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Recent advances in the discovery, biosynthesis, and therapeutic potential of isocoumarins derived from fungi: a comprehensive update†

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Microorganisms still remain the main hotspots in the global drug discovery avenue. In particular, fungi are highly prolific producers of vast structurally diverse specialized secondary metabolites, which have displayed a myriad of biomedical potentials. Intriguingly, isocoumarins is one distinctive class of fungal natural products polyketides, which demonstrated numerous remarkable biological and pharmacological activities. This review article provides a comprehensive state-of-the-art over the period 2000–2022 about the discovery, isolation, classifications, and therapeutic potentials of isocoumarins exclusively

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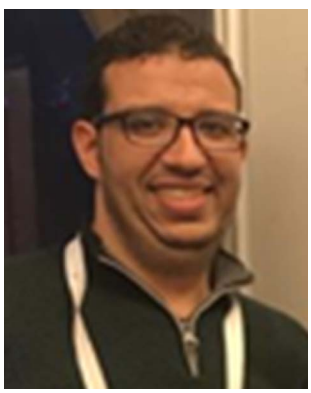

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reported from fungi. Indeed, a comprehensive list of **351** structurally diverse isocoumarins were documented and classified according to their fungal sources [16 order/28 family/55 genera] where they have been originally discovered along with their reported pharmacological activities wherever applicable. Also, recent insights around their proposed and experimentally proven biosynthetic pathways are also briefly discussed.

1. Introduction

Natural products have long been recognized as a crucial mine for drug discovery. Indeed, they have been traditionally used for centuries for their biological significance that have been extended through a wide era of therapeutic fields including inflammatory disorders, cancer immunodeficiency, infectious, hepatic, cardiovascular, renal, and skin diseases.[1,2] Besides, natural products are always a preferable source of bioactive drugs on account of their safety profile associated with their therapeutic potency compared to conventional synthetic drugs.[3,4] Terrestrial plants, despite being a rich source of secondary metabolites and a major fundamental for traditional folk medicine for thousands of years, their overuse made them susceptible to overharvesting, depletion, and extinction of many rare species of high medicinal value.[5] Hence, microorganisms, especially fungi, have recently received remarkably growing attention for discovering an enormous scaffold of natural products of indispensable medicinal values.[6,7] Fungi constitute a broadly diverse class of eukaryotes, which inhabit a wide range of ecosystems including soil, air, and water, in addition to the fungal endophytes that dwell within their hosts of terrestrial and marine habitats.[8,9] They are recognized as an abundant reservoir of bioactive metabolites that have demonstrated stunning therapeutic potentials for both human and animals.[7,10] Dating back to 1929, Alexander Fleming explored the antibacterial activity of the mould *Penicillium rubens*, naming it Penicillin, which was the first of a series of antimicrobial agents isolated from fungi, marking the emergence of the golden era of antibiotics discovery.[11] In addition, further β-lactam antibiotics were discovered from different fungi, causing substantial changes in the global health and the world pharmaceutical industry.[12,13] Moreover, various fungal metabolites were identified and approved as commercial drugs with

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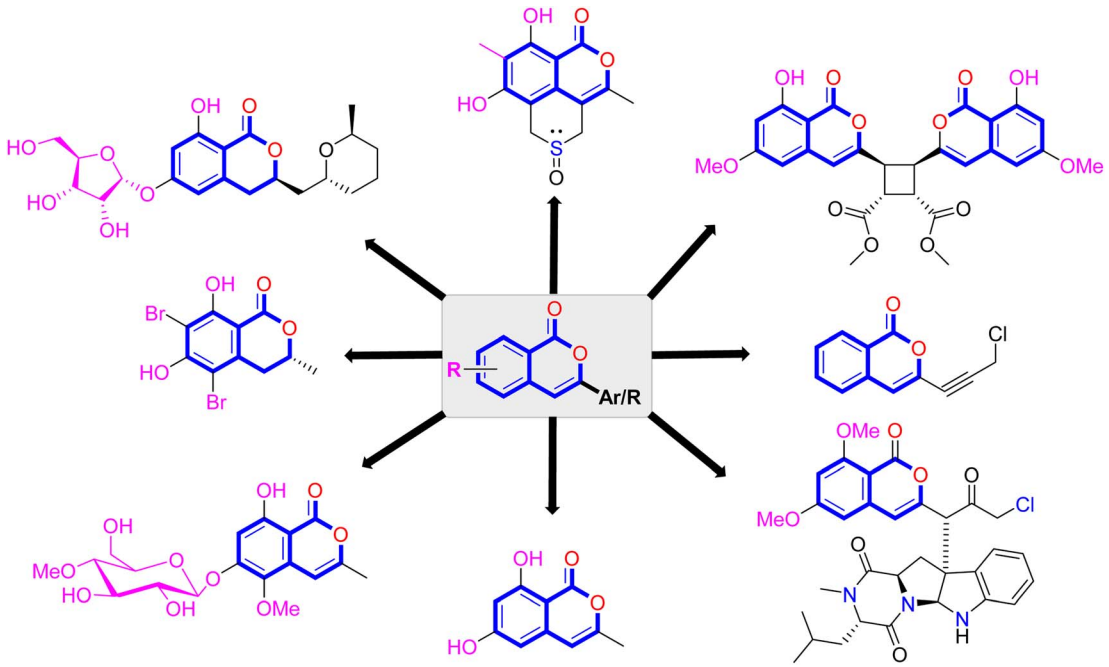
Dr Amr El-Demerdash received his BSc degree (excellent with honors) in chemistry from the Faculty of Sciences, Mansoura University (Egypt) in 2004 and his MSc degree in organic chemistry (natural product chemistry) from the same university in 2009, before getting his PhD in organic chemistry (discovery of pharmacologically active marine natural products and biomimetic total synthesis) from the prestigious French chemical institution CNRS-ICSN (Institute of Natural Products' Chemistry), University of Paris-Saclay (France), under the supervision of Dr Ali Al-Mourabit, in May 2016. After pursuing his PhD in France, Dr El-Demerdash was affiliated to Mansoura University (Egypt) as an assistant professor while also conducting his first postdoctoral training (October 2017 to March 2019) within the fungal natural products chemistry group, CNRS/MNHN, Sorbonne Universities (France). Since April 2019 to date, Dr El-Demerdash is conducting his second postdoctoral training, working on the biosynthesis of pharmacologically active plant natural products (Professor Anne Osbourn's group) at the John Innes Centre, Norwich Research Park, United Kingdom. Later, in December 2021, Dr El-Demerdash was promoted to an associate professorship in organic and natural products chemistry at Mansoura University, Egypt. Dr El-Demerdash's work covers natural products chemistry-based drug discovery including isolation, structure elucidation, biomimetic synthesis, and biosynthesis.



Scheme 1 The isocoumarin core and representative isolated derivatives.

different biological activities, including the immunosuppressant cyclosporine, statins, the inhibitors of cholesterol synthesis, the antifungal, Griseofulvin, and kojic acid, the tyrosinase inhibitor, in addition to chemotherapeutic agents, such as, vincristine, paclitaxel, and camptothecin.[13–15] Secondary metabolites isolated and identified from fungi are sorted to different chemical classes including peptides, steroids, quinones, terpenes, alkaloids, and isocoumarins.[4,16–18] Isocoumarins constitute a distinguished class of secondary metabolites widely abundant in fungi, bacteria, and terrestrial plants. Chemically, as their name implies, isocoumarins are characterized by their inverted α-pyrone lactone nucleus, with substituted or unsubstituted 3-phenyl ring attached on the lactone ring, usually demonstrating 3-alkyl substitution (C1–C7), and possible oxygenation at 6 and 8 positions (Scheme 1).[19,20] Their variant chemical substitution patterns account for their great chemical diversity that influence their wide array of biological and pharmacological activities. Isocoumarins were reported to possess antimicrobial, antifungal, insecticidal, antioxidant, anticancer, anti-inflammatory, and antidiabetic activities.[21–25] Besides, isocoumarins constitute key intermediates in the synthesis of important heterocyclic compounds, *viz.*, isochromenes, isoquinolines, and isocarbostyrils.[26] Consequently, isocoumarins have recently gained great attention in the medicinal, synthetic, and drug discovery research fields. Various captivating reviews addressed natural isocoumarins, namely, the reviews by Saeed A., *et al.*, which focused on the chemical structural diversity among isocoumarins and their associated pharmacological activities reported before 2016.[27,28] Besides, Saddiqa *et al.* reviewed the isolated isocoumarins from natural sources before 2017 with highlights on their bioactivities and chemical synthesis.[29] Noor *et al.* reported the isocoumarins isolated from endophytic fungi between 2019–2020 stressing on their chemistry, biosynthesis, and their pharmacological activities.[31] Meanwhile, the recent review by Shabir *et al.*, reported the natural isocoumarins isolated in the period of 2016–2020, focusing on their chemistry and their bioactivities.[31] As a part of our ongoing research on biologically active natural products[32–34] and with emphasis on pharmacologically active fungal natural products (FNPs),[4,16,35–37] herein, we comprehensively present an up-to-date literature review for the period 2000–2022 on the chemical diversity and biological activities reported for isocoumarins isolated exclusively from different fungal strains. Indeed, the review systematically documents the distribution of a list of 351 isocoumarins among the various fungal genera, their chemical diversities along with their therapeutic potentialities. Furthermore, insights into their biogenesis are briefly discussed.

2. General biosynthetic pathway of fungal isocoumarin

The chemistry of isocoumarin has been extensively studied since the 1950 or before, as reported by Barry.[38] Isocoumarin is a well-known polyketide that had been biosynthesized by the polyketide synthase (PKS) pathway.[39,40] The biosynthetic pathway of isocoumarin derivates had been studied by Birch's group.[41,42] Their study investigated the biosynthesis of canescin from *Penicillium canescens* using stable isotopes (^{13}C labelled) and NMR spectroscopy to determine the sites of incorporation. They pointed out that the isocoumarin portion of the canescin molecule was generated through the acetate/malonate pathway.[42,43] Indeed, Birch *et al.*, discovered that canescin's C-

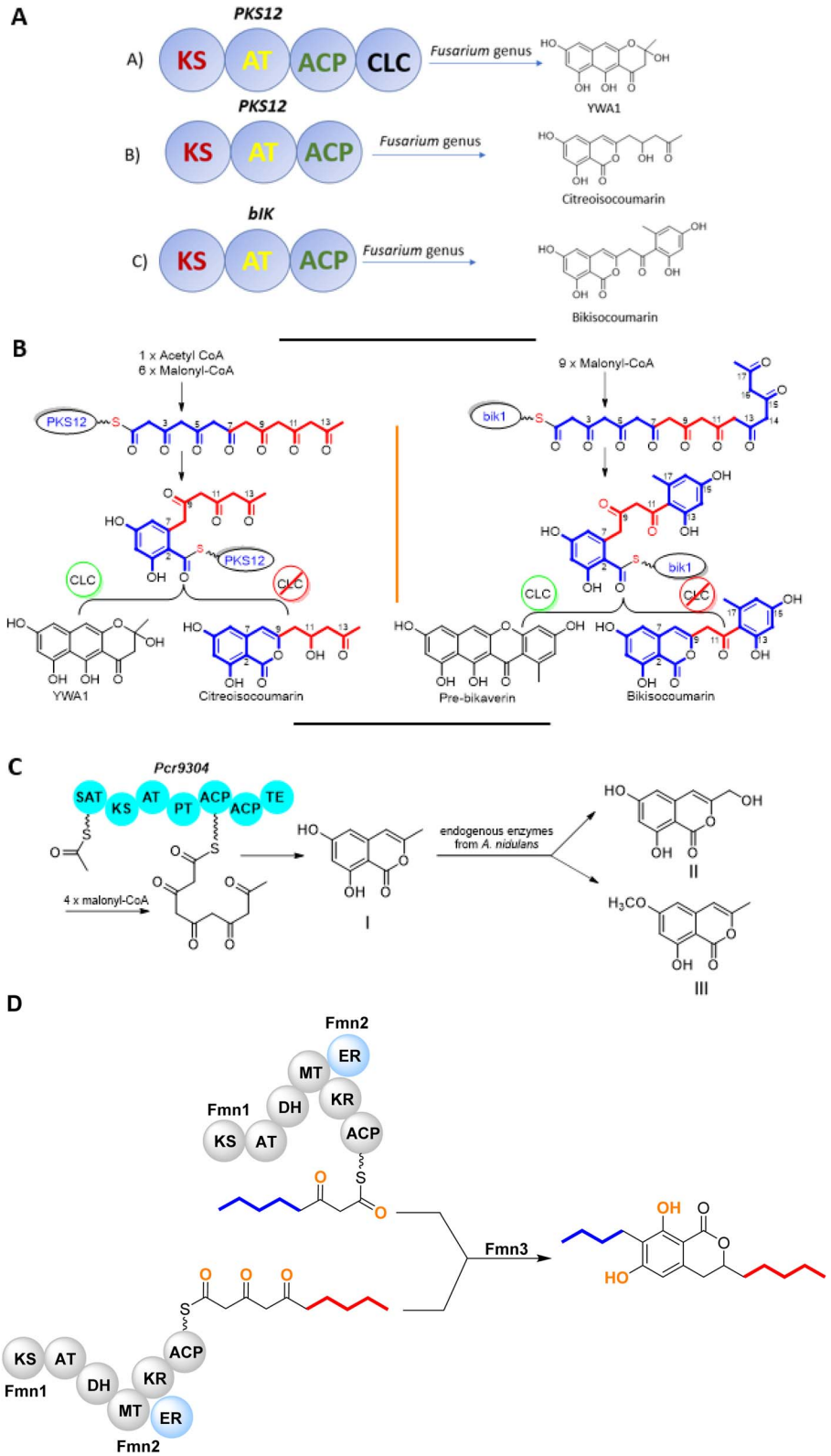


Fig. 1 (A) Domain architecture of various PKS producing isocoumarin derivatives; KS (β-ketoacyl sythase), AT (acetyltransferase), ACP (acyl carrier protein), and CLC (claisen-type cyclase). (B) Biosynthesis of citreoisocoumarin and bikisocoumarin through different PKS architecture domains. (C) Successful heterologous expression of three isocoumarin derivatives by non-reducing polyketide synthase (NR-PKS) in *Aspergillus nidulans* as a host. (D) Proposed biosynthetic pathway of FMN.

10 and C-14 were generated from methionine. Further study by Lewis's group confirmed canescin biosynthesis using the feeding experiment of [$^{13}C,2H_3$] methionine that was administered to *Aspergillus malignus* using batch-wise method over 5 days of incubation.[43] Advances in bioinformatic analysis, genetic transformation experiments, and the progress in genome sequencing revealed that isocoumarins in *Fusarium graminearum* had been synthesized by polyketide synthase 12 (PKS12), a transcription factor (aurR1), and several tailoring enzymes.[44–47] This type of PKS domain architecture consists of a β-ketoacyl synthase (KS), an acetyltransferase (AT), an acyl carrier protein (ACP), and a claisen-type cyclase (CLC), as shown in Fig. 1A. The biosynthetic pathway could be considered as a unified gate to generate different natural compounds by the modification of the PKS domain architecture. Enzymatically, the biosynthetic cascade begins with the condensation of one acetyl-coenzyme A (CoA) molecule and six malonyl-CoA molecules, which is mediated by PKS12 with the active CLC domain to furnish the naphthopyrone YWA1.[48] However, the absence of the CLC domain tragically led to the biosynthesis of citreoisocoumarin.[49,50] This demonstrates that similar PKS domain architectures in different species can lead to the biosynthesis of various polyketide derivatives.[51] In addition, bikisocoumarin is another type of isocoumarin that biosynthesized by similar PKS named bIK[45] which shared a similar architecture domain to previously mentioned PKS12. Nine malonyl-CoA molecules were employed to form pre-bikaverin with the presence of active CLC domain[52,53] (Fig. 1B) while bikisocoumarin was only obtained with the deletion of CLC domain. Furthermore, Ma *et al.*, 2008[52] was able to produce bikisocoumarin by heterologous expression in *E. coli* of a mutated bIK gene. Moreover, a successful heterologous expression insights has been done to elucidate the biosynthesis of some isocoumarins.[54] Three isocoumarins derivatives (I–III) were accumulated as a result of the expression of the non-reducing polyketide synthase (NR-PKS) gene from *Penicillium crustosum* in *Aspergillus nidulans*. The domain architecture of this isocoumarin synthase consists of the SAT-KS-AT-PT-ACP-ACP-TE domain. Meanwhile, Xiang *et al.*, in 2020 elucidated the structure of the three generated isocoumarins by ^{1}H-NMR analysis.[54] They concluded that compounds II–III are modification products obtained by endogenous host enzymes during the heterologous expression (Fig. 1C).

In addition, fusamarins (FMN) is another type of dihydroisocoumarins, which is isolated from the plant-pathogenic fungus *Fusarium mangiferae*. Although it was reported 50 years ago, the biosynthetic pathway has not been revealed yet. Indeed, Atanasoff-Kardjalieff *et al.*,[55] managed to investigate the gene cluster involved in fusamarins biosynthesis. They showed that the FmPKS8 biosynthetic gene cluster (FMN BGC) leads the biosynthesis, which is composed of FmPKS8 (FmFMN1), followed by FmFMN2, FmFMN3, and FmFMN4. Interestingly, PKS8 exhibits the characteristic domains of a highly reducing (HR)-PKS containing a dehydratase (DH), intrinsic *S*-adenosylmethionine (SAM)-dependent methyltransferase (CMet), and keto reductase (KR) domain. They observed that the C-Met domain is not functional in the FMN BGC as the isolated metabolites were not C-methylated; it is conventional for HR-PKS to have the inactive CMet domain.[56] On the other hand, FmFmn3 possesses a peptidase domain with α/β hydrolase fold, FmFmn2 has an ER domain, as well as domains with putative alcohol dehydrogenase activity (ADH). The isolated FMN's structural characteristics imply that two different carbon chains are fused during their production. It was hypothesized that (FmFMN1) produces two distinct polyketides, a tetra and a pentaketide, with changing numbers of double bonds dependent on the selective activities of the trans-acting ER FmFmn2 as only one PKS is expressed inside the FMN BGC (Fig. 2).

Fig. 2 Chemical structure of **1–2**.

3. Chemistry and pharmacological potentials of isocoumarins isolated from fungi

3.1. Fungi of the order Agaricales

3.1.1. Fungi of the family Omphalotaceae

3.1.1.1. Genus Gymnopus (Marasmiaceae). Two chlorinated isocoumarin derivatives previously unreported, namely, gymnopalynes A (**1**) and B (**2**) (Fig. 2), were obtained from the fungus *Gymnopus* sp., isolated from the basidiomycete collected from the rain forest of Thailand. Compounds **1–2** were tested for their antimicrobial activity by assessing their MIC against several bacterial and fungal strains (oxytetracycline hydrochloride, gentamicin, and nystatin were used as positive controls), which exhibited weak to moderate activity against some of the examined strains. In addition, compounds **1–2** showed cytotoxic effect toward the mouse fibroblast cell line L-929 with IC_{50} values of 3.7 and 14.0 μM, respectively.[57]

3.2. Fungi of the order Botryosphaeriales

3.2.1. Fungi of the family Botryosphaeriaceae

3.2.1.1. Fungi of the genus Botryosphaeria. The chemical examination of the EtOAc extract of the marine-derived fungus *Botryosphaeria* sp. KcF6 isolated from the fruit of the mangrove *K. candel*, collected from the bay of Daya, China, led to the isolation of the previously unreported 3*S*-5,8-dihydroxy-3-hydroxymethyldihydroisocoumarin (**3**) as well as other four previously reported isocoumarin derivatives, namely, monocerin (**4**), 3-methyl-6,8-dihydroxyisocoumarin (**5**), 8-methoxymellein (**6**), and *trans*-4-hydroxymellein (**7**) (Fig. 3). Though none of the isolated compound showed any cytotoxic effect against the studied cancer cell lines (K562, MCF-7, A549, U937, HeLa, DU145, HL60, BGC823, MOLT-4, and H1975), compound **3** showed antiinflammation properties through the inhibition

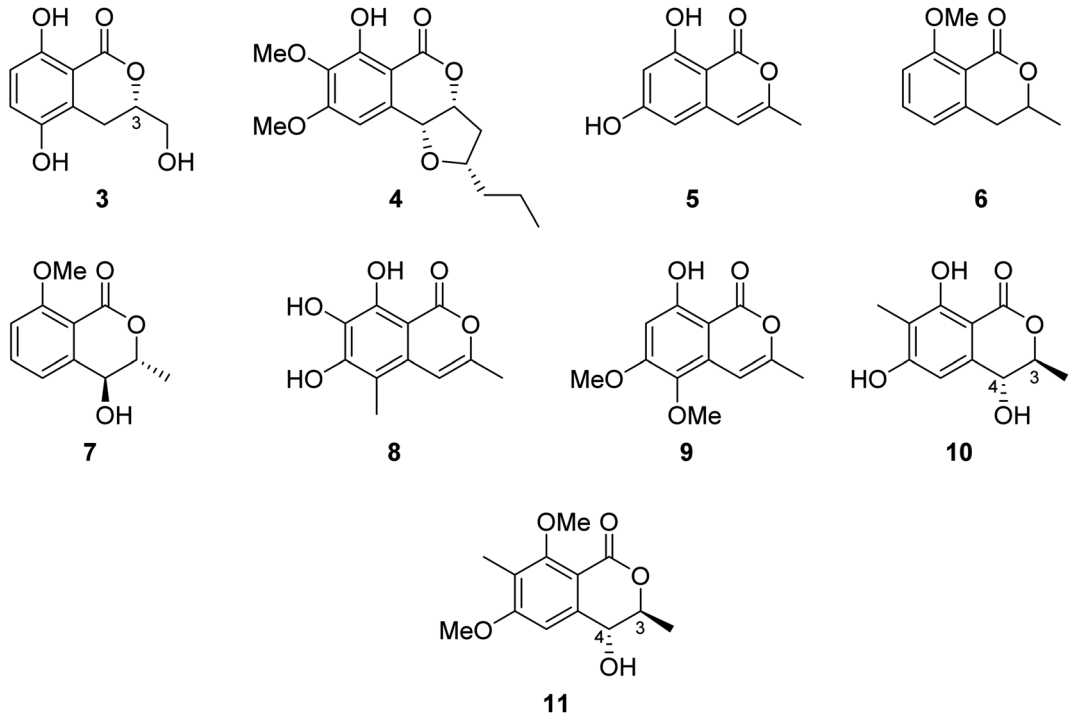


Fig. 3 Chemical structures of **3–11**.

of COX-2 activities with $IC_{50} = 6.51$ μM.[58] Other four previously unreported isocoumarin derivatives, namely, botryospyrones A–D (**8–11**) (Fig. 3), were obtained from the EtOAc extract of the marine endophytic fungus *Botryosphaeria ramosa* L29 isolated from the leaf of *Myoporum bontioides*, collected from the mangrove of Leizhou Peninsula, China. The antifungal properties of compounds **8–10** against three phytopathogenic fungi, *i.e.*, *Fusarium oxysporum*, *Penicillium italicum*, and *Fusarium graminearum*, were tested (triadimefon was used as the positive control). They showed antifungal activity ranging from weak to strong with MIC values ranging from 900 to 105.8 μM, except for compound **9**, which showed no activity toward *Penicillium italicum* with MIC value >900.0 μM. Also, it is worth mentioning that compound **11** was not examined as it was obtained in a very minute amount.[59]

3.3. Fungi of the order Cladosporiales

3.3.1. Fungi of the family Cladosporiaceae

3.3.1.1. Fungi of the genus Cladosporium. Chemical investigation of the marine sponge-derived fungus *Cladosporium* sp. SCSIO41007 isolated from the sponge *Callyspongia* sp., collected from the sea near to the province of Guangdong, China, led to the isolation of the previously unreported dihydroisocoumarin derivatives, namely, (3*R*)-3-(2-hydroxypropyl)-6,8-dihydroxy-3,4-dihydroisocoumarin (**12**) (Fig. 4). It is worth mentioning that compound **12** was not assessed for any biological activity.[60]

3.4. Fungi of the order Chaetothyriales

3.4.1. Fungi of the family Herpotrichiellaceae

3.4.1.1. Fungi of the genus Exophiala. The previously unreported exophiarin (**13**) (Fig. 5) was isolated from the EtOAc extract of the soil derived fungus *Exophiala* sp. obtained from a dumped organic waste collected from Kaziranga, Assam. Compound **13** exhibited moderate activity in the glucose uptake

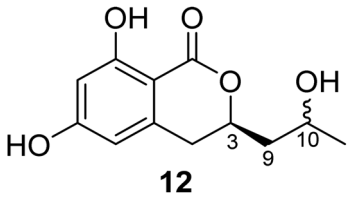


Fig. 4 Chemical structure of **12**.

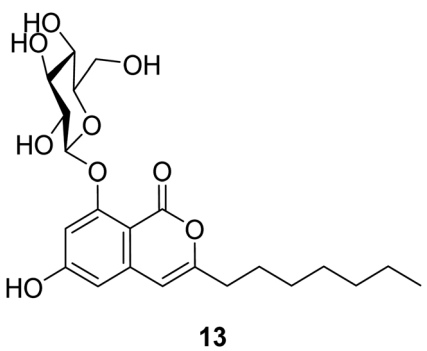


Fig. 5 Chemical structure of **13**.

