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REVIEW

Secondary metabolites of fungi from marine habitats†

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Covering: 2006 to mid-2010

Marine-derived fungi continue to produce structurally unique secondary metabolites, a considerable number of which display promising biological and pharmacological properties. This review gives an overview of new natural products from marine-derived fungi and their biological activities, focusing on the period from 2006 until mid-2010. Overall, 690 structures and 478 references are presented.

1 Introduction

In recent years, secondary metabolites obtained from marine-derived fungi have gained considerable attention, as many of them are structurally unique and possess interesting biological and pharmacological properties. From the time of the more-or-less accidental discovery of cephalosporin C in 1949, which was produced by a culture of a *Cephalosporium* species obtained off the Sardinian coast, it took another thirty years for marine-derived fungi to be more systematically evaluated for their chemical potential. A sharp increase in the number of published structures from this source occurred at the beginning of the 1990s, and this trend continues today. It is the aim of this review to give an overview on secondary metabolites from marine-derived fungi and their biological activities, focusing on the period from 2006 until mid-2010. For earlier years, review papers with a similar scope have been published in *NPR*, including those by Bugni & Ireland in 2004,[1] and Saleem *et al.* in 2007.[2] We also mention briefly important developments that have occurred in terms of characterisation of microbial (and most importantly fungal) communities by molecular biological methods, first from algae, but recently also from sponges. Sponges and algae are the top-ranking sources of marine fungal diversity, as expressed in the number of new structures reported. On the other hand, the true origin of these fungal strains has been the subject of controversy, with the extreme positions being that they are true symbionts to that they are mere contaminants washed into the sea from terrestrial habitats. Very recent reports, however, provide increasing evidence that, similar to the case of marine bacteria, fungal diversity assessed by molecular methods considerably exceeds culturable diversity, and also that specifically adapted fungal associates might exist.

2 Definition of marine fungi

Marine fungi are an ecologically rather than physiologically or taxonomically defined group of organisms. According to the "classic" definition that appears to be universally accepted in the scientific community, marine fungi are divided into two groups, obligate and facultative marine fungi – *obligate* marine fungi are those that grow and sporulate exclusively in a marine or estuarine habitat, while *facultative* marine fungi are those from freshwater or terrestrial milieus able to grow (and possibly also to sporulate) in the marine environment.[3] It has been suggested that indigenous marine species (obligate and facultative) should be separated from non-indigenous species (sometimes referred to as "contaminants" or "transients", *i.e.* terrestrial or freshwater species that are dormant in marine habitats) based on their germination ability,[3] but in practical terms this is difficult to achieve. Moreover, there is

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an increasing tendency to identify marine fungi by molecular biological methods that do not require sexually reproducing life stages, for example sequencing of rDNA, instead of traditional approaches based on morphological characteristics.

3 Biology of marine fungi

3.1 Taxonomy and biological diversity

Based on the distinction between obligate and facultative marine fungi, it can clearly be stated that among the former there are taxa which are exclusively found in the marine environment, while by definition, this is not the case for the latter. A recent monographic treatment of filamentous marine fungi listed at total of 530 species in 321 genera, among them 424 species within Ascomycota (in 251 genera), 94 species of anamorphic fungi (in 61 genera) and only 12 species within Basidiomycota (in 9 genera).[4] These figures apply to those marine taxa that can be isolated or cultivated by classical microbial techniques, and that have been studied in detail and taxonomically described by marine mycologists, while the overall figures are expected to be much higher. For example, analysis of the mangrove plant *Kandelia candel*, sampled at a single nature reserve in Hong Kong, resulted in more than 50 taxonomically distinct isolates for this one host species.[5] It has also been suggested that the fungal diversity in individual habitats so far has been underestimated considerably, exemplified by the situation of sediment-borne marine fungi which avoid microscopic detection due to their tendency to form aggregates.[6]

On the other hand, there is a pronounced difference regarding the biological diversity accessible by cultivation-based methods, and the diversity evident from molecular biological studies which rely on gene sequences present in environmental samples. This phenomenon has been demonstrated when analysing methane hydrate bearing deep-sea marine sediments for fungal gene sequences,[7] but is by no means restricted to marine fungi. On the contrary, similar observations have been made in virtually all microbiological disciplines, with molecular studies giving evidence for the presence of taxonomic groups which have no known closely related cultivated representatives.

In terms of global fungal diversity, a commonly used estimate is that while 74,000 fungal species have been described, the overall expected diversity amounts to 1.5 million species.[8] While critics have questioned the validity of this figure, a more recent "rigorous, minimum estimate of global fungal diversity" came to the conclusion that there are at least 712,000 extant fungal species worldwide.[9]

3.2 Ecology of fungal communities

Marine fungal strains have been obtained from virtually every possible marine habitat, including inorganic matter (soil, sediments, sandy habitats, artificial substrates, and the water column), marine microbial communities, marine plants (algae, sea grasses, driftwood and other higher plants, especially mangrove plants), marine invertebrates (most notably sponges, but also corals, ascidians, holothurians, bivalves, crustaceans) and vertebrates (mainly fishes). However, it is worth mentioning that the fraction of culturable isolates is very low, *i.e.* in the range of 1% or less, with regard to the overall estimated biodiversity, similar to the situation with bacteria. As described above, marine plants, especially from mangrove habitats, harbor an enormous diversity of fungal associates. Since algae are the most prevalent source of marine fungi for chemical studies (see below), it is not surprising that they have been the subject of meticulous studies regarding their fungal communities. Using molecular techniques such as denaturing gradient gel-electrophoresis (DGGE), it has been demonstrated that the brown alga *Fucus serratus* harbours a distinct pattern of fungi which based on their rDNA sequences belonged to the *Lindra*, *Lulworthia*, *Engyodontium*, *Sigmoidea*/*Corollospora* complex, and *Emericellopsis*/*Acremonium*-like ribotypes. In a parallel culture-based approach, 336 isolates representing 35 genera of the Ascomycota and Zygomycota were obtained, including *Sigmoidea marina* and *Dendryphiella salina*, together with members of the genera *Acremonium* (most of them

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Rainer Ebel

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representing the new endophytic species *Acremonium fuci*), *Cladosporium* and *Fusarium*.[10–12]

On the other hand, marine animals, especially sponges, have also been demonstrated to represent a rich source of fungal diversity. The ecological role of fungal associates within sponges has been controversial from the very beginning, since due to their enormous filtering capacities, sponges are to be expected to effectively concentrate microorganisms from the surrounding water column. However, for sponge-associated bacteria, it has been shown that most of the bacterial strains present within sponges (where they can contribute to up to 40% of the volume) are highly adapted and specialized symbionts, with sponge-derived taxa collected from various geographic locations and different sponge hosts being more closely related to each other than to any other free-living taxa.[13–15] Numerous cultivation-based studies with marine sponges have shown enormous biological diversity for the isolates obtained, with at least some of them displaying close affiliation with fungi from marine habitats, although in most cases genera already described from terrestrial habitats were dominating.[16–21] However, a recent DGGE-based study provided evidence for sponge-specific patterns of distribution, and possibly even for the existence of sponge-specific fungal clades.[22]

4 Chemistry and biological activity

4.1 Sources of fungi for chemical studies

Fig. 1 gives an overview of new chemical structures from marine-derived fungi reported in the literature until mid-2010. It should be noted that it is not always possible to assign a given report to a given source, since there is a deplorable general trend to disclose little to virtually no information at all, especially for fungi from mangrove habitats.[23] Thus, while it was possible to assign publications until 2002 to categories such as plants or sediments,[1] this is no longer possible in recent years, as reflected by the introduction of an additional category "mangrove habitats" in the key report on marine natural products published annually in this journal.[23] Based on these considerations, it can be estimated that roughly two-thirds of all new compounds reported from marine fungi are derived from isolates from living matter, with an approximately even split between plant and animal sources in the broadest term, while the remaining compounds are due to fungi from non-living sources, most notably sediments. Within the individual groups, algae are the predominant sources for fungal diversity, closely followed by sponges and mangrove habitats. An interesting newly emerging source is the deep sea, and only a handful of reports exist describing new secondary metabolites from fungi derived from this habitat, all of them actually obtained from deep sea sediments, which consequently have been assigned to the sediment category. It is interesting to compare the present chart to the one provided 8 years ago by Bugni and Ireland.[1] The most dramatic change that has occurred in the meantime is certainly the dramatic increase in reports from Chinese scientists, with most of them studying fungal isolates from mangrove areas on the subtropical island of Hainan.

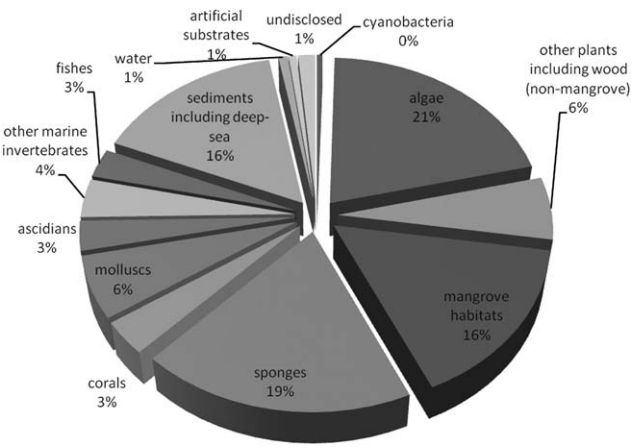


Fig. 1 New compounds from marine-derived fungi until mid-2010, divided by sources of the fungal strains.

4.2 General aspects of secondary metabolism

From the number of new compounds published each year (Fig. 2), it is evident that natural products chemistry of marine-derived fungi is rapidly developing, and still has not reached its climax. While in the period covered by the first review of this series, *i.e.* from the beginning until 2002, 272 new structures had been reported, in 2009 alone more than two-thirds of this figure was reached, and it can be projected that in 2010, approximately 200 new structures will be reported. The total number of new natural products from marine-derived fungi currently exceeds 1000.

Fig. 3 gives an overview of new chemical structures from marine-derived fungi reported in the literature until mid-2010, based on their putative biogenetic origin. In most cases, assignments of a given metabolite to a certain category is only based on structural considerations, and only represents the authors' personal judgement. It is also clear that any approach to classify the enormous structural diversity of marine fungal-derived metabolites according to biogenetic categories is somewhat arbitrary, since there are numerous examples of mixed biogenesis, such as PKS–NRPS (polyketide synthase–non-ribosomal peptide synthase) hybrids, *e.g.* responsible for the generation of pseurotin congeners,[24] or the numerous cases of prenylated alkaloids and prenylated polyketides. Obviously, for some groups of compounds it was necessary to compromise in order to avoid too many different categories, as exemplified by the very

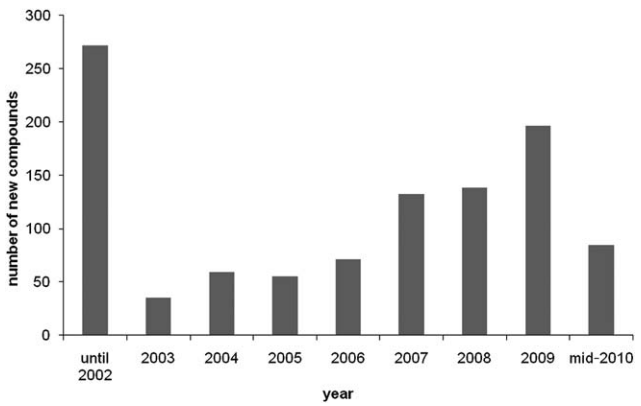


Fig. 2 New compounds from marine-derived fungi, according to year of publication.

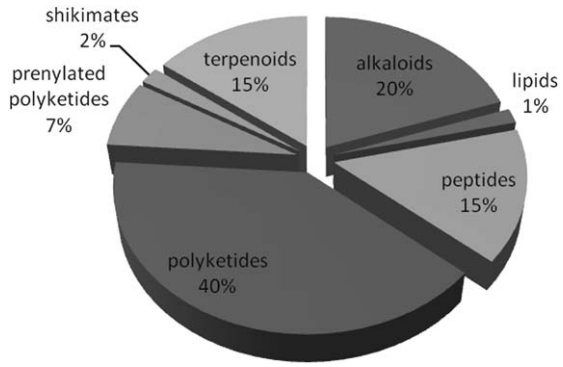


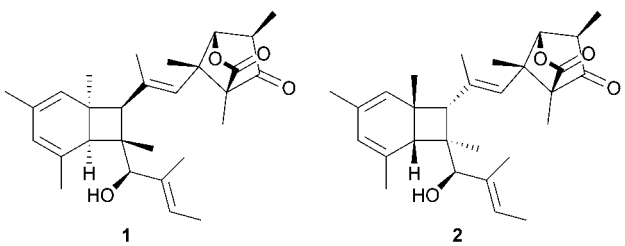
Fig. 3 New compounds from marine-derived fungi until mid-2010, divided by structural/biogenetic types.

common diketopiperazines, which have been listed as (di-)peptides, rather than alkaloids.

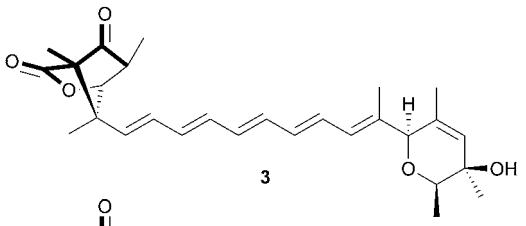
As evident from Fig. 3, polyketides play a dominant role, and if prenylated polyketides and nitrogen-containing polyketides (grouped as alkaloids in this overview) are taken into account, their total share will exceed 50% of all new natural products from marine-derived fungi, which is similar to the situation of terrestrial fungi. A clearly emerging picture based on molecular sequence data is that fungal polyketide synthases (PKS) can be grouped into three subtypes, *i.e.* non-reducing, partially-reducing and highly-reducing, and for the limited number of fungal secondary metabolites for which biogenetic gene clusters have been identified and characterised, this division is also reflected in the relevant structures of the natural products.[25] However, no attempt was undertaken in this review to further divide the large group of polyketides along these lines, since the vast number of reported structures would have required extensive speculation.

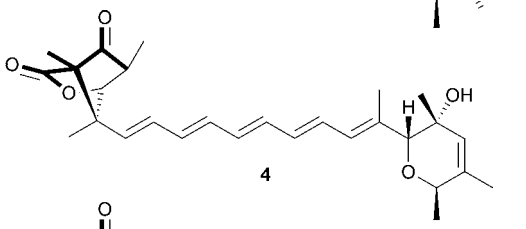
4.3 Polyketides

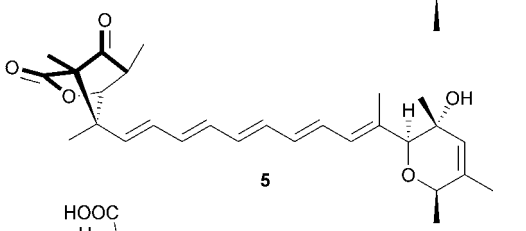
Shimalactones A (**1**) and B (**2**) are unusual polyketides with a novel carbon framework containing a bicyclo[4.2.0]octadiene and an oxabicyclo[2.2.1]heptane unit.[26,27] They are produced by an isolate of *Emericella variecolor* which was obtained from a sediment sample collected in Japan. **1** and **2** induced neuritogenesis in neuroblastoma Neuro2A cells at a concentration of 10 μg mL^{-1}, but were cytotoxic at higher concentrations.

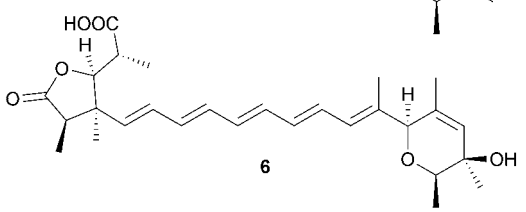


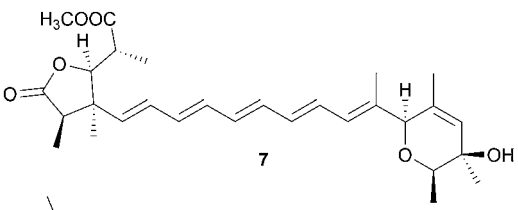
Chemical analysis of the fungus *Penicillium rugulosum*, isolated from the Mediterranean sponge *Chondrosia reniformis*, yielded a series of structurally unusual tricyclic and bicyclic pentaenes, prugosenes A1 (**3**), A2 (**4**), A3 (**5**), B1 (**6**), B2 (**7**), C1 (**8**), and C2 (**9**).[28] Through feeding studies labelled precursors, **3** was established as an undecaketide, with all branching methyl groups being derived from *S*-adenosyl-methionine. The oxabicyclo[2.2.1]-heptane core present in **3–5** had previously only been reported for shimalactones A (**1**) and B (**2**) from an marine-derived *Emericella variecolor*,[26,27] and more recently for coccidiostatin A, a metabolite from a terrestrial isolate of *Penicillium rugulosum*.[29] Upon treatment of **3** with diluted alkali, **6** was obtained as a major and **8** as a minor product, suggesting that **6** is formed by hydrolytic cleavage of the C-2–C-3 bond, while the formation of the cyclopentenone system of **8** and **9** should include decarboxylation of the bicyclic system of the A-type prugosenes (**3–5**). None of the compounds were active when tested for antimicrobial activity against several bacterial and one fungal strain.

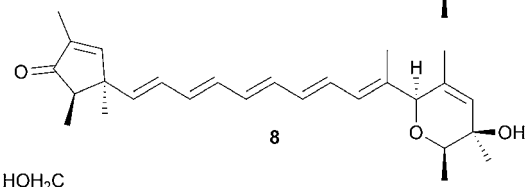


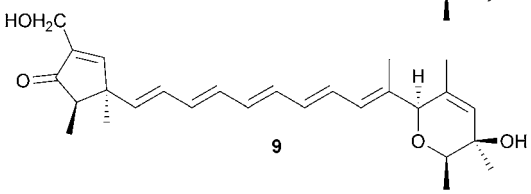






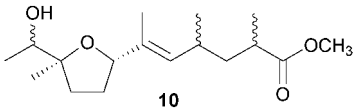






The fungus *Rhizopus* sp. was isolated from the Chinese bryozoan *Bugula* sp., and was found to produce aspericins A–C

(**10–12**), along with the related asperic acid.[30] Asperic acid, so far the only compound reported from nature with the same carbon skeleton as present in **10–12**, had previously been obtained from a saltwater culture of sponge-derived *Aspergillus niger*.[31] When tested for cytotoxic properties against four different cell lines, only **12** displayed moderate activity.



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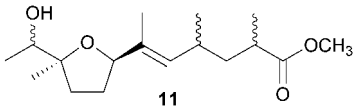

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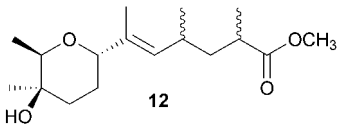

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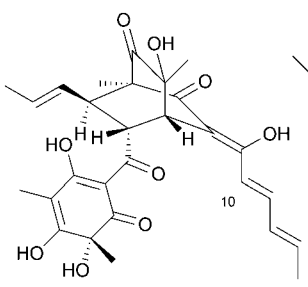
Bisorbicillinoids have frequently been reported from marine-derived fungi, and are thought to arise biosynthetically *via* a Diels–Alder cycloaddition of two sorbicillinol or oxosorbicillinol moieties. Oxosorbiquinol (**13**) and its 10,11-dihydro derivative (**14**) were discovered when investigating a deep-sea isolate of *Phialocephala* sp., collected from sediments at a depth of 5059 m.[32] Compounds **13** and **14** displayed weak cytotoxic activity against five different cancer cell lines. Apart from sorbiquinol,[33] previously reported form a terrestrial *Trichoderma longibrachiatum*, **13** and **14** are the only bisorbicillinoids connected through the six-membered ring of one monomer and the unsaturated side chain of the other one. The same strain also yielded the first sorbicillin trimer, trisorbicillinone A (**15**), which displayed moderate cytotoxicity against P388 and HL60 cells.[34] A recent re-examination of the fermentation broth yielded three further congeners, trisorbicillinones B–D (**16–18**), all of which exhibited only very weak cytotoxicity.[35] The sorbicillinoid 6-demethylsorbicillin (**19**) and the bisorbicillinoid 10,11-dihydrobisvertinolone (**20**) were isolated together with nine known sorbicillinoids and bisorbicillinoids from the fungus *Trichoderma* sp. which was obtained from a Chinese sediment sample.[36] All compounds exhibited mild cytotoxicity towards the HL-60 cell line, and also led to an increase in the percentage of cells in the sub-G_1 fraction, compared to the control.



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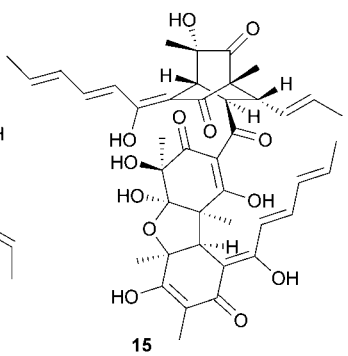
14 (10,11-dihydro)



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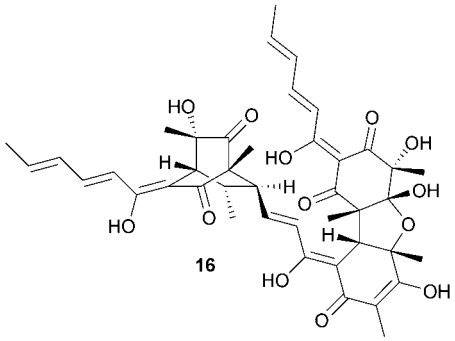

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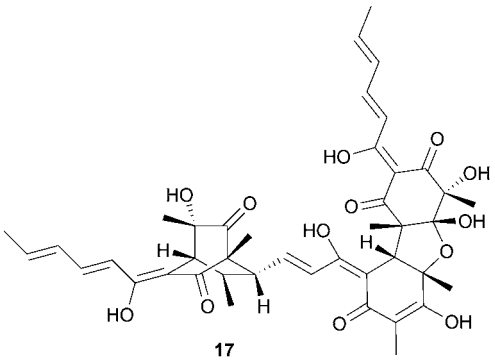

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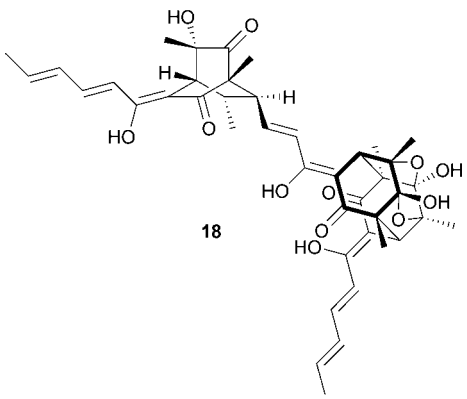

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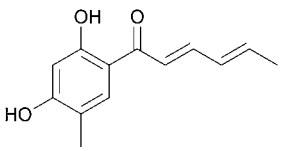

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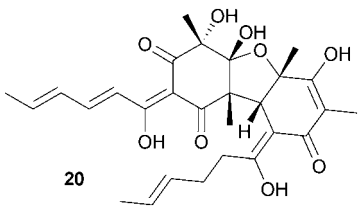

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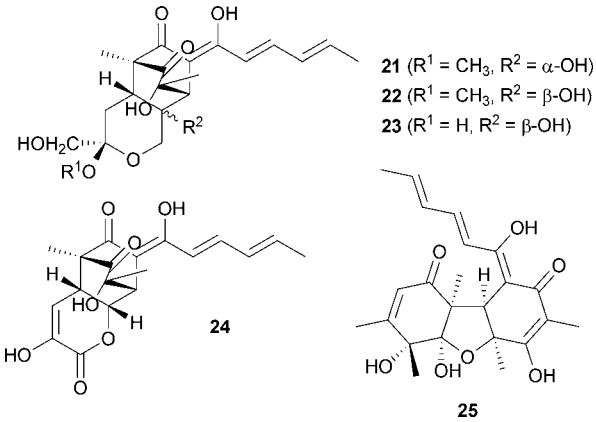
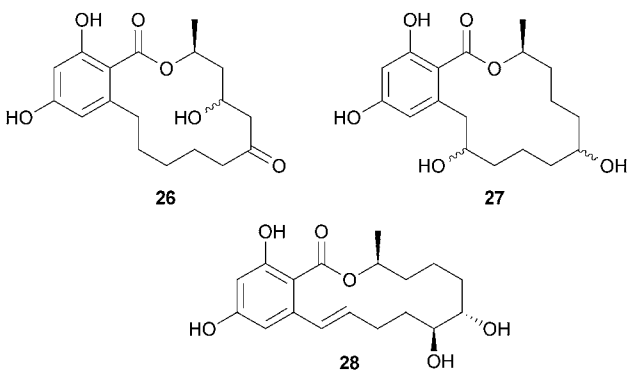
Trichodermanones A–D (**21–24**) are new sorbicillinoid polyketide derivatives with an unprecedented tricyclic ring system produced by the fungus *Trichoderma* sp. isolated from the Caribbean sponge *Agelas dispar*.[37] Compounds **21–23** exhibited moderate radical scavenging activity in the DPPH assay, but were devoid of antimicrobial, antiparasitic and cytotoxic properties, or inhibitory properties toward phosphatase, acetylcholine esterase and trypsin. Based on structural considerations, **21–24** are thought to be biosynthesised by Diels–Alder cycloaddition of the hexaketide sorbicillinol with a triketide unit. An isolate of *Penicillium citrinum*, obtained from an unidentified

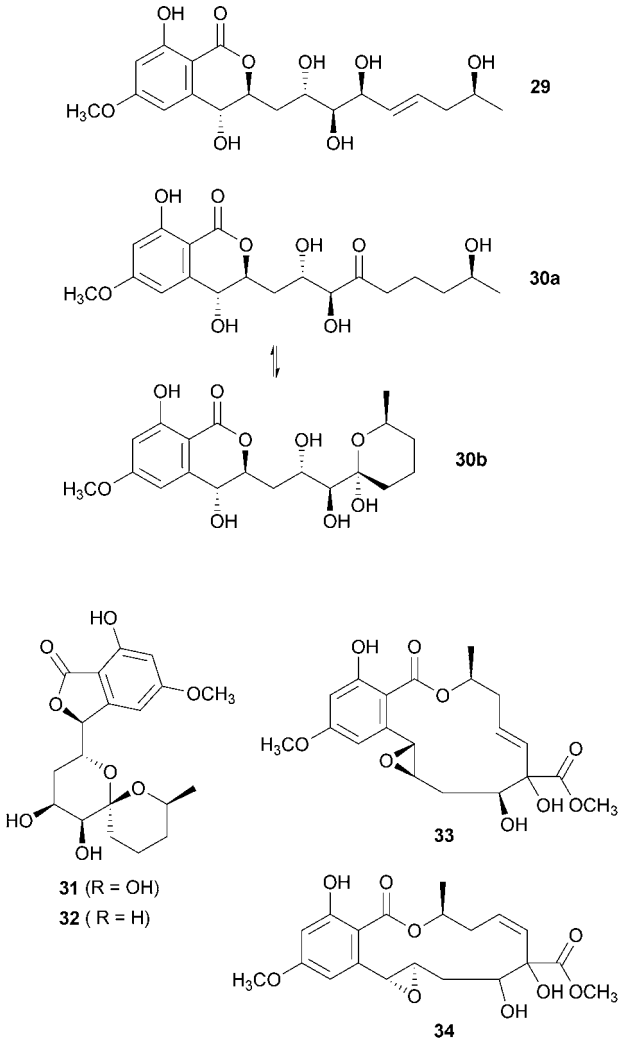
Japanese demosponge, yielded JBIR-59 (**25**), along with a series of known sorbicillinoids.[38] Based on structural considerations, **25** is assumed to be formed by reaction of sorbicillin and the known trihydroxyquinol USF 406A,[39] a metabolite of the soil-borne fungus *Mortierella* sp.



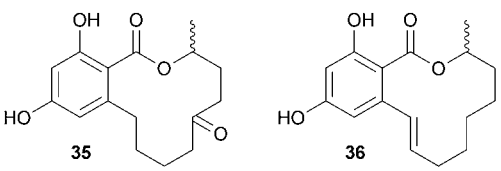
The fungus *Penicillium* sp. which was isolated from the surface of the drifting cotton clothing collected off an island in Korea, was found to produce two new resorcylic acid-containing 14-membered lactones, 8′-hydroxyzearalanone (**26**) and 2′-hydroxy-zearalanol (**27**).[40] Zearalanone, originally described from a terrestrial *Gibberella zeae*,[41] and three further known congeners were also detected in the culture broth. Compounds **26** and **27** did not possess radical scavenging activity, antibacterial activity, or inhibitory properties toward tyrosinase, even though similar biological activities had previously been reported for zear-alanones. Compound **26**, zearalenone and zearalenol were like-wise identified as metabolites of a *Fusarium* sp. derived from an undisclosed Japanese sponge, together with the new derivative 5′-hydroxyzearalenol (**28**),[42] which was devoid of antifungal or antimitotic activity.



A strain of the lignicolous mangrove ascomycete *Aigialus parvus* was reinvestigated and yielded six new nonaketide metabolites, aigialomycins F (**29**) and G (**30a/30b**), 7′,8′-dihy-droaigialospirol (**31**), 4′-deoxy-7′,8′-dihydroaigialospirol (**32**), and rearranged macrolides **33** and **34**,[43] along with the known compounds hypothemycin, aigialomycins A and B, aigialospirol, 4-*O*-demethylhypothemycin, and aigialone, previously reported from the same fungus.[44,45] None of the new metabolites displayed antimalarial or cytotoxic properties. Hypothemycin is a resor-cylic macrolide that was first reported from a terrestrial specimen of *Hypomyces trichothecoides*,[46] and has attracted considerable attention due to its protein kinase inhibitory profile.[47]

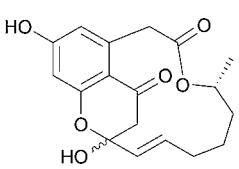


Two new 12-membered lactones of the lasiodiplodin-type, **35** and **36**, in addition to known lasiodiplodins, were identified as metabolites of an unidentified endophytic fungus, which was isolated from the Chinese brown alga *Sargassum* sp.[48] Only the known congeners displayed various degrees of antimicrobial activity.

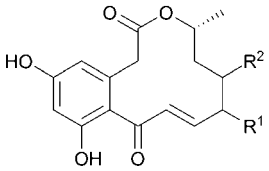


Chemical analysis of the marine fungus *Curvularia* sp., isolated from the red alga *Acanthophora spicifera* collected in Guam, resulted in the discovery of the novel macrolide apralactone A (**37**), together with the antipodes of known curvularin macrolides (**38–43**).[49] The dimeric curvularin (**44**) was recognised as an artefact. Compound **37** is a 14-membered phenyl acetic acid macrolactone, and the first such compound with a 4-chromanone substructure. Compounds **37**, **38**, and **40–42** displayed varying

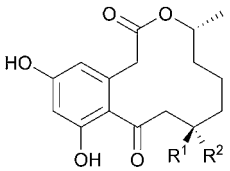
degrees of cytotoxicity towards a panel of 36 human tumour cell lines, with mean IC_{50} values in the range 1.25 to 30 μM.



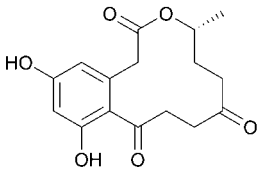
37



38 (R^1 = H, R^2 = H)
39 (R^1 = OH, R^2 = H)
40 (R^1 = H, R^2 = OH)



41 (R^1 = H, R^2 = OH)
42 (R^1 = OH, R^2 = H)



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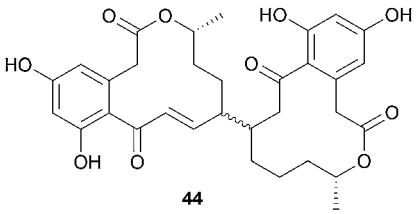
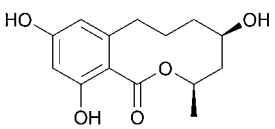
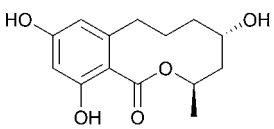


44

An unidentified endophytic fungus, isolated from the Chinese mangrove plant *Sonneratia apetala*, produced two new 10-membered lactones, (3*R*,5*R*)-sonnerlactone (**45**) and its (3*R*,5*S*) diastereoisomer (**46**).[50] Both **45** and **46** displayed weak inhibitory effects towards the multi-drug resistant cancer cell line KV/MDR.

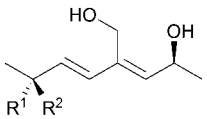


45

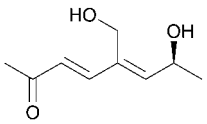


46

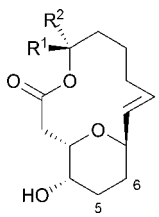
Three pentaketides, aspinotriols A (**47**) and B (**48**) and aspinonediol (**49**), together with the known aspinonene[51] and dihydroaspyrone,[52] metabolites from a terrestrial isolate of *Aspergillus ochraceus*, were obtained from the culture of an *Aspergillus ostianus* strain isolated from an unidentified marine sponge at Pohnpei, Micronesia.[53] Since the same strain previously had produced new chlorinated pentaketides when fermented in natural seawater,[54] a culture medium containing large amounts of bromine was used. Even though no brominated compounds were detected, the metabolite profile of the fungus changed considerably compared to the previous study. When screened for activity towards MRSA and cytotoxic properties, only aspinonene displayed mild inhibitory properties towards mouse lymphocytic leukemia cells.[53] A further chemical investigation of the same fungus under identical culture conditions led to the discovery of three new 14-membered macrolides, aspergillides A–C (**50–52**).[55] Even though 14-membered macrolides in general are frequently reported from fungi, **50–52** are unusual since they represent the first congeners with an additional tetrahydropyran or dihydropyran ring, respectively. All three proved inactive when tested for antimicrobial activity toward MRSA, however, the compounds exhibited moderate cytotoxicity toward mouse lymphocytic leukemia cells (L1210).



47 (R^1 = OH, R^2 = H)
48 (R^1 = H, R^2 = OH)

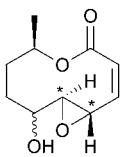


49

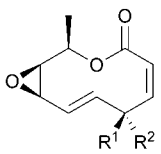


50 (R^1 = CH_3, R^2 = H)
51 (R^1 = H, R^2 = CH_3)
52 (R^1 = CH_3, R^2 = H, $\Delta_{5,6}$)

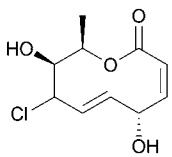
The fungus *Curvularia* sp., obtained from the red alga *Acanthophora spicifera* collected in Guam, produced four ten-membered lactones, curvulide A (**53**), a mixture of curvulides B_1 (**54**) and B_2 (**55**) and another congener **56**.[56] Compounds **53–56** are related to other lactones including modiolides[57] or decarestrictines,[58] previously reported from a marine-derived *Paraphaeosphaeria* sp. and from terrestrial *Penicillium* spp., respectively, but differ with regard to their oxygenation pattern. None of the new congeners was active when tested for antibacterial, antifungal, or antialgal properties.



