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Novel secondary metabolites from endophytic fungi: synthesis and biological properties

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Abstract Plant-associated endophytic fungi are rich sources of novel bioactive and structurally diverse secondary metabolites and other natural products. Newly synthesized secondary metabolites of endophytes in terrestrial plants and their biological properties are presented and reviewed herein. The review highlights natural products from plant-associated fungal endophytes that demonstrate significant inhibition against pathogenic strains, human cancer cell lines and other biological targets. We have summarized 221 recently isolated, structurally diverse and novel secondary metabolites. Secondary metabolites that failed to demonstrate activity in the bioassays are not included. The review is intended to assist scientists in the fields of phytochemistry, organic chemistry, and pharmacology.

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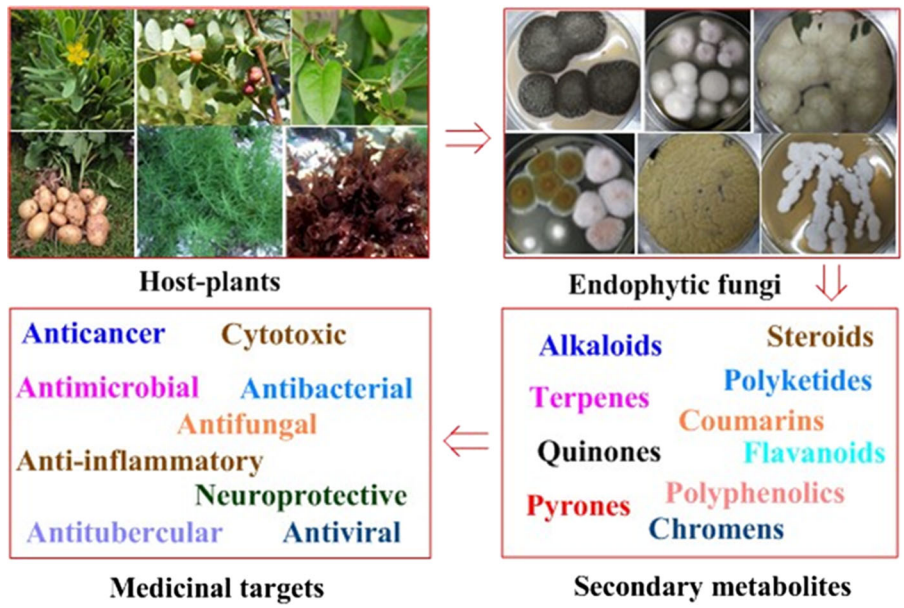
Graphic abstract



Keywords Endophytic fungi · Secondary metabolite · Natural product · Biological activity · Antimicrobial activity

Introduction

Endophytic fungi are microorganisms that inhabit the internal tissues of the plants without causing apparent disease symptoms (Nisa et al. 2015). Differences between pathogenic and endophytic microorganisms are sometimes difficult to define, especially when both present similar genetic signatures. Many fungal species comprise individual subspecies having both endophytic and pathogenic properties (Schouten 2019a, b). However, most pathogenic microorganisms produce toxins harmful to the host plant, while secondary metabolites produced by endophytic strains—usually antimicrobial agents—protect their host plants by blocking or inhibiting the appropriate pathogenic microorganisms (Schouten 2019a; Ludwig-Müller 2019). Endophytic microorganisms may also control growth and development of host plants (Neilson et al. 2013). Importantly, endophytic microorganisms living inside their host can often be cultured and grown after isolation from their host plants.

The isolation of endophytic fungi is normally carried out using surface sterilization, vacuuming (particularly for wood plants) and other accepted methods (Martinez-Klimova et al. 2017). Among these, most common approach is the screening of surface-sterilized plant tissue placed on growth media suitable for fungi (Schouten 2019b); antibacterial agents may be added to prevent proliferation of endophytic bacteria. Identification of endophytic microorganisms can be performed by morphological and molecular phylogenetics (rDNA, 16S rDNA sequences) techniques (Ko Ko et al. 2011; Rustamova et al. 2020).

One approach to efficient production of secondary metabolites is represented by fermentation, a microorganism-driven process that enzymatically converts substrates into bioactive compounds (Parvez et al. 2006). Endophytic strains sometimes produce novel pharmacologically active and structurally diverse secondary metabolites not present in their host's tissues. In this way endophytes can live independently and produce secondary metabolites in the host plant (Tawfike et al. 2019). Because plant-associated endophytic fungi are rich sources of novel bioactive compounds (Andrés et al. 2017), they provide an

important alternative to exploiting the plant itself (Obermeier and Christina 2019). This is of particular interest when (a) the bioactive secondary metabolites are not commercially available, (b) the bioactive secondary metabolites are derived from slow-growing or rare plants, or (c) total synthesis of the bioactive secondary metabolite is difficult or expensive due to its high molecular weight or complex structure.

Further research is needed to elucidate which partner (host-plant or endophytic strain) contributes to the biosynthesis of secondary metabolites, and to what extent. For example, it remains unclear which secondary metabolites are exclusively produced from plants, from the endophytic strain, or from both partners (Ludwig-Müller 2019). We do know that particular secondary metabolites can be exchanged with the partner and then further metabolized, either by the plant or by the endophytic fungus (Ludwig-Müller 2015). It has also been confirmed that endophytic strains can transform host-synthesized metabolites into multi-functional products (Schouten 2019c), and therefore particular fungi could be used as catalysts during biotransformation processes producing oxygenated compounds (Wang and Dai 2011).

The structurally unique natural compounds produced by plant endophytic fungi include alkaloids (Panaccione et al. 2014; Rustamova et al. 2019), terpenoids (Souza et al. 2011), various polyketides (El-Neketi et al. 2013), isocoumarins (Saeed 2016), flavonoids (Wang et al. 2011), lactones (Shen et al. 2015), and other such compounds (Martelli and Giacomini 2018). Endophytic secondary metabolites and their biological properties have been studied in terrestrial plants as well as marine organisms (Hou et al. 2019). Biochemistry and molecular biology techniques (e.g., biotransformation, exploration of biosynthetic pathways, and heterologous expression of enzymes in microorganisms) have been developed for the large-scale production of natural products. For example, between 2014 and 2016 there was a continual increase in the number of new secondary metabolites isolated from mangrove-associated fungi (103 in 2014, 133 in 2015 and 149 in 2016), mostly from endophytic species (Carroll et al. 2019). These data illustrate the potential of secondary metabolites isolated from endophytic strains.

Over the past decade the chemistry and biology of plant-associated endophytic fungi have emerged as topics of increasingly vital importance to our understanding of plant and microbial ecosystems, as well as to their potential applications in the pharmaceutical and other industries. Understanding of the chemistry of these fungi leads directly to better knowledge of their phytochemistry vis-a-vis isolation, analysis, biosynthesis, biotransformation and diversity of fungal components, while biological studies allow improvement in methods of strain isolation, microbiological characterization, and understanding of mechanisms of biological diversity and plant-fungal symbiosis. A literature search of Scopus (www.scopus.com) and Web of Science (www.webofknowledge.com) databases covering the period of January 2018 to June 2019 and using the search terms "endophyte" "endophytic fungi," "endophytic fungus," and "secondary metabolites from endophytic fungus" as keywords revealed nearly 1000 peer-reviewed scientific reports, including up to 150 research studies dedicated to the phytochemistry and medicinal chemistry of plant-associated natural compounds produced by endophytic fungi. This review significantly expands this body of work by summarizing 221 new secondary metabolites isolated from plant-associated endophytic fungi, along with their taxonomy (Fig. 1) and discussion of their biological properties.

Terpenes and terpenoids

Structurally unique and biologically active terpenes and terpenoids provided in this section include sesquiterpenes/sesquiterpenoids, diterpenes/diterpenoids, triterpenoids, and meroterpenoids, as well as steroids exhibiting various biological activities. All of the natural compounds we've isolated and characterized fall within these categories, are novel, and were isolated from endophytic strains belonging to defined fungal genera.

Sesquiterpenoids

Novel phenolic bisabolane sesquiterpenoids, (7*R*,10*S*)-7,10-epoxysydonic acid (**1**), (7*S*,10*S*)-7,10-epoxysydonic acid (**2**), (7*R*,11*S*)-7,12-epoxysydonic acid (**3**), (7*S*,11*S*)-7,12-epoxysydonic acid (**4**), 7-deoxy-7,14-didehydro-12-hydroxysydonic acid (**5**), (*Z*)-7-deoxy-7,8-didehydro-12-hydroxysydonic acid (**6**), and (*E*)-7-deoxy-7,8-didehydro-12-hydroxysydonic acid (**7**), were obtained from a culture of the

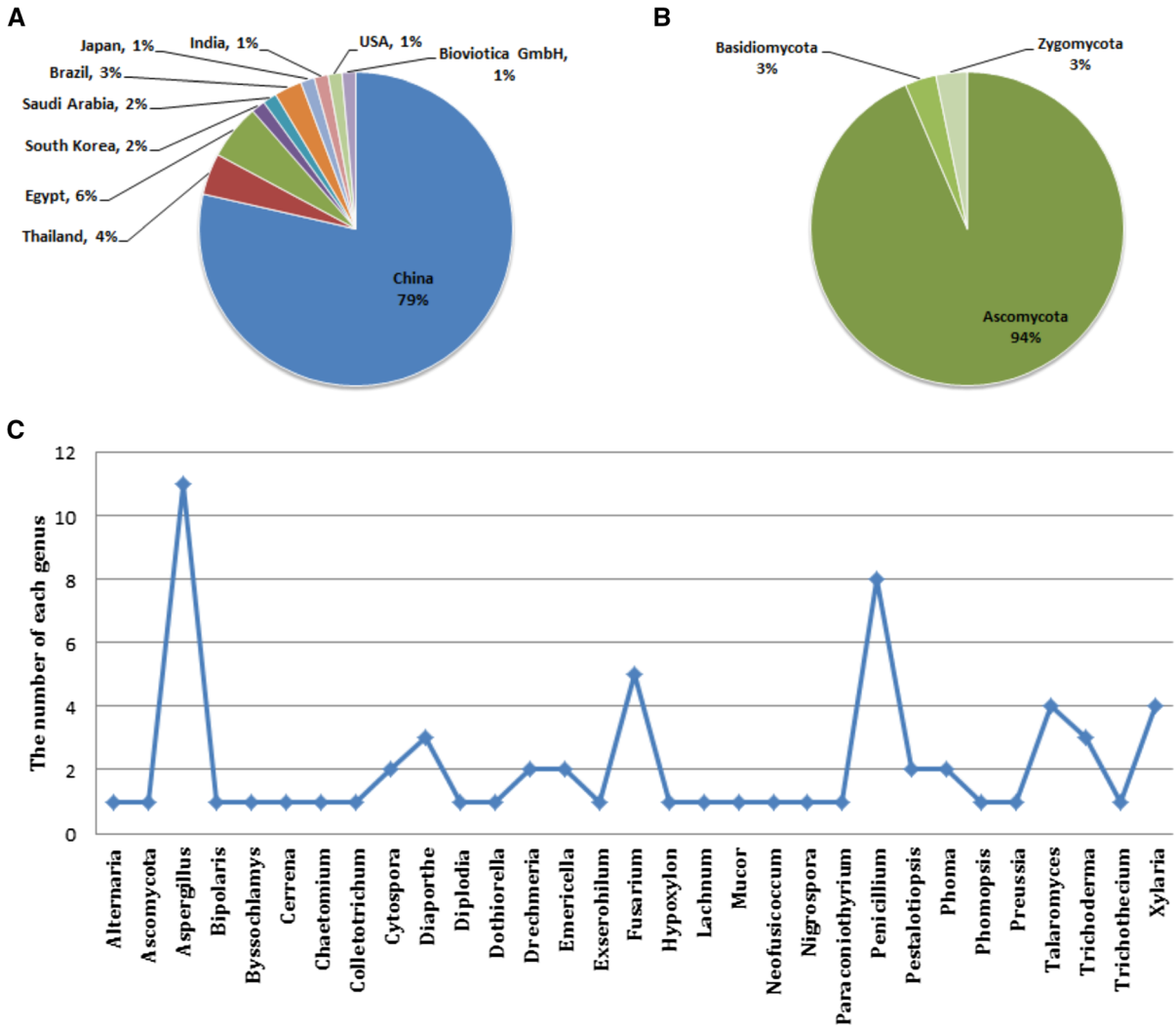


Fig. 1 Locations and ratios of the endophytic fungi that have been collected (**a**), percentages of endophytic fungi belonging to various phyla (**b**) and the number of endophytic fungi studied in each genus (**c**)

endophytic fungus *Aspergillus* sp. xy02 isolated from the leaves of a Thai mangrove *Xylocarpus moluccensis* (Fig. 2) (Wang et al. 2018a). Four derivatives (**2**, **3**, **5** and **7**) showed moderate antibacterial activities against *Staphylococcus aureus* ATCC 25,923 with IC_{50} values ranging from 31.5 to 41.9 μM, with none of the novel sesquiterpenoids demonstrating DPPH scavenging antioxidant potential.

Another fourteen novel secondary metabolites [one 2,3-seco-protoilludane-type sesquiterpenoid (**8**), eight protoilludane-type sesquiterpenoids (**9**–**16**), four illudalane-type sesquiterpenoids (**17**–**20**), and one botryane-type sesquiterpenoid (**21**)] were obtained from the strain *Phomopsis* sp. TJ507A, an endophytic fungus isolated from the leaves of the medicinal plant *Phyllanthus glaucus* (Fig. 2) (Xie et al. 2018b). All sesquiterpenoids were evaluated for their BACE1 inhibitory activities. Among them, eight isolates **8**–**14** and **16** showed BACE1 inhibitory activities ranging from 19 to 43% at a concentration of 40 μM, while the positive control LY2811376 revealed an inhibitory activity of 38.6%.

