7 Insecticidal and Nematicidal Metabolites from Fungi

Heidrun Anke[1]

CONTENTS

I. Introduction

In our last review (Anke and Sterner 2002), published in the first edition of this volume, we focused on the chemical diversity of nematicidal and insecticidal fungal metabolites and the producing organisms. Since then, only a few novel compounds have been described. However, many publications have appeared which describe the biological activities of some of the described compounds (other than insecticidal/nematicidal) or their mode of action. In addition, the ecological significance of some of the compounds has been partly elucidated, e.g. their role in insect pathogens during the colonization of the host. Therefore this chapter also includes some of these aspects.

II. Novel Compounds and Their Producers

A. Peptides, Cyclic Peptides, and Cyclic Depsipeptides

Cyclic peptides and depsipeptides produced by fungi, among them insect pathogenic fungi (e.g. members of the genera *Aschersonia*, *Beauveria*, *Isaria*, *Metarhizium*, *Paecilomyces*, *Verticillium*), and their occurrence have been summarized in four comprehensive review articles (Anke and Sterner 2002; Zimmermann 2007a, b; Anke and Antelo 2009).

Since 2000, new producers of bioactive depsipeptides have been reported, for example, *Beauveria fellina* strains of marine origin (Lira et al. 2006), *Verticillium* sp. FKI-1033 (Monma et al. 2006), *Aspergillus carneus* (Capon et al. 2003), *Torrubiella luteorostrata* and its anamorph *Paecilomyces cinnamomeus* (both isolated from a scale insect; Isaka et al. 2007), *Verticillium hemipterigenum* (Nilanonta et al. 2003; Supothina et al. 2004), an *Aureobasidium* species from the tropical rain forest (Boros et al. 2006), an unidentified endophytic fungus (Huang et al. 2007), and a soil-borne *Phoma* species (Aoyagi et al. 2007). For a compilation of beauvericins and enniatins produced by *Cordyceps* species and their anamorphs as well as other insect pathogens, see Isaka et al. (2005a, b). Pseudodestruxins were found in *Nigrosabulum globosum* (Che et al. 2001) and reviews on destruxins and the producing organisms were published by Pedras et al. (2002) and Zimmermann (2007b). Some of the relevant compounds are listed in Table 7.1.

Chemical screening by HPLC-MS techniques led to the identification of five novel beauverolides from *Beauveria bassiana* and *Paecilomyces* spp. (Kuzma et al. 2001; Jegorov et al. 2004). Specific protocols for the detection and quantification of insecticidal cyclodepsipeptides in fungal cultures are now available (Jegorov et al. 2003).

Besides cyclopeptides and depsipeptides, fungi can also produce linear peptides with insecticidal activity; recently reported examples are efrapeptin G and methylated peptides from a marine fungus associated with a sponge, neoefrapeptins from *Geotrichum candidium* (Nagaraj et al. 2001; Fredenhagen et al. 2006) and the Aib-containing

[1]Institute for Biotechnology and Drug Research, IBWF e.V., Erwin-Schroedinger-Str. 56, 67663 Kaiserslautern, Germany; e-mail: anke@ibwf.de

Industrial Applications, 2nd Edition
The Mycota X
M. Hofrichter (Ed.)

Table 7.1. Examples of insecticidal and nematicidal compounds reported lately. The structures are given in Figs. 7.1–7.5

Producing fungus	Compound	Structure	References
Geotrichum candidium	Neoefrapeptin A	Fig. 7.1	Fredenhagen et al. (2006)
Marine isolate	Efrapeptin G	Fig. 7.1	Nagaraj et al. (2001)
Cordyceps heteropoda	Cicadapeptin I	Fig. 7.1	Krasnoff et al. (2005)
Paecilomyces lilacinus	Leucinostatin B	Fig. 7.1	Park et al. (2004)
Omphalotus olearius	Omphalontins E–I	Fig. 7.2	Liermann et al. (2009)
Nigrosabulum globosum	Pseudodestruxin A	Fig. 7.2	Che et al. (2000)
Beauveria bassiana	Beauverolide N	Fig. 7.2	Kuzma et al. (2003)
Verticillium sp. FKI-1033	Verticilide	Fig. 7.2	Momna et al. (2006)
Gliocladium sp. FTD-0668	Argifin	Fig. 7.3	Arai et al. (2000)
Laeptosphaeria maculans	Sirodesmin PL	Fig. 7.3	Boudart (1989)
Metarhizium anisopliae	Serinocyclin	Fig. 7.3	Krasnoff et al. (2007)
Epichloe typhina	Epichlicin	Fig. 7.3	Seto et al. (2007)
Fusarium sp.	Apicidin	Fig. 7.3	Singh et al. (2002)
Penicillium cluniae	Paraherquamides H, I	Fig. 7.4	López-Gresa et al. (2006)
Galiella rufa	Pregaliellalactone	Fig. 7.4	Köpcke et al. (2002a, b)
Penicillium sp. FKI-2140	Quinolonone B, yaequinolones D, F	Fig. 7.4	Uchida et al. (2006a, b)
Penicillium bilaiae	Penipratynolene, 2, 6-pyridinedicarboxylic acid	Fig. 7.4	Nakahara et al. (2004)
Penicillium citrinum	Quinolactacide	Fig. 7.4	Abe et al. (2005)
Penicllium simplicissium	Peniprequinolone	Fig. 7.4	Kusano et al. (2000)
Aspergillus niger	Nafuredin-γ	Fig. 7.4	Omura et al. (2001)
Nodulisporium sp.	Nodulisporic acids B_2, C	Fig. 7.5	Onydeyka et al. (2003)
Coronophora gregaria	MK7924	Fig. 7.5	Kumazawa et al. (2003)
Penicillium expansum	Communesins C, D, E	Fig. 7.5	Hayashi et al. (2004)

cicadapeptins I and II from *Cordyceps heteropoda* (Krasnoff et al. 2005). Structures of some linear peptides are shown in Fig. 7.1, cyclic peptides and depsipeptides in Figs. 7.2 and 7.3. The neoefrapeptins comprise a large group of ten 16-residue and two 13-residue peptides containing also non-proteinogenic amino acids (Fredenhagen et al. 2006).

From protoplasts of a monokaryotic strain of the basidiomycete *Omphalotus olearius*, five novel hydroxylated omphalotin derivatives (omphalotin E–I) were isolated, complementing the already known omphalotins.

Interestingly the monokaryotic strain grew faster and produced higher amounts of these compounds than the dikaryotic parental strain from which it was obtained (Liermann et al. 2009). All *O. olearius* strains, irrespective of their geographical origin, seem to produce omphalotin derivatives (Anke et al., unpublished data). In fruiting bodies, omphalotins could not be detected. Omphalotins E-I exhibited similar nematicidal activities against *Meloidogyne incognita* (Kofoid & White) as omphalotin A. Antibacterial or antifungal activities were not detected and none of the compounds showed cytotoxic effects towards mouse leukemia cells (L1012 cells) or human colon adenocarcinoma cells (Colo 320 cells) at concentrations up to 50 µg/ml. The novel compounds were seemingly produced at the expense of the known omphalotins, including omphalontin A, the amount of which decreased drastically towards the end of the fermentation (Liermann et al. 2009).

B. Novel Metabolites and New Derivatives of Insecticidal or Nematicidal Metabolites

A screening of some 500 endophytic fungi for the production of nematicidal metabolites led to the selection of 17 strains with selective activity towards *Meloidogyne incognita*, while *Caenorhabditis elegans* was less affected (Schwarz et al. 2004). In five strains identified as *Phomposis phaseoli* and *Melanconium betulinum* (four strains), the nematicidal principle was found to be the simple metabolite 3-hydroxypropionic acid (Schwarz et al. 2004).

In the Sarcosomataceae (teleomorphs of the genera *Galiella*, *Urnula*, *Strumella*), the production of the galiellalactone precursors pregaliellalactone (Fig. 7.4) and structurally related hexaketides accounted for the nematicidal activity. Interestingly an endophytic strain of *Cistus salviifolius*, which according to its 18S rDNA sequences also belongs to the Sarcosomataceae, produced the same compounds (Köpcke et al.

