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REVIEW

Non-lipopeptide fungi-derived peptide antibiotics developed since 2000

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Abstract The 2,5-diketopiperazines (DKPs) are the smallest cyclopeptides and their basic structure includes a six-membered piperazine nucleus. Typical peptides lack a special functional group in the oligopeptide nucleus. Both are produced by at least 35 representative genera of fungi, and possess huge potential as pharmaceutical drugs and biocontrol agents. To date, only cyclosporin A has been developed into a commercial product. This review summarises 186 fungi-derived compounds reported since 2000. Antibiotic (antibacterial, antifungal, synergistic antifungal, antiviral, antimycobacterial, antimalarial, antileishmanial, insecticidal, antitrypanosomal, nematicidal and antimicroalgal) activities are discussed for 107 of them, including 66 DKPs (14 epipolythiodioxopiperazines, 20 polysulphide bridge-free thiodiketopiperazines, and 32 sulphur-free prenylated indole DKPs), 15 highly *N*-methylated, and 26 non-highly *N*-methylated typical peptides. Structure–activity relationships, mechanisms of action, and research methods are covered in detail. Additionally, biosynthases of tardioxopiperazines and neoechinulins are highlighted. These compounds have attracted considerable interest within the pharmaceutical and agrochemical industries.

Keywords Antibiotic activity · DKP · Fungi · Mechanism of action · Structure–activity relationship · Typical peptide · Biosynthesis

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Introduction

Fungi are well-known producers of bioactive secondary metabolites, especially short peptides of 30 residues or fewer, with interesting structures and antibiotic properties (Brase et al. 2009; Jia et al. 2015; Li et al. 2017; Wang et al. 2017a, b; Yu et al. 2012). Herein, we focus on fungal cyclodipeptides known as 2,5-diketopiperazines (DKPs), as well as typical

peptides and their analogs, reported since 2000. Genera of fungi known to produce these compounds include *Alternaria*, *Aspergillus*, *Asteromyces*, *Bionectra*, *Chaetomium*, *Clonostachys*, *Cordyceps*, *Cryptosporiopsis*, *Epicoccum*, *Eurotium*, *Eutypella*, *Fusarium*, *Gliocladium*, *Graphium*, *Lasiodiplodia*, *Metarhizium*, *Microascus*, *Mortierella*, *Myrothecium*, *Nectria*, *Omphalotus*, *Penicillium*, *Pestalotiopsis*, *Phoma*, *Phomopsis*, *Pseudallescheria*, *Pseudoxylaria*, *Schizophyllum*, *Simplicillium*, *Stagonospora*, *Stereum*, *Talaromyces*, *Trichoderma*, *Verticillium* and *Xylaria*. Some of these molecules have been explored for potential applications (Wang et al. 2013a).

DKPs are the smallest cyclopeptides, and generated by the condensation of two amino acids (e.g. Try, Pro, Ala, His, Leu, Ile, Phe, Ser, Tyr, and Gly) (Wang et al. 2013a, 2017a). Their basic structure includes a six-membered piperazine nucleus, and based on structural characteristics, they are classified as thiodiketopiperazines (TDKs) and sulphur-free DKPs. TDKs feature *S*-methyl (Me) groups and/or transannular polysulphide bridges (epipolythiodioxopiperazines, ETPs) (Guo et al. 2009; Li et al. 2013a; Meng et al. 2015a). Biosynthesis of DKPs can be achieved either by cyclodipeptide synthases (CDPSs) or non-ribosomal peptide synthases (NRPSs) that differ in the mode of activation of their amino acid substrates (Belin et al. 2012). To date, only six DKPs synthesized by CDPSs have been reported (albonoursin, mycocyclosin, pulcherriminic acid, bicyclomycin, drimentines, and nocazine XR334 and E) (Lautru et al. 2002; Belin et al. 2009; Cryle et al. 2010; Vior et al. 2018; Yao et al. 2018; Giessen et al. 2013; Zhang et al. 2013). To the best of our knowledge, the formation of fungi-derived DKPs is catalysed by NRPSs. Structural modification of the DKP backbone is subsequently achieved by various tailoring enzymes including oxidoreductases, methyltransferases, prenyltransferases, cyclases and others (Wohlgemuth et al. 2018). Table 1 shows fungi-derived DKPs for which biosynthases have been identified (Saruwatari et al. 2014; Guo et al. 2013; Yin et al. 2009; Chankhamjon et al. 2014; Maiya et al. 2006, 2009; Mundt et al. 2012; Gerken and Walsh 2013; Oide et al. 2006; Wilhite et al. 2001; Wohlgemuth et al. 2017, 2018; Lazos et al. 2010; Lim et al. 2014; Gardiner and Howlett 2005; Sherkhane et al. 2017; Chu et al. 2010; García-Estrada et al. 2011; Ali et al.2013; Gardiner et al. 2004; Dopstadt et al. 2016; Wang et al. 2017c; Quezada et al. 2017). Peptides lacking special functional groups in the short oligopeptide nucleus are herein referred to as typical peptides. This review highlights their sources, biosynthesis, structural and sequence features, antibiotic activities, structure–activity relationships (SARs), mechanisms of action, and related research methods since 2000 in order to assist their future exploration and exploitation as novel pharmaceutical drugs or biocontrol agents.

ETPs

Research suggests that the crucial structural element of ETPs responsible for the observed biological properties is the polysulphide linkage (Li et al. 2012a; Onodera et al. 2004). Based on differences in the amino acid composition of the ETP parent nucleus and further structural modification, 37 ETPs can be classified into 12 families: aspirochlorine, emestrins, epicorazines, gliotoxins, gliocladine C, hyalodendrin, chetomins, verticillins, vertihemiptellides, aranotins, eutypellazine and gliovirins (Table 2 and Fig. 1).

The aspirochlorine tetrathiol analog tetrathioaspirochlorine from *Aspergillus flavus* 0G0S0151 is a potent antifungal agent against azole-resistant *Candida albicans*, with a 50% inhibitory concentration (IC_{50}) of 0.083 μM, stronger the three standard compounds amphotericin B, gliotoxin and griseofulvin, but less active than aspirochlorine (Klausmeyer et al. 2005). The 7-membered disulphide ring appears to play a key role in antifungal activity. Aspirochlorine antifungal activity is related to its ability to inhibit protein biosynthesis. Four 2″-*O*-Me derivatives of emestrin and one 7″-deoxy analog of emestrin named emestrin C (MPC1001), MPC1001C and emestrins D (MPC1001D)–F have been isolated. Emestrin C and MPC1001C, isolated from *Cladorrhinum* sp. KY4922 and *Podospora australis* TTI-0248, contain one disulphide bridge and two *O*-Me groups, and both show significant activity against *Cryptococcus neoformans* with minimum inhibitory concentrations (MICs) of 0.8 and 1.6 μg ml^{-1}, respectively, close to that of amphotericin B (Li et al. 2016a; Onodera et al. 2004; Tsumagari et al. 2004). Nevertheless, the trisulphide-bridged emestrin D (*Cladorrhinum* sp. KY4922 and *P. australis* TTI-0248), tetrasulphide-bridged emestrin E (*Verticimonosporium ellipticus* MF6822 and *P. australis* TTI-0248), and the disulphide bridge- single *O*-

Table 1 Biosynthases of fungi-derived DKPs

DKPs	Sources	Biosynthases	Antibiotic activity
(-)-Ditryptophenaline	*Aspergillus*	Dtp**A**BC	None
Acetylaranotins	*Aspergillus*	AtaA, TC, J, IMG and F**P**LYH	Antiviral
Acetylaszonalenin	*Aspergillus* and *Neosartorya*	Ana AT, **PS** and PT	None
Aspirochlorine	*Aspergillus*	AclA–**P** and QSTUZ	Antifungal
Brevianamide F	*Aspergillus*	Ftm**A**B	Antibacterial
Fumitremorgins	*Aspergillus*	Ftm**A**–E, Ox1 and FtmPT3	Antibacterial
Verruculogen	*Aspergillus*	Ftm**A**–E and Ox1	Antifungal
Tryprostatins	*Aspergillus*	Ftm**A**–D	Antibacterial
Chaetocin	*Chaetomium*	ChaABCEGIJKMN**P**TZ	None
Coprogens	*Cochliobolus*	NPS6	None
Dimerumic acid	*Trichoderma*	Psy1	None
Echinulin	*Aspergillus*	Ech**PS**, PT1 and PT2	Antimycobacterial
Tardioxopiperazines	*Aspergillus*	Ech**PS**, PT1 and PT2	Antibacterial
Neoechinulins	*Aspergillus*	Ech**PS**, PT1 and P450	Antiviral
Erythrochelin	*Saccharopolyspora*	ErcABC**D**EF	None
Fumiquinazoline	*Aspergillus*	Fmq**A**B**C**DE	None
Gliotoxin	*Aspergillus*	GliTFNAKGMC**P**JIZ	Antimycobacterial, antifungal, anti-trypanosomal
Gliovirin	*Trichoderma*	Glv1–**21** and 22	Antifungal
Notoamides/stephacidin	*Aspergillus*	NotA–**E** and F–R	None
Roquefortine/Meleagrin	*Penicillium*	Roq**A**RMONDT	None
Sirodesmin PL	*Leptosphaeria*	SirA–E, G–J, M–**P** and QRSTZ	Antibacterial, antiviral
Thioclapurine	*Claviceps*	TcpACDGJKN**P**TZ	None
Verticillin	*Clonostachys*	VerATLMNIC**P**KJGZB	Antibacterial, anti-trypanosomal
Waspergillamide A	*Aspergillus*	PABA as the starter unit	None