Sesquiterpenes, including three cyclonerane sesquiterpenes, 11-methoxy-9-cycloneren-3,7-diol (**22**), 10-cycloneren-3,5,7-triol (**23**), and methyl 3,7-dihydroxy-15-cycloneranate (**24**), as well as one

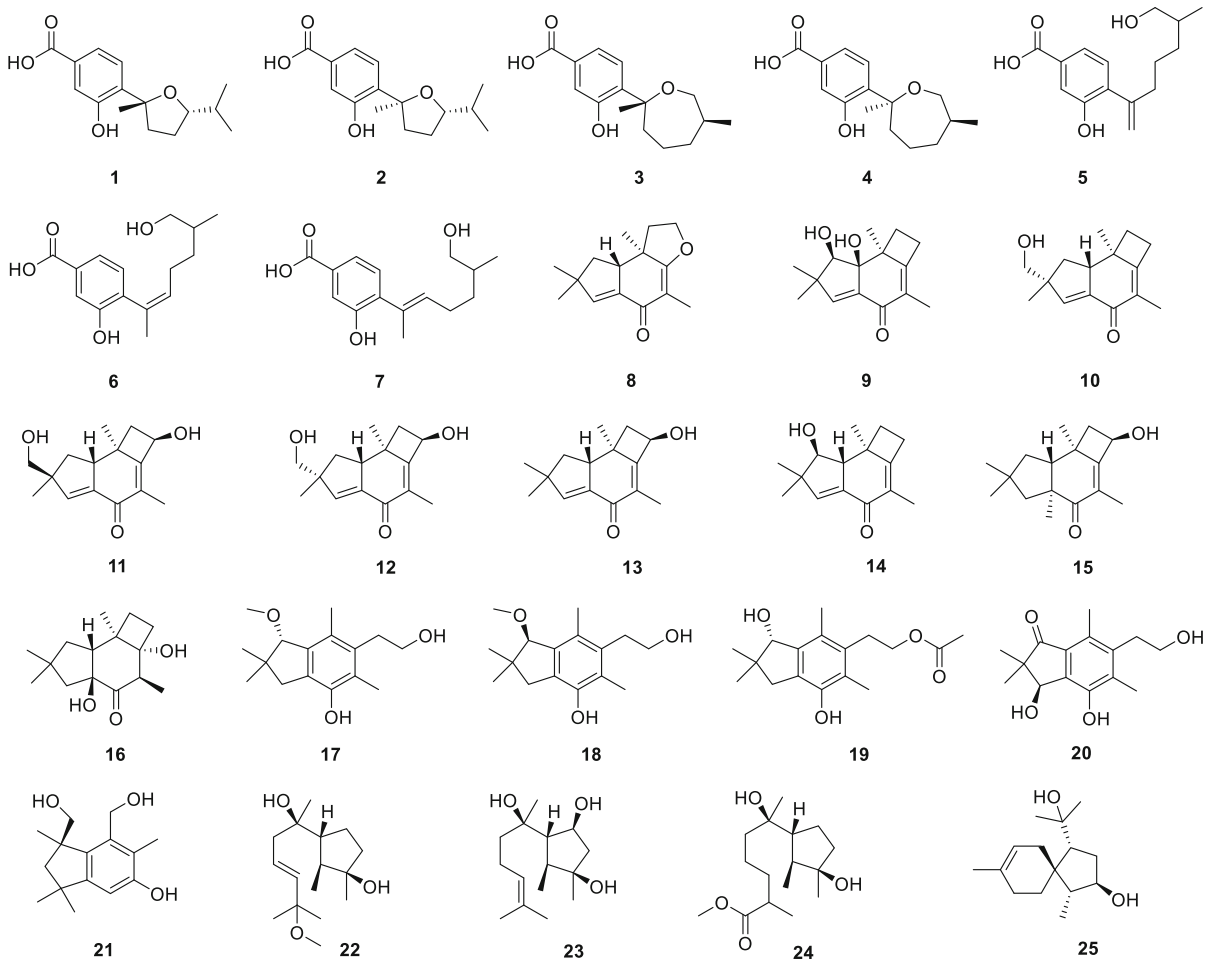


Fig. 2 The structures of novel sesquiterpenoids (**1**–**25**) isolated from endophytic fungi

acorane sesquiterpene, 8-acoren-3,11-diol (**25**), were isolated from a culture of *Trichoderma harzianum* X-5, an endophytic fungus obtained from the marine brown alga *Laminaria japonica* (Fig. 2) (Song et al. 2018b). The isolates have been evaluated for their antimicroalgal activities against *Chattonella marina*, *Heterosigma akashiwo*, *Karlodinium veneficum,* and *Prorocentrum donghaiense* phytoplankton species, as well as their antibacterial activity against *Vibrio anguillarum*, *Vibrio harveyi*, *Vibrio parahemolyticus,* and *Vibrio splendidus* marine-derived pathogenic bacteria. Compound **22** was the most active against *C. marina* (IC_{50} = 0.66) and *K. veneficum* (IC_{50} = 2.2) compared to the other obtained products. All four metabolites failed to demonstrate significant activity against bacterial strains of the Vibrio genus, with the exception of *V. anguillarum* which displayed only weak potency toward compounds **22**–**25**.

The endophytic fungus *Cytospora* sp., isolated from the hypocotyls of the Chinese mangrove *Ceriops tagal* yielded seiricardine D, a new bicyclic sesquiterpene (**26**) (Fig. 3) (Deng et al. 2018). In vitro antimicrobial activity of metabolite **26** against the human pathogens *Escherichia coli*, methicillin-resistant *S. aureus* (MRSA), *Pseudomonas aeruginosa*, *Candida albicans*, and the plant pathogens *Bacillus subtilis*, *Colletotrichum gloeosporioides*, and *Magnaporthe oryzae* revealed that this compound exhibited weak inhibitory activity only against *M. oryzae* with an MIC of 839 μM.

The fungal strain *Aspergillus fumigatus*, an endophyte of *Ligusticum wallichii*, produced two new sesquiterpenes, fumagillene A (**27**) and fumagillene B

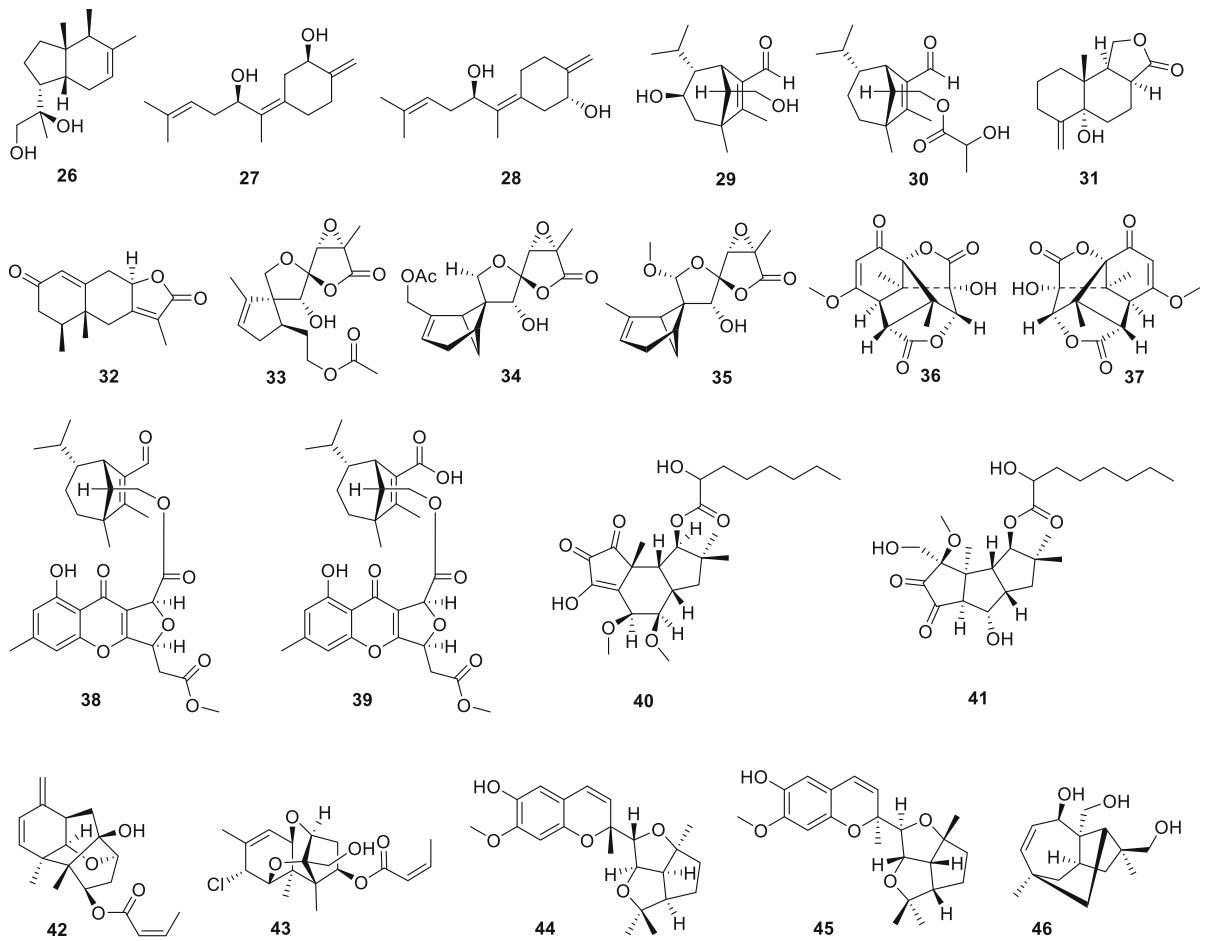


Fig. 3 The structures of new sesquiterpenes (**26–46**) isolated from endophytic fungi

(**28**) (Fig. 3) (Li et al. 2018a). The cytotoxicity evaluation of the novel metabolites against MDA-ME-231 and MV4-11 cancer cell lines revealed that both secondary metabolites showed modest growth inhibition, with derivative **27** displaying IC_{50} values of 8.4 and 14.3 μM and compound **28** having IC_{50} values of 11.2 and 17.3 μM, respectively.

Two novel sativene-type sesquiterpenoids, bipolenins G and H (**29**, **30**, Fig. 3), were obtained from *Bipolaris eleusines*, an endophytic fungus isolated from fresh potatoes (Li et al. 2018c). These metabolites did not demonstrate activity ($IC_{50} > 40$ μM) against three human cancer cell lines (HL-60, A-549 and MCF-7). However, isolate **29** exhibited anti-NO production activity with an IC_{50} value of 23.8 μM. Another new terpenenoid, the first example of 14-nor-drimane-type sesquiterpene, phomanolide (**31**, Fig. 3), was obtained from the culture broth of an endophytic fungus of the *Phoma* sp. isolated from the roots of *Aconitum vilmorinianum* (Liu et al. 2019c). Antiviral screening revealed that sesquiterpene **31** showed anti-influenza activity on influenza A virus (A/Puerto Rico/8/34, H1N1) with an IC_{50} value of 2.96 μg/mL.

The endophytic fungus *Xylaria* sp. GDG-102, isolated from the leaves of *Sophora tonkinensis,* yielded one new eremophilane sesquiterpene, xylareremophil (**32**, Fig. 3) (Liang et al. 2018b). In order to evaluate the antibacterial potential of compound **32**, several strains were selected for the antibacterial assay, including *S. aureus*, *Micrococcus lysodeikticus*, *Micrococcus luteus*, *B. subtilis*, *Enterobacter aerogenes*, *Salmonella paratyphi* B, and *Proteus vulgaris*. Metabolite **32** exhibited moderate inhibition of *M. luteus* and *P. vulgaris* with an MIC value of 25 μg/mL.

Three novel sesquiterpene lactones, purpurolides A–C (**33**–**35**, Fig. 3), with significant inhibitory activity against pancreatic lipase, were produced from the strain *Penicillium purpurogenum* IMM003, an endophytic fungus obtained from fresh and healthy leaves of *Edgeworthia chrysantha* (Wang et al. 2018c). The new metabolites **33**–**35** potently inhibited the pancreatic lipase demonstrating IC_{50} values of 2.83, 5.45, and 6.63 μM, respectively, compared to the standard kaempferol (1.50 μM).

Preussia isomera XL-1326, an endophyte isolated from the stems of *Panax notoginseng*, produced a pair of norsesquiterpenoidal enantiomers, (+-(**36**) and (−-(**37**) preuisolactone A (Fig. 3) (Xu et al. 2019a). These metabolites failed to demonstrate cytotoxic activity against the human A549, Huh7, MGC803, HCT116, and LN229 cancer cell lines ($IC_{50} > 100$ μM). However, they showed moderate to weak antibacterial activities against *M. luteus* and *Bacillus megaterium* with MIC values of 10.2 and 163.4 μM, respectively. Notably, the antimicrobial screening led to the selection of a total of 16 microbial strains, including eight bacterial and eight fungal species.

The endophytic fungus *Bipolaris eleusines,* isolated from potato, also yielded two novel anti-phytopathogenic (*Alternaria solani*) sesquiterpenoid-xanthone hybrids, namely bipolins I and J (**38** and **39**, Fig. 3) (He et al. 2019). These hybrids were evaluated for their anti-phytopathogenic activities against four plant pathogens including *Phytophthora infestane*, *A. solani*, *Rhizoctonia solani,* and *Fusarium oxysporum*. Both, metabolites **38** and **39** displayed potent inhibitory activity towards *A. solani*, with MIC values of 8 and 16 μg/mL, respectively. Compound **38** also weakly inhibited *F. oxysporum* with an MIC value of 64 μg/mL.

Two new triquinane-type sesquiterpenoids, named cerrenins D (**40**) and E (**41**) (Fig. 3), were isolated from endophytic *Cerrena* sp. A593, which was obtained from the plant *Pogostemon cablin* (Liu et al. 2019a). The new metabolite **40** was evaluated for its cytotoxic activity in four cancer cell lines (SF-268, MCF-7, NCI-H460 and HepG-2) and compared with cisplatin as positive control drug. The results revealed that cerrenins D displayed moderate activity against the breast cancer MCF-7 cell line with an IC_{50} value of 14.43 μM. Only weak cytotoxic activities were observed toward the other cell lines.

Novel secondary metabolites, including two trichothecene sesquiterpenoids, trichothecrotocins A (**42**) and B (**43**), and merosesquiterpenoid racemate, (±)-trichothecrotocin C (**44** and **45**), were detected in the potato (*Solanum tuberosum*) endophytic fungus *Trichothecium crotocinigenum* (Fig. 3) (Yang et al. 2018a). All isolated sesquiterpenoids were evaluated for their anti-phytopathogenic properties against four potato pathogens, including *Phytophthora infestans* (late blight), *A. solani* (early blight), *R. solani* (black scurf), and *F. oxysporum* (blast). It should be noted that several potato diseases are caused by the plant pathogens described above. Additionally, they are known to cause substantial problems in the production of potatoes. Notably, (±)-trichothecrotocin C weakly inhibited *P. infestans* and *R. solani*, while all metabolites of the new isolates demonstrated potent inhibitory activities against *A. solani* (MIC = 12, 16, 8 μg/mL) and *F. oxysporum* (MIC = 32, 16, 16 μg/mL).

An endophytic fungus, *Pestalotiopsis adusta,* collected from the stem bark of the wild and rare medicinal plant *Sinopodophyllum hexandrum* (Royle), produced one novel sesquiterpene pestalustaine A (**46**, Fig. 3), with an unusual 5/6/7-fused tricyclic system (Xiao et al. 2018). The cytotoxic activities of the new isolate against HeLa, HCT116, and A549 cell lines were weak to moderate, with the IC_{50} values ranging from 29.58 to 58.75 μM.

Diterpenoids

Drechmerin H, a novel 1(2), 2(18)-disecoindole diterpenoid (**47**), and new indole diterpenoid, 2′- epiterpendole A (**48**), was reportedly produced by the endophytic fungus of *Drechmeria* sp. SYPF 8335, isolated from the root of *Panax notoginseng* (Fig. 4) (Zhao et al. 2018a). The isolates were assayed for agonistic effects on the pregnane X receptor (PXR) and metabolite **47**. A significant agonistic effect on PXR was measured with an EC_{50} value of 134.91 nM. Further, seven new indole diterpenoids, drechmerins A–G (**49**–**55**, Fig. 4) were derived from the fungal strain *Drechmeria* sp., which is an endophyte isolated from the root of *Panax notoginseng* (Zhao et al. 2018b). The antimicrobial screening revealed that drechmerin B (**50**) displayed significant inhibition of *C. albicans*, with an MIC value of 12.5 μg/mL, while other metabolites demonstrated only weak antimicrobial effects.

