13 Cyclic Peptides and Depsipeptides from Fungi

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I. Introduction

Cyclic peptides and depsipeptides are widely distributed in nature. They are found in plants (Gournelis et al. 1998; Tan and Zhou 2006), sponges and other lower sea animals (Bertram and Pattenden 2007), cyanobacteria (Welker and von Döhren 2006), bacteria and fungi alike and their bioactivities range from antimicrobial, insecticidal, nematicidal, antiviral, hepatotoxic, cytotoxic/cytostatic to immunosuppressive and other pharmacological properties (Kleinkauf and von Döhren 1997; Pomilio et al. 2006).

Some of the peptides and depsipeptides produced by fungi have gained entrance into the pharmaceutical market, like cyclosporins (Kürnsteiner et al. 2002), ergopeptides (Keller and Tudzynski 2002), penicillins (Demain and Elander 1999) and cephalosporins (Schmidt 2002), or are currently undergoing clinical trials, like the candines, promising antifungal drugs against aspergillosis and candidiasis (Denning 2002; Johnson and Perfect 2003; Pasqualotto and Denning 2008). Caspofungin derived from pneumocandin and micafungin derived from FR901379 are examples of those novel drugs targeting fungal cell wall synthesis, e.g. biosynthesis of 1,3-β-glucan (Odds et al. 2003; Butler 2004). For a recent review, see Hashimoto (2009). Emodepsin, a semi-synthetic depsipeptide, is used in veterinary medicine against helminths (von Samson-Himmelstjerna et al. 2005). The drug is derived from PF1022A, a metabolite of an endophytic fungus from *Camellia japonica* (Sasaki et al. 1992; Scherkenbeck et al. 2002). As these groups of compounds are well covered in the literature, they are not addressed here in detail.

The biosynthesis of cyclic peptides and depsipeptides has attracted the interest of biochemists since the mid1960s (Gevers et al. 1968). Today, the focus has shifted from enzymology to genetics, e.g. the biosynthetic genes and their regulation. Therefore Chap. 15 is dedicated to this topic, to which the reader is referred.

A special group of cyclopeptides are the diketopiperazines, which consist of two amino acids linked by two peptide bonds. In the related epipolythiodioxopiperazines the 6-ring is bridged by one to four sulfur atoms. The structural diversity of diketopiperazines (more than 100 different compounds are known from fungi; Buckingham 2008) is matched by their biological activities. Recently published reviews are available (Cole and Schweikert 2003; Gardiner et al. 2005). Interestingly, functions in the producing organisms have been detected for some of these compounds, e.g. gliotoxin and related compounds play a role as virulence factors in invasive aspergillosis (Sugui et al. 2007) and coprogens in host invasion of plant-pathogenic fungi (Oide et al. 2006; Hof et al. 2007). The reported biological activities of gliotoxin are very broad and diverse. Antibacterial, antifungal, antiviral, amoebicidal and

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immunosuppressive properties have been described (see below). Most of these activities are based on interactions with essential thiol groups in proteins (Waring and Beaver 1996). Iron chelators like dimerumic acid, rhodotorulic acid, coprogen and its derivatives are involved in iron uptake (Winkelmann and Drechsler 1997; Renshaw et al. 2002; Antelo et al. 2006), while other siderophores, e.g. the hexapeptides ferrichrome or ferricrocin, in addition to iron transport or storage functions act as virulence factors in some human and plant pathogens similar to coprogens (Howard 1999; Haas et al. 2008).

The group of peptaibiotics, a constantly growing family of linear α-aminobutyric acid (Aib)-containing linear peptides has been enlarged by a small group of cyclic peptides also containing Aib, now called cyclopeptaibiotics. Whereas the linear group comprises more than 800 compounds, only nine cyclic compounds have been reported to date. These are seven tetrapeptides structurally related to chlamydocin (Degenkolb et al. 2008) and the scytalidamides, two heptapeptides containing Aib residues (Tan et al. 2003).

II. Occurrence of Cyclic Peptides and Depsipeptides Within the Kingdom Eumycota (True Fungi)

A. Siderophores

The occurrence and distribution of siderophores among the taxonomic groups of fungi is very well covered by the reviews of Renshaw et al. (2002) and Haas et al. (2008). Zygomycetes very rarely produce cyclic peptide or depsipeptide siderophores. Up to now the hexapeptide ferrichrysin seems to be the only example. It is produced by *Cunninghamella blakesleeana* (Patil et al. 1995). The production of diketopiperazine and hexapeptide siderophores is common among asco- and basidiomycetes (Renshaw et al. 2002). The fact that members of some orders have not yet been reported to produce siderophores reflects a lack of investigation rather than presence. There are a few fungi, however, which do not produce siderophores: the ascomycetous yeasts *Saccharomyces cerevisiae* and *Candida albicans* or *Geotrichum candidum* and the basidiomycete *Cryptococcus neoformans* (teleomorph *Filobasidiella*; Howard 1999; Haas et al. 2008). The investigation of basidiomycetes is difficult because iron-free media, which upregulate the biosynthesis of siderophores, often hardly support mycelial growth, requiring incubation times of eight to ten weeks (Welzel et al. 2005). In contrast, modern analytical techniques like HPLC-MS^n are sensitive enough to allow the detection and characterization of very small amounts (μg/l of culture). In addition, as more fungal genomes and NRPS genes and products become available, it is clear that siderophores and iron metabolism are important virulence determinants (Eichhorn et al. 2006; Oide et al. 2006; Haas et al. 2008).

It is remarkable that extracellular and intracellular siderophores are not identical and that the synthesis of intracellular siderophores is often not iron-dependent.

As an example, most *Trichoderma* species excrete coprogen-type siderophores and ferricrocin for the capture and transport of iron and use palmitoylcoprogen located within the mycelia as storage compound. In *T. pseudokoningii* and *T. longibrachiatum* however, palmitoylcoprogen was not detected, but these two species excrete fusigen-type siderophores in addition to coprogen and fericrocin (Anke et al. 1991). *Magnaporthe grisea* uses intracellular ferricrocin for iron storage and under iron deprivation excretes four coprogen derivatives (Hof et al. 2007). In other plant-pathogenic fungi like *Fusarium graminearum*, *F. culmorum*, *F. pseudograminearum*, *Cochliobolus heterostrophus* and *Gibberella zeae* ferricrocin has also been reported as intracellular siderophore (Oide et al. 2007; Tobiasen et al. 2007). The situation in the human pathogen *Aspergillus fumigatus* is similar. Ferricrocin is located in the mycelia, a hydroxylated derivative in the conidia and triacetylfusigen is excreted (Schrettl et al. 2007).

The structures of several iron-free siderophores, e.g. rhodotorulic acid, 2-*N*-methylcoprogen, palmitoylcoprogen, ferricrocin and ferrichrome are given in Fig. 13.1.

B. Diketopiperazines

Simple diketopiperazines may be detected in fermentations of many fungi. Sometimes it is difficult to decide whether these are degradation products of proteins and peptides or synthesized de novo (Prasad 1995). In the future, this problem might be solved by molecular genetics, since the presence of the relevant biosynthetic genes can be

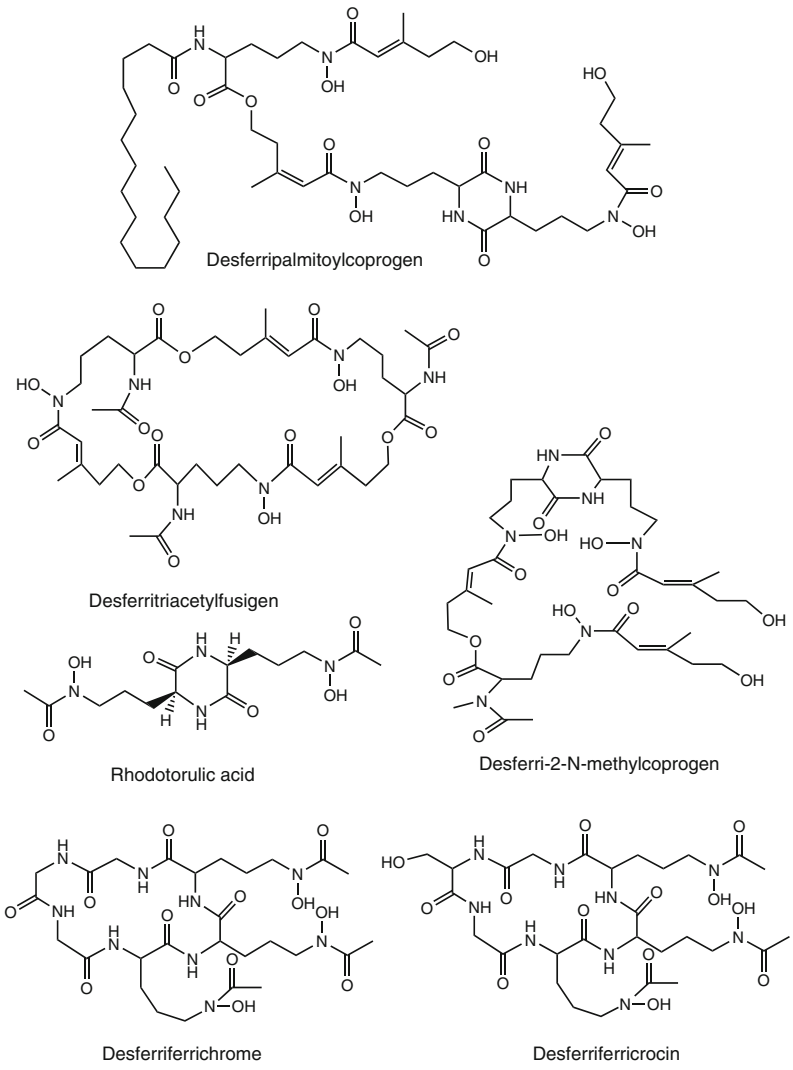

Fig. 13.1. Structures of some intracellular and extracellular siderophores produced by fungi