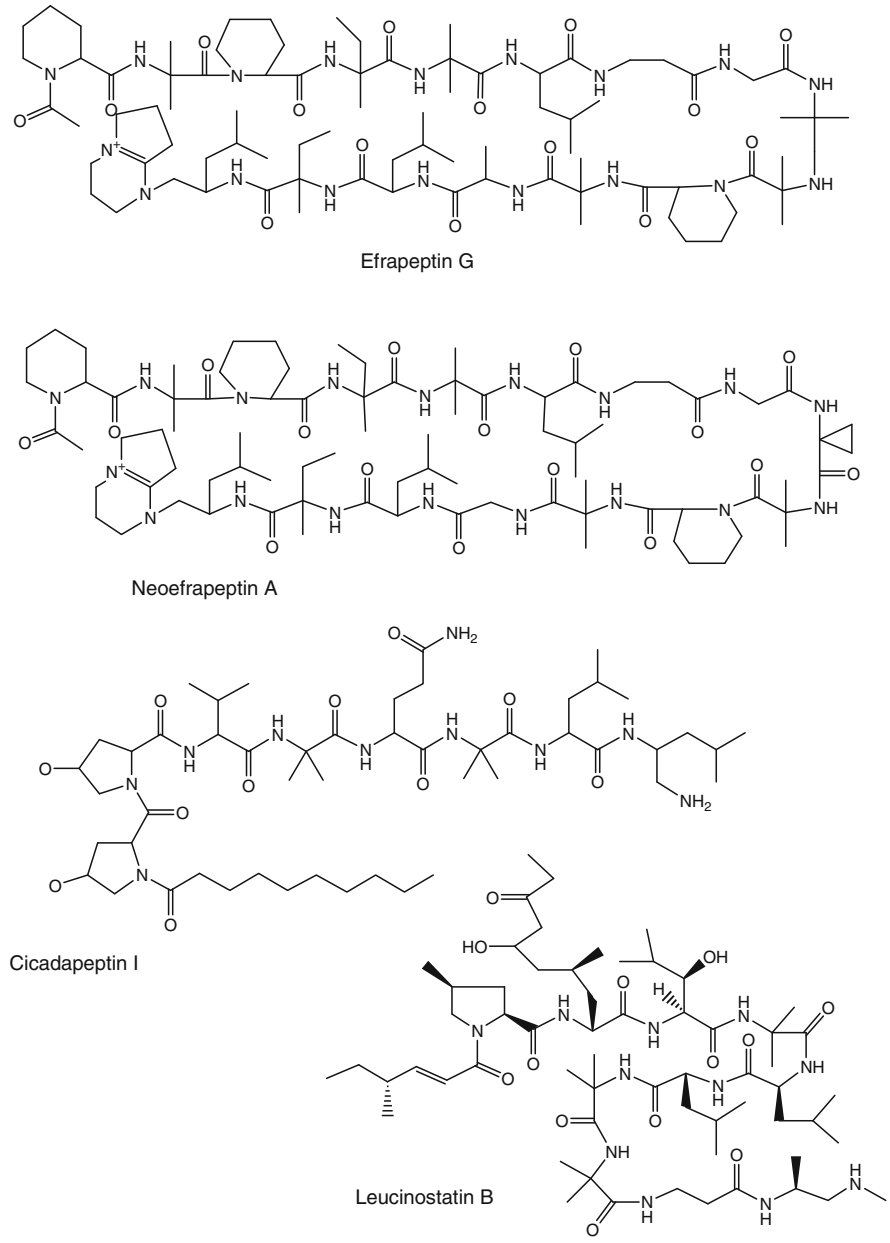

Fig. 7.1. Neofrapeptin A (produced by *Geotrichum candidium*). Efrapeptin G (from a marine isolate). Cicadapeptin I (from *Cordyceps heteropoda*). leucinostatin B (from *Paecilomyces lilacinus*)

2002a, b). A further nematicidal metabolite, MK7924 (Fig. 7.5), with weak activity against *Aspergillus niger* and *Caenorhabditis elegans* was isolated from *Coronophora gregaria* (Kumazawa et al. 2003).

Quinolactacide (Fig. 7.4), an insecticidal quinolone, was isolated from solid-state cultures of *Penicillium citrinum* (Abe et al. 2005). Using *Artemia salina* as test organism, seven novel yaequinolones were isolated from *Penicillium* sp. FKI-2140, together with nine known and structurally related compounds, among them quinolinones A and B, penigequinolones A and B, and peniprequinolone (Uchida et al. 2006a, b).

Quinolone derivatives were also obtained from other *Penicillium* species, e.g. *P. janczewskii* (He et al. 2005) and *P. simplicissimum* (Kusano et al. 2000). Peniprequinolone, in addition to its strong insecticidal properties,

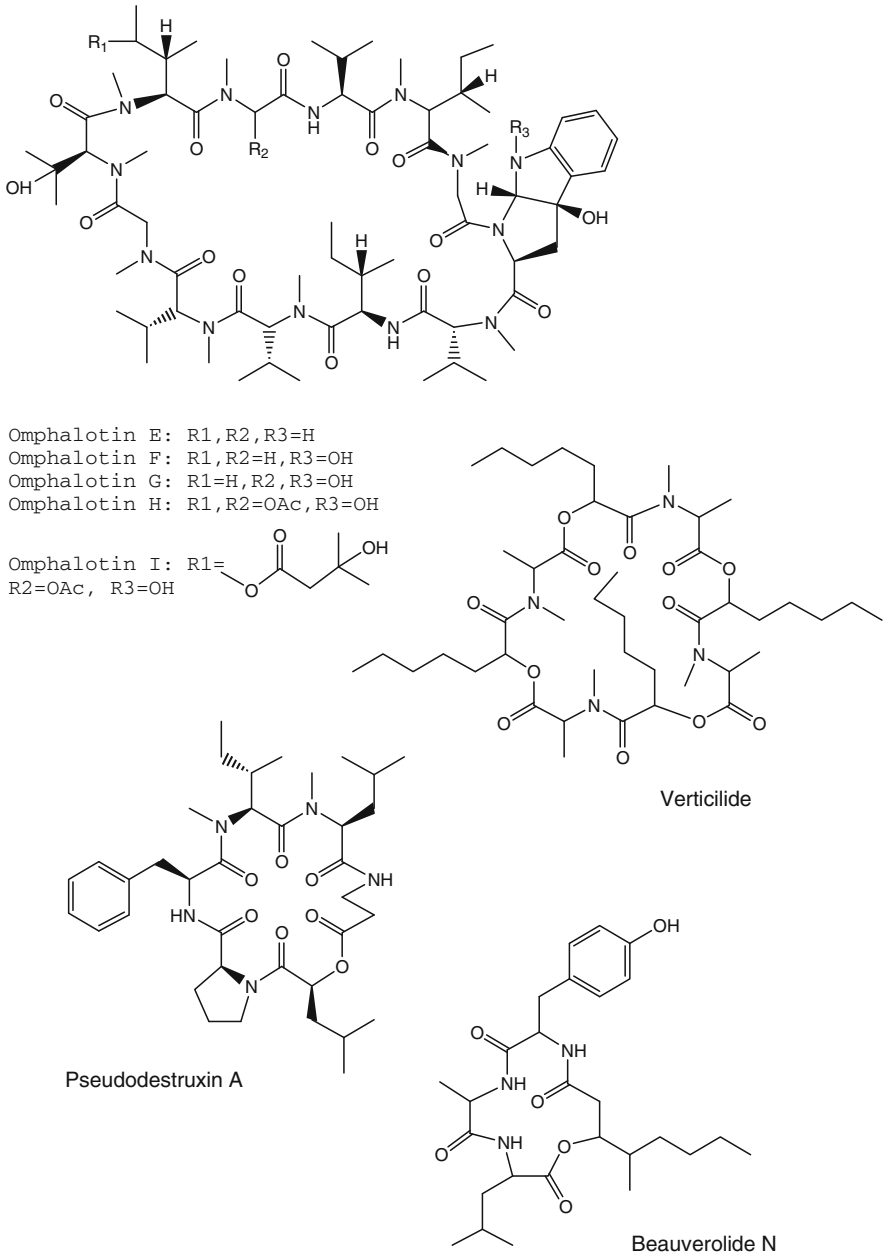

Fig. 7.2. Omphalontins E–I (from *Omphalotus olearius*). Pseudodestruxin A (from *Nigrosabulum globosum*). Beauverolide N (from *Beauveria bassiana*). Verticilide (from *Verticillium* sp. FKI-1033)

inhibits the root-lesion nematode *Pratylenchus penetrans* (Kusano et al. 2000). Some of the quinolones and their producers are listed in Table 7.1, and their structures are given in Fig. 7.4. Another *Penicillium* metabolite active against the nematode *Pratylenchus penetrans* is penipratynolene (Nakahara et al. 2004). The compound was isolated together with 6-methoxy-carbonylpicolinic acid and 2,6-pyridinedicarboxylic acid (Fig. 7.4) from *Penicillium bilaiae*.