Three new diterpenes, koninginols A–C (**56**–**58**, Fig. 4), produced by the endophytic fungus

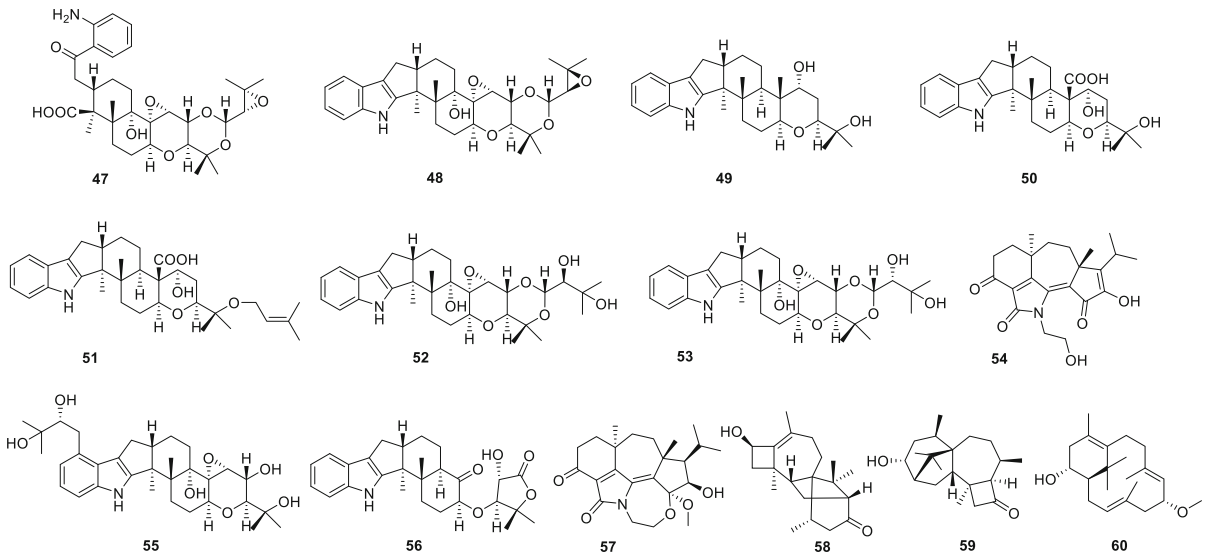


Fig. 4 The structures of novel diterpenoids (**47**–**60**) produced by endophytic fungi

Trichoderma koningiopsis A729, were derived from the fresh branches of the medicinal plant *Morinda officinalis* (Chen et al. 2019b). Regarding their biological screening, the novel isolates **56** and **57** exhibited significant antibacterial activity against *B. subtilis* with MIC values of 10 and 2 μg/mL, respectively. Furthermore, in their antitumor evaluation using HepG-2, MCF-7, SF-268, and A549 cell lines, only diterpene **57** displayed an antiproliferative activity in A549 with an IC_{50} value of 46.6 μM.

One harziane diterpene, 3*R*-hydroxy-9*R*,10*R* dihydroharzianone (**59**), and one proharziane diterpene, 11*R*-methoxy-5,9,13-proharzitrien-3-ol (**60**), were obtained from endophytic *Trichoderma harzianum* X-5 of the marine brown alga *Laminaria japonica* (Fig. 4) (Song et al. 2018b). In anti-microalgal and antibacterial assays, compound **60** exhibited modest activity against *C. marina*. This compound also showed weak activity against *V. harveyi,* with an IC_{50} value of 6.8 μM at 20 μg/disk.

Triterpenoids

Nine novel triterpenoids, named as kadhenrischinins A–H (**61**–**68**) and 7β-schinalactone C (**69**) were isolated from *Kadsura angustifolia* fermented by a symbiont endophytic fungus, *Penicillium* sp. SWUKD4.1850 (Fig. 5) (Qin et al. 2019). This was the first report on the fermentation of *Kadsura angustifolia* and the first discovery of highly oxygenated schitriterpenoids using microbial technology. All metabolites were evaluated for their cytotoxicity in human hepatocellular liver carcinoma cells (HepG2). The triterpenoids **61**–**68** demonstrated moderate cytotoxic activity with IC_{50} values ranging from 14.3 to 21.3 μM, while derivative **69** displayed weak activity ($IC_{50} > 40$ μM) in the HepG2 cells.

Two new tetracyclic triterpenoids, integracide E (**70**) and isointegracide E (**71**), were obtained from the mycelium of the endophytic fungus *Hypoxylon* sp. 6269, which was isolated from medicinal plant *Artemisia annua* (Fig. 5) (Liang et al. 2018a). These novel secondary metabolites were tested for their anti-HIV-1 integrase potential in coupled and strand transfer assays. Herein, derivative **70** displayed weak activity in both assays with IC_{50} values of 31.63 and 29.06 μM, respectively, while metabolite **71** was inactive in all performed tests.

One new pentanortriterpenoid, 23,24,25,26,27-pentanorlanost-7,9(11)-dien-3b,22-diol (**72**), and one new triterpenoid, lanost-8-en-3b,22S,23S-triol (**73**), were derived from the endophytic fungus *Diplodia cupressi*, isolated from the healthy tissues of *Polytrichum commune* (Fig. 5) (Liu et al. 2019d). The cytotoxicity of these compounds in human cancer cell lines (A549, Hep G2, Hepa 1c1c7, and HeLa) was evaluated, and derivative **73** displayed weak inhibitory

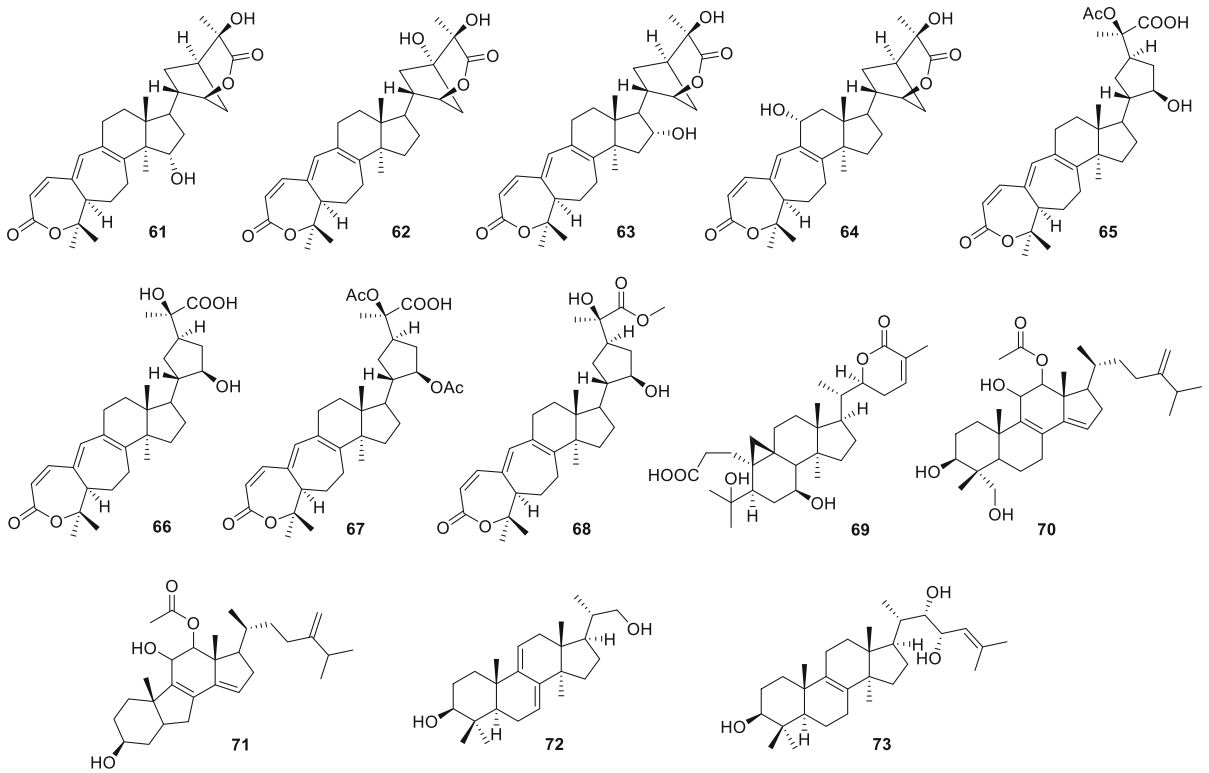


Fig. 5 The structures of novel triterpenoids (**61**–**73**) isolated from endophytic fungi

activity with an IC_{50} value of 35.0 μM against the proliferation of Hepa 1c1c7 cells.

Meroterpenoids

The endophytic fungus *Fusarium* sp. YD-2, obtained from the twigs of *Santalum album*, produced two new spiromeroterpenoids, namely fusariumin A (**74**) and B (**75**) (Fig. 6) (Yan et al. 2018). These terpenoids were evaluated for their potential anti-inflammatory and antibacterial properties. Fusariumin A exhibited significant activity against *S. aureus* and *P. aeruginosa* with an MIC value of 6.3 μg/mL, while fusariumin B showed modest anti-inflammatory activity in vitro by inhibiting the nitric oxide (NO) production in lipopolysaccharide (LPS)-activated RAW264.7 cells with an IC_{50} value of 50 μM. For antibacterial screening, eight bacterial species (*S. aureus*, *Staphylococcus albus*, *B. subtilis*, *Bacillus cereus*, *M. luteus*, *E. coli*, *P. aeruginosa*, *Salmonella enteritidis*) were selected for the evaluation of **74** and **75**.

The chemical investigation of the fungal strain *Talaromyces amestolkiae* YX1, an endophyte isolated from healthy leaves of the marine mangrove *Kandelia obovata*, produced four new meroterpenoids, amestolkolides A-D (**76**–**79**, Fig. 6) (Chen et al. 2018). Meroterpenoids were tested for their inhibitory activities against LPS-activated NO production in RAW264.7 cells using the Griess assay, with indomethacin as the positive control (IC_{50} = 26.3 μM). Amestolkolide B (**77**) displayed strong inhibitory effects on the NO production with IC_{50} values of 1.6 μM, while amestolkolide A (**76**) demonstrated weaker activity (30 μM).

The fungal strain *Emericella* sp. TJ29, an endophyte derived from the root of the plant *Hypericum perforatum*, produced emeridones A–F (**80**–**85**, Fig. 6), six new 3,5-demethylorsellinic acid-based meroterpenoids (Li et al. 2019). The anticancer screening of the novel secondary metabolites in five human cancer cell lines (HL-60, SMMC-7721, A549, MCF-7, and SW-480) revealed that meroterpenoids **81**, **83**, and **85** displayed modest cytotoxic activities against SMMC-7721 cells with IC_{50} values of 18.80,

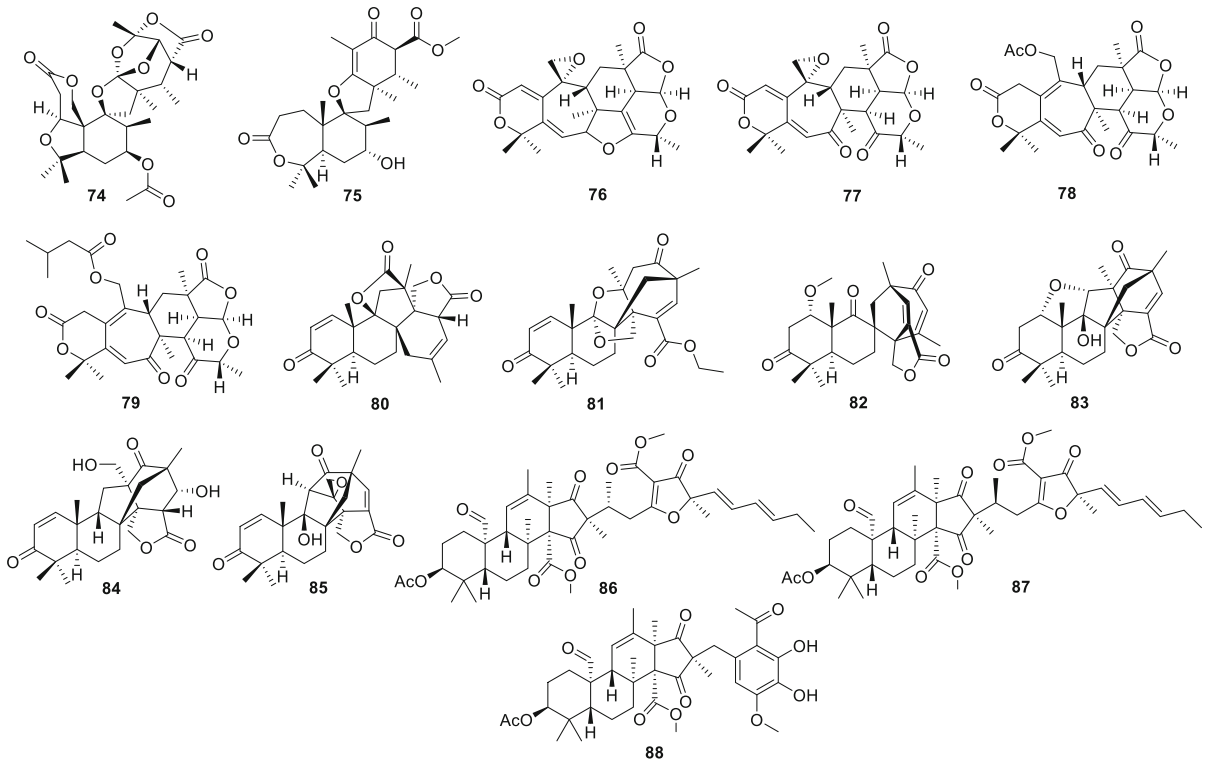


Fig. 6 The structures of new natural meroterpenoids (**74**–**88**) isolated from endophytic fungi

8.19, and 17.49 μM, respectively. These three isolates also demonstrated cytotoxicity towards SW-480 cells (IC_{50} = 18.35, 14.67, and 16.84 μM, respectively), while emeridone D (**83**) was active against A-549 cells with an IC_{50} of 11.33 μM.

The endophytic fungus *Penicillium* sp. sh18 was isolated from the fresh stems of *Isodon eriocalyx var. laxiflora.* Three novel meroterpenoids, isopenicins A–C, were derived from this endophyte (**86**–**88**, Fig. 6), which contained terpenoid-polyketide hybrid skeletons (Tang et al. 2019a). These secondary metabolites were evaluated for their inhibitory activity towards the Wnt/β-catenin signaling pathway using HEK293 cells stably transfected with Wnt3a, Renilla, and Super-Topflash luciferase (ST-Luc). Metabolite **86** was identified as a potent inhibitor of the Wnt signaling pathway. The Wnt signaling inhibitory activity of metabolite **86** was also investigated in Wnt-dependent colorectal cancer cells, SW620 and HCT11610. The elevated ST-Luc activity was significantly decreased by derivative **86** in both SW620 and HCT116 cells. Further experiments evaluating the effect of compound **86** on the expression of endogenous Wnt target genes revealed that the expression of Axin 2, c-myc, and survivin was considerably suppressed in SW620 and HCT116 cells exposed to isopenicin A.