proof of de novo synthesis (Chap. 15). The recently demonstrated behavioral effects and occurrence in humans of cyclo(His-Pro) stimulated research on such compounds which are easily accessible by chemical synthesis. However, cyclo(His-Pro) has not yet been reported from fungi. This may be due to the fact that its bioactivities, e.g. inhibition of food intake and inhibition of prolactin secretion or modulation of pain perception (Prasad 1995) are not suited for a screening of microbial cultures. Usually these compounds are detected during the isolation of other metabolites and described as side-products. A recent example is L-alanyl-L-tryptophan anhydride isolated together with golmaenone, a radical scavenger compound, and neoechinulin from an marine *Aspergillus* species (Li et al. 2004). As in many other cases, the simple alkaloid is the biogenetic precursor of the other two compounds. With antimicrobial, cytotoxic, phytotoxic, insecticidal and other test systems which have been extensively used in screenings for bioactive natural products, simple diketopierazines are less frequently detected. One example is the fungistatic mactanamide from a marine *Aspergillus* species (Lorenz et al. 1998). Simple diketopiperazines have been described from hetero- and homobasidiomycetes, for example *Ustilago cynodontis*, *Entoloma haastii* and *Stereum hirsutum* (Turner and Aldridge 1983), ascomycetes like *Rosellinia necatrix*,

Claviceps species, *Eurotium* and *Emericella* species, *Leptosphaeria* species including their anamorphs, *Aspergillus*, *Phoma* and *Coniothyrium* species (Turner and Aldridge 1983; Cole and Schweikert 2003; Blunt et al. 2006).

Aspergillus and *Penicillium* species are very prolific producers of cyclic dipeptide-derived mycotoxins like fumitremorgins, verruculogens or roquefortine C, while sporidesmins, mycotoxins that cause facial eczema in grazing sheep, are produced by *Pithomyces chartarum* (Betina 1989). From several *Penicillium* species, mycelianamide, one of the very "old" diketopiperazines, has been known since 1931. This compound was detected during early screenings after the discovery of penicillin G. The recently described sulfur-containing gliovictin was obtained from an endophytic *Penicillium janczewskii* (Gunatilaka 2006) and diketopiperazine-derived rostratins from a marine *Exserohilium rostratum* (Tan et al. 2004). To the long list of *Penicillium* species producing diketopiperazines, *P. dipodomyis*, *P. nalgiovense*, *P. fellutanum* and *P. simplicissimum* were recently added (Lewis 2002).

Examples for structures of simple and complex diketopiperazines are found in Fig. 13.2.

From cultures of a number of fungi producing cyclic depsipeptides, e.g. *Beauveria bassiana*, dipeptides composed of the amino acids occurring in the depsipeptides have been

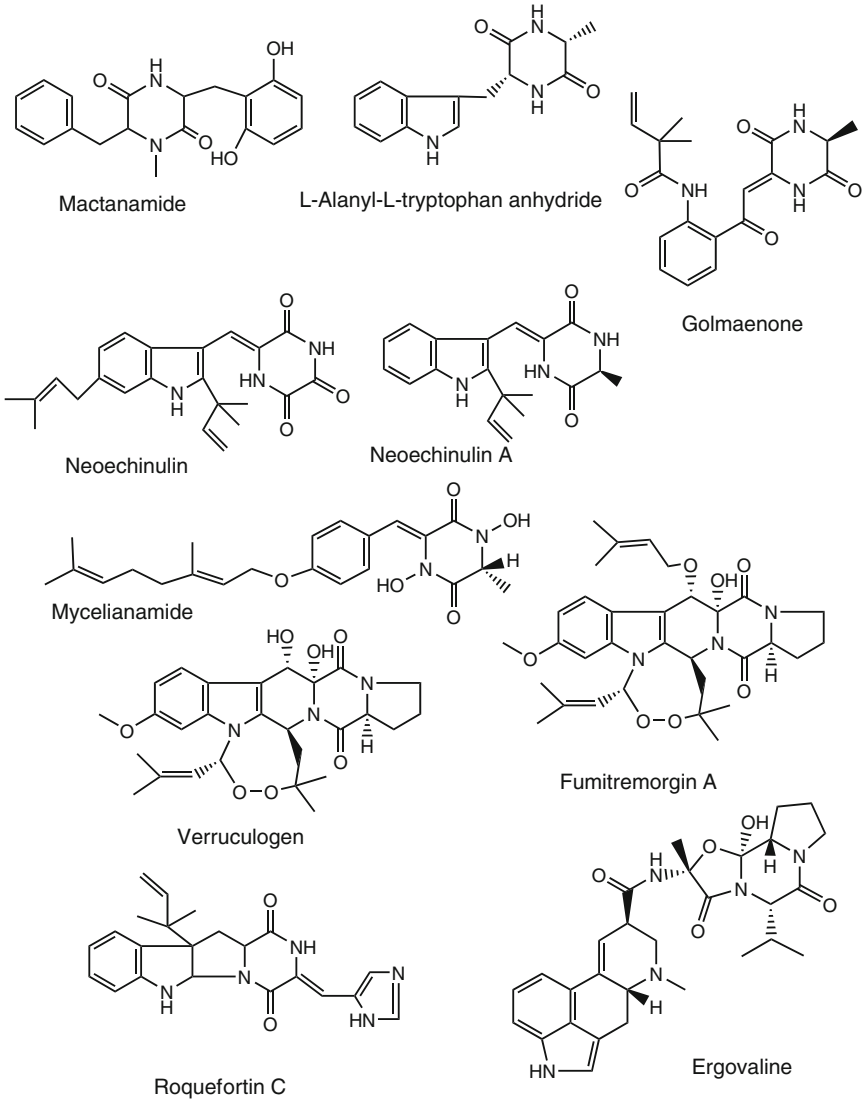

Fig. 13.2. Structures of some diketopiperazines

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* produce dipeptides. An unidentified endophyte from mangrove leaf produces two cyclic depsipeptides and three diketopiperazines (Huang et al. 2007). The role of the compounds, dipeptides and depsipeptides, in insect and plant-pathogenicity has not yet been completely elucidated. As molecular tools become more easily available, this question might be addressed or even answered in the near future, especially since the elucidation of the ecological function of secondary metabolites for the producers becomes more interesting (see below).

Epipolythiopiperazines with more than 60 members, gliotoxin being the most prominent, are widely distributed in nature. Their producers are mainly found among the ascomycete genera *Aspergillus*, *Penicillium*, *Gliocladium*, *Verticillium*, *Chaetominum*, *Emericella*, *Acrostalagmus* (syn. *Verticillium*), *Pithomyces*, *Bionectria*, *Leptosphaeria*, *Hyalodendron*, *Trichoderma*, *Sirodesmium* (syn. *Coniosporium), Epicoccum, Arachniotus* and *Pseudallescheria* (Turner and Aldridge 1983; Betina 1989; Takahashi et al. 1994; Gardiner at al. 2005; Li et al. 2006; Zheng et al. 2007). There is one report on the occurrence of an epipolythiopiperazine in lichens, e.g. *Xanthoparmelia scabrosa* (Ernst-Russell et al. 1999). As is true for many lichen metabolites, it may be also in this case the ascomycetous fungal