Bold type denoting nonribosomal peptide synthase

None having no antibiotic activity, *PABA* *p*-aminobenzoic acid

Me-containing emestrin F (*Armillaria tabescens* JNB-OZ344) display weaker anti-*Cryptococcus* activity (Herath et al. 2005, 2013; Li et al. 2016a). In addition, MPC1001 also exhibits good antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Enterococcus hirae* and *C. albicans*, especially *B. subtilis*, for which the MIC is 2.1 μg ml^{-1} (Li et al. 2016a; Tsumagari et al. 2004). Emestrin F is also potently active against *Mycobacterium intracellulare* (MIC = 1.25 μg ml^{-1}; IC_{50} = 1.18 μg ml^{-1}) (Herath et al. 2013). This led to the conclusion that the *O*-Me groups and disulphide bridges are essential for potency. Mechanistic studies on the effects of emestrins led to the hypothesis that antimicrobial activity is due to inhibition of ATP synthesis in mitochondria, causing an uncoupling of oxidative phosphorylation and depression of respiration (Li et al. 2016a; Herath et al. 2013). Brocazine G from *Penicillium brocae* MA-231 belongs to the epicorazine family and exhibits potent inhibitory activity against *S. aureus* (MIC = 0.25 μg ml^{-1}), stronger than chloromycetin (Meng et al. 2016). Glionitrin A from *Sphingomonas* sp. KMK-001 and *Aspergillus fumigatus* KMC-901 belongs to the gliotoxin family and displays differential antibiotic activity against a range of microbes, especially *Micrococcus leuteus* and methicillin-resistant *S. aureus* (MRSA; MIC = 0.78 μg ml^{-1}) (Park et al. 2009). Furthermore, gliotoxin addition can perturb the proteome and induce redox stress in fungi (Carberry et al. 2012; Pereira-Neves et al. 2016).

Gliocladine C-type GG1F1-1 and 2 from *Phoma* sp. GG1F1 were shown to be effective against 16

Table 2 Epipolythiodioxopiperazines (ETPs) with antibiotic activities

Class/name	Biosynthetic precursors	Antibiotic activity
Aspirochlorine/tetrathioaspirochlorine	Cyclo-(Gly-Tyr)	Antifungal
Emestrin/emestrin C (MPC1001), MPC1001C and emestrins D (MPC1001D)–F	Cyclo-(Phe-Phe)	Antifungal, antibacterial, antimycobacterial
Epicorazine/brocazine G	Cyclo-(Phe–Phe)	Antibacterial
Gliotoxin/glionitrin A	Cyclo-(Phe-Ser)	Antifungal, antibacterial
Gliocladine C/GG1F1-1 and 2	Cyclo-(Trp-Ser)	Antibacterial, antifungal
Hyalodendrin/1-demethyl-hyalodendrin tetrasulfide	Cyclo-(Phe-Ser)	Antimalarial
Chetomin/chaetocochin J	Dimer: cyclo-(Trp-Ser)-cyclo-(Trp-Ser)	Antibacterial
Chetoseminudin A		
6-Formamide-chetomin		
Verticillin/gliocladines A and B	Dimer: cyclo-(Trp-Ala)-cyclo-(Trp-Ala)	Antinematodal
11'-Deoxyverticillin A		
Sch52900 and Sch52901	Dimer: cyclo-(Trp-Abu/Thr)-cyclo-(Trp-Ala)	
Gliocladine C/gliocladines C–E	cyclo-(Trp-Ala)	Antinematodal
Verticillin/Verticillin G	Dimer: cyclo-(Trp-Ser)-cyclo-(Trp-Gly)	Antibacterial
Epicorazine/epicoccins A and U	Cyclo-(Phe-Phe)	Antibacterial
Eutypellazine/eutypellazine Q	Cyclo-(Phe-Phe)	Antibacterial
Gliocladine C/bionectins A and B	Cyclo-(Trp-Gly/Thr)	Antibacterial
Gliovirin/outovirin C	Cyclo-(Phe-Tyr)	Antifungal
Vertihemiptellide/vertihemiptellides A and B	Dimer: cyclo-(Phe-Ser)-cyclo-(Phe-Ser)	Antimycobacterial
Gliovirin/pretrichodermamide A	Cyclo-(Phe-Tyr)	Antimycobacterial
Gliovirin/adametizines A and B	Cyclo-(Phe-Tyr)	Antibacterial, antifungal
Epicorazine/epicorazine C	Cyclo-(Phe-Phe)	Antimycobacterial, antibacterial, antifungal
Aranotin/graphiumins A and I	Cyclo-(Phe–Phe)	Anti-virulence

Classes are indicated in bold

Abu aminobutyric acid

pathogens, especially *S. aureus*, MRSA, *Bacillus cereus*, *Staphylococcus warneri* and *Streptococcus pyogenes*, with IC_{50} values < 10 μM (Arora et al. 2016). In addition, GG1F1-1 inhibits *Klebsiella pneumonia* ($IC_{50} = 4.5$ μM). Interestingly, they also strongly inhibit biofilm formation in *S. aureus* and *S. pyogenes*, and were found to act synergistically with streptomycin while exerting varying effects in combination with ciprofloxacin and ampicillin. 1-demethyl-hyalodendrin tetrasulphide from *Verticillium hemipterigenum* BCC 1449 belongs to the hyalodendrin family (Nilanonta et al. 2003). This compound significantly inhibits the proliferation of multi-drug resistant *P. falciparum* ($IC_{50} = 2.5$ μg ml^{-1}), but its bisdimethylthio ether is inactive, indicating that the tetrasulphide bridge is crucial for achieving high antimalarial activity. Three ETP dimeric members of the chetomin family have been identified (chaetocochin J, chetoseminudin A and 6-formamide-chetomin). Chetoseminudin A from *Chaetomium seminudum* 72-S-204-1 and *Chaetomium globosum* CIB-G3604 contains one disulphide and one trisulphide bridge (Fujimoto et al. 2004; Xu et al. 2015), and displays strong activity against *B. subtilis* (MIC = 0.78 μg ml^{-1}), more active than chaetocochin J containing only one tetrasulphide bridge (Xu et al. 2015). These results suggest that the number of sulphur bridges is important for maintaining high anti-*Bacillus* activity. 6-formamide-chetomin from *Chaetomium* sp. M336 has strong antibacterial activity

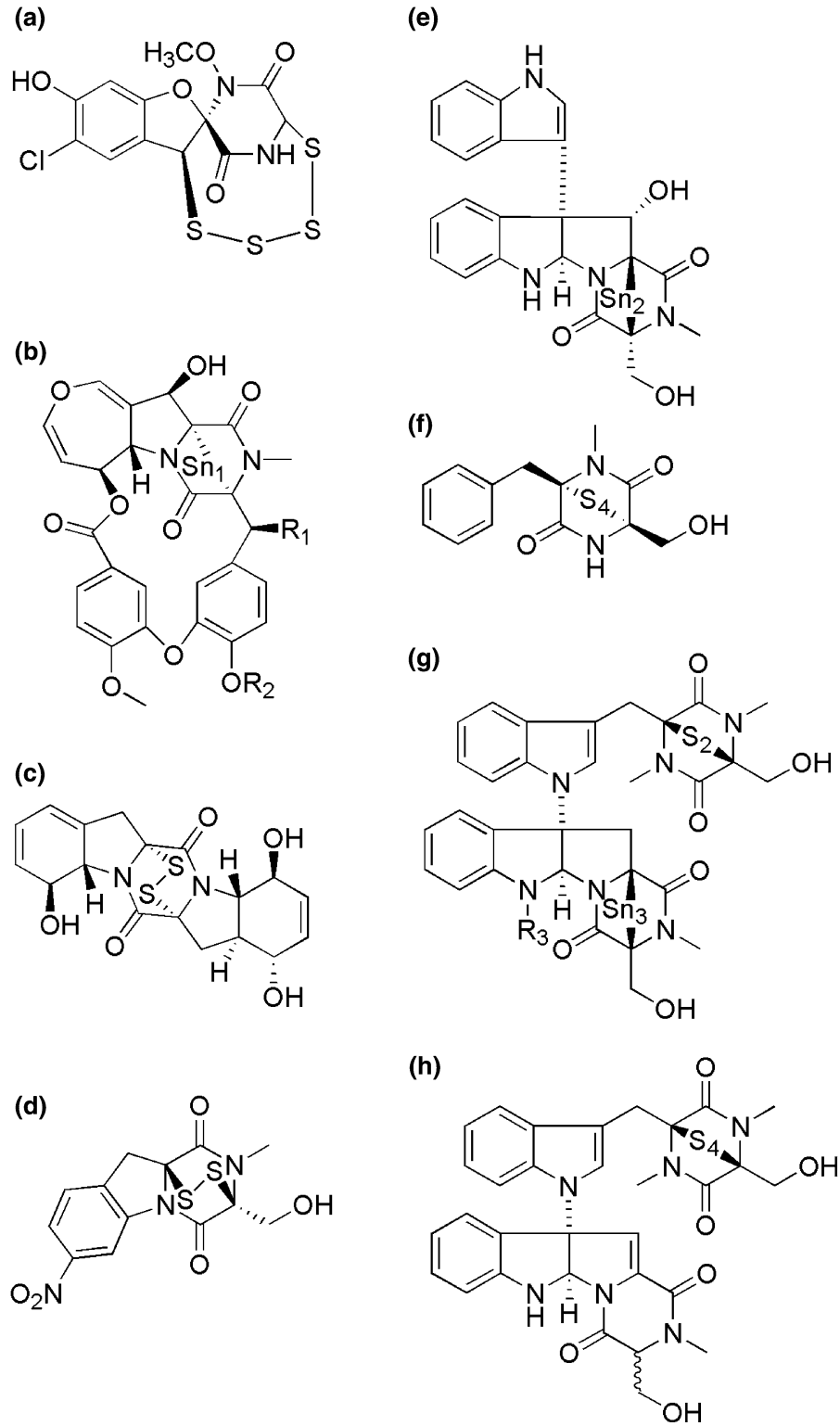

Fig. 1 Structure of partial ETPs. **a** Aspirochlorine/tetrathioaspirochlorine. **b** Emestrin C ($n_1 = 2$, $R_1 = OH$, $R_2 = CH_3$); MPC1001C ($n_1 = 2$, $R_1 = H$, $R_2 = CH_3$); emestrin D ($n_1 = 3$, $R_1 = OH$, $R_2 = CH_3$); E ($n_1 = 4$, $R_1 = OH$, $R_2 = CH_3$); F ($n_1 = 2$, $R_1 = H$, $R_2 = H$). **c** Epicorazine/brocazine G. **d** Gliotoxin/glionitrin A. **e** Gliocladine C/GG1F1-1 ($n_2 = 2$); GG1F1-2 ($n_2 = 3$). **f** Hyalodendrin/1-demethylhyalodendrin tetrasulphide. **g** Chetomins/chetoseminudin A ($R_3 = H$, $n_3 = 3$); 6-formamide-chetomin ($R_3 = CHO$, $n_3 = 2$). **h** Chaetocochin J (Klausmeyer et al. 2005; Li et al. 2016a; Herath et al. 2013; Meng et al. 2016; Park et al. 2009; Arora et al. 2016; Nilanonta et al. 2003; Xu et al. 2015; Yu et al. 2018)

