Nematicidal Substances from Fungi

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Abstract: This review summarizes the 179 compounds from fungi that have shown to possess nematicidal activities. These compounds belong to diverse chemical groups and they are mainly isolated from a variety of deuteromycete, ascomycete and basidiomycete fungi. Some of them have been patented as nematicidal agents. We review and classify these compounds based on their structural types. Their nematicidal activities are described and their potential roles in natural environments and in the biocontrol of nematodes are discussed.

Keywords: Nematode, fungus, compound, nematicidal activity, biocontrol.

INTRODUCTION

Nematodes can attack and destroy a wide variety of organisms, including animals, microorganisms and plants. Among the species susceptible to nematode infections, plants with significant agricultural and forestry importance have probably attracted the most attention. This is because plant parasitic nematodes can cause serious damages to agriculture and forestry [1]. For example, it has been estimated that plant root-knot nematodes cause around US $ 80 billion worth of damages to the global agricultural crops annually [2]. As a result, there have been significant financial and scientific investments to find effective solutions to control parasitic nematodes.

In the recent past, the use of synthetic chemical compounds has been the most common strategy for controlling plant parasitic nematodes. While effective in certain circumstances, the widespread use of man-made chemical nematicides has caused significant problems to both the environment and human health. Consequently, their use has been reduced significantly for pest control in agriculture and forestry in the past few years. The reduced use of synthetic chemical nematicides has generated significant demands for environmentally friendly alternative strategies. Biological control is a potentially effective alternative for the management of nematode pests. Consequently, nematophagous fungi, a group of natural enemies of nematodes, have become the major target organisms from which to develop biological agents to control the parasitic nematodes.

Biological agents include both live organisms as well as their metabolic products. Fungi are known to possess a huge diversity of metabolic pathways and they have provided several large classes of commercial compounds, including many antibiotics used in medicine [3]. Therefore, secondary metabolites in fungi could have much potential in their novel structures and nematicidal activities. Indeed, the evaluation and commercial development of such natural chemicals, including nematicidals, are pursued by many research groups and biotech companies.

Because of significant research in this area in the recent past, many nematicidal compounds have been found from fungi. Though no major commercial product based on these natural fungal compounds has been developed yet for wide use, there have been several exciting discoveries. For example, a new peptide called omphalotin was obtained from the fungus *Omphalotus olearius* and this peptide has shown to have a nematicidal activity similar to the commercial nematicide ivermectin [4].

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There have been two reviews on natural nematicidal metabolites in the past. In the first, Anke and Sterner (1997) [5] reviewed nematicidal metabolites from higher fungi and discussed those metabolites from the perspective of fungal taxonomic groups. In the second, Chitwood (2002) [6] reviewed the phytochemicals that showed antagonism against nematodes. However, Chitwood's focus was on natural compounds from higher plants. In our current review, we summarize all natural products isolated from fungi that have shown to contain nematicidal activities. Our list includes both new compounds as well as 'old' compounds but that have been isolated from fungi and been 'rediscovered' to have nematicidal activities. Our review covers a total of 179 compounds and these compounds are discussed with regard to their chemical structures and nematicidal activities.

ALKALOIDS

This group of compounds included 33 nematicidals from fungi. More than half of the compounds were isolated from two genera, *Penicillium* and *Aspergillus*. The oxindole alkaloid paraherquamide (**1**) was originally isolated from *Penicillium paraherquei* and its structure was determined by X-ray diffraction analysis [7]. Subsequently, paraherquamide and its novel analogs paraherquamides B (**2**), C (**3**), D (**4**), E (**5**), F (**6**), G (**7**) were obtained from another species of *Penicillium*, *P. charlesii* (ATCC 20841) [8,9]. All these seven metabolites possessed nematicidal activities against the model nematode *Caenorhabditis elegans* with LD_{50} (Lethal Dose required to cause the death of 50% of the tested organism) values in the range of 2.5-160 μg mL^{-1}. Among them, paraherquamide was the most potent with an LD_{50} value of 2.5 μg mL^{-1} [8]. From another strain of *Penicillium*, IMI332995, paraherquamide and its seven novel analogues VM55594 (**8**), VM54158 (**9**), VM54159 (**10**), VM55595 (**11**), VM55596 (**12**), VM55597 (**13**) and VM55599 (**14**) were found [10,11]. The nematicidal activities of compounds **1** and **8-10** were assayed against both *Haemonchus contortus* larvae and *Trichostrongylus colubriformis* adults *in vitro*. The results showed that compounds **1** and **10** were more active than compounds **8** and **9,** with MIC_{50} (Minimum Inhibitory Concentration required to inhibit the growth of 50% of the tested organism) values of 31.2 and 25.6 μg mL^{-1} against *H. contortus* for compounds **1** and **10** respectively. In addition, compounds **1** and **10** could cause 99.5% and 100% reductions in faecal egg counts of the nematode *T. colubriformis* at 4 mg kg^{-1}. These results indicated that the 14-dehydroxy in compounds **1** and **10** was more potent than their corresponding 14-hydroxy in analogues **8** and **9** [10]. Compound **12** was the first *N*-oxide member in the paraherquamide family and it was found capable of eliminating 94% faecal eggs of *T. colubriformis* when dosed at 2.0 mg kg^{-1} [11].

In 1997, two members of a new class of anthelmintics, aspergillimide (VM55598) (**15**) and 16-keto aspergillimide (SB202327)

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(**16**), were isolated from *Aspergillus* sp. IMI 337664 [12]. In addition, three new paraherquamides SB203105 (**17**), SB200437 (**18**) and VM54159 (**10**) were also isolated from this strain. This study was the first to report paraherquamides from an organism outside the fungal genus *Penicillium*. These compounds were shown to have weak to moderate activities against adult *T. columbriformis*. Tests conducted during bioassay-guided extraction procedures showed that the 16-keto analogue of aspergillimide was active against *Haemonchus contortus* L_3 larvae *in vitro* but not *in vivo* [12].

Three new alkaloids marcfortine A (**19**), B (**20**) and C (**21**) were obtained from the mycelium of *Penicillium roqueforti* [13,14]. The chemical structures of marcfortine A and C were established by X-ray analysis. These three compounds possessed potent anthel-mithic properties against plant-parasitic and animal-endoparasitic nematodes [15].

The alkaloid phenoxazone (**22**) was isolated from the mycelial cultures of *Calocybe gambosa* and fruiting bodies of *Pycnoporus sanguineus* [16,17]. This compound showed nematicidal activity against *Meloidogyne incognita* ($LD_{50:}$ 50 μg mL^{-1}) [18]. A novel alkaloid 2-aminoquinoline (**23**) was isolated from the fruiting bodies of *Leucopaxillus albissimus* var. *paradoxus* form *albiformis* (Murr.) Sing. & Sm. [19]. At the concentration of 50 μg mL^{-1}, compound **23** caused the reductions of 50% motility, 74% viability, and 52% cast formation in nematode *Nippostrongylus braziliensis* [19].

Three nitrogen-containing compounds including two novel ones [1-(1-((2E,6Z)-6-amino-5-methylnona-2,6-dien-4-yl)-4-methylpiperidin-2-yloxy)heptan-2-one (**24**), 2-(1H-pyrrol-1-yl)ethanol (**25**)] and a known one [1-methyl-1H-pyrrole-2-carboxylic acid (**26**)] were obtained from solid fermentation cultures of the basidiomycete *Coprinus xanthothrix* [20]. These three compounds have shown nematicidal activities against *Panagrellus redivivus* and *Meloidogyne arenaria* at 500 ppm. Among them, compounds **25** and **26** showed LD_{50} values at a concentration of 125 ppm after 12 hours [20]. Gliotoxin (**27**), a known antibiotic, was also weakly active against *Anguillula aceti* [21]. Gliotoxin has been isolated from a large number of fungi including *Trichoderma virens* [22], *Penicillium obscurum* [23], *Gliocladium fimbriatum* [24], *Candida albicans* [25] and *Aspergillus fumigatus* [26].

Two known compounds, 6-methoxy-carbonylpicolinic acid (**28**) and 2,6-pyridinedicarboxylic acid (**29**), were obtained from the culture filtrate of *Penicillium bilaiae*. By a bioassay at 300 mg L^{-1}, both **28** and **29** showed nematicidal activities with a mortality of 52% and 98% respectively against the root-lesion nematode *Pratylenchus penetrans* [27]. Author suggested that the carboxy groups in compounds **28** and **29** likely played important roles in their nematicidal activities [27].

A new alkaloid, peniprequinolone (**30**), together with the known compounds penigequinolones A (**31**), B (**32**) and 3-methoxy-4,6-dihydroxy-4-(4'-methoxyphenyl) quinolinone (**33**) were isolated from the liquid culture of *Penicillium* cf. *simplicissimum* [28]. Compounds **31**, **32** and **33** were first isolated from other species of the genus *Penicillium* [29,30]. These compounds were active against the nematode *P. penetrans* at the killing rates of 82.4%, 69.2% and 57.7% respectively at the concentration of 1000 mg L^{-1}. These results indicated that either a phenolic hydroxyl group at C-5 or a tetrahydropyran ring in these compounds might be necessary for their nematicidal activities against *P. penetrans* [28].

PEPTIDE COMPOUNDS

This group of nematicidal compounds includes 26 chemicals. Four of them were isolated from the mycelium of *Apiocrea chrysosperma* Ap101 [31]. These four were linear lipophilic peptides called chrysospermins A (**34**), B (**35**), C (**36**) and D (**37**) (Table **1**). These compounds have been patented as nematicidal and anthelminthic agents [32]. The chrysospermins are homologous to members of the peptaibol family and share structural similarities to trichorzianine isolated from the fungus *Trichoderma harzianum*. Each of these four peptides contains 19 amino acids and possesses a C-terminal Trpol and one labile Aib-Pro bond [33].

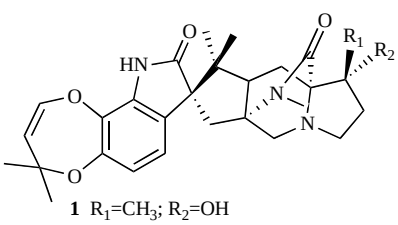
The N-terminally acetylated lipophilic linear polypeptide antiamoebin I (**38**) have been obtained from three fungal species *Emericellopsis poonensis, E. synnematicola* and *Cephalosporium pimprina* [34]. The structure of **38** was determined by several spectral methods including X-ray crystallography. Compound **38** has been shown activity against helminthes [35-37].

Peptidal compounds omphalotin A (**39**) and its derivatives omphalotin B (**40**), C (**41**) and D (**42**) were obtained from *Omphalotus olearius*. All four compounds have been shown to possess strong nematicidal activities against nematodes [4,38,39]. Omphalotin A (**39**), a cyclic dodecapeptide, was highly toxic (LD_{90}: 0.76 μM) towards the plant parasitic nematode *Meloidogyne incognita*. However, it was approximately 50 times less active against the saprophytic nematode *C. elegans* (LD_{90}: 38 μM) [4,38]. The corresponding LD_{90} values for the commercially available nematicide ivermectin were 4.6 μM and 0.46 μM respectively against *M. incognita* and *C. elegans*. Compound **39** lacks any antimicrobial and phytotoxic activities, and contains only weak cytotoxic activity, making it a potentially useful nematicide. The three derivatives omphalotin B (**40**), C (**41**) and D (**42**) all possessed nematicidal activities similar to that of omphalotin A [39].