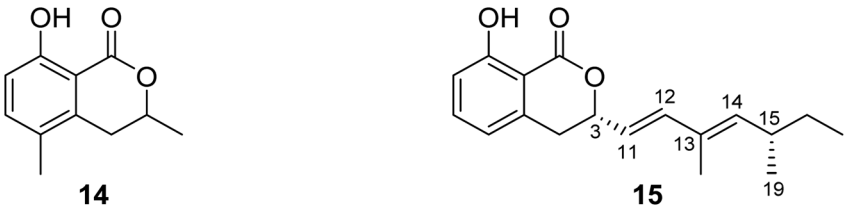


Fig. 6 Chemical structures of 14–15.

activity when tested *in vitro*, using Rosiglitazone as a positive control.[61]

3.5. Fungi of the order Diaporthales

3.5.1. Fungi of the family Diaporthaceae

3.5.1.1. Fungi of the genus Diaporthe. (−)3,4-Dihydro-8-hydroxy-3,5-dimethyl-isocoumarin (**14**) (Fig. 6), also known as (−)5-methylmellein, a previously reported phytotoxic isocoumarin derivative, was isolated from the EtOAc extract of the pathogenic fungus *Diaporthe eres* obtained from *Hedera helix* infected leaf collected from Oxford, Mississippi. Compound **14** was examined for its phytotoxicity against *Agrostis stolonifera* (bentgrass) and *Lactuca sativa* (lettuce), and it was found to be more phytotoxic toward bentgrass than lettuce with IC_{50} ~100 μM. It is worth mentioning that compound **14** is well known to be more active on monocots than dicots.[62] A previously unreported dihydroisocoumarin derivative Diaporone A (**15**) (Fig. 6) was obtained from the EtOAc extract of the endophytic fungus *Diaporthe* sp., isolated from *Pteroceltis tatarinowii* Maxim collected from Nanjing, China. Compound **15** was examined for its antimicrobial activity against several bacterial strains including *B. subtilis* (ATCC 6633), *Staphylococcus aureus* (CGMCC 1.2465), *Streptococcus pneumoniae* (CGMCC 1.1692), *Escherichia coli* (CGMCC 1.2340), and the fungal strains *Saccharomyces cerevisiae* (ATCC 18824) and *Candida albicans* (CGMCC 2.2086) using gentamycin as a positive control, showing a moderate antibacterial activity toward *B. subtilis* with an MIC value of 66.7 μM. In addition, compound **15** was tested for its cytotoxic activity against a panel of human cancer cell lines including human glioma cell lines (SH-SY5Y), cervical epithelial cells (HeLa), human colon cancer cells (HCT116), human hepatocellular carcinoma cells (HepG2), human lung cancer cells (A549), and human breast cancer cells (MCF7). It was found to be a weak cytotoxic agent against HeLa cell lines with IC_{50} = 97.4 μM.[63]

3.5.2. Family of the family Valsaceae

3.5.2.1. Fungi of the genus Phomopsis. The chemical examination of the EtOAc extract of the endophytic fungus *Phomopsis prunorum* isolated from the leaves of *Hypericum ascyron*, collected in Hubei, China, led to the isolation of two previously unreported isocoumarins, namely, phomoisocoumarins C–D (**16–17**) (Fig. 7). Compounds **16–17** were tested for their antibacterial activity toward a list of plant pathogenic bacterial strains including *Pseudomonas syringae* pv. *Lachrymans*, *Xanthomonas citri* pv. *phaseoli* var. *fuscans*, and the pathogenic bacteria *E. coli*, as well as the marine-derived bacteria *Vibrio parahaemolyticus* and *Vibrio anguillarum* using microplate assay and streptomycin as the positive control. They exhibited weak to moderate inhibition effect against *P. syringae* pv. *Lachrymans* with MIC values of 31.2 and 15.6 μg mL^{-1}, respectively, and toward *X. citri* pv. *phaseoli* var. *fuscans* with MIC value of 31.2 μg mL^{-1}.[64] Chemical investigations of the organic extract of the endophytic fungus *Phomopsis prunorum* (F4-3) obtained from *Hypericum ascyron* leaves collected in Hubei, China, led to the isolation of three pairs of enantiomeric isocoumarin derivatives, including the previously unreported (±)-prunomarin A (**18**), (+)-pestalactone B (**19**) along with its known enantiomer (−)-pestalactone B (**20**), together with the known enantiomers

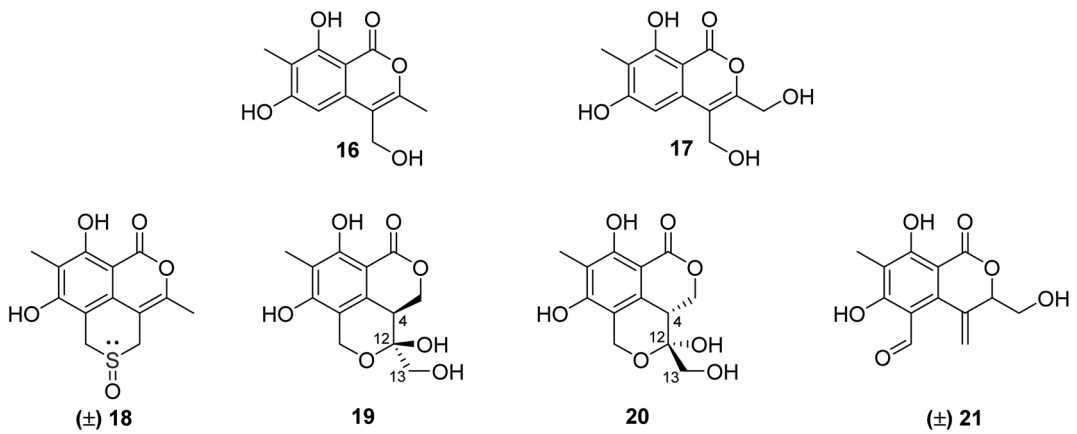


Fig. 7 Chemical structures of 16–21.

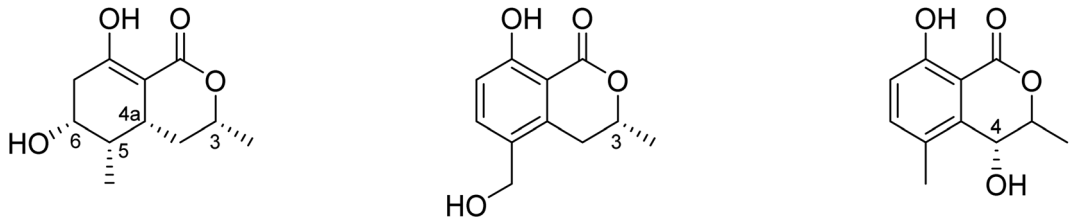


Fig. 8 Chemical structures of 22–24.

pestalactone C (+)-(**21**) and oxoisochromane (−)-(**21**) (Fig. 7). Only compound **18** exhibited anti-inflammatory activity by the inhibition of nitric oxide (NO) production in the lipopolysaccharide (LPS)-stimulated mouse macrophage RAW 264.7 with IC_{50} = 84.2 μM, and the rest of the isolated compounds were found to be inactive.[65]

3.5.2.2. Fungi of the genus Valsa. (3*R*,4a*R*,5*S*,6*R*)-6-Hydroxy-5-methylramulosin (**22**), a previously unreported isocoumarin along with three other known derivatives, including the previously mentioned (−)5-methylmellein (**14**), (−)-5-hydroxymethylmellein (**23**), and (−)-(3*R*,4*R*)-*cis*-4-hydroxy-5-methylmellein (**24**) (Fig. 8), were isolated from the marine alga-derived fungus *Valsa ceratosperma* obtained from the green alga *Codium fragile* (SURINGAR) HARIOT, collected from the Japan sea at the bay of Toyama. While compounds **14**, **23**, and **24** showed no cytotoxic activity against HeLa cell lines, compound **22** displayed 65% inhibitory activity against HeLa cells growth at a concentration of 50 μg mL^{-1}.[66]

3.6. Fungi of the order Eurotiales

3.6.1. Fungi of the family Aspergillaceae

3.6.1.1. Fungi of the genus Aspergillus. The chemical investigation of the marine-derived fungus *Aspergillus* sp. associated with the ascidian *Eudistoma vannamei*, obtained from Northeast Brazil, led to the isolation of two previously reported isocoumarins, namely, mullein (**25**) and *cis*-4-hydroxymellein (**26**), along with the previously mentioned *trans*-4-hydroxymellein (**7**) (Fig. 9). All the isolated compounds exhibited no cytotoxicity once they were examined against two tumor cell lines HCT-8 and MDA-MB-435.[67] Other four isocoumarins were isolated from the EtOAc extract of the marine-derived fungus *Aspergillus similanensis* sp. nov. KUFA 0013, obtained from the marine sponge *Rhabdermia* sp., collected in Thailand, from the Similan Islands coral reef, including the previously reported 6,8-dihydroxy-3-methylisocoumarin (**27**) and reticulol (**29**), along with previously unreported derivatives 6,8-dihydroxy-3,7-dimethylisocoumarin (**28**) and 5-hydroxy-8-methyl-2*H*,6*H*-pyrano[3,4-*g*]chromen-2,6-dione (**30**), which is also known as similanpyrone A (Fig. 9). Compounds **27–30** showed neither antifungal nor antibacterial when tested against *C. albicans* ATCC 10231, Gram-negative bacteria (*E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853), and Gram-positive bacteria (*S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633).[68] In addition, four previously reported isocoumarin derivatives, namely, angelicoin A (**31**), periplanetin D (**32**), (3*S*,4*S*)-dihydroascochin (**33**), and phomolactone B (**34**) together with three previously unreported congeners, including versicoumarins A (**37**), B (**35**), and C (**36**) (Fig. 9), were obtained from the endophytic fungus of *Aspergillus versicolor* isolated from *P. marmorata* stearn rhizome, collected from Yunnan, China. Compounds **31–37** were examined for their antiviral activity (anti-TMV activity) using the half-leaf method and ningnanmycin as a positive control. They exhibited an inhibition activity in the range from 11.5 to 28.6%. Furthermore, it is worth mentioning that compound versicoumarins A (**37**) exhibited the highest inhibitory activity of 28.6%. In addition, they were also tested for their cytotoxicity against MCF7, NB4, PC3, SHSY5Y, and A549 cancer cell lines using the MTT-assay and taxol as the positive control. Compounds **31–36** exhibited moderate cytotoxic effect against the examined cell lines with IC_{50} <10 μM; however, compound versicoumarins A (**37**) displayed strong cytotoxic effect toward MCF7 and A549 tumor cell lines with IC_{50} values of 4.0 and 3.8 μM, respectively.[69] (*S*)-(−)-6,8-Di-*O*-methylcitreoisocoumarin (**38**) (Fig. 9), a previously unreported isocoumarin derivative, was isolated from the marine-derived fungus *Aspergillus flavus* OUCMDZ-2205 isolated from the prawn, *Penaeus vannamei*, collected in China from the sea area of Lianyungang. Compound **38** was not examined for any relevant biological activity.[70] The chemical examination of the algicolous-derived endophytic fungus *Aspergillus* sp. F00785 isolated from the alga, *Enteromorpha prolifera*, collected in China from the Saltern of Jinjiang, afforded nine asperentin derivatives, including the previously reported asperentin (**39**), which is also known as cladosporin, 5′-hydroxyasperentin (**40**), 4′-hydroxyasperentin (**41**), asperentin-8-methyl ether (**42**), 5′-hydroxyasperentin-8-methyl ether (**43**), and 4′-hydroxyasperentin-6-methyl ether (**44**), together with three previously undescribed derivatives, *i.e.*, 5-hydroxyl-6-*O*-methylasperentin (**45**), 6-*O*-α-D-ribosylasperentin (**46**), and 6-*O*-α-D-ribosyl-8-*O*-methylasperentin (**47**) (Fig. 9). Compounds **39–47** were examined for their antifungal effect against three crop pathogenic fungi, *B. cinerea* Pers, *C. gleosporioides* Penz., and *C. gleosporioides* (Penz.) Sacc., using the filter-paper disk method and as a positive control amphotericin has been used. Compounds **41–47** exhibited no antifungal effect against the examined fungi, but compound **39** displayed strong inhibition effect against *C. gleosporioides* Penz. at a concentration of 5 μg mL^{-1} with an inhibition zone of 19.7 mm.[71] Six dihydroisocoumarins derivatives including the previously mentioned asperentin (**39**), 5′-hydroxyasperentin (**40**), 4′-

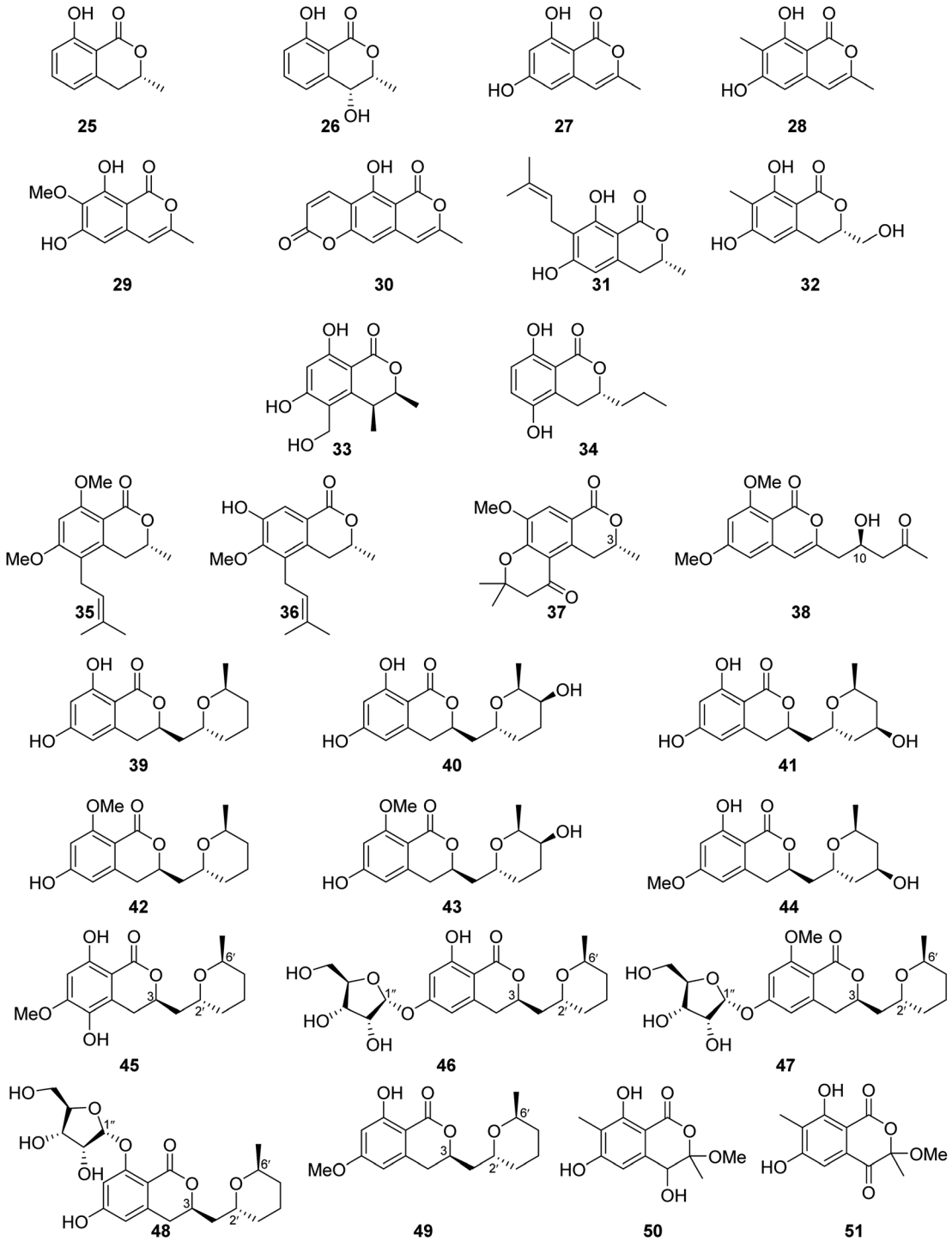


Fig. 9 Chemical structures of **25–51**.

hydroxyasperentin (**41**), asperentin-8-methyl ether (**42**), along with two previously undescribed derivatives, including cladosporin 8-*O*-α-ribofuranoside (**48**), and asperentin 6-*O*-methyl ether (**49**) (Fig. 9), were obtained from EtOAc extract of the marine-derived fungi *Aspergillus* sp. SF-5974 and *Aspergillus* sp. SF-5976, isolated from an unidentified red algae, collected from the Ross Sea at a depth of 300 m. Compounds **39–42** and **48–49**, were tested for their antineuro–inflammatory activity, and they displayed inhibition activity toward prostaglandin E2 (PGE2) and LPS-induced nitric oxide (NO) production through inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) expression, with IC_{50} values ranging from 10 to 80 μM.[72] The chemical examination of the MeOH extract of the mangrove-derived fungus *Aspergillus* sp. 16-5B isolated from *Sonneratia apetala*

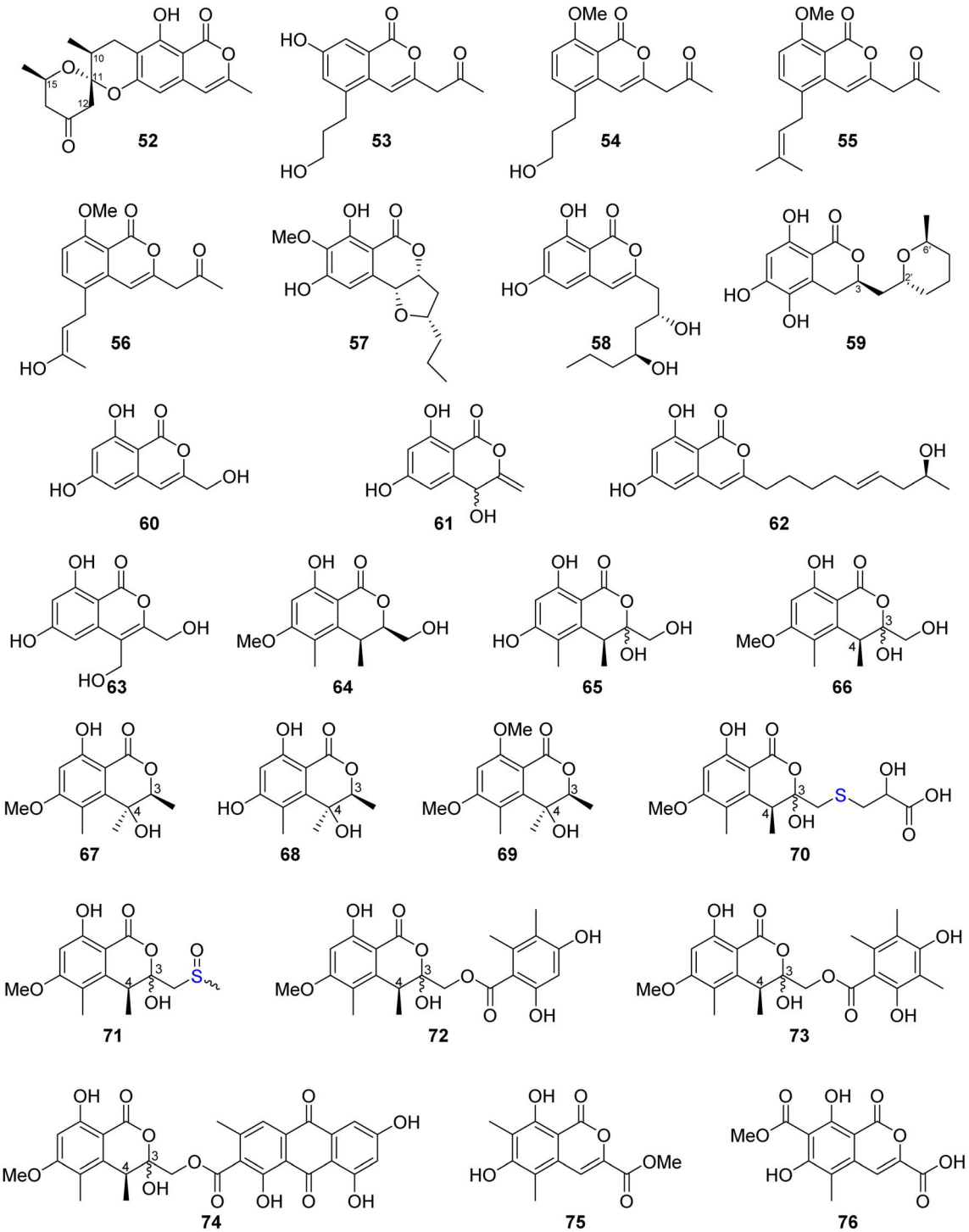


Fig. 10 Chemical structures of 52–76.

leaves, collected in China, in Hainan Island, led to the isolation of two previously unidentified isocoumarin derivatives as a racemic mixture of the possible enantiomer. *i.e.,* (±) **50** and (±) **51** (Fig. 9). Compounds **50–51** were tested for their ability to inhibit the enzyme α-glucosidase (using acarbose as a positive control); while compound **51** was inactive, compound **50** displayed inhibition activity with IC_{50} values of >200 and 90.4 μM, respectively.[73]

Similanpyrone C (**52**) (Fig. 10), a previously undescribed isocoumarin derivative, was isolated from the marine associated fungus *Aspergillus similanensis* KUFA 0013, obtained from the unidentified marine sponge. Compound **52** was not tested for any biological activity as it was obtained in a very minute amount.[74] The chemical investigation of the endophytic fungus *Aspergillus oryzae* organic extract obtained from the rhizome of *P. polyphylla* var. *yunnanensis*, collected in Yunnan, China

afforded six isocoumarin derivatives, including the previously unreported oryzaeins A (**53**) and B (**54**), together with the known derivatives, tabaisocoumarin A (**55**), caudacoumarin C (**56**), exserolide D (**57**), and exserolide F (**58**) (Fig. 10). Intriguingly, the presence of the unusual 2-oxopropyl group and a rare 3-hydroxypropyl group shows privileged compounds **53–54** to be the first examples of an isocoumarin possessing these unusual structural features. Only compounds **53–54** were examined for their antiviral effect toward tobacco mosaic virus (anti-TMV) using the half-leaf method and ningnanmycin as a positive control, showing an inhibition rate of 28.4 and 30.6, respectively, at a concentration of 20 μM. Moreover, they were tested for their cytotoxic ability against NB4, A549, SHSY5Y, PC3, and MCF7 cancer cell lines by the MTT method, exhibiting weak to moderate cytotoxic effect with IC_{50} values in the range of 2.8–8.8 μM.[75] Asperentin B (**59**) (Fig. 10), a previously undescribed isocoumarin derivative of the asperentin-type, and the previously mention asperentin (**39**) were isolated from the marine-derived fungus *Aspergillus sydowii* obtained from the deep Mediterranean sea sediment (2769 m). Asperentin B (**59**) was found to display potent inhibitory activity against PTP1B enzyme with an IC_{50} value of 2.05 μM, when compared with suramin as a positive control that exhibited an IC_{50} value of 11.85 μM. In addition, **59** exhibited weak inhibitory activity against *Propionibacterim acnes* with an inhibition rate of 57% at a concentration of 100 μM. Moreover, compound **59** displayed no antimicrobial effect when tested against *X. campestris*, *S. tritici*, *C. albicans*, *B. subtilis*, and *S. lentus* at a concentration of 100 μM. Furthermore, **59** showed no cytotoxic effect at a concentration of 50 μM when tested against the HepG2 and HT29 tumor cell lines. On the other hand, while compound **39** showed no inhibition effect against the activity of PTP1B enzyme as well as exhibited no cytotoxic effect against HepG2 and HT29, it inhibited the growth of *X. campestris*, *S. tritici*, *B. subtilis*, *T. mentagrophytes*, and *S. lentus* with an inhibition rate in the range of 83–100% when compared with the positive control clotrimazole, which also displayed a very weak antifungal activity.[76] The previously mentioned 6,8-dihydroxy-3-methylisocoumarin (**27**), along with four previously reported isocoumarin derivatives, namely, 6,8-dihydroxy-3-hydroxymethylisocoumarin (**60**), 4,6-dihydroxy-3,9-dehydromellein (**61**), fusariumin (**62**), and penicimarin F (**63**) (Fig. 10), were obtained from the EtOAc extract of the fermentation product of the endophytic fungus *Aspergillus versicolor*,