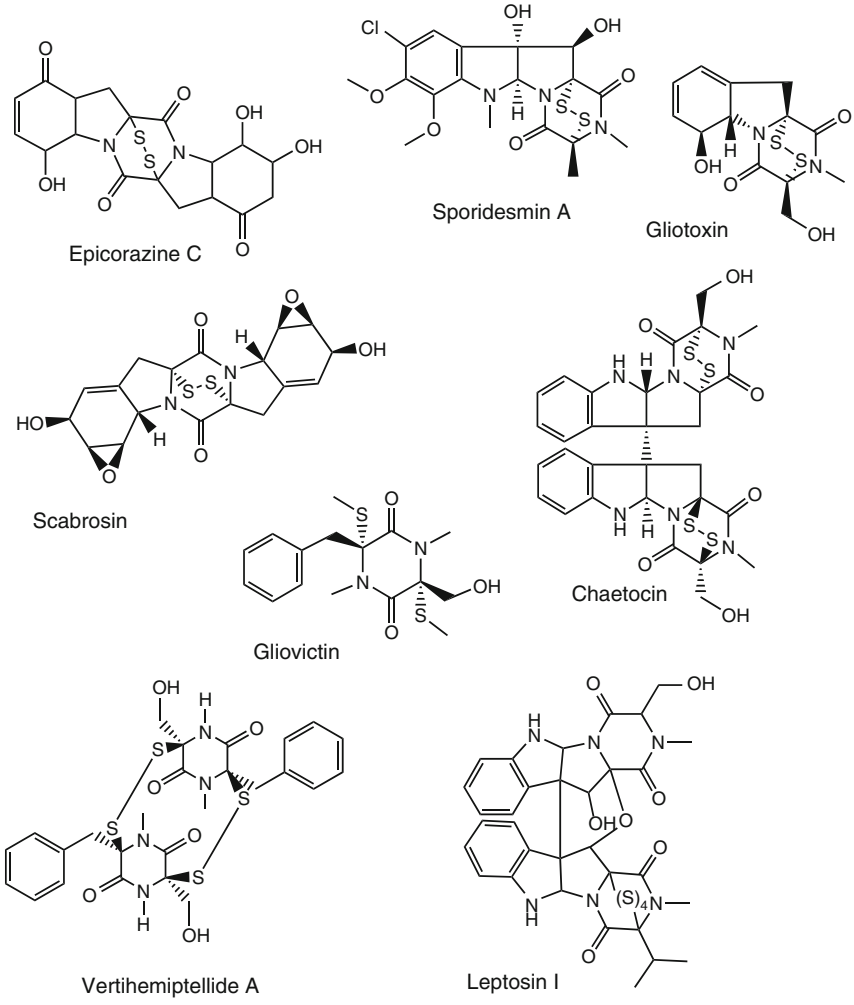

Fig. 13.3. Structures of some epipolythiopiperazines

partner which is responsible for the production of scabrosin. The production of epicorazine C by *Stereum hirsutum*, a basidiomycete, seems a bit questionable since related epicorazines are produced by *Epicoccum nigrum* and *E. purpurascens* (Kleinwachter et al. 2001). Overlaps between metabolites from basidiomycetes and ascomycetes are fairly rare but do occur occasionally. Other examples may be beauvericin and chlamydocin (see below). The structures of gliotoxin, epicorazines, scabrosin, vertihemiptellide A and other epipolythiopiperazines are given in Fig. 13.3.

C. Cyclic Peptides

Cyclic peptides are mainly produced by ascomycetes and their anamorphs. Among cyclic peptides, the immunomodulating cyclosporins constitute the largest group with 46 members. The producing organisms are found mainly in the ascomycetous families *Hypocreaceae* and *Clavivipitaceae* and their anamorphs *Tolypocladium inflatum*, *T. tundrense* and *T. terricola*. In addition, three soil-borne insect pathogens, *Neocosmospora vasinfecta*, *Acremonium luzulae*, a *Cyclindrotrichum* species, *Stachybotrys chartarum*,

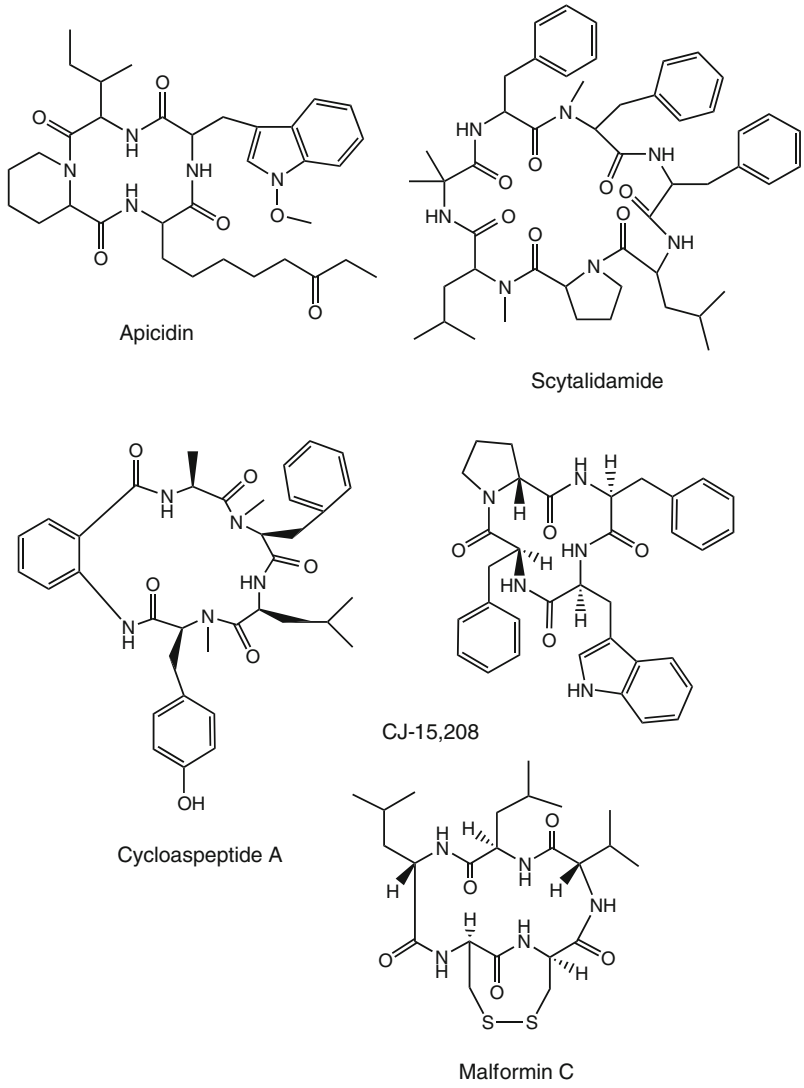

Fig. 13.4A. Structures of some simple cyclopeptides

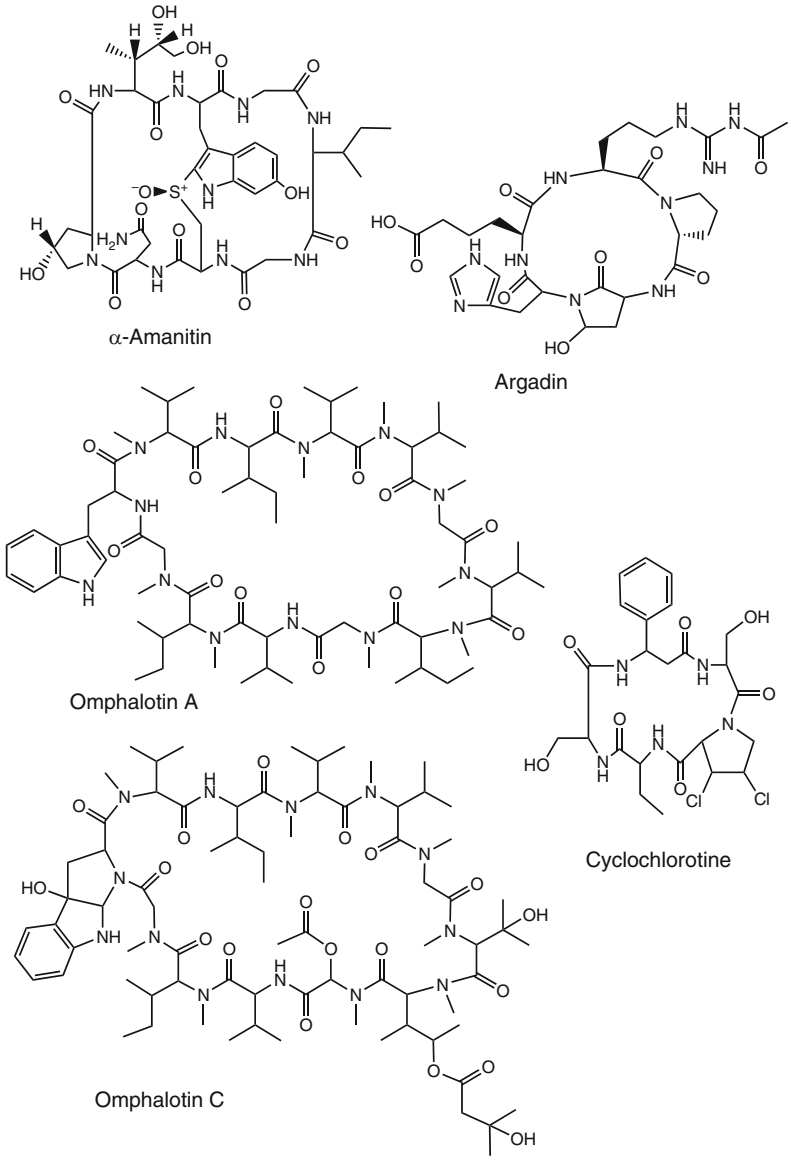

Fig. 13.4B. Structures of some complex cyclopeptides.

Trichoderma viride, a *Leptostroma* anamorph of *Hypoderma eucalyptii*, *Chaunopycnis alba* and an unidentified mycelium sterilium have been reported to produce cyclosporins (Matha et al. 1992; Traber and Dreyfuss 1996). The structure of cyclosporin A is found in Fig. 13.4C. Figure. 13.4A shows examples of simpler cyclospeptides.

