RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Bioactive natural products derived from Mangrove-Associated Microbes

Jing Xu[1] *

[1] Key Laboratory of Protection and Development Utilization of Tropical Crop Germplasm Resources, Ministry of Education, College of Material and Chemical Engineering, Hainan University, Haikou 570228, P. R. China

Jing Xu obtained her BS and MS degrees from Hainan University. In 2006, she began her doctoral research with Professor Huashi Guan at the College of Medicine and Pharmaceutics, Ocean University of China. In 2007, she continued with her doctoral research in a group working with Professor Peter Proksch and received her PhD degree in 2010 at Heinrich-Heine-Universität Düsseldorf, Germany. She joined the faculty at Hainan University after her graduation where she is currently an Associate Professor of Pharmaceutical Chemistry. Simultaneously, she undertook a postdoctoral appointment at Nanjing University, with Professor Renxiang Tan from 2011 to 2014. Her research interests are focused on natural products originating from endophytic microbes and medicinal plants.

* To whom correspondence should be addressed. Tel: ++86 898 6627 9226; Fax: ++86 898 6627 9010;
Email: happyjing3@163.com

Abstract

This review summarizes new findings concerning the sources and characteristics of various natural products that can be extracted from mangrove-associated microbes over the past three years (January 2011-December 2013). The natural products are discussed with a focus on bioactivity, highlighting the unique chemical diversity of these metabolic products.

Keywords

Mangrove-associated microbes, actinomycetes, bacteria, fungus, biomolecules, polyketides, terpenoids, nitrogenated compounds, biological activities, synthesis, biosynthetic origin

Contents

1. Introduction

Microorganisms from special ecological niches such as the mangrove endosymbionts are a rich source of diverse and structurally unique bioactive natural products. Microbes inhabiting mangrove ecosystems adapt to frequent and sporadic environmental changes, including high salinity, low oxygen, nutrient limitation, tidal gradients, high temperatures, excessively high light, and drought [1]. The warm and damp conditions result in an active microbial community, which can act as an effective selector for metabolic pathway adaptations via generation of unique functional metabolites of pharmaceutical importance.

Mangrove forests are complex ecosystems that harbor diverse groups of microorganisms including actinomycetes, bacteria, fungi, cyanobacteria, microalgae, macroalgae and fungus-like protozoa. In the tropical mangrove microbial community, bacteria and fungi constitute 91% of the total microbial biomass, whereas algae and protozoa represent only 7% and 2%, respectively. Although the mangrove ecosystem has extensive microbial diversity, culture-dependent technologies reveal only a small percentage (<1 %) of the microbial community while 99 % of the microorganisms remain undiscovered. Among the isolated microbes, less than 5% of species have been presently chemically estimated, and these include the actinomycetes, bacteria and fungi. The advent of modern techniques provides the opportunity to find novel metabolites [2].

Mangrove associated microbial natural products have been the subject of several review articles. Advances in the chemistry and bioactivity of fungi from mangroves have been reviewed periodically in *Natural Product Reports* by Blunt and his co-workers [3, 4]. Wang et al. reviewed the studies on structure and bioactivity of metabolites isolated from

mangrove-derived fungi in the South China Sea [5]. Prof. Proksch' group compiled a comprehensive review detailing a decade of studies on potential of mangrove-derived endophytic fungi as promising bioactive natural products [6, 7]. Our previous review discussed the role of these endophytic fungi as a major source of antimicrobial agents. These fungi produce a wide range of medicinal compounds, including antitumor, neuroprotective, antioxidant, anti-AChE, anti-BK_{Ca} channel agents, and 348 molecules were discovered before 2011 [8].

However, 464 new metabolites have been discovered recently; therefore, we describe here the source, chemistry, and biology of the newly discovered biomolecules from the mangrove-associated microbes. We also summarize the chemical synthesis and the biosynthetic relationship of metabolites. All relevant studies focusing on known secondary metabolites in terms of bioactivity, the source of the microorganism, and the location of collection are examined, and particular emphasis is given to their potential use as drug leads. The running titles are presented in the following order: actinomycetic, bacterial, and fungal producers with structures classified within a biogenetic context as polyketides, terpenes, and nitrogenated compounds. Bioassays showed that the antitumor, anti-influenza A H1N1, anti-enzyme, anti- or activate- subintestinal vessel plexus and brine shrimp lethality activities were the most notable bioactivities of secondary metabolites isolated during 2011-2013. Possible biogenetic relationships between several alkaloids, quinones, phenols, lactones, sesquiterpenes, sesterterpenoids, and meroterpenes are discussed. The biomacromolecules originating from the title microbes were not within the scope of this review. The Metabolites Name Index in conjunction with the Microbial and Host Source Index, the Bioactivity Index and the Leading References on isolation in

the accompanying Tables, will help understand the fascinating chemistry and biology of naturally occurring mangrove-associated microbial metabolites.

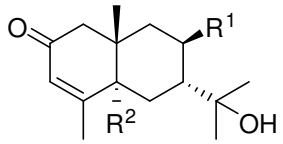
2. Actinomyces-derived molecules

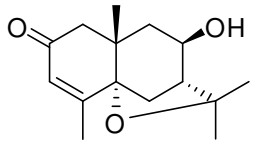
Due to the high rediscovery rate of known compounds from *Actinomycetes*, there has been a renewed interest in the development of new antimicrobial agents from this species. These compounds can help combat the increasing number of multidrug-resistant human pathogens [9]. Mangrove-derived actinomycetes are a potentially vast resource of structurally diverse natural products with unusual biological activity. *Streptomyces* are Gram-positive bacteria known for the production of an enormous variety of biologically active secondary metabolites, including antibiotics, immunosuppressants, and anticancer agents and have been become the focus of antibiotic research in the past three years.

2.1. Terpenoids

Eudesmene sesquiterpenes are proposed to be originated from further cyclization of the monocyclic germacranes [10]. They are most abundant as eukaryotic secondary metabolites and may be referred to as selinanes, commonly metabolized by a variety of plants, such as *Inula japonica* [11], *Blumea balsamifera* [12], and *Nectandra cissiflora* [13]. The only examples from prokaryotes are the recently described selina-4(14),7(11)-diene-8,9-diol from a marine *Streptomyces* sp. [14]; and 1,6,11-eudesmanetriol and 11-eudesmene-1,6-diol from an endophytic *Streptomyces* sp. of *Drymaria diandra* [15]. Five new members of this family, kandenols A-E (**1–5**), were characterized from a culture filtrate of endophytic *Streptomyces* sp. HKI0595 isolated from *Kandelia candel* (L.) (Xiamen, Fujian, China) using an HPLC-MS hyphenated system. The configuration of these eudesmenes was rigorously established by a

combination of the Mosher method and comparison of CD spectra with α-rotunol and β-rotunol. Hydroperoxide moieties are relatively rare in compounds **3** and **4**. Metabolite **5** is the first actinomycete agarofuran, which belongs to an important group of antibiotics. Unfortunately, none of these sesquiterpenes exhibited any cytotoxicity against the 12 selected human cell lines tested. However, weak to moderate antimicrobial activities were detected against *Bacillus subtilis* ATCC 6633 and *Mycobacterium vaccae* IMET 10670, with MIC values ranging from 12.5–50 μg/mL [16].





1 kandenol A, R^1 = OH, R^2= H
2 kandenol B, R^1 = OH, R^2= OH
3 kandenol C, R^1 = OH, R^2= O-OH
4 kandenol D, R^1 = H, R^2= O-OH

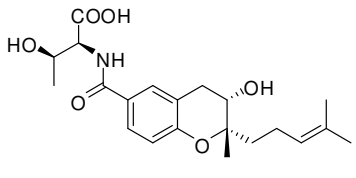
5 kandenol E

2.2. Nitrogenated compounds

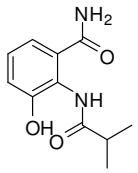
Indole terpenoids encompass a highly diverse group of natural products, including infamous psychotropic agents such as lysergic acid derivatives, the aphrodisiac yohimbine, and the potassium channel blockers paxilline and lolitrem. A remarkable fact about this multifarious class is that practically all indole terpene alkaloids have been isolated from plants and fungi. Further work on the aforementioned *Streptomyces* sp. HKI0595 endophyted in *K. candel* and another endophyte *Streptomyces* sp. GT2002/1503 associated in *Bruguiera gymnorrhiza* revealed five new pentacyclic indolosesquiterpene congeners, xiamycin A (**6**) and its methyl ester (**7**), xiamycin B (**8**), the seco-derivative indosespene (**9**), and the novel bridged spiro compound sespenine (**10**) by the same research team [17, 18]. Their most likely biosynthetic pathway and interrelationship are proposed based on the heterologous gene expression and mutational analysis as shown in

Scheme 1 [19]. A broad bioactivity screen revealed that compound **6** was moderately active against HIV, specifically blocked R5, but had no effects on X4 tropic HIV-1 infection. Compound **7** exhibited potential cytotoxicity compared with **6** in a modified propidium iodide assay, with IC_{50} values of 10.13 μM. Compound **8-10** showed moderate to strong antimicrobial activities in agar diffusion assays against several bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*; however, these compounds did not show cytotoxicity against human tumor cell lines. These rare endophyte metabolites likely play an ecological role in their habitat because their diverse antiviral, antibacterial, and antifungal activities may contribute to the antibiotic reservoir of the mangrove plants [18]. It is intriguing that these prokaryotes are endophytes producing typical plant metabolites. A unique diazaphenanthrene alkaloid, named 1-*N*-methyl-3-methylamino-[*N*-butanoic acid-3′-(9′-methyl-8′-propen-7′-one)-amide]-benzo[f][1,7]naphthyridine-2-one (**11**) and a known metabolite *N*-[[3,4-dihydro-3*S*-hydroxy-2*S*-methyl-2-(4′R-methyl-3′S-pentenyl)-2*H*-1-benzopyran-6-yl]carbonyl]-threonine (**12**) were isolated from *Streptomyces albogriseolus* and *Streptomyces xiamenensis*, respectively. Both of these compounds were obtained from mangrove sediments collected in the national mangrove reserve in Fujian province of China. A bioassay disclosed that the compound **12** inhibited the proliferation of human lung fibroblasts (WI26); blocks adhesion of human acute monocytic leukemia cells (THP-1) to a monolayer of WI26 cells; and reduces the contractile capacity of WI26 cells in three-dimensional free-floating collagen gels [20, 21]. The total synthesis of **11** was accomplished by coupling the tricyclic heteroaromatic carboxylic acid with the chiral

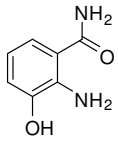
unsaturated amino ketoacid to yield a fused tricyclic heteroaromatic system as shown in Scheme 2 and the absolute configuration of **11** was firstly determined [22]. A new benzamide, 3-hydroxyl-2-*N*-iso-butyryl-anthranilamide (**13**), together with two known benzamides (**14**, **15**) and three known quinazolines (**16-18**), was isolated from a mangrove actinomycetes *Streptomyces* sp. No.061316 isolated from mangrove soils (Wenchang, Hainan, China). Although the extract from which it was isolated displayed *in vitro* inhibitory Caspase-3 activity, the pure natural products only **14** and **18** were found to be moderately active with IC_{50} values of 32 and 36 μM, respectively [23]. Several studies have demonstrated that *Streptomyces* is a successful source of bioactive benzoxazole metabolites, such as antitumor agents UK-1 [24] and nataxazole [25], antibiotics A33853 [26] and caboxamycin [27]. An antitumour benzoxazole derivative AJI956 (**19**), originally obtained from the actinomycete strain *Streptomyces* sp., was purified from *Streptomyces* sp. A1626 in *Kandelia candel* [28]. Micro-broth dilution assay disclosed its additional strength in moderating antifungal activity against fungal strains *Candida albicans* ATCC90028, *Cryptococcus neoformans* SLA1017 and *Aspergillus fumigatus* SIA1524, with IC_{50}/MIC values of 0.78/1.25, 1.5/2.5, and 15/20 μg/mL. Halogenation was reported to be an important feature for the bioactivity of a large number of distinct natural products. Chlorination was the most frequently found modification, followed by bromination, while iodination and fluorination are rare in nature [29]. Using PCR-based genetic screening techniques on mangrove sediments, 163 strains of actinomycetes were isolated and investigated for their potential to produce halogenated metabolites. A previously known antibiotic, enduracidin (**20**), was identified in the mangrove-derived *Streptomyces atrovirens* MGR140 [30, 31].



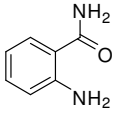
12



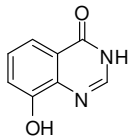
13



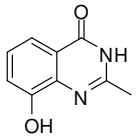
14



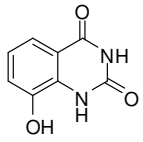
15



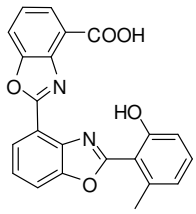
16



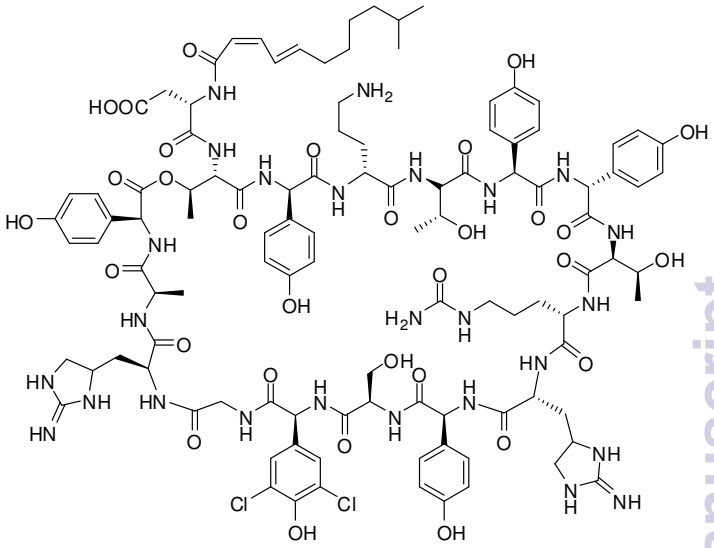
17



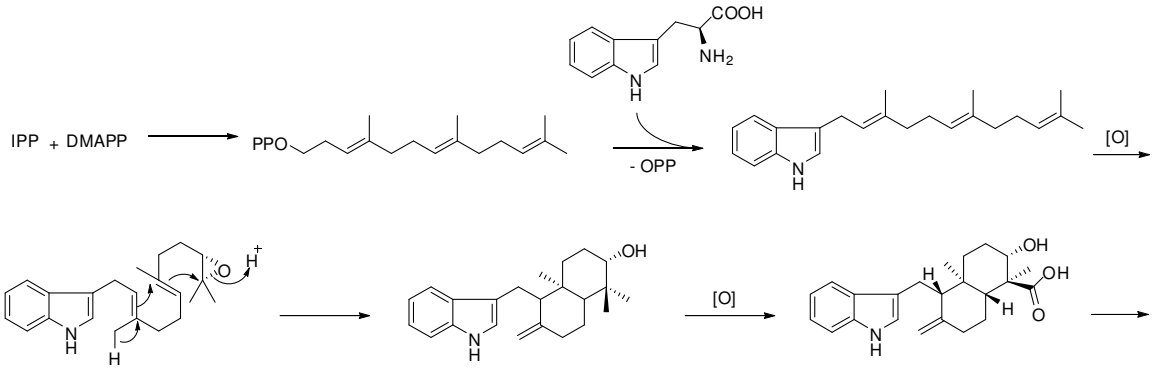
18



19 AJI956



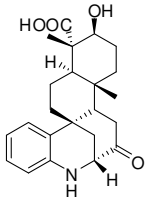
20



9 indosespene

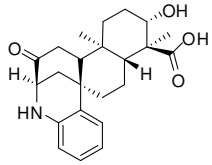
6 xiamycin A, R = H
8 xiamycin B, R = OH