New nodulisporic acids were isolated from a *Nodulisporium* sp., namely nodulisporic acids B, B_1, B_2, and C, C_1, C_2, and Δ^{23} nodulisporic acid C_4 (Ondeyka et al. 2002, 2003; Singh et al. 2004). The compounds are active against fleas on dogs (Shoop et al. 2001) and comprise complex chemical structures (see Fig. 7.5). From *Penicillium expansum* Link MK-5, communesins C, D, and E (Fig. 7.5) were

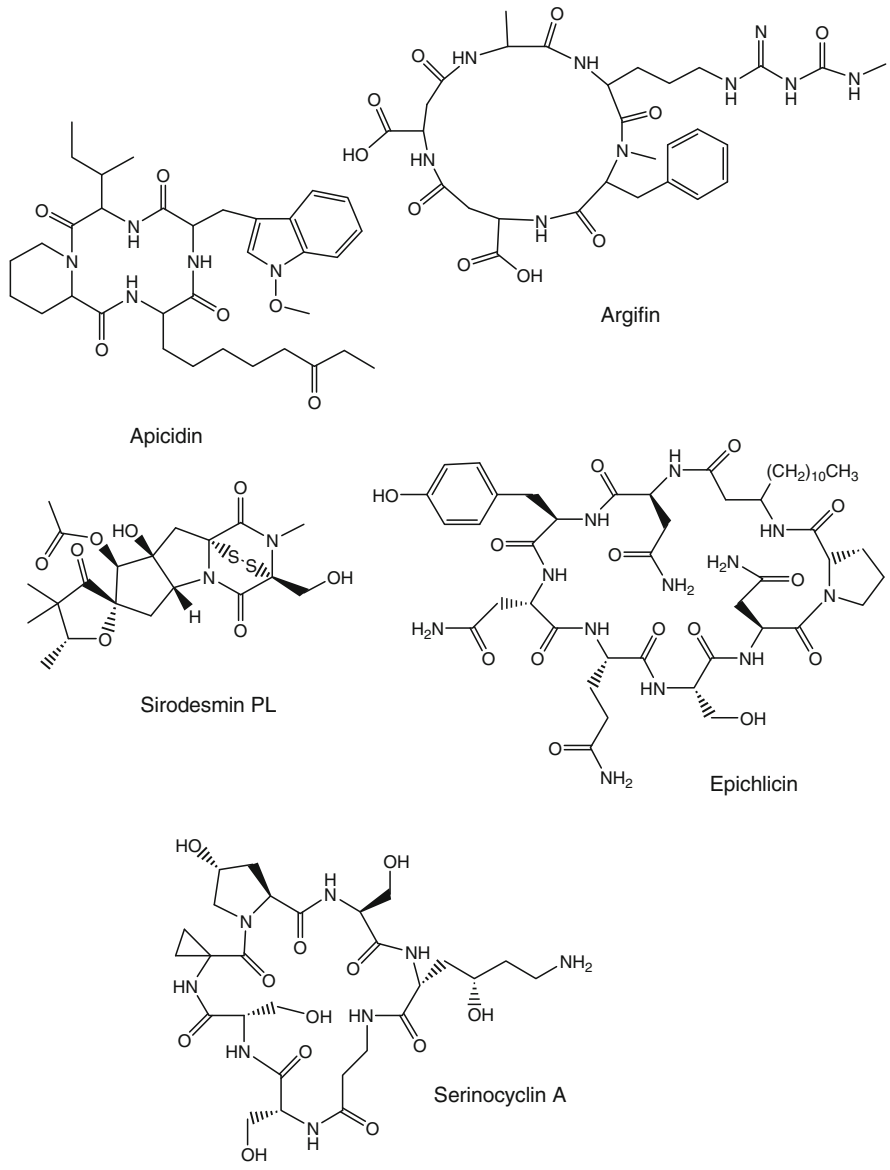

Fig. 7.3. Argifin (from *Gliocladium* sp. FTD-0668). Sirodesmin PL (from *Laeptosphaeria maculans*). Serinocyclin (from *Metarhizium anisopliae*). Epichlicin (from *Epichloe typhina*). Apicidin (from *Fusarium* sp.)

obtained, along with two known communesins (A, B). All novel communesins showed selective insecticidal activity against silkworms (Hayashi et al. 2004).

The large family of paraherquamide metabolites has gained new members from *P. cluniae* Quintanilla: paraherquamide H and I (Fig. 7.4) together with five known derivatives. Structure–activity relationships revealed paraherqueamide E to be the most potent member, with a LD_{50} of 0.089 μg/nymph of the milkweed bug *Oncopeltus fasciatus* Dallas (López-Gresa et al. 2006).

Nafuredin is one of the few insecticidal metabolites that does not contain nitrogen, i.e. it is not an alkaloid. The substance was isolated from a marine-derived *Aspergillus niger* strain using mitochondria of *Ascaris suum* as test system with the aim to find inhibitors of NADH-fumarate reductase from helminths (Omura et al. 2001). By weak alkaline treatment the compound was converted to its γ-lactone (Fig. 7.4) which also inhibits NADH-fumarate reductase (Shiomi et al. 2005).