against *Escherichia coli*, *S. aureus*, *Salmonella typhimurium* and *E. faecalis* (MICs = 0.78 μg ml^{-1}) (Yu et al. 2018). Antibiotic activities of other ETPs are listed in Table 2 (Chunyu et al. 2017; Dong et al. 2005; Fukuda et al. 2015a, b; Isaka et al. 2005; Kajula et al. 2016; Kleinwächter et al. 2001; Liu et al. 2015a; Niu et al. 2017a; Park et al. 2009; Seephonkai et al. 2006; Zhang et al. 2007a; Zheng et al. 2006, 2007a).

Polysulphide bridge-free TDKs

Since 2000, 40 polysulphide bridge-free TDKs have been reported (Table 3 and Fig. 2). Chetoseminudin B from *C. seminudum* 72-S-204-1 and *A. fumigatus* 030402dZa possesses one dethio-dimethylthio-dioxopiperazine moiety (Fujimoto et al. 2004; Watts et al. 2010). Compared with the nM activity exhibited by gliotoxin, verticillin B and chaetocin, the μM activity of chetoseminudin B confirms the role of the disulphide bridge in the remarkable potency against *Trypanosoma brucei*. Epicoccins G and H from *E. nigrum* XZC04-CS-302 show differential inhibitory effects on HIV-1 replication in C8166 cells, indicating that two hydroxyl substitutions at C-7 and C-7′ significantly increase activity (Guo et al. 2009). Anti-HIV bioassays indicated that eutypellazines A–L from *Eutypella* sp. MCCC 3A00281 exhibit inhibitory effects against pNL4.3.Env-.Luc co-transfected 293T cells (HIV-1 model cells) with low cytotoxicity, and the E form exerts the highest activity (IC_{50} = 3.2 μM) (Niu et al. 2017b). A preliminary SAR study revealed that analogs with an *S*-Me group at C-2′ (D and E) are more active than those with one monosulfide bridge between C-2′ and C-7′ (A–C and F–H). Comparison of the inhibitory effects of D and E revealed a double bond at C-6′/C-7′ in E that enhances activity. Regarding eutypellazines I–M, analogs with two *S*-Me groups at C-2 and C-2′ (J) exert a stronger effect than those with *O*-Me/hydroxyl substitution (K–M) or with a double bond at C-2′/C-3′ (I). In addition, both eutypellazine J and epicoccin A can reactivate latent HIV-1 transcription at a dose of 80 μM in a dose-dependent manner.

Lasiodipline E from *Lasiodiplodia pseudotheobromae* F2 possesses two *S*-Me and one *N*-Me groups, and this compound exerted antibacterial activity against five clinical strains, of which the most susceptible were *Streptococcus* sp., *Bacteroides vulgates* and *Peptostreptococcus* sp. (MICs = 0.12 μg ml^{-1}), superior to tinidazole (Wei et al. 2014). Lasiodipline E is also active against *Veillonella parvula* (MIC = 0.25 μg ml^{-1}) and *Actinomyces israelii*. Penicibrocazines B–E from *P. brocae* MA-231

Table 3 Polysulphide bridge-free thiodiketopiperazines (TDKs) with antibiotic activities

Name	Biosynthetic precursors	Antibiotic activity
Chetoseminudin B	Cyclo-(Trp-Ser)	Anti-trypanosomal
Epicoccins G and H	Cyclo-(Phe-Phe)	Antiviral
Eutypellazines A–L	Cyclo-(Phe-Phe)	Antiviral
Lasiodipline E	Cyclo-(Trp-Ala)	Antibacterial
Penicibrocazines B–E	Cyclo-(Phe-Phe)	Antibacterial, antifungal
Dehydroxybisdethiobis(methylthio)gliotoxin	Cyclo-(Phe-Ala)	Antibacterial
Eutypellazines N–P, R and S	Cyclo-(Phe-Phe)	Antibacterial
Glioperazine B	Cyclo-(Trp-Thr)	Antibacterial
Spirobrocazine A	Cyclo-(Phe-Phe)	Antibacterial
Haematocin	Cyclo-(Phe-Phe)	Antifungal
Peniciadametizines A and B	Cyclo-(Phe-Phe)	Antifungal
Alternarosin A	Cyclo-(Phe-Phe)	Antibacterial, antifungal
Bis-*N*-norgliovictin	Cyclo-(Phe-Ser)	Antibacterial, antifungal
Bisdethiobis(methylsulfanyl)apoaranotin	Cyclo-(Phe-Phe)	Antimycobacterial
Bisdethiodi(methylthio)-1-demethylhyalodendrin	Cyclo-(Phe-Ser)	Antimycobacterial
Graphiumins D, E, G, H and J	Cyclo-(Phe-Phe)	Anti-virulence

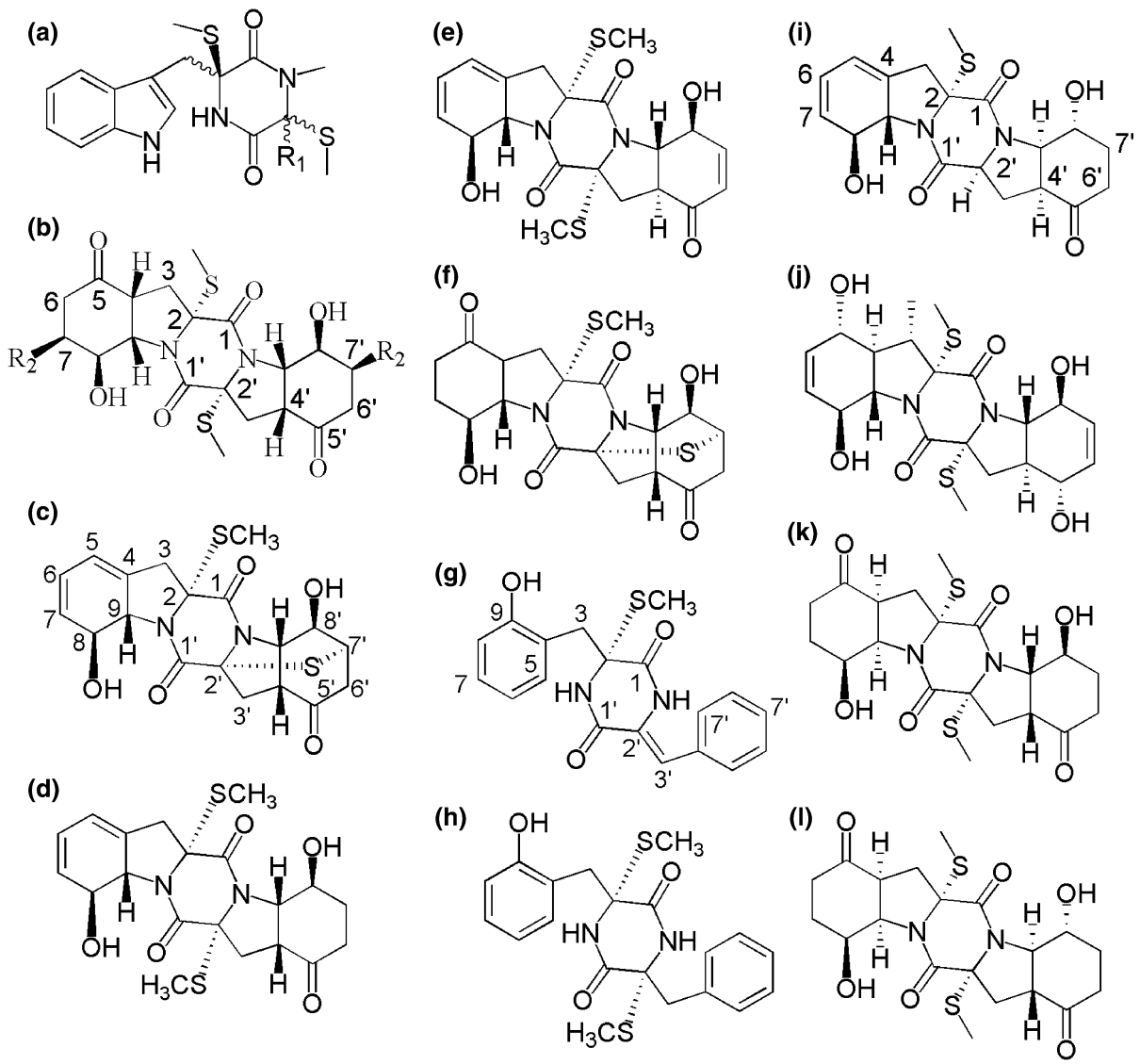

Fig. 2 Structure of partial polysulphide bridge-free TDKs. **a** Chetoseminudin B ($R_1 = CH_2OH$) and lasiodipline E ($R_1 = CH_3$). **b** Epicoccins G ($R_2 = H$) and H ($R_2 = OH$). **c**–**h** Eutypellazines A, D–F, I and J. **i**–**l** Penicibrocazines B–E (Fujimoto et al. 2004; Wei et al. 2014; Guo et al. 2009; Niu et al. 2017b; Meng et al. 2015a)