methylation

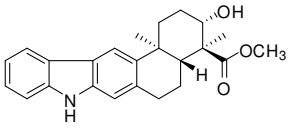


10 sespenine

=

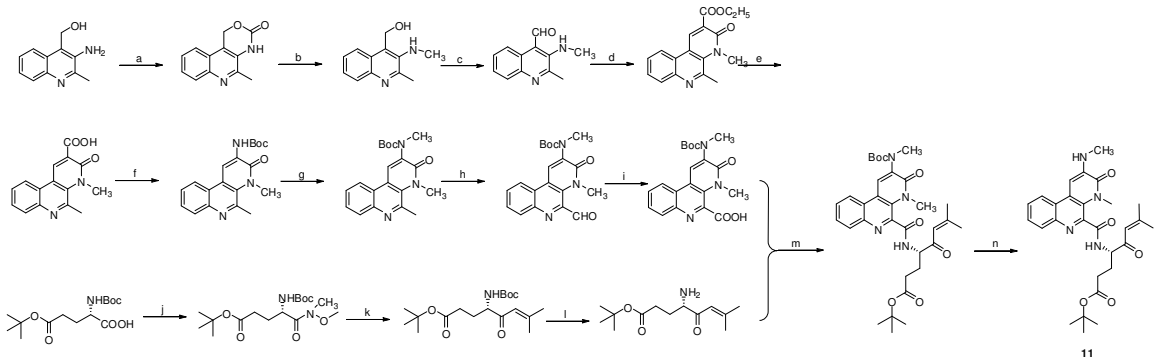


10 sespenine



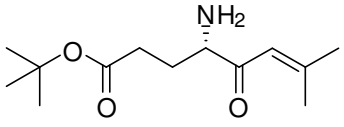
7

Scheme **1**. Biosynthetic pathways for the generation of compounds **6**-**10**



Scheme **2**. Synthesis of benzonaphthyridine alkaloid **11**.

Reagents and conditions: (a) triphosgene, Et_3N, THF, 0°C, 2 h, 78%; (b) $LiAlH_4$, THF, reflux, 2 h, 68%; (c) MnO_2, THF, rt, 20 h, 77%; (d) diethyl malonate, piperidine, 170°C, 5 h, 74%; (e) KOH, ethanol, reflux, 0.5 h, then glacial acetic acid, 87%; (f) DPPA, Et_3N, *t*-BuOH, reflux, 5 h, 73%; (g) CH_3I, Cs_2CO_3, DMF, 0°C to rt, overnight, 96%; (h) SeO_2, 70% TBHP, 1,4-dioxane, 50°C, 5 h, 82%; (j) *N*,*O*-dimethylhydroxylaminehydrochloride, $ClCO_2$-*i*-Bu, NMM, CH_2Cl_2, −15°C to rt, 2.5 h, 96%; (k) 2-methyl-1-propenyl magnesium bromide solution (0.5 M in THF), THF, 0°C, 4 h, 73%; (l) concentrated H_2SO_4, *tert*-butyl acetate, 0°C, 2 h, then saturated $NaHCO_3$, 80%; (m) (i) Ag_2O, KOH, H_2O, ethanol, rt, 1 h, then filtered through Celite and dried; (ii) HATU, DIPEA,

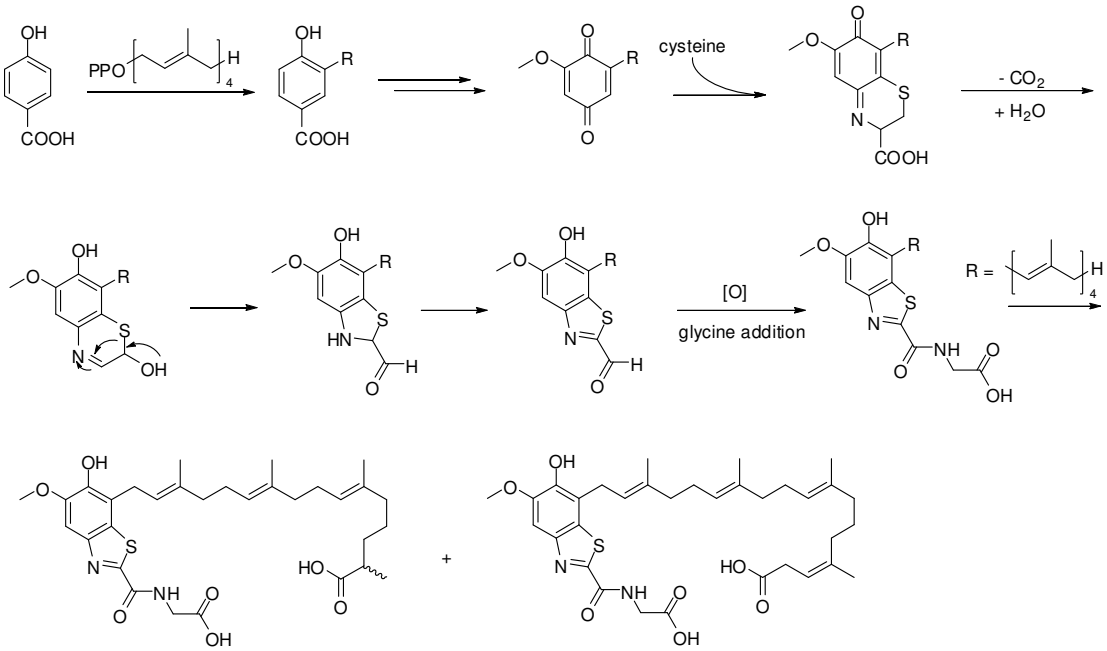


, DMF, rt, overnight, 45% over two steps; (n) CF_3COOH, CH_2Cl_2, rt, 5 h, 89%.

3. Bacterial metabolites

Information on bacterial strains, hosts, natural products, their biological activities, and relevant articles is included in Table 1. A predominant focus of natural products study of mangrove-associated bacteria has been on species of the genus *Bacillus*.

However other bacteria, such as gram-negative *Erythrobacter* have also proven to be an additional source of biologically and chemically interesting natural products. Chemical examination of an extract from an *Erythrobacter* sp. isolated from mangrove sediments yielded erythrazoles A (**21**) and B (**22**). The erythrazoles are of mixed biosynthetic origin containing a tetrasubstituted benzothiazole, an appended diterpene side chain, and a glycine unit. Based on the structural analysis, formation of the benzothiazole moiety was proposed to include a series of well precedented steps found in ubiquinone biosynthesis, *i.e.* prenylation, decarboxylation, hydroxylation, methylation, oxidation, and cyclisation. Their most likely biosynthetic pathway and interrelationship are shown in Scheme 3. Compound **21** is cytotoxic to a panel of non-small cell lung cancer (NSCLC) cell lines, with IC_{50} values of 1.5, 2.5, and 6.8 μM against H1325, H2122, and HCC366, respectively [32]. This encouraged subsequent efforts to investigate other bacteria that were not necessarily scarce in nature, but were rarely ever brought into culture and study.



21 **22**

Scheme 3. Possible biosynthetic pathway of the formation of compounds **21** and **22**.

Table 1. Actinomycetic and bacterial metabolites

bacterial species	host(s)	natural product(s)	biological activity	ref
Erythrobacter sp.	sediments	erythrazole A (**21**) erythrazole B (**22**)	cytotoxic	32
Streptomyces albogriseolus	sediments	1-*N*-methyl-3-methylamino-[*N*-butanoic acid-3′-(9′-methyl-8′-propen-7′-one)-amide]-benzo[f][1,7] naphthyridine-2-one (**11**)		20
Streptomyces xiamenensis	sediments	*N*-[[3,4-dihydro-3*S*-hydroxy-2*S*-methyl-2-(4′*R*-methyl-3′*S*-pentenyl)-2*H*-1-benzopyran-6-yl]carbonyl]-threonine (**12**)	anti-Fibrotic	21
Streptomyces sp. A1626	*Kandelia candel*	AJI956 (**19**)	antitumour; antifungal	28
Streptomyces sp. GT2002/1503	*Bruguiera gymnorrhiza*	xiamycin B (**8**) indosespene (**9**) sespenine (**10**)		18
Streptomyces sp. HKI0595	*Kandelia candel*	kandenol A (**1**) kandenol B (**2**) kandenol C (**3**) kandenol D (**4**) kandenol E (**5**) xiamycin A (**6**) xiamycin A methyl ester (**7**)	moderate antimicrobial moderate antimicrobial moderate antimicrobial waek antimicrobial moderate antimicrobial selective anti-HIV cytotoxic	16 17
Streptomyces atrovirens MGR140		enduracidin (**20**)	antibiotic	30
Streptomyces sp. No.061316	soil	3-hydroxyl-2-*N*-iso-butyryl-anthranilamide (**13**) 3-hydroxyl-anthranilamide(**14**) anthranilamide (**15**) 8- hydroxy -4(3H)-quinazoline(**16**) 8- hydroxy -2-methyl-4(3H)-quinazoline (**17**) 8- hydroxy-2,4-dioxoquinazoline (**18**)	 caspase-3 catalytic inhibitor caspase-3 catalytic inhibitor	23

4. Fungal metabolites

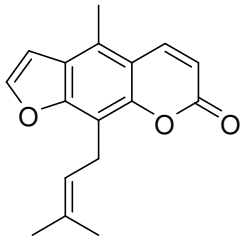
Mangrove-associated fungi produce a larger number of secondary metabolites

compared to any other mangrove-derived microbes, especially the endophytic fungi [8]. Many of these fungi are capable of synthesizing bioactive compounds that may contribute to their adaptation to harsh environmental factors such as predation and microbial infection during long co-evolution. An ever-increasing number of compounds are being reported from fungi associated with mangrove plants and soils. Some of these compounds have been shown to have a broad spectrum of biological activity, and they can be grouped into several categories, including isocoumarins, chromones, flavonoids, quinones, xanthones, phenols and phenolic acids, lactones, terpenoids, nitrogenated compounds, steroids, etc. Table 2 lists the hosts, natural products, biological activities, and articles related to these fungi and their products.

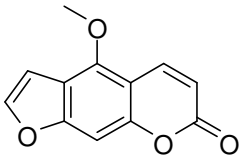
4.1. Polyketides

4.1.1 Coumarins

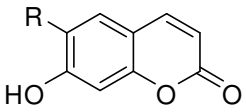
Only one previously unknown furanocoumarin, named 5-methyl-8-(3-methylbut-2-enyl) furanocoumarin (**23**), together with three known metabolites, bergapten (**24**), scopoletin (**25**), and umbelliferone (**26**), were identified from mangrove sources from 2011-2013. These metabolites were isolated from *Penicillium* sp. ZH16, which is an endophytic fungus from the mangrove tree *Avicennia* (Hainan, China). Compound **23** showed modest cytotoxic activity against the human tumor cell line KB and KBV200 with IC_{50} values of 5 and 10 μg/mL, respectively [33].



23



24

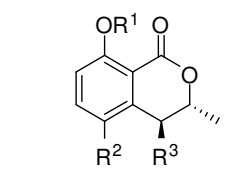


25 R = OCH_3
26 R = H

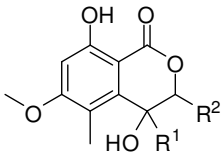
4.1.2 Isocoumarin derivatives

Naturally occurring isocoumarin and 3,4-dihydroisocoumarin derivatives abound in a wide variety of microbial sources and have been shown to possess an impressive array of biological activities. Many of these are known to have substituents at C-3 [34]. A new isochroman, (3*R*, 4*S*)-3,4-dihydro-4,5,8-trihydroxy-3-methylisocoumarin (**27**), isolated from mangrove sediment was characterized from *Phomopsis* sp. (No. ZH-111) (ZhuHai, China). This metabolite was tested on zebrafish embryo collections in a primary antibacterial assay wherein it was shown to accelerate the growth of blood vessel markedly. Furthermore, it showed weak cytotoxicity against Hep-2 and HepG2 cells [35]. In mixed fermentation, co-cultured microbes may activate the silent genes related to metabolite biosynthesis for new biomolecules, which cannot be otherwise detected in individual strain cultures. This approach can be used to fully exploit the metabolic potential of cultivable microbes [36]. Application of mixed fermentation technique on unidentified mangrove fungal strains *Kandelia candel* endophytic K38 and *Eucheuma muricatum* endophytic E33 yielded a representative 4-substituted 3-nonsubstituted known isocoumarin, 6, 8-dihydroxy-4-acetylisocoumarin (**28**) (Zhanjiang, South China Sea, China) [37]. Three previously known mellein derivatives (**29-31**) were isolated from *Xylaria cubensis* PSU-MA34, an endophyte obtained from a branch of *Bruguiera*

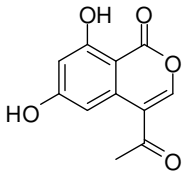
parviflora (Suratthani, Thailand). Even the crude extract from the culture broth exhibited cytotoxic activity against KB cells derived from the epidermoid carcinoma of the oral cavity, with an IC_{50} value of 2.79 μg/mL. Moreover, the crude extract showed antibacterial activity against *Staphylococcus aureus* ATCC 25923 and methicillin-resistant *Staphylococcus aureus* (MRSA) with equal MIC values of 200 μg/mL. None of **29-31** exhibited either cytotoxic or antibacterial activities [38]. Two new dihydroisocoumarin derivatives, aspergillumarins A (**32**) and B (**33**), were isolated from the liquid culture of *Aspergillus* sp., an endophytic fungus isolated from the leaf of Chinese mangrove plant *Bruguiera gymnorrhiza* (South China Sea, China). Both compounds exhibited a weak antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* at a concentration of 50 μg/mL [39]. Chromatographic analysis of *Rhizophora apiculata* (Satun, Thailand) endophytic *Acremonium* sp. PSU-MA70 yielded seven new analogues, acremonones B–H (**34-40**) [40]. A previously unknown isocoumarin (**41**), bearing an exocyclic double bond, was identified from an endophytic fungus *Xylaria* sp. BL321, present in *Acanthus ilicifolius* L. (Guangdong, South China Sea, China) [153]. Another two known analogues, phytotoxic diaporthin (**42**) and 5-carboxymellein [8], were also found to occur in a fungal endophyte *Sporothrix* sp. (#4335) of *Kandelia candel* (South China Sea, China). Compound **42** was found to be toxic to tumor cell line HepG2, giving an IC_{50} value of 23 μM [41].