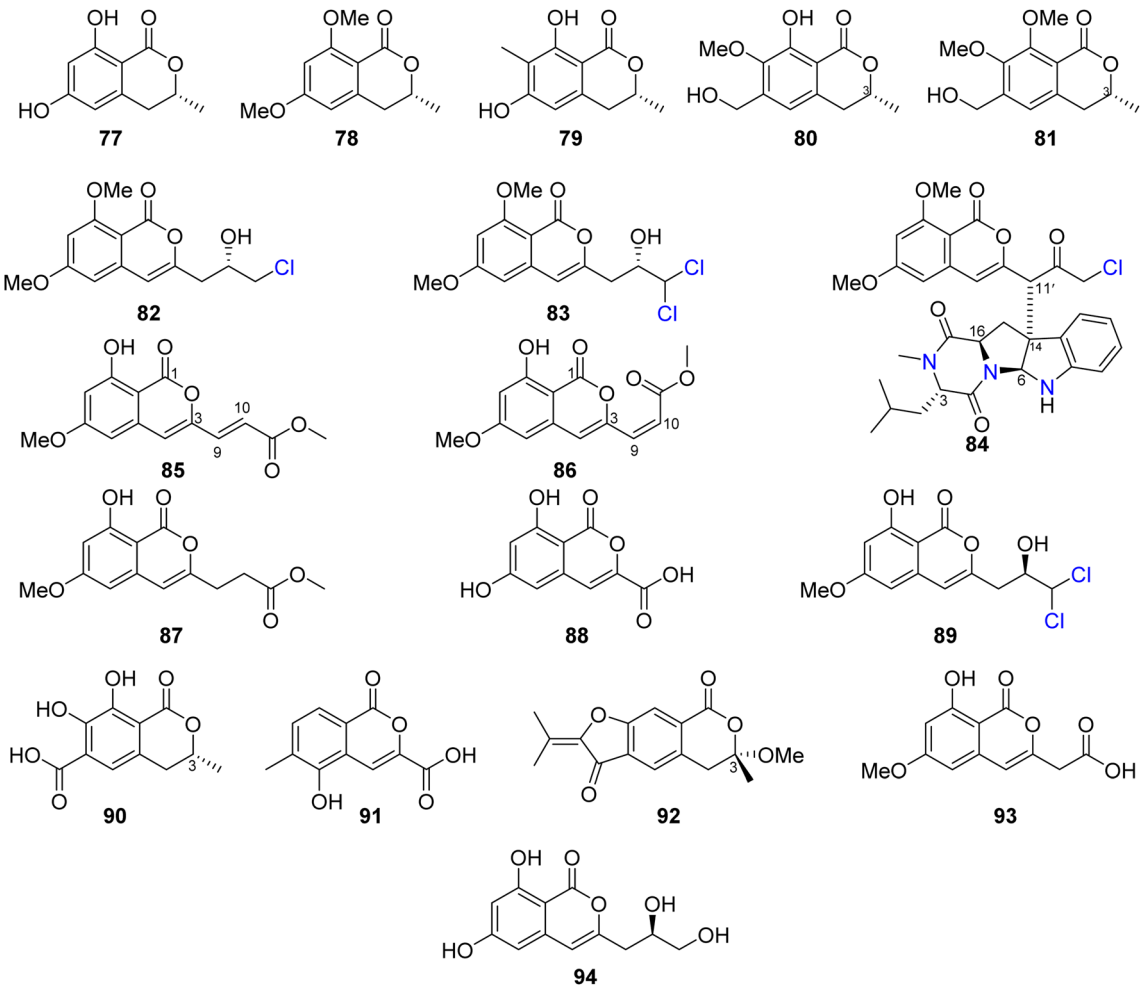


Fig. 11 Chemical structures of **77–94**.

obtained from the rhizome of *Paris polyphylla* var. *yunnanensis*, collected in Yunnan, China. No relevant biological activity was reported for **60–63**.[77] The chemical investigation of the fungus *Aspergillus banksianus* obtained from *Banksia integrifolia* collected from Australia in New South Wales led to the isolation of three previously described isocoumarin derivatives, namely, clearanol I (**64**), dothideomynone A (**65**), and banksialactone A (**66**), together with ten previously undescribed derivatives, including eight isocoumarins, namely, banksialactones B–I (**67–74**), as well as two new isocoumarins, named banksiamarins A–B (**75–76**) (Fig. 10). Compounds **64–76** were examined for their antibacterial activity against *B. subtilis* (ATCC6633), *E. coli* (ATCC25922), *C. albicans* (ATCC 10231), and *S. cerevisiae* (ATCC 9763), as well as for their antiprotozoal ability against *T. fetus* (KV-1) and for their cytotoxicity against the NS-1 cancer cell line using ampicillin, clotrimazole, mebendazole, and 5-fluorouracil, respectively, as positive controls. Though compounds **64–65**, **67–71**, and **75–76** displayed no activity in any of the investigated biological activity, compounds **72–74** exhibited weak to moderate activity on all the aforementioned biological assays.[78]

Three previously reported isocoumarins (*R*)-6-hydroxymellein (**77**), 6,8-dimethoxy-3-methyl-3,4-dihydro-1*H*-isochromen-1-one (**78**), and periplanetin B (**79**), along with the previously undescribed derivatives (3*R*)-methyl-8-hydroxy-6-(hydroxymethyl)-7-methoxydihydroisocoumarin (**80**) and (3*R*)-methyl-7,8-dimethoxy 6-(hydroxymethyl)dihydroisocoumarin (**81**) (Fig. 11), were isolated from the endophytic fungus *Aspergillus versicolor* derived from the *Nicotiana tabacum* rhizome, collected from Yunnan, China. Compounds **80–81** were tested for their antiviral activity against the TMV using the half leaf method and ningnanmycin as a positive control, showing an inhibition effect with an inhibition rate 21.8 and 18.6%, respectively.[79] The chemical examination of the terrestrially-derived fungus *Aspergillus* sp. CPCC 400810, an endolichenic fungus obtained from *Cetrelia* sp., collected in Yunnan, China from the mount of Laojun, led to the isolation of the two previously identified isocoumarin derivatives 8-methyl-11-chlorodiaporthin (**82**) and 8-methyl-11,11-dichlorodiaporthin (**83**), along with one previously unreported isocoumarindole A (**84**), a hybrid molecule, featuring a polyketide-nonribosomal peptide (PKS-NRPS) biogenesis pathway (Fig. 11). Compound **84** displayed moderate antifungal effect toward *C. albicans* using caspofungin as a positive control, with MIC value of 32.0 μg mL^{-1}. In addition, it exhibited potent cytotoxicity against MIA-PaCa-2 and AsPC-1 with IC_{50} values of 1.63 and 5.53 μM, respectively.[80] Three previously undescribed isocoumarins, namely, apergisocoumrins A–C (**85–87**), along with the previously identified 8-dihydroxyisocoumarin-3-carboxylic acid (**88**) and dichlorodiaportin (**89**) (Fig. 11), were isolated from the mangrove-derived endophytic fungus *Aspergillus* sp. HN15-5D isolated from *A. ilicifolius* fresh leaves, collected from Hainan Island, China. Compounds **85–89** were tested for their cytotoxicity (using epirubicin as the positive control) against MDA-MB-435, HepG2, HCT116, H460, and MCF10A cancer cell lines. While **87–89** showed no cytotoxic activity against the examined tumor cell lines, **85** exhibited potent cytotoxic activity against MDA-MB-435, HepG2, H460, and MCF10A with IC_{50} value in the range of 5.08–43.7 μM; however, **86** displayed moderate cytotoxicity against MCF10A and MDA-MB-435 cancer cell lines with IC_{50} values of 21.4 and 4.98, respectively. Furthermore, **85–89** were tested for their antibacterial ability against *S. aureus*, *S. epidermidis*, *E. coli*, *K. pneumoniae*, and *B. subtilis*; only **89** displayed moderate antibacterial activity against with MIC values of 25 μg mL^{-1}.[81] Two previously unreported isocoumarins, namely, aspergillspins F–G (**90–91**) (Fig. 11), were reported from the gorgonian-derived fungus *Aspergillus* sp. SCSIO 41501 isolated from the soft coral *Melitodes squamata* collected from the South China Sea. Compounds **90–91** displayed neither cytotoxicity when examined against HL60, HepG2, and MCF-7 cancer cell lines using MTT methods nor antibacterial effect toward *B. subtilis* and *E. coli* using the standard disc diffusion.[82] Asperisocoumarin G (**92**) (Fig. 11), a previously undescribed isocoumarin, was isolated from MeOH extract of the marine derived fungus *Aspergillus* sp. 085 242 isolated from the mangrove plant collected in China. Compound **92** exhibited moderate inhibition effect against α-glucosidase activity when compared with clinical acarbose as a positive control. In addition, it showed no antibacterial activity against *S. aureus* ATCC 6538, *B. Subtilis* ATCC 6633, *E. coli* ATCC 8739, *P. Aeruginosa* ATCC 9027, and Salmonella ATCC 14028.[83] The chemical examination of the marine-derived fungus *Aspergillus falconensis* isolated from the marine sediment collected from Red Sea, Egypt from the Canyon at Dahab at 25 m depth led to the isolation of the previously mentioned dichlorodiaportin (**89**) along with the previously synthesized derivative 2-(8-hydroxy-6-methoxyisochromen-3′-yl)acetic acid (**93**) and the previously described desmethyldiaportinol (**94**). *In silico* studies of compounds **89** and **93–94** on human cyclin-dependent kinase 2 revealed a certain degree of stability in the active sites of CDK-2 ($\Delta G = -20.32$, -22.30, and -20.46, respectively).[84]

3.6.1.2. Fungi of the genus Penicillium. Dihydrocitrinone (**95**) (Fig. 12), a previously described isocoumarin, was reported from the marine-derived fungus *Penicillium notatum* B-52 isolated from the sediments, collected from the Lake of Qinghai, China. In addition, the chemical investigation of the marine-derived fungus *P. stoloniferum* QY2-10 isolated from an unidentified sea squirt collected from the bay of Jiaozhou, China, led to the isolation of two previously unreported derivatives, namely, stoloniferols A–B (**96–97**) (Fig. 12). Compounds **95–97** displayed no activity when tested for their cytotoxicity by the MTT method against P388, BEL-7402, A-549, and HL-60 tumor cell lines.[85] *Cis*-4-hydroxymellein (**26**), a previously mentioned derivative (Fig. 9), was isolated from the marine-derived fungus *P.* sp., obtained from the green alga *Ulva pertusa* collected from the island of Beijing, Korea. No biological activity was reported for this compound.[86] In addition, the chemical investigation of the marine derived endophytic fungus *P.* sp., 091 402 isolated from the roots of the mangrove *Bruguiera sexangular* Linn collected in China, Qinglan Port, Hainan led to the isolation of one previously unreported derivative, (3*R**,4*S**)-6,8-dihydroxy-3,4,7-trimethylisocoumarin (**98**), along with the known isocoumarin derivative, (3*R*,4*S*)-6,8-dihydroxy-3,4,5-trimethylisocoumarin (**97**) (Fig. 12). Compound **97** was not tested for any relevant

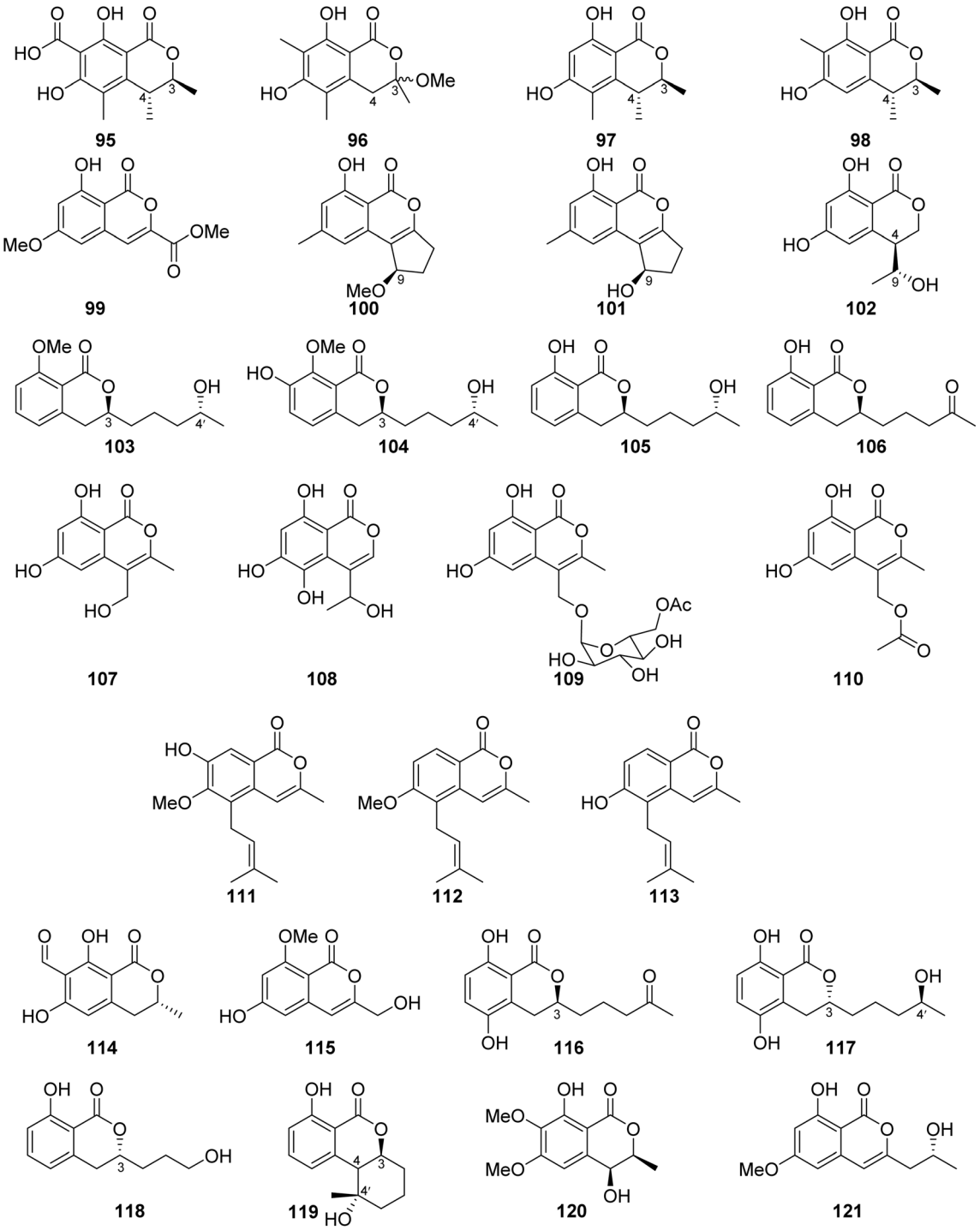


Fig. 12 Chemical structures of **95–121**.

bioactivity, while compound **98** displayed mild cytotoxic activity against K562 cancer cell line with $IC_{50} = 18.9\ \mu g\ mL^{-1}$.[87] Penicilisorin (**99**) (Fig. 12), a previously undescribed isocoumarin, was isolated from the terrestrial endophytic fungus *P. sclerotiorum* PSUA13, isolated from *G. Atroviridis* leaves, collected in Thailand from Yala Province. Due to the minute quantity of **99**, it was not subjected for any relevant biological activity.[88] A previously unidentified citrinolactone D (**100**) along with the previously described citrinolactone B (**101**) (Fig. 12) was isolated from the marine sediment-derived fungus *P.* sp., ML226, isolated from the sediment of the mangrove region, Long Hai, China.

Compound **100** was tested for its cytotoxicity against the tumor HeLa and HepG-2 cell line (using the MTT method and

cis-platinum as positive control) as well as evaluated for its antimicrobial activity against *S. aureus* (CMCC26003), *E. coli* (CMCC44103), *C. albicans* (AS2.538), and *A. niger* (ACCC30005) using the paper diffusion method. Compound **100** displayed neither cytotoxicity nor antimicrobial activities.[89] The chemical examination of the sponge-derived fungus *P.* sp., (MWZ14-4), isolated from an unidentified sponge collected from the coral reef of the South China Sea, afforded ten isocoumarin derivatives, including five previously unreported hydroisocoumarins, namely, penicimarins A–C (**102–104**), penicimarins D–E (**109–110**), along with known congeners aspergillumarins B (**105**) and A (**106**), sescandelin B (**107**), 5,6,8-trihydroxy-4-(1′-hydroxyethyl) isocoumarin (**108**) (Fig. 12), and previously mentioned derivative penicimarin F (**63**) (Fig. 10). Compounds **63** and **102–110** were tested for their antibacterial activity against the terrestrial pathogenic bacteria *E. coli*, *S. aureus*, *S. albus*, *B. subtilis*, *B. cereus*, *M. tetragenus*, and *K. rhizophila*, as well as the marine-derived pathogenic bacteria *V. parahemolyticus* and *V. anguillarum* (using the conventional broth dilution method and ciprofloxacin as a positive control). Among all of them, **108** displayed the most potent activity against *B. cereus* and *V. parahemolyticus*, with MIC values of 6.25 μM. Furthermore, **63** and **102–110** displayed no cytotoxicity against HeLa, A549, K562, and HL-60 when examined by the MTT method.[90]

Terrecoumarins A–C (**111–113**), three previously unreported isocoumarins along with known ones including, periplanetin A (**114**), 6-hydroxy-3-hydroxymethyl-8-methoxyisocoumarin (**115**) (Fig. 12), periplanetin D (**32**) (Fig. 9), and 6,8-dihydroxy-3-hydroxymethylisocoumarin (**60**) (Fig. 10), were reported from the terrestrial-derived fungus *P. oxalicum* 0403 isolated from *Nicotiana sanderae* leaves collected in Yunnan Province, China. Compounds **32**, **60**, and **111–115** were tested for their antiviral activity against tobacco mosaic virus (using ningnamycin as a positive control).

Only **111** displayed strong anti-TMV activity with an inhibition rate of 25.4%, while all the other compounds displayed weak antiviral effect with an inhibition rate in the range of 11.3–18.9%.[91] In addition, the chemical examination of the EtOAc extract of the marine sediment-derived fungus *P. citrinum*, isolated from the marine sediment collected in China, from the Island of Langqi, afforded a previously mentioned (3*R*,4*S*)-6,8-dihydroxy-3,4,5-trimethylisocoumarin (**97**) (Fig. 12). No relevant biological activity was reported for **97** obtained from this species.[92] Furthermore, the chemical investigation of the EtOAc of the marine-derived fungus *P.* sp., (KY620115), isolated from the hydrothermal vent sediment, collected in Taiwan, from the Island Kueishantao, led to the isolation of six isocoumarin derivatives, including two previously reported analogues, aspergillumarins B (**105**) and A (**106**) together with four previously unreported derivatives, penicillisocoumarins A–D (**116–119**) (Fig. 12).

All the isolated compounds displayed no cytotoxicity against HepG2, SMMC-7721, and Bel-7402 cancer cell lines. However, **116–117** and **119** exhibited weak antibacterial activity against *E. coli*, with MIC value of 32 μg mL^{-1}.[93] Chen *et al.,* 2017[94] recorded the chemical examination of the marine-derived fungus *P. chrysogenum* SCSIO 41001 obtained from the deep-sea sediment collected in the Indian Ocean, which led to the isolation of three known compounds, stoloniferol A (**96**), 4-hydroxykigelin (**120**), and diaporthin (**121**) (Fig. 12). Though Xin *et al.,* 2007[85] suggested before that stoloniferol A (**96**) was reported as one pure compound, Chen *et al.,* 2017 [94]succeeded in its isolation in the form of two enantiomers such as stoloniferol A (**96**), *i.e.*, *R*-(−)-stoloniferol A and *S*-(+)-stoloniferol A (**96**). Compounds **96** and **120–121** displayed no activity when examined for their antibacterial, cytotoxic, antiviral, and anti-inflammatory (COX-2) activities.

Dichlorodiaportin (**89**) (Fig. 11) and diaporthin (**121**) (Fig. 12), two previously reported derivatives, along with previously undescribed peniisocoumarins A–J (**122–131**), together with the previously reported (+)-6-*O*-methylcitreoisocoumarin (**132**) (Fig. 13), were obtained from the EtOAc extract of the mangrove-derived fungus *P. commune* QQF-3, isolated from *Kandelia candel* collected in Guangdong municipality, China.

Compounds **89** and **121–132** were tested for their α-glucosidase inhibition activity using acarbose as a positive control. Indeed, **89** and **126–127** displayed mild inhibitory effect with IC_{50} values of 102.4, 110.3, and 158.4 μM, respectively. Moreover, **124**, **128**, and **130–131** were found to be more potent than the positive control acarbose with IC_{50} values of 38.1, 40.5, 78.1, 45.1, and 478.4 μM, respectively. In addition, they were evaluated for their inhibition effect against MptpB, using oleanolic acid and *p*-nitrophenyl phosphate as a positive control/substrate. Compound **128** displayed a moderate inhibitory activity with an IC_{50} value of 20.7 μM, but the remaining compounds exhibited weak or no activity. Moreover, none of the isolated compounds exhibited cytotoxicity against A549, HepG2, HeLa, MCF-7, and HEK293T tumor cell lines using the MTT method.[95] The chemical examination of the EtOAc of the marine-derived fungus *P. piltunense* KMM 4668, isolated from the subaqueous soil collected in Russia from the Island of Sakhalin, led to the isolation of the previously mentioned asperentin, also known as cladosporin (**39**), 5′-hydroxyasperentin (**40**) (Fig. 9). Compound **39** displayed cytotoxicity against the 22Rv1 cancer cell line with a high selectivity index. In addition, it displayed anti-inflammatory effect by decreasing the NO production by 24.1% in LPS-stimulated macrophages.[96]

A previously undescribed penicitol D (**133**), along with four known derivatives, stoloniferol B (**97**) (Fig. 12), (3*S*,4*S*)-sclerotinin A (**134**), (3*R*)-6-methoxymellein (**135**), and (3*R*)-6-methoxy-7-chloromellein (**136**) (Fig. 13), were isolated from the deep sea-derived fungus *P. citrinum* NLG-S01-P1. Compounds **97** and **133–136** were tested for their antibacterial activity using continuous dilution in 96-well plates method against *V. rotiferianus* (MCCC E385), MRSA (ATCC 43300, CGMCC 1.12409), *V. campbellii* (MCCC E333), and *V. vulnificus* (MCCC E1758). Among them, **133** exhibited a potent antibacterial effect toward MRSA (ATCC 43300, CGMCC 1.12409), and **134** showed relatively stronger effect in comparison with the other compounds. In addition, **97** and **133–136** displayed weak cytotoxic effect when tested for their cytotoxicity against A549 and HeLa tumor cell lines (using the Cell Counting Kit-8 (CCK-8) (DOJINDO) method and as a positive control, doxorubicin was used).[97]

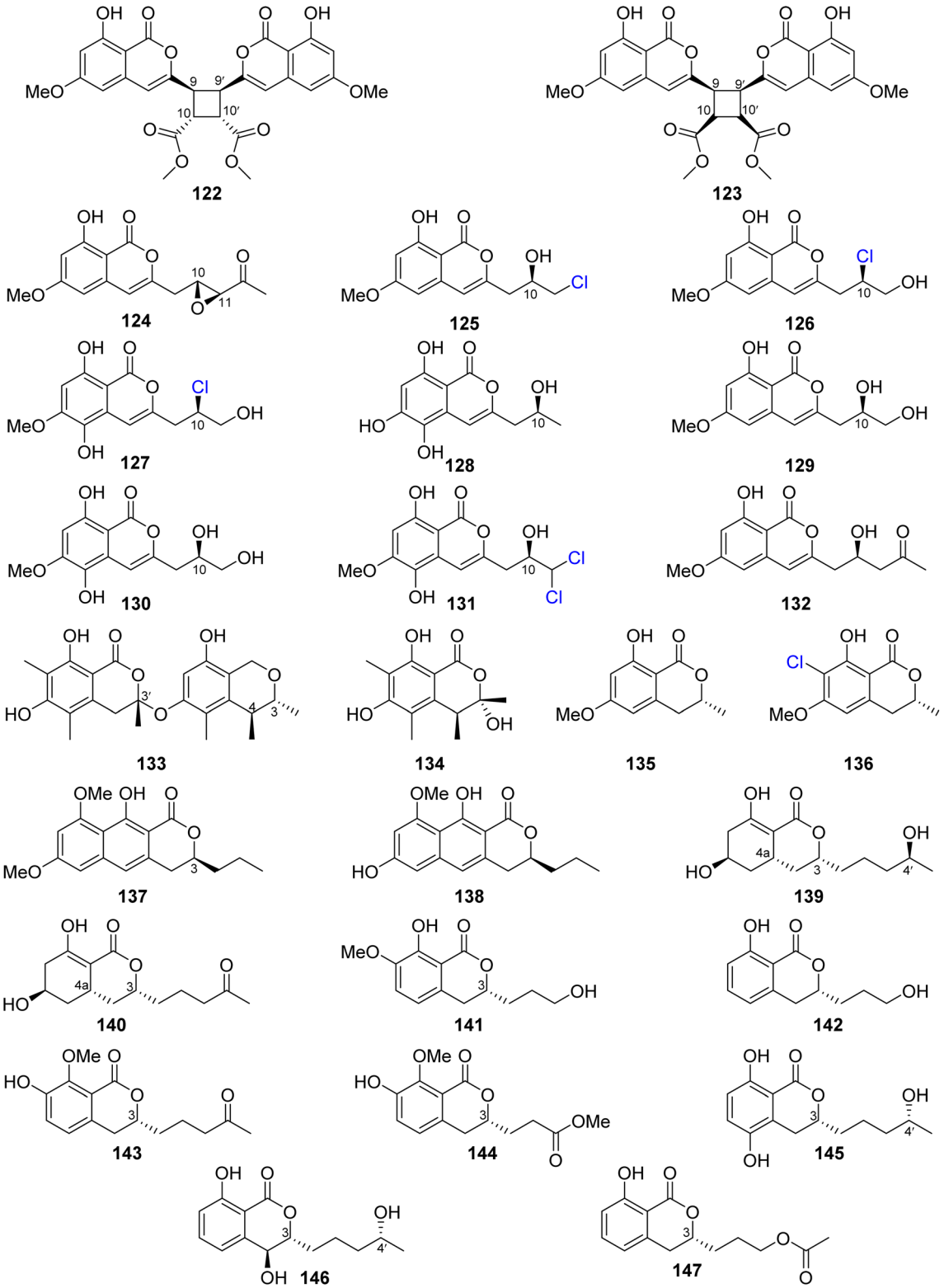


Fig. 13 Chemical structures of 122–147.

A chemical investigation of the sponge-derived fungus *P.* sp., XWS02F62, isolated from the marine sponge *Callyspongia* sp., collected in Guangdong, China, afforded one previously unrecorded isocoumarin, named 7-*O*-methylpenicitor A (**137**), along with previously reported aspergillumarins B (**105**) and A (**106**), and penicitor A (**138**) (Fig. 13). Compounds **105**, **106**, and **137**–**138** were examined for their cytotoxicity against MDA-MB-231, 143B, C4–2B, MGC803, and A549 cancer cell lines. Only **138**

exhibited a moderate inhibitory activity against MDA-MB-231 and C4–2B tumor cells with inhibition rates of 31.3% and 25.7% at a concentration of 5 μM, respectively.[98] Three previously mentioned derivatives, penicimarin C (**104**), aspergillumarin A (**106**), and (*R*)-3-(3-hydroxypropyl)-8-hydroxy-3,4-dihydroisocoumarin (**142**) (Fig. 12), along with eight new derivatives, peniciisocoumarins A (**139**), B (**140**), C (**141**), D (**143**), E (**144**), F (**145**), G (**147**), and H (**146**) together with the previously described (Fig. 13), were obtained from the marine-derived fungus *P.* sp., TGM112, isolated from the mangrove plant *B. sexangula* var. *rhynchopetala*, collected in China, from the South China Sea.