The malformins, a group of nine phytotoxic compounds, are only found within the *Aspergillus niger* group (Kobbe et al. 1977). Some authors classify the compounds as mycotoxins even so they are rarely found in food or feed stuff.

The antifungal echinocandins comprising different compounds (aculeacin A, echinocandin B, pneumocandins, mulundocandins, FR901379, WF11899A, B, C, FR227673, FR190293, etc.) have been reported from several Aspergilli, *Coleophoma empetri*, *C. crateriformis*, *Chalara* species, *Tolypocladium parasiticum* and *Zalerion arboricola* (Iwamoto et al. 1994b; Anke and Erkel 2002; Denning 2002; Kanasaki et al. 2006a, b, c,).

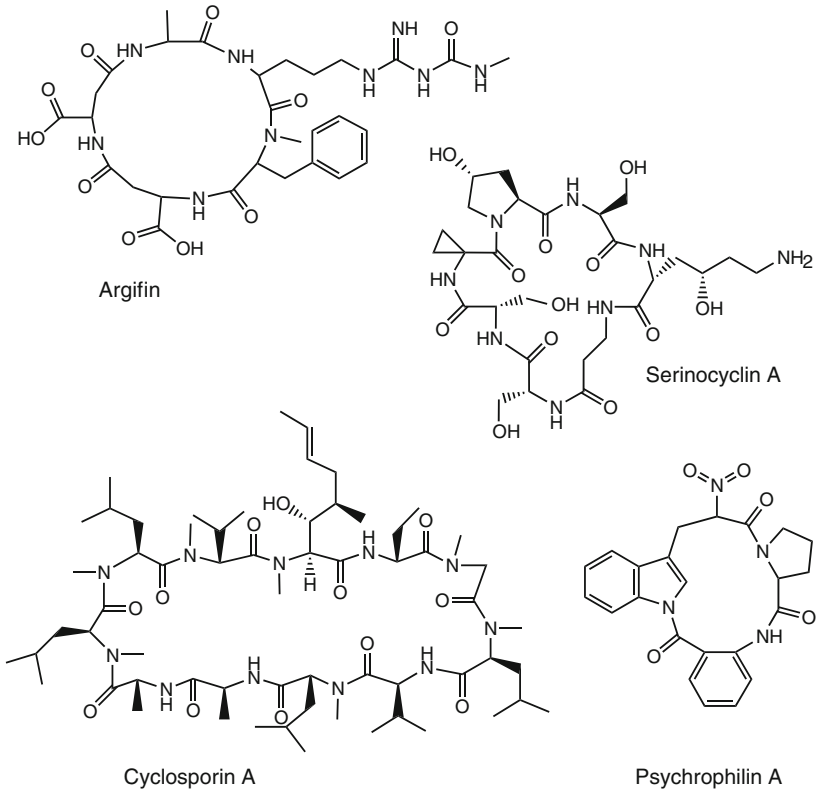

Fig. 13.4C. Structures of other complex cyclopeptides

The *Zalerion* strain producing echinocandin B was later reclassified as *Glarea lozoyensis*, a new anamorph genus and species within the Leotiales (Bills et al. 1999). The fungus producing arborcandins (Ohyama et al. 2000), has not been identified.

The structures of some of these compounds can be found in Fig. 13.5.

Producers of various cyclic peptides are found in many other families and genera, for example *Diheterospora*, *Gliocladium*, *Cylindrocarpon*, *Clonostachys*, *Cochliobolus* and *Fusarium* (Lewis 2002; Adachi et al. 2005; Weber et al. 2006; Degenkolb et al. 2008).

As endophytic fungi have recently come into focus as producers of bioactive natural compounds, it is not astonishing that also novel cyclic peptides have been reported from these fungi.

A pentapeptide was isolated from an unidentified endophyte from the seed of *Avicinnia marina* (Gunatilaka 2006), other cyclopeptides from endophytic *Fusarium* species (Shiono et al. 2007), *Epichloe typhina* (Seto et al. 2007) or endophyte "2221" from *Castaniopsis fissa* (Yin et al. 2005). More than 450 cyclic peptides are known from plants (Tan and Zhou 2006); some of these actually may be produced by endophytic fungi in planta.

In recent years, marine habitats have drawn much interest as ecological niches for producers of novel bioactive metabolites. The unguisins were isolated from a marine-derived strain of *Emericella unguis* (Malstrom 2002). Among cyclic peptides from obligate marine ascomycetes are the highly cytotoxic trapoxin A produced by *Corollospora intermedia* (Daferner 2000) or scytalidamides from a *Scytalidium* species from a marine alga (Tan et al. 2003). JM47, structurally related to HC-toxins and trapoxin, was isolated together with enniatin from a marine-derived *Fusarium* species (Jiang et al. 2002). Trapoxins are also known from terrestrial fungi, e.g. *Helicoma ambiens*, the anamorph of *Thaxteriella pezicula* (Itazaki et al. 1990) and structurally related metabolites have been described from the phytopathogenic *Cyclindrocladium scorparium* (teleomorph *Calonectria morganii*) and *Cochliobolus carbonum* (Degenkolb et al. 2008).

For structures see Fig. 13.6.

The only cyclopeptides, besides the siderophores, known from *submerged cultures* of basi-

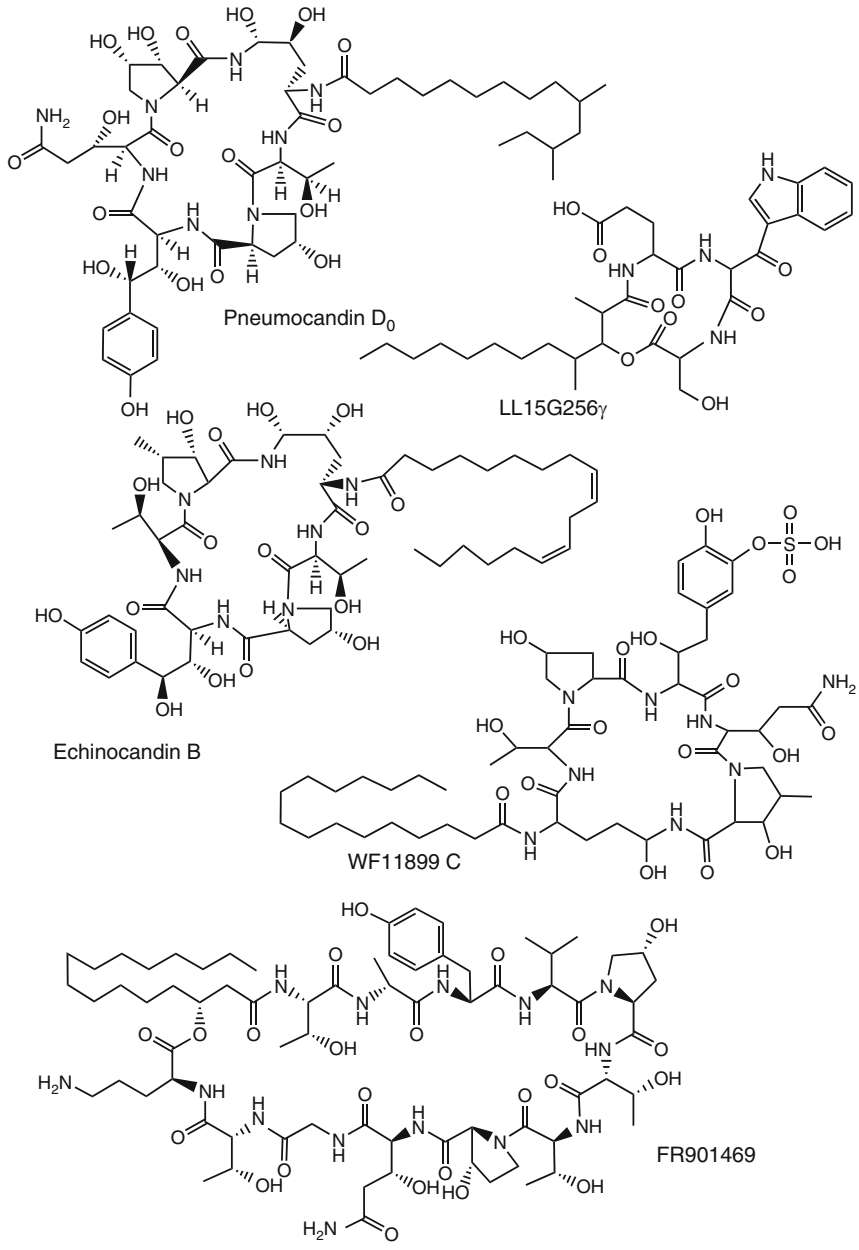

Fig. 13.5. Structures of some β-1,3-glucan synthase inhibitors

diomycetes are the omphalotins from *Omphalotus olearius* (Büchel et al. 1998a,b), amanitins from *Amanita exitialis* (Zhang et al. 2005) and chlamydocins from a *Peniophora* strain isolated from soil (Tani et al. 2001). The chlamydocins are tetrapeptides with Aib and an unusual amino acid. Most of these are produced by ascomycetes, e.g. *Diheterospora chlamyydosporia* (Closse and Huguenin 1974) and *V. coccosporum* (Gupta et al. 1994). Interestingly, the omphalotins produced by a monokaryotic strain differ from those found in the dikaryotic parental strain (Liermann et al. 2009). However, all *O. olearius* strains irrespective of their geographical origin produce omphalotin derivatives (Anke et al., unpublished data). In fruiting bodies omphalotins could not