possess a 6-5-6-5-6 DKP skeleton and one or two *S*-Me groups at C-2/C-2′ (Meng et al. 2015a). They exhibit selective antimicrobial activity against some of the tested strains; B–D show activity against *S. aureus*, with C the most potent (MIC = 0.25 μg ml^{-1}), more active than chloromycetin; C also displays potent activity against *Micrococcus luteus* (MIC = 0.25 μg ml^{-1} compared with 2.0 μg ml^{-1} for chloromycetin); B, D and E exhibit activity against *Gaeumannomyces graminis*, especially B and E (MICs = 0.25 μg ml^{-1} compared with 16.0 μg ml^{-1} for amphotericin B). These findings indicate that the double bonds at C-6/C-7 and C-6′/C-7′ increase activity against *S. aureus*. In addition, more *S*-Me groups likely strengthen activity against *G. graminis*, and keto groups at C-5/5′ also enhance activity. Antibiotic activities of other polysulphide bridge-free TDKs are listed in Table 3 (Fukuda et al. 2015a, b; Gulder et al. 2012; Haritakun et al. 2012; Isaka et al. 2005; Li et al. 2006; Liu et al. 2015b; Meng et al. 2016; Niu et al. 2017a; Suzuki et al. 2000; Wang et al. 2009; Zheng et al. 2007b).

Sulphur-free DKPs

Prenylated indole DKPs, the largest family of sulphur-free compounds, are mainly produced by *Aspergillus* and *Penicillium*. They have three hallmark features; common biogenesis from tryptophan, one to three isopentenyl units, and a DKP nucleus (Chang et al. 2016). To date, 60 sulphur-free DKPs, including 42 prenylated indoles, have been identified (Tables 4 and 5; Fig. 3).

Dimeric brevianamide S dimerised via a C-8-C-8′ bond was isolated together with monomeric brevianamides T–V from *Aspergillus versicolor* MF030, and all four exhibit selective activity against Bacille Calmette-Guerin (BCG), although activity for S was modest, indicating that the dimeric structure is important for enhancing antimycobacterial activity (Song et al. 2012). Diketopiperazine M-3 from the fungus M-3 strongly inhibits the mycelial growth of *P. oryzae* by inducing curling and swelling (MIC = 0.36 μM), and it triggers morphological changes in the mycelia via similar mechanisms to those of the commercial antifungicidal agent rhizoxin (Byun et al. 2003). Therefore, M-3 may prove to be a valuable anti-fungicidal agent against rice blast disease. Neoechinulin B from *Aspergillus amstelodami* and *E. rubrum* F33 are structural analogs of rubrumlines A–O from *E. rubrum* F33 (Chen et al. 2015). These compounds reduce cytopathic effects on influenza A/WSN/33 virus, especially neoechinulin B which is the most potent (IC_{50} = 27.4 μM), and they are also effective against two clinical influenza virus isolates (oseltamivir-resistant LN/1109 and amantadine- and ribavirin-resistant HN/1222 strains). Analysis of the mechanism of action indicated binding to hemagglutinin in the influenza envelope, disrupting its interaction with the sialic acid receptor and the attachment of viruses to host cells. Further SAR analysis revealed that the $\Delta^{8,9}$ bond and a $\Delta^{12,15}$ unit of rubrumline D significantly enhance antiviral activity. Rubrumline N, which has an *O*-Me group at C-8, has a stronger antiviral effect than rubrumline M in which a hydroxyl group is substituted at C-8. In addition, based on neoechinulin B, an isopentenyl or oxygenated isopentenyl group attached to the indole ring in the scaffold of indole-bearing DKPs appears to be unfavourable for antiviral activity. Furthermore, neoechinulin B biosynthase consists of one NRPS (EchPS), a prenyltransferase (EchPT1) and a cytochrome P450 enzyme (EchP450) that catalyses dehydrogenation forming two olefin bonds (Table 1). Okaramine Q from *Penicillium simplicissimum* ATCC 90288 is a demethoxy derivative of okaramine B possessing an octacyclic ring system, including a four-membered azetidine ring and an eight-membered azocine ring (Shiono et al. 2000). This compound shows insecticidal activity against silkworms, albeit less than okaramine B, suggesting that the *O*-Me group at C-3 enhances this activity. Additionally, an azocine ring moiety with an appropriate conformation and an *N*-aliphatic group attached to the indole are important for activity. Furthermore, the molecular target in *Bombyx mori* is the glutamate-gated chloride channel, also the molecular target of ivermectin (Furutani et al. 2014; Kato et al. 2018). However, unlike ivermectin, this agent exerts minimal toxicity toward human glycine or γ-aminobutyric acid receptors, even at high concentrations. Speramide A from freshwater-derived *A. ochraceus* KM007 possesses an aza-spiro structure, and has potent activity against *Pseudomonas aeruginosa* (MIC = 0.8 μM) (Chang et al. 2016).

Tardioxopiperazine A from *Microascus tardifaciens* IFM4564 and *E. cristatum* EN-220 displays potent inhibitory activity against *S. aureus* (MIC = 8 μg ml^{-1}), more than its analogs cristatumin A and isoechinulin A (Du et al. 2012; Fujimoto et al. 1999). The structures only differ at C-8/C-9, indicating that the single bond between C-8/C-9 is essential to antibacterial activity. Like neoechinulin B, tardioxopiperazine A biosynthase contains one NRPS (EchPS) and two prenyltransferases (EchPT1 and PT2; Table 1). The Trp-derived alkaloid cyclo-*N*-Me-anthranilic acid-*N*-hydroxy-2-one-3-isopentenyl-Trp from Mediterranean *Aspergillus* sp. strongly inhibits *V. harveyi*, *V. natriegens*, *V. proteolyticus* and *V. carchariae* (MICs = 0.1–1 μg ml^{-1}) (Zhou et al. 2014). Waikialoids A and B from *Aspergillus* sp. JQ693975 are asymmetric dimeric DKPs, and both are complex prenylated indole alkaloids, but only the B form has a nitrone at N-39 and a hydroxyl group at C-50 (Wang et al. 2012). These compounds display dose-dependent activity against *C. albicans* in biofilm inhibition assays, and the A form is especially active (IC_{50} = 1.4 μM). Both inhibit cell adherence, hyphal development, and biofilm assembly during the early stages of surface colonisation. 12β-hydroxy-13α-methoxyverruculogen TR-2 from *A. fumigatus* LN-4 is a methylated derivative of verruculogen TR-2 and

Table 4 Sulphur-free prenylated indole diketopiperazines (DKPs) with antibiotic activities

Name	Biosynthetic precursors	Antibiotic activity
Brevianamide S	Dimer: cyclo-(Pro-Trp)-cyclo-(Pro-Trp)	Antimycobacterial
Brevianamides T–V	Cyclo-(Pro-Trp)	
Diketopiperazine M-3	Cyclo-(Trp-Val)	Antifungal
Neoechinulin B	Cyclo-(Ser-Trp)	Antiviral
Rubrumlines A–O		
Okaramine Q	Cyclo-(Trp-Trp)	Insecticidal
Speramide A	Cyclo-(Pro-Trp)	Antibacterial
Tardioxopiperazine A	Cyclo-(Ala-Trp)	Antibacterial
Trp derived alkaloid	Cyclo-(^{1}ATA-Trp)	Antibacterial
Waikialoids A and B	Dimer: cyclo-(Pro-Trp)-cyclo-(Pro-Trp)	Anti-biofilm
12β-hydroxy-13α-methoxyverruculogen TR-2	Cyclo-(Pro-Trp)	Antifungal
12,13-dihydroxyfumitremorgin C	Cyclo-(Pro-Trp)	Antibacterial, antimycobacterial, anti-trypanosomal
6-Methoxyspirotryprostatin B	Cyclo-(Pro-Trp)	Anti-trypanosomal
BOC derivatives of fumitremorgin C and tryprostatin B	Cyclo-(Pro-Trp)	Antibacterial
Avrainvillamide (CJ-17,665)	Cyclo-(Pro-Trp)	Antibacterial
Cyclo-(glycyl-L-tyrosyl)-4,4-dimethylallyl ether	Cyclo-(Gly-Tyr)	Antibacterial
Cristatumin A	Cyclo-(Ser-Trp)	Antibacterial
Dihydroxyisoechinulin A	Cyclo-(Ala-Trp)	Antibacterial
Novoamauromine	Cyclo-(Trp-Trp)	Antifungal
Ent-cycloechinulin	Cyclo-(Trp-Ala)	
Piscarinines A and B	Cyclo-(Pro-Trp)	Antibacterial, antifungal
Talathermophilins A and B	Cyclo-(Gly/Ala-Trp)	Nematicidal