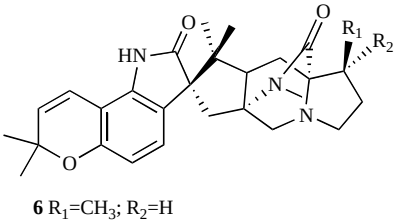
The cyclic depsipeptide beauvericin (**43)** was weakly active against *M. incognita* [18]. This peptide was isolated from the basidiomycete *Polyporus sulphureus* [40], as well as from several deuteromycetes *Beauveria bassiana* [41], *Paecilomyces fumosoroseus*, *Fusarium* spp. [42] and *Beauveria* sp. FKI-1366 [43]. Other two cyclodepsipeptides, enniatin A (**44**) and enniatin B (**45**), were isolated from the culture broth of *Fusarium* spp. [44,45], and both were weakly active against *M. incognita* [18]. Enniatin B was also reported to possess a nematicidal activity against *A. aceti* [26]. Two novel depsipeptides bursaphelocides A (**46**) and B (**47**) were isolated from an imperfect fungus, strain D1084 that belongs to Mycelia sterilia. These two compounds (**46** and **47**) were active against *Bursaphelenchus xylophilus* at a dose of 100 μg per ball

Table 1. Primary Structures of Chrysospermin A, B, C and D

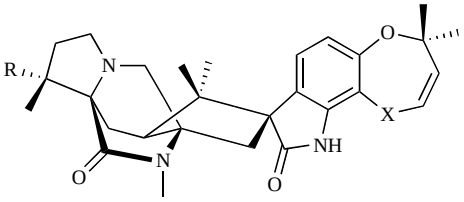
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
34	AcPhe-	Aib-	Ser-	Aib-	**Aib-**	Leu-	Gln-	Gly-	Aib-	Aib-	Ala-	Ala-	Aib-	Pro-	**Aib-**	Aib-	Aib-	Gln-	Trpol
35	AcPhe-	Aib-	Ser-	Aib-	**Aib-**	Leu-	Gln-	Gly-	Aib-	Aib-	Ala-	Ala-	Aib-	Pro-	**Iva-**	Aib-	Aib-	Gln-	Trpol
36	AcPhe-	Aib-	Ser-	Aib-	**Iva-**	Leu-	Gln-	Gly-	Aib-	Aib-	Ala-	Ala-	Aib-	Pro-	**Aib-**	Aib-	Aib-	Gln-	Trpol
37	AcPhe-	Aib-	Ser-	Aib-	**Iva-**	Leu-	Gln-	Gly-	Aib-	Aib-	Ala-	Ala-	Aib-	Pro-	**Iva-**	Aib-	Aib-	Gln-	Trpol



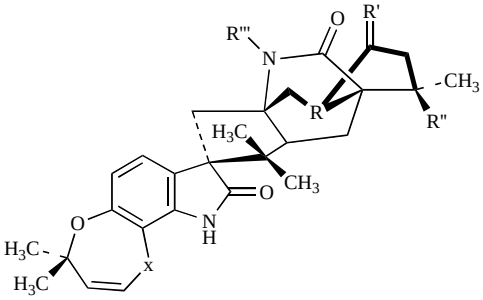
1 R_1=CH_3; R_2=OH
2 R_1=R_2=H
3 R_1=R_2=CH_2
4 R_1=R_2=CH_2O
5 R_1=CH_3; R_2=H



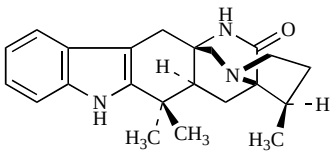
6 R_1=CH_3; R_2=H
7 R_1=CH_3; R_2=OH



8 R=H X=Absent
9 R=OH, X=Absent
10 R=H, X= -O-



11 R= N R'=H_2, R"=H, R'"=H, X=Absent
12 R= N^+-O^- R'=H_2, R"=OH, R'"=Me, X=O
13 R= N R'=O, R"=OH, R'"=Me, X=O



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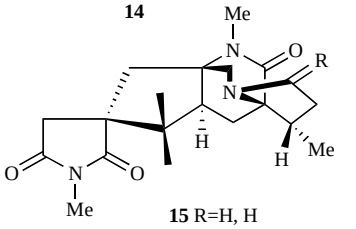
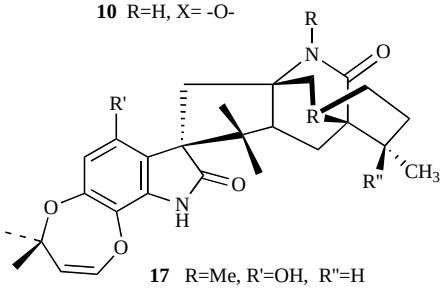
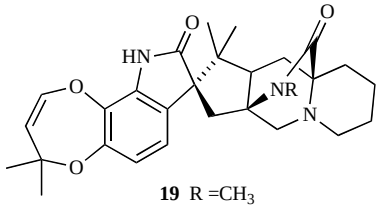


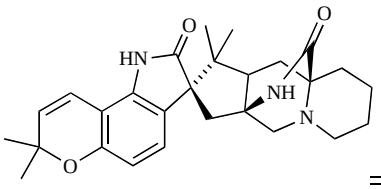
15 R=H, H
16 R=O



17 R=Me, R'=OH, R"=H
18 R=H, R'=H, R"=H



19 R =CH_3
20 R =H



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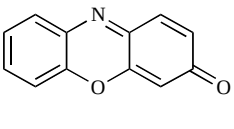

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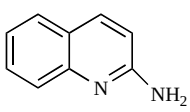

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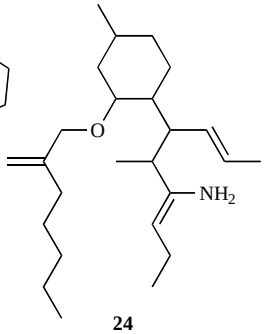

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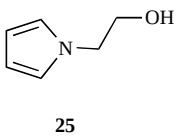

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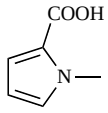

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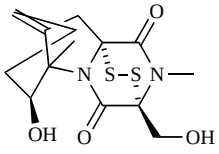

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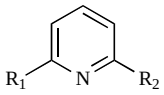
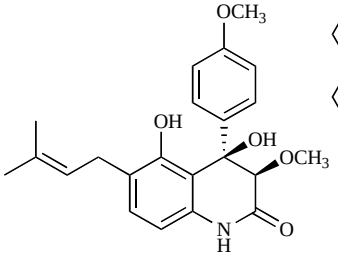


28 R_1= $COOCH_3$ R_2= COOH
29 R_1= COOH R_2= COOH



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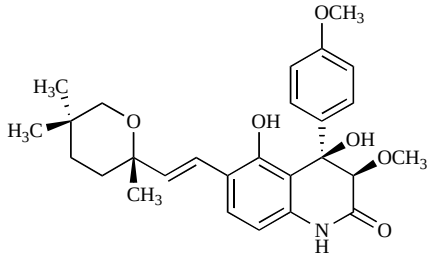

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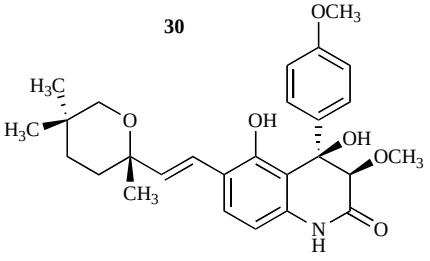

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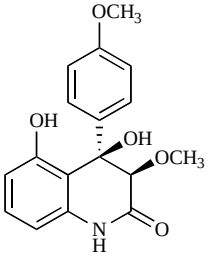

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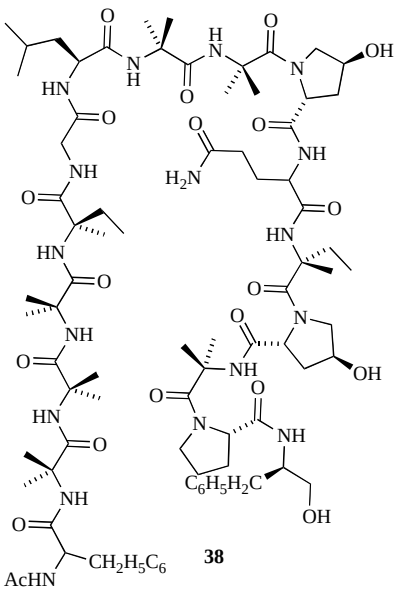
using the "cotton ball on the fungal mat method" [46]. It was the first description of destruxin analogues exhibiting nematicidal activity. From another imperfect fungal strain PF1022, a novel cyclodepsipeptide PF1022A (**48**) was obtained and shown to exhibit potent anthelmintic activity against *Ascaridia galli* in chickens with the dose of LD_{90} at 2 mg kg^{-1} [47]. Importantly, no toxic effect was observed to the host animals. The efficacy of compound **48** against anthelmintic-resistant nematodes in sheep and cattle was investigated and the result confirmed that PF1022A (**48**) was fully effective against these parasitic nematode populations [48].

Cyclosporin A (**49**) was reported to possess nematicidal activity against *M. incognita* although it was approximately 100 times less potent than omphalotin A [18]. Cyclosporin A has been isolated from *Tolypocladium inflatum* (originally named *Trichoderma polysporum*), *Fusarium solani* and *Cylindrocarpon lucidum* [49].



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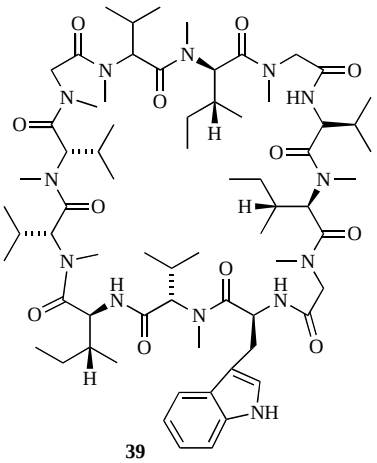

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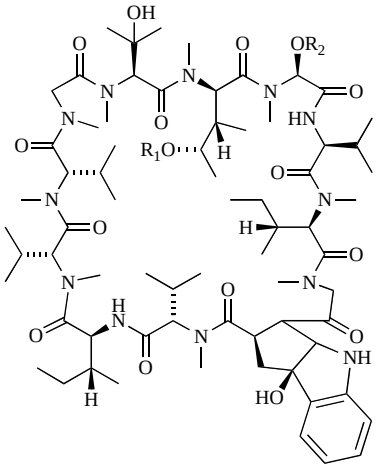

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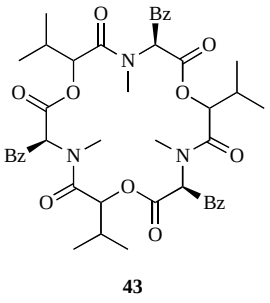
41 R_1=3-hydroxy-3-methylbutanoyl, R_2=acetyl
42 R_1=R_2=acetyl



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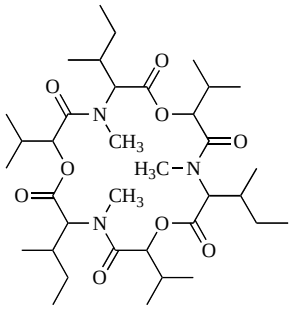

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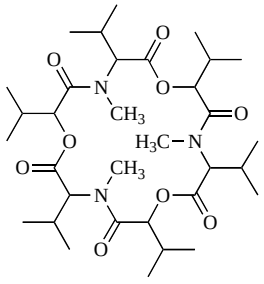

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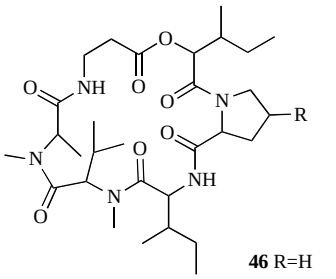
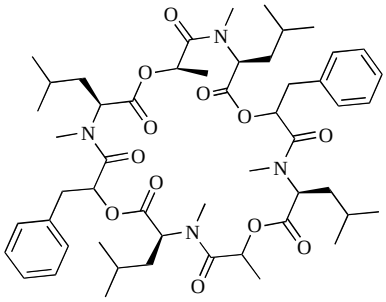


46 R=H
47 R=CH_3



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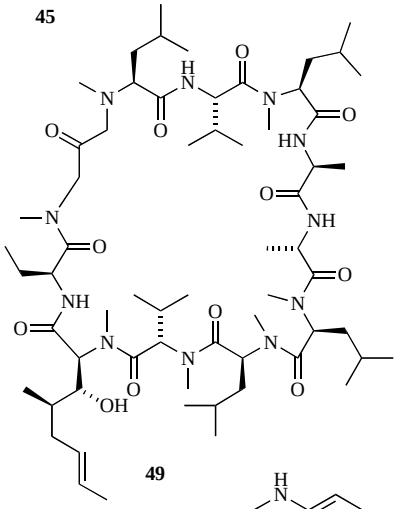