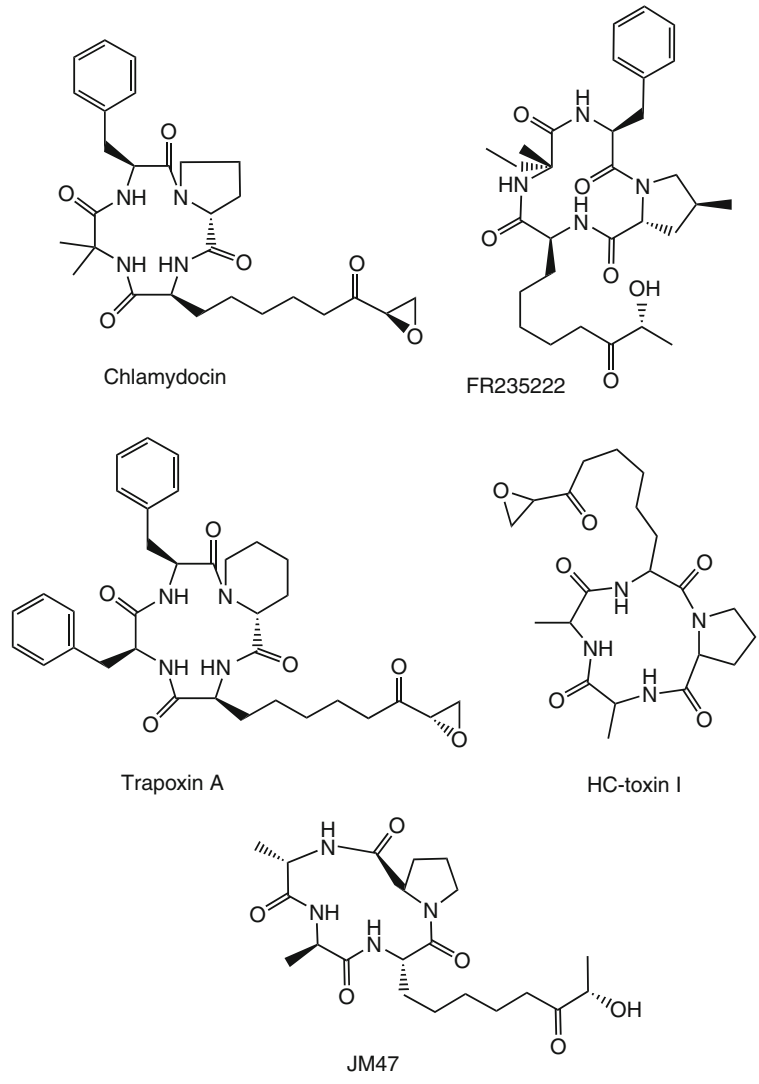

Fig. 13.6. Structures of some histone deacetylase inhibitors

be detected, contrary to *Amanita exitialis* carpophores which contained tenfold more α- and β-amanitin as compared to the slow growing mycelial cultures (Zhang et al. 2005). For recent surveys of *Amanita* toxins from fruiting bodies see Li and Oberlies (2005), Liu (2005) and Pomilio et al. (2006). Figure 13.4B shows the structures of omphalotins and α-amanitin.

D. Cyclic Depsipeptides

Most depsipeptides are metabolites from ascomycetes and their anamorphs. They are widespread in phytopathogens (e.g. *Cochliobolus* with anamorphs *Helminthosporium* and *Bipolaris*, *Calonectria* and its anamorph *Cyclindrocladium*, as well as *Fusarium* and *Alternaria*), insect pathogens (*Aschersonia*, *Beauveria*, *Cordyceps*, *Diheterospora*, *Fusarium*, *Hirsutella*, *Isaria*, *Metharizium*, *Paecilomyces*, *Verticillium*) and others (Zimmermann 2007a, b; Buckingham 2008). 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). Figure 13.7 gives the structures of some cyclodepsipeptides.

Up to now the pteratides (Fig. 13.7C) are the only depsipeptides reported from basidiomycetes, namely from the fruiting bodies of a

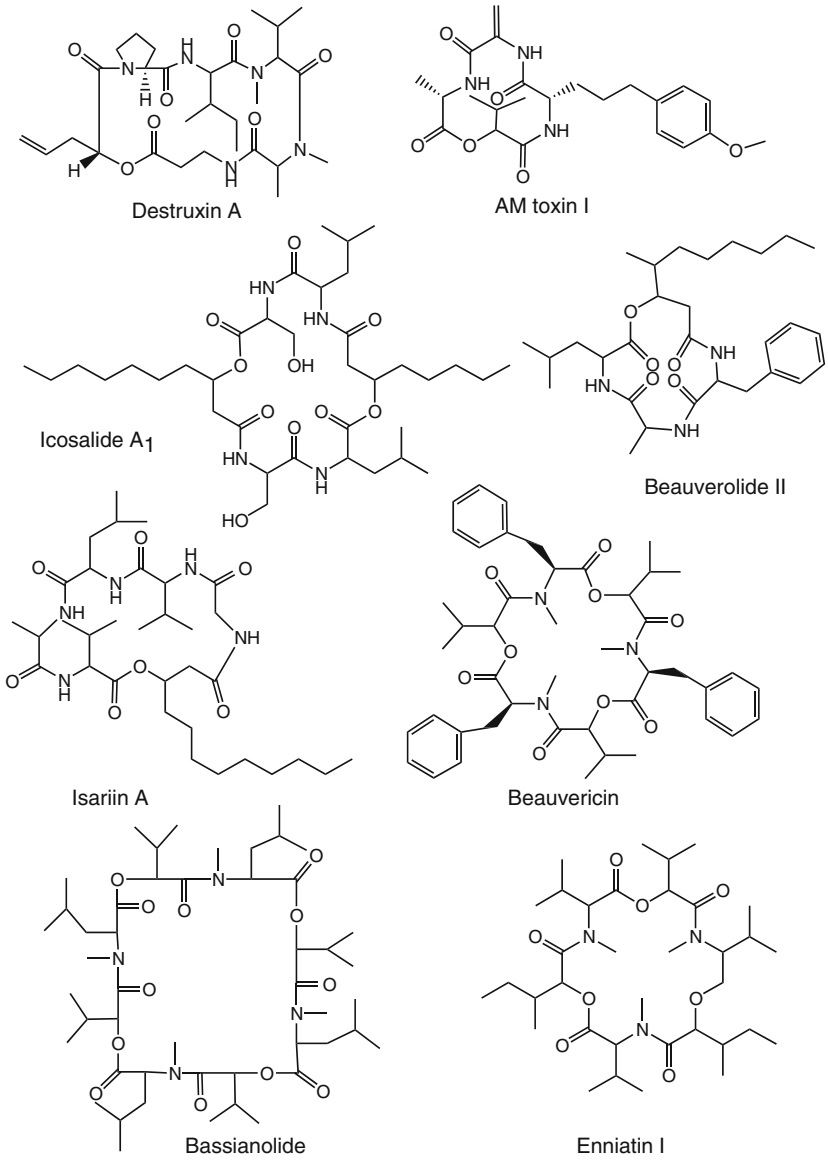

Fig. 13.7A. Structures of some simple cyclodepsipeptide

Pterula species (Chen et al. 2006). From zygomycetes none have been described. One report on the production of beauvericin by *Laetiporus sulfureus* (Badan et al. 1978) could not be confirmed by other groups. In our cultures from *L. sulfureus* from different locations we could only detect laetiporic acid and its derivatives (Davoli et al. 2005).