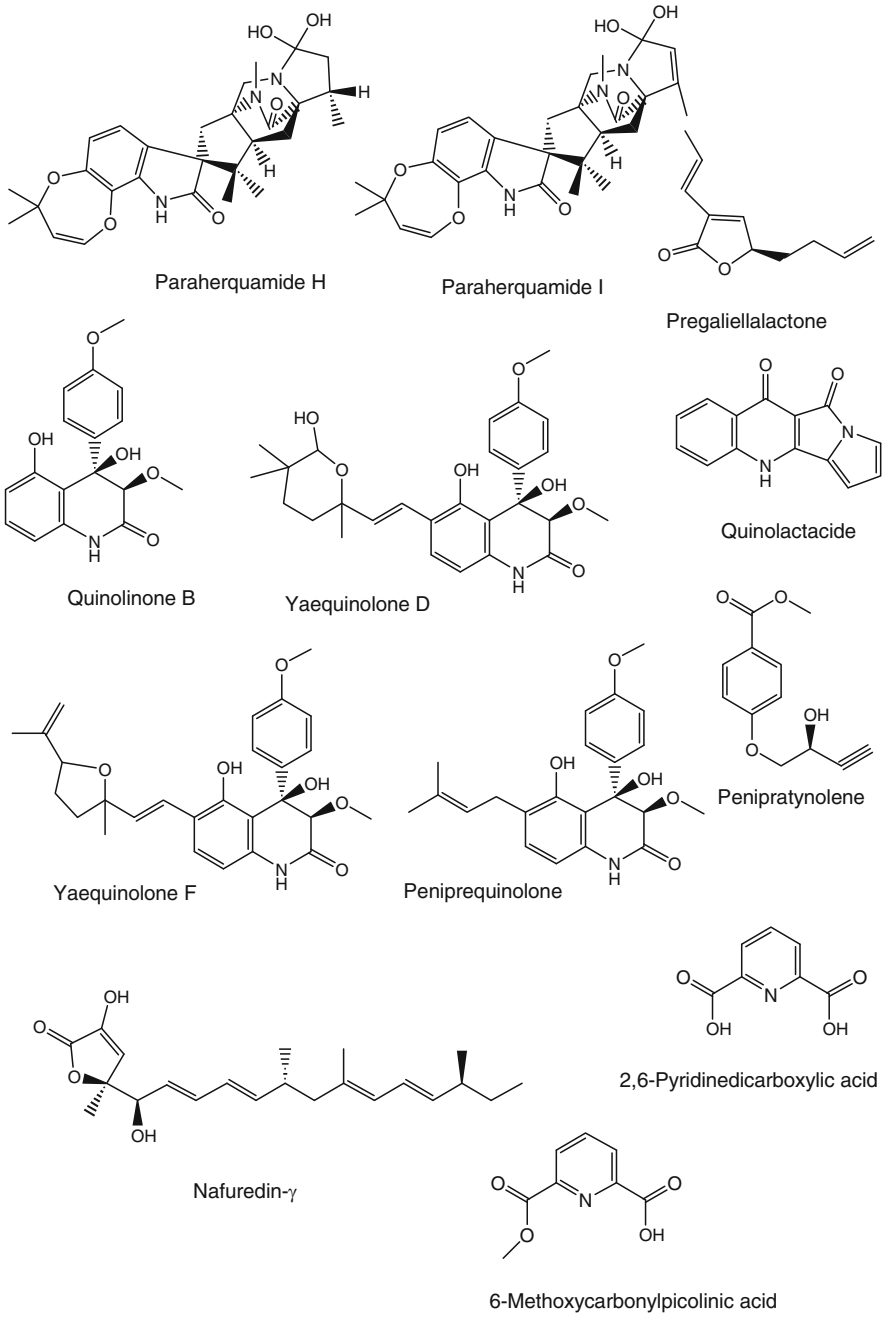

Fig. 7.4. Paraherquamides H, I (from *Penicillium cluniae*). Pregaliellalactone (from *Galiella rufa*). Quinolonone B, yaequinolones D, F (from *Penicillium* sp. FKI-2140). Penipratynolene and 2,6-pyridinedicarboxylic acid (from *Penicillium bilaiae*). Quinolactacide (from *Penicillium citrinum*). Peniprequinolone (from *Penicllium simplicissium*). Nafuredin-γ (from *Aspergillus niger*)

Several reports on insecticidal activities of extracts obtained from fungal culture filtrates have been published without identification of the active components (Meyer et al. 2004; Mohanty and Prakash 2008). Thus, Chen et al. (2003) reported on an extract obtained from an endophytic fungus with high activities against *Heliothis armigera*; the metabolites isolated, however, were not insecticidal (Yasui et al. 2006).

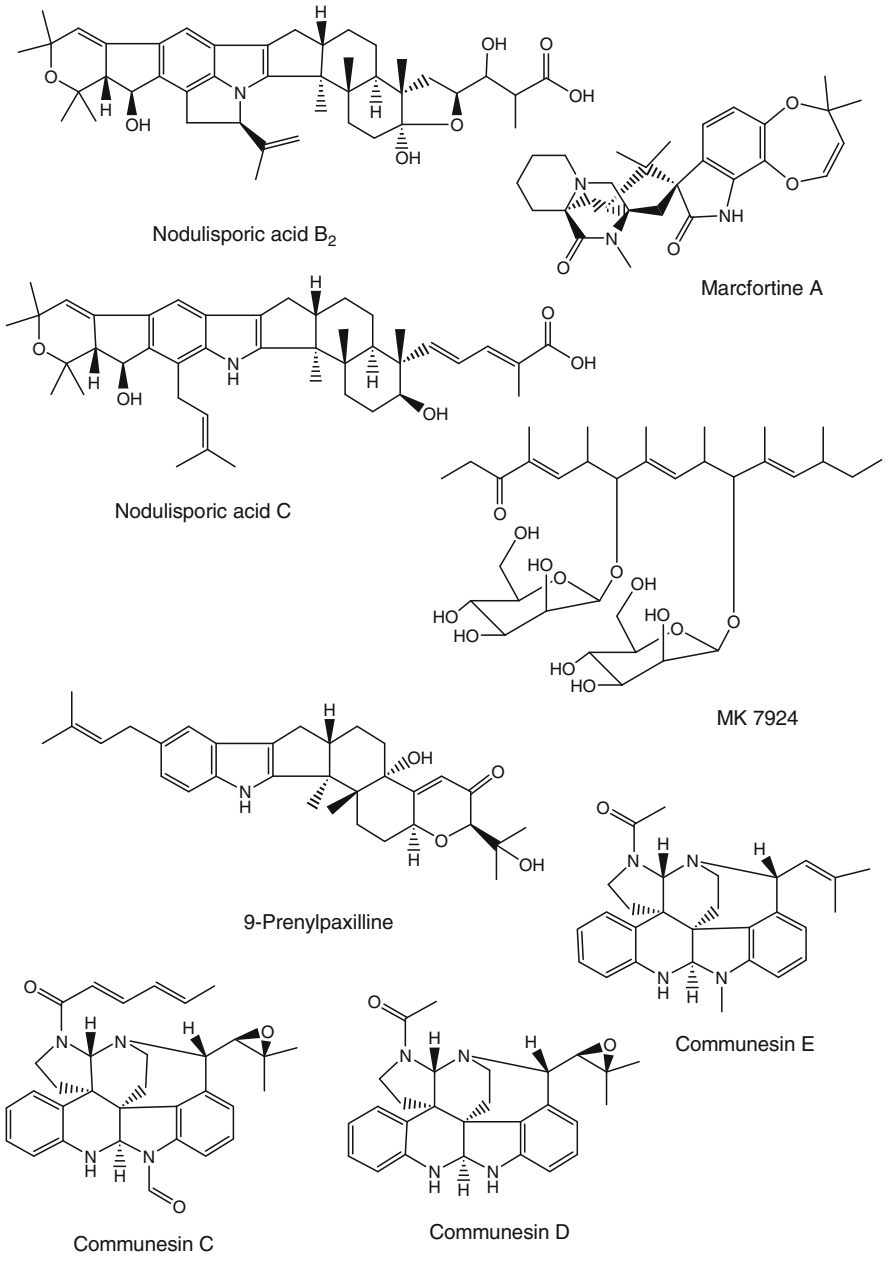

Fig. 7.5. Nodulisporic acids B_2, C (from *Nodulisporium* sp.). MK7924 (from *Coronophora gregaria*). Communesins C, D, E (from *Penicillium expansum*)

Many insecticidal or nematicidal metabolites, despite their complex structures, have been chemically synthesized during the last few years, for example, 9-prenylpaxilline (Smith and Cui 2003), marcfortine A, and structurally related metabolites of the paraherquamide group, many of which have potent insecticidal and antihelmintic properties (Williams 2002; Williams et al. 2003; Trost et al. 2007): quinolactacide (Abe et al. 2006), nafuredin-γ (Nagamitsu et al. 2003), and verticilide (Momna et al. 2006).

The successful in vitro synthesis of enniatins with the multienzyme enniatin synthetase may open the way to novel derivatives, since the substrate binding pocket for the α-hydroxy carboxylic acid accepts chemically different acids (Glinski et al. 2001; Feifel et al. 2007).

III. Biological Activities and Mode of Action

Cyclic depsipeptides and their biological activities were thoroughly reviewed by Sarabia et al. (2004), insecticidal and other biological activities of destruxins, isariins, enniatins, and beauverolides by Anke and Sterner (2002), by Anke and Antelo (2009), and by Zimmermann (2007a, b).

Sirodesmin PL produced by *Leptosphaeria maculans* was found to have phytotoxic, antibacterial, and insecticidal properties (Rouxel et al. 1988; Boudart 1989). Serinocyclin A isolated from *Metarhizium anisopliae* condia produced a sublethal locomotory defect in mosquito larvae (Krasnoff et al. 2007). Argifin and argadin, two cyclopentapeptides from a *Gliocladium* sp. and a *Clonostachys* sp. turned out to be potent inhibitors of chitinase B from the gram-negativ bacterium *Serratia marcescens* (Arai et al. 2000). When injected into cockroach larvae, their moult was arrested (Houston et al. 2002).

Like many peptaibols, the efrapeptins act as channel-forming ionophores and have insecticidal, antimalarial, and antiprotozoal activities (Nagaraj et al. 2001). In addition, they inhibit exocytosis but not endocytosis in eukaryotic cells (Muroi et al. 1996) and exhibit antibacterial and antifungal activities (Bandani et al. 2000).

Efrapeptins bind strongly to V-ATPases in the brush border membrane of the mid-gut of the wax moth *Galleria mellonella* (Bandani et al. 2001). Leucinostatins A and B originally isolated from *Penicillium lilacinum* [now *Paecilomyces lilacinus* (Thom) Samson] were found to have nematicidal activities (Arai et al. 1973; Park et al. 2004). Like other peptaibols they act on bacteria, are uncouplers in the inner mitochondria membrane and inhibit mitochondrial ATP synthesis. Recently interesting and potent in vivo and in vitro antitrypanosomal activities of these compounds have been reported. Despite its toxicity, the strong in vivo antitrypanosomal activity of leucinostatin B makes the compound a promising lead structure for the development of drugs with a new type of action mode (Ishiyama et al. 2009).

