Recent Advances in Discovery, Biosynthesis and Therapeutic Potentialities of Isocoumarins Derived from Fungi: A Comprehensive Update

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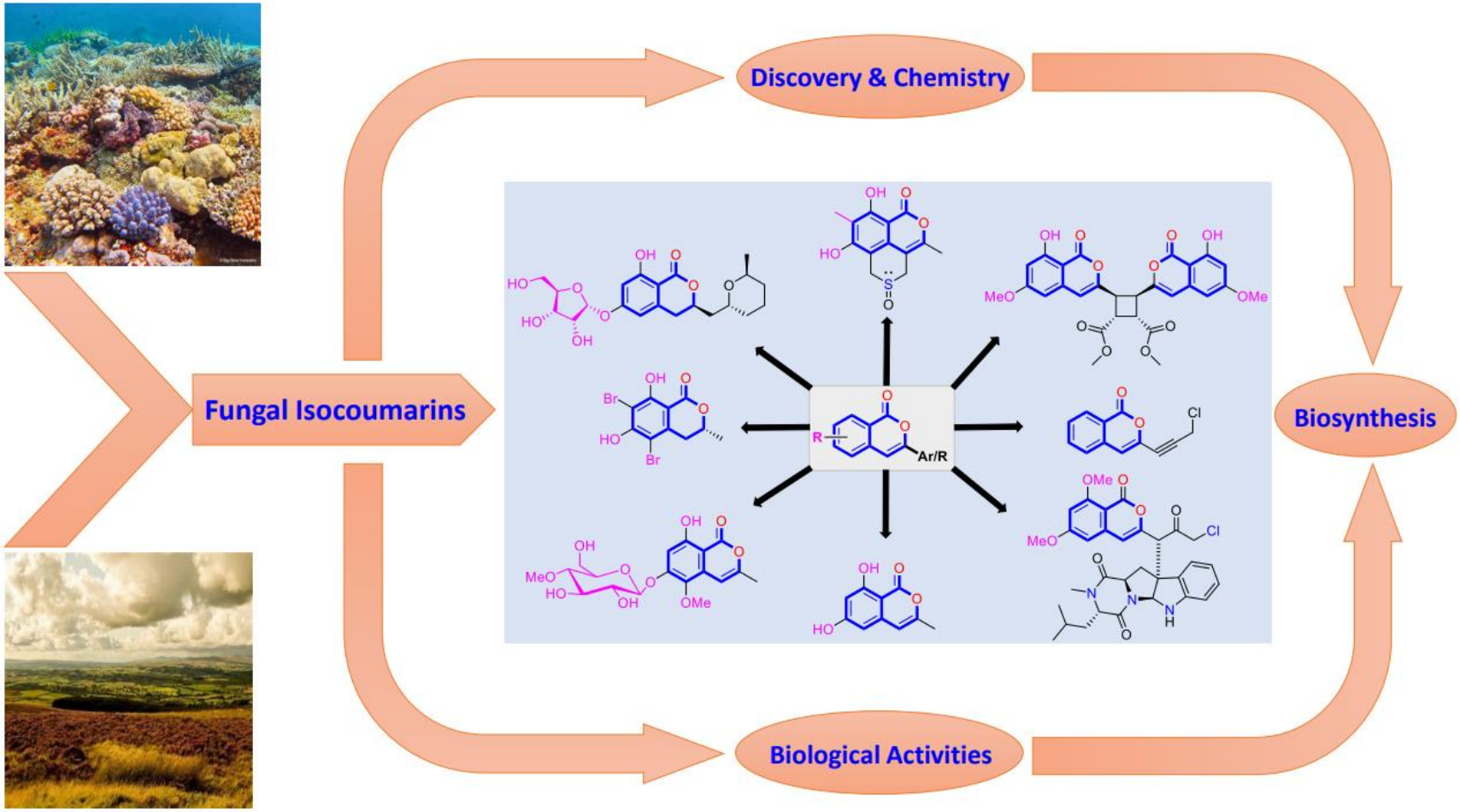
Graphical Abstract:

This review article provides an intensive state-of-the-art over the period 2000-2022 centred around the discovery, classifications, and therapeutic potentialities of fungal containing-isocoumarins. Indeed, a comprehensive list of 351 structurally diverse compounds were documented, taxonomically classified according to their fungal sources, alongside their reported pharmacological activities wherever applicable. Also, recent insights around their proposed and experimentally proven biosynthetic pathways are also briefly discussed.



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Abstract: Microorganisms still remain as main hotspots in the global drug discovery avenue. In particular, fungi are highly prolific producers of a vast of structurally divers specialised secondary metabolites, which have displayed a myriad of biomedical potentialities. 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 potentialities of isocoumarins exclusively reported from fungi. Indeed, a comprehensive list of 351 structurally diverse isocoumarins were documented, classified according to their fungal sources [16 order/ 28 family/ 55 genera] where they have been originally discovered, alongside, their reported pharmacological activities wherever applicable. Also, recent insights around their proposed and experimentally proven biosynthetic pathways are also briefly discussed.

Keywords: Isocoumarin, Microbial Natural Products; Fungi; Therapeutic potentialities; bioactivity; Spectroscopy; Biosynthesis

List of abbreviations:

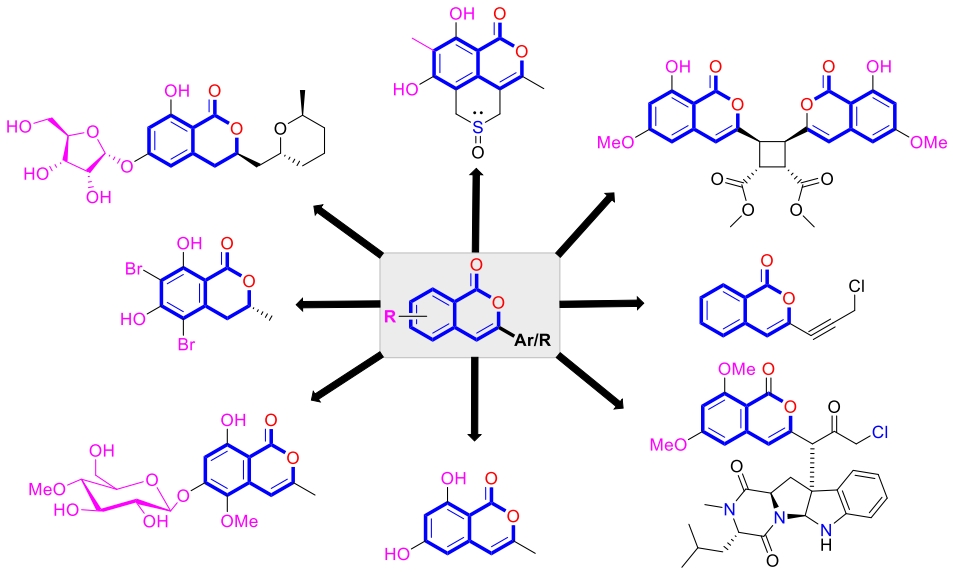
A549	Human lung cancer cells
AChE	Acetylcholinesterase
AsPC-1	Xenograft model pancreatic cancer
BEL-7402	Hepatoma cell line
BGC823	Human gastric cancer cell line
BHT	Butylated hydroxytoluene
BT474	Human breast cancer cell line
CCD25sk	Cellosaurus cancer cell line
CDK-2	Human cyclin-dependent kinase 2
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
tBHQ	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

1. Introduction

Natural products have long been recognized as a crucial mine for drug discovery. Indeed, they are traditionally used for centuries for their biological significance that 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 the 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 for overharvesting, depletion and extinction of many rare species of high medicinal value [5]. Hence, microorganisms, especially fungi, have recently received a 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, that 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 a copious 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]. Additionally, further *β*-lactam antibiotics were discovered from different fungi followed 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 different biological activities, including the immunosuppressant cyclosporine; statins, the inhibitors of cholesterol synthesis; the antifungal, Griseofulvin; kojic acid, the tyrosinase inhibitor besides many chemotherapeutic agents viz. vincristine, paclitaxel, camptothecin and others [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 viz the reviews by Saeed A., *et al*. that 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 [30]. Meanwhile, the recent review by Shabir *et al*., reported the natural isocoumarins isolated in the period between 2016–2020 focusing on their chemistry and their bioactivities [30]. As a part of our ongoing research on biologically active natural products [31–33] and with emphasize on pharmacologically active fungal natural products (**FNPs**) [4,16,34–36], herein, we present comprehensively over the period 2000-2022 un up-to-date literature reviewing on the chemical diversity and biological activities reported for isocoumarins isolated exclusively from different fungal strains. Indeed, the review is systematically documenting 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 discussed briefly.



Scheme 1: The isocoumarin core and representative isolated derivatives

2. General Biosynthetic Pathway of Fungal Isocoumarin

The chemistry of isocoumarin has been extensively studied since the 1950 or before as reported by Barry [37]. Isocoumarin is a well-known polyketide that had been biosynthesized by the polyketide synthase (PKS) pathway [38,39]. The biosynthetic pathway of isocoumarin derivates had been studied by Birch's group [40,41]. Their study investigated the biosynthesis of canescin from *Penicillium canescens* using stable isotopes (^{13}C labelled) and NMR spectroscopy to determine sites of incorporation. They pointed out that the isocoumarin portion of the canescin molecule being generated through the acetate/malonate pathway [41,42]. Indeed, Birch *et al*., discovered that canescin's C-10 and C-14 are generated from methionine. Further study by Lewis's group confirmed the canescin biosynthesis using the feeding experiment of [$^{13}C^{2}H_3$] methionine that administered to *Aspergillus malignus* using batch-wise method over 5 days incubation [42]. Advances in bioinformatic analysis, genetic transformation experiments and the progress in genome sequencing had revealed that isocoumarins in *Fusarium graminearum* had been synthesised by polyketide synthase 12 (*PKS12*), a transcription factor (*aurR1*) and several tailoring enzymes [43–46]. This type of PKS domain architecture consists of a *β*-ketoacylsynthase (KS), an acetyltransferase (AT), an acyl carrier protein (ACP) and a claisen-type cyclase (CLC) as shown in (**Figure 1A**). The biosynthetic pathway could be considered as a unified gate to generate different natural compounds by the modification of 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 active CLC domain to furnish the naphthopyrone YWA1 [47]. However, the absence of CLC domain has tragically led to the biosynthesis of citreoisocoumarin [48,49]. This demonstrates that similar PKS domain architectures in different species can lead to the biosynthesis of various polyketide derivatives [50]. Additionally, bikisocoumarin is another type of isocoumarin that biosynthesised by similar PKS named *bIK* [44] 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 [51,52] (**Figure 1B**) while bikisocoumarin was only obtained with the deletion of CLC domain. Furthermore, Ma *et al*., 2008 [51] 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 in order to elucidate the biosynthesis of some isocoumarins [53]. 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 is

consist of SAT-KS-AT-PT-ACP-ACP-TE domain. Meanwhile, Xiang *et al.*, 2020 has elucidated the structure of the three generated isocoumarins produced by ^{1}H-NMR analysis [53]. They concluded that compounds II-III are modification products obtained by endogenous host enzymes during the heterologous expression (**Figure 1C**). Additionally, fusamarins (FMN) are another type of dihydroisocoumarins which is isolated from the plant-pathogenic fungus *Fusarium mangiferae*. Although it was reported 50 years ago, the biosynthetic pathway was not revealed yet. Indeed, Atanasoff-Kardjalieff *et al.*, [54], managed to investigate the gene cluster involved in the fusamarins biosynthesis. They represented that FmPKS8 biosynthetic gene cluster (FMN BGC) is leading the biosynthesis which is composed of FmPKS*8* (*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*-adenosyl-methionine (SAM)-dependent methyltransferase (CMet) and keto reductase (KR) domain. They observed that C-Met domain is not functional in the FMN BGC as the isolated metabolites were not C-methylated, which is conventional for HR-PKS to have inactive CMet domain [55]. Whereas *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 hypothesised 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 (**Figure 1D**).

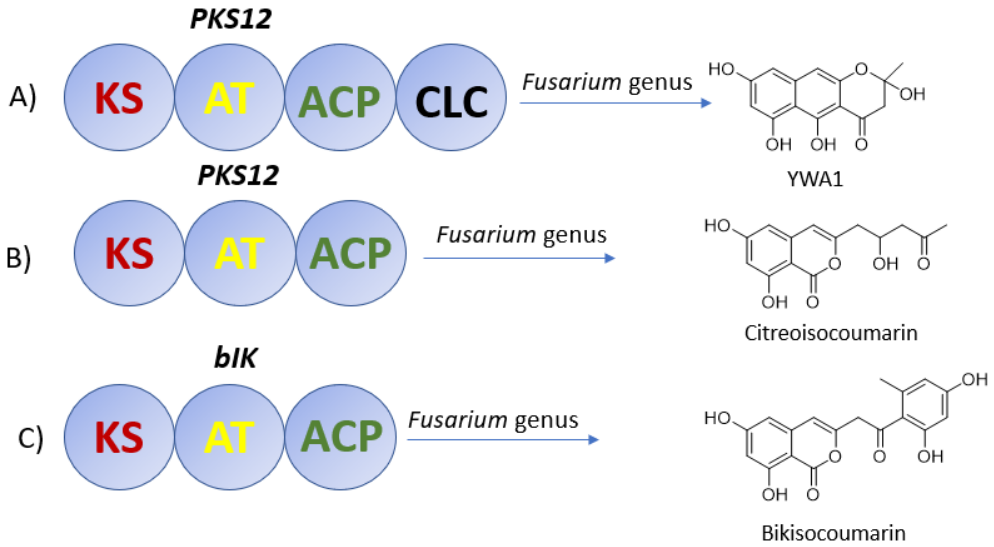
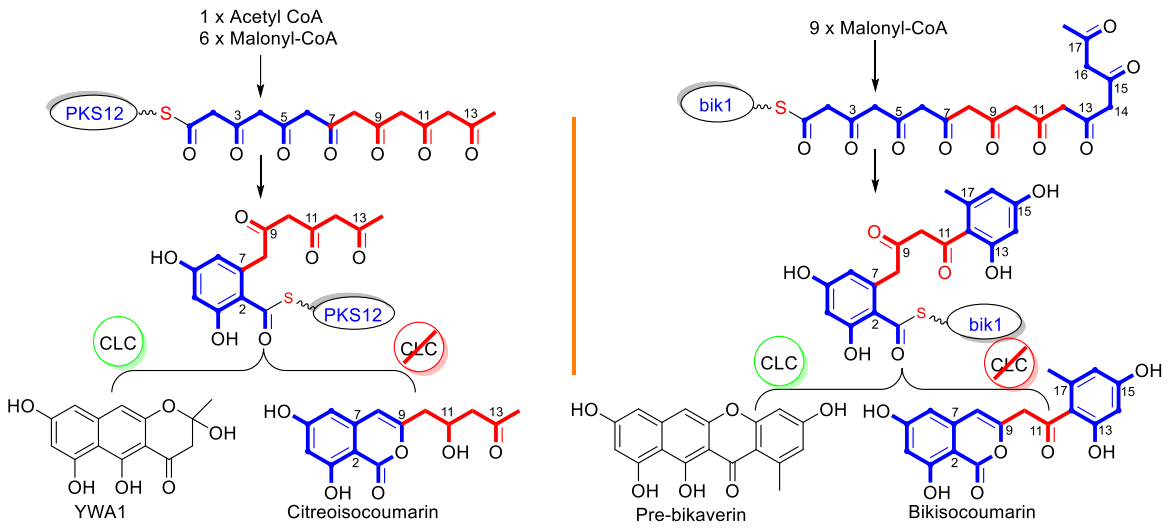


Figure 1A: Domain architecture of various PKS producing isocoumarin derivatives; KS (β-ketoacylsythase), AT (acetyltransferase), ACP (acyl carrier protein) and CLC (claisen-type cyclase).



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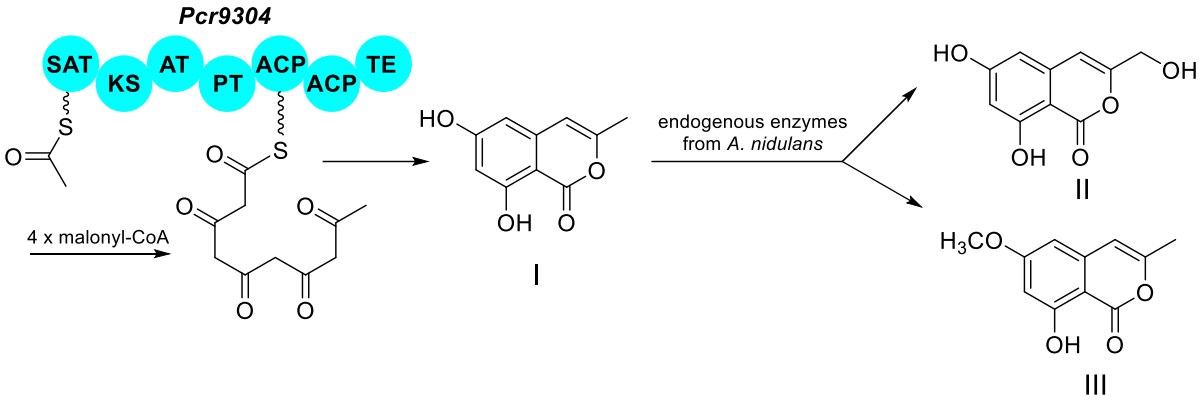
191 **Figure 1B**: Biosynthesis of citreoisocoumarin and bikisocoumarin through different PKS architecture
192 domains.