53

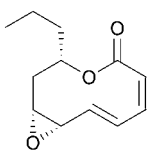


54 (R^1 = OH, R^2 = H)
55 (R^1 = H, R^2 = OH)

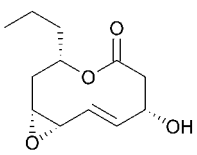


56

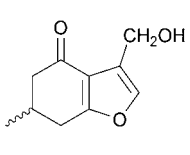
The strain *Phomopsis* sp. of undisclosed marine origin produced two very closely related new 10-membered macrolides, phomolides A (**57**) and B (**58**), and the new 3-(hydroxymethyl)-6-methyl-6,7-dihydrobenzofuran-4(5*H*)-one (**59**).[59] All compounds were devoid of cytotoxic activity, but displayed antimicrobial activity against *Escherichia coli*, *Candida albicans*, and *Saccharomyces cerevisiae*, while **59** also showed strong activity against *Bacillus subtilis*.



57



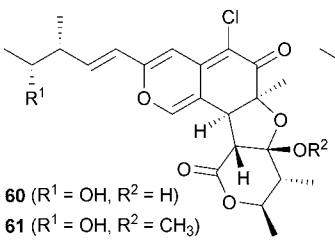
58



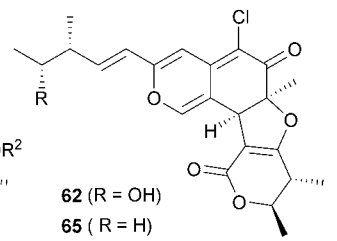
59

The fungus *Chaetomium globosum*, originally isolated from the Japanese fish *Mugil cephalus*, is the source of a complex series of

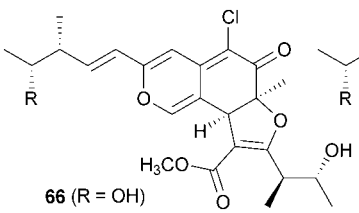
azaphilones, chaetomugilins. Initially, chaetomugilins A–C (**60–62**) were reported, of which **60** and **62** exhibited significant cytotoxic activity against P388 and HL-60 cell lines.[60] A subsequent report disclosed the structures of chaetomugilins D–F (**63–65**), and all compounds were tested for cytotoxic activity profiles against a panel of 39 human cancer cell lines.[61] Compound **65** exhibited remarkable growth inhibition in combination with selective cytotoxic activity, and evaluation of the activity profiles with the COMPARE program suggested that the mode of action for **60**, **62** and **65** might be different from any other anticancer drug developed to date. Further chemical analysis revealed chaetomugilins G (**66**) and H (**67**), with **66** exhibiting significant cytotoxicity against the P388 and HL-60 cell lines, while **67** was moderately active against KB cell line.[62] Furthermore, seco-chaetomugilins A (**68**) and D (**69**) were discovered, of which **69** exhibited significant cytotoxic activity against the cell lines P388, HL-60, L1210 and KB.[63] Investigations into the stability and the chemical reactivity indicated that neither of compounds **66–69** was an artefact resulting from degradation of **60** or **61**. The next additions to this series of azaphilones were chaetomugilins I–O (**70–76**), and all compounds apart from **74** exhibited significant cytotoxic activity against various cancer cell lines.[64] Compound **70** was subjected to detailed activity profiling in a panel of 39 human cancer cell lines, and the COMPARE program suggested that it possessed a novel mechanism of action. Recently, the two stereoisomers of **60**, 11-*epi*-chaetomugilin A (**77**) and 4′-*epi*-chaetomugilin A (**78**), were discovered upon reinvestigation of the same fungus.[65] Compound **77** exhibited moderate activity against P388 and HL-60 cell lines, but marginal activity against L1210 and KB cell lines, whereas **78** was only marginally active against all cell lines.



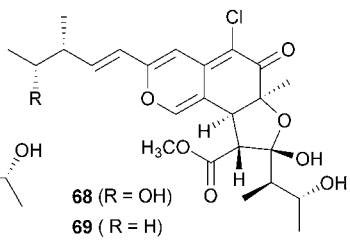
60 (R^1 = OH, R^2 = H)
61 (R^1 = OH, R^2 = CH_3)
63 (R^1 = H, R^2 = H)
64 (R^1 = H, R^2 = CH_3)



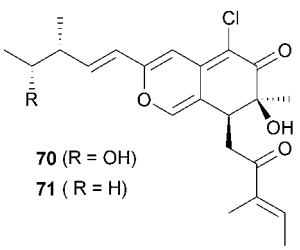
62 (R = OH)
65 (R = H)



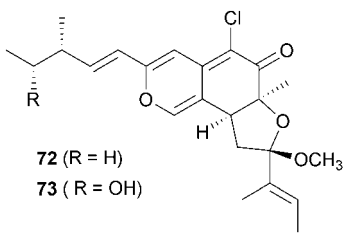
66 (R = OH)
67 (R = H)



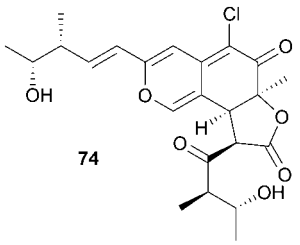
68 (R = OH)
69 (R = H)



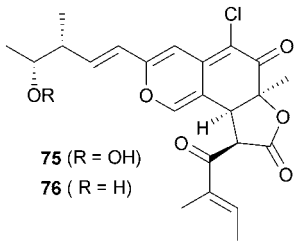
70 (R = OH)
71 (R = H)



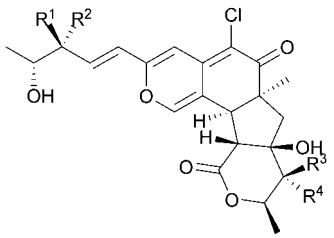
72 (R = H)
73 (R = OH)



74

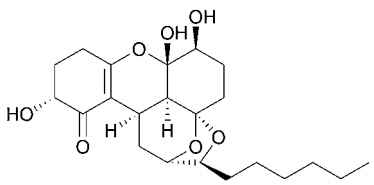


75 (R = OH)
76 (R = H)



77 (R^1 = CH_3, R^2 = H, R^3 = H, R^4 = CH_3)
78 (R^1 = H, R^2 = CH_3, R^3 = CH_3, R^4 = H)

Trichodermatides A–D (**79–82**) have been characterised from the fungus *Trichoderma reesei*, obtained from a Chinese sediment sample.[66] Compound **79** is the first example of a pentacyclic polyketide with a ketal moiety, and similar to the remaining compounds, displayed mild cytotoxic activity against the A375-S2 (human melanoma) cell line. Octaketide derivatives with an α,β-unsaturated cyclohexenone fused to a pyran ring such as **79–82** have so far been reported from the terrestrial fungus *Trichoderma harzianum*,[67,68] but do not appear to occur elsewhere in Nature.



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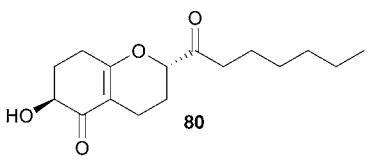

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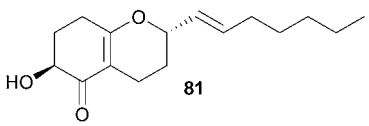

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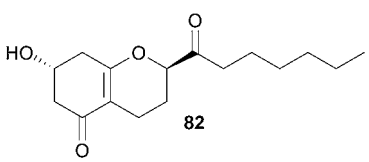
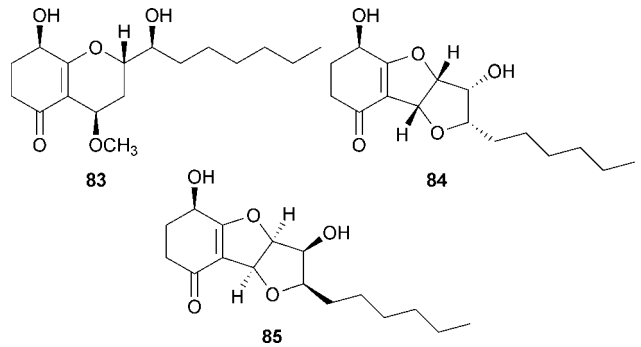


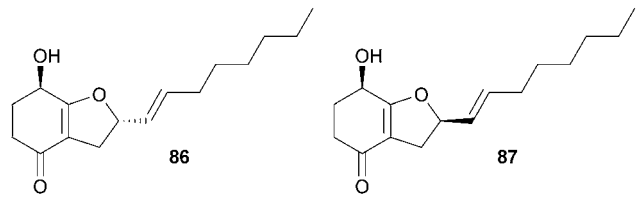
82

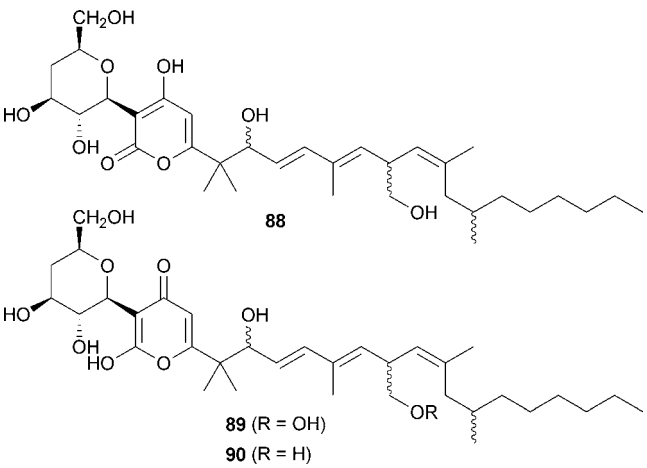
The fungus *Trichoderma koningii*, isolated from marine mud of the South China Sea, produced 7-*O*-methylkoninginin D (**83**) and trichodermaketones A–D (**84–87**), together with four koninginin derivatives.[69] Koninginin D had previously been reported form a terrestrial strain of *Trichoderma koningii*.[70]

Compounds **83–87** did not display antimicrobial activity against methicillin-resistant *Staphylococcus aureus* or *Candida albicans*, but **84** showed synergistic antifungal activity against *C. albicans* with ketoconazole, albeit at rather high concentrations.

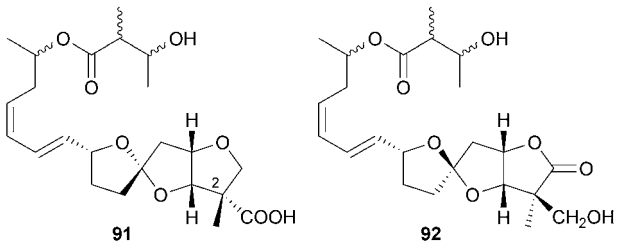
An isolate of the fungus *Fusarium* sp. (section *Liseola*), which was obtained from driftwood collected in Japan, yielded neofusapyrone (**88**), fusapyrone (**89**), and deoxyfusapyrone (**90**).[71] Compounds **89** and **90** had initially been described from *Fusarium semitectum* and were thought to be α-pyrones,[72] while their structures were revised to γ-pyrones in the present investigation. All three displayed weak antifungal activity against *Aspergillus clavatus*.

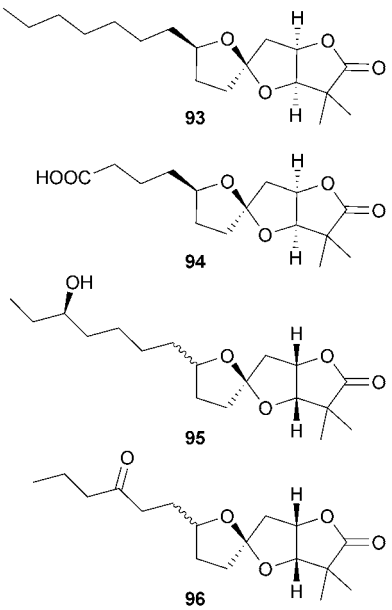




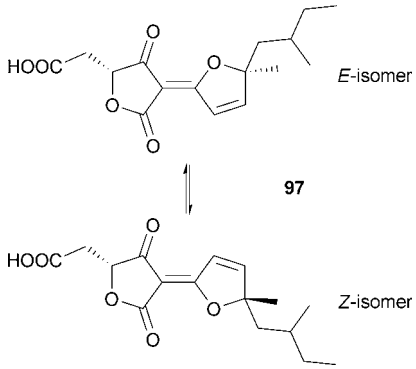


The endophytic fungus *Ascochyta salicorniae* was obtained from the green alga *Ulva* sp., collected from the German North Sea. A reinvestigation of this strain, which previously had the tetramic acids ascosalipyrrolidinone A and B as well as the polyketide ascosalipyrone,[73] resulted in the discovery of biogenetically unique cycloethers, ascospiroketals A (**91**) and B (**92**),[74] composed of a methylated diketide attached to a highly modified octaketide *via* an ester link. From a biosynthetic point of view, the presence of two additional carbon atoms attached to C-2 of the octaketide part is striking, since extender units other than malonyl-CoA are not known from fungal polyketides, and these two carbons thus most probably arise from geminal biomethylation *via* *S*-adenosyl-methionine, a very rare process that seems to be unprecedented in the context of fungal polyketides. Two closely related metabolites, cephalosporolides H (**93**) and I (**94**), were obtained from a *Penicillium* sp. isolated from the Chinese mangrove plant *Kandelia candel*,[75] and shortly after, the same group of authors also reported penisporolides A (**95**) and B (**96**) from a *Penicillium* sp. isolated from the same source,[76] although it is not clear whether or not both strains were identical. Compounds **95** and **96** showed mild inhibitory activity toward xanthine oxidase and 3α-hydroxysteroid dehydrogenase, while **93** and **94** were inactive.

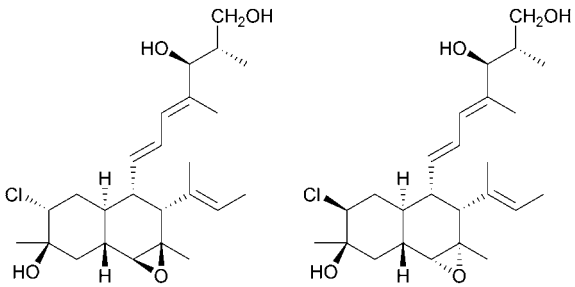




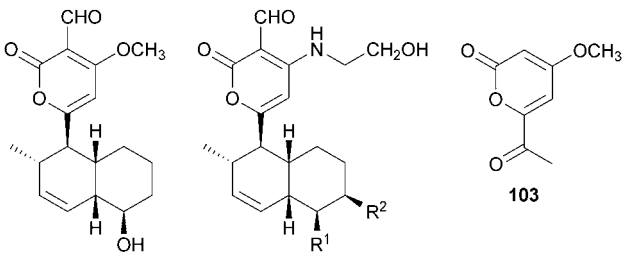
The fungus *Nodulisporium* sp., obtained from a soft coral from Thailand, produced a tetronic acid, nodulisporacid A (**97**).[77] The same communication also reported the presence of vermelhotin,[78] previously described from an unidentified terrestrial fungal strain, in the culture broth of an unidentified sponge-derived fungal strain. Both compounds occurred as equilibrium *E*/*Z* mixtures. Compound **97** is structurally related to lowdenic acid, a metabolite from a terrestrial *Verticillium* sp.[79] When tested for cytotoxic properties, **97** was inactive, but its methyl and benzyl ester displayed a pronounced increase in activity, similar in potency to vermelhotin. Both **97** and vermelhotin also exhibited moderate antiplasmodial activity.



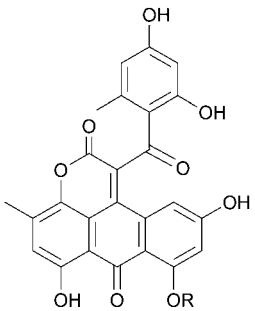
Dehydroxychlorofusarielin B (**98**) is a decalin derivative of *Aspergillus* sp., obtained from the surface of the Korean marine brown alga *Sargassum horneri*.[80] The structure of **98** was established by X-ray crystallography, and it is structurally closely related to fusarielins A and B, previously described from a soil-borne *Fusarium* sp.[81] that were also detected in the culture broth. All three compounds displayed moderate antibacterial activity against *Staphylococcus aureus*, methicillin-resistant *S. aureus*, and multidrug-resistant *S. aureus*. Shortly after this report, fusarielin E (**99**) was described from the culture broth of a marine-derived *Fusarium* sp. of undisclosed origin by a Chinese research group.[82] Even though **99** is claimed to differ from **98** with regard to the configuration at C-11, C-15 and C-16, their NMR data are virtually identical, and it is thus very likely that both compounds are actually identical. At high concentrations, **99** inhibited the conidia growth of *Pyricularia oryzae* by a swelling effect and induced curling deformation of the mycelia.

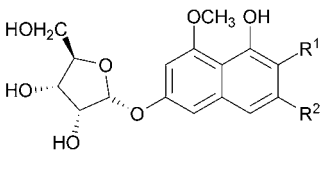


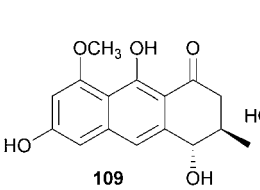
Nigrosporapyrones A–D (**100–103**) were reported, together with a series of known metabolites, from the fungus *Nigrospora* sp. isolated from the sea fan *Annella* sp. in Thailand.[83] Compound **100** exhibited mild antibacterial activity against *Staphylococcus aureus* and methicillin-resistant *S. aureus*.

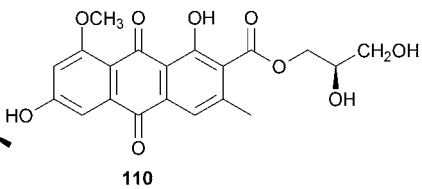


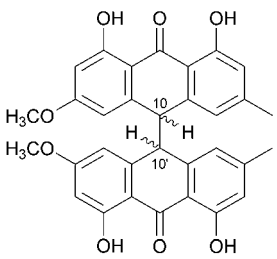
The fungus *Aspergillus glaucus*, which was cultured from sediment around mangrove roots in China, yielded aspergiolide A (**104**), a novel anthraquinone derivative with an unprecedented naphtho[1,2,3-*de*]chromene-2,7-dione skeleton, the structure of which was secured by X-ray diffraction analysis.[84] Compound **104** displayed pronounced cytotoxicity at submicromolar concentrations towards A-549 and HL-60 cells, while it was less active against BEL-7402 and P388 cell lines by approximately two orders of magnitude. More recently, through feeding experiments with labelled acetate units, the biosynthesis of **104** was demonstrated to follow the classical acetate–malonate pathway of aromatic polyketides, and to proceed *via* coupling of an octaketide and a pentaketide precursor.[85] A subsequent study yielded a further congener, aspergiolide B (**105**), together with seven new polyketides.[86] Compounds **106–108** are unusual naphthyl furanosides, isoasperflavin (**109**) is a constitutional isomer of the known asperflavin from a terrestrial-derived *Aspergillus flavus*,[87] **110** was identified as the (+)-enantiomer of the recently described variecolorquinone A from the halotolerant Chinese fungus *Aspergillus variecolor*,[88] while **111** and **112** are new physicon–emodin bisanthrones. When tested against the most susceptible cell lines A-549 and HL-60 of the previous study, the activity of **105** was comparable to **104**, whereas **111** and **112** were only moderately active.





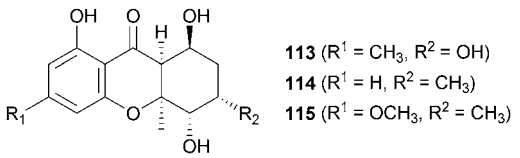




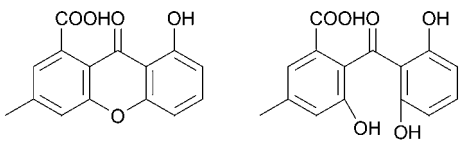


Secondary metabolites produced by the endophytic fungus *Monodictys putredinis*, obtained from an undisclosed green alga,

collected in Tenerife, Spain, were subjected to an in-depth evaluation for potential cancer chemopreventive effects.[89,90] Initially, four new monomeric xanthones, monodictysins A–C (**113–115**) and monodictyxanthone (**116**), and the benzophenone monodictyphenone (**117**) were obtained, all of them thought to be biogenetically derived by oxidative cleavage of a common anthraquinone precursor either between C-4a or C-10a and carbonyl C-10.[89] A more recent reinvestigation resulted in the two dimeric chromanones monodictyochromes A (**118**) and B (**119**), consisting of two unusual naphthoquinone units, which are probably also derived from an anthraquinone precursor *via* a xanthone intermediate, and which are connected by phenol oxidative coupling in a regioselective manner. This coupling should also occur under strict stereoselectivity, since **118** was identified as the (*P*)-atropisomer, while **119** represents the (*M*)-stereoisomer as was deduced by comparison of the pertaining CD spectra with the model compounds, (*P*)- and (*M*)-orsellinic acid camphanate.[90] The cancer chemopreventive potential of **113–119**, expressed as their ability to either inhibit or induce certain enzymes involved in biotransformation of potential carcinogenic agents, was studied using a series of assay systems. At concentrations in the lower micromolar range **114**, **118** and **119** were found to inhibit cytochrome P450 1A, an enzyme that is involved in the metabolic conversion of procarcinogens into carcinogens. Similarly, **114**, **115**, **118** and **119** also moderately induced NAD(P)H:quinone reductase, a carcinogen-detoxifying enzyme. Furthermore, **115**, **118** and **119** were weak inhibitors of aromatase activity, which is essential for the biosynthesis of estrogens.

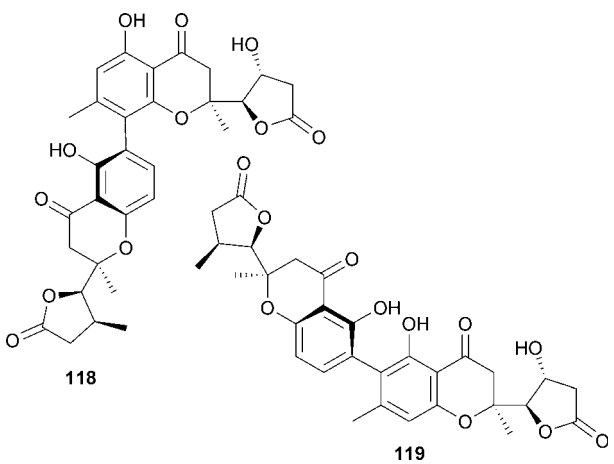


113 (R^1 = CH_3, R^2 = OH)
114 (R^1 = H, R^2 = CH_3)
115 (R^1 = OCH_3, R^2 = CH_3)



116

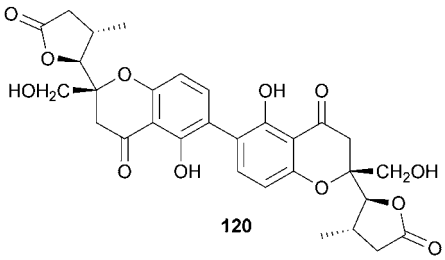
117



118

119

The endophytic fungus *Phomopsis* sp., isolated from the Chinese mangrove tree *Excoecaria agallocha*, produced phomopsis-H76 A (**120**), a dimeric chromanone closely related to monodictyochrome B (**119**), as well as phomopsis-H76 B (**121**), and C (**122**), structurally unique dimeric pyrano[4,3-*b*]pyran-5(2*H*)-ones.[91] In zebra fish embryos, **113** led to a significant acceleration of sub-intestinal vessel plexus (SIV) branching, and all three compounds lacked cytotoxic or antibacterial properties.



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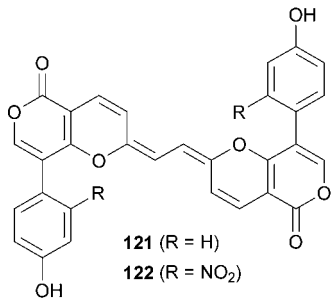
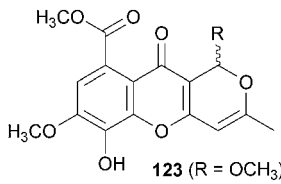
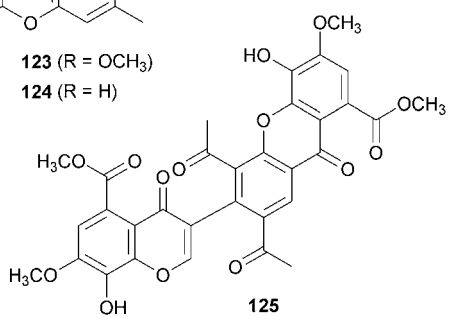


121 (R = H)
122 (R = NO_2)

Chaetocyclinones A–C (**123–125**) were obtained from the culture broth of *Chaetomium* sp., isolated from an undisclosed marine alga.[92] Compound **125** was active towards selected phytopathogenic fungi, but was not found to be cytotoxic. Compound **123** is closely related to anhydrofulvic acid, a metabolite of *Carpenteles brefeldianum* (now named *Eupenicillium brefeldianum*),[93] while **125** differs from vinaxanthone, previously described from *Penicillium vinaceum*[94] only with regard to the oxygenation pattern. Using feeding experiments with ^{13}C-labelled acetate, the biosynthesis of **123** was shown to proceed *via* a linear heptaketide intermediate, which would then undergo oxidative cleavage and recyclisation. Accordingly, the biosynthesis of **125** should involve an unusual two-fold aldol condensation of two highly reactive heptaketide intermediates, but it could not be ruled out that this reaction could occur spontaneously, and that **125** thus represents an artefact.[92]



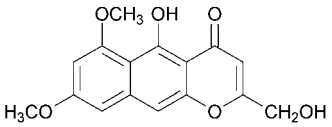
123 (R = OCH_3)
124 (R = H)



125

An endophytic *Aspergillus niger*, isolated from the Chinese brown alga *Colpomenia sinuosa*, yielded three new naphtho-γ-pyrones,

nigerasperone A–C (**126–128**).[95] Compound **126** is a linear naphtho-γ-pyrone, while **127** and **128** are dimers of two angular and two linear naphtho-γ-pyrones, respectively. Compound **128** showed weak antifungal activity against *Candida albicans* and moderate antioxidant activity in the DPPH assay, but none of the compounds exhibited cytotoxic activity.



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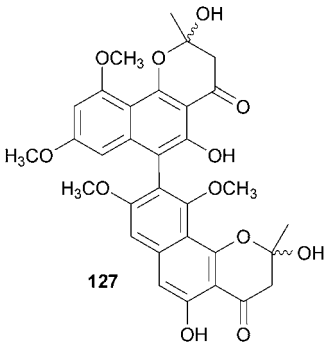
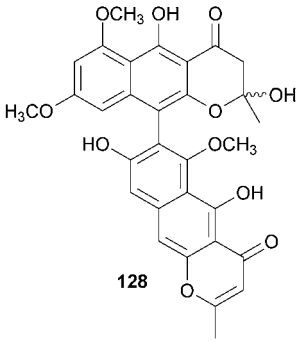


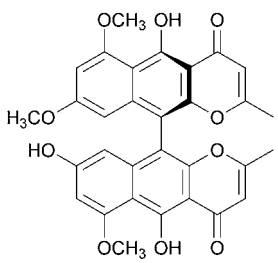
127



128

8′-*O*-Demethylnigerone (**129**) and 8′-*O*-demethylisonigerone (**130**) are two new structurally related dimeric naphtho-γ-pyrones which were detected in the culture broth of the fungus *Aspergillus carbonarius*, isolated from a Chinese sediment sample.[96] Both compounds exhibited mild inhibitory activity against *Mycobacterium tuberculosis*. In a screening effort directed at discovering tyrosine kinase inhibitors using human umbilical vein endothelial cell lysate, out of a total of 200 fungal strains tested, only the fungus *Hypocrea vinosa* isolated from beach sand collected in Japan displayed activity. Chemical analysis revealed the presence of two new bisnaphtho-γ-pyrones, hypochromins A (**131**) and B (**132**), besides the closely related known SC2051, the diketocongener of **131** which so far has only been reported in the patent literature.[97] All three compounds inhibited tyrosine kinase activity in HUVEC lysate, and in addition also inhibited HUVEC proliferation, migration, and tubule formation, thus displaying antiangiogenic potential.

A new naphtho-γ-pyrone, 2-benzyl-5-hydroxy-6,8-dimethoxy-4*H*-benzo[*g*]chromen-4-one (**133**), was reported from the endophytic fungus *Phomopsis* sp., isolated from the Chinese mangrove tree *Excoecaria agallocha*.[98] Compound **133** exhibited moderate cytotoxicity against HEp-2 and HepG2 cell lines. In a screening program aimed at discovering inhibitors of the bacterial two-component regulatory system (TCS), an isolate of



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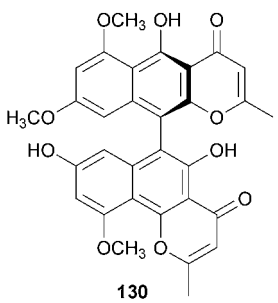

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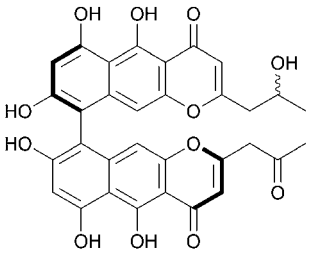

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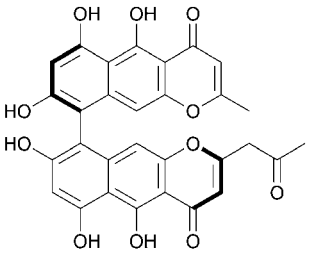
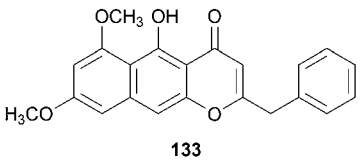


132

Ascochyta sp. from a floating scrap of festering rope in a Japanese fishing port yielded the spirodioxynaphthalene ascochytatin (**134**).[99] **134** which is structurally related to palmarumycins,[100,101] exhibited stronger activity against the temperature-sensitive mutant *Bacillus subtilis* CNM2000 than against wild-type strain 168, suggesting that the compounds inhibited the function of the YycG/YycF-TCS in the bacterium. Furthermore, **134** displayed strong antimicrobial activity against Gram-positive bacteria and *Candida albicans*, and displayed cytotoxicity toward two mammalian cancer cell lines with IC_{50} values in the lower micromolar range.



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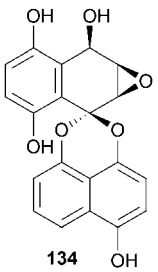
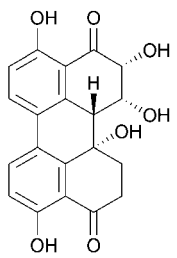


134

7-*epi*-8-Hydroxyaltertoxin I (**135**) and 6-*epi*-stemphytriol (**136**), together with the known perylenequinones altertoxin I and stemphyperylenol, were discovered during chemical analysis of the fungus *Alternaria alternata*, which was cultivated from the inner tissue of the Chinese red alga *Laurencia* sp.[102] Altertoxin I is a known mycotoxin from the plant pathogenic *Alternaria alternata*,[103] while stemphyperylenol was initially reported from *Stemphylium botryosum* var. *lactucum*.[104] None of the compounds displayed any significant antibacterial or antifungal activity.



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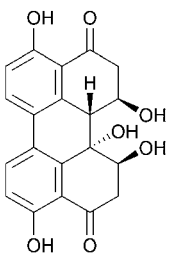
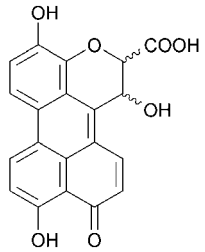


136

The fungus *Alternaria* sp. was isolated from the Chinese mangrove plant *Sonneratia alba*, and identified as a source xanalteric acids I (**137**) and II (**138**), besides a series of known compounds including perylenequinones such as altertoxin I.[105]

Compounds **137** and **138** appear to represent the first natural products with a 10*H*-phenaleno[1,2,3-*de*]chromene skeleton, the only other report of which being that of xanalteric acid, a degradation product of the fungal toxin cercosporin which was obtained following addition of the latter to cultures of the bacterium *Xanthomonas campestris* pv. *zinnia*.[106,107] Compounds **137** and **138** exhibited weak antibiotic activity against multidrug-resistant *Staphylococcus aureus* and only marginal cytotoxicity against L5178Y cells.



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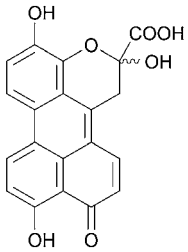
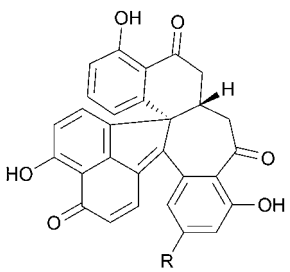
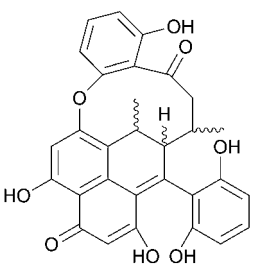


138

The endophytic fungus *Sporothrix* sp., isolated from the Chinese inshore mangrove tree *Kandelia candel*, produced three metabolites with unique ring systems, sporothrins A–C (**139–141**), besides the known 1-hydroxy-8-methoxynaphthalene and 1,8-dimethoxynaphthalene.[108] Biogenetically, **139** and **140** are assumed to arise *via* multiple oxidative coupling reactions of three 1,8-dihydroxynaphthalene units. This assumption was supported by molecular biological investigations revealing the presence of a non-reducing polyketide synthase gene in the genomic DNA of *Sporothrix* sp., which based on BLAST homology search is very likely to be involved in 1,3,6,8-tetrahydroxynaphthalene (T4HN) biosynthesis. Compounds **139** and **140** displayed modest cytotoxic activity against the hepG2 cell line, whereas **139** additionally strongly inhibited acetylcholine esterase (AChE) activity.

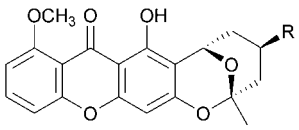


139 (R = H)
140 (R = OH)

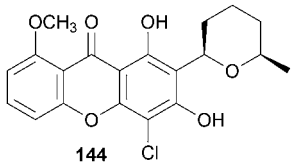


141

The fungal strain *Chaetomium* sp., isolated from an undisclosed Greek alga, was found to produce three structurally unusual xanthones, chaetoxanthones A–C (**142–144**).[109] The dioxane/tetrahydropyran moieties present in **142** and **143** are reminiscent of intermediates of aflatoxin biosynthesis, while **144** is a chlorinated xanthone substituted with a tetrahydropyran ring. Compound **143** displayed selective activity against *Plasmodium falciparum*, with an IC_{50} value of 0.5 μg mL^{-1} without being cytotoxic, whereas **144** was moderately active against *Trypanosoma cruzi*, with an IC_{50} value of 1.5 μg mL^{-1}.