Compounds **139**, **140**, **144**, and **146** displayed insecticidal effect against *H. armigera* Hubner (using azadirachtin as a positive control) with IC_{50} values of 200, 200, 100, and 100 μg mL^{-1} respectively. Moreover, none of the isolated compound exhibited cytotoxicity toward A549, HeLa, and HepG2 tumor cell lines. Furthermore, they displayed no antibacterial ability against *E. coli* (ATCC 25922), *S. aureus* (ATCC 25923), Methicillin-resistant *S. aureus* MRSA (ATCC 33591), *Bacillus cereus* (ATCC 11778), *V. parahaemolyticus* (ATCC 17802), and *V. alginolyticus* (ATCC 17749), using the microplate assay method and ciprofloxacin as the positive control. In addition, they showed no anti-inflammatory properties as they displayed no inhibitory activity against nitric oxide (NO) production in lipopolysaccharide (LPS)-induced RAW 246.7 mouse macrophages.[99]

The chemical analysis of the EtOAc extract of the mangrove-derived endophytic fungus *P. coffeae* MA-314 isolated from *Laguncularia racemosa* leaves collected in China from the Island of Haninan afforded five previously reported known derivatives including 6,8-dihydroxy-3-methylisocoumarin (**27**), 4,6-dihydroxy-3,9-dehydromellein (**61**), 3-methoxy-6,8-dihydroxy-3-methyl-3,4-dihydroisocoumarin (**150**), *cis*-4,6-dihydroxymellein (**151**), and *O*-demethyldiaporthin (**152**) along with two previously unreported enantiomers, penicoffrazins B (**148**) and C (**149**) (Fig. 14). The isolated compounds were tested for their antioxidant activity by measuring their ability to scavenge the DPPH free radical, and butylated hydroxytoluene (BHT) was used as a positive control. Only **150** displayed weak antioxidant effect with $IC_{50} = 159$ μM; however, the remaining compounds exhibited almost no antioxidant activity with IC_{50} >900 μM.[100] A previously described isocoumarin, monaschromone (**153**), along with three previously non-recorded derivatives, namely, (*S*)-6,8-dihydroxy-5-(methoxymethyl)-3,7-dimethylisochroman-1-one (**154**), (*S*)-6,8-dihydroxy-3,5,7-trimethyl-isochroman-1-one (**155**), and (*R*)-2-chloro-3-(8-hydroxy-6-methoxy-1-oxo-1*H*-isochromen-3-yl) propyl acetate (**156**) (Fig. 14), was isolated from the MeOH extract of the marine endophytic fungus *P.* sp., YYSJ-3, isolated from *Heritiera littoralis* steam, collected from Guangdong Province, China. Compounds **153–156** were examined for their inhibitory activity toward α-glucosidase activity. Compound **153** displayed no effect, but **154–155** exhibited weak

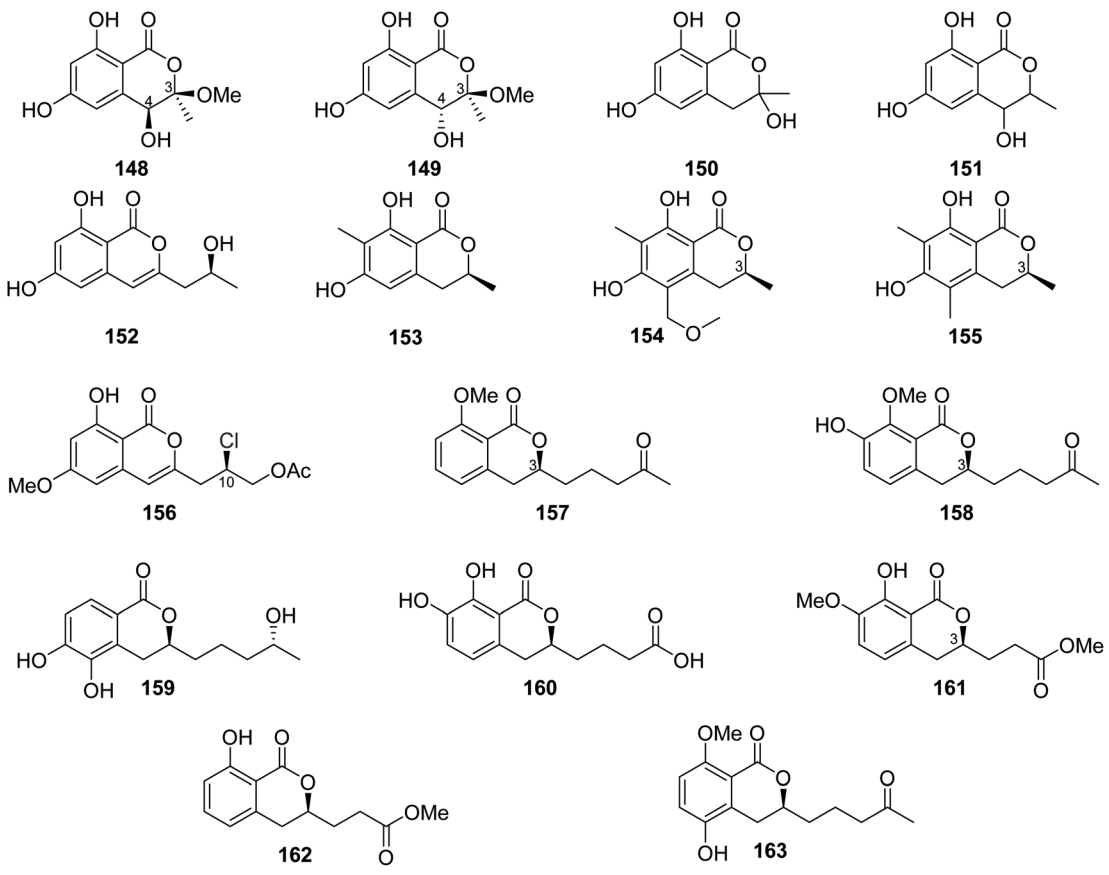
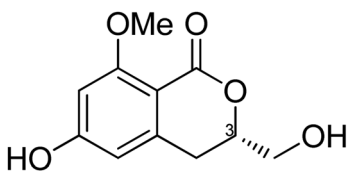


Fig. 14 Chemical structures of **148–163**.

inhibition activity with IC_{50} values of 309.6 and 237.4 μmol L^{-1}, respectively. In addition, among them, **156** was the most potent enzyme inhibitor with an IC_{50} value of 100.6 μmol L^{-1}.[101] Phytochemical examination of the marine-derived fungus *P.* sp., XR046, obtained from the soil collected from the area of Xinren coal area in the province of Guizhou, China, led to the isolation of five known derivatives, including penicimarins B–C (**103–104**), penicillisocoumarin A (**116**) (Figure 12), 5,6-dihydroxy-3*R*-(4*S*-hydroxypentyl)-isochroman-1-one (**159**), and 3*R*-(7,8-dihydroxy-1-oxoisochroman-3-yl)propanoic acid (**160**) (Fig. 14), along with two previously undescribed congeners, namely, 3*R*-8-methoxy-3-(4-oxo-pentyl) isochroman-1-one (**157**) and 3*R*-7-hydroxy-8-methoxy-3-(4-oxopentyl) isochroman-1-one (**158**) (Fig. 14). Compounds **103–104** and **157–160** were tested for their antimicrobial activity against *C. albicans* ATCC 5314, *S. epidermidis*, *E. coli* ATCC 25922, *S. aureus* ATCC 25923, and *B. subtilis* ATCC 6633. While **103–104** and **157–160** displayed mild antifungal effect against *C. albicans* ATCC 5314, **103–104** and **157–159** displayed weak antibacterial ability against *S. epidermidis*. Moreover, only **159–160** showed weak antibacterial activity toward *B. subtilis* ATCC 6633. In addition, among all the tested compounds, only **160** displayed weak antibacterial activity against *E. coli* ATCC 25922. The remaining isolated metabolites were inactive against *S. aureus* ATCC 25923.[102] A previously undescribed penicimarin N (**161**) along with three previously reported derivatives, penicimarins I–H (**162–163**) (Fig. 14) and aspergillumarin A (**106**) (Fig. 12), was obtained from the EtOAc extract of the mangrove-derived fungus *P.* sp., TGM112 isolated from *B. sexangula* var. *rhynchopetala*, collected South China Sea, China. Compounds **106** and **161–163** were evaluated for their antioxidant activity (using Trolox as a positive control), antibacterial activity against *S. aureus*, methicillin-resistant *S. aureus*, *S. albus*, *V. alginolyticus*, and *V. parahemolyticus* as well as α-glucosidase initiatory activities. While **163** showed weak antioxidant ability, **161** displayed strong antioxidant effect with IC_{50} values of 9.0 and 0.1 mM, respectively. None of the examined metabolites exhibited antibacterial activity against the bacterial strains under investigation. Among the tested isocoumarin derivatives, **161** displayed moderate enzyme inhibitory effect toward α-glucosidase.[103]

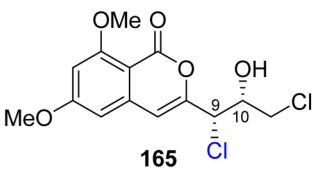
3.6.1.3. Fungi of the genus Eupenicillium. A chemical study of the marine-derived fungus *Eupenicillium* sp. 6A–9 obtained from the inner part of the marine sponge *Plakortis simplex*, collected from the Island of Yongxing, China, afforded the previously unreported isocoumarin derivative eupenicillin A (**164**) (Fig. 15). Compound **164** displayed no antibacterial activity against *S. aureus* ATCC 25923, methicillin-resistant *S. aureus* (MRSA) ATCC4330, and *A. baumannii* ATCC19606, but it exhibited moderate cytotoxic effect against MCF7 with an IC_{50} value of 53.48 μM.[104]

3.6.1.4. Fungi of the genus Hamigera. A previously described derivative, 8-methyl-11,11-dichlorodiaporthin (**83**) (Fig. 11), alongwith with two previously unidentified chlorinated congeners, (9*R**)-8-methyl-9,11-dichlorodiaporthin (**165**) and (9*S**)-8-methyl-9,11-dichlorodiaporthin (**166**) (Fig. 16), was isolated from the soil-derived fungus *Hamigera fusca* NRRL 35721, obtained from a soil sample treated with phenol collected from a banana tree in the Island of Grande Comore. Compounds **83** and **165–166** were tested for their cytotoxic activity against CCD25sk, SHSY5, MiaPaca-2, MCF-7, HepG2, A2058, and A549 cancer cell lines colorimetrically using the MTT assay and doxorubicin as a positive control. Compound **83** displayed moderate cytotoxicity toward the CCD25sk tumor cell line with a CC_{50} value of 27.0 μM. Furthermore, **83** and **165–166** exhibited moderate cytotoxicity against SHSY5y cells with the CC_{50} values ranging from 19.4 to 36.2 μM.[105]



164

Fig. 15 Chemical structure of **164**.



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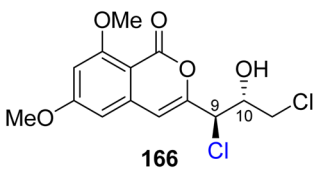
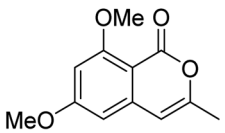


166

Fig. 16 Chemical structures of **165–166**.



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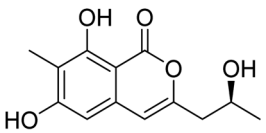

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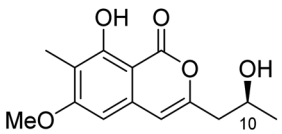


169

Fig. 17 Chemical structures of **167–169**.

3.6.1.5. Fungi of the genus Monascus. A chemical inspection of the marine-derived fungus *Monascus ruber* BB5, isolated from the shellfish *Meretrix* collected in Yangjiang, from the Island of Hailing, China, led to the isolation of two previously described derivatives 6,8-dimethoxy-3-methylisocoumarin (**167**) and lunatinin (6,8-dihydroxy)-3-(2-hydroxypropyl)-7-methyl-1*H*-isochromen-1-one (**168**), together with one previously unreported derivative (*S*)-8-hydroxy-3-(2-hydroxypropyl)-6-methoxy-7-methyl-1*H*-isochromen-1-one, also known as monarubin B (**169**) (Fig. 17).

Compounds **167–168** were examined for their cytotoxic activity toward CNE1, CNE2, SUNE1, HONE1, HepG2, and QGY7701 cancer cell lines (using the MTT colorimetric assay and hirsutanol A as a positive control). Though all the isolated compounds displayed no cytotoxicity against CNE1 and HONE1, **168–169** showed weak cytotoxic effect toward CNE2 with IC_{50} values of 85.66 and 75.70 μM, respectively. Furthermore, they exhibited weak to potent cytotoxicity against the rest of the examined cell lines with IC_{50} values in the range of 0.71–72.07 μM.[106]

3.6.2. Fungi of the family Trichocomaceae

3.6.2.1. Fungi of the genus Talaromyces. A previously unreported isocoumarin derivative, named 8-hydroxy-3-(4-hydroxypentyl)-3,4-dihydroisocoumarin (**170**) (Fig. 18), was discovered from the plant-derived fungus *Talaromyces verruculosus* isolated from *Stellera chamaejasme* L. rhizosphere soil, collected from the Mountains of Qinling in the Province of Shaanxi, China. Compound **170** showed potent antibacterial ability against *E. coli* and *S. aureus* with MIC values of 2.5 and 5.0 μg mL^{-1}, respectively. Furthermore, **170** displayed weak antifungal activity against *A. solani, V. mali, C. lunata*, and *B. berengeriana* with the growth inhibition percentage ranging from 87.2 to 97.3%.[107] A chemical investigation of the marine sponge-derived fungus *T. tratensis*, obtained from the marine sponge *Mycale* sp., collected from the coral reefs of the Island of Samae San, Thailand, led to the isolation of the unreported previously tratenopyrone (**171**) (Fig. 18). Compound **171** displayed neither antibacterial nor anti-quorum sensing activities. In addition, it showed no cytotoxic and fungicidal activities.[108] Five previously unreported isocoumarin derivatives including **172**, **173**, 6-hydroxy-8-methoxy-3,4-dimethylisocoumarin (**174**), *S*-(−)-5-hydroxy-8-methoxy-4-(10-hydroxyethyl)-isocoumarin (**175**), and **180**, along with ten previously described compounds, including *S*-(−)-5,6,8-trihydroxy-4-(10-hydroxyethyl) isocoumarin (**176**), 6-hydroxy-4-hydroxymethyl-8-methoxy-3-methyl-isocoumarin (**177**), 3,4-dimethyl-6,8-dihydroxyisocoumarin (**178**) and sescandelin (**179**) (Fig. 18), penicimarins B (**103**), C (**104**), aspergillumarins B (**105**), A (**106**), sescandelin B (**107**), and 5,6-dihydroxy-3*R*-(4*S*-hydroxypentyl)-isochroman-1-one (**159**), were isolated from the marine endophytic fungus *T. amestolkiae,* isolated from the mangrove leaf of *Kandelia obovate*, collected from the Guangdong Province, China. Compounds **103–107**, **159**, and **172–180** exhibited moderate to weak inhibitory activities toward the enzyme α-glucosidase with IC_{50} ranging from 17.2 to 585.7 μM. Moreover, all the isolated compounds displayed no antibacterial activity when tested against *S. aureus*, *S. epidermidis*, *E. coli*, *K. pneumoniae*, and *B. subtilis*.[23] A chemical investigation of the methanolic extract of the mangrove endophytic fungus *T.* sp., SCNU-F0041, obtained from *Kandelia* leaf, collected from Guangdong Province, China, afforded three previously mentioned aspergillumarins B (**105**), A (**106**) (Fig. 12), and 3*R*-(7,8-dihydroxy-1-oxoisochroman-3-yl) propanoic acid (**160**) (Fig. 14), along with a previously undescribed isocoumarin derivative

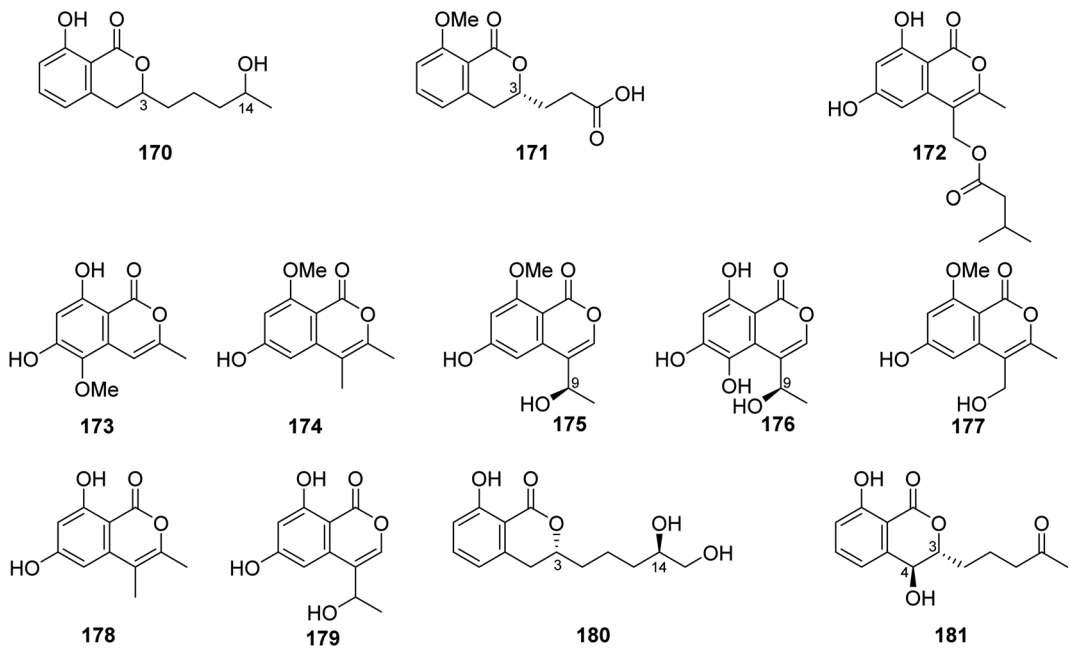


Fig. 18 Chemical structures of **170–181**.

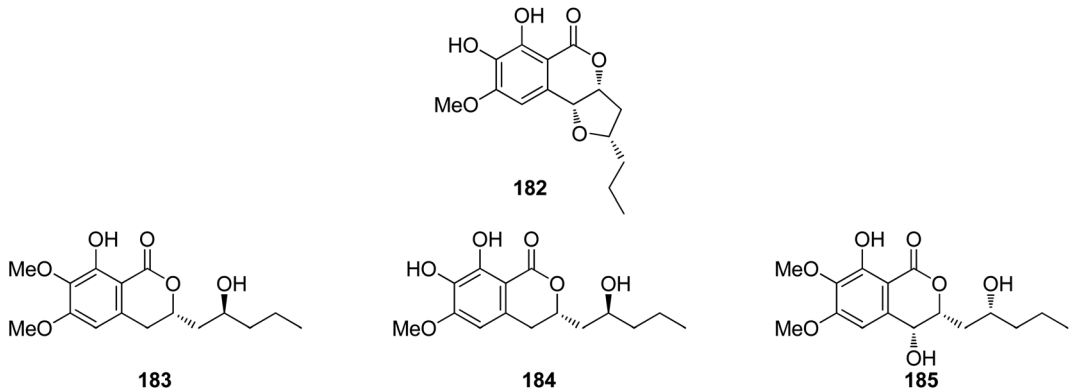


Fig. 19 Chemical structures of 182–185.

aspergillumarin C (**181**) (Fig. 18). Compound **181** displayed no inhibitory effect toward AChE (acetylcholinesterase).[109]

3.7. Fungi of the order Glomerellales

3.7.1. Fungi of the family Glomerellaceae

3.7.1.1. Fungi of the genus Colletotrichum. A previously mentioned derivative **4** (Fig. 3), along with other four previously reported isocoumarin derivatives, namely, monocerin demethylated (**182**), fusarentin-6,7-dimethyl ether (**183**), fusarentin-6-methyl ether (**184**), and fusarentin derivative (**185**) (Fig. 19), were obtained from the endophytic fungus *Colletotrichum* sp., CRI535-02, isolated from *Piper ornatum*, collected from the Province of Surat Thani. Compounds **4** and **182–185** were tested for their cytotoxicity against the HepG2, HuCCA-1, and A549 tumor cell lines (using the MTT assay) as well as toward the MOLT-3 cancer cell line (using the XTT assay). Though all the isolated compounds exhibited weak cytotoxicity or no activity against the examined cell lines, **182** displayed potent anticancer ability toward HepG2 with an IC_{50} value of 23.7 μM when compared with the positive control etoposide (IC_{50} = 15.8 μM). In addition, the potential cancer chemo-preventive characteristics of the isolated compounds were examined by determining their antioxidant activity and their inhibition activity against aromatase (CYP19). Indeed, among the isolated compounds, **182** and **184** displayed moderate DPPH free radical scavenging activities with IC_{50} values of 23.4 and 16.4 μM, respectively. In addition, **182** and **184** showed significant inhibitory activity against the formation of the superoxide anion radical with IC_{50} values of 52.6 and 4.3 μM, respectively. Moreover, none of the isolated compounds suppressed superoxide anion generation

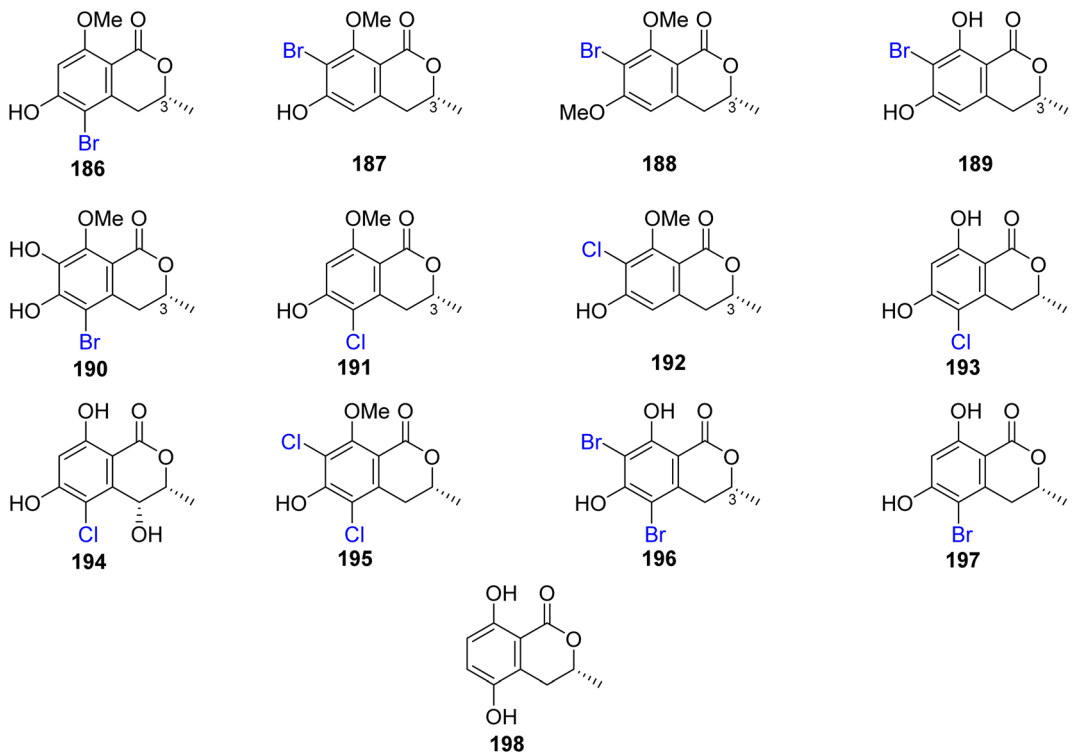


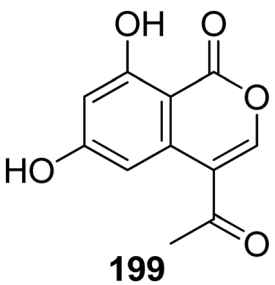
Fig. 20 Chemical structures of 186–198.

induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in differentiated HL-60 human promyelocytic leukemia cells. Furthermore, compounds **4**, **182**, and **183** displayed potent ORAC antioxidant properties with ORAC units in the range of 10.8–14.4 ORAC units.[110]

3.8. Fungi of the order Helotiales

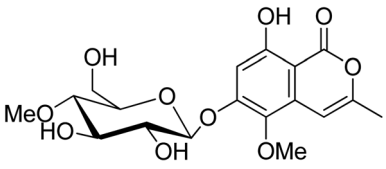
3.8.1. Fungi of the family Lachnaceae

3.8.1.1. Fungi of the genus Lachnum. The chemical examination of the endophytic fungus *Lachnum palmae* isolated from *Przewalskia tangutica* Maxim. fresh tissue, collected Linzhou, China, led to the isolation of the previously mentioned derivatives, including *trans*-4-hydroxymellein (**7**), mullein (**25**), *cis*-4-hydroxymellein (**26**), (*R*)-6-hydroxymellein (**77**), and (3*R*)-6-methoxymellein (**135**), along with seven previously unreported palmaerones A–G (**186–192**), together with six previously described compounds, namely, (*R*)-5-cholro-6-hydroxymellein (**193**), (3*R*,4*R*)-5-cholro-4,6-dihydroxymellein (**194**), palmaerins A (**195**), B (**196**), D (**197**), and (*R*)-5-hydroxymellein (**198**) (Fig. 20). Compounds **186–192** were examined for their antimicrobial properties against three fungal strains, namely, *C. neoformans*, *Penicillium* sp., and *C. albicans* and two bacterial strains *B. subilis* and *S. aureus* (using the broth microdilution method, and amphotericin B and kanamycin as a positive controls). Generally, the brominated derivatives were found to be more potent as antimicrobial agents than the chlorinated congeners. Among them, **190** displayed the most powerful antimicrobial effect against the examined fungal and bacterial strains with MIC value ranging from 10 to 55 μg mL^{-1}. In addition, **186–192** were tested for their anti-inflammatory activity (SMT; 2-methyl-2-thiopseudourea sulphate was used as a positive control). Compounds **186** and **190** exhibited mild no inhibitory activity with IC_{50} values of 26.3 and 38.7 μM, respectively. Further, only **190** displayed a weak cytotoxicity toward HepG2 with an IC_{50} value of 42.8 μM.[111]



199

Fig. 21 Chemical structure of **199**.