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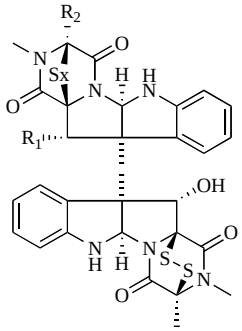
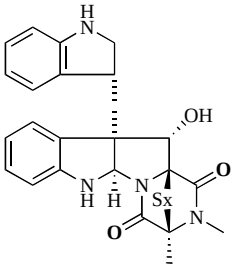
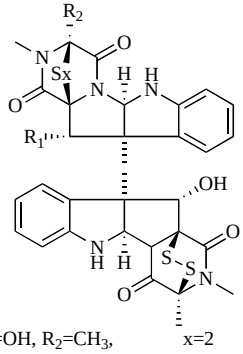


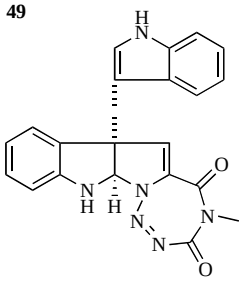
50 R_1=OH, R_2=CH_3, x=3
51 R_1=OH, R_2=CH_3, x=4



52 x=2
53 x=3
54 x=4



55 R_1=OH, R_2=CH_3, x=2
56 R_1=H, R_2=CH_3, x=2
57 R_1=OH, R_2=CH_2CH_3, x=2
58 R_1=OH, R_2=$CH(OH)CH_3$, x=2



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A series of diketopiperazine compounds were isolated from the solid-substrate fermentation cultures of the fungus *Gliocladium roseum* [50,51]. These compounds include gliocladine A (**50**), B (**51**), C (**52**), D (**53**), E (**54**), verticillin A (**55**), 11'-deoxyverticillin A (**56**), Sch52900 (**57**), Sch52901 (**58**) and glioclasine (**59**). Compounds **50**-**54** and **58** were new, and the other compounds in

this group had previously been reported as fungal antibiotics [52,53]. Compounds **50-58** showed nematicidal activities against *C. elegans* and *P. redivivus*. However, they showed little activity against *B. xylophilus*. The nematicidal experiment indicated that monomeric epipolysulfanydioxopiperazines (**52-54**) were less active than dimeric compounds (**50-51**, **55-58**) [51]. Compared to the other compounds in this group, glioclasine (**59**) showed the strongest activities against *C. elegans*, *P. redivivus*, and *B. xylophilus*, with LD_{50} values at 15, 50 and 200 μg mL^{-1}, respectively [50].

TERPENOIDS

There are **35** fungal terpenoids with reported nematicidal activities. Six new bisabolane sesquiterpenes cheimonophyllons A (**60**), B (**61**), C (**62**), D (**63**), E (**64**) and cheimonophyllal (**65**) were obtained from the submerged cultures of the basidiomycete *Cheimonophyllum candidissimum* TA 8644. These compounds were active against *C. elegans* with LD_{50} between 10 and 100 μg mL^{-1} [54,55]. However, none of these six compounds exhibited phytotoxic activities towards either *Setaria italica* or *Lepidium sativum* [54]. In a further study, compound 1,2-dihydroxy-mintlactone (**66)** was isolated as a minor metabolite from the same fungus [56]. Compound **66** was a new menithol monoterpene and possessed nematicidal activity. The LD_{50} of compound **66** against *C. elegans* was 25 μg $mL.^{-1}$ This was the first compound in the *p*-menthane group reported from a Basidiomycete [56].

Marasmane sesquiterpene isovelleral (**67**) could be found in injured fruiting bodies of the mushroom *Lactarius vellereus*. This compound was considered a key component of the chemical defense system against nematodes in this mushroom species [57,58]. Compound **67** has shown nematicidal activity against *M. incognita* with LD_{30} at 100 μg mL^{-1} and against *C. elegans* with LD_{50} at 50 μg mL^{-1} [18]. Aside from being found in *L. vellereus*, compound **67** has also been found in injured fruiting bodies of other mushrooms such as *Russula cuprea* [59]. Another sesquiterpene marasmic acid (**68**) was also reported to have a weak activity against *M. incognita* by Mayer [18]. Compound **68** was originally isolated from the mushroom *Marasmius conigenus* [60] and its structure was elucidated by Dagan [61]. Subsequently, marasmic acid was obtained from several other basidiomycetes *Lachnella villosa*, *Lachnella* sp. and *Peniophora laeta* [62].

Three furan sesquiterpenoids lactarorufin A (**69**), lactarorufin B (**70**) and furantriol (**71**) were isolated from the mushroom *Lactarius mitissimus* and the all three compounds had shown nematicidal activities against *C. elegans* with LD_{50} values at around 100 μg mL^{-1} [63,64].

A new aromadendrane, 2β,13-dihydroxyledol (**72**) was isolated from the solid mycelial cultures of *Dichomitus squalens* and this compound exhibited potent activity against the pine wood nematode *B. xylophilus* with LC_{50} at 35.6 μg mL^{-1} [65]. Five new cadinane sesquiterpenoids, named stereumin A (**73**), B (**74**), C (**75**), D (**76**) and E (**77**) were isolated from the culture broth of the fungus *Stereum* sp. YMF1.1587. Compounds **73-77** all showed nematicidal activities against *P. redivivus* at 400 mg L^{-1}. Among them, compounds **75** and **76** killed 84.4% and 94.9% of *P. redivivus* in 48 h respectively [66]. Two known compounds 7,8,11-drimanetriol (**78**) and 8,11-drimanediol (**79**) were isolated from the fungus *Coprinus xanthothrix* and both had nematicidal activities against *P. redivivus* and *M. arenaria* at a concentration of 500 ppm [20].

The ophiobolins are the ophiobolane-type sesterterpenes [67] and they have been found in several fungal sources. These compounds include two new nematicidal ophiobolins ophiobolin K (**80**) and 6-epiophiobolin K (**81**). These two were obtained from *Aspergillus ustus* [68]. In addition to these two compounds, ophiobolin M (**82**), 6-epiophiobolin M (**83**), ophiobolin C (**84**) and 6-epiophiobolin C (**85**) have also been isolated from the ascomycete *Cochliobolus heterostrophus* [69]. Ophiobolin C was first obtained from *Helminthosporium* species [70] and it was the most active compound among these six with an LD_{50} value of 5 μM against *C. elegans*. Ophiobolin K and ophiobolin M had similar nematicinal activities with LD_{50} values of 26 μM and 13 μM respectively. The epimers 6-epiophiobolin C and M were less potent with LD_{50} values around 130 μM. These compounds are non-competitive inhibitors of ivermectin binding to membranes prepared from *C. elegans* [69].

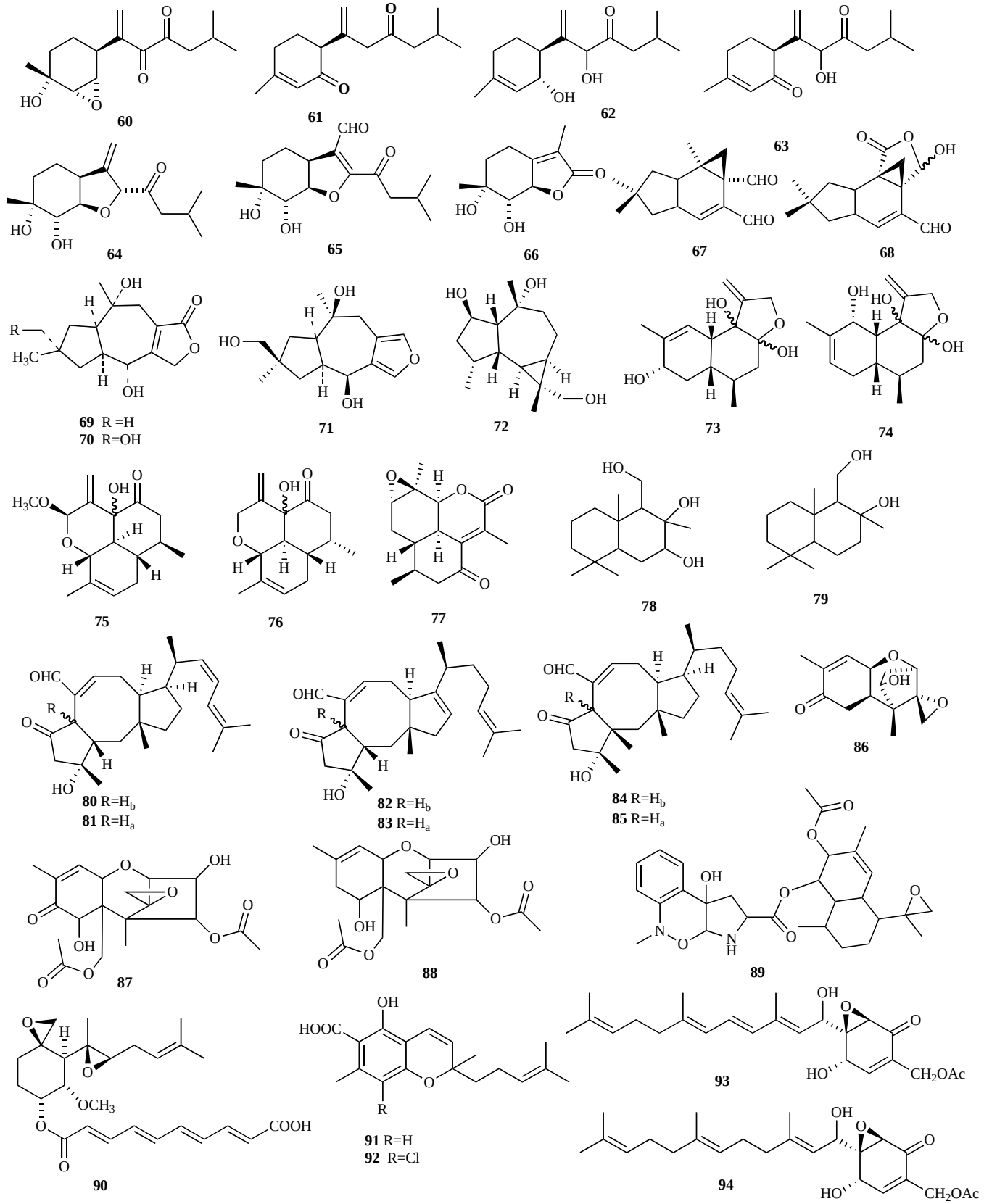
Trichothecolone (**86**), isolated from *Trichothecium roseum* [71,72], was weakly active against *Anguillula aceti* [26]. Two tricyclic sesquiterpenes 4,15-diacetylnivalenol (**87**) and diacetoxy-scirpenol (**88**) were obtained from *Fusarium equiseti* isolated from a soybean cyst nematode (*Heterodera glycines*) [73]. The two compounds could inhibit egg hatch and immobilize second-stage juveniles of nematode *M. incognita* [73]. The two trichothecene compounds have been found in several other *Fusarium* species [74-77]. A new macrocyclic lactone derivative paeciloxazine (**89**) with the pyrrolobenzoxazine skeleton was isolated from the culture broth of *Paecilomyces* sp. BAUA3058 [78]. Biological assay showed that the compound was active against *Rhabditis pseudoelongata* at 50 μg mL^{-1}. Interestingly, paeciloxazine (**89**) also had a significant insecticidal activity against the insect *Plutella xylostella* which could kill 100% *P. xylostella* at the concentration of 500 μg mL^{-1} [78]. Fumagillin (**90**) [79], isolated from both *Aspergillus fumigatus* and *Penicillium nigricans* [80,81], was reported to be moderately active against nematode *A. aceti* [26]. Two nematicidal compounds cannabiorcichromenic acid (**91**) and its 8-chloro derivative (**92**) were isolated from *Cylindrocarpon olidum* [82]. The mixture of these two could kill 50% of *Heterorhabditis* nematodes at 20 μg mL^{-1} [82].

Two isoepoxydon compounds oligosporon (**93**) and its dihydro-derivative 4',5'-dihydro-oligosporon (**94**) were isolated from the predacious fungus *Arthrobotrys oligospora* [83]. These two compounds were active against the intestinal parasitic nematode *Haemonchus contortus* with LD_{50} values of 25 and 50-100 μg mL^{-1}. However, they were inactive against the nematode *C. elegans* at concentrations up to 100 μg mL^{-1} [83,84].