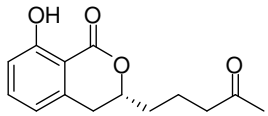
27 R^1 = H, R^2= OH, R^3= OH
29 R^1 = R^3= H, R^2= COOH
30 R^1 = R^3= H, R^2= $COOCH_3$
31 R^1 = CH_3, R^2= R^3= H



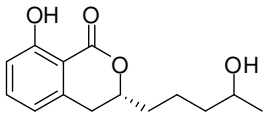
34 R^1 = $COCH_3$, R^2 = H
35 R^1 = CH_2OH, R^2 = CH_3
36 R^1 = $CH(OH)CH_3$, R^2 = H



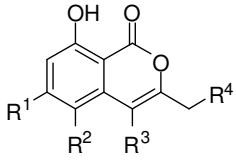
28

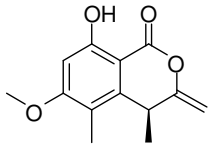


32

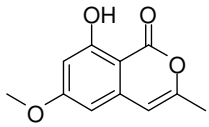


33



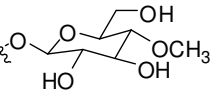


41



42

37 R^1 = OCH_3, R^2 = CH_3, R^3 = CH_2OH, R^4 = OH
38 R^1 = R^4 = OH, R^2 = CH_3, R^3 = CH_2OH
39 R^1 = R^4 = OH, R^2 = H, R^3 = CH_3
40 R^1 = OCH_3, R^2 = R^3 = CH_3, R^4 =

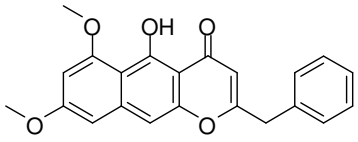


4.1.3 Chromones

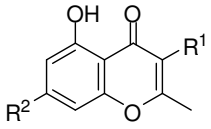
Naphthopyrones combining naphthalene and a γ-pyrone moiety exist as naturally occurring scaffolds with broad biological activity ranging from antimicrobial, antiviral, insecticidal and anti-estrogenic activity [42]. A new cytotoxic naphtho-γ-pyrone, 5-hydroxy-6,8-dimethoxy-2-benzyl-4*H*-naphtho[2,3-*b*]-pyran-4-one (**43**), was characterized from the fungal strain *Phomopsis* sp. ZSU-H26 residing in *Excoecaria agallocha* (DongZhai, Hainan, China). Two other well- known metabolites 5,7-dihydroxy-2-methylbenzopyran-4-one (**44**) and 3,5-dihydroxy-2,7-dimethylbenzopyran-4-one (**45**) were also discovered from *Phomopsis* sp. ZSU-H26 alongside the above described compound. Compound **43** showed cytotoxic activity against Hep-2 and HepG2 cells, with IC_{50} values of 10 and 8 μg/mL, respectively [43]. Chemical investigation of another *Excoecaria agallocha* (DongZhai, Hainan, China) endophytic fungal strain *Phomopsis* sp. (#zsu-H76) yielded a unique dimer metabolite,

phomopsis-H76 A (**46**), which could accelerate the growth of subintestinal vessel plexus (SIV) branch [44]. "One strain many compounds" (OSMAC) is an effective approach to activate the biosynthetic pathway of microorganisms [45] and has been successfully applied towards the discovery of new metabolites from *Aspergillus tubingensis* (GX1-5E). *A. tubingensis* (GX1-5E) obtained from the radix of *Pongamia pinnata* (Guangxi, China), yielded seven dimeric naphtho-γ-pyrones, rubasperone A-G (**47-53**), which co-exist with their biosynthetically related monomers, rubrofusarin (**54**), rubrofusarin B (**55**), TMC 256 A1 (**56**), fonsecin (**57**), and flavasperone (**58**) by solid-substrate fermentation cultures. The absolute configurations of compounds **47** and **48** were determined by X-ray crystallography. Compounds **52/53** were obtained as an inseparable mixture of two slowly equilibrating atropisomers, which could be distinguished by NMR spectroscopy. The hindered internal rotation allows distinguishing these compounds, thus, indicating a non-enzymatic biosynthesis or a particularly facile mode of racemization. Among these metabolites, compound **54** displayed moderate tyrosinase inhibitory activity, with an IC_{50} value of 65.6 μM, and compound **55** exhibited mild α-glucosidase inhibitory activity, with an IC_{50} value of 97.3 μM. Compound **56** was found to be toxic towards a small panel of tumor cell lines such as MCF-7, MDA-MB-435, Hep3B, Huh7, SNB19, and U87 MG, with IC_{50} values ranging from 19.92 to 47.98 μM while compounds **50**, **55**, and **58** showed mild cytotoxicities [46, 47]. Further investigation of the aforementioned mixed culture of the two unidentified fungal strains K38 and E33 isolated from mangrove plants *Kandelia candel* endophytic and *Eucheuma muricatum*, yielded another previously known naphtho-γ-pyrone, 5-hydroxy-6, 8-dimethoxy-2, 3-dimethyl-4*H*-naphtho-[2，3-*b*]-pyran-4-one (**59**) [37]. Nonchlorinated chromones are common metabolites

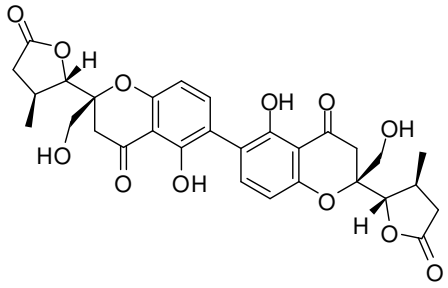
encountered in mangrove fungi [8]. Three previously unknown chlorinated tetrahydrochromanone derivatives, pestalochromones A–C (**60–62**), were recently identified in a mangrove plant *Rhizophora apiculata*-derived fungus *Pestalotiopsis* sp. PSU-MA69 (Satun, Thailand). The biosynthetic pathway for compounds **60–62** is proposed as shown in Scheme 4 [48]. Several ubiquitous microbial chromone derivatives were also isolated, including 5-hydroxy-3-hydroxymethyl-7-methoxy-2-methyl-4H-1-benzopyran-4-one (**63**) from *Penicillium* sp. ZH58 obtained from the leaves of the mangrove tree *Avicennia* (Hainan, China) [49]; and 5-hydroxy-2-methylchromanone (**64**) and 5-methoxy-2-methylchromanone (**65**) from *Sporothrix* sp. (#4335) of *Kandelia candel* [41].



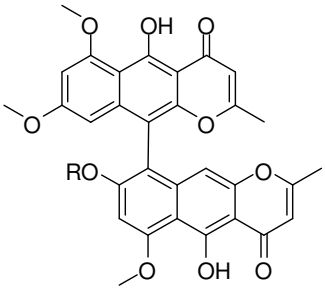
43



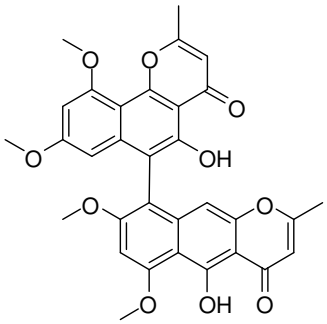
44 R^1 = H, R^2= OH
45 R^1 = OH, R^2= CH_3



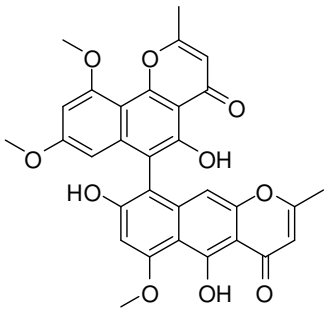
46



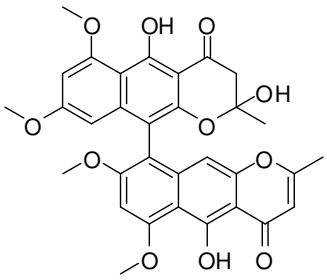
47 rubasperone A, R = H
48 rubasperone B, R = CH_3



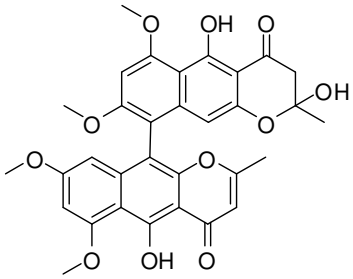
49 rubasperone C



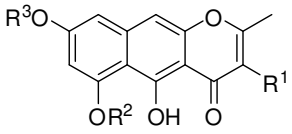
50 rubasperone D



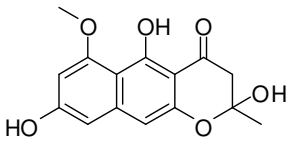
51 rubasperone E



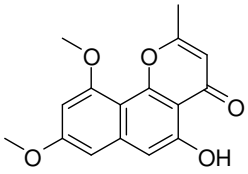
52, **53** atropisomers



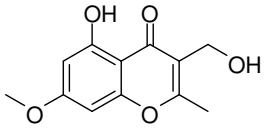
54 R^1=R^2 =H, R^3=CH_3
55 R^1=H, R^2 =R^3=CH_3
56 R^1=R^3 =H,R^2=CH_3
59 R^1=R^2 =R^3=CH_3



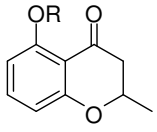
57



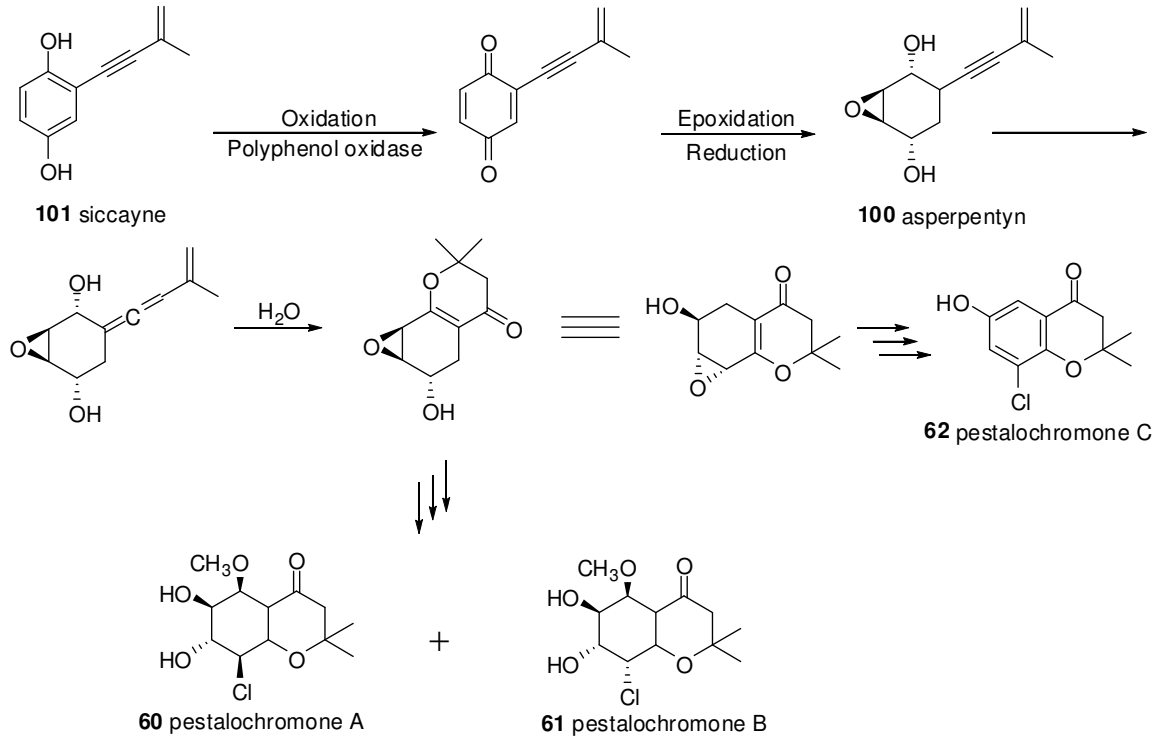
58



63



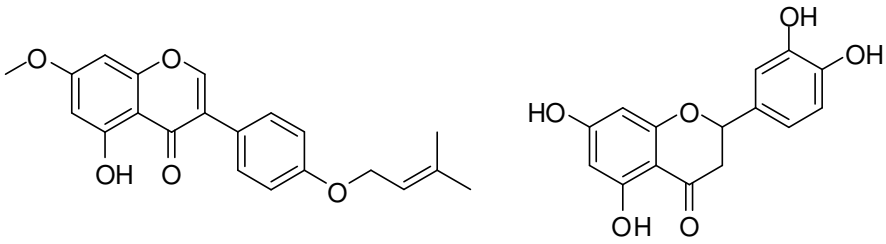
64 R = H
65 R = CH_3



Scheme 4. Proposed pathways of compounds **100**-**101** to compounds **60–62**

4.1.4 Flavonoids

An isoflavone, 5-hydroxy-7-methoxy-4′-*O*-(3-methylbut-2-enyl) isoflavone (**66**) and a structurally related known vasodilatory agent eriodictyol (**67**) were identified from the cultures of *Fusarium* sp. ZZF60 inhabiting the leaves of *Kandelia candel* (Hainan, China) [50]. Huang et al. (2012) reported these metabolites for the first time in mangrove microbes.



66 **67**

4.1.5 Quinones

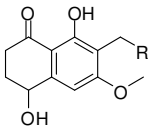
The widespread occurrence and function of quinone and semiquinone derivatives in

mangrove-derived fungi has been well established. These compounds have anticancer, antibacterial, antimalarial and fungicidal properties. Two previously reported semiquinones, 3,4-dihydro-4,8-dihydroxy-7-(2-hydroxyethyl)-6-methoxy-1(2*H*)-naphthalen-1-one (**68**) and an anti-influenza virus antibiotic 10-norparvulenone (**69**) were isolated from an unidentified plant endophyte Zh6-B1, obtained from the bark of *Sonneratia apetala* (Guangdong, China) [51]. Three newly identified bianthraquinone derivatives, alterporriols K-M (**70-72**), and four co-occurring anthraquinones (**73-76**) were obtained from extracts of the endophytic fungus *Alternaria* sp. ZJ9-6B isolated from *Aegiceras corniculatum* (Guangdong, China). Compounds **70-72** were the first isolated alterporriols featuring a rarely encountered a C-2-C-2′ linkage. Compounds **70** and **71** were found to be moderately toxic towards MDA-MB-435 and MCF-7 cells with IC_{50} values ranging from 13.1 to 29.1 μM [52]. The anticancer mechanism of compound **71** towards breast cancer cells lines was estimated, and it is known to play a vital role in breast cancer cells by destroying the mitochondrial membrane [53]. Early studies on *Kandelia candel* endophytic fungus *Nigrospora* sp. No.1403 revealed the presence of five cytotoxic anthracenediones [54]. Further investigation of this fungus yielded an additional multi-active substance deoxybostrycin (**77**), which is a known phytotoxin, also an antibacterial agent bostrycin 1403P-3 and a deoxy-analogue 1403P-2 nigrosporin. Bioassay indicated that **77** could significantly suppress the growth of six human tumor cell lines: A549, Hep-2, Hep G2, KB, MCF-7, and MCF-7/Adr, with IC_{50} values of 2.44, 3.15, 4.41, 3.15, 4.76, and 5.46 μg/mL, respectively. Moreover, its 21 synthetic derivatives also exhibited strong to moderate cytotoxicity while some displayed remarkable activity against MDA-MB-435,