Steroids

The *Fusarium* sp. is a rich source of ergosterol derivatives and other metabolites of diverse classes. Three new ergosterol derivatives [Fusaristerol B ((22E,24R)-3-palmitoyl-19(10 → 6)-abeo-ergosta-5,7,9,22-tetraen-3β-ol) (**89**), Fusaristerol C [(22E,24R)-ergosta-7,22-diene-3β,6β,9R-triol] (**90**) and Fusaristerol D [(22E,24R)-ergosta-7,22-diene-3β,5α,6β,9α-tetraol 6-acetate] (**91**)] were isolated from the endophytic fungus *Fusarium* sp., separated from the interior tissues of the *Mentha longifolia* L. (Labiatae) roots (Fig. 7) (Khayat et al. 2019). The 5-lipoxygenase (5-LOX) inhibitory activity of the secondary metabolites from *Fusarium* sp. was assessed, with isolate **89** displaying strong 5-LOX inhibitory activity with the IC_{50} value of 3.61 μM compared to that of indomethacin (IC_{50} 1.17 μM),

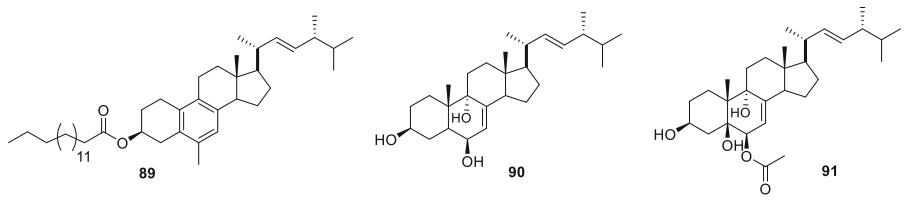


Fig. 7 The structures of new steroids (**89–91**) endophytic fungi

while isolates **90** and **91** demonstrated moderate activity with IC_{50} values of 7.01 and 4.79 μM, respectively. Therefore, ergosterol derivatives could be lead compounds in the development of 5-LOX inhibitory agents to treat various inflammatory disorders.

Polyketides

Many of the secondary metabolites produced from endophytic fungi are polyketides. These are widely distributed in other microorganisms and plants, and many of them exhibit various biological activities. This class of compounds includes coumarins, isocoumarins, α-pyrones, chromens, quinones, anthrones, and other related polyketides. This section describes recent developments in the chemistry and biology of polyketides in phytochemistry along with their medicinal uses.

Coumarins

One rare coumarin derivative, pestalustaine B (**92**, Fig. 8), with an unprecedented 6/6/5/5-fused tetracyclic system was isolated from the endophyte *Pestalotiopsis adusta* of the plant *Sinopodophyllum hexandrum* (Xiao et al. 2018). The anticancer activity of this coumarin has been evaluated in HeLa, HCT116, and A549 cancer cell lines, and moderate cytotoxic activities against all selected cell lines was observed with IC_{50} values of 21.18, 21.04, and 37.33 μM, respectively.

Isocoumarins

Pestalotiopsis sp., an endophytic fungus isolated from the fresh, healthy branches of the Chinese mangrove plant *Rhizophora stylosa*, yielded one new isocoumarin derivative, pestalotiopisorin B (**93**, Fig. 8) (Xu et al. 2019b). For antimicrobial screening, five types of microorganisms were selected (*P. aeruginosa*, *Enterococcus faecalis*, MRSA, *E. coli* and *C. albicans*). This secondary metabolite displayed moderate antibacterial activity towards *E. coli* and *P. aeruginosa* with MIC values of 12.5 and 50 μg/mL, respectively.

Seven new dihydroisocoumarins, including five brominated (**94–98**) and two chlorinated (**99** and **100**) metabolites were produced by the endophytic fungus *Lachnum palmae*, isolated from the fresh tissue of the surface-sterilized *Przewalskia tangutica* (Fig. 8) (Zhao et al. 2018c). All novel isolates were evaluated for antimicrobial activity against *Cryptococcus neoformans*, *Penicillium* sp., *C. albicans*, *B. subtilis,* and *S. aureus* strains. Coumarin **98** possessed antimicrobial activities against all the tested strains with MIC values in the range of 10–55 mg/mL. However, HepG2 cells revealed only weak cytotoxicity with an IC_{50} value of 42.8 μM. Regarding the anti-inflammatory properties, palmaerones A and E (**94** and **98**) exhibited moderate inhibitory effects on NO production in LPS-induced RAW 264.7 cells, with IC_{50} values of 26.3 and 38.7 μM, respectively, with no obvious toxicities observed at 50 μM.

Ten new isocoumarins, named peniisocoumarins A–J (**101–110**, Fig. 8), were obtained through the fermentation of an endophytic fungus *Penicillium commune* QQF-3, isolated from fresh fruits of the mangrove plant *Kandelia candel* (Cai et al. 2018). These new coumarins were tested for their inhibitory activities against α-glucosidase in vitro, and metabolites **101**, **105**, **107**, and **108** demonstrated potential inhibitory activity comparable to the positive control acarbose. The IC_{50} values ranged from 38.1 to 78.1 μM. In addition, all coumarins were tested for their MptpB inhibitory activity, and cytotoxicity using human tumor cell lines including A549, HepG2, HeLa, MCF-7, and HEK293T. Herein, isolate **105** showed potent MptpB inhibitory activity with an IC_{50}

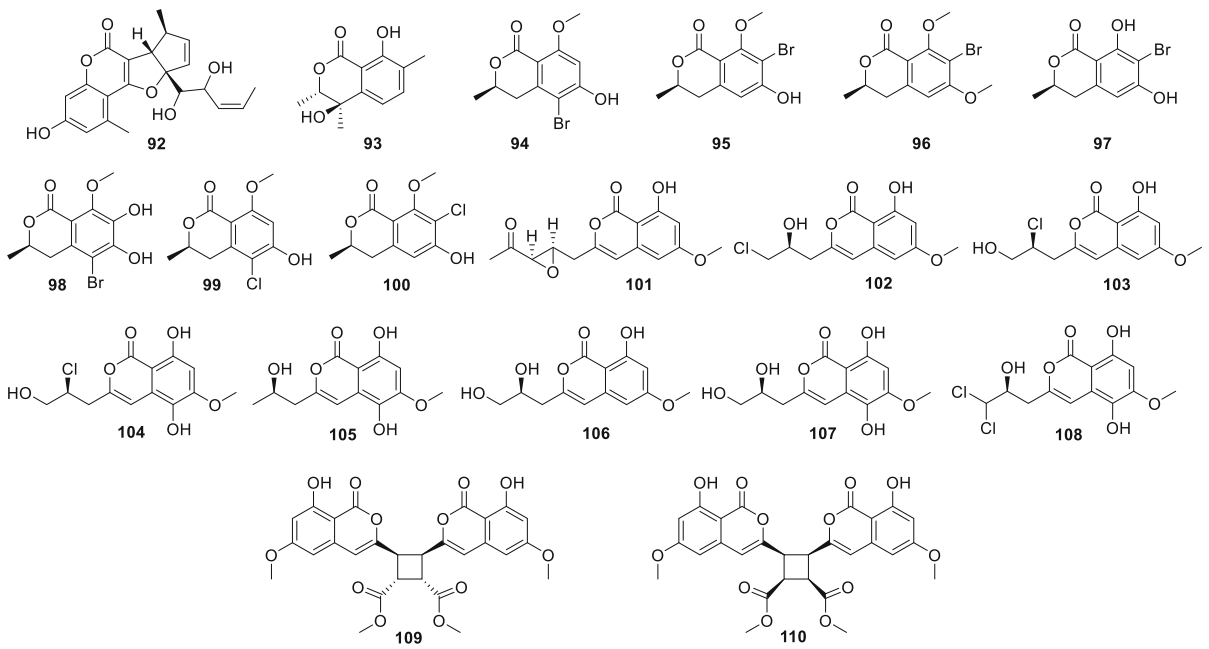


Fig. 8 The structures of coumarins **92**, isocoumarins **93–110** produced by endophytic fungi

value of 20.7 μM compared to the positive control oleanolic acid. However, none of the metabolites displayed cytotoxicity against the tested human cell lines at 100 μM.

α-Pyrones and chromens

In continuing pursuit of new bioactive metabolites from endophytic fungi of endemic plants around the Three Gorges area, four new α-pyrone type derivatives (**111–114**, Fig. 9) were obtained from an ethyl acetate extract of *Xylariales* sp. (HM-1), an endophytic fungi isolated from the healthy leaves of *Distylium chinense* (Guo et al. 2018). The preliminary cytotoxicity of the novel isolates in four cancer cell lines (A549, HepG2, Caski and MDA-MB-231) failed to reveal significant activity. However, xylariaopyrones A–D (**111–114**) displayed antimicrobial inhibitory activity with MIC values ranging between 20.5 and 50.6 μg/mL. In addition, the results of the brine shrimp inhibiting activity from four new metabolites displayed inhibition percentages ranging from 42 to 82%.

Three new 3,4,6-trisubstituted α-pyrone derivatives, namely 6-(2′rhydroxy-3′*E*,5′*E*-diene-1′-heptyl)-4-hydroxy-3-methyl-2*H*-pyran-2-one (**115**), 6-(2′*S*-hydroxy-5′*E*-ene-1′-heptyl)-4-hydroxy-3-methyl-2*H*-pyran-2-one (**116**), and 6-(2′*S*-hydroxy-1′-heptyl)-4 -hydroxy-3-methyl-2*H*pyran-2-one (**117**) were derived from the endophytic fungi *Penicillium ochrochloronthe* associated with the roots of *Taxus media* (Fig. 9) (Zhao et al. 2018d). Although these secondary metabolites exhibited minimal cytotoxic activity in seven human cancer cells (A549, LN229, MGC, LOVO, Huh7, MHCC97H and MDA231), all the novel α-pyrones demonstrated significant antifungal activity when tested in fungal strains including *Cercospora arachidicola* Hori, *A. solani*, *Bipolaris carbonum* Wilson, *Fusarium graminearum*, *Cylindrocladium parasiticum*, *Alternaria alternata f.* sp. mali, *Cercospora personata,* and *Botrytis cinerea* Pers. with MIC values ranging between 12.5–50 μg/mL, and weak to modest antibacterial activity against 20 fungal and 10 bacterial strains.

Three new α-pyrone derivatives, namely (*S*)-6-(sec-butyl)-5-(hydroxymethyl)-4-methoxy-2*H*-pyran-2-one (**118**), (5*S*,7*R*)-7-ethyl-4,5-dimethoxy-7-methyl-5,7-dihydro-2*H*-furo[3,4-*b*]pyran-2-one (**119**) and (5*R*,7*R*)-7-ethyl-4,5-dimethoxy-7-methyl-5,7-dihydro-2*H*-furo[3,4-*b*]pyran-2-one (**120**), were induced by chemical epigenetic manipulation of the endophytic fungus *Penicillium herquei*, isolated from the fruiting body of *Cordyceps sinensis* (Fig. 9) (Guo et al. 2019). The cytotoxicity of these metabolites in MDA-ME-231 and MV4-11 cancer cell lines revealed

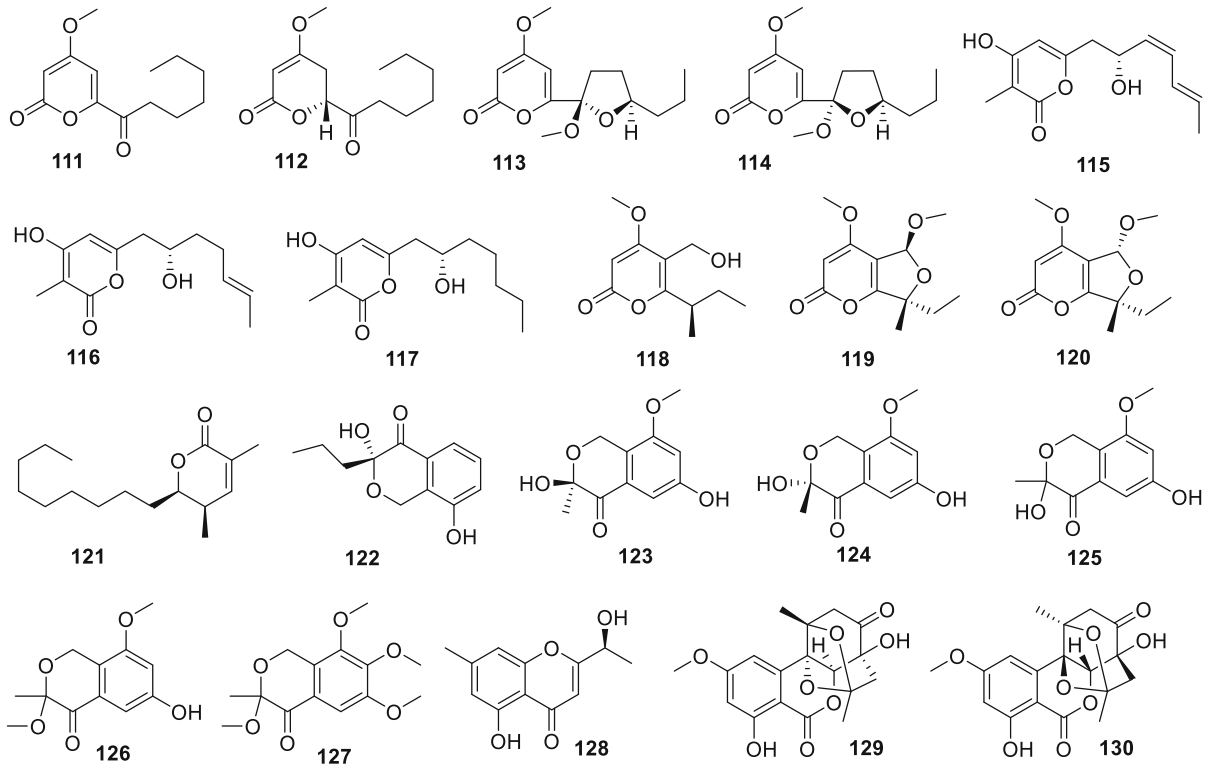


Fig. 9 The structures of novel α-pyrones (**111**–**122**), and chromens (**123**–**130**) isolated from endophytic fungi

that α-pyrones **118**–**120** exhibited weak growth inhibition in the MV4-11 cell line with IC_{50} values of 90.09, 74.16 and 70.00 μM, respectively.

Two new pyranones, Wortmannine F (**121**) and G (**122**) (Fig. 9), were isolated from *Talaromyces wortmannii* LGT-4, which is an endophytic fungus derived from *Tripterygium wilfordii* (Zhao et al. 2019). These new isolates were tested for monoamine oxidase (MAO), AChE, and phosphoinositide 3-kinase α (PI3Kα) inhibitory activities, and metabolites **121** and **122** demonstrated potent PI3Kα inhibition with IC_{50} values of 25 and 5 μM, respectively.

Novel isochromanes, named (*S*)-3,6-dihydroxy-8-methoxy-3-methylisochroman-4-one(**123**) and (*R*)-3,6-dihydroxy-8-methoxy-3-methylisochroman-4-one(**124**), as well as 6-methoxy-3-methylisochromane-3,8-diol (**125**), 3,6-dimethoxy-3-methylisochroman-8-ol (**126**) and 3,6,7,8-tetramethoxy-3-methylisochromane (**127**), were derived from the endophytic fungus *Aspergillus fumigatus*, isolated from the fruiting body of *Cordyceps sinensis* (Fig. 9) (Li et al. 2018b). The antitumor activity of these novel metabolites was evaluated in MV4-11 and MDA-ME-231 cancer cell lines. Compounds **123** and **125** demonstrated intermediate activity in the MV4-11 cell line with the IC_{50} values of 38.39 μM and 30.00 μM, respectively.