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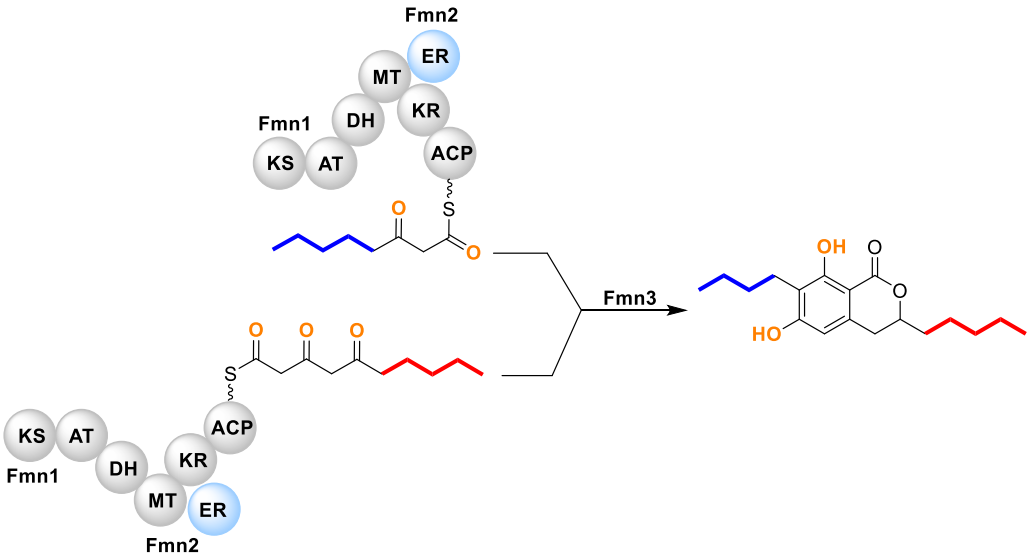
194 **Figure 1C**: Successful heterologous expression of three isocoumarin derivatives by non-reducing
195 polyketide synthase (NR-PKS) in *Aspergillus nidulans* as a host.



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197 **Figure 1D**: Proposed biosynthetic pathway of FMN.

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**) (**Figure 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) exhibited weak to moderate activity against some of the examined strains. Additionally compounds **1-2** showed cytotoxic effect toward the mouse fibroblast cell line L-929 with IC_{50} values 3.7 and 14.0 μM, respectively [56].

1 **2**

Figure 2. Chemical structure of **1-2**.

3.2. Fungi of the order Botryosphaeriales

3.2.1. Fungi of the family Botryosphaeriaceae

3.2.1.1. Fungi of the genus *Botryosphaeria*

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**) (**Figure 3**). Despite, none of the isolated compound showed any cytotoxic effect against the following cancer cell lines (K562, MCF-7, A549, U937, HeLa, DU145, HL60, BGC823, MOLT-4 and H1975), compound **3**, showed antiinflammation properties through the inhibition of COX-2 activities with IC_{50} 6.51 μM [57]. Other four previously unreported isocoumarin derivatives namely botryospyrones A-D (**8-11**) (**Figure 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 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 towards *Penicillium italicum* with MIC value > 900.0 μM. Also, it is worth to mention that compound **11** was not examined as it was obtained in a very minute amount [58].

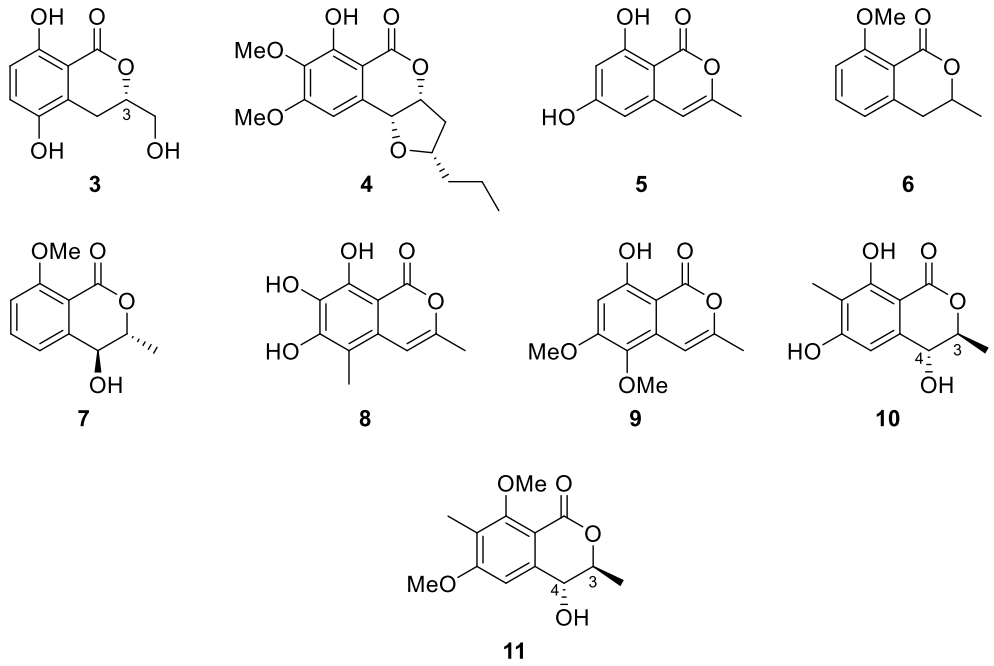


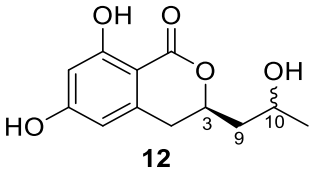
Figure 3. Chemical structure of **3-11**.

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**) (**Figure 4**), it is worth mention that compound **12** was not assessed for any biological activity [59].



12

Figure 4. Chemical structure of **12**.

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)** (**Figure 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 glucose uptake activity when tested *in vitro*, using Rosiglitazone as a positive control [60].

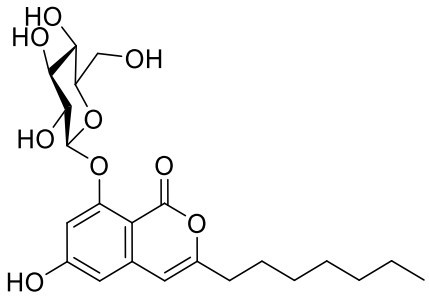


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Figure 5. Chemical structure of **13**.

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)** (**Figure 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 to mention that compound **14** is well known to be more active on monocots than dicots [61]. A previously unreported dihydroisocoumarin derivative namely Diaporone A **(15)** (**Figure 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 MIC value 66.7 μM. Additionally, 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 displayed found to a weak cytotoxic agent against Hela cell lines with IC_{50} 97.4 μM [62].

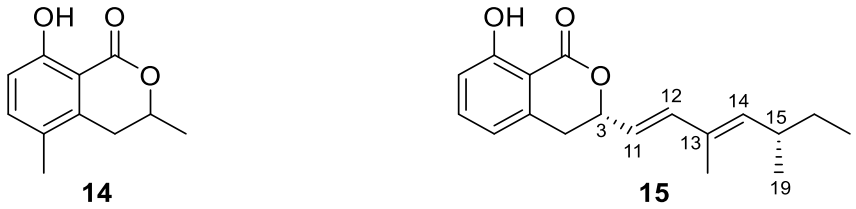


Figure 6. Chemical structure of **14**-**15**.

3.5.2. Family of the family Valsaceae

3.5.2.1. Fungi of the genus *Phomopsis*

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**) (**Figure 7**). Compounds **16-17** were tested for their antibacterial activity towards 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 the microplate assay and streptomycin as a 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, respectively; and towards *X. citri* pv. *phaseoli* var. *fuscans* with MIC value of 31.2 μg/ml [63]. 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 pestalactone C (+)-(**21**) and oxoisochromane (-)-(**21**) (**Figure 7**). Only compound **18** exhibited anti-inflammatory activity by the inhibition of the 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 [64].

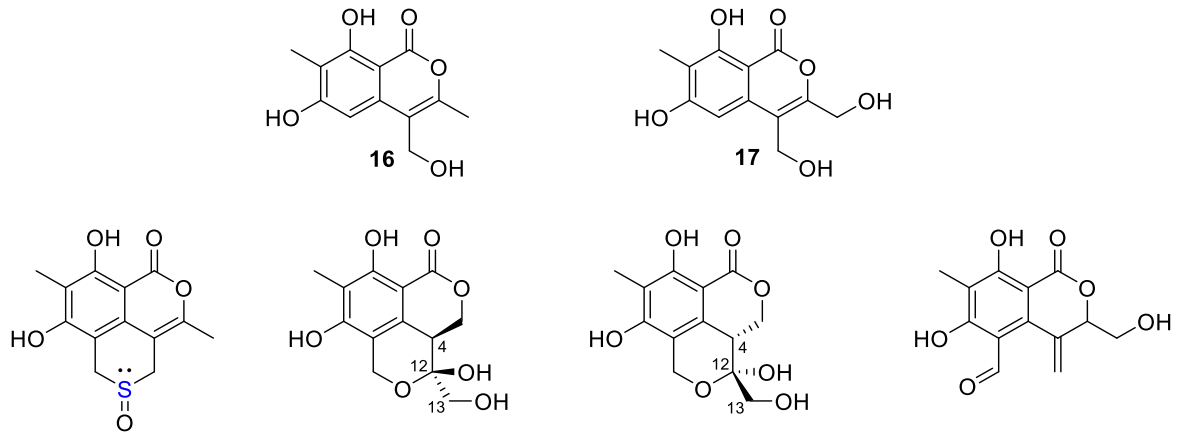


Figure 7. Chemical structure of **16-21**

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 mention (–)5-methylmellein (**14**), (–)-5-hydroxymethylmellein (**23**) and (–)-(3*R*,4*R*)-*cis*-4-hydroxy-5-methylmellein (**24**) (**Figure 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 concentration 50 μg/ml [65].

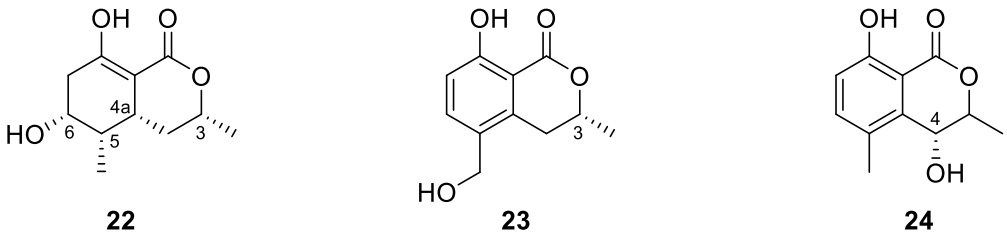


Figure 8. Chemical structure of **22-24**

3.6. Fungi of the order Eurotiales

3.6.1. Fungi of the family Aspergillaceae

3.6.1.1. Fungi of the genus *Aspergillus*

Chemical investigation of the marine derived fungus *Aspergillus* sp associated to 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 mention *trans*-4-hydroxymellein (**7**) (**Figure 9**). All the isolated compounds exhibited no cytotoxicity once examined against two tumour cell lines HCT-8 and MDA-MB-435 [66]. Another 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 at 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 also known as similanpyrone A (**Figure 9**). Compounds **27**-**30** showed neither antifungal nor antibacterial when tested against *C. albicans* ATCC 10231, the Gram-negative bacteria (*E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) and the Gram-positive bacteria (*S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633) [67]. Additionally, 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)** (**Figure 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 ranged from 11.5 to 28.6%. Furthermore, it is worth mention that compound versicoumarins A (**37**) exhibited the highest inhibitory activity 28.6%. Additionally, they also tested for their cytotoxicity against MCF7, NB4, PC3, SHSY5Y, 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 towards MCF7 and A549 tumor cell lines with IC_{50} values of 4.0 and 3.8 μM, respectively [68]. (*S*)-(−)-6,8-Di-*O*-methylcitreoisocoumarin (**38**) (**Figure 9**), a previously non-reported 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 [69]. 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 also known 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**) (**Figure 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 5μg/ml with an inhibition zone 19.7 mm [70]. Six dihydroisocoumarins derivatives including the previously mentioned asperentin (**39**), 5′-hydroxyasperentin (**40**), 4′-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**) (**Figure 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 300 m respectively. Compounds **39**-**42**, **48**-**49**, were tested for their antineuro-inflammatory activity, and they displayed inhibition activity towards 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 ranged from 10 to 80 μM [71]. Chemical examination of MeOH extract of the mangrove derived fungus *Aspergillus* sp. 16-5B isolated from *Sonneratia apetala* leaves, collected in China, in Hainan Island, led to the isolation of two previously unidentified isocoumarin derivatives as racemic mixture of the possible enantiomer. *i.e.,* (±) **50** and (±) **51** (**Figure 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 in active, compound **50** displayed an inhibition activity with IC_{50} values of >200 and 90.4 μM, respectively [72].

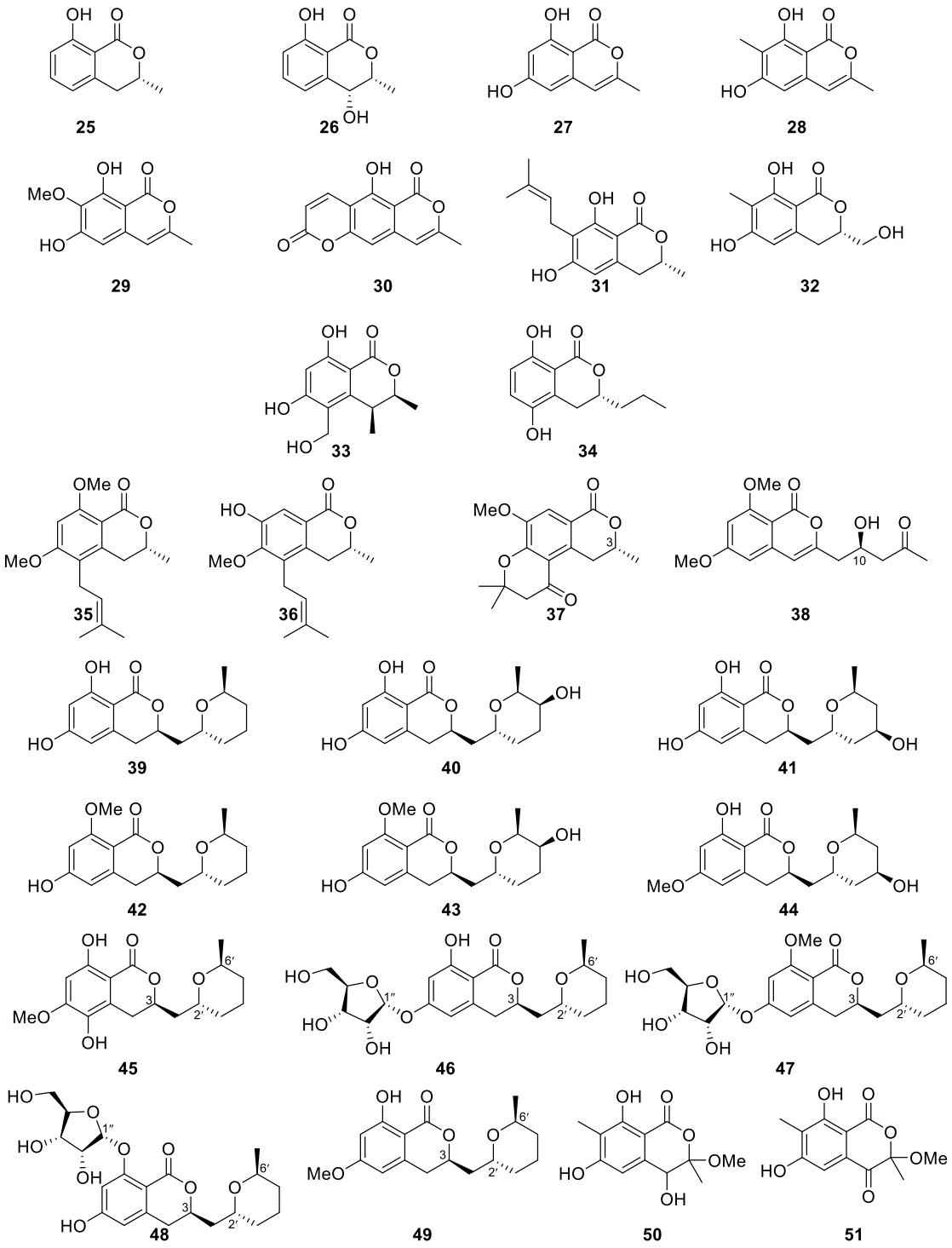


Figure 9. Chemical structure of **25-51**

Similanpyrone C **(52)** (**Figure 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 [73]. 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**) (**Figure 10**). Intriguingly, the presence of the unusual 2-oxopropyl group and a rare 3-hydroxypropyl group, has 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 towards 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 ranged from 2.8-8.8 μM [74]. Asperentin B (**59**) (**Figure 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 IC_{50} value of 2.05 μM, when comparing with suramin as a positive control with exhibited with an IC_{50} value of 11.85 μM. Additionally, **59** exhibited weak inhibitory activity against *Propionibacterim acnes* with an inhibition rate of 57% at 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 tumour 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 ranged from 83-100 % when compared with the positive control clotrimazole, which also it displayed a very weak antifungal activity [75].The previously mention 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**) (**Figure 10**), were obtained from the EtOAc extract of the fermentation product of the endophytic fungus *Aspergillus versicolor*, obtained from the rhizome of *Paris polyphylla* var. *yunnanensis*, collected in Yunnan, China. No relevant biological activity was reported for **60**-**63** [76]. 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**) (**Figure 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 NS-1 cancer cell line using ampicillin, clotrimazole, mebendazole and 5-fluorouracil, respectively as positive controls. Despite, 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 aforementioned biological assays [77].