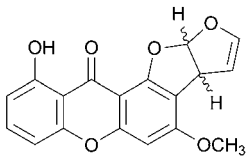


142 (R = OH)
143 (R = H)

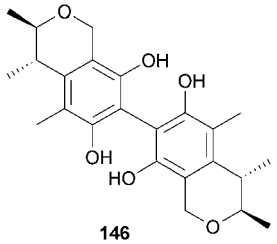


144

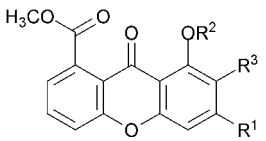
An *Aspergillus* sp. strain that was isolated from sea water in China, yielded a bifuran-substituted xanthone, asperxanthone (**145**) and a biphenyl, asperbiphenyl (**146**), together with a series of known fatty acid monoglycerides.[110] Compounds **145** and **146** moderately inhibited the multiplication of tobacco mosaic virus (TMV). Two new xanthones, 8-(methoxycarbonyl)-1-hydroxy-9-oxo-9*H*-xanthene-3-carboxylic acid (**147**) and dimethyl 8-methoxy-9-oxo-9*H*-xanthene-1,6-dicarboxylate (**148**) were obtained, together with one known congener, methyl 8-hydroxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylate (**149**), from the culture broth of the fungus *Penicillium* sp. that was isolated from the bark of the Chinese mangrove plant, *Acanthus ilicifolius*.[111] The spectral data of **149** indicated that it is in fact identical to janthinone, reported initially as a lactone from a terrestrial endophytic *Penicillium janthinellum*,[112] but in the current study, its structure was revised to **149**, which was secured by X-ray crystallographic analysis. Compound **148** exhibited modest antifungal activity against *Fusarium oxysporum* f. sp. *cubense*. More recently, 7-hydroxyjanthinone (**150**) was isolated from *Penicillium* sp., an endophyte from *Melia azedarach* growing in a Chinese mangrove habitat, and proved to be devoid of cytotoxic activity.[113]



145



146

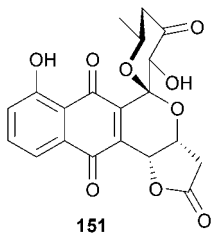


147 (R^1 = COOH, R^2 = H, R^3 = H)
148 (R^1 = $COOCH_3$, R^2 = CH_3, R^3 = H)
149 (R^1 = CH_3, R^2 = H, R^3 = H)
150 (R^1 = CH_3, R^2 = H, R^3 = OH)

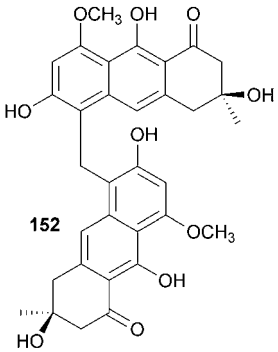
Griseusin C (**151**) is a new, structurally unusual naphthoquinone derivative which was produced by a strain of *Penicillium* sp., an endophyte from the Chinese mangrove plant *Kandelia candel*. Compound **151** displayed very mild inhibitory activity towards 3α-hydroxysteroid dehydrogenase, but was inactive against xanthin oxidase and horseradish peroxidase.[114]

An endophytic fungal strain *Eurotium rubrum*, isolated from the Chinese mangrove plant *Hibiscus tiliaceus*, yielded four new anthraquinone derivatives including the bisdihydroanthracenone eurorubrin (**152**), two seco-anthraquinones 2-*O*-methyl-9-dehydroxyeurotinone (**153**) and 2-*O*-methyl-4-*O*-(α-D-ribofuranosyl)-9-dehydroxyeurotinone (**154**) and the anthraquinone glycoside 3-*O*-(α-D-ribofuranosyl)questin (**155**), together with three known

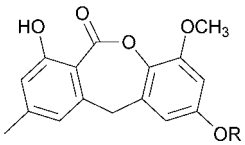
compounds.[115] Compound **152** displayed strong radical scavenging activity in the DPPH assay, exceeding that of the positive control, butylated hydroxytoluene (BHT), whereas the remaining compounds were moderately active.



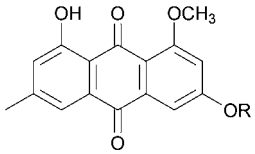
151



152

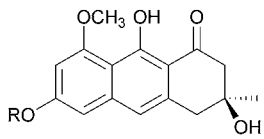


153 (R = H)
154 (R = α-D-ribofuranosyl)



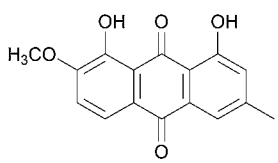
155 (R = α-D-ribofuranosyl)

The fungus *Microsporum* sp. was isolated from the surface of the Korean red alga *Lomentaria catenata*, and was shown to produce the anthracene glycoside, asperflavin ribofuranoside (**156**).[116] This compound exhibited considerable radical scavenging activity in the DPPH assay, and also showed moderate antibacterial activity against methicillin-resistant and multidrug-resistant *Staphylococcus aureus*.



156 (R = α-D-ribofuranosyl)

Monodictyquinone A (**157**) is an anthraquinone that, together with three known congeners was isolated from the marine-derived *Monodictys* sp., obtained from the Japanese sea urchin, *Anthocidaris crassispina*.[117] Compound **157** showed antimicrobial activity against *Bacillus subtilis*, *Escherichia coli* and *Candida albicans*, but was not cytotoxic toward HeLa cells even at high concentrations. The endophytic fungus *Fusarium* sp. from an undisclosed Chinese mangrove plant was reported as a source of the new anthraquinone, 5-acetyl-2-methoxy-1,4,6-trihydroxy-anthraquinone (**158**), besides a series of known naphthoquinones.[118]



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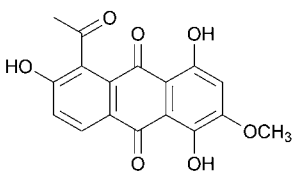
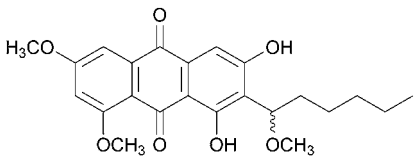


158

6,8,1′-Tri-*O*-methylaverantin (**159**) was isolated, besides a series of known anthraquinones, from an unidentified fungus obtained from the Chinese mangrove plant *Acanthus ilicifolius*.[119] Two new hexahydroanthrones, tetrahydrobostrycin (**160**) and its 1-deoxy congener (**161**), were isolated from the fungus *Aspergillus* sp. obtained from an unidentified Indonesian alga, together with the known pigment bostrycin and the plant hormone abscisic acid.[120] Compound **160** displayed weak antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, while **161** was active against *S. aureus*. Both compounds displayed no antifungal activity against yeasts.



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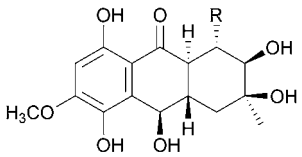
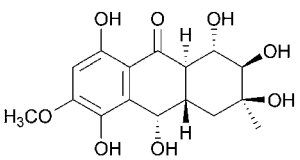


160 (R = OH)
161 (R = H)

The fungus *Halorosellinia* sp., isolated from decayed wood in Hong Kong and a salt lake in the Bahamas, yielded two new anthraquinones **162** and **163**, besides three known derivatives.[121] Three new hehahydroanthraquinones, fusaquinones A–C (**164–166**) were isolated from the fermentation medium of the fungus *Fusarium* sp., obtained from mangrove sediment in China.[122] Compound **164** is characterized by an unusual 7,9-epoxide bridge. Compounds **164–166** were inactive when tested for cytotoxic properties.



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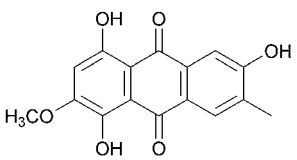

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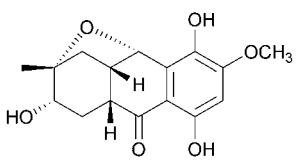

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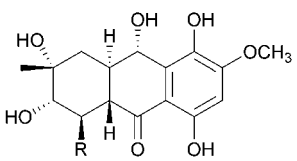
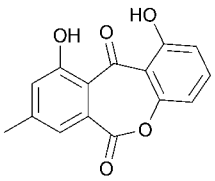


165 (R = OH)
166 (R = H)

An unidentified endophytic fungal strain isolated from the Chinese mangrove *Bruguiera gymnorrhiza* produced two new aromatic lactones, 1,10-dihydroxy-8-methyldibenzo[*b*,*e*]oxepine-6,11-dione (**167**) and 3-(hydroxymethyl)-6,8-dimethoxy-2*H*-chromen-2-one (**168**), along with a known coumarin derivative and the 8-demethyl congener of **168**, which so far had only been obtained synthetically, but not as a natural product.[123]

A new lactone, 1,8-dihydroxy-10-methoxy-3-methyldibenzo[*b*,*e*]oxepine-6,11-dione (**169**), and two new xanthones, 1-hydroxy-8-(hydroxymethyl)-6-methoxy-3-methyl-9*H*-xanthen-9-one (**170**) and 1-hydroxy-8-(hydroxymethyl)-3-methoxy-6-

methyl-9*H*-xanthen-9-one (**171**) were reported from the endophytic fungus *Phoma* sp., isolated from the roots of the Chinese mangrove plant *Avicennia marina*.[124] Compounds **169–171** were inactive when tested for cytotoxic properties.



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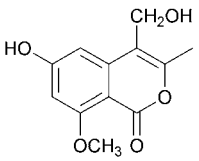

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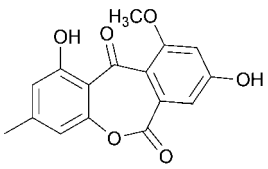

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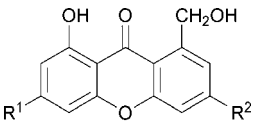
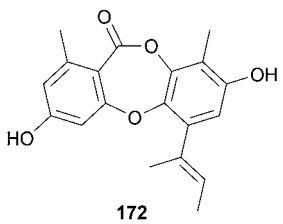


170 (R^1 = CH_3, R^2 = OCH_3)
171 (R^1 = OCH_3, R^2 = CH_3)

The known depsidone unguinol (**172**), a metabolite of *Aspergillus unguis*[125] and *A. nidulans*,[126] was identified as an inhibitor of the C_4 plant enzyme pyruvate phosphate dikinase (PPDK), a potential herbicide target, in the course of a systematic screening of more than 2000 extracts generated from approximately 450 marine-derived fungal strains from the collection of the Australian Institute of Marine Sciences (AIMS).[127] The producing strain was originally obtained from the Australian sponge *Ianthella reticulata*, and by molecular methods was identified as being related to both *A. unguis* and *A. nidulans*, with the analysis of 18S rDNA sequences giving a slightly different result from that of ITS sequences.

(–)-Byssochlamic acid (**173**), previously only known as a synthetic product, was described as a metabolite of an unidentified mangrove fungus obtained from an undisclosed Chinese location.[128] The same strain also yielded the hydroxylated congener, 1-hydroxybyssochlamic acid (**174**).[129] Compound **173** displayed mild cytotoxic effects towards HEp-2 and HepG2 cells, while **174** was inactive.



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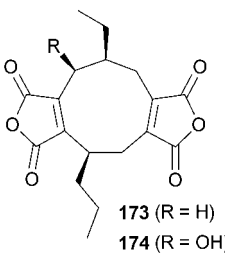
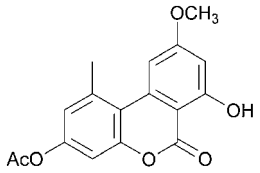


173 (R = H)
174 (R = OH)

2240B (**175**) is a new alternariol derivative that was isolated, together with alternariol and two further known congeners, from the culture of an unidentified fungus obtained from an undisclosed Chinese mangrove habitat.[130] An endophytic *Guignardia* sp. was isolated from the bark of the Chinese mangrove plant *Kandelia candel*.[131] Besides the known vermistatin (**176**), a metabolite of *Penicillium vermiculatum*,[132] the two new oxygenated congeners **177** and **178** were detected. Compound **176** exhibited weak and **177** moderate cytotoxic activity, but both compounds were devoid of antimicrobial activity. A later reinvestigation additionally yielded 6-demethylvermistatin (**179**).[133]



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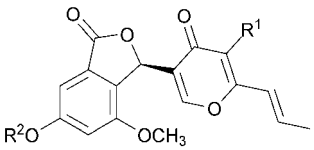
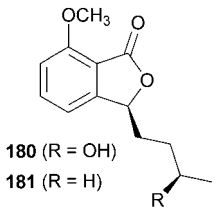


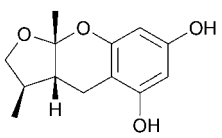
176 (R^1 = H, R^2 = CH_3)
177 (R^1 = OCH_3, R^2 = CH_3)
178 (R^1 = OH, R^2 = CH_3)
179 (R^1 = H, R^2 = H)

(3*S*,3′*R*)-3-(3′-Hydroxybutyl)-7-methoxyphthalide (**180**) and (*S*)-3-butyl-7-methoxyphthalide (**181**) were isolated from the culture broth of the fungal strain CRIF2 belonging to the order Pleosporales, obtained from an unidentified sponge in Thailand.[134] **181** which was obtained synthetically before, but was isolated for the first time as a natural product, exhibited mild cytotoxicity towards several cell lines. **180** and **181** are closely related to known phthalides such as (–)-3-butyl-7-hydroxyphthalide, a cytotoxic metabolite of *Penicillium vulpinum*.[135,136]



180 (R = OH)
181 (R = H)

Xyloketal H (**182**), previously only known as a synthetic intermediate, is a metabolite of the fungus *Xylaria* sp., obtained from the seeds of an undisclosed angiosperm mangrove tree from Hong Kong.[137] Reinvestigation of the same fungus yielded the new congener **183**, to which unfortunately the same name was assigned.[138] Subsequently, the new analogues xyloketal J (**184**), xyloester A (**185**) and xyloallenolide B (**186**) were discovered, together with (2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran-5-yl)methanol, the benzofuran moiety present in **185** and **186**,



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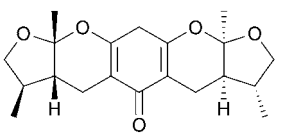

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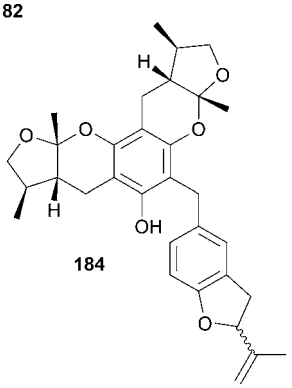

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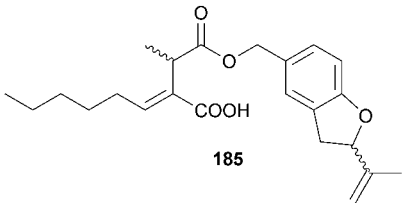

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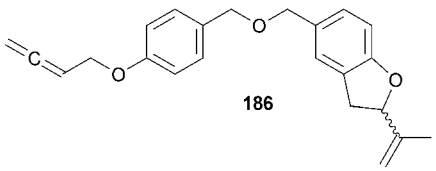
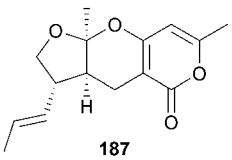


186

which had previously only been obtained synthetically,[139] but apparently was not known as a natural product.[140] Compounds **184–186** were inactive when tested for antibacterial activity.

The fungus *Penicillium* sp. was isolated from the sea fan *Annella* sp., collected in Thailand, and found to produce the ketal penicipyrone (**187**) and the γ-lactone, penicilactone (**188**), together with three known brefeldin-type macrolides.[141] Only one of the known compounds displayed mild antifungal activity.



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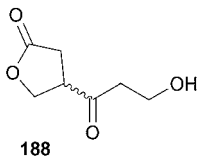
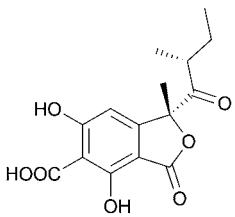


188

An endophytic strain of *Ascochyta salicornia* was cultivated from the inner tissue of the green alga *Ulva* sp., collected from the German North Sea coast. Upon fermentation on a solid seawater-based medium, two new lactones ascolactones A (**189**) and B (**190**),[142] were detected besides two previously described polyketides – ascochital, a metabolite previously reported from the marine fungus *Kirschsteiniothelia maritima*,[143] and the well-known phytotoxin ascochitine, produced by terrestrial *Ascochyta* spp.[144] The absolute configurations of **189** and **190** were assigned based on a combination of quantum-chemical CD calculations and chemical degradation.[142,145] When tested for inhibitory properties against a series of protein phosphates, which were predicted by *in silico* screening, the known ascochitine was moderately active against MPtpB (mycobacterial protein tyrosine phosphatase B), while **189** and **190** were inactive. The fungus *Sporothrix* sp., isolated from an undisclosed mangrove at the South China Sea coast, yielded the new griseofulvin derivative **191**.[146]



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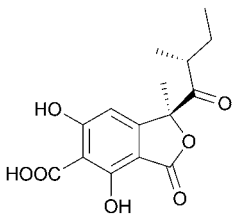

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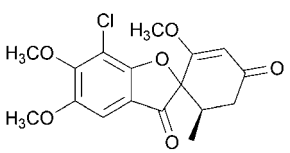
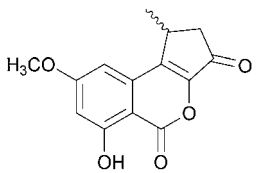


191

1-Deoxyrubralactone (**192**) was obtained, besides the known talaroflavone, from an unidentified fungal strain isolated from undisclosed Japanese algae.[147] Compound **192** is a deoxy derivative of the known rubralactone, a metabolite of the terrestrial fungus *Penicillium rubrum*,[148] while talaroflavone had previously been reported from the terrestrial *Talaromyces flavus*.[149] Compound **192** and talaroflavone selectively inhibited eukaryotic DNA polymerases of the X and Y families, but were inactive against other eukaryotic or prokaryotic polymerases, or other DNA metabolic enzymes.

Stoloniferols A (**193**) and B (**194**) are two new isocoumarin derivatives, produced by the fungus *Penicillium stoloniferum* which was isolated from an unidentified Chinese sea squirt.[150] In the same study, the halophilic fungus *Penicillium notatum*, obtained from sediments of Qinghai Lake, a saline lake in China, yielded the known dihydrocitrinone, previously described from *Aspergillus carneus*.[151] None of the compounds exhibited cytotoxicity against various cell lines. The closely related 6,8-dihydroxy-3,4,7-trimethylisochroman-1-one (**195**) was reported from *Penicillium* sp., an endophyte of the Chinese mangrove *Bruguiera sexangula*, and demonstrated to possess moderate cytotoxic activity towards the K562 cell line.[152]



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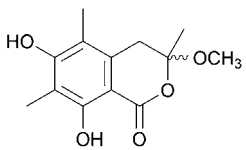
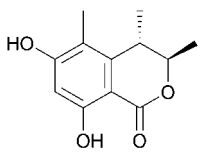


193



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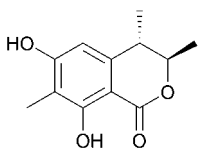
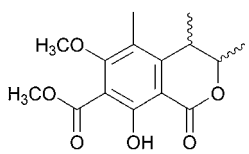


195

Methyl 8-hydroxy-6-methoxy-3,4,5-trimethyl-1-oxoisochroman-7-carboxylate (**196**) was obtained from an unidentified endophytic fungus obtained from an undisclosed Chinese mangrove.[153] From a culture of a sterile mycelium, isolated from the Japanese green alga *Codium fragile*, (3*R*,4a*R*,5*S*,6*R*)-6-hydroxy-5-methylramulosin (**197**) and three known mellein congeners were obtained.[154] **197** displayed weak cytotoxic activity toward HeLa cells, whereas the remaining compounds were inactive.



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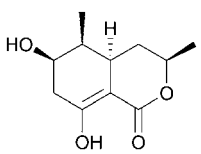
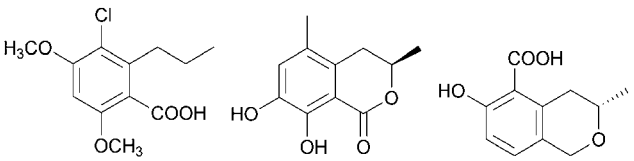


197

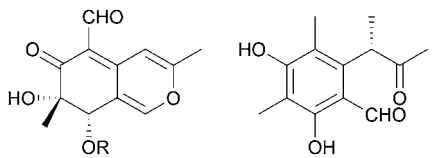
Two endophytic fungi of algae, *Acremonium* sp. from the German red alga *Plocamium* sp. and *Nodulisporium* sp. from a Greek algal species of unknown taxonomy, yielded

acremonisol A (**198**) and (3*R*)-7-hydroxy-5-methylmellein (**199**), respectively. Compounds **198** and **199** were inactive in several bioassays, including tests for antibacterial, antifungal, antialgal, or cytotoxic properties.[155] An unidentified endophytic strain, obtained from the dropper of *Kandelia candel* growing in an estuarine mangrove in China, was found to produce the new isochroman 6-hydroxy-3-methylisochroman-5-carboxylic acid (**200**), besides a series of known natural products.[156]



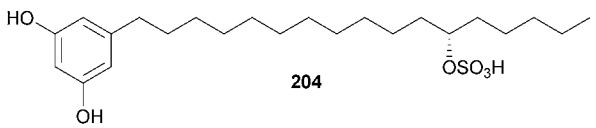
198 **199** **200**

The endophytic fungus *Talaromyces* sp., isolated from the Chinese mangrove plant *Kandelia candel*, yielded two new isochromenones 7-epiaustdiol (**201**) and 8-*O*-methylepiaustdiol (**202**), besides a diverse series of known polyketides.[157] The fungus *Penicillium* sp., obtained from the surface of the Korean green alga *Ulva pertusa*, yielded the new redoxcitrinin (**203**)[158] together with the structurally related known phenol A[159] and citrinin H2,[160] all of them being derivatives of the well-known citrinin.[161,162] All compounds were found to possess moderate radical scavenging activity in the DPPH assay.



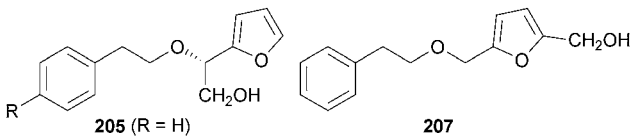
201 (R = H)
202 (R = CH_3)
203

In the course of a screening for antimicrobial substances targeting FtsZ, which is a structural homolog of eukaryotic tubulin, the new sulfoalkylresorcinol (**204**), was identified in the culture extract of the fungus *Zygosporium* sp., isolated from an undisclosed hard coral in Palau.[163] At very high concentrations, **204** inhibited the GTPase activity of FtsZ and also inhibited FtsZ polymerization, in addition to exhibiting antimicrobial activity against various bacterial strains.

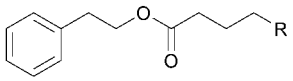


204

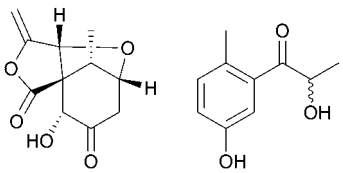
Pichiafurans A–C (**205–207**) and pichiacins A (**208**) and B (**209**) have been characterised from the yeast *Pichia membranifaciens* which was obtained from the Korean marine sponge *Petrosia* sp.[164] Compounds **205–207** are furyl ethers with 2-phenylethanol (likely to be derived from the shikimate pathway), while **208** and **209** are esters consisting of 2-phenylethanol and short-chain ω-hydroxy acids. The fungus *Massarina* sp., isolated from a marine mud sample collected at low depth in the Palau Islands, yielded spiromassaritone (**210**) and massariphenone (**211**), which did not exhibit significant antimicrobial or cytotoxic activity.[165] Compound **210** is a stereoisomer of V214w, previously reported from an unidentified fungus.[166] For the related metabolite arthropsolide A, produced by *Arthropsis truncata*, it has been proposed that its biogenesis includes the condensation of a pentaketide precursor and malic acid.[167]



205 (R = H)
206 (R = OH)
207

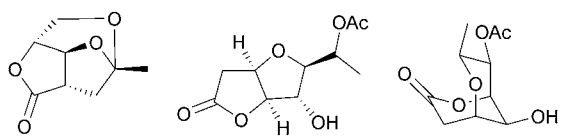


208 (R = CH_2OH)
209 (R = OH)



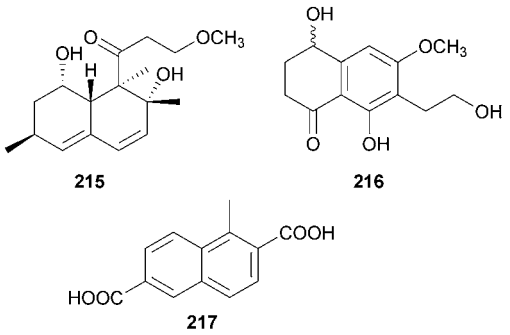
210 **211**

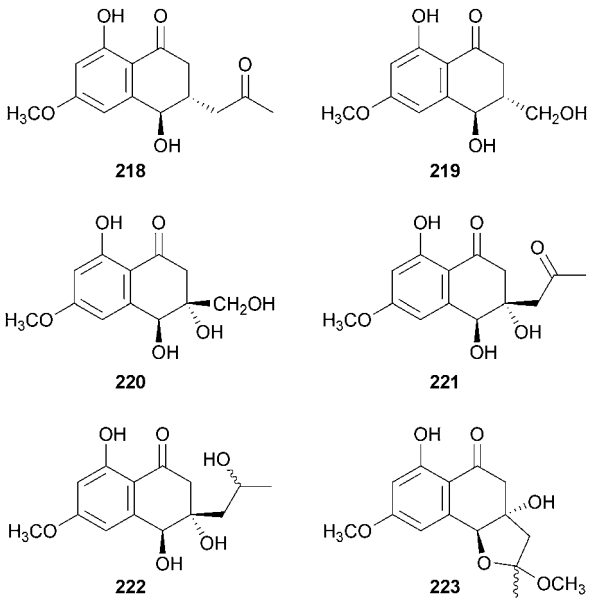
The unusual tricyclic compound 2106 A (**212**) was obtained from the culture broth of an unidentified fungus from the mangrove *Avicennia marina* in Hong Kong, and its structure was established by X-ray diffraction analysis.[168] Protulactones A (**213**) and B (**214**) were reported from the fungus *Aspergillus* sp., isolated from an inter-tidal sediment sample collected in Korea.[169] Both the unusual furo[3,2-*b*] furan ring system present in **213** and the dioxabicyclo[3.3.1]nonane ring system as found in **214** appear to be unprecedented in fungi, at least in the genus *Aspergillus*, but are present in plant-derived metabolites such as goniofufurone from *Goniothalamus giganteus*,[170] or a tetraketide from *Euscaphis japonica*.[171]



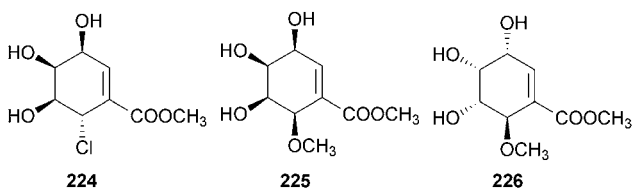
212 **213** **214**

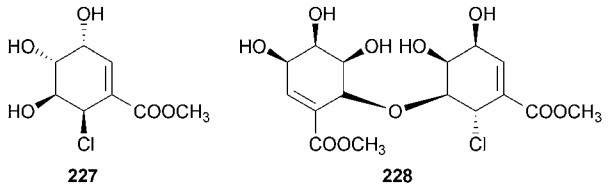
A sterile mycelium obtained from an undisclosed sponge of unknown geographic origin produced three new metabolites, 1-((1*R*,2*R*,6*S*,8*S*,8a*S*)-2,8-dihydroxy-1,2,6-trimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl)-3-methoxypropan-1-one (**215**), 4,8-dihydroxy-7-(2-hydroxyethyl)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**216**) and 1-methylnaphthalene-2,6-dicarboxylic acid (**217**).[172] A fungal strain, identified as belonging to the Pleosporales (Ascomycota), was isolated from driftwood from the Baltic coast in Germany, and subsequent chemical analysis led to the discovery of six naphthalenone derivatives, balticols A–F (**218–223**),[173] besides the known altechromone A, previously described from *Alternaria* sp.[174] At non-cytotoxic concentrations, all compounds displayed antiviral activity against influenza A virus or Herpes simplex virus (HSV) type I, most notably **221** and **222**, with IC_{50} values ranging between 0.01 and 0.1 μg ml^{-1}.



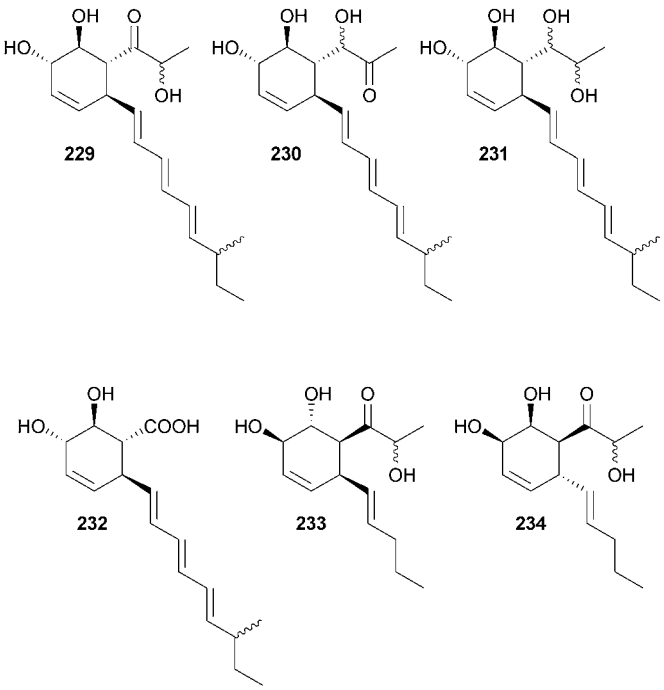


An isolate of *Periconia byssoides*, obtained from the sea hare *Aplysia kurodai*, and which is the well-established source of peribysins with cell-adhesion inhibitory properties,[175,176] was subjected to further chemical study, resulting in the discovery of pericosines A–E (**224–228**).[177] A preliminary report[178] of the structures for **224** and **225** had been revised with regard to the relative stereochemistry based on the synthesis of the enantiomer of **224**.[179] The absolute configuration of pericosine D (**227**) was later established by total synthesis.[180] Compounds **224**, **225** and **227** exhibited significant growth inhibition against the murine P388 cell line, whereas **226** and **228** were inactive. In a disease-oriented panel of human cancer cell lines (HCC panel) in the Japanese Foundation for Cancer Research, **224** and **228** displayed moderate activity in general, but **224** was selective for HBC-5 and SNB-75 cell lines, and also showed significant *in vivo* tumour inhibitory activity. Likewise, **224** was found to inhibit EGFR protein kinase and topoisomerase II.[177]

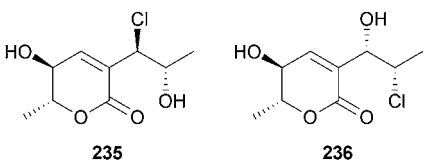




The fungus *Phaeosphaeria spartinae*, an endophyte of the German alga *Ceramium* sp., produced spartinols A–D (**229–232**).[181] Compound **231** exhibited weak inhibitory activity towards human leukocyte elastase (HLE). Nigrosporanenes A (**233**) and B (**234**) were isolated from fungus *Nigrospora* sp, which was obtained from the sea fan *Annella* sp. collected Thailand.[182] Compound **233** displayed moderate cytotoxicity towards MCF-7 and Vero cells, while **233** and **234** also showed weak radical scavenging activity.

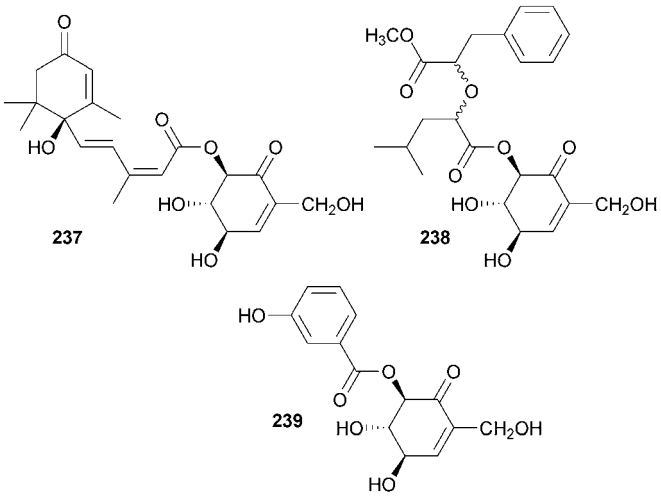


The fungal strain *Exophiala* sp., isolated from the surface of the Korean sponge *Halichondria panicea*, was the source of chlorohydroaspyrones A (**235**) and B (**236**),[183] besides three known polyketides including aspyrone, an epoxide which yielded **235** and **236** upon hydrolysis with HCl. Compounds **235** and **236** exhibited mild antibacterial activity against *Staphylococcus aureus*, methicillin-resistant *S. aureus*, and multidrug-resistant *S. aureus*.

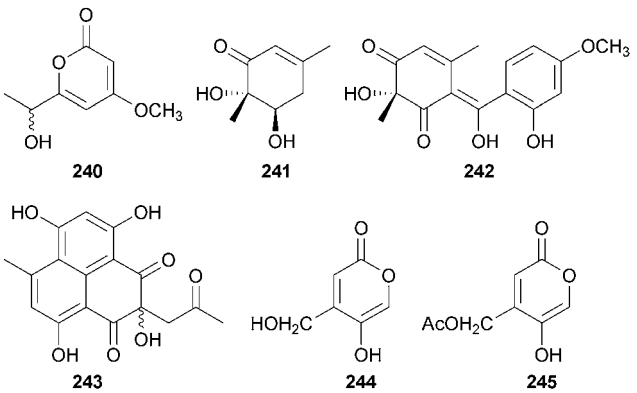


Three new epoxydon esters, nigrospoxydons A–C (**237–239**), and the new pyrone, nigrosporapyrone (**240**), were reported from the fungus *Nigrospora* sp. which was isolated from the sea fan *Annella* sp. in Thailand.[184] Compound **237** is an ester of abscisic

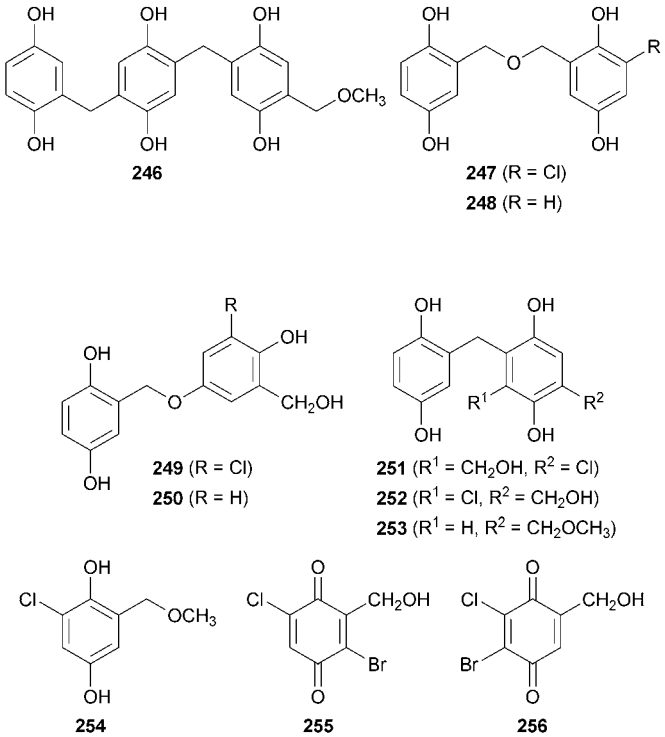
acid and epoxydon, a well-known metabolite from originally described from a terrestrial *Phoma* sp.[185] Both abscisic acid and epoxydon were also detected in the culture medium, and the latter as well as **237** displayed mild antibiotic activity against *Staphylococcus aureus* and methicillin-resistant *S. aureus*.