ATA anthranilic acid, *BOC tert*-butyloxycarbonyl

12β-hydroxyverruculogen TR-2 (Li et al. 2012b). It displays varying degrees of activity against *B. cinerea*, *Alternaria solani*, *Alternaria alternata*, *Colletotrichum gloeosporioides*, *Gibberella saubinettii*, *Fusarium solani* and *F. oxysporum*, especially the former five strains (MICs = 6.25 μg ml^{-1}). It is more active than verruculogen TR-2 and 12β-hydroxyverruculogen TR-2, as well as the commercial fungicides carbendazim and hymexazol. In addition, this compound has a 2-methylpropan-2-ol group at C-3, and it has higher antifungal activity than cyclotryprostatin B that has an isobutenyl group at C-3. These observations suggest that the introduction of an *O*-Me group at C-13 yields higher activity, regardless of the configuration of the hydroxy group at C-12. The 2-methylpropan-2-ol substituent at C-3 on ring C of this family also appears to be necessary for activity. 12,13-dihydroxyfumitremorgin C from *Aspergillus* sp. SCSIOInd09F01, *A. fumigatus* 30402dZa and *Pseudallescheria* sp. MFB262 belongs to the fumitremorgin class that has a similar structure to 12β-hydroxy-13α-methoxyverruculogen TR-2 (Luo et al. 2017; Watts et al. 2010; Zhang et al. 2007b). It exhibits weak antibacterial activity, but strong inhibitory activity towards *M. tuberculosis* and *T. brucei* with 50% minimun inhibitory concentration (MIC_{50}) and IC_{50} values of 2.41 and 6.4 μM, respectively (superior to verruculogen and fumitremorgin B), demonstrating that the peroxide ring is not the bioactive pharmacophore. Furthermore, comparing with cyclotryprostatin A underscores the importance of the C-12 *R* configuration. 6-methoxyspirotryprostatin B from

Table 5 Sulphur-free-non-prenylated indole DKPs with antibiotic activities

Name	Biosynthetic precursors	Antibiotic activity
DKP isomers 1 and 2	Cyclo-(Leu-norvaline)	Antileishmanial
Diphenylalazines A and C	Cyclo-(Phe-Phe)	Antiviral, antibacterial, antifungal
Penicillatide B	Cyclo-(Phe-Pro)	Antibacterial, antifungal
Pinodiketopiperazine A	Cyclo-(Phe-norvaline)	Antibacterial
Spirobrocazine C	Cyclo-(Phe-Phe)	Antibacterial
Trichocyclodipeptides A–C	Cyclo-(Orn-Orn)	Antibacterial, antifungal
Aspergilazine A	Dimer: cyclo-(Pro-Trp)-cyclo-(Pro-Trp)	Antiviral
Cristatumin E	Dimer: cyclo-(Val-Trp)-cyclo-(Val-Trp)	Antibacterial
Pestalazine A	Dimer: cyclo-(Phe-Trp)-cyclo-(Leu-Trp)	Antiviral
Haenamindole	β-Phe-cyclo-(Trp-Phe)	Insecticidal
2'-epi-fumiquinazoline D	ATA-cyclo-(Ala-Trp)-Ala	Insecticidal
Neosartoryadins A and B	ATA-cyclo-(Val-Trp)-Aib	Antiviral
3-hydroxyfumiquinazoline A	ATA-cyclo-(Ala-Trp)-Ala	Antifungal

Orn ornithine, *Aib* 2-aminoisobutyric acid

Aspergillus sydowi PFW1-13 and *A. fumigatus* 030402dZa belongs to the spirotryprostatin class of alkaloids (Zhang et al. 2008). This compound is active against *T. brucei* (IC_{50} = 5.7 μM), unlike its derivatives spirotryprostatin A, *N*-Me-6-methoxyspirotryprostatin B and *N*-Me-spirotryprostatin A. Also, two *tert*-butyloxycarbonyl (BOC) derivatives of fumitremorgin C and tryprostatin B from *A. fumigates* MR2012 display potent activity against *S. aureus* and *B. subtilis* (MICs = 2.1–3.3 μg ml^{-1}), more than the parent compounds and comparable to tetracycline (El-Gendy and Rateb 2015). Therefore, the introduction of a BOC group significantly increases antibacterial activity against Gram-positive strains. It is likely that capping the NH groups with BOC groups makes these compounds more lipophilic, lowering their tendency to ionise, and thereby enhancing membrane penetration. Antibiotic activities of other prenylated indole DKPs and 18 sulphur-free-non-prenylated DKPs are listed in Tables 4 and 5 (Baran et al. 2005, 2006; Cai et al. 2012; Chen et al. 2017; Chu et al. 2010; Chunyu et al. 2017; Ding et al. 2008; Du et al. 2012; Guo et al. 2009; Hwang et al. 2016; Ishikawa et al. 2010; Kim et al. 2015; Koolen et al. 2012; Kozlovsky et al. 2001; Li et al. 2004, 2012b, 2013b; Meng et al. 2015b, 2016; Metwaly et al. 2015; Wang et al. 2013b; Youssef and Alahdal 2018; Yu et al. 2016).

Highly *N*-methylated typical peptides

Numerous structural modifications in the biosynthesis of antibiotic peptide products have been identified, of which *N*-methylation is the most common (Räder et al. 2018). Some studies have shown that *N*-methylation of amides removes H-bond donor capacity, affects the backbone conformation, and introduces differences in lipophilicity and antibiotic properties, and the effects are more obvious with an increasing number of *N*-methylated sites (Chatterjee et al. 2006, 2012; Räder et al. 2018; van der Velden et al. 2017). As shown in Table 6, 17 highly *N*-methylated typical peptides have been identified (represented by the structure of omphalotins in Fig. 4).

Phe-rich cordyheptapeptide A from *Cordyceps* sp. BCC1788 and BCC 16173 exhibits potent activity against *P. falciparum* (IC_{50} = 3.8–5.35 μM), while the B form has an *N*-Me-Phe residue instead of the *N*-Me-Tyr in A and is inactive, suggesting that the hydroxyl group in the aromatic ring is crucial for the antimalarial activity of this class (Isaka et al. 2007; Rukachaisirikul et al. 2006). Also, the A form is active against eight microbial strains, especially the Gram-negative bacteria *P. aeruginosa* and *Klebsiella pneumoniae*, as well as the dermatophytes *Trichophyton mentagrophytes* and *Microsporum audouinii* (MICs = 6 μg ml^{-1}; the diameters of inhibition zones: DIZs = 25, 26, 20 and 22 mm, respectively),

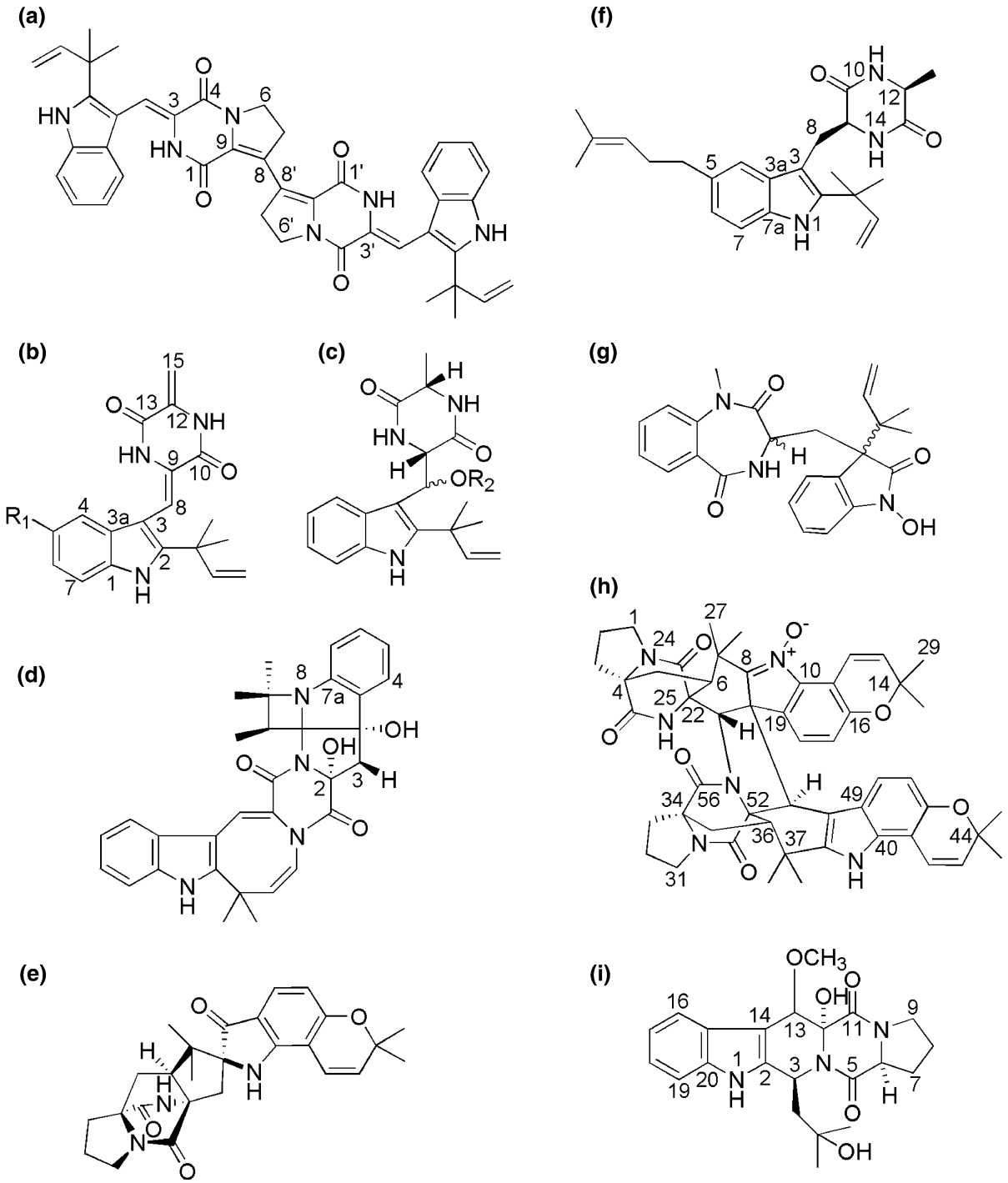

Fig. 3 Structure of partial sulphur-free prenylated indole DKPs. **a** Brevianamide S. **b** Rubrumlines D [R_1 = $CH_2CH(OH)C(OH)(CH_3)_2$] and neoechinulin B (R_1 = H). **c** Rubrumlines M (R_2 = H) and N (R_2 = CH_3). **d** Okaramine Q. **e** Speramides A. **f** Tardioxopiperazine A. **g** cyclo-*N*-Me-anthranilic acid-*N*-hydroxy-2-one-3-isopentenyl-Trp. **h** Waikialoid A. **i** 12β-hydroxy-13α-methoxyverruculogen TR-2 (Song et al. 2012; Chen et al. 2015; Shiono et al. 2000; Chang et al. 2016; Du et al. 2012; Zhou et al. 2014; Wang et al. 2012; Li et al. 2012b)