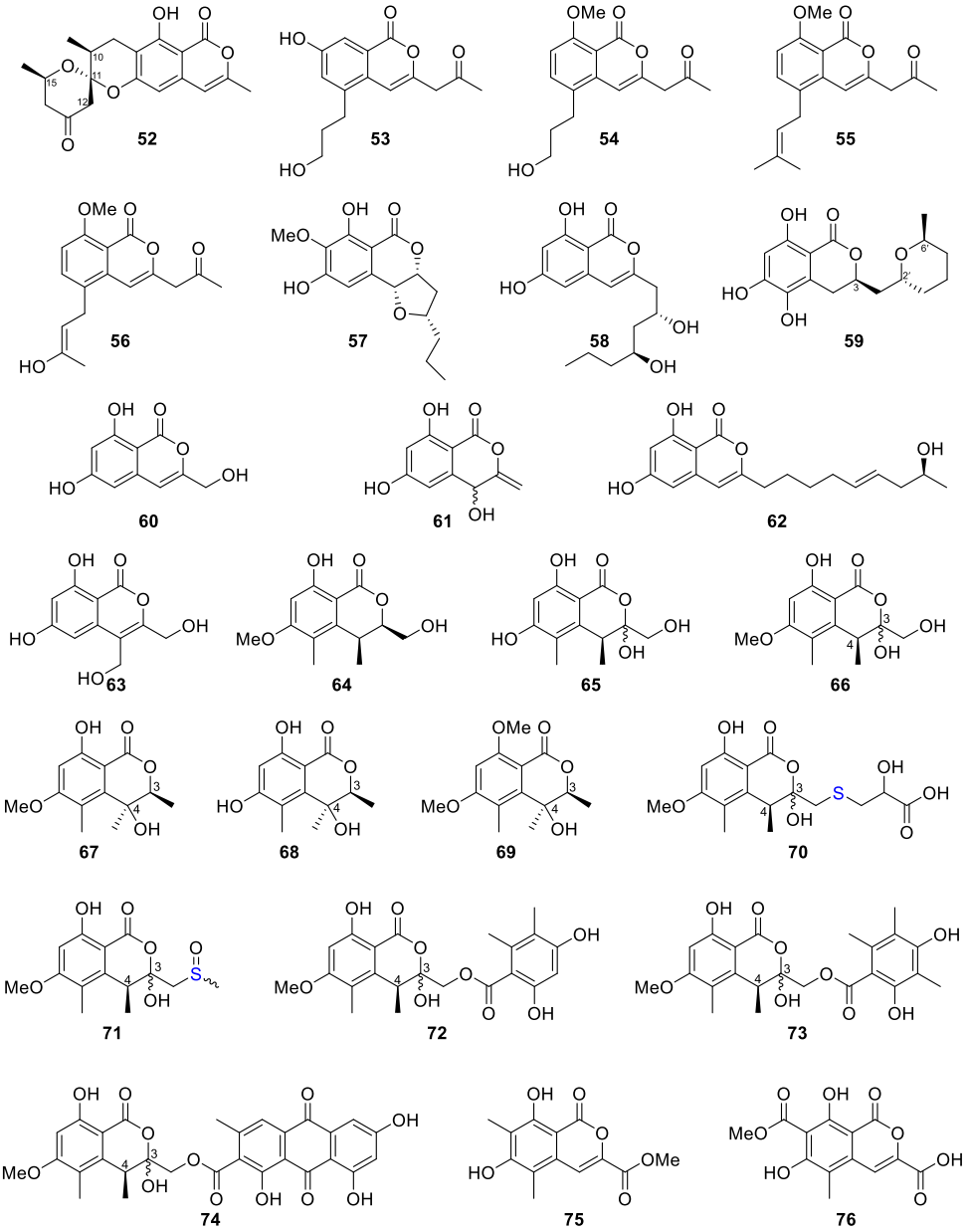


Figure 10. Chemical structure of **52-76**

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**) (**Figure 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 [78]. Chemical examination of the terrestrial 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, which is featuring a polyketide-nonribosomal peptide (PKS-NRPS) biogenesis pathway (**Figure 11**). Compound **84** displayed a moderate antifungal effect towards *C. albicans* using caspofungin as a positive control, with MIC value of 32.0 μg/ml. Additionally, it exhibited potent cytotoxicity against MIA-PaCa-2 and AsPC-1 with IC_{50} values of 1.63 and 5.53 μM, respectively [79]. Three previously undescribed isocoumarins, namely apergisocoumrins A-C (**85-87**), along with the previously identified, 8-dihydroxyisocoumarin-3- carboxylic acid (**88**) and dichlorodiaportin (**89**) (**Figure 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 tumour cell lines, **85** exhibited potent cytotoxic activity against MDA-MB-435, HepG2, H460, and MCF10A with IC_{50} value ranged from 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 [80]. Two previously unreported isocoumarins namely aspergillspins F-G (**90-91**) (**Figure 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 towards *B. subtilis* and *E. coli* using the standard disc diffusion [81]. Asperisocoumarin G (**92**) (**Figure 11**), a previously undescribed isocoumarin, was isolated from MeOH extract of the marine derived fungus *Aspergillus* sp. 085242 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. Additionally, 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 [82]. 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 mention dichlorodiaportin (**89**) along with the previously synthetic 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 (ΔG = -20.32, -22.30 and -20.46, respectively) [83].

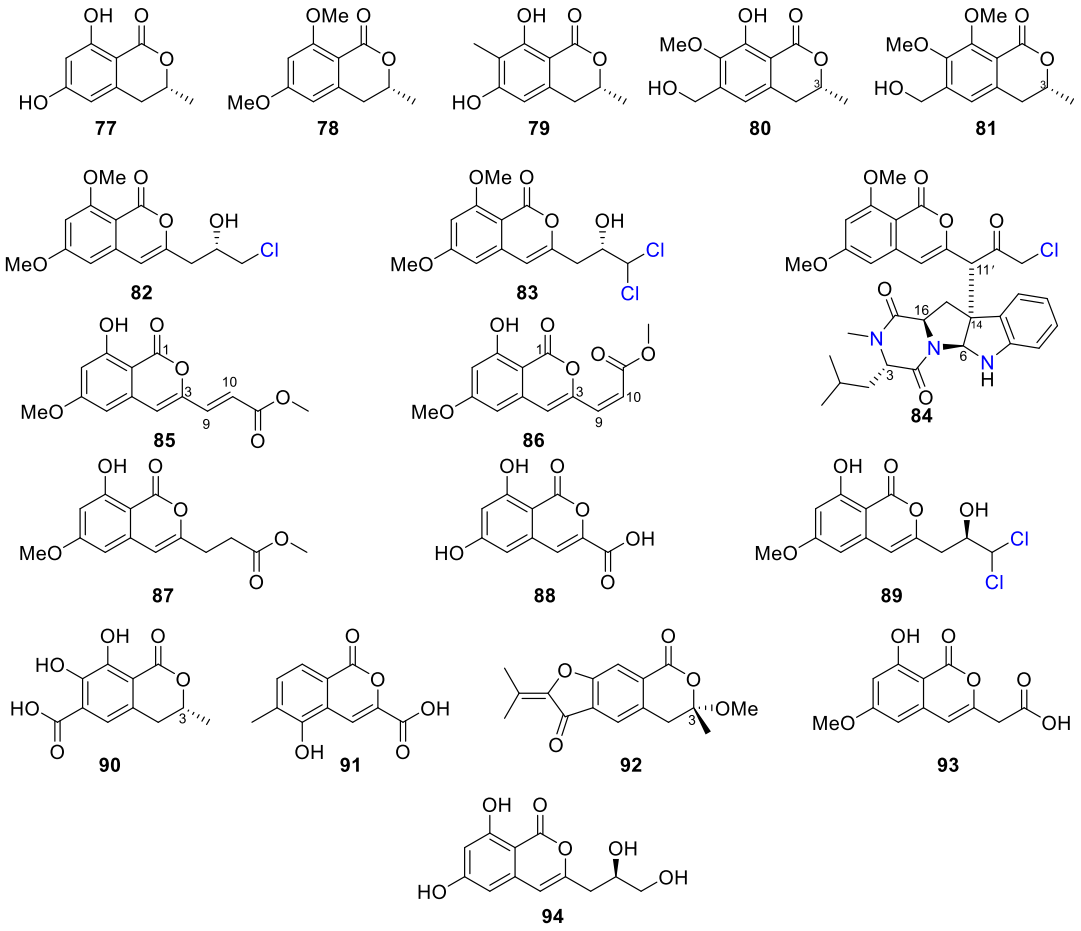


Figure 11. Chemical structure of **77-94**

3.6.1.2. Fungi of the genus *Penicillium*

Dihydrocitrinone (**95**) (**Figure 12**), a previously described isocoumarin was reported from the marine derived fungus *Penicillium notatum* B-52 isolated from the sediments, collected in the Lake of Qinghai, China. Additionally, 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**) (**Figure 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 tumour cell lines [84]. *Cis*-4-hydroxymellein (**26**), a previously mention derivative (**Figure 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 this compound [85]. Additionally, chemical investigation of the marine derived endophytic fungus *P.* sp., 091402 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**) (**Figure 12**). Compound **97** was not tested for any relevant bioactivity, compound **98** displayed mild cytotoxic activity against K562 cancer cell line with IC_{50} 18.9 μg/ml [86]. Penicilisorin (**99**) (**Figure 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 [87]. A previously unidentified citrinolactone D (**100**) along with and the previously described citrinolactone B (**101**) (**Figure 12**), were isolated from the marine sediment derived fungus *P.* sp., ML226, isolated from the sediment of mangrove region, China, Long Hai.

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 was 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 [88]. 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 non-reported 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**) (**Figure 12**) and previously mentioned derivative penicimarin F **(63)** (**Figure 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 by 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 [89].

Terrecoumarins A-C (**111-113**), three previously unreported isocoumarins along with known ones including, periplanetin A (**114**), 6-hydroxy-3-hydroxymethyl-8-methoxyisocoumarin (**115**) (**Figure 12**), periplanetin D (**32**) (**Figure 9**) and 6,8-dihydroxy-3-hydrox ymethylisocoumarin (**60**) (**Figure 10**), were reported from the terrestrial derived fungus *P. oxalicum* 0403 isolated from *Nicotiana sanderae* leaves collected in China, Yunnan Province. 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 ranged from 11.3-18.9% [90]. Additionally, the chemical examination of 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**) (**Figure 12**). No relevant biological activity was reported for **97** obtained from this species [91]. Furthermore, 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**) (**Figure 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 [92]. Chen *et al.*, 2017 [93] 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)** (**Figure 12**). Despite Xin *et al.*, 2007 [84], suggested before that stoloniferol A (**96**) was reported as one pure compound, Chen *et al.*, 2017 [93] succeeded in its isolation in form of two enantiomers as stoloniferol A (**96**) i.e., *R*-(−)- stoloniferol A, *S*-(+)- stoloniferol A (**96**). Compounds **96**, **120**-**121** displayed no activity when examined for their antibacterial, cytotoxic, antiviral, and anti-inflammatory (COX-2) activities.

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

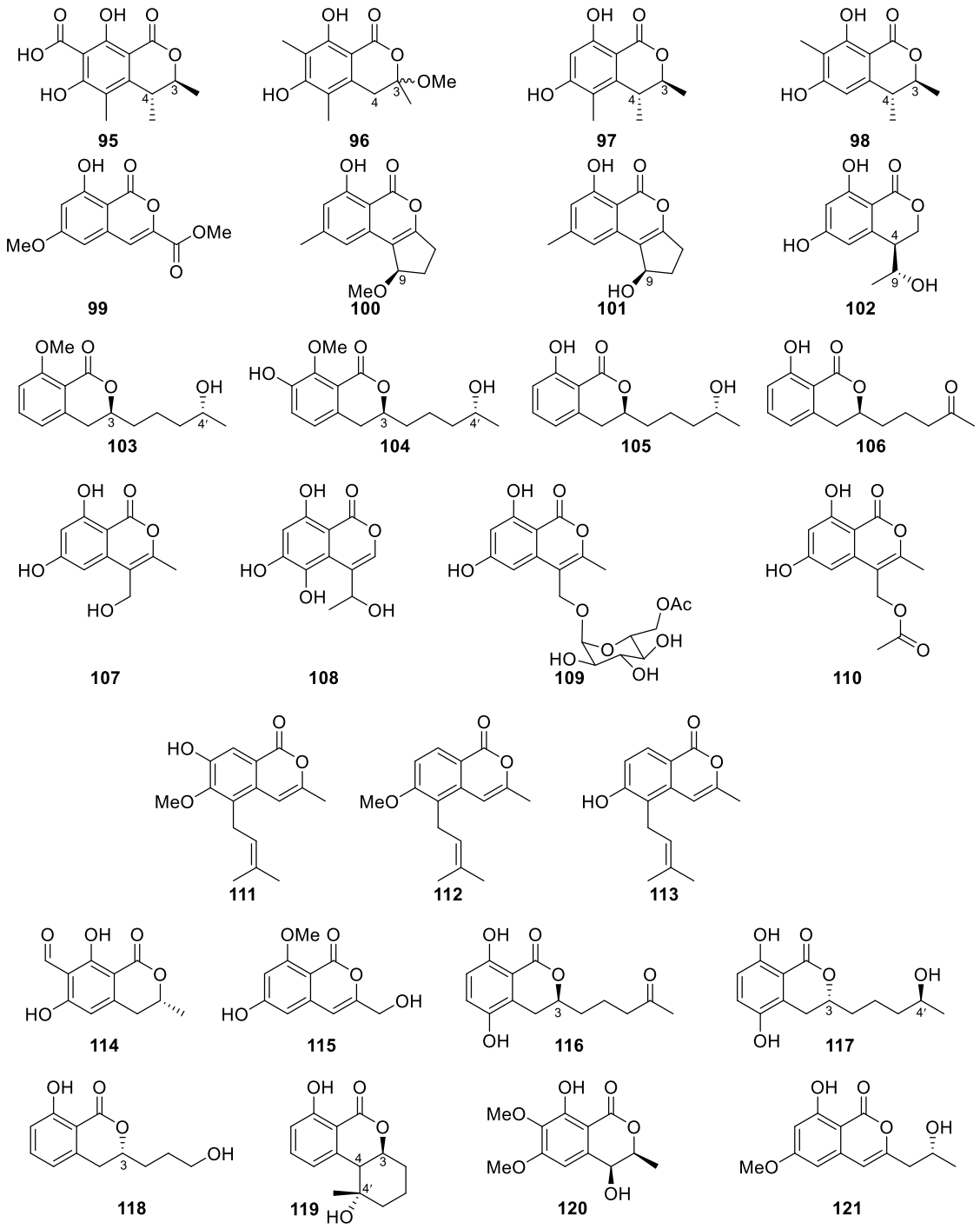
Compounds **89** and **121**-**132** were tested for their α-glucosidase inhibition activity using acarbose as a positive control. Indeed, **89** and **126**-**127** displayed mild inhibitory effect with IC_{50} values of 102.4, 110.3 and 158.4 μM, respectively. Moreover, **124**, **128** and **130**-**131** 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. Additionally, 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 IC_{50} value of 20.7 μM, but the rest compounds exhibited weak or no activity. Moreover, none of the isolated compounds exhibited cytotoxicity against A549, HepG2, HeLa, MCF-7, and HEK293T tumour cell lines using the MTT method [94]. 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 mention asperentin also known as cladosporin (**39**), 5′-hydroxyasperentin (**40**) (**Figure 9**). Compound **39** displayed cytotoxicity against 22Rv1 cancer cell line with high selective index. Additionally, it displayed anti-inflammatory effect by decreasing the NO production by 24.1% in LPS-stimulated macrophages [95].

A previously undescribed penicitol D (**133**)**,** along with four known derivatives, stoloniferol B (**97**) (**Figure 12**), (3*S*,4*S*)-sclerotinin A (**134**), (3*R*)-6-methoxymellein (**135**) and (3*R*)-6-methoxy-7-chloromellein (**136**) (**Figure 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 the 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 towards MRSA (ATCC 43300, CGMCC 1.12409) and **134** showed relatively stronger effect in comparison with the other compounds. Additionally, **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, has been used) [96].

A chemical investigation of the sponge derived fungus *P.* sp., XWS02F62, isolated from the marine sponge *Callyspongia* sp, collected in China, Guangdong, afforded one previously no-recorded isocoumarin, named 7-*O*-methylpenicitor A (**137**) along with previously reported aspergillumarins B (**105**) and A (**106**), and penicitor A **(138)** (**Figure 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 inhibitions rate of 31.3% and 25.7% at concentration of 5 μM, respectively [97]. Three previously mentioned derivatives, penicimarin C (**104**), aspergillumarin A (**106**) and (*R*)-3-(3-hydroxypropyl)-8-hydroxy-3,4-dihydroisocoumarin (**142**) (**Figure 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 (**Figure 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 respectively. Moreover, none of the isolated compound exhibited cytotoxicity towards 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 cereu*s (ATCC 11778), *V. parahaemolyticus* (ATCC 17802) and *V. alginolyticus* (ATCC 17749), using the microplate assay method and Ciprofloxacin as the positive control. Additionally, 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 [98].



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612 **Figure 12**. Chemical structure of **95-121**