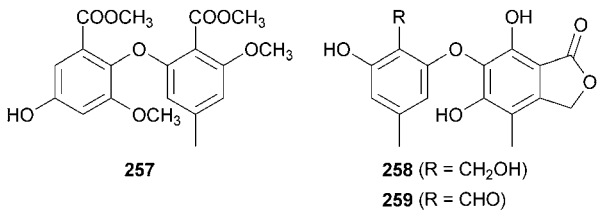
The endophytic fungus *Penicillium* sp., isolated from the Chinese mangrove plant *Aegiceras corniculatum*, was found to produce a diverse suite of metabolites including the new leptosphaerone C (**241**), penicillenone (**242**) and 9-demethyl FR-901235 (**243**), besides the new prenylated polyketide arugosin I (**311**). Compounds **241** and **242** displayed marked cytotoxicity towards P388 cells.[186] A strain of *Aspergillus flavus*, obtained from the Chinese marine alga *Enteromorpha tubulosa*, yielded two new 5-hydroxy-2-pyrones, **244** and **245**.[187] Compound **244** induced the production of cAMP on GPR12 transfected CHO and HEK293 cells in a dose-dependent manner, indicating that the compound might be a possible ligand for GPR12.



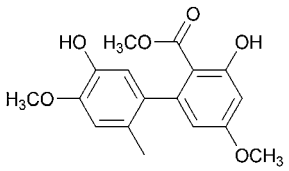
A strain of *Penicillium terrestre*, obtained from a sediment sample in China, yielded a series of new gentisyl alcohol polymers, including the trimeric terrestriol A (**246**), the dimeric terrestrols B–H (**247–253**) and the monomer **254**.[188] All compounds displayed moderate levels of cytotoxicity against four different cancer cell lines, and were also moderately active as radical scavengers. In addition, **252** displayed moderate inhibitory activity against protein tyrosine kinases Src and KDR. Bromochlorogentisylquinones A (**255**) and B (**256**) are metabolites of the fungus *Phoma herbarum*, isolated from the Korean red alga *Gloiopeitis tenax*, which were formed upon addition of calcium bromide to the culture medium, together with the known chlorogentisyl alcohol and gentisyl alcohol.[189] All compounds displayed significant radical scavenging properties in the DPPH assay.



The fungus *Aspergillus* sp., isolated from a Chinese sediment sample, was found to produce the diphenyl ether dimethyl 2,3′-dimethylosoate (**257**), together with three known compounds.[190] Compound **257** displayed weak cytotoxic properties towards K562 cells, which might be due to arresting the cell cycle in the S phase, as demonstrated by flow cytometry, and also a marked increase in apoptotic cells. Two new diaryl ethers, phomopsides A (**258**) and B (**259**), were reported from the endophytic fungus *Phomopsis* sp., isolated from an undisclosed Chinese mangrove plant.[191] In addition, the known excelsione, a depsidone previously described from an endophytic fungus of the New Zealand endemic tree *Knightia excelsa*, was also detected.[192]



An unidentified fungus collected from the rhizosphere in a Chinese mangrove habitat yielded the new biphenyl derivative methyl 3,5′-dihydroxy-4′,5-dimethoxy-2′-methylbiphenyl-2-carboxylate (**260**).[193] The endophytic fungus *Penicillium commune*, which was isolated from the Chinese semi-mangrove plant *Hibiscus tiliaceus*, afforded a new ester of orsellinic acid with glycerol (**261**), besides a suite of mostly structurally simple known metabolites.[194]



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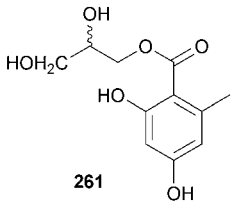
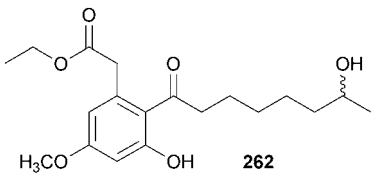


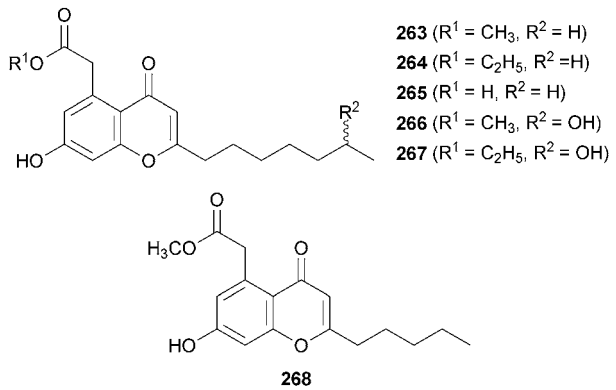
261

Ethyl 2-(3-hydroxy-2-(7-hydroxyoctanoyl)-5-methoxyphenyl)acetate (**262**) was produced by the endophytic fungus *Phomopsis* sp., isolated from the Chinese mangrove tree *Excoecaria agallocha*.[195] In addition, the closely related dothiorelones A–C, previously described from the mangrove endophytic fungus *Dothiorella* sp.,[196] were also detected. Compound **262** displayed weak cytotoxicity against HEp-2 and HepG2 cells.



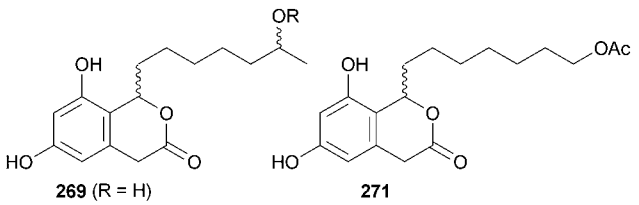
262

The fungus *Pestalotiopsis* sp., isolated from the Chinese mangrove plant *Rhizophora mucronata*, proved to be a prolific source of new secondary metabolites. At first, six new chromones, pestalotiopsones A–F (**263–268**) were characterized, together with a closely related known congener.[197] Compound **268** displayed moderate cytotoxicity towards the murine cancer



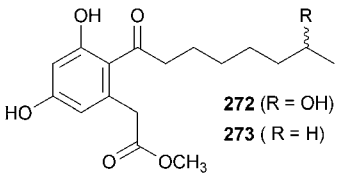
263 (R^1 = CH_3, R^2 = H)
264 (R^1 = C_2H_5, R^2 =H)
265 (R^1 = H, R^2 = H)
266 (R^1 = CH_3, R^2 = OH)
267 (R^1 = C_2H_5, R^2 = OH)

268

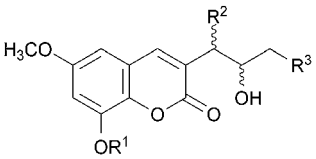


269 (R = H)
270 (R = Ac)

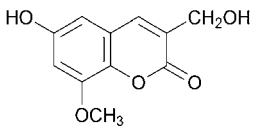
271



272 (R = OH)
273 (R = H)



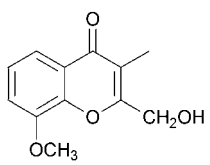
274 (R^1 = CH_3, R^2 = H, R^3 = H)
275 (R^1 = CH_3, R^2 = OH, R^3 = H)
276 (R^1 = CH_3, R^2 = H, R^3 = OH)
277 (R^1 = H, R^2 = H, R^3 = OH)



278

cell line L5178Y, while the remaining compounds were inactive. A later reinvestigation yielded new cytosporone derivatives, cytosporones J–N (**269–273**) and five new coumarins, pestalasins A–E (**274–278**), together with the known cytosporone C, dothiorelone B and the new alkaloid pestalotiopsoid A (**647**).[198] Cytosporone C was initially described from an endophytic *Cytospora* sp.,[199] while dothiorelone B was reported from the mangrove endophytic fungus *Dothiorella* sp.[196] None of the new compounds exhibited significant cytotoxic effects.

Chromanone A (**279**) was produced by an endophytic *Penicillium* sp, isolated from the Egyptian green alga *Ulva* sp.[200] Besides a potent scavenging activity against hydroxyl radicals, **279** was found to inhibit cytochrome P450 1A, and to induce mEH (epoxide hydrolase) as well as glutathione *S*-transferase, enzymes involved in carcinogen metabolism. The fungal strain *Botrytis* sp., isolated from the surface of the Korean red alga *Hyalosiphonia caespitosa*, gave a new α-pyrone, (*E*)-6-(hept-1-enyl)-2*H*-pyran-2-one (**280**),[201] together with (*E*)-6-(pent-1-enyl)-2*H*-pyran-2-one, which had so far only been obtained synthetically.[202] Compound **280** exhibited tyrosinase inhibitory activity with an IC_{50} value of 4.5 μM, and was thus more active than the positive control, kojic acid.



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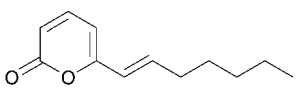
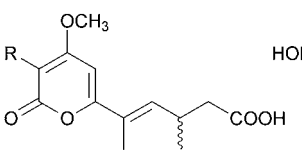
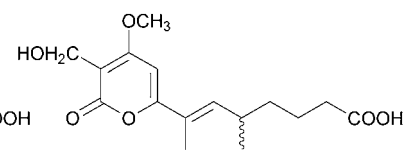


280

Three new derivatives (**281–283**) of the known α-pyrone infectopyrone were isolated from the culture broth of the fungus *Petriella* sp., obtained from the Mediterranean sponge *Suberites domuncula*.[203] Their parent compound infectopyrone had previously been described from the plant pathogenic fungus



281 (R = H)
282 (R = OH)



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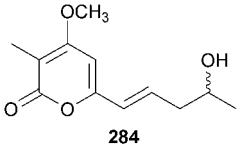
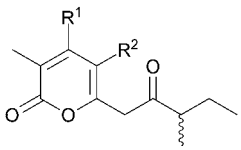


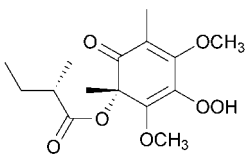
284

Alternaria infectoria.[204] Its 2,3-dihydro congener **281** exhibited pronounced cytotoxicity towards the L5178Y cell line.[203]

The fungus *Trichoderma viride*, isolated from the Caribbean sponge *Agelas dispar*, was identified as the source of a new α-pyrone, trichopyrone (**284**), together with ten known compounds, most of them sorbicillinoids and bisorbicillinoids.[205] Compound **284**, which is closely related to the previously described xylarone from *Xylaria hypoxylon*,[206] did not display significant biological activity when tested for antiviral, antimicrobial, estrogenic, antioxidative or cytotoxic properties. The fungus *Paecilomyces lilacinus*, derived from the Korean sponge *Petrosia* sp., produced two new α-pyrones, paecilopyrones A (**285**) and B (**286**), and two cyclohexenone hydroperoxides (**287** and **288**).[207]



285 (R^1 = OH, R^2 = CH_3)
286 (R^1 = CH_3, R^2 = H)



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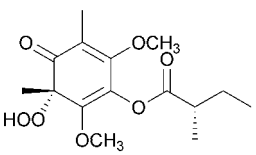
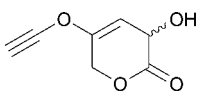


288

5-(Ethynyloxy)-3-hydroxy-3,6-dihydro-2*H*-pyran-2-one (**289**) and 4-(butoxymethyl)benzene-1,2-diol (**290**), the latter due to its C_6–C_1 motif and its hydroxylation patterns probably rather representing a phenylpropanoid instead of a polyketide, were reported together with a suite of structurally simple known aromatic compounds from an unidentified fungal strain obtained from the tree *Clerodendrum inerme* growing in the intertidal zone of a Chinese coastal region.[208] The methoxylated (instead of butoxylated) analogue of **290** was also among the isolated compounds, and is a compound which up to that point was only known synthetically.



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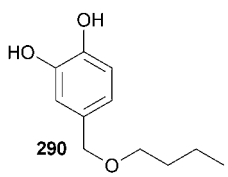
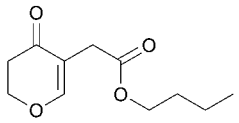


290

The fungus *Penicillium* sp., isolated from the tree *Clerodendrum inerme* growing in the inter-tidal zone of the South China Sea, yielded three new esters of desoxypatulinic acid **291**–**293**.[209] Desoxypatulinic acid, which was also detected in the culture broth, is a common mycotoxin initially reported from *Penicillium patulum*.[210] The fungal strain *Trichoderma atroviride*, isolated from sediment near the Chinese mangrove *Ceriops tagal*, produced the new compound 3-hydroxy-5-(4-hydroxybenzyl)dihydrofuran-2(3*H*)-one (**294**).[211]

Two new benzaldehyde derivatives, 6-ethyl-2-hydroxy-4-methoxy-3-methylbenzaldehyde (**295**) and 6-ethyl-2,4-dihydroxy-3-methylbenzaldehyde (**296**), were obtained from an



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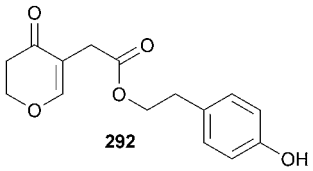

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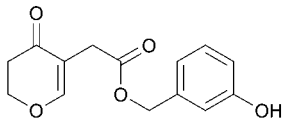
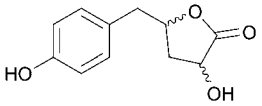
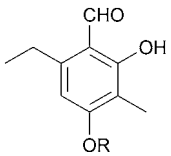


293



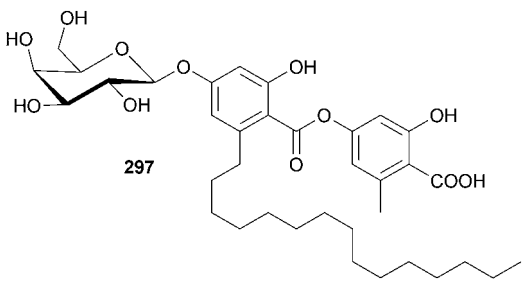
294

undisclosed fungus, supposedly endophytic to an undisclosed Chinese mangrove plant.[212] Based on the strain designation, it could actually be a previously studied *Penicillium* sp. isolated from *Acanthus ilicifolius*, although this was not specifically stated in this communication.



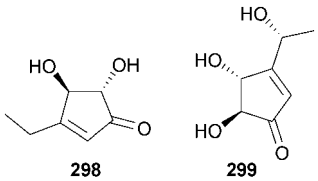
295 (R = CH_3)
296 (R = H)

The known aquastatin A (**297**), produced by the Korean sediment-borne fungus *Cosmospora* sp., was isolated as a potent protein tyrosine phosphatase 1B (PTP1B) inhibitory component.[213] **297** is an orcinol depside that had previously been reported from the fungus *Fusarium aquaeductuum*, but the absolute configuration of its galactose moiety had not been determined.[214] The fungus *Trichoderma* sp. was isolated from marine sediment in the South China Sea and found to produce a new cyclopentenone, trichoderone (**298**), besides a known steroid.[215] Compound **298** displayed selective cytotoxicity towards six cancer cell lines and was moderately active, probably by inducing apoptosis.



297

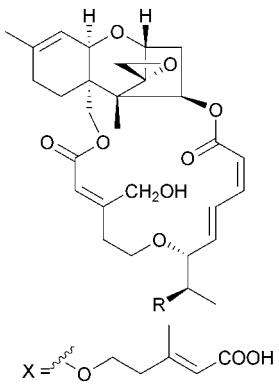
In the culture extract of the fungus *Botrytis* sp., obtained from the surface of the Korean green alga *Enteromorpha compressa*, the new cyclopentenone botrytinone (**299**) was detected, besides the new nitrogen-containing cyclopentenone bromomyrothenone B (**661**).[216] Compound **299** did not display significant activity during a screening for radical scavenging, tyrosinase inhibitory and antimicrobial properties. Subsequently, **299** and **661** were also detected in the culture medium of *Rhizopus stolonifer*, isolated from the surface of the Korean brown alga, *Sargassum horneri*.[217]



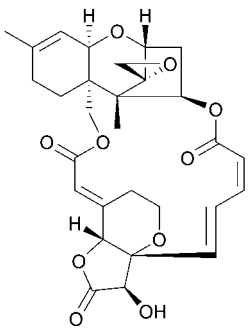
298 299

4.4 Prenylated polyketides/meroterpenoids

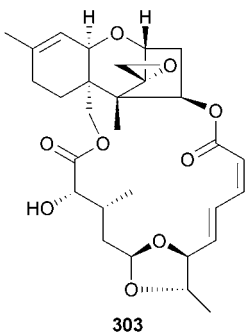
An isolate of *Myrothecium roridum*, obtained from a wood sample collected in Palau, was reported to produce three new macrocyclic trichothecenes, 12′-hydroxyroridin E (**300**), roridin Q (**301**), and 2′,3′-deoxyroritoxin D (**302**), while one new compound, roridin R (2′,3′-dihydro-2′-hydroxyroridin H (**303**), was isolated from *Myrothecium* sp. which was obtained from an unidentified Indonesian sponge.[218] Compound **301** is characterized by a unique ether moiety at position C-13′ and thus contains a third hydroxyacid moiety not present in other trichothecenes. Compounds **300**, **301** and **303** displayed cytotoxic activity towards the murine leukemia cell line L1210 with IC_{50} values of 0.19, 31.2, and 0.45 μM, respectively, while **303** showed antifungal activity against *S. cerevisiae* at 1 μg per disc.



300 (R = OH)
301 (R = X)

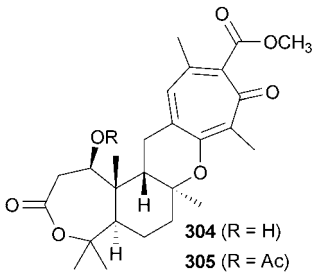


302

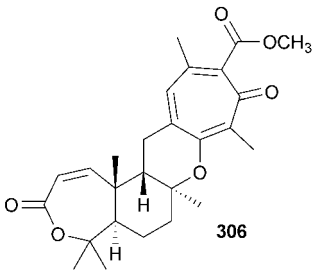


303

Chemical analysis of the culture broth of a fungus of the genus *Aspergillus*, isolated from an unidentified Hawaiian sponge, resulted in the characterisation of four new meroterpenoids, tropolactones A–D (**304–307**).[219] **304–306** contain a substituted 2,4,6-cycloheptatriene-2-one (tropone) ring, which is presumed to arise from an oxidative ring expansion of the 2,5-cyclohexadiene-2-one ring system of **307**. Tropolactones A–C (**304–306**) showed weak cytotoxicity against HCT-116 human colon adenocarcinoma cells.



304 (R = H)
305 (R = Ac)



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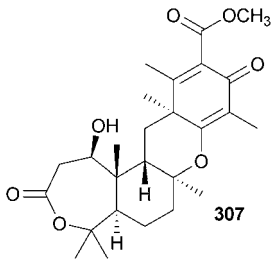
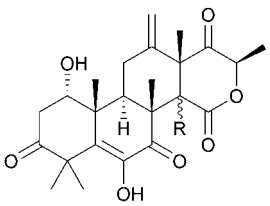
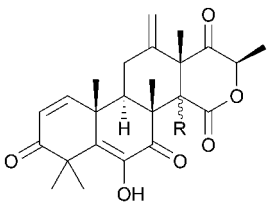


307

The fungus *Aspergillus insuetus*, isolated from the Mediterranean sponge *Petrosia ficiformis*, yielded two new meroterpenoids terretonins E (**308**) and F (**309**), together with the known diketopiperazine aurantiamine.[220] Compounds **308** and **309** are derivatives of the previously reported terretonin[221] and terretonins A–D[222] isolated from *A. terreus*. Compounds **308** and **309** showed midrange potency as mammalian mitochondrial respiratory chain inhibitors, interacting with NADH oxidase activity.

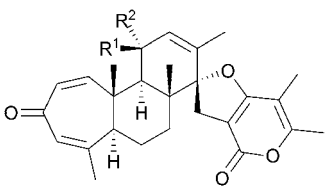


308 (R = $COOCH_3$)

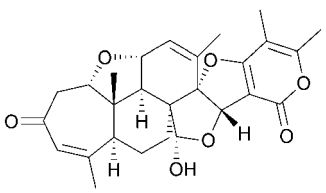


309 (R = $COOCH_3$)

Breviones F–H (**310–312**) are new spiroditerpenoid-type meroterpenoids which were produced by the deep-sea fungus *Penicillium* sp., obtained from a sediment sample which was collected at a depth of 5115 m.[223] They are structurally related to breviones A–E, allelopathic agents from a terrestrial isolate of *Penicillium brevicompactum*.[224,225] Compounds **310–312** displayed moderate cytotoxicity towards HeLa cells, while **310** also inhibited replication of HIV-1 in C8166 cells.



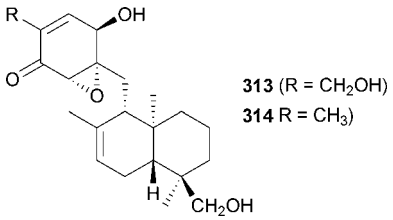
310 (R^1 = OH, R^2 = H)
311 (R^1 = H, R^2 = OH)



312

The fungus *Phoma* sp. was obtained from the Caribbean sponge *Ectyplasia perox*, and identified as the producer of two unusual cyclohexenone sesquiterpenoids, epoxyphomalins A (**313**) and B (**314**).[226] Based on structural considerations, their biosynthesis is assumed to proceed *via* a farnesylated epoxydon

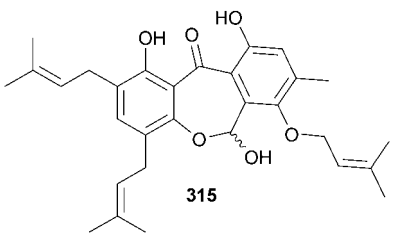
derivative, yielding an analogue of the known 22-deactylyanuthone A, reported from a marine-derived *Aspergillus niger*,[227] which upon cyclisation and hydroxylation would yield **313**. Cytotoxic properties were investigated using a panel of 36 human tumour cell lines, and mean IC_{50} values of **313** and **314** were 0.11 and 1.25 μg mL^{-1}, respectively. The observed cytotoxic selectivity pattern of **313** did not correlate with those of reference anticancer agents with known mechanisms of action in the COMPARE analysis.



313 (R = CH_2OH)
314 R = CH_3)

Arugosins G (**315**) and H (**316**) are prenylated benzophenones produced by the fungus *Emericella nidulans* var. *acristata*, which was isolated from an undisclosed Mediterranean green alga.[228] Compounds **315** and **316** were tested in a variety of assays for antibacterial, antifungal and antialgal activities, but only **316** displayed mild activity towards *Mycotypha microspora* and *Chlorella fusca*. In addition, **315** and **316** were devoid of cytotoxic or immunostimulating activity. The endophytic fungus *Penicillium* sp., isolated from the Chinese mangrove plant *Aegiceras corniculatum*, was found to produce arugosin I (**317**), besides further new polyketides leptosphaerone C (**241**), penicillenone (**242**) and 9-demethyl FR-901235 (**243**).[186]

The fungus *Paecilomyces* sp. was isolated from the bark of an undisclosed Taiwanese mangrove tree, and was found to produce the prenylated xanthone, paeciloxanthone (**318**).[229] **318** displayed pronounced cytotoxicity against hepG2 (human liver cancer) cells, was active against the fungi *Curvularia lunata* and *Candida albicans*, and also inhibited acetyl choline esterase (AChE) activity. 1,7-Dihydroxy-2-methoxy-3-(3-methylbut-2-enyl)-9*H*-xanthen-9-one (**319**) and 1-hydroxy-4,7-dimethoxy-6-(3-oxobutyl)-9*H*-xanthen-9-one (**320**) were reported from an unidentified endophytic fungus, isolated from the Chinese mangrove tree *Avicennia marina*.[230] Compounds **319** and **320** displayed mild cytotoxicity towards the KB and KB_V200 cell lines.



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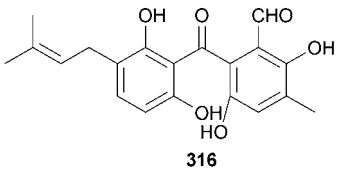

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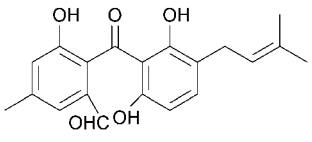
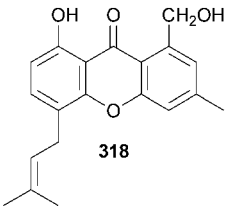
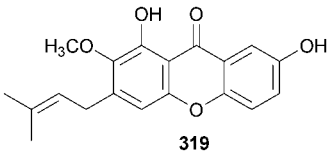


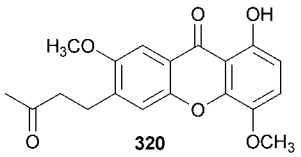
317



318

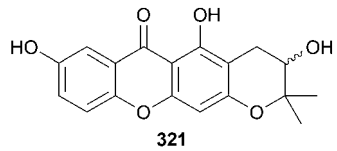


319

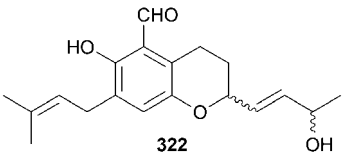


320

3,5,8-Trihydroxy-2,2-dimethyl-3,4-dihydropyrano[3,2-*b*]xanthen-6(2*H*)-one (**321**) was reported from an unidentified endophytic fungus, obtained from a Chinese mangrove tree of the genus *Avicennia*.[231] Cultivation of the endophytic fungus *Chaetomium globosum*, isolated from the Chinese red alga *Polysiphonia urceolata*, resulted in the isolation of the new benzaldehyde derivative chaetopyranin (**322**), together with ten known compounds.[232] Compound **322** displayed moderate radical-scavenging properties, and also exhibited moderate to weak cytotoxic activity toward several tumour cell lines.

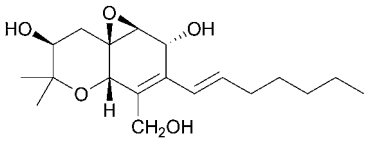


321



322

Cytosporins D (**323**) and cytosporin E (**324**) are metabolites of the fungus *Eutypella scoparia*, isolated from the marine pulmonate mollusc *Onchidium* sp.[233] Compounds **323** and **324** are derivatives of cytosporins A–C, angiotensin II binding inhibitors previously described from an endophytic *Cytospora* sp.[234] When tested for antimicrobial properties, **323** and **324** proved inactive towards *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*.



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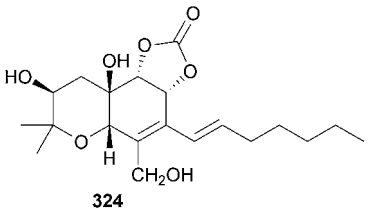
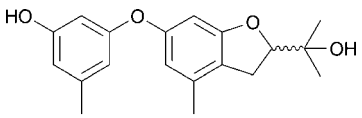


324

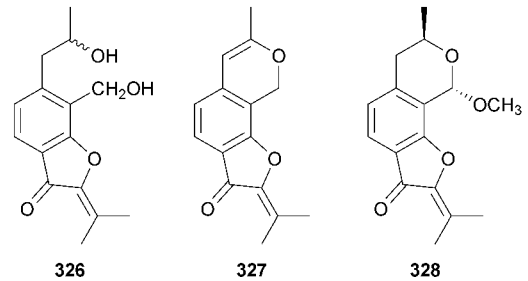
Awajanoran (**325**) is a new dihydrobenzofuran derivative, produced by the fungus *Acremonium* sp. which was obtained

from a sea mud sample in Japan.[235] Compound **325** displayed moderate cytotoxic activity towards the A549 (human lung adenocarcinoma) cell line, and was also moderately active against five different bacterial strains as well as *Candida albicans*.

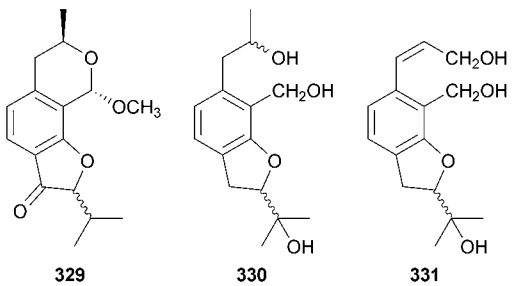


325

An isolate of *Aspergillus ustus*, obtained from the rhizosphere soil of the mangrove plant *Bruguiera gymnorrhiza* in China, produced ustusoranes A–F (**326–331**) together with the closely related known pergillin and eight new drimane sesquiterpenes.[236] Pergillin had initially been reported as a plant growth inhibitor from a terrestrial isolate of *Aspergillus ustus*.[237] Compound **330** displayed significant cytotoxicity against HL-60 cells, with an IC_{50} value of 0.13 μM.

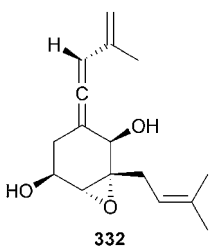


326 **327** **328**



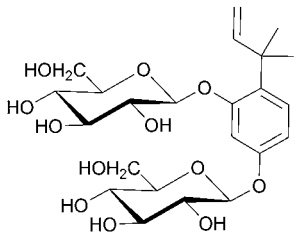
329 **330** **331**

The endophytic fungus *Phaeosphaeria spartinae*, isolated from a German red alga of the genus *Ceramium*, was the source of spartinoxide (**332**), which is the enantiomer of the known compound A82775C.[238] The latter was previously reported from an unknown fungus of the order Sphaeropsidales.[239] Compound **332** showed potent inhibition of human leukocyte elastase (HLE), but was inactive against bovine trypsin acetyl cholinesterase from *Electrophorus electricus*, and porcine cholesterol esterase.

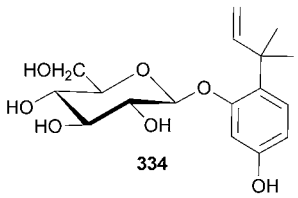


332

JBIR-37 (**333**) and JBIR-38 (**334**) are glucosylated benzenediols that were obtained from the culture broth the fungus *Acremonium* sp., isolated from an undisclosed Japanese sponge of the class Demospongiae.[240] **333** and **334** were inactive when tested for cytotoxicity towards two cell lines. The endophytic fungus *Talaromyces* sp., isolated from the mangrove *Kandelia candel* in Hong Kong, yielded tenelate A (**335**) and B (**336**), together with the known compound, tenellic acid.[241] The latter had previously been reported from the aquatic fungus *Dendrospora tenella*.[242]



333



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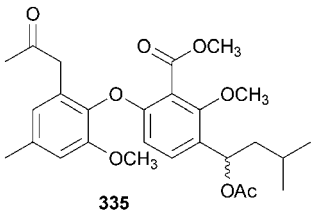

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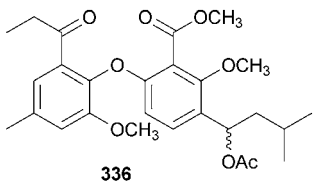
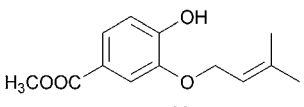


336

An unidentified fungus from an undisclosed Chinese mangrove habitat was reported to produce methyl 4-hydroxy-3-(3-methylbut-2-enyloxy)benzoate (**337**), exhibiting moderate antibacterial, antifungal and cytotoxic properties.[243] 8-Hydroxy-3-methyl-5-(3-methylbut-2-enyloxy)isochroman-1-one (**338**) was detected in the culture broth of the fungus *Cephalosporium* sp., isolated from an undisclosed Chinese mangrove plant.[244]



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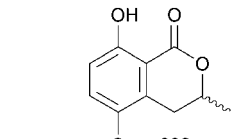
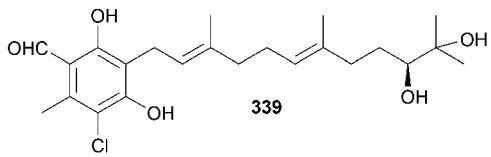
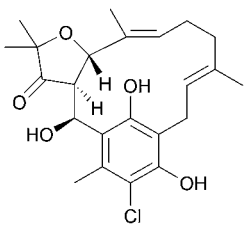


338

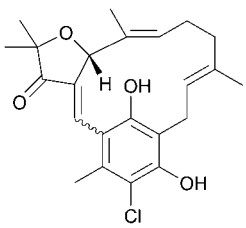
The fungus *Acremonium* sp., isolated from the Korean sponge *Stelletta* sp., produced three new meroterpenoids,



339



340

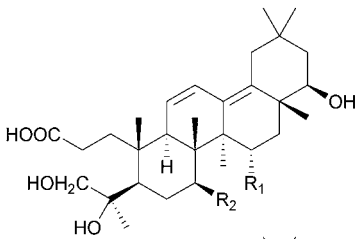


341

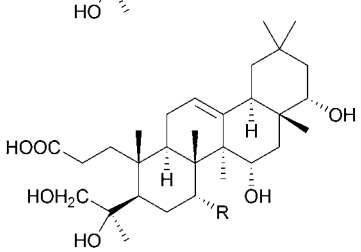
chlorocylindrocarpol (**339**), acremofuranone A (**340**) and acremofuranone B (**341**), besides the new sesquiterpenoid dihydroxybergamotene (**414**) and nine known sesquiterpenoids.[245] Compound **339** is a chlorinated analogue of cylindrocarpol, previously described from *Cylindrocarpon lucidum*,[246] while the cyclic skeleton of **340** and **341** is unprecedented in Nature. Although some of the known metabolites exhibited various anti-inflammatory properties, **339–341** were inactive in the respective bioassays.