Among nine beauverolides tested for acyl-CoA:cholesterol acyltransferase (ACAT) inhibitory activity in CHO-cells expressing ACAT1 or ACAT2, beauverolides I and III inhibited ACAT1 rather selectively, and no antimicrobial or cytotoxic activities were detected.

Both compounds produced by the entomopathogenic fungus *Beauveria bassiana* exert anti-atherogenic activity in low-density lipoprotein receptor- and apolipoprotein E-knockout mice without any side effects and thus may serve as lead structures for new anti-atherosclerotic agents (Namatame et al. 2004). Contrary to the beauverolides, related beauvericin was clearly cytotoxic (Matsuda et al. 2004; Ohshiro et al. 2007). Cell lines derived from insects, e.g. *Spodoptera frugiperda* SF-9 cells, were also inhibited by beauvericin (Calo et al. 2003; Fornelli et al. 2004). The compounds induced rapid cell death in *Xenopus* oocytes via influx of Ca^{2+} (Tang et al. 2005).

Furthermore, significant effects were detected for destruxin E on insect haemocytes (Vey et al. 2002) and for different destruxins, e.g destruxins A, B, and E, on human and insect cell lines (Skrobek and Butt 2005). Verticilide from moulds of the genus *Verticillium* inhibits the binding of ryanodine to its receptor (RyR) and, hence, has insecticidal activity (Monma et al. 2006).

The target of PF1022A, a fungal cyclooctadepsipetide, is a latrophilin-like receptor from the parasitic nematode *Haemonchus contortus* (Saeger et al. 2001). Emodepsin, a semi-synthetic depsipeptide derived from PF1022A, has already been successfully used against helminths in veterinary medicine (Conder et al. 1995; Dyker et al. 2004; Samson-Himmelstjerna et al. 2005). Due its limited availability and therefore a rather high price, its use is restricted to small pets. PF1022A is a metabolite of an endophytic fungus from the ornamental plant *Camellia japonica* (Sasaki et al. 1992; Scherkenbeck et al. 2002). Based on its 18S rRNA gene sequence, the endophyte was tentatively identified as a member of the ascomycetous family Xylariaceae close to *Xylaria polymorpha* and *Rosellinia necatrix* (Miyado et al. 2000).

Selective nematicidal properties were only reported for the omphalotins with high inhibitory activity towards *Meloidogyne incognita* and lower activities against *Caenorhabditis elegans* (Mayer et al. 1999). The nematicidal properties of hydroxylated omphalotins, some of which can be produced by monokaryotic strains generated from dikaryotic parent mycelia, were found to be higher than those of the unsubstituted compound, but unfortunately they were not stable (Büchel et al. 1998; Liermann et al. 2009). Their mode of action has not yet been elucidated.

Paraherquamides, potent anthelmintic agents isolated from various *Penicillium* species, were reported to possess promising activities against drug-resistant intestinal parasites (Williams et al. 2003).

Quinolactacide was also strongly active against *Myzus persicae*, and 250 ppm were lethal to 88% of the aphides tested; and, at a concentration of 500 ppm, 42% mortality towards the diamondback moth (*Plutella xylostella*) was recorded (Abe et al. 2006).

Nafuredin is a selective inhibitor of the helminth complex I (NADH-fumarate reductase). It showed only very weak inhibition of the mammalian complex I (NADH ubiquinone reductase from bovine liver) but was selectively active in vivo against the stomach worm *Haemonchus contortus* in sheep (Omura et al. 2001). The γ-lactone was almost equally active in the helminth complex I assay but less active in the in vivo tests (Shiomi et al. 2005). The differences between the human and helminth complex I make this an interesting target for the development of novel selective drugs against parasitic nematodes.

IV. Ecological Significance

Many secondary metabolites play a crucial role for fungi in their natural habitats. For example, endophytic fungi of grasses belonging to the genera *Neotyphodium*/*Epichloe* confer protection from mammalian and insect herbivores, or enhanced resistance to nematodes and phytopathogenic fungi (Schardl et al. 2004; Panaccione et al. 2006). Some of these beneficial effects are due to secondary metabolites.

Loline and peramine have been identified among the fungal metabolites with insecticidal activities in the plant host. Another metabolite from *Epichloe typhina*, epichlicin, efficiently prevents the germination (IC_{50} value of 22 nM) of *Cladosporium phlei* spores, a host plant pathogen (Seto et al. 2007). Likewise, sirodesmin PL or zearalenone and other mycotoxins produced by *Leptoshaeria maculans* and *Fusarium* species, respectively, were detected in the plant hosts (Laser et al. 2003; Elliott et al. 2007). Some endophytic fungi produce 3-hydroxypropionic acid as a nematicidal principal (Schwarz et al. 2004). This might be the natural nematicide with the simplest chemical structure; however it remains to be elucidated whether the compound is also produced in planta.

The function of shearamide A, an insecticidal cyclopeptide isolated from the ascostromata of *Eupenicillium shearii* (Belofsky et al. 1998), and likewise sclerotiamide from *Aspergillus sclerotiorum* sklerotia (Whyte et al. 1996), may be to protect the reproductive or survival structures of the fungi against insects or nematodes, similar to ergopeptides in the sclerotia of *Claviceps* species (Leistner and Steiner 2009).

Investigations on the role of destruxins in the pathogenicity of *Metarhizium anisopliae* against three species of insects revealed a direct relationship between the titre of destruxins produced by the strains in vitro and their destructive action (Kershaw et al. 1999).

However, in *M. anisopliae* mutants, incapable of destruxin production, virulence towards *Galleria mellonella* was unaltered (Amiri-Besheli et al. 2000). In the plant pathogenic mould *Alternaria brassicae*, destruxin B is a host-specific toxin. In three *Brassica* species the degree of their sensitivity to destruxin B positively correlated with their degree of susceptibility (Pedras et al. 2002).

From cultures of a number of fungi producing cyclic depsipeptides (e.g. *Beauveria bassiana*), also dipeptides composed of the same amino acids as the depsipeptides were isolated.

Other insect pathogens like *Verticillium* species and *Metarhizium anisopliae* as well as plant pathogenic fungi, e.g. *Colletotrichum gloeosporioides*, *Exserohilum holmi*, *Gliocladium deliquenscens*, *Alternaria* and *Trichoderma* spp. were also found to produce dipeptides. An unidentified endophyte from mangrove leafs (*Rhizophora* spp.) produced two cyclic depsipeptides and three diketopiperazines (Huang et al. 2007).

It might be interesting to elucidate the insecticidal and nematicidal activities exhibited by cocktails of all these secondary metabolites of a pathogen. Such synergistic effects of different fungal metabolites have been largely neglected so far. In general, the role of dipeptides and depsipeptides in insect and plant pathogenicity is not fully understood. Further, it is intriguing that depsipeptides are widespread in phytopathogens (e.g. *Cochliobolus* with anamorphs *Helminthosporium* and *Bipolaris*, *Calonectria* with its anamorph *Cyclindrocladium*, as well as *Fusarium* and *Alternaria*), insect pathogens (*Aschersonia*, *Beauveria*, *Cordyceps*, *Diheterospora*, *Fusarium*, *Hirsutella*, *Isaria*, *Metharizium*, *Paecilomyces*, *Tolypocladium*, *Verticillium*), and others (Zimmermann 2007a, b; Buckingham 2008). As molecular tools become more and more available, this question may be correctly addressed and respectively answered in the near future.

The efrapeptins produced by insect pathogenic *Tolypocladium* species are also produced

in vivo; the amounts, however, were found to be too small to cause the death of insects. Therefore, it was suggested that the compounds act in concert with additional, not yet known, pathogenicity factors (Bandani et al. 2000).

For the function of enzymes in entomopathogenic fungi and their role in disease development, see Khachatourians and Qazi (2008) in this context. The effects of secondary metabolites on the enzymes involved in pathogenesis in plants and insects alike is another innovative field, in which interesting results still wait to be elucidated.