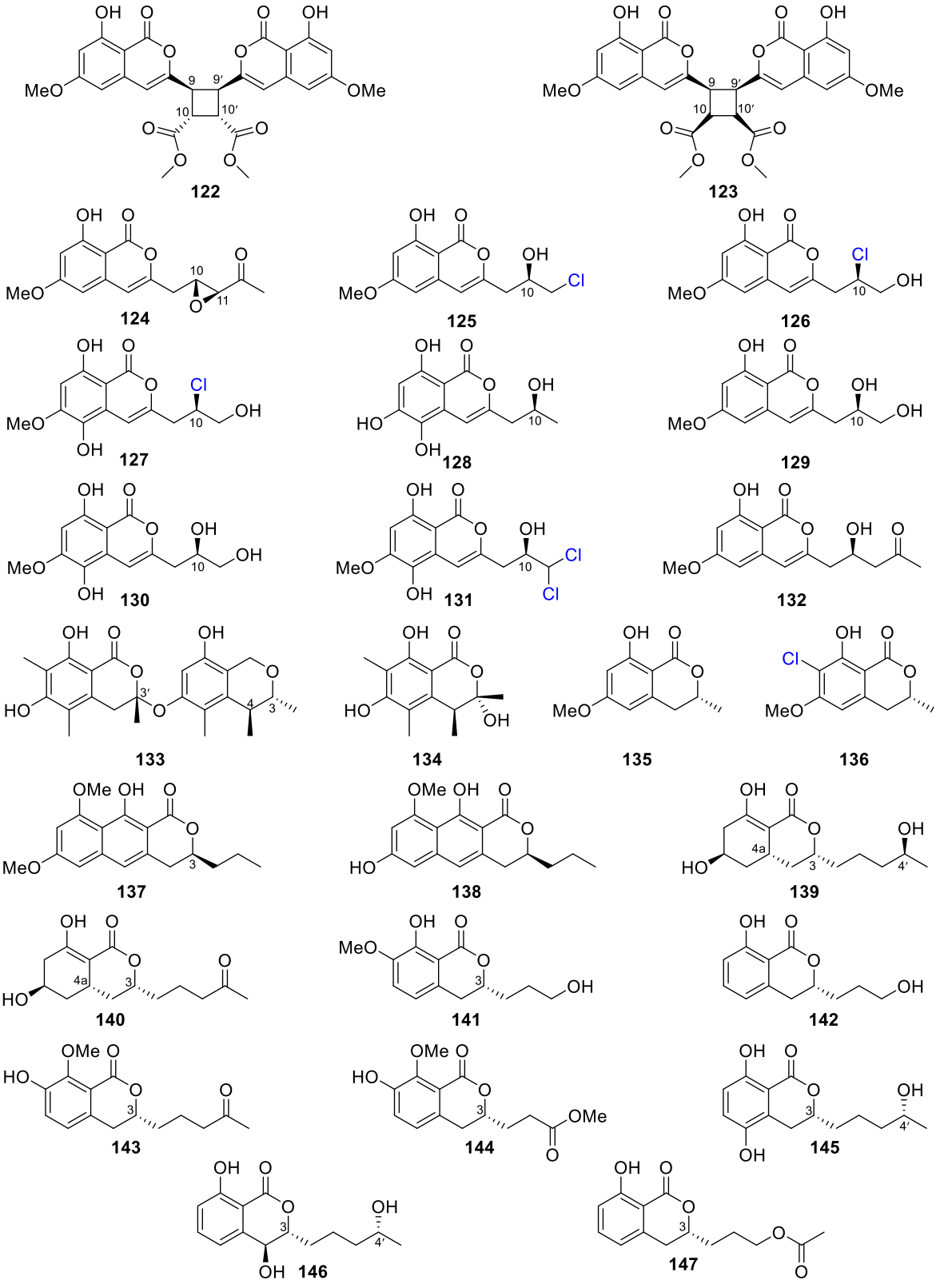


Figure 13. Chemical structure of **122-147**

A chemical analysis of the EtOAc extract of the mangrove derived endophytic fungus *P. coffeae* MA-314 isolated from *Laguncularia racemosa* leafs 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 non-reported enantiomers, penicoffrazins B (**148**) and C (**149)** (Figure 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 rest of compounds exhibited almost no antioxidant activity with IC_{50} > 900 μM [99]. 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-1H-isochromen-3-yl) propyl acetate **(156)** (**Figure 14**), were isolated from the MeOH extract of the marine endophytic fungus *P.* sp., YYSJ-3, isolated from *Heritiera littoralis* steam, collected from China, in the Province of Guangdong. Compounds **153-156** were examined for their inhibitory activity towards α-glucosidase activity. Compound **153** displayed no effect, but **154-155** exhibited weak inhibition activity with IC_{50} values of 309.6 and 237.4 μmol/L, respectively. Additionally, among them, **156** was the most potent enzyme inhibitor with IC_{50} value of 100.6 μmol/L [100]. 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)** (**Figure 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)** (**Figure 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 towards *B. subtilis* ATCC 6633. Meanwhile, among all the tested compounds, only **160** displayed weak antibacterial activity against *E. coli* ATCC 25922. The rest of the isolated metabolites were inactive against *S. aureus* ATCC 25923 [101]. A previously undescribed penicimarin N **(161)** along with three previously reported derivatives, penicimarins I-H **(162-163)** (**Figure 14**), aspergillumarin A **(106)** (**Figure 12**), were obtained from the EtOAc extract

of the mangrove derived fungus *P.* sp., TGM112 isolated from *B. sexangula var. rhynchopetala*, collected in China, from the South China Sea. Compounds **106** and **161**-**163** were evaluated for their antioxidant (using Trolox as a positive control), antibacterial 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 towards *α*-glucosidase [102].

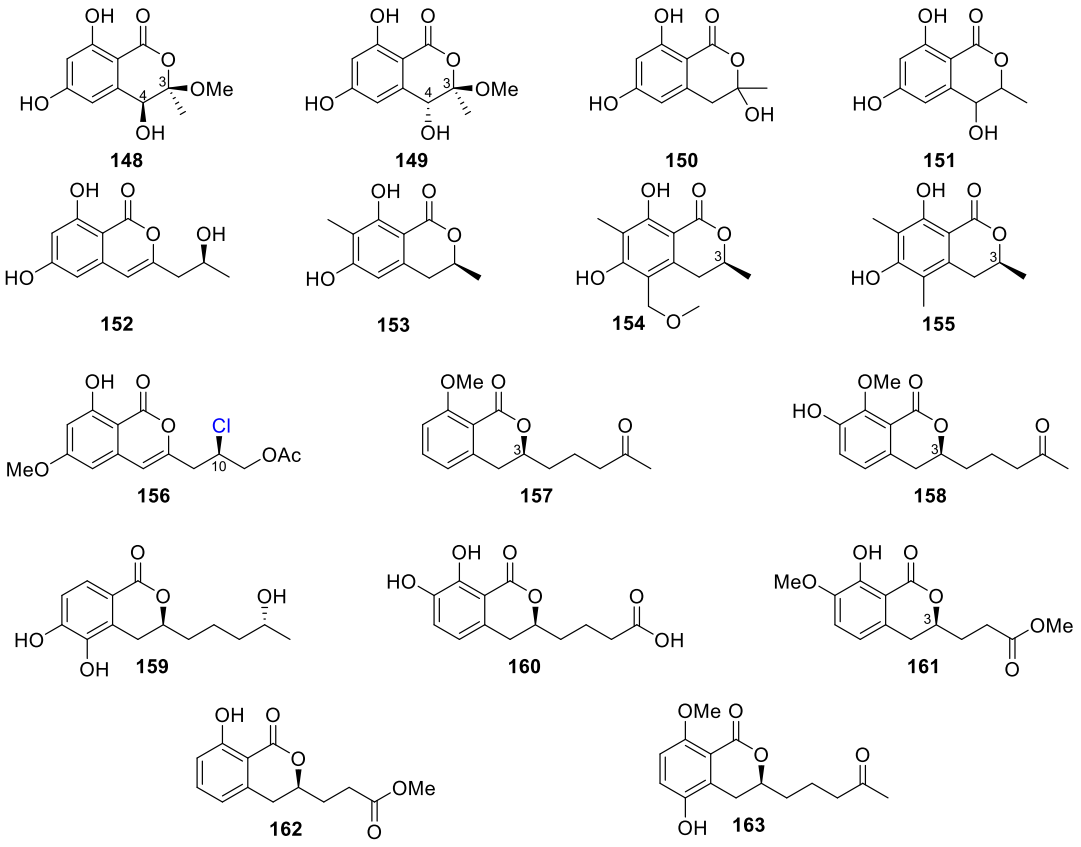
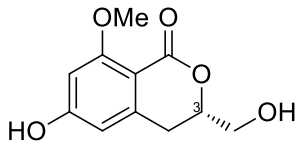


Figure 14. Chemical structure of **148**-**163**

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 in China from the Island of Yongxing, afforded the un previously reported isocoumarin derivatives eupenicillin A (**164**) (**Figure 15**). Compound **164** displayed no antibacterial activity against *S. aureus* ATCC25923, methicillin-resistant *S. aureus* (MRSA) ATCC4330, and *A. baumannii* ATCC19606, but it exhibited moderate cytotoxic effect against MCF7 with IC_{50} value of 53.48 μM [103].

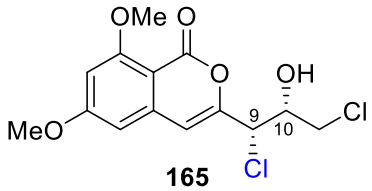


164

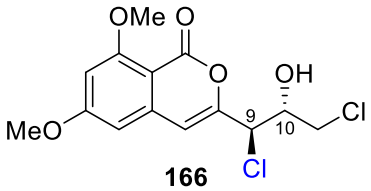
Figure 15. Chemical structure of **164**

3.6.1.4. Fungi of the genus *Hamigera*

A previously described derivative, 8-methyl-11,11-dichlorodiaporthin (**83**) (**Figure 11**), alongside with two previously unidentified chlorinated congeners, (9*R**)-8-methyl-9,11-dichlorodiaporthin (**165**) and (9*S**)-8-methyl-9,11-dichlorodiaporthin (**166**) (**Figure 16**), were isolated from the soil derived fungus *Hamigera fusca* NRRL 35721, obtained from a soil sample treated with Phenol collected from the Island of Grande Comore, at a banana tree. Compounds **83** and **165-166**, were tested for their cytotoxicity 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 towards CCD25sk tumour cell line with CC_{50} value of 27.0 μM. Furthermore, **83**, **165-166**, exhibited moderate cytotoxicity against SHSY5y cells with CC_{50} values ranged from 19.4 to 36.2 μM [104].



165



166

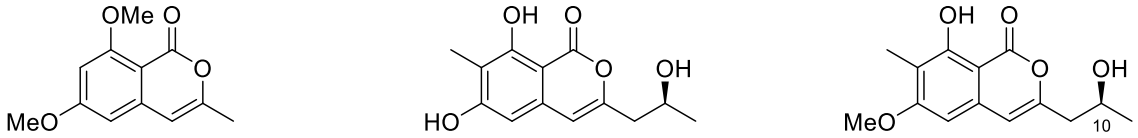
Figure 16. Chemical structure of **165-166**

3.6.1.5. Fungi of the genus *Monascus*

A chemical inspection of the marine associated fungus *Monascus ruber* BB5, isolated from the shellfish *Meretrix* collected in China, Yangjiang, from the Island of Hailing, 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)** (**Figure 17**).

Compounds **167-168** were examined for their cytotoxicity activity against CNE1, CNE2, SUNE1, HONE1, HepG2 and QGY7701 cancer cell lines (using the MTT colorimetric assay and hirsutanol A as a positive control). Despite, all the isolated compounds displayed no

cytotoxicity against CNE1 and HONE1, **168-169** showed weak cytotoxic effect towards 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 ranged from 0.71-72.07 μM [105].



167 **168** **169**

Figure 17. Chemical structure of **167-169**

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**) (**Figure 18)** was discovered from the plant associated 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, respectively. Furthermore, **170** displayed weak antifungal activity against *A. solani, V. mali, C. lunata* and *B. berengeriana* with growth inhibition percentage ranged from 87.2 to 97.3 % [106]. A chemical investigation of the marine sponge derived fungus *T. tratensis*, obtained from the marine sponge *Mycale* sp, collected at Thailand, from the coral reefs of the Island of Samae San, led to the isolation of the unreported previously tratenopyrone (**171**) (**Figure 18**). Compound **171** displayed neither antibacterial nor anti-quorum sensing activities. Additionally, it showed no cytotoxicity and fungicidal activities [107]. 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**) (**Figure 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 in China from the province of Guangdong. Compounds **103-107**, **159** and **172-180** exhibited moderate to weak inhibitory activities towards the enzyme α-glucosidase

with IC_{50} ranged 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 in China from the province of Guangdong, afforded three previously mentioned aspergillumarins B (**105**), A (**106**) (**Figure 12**), and 3*R*-(7, 8-dihydroxy-1-oxoisochroman-3-yl) propanoic acid (**160**) (**Figure 14**) along with a previously undescribed isocoumarin derivative aspergillumarin C (**181**) (**Figure 18**). Compound **181** displayed no inhibitory effect towards AChE (acetylcholinesterase) [108].

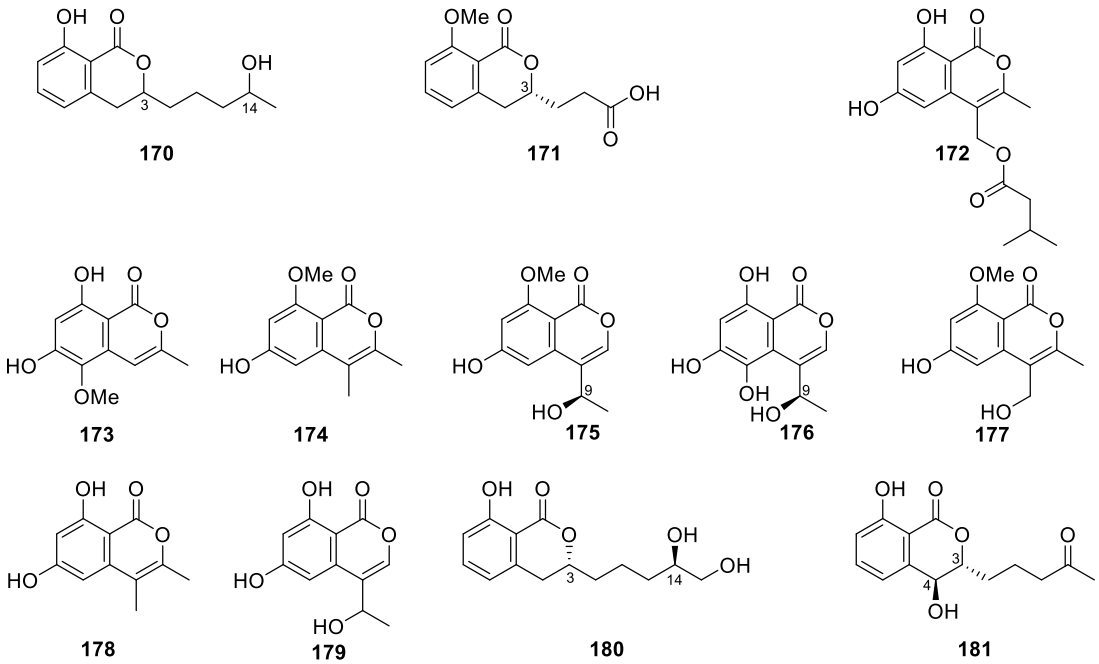


Figure 18. Chemical structure of **170-181**

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** (**Figure 3**), along with other four previously reported isocoumarin derivative, namely monocerin demethylated (**182**), fusarentin 6,7-dimethyl ether (**183**), fusarentin 6-methyl ether (**184**) and fusarentin derivative (**185**) (**Figure 19**), were recorded from the endophytic fungus *Colletotrichum* sp., CRI535-02, isolated from *Piper ornatum*, collected from the Province of Surat Thani. Compounds **4**, **182-185** were tested for their cytotoxicity against HepG2, HuCCA-1, and A549 tumor cell lines (using the MTT assay) as well as towards MOLT-3 cancer cell line (using the XTT assay). Despite that all the isolated

compounds exhibited weak cytotoxicity or no activity against the examined cell lines, **182** displayed potent anticancer ability towards HepG2 with IC_{50} value of 23.7 μM when compared with the positive control etoposide (IC_{50} = 15.8 μM). Additionally, 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. Additionally, **182** and **184** showed a significant inhibitory activity against the formation of superoxide anion radical with IC_{50} values of 52.6 and 4.3 μM, respectively. Moreover, none of the isolated compounds suppress superoxide anion generation 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 ranged from 10.8-14.4 ORAC units [109].

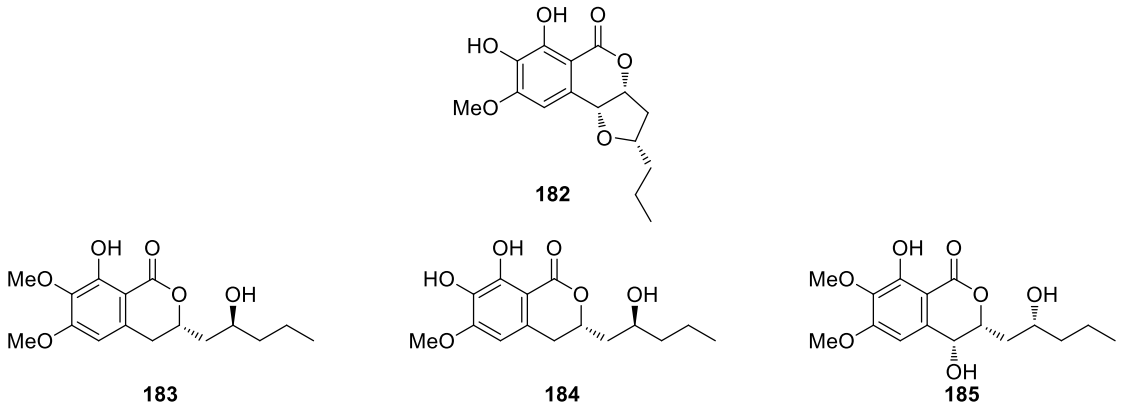


Figure 19. Chemical structure of **182-185**.

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 on China from the country of Linzhou, 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 the seven previously unreported palmaerones A-G (**186-192**), together with six previously described (*R*)-5-cholro-6-hydroxymellein (**193**), (3*R*,4*R*)-5-cholro-4,6-dihydroxymellein (**194**), palmaerins A (**195**), B (**196**) and D (**197**) and (*R*)-5-hydroxymellein (**198**) (**Figure 20**). Compounds **186-192** were examined for their antimicrobial

properties against three fungal strains *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 agent than the chlorinated congeners. Among them, **190** displayed the most powerful antimicrobial effect against the examined fungal and bacterial strains with MIC value ranged from 10 to 55 μg/ml. Additionally, **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. Furthermore, only **190** has displayed a weak cytotoxicity towards HepG2 with IC_{50} value of 42.8 µM [110].

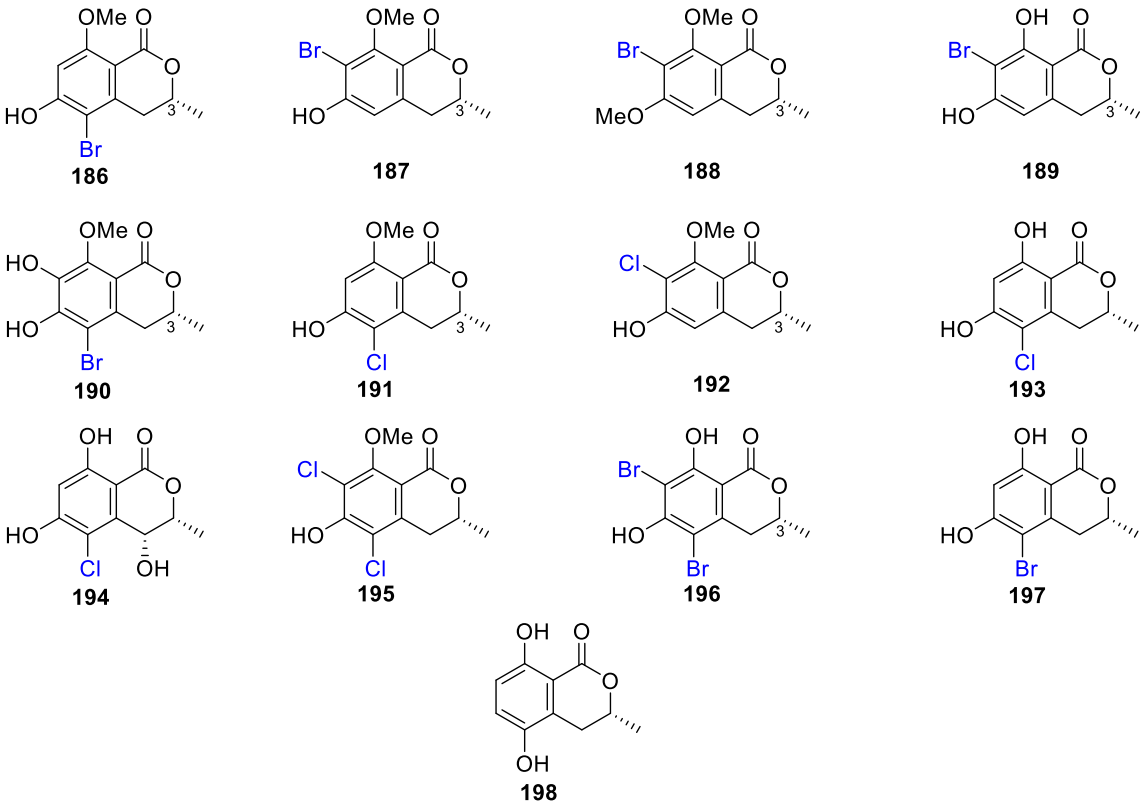


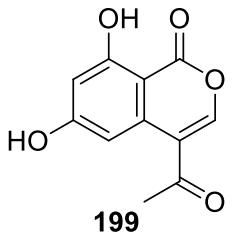
Figure 20. Chemical structure of **186-198**

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**) (Figure 21), was isolated from the fungus *Bionectria* sp. (MSX 47401), isolated from leaf litter and leaves collected from a forest of humid mountain. Compound **199** displayed no cytotoxicity against NCI-H460, MCF-7 and SF-268 cancer cell lines [111].