4.5 Terpenoids

The fungus *Phomopsis* sp., isolated from the Chinese mangrove plant, *Hibiscus tiliaceus*, produced four new unusual ring A-seco-oleanes, namely 3,4-seco-olean-11,13-dien-4,15α,22β,24-tetraol-3-oic acid (**342**), 3,4-seco-olean-11,13-dien-4,7β,22β,24-tetraol-3-oic acid (**343**), 3,4-seco-olean-13-en-4,7α,15α,22α,24-pentaol-3-oic acid (**344**), and 3,4-seco-olean-13-en-4,15α,22α,24-tetraol-3-oic acid (**345**).[247] This is the first report of A-seco-oleanes in fungi, while oleane-type triterpenes, frequently found in terrestrial plants, have only rarely been reported from microbial including fungal sources. Interestingly, it has been demonstrated that some fungi are able to convert oleananes into A-seco-oleanes, which might be relevant with regard to the biosynthetic origin of **342–345**.[248,249]

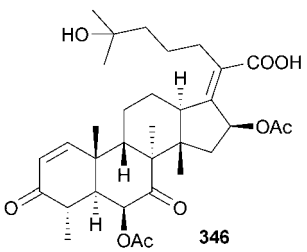


342 (R^1 = OH, R^2 = H)
343 (R^1 = H, R^2 = OH)



344 (R = OH)
345 (R = H)

The rearranged triterpene, 6β,16β-diacetoxy-25-hydroxy-3,7-dioxy-29-nordammara-1,17(20)-dien-21-oic acid (**346**) was isolated as well as a new pseurotin congener and three new diketopiperazines from a culture of the fungus *Aspergillus sydowi*, obtained from a driftwood sample collected in China.[250] Compound **346** displayed significant antibiotic activity towards *Escherichia coli*, *Bacillus subtilis* and *Micrococcus lysoleikticus*. The new friedelane triterpene, 3β-hydroxyfriedelan-17β-carboxylic acid (**347**) was isolated from an unidentified mangrove endophytic fungus.[251]



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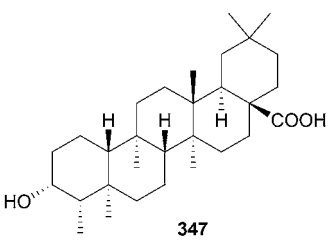
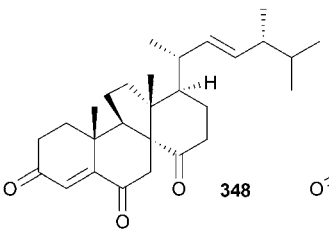


347

The fungus *Gymnascella dankaliensis* was isolated from the Japanese sponge *Halichondria japonica*, and yielded a series of structurally unusual steroid-type compounds, the pattern of which varied depending on media composition.[252] Dankasterones A (**348**)[253] and B (**349**) were obtained when glucose in the original medium was replaced by soluble starch, while gymnasterones A–D (**350–353**) were isolated from malt–glucose–yeast media.[252] **348** and **349** are most unusual steroids possessing a 13(14→8)*abeo*-8-ergostane skeleton, which so far only has been described once from Nature, resulting from a photochemical reaction of the insect molting hormone, (20*R*)-hydroxyecdysone.[254] On the other hand, **350** is structurally intriguing since it represents an unprecedented steroid alkaloid with an additional ring and an amide-linked side chain derived from gymnastatins, a group of polyketides likewise described from *Gymnascella dankaliensis*. Compounds **348**, **349** and **351–353** exhibited significant growth inhibition against the murine P388 cancer cell line, whereas **348** also exhibited potent growth inhibition against human cancer cell lines.



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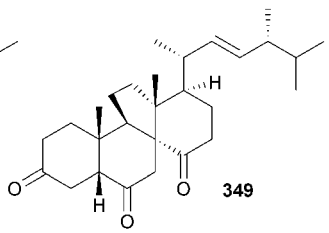
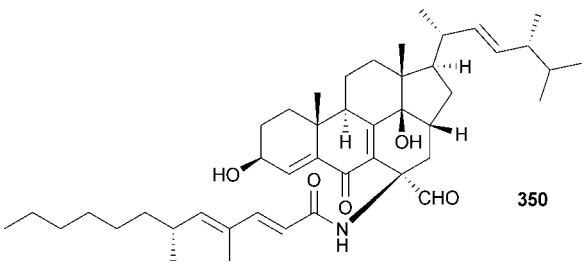
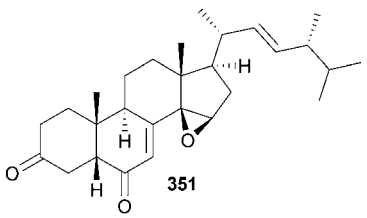


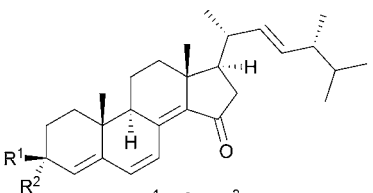
349



350



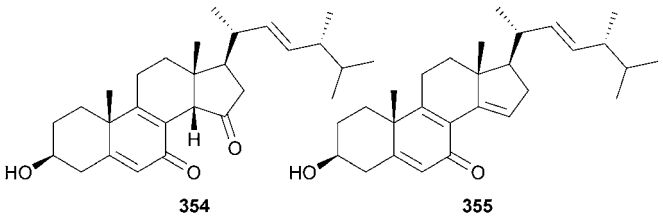
351



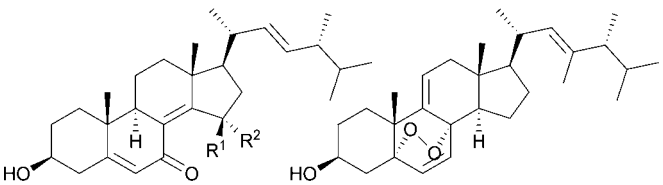
352 (R^1 = OH, R^2 = H)
353 (R^1, R^2 = O)

The marine-derived fungus *Rhizopus* sp., isolated from the Chinese bryozoan *Bugula* sp., yielded six new ergosterols,

3β-hydroxy-(22*E*,24*R*)-ergosta-5,8,22-trien-7,15-dione (**354**), 3β-hydroxy-(22*E*,24*R*)-ergosta-5,8,14,22-tetraen-7-one (**355**), 3β,15β-dihydroxy-(22*E*,24*R*)-ergosta-5,8(14),22-trien-7-one (**356**), 3β,15β-dihydroxy-(22*E*,24*R*)-ergosta-5,8(14),22-trien-7-one (**357**), 3β-hydroxyl-(22*E*,24*R*)-ergosta-5,8(14),22-trien-7,15-dione (**358**), and 5α,8α-epidioxy-23,24(*R*)-dimethylcholesta-6,9(11),22-trien-3β-ol (**359**).[255] All compounds showed cytotoxic activity to varying degrees against four different cancer cell lines.



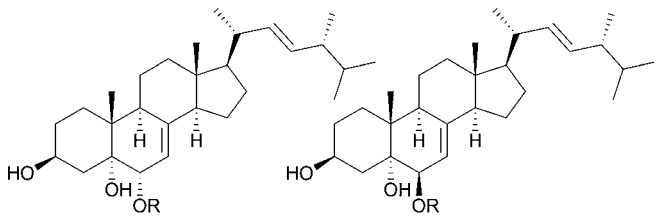
354 **355**



356 (R^1 = OH, R^2 = H)
357 (R^1 = H, R^2 = OH)
358 (R^1, R^2 = O)

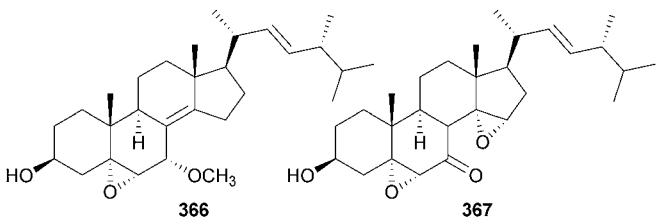
359

Six new fatty acid esters of the known steroids (22*E*)-ergosta-7,22-diene-3β,5α,6α-triol (**360–363**) and (22*E*)-ergosta-7,22-diene-3β,5α,6β-triol (**364**, **365**) were isolated from the fungus *Aspergillus awamori* isolated from soil around the mangrove plant *Acrostichum speciosum* in Hainan, China, besides various known steroids and their esters.[256] All compounds exhibited mild cytotoxic activity against B16 and SMMC-7721 cell lines. Further analysis yielded the two new oxidized sterols, (22*E*)-7α-methoxy-5α,6α-epoxyergosta-8(14),22-dien-3β-ol (**366**) and (22*E*)-3β-hydroxy-5α,6α,8α,14α-diepoxyergosta-22-en-7-one (**367**), both of which displayed weak cytotoxic activity towards the lung cancer cell line A549.[257] Conformational analysis on the basis of the observed NOEs in the ROESY spectrum indicated that the cyclohexene oxide system in ring B of **366** adopted an *endo*-boat rather than a half-chair conformation.



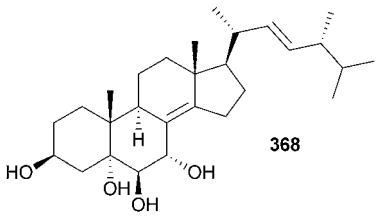
360 (R = palmitoyl)
361 (R = stearoyl)
362 (R = oleooyl)
363 (R = linoleoyl)

364 (R = palmitoyl)
365 (R = stearoyl)



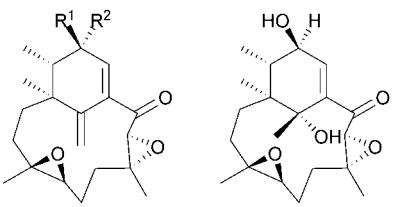
366 **367**

The fungus *Penicillium* sp. was obtained from an undisclosed moss collected from the South Pole. Chemical analysis revealed the presence of a new sterol, ergosta-8(14),22-diene-3β,5α,6β,7α-tetraol (**368**), together with four known sterols. **368** exhibited pronounced cytotoxicity against the human liver cancer cell line Hep G with an IC_{50} value of 10.4 μg mL^{-1}.[258]



368

An unidentified fungus that was isolated from the surface of the Japanese brown alga *Ishige okamurae*, and based on DNA sequence analysis was grouped into the order Dothideales was identified as the producer of phomactin I (**369**), 13-*epi*-phomactin I (**370**) and phomactin J (**371**).[259] Phomactins are an intriguing class of fungal diterpenes which have raised considerable attention due to their activity as platelet-activating factor (PAF) antagonists,[260] and were initially discovered in cultures of the fungus *Phoma* sp. obtained from the shell of the crab *Chionoecetes opilio*,[261,262] and it is therefore remarkable that the unidentified fungus in this study was taxonomically not closely related to the genus *Phoma*.

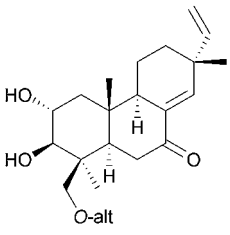


369 (R^1 = OH, R^2 = H)
370 (R^1 = H, R^2 = OH)

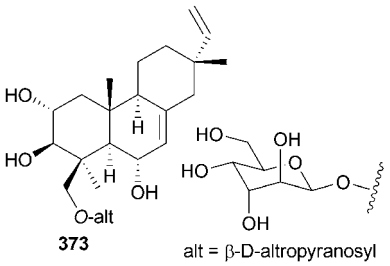
371

The fungus *Acremonium striatisporum* was isolated from superficial mycobiota of the sea cucumber *Eupentacta fraudatrix* collected from the Sea of Japan. Over the course of eight years, it was repeatedly studied and proved to be an exceptionally rich source of new isopimaradiene diterpene glycosides, virescenosides. The latest addition to this series were virescenosides V–X (**372–374**), which like most of the remaining virescenosides are substituted with an unusual β-D-altropyranose moiety.[263]

The marine fungus *Cryptosphaeria eunomia* var. *eunomia*, isolated from an unidentified Micronesian sponge, was found to produce the new pimarane-type diterpene 11-deoxydiaporthein A (**375**),[264] together with known compounds from terrestrial fungi, diaporthein A and B, metabolites of *Diaporthe* sp.[265] and scopararane A, previously described from *Eutypella scoparia*.[266]

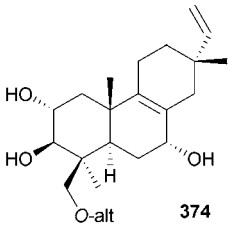


372



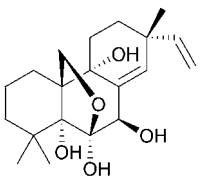
373

alt = β-D-altropyranosyl



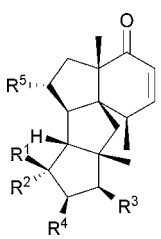
374

Recrystallisation experiments were undertaken using chloroform, and inspection of the crystals obtained for **375**, diaporthein A and scopararane A revealed that chloroform molecules were incorporated into their crystal lattices, so that their absolute configurations could unambiguously be determined.



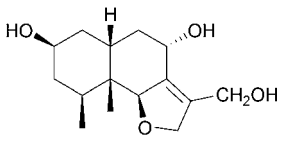
375

A deep sea sediment-borne *Penicillium* sp., obtained from a depth of 5080 m, was found to produce a series of new diterpenes, conidiogenones B–G (**376–381**), besides four new diketopiperazine-type alkaloids (**501–504**).[267] **376–381** are structurally related to conidiogenol and conidiogenone, metabolites from a terrestrial isolate of *Penicillium cyclopium* which were reported to possess potent conidiation-inducing activity.[268] When tested for cytotoxic properties against four different cell lines, **376–381** displayed various degrees of activity, with **377** exhibiting potent activity towards HL-60 and BEL-7402 cells.



376 ($R^1 = R^2 = CH_3$, $R^3 = R^4 = R^5 = H$)
377 ($R^1 = CH_2OH$, $R^2 = CH_3$, $R^3 = R^4 = R^5 = H$)
378 ($R^1 = CH_3$, $R^2 = CH_2OH$, $R^3 = R^4 = R^5 = H$)
379 ($R^1 = R^2 = CH_3$, $R^3 = OH$, $R^4 = R^5 = H$)
380 ($R^1 = R^2 = CH_3$, $R^3 = H$, $R^4 = OH$, $R^5 = H$)
381 ($R^1 = R^2 = CH_3$, $R^3 = R^4 = H$, $R^5 = OH$)

Peribysins H[269] (**382**), I (**383**)[269] and J (**384**)[270] are eremophilane-type sesquiterpenoids produced by the fungus *Periconia byssoides* which was originally isolated from the Japanese sea hare, *Aplysia kurodai*. Similar to most other peribysins A–G[175,176] which have been established as cell-adhesion inhibitors, **382** and **383** inhibited the adhesion of HL-60 cells to HUVEC (human umbilical vein endothelial cells) more potently than the standard control in this assay system, herbimycin A.



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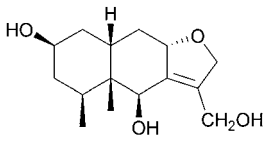

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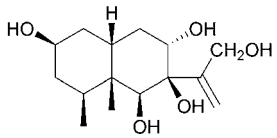
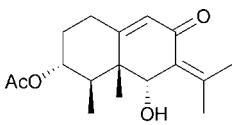
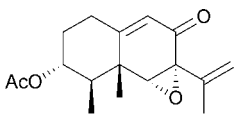


384

The fungus *Penicillium* sp., isolated from sea mud in the Bering Sea, yielded two new eremophilane sesquiterpenes, 3-acetyl-9,7(11)-dien-7α-hydroxy-8-oxoeremophilane (**385**) and 3-acetyl-13-deoxyphomenone (**386**).[271] Compound **386** had been synthesized in the course of the structure elucidation of sporogen A0 I from a mycophilic *Hansfordia* sp.,[272] but had not been previously reported as a natural product. The epoxide **386** exhibited pronounced cytotoxic activity in the nanomolar range against three different cell lines, while the ring-opened alcohol **385** was less active by several orders of magnitude.

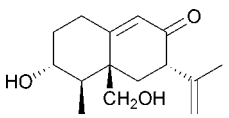


385

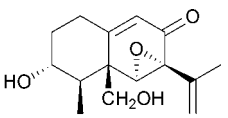


386

JBIR-27 (**387**) and JBIR-28 (**388**) were reported from the fungus *Penicillium* sp. which was obtained from the Japanese tunicate *Didemnum molle*.[273] In addition, the closely related eremophilanes phomenone[274] and its 13-deoxy congener,[275] also known as sporogen-A01, were also obtained, which previously had been described from *Phoma exigua* var. *non-oxydabilis* and *Hansfordia pulvinata*, respectively. Compound **388** and the two known compounds showed moderate cytotoxicity towards the HeLa cell line, whereas **387** was inactive.



387

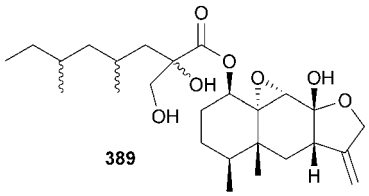


388

A marine-derived ascomycete related to the genus *Cryptosphaeria*, isolated from an unidentified ascidian in the Bahamas, produced cryptosphaerolide (**389**), an eremophilane type sesquiterpenoid bearing both an *exo*-methylene and an ester function.[276] **389** is related to berkleasmin A, a metabolite of the terrestrial saprobic fungus, *Berkleasmium nigroapicale*.[277] In the Mcl-1/Bak fluorescence resonance energy transfer (FRET) assay, **389** displayed inhibitory activity towards the Mcl-1 protein, a cancer drug target involved in apoptosis. In addition, **389** also showed significant cytotoxicity against the HCT-116 human colon carcinoma cell line, with IC_{50} values in the lower μM range.

An undisclosed mangrove endophytic fungal strain yielded the sesquiterpene microsphaeropsisin A (**390**),[278] closely related to microsphaeropsisin described previously from a sponge-derived *Microsphaeropsis* sp.[279] Due to its instability neither the relative

stereochemistry nor the biological activity of **390** could be investigated.



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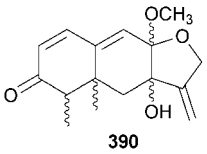
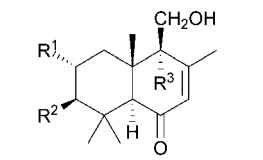
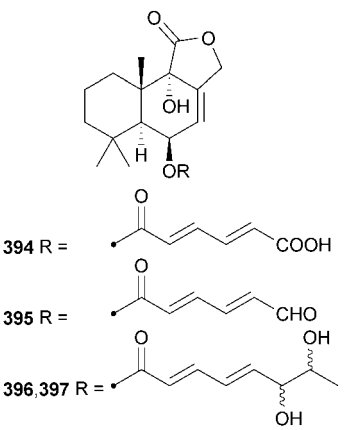


390

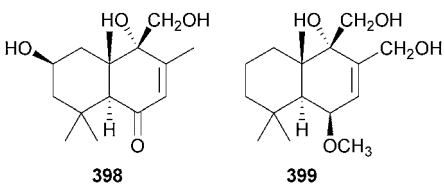
Seven new drimane sesquiterpenoids, hydroxylated derivatives of drim-7-en-6-one (**391–393**) and esters of 6β,9α-dihydroxy-5α-drim-7-en-11,12-olide with polyunsaturated acid substituents at C-6 (**394–397**), together with the related known compounds deoxyuvidin B, strobilactone B and RES-1149-2, were obtained from cultures of the fungus *Aspergillus ustus*, which was isolated from the Mediterranean sponge *Suberites domuncula*.[203,280] Compounds **394**, **395**, and RES-1149-2 showed cytotoxic activity against a panel of tumour cell lines, and **395** was the most active, with an EC_{50} value of 0.6 μg mL^{-1} against the L5178Y cell line. In a study which was published almost simultaneously, another isolate of *Aspergillus ustus*, obtained from the rhizosphere soil of the mangrove plant *Bruguiera gymnorrhiza* in China, produced eight drimane sesquiterpenes, termed ustusols A–C (**391**, **398**, **399**) and ustusolates A–E (**400–403**, **395**), out of which two proved to be identical to the ones reported from the sponge-derived fungal strain mentioned above, besides another occurrence of RES-1149-2, and six new isochromane derivatives.[236] In



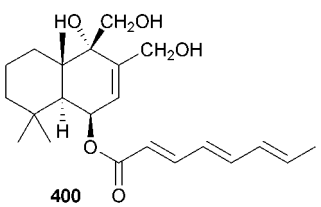
391 R^1 = H, R^2 = OH, R^3 = OH
392 R^1 = OH, R^2 = H, R^3 = OH
393 R^1 = OH, R^2 = H, R^3 = H



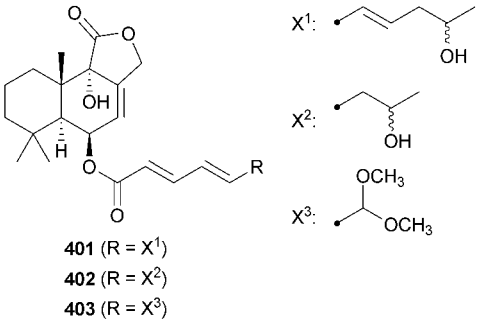
394 R =
395 R =
396,**397** R =



398 **399**



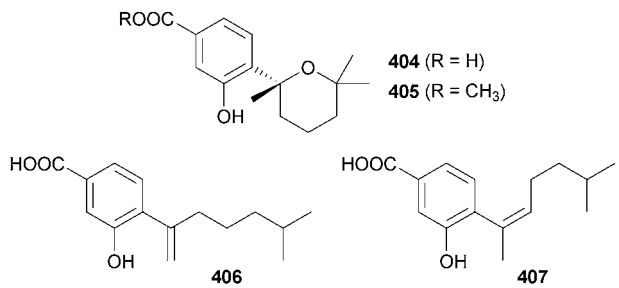
400



401 (R = X^1)
402 (R = X^2)
403 (R = X^3)

this latter report, the absolute configuration of **391** was established based on its CD spectrum and the octant rule for cyclohexenones, and **395** and **402** were found to exhibit moderate cytotoxicity, while **400** was weakly active. It is noteworthy that compounds **392** and **398**, reported from the two research groups as C-2 epimers, displayed virtually identical ^{13}C NMR data, and are thus very likely to be identical. RES-1149-2 had previously been described as a metabolite from *A. ustus* var. *pseudoreflectus* isolated from a soil sample,[281,282] and was found to act as endothelin type B receptor antagonist.[283]

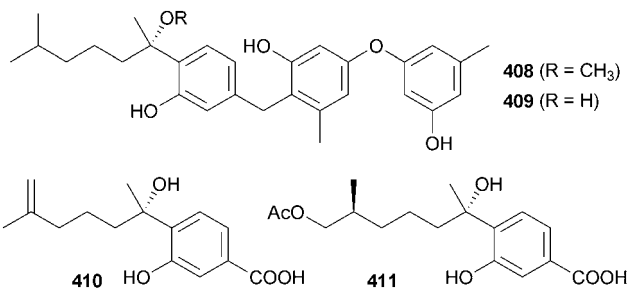
Four new phenolic bisabolane-type sesquiterpenoids, (+)-sydowic acid (**404**), (+)-methyl sydowate (**405**), 7-deoxy-7,14-didehydrosydonic acid (**406**) and 7-deoxy-7,8-didehydrosydonic acid (**407**), together with the known (+)-sydonic acid were isolated from a marine-derived *Aspergillus* sp., obtained from the Chinese gorgonian *Dichotella gemmacea*.[284] The enantiomer of **404** ((−)-sydowic acid), as well as the corresponding racemate and sydonic acid, had previously been obtained from terrestrial strains of *Aspergillus sydowi*.[285–287] Compounds **404**, **405** and sydonic acid exhibited weak antibacterial activity against *Staphylococcus aureus*, but were inactive against methicillin-resistant *S. aureus*.



404 (R = H)
405 (R = CH_3)

406 **407**

The fungus strain *Penicillium expansum* was isolated from the roots of the Chinese mangrove plant *Excoecaria agallocha*, and identified as the producer of expansols A (**408**) and B (**409**),



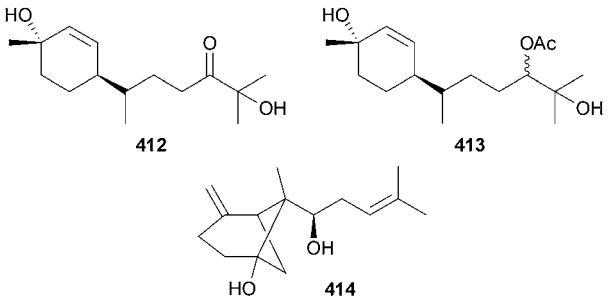
408 (R = CH_3)
409 (R = H)

410 **411**

bisabolane sesquiterpenoids substituted with a diphenyl ether unit, and two new phenolic bisabolane sesquiterpenoids, (*S*)-(+)-11-dehydrosydonic acid (**410**) and (7*S*,11*S*)-(+)-12-acetoxysydonic acid (**411**).[288] Compound **408** exhibited moderate cytotoxicity against the HL-60 cell line, while **409** inhibited the proliferation of A549 and HL-60 cells, while **410** and **411** were inactive.

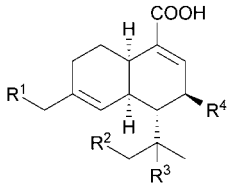
Verticinols A (**412**) and B (**413**) are two new hydroxylated bisabolane-type sesquiterpenes which were reported from the fungus *Verticillium tenerum*, isolated from an unidentified marine alga.[289] Although **412** and B **413** were tested for a variety of effects, *i.e.* antibacterial, antifungal, antialgal, antiplasmodial, antiviral, and cytotoxic activity as well as protein kinase inhibition or fat-accumulation inhibitory activity against 3T3-L1 murine adipocytes, they did not display significant activity in any of these test systems.

The fungus *Acremonium* sp., isolated from the Korean sponge *Stelletta* sp., produced the new sesquiterpenoid dihydroxybergamotene (**414**) and nine known sesquiterpenoids, together with three new meroterpenoids (**339–341**).[245] **414** is a dihydroxylated congener of β-*trans*-bergamotene, which was reported from a terrestrial strain of *Aspergillus fumigatus*,[290] but otherwise has widespread occurrence in essential oils of higher plants. Although some of the known metabolites exhibited various anti-inflammatory properties, **414** was inactive in the respective bioassays.

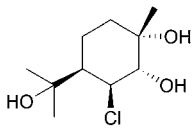


Four new hydroxylated sclerosporin derivatives 15-hydroxysclerosporin (**415**), 12-hydroxysclerosporin (**416**), 11-hydroxysclerosporin (**417**) and 8-hydroxysclerosporin (**418**), besides the known (+)-sclerosporin were produced by the fungus *Cadophora malorum*, isolated from the green alga *Enteromorpha* sp. upon long-term fermentation in a medium supplemented with artificial sea salt.[291] Sclerosporin was initially characterised as a sporogenic metabolite of a terrestrial isolate of *Sclerotinia fruticula*, and is a rare example of a fungal-derived cadinane-type sesquiterpene.[292,293] Compounds **415–418** were subjected to a variety of assays, but were found devoid of significant biological activity, apart from **418** which showed a weak fat-accumulation inhibitory activity against 3T3-L1 murine adipocytes.

A large-scale fermentation of the fungus *Tryblidiopycnis* sp., an endophyte from woody tissue of a *Kandelia* sample from Hong Kong, yielded the new chlorinated monoterpene, (1*S*,2*S*,3*S*,4*R*)-3-chloro-4-(2-hydroxypropan-2-yl)-1-methylcyclohexane-1,2-diol (**419**).[294]



415 (R^1 = OH, R^2 = H, R^3 = H, R^4 = H)
416 (R^1 = H, R^2 = OH, R^3 = H, R^4 = H)
417 (R^1 = H, R^2 = H, R^3 = OH, R^4 = H)
418 (R^1 = H, R^2 = H, R^3 = H, R^4 = OH)



419

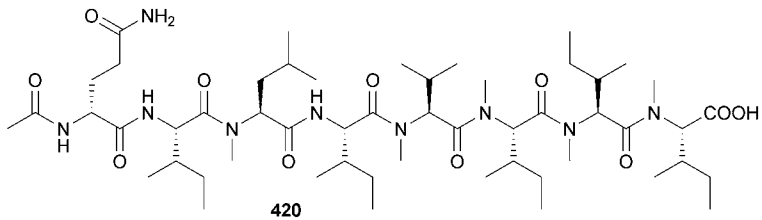
4.6 Peptides including diketopiperazines

RHM1 (**420**) and RHM2 (**421**) are highly *N*-methylated linear octapeptides produced by the fungus *Acremonium* sp., which was isolated from the sponge *Teichaxinella* sp. collected in Papua New Guinea.[295] The fungus was considered by the authors "a notably atypical *Acremonium* sp.", since its unusual morphological characteristics were in disagreement with the results of the molecular biological identification which suggested a close similarity to *Leucosphaerina indica*. Compounds **420** and **421** exhibited mild cytotoxicity against murine L1210 cells, while **420** additionally possessed antibiotic properties against *Staphylococcus epidermidis*. Reinvestigation of the same fungal strain revealed the presence of additional RHM congeners, RHM3 (**422**) and RHM4 (**423**).[296] In addition, two new efrapeptin derivatives, efrapeptin Eα (**424**) and H (**425**), were characterised, besides the known efrapeptides E, F and G, so far only known from terrestrial sources. Efrapeptins are linear pentadecapeptides produced by the soil hyphomycete *Tolypocladium niveum* that have attracted considerable attention due to their ability to inhibit the soluble (F_1) part of the mitochondrial ATPase.[297] The structure elucidation of **424** and **425**, most importantly establishing their amino acids sequence, heavily relied on MS and MS^n analysis, while NMR spectroscopy was mainly used to establish the presence or absence of individual amino acids by individual characteristic signals.

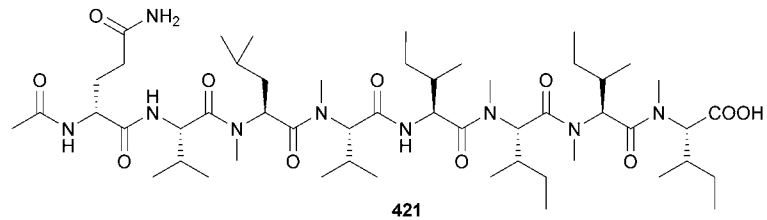
The fungus *Tolypocladium* sp., obtained from sea mud in Japan, was recently identified as a source of the new efrapeptin analogue, efrapeptin J (**426**), together with the known efrapeptins F and G.[298] In a reporter gene assay, all three compounds were shown to inhibit the expression of luciferase controlled by the GRP78 promoter in a dose-dependent manner. Furthermore, **426** also inhibited the protein expression of GRP78 in HT1080 cells and MKN-74 human gastric cancer cells, and induced cell death in HT1080 cells under endoplasmic reticulum stress.

The fungal strain *Trichoderma* sp., isolated from an unidentified marine sponge of undisclosed geographic origin, produced three new aminolipopeptides, trichoderins A (**427**), A1 (**428**) and B (**429**).[299] Compounds **427–429** are characterized by the presence of an 2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid (AHMOD) moiety, which they share with previously described aminolipopeptides such as the leucinostatins or trichopolyns, metabolites of *Penicillium lilacinum*[300] and *Trichoderma polysporum*,[301] respectively. Compounds **427–429** showed potent anti-mycobacterial activity against *Mycobacterium smegmatis*, *M. bovis* and *M. tuberculosis*, with MIC values in the range 0.02–2.0 μg mL^{-1}, and were effective against both actively growing and dormant states.

Six new peptaibols, asperelines A–F (**430–435**), characterised by an uncommon prolinol residue at the C-terminus, were produced by the psychrophilic fungus *Trichoderma asperellum*,



420



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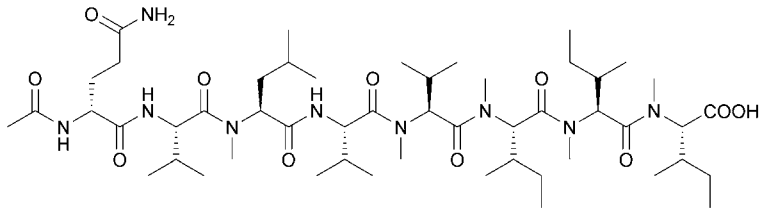

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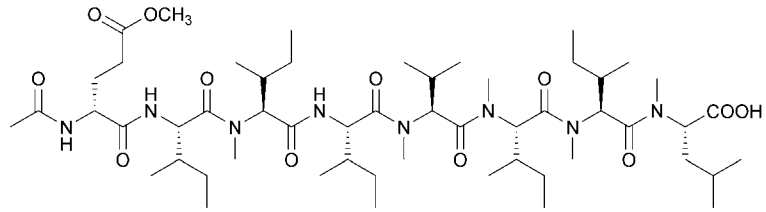

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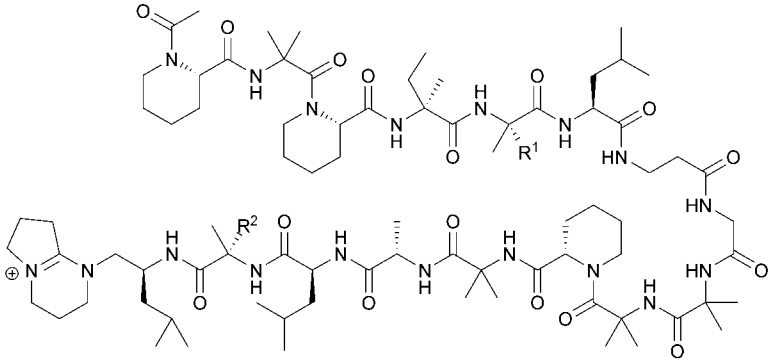
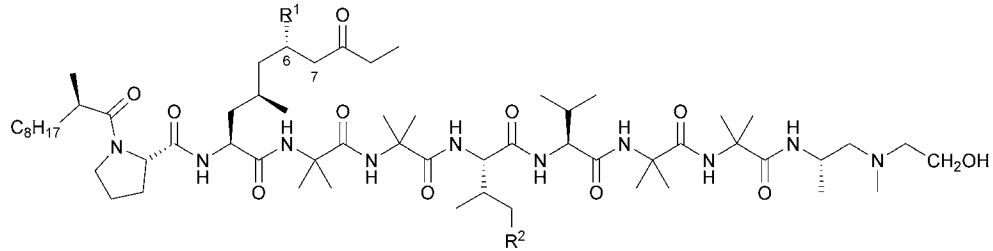
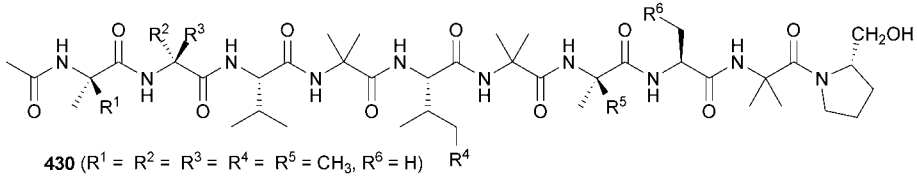


424 (R^1 = C_2H_5, R^2 = CH_3, R^3 = CH_3)
425 (R^1 = C_2H_5, R^2 = C_2H_5, R^3 = C_2H_5)
426 (R^1 = CH_3, R^2 = CH_3, R^3 =CH_3)



427 (R^1 = OH, R^2 = CH_3)
428 (R^1 = H, R^2 = CH_3; $\Delta_{6,7}$)
429 (R^1 = OH, R^2 = H)



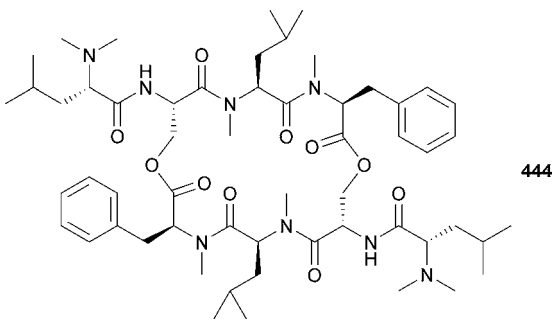
430 (R^1 = R^2 = R^3 = R^4 = R^5 = CH_3, R^6 = H)
431 (R^1 = R^6 = H, R^2 = R^3 = R^4 = R^5 = CH_3)
432 (R^1 = R^2 = R^3 = R^4 = CH_3, R^5 = R^6 = H)
433 (R^1 = R^2 = R^3 = R^5 = CH_3, R^4 = R^6 = H)
434 (R^1 = R^2 = R^3 = R^4 = R^5 = CH_3, R^6 = OH)
435 (R^1 = R^4 = R^5 = CH_3, R^2 = R^6 = H, R^3 = $CH(CH_3)_2$)

436 Ac—Aib—Asn—Leu—Leu—Aib—Pro—Leu—Aib—Aib—Pro-Leuol
437 Ac—Aib—Asn—Leu—Leu—Aib—Pro—Val—Leu—Aib—Pro-Valol
438 Ac—Aib—Asn—Val—Leu—Aib—Pro—Leu—Leu—Aib—Pro-Valol
439 Ac—Aib—Asn—Leu—Val—Aib—Pro—Leu—Leu—Aib—Pro-Valol
440 Ac—Aib—Asn—Leu—Leu—Aib—Pro—Val—Aib—Val—Pro-Leuol
441 Ac—Aib—Asn—Val—Leu—Aib—Pro—Leu—Aib—Val—Pro-Leuol
442 Ac—Aib—Asn—Leu—Val—Aib—Pro—Leu—Aib—Val—Pro-Leuol
443 Ac—Aib—Asn—Leu—Leu—Aib—Pro—Leu—Aib—Val—Pro-Valol

collected from a sediment sample in the Antarctic.[302] The absolute configurations of some of the amino acid residues were determined using a new method of ^{1}H NMR spectroscopic comparison of complexes formed with the chiral shift reagent Ru(D_4-Por*)CO. **430–435** exhibited weak inhibitory activity towards the phytopathogenic fungi *Alternaria solani* and *Pyricularia oryzae*, as well as against the bacteria *Staphylococcus aureus* and *Escherichia coli*.