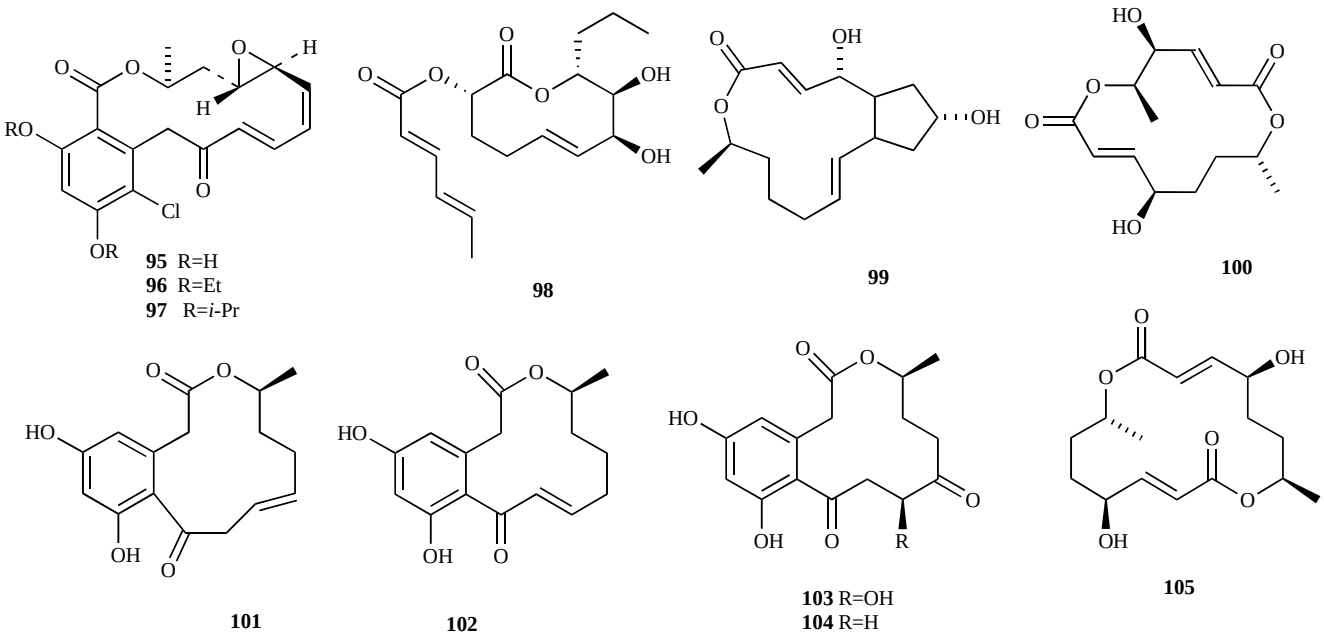
MACROLIDE COMPOUNDS

Eleven nematicidal compounds from fungi are included into the macrolide group. Among these, radicicol (**95**) produced by *Nectria radicicola* was a highly cytotoxic antiprotozoal and antineoplastic agent [85]. This compound has also been isolated from other fungal species such as *Monosporium bonorden*, *Pencicillium luteo-aurantium* [86] and *Chaetomium chiversii* [87]. Its two dialkoxy derivatives radicicol B (**96**) and radicicol C (**97**) also possessed nematicidal activities against an unidentified soil nematode with an LD_{50} value at 200 μg mL^{-1} [88]. A 9-lactide decane compound lethaloxin (**98**) isolated from *Mycosphaerella lethalis* [89] was also proven capable of killing *C. elegans* with an LD_{50} at 25 μg mL^{-1} [88]. Brefeldin A (**99**) is identical to two known chemicals ascotoxin and decumbin. It was first obtained from *Penicillium decumbens* [90] and subsequently isolated from several other fungal species *Penicillium brefeldianis* [91], *Penicillium camemberti* [92], *Hemicarpenteles paradoxus* (teleomorph of *Aspergillus paradoxus*), *Alternaria carthami*, *Alternaria zinniae* [93], *Paecilomyces* sp., *Aspergillus clavatus* [94], *Ascochyta imperfecta* [95]. In a screening against the nematode *Anguillula aceti*, brefeldin A (**99**) was found to possess significant nematicidal activity [26].

A 14-membered macrodiolide clonostachydiol (**100**) was isolated from the ascomycete *Clonostachys cylindrospora* [96]. This compound is related to the macrodiolides of the colletodiol family and its synthesis *in vitro* has been achieved [97]. A dose of 2.5 mg kg^{-1} subcutaneously administered to sheep artificially infected with the nematode *Haemunchus cortortus* caused 80 to 90% reduction of abomasum nematodes [96]. Four macrolides including a new compound $\beta\gamma$–dehydrocurvularin (**101**) and three



known ones *αβ*-dehydrocurvularin (**102**), 8-*β*-hydroxy-7-oxocurvularin (**103**) and 7-oxocurvularin (**104**) were obtained from *Aspergillus* spp. These four macrolides have shown nematicidal activities against the root-lesion nematode *Pratylenchus penetrans* with killing rates of 35%, 80%, 23% and 33% respectively at the concentration of 300 mg L^{-1}, and rates of 87%, 88%, 35%, 59% respectively, at the concentration of 1000 mg L^{-1} [98]. However, none of the four compounds had any observable effects on *C.*



elegans at the tested concentrations (1-1000 mg L^{-1}). Compounds **102-104** were produced by many phytopathogenic fungal species in the genera of *Curvularia*, *Penicillium*, *Cochliobolus* and *Alternaria* [99-107]. A symmetric 16-membered macrodiolide helmidiol (**105**) was produced by *Alternaria alternate* [108]. Coproscopic investigations before and after 14 days of application of 2.5 mg kg^{-1} of helmidiol (**105**) subcutaneously in sheep identified a 50% reduction of the population of nematode *H. cortortus* [108].

OXYGEN HETEROCYCLE AND BENZO COMPOUNDS

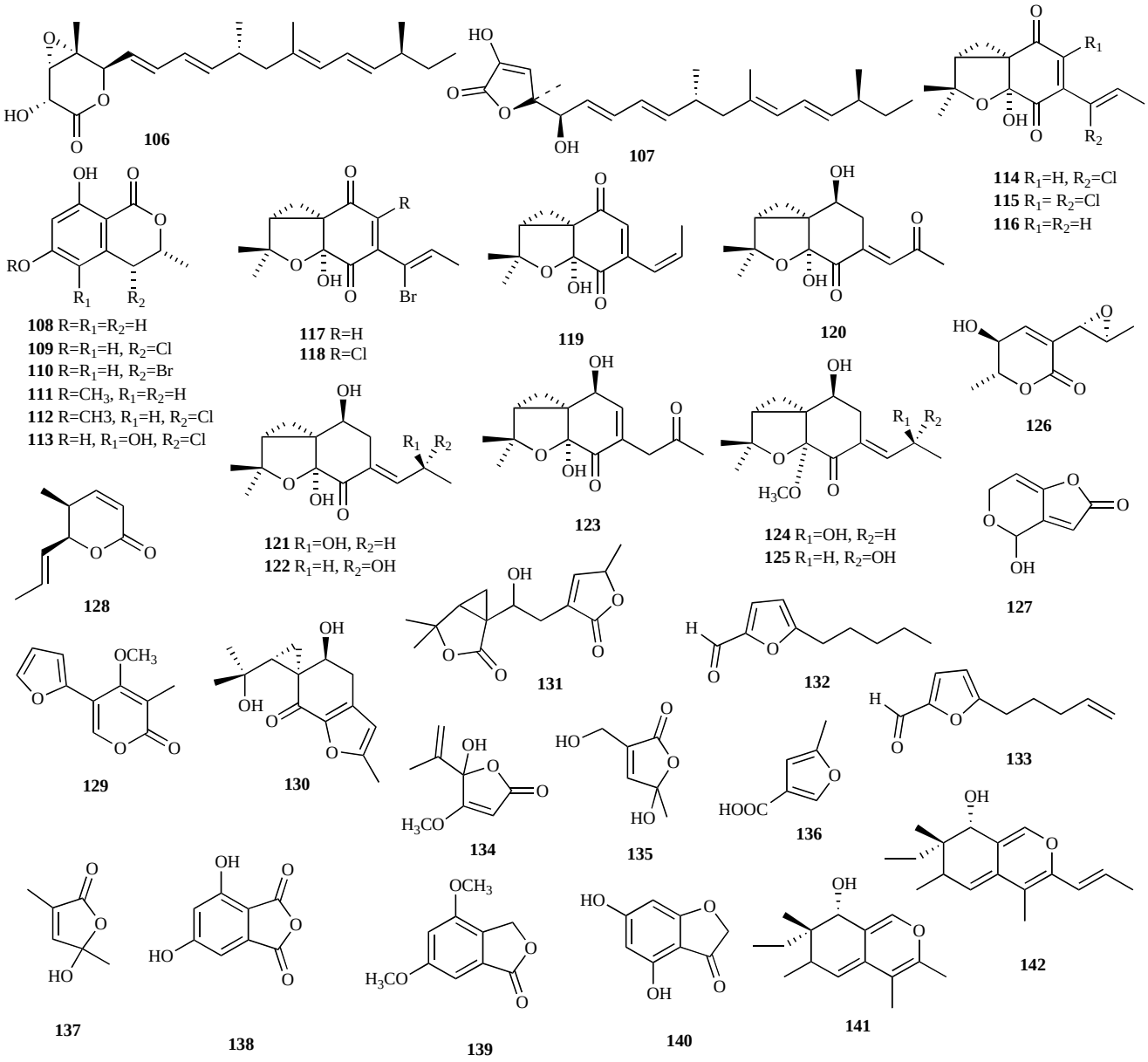
Compound nafuredin (**106**) was isolated as an inhibitor of an anaerobic electron transporter from the culture broth of *Aspergillus niger* FT-0554 [109,110]. Its chemical configuration was subsequently elucidated [111]. *In vivo* trials with sheep identified that this compound had a significant nematicidal activity against *H. cortortus*. Specifically, 2 mg kg^{-1} of nafuredin could exert a significant anthelmintic effect against *H. cortortus*. It suppressed the egg output of female worms within 11 days after treatment, and greater than 90% egg reduction was observed at day 11 [110]. Nafuredin could be easily converted to nafuredin-γ (**107**) by weak alkaline treatment. The latter also showed an inhibitory activity similar to nafuredin [112]. The IC_{50} values were 9.7 nM and 6.4 nM respectively for compounds **106** and **107** in their inhibition against NADH-fumarate reductase (NFRD) of *Ascaris suum* [112].

During the investigations of the influences of $CaBr_2$ on the biosynthesis of chlorinated secondary metabolites in *Lachnum papyraceum*, six isocoumarin derivatives, 6-hydroxymellein (**108**), 4-chloro-6-hydroxymellein (**109**), 4-bromo-6-hydroxymellein (**110**), 6-methoxymellein (**111**), 4-chloro-6-methoxymellein (**112**) and 4-chloro-6,7-dihydroxymellein (**113**) were obtained. Among them, compounds **109**, **110**, **111** and **113** were isolated for the first time from a natural source [113,114]. Compared with other compounds such as lachnumol A and mycorrhizin A isolated from the same fungus, these isocoumarin derivatives showed only weak nematicidal effects and the ND_{90} values of these compounds against *C. elegans* were all about 100 μg mL^{-1} [113]. In addition, from fermentations of *Lachnum papyraceum*, a series of mycorrhizins (**114-125**) were isolated [113,115-119]. Three mycorrhizins, mycorrhizin A (**114**), chloromycorrhizin A (**115**) and (1'-E)-dechloromycorrhizin A (**116**) were commonly found in normal fermentations of the fungus [115]. However, in fermentations in media containing of $CaBr_2$, additional mycorrhizins could be found. These included two brominated derivatives mycorrhizin B1 (**117**) and mycorrhizin B2 (**118**) as well as (1'Z)-dechloromycorrhizin A (**119**) [116-119]. These mycorrhizins were all toxic towards *C. elegans* but were only weakly active against *M. incognita*. Among these mycorrhizins, mycorrhizin A showed the highest activity against *C. elegans* with an LD_{50} at 1 μg mL^{-1}. Based on structural and functional comparisons, it was suggested that chlorine substitutions in the side chains could increase their biological activities, whereas chlorine substitutions within the ring systems seem to weaken their activities [113]. The brominated mycorrhizins showed weaker activities than their chlorinated analogues. However, these differences were not statistically significant [116]. In addition to the above-mentioned compounds, several minor metabolites, papyracons A (**120**), B (**121**), C (**122**) and D (**123**), 6-*O*-methylpapyraceum B (**124**) and 6-*O*-methylpapyraceum C (**125**) have also been isolated from *Lachnum papyraceum* and they are all weakly active against *C. elegans* [116-119]. Among above-described compounds (**108-125**), 6-hydroxymellein (**108**) was also obtained from other fungi including *Discula* spp. [120] and *Myxotrichum stipitatum* [121]. In addition, mycorrhizin A (**114**) and chloromycorrhizin A (**115**) have been isolated from a mycorrhizal fungus *Monotropa hypopitys* [122,123].