The potato endophytic fungus, *Bipolaris eleusines,* yielded a novel chromone (*S*)-5-hydroxyl-2-(1-hydroxyethyl)-7-methylchromone (**128**, Fig. 9) when the fungal strain was cultured on potato dextrose agar (PDA) medium (He et al. 2018). This secondary metabolite displayed weak inhibitory activity towards *S. aureus* subsp. with an inhibition rate of 56.3%, at a concentration of 128 μg/mL (penicillin G: 99.9% at 5 μg/mL).

A pair of enantiomers (+)- and (−)-alternarilactone A (**129** and **130**, Fig. 9) were derived from the fungal strain *Alternaria* sp. hh930. This endophyte was isolated from fresh stems of *Isodon sculponeatus* (Tang et al. 2019b). These enantiomers were evaluated for their inhibitory potential in corticosterone-induced apoptosis in PC12 cells, together with their antimicrobial activities. Both derivatives failed to demonstrate significant antibacterial or antifungal effects against the Gram-positive pathogen *S. aureus*, the

Gram-negative pathogen *Salmonella typhi*, and the plant pathogenic fungi *Gaeumannomyces graminis* and *Verticillium cinnabarium*. However, these metabolites possessed weak cytoprotective activity (cell survival (%) of **129** and **130** revealed as 64.86 and 61.86%, respectively) against corticosterone-induced apoptosis in PC12 cells. These secondary metabolites are the first examples of dibenzo-α-pyrones possessing a diepoxy-cage-like moiety.

Quinones, anthrones and related secondary metabolites

A new hydroanthraquinone, nigrosporone A (**131**), and a new naturally isolated nigrosporone B (**132**) (Fig. 10) were produced by the strain *Nigrospora* sp. BCC 47789, an endophytic fungi isolated from the leaf of *Choerospondias axillaris* (Roxb.) (Kornsakulkarn et al. 2018). The two novel isolates were subjected to assays to assess their antiplasmodial (*P. falciparum*, K1), antimycobacterial (*M. tuberculosis* H37Ra), antibacterial (*B. cereus* and *Enterococcus faecium*) activities and cytotoxic potential in cancer cell lines (KB, MCF-7, and NCI-H187) and non-cancerous Vero cells. Metabolite **132** showed significant biological activities against *P. falciparum* (IC_{50} 10.81 μM), *M. tuberculosis* (MIC 172.25 μM), *B. cereus* (MIC 21.53 μM), and *E. faecium* (MIC 10.78 μM). It also demonstrated selective cytotoxicity in NCI-H187 and Vero cells with IC_{50} values of 0.25 and 0.72 μM, respectively. Additionally, isolate **131** demonstrated only moderate to weak cytotoxicity in MCF-7 and NCI-H187 cancer cells (IC_{50} 110.36 and 13.69 μM).

The fungus *Neofusicoccum austral* SYSU-SKS024, an endophyte isolated from the branches of the mangrove plant *Kandelia candel*, produced three new ethylnaphthoquinone derivatives, neofusnaphthoquinone A (**133**), 6-(1-methoxylethy1)-2,7-dimethoxyjuglone (**134**), and (3*R*,4*R*)-3-methoxylbotryosphaerone D (**135**) (Fig. 10) (Cui et al. 2018). These metabolites were evaluated for their indoleamine 2,3-dioxygenase (IDO) inhibitory activity. All isolates displayed promising effects against IDO. In particular, compound **134** revealed superior cytotoxicity with an IC_{50} value of 0.11 μM.

A new anthraquinone (**136**, Fig. 10), isolated and identified from the cultures of *Colletotrichum* sp. JS-0367, an endophytic fungus isolated from the leaves of the mulberry tree *Morus alba* L. (Song et al. 2018a), and an analogue of this metabolite, evariquinone (Song et al. 2018a), which was also derived from *Colletotrichum* sp., demonstrated potent neuroprotection against excessive glutamate-induced apoptosis in the immortalized murine HT22 hippocampal neuronal cell line. With regards to the difference between metabolite **136** and evariquinone, compound **136** contains a methoxy substituent at position C-2, while evariquinone has a hydroxyl group at the same position.

Two new cryptic 3,4-dihydronaphthalen-(2*H*)-1-one (1-tetralone) derivatives, aspvanicin A (**137**) and its epimer aspvanicin B (**138**) (Fig. 10) were obtained from the ethyl acetate extract of a co-culture of the

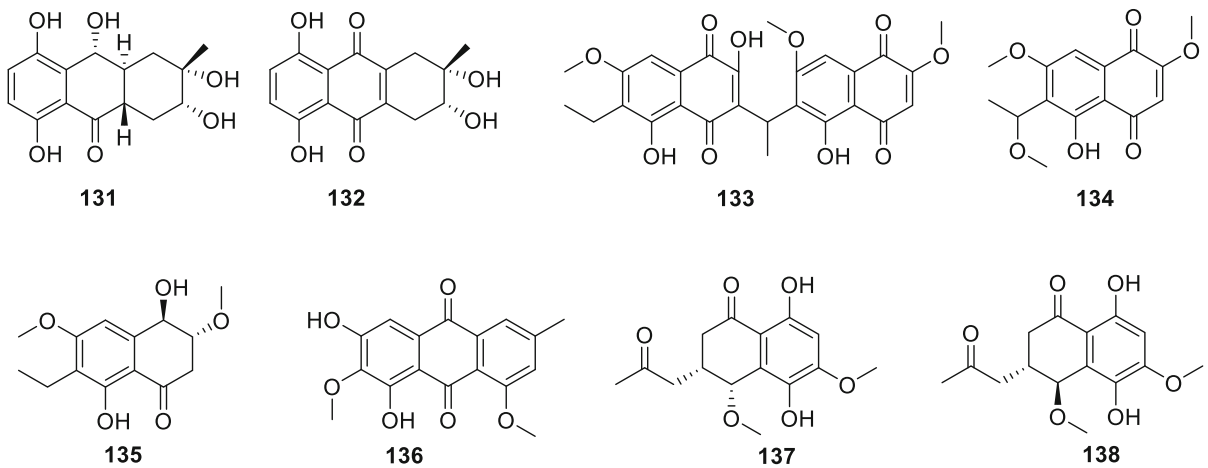


Fig. 10 The structures of novel quinones (**131–135**, **136–138**) isolated from endophytic fungi

endophytic fungus *Aspergillus versicolor* KU258497 (an endophyte isolated from fresh, healthy leaves of *Eichhornia crassipes*, family Pontederiaceae, from the shores of the River Nile in Mansoura, Egypt) and the bacterium *B. subtilis* 168 trpC2 on a solid rice medium (Abdelwahab et al. 2018). The isolates were assessed for their antiproliferative activity in the mouse lymphoma cell line L5178Y. Aspvanicin B (**138**) demonstrated cytotoxic potential with an IC_{50} value of 22.8 μM when compared to kahalalide F as a standard antiproliferative agent (IC_{50} = 4.3 μM).

Other polyketides

A new xanthoquinodin B9 (**139**, Fig. 11) was isolated from the endophytic fungus *Chaetomium globosum* 7s-1, obtained from the leaves of *Rhapis cochinchinensis* (Tantapakul et al. 2018). The antibacterial (against Gram-positive bacteria *B. cereus*, *S. aureus,* and MRSA, as well as Gram-negative bacteria *E. coli*, *P. aeruginosa,* and *Salmonella typhimurium*), antimalarial (against *Plasmodium falciparum*), anti-mycobacterial (against *Mycobacterium tuberculosis* H37Ra) and antitumor (in KB, MCF7, and NCI-H187) activities of this novel xanthoquinodin were evaluated. Compound **139** showed significant activity against *B. cereus* with an MIC value of 0.87 μM, as well as against *S. aureus* and *MRSA* with MIC values ranging from 0.87 to 1.75 μM. Moreover, the antimalarial activity against *Plasmodium falciparum* (IC_{50} = 2.57 μM) demonstrated satisfactory inhibition, with only weakly activity in the anti-TB assay. Isolate **139** showed promising cytotoxicity in the selected cancer cell lines (KB, MCF-7, and NCI-H187) with IC_{50} values of 7.04, 18.40, and 0.98, respectively.

Aspergillus sp. TJ23, isolated from fresh leaves of *Hypericum perforatum* L., yielded a new polyketide, asperetide (**140**), and a new prenylxanthone derivative, asperanthone (**141**) (Fig. 11) (Qiao et al. 2018). These two novel metabolites have been evaluated for their anticancer activities in B16, MDA-MB-231, 4T1, HepG2, and LLC cells. Compound **141** displayed a weak inhibitory activity in HepG2 cells with an IC_{50} value 35.5 μM.

Four novel polyketide heterodimers, cytorhizins A–D (**142–145**) (Fig. 11), were obtained from the endophytic fungus *Cytospora rhizophorae* A761, isolated from the plant *Morinda oficinalis* (Liu et al. 2019b). These polyketides were evaluated for cytotoxicity in human cancer cell lines (HepG-2, MCF-7, SF-268, and NCIH460). Cytorhizin A and cytorhizin D displayed weak cytotoxic activity with IC_{50} values ranging from 29.4 to 68.6 μM. In the *E. coli* and *S. aureus* antibacterial screening, these isolates failed to demonstrate any significant antimicrobial activity at a concentration of 100 μM.

The fungal isolate *Emericella* sp. XL029 was obtained from the leaves of *Panax otoginseng* and yielded four novel polyketides, emericelactones A–D (**146–149**) (Fig. 11) (Pang et al. 2018). The one strain-many compounds (OSMAC) approach was applied to *Emericella* sp. XL029, indicating that more diverse secondary metabolites were produced, including compounds **146–149**, when cultivated in the solid medium of rice plus malt extract broth. All isolated secondary metabolites demonstrated moderate antimicrobial activities against three agricultural pathogenic fungi (*Verticillium dahliae Kleb*, *R. solani, and Gibberella*

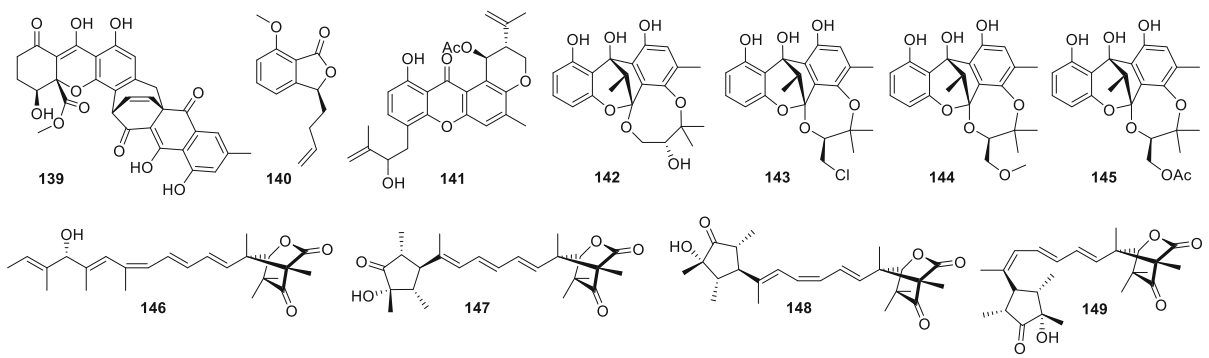


Fig. 11 The structures of novel polyketides (**139–149**) isolated from endophytic fungi

saubinetii) and two human pathogenic bacteria (*M. lysodeikticus* and *S. typhi*) with MIC values ranging between 25 and 50 μg/mL.

Four new polyketides, namely bellidisins A–D (**150–153**, Fig. 12), were isolated from the rice fermentation extract of the fungus *Phoma bellidis*, an endophyte isolated from the healthy leaf tissue of *Tricyrtis maculate* (Wang et al. 2019b). All novel secondary metabolites evaluated in human cancer cell lines (HL-60, A549, SMMC-7721, MCF-7, and SW480). Derivative **153** demonstrated considerable cytotoxicity with IC_{50} values ranging from 3.40 to 15.25 μM, stronger than that of cisplatin (4.86–27.70 μM).

Paraconiothyrium sp. SW-B-1, an endophytic fungus isolated from the seaweed *Chondrus ocellatus* Holmes, produced five new polyketides, designated as paralactonic acids A–E (**154–158**) (Fig. 12) (Suzuki et al. 2019). All metabolites were evaluated for potential antimicrobial activity against Gram-positive and Gram-negative bacteria, yeast, and other fungal strains by the agar diffusion assay. Only paralactonic acid E (**158**) showed moderate antibacterial activity against *S. aureus* NBRC 13276 (24 mm) at a concentration of 100 μg/disk (MIC value: 3.2 μg/mL). In addition, all isolates were tested for their inhibitory effect against Ca^{2+} signal transduction using the hypersensitive drug screening procedure based on the YNS17 [*Saccharomyces cerevisiae* (*zds1*Δ *erg3*Δ *pdr1*Δ *pdr3*Δ)] strain. Notably, only derivative **158** exhibited a dose-dependent growth-restoring activity around the inhibition zone in the mutant yeast strain YNS17.

Two new secondary metabolites, the polyketide paecilin D (**159**) and the maleic anhydride cordyanhydride A methyl ester (**160**), were obtained from fungal strains *Talaromyces stipitatus* DgCr2 2.1b and *Talaromyces* sp. VrTrb2 1.1, respectively (Fig. 12) (Silva et al. 2018). The endophyte of *Talaromyces stipitatus* DgCr2 2.1b was isolated from the medicinal plant roots of *Duguetia stelechantha*, while the endophyte of *Talaromyces* sp. VrTrb2 1.1 strain was isolated from *Victoria amazonica*, collected in the Amazonian rainforest. Novel metabolites have been isolated from the antimicrobial extracts of the examined strains. Paecilin D (**159**) was reportedly active against *C. albicans* and *Candida tropicalis* (MIC: 15.6 and 31.3 μg/mL).

The endophytic fungus *Byssochlamys spectabilis*, isolated from leaf tissue of the traditional Chinese medicinal plant *Edgeworthia chrysantha*, yielded a polyketide-derived octaketide dimer with a novel carbon skeleton, designated bysspectin A (**161**), and two new precursor derivatives, bysspectins B and C (**162** and **163**) (Fig. 12) (Wu et al. 2018). Only derivative **163** displayed weak inhibition on strains including *E. coli* and *S. aureus* with MIC values of 32 and 64 μg/mL, respectively. The novel octaketide dimer (**161**) possessed highly hydrophobic properties in terms of its two long and bulky aliphatic ketone carbon chains coupled with a 2-phenylbenzo[*b*]furan core. Therefore, compound **161** was assayed for its inhibitory effects towards human carboxylesterases

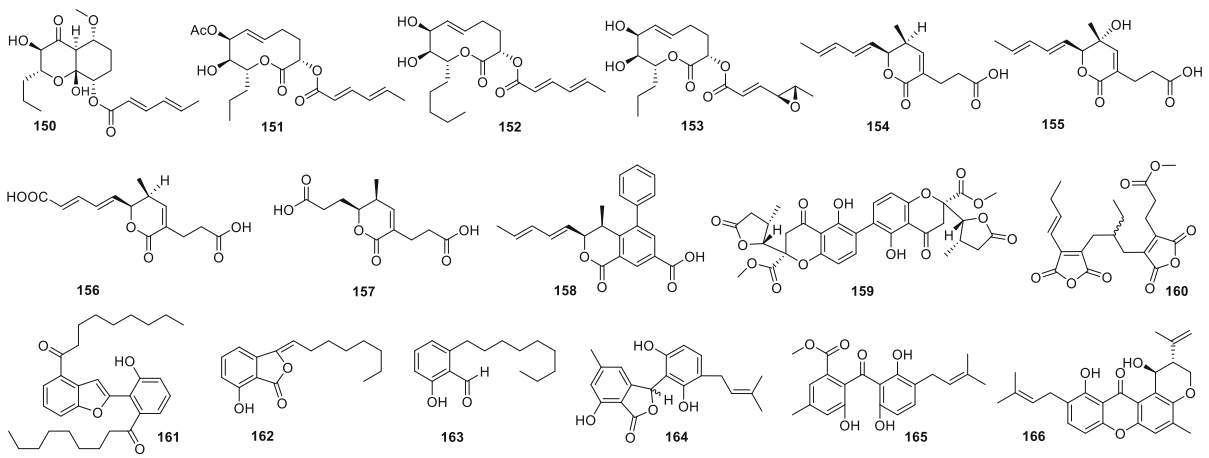


Fig. 12 The structures of novel polyketides (**150–166**) isolated from endophytic fungi

hCE1 and hCE2. Notably, bysspectin A (**161**) was a novel and highly selective inhibitor against hCE2 with an IC_{50} value of 2.01 μM.