Table 6 Highly *N*-methylated typical peptides with antibiotic activities

Name	Sequence	Antibiotic activity
Cordyheptapeptide A	*N*-Me-Phe*-Pro-*N*-Me-Gly-Phe-*N*-Me-Tyr-Ile-Leu*	Antimalarial, antibacterial, antifungal
IB-01212	*N*, *N*-diMe-Leu-Ser*-*N*-Me-Leu-*N*-Me-Phe-Ser(*N*, *N*-diMe-Leu)-*N*-Me-Leu-*N*-Me-Phe*	Antileishmanial
Omphalotins E and F	*N*-Me-Ile*-*N*-Me-Gly-Val-*N*-Me-Ile-*N*-Me-Gly-Trp derive/*N*-hydroxy-Trp derive-*N*-Me-Val-Ile-*N*-Me-Val-*N*-Me-Val-*N*-Me-Gly-*N*-Me-3-hydroxy-Val*	Nematicidal
Omphalotin G	*N*-Me-Ile*-*N*-Me-2-hydroxy-Gly-Val-*N*-Me-Ile-Sar-*N*-hydroxy-Trp derive-*N*-Me-Val-Ile-*N*-Me-Val-*N*-Me-Val-*N*-Me-Gly-*N*-Me-3-hydroxy-Val*	
Pseudoxylallemycin A	Phe*-*N*-Me-Leu-Phe-*N*-Me-Leu*	Antibacterial, antimycobacterial, anti-trypanosomal, antileishmanial, antimalarial
Pseudoxylallemycin B	*O*-(buta-2,3-dienyl)-Tyr*-*N*-Me-Leu-*O*-(buta-2,3-dienyl)-Tyr-*N*-Me-Leu*	
Pseudoxylallemycin C	Phe*-*N*-Me-Leu-*O*-(buta-2,3-dienyl)-Tyr-*N*-Me-Leu*	
Pseudoxylallemycin D	Phe*-*N*-Me-Leu-5-hydroxy-*O*-(buta-2,3-dienyl)-Tyr-*N*-Me-Leu*	
Verrucamides A and B	*N*-Me-Phe*-Gly-Val-*N*-Me-Thr-Val-*N*-Me-Thr-Val-*N*-Me-Ala-Gly-Ile-*N*-Me-Ser-*N*-Me-Ile/*N*-Me-Val-Ser-Val*	Antibacterial
Verrucamides C and D	*N*-Me-Phe*-Gly-Val-*N*-Me-Thr-Val-*N*-Me-Thr-Val-*N*-Me-Ala-Gly-Val-*N*-Me-Ser-*N*-Me-Ile/*N*-Me-Val-Ser-Val*	
Talaropeptide A	*N*-Me-Ala-*N*-Me-Val-Val-Thr-*N*-Me-Val-Pro-*N*-Me-Val-*N*-Me-Val-*N*-Me-Phe-*N*-Me-Ile-Leu	Antibacterial
Talaropeptide B	*N*-Me-Ala-*N*-Me-Val-Val-Thr-Val-*N*-Me-Val-Pro-*N*-Me-Val-*N*-Me-Val-*N*-Me-Phe-*N*-Me-Ile-Leu	
Clonostachysins A and B	*N*-Me-Gly*-*N*-Me-Leu-Pro-*O*-Me-Tyr-Ala-*N*-Me-Val/*N*-Me-Ile-*N*-Me-Leu-*N*-Me-Ile-*N*-Me-Ala*	Antimicroalgal

Trp derive tricyclic tryptophan derivative, 3a-hydroxy-pyrrolidino[2,3-b]indole-2-carboxylic acid

*Denoting the linkage position of the ring formation

with potency greater than gatifloxacin and griseofulvin (Kumar et al. 2017). In addition, cordyheptapeptide A displays greater bioactivity against these pathogenic microbes than its linear form due to a reduction in the degree of freedom for each constituent within the ring resulting from cyclisation of the peptide. IB-01212 from marine sponge-derived *Clonostachys* sp. ESNA-A009 features C_2 symmetry, and displays Leishmanicidal activity in the low micromolar range against promastigotes *Leishmania pifanoi* and amastigote forms of the parasite *L. donovani*, with greater activity against amastigotes (Cruz et al. 2006; Luque-Ortega et al. 2010). Ten derivatives of IB-01212 were synthesised through the original ester linkages between the hydroxyl groups of Ser residues and the *C*-terminal carboxyl group of *N*-Me-Phe replaced by a thioester (Ser → Cys) or an amide such as Ser → 2,3-diaminobutyric acid (Dab), 2,3-diaminopropionic acid (Dap), ornithine (Orn) or Lys. In general, monosubstituted analogs are more active than bisubstituted ones, suggesting that perturbation of C_2 symmetry improves leishmanicidal activity. Therefore, the nature of the two hydroxyl groups that form the original peptide linkages of the two tetrapeptide moieties modulates activity. Furthermore, three analogs display higher activity against amastigotes than IB-01212, indicating that ring size affects leishmanicidal activity. Ruling out massive disruption of the plasma membrane suggested the involvement of intracellular targets such as mitochondrial dysfunction that eventually causes parasite death through an apoptotic-like process. Oxidatively modified omphalotins E–G from *Omphalotus olearius* TA90170 contain a tricyclic Trp derivative, and all exhibit strong and selective nematicidal activity against *Meloidogyne incognita*, especially G

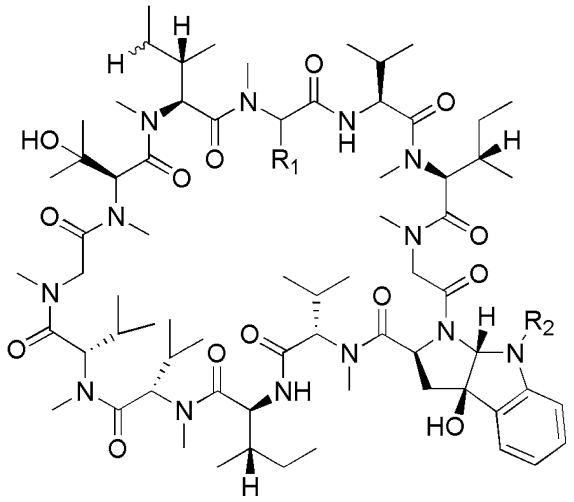

Fig. 4 Structure of omphalotins E–G (highly *N*-methylated typical peptides). E: R_1, R_2 = H; F: R_1 = H, R_2 = OH; G: R_1 = OH, R_2 = OH (Liermann et al. 2009)

(LD_{50} = 1 μg ml^{-1}; LD_{90} = 2 μg ml^{-1}), which is more active than ivermectin and comparable to its lipopeptide analogs omphalotins H and I (Liermann et al. 2009). It was suggested that both hydroxylation at *N*-Me-Gly and Trp derivatisation may improve nematicidal effects, while *O*-acetyl and *O*-(3-hydroxy-3-Me-butyl) groups in *N*-Me-Gly and *N*-Me-Ile residues do not appear to influence the activity of the omphalotin class.

Pseudoxylallemycins A–D from *Pseudoxylaria* sp. X802 contain an alternating pattern of *N*-methylation, with *N*-Me groups present at Leu but not Phe or Tyr residues (Guo et al. 2016). Specifically, B–D also carry one or two allenyl modifications at the aromatic ring of Tyr moieties. All show moderate activity against *P. aeruginosa* and *Mycobacterium vaccae*. A–C also display antiparasitic activity against *Trypanosoma brucei rhodesiense*, *Trypanosoma cruzi*, *L. donovani* and *P. falciparum*, especially B which is the most potent (IC_{50} = 0.64, 1.88, 2.01 and 1.23 μM, respectively), indicating that allenyl groups significantly affect antiparasitic activity (Guo et al. 2018). Verrucamides A–D from *Myrothecium verrucaria* XZ04-18-2 feature six *N*-methylated amino acid residues (Zou et al. 2011). They show significant activity against *S. aureus*, with A the most potent (IC_{50} = 3.59 μg ml^{-1}; MIC = 10 μg ml^{-1}). These findings demonstrated that extension of the carbon chain of *N*-Me-Val is conducive to maintaining higher antibacterial activity. Two 11–12 residue linear peptides, talaropeptides A and B from *Talaromyces* sp. CMB-TU011 lack mammalian cell cytotoxicity but exhibit promising growth inhibitory activity against *B. subtilis* (IC_{50} = 1.5 and 3.7 μM, respectively), indicating that enhanced activity is due to *N*-methylation of the Val residue in A (Dewapriya et al. 2018). Antimicroalgal activity of clonostachysins is shown in Table 6 (Adachi et al. 2005).