200

Fig. 22 Chemical structure of **200**.

3.9. Fungi of the order Hypocreales

3.9.1. Fungi of the family Bionectriaceae

3.9.1.1. Fungi of the genus Bionectria. A previously described isocoumarin derivative AGI-7 (**199**) (Fig. 21) was isolated from the fungus *Bionectria* sp. (MSX 47401), isolated from leaf litter and leaves collected from a humid mountain forest. Compound **199** displayed no cytotoxicity against NCI-H460, MCF-7, and SF-268 cancer cell lines.[112]

3.9.1.2. Fungi of the genus Clonostachys. Chemical examination of the EtOAc extract of the marine-derived fungus *Clonostachys* sp. (AP4.1) isolated from the marine sponge *Axinella polypoides*, collected at a depth of 30 m from İlyosta–Ayvalık, Turkey, led to the isolation of two previously mentioned isocoumarin derivatives, dichlorodiaportin (**89**) and peniisocoumarin D (**125**). Compound **125** displayed no cytotoxicity against the L5178Y cancer cell line.[113]

3.9.2. Fungi of the family Clavicipitaceae

3.9.2.1. Fungi of the genus Conoideocrella. A previously unreported isocoumarin glycoside (**200**) (Fig. 22) was isolated from the organic extract of the insect pathogenic fungus *Conoideocrella tenuis* BCC 18627, obtained from Hemiptera scale, collected in Nakhon Nayok Province from the national park of Khao Yai. In addition, as a result of its limited abundance, **200** was not subjected to any relevant biological activity test.[114]

3.9.2.2. Fungi of the genus Metarhizium. The chemical exploration of the soil-derived fungus *Metarhizium anisopliae* (No. DTH12-10), isolated from a soil sample collected in China from the Province of Hunan, led to the isolation of eight previously undescribed isocoumarin glycosides (Fig. 23), namely, (3*S*)-6-*O*-(4′-*O*-methyl-6′-acetyl-β-D-glucopyranoside)-7-*O*-methyl-8-hydroxyl-3-[(3*E*)penta-3-enyl]-3,4-dihydroisocoumarin (**201**), (3*S*)-7-*O*-(4′-*O*-methyl-β-D-glucopyranoside)-6,8-dihydroxyl-3-[(3*E*)penta-3-enyl]-3,4-dihydroisocoumarin (**202**), (3*S*)-6-*O*-(4′-*O*-methyl-β-D-glucopyranoside)-7-*O*-methyl-8-hydroxyl-3-[(3*E*)-pent-3-enyl]-3,4-dihydroisocoumarin (**203**), (3*S*)-6-*O*-(4′-*O*-methyl-β-D-glucopyranoside)-8-hydroxyl-3-[(3*E*)-pent-3-enyl]-3,4-dihydroisocoumarin (**204**), (3*S*)-6-*O*-(4′-*O*-methyl-β-D-glucopyranoside)-5,8-dihydroxyl-3-[(3*E*)-pent-3-enyl]-3,4-dihydroisocoumarin (**205**), 6-*O*-(4′-*O*-methyl-β-D-glucopyranoside)-7-*O*-methyl-8-hydroxyl-3-[(3*E*)-penta-3-enyl]-isocoumarin (**206**), (3*R*)-6-*O*-(4′-*O*-methyl-β-D-glucopyranoside)-8-hydroxyl-3-[(1*E*,3*E*)-penta-1,3-dienyl]-dihydroisocoumarin (**207**), and (3*R*)-6-*O*-(4′-*O*-methyl-β-D-glucopyranoside)-7-*O*-methyl-8-hydroxyl-3-[(1*E*,3*E*)-penta-1,3-dienyl]-dihydroisocoumarin (**208**). Compounds **201–208** were tested for their biofilm and virulence factor secretion inhibition activities of toward *P. aeruginosa* strain PAOA (clinical isolates). Among them, **201** displayed antibacterial effect in comparison with (*Z*)-4-bromo-5-(bromomethylene)-2(5*H*)-furanone (BF as positive control).[115]

3.9.2.3. Fungi of the genus Torrubiella. Two previously described isocoumarin derivatives, including 6,8-dihydroxy-3-methylisocoumarin (**27**) and 6,8-dihydroxy-3-

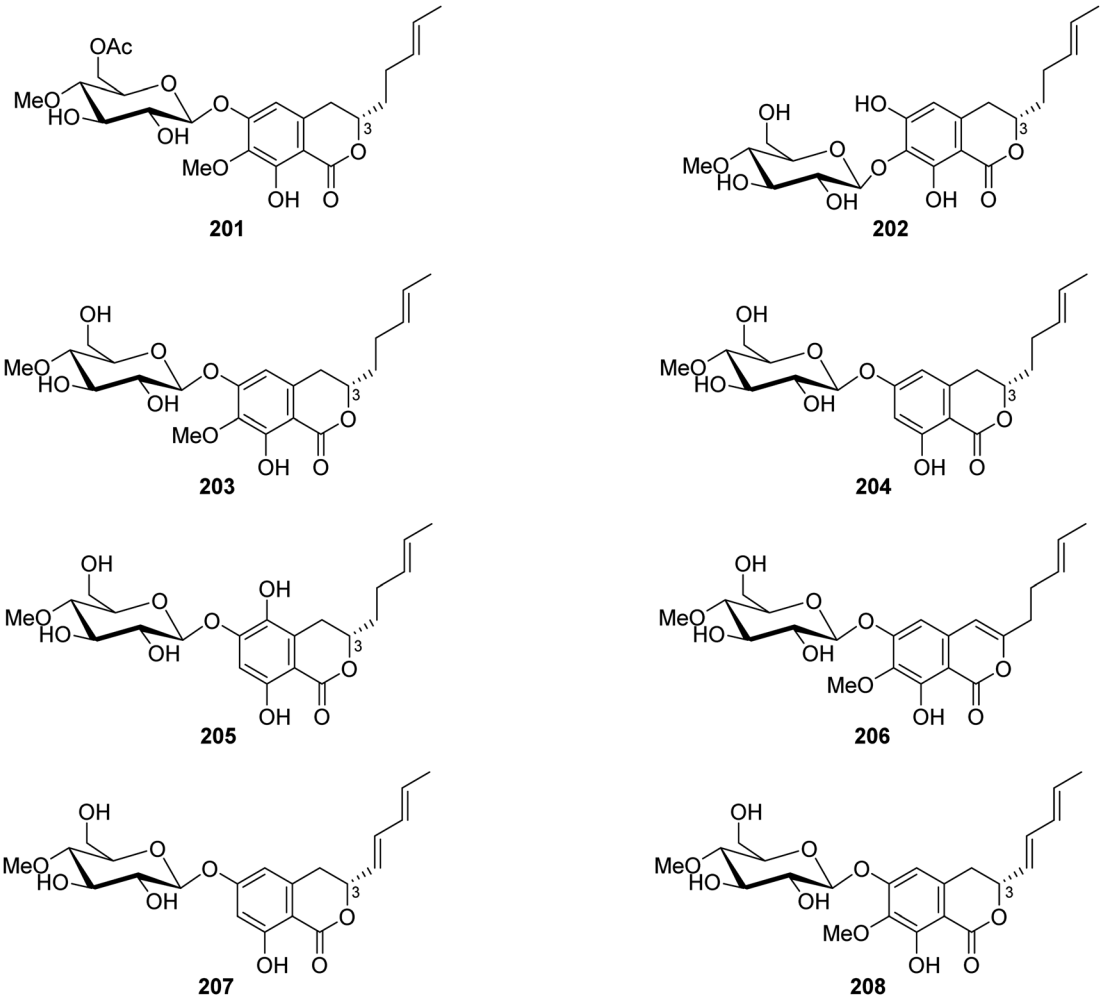


Fig. 23 Chemical structures of **201–208**.

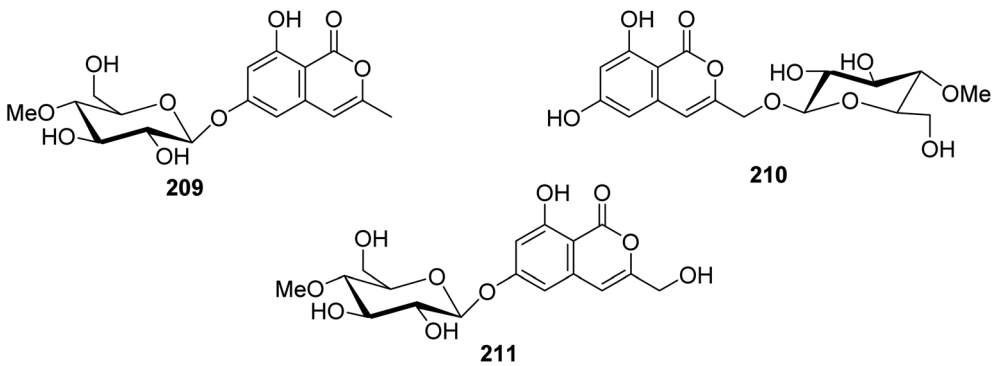


Fig. 24 Chemical structures of **209–211**.

hydroxymethylisocoumarin (**60**), along with three previously undescribed isocoumarin glucosides **209–211** (Fig. 24), were obtained from the fungus *Torrubiella tenuis* BCC 12732, isolated from the scale of Homoptera, collected from the province of Chiang Mai, Thailand. Compounds **27**, **60**, and **209–211** were tested for their antimalarial, anti-mycobacterium, antiviral (against Herpes simplex virus-1), and cytotoxic activities against KB, MCF-7, NCI-H187, and Vero cells. Though all the isolated compounds displayed no biological activity, **60** displayed mild growth inhibitory activity against *Mycobacterium tuberculosis* H37Ra and Herpes simplex virus-1 with IC_{50} values of 25 and 50 μg mL^{-1}, respectively.[116]

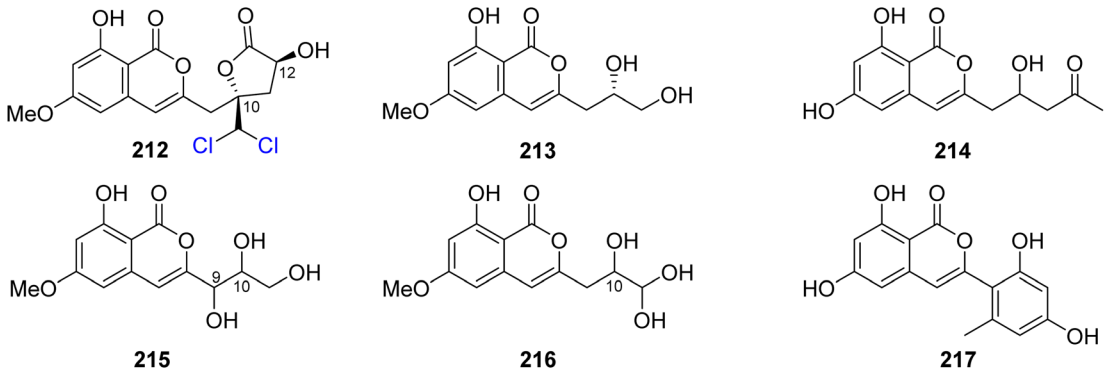


Fig. 25 Chemical structures of 212–217.

3.9.3. Fungi of the family Hypocreaceae

3.9.3.1. Fungi of the genus Trichoderma. Dichlorodiaportinolide (**212**), a previously undescribed derivative along with three previously reported congeners, including diaportinol (**213**), dichlorodiaportin (**89**), and diaporthin (**121**) (Fig. 25), was obtained from the endophytic fungus *Trichoderma* sp., 09, isolated from *Myoporum bontioides* A. Gray roots, collected from Guangdong Province, China. Compounds **121** and **213** were not tested for any relevant biological activity due to their minute available quantities; however, **89** and **212** were tested for their antifungal activity against a list of phytopathogenic fungi, including *C. musae*, *F. graminearum*, *P. italic*, and *R. solani* (using the broth dilution method and carbendazim as a positive control). Compound **212** displayed strong to mild antifungal properties against *R. solani* and *C. musae*, with MIC values of 6.25 and 25 μg mL^{-1}, respectively. In addition, **89** displayed weak antifungal activity against *R. solani* and *C. musae*, with MIC values of 150 μg mL^{-1}.[117] A chemical investigation of the marine-derived fungus *T.* sp., HPQJ-34, isolated from the marine sponge *Hymeniacidon perleve*, collected from the Island of Dongji, China, led to the isolation of two previously described derivatives, including citreoisocoumarin (**214**) (Fig. 25) and (+)-6-*O*-methylcitreoisocoumarin (**132**). Compounds **132** and **214** were not subjected to any relevant biological activity test.[118] In addition, two previously unreported isocoumarin derivatives (**215**) and (**216**) (Fig. 25), were recovered from the EtOAc extract of the endophyte fungus *T. harzianum* isolated from the fresh leaves of *F. elastic*. The antimicrobial activity of **215–216** was tested against *B. subtilis*, *C. albicans*, *E. coli*, *P. aeruginosa*, and *S. aureus* (using the well diffusion method, and chloramphenicol and fluconazole as positive controls). Compounds **215–216** showed moderate antibacterial effect against *E. coli* with MIC values of 32 μg mL^{-1}.[119] A chemical exploration of the marine-derived fungus *T. citrinoviride* A-WH-20-3, isolated from the inner tissue marine alga *Laurencia okamurai*, collected from the coast of Weihai, China, led to the isolation of a previously undescribed trichophenol A (**217**) (Fig. 25). Compound **217** displayed anti-microalgal activity against the marine phytoplankton *Heterosigma akashiwo*, *Prorocentrum donghaiense*, *Karlodinium veneficum*, and *Chattonella marina* with IC_{50} values of 9.1, 5.9, 20, and 4.4 μg mL^{-1}, respectively. Furthermore, it displayed antibacterial activity against the marine-derived pathogenic bacterial strains including *P. citrea*, *V. splendidus*, *V. harveyi*, *V. anguillarum*, and *V. parahaemolyticus* with an inhibition zone of 21, 7.5, 7.0, 8.0, and 7.0 mm, respectively, at a concentration of 50 μg per disk.[120]

3.9.4. Fungi of the family Nectriaceae

3.9.4.1. Fungi of the genus Fusarium. Four previously unreported isocoumarin derivatives, including fusarimarins A–C (**218–220**), along with a previously described aspergisocoumrin A (**221**) (Fig. 26), were isolated from the mangrove-derived fungus

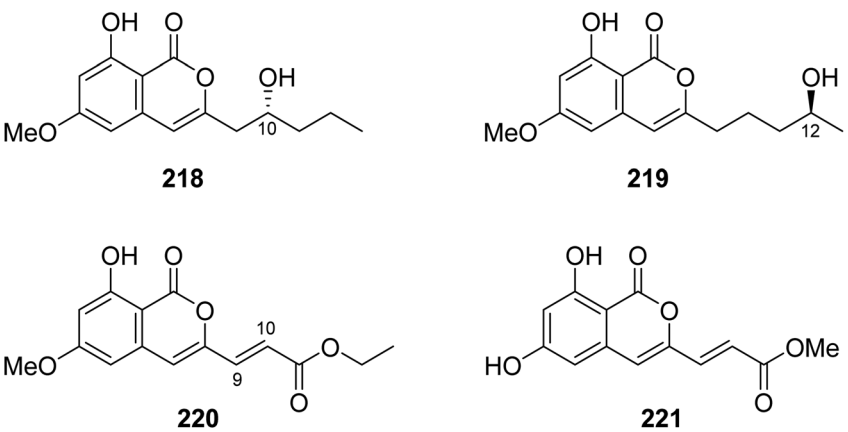


Fig. 26 Chemical structures of 218–221.

Fig. 27 Chemical structures of 222–223.

Fusarium sp., 2ST2, isolated from the leaves of *Kandelia candel*, collected from the South China Sea, China. Compounds **219–220** were tested for their cytotoxicity against A549, HELA, KYSE150, PC-3, and MDA-B-435 tumor cell lines (using the MTT method and DDP as a positive control). Only **221** displayed significant cytotoxicity toward A549 and MDA-B-435, with IC_{50} values of 6.2 and 2.8 μM, respectively. In addition, **220** showed weak cytotoxicity against MDA-B-435, with an IC_{50} value of 30.5 μM.[121]

3.9.4.2. Fungi of the genus Nectria. 3,4-dimethyl-6,8-dihydroxyisocoumarin (**178**), a previously mentioned derivative, along with two previously undescribed congeners, namely, nectriapyrones A–B (**222–223**) (Fig. 27), was obtained from the endophytic fungus *Nectria pseudotrichia* 120-1NP, isolated from *Gliricidia sepium* stem, collected from the forest of Wanagama, Indonesia. Compounds **178** and **222–223** were tested for their cytotoxicity, phytotoxicity, and antimicrobial activity, but they showed no activity.[122]

3.9.5. Unidentified in the level of the family

3.9.5.1. Fungi of the genus Acremonium. Phytochemical examination of the mangrove-derived fungus *Acremonium* sp., PSU-MA70, isolated from *R. apiculata* branch, collected from the Province of Satun, Thailand, afforded seven previously unreported isocoumarin derivatives, namely, acremonones B–H (**224–230**) (Fig. 28). Indeed, due to the lack of isolated quantities, only **227**, was examined for its antifungal activity against *C. albicans* NCPF3153 and *C. neoformans* ATCC90113, but it showed no activity.[123]

3.10. Fungi of the order Hysteriales

3.10.1. Fungi of the family Hysteriaceae

3.10.1.1. Fungi of the genus Rhytidhysteron. Two pairs of previously unreported enantiomers (±) **231** and (±) **232** (Fig. 29)

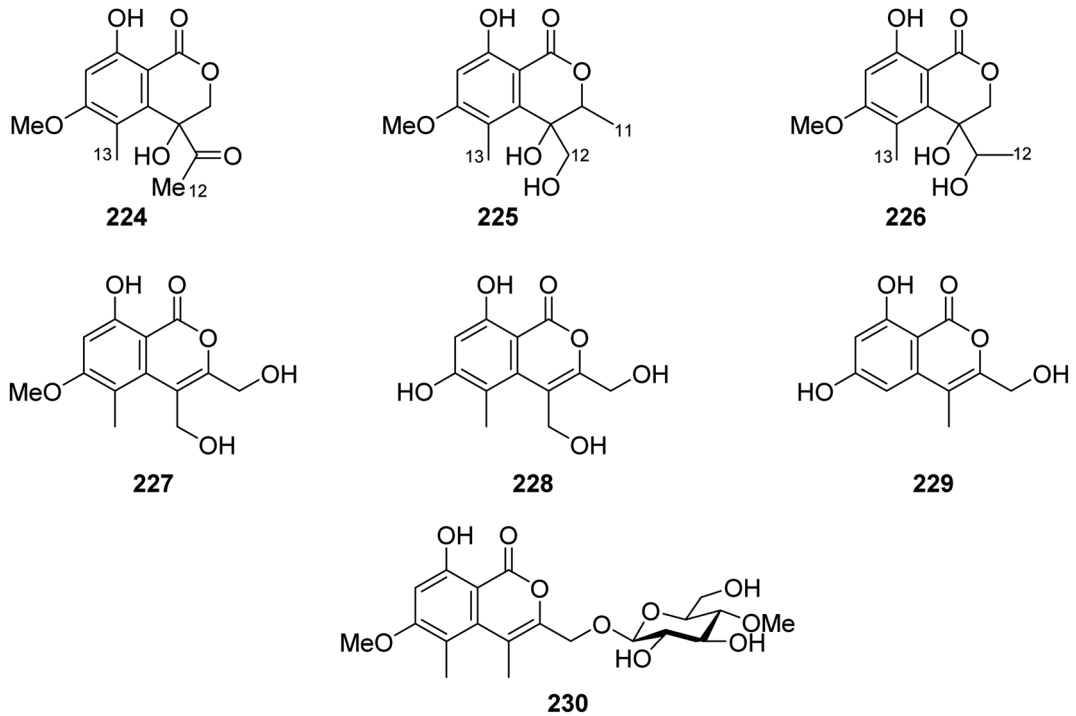


Fig. 28 Chemical structures of 224–230.

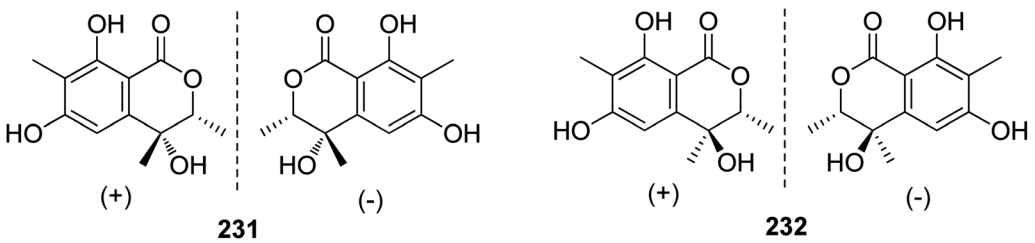


Fig. 29 Chemical structures of 231–232.

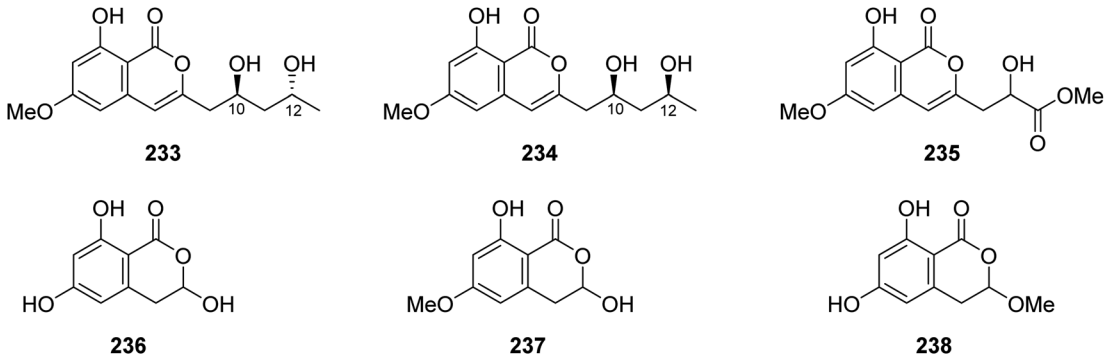


Fig. 30 Chemical structures of **233–238**.

were isolated from the fungus *Rhytidhysteron* sp., BZM-9. Compounds **231–232** displayed no cytotoxicity.[124]

3.11. Fungi of the order Mucorales

3.11.1. Fungi of the family Mucoraceae

3.11.1.1. Fungi of the genus Mucor. Chemical inspection of the soil-derived fungus *Mucor* sp., (No. XJ07027-5), obtained from a mountainous soil collected from the region of Sinkiang Uyghur, China, led to the discovery of three previously unreported mucorisocoumarins A–C (**233–235**), along with seven previously described isocoumarin derivatives including **236–238** (Fig. 30), dichlorodiaportin (**89**), (+)-6-methylcitreoisocoumarin (**132**), *O*-demethyldiaporthin (**152**), and diaportinol (**213**). Compounds **89**, **152**, **213**, and **233–23**, were tested for their toxicity using a zebrafish model. Only **235** displayed toxicity toward the zebrafish embryos, while all the other compounds showed no toxicity.[125]

3.12. Fungi of the order Onygenales

3.12.1. Fungi of the family Spiromastigoidaceae

3.12.1.1. Fungi of the genus Spiromastix. Three previously unreported isocoumarin derivatives, namely, spiromastols G–I (**239–241**), (Fig. 31), were obtained from the EtOAc extract of the deep sea-derived fungus *Spiromastix* sp. MCCC 3A00308, isolated from the sediment of the deep ocean, collected from the South Atlantic Ocean. Compounds **239–240** were tested for their antibacterial activity against *X. vesicatoria* ATCC 11633, *P. lachrymans* ATCC11921, *A. tumefaciens* ATCC11158, *R. solanacearum* ATCC11696, *B. thuringensis* ATCC 10792, *S. aureus* ATCC 25923, and *B. subtilis* CMCC 63501 (using chloramphenicol as a positive control). While **239–240** displayed no effect against the examined bacterial strains, **241** showed mild antibacterial activity with MIC values ranging from 8 to 64 μg mL^{-1}.[126] A chemical examination of the marine-derived fungus *S.* sp. MCCC 3A00308, isolated from the sediment collected from the South Atlantic Ocean at a depth of 2869 m, led to the isolation of two previously undescribed chlorinated derivatives namely, spiromastimelleins A–B (**242–243**) (Fig. 31). Compounds **242–243** were evaluated for their antibacterial activity against the Gram-positive bacteria (*S. aureus* ATCC 25923, *B. thuringiensis* ATCC 10792, and *B. subtilis* CMCC 63501) and the Gram-negative bacterium (*E. coli* ATCC 25922) (using chloramphenicol as a positive control). While both compounds showed no activity against *E. coli* ATCC 25922, they displayed significant effect against *S. aureus* ATCC 25923, *B. thuringiensis* ATCC 10792, and *B. subtilis* CMCC 63501, with MIC values ranging from 4 to 32 μg mL^{-1}.[127]

3.13. Fungi of the order Pezizales

3.13.1. Fungi of the family Sarcosomataceae

3.13.1.1. Fungi of the genus Sarcosomataceae. Three previously mentioned derivatives, including methoxymellein (**6**),

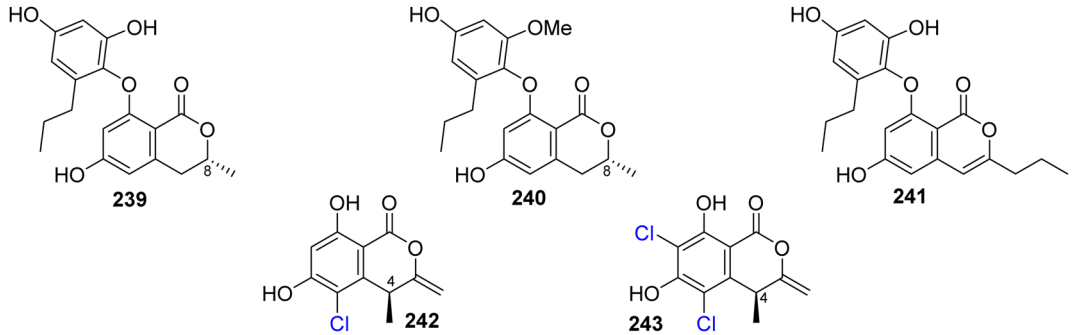


Fig. 31 Chemical structures of **239–243**.