Since the review of Anke and Sterner (2002), additional producers of bioactive depsipeptides have been reported, for example marine-derived strains of *Beauveria fellina* (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* (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). Pseudodestruxins have been

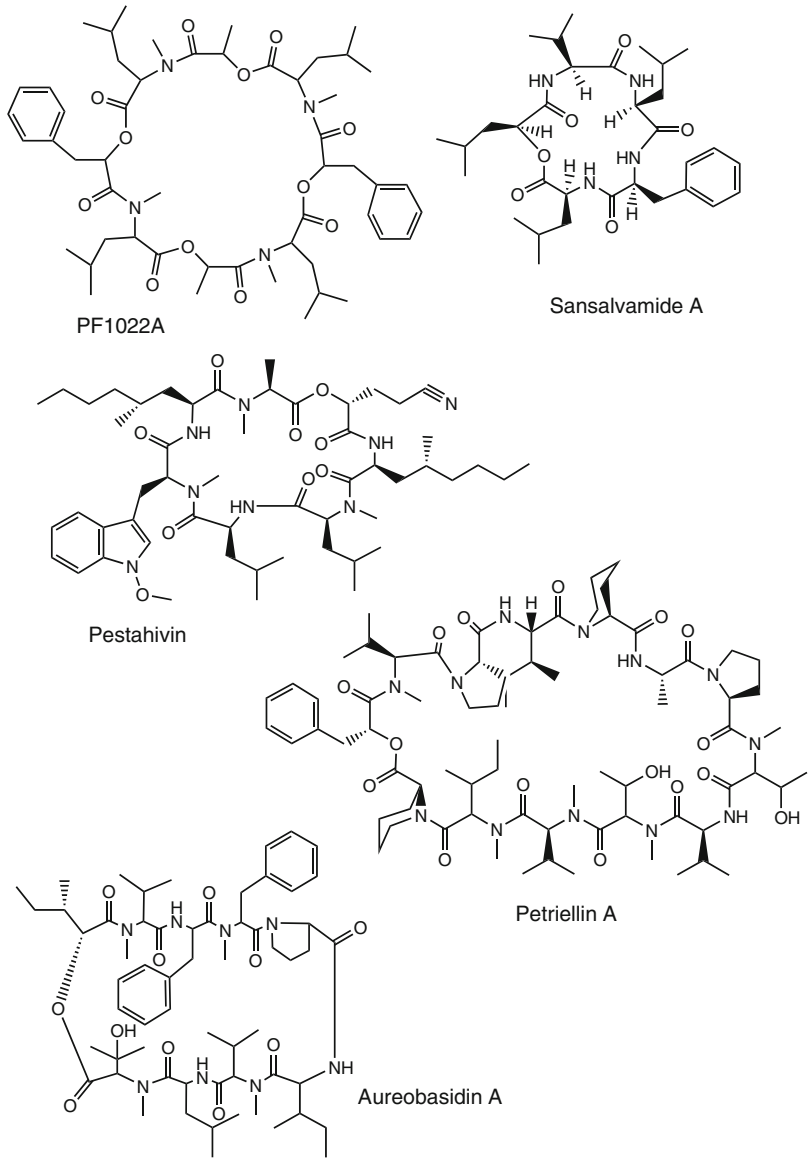

Fig. 13.7B. Structures of some complex cyclodepsipeptides

reported from *Nigrosabulum globosum* (Che et al. 2001) and reviews on destruxins and the producing organisms have been published by (Pedras et al. 2002) and Zimmermann (2007b).

The endophyte-producing PF1022A (and related anthelmintic cyclooctadepsipeptides) isolated from leaves of a camellia has been identified based on its 18S rRNA gene sequence as a member of the Xylariaceae close to *Xylaria polymorpha* and *Rosellinia necatrix* (Miyado et al. 2000).

One of the few aquatic fungi investigated for secondary metabolite production is *Clavariopsis aquatica* from which the antifungal clavariopsins A and B were isolated (Kaida et al. 2001).

Analogues of the lipopeptides with 1,3-β-glucan synthase inhibitory activity are the lipodepsipeptides FR901469 or LL15G256γ (see Fig. 13.5). The former is produced by an unidentified fungus, the latter (identical to arthrichitin from *Arthrinum*

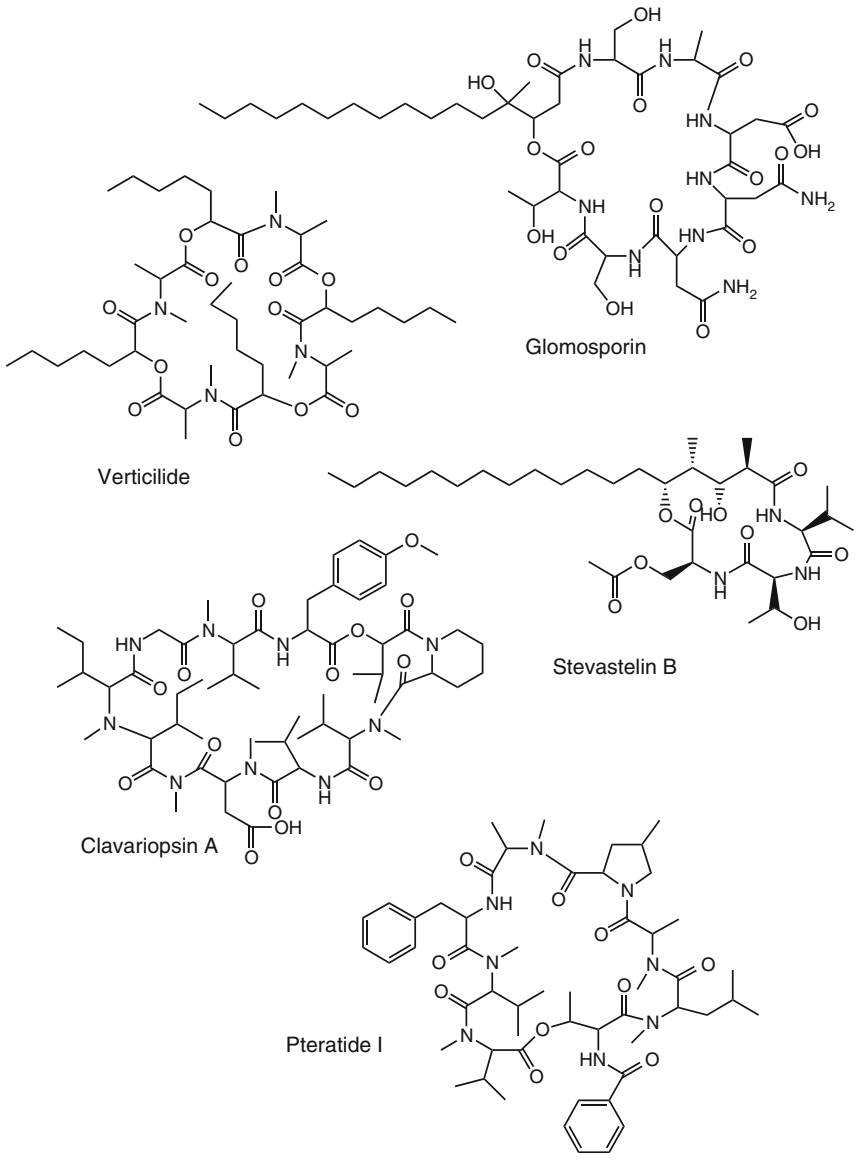

Fig. 13.7C. Structures of other complex cyclodepsipeptides

spaeospermum) by *Hypoxylon oceanicum* (Abbanat et al. 1998; Fujie et al. 2000).

III. Chemical and Biological Diversity of Cyclic Peptides and Depsipeptides

A. Diversity of Building Blocks

Cyclic peptides and depsipeptides constitute a class of natural compounds with an enormous structural diversity. This diversity is brought upon by the different building blocks in the ring: proteinogenic amino acids including their D-isomers, nonproteinogenic amino acids, branched or unbranched lipoamino acids and hydroxylated short-, medium- and long-chain fatty acids. The diversity of the building blocks can be deduced from Tables 13.1–13.3, which give a compilation of unusual building blocks (Table 13.1 unusual amino acids, Table 13.2 unusual fatty acids) and various modifications (Table 13.3).

Table 13.1. Diversity of amino acid building blocks in cyclic peptides and depsipeptides

Amino acid	Example	Figure	Reference
α-Aminoadipic acid	Argadin	13.4B	Arai et al. (2000)
Prolyl-homoserine	Argadin	13.4B	Arai et al. (2000)
β-Keto tryptophan	LL15G256γ	13.5	Abbanat et al. (1996)
Propylleucine	Pestahivin	13.7B	Hommel et al. (1996)
Dehydroalanine	AM-toxin I	13.7A	Ueno et al. (1975)
α-Amino-p-methoxyphenylvaleric acid	AM-toxin I	13.7A	Ueno et al. (1975)
N^5-Hydroxyornithine	Siderophores	13.1	Renshaw et al. (2002)
4-Methylproline	FR-235222	13.6	Mori et al. (2003)
2-Butenyl-4-methylthreonine	Cyclosporin A	13.4C	Rüegger et al. (1975)
α-Aminobutyric acid	Cyclosporin A	13.4C	Rüegger et al. (1975)
3-Hydroxyhomotyrosine	WF-11899C	13.5	Iwamoto et al. (1994b)
5-Hydroxyornithine	WF-11899C	13.5	Iwamoto et al. (1994b)
Dichloro-proline	Cyclochlorotine	13.4B	Yoshioka et al. (1973)
β-Phenyl-β-aminopropionic acid	Cyclochlorotine	13.4B	Yoshioka et al. (1973)
β-Alanine	Destruxin A	13.7A	Rees et al. (1996)
β-Aspartic acid	Argifin	13.4C	Arai et al. (2000)
α-Aminoisobutyric acid	Chlamydocin	13.6	Closse and Huguenin (1974)
Isovaline	FR-235222	13.6	Mori et al. (2003)
1-Aminocyclopropane-1-carboxylic acid	Serinocyclin A	13.4C	Krasnoff et al. (2007)
Pipecolinic acid	Trapoxin A	13.6	Itazaki et al. (1990)
Anthranilic acid	Psychrophilin D	13.4C	Dalsgaard et al. (2005)
2-Amino-8-oxo-9-hydroxydecanoic acid	JM47	13.6	Jiang et al. (2002)
2-Amino-9,10-epoxy-8-oxodecanoic acid	HC-toxin I	13.6	Gross et al. (1982)