A strain of *Trichoderma longibrachiatum* was isolated from blue mussel, *Mytilus edulis*, collected in France. Using various mass spectrometric techniques, eight new short peptaibols were identified, each of them comprising 11 amino acids, trichobrachins A I–IV (**436–439**) and trichobrachins B I–IV (**440–443**).[303] Reinvestigation of the same strain led to the partial characterisation by mass spectrometry of a further microheterogenous mixture of 30 peptaibols, out of which 21 were new.[304] All shared the common motif Ac-Aib-xxx-xxx-xxx-Aib-Pro-xxx-xxx-Aib-Pro-xxol, and were assigned the names trichobrachins A when the residue in position 2 was an asparagine, and trichobrachin C when it was a glutamine.

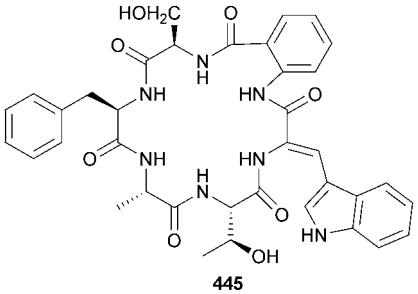
The fungus *Clonostachys* sp., isolated from an unidentified Japanese sponge, yielded the symmetric cyclodepsipeptide IB-01212 (**444**).[305] When its cytotoxic activity was evaluated against a panel of 14 different human tumour cell lines, **444** was most active against LN-caP (prostate cancer), SK-BR3 (breast cancer), HT29 (colon cancer), and HELA (cervix cancer) cell lines, with GI_{50} values ranging in the order of 10^{-8} M.



444

Sclerotides A (**445**) and B (**446**), cyclic hexapeptides containing anthranilic acid and a dehydrotryptophan unit, were isolated in a nutrient-limited hypersaline medium from the marine-derived halotolerant *Aspergillus sclerotiorum*, isolated from a Chinese salt field.[306] Compounds **445** and **446** exhibited moderate antifungal activity against *Candida albicans*, while **434** also showed weak cytotoxic activity against the HL-60 cell line and antibacterial activity against *Pseudomonas aeruginosa*. Compounds **445** and **446** were photointerconvertible *via* a radical mechanism.

From the brown alga *Durvillaea antarctica*, collected off the coast of New Zealand, an endophytic strain of *Gliocladium* sp. was obtained. Bioactivity profiling using a coupled HPLC/microtiter assay system revealed that both the antimicrobial and the cytotoxic activity of the fungal crude extract were due to the presence of the known compound, 4-keto-clonostachydiol, a 14-membered macrodiolide previously reported in the patent literature. In addition, the new cyclodepsipeptide gliotide (**447**) was characterised, which proved inactive in the cytotoxicity and antimicrobial assays.[307]



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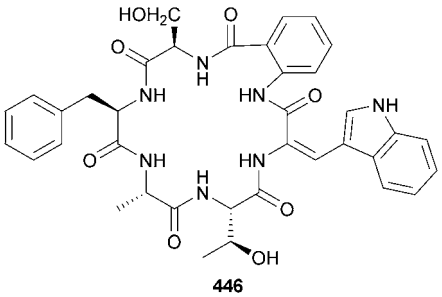

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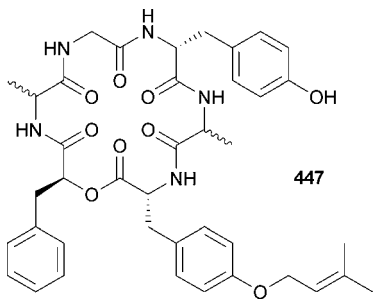
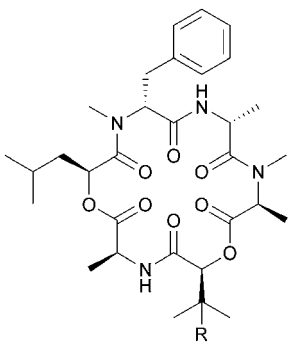
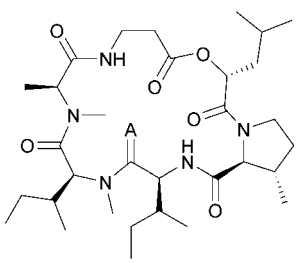


447

An unidentifiable fungus was isolated from the sponge *Ianthella* sp. collected in Papua New Guinea. In a seawater-based medium, it was found to produce two new guangomides A (**448**) and B (**449**), together with a new destruxin derivative, homodestcardin (**450**).[308] Compounds **448** and **449** are unusual due to the presence of two lactone moieties, while **450** is the first example of a destruxin analogue obtained from marine-derived fungi. Both **448** and **449** were devoid of cytotoxic activity, but displayed weak antibacterial activity against *Staphylococcus epidermidis* and *Enterococcus durans*.



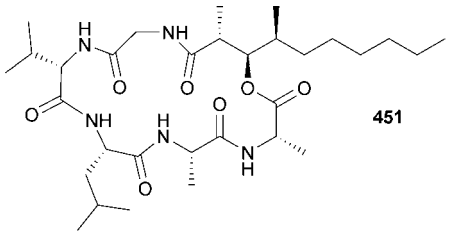
448 (R = OH)
449 (R = H)



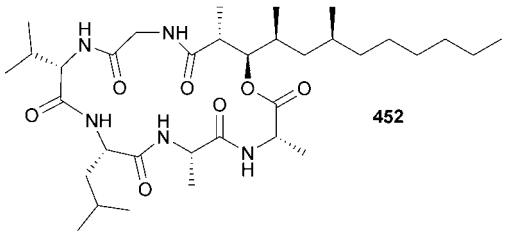
450

Emericellamides A (**451**) and B (**452**) are cyclic lipodepsipeptides that were found to be produced by competing

co-culture of the fungus *Emericella* sp., isolated from the surface of the green alga *Halimeda*. sp. collected in Papua New Guinea, in the presence of the marine actinomycete *Salinispora arenicola*.[309] Compounds **451** and **452** were produced in low yields by *Emericella* sp. alone, but upon co-culture their levels were enhanced by 100-fold. Both compounds showed modest antibacterial activities against methicillin-resistant *Staphylococcus aureus*. More recently, the biogenetic gene cluster for the production of **451** comprising a PKS–NRPS hybrid synthase has been identified through genomic data mining in the fully sequenced genome of *Aspergillus nidulans*.[310]

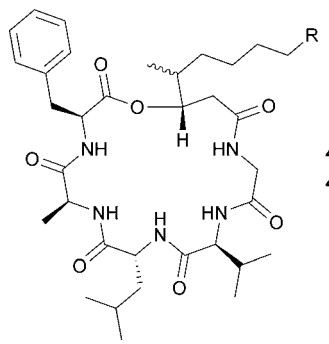


451



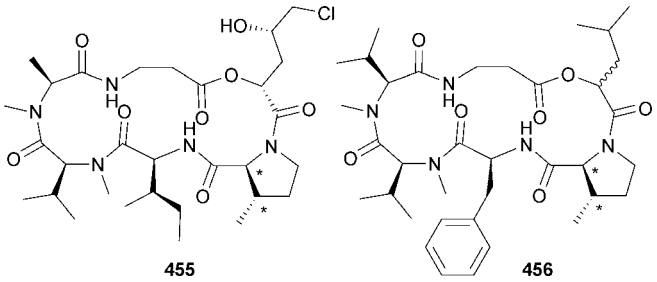
452

The fungus *Scopulariopsis brevicaulis* was isolated from the Mediterranean sponge *Tethya aurantium*, and was shown to produce the two cyclodepsipeptides, scopularides A (**453**) and B (**454**).[311] Their 3-hydroxy-4-methylalkanoic acid moiety is similar to the corresponding moiety in emericellamides A (**451**) and B (**452**), and both compounds displayed only weak antibacterial activity, but significantly inhibited growth of several tumour cell lines.



453 (R = C_2H_5)
454 (R = H)

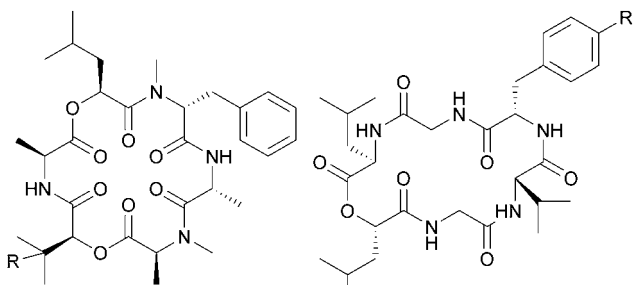
The fungus *Beauveria felina* was isolated from the green alga *Caulerpa* sp. collected off the coast of Brazil. Chemical investigation of its cytotoxic and anti-tuberculosis active butanone extract led to the discovery of two new destruxins, [β-Me-Pro] destruxin E chlorohydrin (**455**) and pseudodestruxin C (**456**), along with five known cyclic depsipeptides.[312] The absolute configuration of the (2*R*,4*S*)-5-chloro-2,4-dihydroxypentanoic acid residue in **455** was established by the *J*-based configuration method in combination with chiral derivatisation. In a subsequent communication, the multi-screening approach leading to the discovery of destruxins including **455** and **456** was explained in more detail.[313]



455 **456**

The fungal strain *Spicellum roseum*, isolated from the Caribbean sponge *Ectyplasia perox*, yielded two new cyclohexadepsipeptides, spicellamides A (**457**) and B (**458**).[314] Both compounds displayed moderate cytotoxicity against neuroblastoma cells, but were inactive when assayed for antimicrobial effects against various test bacteria, fungi and algae. Since hydrolysis using Marfey's method revealed the presence of both D- and L-alanine in **457** and **458**, the position of this amino acid was determined by using a NOESY data in combination with molecular modelling.

Two new cyclic depsipeptides, 1962A (**459**) and 1962B (**460**), were produced by an unidentified fungal endophyte, obtained from the mangrove plant *Kandelia candel* collected in Hong Kong.[315] **459** and **460** were both found to contain one D-amino acid each. **459** exhibited mild cytotoxic activity towards human breast cancer MCF-7 cells.



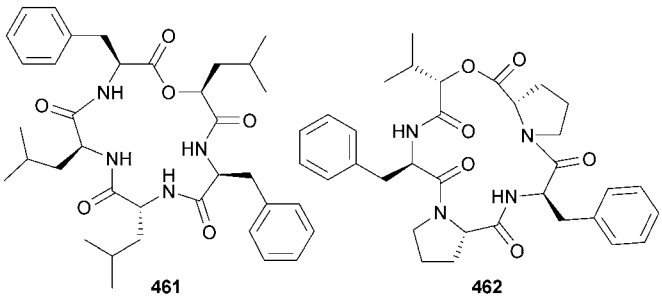
457 (R = H)
458 (R = OH)

459 (R = OH)
460 (R = H)

Zygosporamide (**461**) is a new cyclic pentadepsipeptide which was obtained upon seawater-based fermentation of the fungus *Zygosporium masonii*.[316] Interestingly, the fungal strain was isolated from a cyanobacterium collected off Maui, Hawaii. So far, cyanobacteria have largely been neglected as a potential source of fungal diversity. **461** proved inactive against various drug-resistant bacteria, but displayed highly selective cytotoxicity in the National Cancer Institute cell line assay, with GI_{50} values ranging in the nanomolar range.

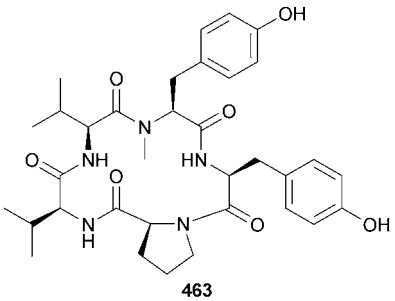
The cyclic pentadepsipeptide alternaramide (**462**) was detected in the culture broth of the fungus *Alternaria* sp. which was isolated from Korean sediment sample.[317] Compound **462** displayed weak antimicrobial activity against *Bacillus subtilis* and *Staphylococcus aureus*, and also inhibited protein tyrosine phosphatase 1B (PTP1B).

An Australian marine-derived isolate of *Aspergillus versicolor*, recovered from beach sand, was grown on a cellophane raft over



461 462

nutrient-rich media, and by this treatment was induced to produce two new cyclopentapeptides, cotteslosins A (**463**) and B (**464**), besides a new quinazoline-type alkaloid.[318] Compound **463** and **464** display structural similarities to the cyclic pentadepsipeptide sansalvamide A, previously reported from a seagrass-derived *Fusarium* sp.,[319] and **464** was found to exhibit weak cytotoxicity against several cancer cell lines.



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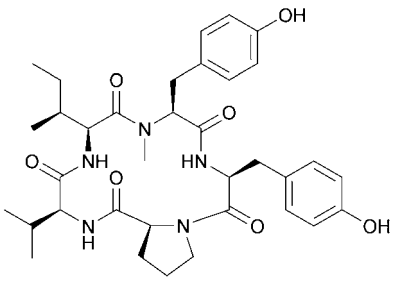
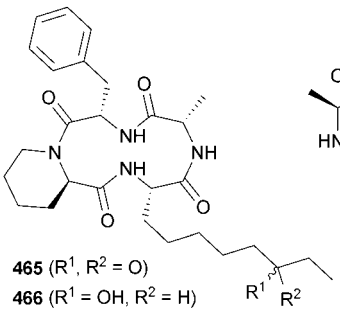


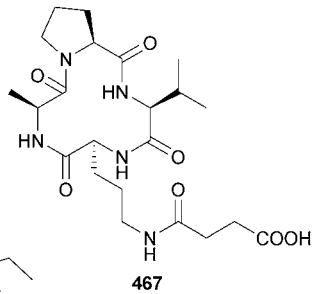
464

The fungus *Microsporum cf. gypseum*, obtained from a sample of the bryozoan *Bugula* sp. collected in the U.S. Virgin Islands, was found to produce two new cyclic tetrapeptides, microsporins A (**465**) and B (**466**).[320] Compound **465** was synthesised by solid-phase synthesis using a sulfonamide linker resin. **465** and **466** displayed marked inhibitory properties towards histone deacetylase, exhibited cytotoxic activity against HCT-116 cells (human colon adenocarcinoma), and were active in the National Cancer Institute's 60-cancer-cell panel. **465** contains the unusual amino acid, (2*S*)-2-amino-8-hydroxydecanoic acid, while **466** contains its oxidised derivative, (*S*)-2-amino-8-oxodecanoic acid (Aoda), respectively. The latter is present in other fungal cyclic tetrapeptides including the potent protozoan HDAC inhibitors apicidin[321] and 9,10-deepoxy-chlamydocin,[322] described from *Fusarium pallidoroseum* and *Peniophora* sp., respectively.

A strain of *Trichoderma reesei* separated from sea mud in China was found to produce the cyclotetrapeptide trichoderide A (**467**) which exhibited moderate cytotoxicity towards the A375-S2 melanoma cell line.[323]

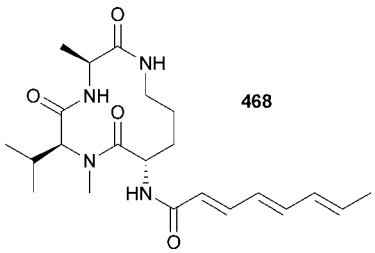


465 (R^1, R^2 = O)
466 (R^1 = OH, R^2 = H)



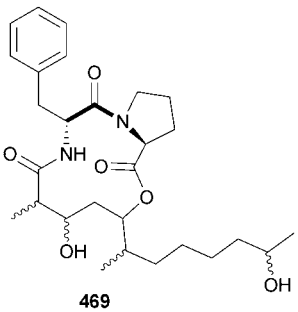
467

The new JBIR-15 (**468**), together with the known aspochracin, were obtained from the culture broth of the fungus *Aspergillus sclerotiorum* which was isolated from the Japanese sponge *Mycale* sp.[324] Aspochracin, an insecticidal cyclic tripeptide which differs from **468** by an *N*-methylated alanine residue, was originally reported from *A. ochraceus*.[325] Both **468** and asprochacin were inactive when tested for cytotoxicity towards two cell lines.



468

The Australian sediment-derived fungus *Acremonium* sp. produced a novel family of lipodepsipeptides, acremolides A–D (**469–472**), together with known chaetoglobosins.[326] Compounds **469–472** were devoid of antibacterial, antifungal or cytotoxic properties, nor did they synergize the cytotoxicity of the chaetoglobosins. The absolute stereochemistry of amino acid residues in **469–472** was established using a new C_3 Marfey's method, capable of discriminating between diastereomeric amino acid pairs such as isoleucine and *allo*-isoleucine, which are otherwise hard to resolve.



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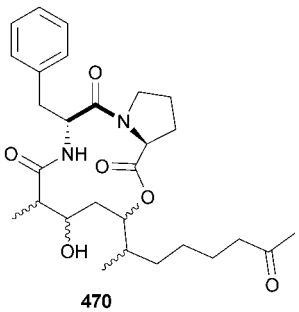

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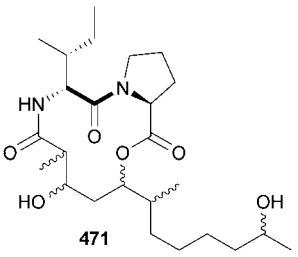

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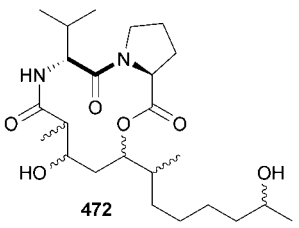
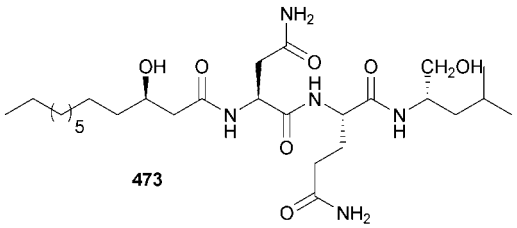


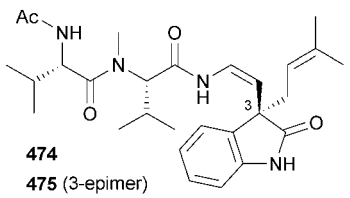
472

A new lipopeptide, fellutamide C (**473**), was isolated from a strain of *Aspergillus versicolor* which was obtained from the Korean sponge *Petrosia* sp.[327] Compound **473** displayed mid-range cytotoxicity against several cancer cell lines, and is a derivative of the previously described fellutamides A and B, metabolites of a marine fish-derived *Penicillium fellutanum*,[328] which however were not detected in the extract of *Aspergillus versicolor*.

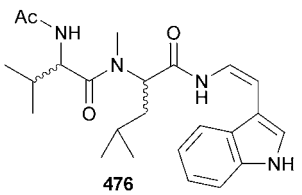


473

Two new indolic enamides, terpeptins A (**474**) and B (**475**), were characterised from the fungus *Aspergillus* sp., an endophyte of the Chinese mangrove plant *Acanthus ilicifolius*, together with the known terpeptin.[329] The latter is a mammalian cell cycle inhibitor initially described from *Aspergillus terreus*.[330] All three compounds exhibited moderate cytotoxicity towards the A-549 cell line. Two further derivatives, JBIR-81 (**476**) and JBIR-82 (**477**), in addition to terpeptin, were reported recently from another *Aspergillus* sp., isolated from the Japanese brown alga *Sargassum* sp.[331] All three terpeptins displayed free radical scavenging activities as expressed by their ability to protect N18-RE-105 cells against L-glutamate toxicity, and were considerably more potent than the positive control, α-tocopherol.



474
475 (3-epimer)



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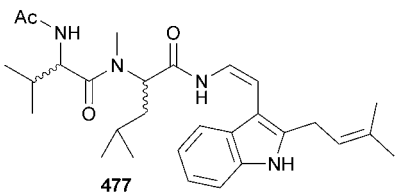


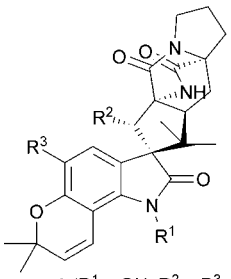
477

The fungus *Aspergillus* sp., which was isolated from the common mussel, *Mytilus edulis*, yielded a series of complex prenylated diketopiperazines, notoamides A–D (**478–481**)[332] and F–K (**486–491**),[333] with diverse modifications in their backbones. Compounds **478**, **479** and **488** contain the same intriguing spiro-indolinone skeleton as encountered in sclerotiamide, previously reported as a metabolite of a terrestrial *Aspergillus sclerotiorum*,[334] or in paraherquamide, a toxin produced by *Penicillium paraherquei*.[335] Compounds **486**, **487** and **489** are related to stephacidin A (**492**), earlier described from an Indian isolate of *Aspergillus ochraceus*.[336] The remaining congeners could be considered biosynthetic intermediates, since all of them are characterised by the presence of a rearranged isoprenyl moiety either at C-2 or C-3 of the indole, but lack additional cyclisation steps which link this substituent to the pyrrolo[1,2-*a*]pyrazine system in **478**, **479** and **486–489**, possibly by means of an intramolecular Diels–Alder reaction.[337] Compounds **478–480** and **489** showed moderate cytotoxicity against HeLa cells, while the remaining congeners proved inactive. Moreover, **480** was found to induce G2/M-cell cycle arrest. Reinvestigation of the same fungus yielded notoamide E (**482**) which represents a short-lived biogenetic intermediate, and feeding studies with synthetic doubly ^{13}C-labeled **482** resulted in the discovery of notoamides E2 (**483**), E3 (**484**) and E4 (**485**).[338] A subsequent report[339] disclosed the structures of notoamides L–N (**493–495**) and (−)-versicolamide B (**496**), the antipode of (+)-versicolamide B which was previously reported from a terrestrial fungicolous isolate of *A. versicolor*.[340] Interestingly, a marine isolate of *A. ostianus*, obtained from an unidentified Japanese sponge, likewise yielded related congeners, including the new 21-hydroxy-stephacidin A (**497**), besides notoamide F (**486**).[341] Very recently, further notoamide derivatives, notoamides O–Q (**498–500**) and notoamide R were reported from the original producer *Aspergillus* sp., but the latter compound appears to be identical to **497**.[342] Compound **498** possesses a hemiacetal/hemiaminal ether function which is unprecedented in the notoamide class of compounds.

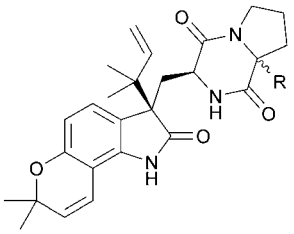
A deep sea sediment-borne *Penicillium* sp., obtained from a depth of 5080 m, was found to produce the new diketopiperazine-type alkaloids meleagrins B (**501**) and C (**502**), roquefortins F (**503**) and G (**504**), besides a series of new diterpenes, conidiogenones B–G (**376–381**).[267] Compounds **501** and **502** are related to meleagrin (a compound initially described from *Penicillium meleagrinum*,[343] and since then rather frequently detected in various terrestrial and marine isolates of the genus *Penicillium*), but **501** is structurally most unusual since it also contains a diterpene-derived moiety. **503** and **504** are derivatives of roquefortin C, a very common mycotoxin from various species of *Penicillium* subgenus *Penicillium*.[344] When tested for cytotoxic properties against four different cell lines, **501** displayed moderate activity against all cells, while the remaining compounds were less active.

The fungus *Aspergillus fumigatus*, isolated from the Chinese holothurian *Stichopus japonicus*, also produced a diverse suite of seven new prenylated indole diketopiperazine alkaloids.[345] Compound **505** was identified as a structurally unique spiro-3-indolinone derivative, while spirotryprostatins C–E (**506–508**) are spiro-2-indolinones related to spirotryprostatins A and B, previously described as mammalian cell cycle inhibitors from a terrestrial isolate of *Aspergillus fumigatus*.[346,347] Compounds **509** and **510** which were obtained as an inseparable mixture of diastereomers, display the same skeleton as present in fumitremorgin, another well-known tremorgenic toxin from *A. fumigatus*.[348] 13-Oxoverruculogen (**511**) contains a 1,2,4-dioxazocane ring formed from two isoprene moieties cross-linked by a peroxide bridge, and is a derivative of the known verruculogen, a metabolite from *Penicillium verruculosum*.[349] Compounds **506–511** displayed moderate cytotoxic activity against four different cell lines.

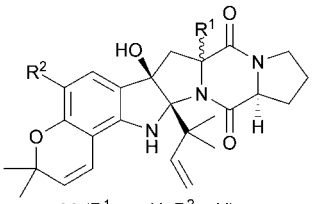
Brevicompanines D–H (**513–517**) along with the known *allo*-brevicompanine B (**512**) and fructigenine, were produced by the fungus *Penicillium* sp., obtained from a deep ocean sediment sample collected at a depth of 5080 m.[350] Compound **512** was up to that point known as a synthetic product, and had not been reported as a natural product before. Brevicompanine alkaloids



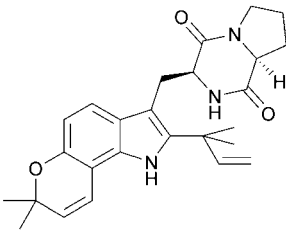
478 (R^1 = OH, R^2 = R^3 = H)
479 (R^1 = R^2 = R^3 = H)
488 (R^1 = R^2 = OH, R^3 = H)
495 (R^1 = R^2 = H, R^3 = Cl)



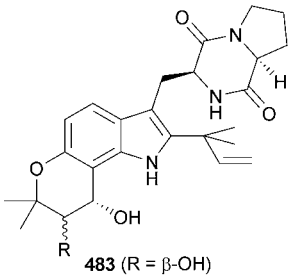
480 (R = α-H)
494 (R = OH)
500 (R = OCH_3)



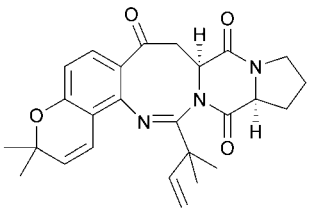
481 (R^1 = α-H, R^2 = H)
491 (R^1 = β-OH, R^2 = H)
499 (R^1 = β-OH, R^2 = Br)



482



483 (R = β-OH)
484 (R = α-OH)



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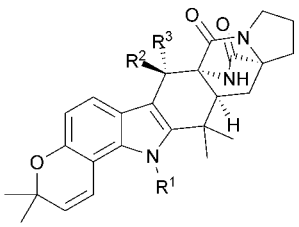
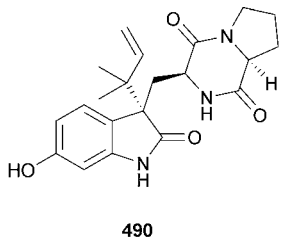
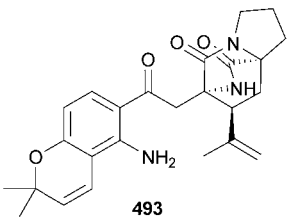


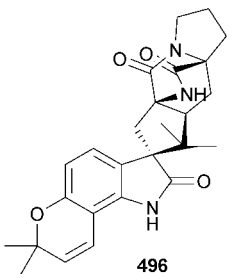
486 (R^1 = R^2 = H, R^3 = OCH_3)
487 (R^1 = OH, R^2 = H, R^3 = OCH_3)
489 (R^1 = H, R^2, R^3 = O)
492 (R^1 = R^2 = R^3 = H)
497 (R^1 = R^2 = H, R^3 = OH)



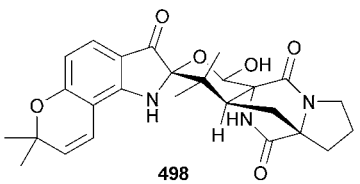
490



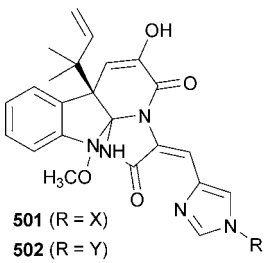
493



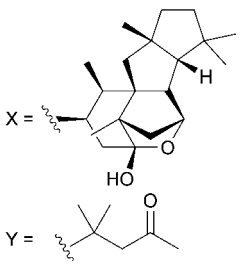
496

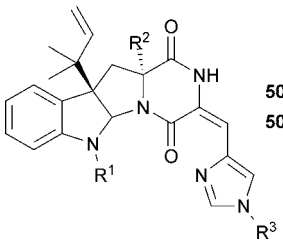


498

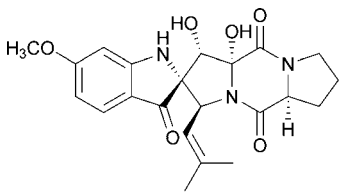


501 (R = X)
502 (R = Y)

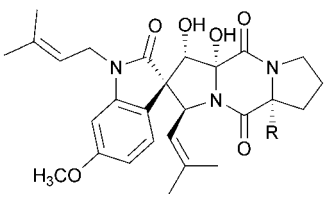




503 (R^1 = OCH_3, R^2 = R^3 = H)
504 (R^1 = H, R^2 = OCH_3, R^3 = Y)



505

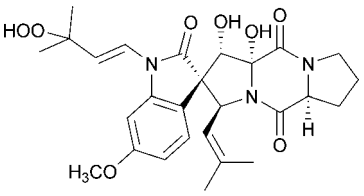


506 (R = H)
507 (R = OH)

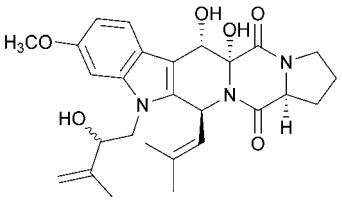
were first reported as plant growth regulators from *Penicillium brevicompactum*.[351,352] Compounds **514** and **517** were found to inhibit lipopolysaccharide (LPS)-induced nitric oxide production in BV2 microglial cells at concentrations at which they did not exhibit cytotoxic effects.

Eurotium rubrum, an endophytic fungus from the Chinese mangrove plant *Hibiscus tiliaceus*, was found to produce two new threefold prenylated diketopiperazine derivatives, dehydrovariecolorin L (**518**) and dehydroechinulin (**519**).[353] Both compounds displayed neither cytotoxicity nor radical scavenging activity. Compound **518** is the 8,9-dehydro derivative of variecolorin L, recently described from a halotolerant strain of *Aspergillus variecolor*,[354] while **519** is the 8,9-dehydro congener of echinulin, described 50 years ago from *Aspergillus glaucus*.[355]

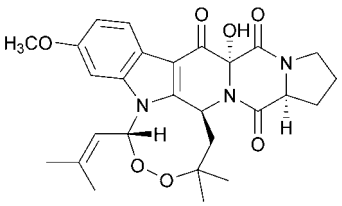
A series of prenylated diketopiperazines, 6-methoxyspirotryprostatin B (**520**), 18-oxotryprostatin A (**521**), and



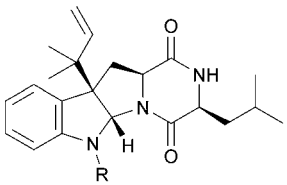
508



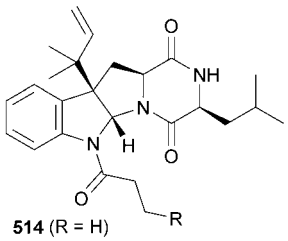
509, 510



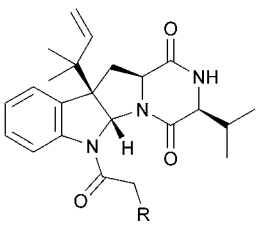
511



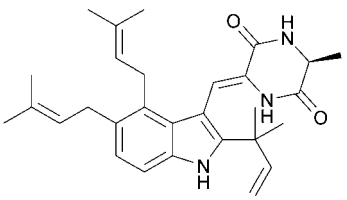
512 (R = H)
513 (R = CH_2OCH_3)



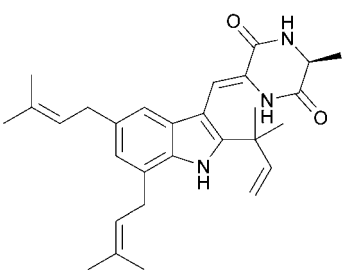
514 (R = H)
515 (R = CH_3)



516 (R = H)
517 (R = CH_3)

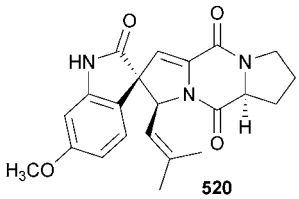


518

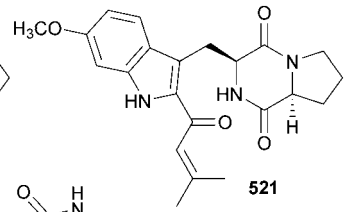


519

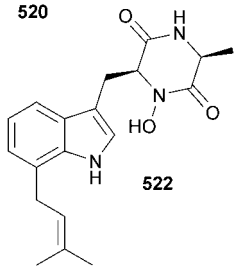
14-hydroxyterezine (**522**), together with a new pseurotin congener and a new rearranged dammarane triterpene, were isolated from a culture of the fungus *Aspergillus sydowi*, obtained from a driftwood sample collected in China.[250] Spirotryprostatin B and tryprostatin A have originally been described from *Aspergillus fumigatus* BM939, isolated from a sea sediment sample in Japan, and were identified as mammalian cell cycle inhibitors,[347,356] while terezine D is a metabolite of the coprophilous fungus *Sporormiella teretispora*.[357] Compounds **520–522** displayed mild cytotoxic activity towards the A-549 cell line.