Non-highly *N*-methylated typical peptides

In addition to highly *N*-methylated typical peptides, since 2000, another 32 typical peptide products have been reported (Table 7). Figures 5 and 6 show the structures of arborcandins and calpinactam as representative examples. Seven apicidin-like compounds named apicidins A–C, D_1–D_3 and F have been identified. Apicidins A–C and D_1–D_3 from *Fusarium pallidoroseum* MF6040 and *Fusarium* sp. MF6058 have a C_8-keto or C_8/C_9-hydroxyl group at a 2-aminodecanoic acid (Ada) substituent linked to a β-turn amino acid residue, namely piperazic acid (Pip) or Pro (Singh et al. 2001, 2002). These compounds show potent and selective activity against *P. falciparum* and *Eimeria tenella*. Apicidins A and D_1 are among the most active compounds of the series (IC_{50} = 59 and 34 nM; MICs = 52 and 13 nM). Additionally, two synthesised C-8 hydroxyl compounds were over tenfold less active than apicidins A and D_1, and chemical modification of the Trp residue led to compounds exhibiting significant parasite selectivity. These results indicate that the C-8 keto group and Trp are both critical for activity. Apicidins B and C are also strongly and selectively active against *Besnoitia jellisoni* (MICs = 12.8 and 0.8 nM, respectively). Apicidin F has a 2-aminooctanedioic acid instead of Ada incorporated into the tetrapeptide, and it displays good in vitro activity against *P. falciparum* (IC_{50} = 0.67 μM) (von Bargen et al. 2013). Apicidins are potent and broad spectrum antiprotozoal agents that reversibly inhibit histone deacetylase (HDAC) activity (Kwon et al. 2003; Singh et al. 2001). HDACs regulate gene transcription by controlling the dynamic acetylation and deacetylation of Lys residues. Blockade of deacetylation causes hyperacetylation of histones, leading to untimely cell death. Arborcandins A–F from the fungus SANK17397 contain one 2-amino-5-

Table 7 Non-highly *N*-methylated typical peptides with antibiotic activities

Name	Sequence	Antibiotic activity
Apicidins A and B	Trp*/*N*-methoxy-Trp*-Ile-Pip/Pro-AODA*	Antimalarial, anti-*Eimeria*, anti-*Besnoitia*
Apicidin C	*N*-methoxy-Trp*-Val-Pip-AODA*	
Apicidins D_1–D_3	*N*-methoxy-Trp*-Ile-Pip-AOHA*/AHDA*/ANDA*	
Apicidin F	*N*-methoxy-Trp*-Phe-Pip-AOEA*	
Arborcandins A–D	AHTA*-Gly-β-Ala-ATDA/AHPA/AH HA/AOHDA-Asn-Asn-Ala-4-hydroxy-Gln-Thr–Thr*	Antifungal
Arborcandins E and F	APDA*/AHAA*-Gly-β-Ala-AHHA-Asn-Asn-Ala-4-hydroxy-Gln-Thr–Thr*	
LG53-R5	Leu*–Leu–Leu–Leu–Val*	Antifungal
Malformins A_1 and A_2	S**-Cys*-Val-Leu-Ile/Val-Cys*-S**	Antimalarial, anti-trypanosomal, anti-TMV, anti-HIV-1
Malformins B_2 and C	S**-Cys*-Val-Val/Leu-Leu-Cys*-S**	
Malformin E	S**-Cys*-Ile-Val-Leu-Cys*-S**	Antibacterial, antifungal
Serinocyclin A	Acc*-4-hydroxy-Pro-Ser-4-hydroxy-Lys-β-Ala-Ser-Ser*	Antimosquito
Xylapeptides A and B	*N*-Me-Phe*-Val-Ala-Leu-Pip*/Pro*	Antibacterial, antifungal
Aspergillipeptide D	*N*-Me-Tyr*-Val-Pro-*O*-Me-Tyr-*O*-Me-Tyr*	Anti-^{16}HSV-1
Aspergillipeptide E	Tyr-Trp-Val	
Calpinactam	Phe-Leu-His-Glu-Ile-Lys	Antimycobacterial
Trichodermamide B	A modified dipeptide	Antifungal, antibacterial
CAFT122-1	Ile*-Leu-Leu-Leu-Leu*	Antifungal
Tetrapeptides K38 and E33	Pro*/Gly*-Tyr/Phe-Pro-Tyr*	Antifungal
Pentapeptide 75-1-3-1	*N*-Me-Phe*-Val-Ile-Leu-Pro*	Synergistic antifungal
Lajollamide A	*N*-Me-Leu*-Leu-Leu-Leu-Val*	Antibacterial
Tetrapeptide BAFC 3291	Phe-Val-Val-Tyr	Antifungal, antibacterial

Pip piperazic acid, *AODA* 2-amino-8-oxodecanoic acid, *AOHA* 2-amino-8-oxo-9-hydroxy-decanoic acid, *AHDA* 2-amino-8-hydroxy-decanoic acid, *ANDA* 2-amino-9-hydroxy-decanoic acid, *AOEA* 2-aminooctanedioic acid, *AHTA* 2-amino-5-hydroxy-tetradecanoic acid, *ATDA* 2-amino-10-hydroxy-tetradecanoic acid, *AHPA* 2-amino-10-hydroxy-pentadecanoic acid, *AHHA* 2-amino-10-hydroxy-hexadecanoic acid, *AOHDA* 2-amino-10-oxohexadecanoic acid, *APDA* 2-amino-5-hydroxy-pentadecanoic acid, *AHAA* 2-amino-5-hydroxy-hexadecanoic acid, *TMV Tobacco mosaic* virus, *Acc* 1-aminocyclopropane-1-carboxylic acid, *HSV-1* herpes simplex virus type 1

*, **Denoting the linkage position of the first and second ring formation, respectively

hydroxyl acid (AHA) and one 2-amino-10-hydroxyl/10-oxo acid (AHOA), connected to Gly and β-Ala residues, respectively (Ohyama et al. 2000, 2003). They possess strong growth inhibitory activity against *A. fumigatus*, of which C, E and F are the most potent, with minimum effective concentrations (MECs) of 0.063 μg ml^{-1}, considerably superior to pneumocandin A_0; However, against *Candida* spp. (*C. albicans*, *Candida parapsilosis* and *Candida tropicalis*), F is the most potent (MICs = 0.25–2 μg ml^{-1}), comparable to the MICs of fluconazole (Ohyama et al. 2000). This suggests that the hydroxyl group and carbon chain extension of the two unusual AHA and AHOA units are important for enhancing the antifungal activity of arborcandins. In addition, activity of these compounds against *Candida* spp. is due to inhibition of 1,3-β-glucan synthase, and they cause a change in the hyphal growth of *A. fumigates* (Ohyama et al. 2000, 2004).

LG53-R5 from *Fusarium decemcellulare* LG53 and *Fusarium* sp. R5 exhibits broad spectrum antifungal activity against *C. gloeosporioides*, *C. musae* and *F. oxysporum*, among which activity toward *F. oxysporum* (MIC = 23 μM) is superior to carbendazim that is used globally as an agricultural and horticultural fungicide (Li et al. 2016b; Zhu et al. 2018). Malformins A_1 (*A. niger* 56-39 and *Aspergillus tubingensis* FJBJ11), A_2 (*A. niger* 56-39), B_2 (*A. niger* 56-30), C (*A. niger* AN-1, # 94-1212 and SCSIO Jcsw6F30) and E (*Aspergillus tamari* FR02) are cyclicpentapeptides with a disulphide bond between

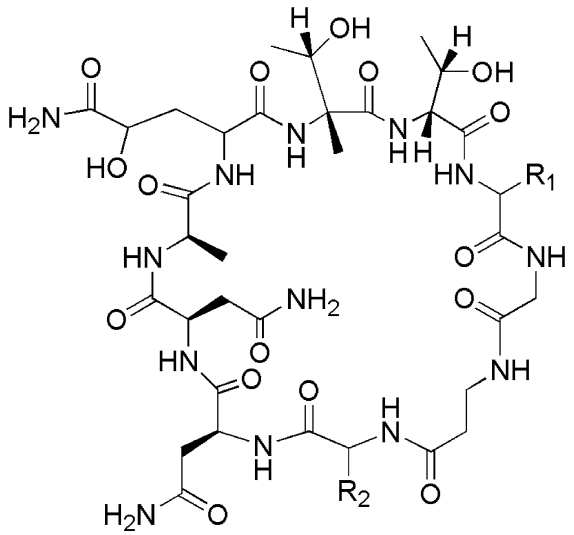

Fig. 5 Structure of arborcandins A–F (non-highly *N*-methylated typical cyclic peptides). A: $R_1 = (CH_2)_2CH(OH)(CH_2)_8CH_3$, $R_2 = (CH_2)_7CH(OH)(CH_2)_3CH_3$; B: $R_1 = (CH_2)_2CH(OH)(CH_2)_8CH_3$, $R_2 = (CH_2)_7CH(OH)(CH_2)_4CH_3$; C: $R_1 = (CH_2)_2CH(OH)(CH_2)_8CH_3$, $R_2 = (CH_2)_7CH(OH)(CH_2)_5CH_3$; D: $R_1 = (CH_2)_2CH(OH)(CH_2)_8CH_3$, $R_2 = (CH_2)_7CO(CH_2)_5CH_3$; E: $R_1 = (CH_2)_2CH(OH)(CH_2)_9CH_3$, $R_2 = (CH_2)_7CH(OH)(CH_2)_5CH_3$; F: $R_1 = (CH_2)_2CH(OH)(CH_2)_{10}CH_3$, $R_2 = (CH_2)_7CH(OH)(CH_2)_5CH_3$ (Ohyama et al. 2000, 2003)