Aspyrone (**126**) was isolated from *Aspergillus melleus* and it showed a nematicidal activity against *Pratylenchus penetrans* with killing rates of 39.0% and 80.8% at concentrations of 100 mg L^{-1} and 300 mg L^{-1}, respectively [124,125]. Patulin (**127**) has been found in several fungi: *Penicilium* spp. [126-128], *Aspergillus* spp. [129] and *Byssochlamys* spp. [130]. Patulin was active against *M. incognita* with the LD_{30} dose at 100 μg mL^{-1} [18].

A nematicidal compound phomalactone (**128)** was obtained by bioassay-directed fractionation from the fungus *Verticillium chlamydosporium* [131]. The mortality of *M. incognita* reached at 84% in 96 hours when the concentration of phomalactone was at 500 mg L^{-1} [131]. This compound has been found from other fungi, e.g the entomopathogenic fungi *Hirsutella thompsonii* var. *synnematosa* [132], and *Nigrospora sphaerica* [133]. Cladobotrin I (**129)** exhibited nematicidal activity toward *M. incognita* with LD_{50} at 100 ug mL^{-1}, and it was isolated from the mycophilic deuteromycete *Cladobotryum rubrobrunnescens* [134].

Two new compounds lachnumfuran A (**130**) and lachnumlactone A (**131**) were obtained from the ascomycete *Lachnum*



papyraceum [119]. Compounds **130** and **131** had relatively weak activities against *C. elegans* with ND_{90} dosages at 100 μg mL^{-1} and 50 μg mL^{-1} respectively [119]. Compound 5-pentyl-2-furaldehyde (**132**) was isolated as the principal nematicide from an unidentified ascomycete belonging to the Dermateaceae family [135,136]. In addition, it has been found from other fungi such as a basidiomycete *Irpex lacteus* [137] and an unidentified fungal strain Kyu-W63 [138]. Compound **132** was one of the few metabolites with nematicidal activity found in both Ascomycetes and Basidiomycetes. This compound was active against *C. elegans* with LD_{50} at 75 μg mL^{-1}, against *M. incognita* with LD_{50} at 60 μg mL^{-1} and against *Aphelencoides besseyi* with LD_{90} at 200 μg mL^{-1} [135,137]. Another new furan compound 5-(4-pentenyl)-2-furaldehyde (**133**) was also produced by the basidiomycete *Irpex lacteus* and it was found active against *A. besseyi* with LD_{50} at 50 μg mL^{-1} [137]. In a screening of compounds with antihelminthic activity in a collection of fungal strains, penicillic acid (**134**) was found to possess weak activities against *A. aceti* [26]. Compound **134** has been isolated from several fungal species and strains belonging to *Penicillium* [139,140], *Aspergillus* [141,142] and *Malbranchea aurantiaca* [143].

A new furan 5-hydroxy-3-(hydroxymethyl)-5-methylfuran-2(5H)-one (**135**), two known furan compounds 5-methylfuran-3-carboxylic acid (**136**) and 5-hydroxy-3,5-dimethylfuran-2(5*H*)-one (**137**), as well as three benzofurans including a new 4,6-dihydroxy-isobenzofuran-1,3-dione (**138**) and two known 4,6-dimethoxyiso-benzofuran-1(3*H*)-one (**139**), and 4,6-dihydroxybenzofuran-3(2*H*)-one (**140**) were all obtained from the fungus *Coprinus comatus* [20]. All compounds had nematicidal activities against *P. redivivus* and *M. arenaria* at 400 ppm [20]. Among them, the LD_{50} values of compounds **136** and **137** were 100 ppm for both at 12 hours [20].

Two new azaphilone metabolites pseudohalonectrin A (**141)** and B (**142)** were produced by the aquatic fungus *Pseudohalo-nectria adversaria* YMF 1.01019 [144]. These two compounds possessed nematicidal activities against the pine wood nematode *B. xylophilus* [144].

QUINONES

This group includes six nematicidal compounds from fungi. Mycenon (**143**) was a chlorinated benzoquinone derivative isolated from the culture broth of a basidiomycete, *Mycena* sp. TA 87202

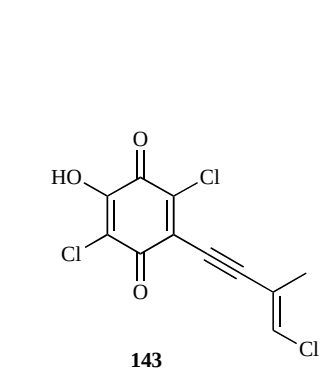
[145]. It was shown active against *C. elegans,* with LD_{50} at 50 μg mL^{-1} [88]. Another quinone cochlioquinone A (**144**) has been isolated from several ascomycetes, *Cochliobolus miyabeanus*, *Helminthosporium leersii* and *Helminthosporium sativum* [146-147]. The ED_{50} (The dose of a drug that is effective for 50% of the tested organism) of compound **144** against *C. elegans* was 135 μM [147]. Cochlioquinone A (**144**) may have a similar mode of action as that of the widely used avermectin because **144** is a competitive inhibitor of [^{3}H]ivermectin and both can bind to the cell membrane of *C. elegans*. This was the first report showing that a non-avermectin compound could interact with an invertebrate avermectin binding site.

Compound 14-epicochlioquinone B (**145**) was isolated as a platelet aggregation inhibitor from the ascomycete *Neobulgaria pura* [148]. This compound had a strong nematicidal activity against *C. elegans* with LD_{50} value at 10 μg mL^{-1} [135]. However, it was approximately 10 times less active against another nematode *M. incognita* [135]. A widely distributed anthraquinone in plants, emodin (**146**) was also obtained from a fungus *Aspergillus glaucus* [149,150]. Compound **146** has shown activity against *M. incognita* [18]. Two photosensitive compounds hypocrellin A (**147**) and elsinochrome A (**148**) were isolated from *Hypomyces* sp. [151]. These two compounds were able to kill 50% of the nematode *B. xylophilus* within 18h at concentrations of 50 μg mL^{-1} for hypocrellin A, and 15 μg mL^{-1} for elsinochrome A [151].

ALIPHATIC COMPOUNDS

A highly methylated polyketide MK7924 (**149**) was isolated from the culture broth of *Coronophora gregaria* L2495 and the compound exhibited significant nematicidal activity against *C. elegans* at 100 μg mL^{-1} [152]. There were significant structural differences between MK7924 and other known anthelmintic agents. Therefore, MK7924 could be developed as a promising new type of anthelmintic. Two sphingolipids including a new (2S,2'R,3R, 3'E,4E,8E)-1-*O*-(β-D-glucopyranosyl)-3-hydroxyl-2-[N-2'-hydroxyl-3'-eicosadecenoyl]amino-9-methyl-4,8-octadecadiene (**150)** and a known (2S,2'R,3R,3'E,4E,8E)-1-*O*-(β-D-glucopyranosyl)-3-hydroxyl-2-[N-2'-hydroxyl-3'-oct adecenoyl]amino-9-methyl-4,8-octadecadiene (**151)** were isolated from a freshwater fungus *Paraniesslia* sp. [153]. Both compounds showed moderately nematicidal activities against *B. xylophilus* [153].

Some fatty acids with nematicidal activities have been isolated from fungi. From an isolate of *Aspergillus niger*, both citric acid (**152)** and oxalic acid (**153)** were obtained as nematicidal components in culture filtrate. However, their activities towards nematode *M. incognita* were weak [154]. Oxalic acid was also produced by the brown-rot fungus *Poria placenta* [155] and the white-rot fungus *Physisporinus rivulosus* [156]. Linoleic acid (**154**) was isolated from both the ascomycete *Chlorosplenium* sp. [135] and the basidiomycete *Pleurotus pulmonarius* [157,158]. The LD_{50} of compound **154** against *C. elegans* was 10 μg mL^{-1} and the LD_{30} against *M. incognita* was 100 μg mL^{-1} [135,157]. This compound has also been detected in the mycelial extracts of several nematode-trapping fungi *Arthrobotrys conoides*, *A. brochopaga*, *A. dactyloides*, *A. oligospora*, *Dctylella candida*, *Monacrosporium doedycoides* [135] as well as in other fungi such as *Pythium ultimum* [159], *Penicillium* spp. [160,161], *Achlya Americana* [162], *Nomuraea rileyi* [163] and *Tricholoma* spp. [164]. Extracts of the mushroom *Pleurotus pulmonarius* contained a different nematicidal fatty acid *S*-coriolic acid (**155**). This fatty acid could kill nematode *C. elegans* with an LD_{50} value at 10 ppm [157]. A nematicidal fatty acid mixture containing linoleic acid (**154**), oleic acid (**156**) and palmitic acid (**157)** were obtained from the culture of *Hericium coralloides*. This mixture showed a nematicidal activity against *C. elegans* [157]. Oleic acid (**156**) has also been isolated from other fungi such as *Achlya Americana* [162], *Nomuraea rileyi* [163] and *Tricholoma* spp. [164]. Similarly, palmitic acid (**157**) was detected as one of the nematicidal components from *Coprinus xanthothrix* [20]. *Trans*-2-decenedioic acid (**158**) was isolated from *Pleurotus ostreatus* as the principal nematicide [165] and this compound was also found in *Penicillium notatum* [166]. Compound **158** could immobilize 95% of the nematode *Panagrellus redivivus* at a concentration of 300 ppm [165]. Compound 3-hydroxypropionic acid (3-HPA) (**159**) was isolated as the main nematicide from the submerged culture of the fungus *Phomopsis phaseoli* originally found on a tropical tree. This compound has also been found in the fungus *Melanconium betulimum* associated with two other plant species *Betula pendula* and *B. pubescens* [167].



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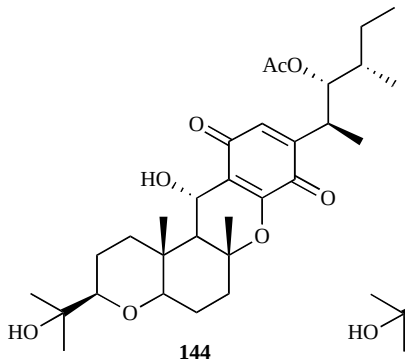

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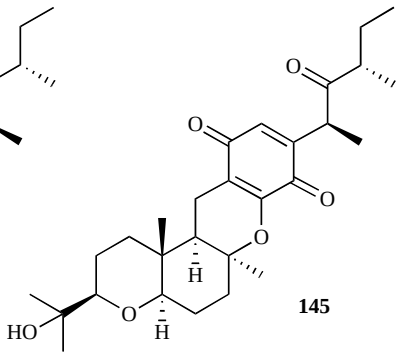

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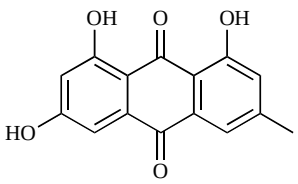

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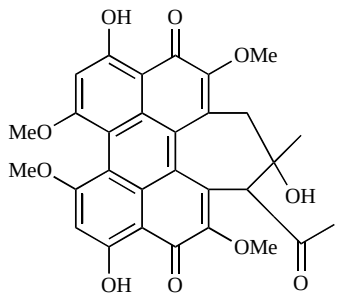

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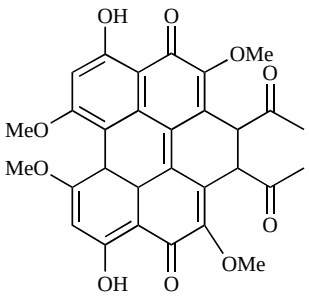


148

Compound **159** showed selective nematicidal activity against *M. incognita* with an LD_{50} value of 12.5-15 μg mL^{-1}, and against *C. elegans* with an LD_{50} value about five times lower [167]. The common acetic acid (**160**) has been isolated from culture filtrates of *Paecilomyces lilacinus* and *Trichoderma longibrachiatum* [168]. Acetic acid (**160**) has been shown to have selective nematicidal activities against certain nematodes [168]. From the widely used traditional medicinal fungus *Poria cocos*, a novel alkyne 2,4,6-triacetylenic octane diacid (**161**) was isolated and found capable of killing 83.9% of the nematode *M. arenaria* and 73.4% of the nematode *P. redivivus* at 500 ppm within 12 hours [169].