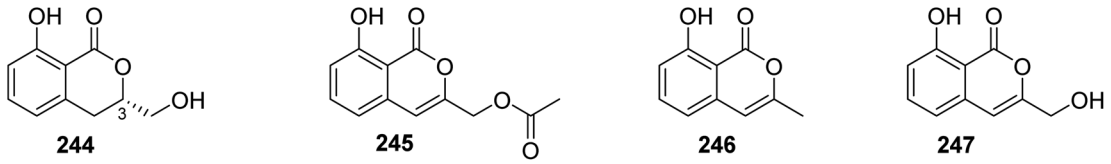


Fig. 32 Chemical structures of 244–247.

trans-4-hydroxymellein (**7**), and mullein (**25**), along with two previously unreported analogues, namely, (3*R*)-3-hydroxymethyl-8-hydroxyl-3,4-dihydroisoucoumarin (**244**) and 3-acetoxyl-8-hydroxyl-isocoumarin (**245**), beside two previously reported congeners, 3-methyl-8-hydroxyisocoumarin (**246**) and 8-hydroxy-3-(hydroxymethyl)-l*H*-2-benzopyran-1-one (**247**) (Fig. 32), were isolated from the EtOAc extract of the endophytic fungus Sarcosomataceae sp., NO. 49-14-2-1, isolated from *E. nepalense*, collected from the province of Panzhihua, Sichuan, China. The isolated compounds were not tested for any relevant biological activity.[128]

3.14. Fungi of the order Pleosporales

3.14.1. Fungi of the family Pleosporaceae

3.14.1.1. Fungi of the genus Alternaria. Three isocoumarin derivatives including two previously reported ones, namely, AI-77-B (**248**) and AI-77-F (**249**), alongwith a previously undescribed derivative Sg17-1-4 (**250**) (Fig. 33), were recorded from the marine-derived fungus *Alternaria tenuis* Sg17-1, isolated from an unidentified marine alga, collected from the island of Zhoushan, China. Compounds **248–250** were tested for their cytotoxicity against A375-S2 and HeLa cancer cell lines. Compound **248** displayed the strongest cytotoxicity followed by **250** with IC_{50} values of (0.1 and 0.02 mM) and (0.3 and 0.05 mM), respectively. In addition, **249** exhibited weak cytotoxicity against HeLa cells only with an IC_{50} value of 0.4 mM.[129] The chemical examination of the endophytic fungus *A. alternata*, isolated from *Camellia sinensis* branches, collected from the Jiangsu Province, China, afforded three previously unreported derivatives, namely, (+)-(10*R*)-7-hydroxy-3-(2-hydroxy-propyl)-5,6-dimethyl-isochromen-1-one (**251**), altenuene-2-acetoxy ester (**252**), and altenuene-3-acetoxy ester (**253**), together with five previously described analogues including altenuene (**254**),

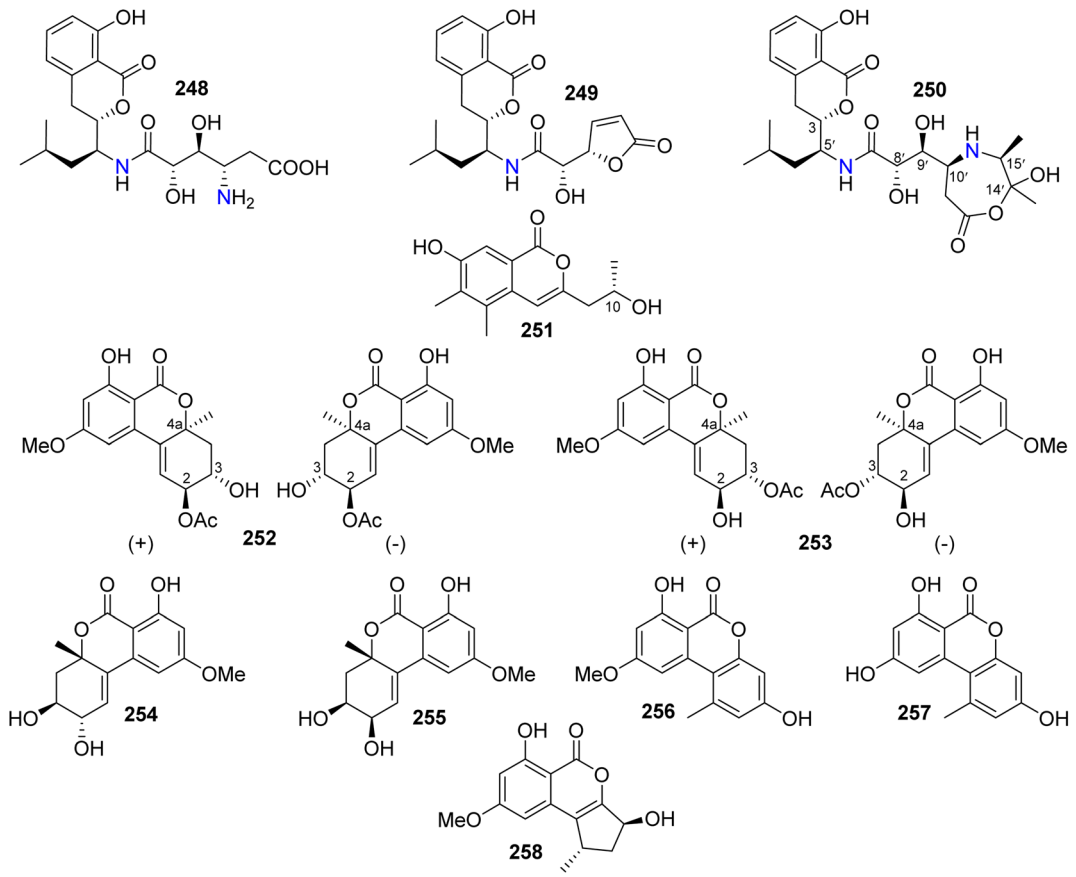
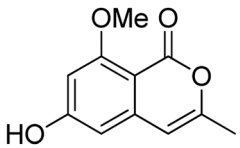


Fig. 33 Chemical structures of 248–258.



259

Fig. 34 Chemical structure of **259**.

5′-epialtenuene (**255**), alternariol 9-methyl ether (**256**), alternariol (**257**), and phialophoriol (**258**) (Fig. 33). Compounds **251–258** were tested for their antimicrobial activity against *S. aureus*, *B. subtilis*, *E. coli*, *C. albicans*, and *T. rubrum* (using initial agar diffusion assay and as a positive control Penicillin and Fluconazole have been used). Among them, **257** exhibited the strongest antibacterial effect against *B. subtilis* with an MIC_{80} of 8.6 μg mL^{-1}. In addition, **251–254** and **258** displayed weak to mild inhibition against the examined pathogenic microorganisms. Moreover, only **256** exhibited moderate cytotoxicity against the U2OS cancer cell line with an IC_{50} value of 28.3 μM.[130]

3.14.1.2. Fungi of the genus Cochliobolus. The phytochemical study of the marine-derived fungus *Cochliobolus lunatus* (TA26-46), isolated from the inner part tissue of zoanthid, collected from the coral reef of Weizhou, South China Sea, led to the isolation of two previously mentioned compounds 3-methyl-6,8-dihydroxyisocoumarin (**5**) and *O*-demethyldiaporthin (**152**), together with a previously described derivative, namely, 6-hydroxy-8-methoxy-3-methylisocoumarin (**259**) (Fig. 34). Compounds **5**, **152**, and **259** were tested for their antibacterial effect against *S. aureus* (ATCC 33591 and ATCC 43300), and for their inhibitory activity against acetylcholinesterase and topoisomerase I (Topo I) enzymes. They displayed neither antibacterial nor enzyme inhibition activities.[131]

3.14.1.3. Fungi of the genus Exserohilum. The previously mentioned monocerin (**4**), together with a previously unreported derivative 11(*R*)-hydroxymonocerin (**260**), alongwith the previously described compound 12(*R*)-hydroxymonocerin (**261**) (Fig. 35), were isolated from the EtOAc extract of the endophytic fungus *Exserohilum rostratum*, derived from *Stemona* sp. leaves and roots, collected from the Province of Ayutthaya, Thailand. Compounds **4** and **260** displayed antimalarial activity against *P. falciparum* with IC_{50} values of 0.68 and 7.7 μM, respectively. In addition, they were evaluated for their cytotoxicity against BT474, CHAGO, Hep-G2, KATO-3, and SW620, but they showed no activity at a concentration of 20 μg mL^{-1}.[132] A chemical investigation of the endophytic fungus *E.* sp., isolated from *A. truncatum* Bunge leaves, collected from the mountain of Dongling, China, afforded three previously mentioned derivatives, namely, monocerin (**4**), 11(*R*)-hydroxymonocerin (**260**), and 12(*R*)-hydroxymonocerin (**261**), along with the previously reported 12(*S*)-hydroxymonocerin (**262**), together with five previously unreported isocoumarin derivatives, named exserolides A (**263**), B (**264**), C (**265**), D (**266**), and F (**267**) (Fig. 35). Compounds **4** and **260–267** were tested for their antibacterial and antifungal effects against *E. coli* (CGMCC 1.2340), *B. subtilis* (ATCC 6633), *S. pneumoniae* (CGMCC 1.1692), and *S. aureus* (CGMCC 1.2465), as well as fungus *F. oxysporum* (CGMCC 3.2830), an example of the plant pathogenic fungi (using ampicillin, gentamicin, and amphotericin B as positive controls, respectively). Compounds **261** and **265** showed moderate antifungal activity against *F. oxysporum* (CGMCC 3.2830) with MIC values of 20 μg mL^{-1}. Meanwhile, **267** exhibited antibacterial effect against the tested

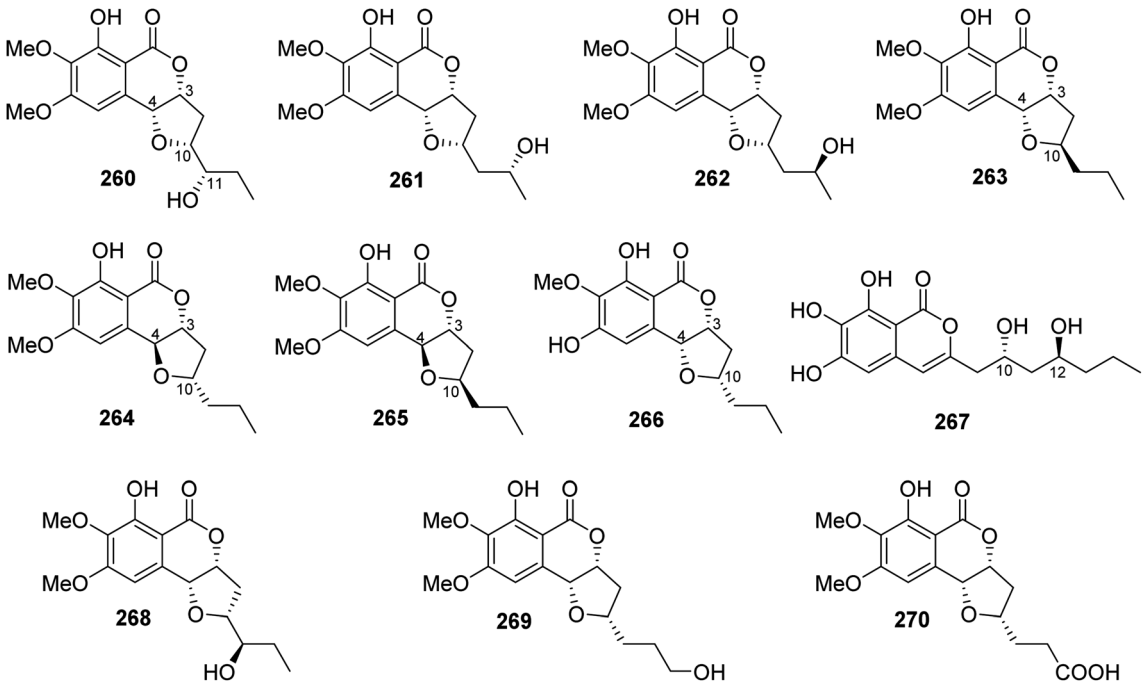


Fig. 35 Chemical structures of **260–270**.

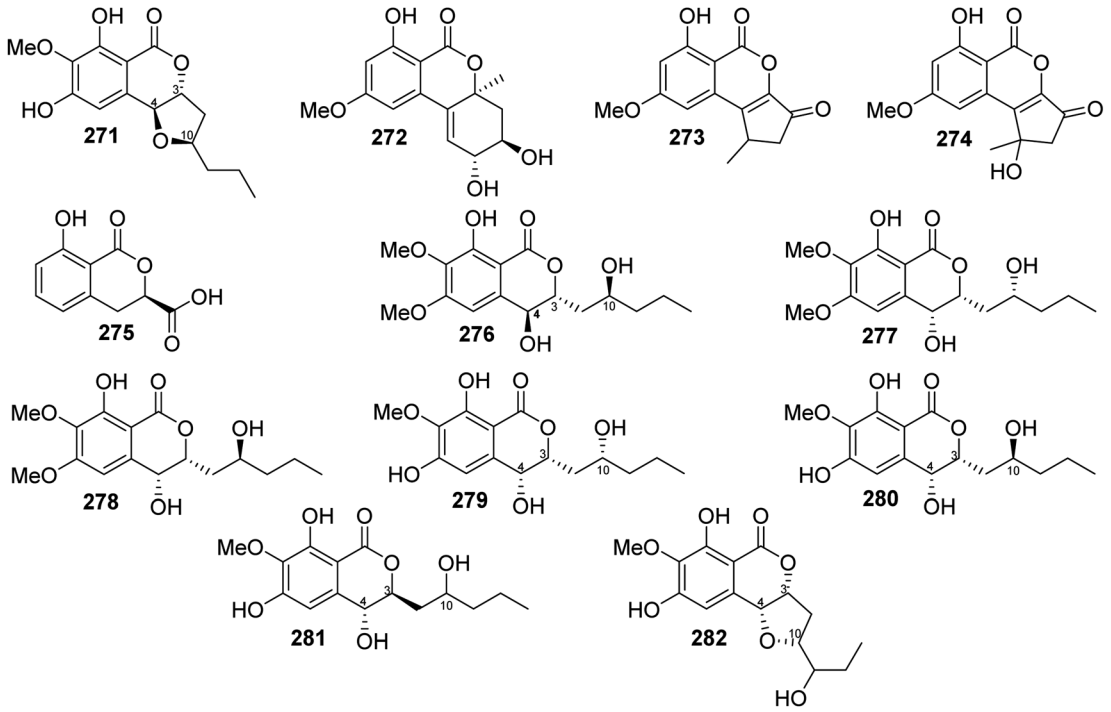


Fig. 36 Chemical structures of 271–282.

bacterial strains with MIC values ranging from 5 to 20 μg mL^{-1}.[133] In addition, the previously mentioned derivatives including monocerin (**4**), 12(*R*)-hydroxymonocerin (**261**), 12(*S*)-hydroxymonocerin (**262**), exserolides B (**264**), and C (**265**), together with the previously described congeners, 11-hydroxymonocerin (**268**), exserolide I (**269**), and exserolide J (**270**) (Fig. 35), were recorded from the EtOAc extract of the marine-derived fungus *E.* sp. (CHNSCLM-0008), isolated from the zoanthid *P. haddoni* inner part tissues, collected from Weizhou coral reefs, South China Sea. Compounds **4** and **262** showed antimalarial activity with IC_{50} values of 1.13 and 11.7 μM, respectively; however **270** was found to be inactive.[134]

3.14.1.4. Fungi of the genus Setosphaeria. A phytochemical investigation of the marine-derived fungus *Setosphaeria* sp. SCSIO41009, isolated from the marine sponge *Callyspongia* sp., collected from the Guangdong Province, China, afforded seven previously mentioned derivatives, including 11(*R*)-hydroxymonocerin (**260**), 12(*R*)-hydroxymonocerin (**261**) exserolides B (**264**), C (**265**), D (**266**), 11-hydroxymonocerin (**268**), exserolides I (**269**), and J (**270**), together with a previously unreported exserolide K (**271**) (Fig. 36). All the isolated metabolites were tested for their antibacterial activity against *S. aureus*, antifungal activity toward *F. oxysporum*, *C. gloeosporioides*, *C. acutatum*, *C. asianum*, and *P. oryza*. Intriguingly, none of these compounds showed either antibacterial or antifungal activities against the examined microbial strains. In addition, the antioxidant activities of the purified compounds were evaluated. Only **266** exhibited moderate anti-radical activity with an IC_{50} value of 38 μM. Furthermore, these compounds were tested for their antiviral and MptpB inhibitory activities, but they showed no activity.[135] Two previously mentioned derivatives, alternariol 9-methyl ether (**256**) and alternariol (**257**), along with four previously reported compounds, including isoaltenuene (**272**), 1-deoxyrubralactone (**273**), rubralactone (**274**), and phomasatin (**275**), together with a previously unreported setosphacohol A (**276**) (Fig. 36), were obtained from the fungus *S.* sp. (strain LGWB-2), isolated from *H. axyridis*, collected from the Hebei Province in Baoding, China. Compounds **256–257** and **272–276** were evaluated for their cytotoxicity against HeLa, A549, MCF-7, MGC-803, Huh-7, and H1975 cancer cell lines (using the MTT method and cisplatin as a positive control). While **272** and **274–276** displayed no cytotoxic activity against the tested cancer cell lines, **256–257** and **273** showed mild cytotoxicity with IC_{50} values ranging from 23.04 to 96.91 μg mL^{-1}.[136] A chemical examination of the *S. rostrate* LGWB-10, obtained from *H. axyridis*, collected from the Hebei Province, China, afforded two previously mentioned derivatives, 12(*R*)-hydroxymonocerin (**261**) and 12(*S*)-hydroxymonocerin (**262**), along with two previously described compounds, including (3*R*,4*R*)-4,8-dihydroxy-3-((*R*)-2-hydroxypentyl)-6,7-dimethoxyisochroman-1-one (**277**) and (3*R*,4*R*)-4,8-dihydroxy-3-((*R*)-2-hydroxypentyl)-6,7-

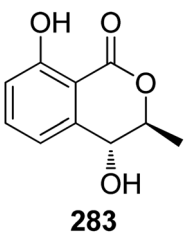


Fig. 37 Chemical structure of 283.

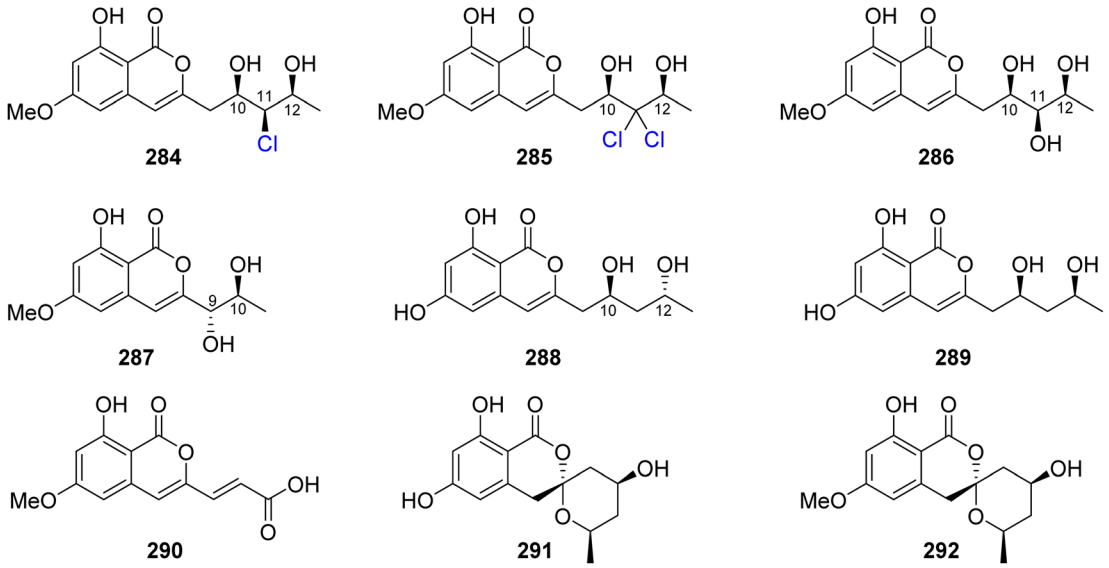


Fig. 38 Chemical structures of 284–292.

dimethoxyisochroman-1-one (**278**) together with four previously undescribed natural products namely, setosphlides A–D (**279–282**) (Fig. 36). Compounds **279–282** displayed no cytotoxicity against MCF-7, MGC-803, HeLa, and Huh-7 with IC_{50} values >200 μM.[137]

3.14.2. Fungi of the family Didymellaceae

3.14.2.1. Fungi of the genus Epicoccum. A previously mentioned (*R*)-5-hydroxymellein (**198**), along with the previously reported (−)-(3*R*,4*S*)-4-hydroxymellein (**283**) (Fig. 37), were obtained from the EtOAc extract of the brown alga-derived fungus *Epicoccum* sp., isolated from *Fucus vesiculous*, collected from the coast of the North Sea, Germany. Compounds **198** and **283** were evaluated for their antioxidant activity (using the DPPH-radical scavenging and TBARS assays and BHT as a positive control). They displayed inhibitory activity in both the assays with an inhibition ratio of 28.4 and 9.6 at a concentration of 50.0 μg mL^{-1}, and 30.4 and 18.4 at a concentration of 37.0 μg mL^{-1}.[138]

3.14.2.2. Fungi of the genus Peyronellaea. The chemical study of the marine-derived fungus *Peyronellaea glomerata* XSB-01-15, obtained from the marine sponge *Amphimedon* sp., collected from the Island of Xisha, South China Sea, afforded five previously undescribed peyroisocoumarins A (**284**), B (**285**), C (**286**), D (**287**), and isocitreoisocoumarinol (**288**), along with four previously reported derivatives including, citreoisocoumarinol (**289**), LL-Z 1640-7 (**290**), demethylcitreoviranol (**291**), and citreoviranol (**292**) (Fig. 38), together with eight previously mentioned (+)-6-*O*-methylcitreoisocoumarin (**132**), *O*-demethyldiaporthin (**152**), diaportinol (**213**), citreoisocoumarin (**214**), mucorisocoumarins A (**233**), B (**234**), alternariol-9-methyl ether (**256**), and alternariol (**257**). All the isolated compounds were tested for their antibacterial activities against *B. thuringiensis*, *S. aureus*, *P. lachrymans*, *X. vesicatoria*, *E. coli*, *A. tumefaciens*, and *R. solanacearum*. Among the isolated metabolites, **257** displayed mild antibacterial activity toward *S. aureus*, *A. tumefaciens*, and *R. solanacearum*, **256** showed weak activity against *A. tumefaciens*, **152** and **299** also exhibited weak activity against *R. solanacearum*. Furthermore, all the isolated compounds showed ARE luciferase activity that was 0.88–2.95 folds more than the negative control (DMSO) when compared with the positive control *t*BHQ with an induction value 4.29 folds more than the solvent (DMSO).[139]

3.14.2.3. Fungi of the genus Phoma. A chemical study of the marine sponge-derived fungus *Phoma* sp. 135, isolated from the sponge *Ectyplasia perox*, collected from the Reef of Lauro Club, Dominica, led to the isolation of one previously mentioned derivative, (3*R*)-6-methoxy-7-chloromellein (**136**), and a previously unreported chlorinated metabolite, (3*R*,4*S*)-4-hydroxy-6-methoxy-7-chloromellein (**293**) (Fig. 39). Compounds **136** and **293** were not tested for any relevant biological assay.[140] A previously mentioned phomasatin (**275**) was obtained from the EtOAc extract of the plant-derived fungus *P.* sp. YN02-P-3, isolated from the *Sumbaviopsis* J. J. Smith, collected from Yunnan, China. Compound **275** was evaluated for its cytotoxicity against HL-60, Molm 13, and PC-3 cancer cell lines (using 5-fluorouracil as a positive control), and it showed no activity.[141] In addition, the chemical investigation of the marine-derived fungus *P.* sp. (TA07-1), isolated from the fresh tissues of the gorgonian *Dichotella gemmacea* (GX-WZ-2008003-4), collected from the

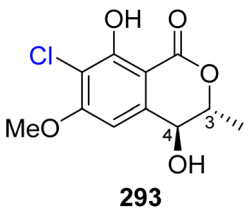


Fig. 39 Chemical structure of 293.