V. Conclusions

Natural products derived from plants, animals, and microorganisms constitute only 7.6% of the global insecticides market (Elbert et al. 2007). However, more than 50 000 microbial metabolites are known. Half of them exhibit bioactivities, first and foremost antibiotic activity. Fungal metabolites represent about 40% of these natural products (Bérdy 2005; Buckingham 2008). So far, no secondary metabolite from a fungus has been developed into a marketable insecticidal or nematicidal product, despite the fact that most insect pathogens are fungi and many have successfully been screened for the production of "soft pesticides". However, as it appears, many of the compounds isolated from these fungi are rather toxic, like the destruxins or efrapeptins. While they fulfil their ecological role very well, i.e. killing the host animal, they do not meet the requirements of modern agricultural pesticides regarding selectiveness, low costs, and environmental safety. Nevertheless, the example of PF1022A shows that fungal metabolites can be developed into drugs useful in agriculture and veterinary medicine. The many synthetic efforts using natural products as lead structures also point in this direction. Taking into account the overall number of fungal species, which is estimated to be around 1.5 million (Hawksworth 2001), and comparing this number with the number of about 50 000 species screened so far, it seems to be only a matter of time until the first insecticide from a fungus is introduced into the market.

Acknowledgements I am grateful to Dr. L. Antelo for preparing the figures. The work in our laboratory was supported by Bayer AG, BASF SE, the State of Rhineland–Palatinate and the BMBF.

References

Abe M, Imai T, Ishii N, Usui M, Okuda T, Oki T (2005) Quinolactacide, a new quinolone insecticide from *Penicillium citrinum*. Biosci Biotechnol Biochem 69:1202–1205

Abe M, Imai T, Ishii N, Usui M (2006) Synthesis of quinolactacide via an acyl migration reaction and dehydrogenation with manganese dioxide, and its insecticidal activities. Biosci Biotechnol Biochem 70:303–306

Amiri-Besheli B, Khambay B, Cameron S, Deadman ML, Butt TM (2000) Inter- and intra-specific variation in destruxin production by insect pathogenic *Metarhizium* spp., and its significance to pathogenesis. Mycol Res 104:447–452

Anke H, Antelo L (2009) Cyclic peptides and depsipeptides from fungi. In: Anke T, Weber D (eds) Physiology and genetics. Mycota XV. Springer, Berlin Heidelberg New York, pp 273–296

Anke H, Sterner O (2002) Insecticidal and nematicial metabolites from fungi. In: Osiewacz HD (ed) Industrial applications. Mycota X. Springer, Berlin Heidelberg New York, pp 109–127

Aoyagi A, Yano T, Kozuma S, Takatsu T (2007) Pleofungins, novel inositol phosphorylceramide synthase inhibitors, from *Phoma* sp. SANK 13899. J Antibiot 60:143–152

Arai N, Shiomi K, Iwai Y, Omura S (2000) Argifin, a new chitinase inhibitor, produced by *Gliocladium* sp. FTD-0668. II. Isolation, physico-chemical properties, and structure elucidation. J Antibiot 53:609–614

Arai T, Mikami Y, Fukushima K, Utsumi T, Yazawa K (1973) A new antibiotic, leucinostatin, derived from *Penicillium lilacinum*. J Antibiot 26:157–161

Bandani AR, Khambay BPS, Faull JL, Newton R, Deadman M, Butt TM (2000) Production of efrapeptins by *Tolypocladium* species and evaluation of their insecticidal and antimicrobial properties. Mycol Res 104:537–544

Bandani AR, Amiri B, Butt TM, Gordon-Weeks R (2001) Effects of efrapeptin and destruxin, metabolites of entomogenous fungi, on the hydrolytic activity of a vacuolar type ATPase identified on the brush border membrane vesicles of *Galleria mellonella* midgut and on plant membrane bound hydrolytic enzymes. Biochim Biophys Acta 1510: 367–377

Belofsky G N, Gloer JB, Wicklow DT, Dowd PF (1998) Shearamide A: a new cyclic peptide from the ascostromata of *Eupenicillium shearii*. Tetrahed Lett 39:5497–5500

Bérdy J (2005) Bioactive microbial metabolites. J Antibiot 58:1–26

Boros C, Smith CJ, Vasina Y, Che Y, Dix AB, Darveaux B, Pearce C (2006) Isolation and identification of the icosalides – cyclic peptolides with selective antibiotic and cytotoxic activities. J Antibiot 59:486–494

Boudart G (1989) Antibacterial activity of sirodesmin PL phytotoxin: application to the selection of phytoxin-deficient mutants. Appl Enivron Microbiol 55:1555–1559

Büchel, E, Martini U, Mayer A, Anke H, Sterner O (1998) Omphalotins B, C, and D, nematicidal cyclopeptides from *Omphalotus olearius*. Absolute configuaration of omphalotin A. Tetrahedron 54:5345–5352

Buckingham J (ed) (2008) Dictionary of natural products on DVD, ver 17.1. Chapman and Hall/CRC, Boca Raton

Calo L, Fornelli F, Nenna S, Tursi A, Caiaffa MF, Macchia L (2003) Beauvericin cytotoxicity to the invertebrate cell line SF-9. J Appl Genet 44:515–520

Capon RJ, Skene C, Stewart M, Ford J, O'Hair RAJ, Williams L, Lacey E, Gill JH, Heiland K, Friedel T (2003) Aspergillicins A-E: five novel depsipeptides from the marine-derived fungus *Aspergillus carneus*. Org Biomol Chem 1:1856–1862

Che Y, Swenson DC, Gloer JB, Koster B, Malloch D (2001) Pseudodestruxins A and B: new cycllic depsipeptides from the coprophilous fungus *Nigrosabulum globosum*. J Nat Prod 64:555–558

Chen G, Lin Y, Wen L, Vrijmoed LLP, Jones EBG (2003) Two new metabolites of a marine endophytic fungus (No. 1893) from an estuarine mangrove on the South China Sea coast. Tetrahedron 59:4907–4909

Chen SY, Dickson DW, Mitchell DJ (2000) Viability of *Heterodera glycines* exposed to fungal filtrates. J Nematol 32:190–197

Conder GA, Johnson SS, Nowakowski DS, Blake TE, Dutton FE, Nelson SJ, Thomas EM, Davis JP, Thompson DP (1995) Anthelmintic profile of the cyclodepsipeptide PF1022A in in vitro and in vivo models. J Antibiot 48:820–823

Dyker H, Harder A, Scherkenbeck J (2004) Chimeric cyclodepsipeptides as mimetics for the anthelmintic PF1022A. Biorg Med Chem Lett 14: 6129–6130

Elbert A, Nauen R, McCaffery A (2007) IRAC, resistance and mode of action classification of insecticides. In: Krämer W, Schirmer U (eds) Modern crop protection compounds. Wiley-VCH, Weinheim, pp 753–771

Elliott CE, Gardiner DM, Thoma G, Cozijnsen A, van de Wouw A, Howlett BJ (2007) Production of the toxin sirodesmin PL by *Leptosphaeria maculans* during infection of *Brassica napus*. Mol Plant Pathol 8:791–802

Feifel SC, Schmiederer T, Hornbogen T, Berg H, Süssmuth RD, Zocher R (2007) In vitro synthesis of new enniatins: Probing the α-D-hydroxy carboxylic acid binding pocket of the multienzyme enniatin synthetase. ChemBioChem 8:1767–1770

Fornelli F, Minervini F, Logrieco A (2004) Cytotoxicity of fungal metabolites to lepidopteran (*Spodoptera frugiperda*) cell line (SF9). J Invert Pathol 85:74–79

Fredenhagen A, Molleyres LP, Böhlendorf B, Laue G (2006) Structure determination of neofrapeptins A to N: peptides with insecticidal activity produced by the fungus *Geotrichum candidum*. J Antibiot 59:267–280

Glinski M, Hornbogen T, Zocher R (2001) Enzymatic synthesis of fungal N-methylated cyclopeptides and depsipeptides. In: Kirst H, Yeh WK, Zmijewski M (eds) Enzyme technologies for pharmaceutical and biotechnological applications. Dekker, New York, pp 471–497

Hawksworth DL (2001) The magnitude of fungal diversity: the 1.5 million species estimate revisited. Mycol Res 105:1422–1432

Hayashi H, Matsumoto H, Akiyama K (2004) New insecticidal compounds, communesins C, D, and E, from *Penicillium expansum* Link MK-57. Biosci Biotechnol Biochem 68:753–756

He J, Lion U, Sattler I, Gollmic FA, Grabley S, Cai J, Meiners M, Schünke H, Schaumann K, Dechert U, Kron M (2005) Diastereomeric quinolinone alkaloids from the marine-derived fungus *Penicllium janczewskii*. J Nat Prod 68:1397–1399

Houston DR, Shiomi K, Arai N, Omura S, Peter MG, Turberg A, Synstad B, Eijsink VG, van Aalten DMF (2002) High-resolution structures of a chitinase complex with natural product cyclopentapeptide inhibitors: mimicry of carbohydrate substrate. Proc Natl Acad Sci USA 99:9127–9132