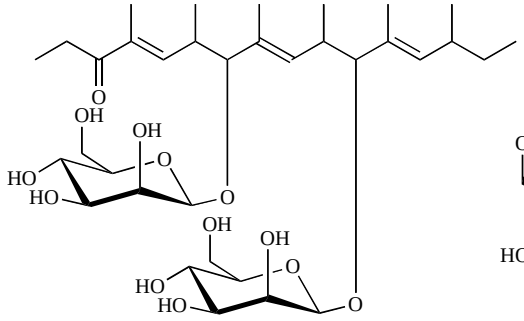
In addition to the above-mentioned acids, some unsaturated dicarboxylic acids and their derivatives have shown to exhibit selective nematicidal activities against phytophagous nematodes and without adversely affecting beneficial entomophagous and saprophagous species. Further experiments suggested that differences in both the physiology of nematodes and the spatial configuration of the compounds are important factors influencing their selective biological activity [170]. Fatty acids with nematicidal activities have been summarized by Anke [5].

Four isoepoxydon compounds were isolated from the ascomycete *Lachnum papyraceum* [115-117,171]. These compounds were lachnumon (**162**), lachnumon A (**163**), lachnumon B1 (**164**) and lachnumon B2 (**165**). Compounds **162** and **163** had similar activities against *C. elegans* with an LD_{50} at 25 μg mL^{-1}. Their activities against *M. incognita* were weak, with LD_{50} exceeding 100 μg mL^{-1} for both [115,171]. The LD_{90} values of **164** and **165** against *C. elegans* were 25 μg mL^{-1} and 50 μg mL^{-1}, respectively. Their activities against *M. incognita* were similar to those of compounds **162** and **163** [116,117].

SIMPLE AROMATIC COMPOUNDS

Four simple nematicidal aromatics were found in the basidiomycete *Pleurotus pulmonarius*. These aromatics were *p*-anisaldehyde (**166**), *p*-anisyl alcohol (**167**), 1-(4-methoxyphenyl)-1,2-propanediol (**168**) and 2-hydroxy-(4'-methoxy)-propiophenone (**169**) [157]. The LD_{50} values of these compounds against *C. elegans* were all similar, at about 100 ppm [157]. Compound **166** has also been reported from a close relative *Pleurotus ostreatus* [172]. Compound **166** was found to possess nematicidal activities against both the root-lesion nematode *Pratylenchus brachyurus* and *Meloidogyne javanica* [173,174].

From the freshwater fungus *Paraniesslia* sp. 83, a new compound 3,5-dicarboxyaldehyde-4-hydroxy-acetophenone (**170**) was obtained. This compound had a nematicidal activity against *B. xylophilus* with an LD_{50} value at 200 ppm in 24 hours [50]. From the fungus *Stereum* sp. 8954, two new aromatics 3,5-dihydroxy-4-(3-methyl-but-2-enyl)-benzene-1,2-dicarbaldehyde (**171**) and 2,4-



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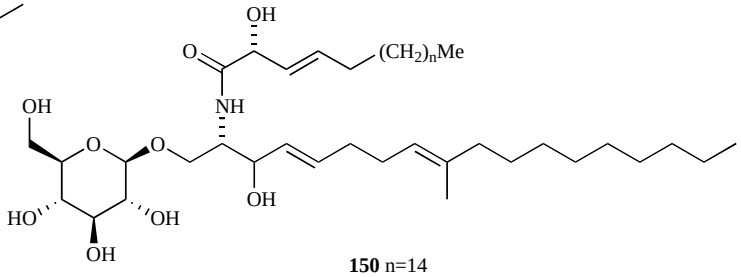
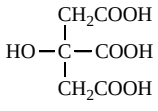


150 n=14
151 n=12



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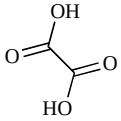

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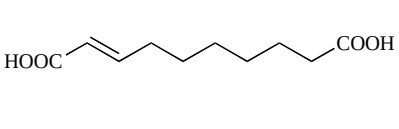

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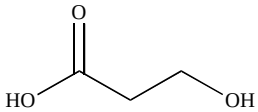

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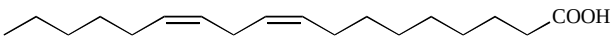

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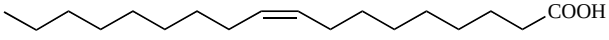

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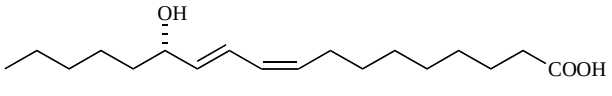

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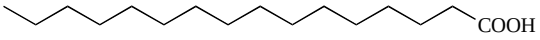

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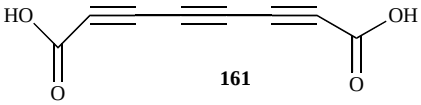

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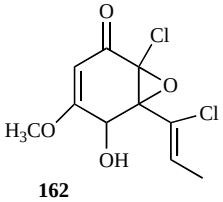

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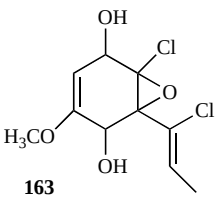

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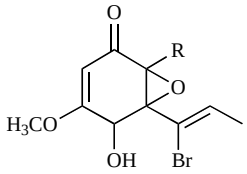

164 R=H
165 R=Cl

dihydroxy-6-methyl-benzoic acid butyl ester (**172**) were obtained. Compound **171** could kill about 90% of *P. redivivus* at 100 ppm in 12 hours, while compound **172** was less active, capable of killing about 50 % of the same nematode at 200 ppm in 24 hours [175]. A new aromatic compound methyl 3-*p*-anisoloxypropionate (**173**) was isolated from *Irpex lacteus* [137]. The LD_{50} value of **173** against *Aphelencoides besseyi* was 25 μg mL^{-1} [137].

3-formyl-2,5-dihydroxybenzyl acetate (**174**) was isolated from *Coprinus comatus* and it was shown to have nematicidal activities to *P. redivivus* and *M. arenaria* at 400 ppm [20]. Flavipin (**175)**, produced by the fungus *Chaetomium globosum*, could inhibit *in vitro* egg hatch and juvenile mobility of *M. incognita*, and could also inhibit the hatch of the soybean cyst nematode *Heterodera glycines* [176]. Compound flavipin was also found in fungi *Epicoccum nigrum* [177] and *Epicoccum purpurascens* [178].

Two naphthalenes 1-methoxy-8-hydroxynaphthalene (**176**) and 1,8-dimethoxynaphthalene (**177**) were isolated from *Daldinia concentrica* [179] and both were active against *C. elegans* with LD_{50} values at 10 μg mL^{-1} and 25 μg mL^{-1} respectively. However, these two compounds were only weakly active against *M. incognita* [135].

A new acetylenic nematicidal compound penipratynolene (**178**) was obtained from the culture filtrate of the fungus *Penicillium bilaiae* [27]. Compound **178** showed a nematicidal activity to the root-lesion nematode *P. penetrans*, capable of killing 77% of the nematode at a concentration of 300 mg L^{-1} [127]. It was suggested that the alkyne carbons likely play an important role in the nematicidal activities of this group of compounds [180,181].

STEROLS

Viridin (**179)** was obtained from *Trichoderma* sp. and *Gliocladium virens* [182], and it has been found to possess weak activity against *A. aceti* [26].

All compounds (**1-179**) described above were summarized in Table **2.**

CURRENT & FUTURE DEVELOPMENTS

The estimate of the number of fungal species on Earth is 1.5 million, and there are 72,000 to 100,000 fungal species have already known [183]. The biodiversity of fungi from soil, sea, plant, animal, insect etc may offer a variety of unexplored fungi [184-186]. In general, secondary metabolism has evolved in response to needs and challenges of the natural environment [187], so abundant fungi isolated from diversiform conditions will produce large numbers of bioactive metabolites.

Among the described nematicidal compounds from fungi, about 60% were obtained and elucidated for the first time. Such a high ratio suggested that there should be a large number of nematicidal compounds in natural, still unexplored fungal species and strains. Our review also indicated that using different model target nematodes and different methods for testing and screening are often necessary and highly productive for the identification of new nematicidals. Most of the reported compounds have shown selective nematicidal activities. For example, 1-methoxy-8-hydroxynaphthalene (**176**) and 1,8-dimethoxynaphthalene (**177**) isolated from *Daldinia concentrica* [179] were highly active against *C. elegans* but only weakly active against *M. incognita* [135]. This pattern was also found for cochlioquinone and the mycorrhizin compounds. In addition to their selective activities against different nematodes, many of these compounds also had selective antibacterial, antifungal, antitumor and/or immunosuppressive activities.

The efforts of optimizing fermentation conditions on the production of nematicidal compounds of fungal strains were rarely made. Only some compounds obtained by feeding special component in the culture medium, for example, several nematicidal compounds from *Lachnum papyraceum*, and few achieved by chemical modification, such as nafuredin-*γ*. Except for the modified compounds, these compounds were natural substances. In comparison with Genetically Modified Organism (GMO) to control parasitic nematodes, the security and validity of natural substances as nematicidal agents had the advantage over GMO (Despite the fact that Genetically Modified Technology should be prevalent in the future).

Aside from producing metabolites that can directly kill nematodes, fungi and their metabolites can also indirectly improve biologic resistance against parasitic nematodes and pathogenic