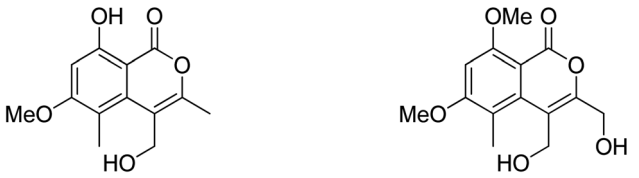


Fig. 40 Chemical structures of 294–295.

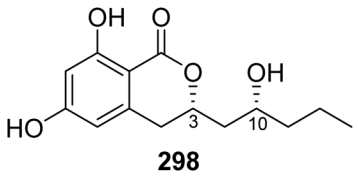


Fig. 42 Chemical structure of 298.

coral reef of Weizhou, South China Sea, afforded four previously mentioned metabolites, including desmethyldiaportinol (**94**), diaportinol (**213**), citreoisocoumarin (**214**), and citreoisocoumarinol (**289**). The isolated compounds were tested for their antibacterial activity against *S. albus*, *S. aureus*, *E. coli*, *V. parahaemolyticus*, and *V. anguillarum* as well as for their lethal activity toward the brine shrimps, but none of them showed antibacterial or any lethal effect.[142]

3.14.3. Fungi of the family Didymosphaeriaceae

3.14.3.1. Fungi of the genus Microsphaeropsis. A previously mentioned isocoumarin derivative **26** was isolated from the marine sponge derived fungus *Microsphaeropsis* sp. (strain number H5-50), isolated from the marine sponge *Myxilla incrustans* Jonnston (1842), collected around Helgoland, Germany. Compound **26** showed no antiplasmodial activity.[143]

3.14.3.2. Fungi of the genus Paraphaeosphaeria. A chemical study of the plant-derived fungus *Paraphaeosphaeria sporulosa*, isolated from *Actinidia chinensis* Planch stem, collected from the Sichuan Province, Cangxi, led to the isolation of two previously mentioned derivatives, acremonones E (**227**) and F (**228**) along with two previously undescribed isocoumarins, paraphaeones E (**294**) and F (**295**) (Fig. 40). Compounds **227–228** and **294–295** were evaluated for their antibacterial effect against *P. syringae* pv. *Actinidiae* (using streptomycin as a positive control). While **228** showed no activity, **227**, **294**, and **295** displayed moderate antibacterial activity with MIC values of 50, 25, and 50 μg mL^{-1}, respectively.[144]

3.14.4. Fungi of the family Leptosphaeriaceae

3.14.4.1. Fungi of the genus Leptosphaeria. Six previously mentioned derivatives, clearanol I (**64**), dothideomynone A (**65**), banksialactone A (**66**), 3,4-dimethyl-6,8-dihydroxyisocoumarin (**178**), acremonone F (**228**), and acremonone G (**229**), along with a previously unreported clearanol J (**296**) together with a previously described (*R*)-4,8-dihydroxy-6-methoxy-4,5-dimethyl-3-methyleneisochromen-1-one (**297**) (Fig. 41), were obtained from the deep sea-derived fungus *Leptosphaeria* sp. SCSIO 41005, isolated from the sediments of the Indian Ocean collected at a depth of 3614 m. All the obtained compounds were tested for their cytotoxicity and antiviral properties against K562, MCF-7, and SGC7901 cancer cell lines, and influenza A virus subtype H3N2, EV71, and HIV viruses. None of them showed either cytotoxicity or antiviral activities.[145]

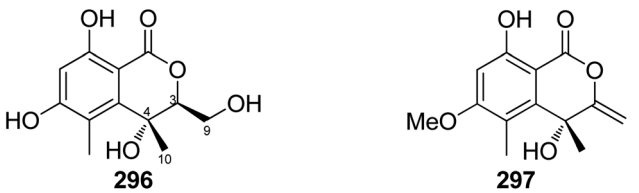


Fig. 41 Chemical structures of 296–297.

3.14.4.2. Fungi of the genus Leptosphaena. A chemical exploration of the plant-derived fungus *Leptosphaena maculans*, isolated from *Osmanthus fragrans*, afforded three previously mentioned derivatives, monocerin (**4**), 12(*R*) hydroxymonocerin (**261**), and exserolide I (**269**) along with the previously unreported maculansline C (**298**) (Fig. 42). Compounds **4**, **261**, **269**, and **298** were evaluated for their α-glucosidase inhibition effect, but none of them displayed any inhibitory activity.[146]

3.14.5. Fungi of the family Phaeosphaeriaceae

3.14.5.1. Fungi of the genus Paraphoma. Paraphamides A–C (**299–301**), three previously unreported isocoumarin derivatives, featuring a rare skeleton coupled with phenylethylamine moiety, along with another six previously unreported derivatives, namely, parapholactone (**302**), 7-hydroxyoospolactone (**303**), 7-methoxyoospolactone (**304**), 7-methoxy-9-hydroxyoospolactone (**305**), 10-acetoxy-9-hydroxyoospolactone 6-dehydroxysescandelin (**306**), and 6-dehydroxysescandelin (**307**), together with five previously described metabolites, including oospolactone (**308**), 8-*O*-methyloospolactone (**309**), 10-hydroxyoospolactone (**310**), 9,10-dihydroxyoospolactone (**311**), and oospoglycol (**312**) (Fig. 43), were discovered from the marine-derived fungus *Paraphoma* sp. CUGBMF180003, obtained from a mud, collected from the Shenzhen intertidal zones, China. All the isolated compounds were evaluated for their antibacterial activities toward *C. albicans* ATCC 10231 and *S. aureus* ATCC 25923. Among them, **302–303** displayed moderate antibacterial activity against *S. aureus* ATCC 25923 with MIC values of 12.5 μg mL^{-1}.[147]

3.15. Fungi of the order Xylariales

3.15.1. Fungi of the family Apiosporaceae

3.15.1.1. Fungi of the genus Arthrinium. The chemical study of the marine-derived fungus *Arthrinium sacchari*, isolated from an identified marine sponge, collected from Atamishi coast, Japan, afforded the isolation of one previously unreported decarboxyhydroxycitrinone (**313**) (Fig. 44). Compound **313** exhibited weak cytotoxicity toward HUVECs and HUAECs cancer cell lines with IC_{50} values of 7.6 and 17.4 μM, respectively.[148]

3.15.2. Fungi of the family Hypoxylaceae

3.15.2.1. Fungi of the genus Hypoxylon. Two previously mentioned (−)-(3*R*,4*R*)-*cis*-4-hydroxy-5-methylmellein (**24**) and

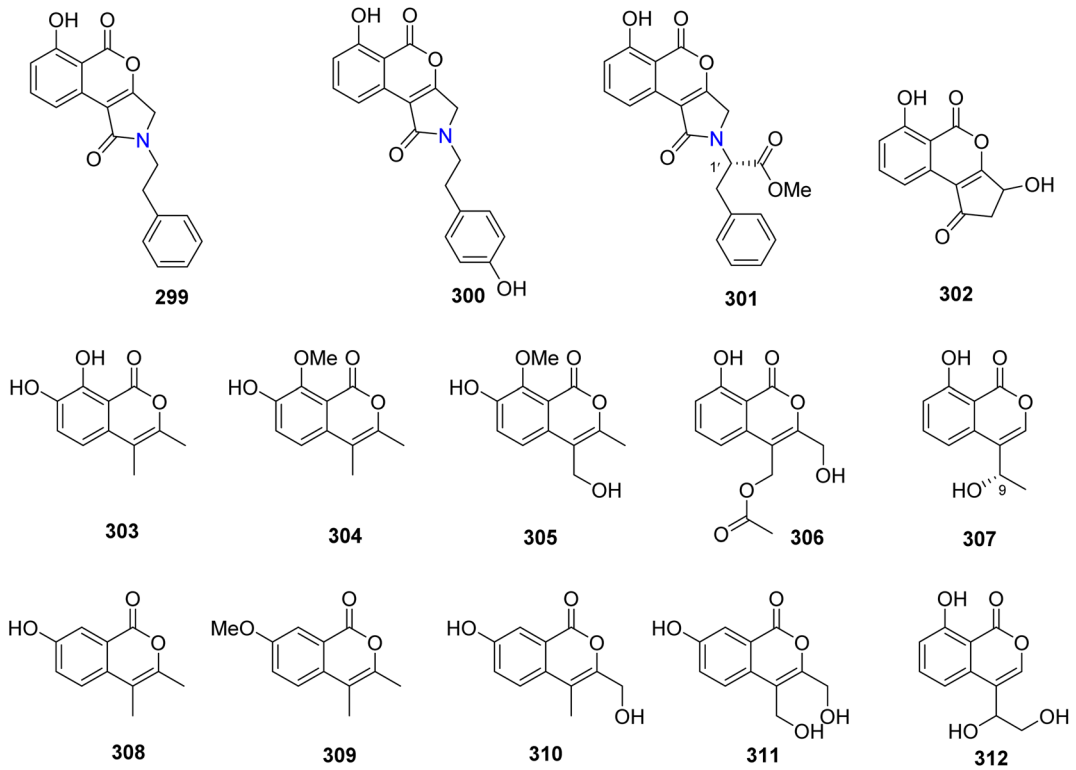


Fig. 43 Chemical structures of 299–312.

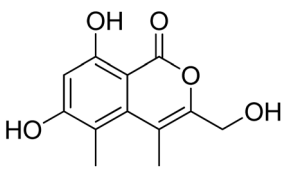


Fig. 44 Chemical structure of 313.

phomasatin (**275**), along with two previously unreported (3*R*,4*R*)-4,8-dihydroxy-5-(hydroxymethyl)-3-methylisochroman-1-one (**314**) and (3*R*,4*S*)-4,8-dihydroxy-5-(hydroxymethyl)-3-methylisochroman-1-one (**315**), together with two previously described 3,5-dimethyl-8-hydroxy-7-methoxy-3,4-dihydroisocoumarin (**316**) and 3,5-dimethyl-8-methoxy-3,4-dihydroisocoumarin (**317**) (Fig. 45), were obtained from the EtOAc extract of the soil derived fungus *Hypoxylon* sp., isolated from a soil sample collected from the Province Heilongjiang Province, the mountain of Da Hinggan, China. It is worth mentioning that none of the obtained compounds was tested for any relevant biological activity.[149]

3.15.3. Fungi of the family Microdochiaceae

3.15.3.1. Fungi of the genus Microdochium. A chemical identification of the plant-derived fungus *Microdochium bolleyi*, isolated from *Fagonia cretica*, collected in Gomera, afforded four previously mentioned derivatives including, monocerin (**4**), 12(*R*)-hydroxymonocerin (**261**), 12(*S*) hydroxymonocerin (**262**), and (3*R*,4*R*)-4,8-dihydroxy-3-((*R*)-2-hydroxypentyl)-6,7-dimethoxyisochroman-1-one (**277**). The isolated metabolites were examined for their inhibitory activity against the fungal strain *M. Violaceum*, the bacterial strains *E. coli* and *B. Megaterium*, and against the algae *C. fusca*, (using the agar diffusion test and as a positive controls penicillin, tetracycline, nystatin, and actidione have been used). While **261** displayed anti-algal

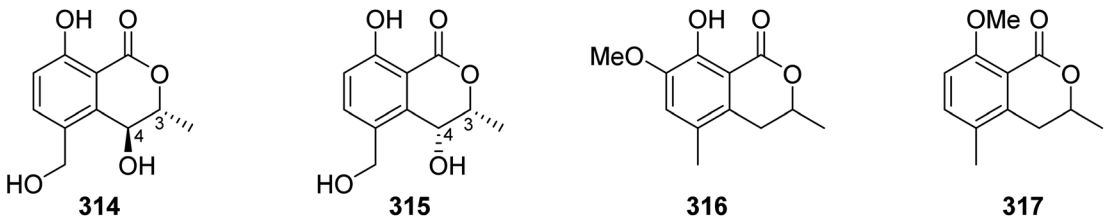


Fig. 45 Chemical structures of 314–317.

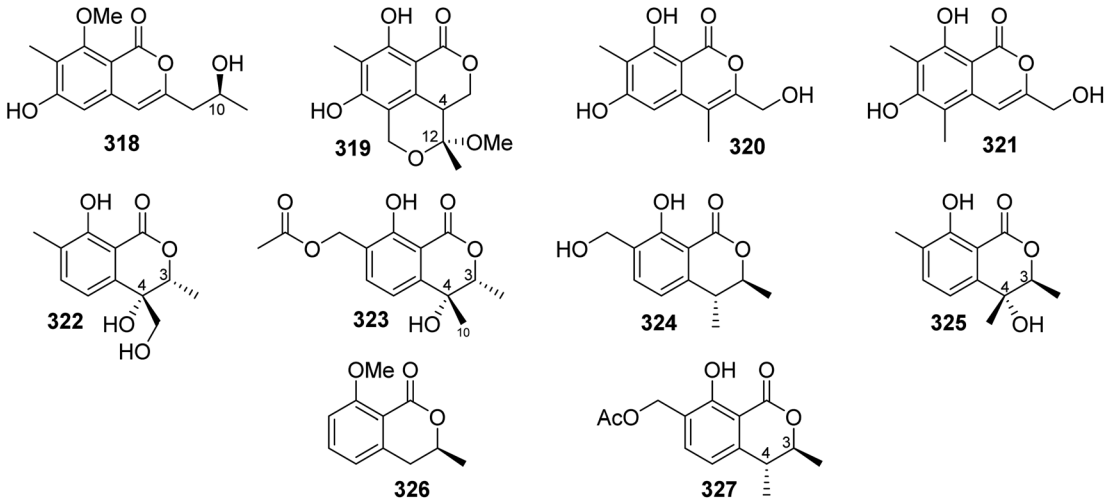


Fig. 46 Chemical structures of 318–327.

and antifungal activities, it showed no antibacterial activity. However, **4**, **262**, and **277** exhibited antifungal, antibacterial, and algal activity against the examined organisms.[150]

3.15.4. Fungi of the family Sporocadaceae

3.15.4.1. Fungi of the genus Pestalotiopsis. Two previously mentioned aspergillumarins B (**105**) and A (**106**), along with the previously unreported pestalotiorin (**318**) (Fig. 46), were obtained from the marine seagrass-derived fungus *Pestalotiopsis* sp. PSU-ES194, isolated from *E. acoroides* leaves, collected in Thailand. Compound **318** was examined for its antimycobacterial, antimalarial, and cytotoxic activities, but it showed no activity.[151] In addition, two previously mentioned (−)-pestalactone B (**20**) and (+)-pestalactone C (**21**), along with three previously unreported derivatives, including pestalactone A (**319**), pestapyrones D (**320**), and E (**321**) (Fig. 46), were isolated from the EtOAc extract of the endophytic fungus *Pestalotiopsis* sp., obtained from *P. frasery* leaves, collected in Jiangsu, Nanjing, China. All the isolated compounds were tested for their antimicrobial effect against *S. aureus* ATCC 25923, *B. subtilis* ATCC 6633, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 9027, and *C. glabrata* ATCC 90030. Among them, only **21** showed antifungal activity against *C. glabrata* ATCC 90030 with an MIC_{50} value of 3.49 μg mL^{-1}.[152] The chemical processing of the marine sponge-derived fungus *P. heterocornis* isolated from the marine sponge *P. fusca* collected in China from the Island of Xisha afforded two previously undescribed pestaloisocoumarins A–B (**322–323**), along with the previously reported gamahorin (**324**) (Fig. 46). Compounds **322–324** showed no cytotoxicity against BGC-823, H460, PC-3, and SMMC-7721 cancer cell lines. However, they exhibited antibacterial activity against *S. aureus* and *B. subtilis* with MIC values ranging from 25 to 100 μg mL^{-1}. In addition, they were tested for their antifungal activity against *C. albicans*, *C. parapsilosis*, and *C. neoformans*, where **322** exhibited weak antifungal activity with MIC values of 100 μg mL^{-1}. Moreover, **323** was found to be inactive against *C. albicans* and *C. parapsilosis* but exhibited weak effect against *C. neoformans* with an MIC value of 100 μg mL^{-1}. Furthermore, **324** displayed weak antifungal ability toward *C. parapsilosis* and *C. neoformans* with MIC values of 100 μg mL^{-1} and was found to be inactive against *C. albicans*.[153] A previously unreported pestalotiopisorin B (**325**), alongwith the co-isolated previously reported (*R*)-(−)-mellein methyl ether (**326**) (Fig. 46), were recorded from the mangrove-derived fungus *Pestalotiopsis* sp. HHL101, isolated from *Rhizophora stylosa* branches, collected from the Island of Hainan, China. Compound **325** was examined for its CN-inhibition activity, but it showed no activity. In addition, it displayed mild antibacterial effect against *E. coli* and *P. aeruginosa*. Moreover, it showed no cytotoxicity against HeLa, A549, and HepG2 cancer cell lines.[154] A previously mentioned gamahorin (**324**), along with the previously undescribed microsporaline D (**327**) (Fig. 46), were reported from the marine-derived fungus *P. microspora* SC3082, isolated from *Scaevola taccada* (Gaertn.) Roxb leaves, collected from the island of Yongxing, China. Compound **327** was tested for its antifungal activity against *C. albicans* ATCC 10231 (using fluconazole as a positive control) but it showed no activity.[155]

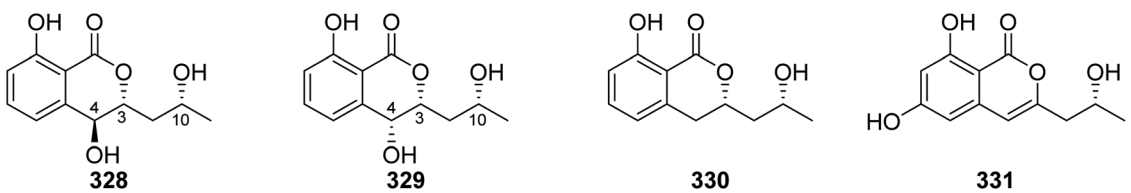


Fig. 47 Chemical structure of 328–331.

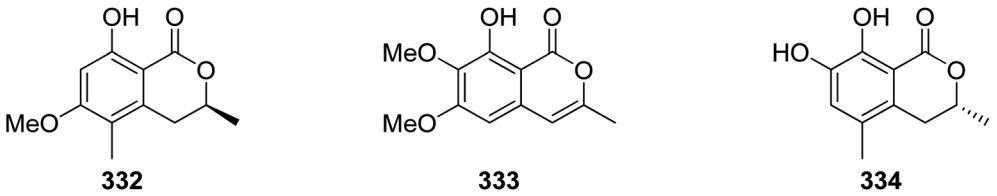


Fig. 48 Chemical structures of 332–334.

3.15.5. Fungi of the family Xylariaceae

3.15.5.1. Fungi of the genus Ascotricha. Two previously undescribed isocoumarin derivatives, namely, ascotrichols A–B (**328–329**), along with the two previously reported 3-(2-hydroxypropyl)-8-hydroxy-3,4-dihydroisocoumarin (**330**) and (*R*)-orthosporin (**331**) (Fig. 47), were reported from the ethanol extract of the marine mud-derived fungus *Ascotricha* sp. ZJ-M-5, isolated from the sea mud, collected from an unidentified location. It is worth mentioning that none of the isolated metabolites were subjected for any relevant biological activity test.[156]

3.15.5.2. Fungi of the genus Biscogniauxia. The previously described 6-methoxy-5-methyl mellein (**332**) (Fig. 48) was reported from the marine-derived fungus *Biscogniauxia mediterranea* strain LF657, isolated from the sediments collected in the Eastern Mediterranean Sea at a depth of 2800 m. Compound **332** displayed weak antifungal effect against the phytopathogenic fungi *Septoria tritici* and *Trichophyton rubrum*.[157] In addition, a chemical examination of the plant endophytic fungus *B. capnodes* isolated from *Averrhoa carambola* L fruits, collected from Kandey, led to the isolation of the previously mentioned (−)-3,4-dihydro-8-hydroxy-3,5-dimethyl-isocoumarin (**14**) and reticulol (**29**), along with two previously described 6-*O*-methylreticulol (**333**) and 7-hydroxy-5-methylmellein (**334**) (Fig. 48). These compounds were tested for their antifungal properties against *C. cladosporioides*, antioxidant activity, their lethal activity against the brine shrimp, and their phytotoxicity. Only **29** displayed mild anti-radical effect with an IC_{50} value of 58 μg mL^{-1}.[158]

3.15.5.3. Fungi of the genus Halorosellinia. A previously mentioned (*R*)-4,8-dihydroxy-6-methoxy-4,5-dimethyl-3-methyleneisochromen-1-one (**297**), along with two previously unreported halorosellins A–B (**335–336**) (Fig. 49), were recorded from the marine-derived fungus *Halorosellinia oceanica*, collected in the Province of Samutsongkram. Compounds **297**, **335**, and **336** displayed no antiviral, anti-mycobacterium, anti-malarial, and cytotoxic effects.[159]

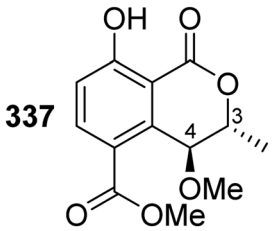


Fig. 50 Chemical structure of 337.

3.15.5.4. Fungi of the genus Nodulisporium. A chemical investigation of the algal-derived fungus *Nodulisporium* sp., isolated from an algal species inner tissue, collected from the island of Corfu, Greece, afforded the previously mentioned 7-hydroxy-5-methylmellein (**334**). Compound **334** was tested using the agar diffusion methods against the bacterial strains *B. megaterium* and *E. coli*, the fungal strains *M. violaceum*, *E. rubrum*, and *M. microspora* as well as the green microalga *C. fusca*, but it showed no activity. In addition, it showed no cytotoxicity when evaluated against a panel of 36 tumor cell lines.[160]

3.15.5.5. Fungi of the genus Xylaria. The previously undescribed xylariamalirin (**337**) (Fig. 50) was recorded from *n*-BuOH fraction of the endophytic fungus *Xylaria mali* isolated from *Lepidagathis stenophylla* C. B. Clarke ex Hayata stems, collected from southern Taiwan. Compound **337** was not evaluated for any relevant biological activity.[161]

3.16. Miscellaneous

3.16.1. Fungi of the genus *Ascomycota*. The chemical exploration of the marine-derived fungus *Ascomycota* sp. CYSK-4, isolated from the *Pluchea indica* branches, collected from the Guangxi Province, China, afforded three previously undescribed

Fig. 49 Chemical structures of 335–336.

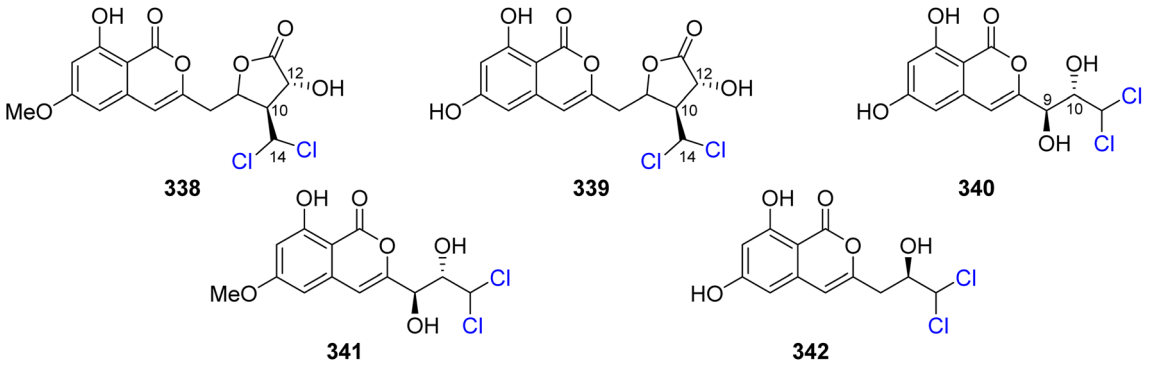


Fig. 51 Chemical structures of 338–342.

dichlorodiaportintone (**338**), desmethyldichlorodiaportintone (**339**), and desmethyldichlorodiaportinol (**340**) along with two previously reported dichlorodiaportinol (**341**) and desmethyldichlorodiaportin (**342**) (Fig. 51), together with four previously mentioned dichlorodiaportin (**89**), diaportinol (**213**), citreoisocoumarin (**214**), and mucorisocoumarins A (**233**). Compounds **89**, **213**, **214**, **233**, and **338–342** were evaluated for their anti-inflammatory activity (using nitric oxide production assay and indomethacin as a positive control). Among them, **89**, **338**, **339**, and **342** displayed inhibitory activity with IC_{50} values of 67.2, 41.5, 15.8, and 33.6 μM, respectively. Moreover, they were evaluated for their antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli*, *K. pneumoniae*, and *A. calcoaceticus* (using conventional broth dilution method and ciprofloxacin and gentamicin as a positive control). Compounds **89** and **342** displayed antibacterial effect against all the examined bacterial strains with MIC values between 25 and 50 μg mL^{-1}. Meanwhile, **338** showed antibacterial activity against *S. aureus*, *E. coli*, *K. pneumoniae*, and *A. calcoaceticus* with an MIC value of 50 μg mL^{-1}, whereas the rest of the isolated compounds displayed no activity at a concentration of 50 μg mL^{-1}.[162]

3.16.2. Fungi of the genus *Scytalidium*. Four previously described isocoumarin derivatives, namely, 4-acetyl-3,4-dihydro-6,8-dihydroxy-5-methylisocoumarin (**343**), 4-acetyl-3,4-dihydro-6,8-dihydroxy-3-methoxy-5-methylisocoumarin (**344**), 4-acetyl-6,8-dihydroxy-5-methyl-2-benzopyran-1-one (**345**), and decarboxycitrinone (**346**), along with two previously unreported analogues, 6,8-dihydroxy-4-hydroxymethyl-3,5-dimethylisochromen-1-one (**347**) and acetic acid 6,8-dihydroxy-3,5-dimethyl-1-oxo-1*H*-isochromen-4-ylmethyl ester (**348**) (Fig. 52) were reported from the EtOAc extract of the endophytic fungus *Scytalidium* sp., isolated from a *Salix* species leaf, collected from the mountains of Lower Saxony, Germany. Compounds **343–348** were not tested for any relevant biological activity.[163]

3.16.3. Fungi of the genus *Xylomelasma*. Two previously mentioned diaporthin (**121**) and (3*R*)-6-methoxymellein (**135**), along with the previously described 8-hydroxy-6-methoxy-3-methylisocoumarin (**349**) (Fig. 53), were reported from the

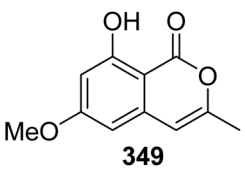


Fig. 53 Chemical structure of 349.