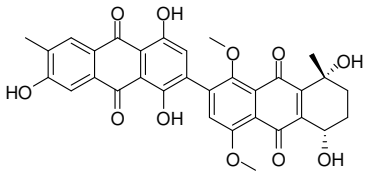
which was comparable with the positive control epirubicin [55]. Further tests disclosed its strong antimicrobial activities against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Sarcina ventriculi*, *Bacillus subtilis* with an IC_{50} of 3.13 μg/mL; it also inhibited *Candida albicans* with an IC_{50} of 12.5 μg/mL [56]. Moreover, **77** exhibited remarkable inhibitory effect on mycobacteria, especially *Mycobacterium tuberculosis*, and this inhibitory effect was much more effective than some of the first line anti-tuberculosis (TB) drugs against clinical multidrug-resistant (MDR) *M. tuberculosis* strains [57]. A new cochlioquinone derivative, 2,3-didehydro-19α-hydroxy-14-epicochlioquinone B (**78**) and a known hydronaphthalenone derivative 4-deoxytetrahydrobostrycin (**79**) were characterized from another endophytic *Nigrospora* sp. strain No. MA75 obtained from the semi-mangrove plant *Pongamia pinnata* in different culture media. This compound (**78**) displayed remarkable antibacterial activity toward MRSA, *E. coli*, *P. aeruginosa*, *P. fluorescens*, and *S. epidermidis*, with MIC values of 8, 4, 4, 0.5, and 0.5 μg/mL, respectively. However, compound **79** exhibited moderate and somewhat selective inhibition of MRSA, *E. coli*, and *S. epidermidis*. Moreover, compound **78** potently inhibited the growth of MCF-7, SW1990, and SMMC7721 tumor cell lines with IC_{50} value of 5 μg/mL [58]. A known phytochemical sterequinone C (**80**) was characterized from *Penicillium* sp. ZH16 from the leaves of *Avicennia* [33] The leaves of *Rhizophora apiculata* (Songkhla, Thailand) harbor the endophytic fungus, *Phomopsis* sp. PSU-MA214 from which a new tetrahydroanthraquinone derivative, (2*R*,3*S*)-7-ethyl-1,2,3,4-tetrahydro-2,3,8-trihydroxy-6-methoxy-3-methyl-9,10-anthracene dione (**81**), and five other known anthraquinones (**82**–**86**), were characterized. Compound

81 is a rare ethyltetrahydroanthraquinone that shows weak cytotoxicity against breast cancer MCF-7 cell lines. Furthermore, it shows antibacterial activity against the standard *Staphylococcus aureus* ATCC25923 and methicillin-resistant *S. aureus* SK1. The proposed biosynthetic pathway of these anthraquinones (**81**–**86**) starts from an octaketide precursor, which is obtained by the condensation reaction of acetate and malonate units as shown in Scheme 5 [59]. A chemical investigation of the ethyl acetate extract of the fermentation broth of *Alternaria tenuissima* EN-192, an endophytic fungus obtained from the stems of *Rhizophora stylosa*, resulted in the isolation of three known tricycloalternarene metabolites (**87**–**89**). In disk diffusion assays, compound **87** was shown have moderate antibacterial activity against the aquaculture pathogenic bacterium *Vibrio anguillarum* [60]. A rare thiophene compound, named 8-hydroxy-2-[1-hydroxyethyl]-5,7-dimethoxynaphtho[2,3-*b*] thiophene-4,9-dione (**90**), and four previously described metabolites anhydrojavanicin (**91**), 8-*O*-methyljavanicin (**92**), botryosphaerone D (**93**), 6-ethyl-5,8-dihydroxy -3,7-dimethoxynaphthoquinone (**94**) were characterized from the liquid culture of *Aspergillus terreus* (No. GX7-3B), an endophyte present in a branch of *Bruguiera gymnoihiza* (Linn.) Savigny (Guangxi, China). Compound **91** displayed remarkable inhibition against α-acetylcholinesterase (AChE) with IC_{50} values 2.01 μM in bioactivity assays *in vitro* [61].

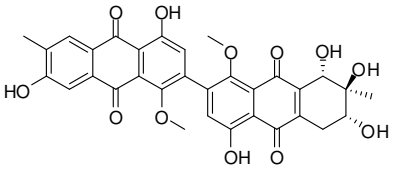
Several known compounds (**96-102**) were also isolated from other endophytes associated with various plants [38, 41, 48, 62, 63]. Amongst, compound **98** exhibited significant inhibitory effect against a panel of human protein kinases, such as IGF1-R and VEGF-R2 with IC_{50} values mostly in the low micromolar range [62].



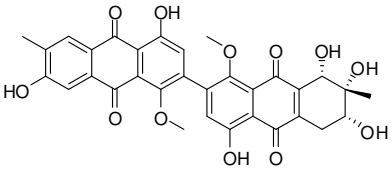
68 R = CH_2OH
69 R = OH



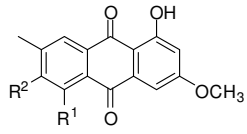
70



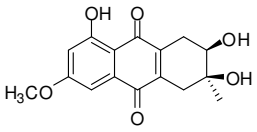
71



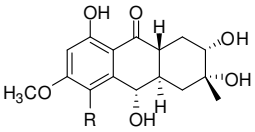
72



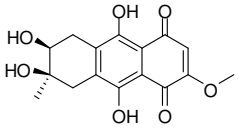
73 R^1 = OH, R^2 = H
74 R^1 = H, R^2 = OH



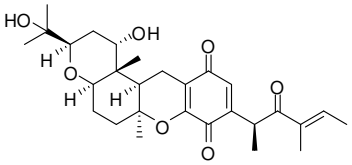
75



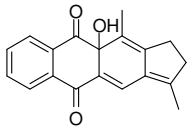
76 R = H
79 R = OH



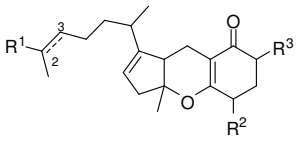
77 deoxybostrycin



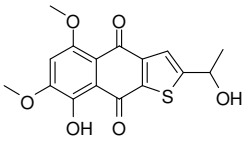
78



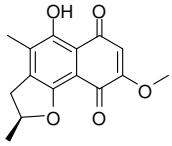
80



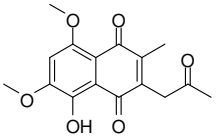
87 R^1 = CH_3, R^2 =OH, R^3 = H, C(2)=C(3)
88 R^1 = CH_2OH, R^2 = H, R^3 = OH
89 R^1 = CH_2OH, R^2 = H, R^3 = OH, C(2)=C(3)



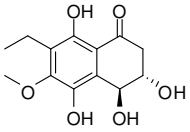
90



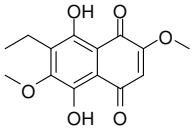
91



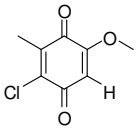
92



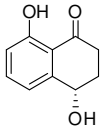
93



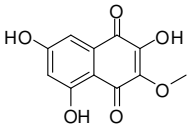
94



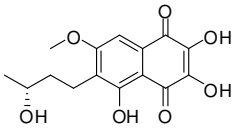
95



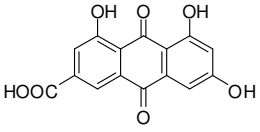
96



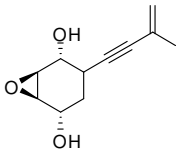
97



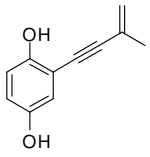
98



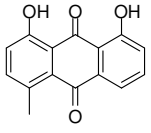
99



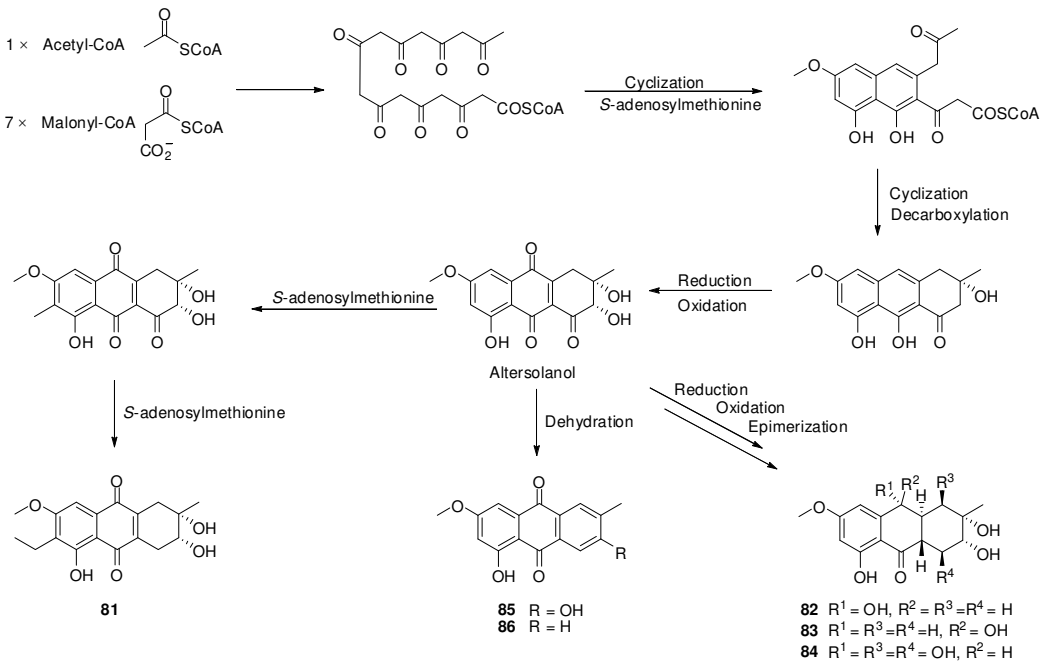
100 asperpentyn



101 siccayne



102



Scheme **5**. A plausible biosynthetic pathway for compounds **81**–**86**.

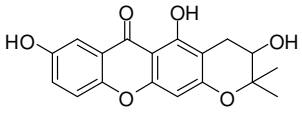
4.1.6 Xanthones

Xanthones are usually polysubstituted and occur as either fully aromatized, dihydro-, tetrahydro-, or, more rarely, hexahydroderivatives. This family of compounds appeals to medicinal chemists because of its members' pronounced biological activity within a notably broad spectrum of disease profiles, a result of their interactions with a correspondingly diverse range of target biomolecules. Studies on structure-activity relationships of xanthone derivatives were reviewed comprehensively [64]. A new xanthone derivative, 3,5,8-trihydroxy-2,2-dimethyl-3,4,4-trihydro-2H,6H-pyrano[3,2-b]-xanthen-6-one (**103**), together with its analogue, 5,8-dihydroxy-2,2-dimethyl-2*H*,6*H*-pyrano[3,2-b]xanthen-6-one (**104**), were found to be produced by unidentified endophytic fungus No. ZSU-H16, which was separated from the leaves of mangrove *avicennia* from the South China Sea coast. Compound

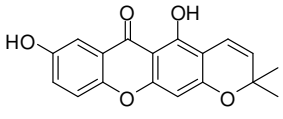
103 was shown to be moderate cytotoxic against KB and KBV 200 cells [65]. On the other hand, two new xanthones, named 1-hydroxy-8-(hydroxymethyl)-6-methoxy-3-methyl-9*H*-xanthen-9-one (**105**) and 1-hydroxy-8-(hydroxymethyl)-3-methoxy-6-methyl-9*H*-xanthen-9-one (**106**), were isolated from endophytic *Phoma* sp. SK3RW1M associated with the roots of *Avicennia marina* (Guangxi, China). This is the first report on xanthone derivatives isolated as metabolites from *Phoma* species [66]. The same collection of a two-endophytic fungi association of unidentified mangrove fungal strains *Kandelia candel* endophytic K38 and *Eucheuma muricatum* endophytic E33 yielded an additional new xanthone antibiotic, 8-hydroxy-3-methyl-9-oxo-9H-xanthene-1-carboxylic acid methyl ester (**107**). Biological investigation demonstrated that compound **107** has broad antifungal activity against some plant pathogens *Gloeosporium musae*, *Blumeria graminearum*, *Fusarium oxysporum*, *Peronophthora cichoralearum* and *Colletotrichum glocosporioides* [67]. Bioassay-guided purification of another endophytic *Nigrospora* sp. strain No. MA75, obtained from the semi-mangrove plant *Pongamia pinnata* on various culture media, resulted in the characterization of three previously known xanthone derivatives (**108–110**). Compound **108** exhibited moderate and somewhat selective inhibition of human tumor cell HepG2, whereas compound **110** was shown to be broad-spectrum antibacterial toward MRSA, *E. coli*, *P. aeruginosa*, *P. fluorescens*, and *S. epidermidis*, with MIC values of 0.5, 2, 0.5, 0.5, and 16 μg/mL, respectively [58]. Four related known derivatives were obtained from the chemical

investigation of *Kandelia candel* endophytic *Fusarium* sp. ZZF60 [50] and *Sporothrix* sp. (#4335) [41], and an endophytic *Penicillium* sp. ZH16 of a mangrove tree *Avicennia* [33]. These were: 3,6,7-trihydroxy-1-methoxyxanthone (**111**), 1,3,6-trihydroxy-8-methylxanthone (**112**) 1,7-dihydroxyxanthone (**113**), and 1,8-dihydroxy-5-methoxy-3-methyl-9*H*-xanthen-9-one (**114**). A new xanthone, pestaloxanthone (**115**) was characterized from *Pestalotiopsis* sp. PSU-MA69, an endophytic fungus living in the interior part of *Rhizophora apiculata* branch [48]. A new xanthone *O*-glycoside, 3-*O*-(6-*O*-*α*-L-arabinopyranosyl)-*β*-D-glucopyranosyl-1,4-dimethoxyxanthone (**116**) was discovered in the endophyte *Phomopsis* sp. (ZH76) isolated from the stem of *Excoecaria agallocha* (Hainan, China). This compound showed modest cytotoxicity against HEp-2 cells with IC_{50} of 9 μg/mL and against HepG2 cells with IC_{50} of 16 μg/mL [68]. A new xanthone, named 2,6-dihydroxy-3-methyl-9-oxoxanthene-8-carboxylic acid methyl ester (**117**), alongside three known compounds lichenxanthone (**118**), griseoxanthone C (**119**) and 1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (**120**) were characterized from *Phomopsis* sp. (No. SK7RN3G1), isolated from the mangrove sediment. Compound **117** displayed modest *in vitro* inhibition of the proliferation of HEp-2 and HepG2 cells lines, giving IC_{50} values of 8 and 9 μg/mL, respectively [69]. Xanthone dimers possess increasingly complex and interesting structures and in many cases have very specific and selective biological properties. Two dimeric tetrahydroxanthones, a known phomoxanthone A (**121**) and a structurally related new

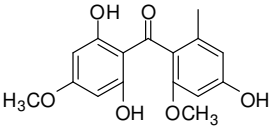
12-*O*-deacetyl-phomoxanthone A (**122**) were obtained from the rice culture of *Phomopsis* sp. IM 41-1 separated from a mangrove plant *Rhizhopora mucronata* (Jakarta, Indonesia). Both of these compounds exhibited moderate antimicrobial activities against *Botrytis cinerea*, *Sclerotinia sclerotiorum*, *Diaporthe medusaea*, and *Staphylococcus aureus*. Furthermore, they are implicated in the protection of the host plant from degradation and disease caused by pathogens. However, in contrast to previous reports [70, 71], the acetylated moiety did not have any significant effect on biological activity. Moreover, the differences in the antimicrobial activities between **121** and **122** were small [72].