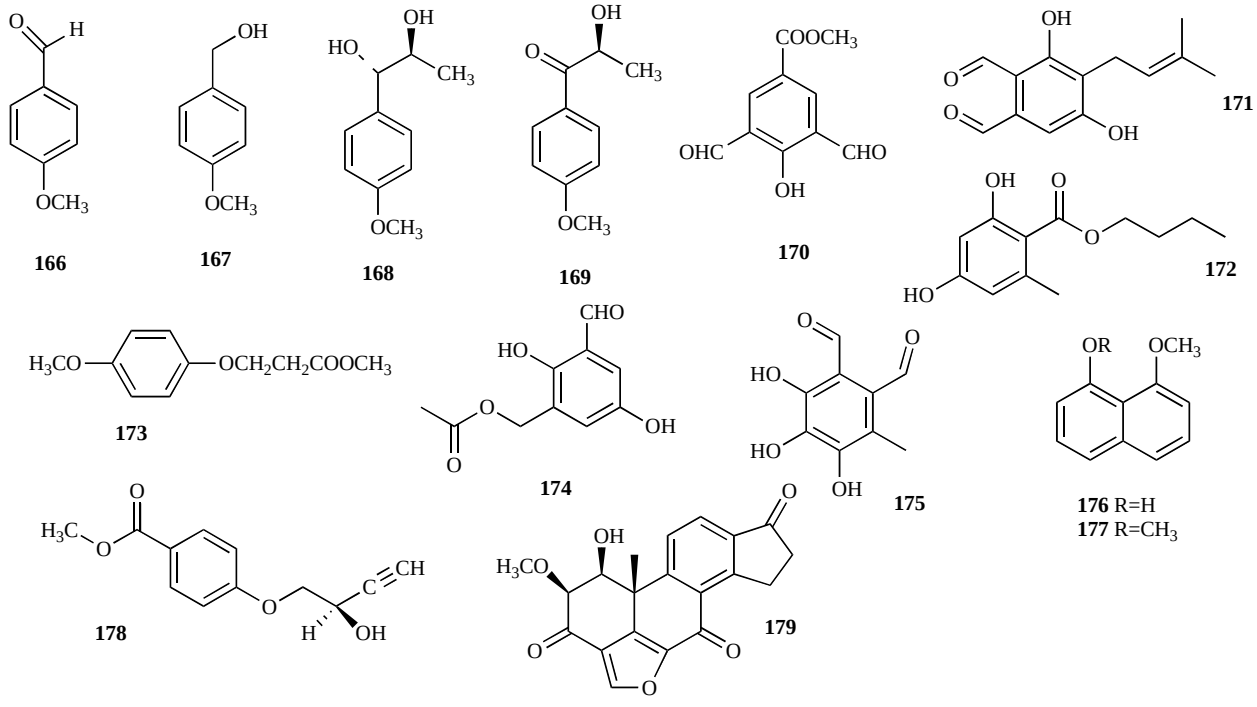

Table 2. Nematicidal Compounds from Fungi

Structural Type	Compound (Number)	Producing Fungus	Tested Organism
Alkaloids	paraherquamide (1)	*Penicillium paraherquei*; *Penicillium charlesii*; *Penicillium* sp. IMI332995	*Caenorhabditis elegans*; *Haemonchus contortus*; *Trichostrongylus colubriformis*
	paraherquamide B (2)	*P. charlesii*	*C. elegans*
	paraherquamide C (3)	*P. charlesii*	*C. elegans*
	paraherquamide D (4)	*P. charlesii*	*C. elegans*
	paraherquamide E (5)	*P. charlesii*	*C. elegans*
	paraherquamide F (6)	*P. charlesii*	*C. elegans*
	paraherquamide G (7)	*P. charlesii*	*C. elegans*
	VM55594 (8)	*Penicillium* sp. IMI332995	*H. contortus*; *T. colubriformis*
	VM54158 (9)	*Penicillium* sp. IMI332995	*H. contortus*; *T. colubriformis*
	VM54159 (10)	*Penicillium* sp. IMI332995	*H. contortus*; *T. colubriformis*
	VM55595 (11)	*Penicillium* sp. IMI332995	*T. colubriformis*
	VM55596 (12)	*Penicillium* sp. IMI332995	*T. colubriformis*
	VM55597 (13)	*Penicillium* sp. IMI332995	*T. colubriformis*
	VM55599 (14)	*Penicillium* sp. IMI332995	*T. colubriformis*
	VM55598 (15)	*Aspergillus* sp. IMI 337664	*T. colubriformis*
	SB202327 (16)	*Aspergillus* sp. IMI 337664	*T. colubriformis*; *H. contortus*
	SB203105 (17)	*Aspergillus* sp. IMI 337664	*T. colubriformis*
	SB200437 (18)	*Aspergillus* sp. IMI 337664	*T. colubriformis*
	marcfortine A (19)	*Penicillium roqueforti*	plant and animal parasitic nematodes
	marcfortine B (20)	*P. roqueforti*	plant and animal parasitic nematodes
	marcfortine C (21)	*P. roqueforti*	plant and animal parasitic nematodes
	phenoxazone (22)	*Calocybe gambosa*; *Pycnoporus sanguineus*	*Meloidogyne incognita*
	2-aminoquinoline (23)	*Leucopaxillus albissimus* var. *paradoxus* form *albiformis*	*Nippostrongylus braziliensis*
	1-(1-((2E,6Z)-6-amino-5-methylnona-2,6-dien-4-yl)-4-methylpiperidin-2-yloxy)heptan-2-one (24)	*Coprinus xanthothrix*	*Panagrellus redivivus*; *Meloidogyne arenaria*
	2-(1H-pyrrol-1-yl)ethanol (25)	*C. xanthothrix*	*P. redivivus*; *M. arenaria*
	1-methyl-1H-pyrrole-2-carboxylic acid (26)	*C. xanthothrix*	*P. redivivus*; *M. arenaria*
	gliotoxin (27)	*Trichoderma virens*; *Penicillium obscurum*; *Gliocladium fimbriatum*; *Candida albicans*; *Aspergillus fumigatus*	*Anguillula aceti*
	6-methoxy-carbonylpicolinic acid (28)	*Penicillium bilaiae*	*Pratylenchus penetrans*
	2,6-pyridinedicarboxylic acid (29)	*P. bilaiae*	*P. penetrans*

(Table 2) Contd….

Structural Type	Compound (Number)	Producing Fungus	Tested Organism
	peniprequinolone (30)	*Penicillium* cf. *simplicissimum*	*P. penetrans*
	penigequinolone A (31)	*Penicillium* cf. *simplicissimum*	*P. penetrans*
	penigequinolone B (32)	*Penicillium* cf. *simplicissimum*	*P. penetrans*
	3-methoxy-4,6-dihydroxy-4-(4'-methoxyphenyl) quinolinone (33)	*Penicillium* cf. *simplicissimum*	*P. penetrans*
Peptide compounds	chrysospermin A (34)	*Apiocrea chrysosperma*	nematode
	chrysospermin B (35)	*A. chrysosperma*	nematode
	chrysospermin C (36)	*A. chrysosperma*	nematode
	chrysospermin D (37)	*A. chrysosperma*	nematode
	antiamoebin I (38)	*Emericellopsis poonensis*; *E. synnematicola*; *Cephalosporium pimprina*	helminth
	omphalotin A (39)	*Omphalotus olearius*	*M. incognita*; *C. elegans*
	omphalotin B (40)	*O. olearius*	*M. incognita*; *C. elegans*
	omphalotin C (41)	*O. olearius*	*M. incognita*; *C. elegans*
	omphalotin D (42)	*O. olearius*	*M. incognita*; *C. elegans*
	beauvericin (43)	*Polyporus sulphureus*; *Beauveria bassiana*; *Paecilomyces fumoso-roseus*; *Fusarium* spp.; *Beauveria* sp.	*M. incognita*
	enniatin A (44)	*Fusarium* spp.	*M. incognita*
	enniatin B (45)	*Fusarium* spp.	*M. incognita*; *A. aceti*
	bursaphelocides A (46)	an imperfect fungus strain D1084 (Mycelia sterilia)	*Bursaphelenchus xylophilus*
	bursaphelocides B (47)	an imperfect fungus strain D1084 (Mycelia sterilia)	*B. xylophilus*
	PF1022A (48)	an imperfect fungus strain PF1022 (Mycelia sterilia)	*Ascaridia galli*; nematodes in sheep and cattle
	cyclosporin A (49)	*Tolypocladium inflatum*; *Fusarium solani*; *Cylindrocarpon lucidum*	*M. incognita*
	gliocladine A (50)	*Gliocladium roseum*	*C. elegans*; *P. redivivus*
	gliocladine B (51)	*G. roseum*	*C. elegans*; *P. redivivus*
	gliocladine C (52)	*G. roseum*	*C. elegans*; *P. redivivus*
	gliocladine D (53)	*G. roseum*	*C. elegans*; *P. redivivus*
	gliocladine E (54)	*G. roseum*	*C. elegans*; *P. redivivus*
	verticillin A (55)	*G. roseum*	*C. elegans*; *P. redivivus*
	11'-deoxyverticillin A (56)	*G. roseum*	*C. elegans*; *P. redivivus*
	Sch52900 (57)	*G. roseum*	*C. elegans*; *P. redivivus*
	Sch52901 (58)	*G. roseum*	*C. elegans*; *P. redivivus*

(Table 2) Contd….

Structural Type	Compound (Number)	Producing Fungus	Tested Organism
	glioclasine (59)	*G. roseum*	*C. elegans*; *P. redivivus*; *B. xylophilus*
Terpenoids	cheimonophyllon A (60)	*Cheimonophyllum candidissimum*	*C. elegans*
	cheimonophyllon B (61)	*C. candidissimum*	*C. elegans*
	cheimonophyllon C (62)	*C. candidissimum*	*C. elegans*
	cheimonophyllon D (63)	*C. candidissimum*	*C. elegans*
	cheimonophyllon E (64)	*C. candidissimum*	*C. elegans*
	cheimonophyllal (65)	*C. candidissimum*	*C. elegans*
	1,2-dihydroxymintlactone (66)	*C. candidissimum*	*C. elegans*
	isovelleral (67)	*Lactarius vellereus*; *Russula cuprea*	*M. incognita*; *C. elegans*
	marasmic acid (68)	*Marasmius conigenus*; *Lachnella villosa*; *Lachnella* sp.; *Peniophora laeta*	*M. incognita*
	lactarorufin A (69)	*Lactarius mitissimus*	*C. elegans*
	lactarorufin B (70)	*L. mitissimus*	*C. elegans*
	furantriol (71)	*L. mitissimus*	*C. elegans*
	2*β*,13-dihydroxyledol (72)	*Dichomitus squalens*	*B. xylophilus*
	stereumin A (73)	*Stereum* sp. YMF1.1587	*P. redivivus*
	stereumin B (74)	*Stereum* sp. YMF1.1587	*P. redivivus*
	stereuminC (75)	*Stereum* sp. YMF1.1587	*P. redivivus*
	stereumin D (76)	*Stereum* sp. YMF1.1587	*P. redivivus*
	stereumin E (77)	*Stereum* sp. YMF1.1587	*P. redivivus*
	7,8,11-drimanetriol (78)	*Coprinus xanthothrix*	*P. redivivus*; *M. arenaria*
	8,11-drimanediol (79)	*C. xanthothrix*	*P. redivivus*; *M. arenaria*
	ophiobolin K (80)	*Aspergillus ustus*; *Cochliobolus heterostrophus*	*C. elegans*
	6-epiophiobolin K (81)	*A. ustus*; *C. heterostrophus*	*C. elegans*
	ophiobolin M (82)	*C. heterostrophus*	*C. elegans*
	6-epiophiobolin M (83)	*C. heterostrophus*	*C. elegans*
	ophiobolin C (84)	*C. heterostrophus*; *Helminthosporium* spp.	*C. elegans*
	6-epiophiobolin C (85)	*C. heterostrophus*	*C. elegans*
	Trichothecolone (86)	*Trichothecium roseum*	*A. aceti*
	4,15-diacetylnivalenol (87)	*Fusarium equiseti*; *Fusarium* spp.	*M. incognita*
	diacetoxyscirpenol (88)	*F. equiseti*; *Fusarium* spp.	*M. incognita*
	paeciloxazine (89)	*Paecilomyces* sp. BAUA3058	*Rhabditis pseudoelongata*
	fumagillin (90)	*Aspergillus fumigatus*; *Penicillium nigricans*	*A. aceti*
	cannabiorcichromenic acid (91)	*Cylindrocarpon olidum*	*Heterorhabditis* nematode

(Table 2) Contd….