199

Figure 21. Chemical structure of **199**

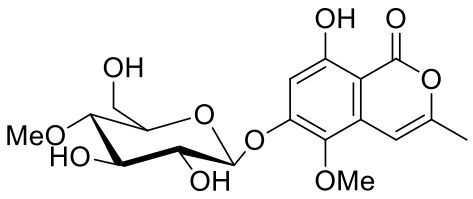
3.9.1.2. Fungi of the genus *Clonostachys*

Chemical examination of the EtOAc extract of the marine derived fungus *Clonostachys* sp. (AP4.1) isolated from the marine sponge *Axinella polypoides*, collected in Turkey at depth of 30 m from İlyosta–Ayvalık, led to the isolation of two previously mentioned isocoumarin derivatives, dichlorodiaportin (**89**) and peniisocoumarin D (**125**). Compound **125** displayed no cytotoxicity against L5178Y cancer cell line [112].

3.9.2. Fungi of the family Clavicipitaceae

3.9.2.1. Fungi of the genus *Conoideocrella*

A previously non-reported isocoumarin glycoside (**200**) (**Figure 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. Additionally, as a result of its limited abundance, **200** was not subjected for any relevant biological activity [113].



200

Figure 22. Chemical structure of **200**

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 (**Figure 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 the virulence factor secretion inhibition activities of towards *P. aeruginosa* strain PAOA (clinical isolates). Among them, **201** displayed antibacterial effect in comparison with (*Z*)-4-bromo-5-(bromomethylene)-2(5H)-furanone (BF as positive control) [114].

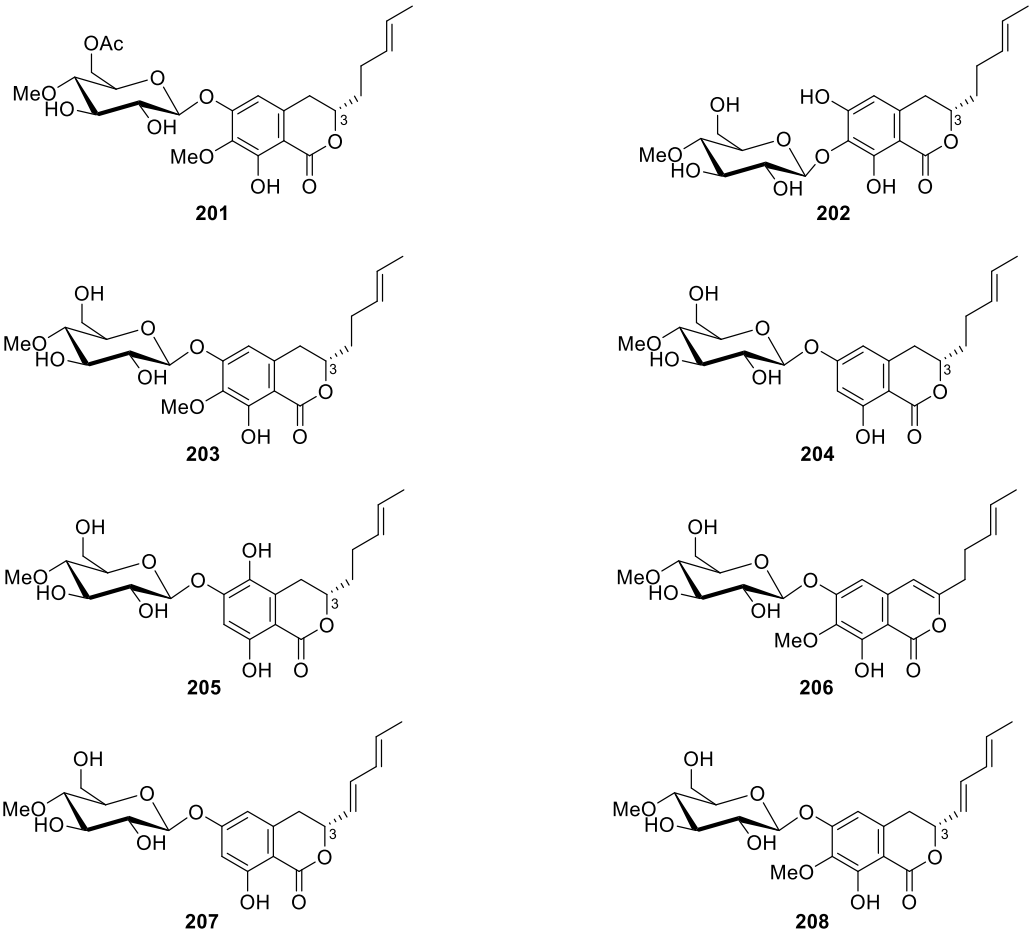


Figure 23. Chemical structure of **201**-**208**

3.9.2.3. Fungi of the genus *Torrubiella*

Two previously described isocoumarin derivatives including, 6,8-dihydroxy-3-methylisocoumarin (**27**), 6,8-dihydroxy-3-hydroxymethylisocoumarin (**60**) along with three previously undescribed isocoumarin glucosides **209**-**211** (**Figure 24**) were obtained from the fungus *Torrubiella tenuis* BCC 12732, isolated from the scale of Homoptera, collected in

Thailand from the province of Chiang Mai. 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. Despite, 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, respectively [115].

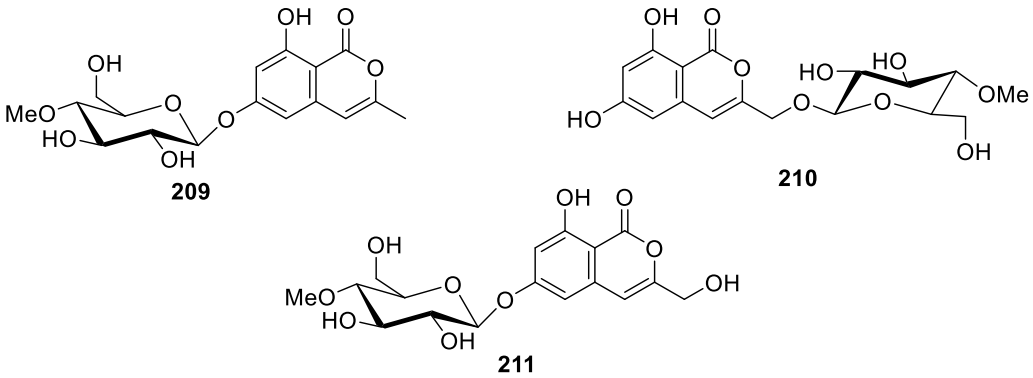


Figure 24. Chemical structure of **209-211**

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**) (**Figure 25**), were obtained from the endophytic fungus *Trichoderma* sp., 09, isolated from *Myoporum bontioides* A. Gray roots, collected in China from the Province of Guangdong. 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. italicm* 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, respectively. Additionally, **89** displayed weak antifungal activity against *R. solani* and *C. musae*, with MIC values of 150 μg/mL [116]. A chemical investigation of the marine derived fungus *T.* sp., HPQJ-34, isolated from the marine sponge *Hymeniacidon perleve*, collected in China from the Island of Dongji led to the isolation of two previously described derivatives, including citreoisocoumarin (**214**) (Figure 25) and (+)-6-*O*-methylcitreoisocoumarin (**132**). Compounds **132** and **214**, were not subjected for any relevant biological activity [117]. Additionally, two previously unreported isocoumarin derivatives (**215**) and (**216**) (**Figure 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**, were tested against *B. subtilis*, *C. albicans*, *E. coil*, *P. aeruginosa S. aureus* (using the well diffusion method, and chloramphenicol and fluconazole as a positive controls). Compounds **215-216** showed moderate antibacterial effect against *E. coil* with MIC values of 32 μg/mL [118]. A chemical exploration of the marine derived fungus *T. citrinoviride* A-WH-20-3, isolated from the inner tissue marine alga *Laurencia okamurai*, collected in China, from the coast of Weihai, led to the isolation of a previously non-described trichophenol A (**217**) (**Figure 25**). Compound **217** displayed anti-microalgal activity against the marine phytoplankton *Heterosigma akashiwo*, *Prorocentrum donations*, *Karlodinium veneficum* and *Chattonella marina* with IC_{50} values of 9.1, 5.9, 20 and 4.4 μg/mL, 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 concentration of 50 µg/disk [119].

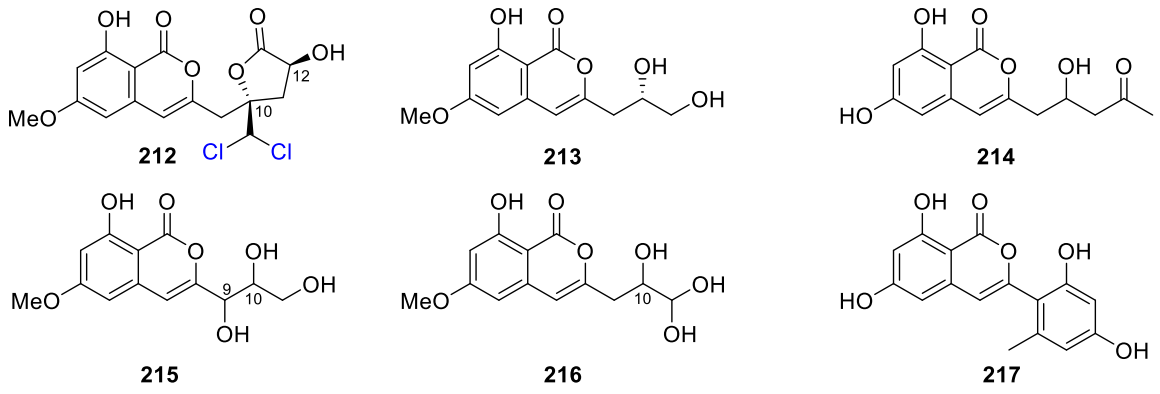


Figure 25. Chemical structure of **212-217**

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**) (**Figure 26**), were isolated from the mangrove derived fungus *Fusarium* sp., 2ST2, isolated from the leaves of *Kandelia candel*, collected in China from the South China Sea. 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 towards A549 and MDA-B-435, with IC_{50} values of 6.2 and 2.8 µM, respectively. Additionally, **220** showed weak cytotoxicity against MDA-B-435, with IC_{50} value of 30.5 µM [120].

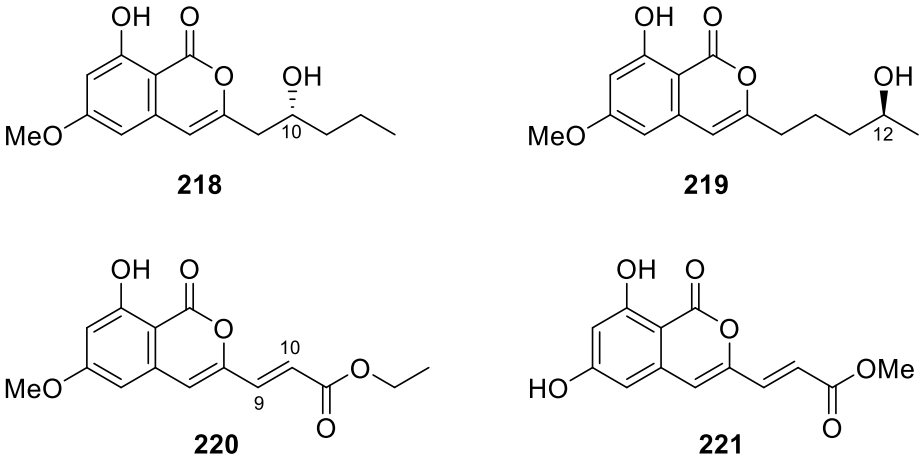


Figure 26. Chemical structure of **218-221**

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**) (**Figure 27**), were obtained from the endophytic fungus *Nectria pseudotrichia* 120-1NP, isolated from *Gliricidia sepium* stem, collected in Indonesia from the forest of Wanagama. Compounds **178** and **222-223** were tested for their cytotoxicity, phytotoxicity and antimicrobial activity, but they showed no activity [121].

Figure 27. Chemical structure of **222-223**

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 in Thailand from the Province of Satun, afforded seven previously unreported isocoumarin derivatives namely, acremonones B-H (**224-230**) (**Figure 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 [122].

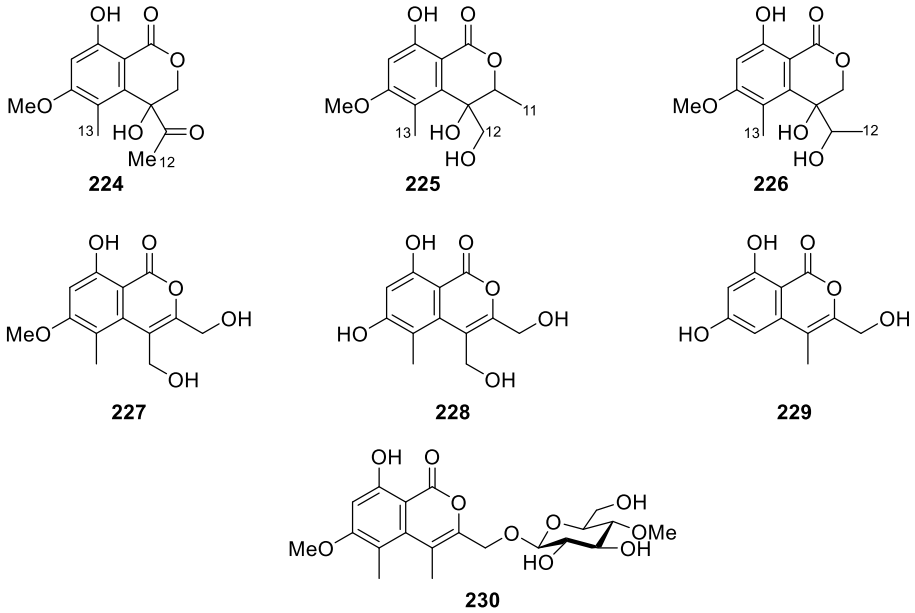


Figure 28. Chemical structure of **224-230**

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** (**Figure 29**), were isolated from the fungus *Rhytidhysteron* sp., BZM-9. Compounds **231-232** displayed no cytotoxicity [123].

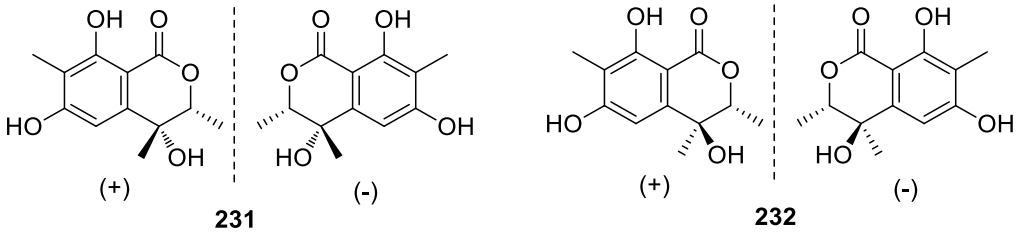


Figure 29. Chemical structure of **231-232**

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 in China, from the region of Sinkiang Uyghur, led to the discovery of three previously unreported mucorisocoumarins A-C (**233-235**), along with seven previously described isocoumarin derivatives including **236-238** (**Figure 30**),

dichlorodiaportin (**89**), (+)-6-methylcitreoisocoumarin (**132**), *O*-demethyldiaporthin (**152**) and diaportinol (**213**). Compounds **89**, **152**, **213** and **233-238**, were tested for their toxicity using a model of Zebrafish model. Only **235** displayed toxicity for the Zebrafish embryos, while all the other compounds showed no toxicity [124].

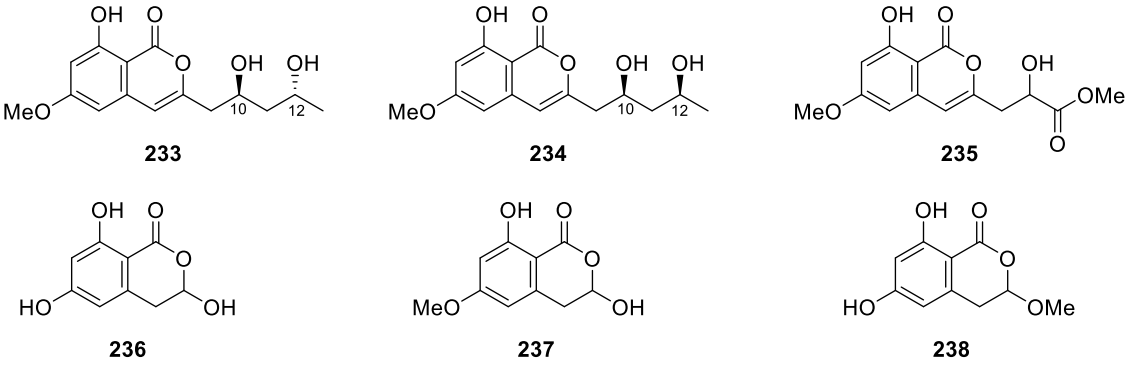


Figure 30. Chemical structure of **233-238**

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**), (**Figure 31**), were obtained from the EtOAc extract of the deep see 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 ranged from 8 to 64 μg/mL [125]. 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, led to the isolation of two previously undescribed chlorinated derivatives namely, spiromastimelleins A-B (**242-243**) (**Figure 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 ranged from 4 to 32 μg/mL [126].