Table 13.2. Diversity of hydroxyacid building blocks in cyclic depsipeptides

Acid	Example	Figure	Reference
2-Hydroxyisovaleric acid	Clavariopsin A	13.7C	Kaida et al. (2001)
3,4-Dihydroxy-4-methylhexadecanoic acid	Glomosporin	13.7C	Ishiyama et al. (2000)
2-Hydroxy-3-methylpentanoic acid	Enniatin I	13.7A	Nilanonta et al. (2003)
2-Hydroxyheptanoic acid	Verticilide	13.7C	Monma et al. (2006)
2-Hydroxy-4-metylpentanoic acid	Sansalvamide A	13.7B	Belofsky et al. (1999)
Phenyllactic acid	PF1022A	13.7B	Sasaki et al. (1992)
Lactic acid	PF1022A	13.7B	Sasaki et al. (1992)
3-Hydroxydodecanoic acid	Isariin A	13.7A	Wolstenholme and Vining (1966)
3-Hydroxy-4-methyldecanoic acid	Beauverolide II	13.7A	Mochizuki et al. (1993)
3-Hydroxydecanoic acid	Icosalide A_1	13.7A	Boros et al. (2006)
3,5-Dihydroxy-2,4-dimethylstearic acid	Stevastelin B	13.7C	Morino et al. (1994)
2-Hydroxy-4-cyanobutyric acid	Pestahivin	13.7B	Hommel et al. (1996)
2-Hydroxy-4-enoylpentanoic acid	Destruxin A	13.7A	Rees et al. (1996)
2,4-Dimethyl-3-hydroxydodecanoic acid	LL15G256γ	13.5	Abbanat et al. (1996)

B. Diversity of Structures

Additional variations are due to the different numbers of building blocks, their arrangement (e.g. sequence in the ring) and their linkage (e.g. amide and ester bonds). Some depsipetides like the enniatins, beauvericins, bassianolide or verticilide show a symmetric arrangement in the ring. The majority however are asymmetric, like the destruxins, beauverolides, isariins or *Alternaria* toxins (Fig. 13.7A,C).

Cyclic peptides including the cyclosporins are asymmetric, as are the echinocandins. The number of building blocks in cyclic peptides varies from two in the diketopiperazines, some of which are symmetric if composed of two residues of the same amino acid, to 12 in the omphalotins, which are at present the largest cyclopeptides known from fungi. In addition, the omphalotins are an example of modifications after ring closure. Omphalotins B, C and D are derived from omphalotin A by hydroxylation followed by acylation to

Table 13.3. Modifications in cyclic peptide and depsipeptides

Modification/substitution	Example	Figure	Reference
O-Methyl	Clavariopsin A	13.7C	Kaida et al. (2001)
N-Methyl	Omphalotin A	13.4B	Sterner et al. (1997)
Methoxy	Pestahivin	13.7B	Hommel et al. (1996)
Acetyl	Omphalotin C	13.4B	Büchel et al. (1998a)
3-Hydroxy-methylbutanoyl	Omphalotin C	13.4B	Büchel et al. (1998a)
Palmitic acid	WF-11899C	13.5	Iwamoto et al. (1994b)
3-Hydroxypalmitic acid	FR 901469	13.5	Fujie et al. (2000)
Linoleic acid	Echinocandin B	13.5	Keller-Juslen et al. (1976)
Sulfate	WF-11899C	13.5	Iwamoto et al. (1994b)
Nitro	Psychrophilin A	13.4C	Dalsgaard et al. (2005)
Halogenation	Sporidesmin A	13.3	Fridrichsons and Mathieson (1962)
Isoprenyl	Roquefortine C	13.2	Scott et al. (1979)
Prenyl	Fumitremorgin A	13.2	Eickman et al. (1975)
Geranyl	Mycelianamide	13.2	Birch et al. (1956)
N-Methylcarbamoyl	Argifin	13.4C	Arai et al. (2000)
Hydroxylation			
3-Hydroxyvaline	Omphalotin C	13.4B	Büchel et al. (1998a)
4,5-Dihydroxyornithine	Echinocandin B	13.5	Keller-Juslen et al. (1976)
3,4-Dihydroxyhomotyrosine	Echinocandin B	13.5	Keller-Juslen et al. (1976)
2,6-Dihydroxyphenylalanine	Mactanamide	13.2	Lorenz et al. (1998)
3,4-Dihydroxyproline	Pneumocandin D_0	13.5	Morris et al. (1994)

the corresponding esters and formation of additional ring structures (Büchel et al. 1998).

Novel omphalotins were recently isolated from a monokaryotic strain. The elucidation of their structures was greatly hampered by their instability (Liermann et al. 2009). These omphalotins bear additional hydroxyl groups, thus bringing the number of known cyclic peptides from *O. olearius* to 11. A second hydroxylation at the tryptophan leads to a novel ring system (Fig. 13.4B). HPLC-MS spectra of enriched extracts indicate the presence of additional members of the group. The psychrophilins are nitropeptides with unusual structures (Fig. 13.4A). The compounds are produced by several psychrotolerant *Penicillium* species (Dalsgaard et al. 2004a, b; 2005). Cyclochlorotine, a mycotoxin from *P. islandicum* contains a dichloroprolyl residue (Betina 1989).

The depsipeptides start with four building blocks (angolide, beauverolides) up to 12 in the antibiotic FR901469 (a member of the 1,3-β-glucan synthase inhibitors; Fujie et al. 2001) and 13 in petriellin A (Lee et al. 1995). The latter contains β-phenyllactic acid, a building block not often found in cyclopeptides and -depsipeptides. Further modifications of cyclic peptides and depsipeptides include N-methylation, hydroxylations, acylation, isoprenylation and the introduction of sulfate-, nitro-chloro- or cyano- groups. These modifications can occur at the beginning of biosynthesis, like N-methylations, or after cyclization, e.g. C- and N-hydroxylations followed by an acylation (Glinski et al. 2001; Chap. 15). In many cases however it is not clear at which step the modifications occur. The low substrate specificity of the NRPS enzymes allows the incorporation of modified ring components. In fact, Zocher and his group have made use of this to produce novel enniatin derivatives in vitro (Feifel et al. 2007).

C. Diversity of Biological Activities

The structural diversity of diketopiperazines, cyclopeptides and -depsipeptides is matched by the diversity of their biological activities. To list all activities and compounds would be beyond of the scope of this chapter. An overview on biological activities of diketopiperazines is given by Martins and Carvalho (2007), cyclic depsipeptides and their biological activities are reviewed by (Sarabia et al. 2004), while insecticidal and other biological activities of destruxins, isariins, enniatins, and beauverolides are reviewed by Anke and Sterner (2002) and by Zimmermann (2007a, b). Some of the compounds exhibit rather selective activities like the antifungal, 1,3-β-glucan synthesis inhibitors (see below) whereas others like gliotoxin show a broad spectrum of activities. While the former (due to fewer side-

effects) generally have a higher potential to be developed into drugs or pesticides, the latter might be of interest as biochemical tools or chemical building blocks. In the following, we attempt to give an overview on the different biological activities exhibited by fungal cyclopeptides and -depsipeptides.

Gliotoxin, already isolated in 1932, recently regained interest not only due to its immunosuppressive and apoptosis-inducing activities (Waring et al. 1988) but moreover due to its occurrence in the blood of aspergillosis patients and its effects on various human cells among them an inhibition of cell adherence in macrophages (Amitani et al. 1995; Kamei and Watanabe 2005). The plethora of biological activities is evident from the number of papers published on gliotoxin and related epipolythiodioxopiperazines (Waring and Beaver 1996; Hume et al. 2002; Gardiner et al. 2005).

The vertihemiptellides A and B and their S-methylated monomers exhibit antimycobacterial and cytotoxic effects (Isaka et al. 2005b). Sirodesmin PL produced by *Leptosphaeria maculans* has phytotoxic, antibacterial and insecticidal properties (Rouxel et al. 1988; Boudart 1989) and the leptosins inhibited the proliferation of P388 lymphocytic leukemia cells with an ED_{50} of 1.1–1.3 μg/ml (Takahashi et al. 1994).

The HC-toxins, host-specific toxins from *Cochliobolus carbonum* (anamorph *Helminthosporium carbonum*), are cyto- and phytotoxic and inhibitors of histone deacetylase (Taunton et al. 1996).

Structurally related tetrapeptides (Fig. 13.6) like apicidin from a *Fusarium* species (Darkin-Rattray et al. 1996; Singh et al. 2002), JM47 from a marine *Fusarium* species (Jiang et al. 2002), FR235222 from an *Acremonium* species (Mori et al. 2003) or the chlamydocins from *Diheterospora chlamydosporia* (Closse and Huguenin 1974) and *Peniophora* sp. (Tani et al. 2001) have been reported to exhibit antiprotozoal activity, to induce apoptosis, to have immunosuppressive effects or to retard plant growth (de Schepper et al. 2003).