Structural Type	Compound (Number)	Producing Fungus	Tested Organism
	8-chloro cannabiorcichromenic acid (92)	*C. olidum*	*Heterorhabditis* nematode
	oligosporon (93)	*Arthrobotrys oligospora*	*H. contortus*; *C. elegans*
	4',5'-dihydro-oligosporon (94)	*A. oligospora*	*H. contortus*; *C. elegans*
Macrolide compounds	radicicol (95)	*Nectria radicicola*; *Monosporium bonorden*; *Pencicillium luteo-aurantium*; *Chaetomium chiversii*	an unidentified soil nematode
	radicicol B (96)	derivative from radicicol	an unidentified soil nematode
	radicicol C (97)	derivative from radicicol	an unidentified soil nematode
	lethaloxin (98)	*Mycosphaerella lethalis*	*C. elegans*
	brefeldin A (99)	*Penicillium decumbens*; *P. brinefeldianis*; *P. camemberti*; *Hemicarpenteles paradoxus*; *Alternaria carthami*; *A. zinniae*; *Paecilomyces* sp.; *Aspergillus clavatus*; *Ascochyta imperfecta*	*A. aceti*
	clonostachydiol (100)	*Clonostachys cylindrospora*	*H. cortortus*
	$\beta\gamma$ –dehydrocurvularin (101)	*Aspergillus* spp.	*P. penetrans*
	$\alpha\beta$-dehydrocurvularin (102)	*Aspergillus* sp.; *Curvularia* sp.; *Penicillium* spp.; *Cochliobolus* sp.; *Alternaria* spp.	*P. penetrans*
	8-β-hydroxy-7-oxocurvularin (103)	*Aspergillus* sp.; *Penicillium* spp.; *Cochliobolus* sp.; *Alternaria* sp.	*P. penetrans*
	7-oxocurvularin (104)	*Aspergillus* sp.; *Penicillium* sp.; *Cochliobolus* sp.;	*P. penetrans*
	helmidiol (105)	*Alternaria alternate*	*H. cortortus*
Oxygen heterocycle and benzo compounds	nafuredin (106)	*Aspergillus niger*	*H. cortortus*; *Ascaris suum*
	nafuredin-γ (107)	derivative from nafuredin	*H. cortortus*; *Ascaris suum*
	6-hydroxymellein (108)	*Lachnum papyraceum*; *Discula* spp.; *Myxotrichum stipitatum*	*C. elegans*
	4-chloro-6-hydroxymellein (109)	*L. papyraceum*	*C. elegans*
	4-bromo-6-hydroxymellein (110)	*L. papyraceum*	*C. elegans*
	6-methoxymellein (111)	*L. papyraceum*	*C. elegans*
	4-chloro-6-methoxymellein (112)	*L. papyraceum*	*C. elegans*
	4-chloro-6,7-dihydroxymellein (113)	*L. papyraceum*	*C. elegans*
	mycorrhizin A (114)	*L. papyraceum*; *Monotropa hypopitys*	*C. elegans*; *M. incognita*

(Table 2) Contd….

Structural Type	Compound (Number)	Producing Fungus	Tested Organism
	chloromycorrhizin A (115)	*L. papyraceum*; *M. hypopitys*	*C. elegans*; *M. incognita*
	(1'-E)-dechloromycorrhizin A (116)	*L. papyraceum*	*C. elegans*; *M. incognita*
	mycorrhizin B1 (117)	*L. papyraceum*	*C. elegans*; *M. incognita*
	mycorrhizin B2 (118)	*L. papyraceum*	*C. elegans*; *M. incognita*
	(1'Z)-dechloromycorrhizin A(119)	*L. papyraceum*	*C. elegans*; *M. incognita*
	papyracon A (120)	*L. papyraceum*	*C. elegans*
	Papyracon B (121)	*L. papyraceum*	*C. elegans*
	papyracon C (122)	*L. papyraceum*	*C. elegans*
	papyracon D (123)	*L. papyraceum*	*C. elegans*
	6-*O*-methylpapyraceum B (124)	*L. papyraceum*	*C. elegans*
	6-*O*-methylpapyraceum C (125)	*L. papyraceum*	*C. elegans*
	aspyrone (126)	*Aspergillus melleus*	*P. penetrans*
	patulin (127)	*Penicilium* spp.; *Aspergillus* spp.; *Byssochlamys* spp.	*M. incognita*
	phomalactone (128)	*Verticillium chlamydosporium*; *Hirsutella thompsonii* var. *synnematosa*; *Nigrospora sphaerica*	*M. incognita*
	cladobotrin I (129)	*Cladobotryum rubrobrunnescens*	*M. incognita*
	lachnumfuran A (130)	*L. papyraceum*	*C. elegans*
	lachnumlactone A (131)	*L. papyraceum*	*C. elegans*
	5-pentyl-2-furaldehyde (132)	*Irpex lacteus*; an unidentified ascomycete; an unidentified fungus Kyu-W63	*C. elegans*; *M. incognita*; *Aphelencoides besseyi*
	5-(4-pentenyl)-2-furaldehyde (133)	*I. lacteus*	*A. besseyi*
	penicillic acid (134)	*Penicillium* spp.; *Aspergillus* spp.; *Malbranchea aurantiaca*	*A. aceti*
	5-hydroxy-3-(hydroxymethyl)-5-methylfuran-2(5H)-one (135)	*Coprinus comatus*	*P. redivivus*; *M. arenaria*
	5-methylfuran-3-carboxylic acid (136)	*C. comatus*	*P. redivivus*; *M. arenaria*
	5-hydroxy-3,5-dimethylfuran-2(5*H*)-one (137)	*C. comatus*	*P. redivivus*; *M. arenaria*
	4,6-dihydroxyisobenzofuran-1,3-dione (138)	*C. comatus*	*P. redivivus*; *M. arenaria*
	4,6-dimethoxyisobenzofuran-1(3*H*)-one (139)	*C. comatus*	*P. redivivus*; *M. arenaria*

(Table 2) Contd….

Structural Type	Compound (Number)	Producing Fungus	Tested Organism
	4,6-dihydroxybenzofuran-3(2*H*)-one (140)	*C. comatus*	*P. redivivus*; *M. arenaria*
	pseudohalonectrin A (141)	*Pseudohalonectria adversaria*	*B. xylophilus*
	pseudohalonectrin B (142)	*P. adversaria*	*B. xylophilus*
Quinones	mycenon (143)	*Mycena* sp. TA 87202	*C. elegans*
	cochlioquinone A (144)	*Cochliobolus miyabeanus*; *Helminthosporium leersii*; *H. sativum*	*C. elegans*
	14-epicochlioquinone B (145)	*Neobulgaria pura*	*C. elegans*; *M. incognita*
	emodin (146)	*Aspergillus glaucus*	*M. incognita*
	hypocrellin A (147)	*Hypomyces* sp.	*B. xylophilus*
	elsinochrome A (148)	*Hypomyces* sp.	*B. xylophilus*
Aliphatic compounds	MK7924 (149)	*Coronophora gregaria*	*C. elegans*
	(2S,2'R,3R,3'E,4E,8E)-1-*O*-(β-D-glucopyranosyl)-3-hydroxyl-2-[N-2'-hydroxyl-3'-eicosadecenoyl]amino-9-methyl-4,8-octadecadiene(150)	*Paraniesslia* sp.	*B. xylophilus*
	(2S,2'R,3R,3'E,4E,8E)-1-*O*-(β-D-glucopyranosyl)-3-hydroxyl-2-[N-2'-hydroxyl-3'-oct adecenoyl]amino-9-methyl-4,8-octadecadiene (151)	*Paraniesslia* sp.	*B. xylophilus*
	citric acid (152)	*Aspergillus nige*	*M. incognita*
	oxalic acid (153)	*A. niger*; *Poria placenta*; *Physisporinus rivulosus*	*M. incognita*
	linoleic acid (154)	*Chlorosplenium* sp.; *Pleurotus pulmonarius*; *Arthrobotrys conoides*; *A. brochopaga*; *A. dactyloides*; *A. oligospora*; *Dctylella candida*; *Monacrosporium doedycoides*; *Pythium ultimum*; *Penicillium* spp. *Achlya Americana*; *Nomuraea rileyi*; *Tricholoma* spp.; *Hericium coralloides*	*C. elegans*
	S-coriolic acid (155)	*P. pulmonarius*	*C. elegans*
	oleic acid (156)	*H. coralloides*; *Achlya Americana*; *Nomuraea rileyi*; *Tricholoma* spp.	*C. elegans*
	palmitic acid (157)	*H. coralloides*; *Coprinus xanthothrix*	*C. elegans*
	Trans-2-decenedioic acid (158)	*Pleurotus ostreatus*; *Penicillium notatum*	*P. redivivus*
	3-hydroxypropionic acid (3-HPA) (159)	*Phomopsis phaseoli*; *Melanconium betulimum*	*M. incognita*; *C. elegans*

(Table 2) Contd….

Structural Type	Compound (Number)	Producing Fungus	Tested Organism
	acetic acid (160)	*Paecilomyces lilacinus*; *Trichoderma longibrachiatum*	Nematodes
	2,4,6-triacetylenic octane diacid (161)	*Poria cocos*	*P. redivivus*; *M. arenaria*
	lachnumon (162)	*Lachnum papyraceum*	*C. elegans*; *M. incognita*
	lachnumon A (163)	*Lachnum papyraceum*	*C. elegans*; *M. incognita*
	lachnumon B1 (164)	*Lachnum papyraceum*	*C. elegans*; *M. incognita*
	lachnumon B2 (165)	*Lachnum papyraceum*	*C. elegans*; *M. incognita*
Simple aromatic compounds	*p*-anisaldehyde (166)	*Pleurotus pulmonarius*; *P. ostreatus*	*C. elegans*; *Pratylenchus brachyurus*; *Meloidogyne javanica*
	p-anisyl alcohol (167)	*P. pulmonarius*	*C. elegans*
	1-(4-methoxyphenyl)-1,2-propanediol (168)	*P. pulmonarius*	*C. elegans*
	2-hydroxy-(4'-methoxy)-propiophenone (169)	*P. pulmonarius*	*C. elegans*
	3,5-dicarboxyaldehyde-4-hydroxy-acetophenone (170)	*Paraniesslia* sp.	*B. xylophilus*
	3,5-dihydroxy-4-(3-methyl-but-2-enyl)-benzene-1,2-dicarbaldehyde (171)	*Stereum* sp.	*P. redivivus*
	2,4-dihydroxy-6-methyl-benzoic acid butyl ester (172)	*Stereum* sp.	*P. redivivus*
	3-*p*-anisoloxypropionate (173)	*Irpex lacteus*	*A. besseyi*
	3-formyl-2,5-dihydroxybenzyl acetate (174)	*Coprinus comatus*	*P. redivivus*; *M. arenaria*
	flavipin (175)	*Chaetomium globosum*; *Epicoccum nigrum*; *Epicoccum purpurascens*	*M. incognita*; *Heterodera glycines*
	1-methoxy-8-hydroxynaphthalene (176)	*Daldinia concentrica*	*C. elegans*; *M. incognita*
	1,8-dimethoxynaphthalene (177)	*Daldinia concentrica*	*C. elegans*; *M. incognita*
	penipratynolene (178)	*Penicillium bilaiae*	*Pratylenchus penetrans*
Sterols	Viridin (179)	*Trichoderma* sp.; *Gliocladium virens*	*A. chydiolaceti*

bacteria. For example, the alkaloid ergocristine can adversely affects the infectivity of *Steinernema carpocapsae* and reduces the growth and pathogenicity of *Xenorhabdus nematophila*, a plant pathogenic bacterium carried by nematodes. The black cutworm, *Agrotis ipsilon* fed on endophyte-infected perennial ryegrass has shown an increased resistance to the nematode *S. carpocapsae* because of the presence of the alkaloids, notably ergocristine, produced by a symbiotic fungus of the cutworm [188].

Some compounds isolated from fungi are interesting in their biological activities. Omphalotin A and its derivatives B, C and D exhibited strong nematicidal activities similar with those of commercially nematicide ivermectin. Omphalotin A lacked anti-microbial and phytotoxic activity, making it as potentially useful nematicide. Unfortunately, the low yields of these compounds (11 mg omphalitin A, 11 mg omphalitin B, 7 mg omphalitin C, and 7 mg omphalitin D in 50 L fermentational mycelia of *O. olearius*) remained the biggest obstacle in the development of these compounds into commercial nematicides [4,38,39].

While many attempts have been made to find potent nematicidal substances that can replace traditional man-made chemical nematicides, few have been developed for wide use. Up to now, no major commercial product based on nematode-toxic fungi or their

metabolites has been developed yet. However, there are several promising trials in progress. Sharma [189] reported that the culture broth of *Pleurotus sajor-caju* could immobilize parasitic nematodes against the button mushroom *Agaricus bisporus*. This study reported that the population of nematode parasitic on *A. bisporus* was reduced by 90% in substrates inoculated with *P. sajor-caju* [189]. Xiang *et al*. reported the positive effects of *Pleurotus ostreatus* on the control of the peanut root-knot nematode *Meloidogyne arenaria* in the greenhouse [190]. Their experiment showed that *P. ostreatus* could markedly reduce the infecting number of nematode. Such a reduction in nematode numbers was accompanied by a reduction of 86.96-94.03% of peanut root knots. These and other trials should result in significant developments in effective biocontrol strategies based on nematode-toxic fungi and the active nematicidal compounds in these fungi, in the near future.

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