Two new prenylated polyketides, ascomfurans C (**164**) and ascomarugosin A (**165**), were isolated from the endophytic fungus *Ascomycota* sp., obtained from the mangrove plant *Kanelia candel* (Fig. 12) (Liu et al. 2018a). Ascomarugosin A exhibited weak anti-inflammatory activity with an IC_{50} value of 72.3 μM. Isoshamixanthone (**166**, Fig. 12), a new stereoisomeric pyrano xanthone was produced from the endophytic fungal strain *Aspergillus* sp. ASCLA obtained from leaf tissues of the medicinal plant *Callistemon subulatus* (Kamel et al. 2019). This metabolite demonstrated moderate to high activities (11–16 mm) against microbial strains including *S. aureus*, *P. aeruginosa*, *C. albicans*, *S. cerevisiae*, *B. cereus,* and *B. subtilis* ATCC 6633. However, in the antitumor screening, compound **166** displayed no cytotoxic effects in KB-3-1 and its multidrug resistant subclone, KB-V1.

Eleven new polyketones named diaporthsins A–K (**167–177**) (Fig. 13) were obtained from the fermentation of *Diaporthe* sp. JC-J7, isolated from the stems of *Dendrobium nobile* (Hu et al. 2018). Amongst new isolated metabolites, compounds **167–169**, **171**, **174** and **176** were evaluated for their antihyperlipidemic activities. Diaporthsin E (**171**) exhibited lipid lowering effects on triglycerides in steatotic L-02 cells, with an inhibition ratio of 26% at a concentration of 5 μg/mL Lovastatin (31.80%) used as positive control drug. All other screened isolates displayed inhibition ratios of < 10%. In addition, most of the new polyketones were esterified products of diaporthsin B (**168**), which occurs in fungal biotransformation.

The chemical investigation on the medicinal mangrove derived endophytic fungus *Dothiorella* sp., isolated from the stem of the mangrove *Xylocarpus granatum* Koenig, resulted in three new cytosporone derivatives, dothiorelones K–M (**178–180**) (Fig. 13) (Zheng et al. 2019). Their inhibitory activities against α-glucosidase, antibacterial activity and cytotoxic activity have been evaluated. In an α-glucosidase inhibitory assay, the new metabolites **178** and **180** exhibited inhibitory activities with IC_{50} values of 22.0 and 77.9 μg/mL, respectively. Moreover, these two compounds demonstrated moderate antibacterial activities against *S. aureus* (MIC = 50 μg/mL). However, none of the new dothiorelones compounds demonstrated cytotoxic activity in the three human cell lines (A549, HeLa, and HepG2) at a concentration of 10 μg/mL.

The symbiotic strain *Fusarium oxysporum* ZZP-R1 is an endophytic fungus derived from the coastal plant *Rumex madaio* Makino, one of the traditional Chinese

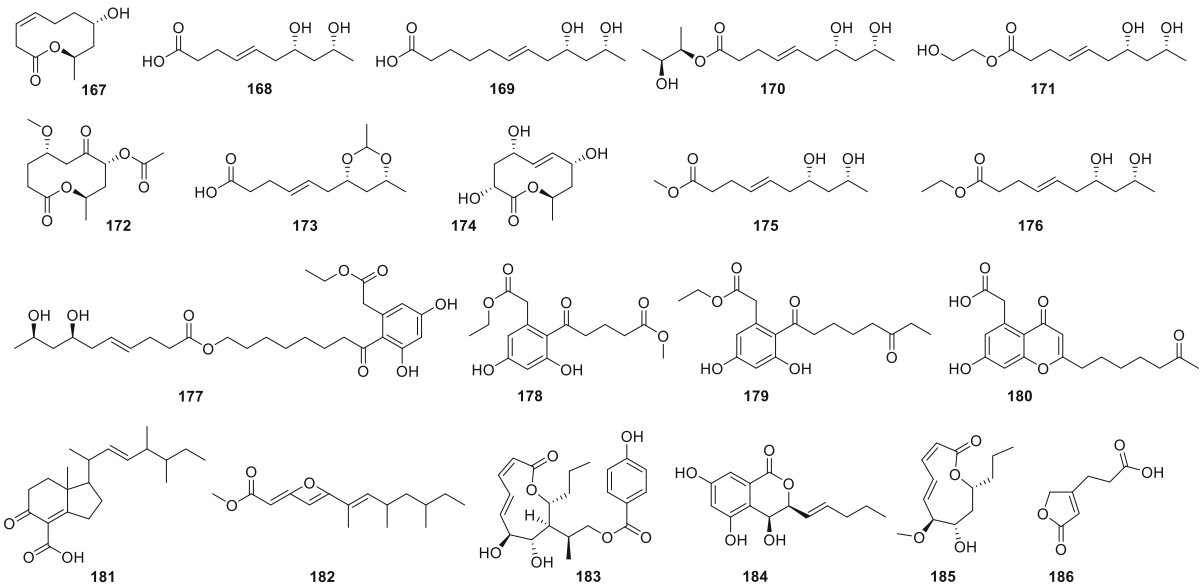


Fig. 13 The structures of new polyketides (**167–186**) produced by endophytic fungi

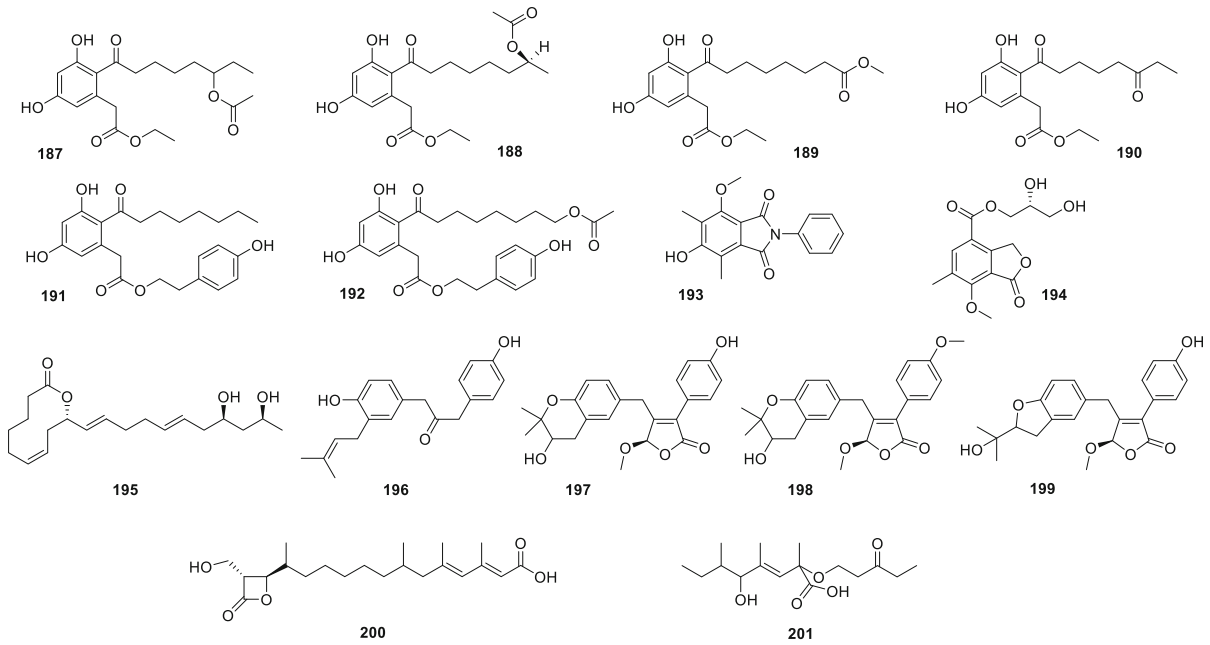


Fig. 14 The structures of new polyketides (**187–201**) produced by endophytic fungi

medicinal herbs used to treat inflammation and intoxication. This fungus produced two novel secondary metabolites, fusariumins C (**181**) and D (**182**) (Fig. 13) (Chen et al. 2019a). Compound **182** displayed a moderate inhibitory effect against *S. aureus* with an MIC value of 25.0 µM, while metabolite **181** showed potent activity against *S. aureus* with an MIC value of 6.25 µM.

Three novel compounds, identified as xylarolide A (**183**), diportharine A (**184**), and xylarolide B (**185**) (Fig. 13), were isolated from the endophytic fungus *Diaporthe* sp., which was obtained from *Datura inoxia* (Sharma et al. 2018). All the derived novel secondary metabolites were screened for their antioxidant, antibacterial and cytotoxicity activities. Xylarolide A (**183**) showed significant growth inhibition in MIA-PaCa-2 and PC-3 cells with IC_{50} values of 20 and 14 µM, respectively. In addition, metabolite **183** displayed significant DPPH scavenging activity (EC_{50}: 10.3 µM) using ascorbic acid as the positive control drug. However, these metabolites failed to demonstrate antibacterial activity against *S. aureus*, *P. aeruginosa,* and *E. coli* at a concentration of 62.5 µM. A new furan derivative named 3-(5-oxo-2,5-dihydrofuran-3-yl)propanoic acid (**186**) (Fig. 13) was isolated from the endophytic *Aspergillus tubingensis* of *Decaisnea insignis* (Griff.) Hook.f. & Thomson (Yang et al. 2018b). This metabolite exhibited potent antifungal activity against *F. graminearum* (MIC = 16 µg/mL) and moderate antibacterial activity against *Streptococcus lactis* (MIC = 32 µg/mL).

Nine new natural compounds, dothiorelones (**187–192**), 5-hydroxy-7-methoxy-4,6-dimethyl-2-phenylisoindoline-1,3-dione (**193**), (13*R*)-diaporphthalide A (**194**) and (9*S*, 17*R*, 19*S*, 6*Z*, 10*E*, 14*E*)-diaporlactone A (**195**) (Fig. 14), were isolated from *Diaporthe pseudomangiferaea*, an endophytic fungus obtained from the leaves of the toxic Chinese plant *Tylophora ouata* (Liu et al. 2018b). All the secondary metabolites were investigated for anti-fibrosis, cytotoxic, antidiabetic, anti-oxidative, antibacterial, and anti-inflammatory activities. Only two metabolites, acetoxydothiorelone B (**187**) and dothiorelone L (**190**), inhibited the transforming growth factor beta (TFG-β) induced activation of the human lung MRC-5 fibroblasts by 17.4% and 59.2% at 10 µM, respectively. The isolates showed moderate to weak activities in other performed assays.

The strain, *Aspergillus* sp. which was isolated from the root of *Tripterygium wilfordii* produced four novel butenolides, terrusnolides A–D (**196–199**) (Fig. 14) (Qi et al. 2018). The in vitro anti-inflammatory effects of these isolates were evaluated using LPS-stimulated RAW264.7 macrophages. The butenolides exhibited

promising inhibitory effects on the production of IL-1β (16.21–35.23 μM), TNF-α (19.83–42.57 μM), and NO (16.78–38.15 μM) in LPS-induced RAW264.7 cells, comparable with the positive control indomethacin. In addition, compounds **198** and **199** showed a weak inhibition against the BACE1 and AChE inhibitory activity.

Two new secondary metabolites, β-lactone polonicin A (**200**) and enoic acid polonicin B (**201**) (Fig. 14), were isolated from *Penicillum polonicum* obtained from the fruits of *Camptotheca acuminate* Decne (Wen et al. 2019). The antidiabetic properties of the isolated novel compounds were examined in L6 cells at a concentration of 30 μg/mL. Both isolates increased the rate of glucose uptake by 1.8 and 1.5 times, respectively. In addition, a L6 cell line stably expressing IRAP-mOrange was used to evaluate the effects of polonicin A on the glucose transporter type 4 (GLUT4) translocation. Incubation with derivative **200** increased the fluorescence intensity in the L6 cell membranes by 2.1-fold.

The fungus *Exserohilum rostratum* LPY-001 has been isolated from leaf tissue of *Gymnadenia conopsea*, a Tibetan medicinal plant known as *wangle* (Chinese), which has been traditionally used for the treatment of cough, asthma, and other syndromes. This fungus produced a new oxacyclododecindione-type macrolactone designated (13*R*,14*S*,15*R*)-13-hydroxy-14- deoxyoxacyclododecindione (**202**, Fig. 15) (Lin et al. 2018). Cytotoxicity assays for compound **202** were performed in the HCT-8, A2780, BGC-823, Bel-7402, and A549 cell lines. This secondary metabolite displayed weak selective cytotoxicity in A549 lung cancer cells with an IC_{50} value of 9.2 μM.

Curtachalasins A (**203**) and B (**204**) (Fig. 15) are a new family of cytochalasans with a 5/6/6/6-fused tetracyclic skeleton, obtained from the endophytic fungus *Xylaria curta* E10, isolated from the healthy stem tissues of potato (*Solanum tuberosum*) (Wang et al. 2018b). These new secondary metabolites were screened against four bacterial strains (*E. coli*, *S. aureus*, *Salmonella enterica*, and *P. aeruginosa*), as well as against four fungal species (*C. albicans*, *Epidermophyton floccosum*, *Trichophyton rubrum*, and *Microsporum gypseum*). Both compounds displayed weak antifungal activity (70.3% and 68.4% inhibitory percentage, respectively) against *M. gypseum* at a concentration of 200 μM. Furthermore, three novel secondary metabolites, curtachalasins C–E (**205**–**207**) (Fig. 15) were also identified from the endophytic fungus *Xylaria* cf. *curta,* derived from the healthy stem tissues of potato (*Solanum tuberosum*) (Wang et al. 2019a). Among these curtachalasins, curtachalasin C and curtachalasin E were screened for their antifungal activities against *C. albicans* with the drug resistant genes Cdr1, Cdr2 and Mdr1; however, in this case the MIC_{50} value of fluconazole was higher than 500 μg/mL. Derivative **205** demonstrated dose-dependent resistant reversal activity when combined with 10 μg/mL fluconazole. The inhibitory ratio against this strain was close to 50%, which was a significant improvement compared to fluconazole

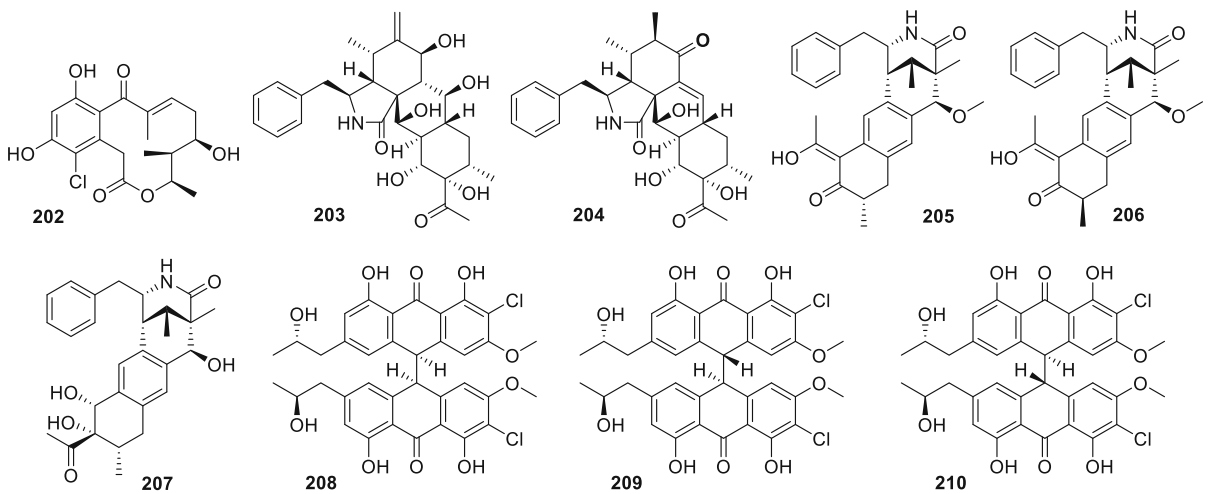


Fig. 15 The structures of novel polyketides (**202**–**210**) produced by endophytic fungi

alone. Regarding the other screened new isolates, curtachalasin E showed no or weak resistance reversal activity at a concentration of 128 μg/mL.