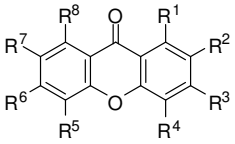
103

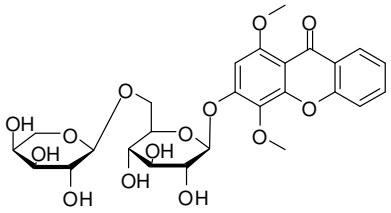


104



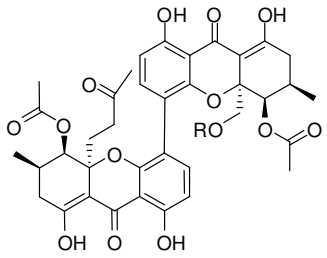
110





116

105 R^1= CH_2OH, R^2=R^4=R^5=R^7=H, R^3=OCH_3, R^6=CH_3, R^8= OH
106 R^1= CH_2OH, R^2=R^4=R^5=R^7=H, R^3=CH_3, R^6=OCH_3, R^8= OH
107 R^1= $COOCH_3$, R^2=R^4=R^5=R^7=H, R^3= CH_3, R^8= OH
108 R^1= CH_3, R^2=R^4=R^5=R^7=H, R^3=R^8=OH, R^6=OCH_3
109 R^1= CH_3, R^2=R^4=R^5=R^7=H,R^3=R^6=R^8= OH
111 R^1= OCH_3, R^2=R^4=R^5=R^8=H,R^3=R^6=R^7= OH
112 R^1= R^3= R^6= OH, R^2=R^4=R^5=R^7=H,R^8= OCH_3
113 R^1= R^7= OH, R^2=R^4=R^6=R^7=H, R^3= CH_3,
114 R^1= R^8=OCH_3, R^2=R^4=R^5=R^6=R^7=H, R^3=OH, R^4=$COOCH_3$
115 R^1= OH, R^2=R^4=R^5=R^7=H, R^3=CH_2OH, R^6=OCH_3, R^8=$COOCH_3$
117 R^1=R^4=R^5=R^7=H, R^2=R^6=OH, R^3=CH_3, R^8=$COOCH_3$
118 R^1= OH, R^2=R^4=R^5=R^7=H, R^3=R^6=OCH_3, R^8=CH_3
119 R^1= R^6=OH, R^2=R^4=R^5=R^7=H, R^3=OCH_3, R^8=CH_3
120 R^1= CH_3, R^2=R^4=R^5=R^7=H, R^3=R^6=R^8=OH



121 R=$COCH_3$
122 R= H

4.1.7 Phenol and phenolic acids

Over 70 natural phenolic acids produced by mangrove fungi were identified during 2011–2013, and since then, their number has steadily increased. Two new

benzofuranoids, deuteromycols A and B (**123**, **124**), were isolated from the fermentation broth of *Deuteromycete* sp., which was isolated by micromanipulation from the mangrove drift wood (Red Sea, El Gouna, Egypt). Although the extract from which it was isolated exhibited *in vitro* antibacterial activity toward pathogenic strains such as *Staphylococcus aureus* (ATCC 6538), *Bacillus subtilis* (ATCC 6051), *Escherichia coli* (ATCC 11229), *Pseudomonas aeruginosa* (ATCC 22853) and multiresistant strains *Staphylococcus aureus* (Northern Germany Epidemic Strain, NGES), *Staphylococcus epidermidis* (LHI, No. 847) and *Staphylococcus haemolyticus* (LHI, No. 535), the pure natural product has not yet been evaluated [73].

Three new *p*-terphenyls, 6′-*O*-desmethylterphenyllin (**125**), 3-hydroxy-6′-*O*-desmethylterphenyllin (**126**), 3″-deoxy-6′-*O*-desmethylcandidusin B (**127**) along with two known *p*-terphenyls (**128**, **129**) were isolated from *Penicillium chermesinum* (ZH4-E2), which is endophytic to *Kandelia candel* (South China Sea, Hainan, China). All of these compounds showed enzyme inhibitory activities. Compounds **125-127** showed strong inhibitory effects against *R*-glucosidase with IC_{50} values of 0.9, 4.9, and 2.5 μM, respectively, whereas compounds **128** and **129** showed inhibitory activity toward acetylcholinesterase, with IC_{50} values of 7.8 and 5.2 μM [53].

Polyhydroxy-*p*-terphenyl-type chemical entities, mainly found in mycomycetes, include scaffolds with a C-18 tricyclic or polycyclic C-18 skeleton and those exhibiting alkylated (methylated or prenylated) side chains [74]. So far, less than 20 polyhydroxy-*p*-terphenyl metabolites have been isolated from lower fungi, with the majority reported from *Aspergillus* section *Candidi* [75]. Members of this family of

natural products include six new prenylated polyhydroxy-*p*-terphenyl metabolites, named prenylterphenyllins A-C (**130-132**) and prenylcandidusins A-C (**133-135**), and one new polyhydroxy-*p*-terphenyl compound with a simple tricyclic C-18 skeleton, named 4″-dehydro-3-hydroxyterphenyllin (**136**). All of these metabolites were obtained together with eight known analogues (**137-144**) from *Aspergillus taichungensis* ZHN-7-07, a root soil fungus isolated from *Acrostichum aureum*. These compounds were evaluated for cytotoxic activity *in vitro* against HL-60, A-549, and P-388 cell lines. It was found that compounds **130** and **137** exhibited moderate activities against all three cell lines, with IC_{50} values ranging from 1.53–10.90 μM, whereas compounds **134** and **136** displayed moderate activities only against the P-388 cell line, with IC_{50} values of 1.57 and 2.70 μM, respectively [76]. Simple halogenated aromatic metabolites are very common in mangrove fungi, thus, reflecting the availability of chloride and bromide ions in seawater [77]. Methyl 3-chloro-6-hydroxy-2-(4-hydroxy-2-methoxy-6-methylphenoxy)-4-methoxybenzoate (**145**) was characterized [56] from *Nigrospora* sp. No.1403, isolated from *Kandelia candel*.

Two new diphenyl ethers, namely, 7-*O*-acetylsecopenicillide C (**146**), and hydroxytenellic acid B (**147**), along with two related derivatives (**148**, **149**) were characterized from the shaken culture of *Penicillium* sp. MA-37, which was obtained from the rhizospheric soil of the mangrove plant *Bruguiera gymnorrhiza* (South China Sea, Hainan, China). The absolute configuration of **147** was determined by the modified Mosher's method. None of these diphenyl ethers exhibited either brine

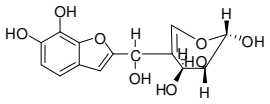
shrimp lethality or antibacterial activity [78]. Epigenetic modification was used to stimulate the biological profile of cytosporones, which induce the generation of additional derivatives. A previously undescribed cytosporone R (**150**) was isolated from the culture medium of *Leucostoma persoonii*, an endophytic fungus obtained from *Rhizophora mangle* (Florida Everglades, USA). The medium was supplemented with histone deacetylase inhibitor (HDAC), sodium butyrate, and a DNA methyltransferase (DNMT) inhibitor, 5-azacytidine to obtain the cytosporone [79].

Apart from previously reported expansols A and B, diorcinol, and *S*-(+)-sydonic acid, four newly discovered polyphenols, expansols C–F (**151**–**154**), and one new diphenyl ether derivative, 3-*O*-methyldiorcinol (**155**), as well as a series of known compounds, (+)-(7*S*)-7-*O*-methylsydonic acid (**156**), 3,7-dihydroxy-1,9-dimethyldibenzofuran (**157**), orcinol (**158**), 2,4-dimethoxyphenol (**159**), and 4-hydroxybenzoic acid (**160**), were isolated from the refermentation broth of *Penicillium expansum* 091006 endogenous with *Excoecaria agallocha*. Compounds **151**–**154** are a group of natural polyphenols featuring a rarely encountered phenolic bisabolane sesquiterpenoid and diphenyl ether moieties of fungal origin. Except **151** and **153,** all compounds showed weak cytotoxicity against HL-60 cell lines, and they showed this activity at IC_{50} values of 18.2 and 20.8 μM, respectively. The co-isolation of known precursors, expansols A and B, further supports the proposed biogenetic pathway for compounds **151**–**156** as illustrated in Scheme 6 [80]. Chlorinated diphenyl ethers are microbially metabolized readily [81], but they rarely occur as fungal metabolites. Culture of *Pestalotiopsis* sp. PSU-MA69, an

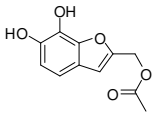
endophytic fungus from *Rhizophora apiculata*, gave four previously unknown diphenyl ethers, pestalotethers A–D (**161**–**164**), together with their biosynthetic precursors, pestheic acid, chloroisosulochrin, chloroisosulochrin dehydrate, isosulochrin and isosulochrindehydrate from *P. theae*, and pestaloxanthone (**115**) [82, 83]. In addition to ring-generating biosynthetic cyclizations, some oxidation and hydrolysis and subsequent adornment reactions (e.g. esterification/decarboxylation/methanolysis) with xanthone precursors were found to be involved in the biosynthesis of the individual diphenyl ethers **161**–**164**. These processes are shown in Scheme 7 [48]. A new polysubstituted benzaldehyde derivative, known as ethyl 5-ethoxy-2-formyl-3-hydroxy-4-methylbenzoate (**165**) was discovered using a mixed fermentation technique on unidentified mangrove endophytic fungal strains Nos. K38 and E33 [84]. It was found to exhibit weak antifungal activity against *Fusarium graminearum*, *Gloeosporium musae*, *Rhizoctonia solani* Kuhn, and *Phytophthora sojae* [57]. An antimicrobial metabolite auroglaucin (**166**), previously characterized from *Aspergillus glaucus* [85], was isolated again from the mangrove rhizosphere soil derived fungus, *Aspergillus effuses* H1-1 [86].

A number of known antifungal phenolic acids, such as vittarin-B (**167**), 3,5-dimethoxybiphenyl (**168**), 3-hydroxy-4-methoxystyrene (**169**), 3,4-dihydroxyphenylethanol (**170**), *p*-tyrosol (**171**), 2-formyl-3,5-dihydroxy-4-methyl-benzoic acid (**172**), 3-methoxy-6-methyl-1,2-benzenediol (**173**), 4-methoxypyrocatechol (**174**), 3,5-dimethylphenol (**175**), and 1-hydroxy-8-methoxynaphthalene (**176**), were first

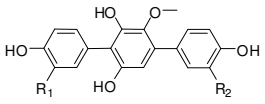
reported to be produced by different mangrove endophytes, as *Kandelia candel* endophytic *Sporothrix* sp. (No. 4335) [41] and *Fusarium* sp. ZZF60 [50], *Avicennia* endophytic *Penicillium* sp. ZH16 [33], *Bruguiera sexangula* endophytic *Pestalotiopsis clavispora* [87], and two unidentified fungal strains K38 and E33 from *Kandelia candel* and *Eucheuma muricatum* [37].



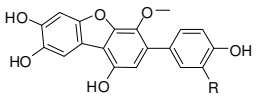
123 deuteromycol A



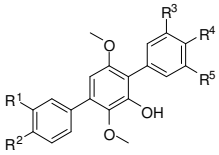
124 deuteromycol B

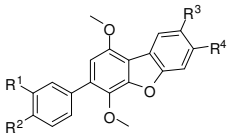


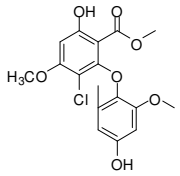
125 $R^1 = R^2 = H$
126 $R^1 = OH$ $R^2 = H$
128 $R^1 = R^2 = OH$



127 R = H
129 R = OH







145

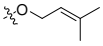
130 R^1 =  $R^2 = R^3 = R^4 = OH$ $R^5 = H$

131 R^1 =  $R^2 = R^4 = OH$ $R^3 = R^5 = H$

132 $R^1 = H$ $R^2 = R^3 = R^4 = OH$ R^5 = 

136 $R^1 = R^2 = R^5 = H$ $R^3 = R^4 = OH$

137 $R^1 = R^5 = H$ $R^2 = R^4 = OH$ R^3 = 

138 $R^1 = R^5 = H$ $R^2 = R^3 = OH$ R^3 = 

139 $R^1 = R^2 = R^3 = R^5 = H$ $R^4 = OH$

140 $R^1 = R^5 = H$ $R^2 = R^3 = R^4 = OH$

141 $R^1 = R^3 = R^5 = H$ $R^2 = R^4 = OH$

142 $R^1 = R^2 = R^3 = R^4 = OH$ $R^5 = H$

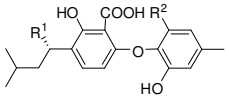
133 R^1 =  $R^2 = R^3 = R^4 = OH$

134 R^1 =  $R^2 = OH$ $R^3 = R^4 = OCH_3$

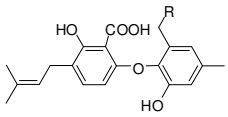
135 R^1 =  $R^2 = R^3 = OH$ $R^4 = OCH_3$

143 $R^1 = H$ $R^2 = R^3 = R^4 = OH$

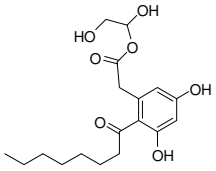
144 $R^1 = H$ $R^2 = OCH_3$ $R^3 = R^4 = OH$



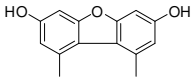
147 $R^1 = OH$, $R^2 = CH_2OH$
148 $R^1 = OCH_3$, $R^2 = CH_2OH$



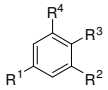
146 R = $OCOCH_3$
149 R = OH



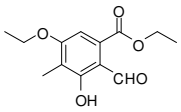
150 cytosporone R



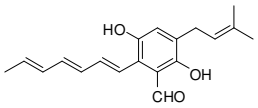
157



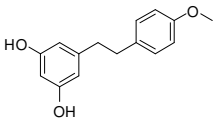
158 $R^1 = CH_3$, $R^2 = R^4 = OH$, $R^3 = H$
159 $R^1 = R^2 = OCH_3$, $R^3 = OH$, $R^4 = H$
160 $R^1 = OH$, $R^2 = R^4 = H$, $R^3 = CO_2H$