Huang H, She Z, Lin Y, Vrijmoed LLP, Lin W (2007) Cyclic peptides from an endophytic fungus obtained from a Mangrove leaf (*Kandelia candel*). J Nat Prod 70: 1696–1699

Isaka M, Kittakoop P, Kirtikara K, Hywel-Jones NI, Thebtaranonth Y (2005a) Bioactive substances from insect pathogenic fungi. Acc Chem Res 38:813–823

Isaka M, Palasarn S, Rachtawee P, Vimuttipong S, Kongsaeree P (2005b) Unique diketopiperazine dimers from the insect pathogenic fungus *Verticillium hemipterigenum* BCC 1449. Org Lett 7:2257–2260

Isaka M, Palasarn S, Kocharin K, Hywel-Jones NI (2007) Comparison of the bioactive secondary metabolites from the scale insect pathogens, anamorph *Paecilomyces cinnamomeus*, and teleomorph *Torrubiella luteorostrata*. J Antibiot 60:577–581

Ishiyama A, Otoguro K, Iwatsuki M, Namatame M, Nishihara A, Nonaka K, Kinoshita Y, Takahashi Y, Masuma R, shiomi K, Yamada H, Omura S (2009) *In vitro and in vivo* antitrypanasomal activities of three peptide antibiotics: leucinostatin A and B, alamethicin I and tsushimycin. J Antibiot 62:303–308

Jegorov A, Paizs B, Zabka M, Kuzma M, Havlièek V, Giannakopulos AE, Derrick PJ (2003) Profiling of cyclic hexadepsipeptides roseotoxins synthesised in vitro: a combined tandem mass spectrometry and quantum chemical study. Eur J Mass Spectrom 9:105–116

Jegorov A, Paizs B, Kuzma M, Zabka M, Landa Z, Sulc M, Barrow MP, Havlicek V (2004) Extraribosomal cyclic tetradepsipeptides beauverolides: profiling and modeling the fragmentation pathways. J Mass Spectrom 39:949–969

Kershaw M, Moorhouse ER, Bateman R; Reynolds SE, Charnley AK (1999) The role of destruxins in the pathogenicity of *Metarhizium anisopliae* for three species of insect. J Invert Pathol 74:213–223

Khachatourians GG, Qazi SS (2008) Entomopathogenic fungi: biochemistry and molecular biology. In: Brakhage AA, Zipfel PF (eds) Human and animal relationship, 2nd edn. Mycota VI. Springer, Berlin Heidelberg New York, pp 33–61

Köpcke B, Johansson M, Sterner O, Anke H (2002a) Biologically active secondary metabolites from the

ascomycete A111-95. 1. Production, isolation and biological activities. J Antibiot 55:36–40

Köpcke B, Weber RWS, Anke H (2002b) Galiellalactone and its biogenetic precursors as chemotaxonomic markers of the Sacrosomataceae (Ascomyceta). Phytochemistry 60:709–714

Krasnoff SB, Reategui RF, Wagenaar MM, Gloer JB, Gibson DM (2005) Cicadapeptins I and II: new Aib-containing peptides from the entomopathogenic fungus *Cordyceps heteropoda*. J Nat Prod 68:50–55

Krasnoff SB, Keresztes I, Gillilan RE, Szebenyi DME, Donzelli BGG, Vhurchill ACL, Gibson DM (2007) Serinocyclins A and B, cyclic heptapeptides from *Metarhizium anisopliae*. J Nat Prod 70:1919–1924

Kumazawa S, Kanda M, Utagawa M, Chiba N, Ohtani H, Mikawa T (2003) MK7924, a novel metabolite with nematocidal activity from *Coronophora gregaria*. J Antibiot 56:652–654

Kusano M, Koshino H, Uzawa J, Fujioka S, Kawano T, Kimura Y (2000) Nematocidal alkaloids and related compounds produced by the fungus *Penicllium* cf. *simplicissium*. Biosci Biotechnol Biochem 64:2559–2568

Kuzma M, Jegorov A, Kacer P, Havlicek V (2001) Sequencing of new beauverolides by high-performance liquid chromatography and mass spectrometry. J Mass Spectrometry 36:1108–1115

Laser H, von Boberfeld WO, Wöhler K, Wolf D (2003) Effects of the botanical composition and weather conditions on mycotoxins in winter forage from grassland. Mycotoxicol Res 19:87–90

Leistner E, Steiner U (2009) Fungal origin of ergoline alkaloids present in dicotyledonous plants (Convolvulaceae) In: Anke T and Weber D (eds) Physiology and genetics**.** Mycota XV. Springer, Berlin Heidelberg New York, pp 197–208

Liermann JC, Kolshorn H, Antelo L, Hof C, Anke H, Opatz T (2009) Omphalotins E-I, five oxidatively modified nematicidal cyclopeptides from *Omphalotus olearius*. Eur J Org Chem 2009:1256–1262

Lira SP, Vita-Marques AM, Seleghim MHR, Bugni TS, LaBarbera DV, Sette LD, Sponchiado SRP, Ireland CM, Berlinck RGS (2006) New destruxins from the marine-derived fungus *Beauveria felina*. J Antibiot 59:553–563

López-Gresa MP, González MC, Ciavatta L, Ayala I, Moya P, Primo J; (2006) Insecticidal activity of paraherquamides, including paraherquamide H and paraherquamide I, two new alkaloids isolated from *Penicillium cluniae*. J Agric Food Chem 54:2921–2925

Matsuda D, Namatame I, Tomoda H, Kobayashi S, Zocher R, Kleinkauf H, Omura S (2004) New beauverolides produced by amino acid-supplemented fermentation of *Beauveria* sp. FO-6979. J Antibiot 57:1–9

Mayer A, Kilian M, Hoster B, Sterner O, Anke H (1999) *In vitro* and *in vivo* nematicidal activities of the cyclic dodecapeptide omphalotin A. Pest Sci 55:27–30

Meyer SLF, Huettel RN, Zhong X, Humber RA, Juba J, Nitao JK (2004) Activity of fungal culture filtrates against soybean cyst nematode and root-knot nematode egg hatch and juvenile motility. Nematology 6:23–32

Miyado S, Kawasaki H, Aoyagi K, Yaguchi T, Okada T, Sugiyama J (2000) Taxonomic position of the fungus producing the anthelmintic PF1022 based on the 18S rRNA gene base sequence. Nippon Kingakukai Kaiho 41:183–188

Mohanty SS, Prakash S (2008) Effects of culture media on larvicidal property of secondary metabolites of mosquito pathogenic fungus *Chrysosporium lobatum* (Moniliales: Moniliaceae) Acta Trop 109:50–54

Monma S, Sunazuka T, Nagai K, Arai T, Shiomi K, Matsui R, Mura S (2006) Verticilide: elucidation of absolute configuration and total synthesis. Org Lett 8:5601–5604

Muroi MN, Kaneko N, Suzuki K, Nishio T, Oku T, Sato T, Takatsuki A (1996) Efrapeptins block exocytic but not endocytic trafficking of proteins. Biochim Biophys Res Commun 227:800–809

Nagamitsu T, Takano D, Shiomi K, Ui H, Yamaguchi Y, Masuma R, Harigaya Y, Kuwajima I, Omura S (2003) Total synthesis of nafuredin-γ, a γ-lactone related to nafuredin with selective activity against NADH-fumarate reductase. Tetrahedron Lett 44:6441–6444

Nagaraj G, Uma MV, Shivayogi MS, Balaram H (2001) Antimalarial activities of peptide antibiotics isolated from fungi. Antimicrob Agents Chemother 45:145–149

Nakahara S, Kusano M, Fujioka S, Shimada A, Kimura Y (2004) Penipratynolene, a novel nematicide from *Penicillium bilaiae* Chalabuda. Biosci Biotechnol Biochem 68:257–259

Namatame I, Zomoda H, Ishibashi S, Omura S (2004) Antiatherogenic activity of fungal beauverolides, inhibitors of lipid droplet accumulation in macrophages. Proc Natl Acad Sci USA 101:737–742

Nilanonta C, Isaka M, Chanphen R, Thongorn N, Tanticharoen M, Thebtaranonth Y (2003) Unusual enniatins produced by the insect pathogenic fungus *Verticillium hemipterigenum*: isolation and studies on precursor-directed biosynthesis. Tetrahedron 59:1015–1020