New chlorinated bianthrones, allianthrone A (**208**) and its two diastereomers (allianthrones B (**209**) and C (**210**) (Fig. 15), were isolated from the co-cultures of two different developmental stages of a marine alga-derived *Aspergillus alliaceus* (teleomorph: *Petromyces alliaceus*) strain (Mandelare et al. 2018). Metabolite **208** showed weak cytotoxic activity in HCT-116 colon cancer and SK-Mel-5 melanoma cell lines with IC_{50} values of 9.0 and 11.0 μM, respectively.

Alkaloids and other nitrogen related compounds

Fungal endophytes are capable of forming biologically active secondary metabolites including alkaloids, various amides and other nitrogen containing compounds. In this section we describe alkaloids and their biological properties from fungal genera such as *Fusarium*, *Penicillium*, *Aspergillus*, and *Mucor*.

The endophytic fungus *Fusarium chlamydosporum*, isolated from the root of *Suaeda glauca*, yielded one new indole alkaloid **211** (Fig. 16) (Wang et al. 2018d). Compound **211** showed significant phytotoxic activity against the radicle growth of *Echinochloa crusgalli* with an inhibition rate above 80%, even at a concentration of 1.25 μg/mL, which was superior to the positive control 2,4-dichlorophenoxyacetic acid. Another endophytic fungus, has been identified as a *Mucor* sp., was obtained from the medicinal plant *Centaurea stoebe*. It produced a new indole compound, terezine E (**212**, Fig. 16) (Abdou et al. 2018). The antiproliferative and cytotoxic activities of the isolate **212** were tested in HUVEC, K-562, and HeLa cancer cell lines. In both assays, terezine E exhibited significant antiproliferative activity with GI_{50} values of 28.02 and 27.31 μM against HUVEC and K-562, respectively. Furthermore, this indole derivative revealed a CC_{50} value of 60.43 μM in the HeLa cancer cells. Compound **212** demonstrated only modest antifungal properties against *A. terreus* strain with an MIC value of 39.7 μg/mL.

Four new aromatic butenolides, asperimides A–D (**213**–**216**, Fig. 16), were derived from solid cultures of the tropical endophytic fungus *Aspergillus terreus*, isolated from fresh, healthy leaves of *Suriana maritima* L. (Liao et al. 2018). Metabolites **215** and **216** inhibited NO production with IC_{50} values of 0.78 and 1.26 μM, respectively, in LPS-stimulated RAW264.7 cells. Another endophytic strain, *Penicillium janthinellum*, isolated from *Panax notoginseng*, produced three new secondary metabolites, including rotational isomers brasiliamide *J*-a (**217**), brasiliamide *J*-b (**218**), and peniciolidone (**219**) (Fig. 16) (Xie et al. 2018a). A total of 180 fungal isolates, belonging to 20 genera and 47 species, were obtained from the roots, stems, and leaves of *Panax notoginseng*. Among the endophytic fungus, *Penicillium janthinellum* SYPF 7899 displayed the strongest antibacterial activity and has been studied for its production of secondary metabolites. Isolates **217**–**219** were screened for antimicrobial effects against several pathogenic bacteria including *S. aureus*, *B. subtilis*, *P. aeruginosa*, *Klebsiella pneumonia,* and *E. coli.* Brasiliamide *J*-a and *J*-b exhibited significant inhibitory activities against *B. subtilis* and

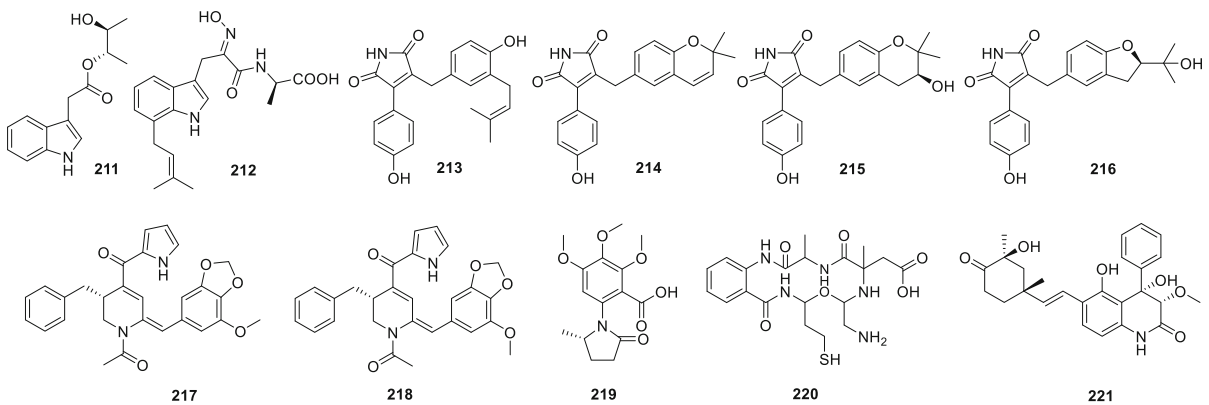


Fig. 16 The structures of the alkaloids and other nitrogen related secondary metabolites (**211**–**221**) isolated from endophytic fungi

S. aureus with MIC values of 15 and 18 μg/mL, respectively. Moderate inhibition against *B. subtilis* (MIC = 35 μg/mL) and *S. aureus* (MIC = 39 μg/mL) was observed with derivative **219**.

Fusarithioamide B (**220**) (Fig. 16), a new aminobenzamide derivative with an unprecedented carbon skeleton, was isolated from the strain *Fusarium chlamydosporium*, an endophytic fungus obtained from *Anvillea garcinii* (Burm.f.) DC. leaves (Asteraceae) (Ibrahim et al. 2018). Compound **220** demonstrated selective antifungal activity against *C. albicans* (MIC = 1.9 μg/mL; inhibition zone diameter = 14.5 mm) when compared to clotrimazole (MIC = 2.8 μg/mL; inhibition zone diameter = 17.9 mm), as well as high antibacterial potential against strains such as *S. aureus* (MIC = 3.1 μg/mL; inhibition zone diameter = 17.4 mm), *B. cereus* (MIC = 2.5 μg/mL; inhibition zone diameter = 23.0 mm), and *E. coli* (MIC = 3.7 μg/mL; inhibition zone diameter = 25.1 mm) compared to ciprofloxacin (MIC = 3.4, 2.9 and 3.9 μg/mL; inhibition zone diameter = 15.3, 21.2 and 25.6 mm). In addition, the strong cytotoxic effects of **220** in KB, HCT-116, BT-549, MCF-7, SKOV-3, and SK-MEL cell lines indicated that the new metabolite displayed selectivity and potential efficacy with IC_{50} values of 0.09, 0.21, 1.23, and 0.59 μM, respectively, compared to doxorubicin (IC_{50} values: 0.046, 0.05, 0.321, and 0.24 μM, respectively).

A new dihydroquinolone derivative, aflaquinolone H (**221**, Fig. 16) was isolated from the endophytic *Aspergillus versicolor*, isolated from the leaves of the Egyptian water hyacinth *Eichhornia crassipes* (Ebada et al. 2018). This secondary metabolite exhibited moderate antiproliferative activity (IC_{50} = 10.3 μM), reporting no potential antimicrobial activity.

Conclusions

In summary, we have outlined a total of 221 novel natural products synthesized by 67 species of endophytic fungi, which belong to three phyla, 31 genera and were collected from 10 countries or sources, along with their various biological properties. Among these 67 strains, five endophyte genera, including *Aspergillus*, *Fusarium*, *Penicillium*, *Xylaria* and *Talaromyces*, were most frequently studied in the year 2018 than any other isolated strains. These endophytic crude extracts (in polar solvents, normally ethyl acetate (EtOAc) extracts) were yielded after appropriate fermentation and exhibited various bioactivities. Most individually purified novel natural products demonstrated promising cytotoxic, antimicrobial, or anti-inflammatory activities. Although some isolated new compounds displayed weak activity, their unique structures could lay interesting ground for further investigations. Thus, these microbial secondary metabolites are valuable as they enrich chemical diversity of bioactive molecules and may support the drug-development process in the pharmaceutical industry. However, plant endophytes remain poorly understood with regard to their pharmaceutical properties, especially those related to their use as potentially novel drug-candidates. Because this potential has been appreciated only recently in the field of medicinal chemistry, phytochemical aspects of these metabolites are still the most thoroughly characterized. New approaches for endophytically synthesized natural compounds include studying their biosynthetic pathways and biotransformation reactions to improve product yields, relationships between host plants and endophytic fungi producing the bioactive compounds, as well as the target evaluation of new secondary metabolites from a medicinal chemistry point of view. In addition, the plethora of novel compounds produced by endophytic fungi will open new avenues to investigate their medicinal utility. We believe that this is a fertile ground for research, which will continue to grow in the coming years.

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References

Abdelwahab MF, Kurtán T, Mándi A et al (2018) Induced secondary metabolites from the endophytic fungus Aspergillus versicolor through bacterial co-culture and OSMAC approaches. Tetrahedron Lett 59:2647–2652

Abdou R, Shabana S, Rateb ME (2018) Terezine E, bioactive prenylated tryptophan analogue from an endophyte of *Centaurea stoebe*. Nat Prod Res. https://doi.org/10.1080/14786419.2018.1489393

Andrés MF, Diaz CE, Giménez C et al (2017) Endophytic fungi as novel sources of biopesticides: the Macaronesian Laurel forest, a case study. Phytochem Rev 16:1009–1022

Cai R, Wu Y, Chen S et al (2018) Peniisocoumarins A–J: isocoumarins from *Penicillium commune* QQF-3, an endophytic fungus of the mangrove plant *Kandelia candel*. J Nat Prod 81:1376–1383

Carroll AR, Copp BR, Davis RA et al (2019) Marine natural products. Nat Prod Rep 36:122–173

Chen S, Ding M, Liu W et al (2018) Anti-inflammatory meroterpenoids from the mangrove endophytic fungus *Talaromyces amestolkiae* YX1. Phytochemistry 146:8–15

Chen J, Bai X, Hua Y et al (2019a) Fusariumins C and D, two novel antimicrobial agents from *Fusarium oxysporum* ZZP-R1 symbiotic on *Rumex madaio* Makino. Fitoterapia 134:1–4

Chen S, Li H, Chen Y et al (2019b) Three new diterpenes and two new sesquiterpenoids from the endophytic fungus *Trichoderma koningiopsis* A729. Bioorg Chem 86:368–374

Cui H, Zhang H, Liu Y et al (2018) Ethylnaphthoquinone derivatives as inhibitors of indoleamine-2, 3-dioxygenase from the mangrove endophytic fungus Neofusicoccum austral SYSU-SKS024. Fitoterapia 125:281–285

Deng Q, Li G, Sun M et al (2018) A new antimicrobial sesquiterpene isolated from endophytic fungus *Cytospora* sp. from the Chinese mangrove plant *Ceriops tagal*. Nat Prod Res. https://doi.org/10.1080/14786419.2018.1512993

Ebada SS, El-Neketi M, Ebrahim W et al (2018) Cytotoxic secondary metabolites from the endophytic fungus *Aspergillus versicolor* KU258497. Phytochem Lett 24:88–93

El-Neketi M, Ebrahim W, Lin W et al (2013) Alkaloids and polyketides from *Penicillium citrinum*, an endophyte isolated from the moroccan plant *Ceratonia siliqua*. J Nat Prod 76:1099–1104

Guo Z-Y, Lu L-W, Bao S-S et al (2018) Xylariaopyrones A–D, four new antimicrobial α-pyrone derivatives from endophytic fungus *Xylariales* sp. Phytochem Lett 28:98–103

Guo D-L, Qiu L, Feng D et al (2019) Three new α-pyrone derivatives induced by chemical epigenetic manipulation of *Penicillium herquei*, an endophytic fungus isolated from *Cordyceps sinensis*. Nat Prod Res. https://doi.org/10.1080/14786419.2018.1544974

He J, Li Z-H, Ai H-L et al (2018) Anti-bacterial chromones from cultures of the endophytic fungus *Bipolaris eleusines*. Nat Prod Res. https://doi.org/10.1080/14786419.2018.1486313

He J, Yang M-S, Wang W-X et al (2019) Anti-phytopathogenic sesquiterpenoid-xanthone adducts from potato endophytic fungus *Bipolaris eleusines*. RSC Adv 9:128–131

Hou X-M, Wang C-Y, Gerwick WH et al (2019) Marine natural products as potential anti-tubercular agents. Eur J Med Chem 165:273–292

Hu M, Yang X-Q, Wan C-P et al (2018) Potential antihyperlipidemic polyketones from endophytic *Diaporthe* sp. JC-J7 in *Dendrobium nobile*. RSC Adv 8:41810–41817

Ibrahim SRM, Mohamed GA, Al Haidari RA et al (2018) Fusarithioamide B, a new benzamide derivative from the endophytic fungus *Fusarium chlamydosporium* with potent cytotoxic and antimicrobial activities. Bioorg Med Chem 26:786–790

Kamel RA, Abdel-Razek AS, Hamed A et al (2019) Isoshamixanthone: a new pyrano xanthone from endophytic *Aspergillus* sp. ASCLA and absolute configuration of epiisoshamixanthone. Nat Prod Res. https://doi.org/10.1080/14786419.2018.1548458

Khayat MT, Ibrahim SRM, Mohamed GA et al (2019) Anti-inflammatory metabolites from endophytic fungus *Fusarium* sp. Phytochem Lett 29:104–109

Ko Ko TW, Stephenson SL, Bahkali AH et al (2011) From morphology to molecular biology: can we use sequence data to identify fungal endophytes? Fungal Divers 50:113