520



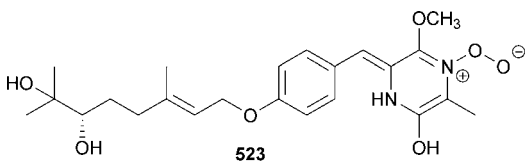
521



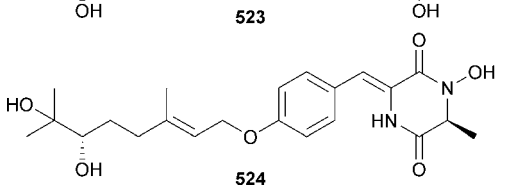
522

The fungus *Penicillium janthinellum*, isolated from the Chinese soft coral *Dendronephthya* sp., was the source of two unusual *N*-oxygenated diketopiperazines, janthinolides A (**523**) and B (**524**).[358] A sediment-borne isolate of *Gliocladium* sp. from China was found to produce the new diketopiperazines, gliocladride (**525**)[359] and the isomeric PJ147 (**526**) and PJ157 (**527**),[360] of which **526** displayed cytotoxicity towards the human A375-S2 melanoma cell line. A later reinvestigation resulted in the discovery of the closely related gliocladrides A (**528**) and B (**529**), both of which exhibited moderate cytotoxicity against three cell lines.[361]

The fungus *Penicillium bilaii* MST-MF667, obtained from a boat ramp on the Huon estuary in Tasmania, was identified as a source of new bis(methylthio)diketopiperazines, bilains A–C (**530–532**).[362] All three proved inactive when tested for antibacterial, antifungal, antiparasitic and cytotoxic properties. Compounds **530–532** are closely related to *cis*-bis(methylthio)-silvatin, described from a terrestrial strain of *Aspergillus silvaticus*,[363] while the corresponding *trans*-stereoisomer of the latter had previously been characterised from a saltwater culture of the terrestrial fungus *Coriolus consors*.[364]



523



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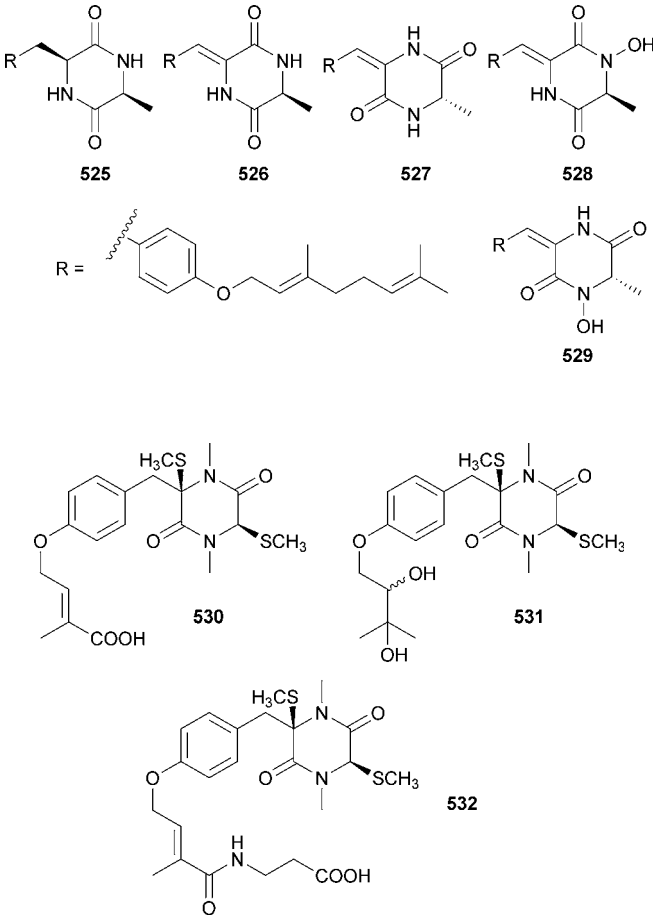
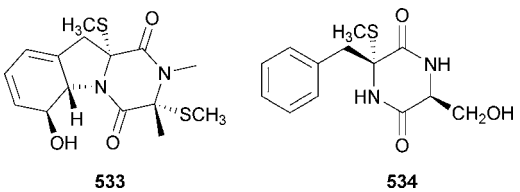
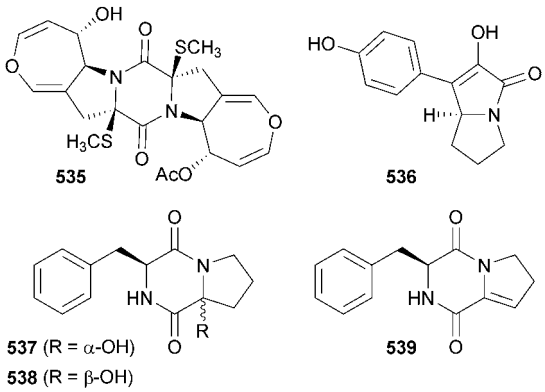


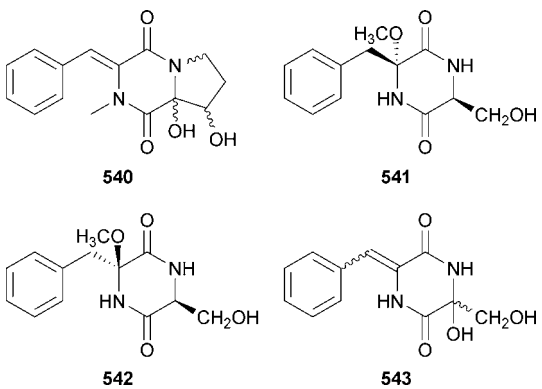
The fungus *Pseudallescheria* sp., isolated from the Korean brown alga *Agarum cribrosum*, was found to produce a new gliotoxin congener, dehydroxybisdethiobis(methylthio)gliotoxin (**533**), besides gliotoxin and a further known derivative.[365] All three compounds displayed antibacterial activity against methicillin-resistant and multidrug-resistant *Staphylococcus aureus*. The related congener **534** was reported from an isolate of *Aspergillus fumigatus* that was cultured from the marine sediments collected China, together with gliotoxin and three known derivatives.[366] Only gliotoxin and one of the known analogues displayed cytotoxic activity, while **534** was inactive.



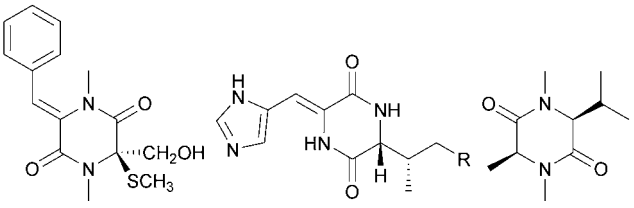
Alternaria raphani, a halotolerant fungal strain isolated from sediment collected in a Chinese sea salt field, produced a new diketopiperazine, alternarosin A (**535**), together with three new cerebrosides.[367] Compound **535** displayed very weak antimicrobial activity against *Escherichia coli*, *Bacillus subtilis* and *Candida albicans*, but was devoid of cytotoxic or radical scavenging activity. Seawater-based fermentation of the fungus *Chromocleista* sp. isolated from a sediment sample collected in the Gulf of Mexico led to the discovery of 4′-hydroxyphenopyrrozin (**536**), two epimeric diketopiperazines **537** and **538** and their decomposition product **539**, in addition to a series of known natural products including diketopiperazines.[368] Only **536** displayed mild antifungal activity against *Candida albicans*, while none of the compounds was active against *Staphylococcus aureus* or possessed cytotoxic properties.



The new diketopiperazine (*Z*)-3-benzylidene-8,8a-dihydroxy-2-methylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**540**) was reported as a metabolite of an unidentified endophytic fungus of the Chinese mangrove plant *Acanthus ilicifolius*, together with a new nicotinamide alkaloid (**653**).[369] Three new dioxopiperazine metabolites **541–543** were isolated from a strain of *Aspergillus fumigatus* which was obtained from marine sediments collected in China. Compounds **541–543** were devoid of cytotoxic activity.[370]

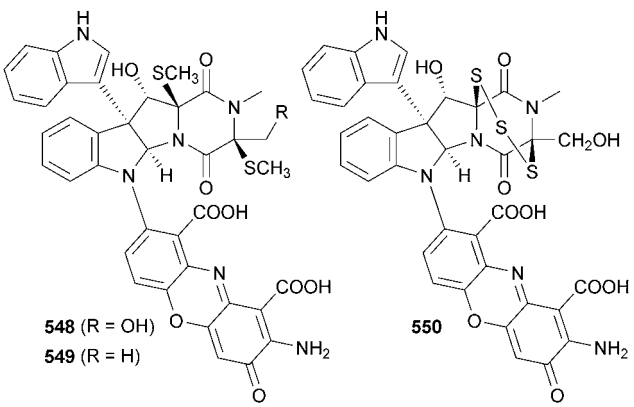


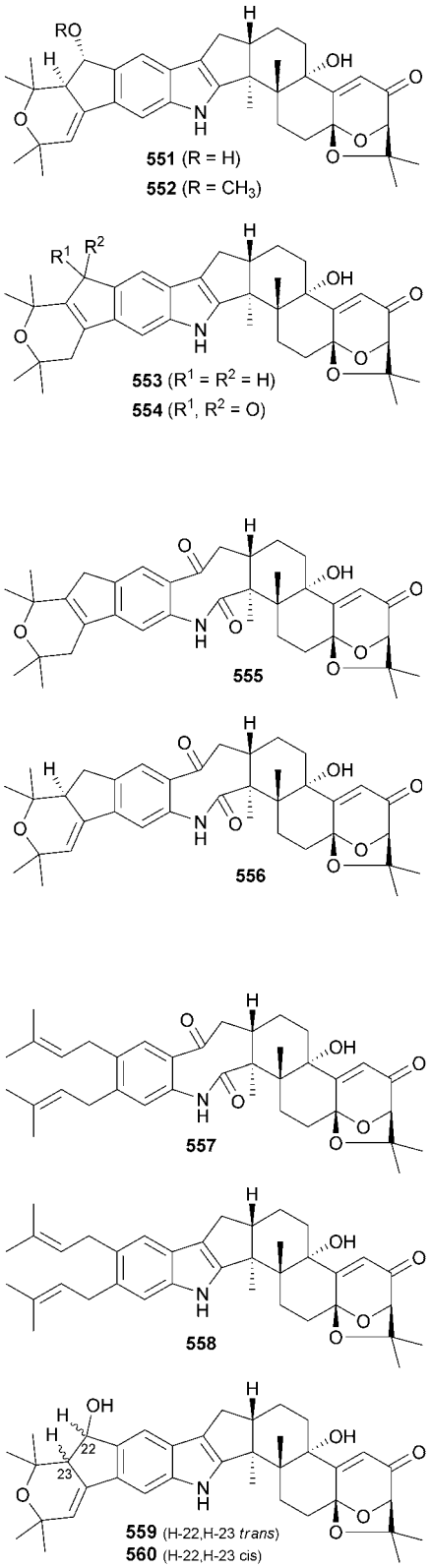
A new diketopiperazine, (*Z*)-6-benzylidene-3-hydroxymethyl-1,4-dimethyl-3-methylsulfanylpiperazine-2,5-dione (**544**), was isolated from the culture broth of the fungal strain CRIF2 belonging to the order Pleosporales, obtained from an unidentified sponge in Thailand.[134] Chemically and biogenetically, **544** is closely related to (3*R*,6*R*)-bisdethiodi(methylthio)hyalodendrin, previously reported from a soil-borne *Penicillium turbatum*,[371] which was also obtained in the current study. Both compounds exhibited weak cytotoxic activity toward various cell lines. The fungus *Aspergillus*, isolated from an unidentified Japanese calcareous sponge, produced JBIR-74 (**545**) and JBIR-75 (**546**) which were devoid of cytotoxic or antimicrobial activity.[372] Cyclo(*N*-MeVal-*N*-MeAla) (**547**) was obtained from the culture broth of an unidentified fungus from the mangrove *Avicennia marina* in Hong Kong, and its structure was established by X-ray diffraction analysis.[168]



4.7 Alkaloids and other nitrogen-containing metabolites

Plectosphaeroic acids A–C (**548–550**) are complex fungal alkaloids produced by *Plectosphaerella cucumerina*, obtained from sediments collected in British Columbia.[373] Biogenetically, they appear to be derived from derived either a serine or an alanine and four tryptophan units, processed in three distinctly different ways, *i.e.* a diketopiperazine, removal of the side chain, and catabolic degradation *via* the kynurenine pathway to give two 3-hydroxyanthranilic acid units, which in turn are oxidatively coupled to give the phenoxazinone heterocycle present in **548–550**. Compounds **548–550** inhibited indoleamine 2,3-dioxygenase (IDO), an emerging molecular target for treating cancer involved in immune escape.[374] The endophytic fungus *Penicillium* sp., isolated from the Chinese mangrove plant *Aegiceras corniculatum*, produced eight new janthitrem-type indole triterpenes, shearinines D–K (**551–558**).[375] Compound **551** is the 22-hydroxy derivative of the known shearinine A, which had previously been described from ascostromata of the terrestrial fungus *Eupenicillium shearii*.[376] Shearinine A and the known ergot alkaloids paspaline[377] and paspalitrem[378] were likewise detected in the culture broth of the fungus under study. Biogenetically, shearinines are suggested to arise from paspaline, which upon prenylation would undergo oxidative ring formation to yield paspalitrem A. The occurrence of **551–558** would then require a further prenylation step, oxidative cyclisation to yield the pyrane ring, and various combinations of olefinic rearrangements or oxidative cleavage of the C-2–C-18 bond, the latter of which might occur spontaneously, since analogous reactions were observed during the NMR measurements. Compounds **551**, **552** and (to a lower extent) **554** exhibited significant *in vitro* blocking activity on large-conductance calcium-activated potassium channels.[375] In a parallel study, a marine isolate of fungus *Penicillium janthinellum* was isolated from a Russian

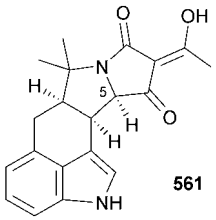




sediment sample.[379] Besides shearinine A three further janthitrem-type alkaloids (**558–560**) were detected, and unfortunately assigned the names shearinines D, E, and F, since the authors were unaware[380] of the parallel publication.[375] "Shearinine F" is

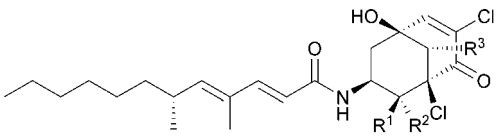
in fact identical to shearinine K (**558**), while **559** and **560** are obviously new compounds and thus should be renamed. Interestingly, the NMR data of the H-22,H-23-*cis* congener **560** differ significantly from shearinine D (**551**), suggesting that both H-22 and H-23 follow the β-orientation. Shearinine A, **559**, and **560** were found to induce apoptosis in human leukemia HL-60 cells, while **560** also inhibited EGF-induced malignant transformation of murine JB6 P^+ Cl 41 cells, indicative of a potential cancer preventive effect.

A strain of *Aspergillus flavus*, isolated from the Chinese green alga *Enteromorpha tubulosa*, yielded a new alkaloid, iso-α-cyclopiazonic acid (**561**), together with α-cyclopiazonic acid, the 5-epimer of **561**.[381] α-Cyclopiazonic acid is a known indole–tetramic acid mycotoxin from the terrestrial fungus, *Penicillium cyclopium*, and is of interest due to its Ca^{2+}–ATPase inhibition.[382] **561** displayed moderate cytotoxic activity against four different cell lines, but was considerably less active than α-cyclopiazonic acid.

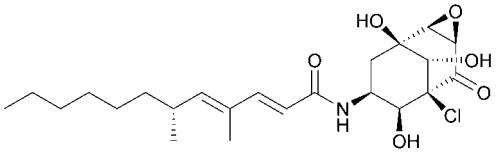


561

The sponge-derived fungus *Gymnascella dankaliensis*, isolated from *Halichondria japonica* collected off Osaka in Japan, had previously been identified as a source of gymnastatins and structurally unusual steroids. Further chemical investigation led to the discovery of gymnastatins F–H (**562–564**), and the fatty acid- or polyketide-derived gymnamide (**565**).[383] Compounds **562** and **563** possess a unique bicyclo[3.3.1]nonane ring system which differs from that of previously reported gymnastatins, and were



562 (R^1 = OH, R^2 = H, R^3 = OCH_3)
566 (R^1 = H, R^2 = OH, R^3 = OCH_3)
567 (R^1 = OH, R^2 = H, R^3 = H)



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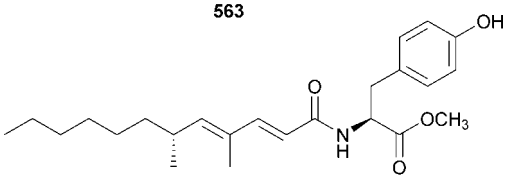

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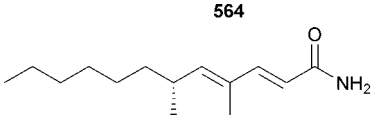

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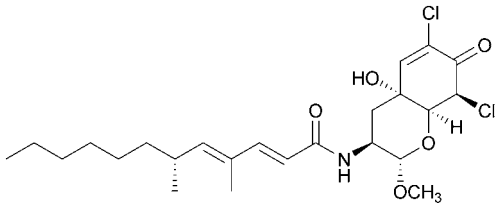

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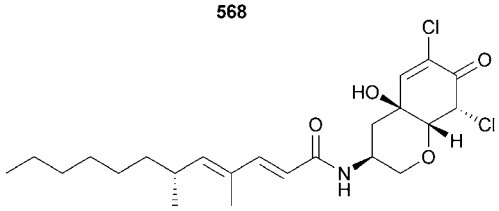

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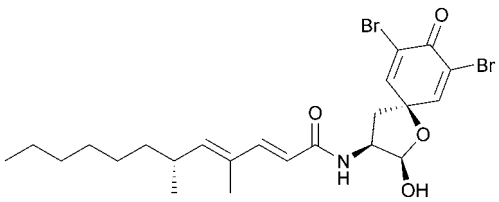

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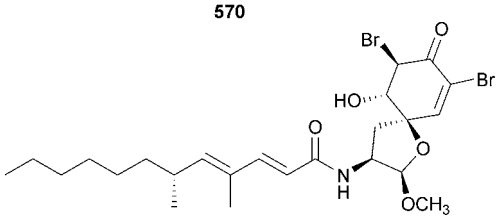

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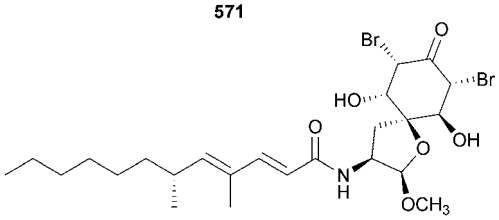
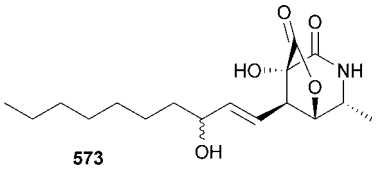


572

found to exhibit pronounced cytotoxic activity against the P388 cancer cell line. In a subsequent communication, additional gymnastatin congeners gymnastatins Q (**566**) and R (**567**) as well as the related dankastatins A (**568**) and B (**569**) were observed, when soluble starch instead of glucose was added to the culture broth.[384] Compounds **566–569** displayed growth inhibition against the P388 cancer cell line, and furthermore, **566** inhibited growth of BSY-1 (breast) and MKN7 (stomach) human cancer cell lines. When cultured in a bromine-containing medium, the same fungus yielded the brominated analogues gymnastatins I–K (**570–572**), all of them exhibiting potent cytotoxicity towards the murine P388 lymphocytic leukemia cell line. Moreover, **570** and **571** displayed pronounced activity against a panel of 39 human cancer cell lines.[385]

Awajanomycin (**573**) is a bicyclic metabolite featuring both a γ-lactone and a δ-lactam ring, produced by the fungus *Acremonium* sp. which was obtained from a sea mud sample in Japan.[386] Compound **573** was also converted into its reduced

congener **574** and its hydrolysis product **575**. Compounds **573** and **574** displayed moderate cytotoxic activity towards the A549 (human lung adenocarcinoma) cell line, but were devoid of antimicrobial activity.



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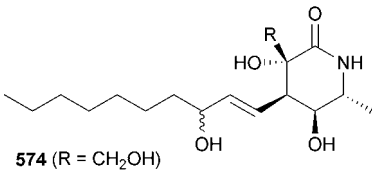
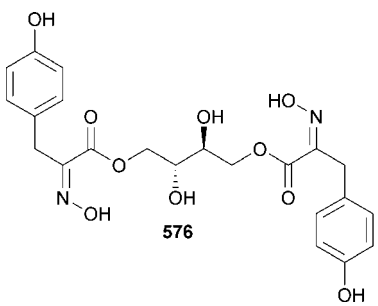


574 (R = CH_2OH)
575 (R = COOH)

A new tyrosine-derived metabolite, aspergillusol A (**576**) was isolated on a gram scale, together with a methyl ester of 4-hydroxyphenylpyruvic acid oxime (**577**) and the known secalonic acid A, from the marine-derived fungus *Aspergillus aculeatus*, obtained from the Thai sponge *Xestospongia testudinaria*.[387] Compound **576** exhibits a striking structural analogy to well-known tyrosine alkaloids from Verongida sponges, most notably psammaplin A,[388] which raises interesting questions regarding the biosynthetic origin of the sponge metabolites. Compound **577** had previously only been known synthetically, and not as a natural product, although it cannot be excluded that it actually represents an artefact derived from methanolysis of **576**. Compound **576** inhibited α-glucosidase from *Saccharomyces cerevisiae*, but was inactive towards α-glucosidase from *Bacillus stearothermophilus*.



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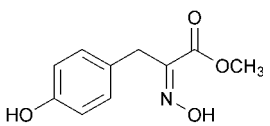
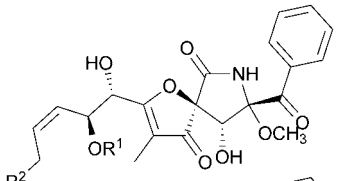
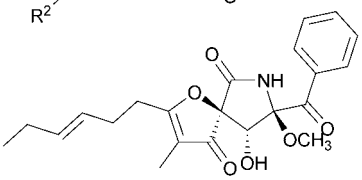


577

Bioassay-guided fractionation of the culture broth of an *Aspergillus fumigatus* isolate which was obtained from a deep-water sediment collected off Vanuatu, using a yeast-halo assay with wild-type and cell-cycle mutant strains of the budding yeast *Saccharomyces cerevisiae*,[389] led to the discovery of 11-*O*-methylpseurotin A (**578**),[390] besides the known but inactive pseurotin A (**579**), initially characterised from *Pseudoeurotium ovalis*.[391] Compound **578** displayed the greatest activity differential *versus* the wild-type strain against the Hof1 (*hof1*Δ) haploid deletion strain, carrying a mutation in a gene involved in cytokinesis. 14-Norpseurotin A (**580**) was discovered along with three new diketopiperazines and a new rearranged dammarane triterpene, from a culture of the fungus *Aspergillus sydowi*, obtained from a driftwood sample collected in China.[250] Compound **580** displayed significant antibiotic activity towards *Escherichia coli*, *Bacillus subtilis* and *Micrococcus lysoleikticus*. Likewise closely related to pseurotin A (**578**) is cephalimysin A (**581**), isolated from a strain of *Aspergillus fumigatus* which was originally separated from the marine fish *Mugil cephalus*.[392] Compound **581** exhibited significant cytotoxic activity against P388 and HL-60 cells.

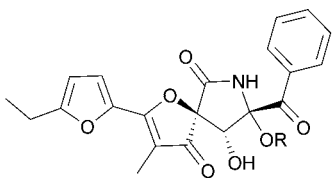


578 (R^1 = CH_3, R^2 = H)
579 (R^1 = H, R^2 = H)
580 (R^1 = H, R^2 = CH_3)



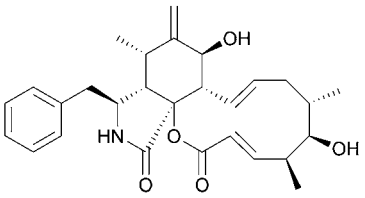
581

The fungus *Aspergillus sydowi*, isolated from marine sediments collected in China, was identified as the producer of two additional pseurotin derivatives, azaspirofurans A (**582**) and B (**583**), characterized by the presence of an additional furan ring in the side chain.[393] Compound **582** exhibited moderate cytotoxicity against the A549 cell line.



582 (R = CH_3)
583 (R = H)

The fungus *Spicaria elegans* was isolated from marine sediments collected in China, and proved to represent a prolific source of new cytochalasin derivatives with various carbon skeletons. Cytochalasins Z_7–Z_9 (**584–586**) are rare examples of cytochalasins with a 12-membered macrolactone ring, exhibiting mild cytotoxicity towards cell lines P388 and A-549 in the MTT assay.[128,394] Reinvestigation of the same fungus resulted in the discovery of cytochalasins Z_{10}–Z_{15} (**587–592**), representing the first cytochalasin congeners from nature with an open 8-carbon side chain instead of the usual 11–14-membered macrocyclic ring.[395] **588** and **589** displayed moderate cytotoxicity toward A-549 cells, whereas the remaining compounds were inactive. By varying the culture conditions according to the OSMAC (one strain–many compounds) approach, a drastically altered metabolite profile was obtained, resulting in the discovery of the novel spicochalasin A (**593**) and aspochalasins M–Q (**594–598**), besides the known aspochalasins B and D.[396] Compound **593** possesses an unusual pentacyclic ring system, and similar to **594** exhibited modest cytotoxic activity against HL-60 cells. On the other hand, treatment of the same fungus with the cytochrome P-450 inhibitor metapyrone resulted in the production of two new 7-deoxycytochalasins, 7-deoxy-cytochalasin Z_7 (**599**) and 7-deoxy-cytochalasin Z_9 (**600**).[397] It is interesting to note that although oxidation at C-7 was prevented, the "Baeyer–Villiger-like" oxidation at C-9 still occurred. Compound **599** displayed moderate cytotoxic activity towards the A-549 cell line, while **600** was inactive. Cytochalasins Z_{16}–Z_{20} (**601–605**) were subsequently reported from an endophytic strain of *Aspergillus flavipes*,



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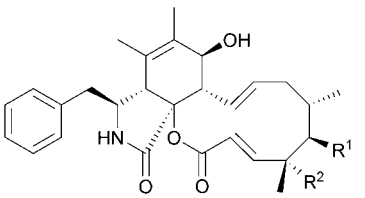
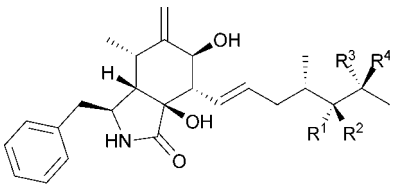
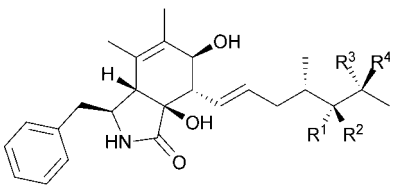


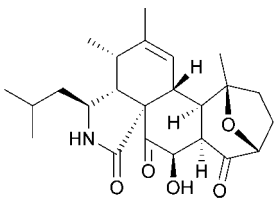
585 (R^1 = OH, R^2 = H)
586 (R^1 = H, R^2 = OH)



587 (R^1 = R^3 = OH, R^2 = R^4 = H)
588 (R^1, R^2 = O, R^3 = H, R^4 = OH)



589 (R^1 = R^3 = OH, R^2 = R^4 = H)
590 (R^1, R^2 = O, R^3 = H, R^4 = OH)
591 (R^1 = H, R^2 = OH, R^3, R^4 = O)
592 (R^1 = OH, R^2 = H, R^3, R^4 = O)



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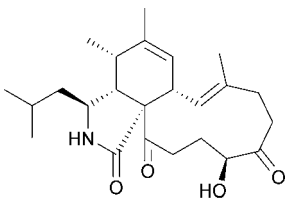

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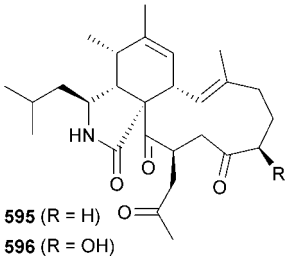
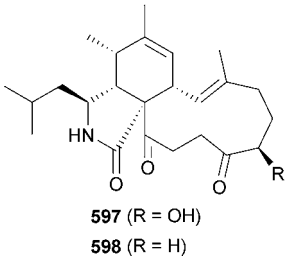
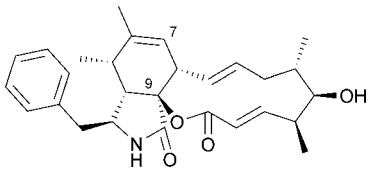


595 (R = H)
596 (R = OH)



597 (R = OH)
598 (R = H)



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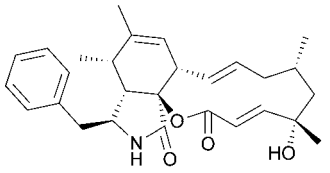

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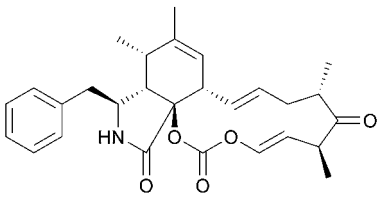

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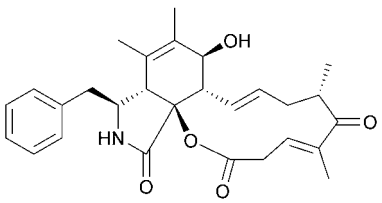

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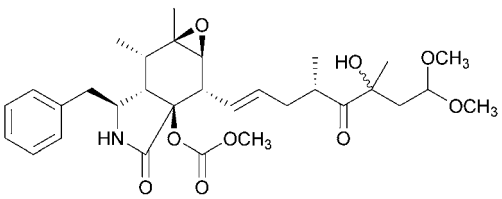

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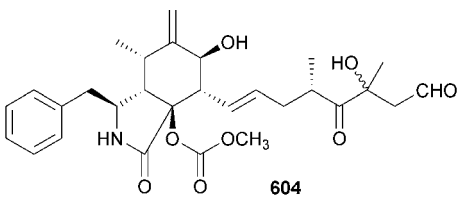

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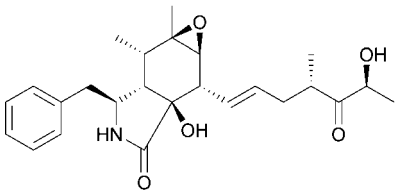

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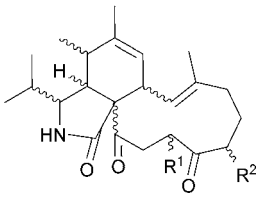
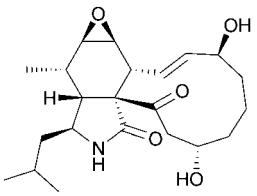


606 (R^1 = OCH_3, R^2 = OH)
607 (R^1 = OH, R^2 = H)
608 (R^1 = OH, R^2 = OH)

isolated from the Chinese mangrove plant, *Acanthus ilicifolius*.[398] When tested for cytotoxicity towards various cell lines, **602** was moderately active, followed by **601** and **604**. A recent reinvestigation of *Spicaria elegans*, using a longer fermentation time, yielded additional aspochalasin congeners, aspochalasins R–T (**606–608**), all of which proved inactive in terms of cytotoxic effects.[399]

Xylarisin (**609**) is a new cytochalasin derivative with a highly substituted perhydroisoindole moiety linked to an 11-membered ring that was produced by the fungus *Xylaria* sp., isolated from the Thai gorgonian sea fan, *Annella* sp.[400] Compound **609** displayed mild antibacterial activity against *Staphylococcus aureus* and methicillin-resistant *S. aureus*. Chemical investigation of the endophytic fungus *Chaetomium globosum* derived from the Chinese green alga *Ulva pertusa* resulted in the discovery of seven new cytochalasan derivatives of the chaetoglobosin class, cytoglobosins A–G (**610–616**), together with the structurally related known compounds, isochaetoglobosin D and chaetoglobosin F_{ex}.[401] The latter two compounds are metabolites of a soil-borne *C. globosum*[402] and *C. subaffine*,[403] respectively. Compounds **612** and **613** exhibited moderate cytotoxic activity against the A-549 cell line.