Ohshiro T, Rudel LL, Omura S, Tomoda H (2007) Selectivity of microbial acyl-CoA:cholesterol acyltransferase inhibitors towards isoenzymes. J Antibiot 60:43–51

Omura S, Miyadera H, Ui H, Shiomi K, Yamaguchi Y, Masuma R, Nagamitsu T, Takano D, Sunazuka T, Harder A, Kölbl H, Namikoshi M, Miyoshi H, Sakamoto K, Kita K (2001) An anthelmintic compound, nafuredin, shows selelctive inhibition of complex I in helminth mitochondria. Proc Natl Acad Sci USA 98:60–62

Ondeyka JG, Dahl-Roshak AM, Tkacz JS, Zink DL, Zakson-Aiken M, shoop WL, Goetz MA, Singh SB (2002) Nodulisporic acid B, B1, and B2: A series of 1′-deoxy-nodulisporic acids from *Nodulisporium* sp. Bioorg Med Chem Lett 12:2941–2944

Ondeyka JG, Byrne K, Vesey D, Zink DL, Shoop WL, Goetz MA, Singh SB (2003) Nodulisporic acids C, C_1, and C_2: a series of D-ring-opened nodulisporic acids from the fungus *Nodulisporium* sp. J Nat Prod 66:121–124

Panaccione DC, Cipoletti JR, Sedlock AB, Blemings KP, Schradl CL, Machado C, Seidel GE (2006) Effects of ergot alkaloids on food preference and satiety in rabbits, as assessed with gene-knockout endophytes

in perennial ryegrass *(Lolium perenne)*. J Agric Food Chem 54:4582–4587

Park JO, Hargreaves JR, McConville EJ, Stirling GR, Ghisalberti EL, Sivasithamparam (2004) Production of leucinostatins and nematicidal activity of Australian isolates of *Paecilomyces lilacinus* (Thom) Samson. Lett Appl Microbiol 38:271–276

Pedras MSC, Zaharia LI, Ward DE (2002) The destruxins: synthesis, biosynthesis, biotransformation and biological activity. Phytochemistry 59:579–596

Rouxel T, Chupeau Y, Fritz R, Kollmann A, Bousquet J-F (1988) Biological effects of sirodesmin PL, a phytotoxin produced by *Leptosphaeria maculans*. Plant Sci 57:45–53

Saeger B, Schmitt-Wrede HP, Dehnhardt M, Benten WP, Krucken J, Harder A, Samson-Himmelstjerna G von, Wiegand H, Wunderlich F (2001) Latrophilin-like receptor from the parasitic nematode *Haemonchus contortus* as target for the anthelmintic depsipeptide PF1022A. FASEB J 15:1332–1334

Samson-Himmelstjerna G von, Harder A, Sangster NC, Coles GC (2005) Efficacy of two cyclooctadepsipeptides, PF022A and emodepside, against anthelmintic-resistant nematodes in sheep and cattle. Parasitology 130:343–347

Sarabia F, Chammaa S, Sánchez Ruiz A, Martín Ortiz L, López Herrera FJ (2004) Chemistry and biology of cyclic depsipeptides of medicinal and biological interest. Curr Med Chem 11:1309–1332

Sasaki T, Takagi M, Yaguchi T, Miyado S, Okada T, Koyama M (1992) A new anthelmintic cyclodepsipeptide, PF1022. J Antibiot 45:692–697

Schardl CL, Leuchtmann A, Spiering MJ (2004) Symbioses of grasses with seedborne fungal endophytes. Annu Rev Plant Biol 55:315–340

Scherkenbeck J, Jeschke P, Harder A (2002) PF1022A and related cyclodepsipeptides – a novel class of anthelmintics. Curr Top Med Chem 7:759–777

Schwarz M, Köpcke B, Weber RWS, Sterner O, Anke H (2004) 3-Hydroxypropionic acid a nematicidal principle of endophytic fungi. Phytochemistry 65:2239–2245

Seto Y, Takahasi K, Matsuura H, Kogami Y, Yada H, Yoshihara T, Nabeta K (2007) Novel cyclic peptide, epichlicin, from the endophytic fungus, *Epichloe typhina*. Biosci Biotechnol Biochem 71:1470–1475

Shiomi K, Ui H, Suzuki H, Hatano H, Nagamitsu T, Takano D, Miyadera H, Yamashita T, Kita K, Miyoshi H, Harder A, Tomoda H, Ōmura S (2005) A γ-lactone from nafuredin, nafuredin-γ, also inhibits helminth complex I. J Antibiot 58:50–55

Shoop WL, Gregory LM, Zaksonaiken M, Michael BF, Haines HW, Ondeyka JG, Meinke RT, Schmatz DM (2001) Systemic efficacy of nodulisporic acid against fleas on dogs. J Parasitol 87:419–423

Singh SB, Zink DL, Liesch JM, Mosley RT, Dombrowski AW, Bills GF, Darkin-Rattray SJ, Schmatz DM, Goetz MA (2002) Structure and chemistry of apicidins, a class of novel cyclic tetrapeptides without a terminal α-keto epoxide as inhibitors of histone deacetylase with potent antiprotozoal activities. J Org Chem 67:815–825

Singh SB, Ondeyka JG, Jayasuriya H, Zink DL, Ha SN, Dahl-Roshak A, Greene J, Kim JA, Smith MM, Shoop W, Tkacz JS (2004) Nodulisporic acids D-F: structure, biological activities, and biogenetic relationships. J Nat Prod 67:1496–1506

Skrobek A, Butt TM (2005) Toxicity testing of destruxins and crude extracts from the insect-pathogenic fungus *Metarhizium anisopliae*. FEMS Microbiol Lett 251:23–28

Smith AB, Cui H (2003) Indole-diterpene synthetic studies: total synthesis of (-)-21-isopentenylpaxilline. Helv Chim Acta 86:3908–3938

Supothina S, Isaka M, Kirtikara K, Tanticharoen M, Thebtaranonth Y. (2004) Enniatin production by the entomopathogenic fungus *Verticillium hemipterigenum* BCC 1449. J Antibiot 57:732–738

Tang CY, Chen YW, Jow GM, Chou CJ, Jeng CJ (2005) Beauvericin activates Ca^{2+-}activated Cl^{-} currents and induces cell deaths in *Xenopus* oocytes via influx of extracellular Ca^{2+}. Chem Res Toxicol 18:825–833

Trost BM, Cramer N, Bernsmann H (2007) Concise total synthesis of (±)-marcfortine B. J Am Chem Soc 129:3086–3087

Uchida R, Imasato R, Yamaguchi Y, Masuma R, Shiomi K, Tomoda H, Omura S (2006a) Yaequinolones, new insecticidal antibiotics produced by *Penicillium* sp. FKI-2140. I. Taxonomy, fermentation, isolation and biological activities. J Antibiot 59:646–651

Uchida R, Imasato R, Tomoda H, Omura S (2006b) Yaequinolones, new insecticidal antibiotics produced by *Penicillium* sp. FKI-2140. II. Structural elucidations. J Antibiot 59:652–658

Vey A, Matha V, Dumas C (2002) Effects of the peptide mycotoxin destruxin E on insect haemocytes and on dynamics and efficiency of the multicellular immune reaction. J Invert Pathol 80:177–187

Whyte AC, Gloer JB, Wicklow DT, Dowd PF (1996) Sclerotiamide: a new member of the paraherquamide class with potent antiinsectan activity from the sclerotia of *Aspergillus sclerotiorum*. J Nat Prod 59:1093–1095

Williams RM (2002) Total synthesis and biosynthesis of the paraherquamides: an intriguing story of the biological Diels–Alder construction. Chem Pharm Bull 50:711–740

Williams RM, Cao J, Tsujishima H, Cox RJ (2003) Asymmetric, stereocontrolled total synthesis of paraherquamide A. J Am Chem Soc 125:12172–12178

Yasiu H, Hirai K, Yamamoto S, Takao K, Tadano K (2006) Total syntheses of (+)-1893B and its three diastereomers and evaluation of their biological activities. J Antibiot 59:456–463

Zimmermann G (2007a) Review on safety of the entomopathogenic fungi *Beauveria bassiana* and *Beauveria brongniartii*. Biocontrol Sci Technol 17:553–596

Zimmermann G (2007b) Review on safety of the entomopathogenic fungus *Metarhizium anisopliae*. Biocontrol Sci Technol 17:879–920