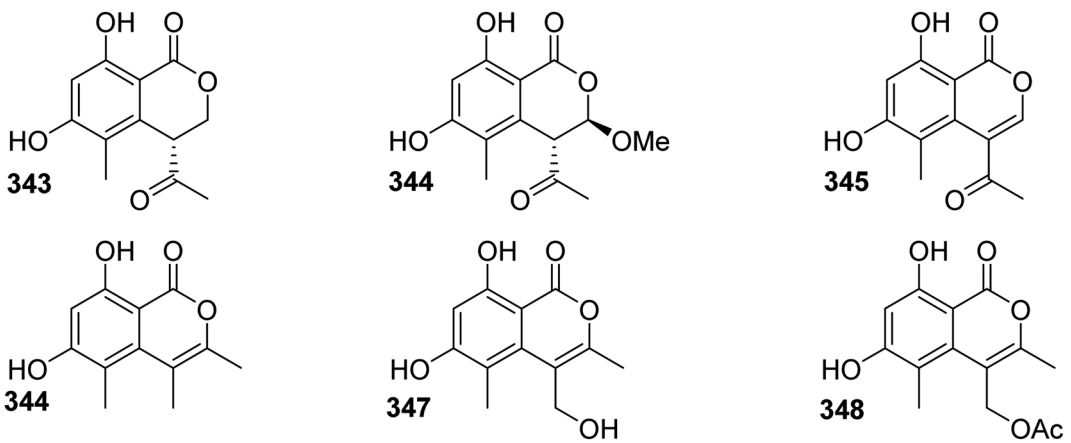


Fig. 52 Chemical structures of 343–348.

endophytic fungus *Xylomelasma* sp. Samif07, obtained from the roots of *Salvia miltiorrhiza* Bunge, collected in China from the medicinal plant garden of Beijing. Compounds **121**, **135**, and **349** were tested for their antibacterial activity against *B. subtilis*, *S. haemolyticus*, *A. tumefaciens*, *E. carotovora*, *R. solanacearum*, and *X. vesicatoria* (using streptomycin as a positive control). Compound **135** displayed no antibacterial activity but **121** exhibited antibacterial ability toward *B. subtilis* with an MIC value of 50 μg mL^{-1}. Moreover, **349** showed antibacterial activity against *B. subtilis*, *A. tumefaciens*, and *X. vesicatoria* with MIC values of 25, 75, and 25 μg mL^{-1}, respectively. Furthermore, they were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* (using rifampicin as a positive control), but none of them exhibited significant inhibitory activity. In addition, they were examined for their antioxidant activity, using hydroxyl radical-scavenging activity test and ascorbic acid as a positive control as well as the Fe^{3+} reducing activity method using BHT as a positive control, **121** displayed significant hydroxyl radical-scavenging and Fe^{3+} reducing activity, but **349** showed weak Fe^{3+} reducing activity.[164]

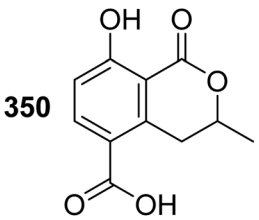


Fig. 54 Chemical structure of **350**.

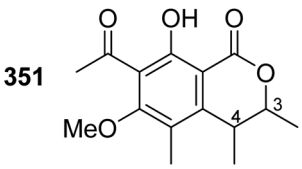


Fig. 55 Chemical structure of **351**.

3.16.4. Unidentified fungal strain

3.16.4.1. Fungal strain No. 1893. The chemical examination of the marine-derived fungal strain No. 1893, isolated from the mangrove *Kandelia candel*, collected from the Sea coast of the South China Sea, afforded the previously mentioned (−)-3,4-dihydro-8-hydroxy-3,5-dimethyl-isocoumarin (**14**) and the previously described 5-carboxylmellein (**350**) (Fig. 54). No biological activity was reported for these metabolites.[165]

3.16.4.2. Fungal strain No. dz17. Two previously mentioned (−)-(3*R*,4*R*)-*cis*-4-hydroxy-5-methylmellein (**24**) and 5-carboxylmellein (**350**), along with the previously unreported 3,4-dihydro-6-methoxy-8-hydroxy-3,4,5-trimethyl-isocoumarin-7-carboxylic acid methyl ester (**351**) (Fig. 55), were recorded from the EtOAc extract of the marine-derived fungal strain No. dz17, obtained from a sample collected from the coast of South China Sea. Compound **351** exhibited cytotoxic effect toward HepG2 and Hep-2 tumor cell lines with IC_{50} values of 55 and 52 μg mL^{-1}, respectively.[166]

3.16.4.3. Fungal strain HJ33moB. The chemical examination of the marine-derived fungal strain HJ33moB, isolated from an unidentified alga, afforded the previously mentioned 1-deoxy-rubralactone (**273**). Compound **273** exhibited strong inhibition effect against families X and Y of eukaryotic pols.[167]

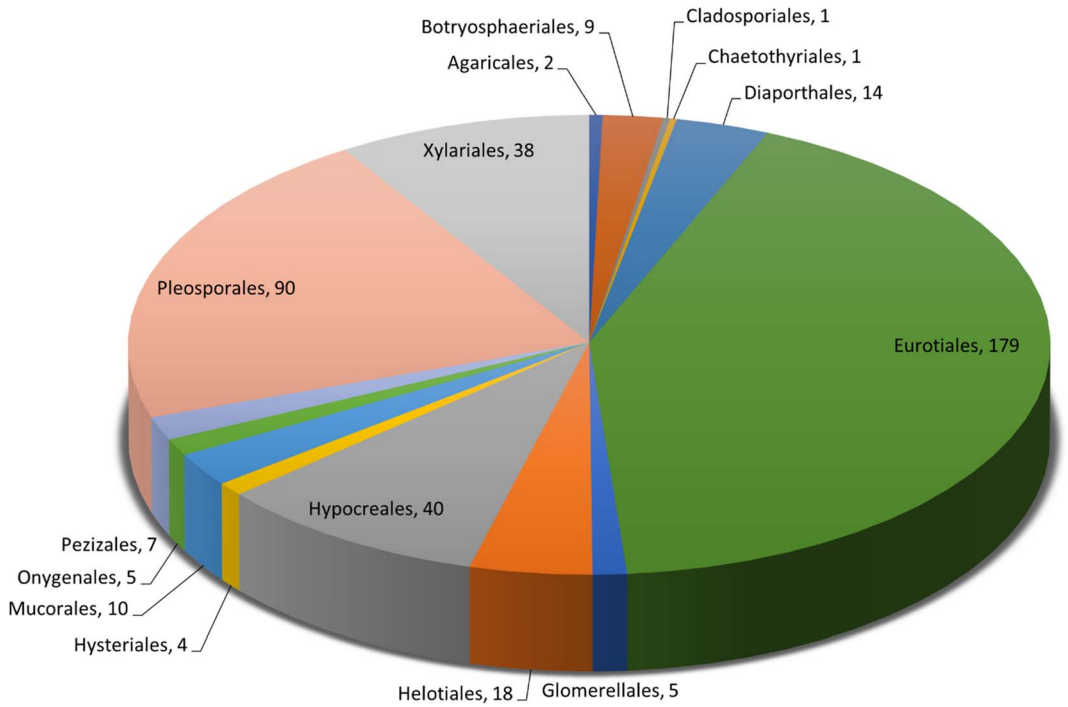


Fig. 56 Contribution of isocoumarins by various fungal orders.

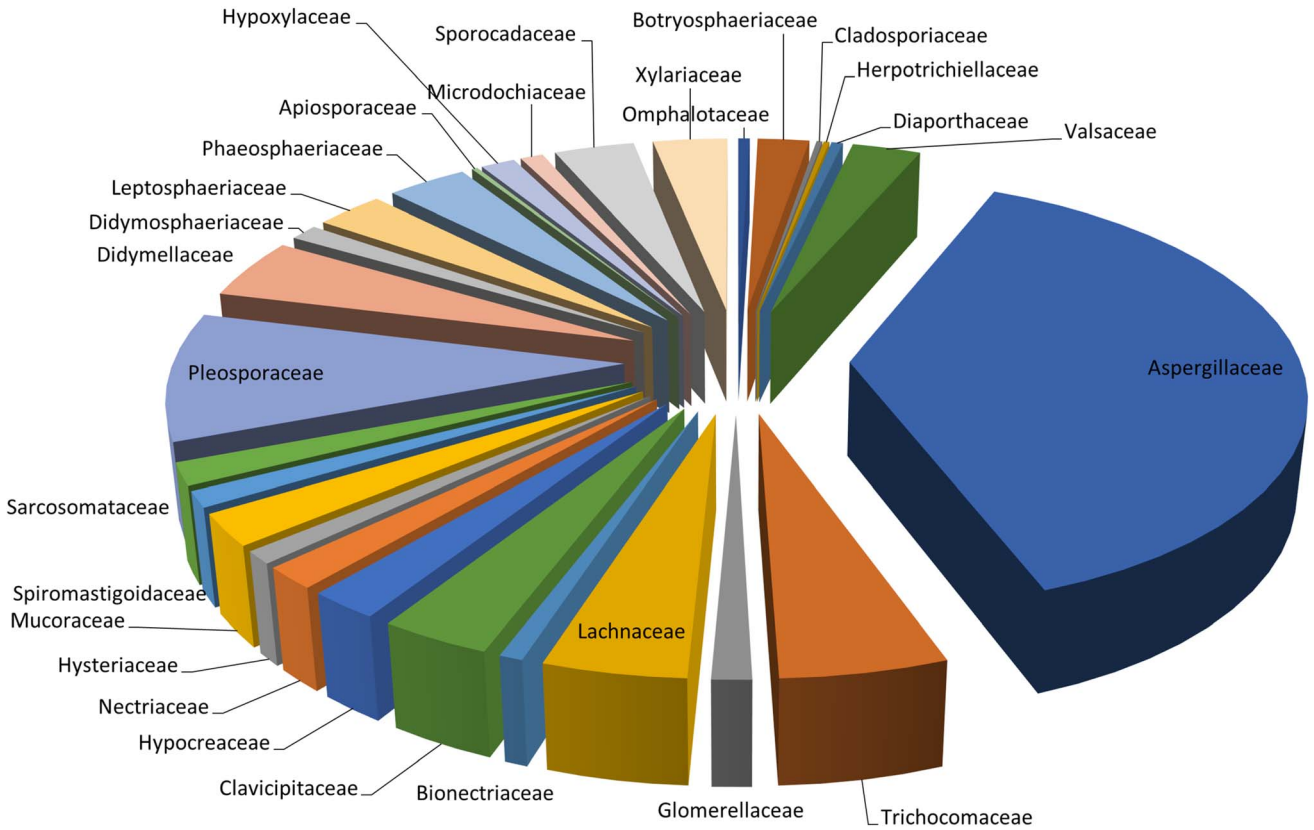


Fig. 57 Contribution of isocoumarins by different fungal families.

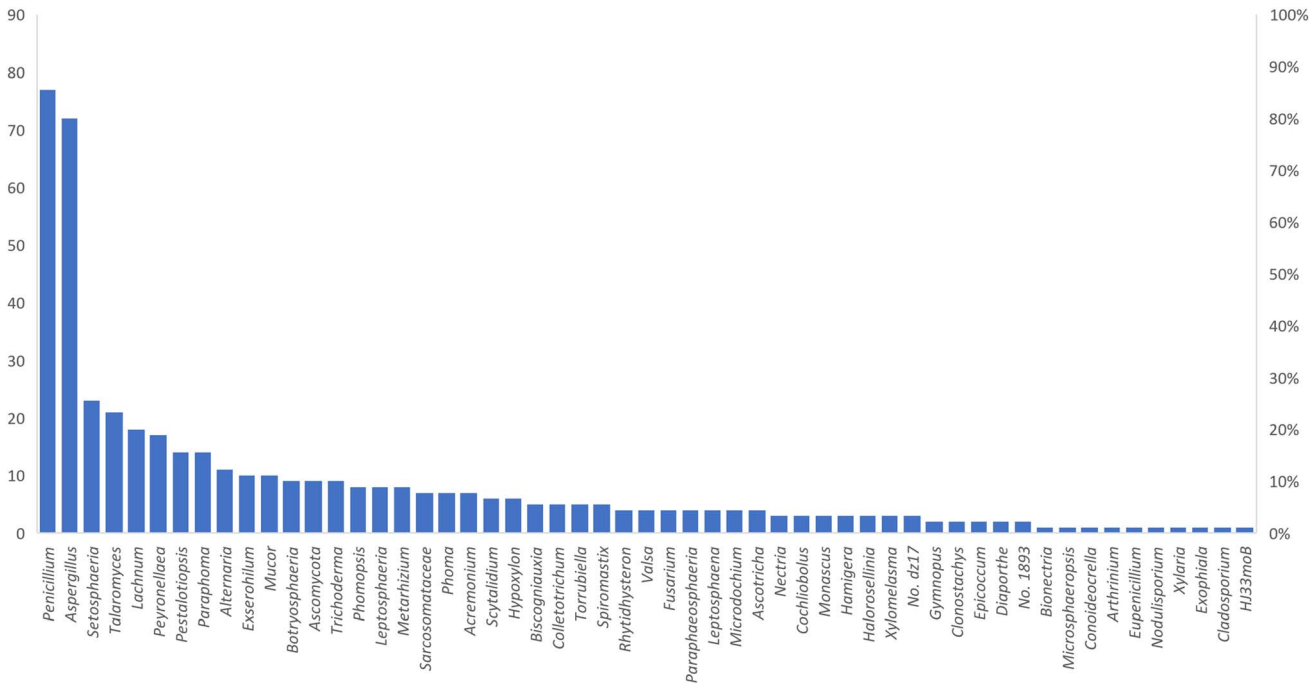


Fig. 58 Contribution of isocoumarins by various fungal genera.

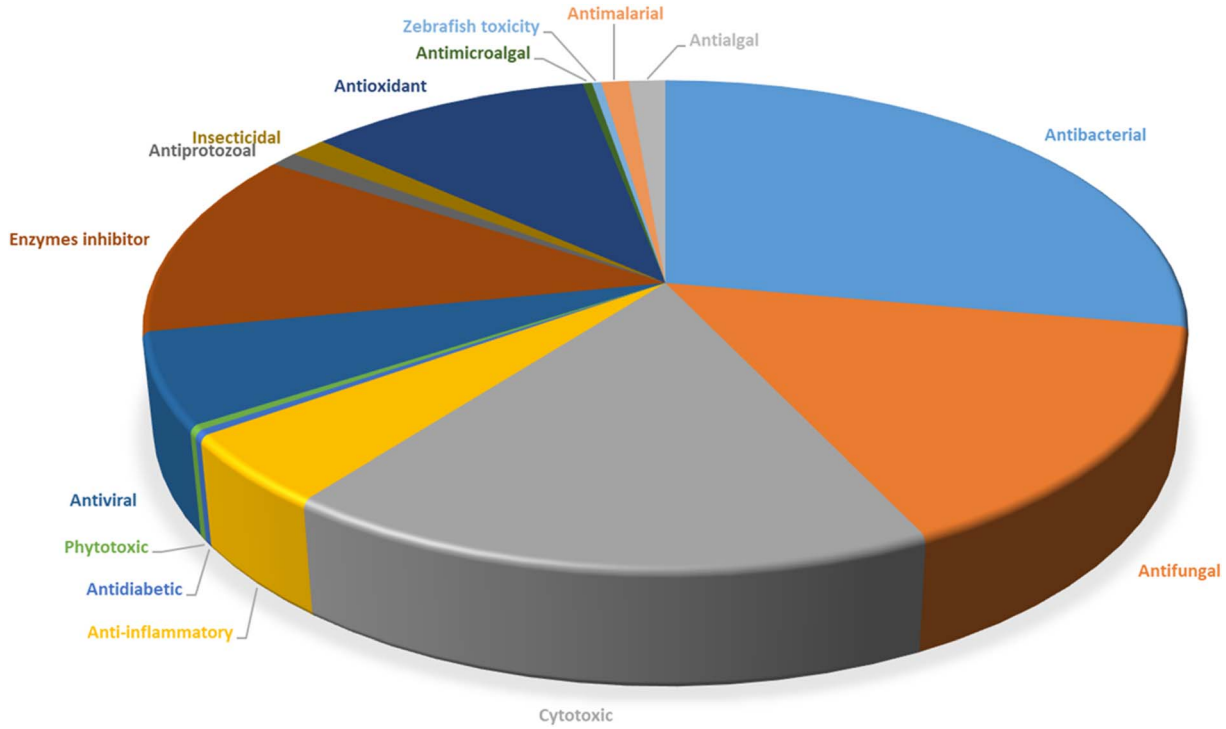


Fig. 59 Total therapeutic activities of various isocoumarins isolated from different fungal species.

4. Conclusion and future prospectives

For decades, natural products have granted medicine an innumerable supply of safe and effective drugs in various medicinal fields. Fungi, the broad diverse class of eukaryotes, is characterized by its variable habitats extending between air, water, soil, and within other marine and terrestrial hosts. Moreover, fungi have been traditionally used in treating various ailments in different old nations, especially Asia. Indeed, notable attention has recently been directed toward fungi as a substantial robust reservoir of pharmacologically active metabolites of crucial value in drug discovery. Among the captivating classes of fungal secondary metabolites are isocoumarins. We hereby present a comprehensive up to date literature reviewing focused on isocoumarins isolated over the period 2000–2022 from different fungal natural sources. A total of **351** structurally diverse isocoumarins isolated from various fungal genera were documented in this current review. Their chemical diversities and biological potentials constituted the focal point of interest of the current review, beside presenting brief highlights on the isocoumarin biosynthetic pathways. Thoroughly, in this manuscript, the analysis of such massive data revealed the richness of the fungal order (Eurotiales) with isocoumarins, representing 51% of the reported isolated compounds (Fig. 56). Meanwhile, on the family level, family (Aspergillaceae) was the most represented fungal family comprising 38% of the reported isocoumarins, followed by (Pleosporaceae) and (Trichocomaceae), from which 10% and 5% of the recorded isocoumarins were reported, respectively (Fig. 57). Intriguingly, the gathered statistical data also revealed the significant contribution of the two fungal species, *Penicillium* and *Aspergillus*, which constitute the prevailing sources of the reported compounds (Fig. 58), where a total of 149 isocoumarins were solely isolated from these two fungal species, representing 42% out of the reported isocoumarins over the specified 23 years period of the review. With emphasis on the therapeutic potentials of the recorded isocoumarins, a broad array of multiple biological activities was documented, including anti-inflammatory, antioxidant, antimicrobial, cytotoxic, and enzyme inhibitory activities. In addition, it is worthy to mention that the cytotoxicity, antibacterial, and antifungal activities were the most profoundly studied biological assays. Moreover, such massive biological screening revealed the evaluation of 155 isocoumarins for their cytotoxic potentials against different cancer cell lines. Furthermore, a total number of 160 and 77 isocoumarins were evaluated for their antibacterial and antifungal activities, respectively (Fig. 58). Noteworthily, a considerable number of isocoumarins, for example, compounds **84**, **108**, **124**, **128**, **130–131**, **134**, and **156**, demonstrated significant biomedical potentials, including antibacterial, cytotoxic, and antidiabetic, respectively, which exceeds the potency when compared to the standards. Moreover, asperentin (**59**) displays numerous potent pharmacological activities, including antifungal, antimicrobial, antiplasmodial, and recently, as inhibitors of the protein tyrosine phosphatase 1B. Actually, such massive linkage between the different chemical architectures and their associated biological significances sheds light on the considerable importance of fungi as a prolific reservoir of promising lead compounds, which are worth future exploration for

pharmaceutical and industrial applications. In-depth study of the pharmacokinetic properties of the fungi-derived isocoumarins is highly recommended as a prerequisite step in enhancing the opportunities for discovering potential drug candidates for different preclinical and clinical trials (Fig. 59).

Abbreviations

A549	Human lung cancer cells
AChE	Acetylcholinesterase
AsPC-1	Xenograft model pancreatic cancer
BEL-7402	Hepatoma cell line
BGC823	Human gastric cancer cell line
BHT	Butylated hydroxytoluene
BT474	Human breast cancer cell line
CCD25sk	Cellosaurus cancer cell line
CDK-2	Human cyclin-dependent kinase 2
CN	Ser/Thr phosphatase calcineurin
CNE1	Cellosaurus CNE-1
CNE2	Cellosaurus CNE-2
COX-2	Cyclooxygenase-2
CYP19 aromatase	Cytochrome P450 aromatase
DDP	*cis*-Diamminedichloroplatinum(II)
DEPT	Distortionless enhancement by polarization transfer
DMSO	Dimethyl sulfoxide
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DU145	Prostate cancer cell line
EtOAc	Ethyl acetate
EV71	Enterovirus 71
H1975	Human lung cancer cells
H_2O_2	Hydrogen peroxide
H_3N_2	Influenzavirus A
H460	Human lung cancer cells
HCT116	Human colon cancer cells
HCT-8	Human colon cancer cells
HEK293T	Human embryonic kidney 293 cells
HeLa	Human cervical cancer cell line
Hep-2	Human hepatocellular cancer cell lines
HepG2	Human hepatocellular cancer cell lines
HIV	Human immunodeficiency virus
HL-60	Human promyelocytic leukemia cells
HOAc	Acetic acid
HONE1	Epithelial tumor cell lines
HT29	Human colon adenocarcinoma cell line
HUAECs	Human amniotic epithelial cells
HuCCA-1	Human cholangiocarcinoma cell line
Huh-7	Human hepatocellular cancer cell lines
HUVECs	Human umbilical vein endothelial cells
IC_{50}	Inhibitory concentration that causes a 50% reduction in cell viability
iNOS	Inducible nitric oxide synthase
K562	Human leukemia cancer cell line
KATO-3	Human gastric cancer cell line
KB	Human epidermoid carcinoma, ATCC CCL-17
KYSE150	Esophageal adenocarcinoma cells
L5178Y	Mouse lymphoma
L-929	Murine fibroblasts cancer cell line
LPS	Lipopolysaccharide
MCF10A	Human breast cancer cells
MCF-7	Human breast cancer cells
MDA-MB-435	Melanoma cell line
MeOH	Methanol
MGC-803	Human gastric cancer cell line
MIA-PaCa-2	Epithelial pancreatic cancer cell line
MIC	Minimum inhibitory concentration
Molm 13	Acute myeloid leukemia
MOLT-3	Human acute T lymphoblastic leukaemia
MOLT-4	T lymphoblast cell line
MptpB	Mycobacterial protein tyrosine phosphatases A and B inhibitors
MTT assay	Colorimetric assay for assessing cell metabolic activity
NCI-H187	Human small cell lung cancer, ATCC CRL-5804
NCI-H460	Human non-small-cell lung cancer cell line
NO	LPS-induced nitric oxide
NS-1	Myeloma cancer cell line
ORAC	Oxygen Radical Absorbance Capacity
PC3	Metastatic human prostate adenocarcinoma cancer cell line
PGE2	Prostaglandin E2
Psa	*P. syringae* pv. *Actinidiae*
PTP1B	Protein Tyrosine Phosphatase 1B
QGY7701	Human hepatocellular cancer cell lines
RAW 264.7	Macrophage-like, Abelson leukemia virus-transformed cell line derived from BALB/c mice
$Rh_2(OCOCF_3)_4$	Rhodium;2,2,2-trifluoroacetic acid
SF-268	Human CNS glioma cancer cell line
SGC7901	Human gastric cancer cell line
SHSY5	Thrice cloned subline of the neuroblastoma cell line
SH-SY5Y	Human glioma cell lines
SMMC-7721	Human hepatocarcinoma
SW620	Human colon cancer cells
TBARS	Thiobarbituric acid reactive substances
*t*BHQ	*tert*-Butylhydroquinone
TDDFT	Time Dependent DFT
TMV	Tobacco mosaic virus
Topo I	Topoisomerase I
TPA	12-*O*-tetradecanoylphorbol-13-acetate
Vero cells	African green monkey kidney fibroblasts, ATCC CCL-81
U2OS	Human Bone Osteosarcoma Epithelial Cells
U937	Monocyte morphology
UV/vis	Ultraviolet-visible spectroscopy
XTT assay	Colorimetric method that uses the tetrazolium dye, 2,3-bis-(2-methoxy-4-nitro-5-sulphenyl)-(2*H*)-tetrazolium-5-carboxanilide

Author contributions

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Conflicts of interest

The authors declare that they have no known competing commercial interests or personal relationships that could have appeared to influence the work reported in this paper.

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