Due to their toxic effects in animal and humans and their occurrence in food and feedstuff, fumitremorgins, verruculogens, roquefortins C and D, sporidesmins, chaetocin, cyclochlorotine and malformins were classified as mycotoxins (Betina 1989). For their different biological activities the reader is referred to the vast online literature on this group of fungal products.

Malformin C (Fig. 13.4), despite its antibacterial, plant-deforming and fibrinolytic activities, recently aroused some interest due to its inhibitory effects on bleomycin-induced G2 arrest, thus potentiating its DNA-damaging action, a mode of action that might be useful for the treatment of cancer (Hagimori et al. 2007).

Cyclosporins are not the only immunomodulating fungal metabolites. Many epipolythiodioxopiperazines, in addition to other biological activities, are immunosuppressants.

Sevastelins, cyclodepsipeptides with a lipophilic side-chain, from a *Penicillium* species blocked human T cell activation in vitro and showed low acute toxicity in mice (Morino et al. 1994). HUN-7293 acts as inhibitor of cytokine-induced expression of vascular cell adhesion molecule-1 on human endothelial cells (Hommel et al. 1996). It is structurally identical to pestahivin.

The depsipeptide aureobasidin A has an interesting mode of action, the inositol phosphoceramide synthase (IPS). The fungal enzyme is considered to be an attractive target for novel fungicides. Further development of aureobasidin A was hampered by its inhibitory effects on ABC transporters in yeasts and humans (Fostel and Lartey 2000). The pleofungins from a *Phoma* species showed antifungal activity towards *Candida albicans*, *Cryptococcus neoformans* and *A. fumigatus* with minimal inhibitory concentrations in the range of 1 μg/ml or lower (Yano et al. 2007). The compounds inhibited the *A. fumigatus* IPS with IC_{50} values of 1 ng/ml (Aoyagi et al. 2007).

Neoechinulin A has protective activity in PC12 cells against lethal effects of peroxynitrite and against 1-methyl-4-phenylpyridine, a neurotoxin capable of inducing neurodegeneration in humans (Kajimura et al. 2008). The cyclic tetrapeptide CJ-15,208 is a kappa opinoid receptor antagonist (Saito et al. 2002) and four depsipeptides were reported to be selective and competitive human tachykinin receptor antagonsits (Hedge et al. 2001).

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, no antimicrobial or cytotoxic activities were detected and beauvericin was cytotoxic (Matsuda et al. 2004; Ohshiro et al. 2007). ACAT is discussed as a target for new antiatherosclerotic agents (Roth 1998; Namatame et al. 2004).

The outstanding anthelmintic activity of PF1022A combined with its mode of action, e.g. binding to the latrophilin-like receptor of

Haemonchus contortus (Conder et al. 1995; Saeger et al. 2001) and low toxicity led to the development of emodepsin, a novel drug used in animal health.

Antiparasitic properties have been reported for cycloaspeptides A and D (Dalsgaard et al. 2004b). Verticilide, a cyclic depsipeptide isolated from the culture broth of *Verticillium* sp. FKI-1033, inhibits the binding of ryanodine to the receptor (RyR) and has insecticidal activity (Monma et al. 2006). Serinocyclin A isolated from *M. anisopliae* condia produced a sublethal locomotory defect in mosquito larvae (Krasnoff et al. 2007). Argifin and argadin, two cyclopentapeptides from a *Gliocladium* and a *Clonostachys* species, are potent inhibitors of chitinase B from *Serratia marcescens* (Houston et al. 2002). When injected into cockroach larvae, the moult was arrested. Besides cyclopeptides and -depsipeptides fungi also produce other peptides with insecticidal activities, recent examples are the neofrapeptins from *Geotrichum candidum* (Fredenhagen et al. 2006). Selective nematicidal properties have been reported only for the omphalotins with high inhibitory activity towards *Meloidogyne incognita* and low activity towards *Caenorhabditis elegans* (Mayer et al. 1997, 1999; Sterner et al. 1997). The nematicidal properties of the hydroxylated omphalotins are higher than those of the parent compound, but unfortunately they are not stable (Büchel et al. 1998a, Liermann et al. 2009).

Antiviral properties have been reported for sansalvamide A, a cyclodepsipeptide from a marine *Fusarium*, which inhibits viral topoisomerase-catalyzed DNA relaxation (Hwang et al. 1999).

The clavariopsins, cyclic depsipetides from *Clavariopsis aquatica*, show selective antifungal activity, bacteria are not affected and mice tolerate 100 mg/kg of clavariopsin A. As mode of action, an inhibition of cell components was proposed (Kaida et al. 2001). Glomosporin from a *Glomospora* species is a lipophilic depsipeptide with antifungal activity (Sato et al. 2000). Whether this compound also inhibits cell wall synthesis was not reported. Antifungal and cytotoxic activities were reported for petriellin A (Lee et al. 1995). Cytotoxic activities are exhibited by many cyclopeptides and -depesipeptides. The destruxins have been intensively investigated (Vey et al. 2002; Skrobek and Butt 2005). Psychrophilin D is weakly cytotoxic towards P388 mouse leukaemia cells with an IC_{50} value of 10 μg/ml (Dalsgaard et al. 2005), while the icosalides inhibit the replication of MDCK cells with LD_{50} of 5–10 μg/ml (Boros et al. 2006). The aspergillicins are weakly cytotoxic with LD_{99} of 25–50 μg/ml (Capon et al. 2003).

As inhibitors of 1,3-β-glucan synthesis have high potential as antimycotic drugs (Fostel and Lartey 2000), fungi have been intensively screened for the production of inhibitors of cell wall synthesis and cyclic peptides as well as cyclic depsipeptides have been found.

The antimycotic drugs already on the market (caspofungin, micafungin, anidulafungin) are derived from lipopeptides (Butler 2004; Morrison 2006). Their spectrum of activity is mainly restricted to *Candida* and *Aspergillus* species. *Cryptococcus neoformans*, *Trichosporon* and *Fusarium* species or Zygomycetes are not affected (Denning 2003), although the glucan synthase from *C. neoformans* is sensitive to echinocandins (Maligie and Selitrennikoff 2005).

IV. Ecological Role of Cyclic Peptides and Depsipeptides

Many secondary metabolites play a crucial role for fungi in their natural habitats. Endophytic fungi of grasses belonging to the genera *Neotyphodium/Epichloe* confer protection from mammalian and insect herbivores, or enhanced resistance against nematodes and phytopathogenic fungi (Schardl et al. 2004; Panaccione et al. 2006). Some of these beneficial effects are due to NRPS products. Ergovaline has been identified among the fungal metabolites in the plant host. Malformins have been detected in onion scales after infection with *A. niger* (Curtis et al. 1974).

The role of siderophores in plant and human pathogens is currently elucidated by many research groups (for a review see Haas et al. 2008). Additional functions of siderophores for the producing organism are acquisition and storage of iron as well as regulation of asexual and sexual development and protection against oxidative stress (Einsendle et al. 2006; Hof et al. 2009). Nonproducing organisms like *Saccharomyces cerevisiae* are able to use, e.g. transport iron-siderophore complexes, thus the compounds might also play a role in fungus–fungus interactions.

In plant-pathogenic fungi cyclic peptides like HC-toxins in *Cochliobolus carbonum*, AM toxins in *Alternaria alternata*, sirodesmin PL in *Leptosphaeria maculans* (anamorph *Phoma lingam*) or enniatins in *Fusarium* species act as putative virulence factors. In some cases this has already been proven, when gene deletions result in apathogenic strains or strains with reduced virulence (Ahn and Walton 1998; Pedley and Walton 2001; Elliott et al. 2007). Likewise the insecticidal depsipetides of insect pathogens have the same function. Investigation on the role of destruxins in the pathogenicity of *Metarhizium anisopliae* against three species of insects revealed a direct relationship between the titer of destruxins produced by the strains in vitro and their destructive action (Kershaw et al. 1999). In the plant-pathogenic *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).

The function of shearamide A, an insecticidal cyclopeptide isolated from the ascostromata of *Eupenicillium shearii* (Belofsky et al. 1998) may be in protecting the fungus against insects, similar to ergopeptides in the sklerotia of *Claviceps* species (Chap. 9).

V. Conclusions

The capability to produce secondary metabolites derived from amino acids by NRPS is widespread among the higher fungi and not dependent on the ecological niches inhabited by them. There are no special habitats from which highly prolific secondary metabolite producers are isolated.

Cyclic peptides and -depsipeptides constitute an interesting class of secondary metabolites with great potential not only in medicine but also in agriculture. This can easily be grasped from the wide array of biological activities exhibited by these compounds. Their chemical diversity is enhanced by the possibility of producing an array of related compounds by precursor-supplemented fermentations of the correspondent fungus. This readily facilitates investigations on structure–activity relationships.

In agriculture, fungally derived pesticides offer ecological advantages and strains with enhanced production of bioactive compounds might be developed as biopesticides. For both agriculture and pharmacology bioactive natural compounds may lead to novel targets and serve as lead structures.

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