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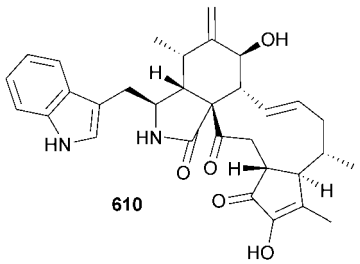

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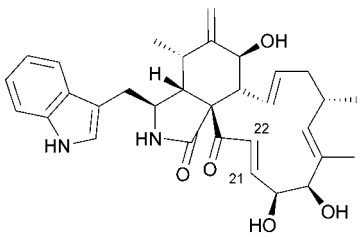
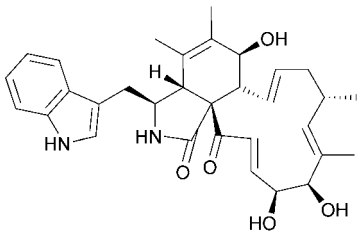


611
616 (21,22-dihydro)



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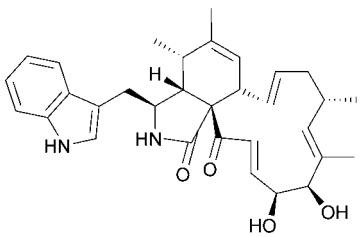

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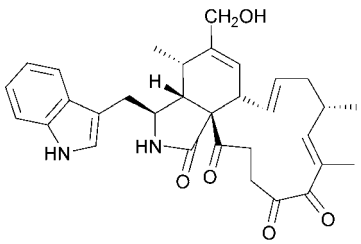

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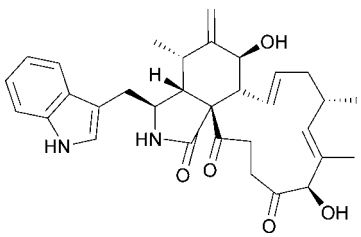
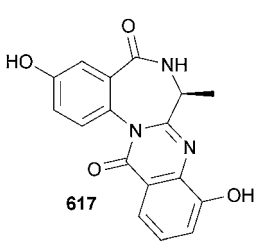


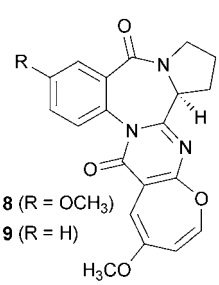
615

The fungus *Exophiala* sp., isolated from the surface of the Korean marine sponge *Halichondria panicea*, yielded circumdatin I (**617**), a member of the circumdatin class of alkaloids,[404] together with the known circumdatins C[405] and G,[406] previously reported from a terrestrial and a marine-derived strain of *Aspergillus ochraceus*, respectively. All three compounds exhibited UV-A protecting activity which exceeded that of the positive control, the commercially applied sunscreen agent oxybenzone. From the culture of an *Aspergillus ostianus* strain isolated from an unidentified marine sponge at Pohnpei, Micronesia, the two known circumdatins A (**618**) and B (**619**) as well as the new circumdatin J (**620**) were obtained.[407] Compound **618** and **619** were initially described as metabolites of from a terrestrial isolate of the fungus *Aspergillus ochraceus*, and their structures reported as zwitterions.[405] In the present study, both structures were revised on the basis of X-ray crystallographic analysis, and **618** and **619** were now found to contain a very unusual oxepin framework in the "Southern" part. Compound **620** is the 15-deoxy congener of circumdatin D, likewise reported from *A. ochraceus*.[408] Compound **618–620** exhibited neither antimicrobial nor cytotoxic properties. An endophytic strain of *A. ochraceus*, obtained from the Chinese brown alga *Sargassum kjellmanianum*, yielded the new 2-hydroxycircumdatin C (**621**), together with the anthranilic acid-containing diketopiperazine **622**, which up to that point was only known synthetically.[409] Compound **621** displayed significant DPPH radical-scavenging activity, and was more potent than butylated hydroxytoluene (BHT), which served as a positive control.

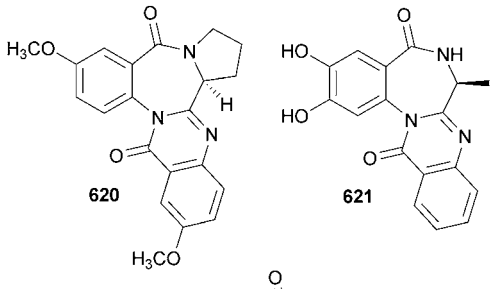
From the Chinese sponge *Mycale plumosa*, the fungus *Penicillium aurantiogriseum* was isolated, which was found to produce three new quinazoline alkaloids, aurantiomides A–C (**623–625**).[410] Compounds **624** and **625** displayed moderate cytotoxicity against several cell lines, while **623** was inactive. All three compounds are closely related to anacine, a metabolite previously described from terrestrial strains of *P. aurantiogriseum*[411] and *P. verrucosum*.[412]

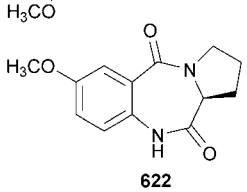


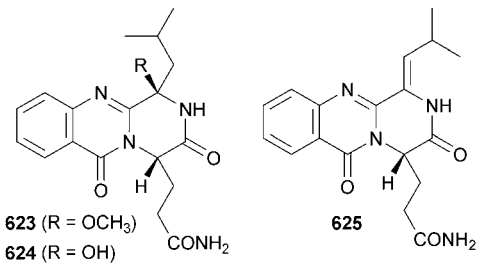
617



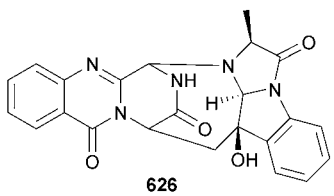
618 (R = OCH_3)
619 (R = H)



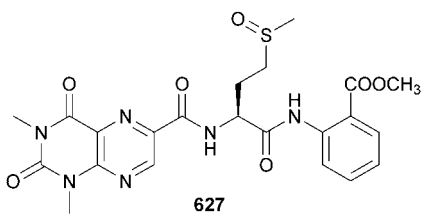




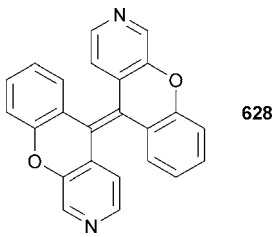
An Australian marine-derived isolate of *Aspergillus versicolor*, recovered from beach sand, was grown on a cellophane raft over nutrient-rich media, and by this treatment was induced to produce a new quinazoline-type alkaloid, cottoquinazoline A (**626**), besides two new cyclopentapeptides.[318] Compound **626** is the 3-nor derivative of the known fumiquinazoline D, previously reported from a strain of *Aspergillus fumigatus* separated from the marine fish *Pseudolabrus japonicus*.[413]



The fungal strain *Penicillium* sp., isolated from the red alga *Laurencia* sp. collected in the Bahamas Islands, yielded penilumamide (**627**), an unusual alkaloid combining a lumazine system with L-methionine sulfoxide and an anthranilic acid ester.[414] The 1,3-dimethyllumazine-6-carboxamide moiety within a natural product had previously only been reported from the freshwater leech *Limnatis nilotica*.[415] The structure elucidation of **627** was severely hampered by the lack of protons in the lumazine part, but was achieved by a combination of 1,1-ADEQUATE and $^{1}H,^{15}N$ HMBC experiments, use of the NMR-based structure generator COCON,[416] and detailed analysis of the ESI-TOF MS fragmentations. Compound **627** was inactive when tested for cytotoxic and antimicrobial properties, and also did not affect cellular Ca^{2+} signalling in neuroendocrine cells.

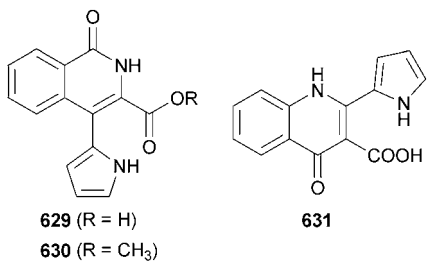


The dimeric alkaloid xylopyridine A (**628**) was isolated from the endophytic fungus *Xylaria* sp., obtained from an undisclosed mangrove in Hong Kong.[417] By fluorescence quenching and spectrophotometric titration experiments, **628** was demonstrated to possess strong DNA-binding affinity, presumably *via* an intercalation mechanism.



In an interesting study, it was shown that marinamide (**629**) and its methyl ester (**630**) are only produced when two unidentified fungal strains, obtained from an undisclosed plant growing in an estuarine mangrove in Hong Kong, were fermented together, but not when either of the two fungi were cultured on their own.[418] It is a bit unfortunate that so little detail about the identity and the origin of the two strains were reported, since while there are very few examples of competing co-culture of fungi and bacteria leading to the production of new secondary metabolites,[419,420] this study seems to represent the first example involving two fungal strains.

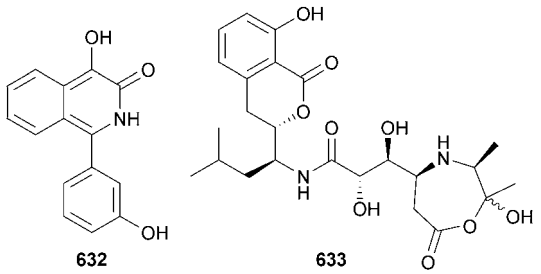
The isomeric pyrrolyl 4-quinolinone alkaloid penicinoline (**631**) was isolated from the endophytic fungus *Penicillium* sp., isolated from the Chinese mangrove plant *Acanthus ilicifolius*.[421] Upon methylation, an *N*-methylated lactam was unexpectedly formed. Compound **631** exhibited potent cytotoxicity towards the 95-D and HepG2 cell lines, and also displayed strong insecticidal activity against *Aphis gossypii*.



The new isoquinoline alkaloid **632** was reported from the endophytic fungus *Phomopsis* sp., isolated from an undisclosed Chinese mangrove plant.[422] However, the trivial name assigned to **632**, phomopsin A, must be rejected, since it is already in use for a cyclic hexapeptide mycotoxin produced by *Phomopsis leptostromiformis*, the causative agent of the disease lupinosis.[423] Compound **632** exhibited mild cytotoxicity towards two cell lines.

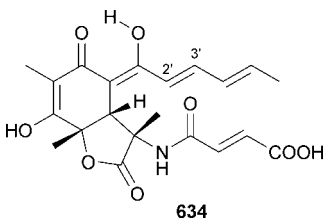
The structurally unique isocoumarin-substituted azepine alkaloid Sg17-1-4 (**633**) is a metabolite of the fungus *Alternaria*

tenuis, which was obtained from an undisclosed Chinese alga.[424] Compound **633** displayed weak and moderate cytotoxic activity towards human malignant A375-S2 and human cervical cancer HeLa cells, respectively.



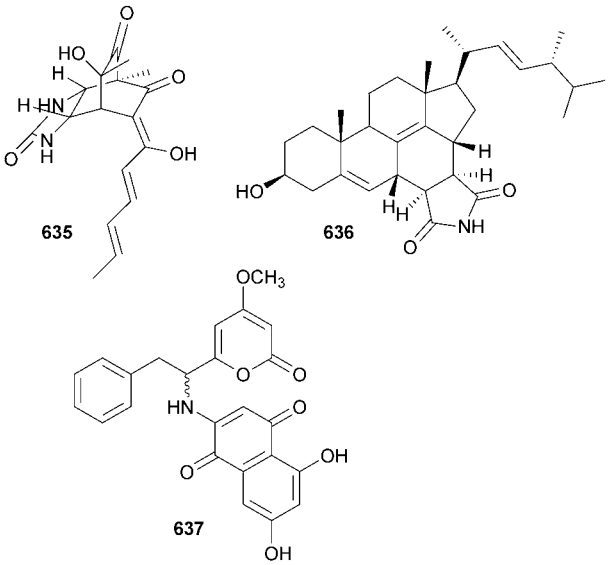
632 **633**

Sorbicillactone A (**634**), produced by marine-derived strains of *Penicillium chrysogenum*, represents the first example of a sorbicillin-derived alkaloid,[425] and its production at a 100 g scale has been achieved, in order to provide sufficient amounts for preclinical evaluation and structure–activity relationship (SAR) studies.[426] Compound **634** has raised considerable interest due to its cytostatic activity against murine leukemic lymphoblasts (L5178y) and the ability to protect human T cells against the cytopathic effects of HIV-1.[427]

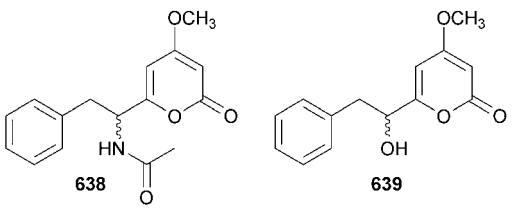


634

The fungus *Paecilomyces marquandii*, isolated from an intertidal sediment sample collected in Argentina, produced an ureido Diels–Alder adduct of sorbicillinol (**635**).[428] Even though a series of sorbicillinoids have been described from fungi previously, this seems to represent the first example of a Diels–Alder adduct of sorbicillinol with another non-sorbicillol-type moiety, in this case maleimide. However, the putative biogenetic precursors were not detected in this study. Interestingly, both the ESI as and the EI mass spectra of **635** were dominated by the corresponding fragments resulting from retro-Diels–Alder fragmentation. Similarly, from the culture broth of the fungus *Aspergillus niger*, endophytic to the Chinese brown alga *Colpomenia sinuosa*, an unusual steroid derivative, ergosterimide (**636**), was obtained.[429] Formally, **636** is a Diels–Alder adduct of (22*E*,24*R*)-ergosta-5,7,14-trien-3β-ol and maleimide. The latter is widely used for technical applications, and due to its high reactivity is commonly used as a reactant for Diels–Alder reactions in synthetic laboratories. If maleimide indeed was a metabolite of the two fungal strains under study, **635** and **636** would represent the first natural Diels–Alder adducts of this type. The same isolate of *Aspergillus niger* also produced a new amino-substituted dihydrostyrylpyrone (**637**) which displayed moderate antifungal activity against *Candida albicans*.[430] This type of fungal natural product seems to be restricted to *Aspergillus* section *Nigri*,[431] and the only reported derivatives reported so far include pyrophen[31,432] and aspernigrin B.[433,434] Subsequently, isopyrophen (**638**) and aspergillusol (**639**) were reported from the same fungus[435] Compound **638** was reported to be a stereoisomer of pyrophen, which would require the existence of stable *cis*/*trans* isomers at the amide bond.

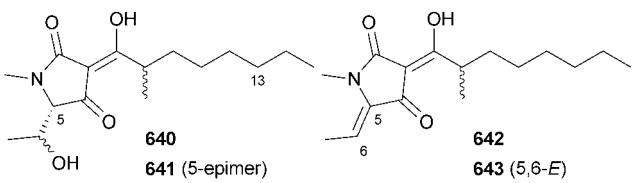


635 **636** **637**



638 **639**

The endophytic fungus *Penicillium* sp., isolated from the bark of the Chinese mangrove plant *Aegiceras corniculatum*, yielded a series of tetramic acids, penicillenol A_1 (**640**), A_2 (**641**), B_1 (**642**), B_2 (**643**), C_1 (**644**) and C_2 (**645**).[436] **640–643** displayed moderate degrees of cytotoxicity towards HL-60 cells, while congeners **644** and **645**, which possess an additional double bond near the chain terminus, were inactive.

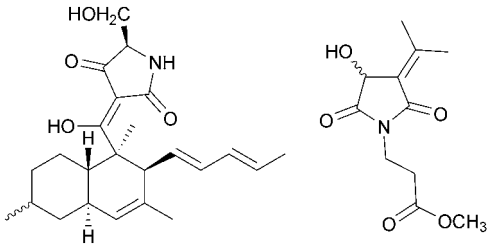


640
641 (5-epimer)
644 (Δ^{13})
645 (Δ^{13}, 5-epimer)

642
643 (5,6-*E*)

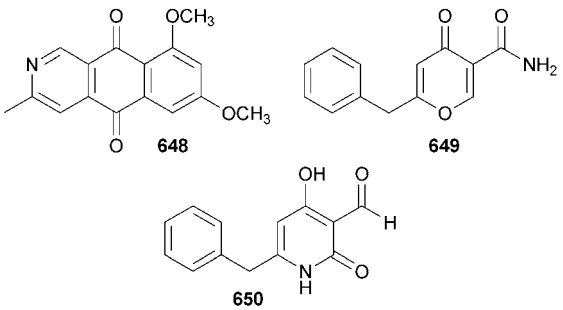
Beauversetin (**646**) is a 3-decalinoyl tetramic acid derivative produced by the fungus *Beauveria bassiana*, isolated from the German sponge *Myxilla incrustans*.[437] Compound **646** exhibited moderate cytotoxic activity towards a panel of 6 cell lines, and is structurally related to equisetin, a metabolite of *Fusarium equiseti*.[438]

The fungus *Pestalotiopsis* sp., isolated from the Chinese mangrove plant *Rhizophora mucronata*, was found to produce a new alkaloid, pestalotiopsoid A (**647**), in addition to a series of new cytosporones and coumarins (**269–278**).[198]

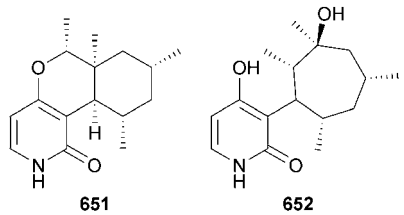


The biosynthesis of the 2-azaanthraquinone, scorpinone (**648**), originally described from the marine sediment-derived fungus *Amorosia littoralis*,[439] has been demonstrated to proceed *via* a regular polyketide pathway with a linear heptaketide as biosynthetic intermediate,[440] which would also account for the presence of the known cyclic hemiketal herbarin, originally isolated from a terrestrial *Torula herbarum*.[441] Thus, it seems clear that at some point late in the biosynthesis of **648**, an exchange of an oxygen for a nitrogen atom has to occur, however, it is not possible to decide whether this nitrogen is derived from inorganic nitrogen or a nitrogen-containing organic precursor.

A sediment-borne *Aspergillus carbonarius* from China yielded carbonarone A (**649**), a new γ-pyrone, and the related α-pyridone derivative carbonarone B (**650**).[442] Both compounds displayed moderate cytotoxic activity against K562 cells.

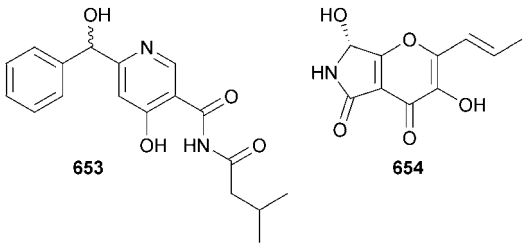


A marine-derived *Penicillium* sp., isolated from the brown alga *Xiphophora gladiata* collected in New Zealand, produced two new *N*-deoxy analogues **651** and **652** of the known *N*-hydroxy-2-pyridone alkaloids, PF1140 and akanthomycin.[443] PF1140, which was also detected in the culture broth, was previously reported from an *Eupenicillium* sp.,[444] while akanthomycin is a metabolite of the entomopathogenic fungus *Akanthomyces gracilis*.[445] PF1140 displayed modest antimicrobial and cytotoxic properties, whereas **651** and **652** were inactive.



The new alkaloid 4-hydroxy-6-(hydroxy(phenyl)methyl)-*N*-(3-methylbutanoyl)nicotinamide (**653**) was reported as a metabolite of an unidentified endophytic fungus of the Chinese mangrove plant *Acanthus ilicifolius*, together with a new diketopiperazine.[369]

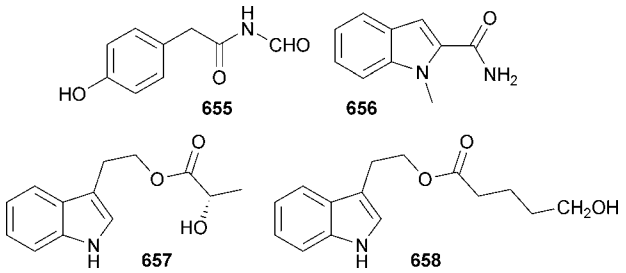
Pyranonigrin A (**654**) was the major UV-active compound in the extract of the fungus *Aspergillus niger*, which was obtained from mangrove wood in Hong Kong.[446] Compound **654** had previously been reported from a sponge-derived *A. niger* strain,[433] but based on extensive analysis of its spectroscopic properties including an ^{1}H–^{15}N HMBC NMR experiment, its structure was revised as given in **654**. Since the initial discovery of **654** in a marine-derived *A. niger*, this metabolite has been shown to occur in at least six different terrestrial species of *Aspergillus* section *Nigri*,[447] and also in rice mold starters used in the manufacturing process of fermented foods.[448,449]



N-Formyl-2-(4-hydroxyphenyl)acetamide (**655**) was described as a metabolite of an unidentified fungus obtained from the Korean brown alga *Ishige okamurae*, together with further known hydroxylated phenylacetic acid derivatives.[450] Compound **655** exhibited pronounced radical scavenging activity in the DPPH assay, and was more active than the positive control, ascorbic acid.

N-Methyl-1*H*-indole-2-carboxamide (**656**) from the fungus *Cladosporium cladosporioides*, isolated from the Chilean sponge *Cliona* sp., has apparently never been reported as a natural product before, but has now been described and its structure determined by single-crystal X-ray diffraction.[451]

Two new indole derivatives, 2-(1*H*-indol-3-yl)ethyl 2-hydroxypropanoate (**657**) and 2-(1*H*-indol-3-yl)ethyl 5-hydroxypentanoate (**658**), were reported from the yeast *Pichia membranifaciens*, isolated from the Japanese sponge *Halichondria okadai*.[452] Chiral HPLC revealed **657** to occur as a 5 : 8 (*S*/*R*) mixture. Both compounds exhibited weak radical scavenging activity in the DPPH assay.

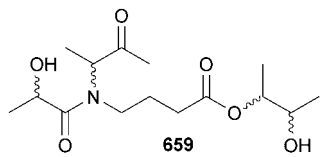


The fungal strain *Trichoderma atroviride*, isolated from sediment near the Chinese mangrove *Ceriops tagal*, produced the new compound 3-hydroxybutan-2-yl 4-(2-hydroxy-*N*-(3-oxobutan-2-yl)propanamido)butanoate (**659**).[211]

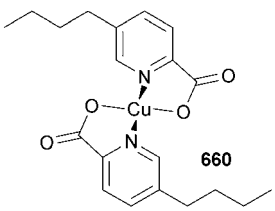
ZZF51(A) (**660**) is a copper complex of two fusaric acid (5-butylpicolinic acid) moieties produced by the fungus *Fusarium* sp., an endophyte of the Chinese mangrove plant *Castaniopsis fissa*.[453] Fusaric acid is a mycotoxin discovered in the 1930s in various *Fusarium* species, and has been shown to possess multiple

effects on the mammalian nervous, cardiovascular and immune system.[454] In culture, the producing strain was able to tolerate concentrations of Cu(II) ions up to 300 ppm, and showed active biosorption of this heavy metal. Compound **660** displayed mild antibiotic activity against 4 bacterial strains, and also displayed cytotoxicity towards 3 different tumour cell lines.

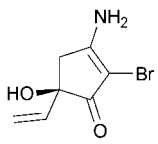
In the culture extract of the fungus *Botrytis* sp., obtained from the surface of the Korean green alga *Enteromorpha compressa*, the new nitrogen-containing cyclopentenone bromomyrothenone B (**661**) was detected, besides the new non-nitrogenated cyclopentenone botrytinone (**299**).[216] Compound **661** did not display significant activity during a screening for radical scavenging, tyrosinase inhibitory and antimicrobial properties. Previously, the debrominated congener of **661**, myrothenone B, had been reported from two independent sources, an algicolous *Myrothecium* sp. from the same algal species,[455] and interestingly, also from an endophytic *Streptomyces* sp. isolated from the Chinese mangrove plant *Aegiceras comiculatum*.[456] Subsequently, **661** and **299** were also detected in the culture medium of *Rhizopus stolonifer*, isolated from the surface of the Korean brown alga, *Sargassum horneri*.[217]



659



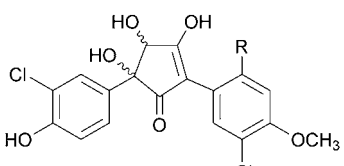
660



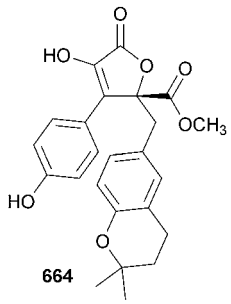
661

4.8 Shikimate-derived metabolites

An endophytic strain of *Aspergillus sydowii* was isolated from the inner tissue of the red alga *Acanthophora spicifera*, collected in India. Chemical analysis revealed the presence of two new chlorinated 2,5-diarylcyclopentenones, sydowin A (**662**) and B (**663**).[457] Two aromatic butenolides, aspernolides A (**664**) and B (**665**), along with known metabolites including butyrolactone I, were obtained from the fermentation broth of the fungus *Aspergillus terreus*, which was isolated from the Indian soft coral *Sinularia kavarattiensis*.[458] Butyrolactone I, assumed to be a biogenetic precursor of **664** and **665**, was originally described from a terrestrial isolate of *A. terreus*.[459] Compound **664** was also shown to be formed from butyrolactone I by heating[458] or treatment with dilute hydrochloric acid,[459] and exhibited mild cytotoxicity against several cancer cell lines.



662 (R = OH)
663 (R = H)



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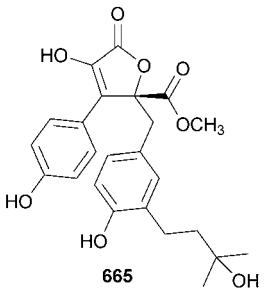
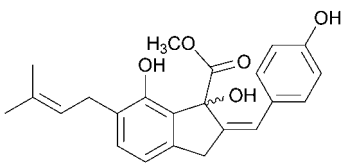


665

Phomoindene A (**666**), a rare example of an indene derivative from Nature, was described from the fungus *Phomopsis* sp., obtained from a sediment sample in a Chinese mangrove habitat, but was inactive when tested for cytotoxic properties.[460]

An isolate of *Aspergillus candidus*, obtained from a sediment sample collected in Japan, yielded prenylterphenyllin (**667**), 4″-deoxyprenylterphenyllin (**668**) and 4″-deoxyisoterprenin (**669**), together with the known 4″-deoxyterprenin, all of which exhibited moderate cytotoxic activity against KB3-1 cells.[461] Compounds **667–669** are analogues of terphenyllin[462] and terprenin,[463] known metabolites from terrestrial strains of *A. candidus*. Through labelling studies with phenylalanine, it has been demonstrated that the biosynthesis of terphenyllin and the related volucrisporin involves self-condensation of two phenylpropanoid units to give the terphenyl ring system.[464]



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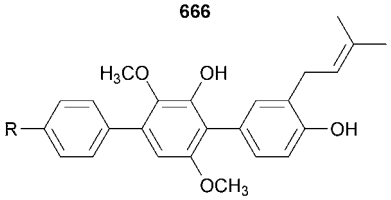
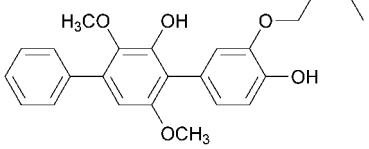
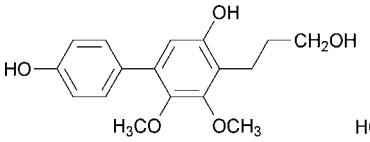


667 (R = OH)
668 (R = H)



669

The biphenyl derivative 4-(3-hydroxypropyl)-5,6-dimethoxybiphenyl-3,4′-diol (**670**) was obtained from the culture broth of the fungus *Penicillium thomi*, an endophyte of the root of the Chinese mangrove *Bruguiera gymnorrhiza*.[465] It displayed moderate cytotoxicity towards three human cancer cell lines, A549, HepG2 and HT29. From the saltwater culture of an *Arthrinium* sp., derived from a marine sediment collected at a depth of 550 m near the U.S. Virgin Islands, the known compound tyrosol (a common degradation product of tyrosine) and its new derivative, tyrosol carbamate (**671**), were obtained.[466]



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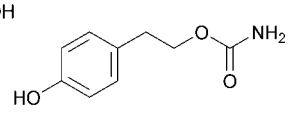
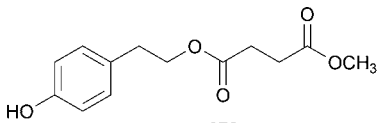


671

The fungus *Penicillium griseofulvum*, isolated from the mangrove *Lumnitzera racemosa*, yielded 4-hydroxyphenethyl methyl succinate (**672**) and 4-hydroxyphenethyl 2-(4-hydroxyphenyl)acetate (**673**), both displaying moderate radical scavenging properties, while **673** also exhibited weak cytotoxic activity.[467] The fungus *Nigrospora sphaerica* was obtained from mud in an intertidal zone in China, and was found to produce 1-(5-oxotetrahydrofuran-2-yl)ethyl 2-phenylacetate (**674**) and 3-hydroxybutan-2-yl 2-hydroxy-3-phenylpropanoate (**675**).[468]



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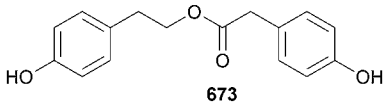

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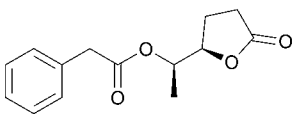

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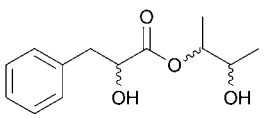
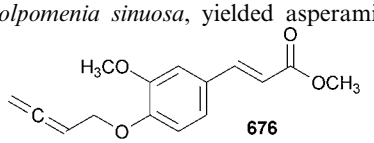


675

Four unusual allenic ethers, (*E*)-methyl 3-(4-(buta-2,3-dienyloxy)-3-methoxyphenyl)acrylate (**676**), (*E*)-methyl 3-(4-(4-(buta-2,3-dienyloxy)benzyloxy)phenyl) acrylate (**677**), (*E*)-methyl 3-(4-(4-(buta-2,3-dienyloxy)benzyloxy)-3-methoxyphenyl)acrylate (**678**), and methyl 4-(4-(buta-2,3-dienyloxy)benzyloxy)benzoate (**679**) have been reported from the fungus *Xylaria* sp., obtained from the seeds of an undisclosed angiosperm mangrove tree from Hong Kong.[469] The allenic ether moiety in **677–679** is also present in xyloallenolide B (**186**), a metabolite from the same fungus.[140]

4.9 Lipids

The fungus *Aspergillus niger*, endophytic to the Chinese brown alga *Colpomenia sinuosa*, yielded asperamides A (**680**) and B (**681**), a sphingolipid and its corresponding cerebroside.[470] Compound **680** showed moderate antifungal activity against *Candida albicans*. While sphingolipids containing a 9-methyl-C_{18}-sphingosine moiety have been described from natural sources on various occasions,[471] **680** and **681** contain a hitherto unreported 9-methyl-C_{20}-sphingosine moiety. Structurally related cerebrosides, asperiamides B (**682**) and C (**683**), were obtained from another strain of *Aspergillus niger*, isolated from seawater in China, together with two known intermediates of aflatoxin biosynthesis, averufin and nidurufin. The latter two displayed moderate antiviral activity against tobacco mosaic virus, while **682** and **683** were inactive.[472] *Alternaria raphani*, a halotolerant fungal strain isolated from sediment collected in a Chinese sea salt field, produced three new cerebrosides, alternarosides A–C (**684–686**), together with a new diketopiperazine.[367] Compounds **684–686** displayed very weak antimicrobial activity against *Escherichia coli*, *Bacillus subtilis* and *Candida albicans*, but were devoid of cytotoxic or radical scavenging activity.



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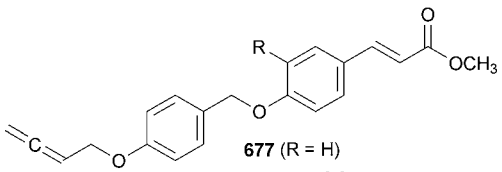
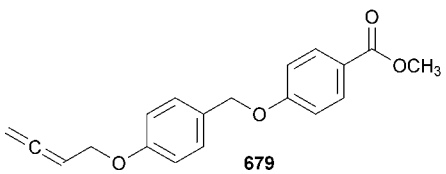


677 (R = H)
678 (R = OCH_3)

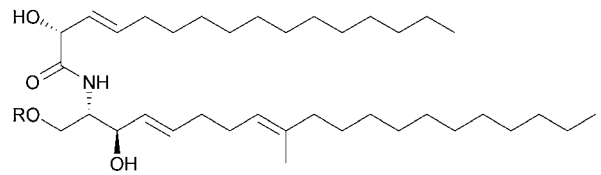


679

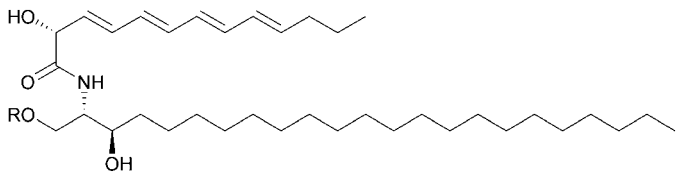
A total of 16 fungal strains were isolated from various tissues of the fish, *Argyrosomus argentatus* (white croaker). Screening for antifungal activity against the human-pathogenic *Candida albicans*, *Aspergillus niger* and *Trichophyton rubrum* identified a *Myrothecium* sp. as the most active isolate, which produced mainly known trichothecenes, but also the new 4,5-ditridecyloctanedioic acid (**687**).[473] Compound **687** was inactive in the antifungal bioassays. The fungus *Aureobasidium* sp., isolated from Neptune Grass, *Posidonia oceanica*, yielded an unusual diester, aureobasidin (**688**), along with two hydroxylated decanoic acids (**689** and **690**).[474] Compounds **688** and **689** inhibited larval settlement of *Balanus amphitrite* larvae, while **690** displayed antifungal activity against *Candida albicans*. All three compounds exhibited antibiotic activity against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis*.

5 Conclusion

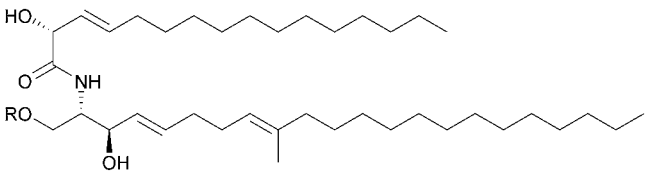
Fungi from marine habitats are a prolific source of new chemical diversity, and so far have provided more than 1000 new natural products, some of them with clinically relevant pharmacological activity. Probably the most important representative is the diketopiperazine halimide, which initially was discovered by Bill Fenical's group in the 1990s,[475] and which acts as a tubulin-depolymerising agent. This molecule served as a lead structure for the closely related synthetic analogue plinabulin (NPI-2358), currently undergoing phase II clinical trials in patients with advanced non-small-cell lung cancer.[476–478] Other important classes of metabolites include for examples the phomactins, the peribysins, or the tryprostatins, all of them mentioned in this review. The study of the secondary metabolite chemistry of marine-derived fungi has gained momentum in recent years, especially with the entry of Chinese researchers into the discipline, and there continues to be a steady increase in the total number of new structures reported in the chemical literature each year. In light of the pronounced discrepancy between the actual number of cultivated strains and the estimated biodiversity of fungi in marine habitats in general, it is to be expected that this trend will continue in the years to come.



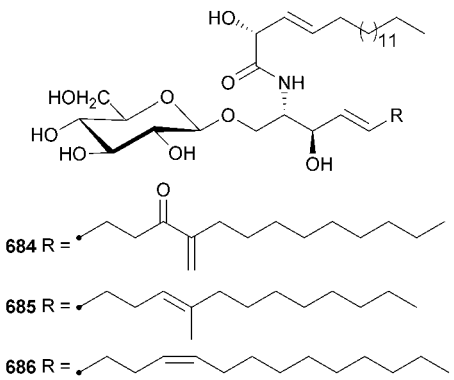
680 (R = H)
681 (R = β-D-glucopyranosyl)



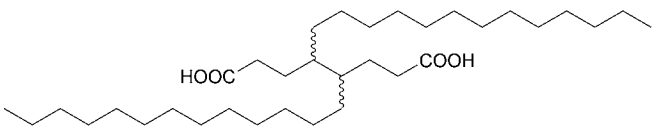
682 (R = β-D-glucopyranosyl)



683 (R = β-D-glucopyranosyl)



684 R =
685 R =
686 R =



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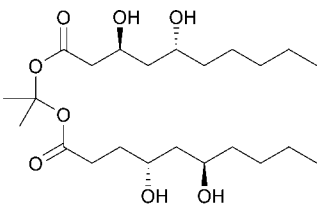

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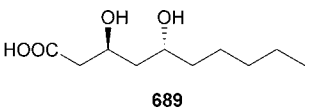

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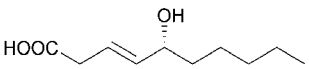

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