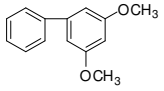
165



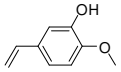
166



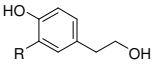
167



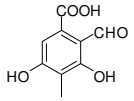
168



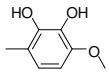
169



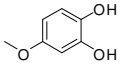
170 R = OH
171 R = H



172

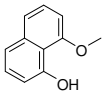


173

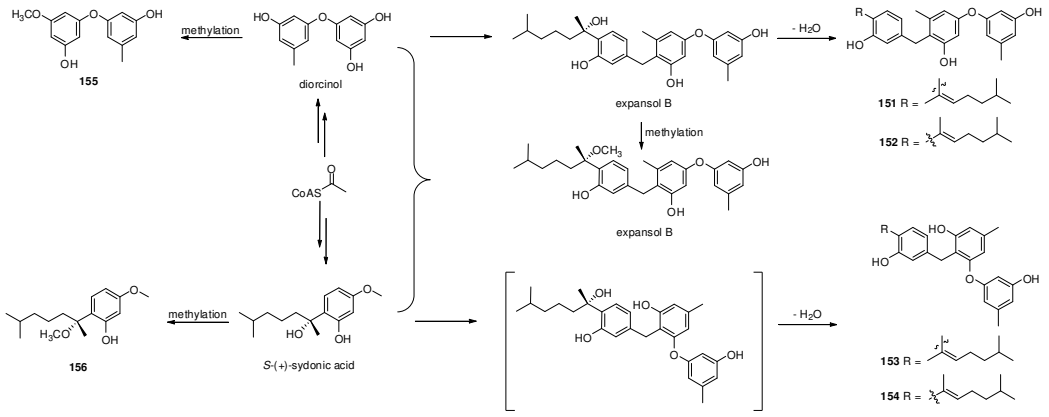


174

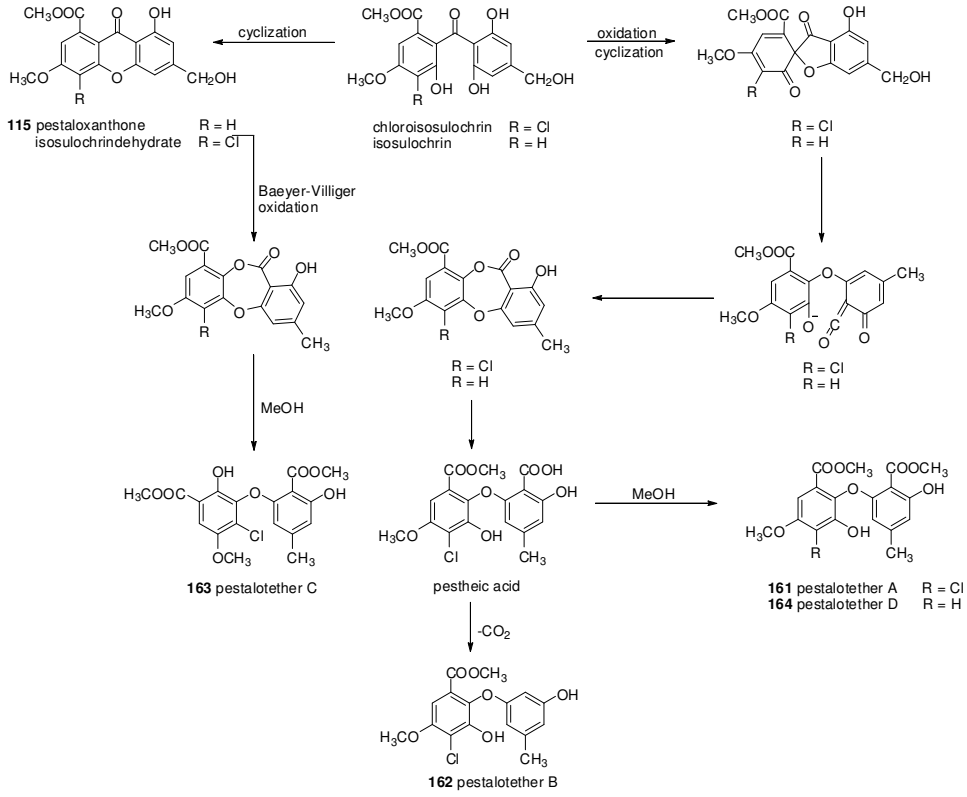
175



176



Scheme **6**. Postulated metabolic relationship between compounds **151**–**156**.



Scheme **7**. A plausible biosynthetic pathway for the generation of compounds **161**–**164**.

4.1.8 Lactones

Lactones continue to be a prominent feature of mangrove-derived secondary metabolism. A unique *δ*-lactone dimer, phomopsis-H76 B (**177**) was obtained from

the liquid culture of *Phomopsis* sp. (#zsu-H76) isolated from *Excoecaria agallocha* [44]. A new dibenzoxepin derivative, 1,8-dihydroxy-10-methoxy-3-methyldibenzo[*b*,*e*]oxepine-6,11-dione (**178**) [66] was identified from the fungus *Phoma* sp. SK3RW1M isolated from *Avicennia marina*. This dibenzoxepin derivative was of interest as it had an aromatic lactone ring framework, which was structurally related to that of possible biosynthetic intermediates in the synthesis of flavones by *Aspergillus variecolor* [88]. Paeciloxocins A and B (**179**, **180**), the two new depsidones, were isolated from an endophytic fungus *Paecilomyces* sp. (Taiwan, China). Interestingly, it was reported that compound **179** exhibits strong cytotoxicity effects against the growth of hepG2 cell line at 1 μg/mL and mildly antimicrobial activity against *Curvularia lunata* (Walker) Boedijn and *Candida albicans* ATCC 10231 [89]. A known isobenzofuran derivative, 4-(hydroxymethyl)-7-methoxy-6-methyl-1(3*H*)-isobenzofuranone (**181**), was found to be produced by *Phomopsis* sp. (No. ZH-111) isolated from the mangrove sediment, which also inhibited the growth of subintestinal vessel plexus (SIV) branches [35]. Two new phthalide glycosides, 7-hydroxy-5-methoxy-4,6-dimethyl-7-*O*-a-L-rhamnosyl-phthalide (**182**) and 7-hydroxy-5-methoxy-4,6-dimethyl-7-*O*-b-D-glucopyranosyl-phthalide (**183**), were isolated from the extract of fermentation broth of an endophyte *Pestalotiopsis heterocornis* (L421) found in the stem of *Bruguiera gymnorrhiza* (Hainan, China). The known related aglycon 7-hydroxy-5-methoxy-4,6-dimethylphthalide (**184**) was also isolated with the abovementioned compounds **182** and **183** [90].

Azaphilones are a structurally diverse family of natural products containing a highly oxygenated bicyclic core and a quaternary center. These molecules exhibit a wide range of significant biological activities, such as inhibitions of monoamine oxidase [91], Gp120-CD4 binding [92], Grb2-SH2 interaction [93], MDM2-p53 interaction [94] and heat shock protein90 (Hsp90) [95], as well as antimicrobial, antiviral, cytotoxic, anticancer, and anti-inflammatory activities [96, 97]. Azaphilones have interesting structural features and biological properties; therefore, a number of synthetic efforts concerning these compounds have been reported during the last four decades [98-101]. Two new members of this product type, named chermesinones B and C (**185**, **186**), were identified from *Penicillium chermesinum* (ZH4-E2) obtained from *Kandelia candel*. Neither of the isolates showed inhibitory effects against *α*-glucosidase or acetylcholinesterase [102]. Eight newly identified α-pyrone derivatives, namely, nigerapyrones A-H (**187-194**), coexisting with two known congeners, asnipyrones A (**195**) and B (**196**), were isolated from *Aspergillus niger* MA-132, an endophytic fungus obtained from the fresh tissue of *Avicennia marina* (Hainan, China). All metabolites were examined by cytotoxicity and antimicrobial bioassays. Nigerapyrone E (**191**) exerted cytotoxicities against SW1990, MDA-MB-231, and A549 cell lines with IC_{50} values of 38, 48, and 43 μM, respectively, which were stronger than that of the positive control fluorouracil. It also showed weak or moderate activity against MCF-7, HepG2, Du145, NCI-H460, and MDA-MB-231 cell lines with IC_{50} values of 105, 86, 86, 43, and 48 μM, respectively. Among these, compound **188** showed selective activity against the HepG2 while **196** showed activity against A549, both

with an IC_{50} of 62 μM. Compound **190** showed moderate or weak activity against the MCF-7, HepG2, and A549 cell lines, with IC_{50} values of 121, 81, and 81 μM, respectively. However, none of the metabolites showed significant antimicrobial activity [103].

A new butyrolactone, 7″-hydroxybutyrolactone III (**197**) and its desoxidation precursor butyrolactone I (**198**), isolated from the culture of *Aspergillus terreus* A8-4 obtained from mangrove-associated sediments, possessed weak cytotoxicity *in vitro* against HCT-8, Bel-7402, BGC-823, A2780 cell lines. Butyrolactone I **198** was reported as a specific inhibitor of eukaryotic cyclin-dependent kinases (CDK) [104]. The putative biosynthetic transformations between these metabolites and conversions can be deduced to the epoxidation of the double bond of **198** on the prenyl side chain to give butyrolactone III, followed by the additional hydroxylation to afford compound **197**, as shown in Scheme 8 [105].

A comprehensive analysis of *Corynespora cassiicola* endophyte from *Laguncularia racemosa*, led to the discovery of four new metabolites, including three decalactones, xestodecalactones D–F (**199-201**), a new depsidone corynesidone C(**202**), as well as two known analogues, corynesidones A (**203**) and B (**204**). Absolute configurations of the optically active compounds **199-201** were determined by TDDFT ECD (Time-Dependent Density Functional Theory, Electronic Circular Dichroism) calculations of their solution conformers. Compound **199** was separated as a mixture of two diastereomers. All compounds were tested against a panel of human protein kinases. Amongst these, compound **204** could inhibit several kinases

such as IGF1-R and VEGF-R2 with IC_{50} values mostly in the low micromolar range. Furthermore, compound **204** inhibited PIM1 with an IC_{50} value of 3.5×10^{-7} M, suggesting a tenfold higher specificity of this naturally occurring inhibitor against this particular protein kinase in comparison to most of the other kinases investigated [62]. Later, a detailed analysis of the minor metabolites obtained from the cultivation of this fungus yielded a series of unusual octalactones, coryoctalactones A–E (**205–209**). It is interesting to note that the absolute configuration of the side chain in **205–207** and **209** were tentatively deduced based on biogenetic consideration in comparison with xestodecalactones as shown in Scheme 9. All isolated compounds were evaluated for their antimicrobial, cytotoxic, and antitrypanosomal activities, and were active in all of the bioassays performed [106].

The endophytic fungus *Eurotium rubrum* has been isolated from a semi-mangrove plant *Hibiscus tiliaceus* and produced a new anthraquinone, 9-dehydroxyeurotinone (**210**) and 2-*O*-methyl-9-dehydroxyeurotinone (**211**). Compound **210** showed weak antibacterial activity against *Escherichia coli* and modest cytotoxic activity against human tumor cell line SW1990 [63].

A novel diphenyl ether derivative, namely, $\Delta^{1',3'}$-1′-dehydroxypenicillide (**212**), was purified from the extracts of *Penicillium* sp. MA-37, which was separated from the rhizospheric soil of the mangrove plant *Bruguiera gymnorrhiza*. Furthermore, three related known compounds, penicillide (**213**), dehydroisopenicillide (**214**), and 3′-*O*-methyldehydroisopenicillide (**215**) were isolated in addition to the compound **212**. All isolated compounds were evaluated in the brine shrimp lethality assay and

compound **213** and **214** were active, with LD_{50} values of 135.9 and 160.0 μM, respectively [78].

Fermentation of an *Acremonium* sp. PSU-MA70, an endophyte from a branch of *Rhizophora apiculata*, yielded a new phthalide derivative acremonide (**216**) and a new depsidone acremonone A (**217**), together with two previously known metabolites, (+)-brefeldin A (**218**) and 5,7-dimethoxy-3,4-dimethyl-3-hydroxyphthalide (**219**). The antiviral antibiotic brefeldin A (BFA) (**218**) could strongly inhibit the protein secretion such as the Golgi membrane enzyme that catalyzes the exchange of guanine nucleotide bound to ribosylation factor (ARF) [107]. BFA was found to display a weak antifungal activity against *Candida albicans* NCPF3153 [40].

Octaketides such as cytosporones are common metabolites found to be produced by three endophytic fungal strains: *Aegiceras corniculatum* endophytic *Dothiorella* sp. HTF3, *Rhizophora mucronata* endophytic *Pestalotiopsis* sp., and *Excoecaria agallocha* endophytic *Phomopsis* sp. ZSU-H76 [8]. Epigenetic tailoring of *Rhizophora mangle* endophytic to *Leucostoma persoonii*, led to the reisolation of a strongly antibacterial trihydroxybenzene cytosporone E (**220**). This compound **220** had previously been isolated by Brady et al. from *Cytospora* sp. CR200 and *Diaporthe* sp. CR146 endophytic in plants *Conocarpus erecta* and *Forsteronia spicata* [108]. This compound displayed anti-infective activity at an IC_{90} of 13 μM toward *Plasmodium falciparum*, with A549 cytotoxicity IC_{90} of 437 μM. Thus, it represented a 90% inhibition therapeutic index (TI_{90} = IC_{90}A459/IC_{90} *P. falciparum*) of 33. Moreover, it was active against MRSA with a minimal inhibitory concentration (MIC) value of 72

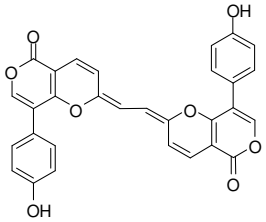
μM; the inhibition of MRSA biofilm at roughly half that value, minimum biofilm eradication counts, $MBEC_{90}$, was found to be 39 μM [79]. Its broad-spectrum biological activity has attracted interest to synthesize this compound. Efficient stereoselective synthesis of the natural enantiomer of this compound was performed by different groups. An overall six-step process starting from 3,4,5-trimethoxybenzoic acid with a yield of 41% is summarized in Scheme 10 [109]. However, in contrast to previous reports, (±)-**220**, (*R*)-**220** and (*S*)-**220** were all found to have weak antimicrobial activities which were similar in all three compounds [110]. Three previously unknown α-pyrones, pestalotiopyrones A–C (**221–223**), together with two previously unknown seiricuprolides, pestalotioprolides A (**224**) and B (**225**), and two known compounds, seiricuprolide (**226**) and 2´-hydroxy-3´,4´-didehydropenicillide (**227**), were characterized from two mangrove-derived fungal strains, *Pestalotiopsis* sp. PSU-MA92 endophytic to *Rhizophora apiculata* (Trang, Thailand) and *Pestalotiopsis* sp. PSU-MA119 endophytic to *Rhizophora mucronata* (Satun, Thailand) [111]. Compounds **221–223** have different structures but they are all called pestalotiopyrones, as described in a previous report [112]. Compound **222** was the only compound obtained in amounts sufficient for antibacterial testing against *Staphylococcus aureus* ATCC25923 and the methicillin resistant *S. aureus* clinical isolate. It was also tested for antifungal activity against *Candida albicans* NCPF3153, *Cryptococcus neoformans* ATCC90113, and *Microsporum gypseum* clinical isolate; however, it showed no antibacterial or antifungal activity [111].