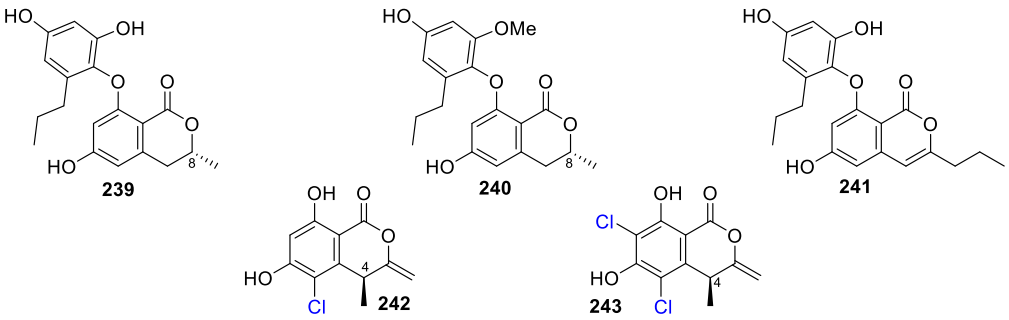


Figure 31. Chemical structure of **239-243**

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**), *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**) (**Figure 32**), were isolated from the EtOAc extract of the endophytic fungus *Sarcosomataceae* sp., NO.49-14-2-1, isolated from *E. nepalense*, collected in China, from the province of Panzhihua, Sichuan. The isolated compounds were not tested for any relevant biological activity [127].

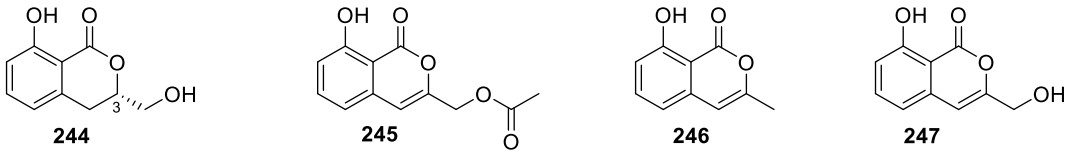


Figure 32. Chemical structure of **244-247**

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 AI-77-B (**248**)**,** AI-77-F **(249)**, alongside a previously undescribed derivative Sg17-1-4 (**250**) (**Figure 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. Additionally, **249** exhibited weak cytotoxicity against Hela cells only with IC_{50} value of 0.4 mM [128]. The chemical examination of the endophytic fungus *A. alternata*, isolated from *Camellia sinensis* branches, collected in China from the Province of Jiangsu, 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**), 5′-epialtenuene (**255**), alternariol 9-methyl ether (**256**), alternariol (**257)** and phialophoriol (**258**) (**Figure 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 MIC_{80} of 8.6 μg/mL. Additionally, **251-254** and **258** displayed weak to mild inhibition against the examined pathogenic microorganisms. Moreover, only **256** exhibited moderate cytotoxicity against U2OS cancer cell line with IC_{50} value of 28.3 μM [129].

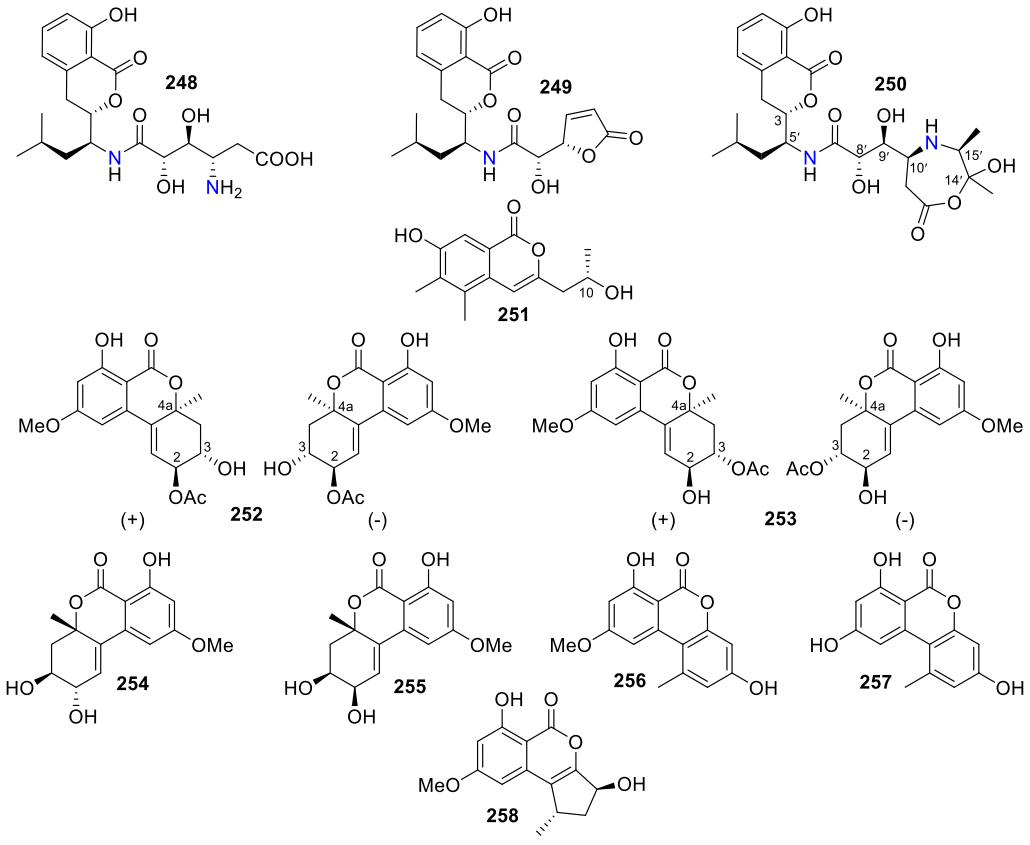
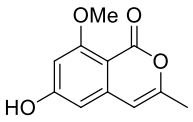


Figure 33. Chemical structure of **248-258**

3.14.1.2. Fungi of the genus *Cochliobolus*

Phytochemical study of the marine derived fungus *Cochliobolus lunatus* (TA26-46), isolated from the inner part tissue of zoanthid, collected in South China Sea from the coral reef of Weizhou, led to the isolation of two previously mentioned compounds including, 3-methyl-6,8-dihydroxyisocoumarin (**5**), *O*-demethyldiaporthin (**152**), together with a previously described derivative, namely 6-hydroxy-8-methoxy-3-methylisocoumarin (**259**) (**Figure 34**). Compounds **5**, **152** and **259** were tested for their antibacterial effect against *S. aureus* (ATCC 33591 and ATCC43300), and for their inhibitory activity against acetylcholinesterase and topoisomerase I (Topo I) enzymes. They displayed neither antibacterial nor enzymes inhibition activities [130].



259

Figure 34. Chemical structure of **259**

3.14.1.3. Fungi of the genus *Exserohilum*

The previously mentioned monocerin (**4**), together with a previously unreported derivative 11(*R*)-hydroxymonocerin (**260**), alongside the previously described compound 12(*R*)-hydroxymonocerin (**261**) (Figure 35), were isolated from the EtOAc extract of the endophytic fungus *Exserohilum rostratum*, derived from *Stemona* sp. leaves and roots, collected in Thailand from the Province of Ayutthaya. Compounds **4** and **260** displayed antimalarial activity against *P. falciparum* with IC_{50} values of 0.68 and 7.7 μM, respectively. Additionally, they were evaluated for their cytotoxicity against BT474, CHAGO, Hep-G2, KATO-3, and SW620, but they showed no activity at concentration of 20 μg/mL [131]. A chemical investigation of the endophytic fungus *E.* sp., isolated from *A. truncatum* Bunge leaves, collected 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**) (**Figure 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. Meanwhile, **267** exhibited antibacterial effect against the tested bacterial strains with MIC values ranged from 5 to 20 μg/mL [132]. Additionally, previously mentioned derivatives including, monocerin (**4**), 12(*R*)-hydroxymonocerin (**261**), 12(*S*)-hydroxymonocerin (**262**), exserolides B (**264**) and C (**265**), together with previously described congeners, 11-hydroxymonocerin (**268**), exserolide I **(269)** and exserolide J (**270**) (**Figure 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 in South China Sea, from Weizhou coral reefs. Compounds **4** and **262** showed antimalarial activity with IC_{50} values of 1.13 and 11.7 μM, respectively, however **270** was found inactive [133].

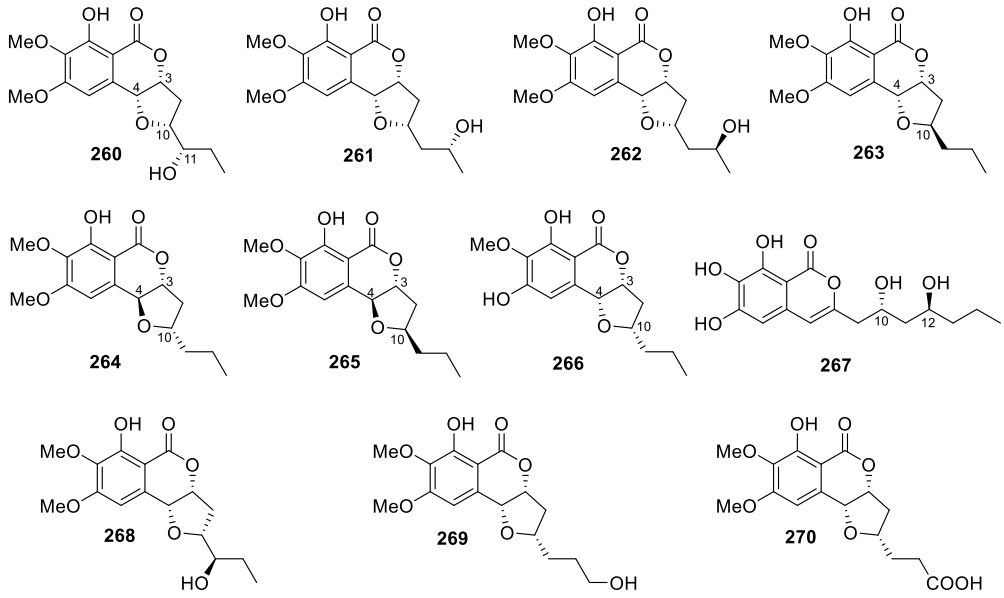


Figure 35. Chemical structure of **260**-**270**

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 in China, from the Province of Guangdong, 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 non-reported exserolide K (**271**) (**Figure 36**). All the isolated metabolites were tested for their antibacterial activity against *S. aureus*, antifungal activity towards *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. Additionally, the antioxidant activities of the purified compounds were evaluated. Only **266**

exhibited moderate anti-radical activity with IC_{50} value of 38 μM. Furthermore, these compounds were tested for their antiviral, and MptpB inhibitory activities, but they showed no activity[134]. 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 non-reported setosphacohol A (**276**) (**Figure 36**), were obtained from the fungus *S.* sp. (strain LGWB-2), isolated from *H. axyridis*, collected in China from the Province of Hebei in Baoding. Compounds **256**-**257** and **272**-**276** were evaluated for their cytotoxicity against HeLa, A549, MCF-7, MGC-803, Huh-7 and H1975 cancers 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 [135]. A chemical examination of the *S. rostrate* LGWB-10, obtained from the *H. axyridis*, collected from the Province of Hebei, 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-dimethoxyisochroman-1-one (**278**) together with four previously undescribed natural products namely, setosphlides A-D (**279**-**282**) (**Figure 36**). Compounds **279**-**282** displayed no cytotoxicity against MCF-7, MGC-803, HeLa, and Huh-7 with IC_{50} values > 200 μM [136].

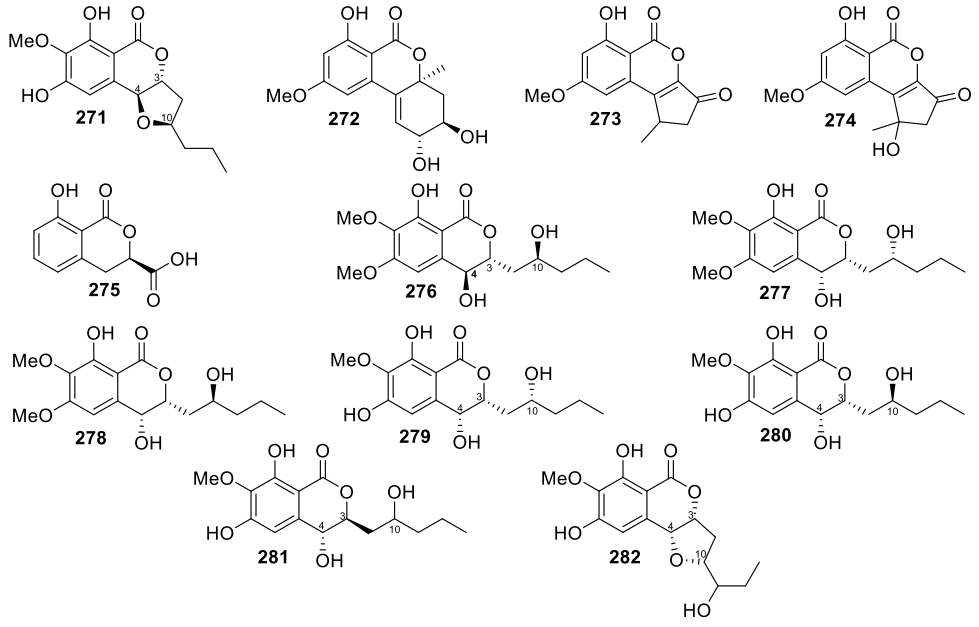
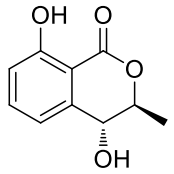


Figure 36. Chemical structure of **271**-**282**

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 a previously reported (-)-(3*R*,4*S*)-4-hydroxymellein (**283**) (**Figure 37**), were obtained from the EtOAc extract of the brown alga derived fungus *Epicoccum* sp., isolated from *Fucus vesiculous*, collected in Germany from the coast of the North sea. 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 assays with an inhibition ratio (28.4 and 9.6 at concentration of 50.0 μg/mL), and (30.4 and 18.4 at concentration of 37.0 μg/mL) %, respectively [137].



283

Figure 37. Chemical structure of **283**

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 in South China Sea from the Island of Xisha, 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**) (**Figure 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 towards *S. aureus*, *A. tumefaciens* and *R. solanacearum*, **256** showed weak activity against *A. tumefaciens*, **152** and **299** exhibited also weak activity against *R. solanacearum*. Furthermore, all the isolated compounds showed ARE luciferase activity with 0.88-2.95 folds more than the negative control (DMSO) when compared with the positive control tBHQ with induction value 4.29 folds more than the solvent (DMSO) [138].

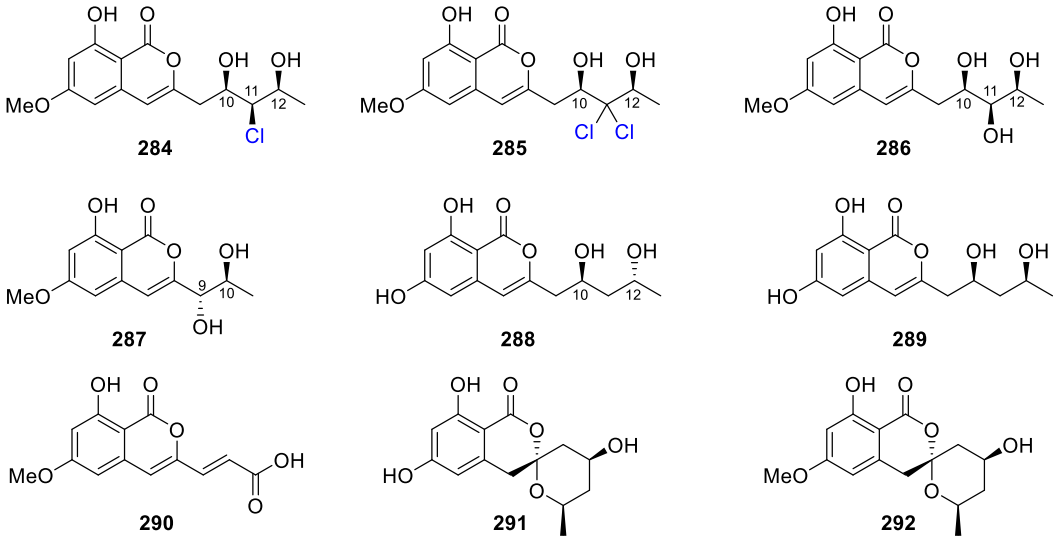
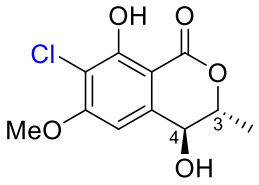


Figure 38. Chemical structure of **284**-**292**

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 non-reported chlorinated metabolite, (3*R*,4*S*)-4-hydroxy-6-methoxy-7-chloromellein (**293**) (**Figure 39**). Compounds **136** and **293** were not tested for any relevant biological assay [139]. A previously mention 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 in China, Yunnan. 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 [140]. Additionally, 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 in South China Sea from the coral reef of Weizhou, 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 towards the brine shrimps, but none of them showed neither antibacterial nor lethal effect [141].



293

Figure 39. Chemical structure of **293**

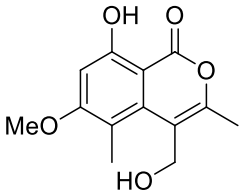
3.14.3. Fungi of the family Didymosphaeriaceae

3.14.3.1. Fungi of the genus *Microsphaeropsis*

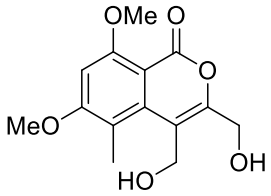
A previously mentioned isocoumarin derivative **26** was isolated from the marine sponge derived fungus *Microsphaeropsis* sp. (strain number H5-50), isolated from the marine sponge *Myxilla incrustans* Jonnston (1842), collected in Germany, around Helgoland. Compound **26** showed no antiplasmodial activity [142].

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 in the Province of Sichuan, 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**) (**Figure 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, respectively [143].