Kornsakulkarn J, Choowong W, Rachtawee P et al (2018) Bioactive hydroanthraquinones from endophytic fungus *Nigrospora* sp. BCC 47789. Phytochem Lett 24:46–50

Li S, Chen J-F, Qin L-L et al (2018a) Two new sesquiterpenes produced by the endophytic fungus *Aspergillus fumigatus* from *Ligusticum wallichii*. J Asian Nat Prod Res. https://doi.org/10.1080/10286020.2018.1540606

Li X-H, Han X-H, Qin L-L et al (2018b) Isochromanes from *Aspergillus fumigatus*, an endophytic fungus from *Cordyceps sinensis*. Nat Prod Res. https://doi.org/10.1080/14786419.2018.1478824

Li Z-H, Ai H-L, Yang M-S et al (2018c) Bioactive sativene sesquiterpenoids from cultures of the endophytic fungus *Bipolaris eleusines*. Phytochem Lett 27:87–89

Li Q, Chen C, Cheng L et al (2019) Emeridones A–F, a series of 3,5-demethylorsellinic acid-based meroterpenoids with rearranged skeletons from an endophytic fungus *Emericella* sp. TJ29. J Org Chem 84:1534–1541

Liang H-Q, Zhang D-W, Guo S-X et al (2018a) Two new tetracyclic triterpenoids from the endophytic fungus *Hypoxylon* sp. 6269. J Asian Nat Prod Res 20:951–956. https://doi.org/10.1080/10286020.2018.1485662

Liang Y, Xu W, Liu C et al (2018b) Eremophilane sesquiterpenes from the endophytic fungus *Xylaria* sp. GDG-102. Nat Prod Res. https://doi.org/10.1080/14786419.2018.1472597

Liao G, Wu P, Xue J et al (2018) Asperimides A–D, anti-inflammatory aromatic butenolides from a tropical endophytic fungus *Aspergillus terreus*. Fitoterapia 131:50–54

Lin P-C, Wu Y-Z, Bao T-W et al (2018) A new cytotoxic 12-membered macrolactone from the endophytic fungus *Exserohilum rostratum* LPC-001. J Asian Nat Prod Res 20:1093–1100

Liu Z, Qiu P, Li J et al (2018a) Anti-inflammatory polyketides from the mangrove-derived fungus *Ascomycota* sp. SK2YWS-L. Tetrahedron 74:746–751

Liu Z, Zhao J, Liang X et al (2018b) Dothiorelone derivatives from an endophyte *Diaporthe pseudomangiferaea* inhibit the activation of human lung fibroblasts MRC-5 cells. Fitoterapia 127:7–14

Liu H-X, Tan H-B, Chen Y-C et al (2019a) Cytotoxic triquinane-type sesquiterpenoids from the endophytic fungus *Cerrena* sp A593. Nat Prod Res. https://doi.org/10.1080/14786419.2018.1539977

Liu H, Tan H, Chen Y et al (2019b) Cytorhizins A–D, four highly structure-combined benzophenones from the endophytic fungus *Cytospora rhizophorae*. Org Lett 21:1063–1067

Liu S-S, Jiang J-X, Huang R et al (2019c) A new antiviral 14-nordrimane sesquiterpenoid from an endophytic fungus *Phoma* sp. Phytochem Lett 29:75–78

Liu X-Y, Wang X-L, Shen T et al (2019d) Two new triterpenoids from the fungus *Diplodia cupressi*. Nat Prod Res. https://doi.org/10.1080/14786419.2019.1578762

Ludwig-Müller J (2015) Plants and endophytes: equal partners in secondary metabolite production? Biotechnol Lett 37:1325–1334

Ludwig-Müller J (2019) Interplay between endophyte and host plant in the synthesis and modification of metabolites. In: Schouten A (ed) Endophyte biotechnology: potential for agriculture and pharmacology, vol 8. CABI, Wallingford, p 180

Mandelare PE, Adpressa DA, Kaweesa EN et al (2018) Coculture of two developmental stages of a marine-derived *Aspergillus alliaceus* results in the production of the cytotoxic bianthrone allianthrone A. J Nat Prod 81:1014–1022

Martelli G, Giacomini D (2018) Antibacterial and antioxidant activities for natural and synthetic dual-active compounds. Eur J Med Chem 158:91–105

Martinez-Klimova E, Rodríguez-Peña K, Sánchez S (2017) Endophytes as sources of antibiotics. Biochem Pharmacol 134:1–17

Neilson EH, Goodger JQD, Woodrow IE et al (2013) Plant chemical defense: at what cost? Trends Plant Sci 18:250–258

Nisa H, Kamili AN, Nawchoo IA et al (2015) Fungal endophytes as prolific source of phytochemicals and other bioactive natural products: a review. Microb Pathog 82:50–59

Obermeier M-M, Christina A (2019) Prospects for biotechnological exploitation of endophytes using functional metagenomics. In: Schouten A (ed) Endophyte biotechnology: potential for agriculture and pharmacology, vol 8. CABI, Wallingford, p 164

Panaccione DG, Beaulieu WT, Cook D (2014) Bioactive alkaloids in vertically transmitted fungal endophytes. Funct Ecol 28:299–314

Pang X-J, Zhang S-B, Chen H-L et al (2018) Emericelactones A–D: Four novel polyketides produced by *Emericella* sp. XL 029, a fungus associated the leaves of *Panax notoginseng*. Tetrahedron Lett 59:4566–4570

Parvez S, Malik KA, Ah Kang S et al (2006) Probiotics and their fermented food products are beneficial for health. J Appl Microbiol 100:1171–1185

Qi C, Gao W, Wang J et al (2018) Terrusnolides A–D, new butenolides with anti-inflammatory activities from an endophytic *Aspergillus* from *Tripterygium wilfordii*. Fitoterapia 130:134–139

Qiao Y, Tu K, Feng W et al (2018) Polyketide and prenylxanthone derivatives from the endophytic fungus *Aspergillus* sp. TJ23. Chem Biodivers 15:e1800395

Qin D, Shen W, Wang J et al (2019) Enhanced production of unusual triterpenoids from *Kadsura angustifolia* fermented by a symbiont endophytic fungus, *Penicillium* sp. SWUKD4.1850. Phytochemistry 158:56–66

Rustamova N, Bobakulov K, Begmatov N et al (2019) Secondary metabolites produced by endophytic *Pantoea ananatis* derived from roots of *Baccharoides anthelmintica* and their effect on melanin synthesis in murine B16 cells. Nat Prod Res. https://doi.org/10.1080/14786419.2019.1597354

Rustamova N, Wubulikasimu A, Mukhamedov N et al (2020) Endophytic bacteria associated with medicinal plant *Vernonia anthelmintica*—diversity and characterization. Curr Microbiol. https://doi.org/10.1007/s00284-020-01924-5

Saeed A (2016) Isocoumarins, miraculous natural products blessed with diverse pharmacological activities. Eur J Med Chem 116:290–317

Schouten A (2019a) Endophyte biotechnology: potential for agriculture and pharmacology. CABI biotechnology series. CABI, Wallingford

Schouten A (2019b) Endophytic fungi: definitions, diversity, distribution and their significance in plant life. In: Schouten A (ed) Endophyte biotechnology: potential for agriculture and pharmacology. CABI biotechnology series. CABI, Wallingford, pp 6–31

Schouten A (2019c) Saving resources: the exploitation of endophytes by plants for the biosynthesis of multi-functional defence compounds. In: Schouten A (ed) Endophyte biotechnology: potential for agriculture and pharmacology. CABI, Wallingford, pp 122–144

Sharma V, Singamaneni V, Sharma N et al (2018) Valproic acid induces three novel cytotoxic secondary metabolites in *Diaporthe* sp., an endophytic fungus from *Datura inoxia* Mill. Bioorg Med Chem Lett 28:2217–2221

Shen W, Mao H, Huang Q et al (2015) Benzenediol lactones: a class of fungal metabolites with diverse structural features and biological activities. Eur J Med Chem 97:747–777

Silva PHFd, Souza MPd, Bianco EA et al (2018) Antifungal polyketides and other compounds from amazonian endophytic talaromyces fungi. J Braz Chem Soc 29:622–630

Song JH, Lee C, Lee D et al (2018a) Neuroprotective compound from an endophytic fungus, *Colletotrichum* sp. JS-0367. J Nat Prod 81:1411–1416

Song Y-P, Fang S-T, Miao F-P et al (2018b) Diterpenes and sesquiterpenes from the marine algicolous fungus *Trichoderma harzianum* X-5. J Nat Prod 81:2553–2559

Souza JJd, Vieira IJC, Rodrigues-Filho E et al (2011) Terpenoids from endophytic fungi. Molecules 16:10604

Suzuki T, Ariefta NR, Koseki T et al (2019) New polyketides, paralactonic acids A–E produced by *Paraconiothyrium* sp. SW-B-1, an endophytic fungus associated with a seaweed. Chondrus ocellatus Holmes Fitoterapia 132:75–81

Tang J-W, Kong L-M, Zu W-Y et al (2019a) Isopenicins A–C: two types of antitumor meroterpenoids from the plant endophytic fungus *Penicillium* sp. sh18. Org Lett 21:771–775

Tang J-W, Xu H-C, Wang W-G et al (2019b) (+)- and (−)-alternarilactone A: enantiomers with a diepoxy-cage-like scaffold from an endophytic *Alternaria* sp. J Nat Prod 82:735–740

Tantapakul C, Promgool T, Kanokmedhakul K et al (2018) Bioactive xanthoquinodins and epipolythiodioxopiperazines from *Chaetomium globosum* 7s–1, an endophytic fungus isolated from *Rhapis cochinchinensis* (Lour.) Mart. Nat Prod Res 34:494–502

Tawfike AF, Romli M, Clements C et al (2019) Isolation of anticancer and anti-trypanosome secondary metabolites from the endophytic fungus *Aspergillus flocculus* via

bioactivity guided isolation and MS based metabolomics. J Chromatogr B 1106–1107:71–83
Wang Y, Dai C-C (2011) Endophytes: a potential resource for biosynthesis, biotransformation, and biodegradation. Ann Microbiol 61:207–215
Wang LW, Zhang YL, Lin FC et al (2011) Natural products with antitumor activity from endophytic fungi. Mini-Rev Med Chem 11:1056–1074
Wang P, Yu J-H, Zhu K et al (2018a) Phenolic bisabolane sesquiterpenoids from a Thai mangrove endophytic fungus, *Aspergillus* sp. xy02. Fitoterapia 127:322–327
Wang W-X, Li Z-H, Feng T et al (2018b) Curtachalasins A and B, two cytochalasans with a tetracyclic skeleton from the endophytic fungus *Xylaria curta* E10. Org Lett 20:7758–7761
Wang Y-N, Xia G-Y, Wang L-Y et al (2018c) Purpurolide A, 5/5/5 spirocyclic sesquiterpene lactone in nature from the endophytic fungus *Penicillium purpurogenum*. Org Lett 20:7341–7344
Wang Z-F, Zhang W, Xiao L et al (2018d) Characterization and bioactive potentials of secondary metabolites from *Fusarium chlamydosporum*. Nat Prod Res. https://doi.org/10.1080/14786419.2018.1508142
Wang W-X, Lei X, Ai H-L et al (2019a) Cytochalasans from the endophytic fungus *Xylaria* cf. curta with resistance reversal activity against fluconazole-resistant *Candida albicans*. Org Lett 21:1108–1111
Wang W-X, Zheng M-J, Li J et al (2019b) Cytotoxic polyketides from endophytic fungus *Phoma bellidis* harbored in *Ttricyrtis maculate*. Phytochem Lett 29:41–46
Wen Y, Lv Y, Hao J et al (2019) Two new compounds of *Penicillium polonicum*, an endophytic fungus from *Camptotheca acuminata* Decne. Nat Prod Res. https://doi.org/10.1080/14786419.2019.1569003
Wu Y-Z, Zhang H-W, Sun Z-H et al (2018) Bysspectin A, an unusual octaketide dimer and the precursor derivatives from the endophytic fungus *Byssochlamys spectabilis* IMM0002 and their biological activities. Eur J Med Chem 145:717–725
Xiao J, Lin L-B, Hu J-Y et al (2018) Pestalustaines A and B, unprecedented sesquiterpene and coumarin derivatives from endophytic fungus *Pestalotiopsis adusta*. Tetrahedron Lett 59:1772–1775
Xie J, Wu Y-Y, Zhang T-Y et al (2018a) New antimicrobial compounds produced by endophytic *Penicillium janthinellum* isolated from *Panax notoginseng* as potential inhibitors of FtsZ. Fitoterapia 131:35–43
Xie S, Wu Y, Qiao Y et al (2018b) Protoilludane, illudalane, and botryane sesquiterpenoids from the endophytic fungus *Phomopsis* sp. TJ507A. J Nat Prod 81:1311–1320
Xu L-L, Chen H-L, Hai P et al (2019a) (+)- and (−)-preuisolactone A: a pair of caged norsesquiterpenoidal enantiomers with a tricyclo[4.4.01,6.02,8]decane carbon skeleton from the endophytic fungus *Preussia isomera*. Org Lett 21:1078–1081
Xu Z, Wu X, Li G et al (2019b) Pestalotiopisorin B, a new isocoumarin derivative from the mangrove endophytic fungus *Pestalotiopsis* sp. HHL101. Nat Prod Res. https://doi.org/10.1080/14786419.2018.1539980
Yan C, Liu W, Li J et al (2018) Bioactive terpenoids from *Santalum* album derived endophytic fungus *Fusarium* sp. YD-2. RSC Adv 8:14823–14828
Yang H-X, Ai H-L, Feng T et al (2018a) Trichothecrotocins A–C, antiphytopathogenic agents from potato endophytic fungus *Trichothecium crotocinigenum*. Org Lett 20:8069–8072
Yang X-f, Wang N-n, Kang Y-f et al (2018b) A new furan derivative from an endophytic *Aspergillus tubingensis* of *Decaisnea insignis* (Griff.) Hook.f. & Thomson. Nat Prod Res 33:2777–2783
Zhao J-C, Luan Z-L, Liang J-H et al (2018a) Drechmerin H, a novel 1(2), 2(18)-diseco indole diterpenoid from the fungus *Drechmeria* sp. as a natural agonist of human pregnane X receptor. Bioorg Chem 79:250–256
Zhao J-C, Wang Y-L, Zhang T-Y et al (2018b) Indole diterpenoids from the endophytic fungus *Drechmeria* sp. as natural antimicrobial agents. Phytochemistry 148:21–28
Zhao M, Yuan L-Y, Guo D-L et al (2018c) Bioactive halogenated dihydroisocoumarins produced by the endophytic fungus Lachnum palmae isolated from *Przewalskia tangutica*. Phytochemistry 148:97–103
Zhao T, Xu L-L, Zhang Y et al (2018d) Three new α-pyrone derivatives from the plant endophytic fungus *Penicillium ochrochloronthe* and their antibacterial, antifungal, and cytotoxic activities. J Asian Nat Prod Res 21:851–858
Zhao J-W, Yang Z-D, Zhou S-Y et al (2019) Wortmannine F and G, two new pyranones from *Talaromyces wortmannii* LGT-4, the endophytic fungus of *Tripterygium wilfordii*. Phytochem Lett 29:115–118
Zheng C-J, Huang G-L, Liao H-X et al (2019) Bioactive cytosporone derivatives isolated from the mangrove-derived fungus *Dothiorella* sp. ML002. Bioorg Chem 85:382–385