Continuous study of *Pestalotiopsis* sp. PSU-MA69 endophytic to *Rhizophora*

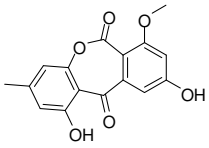
apiculata led to the discovery of a new butenolide pestalolide (**228**) and a known phytotoxic analog seiridin (**229**). Compound **228** showed weak antifungal activity against *Candida albicans* and *Cryptococcus neoformans*, both with MIC values of 128 μg/mL [48]. A previously unknown lactone (**230**), was also isolated from previously described endophyte *Xylaria* sp. BL321 residing in *Acanthus ilicifolius* L. [113]. Two known butenolides, butyrolactones I (**198**) and V (**231**), previously characterized from different *Aspergillus terreus* strains [114, 115], were reisolated from the culture of *Penicillium expansum* 091006, an endophytic fungus from *Excoecaria agallocha* [80]. Butyrolactone V **231** showed moderate antimalarial activity [104, 116, 117]. Aspulvinones, a set of lactones composed of a butenolide unit and substituted by a phenyl group at C-3 and a benzyl group at C-5, were generally produced as pigments by fungi belonging to the *Aspergillus* family. This class of natural products was first reported from *Aspergillus terreus* in 1973 [118]. So far, more than 35 natural analogues, all exhibiting *Z*-configuration for the exocyclic double bond have been isolated. Furthermore, these metabolites were demonstrated to display only moderate biological activities, including antibacterial [119], luciferase inhibitory [120] and glucose-6-phosphate translocase T1 inhibitory [121] effects. Given their intriguing structure and antibacterial activity, they have served as synthetic targets of luciferase inhibitors in recent years [120]. A new member of this group, isoaspulvinone E (**232**), together with two known metabolites aspulvinone E (**233**) and pulvic acid (**234**) were purified from the culture broth of *Aspergillus terreus* Gwq-48 in mangrove rhizosphere soil. Application of bioassay tests revealed that each of these compounds

showed significant anti-influenza A H1N1 virus activities, with IC_{50} values of 32.3, 56.9, and 29.1 μg/mL respectively. Moreover, only compound **232** exhibited effective inhibitory activity against H1N1 viral neuraminidase (NA), and docking of two isomers **232** and **233** into the active sites of NA indicated that the *E* double bond $\Delta^{5(10)}$ was essential to achieve this activity [122]. On the other hand, phomapyrone D (**235**) originally characterized from the fungal pathogen *Leptosphaeria maculans*/*Phoma lingam* [123], might biogenetically result from the methylation of a tetraketide or decarboxylation of a pentaketide. It was isolated as a metabolite from another *Phomopsis* sp. (ZH76) living in *Excoecaria agallocha* [68]. A pair of new spiro-γ-lactone enantiomers, (−)-(4*S*, 8*S*)-foedanolide (**236**) and (+)-(4*R*, 8*R*)-foedanolide (**237**), were isolated from the fermentation broth of the endophytic fungus *Pestalotiopsis foedan* inhabiting the branches of *Bruguiera sexangula* (Hainan, China). Both compounds exhibited moderate inhibition of human tumor cells HeLa, A-549, U-251, HepG2, and MCF-7, giving IC_{50} values between 5.4 and 296 μg/mL [124]. In a survey of *Penicillium* sp. ZH58 of *Avicennia*, a new isobenzofuranone, 4-(methoxymethyl)-7-methoxy-6-methyl-1(3*H*)-isobenzofuranone (**238**) and a known antibiotic curvularin (**239**) were reported [49]. Macrocyclic polyketides are an important feature of the fungi secondary metabolite chemistry. Curvularin and its derivatives have potential antibacterial activity against *Bacillus megaterium* [125], inhibitor of multifunctional cytokine TGF-β [126], antitrypanosomal against *Trypanosoma brucei* [127], and anti-inflammatory through decreasing proinflammatory gene expression in an *in vivo* model of a chronic inflammatory disease [128]. In recent years, they are reported to

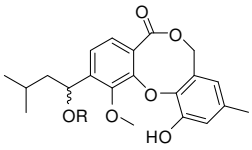
be produced by some fungal species mainly from *Curvularia* [125], *Aspergillus* [129], and *Penicillium* [49]. Sumalarins A–C (**240–242**), the new and rare examples of sulfur-containing curvularin derivatives, along with three known analogues (**239**, **243**, **244**), were identified from the cytotoxic extract of *Penicillium sumatrense* MA-92, a fungus obtained from the rhizosphere of the mangrove *Lumnitzera racemosa*. The absolute configuration of compound **240** was established by X-ray crystallographic analysis. Considering the possible biogenetic pathway for these sulfur-containing compounds **240**–**242**, compounds **240** and **241** can be derived from **242** by esterification or esterification and acylation. However, the putative intermediate **242** is likely produced *via* Michael addition of the cysteine metabolite 3-mercaptolactate to the double bond of dehydrocurvularin **243** as the putative precursor shown in Scheme 11. It is noteworthy that compounds **240–243** showed potent cytotoxicity against some of the tested tumor cell lines. Sulfur substitution at C-11 or a double bond at C-10 significantly increased the cytotoxic activities of the curvularin analogues [130]. Chromatographic analysis of mangrove *Sonneratia caseolaris* (Dongzhai, Hainan, China) endophytic *Pestalotiopsis virgatula* rice culture extracts yielded four new α-pyrone derivatives, pestalotiopyrones I–L (**245–248**), and a new (6*S*,10*S*,20*S*)-hydroxypestalotin (**249**) [131].



177

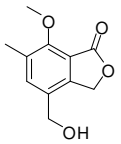


178

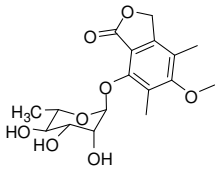


179 paeciloxocin A R = H

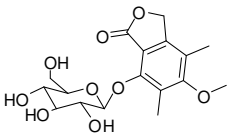
180 paeciloxocin B R = $\overset{O}{\overset{\|}{C}}CH_3$



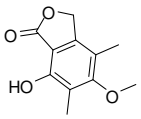
181



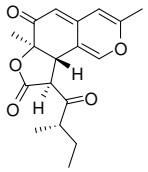
182



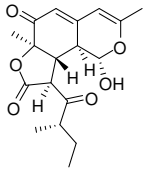
183



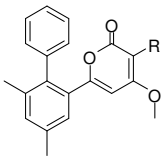
184



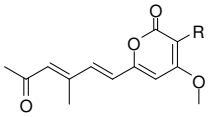
185



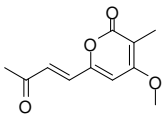
186



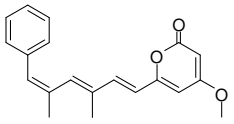
187 R = H
188 R = CH_3



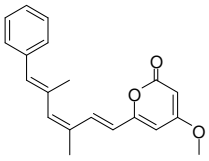
189 R = H
190 R = CH_3



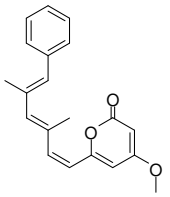
191



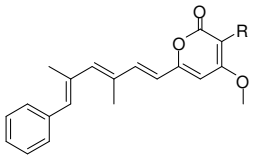
192



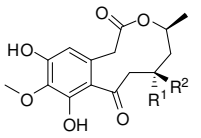
193



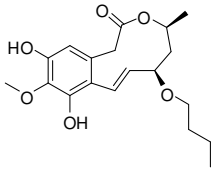
194



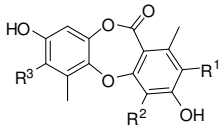
195 R = CH_3
196 R = H



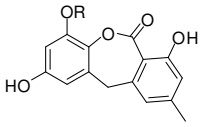
199 R^1 = OH, R^2 = H
199a R^1 = H, R^2 = OH
200 R^1 = H, R^2 =



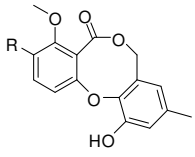
201

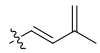


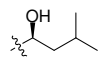
202 R^1 = OH, R^2 = R^3 = H
203 R^1 = R^2 = R^3 = H
204 R^1 = OH, R^2 = H, R^3 = COOH

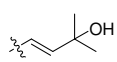


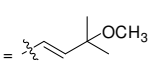
210 R = H
211 R = CH_3

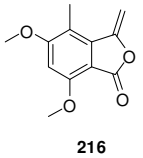


212 R = 

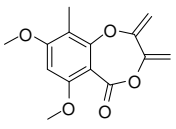
213 R = 

214 R = 

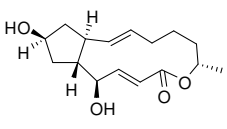
215 R = 



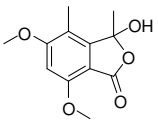
216



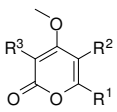
217

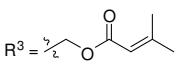


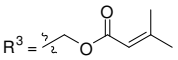
218 (+)-brefeldin A

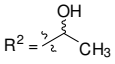


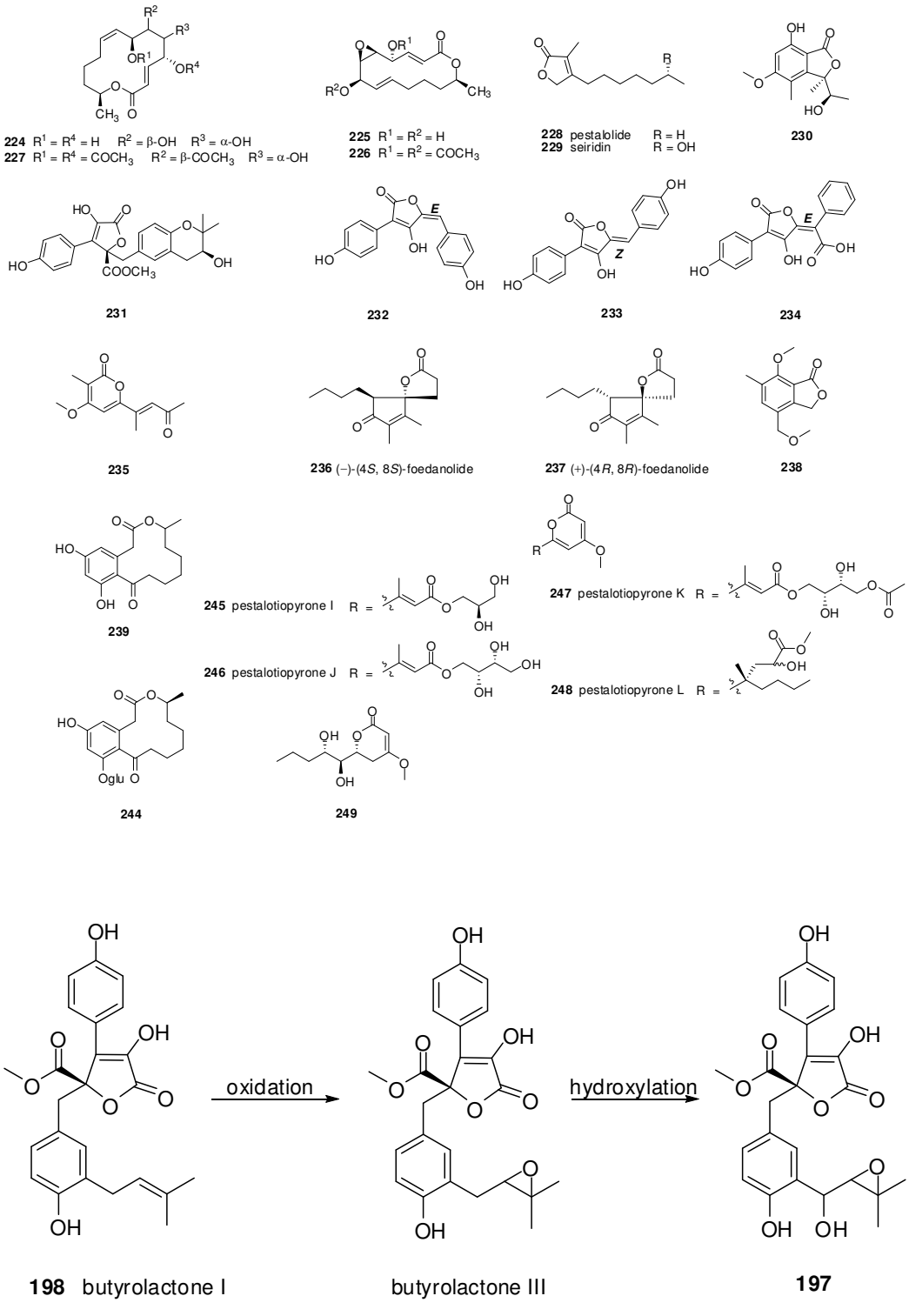
219



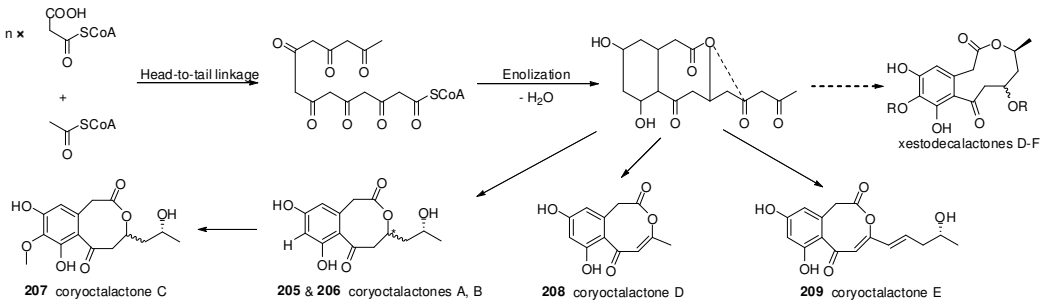
221 pestalotiopyrone A R^1 = H R^2 =  R^3 = 

222 pestalotiopyrone B R^1 = OH R^2 =  R^3 = 

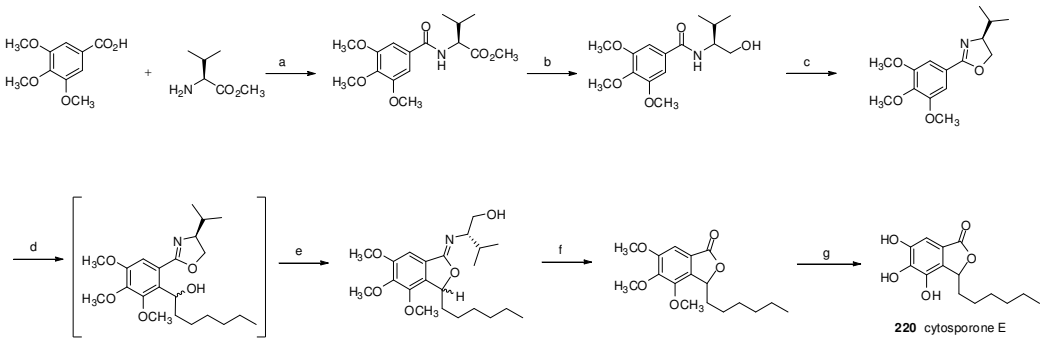
223 pestalotiopyrone C R^1 = H R^2 =  R^3 = CH_3



Scheme 8. A putative biotransformation of precursor compound **198** to **197.**

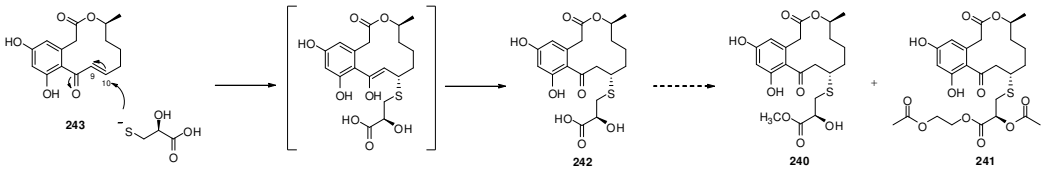


Scheme **9**. Proposed biosynthetic pathway for isolated octalactones (**205-209**).