294



295

Figure 40. Chemical structure of **294**-**295**

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**) (**Figure 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 neither cytotoxicity nor antiviral activities [144].

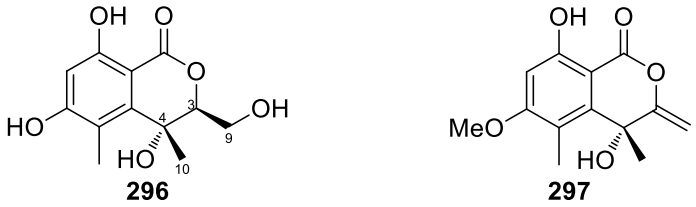


Figure 41. Chemical structure of **296**-**297**

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 non-reported maculansline C (**298**) (**Figure 42**). Compounds **4**, **261**, **269** and **298** were evaluated for their α-glucosidase inhibition effect, but none of them displayed any inhibitory activity [145].

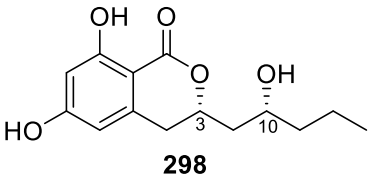


Figure 42. Chemical structure of **298**

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**) (**Figure 43**), were discovered from the marine derived fungus *Paraphoma* sp. CUGBMF180003, obtained from a mud, collected in China from the Shenzhen intertidal zones. All the isolated compounds were evaluated for their antibacterial activities towards *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 [146].

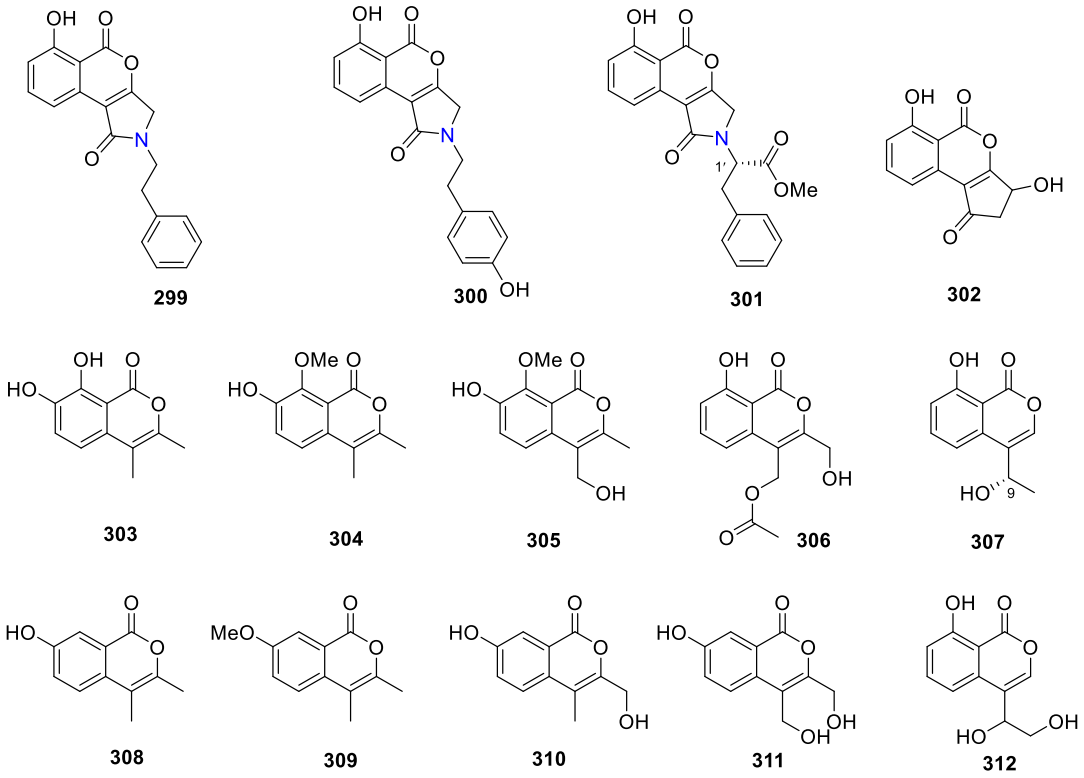


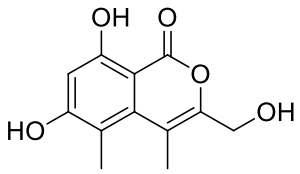
Figure 43. Chemical structure of **299**-**312**

3.15. Fungi of the order Xylariales

3.15.1. Fungi of the family Apiosporaceae

3.15.1.1. Fungi of the genus *Arthrinium*

Chemical study of the marine derived fungus *Arthrinium sacchari*, isolated from an identified marine sponge, collected in Japan, from Atamishi coast, afforded the isolation of one previously unreported decarboxyhydroxycitrinone (**313**) (**Figure 44**). Compound **313** exhibited weak cytotoxicity towards HUVECs and HUAECs cancer cell lines with IC_{50} 7.6 and 17.4 μM, respectively [147].



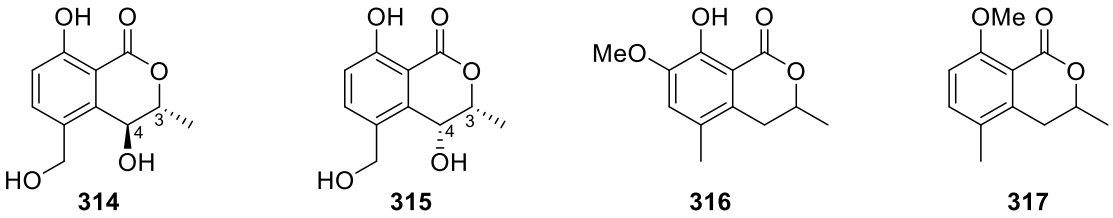
313

Figure 44. Chemical structure of **313**

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 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**) (**Figure 45**), were obtained from the EtOAc extract of the soil derived fungus *Hypoxylon* sp., isolated from a soil sample collected in China, from the Province of Heilongjiang, from the mountain of Da Hinggan. It is worth to mention that none of the obtained compounds was tested for any relevant biological activity [148].



314 315 316 317

Figure 45. Chemical structure of **314**-**317**

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 and antifungal activities, it showed no antibacterial activity. However, **4**, **262** and **277** exhibited antifungal, antibacterial and algal activity against the examined organisms [149].

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**) (**Figure 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 anti-mycobacterial, antimalarial, and cytotoxic activities, but it showed no activity [150]. Additionally, 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**) (**Figure 46**), were isolated from EtOAc extract of the endophytic fungus *Pestalotiopsis* sp., obtained from *P. frasery* leaves, collected in China, Jiangsu, Nanjing. 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, *C. glabrata* ATCC 90030. Among them, only **21** showed antifungal activity against *C. glabrata* ATCC 90030 MIC_{50} value of 3.49 μg/mL [151]. 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**) (**Figure 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*, *B. Subtilis* with MIC values ranging from 25 to 100 μg/mL. Additionally, 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. Moreover, **323** was found to be inactive against *C. albicans* and *C. parapsilosis* but exhibited weak effect against *C. neoformans* with MIC value of 100 μg/mL. Furthermore, **324** displayed weak antifungal ability towards *C. parapsilosis* and *C. neoformans* with MIC values of 100 μg/mL and was found to be inactive against *C. albicans* [152]. A previously unreported pestalotiopisorin B (**325**) along with the co-isolated previously reported (*R*)-(-)- mellein methyl ether (**326**) (**Figure 46**), were recorded from the mangrove derived fungus *Pestalotiopsis* sp. HHL101, isolated from *Rhizophora stylosa* branches, collected in China from the Island of Hainan. Compound **325**

was examined for its CN-inhibition activity, but it showed no activity. Additionally, it displayed mild antibacterial effect against *E. coli* and *P. aeruginosa*. Moreover, it showed no cytotoxicity against Hela, A549 and HepG2 cancer cell lines [153]. A previously mention gamahorin (**324**) along with the previously undescribed microsporaline D (**327**) (**Figure 46**) were reported from the marine derived fungus *P. microspora* SC3082, isolated from *Scaevola taccada* (Gaertn.) Roxb leaves, collected in 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 [154].

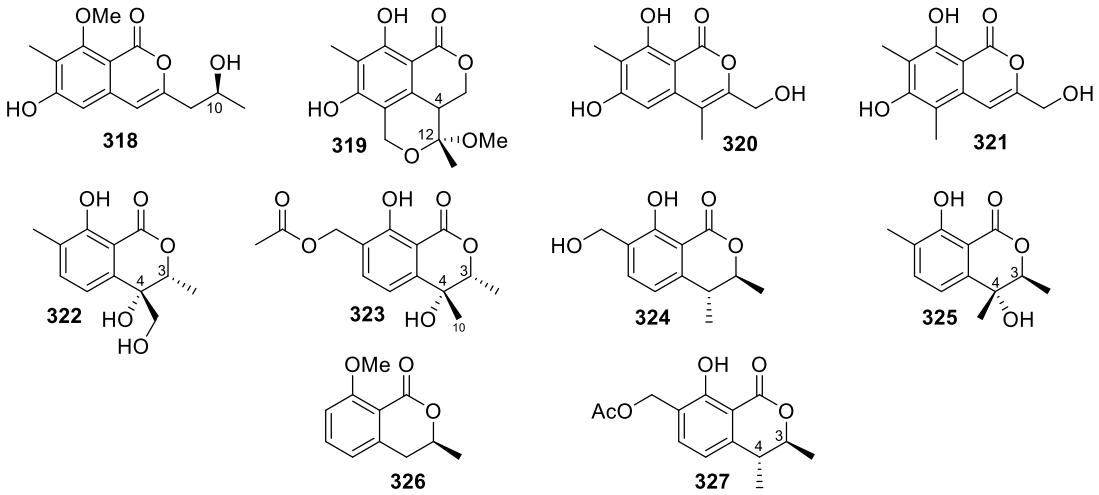


Figure 46. Chemical structure of **318**-**327**

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 two previously reported 3-(2-hydroxypropyl)-8-hydroxy-3,4-dihydroisocoumarin (**330**) and (*R*)-orthosporin (**331**) (**Figure 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 [155].

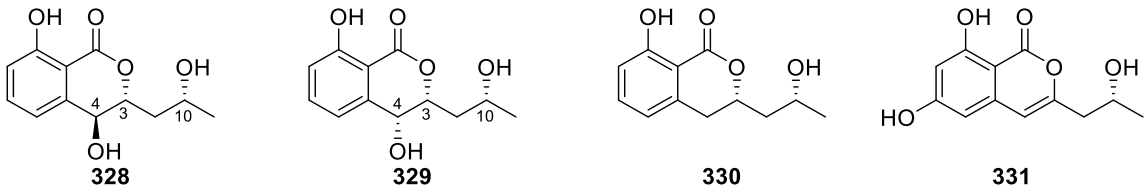


Figure 47. Chemical structure of **328**-**331**

3.15.5.2. Fungi of the genus *Biscogniauxia*

The previously described 6-methoxy-5-methyl mellein (**332**) (Figure 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* [156]. Additionally, a chemical examination of the plant endophytic fungus *B. capnodes* isolated from *Averrhoa carambola* L fruits, collected in 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)** (**Figure 48**). These compounds were tested for their antifungal properties against *C. cladosporioides*, antioxidant activity, their lethial activity against the brine shrimp and their phytotoxicity. Only **29** displayed mild antiradical effect with IC_{50} value of 58 μg/mL [157].

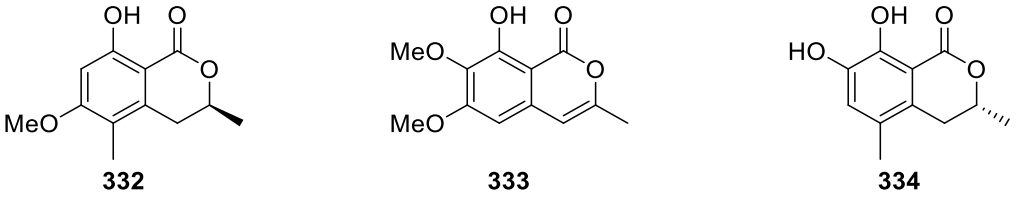


Figure 48. Chemical structure of **332-334**

3.15.5.3. Fungi of the genus *Halorosellinia*

A previously mention (*R*)-4,8-dihydroxy-6-methoxy-4,5-dimethyl-3-methyleneisochromen-1-one (**297**), along with two previously unreported halorosellins A-B (**335-336**) (**Figure 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, antimalarial and cytotoxicity effects [158].

Figure 49. Chemical structure of **335-336**

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 in Greece from the island of Corfu, 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. Additionally, it showed no cytotoxicity when evaluated against a panel of 36 tumor cell lines [159].

3.15.5.5. Fungi of the genus *Xylaria*

The previously undescribed xylariamalirin (**337**) (**Figure 50**), was recorded from *n*-BuOH fraction of the endophytic fungus *Xylaria mali* isolated from *Lepidagathis stenophylla* C. B. Clarke ex Hayata stems, collected in southern Taiwan. Compound **337** was not evaluated for any relevant biological activity [160].

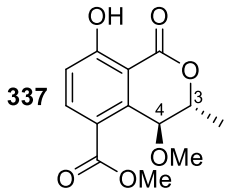


Figure 50. Chemical structure of **337**

3.16. Miscellaneous

3.16.1. Fungi of the genus *Ascomycota*

Chemical exploration of the marine derived fungus *Ascomycota* sp. CYSK-4, isolated from the *Pluchea indica* branches, collected in China from the Province of Guangxi, afforded three previously undescribed dichlorodiaportintone (**338**), desmethyldichlorodiaportintone (**339**) and desmethyldichlorodiaportinol (**340**) along with two previously reported dichlorodiaportinol (**341**) and desmethyldichlorodiaportin (**342**) (**Figure 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 an 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. Meanwhile, **338** showed antibacterial activity against *S. aureus*, *E. coli*, *K. pneumoniae* and *A. calcoaceticus* with MIC value of 50 μg/mL. Whereas the rest of the isolated compounds displayed no activity at a concentration of 50 μg/mL [161].

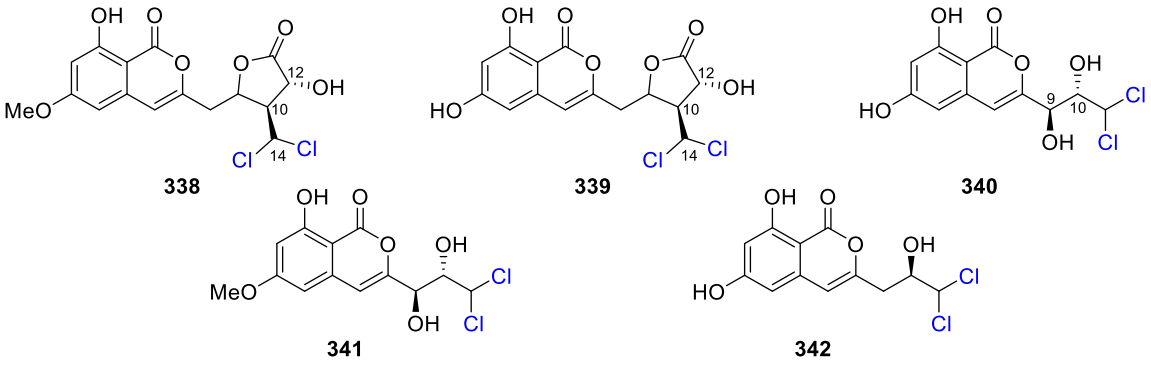


Figure 51. Chemical structure of **338-342**

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-dimethyl-isochromen-1-one (**347**) and acetic acid 6,8-Dihydroxy-3,5-dimethyl-1-oxo-1*H*-isochromen-4-ylmethyl ester (**348**) (**Figure 52**), were reported from the EtOAc extract of the endophytic fungus *Scytalidium* sp., isolated from a *Salix* species leaf, collected in Germany from the mountain of Lower Saxony. Compounds **343-348** were not tested for any relevant biological activity [162].

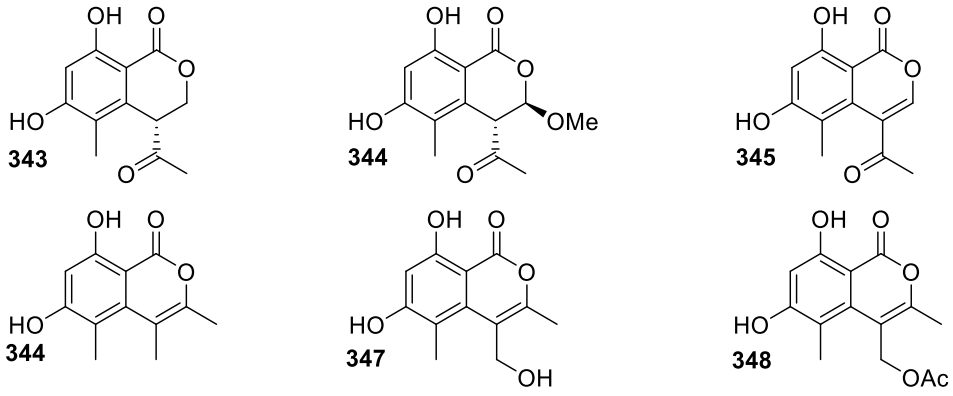
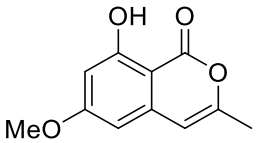


Figure 52. Chemical structure of **343-348**

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**) (**Figure 53**), were reported from the 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 towards *B. subtilis* with MIC value of 50 μg/mL. Moreover, **349** showed antibacterial activity against *B. subtilis*, *A. tumefaciens* and *X. vesicatoria* with MIC values of 25, 75 and 25 μg/mL, 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. Additionally, 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 [163].



349

Figure 53. Chemical structure of **349**

3.16.4. Unidentified fungal strain

3.16.4.1. Fungal strain No. 1893

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**) (**Figure 54**). No biological activity was reported these metabolites [164].

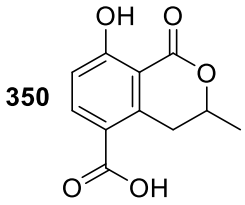


Figure 54. Chemical structure of **350**

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**) (**Figure 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 towards HepG2 and Hep-2 tumour cell lines with IC_{50} values of 55 and 52 μg/mL, respectively [165].