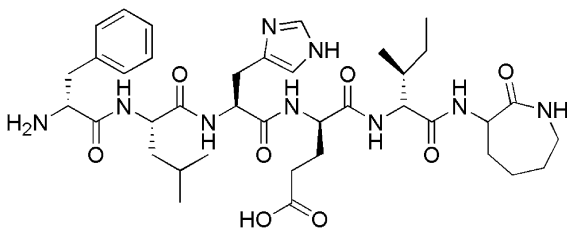

Fig. 6 Structure of calpinactam (non-highly *N*-methylated typical linear peptides) (Koyama et al. 2010a, b)

two cysteine thiols. Malformins A_1, A_2, B_2 and C exhibit potent anti-*P. falciparum* (IC_{50} = 0.056, 0.095, 0.019 and 0.07 μg ml^{-1}, respectively) and anti-*T. brucei brucei* (IC_{50} = 0.19, 0.56, 0.0052 and 0.0016 μg ml^{-1}, respectively) activities, equal to those of pentamidine and artemether, but more active than chloroquine (Sugawara 1990; Tan et al. 2015; Varoglu and Crews 2000; Zhou et al. 2016). Moreover, a modified malformin with a less hindered Ala instead of the Leu present in malformin C exhibits reduced activity against both parasites, as do two disulphide bond-free malformin C derivatives (Kojima et al. 2009). These results indicate that the disulphide bond is essential, and branched amino acids (e.g. Leu, Ile and Val) are also crucial components. Interestingly, malformin A_1 inhibits *Tobacco mosaic* virus (TMV) replication and infection, and is more active than the positive control ningnamycin (Tan et al. 2015). Studies have indicated that the anti-TMV properties of malformin A_1 could possibly be due, at least in part, to its ability to modulate ethylene production, which in turn elicits defence mechanisms in host plants. Malformin C exerts potent anti-HIV-1 activity via SF162 infection in TZM-bl cells, comparable to that of abacavir, a nucleoside reverse transcriptase inhibitor, and ADS-J1, an effective HIV-1 entry inhibitor (Zhou et al. 2016). Malformin E displays significant growth inhibition against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*, more active than gentamicin (Ma et al. 2016). It also has strong antifungal activity against *Penicillium chrysogenum*, *C. albicans* and *F. solani*, equivalent to nystatin. Ser-rich serinocyclin A from *Metarhizium anisopliae* has a cyclopropane amino acid residue along with a charged lysyl side chain and multiple hydroxyl groups that contribute to the polar nature of the compound (Krasnoff et al. 2007). This compound can produce a sublethal locomotory defect in mosquito larvae (EC_{50} = 59 ppm). Xylapeptides A and B from *Xylaria* sp. #GDG-102 have a Pip moiety and Pro residue, respectively (Xu et al. 2017). The A form shows moderate inhibitory activity only against *B. subtilis* and *B. cereus* (MICs = 12.5 μg ml^{-1}), while B exhibits stronger and broader antimicrobial activity against *B. subtilis*, *B. cereus*, *B. megaterium*, *Micrococcus luteus*, *S. aureus*, *Shigella castellani* and *C. albicans*. This suggests that the Pip and Pro moieties play different roles in antimicrobial activity.

Aspergillipeptide D with two *O*-Me-Tyr and one *N*-Me-Tyr residues, and the linear tripeptide aspergillipeptide E from *Aspergillus* sp. SCSIO 41501, display antiviral activity against herpes simplex virus type 1 (HSV-1) with IC_{50} values of 9.5 and 19.8 μM, respectively, and D also shows antiviral activity against acyclovir-resistant clinical isolates of HSV-1-106 and HSV-1-153 (12.5 μM) with a ~ 50% inhibition rate (Ma et al. 2017). The cyclic structure is important for maintaining high anti-HSV-1 activity. Calpinactam from *Mortierella alpina* FKI-4905 has a caprolactam moiety at its *C*-terminus and was found to inhibit the growth of *M. smegmatis*

(MIC = 0.78 μg ml^{-1}; DIZ = 22 mm at 5 μg/disk), more effective than isoniazid, rifampicin, kanamycin, pyrazinamide, lysocin E and propeptin (Koyama et al. 2010a, b; Yagi et al. 2017). Using an in vivo silkworm infection model for *M. smegmatis*, calpinactam exerted moderate therapeutic effects, and it shows moderate inhibition of the growth of *M. tuberculosis* (Yagi et al. 2017). Meanwhile, a series of synthesised calpinactam derivatives with different amino acids exhibited no or significantly reduced antimycobacterial activity, revealing that the side chains, stereochemistry, and the entire peptide chain length are all critical for antimycobacterial activity (Koyama et al. 2010a, b; Nagai et al. 2012). Preliminary analysis of the mechanism of action indicated that calpinactam might act on the cell wall biosynthetic steps in mycobacteria (Koyama et al. 2010b). Trichodermamide B, a modified linear dipeptide from *Trichoderma virens* CNL910 and *Halimeda* sp.-derived CNK266, possesses a cyclic *O*-alkyl-oxime functionality incorporated into a six-membered ring (Garo et al. 2003). It exhibits moderate antimicrobial activity against amphoterocin-resistant *C. albicans*, MRSA and VRE, whereas its dechlorinated derivative trichodermamide A is completely inactive. This suggests that the chlorine atom is an essential part of the pharmacophore. Indeed, chlorination is known to play an essential role in the antibiotic activity of numerous structurally diverse natural products (e.g. vancomycin and chloramphenicol). Antibiotic activities of other non-highly *N*-methylated typical peptides are shown in Table 7 (Bertinetti et al. 2009; Gulder et al. 2012; Huang et al. 2014; Talontsi et al. 2012; Wu et al. 2011).

Conclusions

In this review, we summarise 186 diverse fungi-derived DKPs and typical peptides reported since 2000, and focus of the structural characteristics, SAR and mechanisms of action of 107 of them. These features contribute significantly to antibiotic activity. In the biosynthesis, genetics, total synthesis and research methodologies has grown considerably over this time. However, only biosynthases of tardioxopiperazines and neoechinulins have been reported (Table 1), consistent with the claim that research on DKP biosynthesis tends to move along at a slow pace compared with organic synthesis. With the rapid development of modern biotechnological approaches and high-throughput sequencing technologies, our understanding of the molecular and enzymatic mechanisms of DKP biosynthesis is deepening. Therefore, predictably, more and more NRPSs will be identified, and novel DKPs with high antibiotic activity and low toxicity will likely be designed and tested. Two methods are most often used for the exploration of natural DKPs; traditional approaches and molecular detection. All DKPs mentioned in this review were identified using the former, classical approach, that generally proceeds as follows: (1) fermented cultures are extracted with organic solvent (e.g. acetone, EtOAc, methyl ethyl ketone, methanol, ethanol); (2) extracts are concentrated *in vacuo* and subjected to column chromatography (e.g. silica gel, Sephadex LH-20, Lobar LiChroprep RP-18) or thin layer chromatography on silica gel; (3) active fractions are further separated by reversed-phase high performance liquid chromatography (HPLC); (4) structures are determined mainly by nuclear magnetic resonance (NMR), electrospray ionization mass spectrometry (ESI–MS), infrared ray (IR) or gas chromatography–mass spectrometer (GC–MS). Meanwhile, molecular detection is based on the relationship between DKP biosynthase sequences and structures: (1) biosynthesis-related DKP genes are cloned by PCR amplification using conserved primer pairs and phylogenetic analysis of sequences reveals the structures of DKPs; (2) genes are also screened by phylogenetic analysis of "cryptic gene clusters" in the genome, and structures are derived based on ten conserved specific amino acid residues of adenylation domains in NRPSs.

SAR analysis suggests that the presence of specific groups (e.g., di- and tetrasulphide bridges, double bonds, azocine rings, certain amino acids and their configuration, keto groups, disulfide bonds, and caprolactam), substitutions at some pharmacophore sites (e.g., *O*-Me, hydroxyl, 2-methylpropan-2-ol, *tert*-butyloxycarbonyl, allenyl, the number of *N*-methylations, chlorination and perturbation of C_2 symmetry), dimerisation and its linkage sites, and cyclic structures and ring size are important for endowing activity. Mechanisms of action can be summarised as follows: (1) inhibition of protein biosynthesis for aspirochlorine (a halogenated spiro compound); (2) inhibiting the production of virulence factors for graphiumins; (3) inhibition of ATP synthesis in mitochondria,

causing an uncoupling of oxidative phosphorylation and depression of respiration for emestrins; (4) perturbing the proteome and inducing redox stress in fungi for gliotoxin; (5) inhibiting mycelial growth by inducing curling and swelling, and inducing morphological changes in mycelia for diketopiperazine M-3; (6) binding to hemagglutinin in the influenza envelope, and disrupting its interaction with the sialic acid receptor and the attachment of viruses to host cells for neoechinulin B and rubrumlines; (7) targeting glutamate-gated chloride channels in *Bombyx mori* for okaramines; (8) inhibiting cell adherence, hyphal development, and biofilm assembly during the early stages of surface colonisation for waikialoids; (9) targeting the plasma membrane, causing mitochondrial dysfunction that eventually causes parasite death via an apoptotic-like process for IB-01212; (10) inhibition of enzymes (e.g. HDAC for apicidins and 1,3-β-glucan synthase for arborcandins); (11) modulating ethylene production for malformin A_1; and (12) acting on cell wall biosynthesis in mycobacteria for calpinactam. However, research on SARs and mechanisms of action is limited and often poorly focused, and further detailed studies are clearly needed.

Regardless of future directions, some fungal DKPs and typical peptides can be regarded as promising candidates and lead compounds for drug development in agriculture and medicine due to their potent antimicrobial and antiprotozoal properties. However, to date, only cyclosporin A has been developed as an antifungal drug (Survase et al. 2011; Wang et al. 2017b). Therefore, effective research and development must be undertaken if novel pharmaceutical drugs and biocontrol agents are to be brought to market.

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial interest.

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