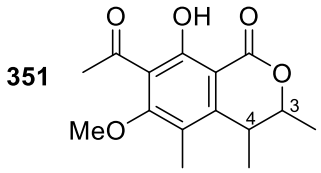


Figure 55. Chemical structure of **351**

3.16.4.3. Fungal strain HJ33moB

Chemical examination of the marine derived fungal strain HJ33moB, isolated from an unidentified alga, afforded the previously mentioned 1-deoxyrubralactone **(273)**. Compound **273** exhibited strong inhibition effect against families X and Y of eukaryotic pols [166].

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, a notable attention has recently been directed towards 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 the isocoumarins isolated over the period **2000-2022** from different fungal natural sources. A total of **351** structurally divers isocoumarins isolated from various fungal genera were documented in this current review. Their chemical diversities and biological potentialities constituted the focal point of interest of the current review besides presenting brief highlights on the isocoumarin biosynthetic pathways. Thoroughly 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 (**Figure 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 (**Figure 57**). Intriguingly, the gathered statistical data also revealed the significant contribution of the two fungal species, *Penicillium* and *Aspergillus* which are constituting the prevailing sources of the reported compounds (**Figure 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 potentialities of the recorded isocoumarins, a broad array of multiple biological activities was documented, including anti-inflammatory, antioxidant, antimicrobial, cytotoxic and enzyme inhibitory activities. Additionally, it is worthy to mention that the cytotoxicity, antibacterial, and antifungal activities were the most profound 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 (**Figure 58**). Noteworthily, a considerable number of isocoumarins, for examples compounds **84**, **108**, **124**, **128**, **130-131**, **134** and **156** demonstrated significant biomedical potentialities including antibacterial, cytotoxic and antidiabetic, respectively, which exceeding the potency when compared to standards. Moreover, asperentin (**59**), displays numerous potent pharmacological activities including antifungal, antimicrobial, antiplasmodial and recently, as Inhibitor of the protein tyrosine phosphatase 1B. Actually, such massive linkage between the different chemical architectures and their associated biological significances sheds the light on the considerable importance of fungi as a prolific reservoir of promising lead compounds that are worth for future exploration for pharmaceutical and industrial applications. In deep studying 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.

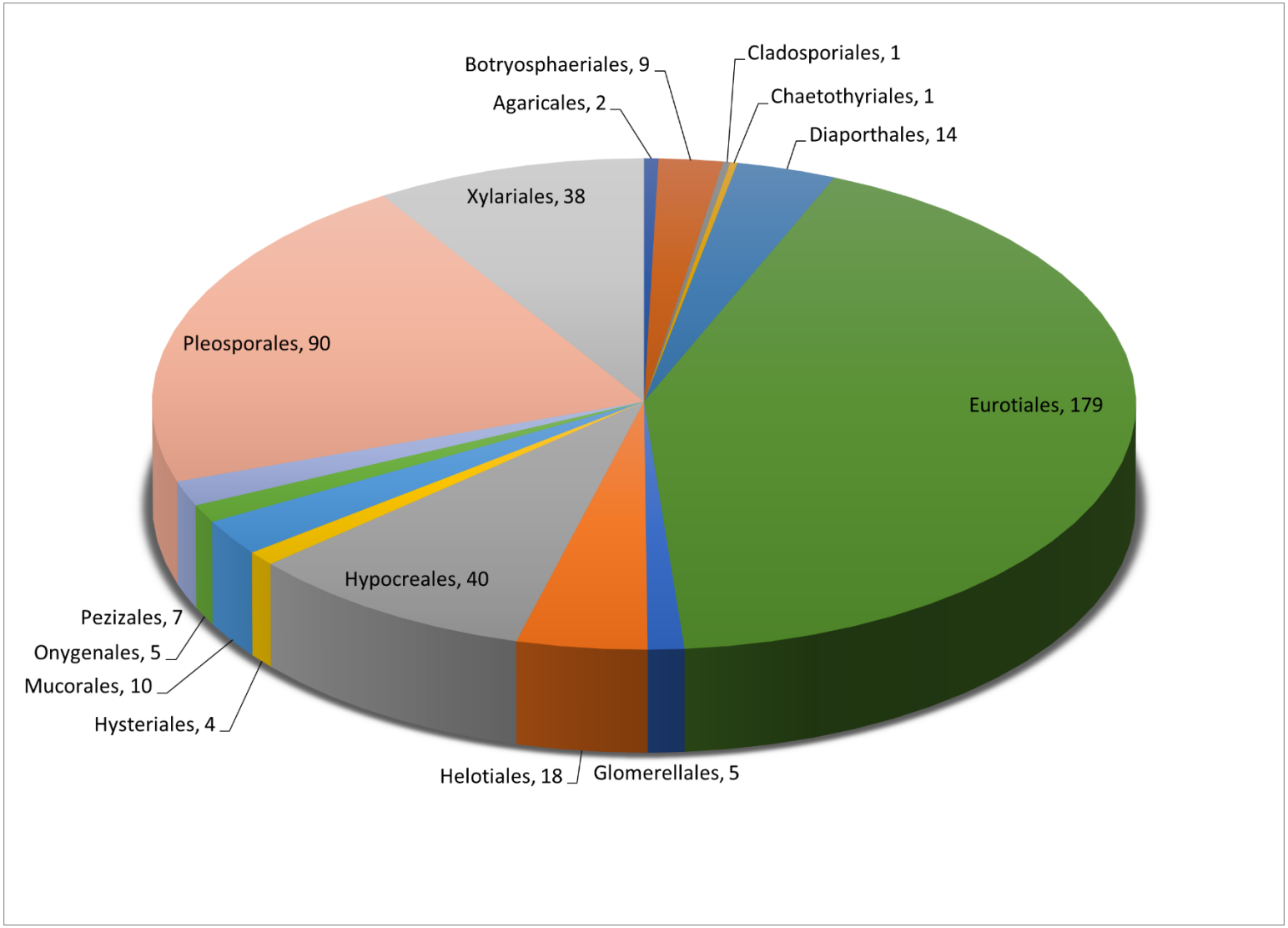


Figure 56. Contribution of isocoumarins by various fungal order

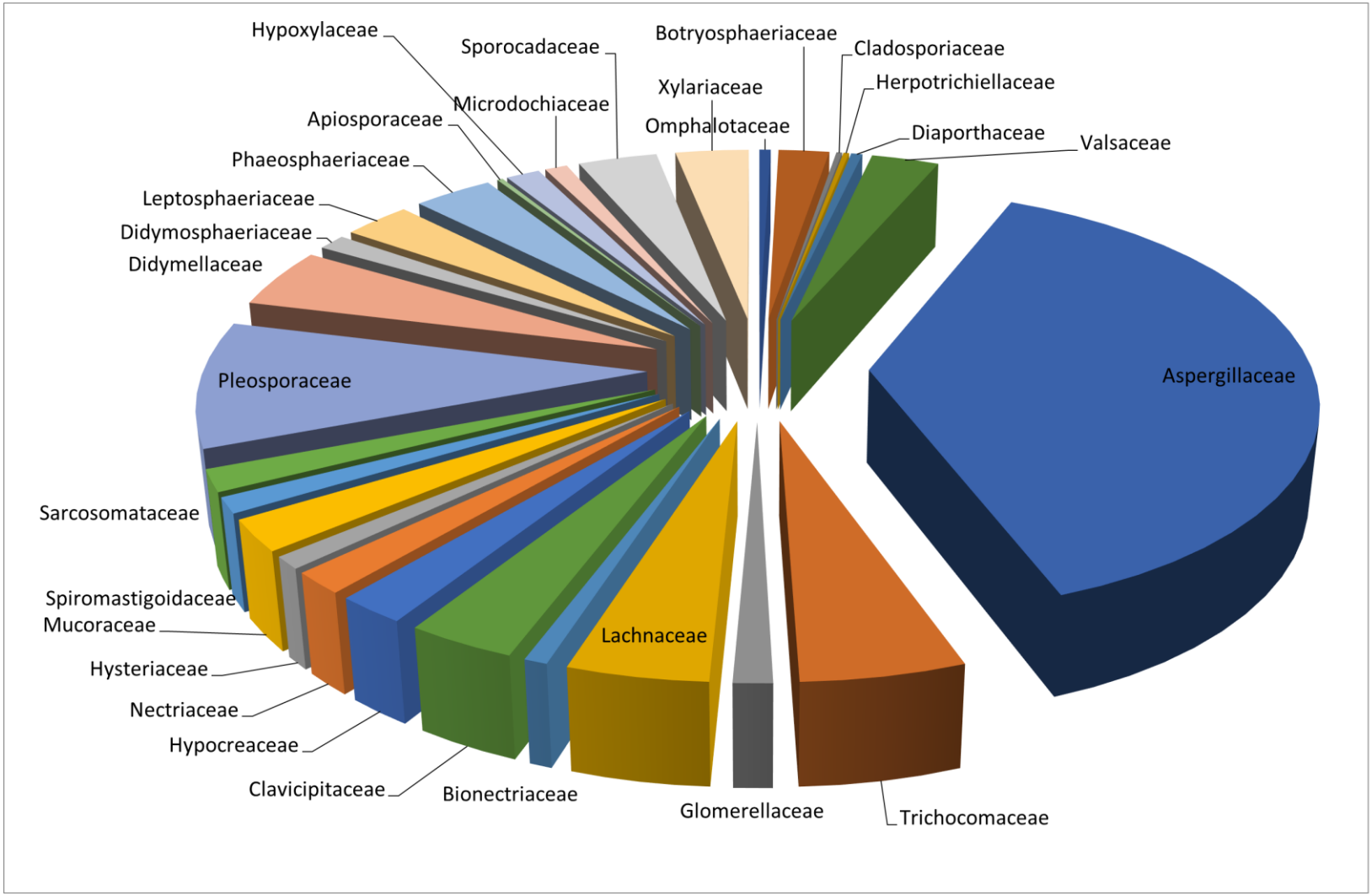


Figure 57. Contribution of isocoumarins by different fungal families.

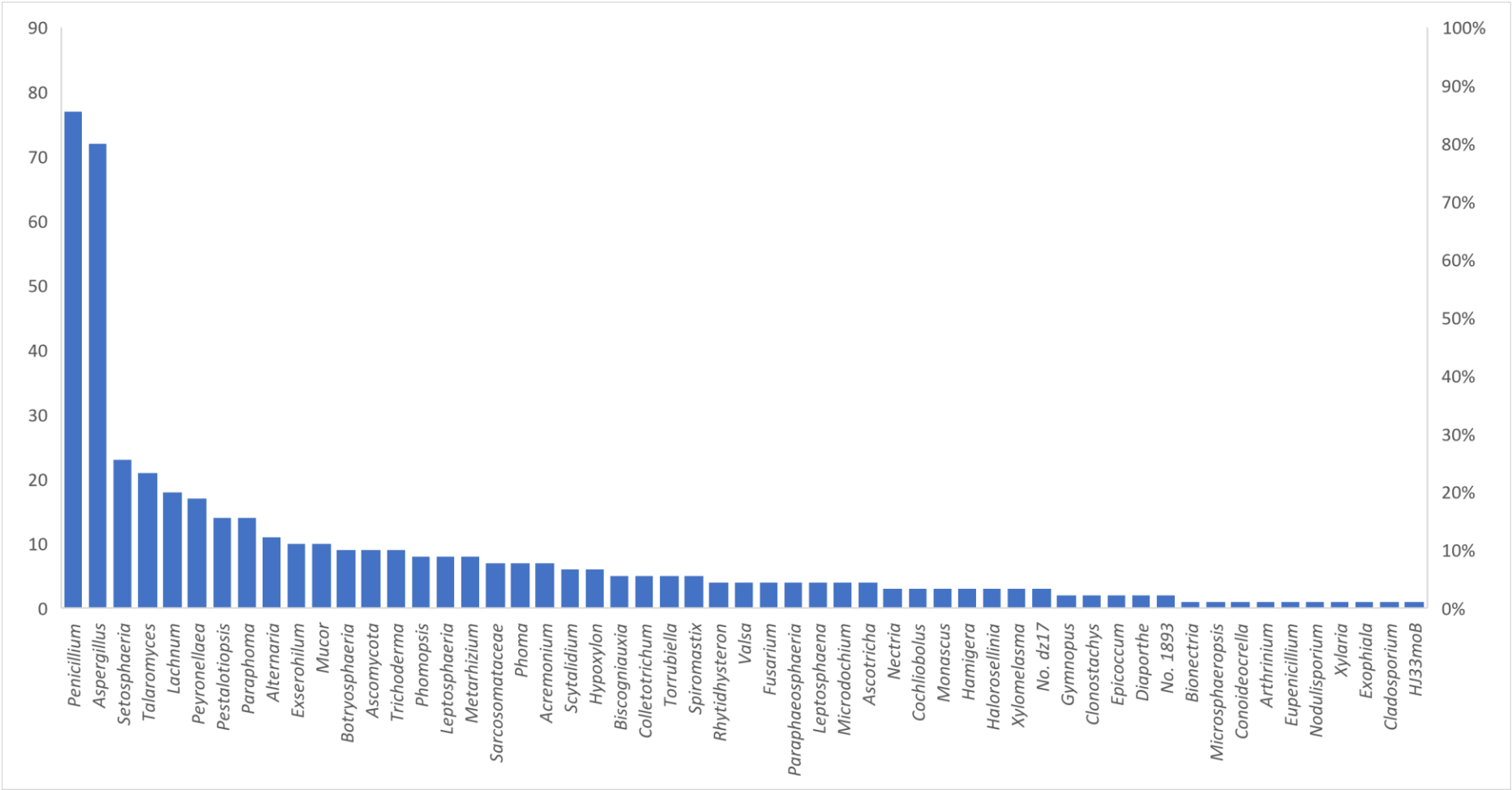


Figure 58. Contribution of isocoumarins by various fungal genera.

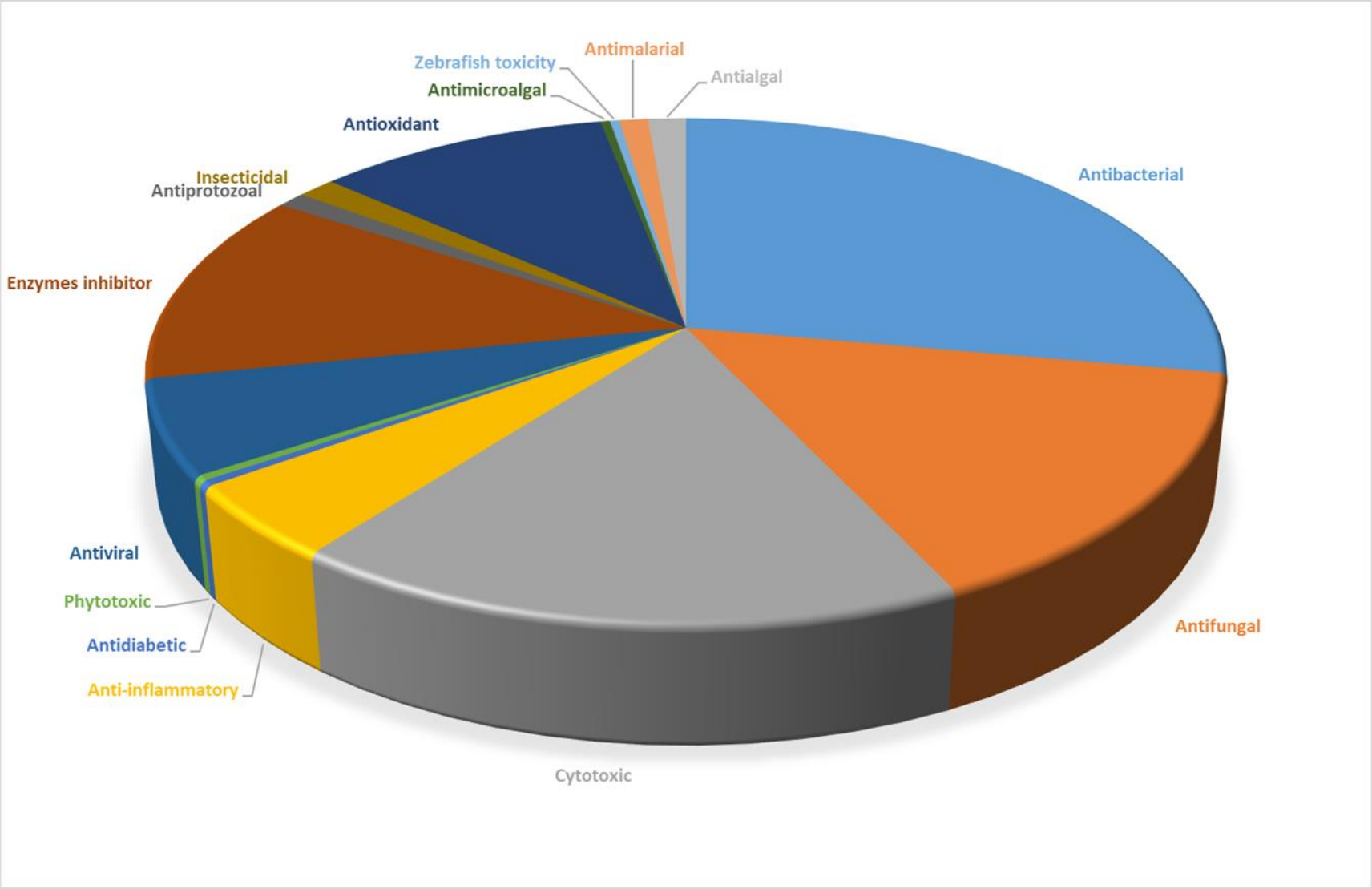


Figure 59. Total Therapeutic activities of various isocoumarins isolated from different fungal species.

Authorship Contribution Statement

Conceptualization: Amr El-Demerdash. **Validation**: Amr El-Demerdash. **Formal analysis**: Mohamed A. Tammam and Amr El-Demerdash. **Investigation**: Mohamed A. Tammam, Mariam I. Gamal El-Din, Amira Abood and Amr El-Demerdash. **Resources**: Mohamed A. Tammam and Amr El-Demerdash. **Data curation**: Mohamed A. Tammam and Amr El-Demerdash. **Writing original draft**: Mohamed A. Tammam, Mariam I. Gamal El-Din, Amira Abood and Amr El-Demerdash. **Writing-review & editing**: Mohamed A. Tammam, Mariam I. Gamal El-Din, Amira Abood and Amr El-Demerdash

Declaration of competing 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.

Data Availability

No data was used for the research described in the article.

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