Scheme **10**. Synthesis of (±)-cytosporone E (**220**).

Reagents and conditions: (a) EDC, HOBt; then CH_2Cl_2, Et_3N, 91%; (b) $LiBH_4$, then THF, room temperature (rt), 94%; (c) MsCl, Et_3N, then CH_2Cl_2, rt, 97%; (d) sec -BuLi, THF, 6h, -78 °C; then b. $CH_3(CH_2)_5CHO$, -78 °C to rt; (e) NH_4Cl (sat.), 56%; (f) 3N HCl, reflux 30 min, 99%; (g) BBr_3, CH_2Cl_2, -30 °C to rt, 90%.



Scheme **11**. Possible pathway for compounds **240**–**242** from **243**.

4.1.9 Miscellaneous polyketides

Griseofulvin is a classic antifungal agent used clinically for the treatment of dermatomycoses. It was originally obtained from the fungal strain *Penicillium griseofulvum* in 1939; however, it was reisolated from the diverse mangrove-derived

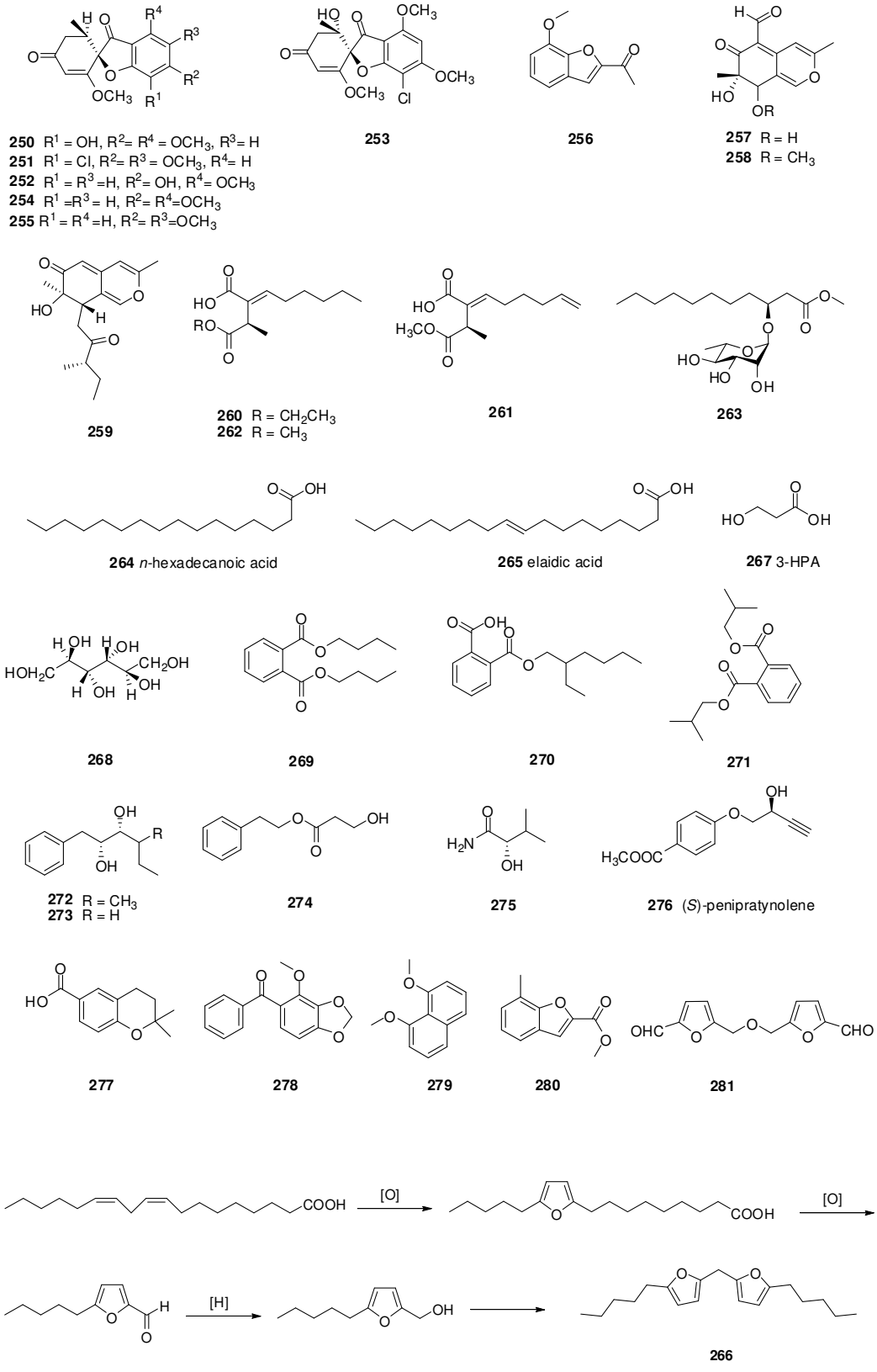
fungi. It was first reported from the unidentified mangrove endophytic fungus No. 1403 [132] and later isolated from *Nigrospora* sp. No.1403 endophyte of *Kandelia candel* [56] and *Pongamia pinnata* endophytic to *Nigrospora* sp. No. MA75 [58]. Its distinct activities have attracted a lot of attention and more than a hundred research papers describe its analogues synthesis. Since 1950, more than 400 analogues have been disclosed covering most positions and many have displayed significantly increased activity [133]. Related metabolites were also discovered recently. Four new griseofulvin derivatives, 7-chloro-2′,5,6-trimethoxy-6′-methylspiro(benzofuran-2(3*H*),1′-(2) cyclohexene)-3,4′-dione (**250**), (2*S*,5′*R*,*E*)-7-hydroxy-4,6-dimethoxy-2-(1-methoxy-3-oxo-5-methylhex-1-enyl)-benz ofuran-3(2*H*)-one (**251**), 6-*O*-desmethyldechlorogriseofulvin (**252**) and 6′-hydroxygriseofulvin (**253**); two known analogue dechlorogriseofulvin (**254**) and 7-chloro-2′,5,6-trimethoxy-6′-methylspiro[benzofuran-2(3*H*),1′-(2)cyclohexene]-3,4′-dione (**255**), were produced by three endophytic fungal strains: *Kandelia candel* endophytic to *Sporothrix* sp. (No. 4335) [41, 132], *Nigrospora* sp. No.1403 [56], and *Pongamia pinnata* endophytic *Nigrospora* sp. strain No. MA75 [58]. Compounds **252-254** were devoid of any significant antibacterial activity toward MRSA, *E. coli*, *P. aeruginosa*, *P. fluorescens*, and *S. epidermidis* [58]. This further confirmed the prediction that the activity of griseofulvin should be strictly related to both its planar structure and spatial configuration. A known metabolite 2-acetyl-7-methoxybenzofuran (**256**) was also isolated from the aforementioned

endophytic fungus *Sporothrix* sp. (No. 4335) [134]. Bioactivity-directed fractionation of the extract of the endophytic *Talaromyces* sp. ZH-154 isolated from the stem bark of *Kandelia candel* (L.) Druce, Rhizophoraceae, afforded two new austdiol analogues, 7-epiaustdiol (**257**) and 8-*O*-methylepiaustdiol (**258**). The absolute configuration of **257** was unequivocally determined by single-crystal X‑ray diffraction. Although, both compounds were found to be moderately cytotoxic against KB and KBv200 cells (IC_{50}＝16.37- 37.16 μg/mL), **257** displayed significant inhibitory activity against *Pseudomonas aeruginosa* with a MIC value of 6.25 μg/mL [135]. Chermesinone A (**259**), a new azaphilone confirmed by X-ray analysis, showed a mild anti-α-glucosidase effect with an IC_{50} value of 24.5μM, was isolated from culture of *Penicillium chermesinum* (ZH4-E2) associated with *Kandelia candel* [74].

Exploration of the *Bruguiera parviflora* endophytic fungus *Xylaria cubensis* PSU-MA34 provided two new succinic acid derivatives, xylacinic acids A (**260**) and B (**261**), along with one known analog, 2-hexylidene-3-methyl succinic acid 4-methyl ester (**262**) [38]. A new fatty acid glycoside was obtained from an unidentified endophytic fungus A1 isolated from *Scyphiphora hydrophyllacea* Gaertn. F., and it was identified as *R*-3-hydroxyundecanoic acid methyl ester-3-*O*-α-L-rhamnopyranoside (**263**). It showed modest inhibitory effect on *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) [136]. A specific fatty acid methyl esters (FAME) profile was also used in taxonomic studies of the *Pestalotiopsis* sp. strain. The specific FAME profile of *Rhizophora mucronata* endophytic *Pestalotiopsis* JCM2A4 was constructed. Meanwhile, two of these

components were isolated and determined to be *n*-hexadecanoic acid (**264**) and elaidic acid (**265**). These compounds (**264** and **265**) were produced by *Pestalotiopsis* JCM2A4, an endophytic fungus originally isolated from leaves of the Chinese mangrove plant [137]. Flavodonfuran (**266**), a new difuranylmethane derivative from another *Rhizophora apiculata* endophytic fungus *Flavodon flavus* PSU-MA201, is proposed to be biosynthesized from linoleic acid. Considering the chemical reactions, a three-step mechanism was proposed that involves the formation of a furan fatty acid. The proposed mechanism involves the oxidation of an unsaturated unit of linoleic acid that would provide 5-pentyl-2-furaldehyde; and reduction of the furaldehyde followed by coupling of two units of the resulting furfuryl alcohol that would furnish the difuranylmethane as shown in Scheme 12 [138]. Another known metabolite reported in this category included 3-hydroxypropionic acid (3-HPA) (**267**), an antibacterial agent from *Diaporthe phaseolorum* obtained from the branches of *Laguncularia racemosa*. In bioassays, 3-HPA showed antimicrobial activities against both *Staphylococcus aureus* and *Salmonella typhi* [139]. Analysis of mixed fermentation of unidentified mangrove fungal strains *Kandelia candel* endophytic K38 and *Eucheuma muricatum* endophytic E33 yielded a common metabolite allitol (**268**) [37]. Two usual phthalate derivatives, dibutylphthalate (**269**) and mono (2-ethylhexyl) phthalate (**270**), were reported from the antibacterial extract of the fungus *Phoma herbarum* VB7 [140]. Diisobutyl phthalate (**271**), a co-occurring metabolite, was reported from the endophytic fungus *Pestalotiopsis clavispora* isolated from *Bruguiera sexangula* [87]. *Acremonium* sp. PSU-MA70 endophytic to *Rhizophora apiculata* was also the source

of two known metabolites, 4-methyl-1-phenyl-2,3-hexanediol (**272**), (2*R*,3*R*)-4-methyl-1-phenyl-2,3-pentanediol (**273**) [40]. A diverse array of compounds was isolated from the *Rhizophora apiculata* endophytic fungus *Phomopsis* sp. PSU-MA214, including a previously known phenethyl alcohol hydracrylate (**274**) and a known butanamide (**275**) [59]. The previously known acetylenic nematicide (*S*)-penipratynolene (**276**) and DNA-damaging active anofinic acid (**277**) were characterized from the endophytic *Pestalotiopsis* sp. PSU-MA69 of *Rhizophora apiculata*. Compound **276** showed more nematicidal potential against *Pratylenchus penetrans* than the positive control, aspyrone. It killed 77% *P. penetrans* at a concentration of 300 μg/mL [48, 141, 142]. Compound **278** isolated from an *Excoecaria agallocha* endophyte *Phomopsis* sp. (ZH76) was identified as a previously known metabolite, 2-methoxy-3,4-methylenedioxybenzophenone [68]. Two known products, 1,8-dimethoxynaphthalene (**279**) and methyl 7-methylbenzofuran-2-carboxylate (**280**) were isolated from *Sporothrix* sp. (#4335) of *Kandelia candel* [41]. A known metabolite 5,5′-oxy-dimethylene-*bis*(2-furaldehyde) (**281**) was purified from *Avicennia* endophytic fungus *Penicillium* sp. ZH58 [49].



Scheme **12**. Possible biosynthetic pathway of the formation of compound **266**.

4.2. Terpenoids

4.2.1 Sesquiterpenes

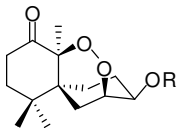
Terpene peroxides possess a wide range of biological activities, including antimalarial, antitumor, antimicrobial, and antiviral activities [143-145]. A typical example of a sesquiterpene peroxide is artemisinin, which has already been clinically applied as an antimalarial drug [146]. A culture of unidentified fungus XG8D, isolated from the leaves of *Xylocarpus granatum* collected from (Samutsakorn, Thailand), yielded a new nor-chamigrane endoperoxide, merulin A (**282**), and two new chamigrane endoperoxides, merulins B and C (**283**, **284**). X-ray crystallographic analysis confirmed the structure of **282** [147]. Reinvestigation of this fungus in a large-scale fermentation experiment led to the isolation of an additional new chamigrane endoperoxide merulin D (**285**) and one known analogue steperoxide A (**286**). Of these, compounds **282** and **284** displayed significant cytotoxicity against human breast cancer line (BT474) with IC_{50} values of 4.98 and 1.57 μg/mL, respectively. These compounds (**282** and **284)** also showed cytotoxicity against colon (SW620) cancer cell lines with IC_{50} values of 4.84 and 4.11 μg/mL, respectively. Moreover, merulin C **284** displayed promising activity in a rat aortic ring sprouting (*ex vivo*) and a mouse Matrigel (*in vivo*) assay. It also exhibited potent antiangiogenic activity mainly by suppression of endothelial cell proliferation and migration in a dose-dependent manner, and its effect is mediated by the reduction in the phosphorylation of Erk1/2 [148]. Species *Talaromyces flavus* from *Sonneratia apetala* was the source of four new norsesquiterpene peroxides, called talaperoxides A-D (**287-290**), and the known

analogue merulin A (steperoxide B) (**282**). The stereochemistries of **287**, **288**, and **282** were fully established through single-crystal X-ray diffraction using Cu Kα radiation. With the exception of **288** and **290**, all of the sesquiterpenes were cytotoxic against human cancer cell lines MCF-7, MDA-MB-435, HepG2, HeLa, and PC-3 with IC_{50} values between 0.70 and 2.78 μg/mL [149]. Cultures of *Diaporthe* sp. from the leaves of *Rhizophora stylosa* produced a unique novel sesquiterpenoid with a tricyclic lactone framework, named diaporol A (**291**); eight new drimane sesquiterpenoids, diaporols B–I (**292–299**); and the known compounds 3β-hydroxyconfertifolin (**300**) and diplodiatoxin (**301**). Structures of **291-295** were further confirmed by low-temperature (100 K), single-crystal X-ray diffraction, thus establishing their absolute configurations using Cu Kα radiation. Neither of the isolated metabolites exhibited significant cytotoxicity against the tested cell lines at a concentration of 20 μM [150].

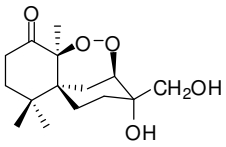
Eremophilane-type sesquiterpenes are well-known secondary metabolites found in both fungi and higher plants and they have been proved to possess phytotoxic, mycotoxic and phytohormonic activity [151, 152]. The mangrove-derived endophytic fungus *Xylaria* sp. BL321 yielded three new eremophilane sesquiterpenes (**302–304**) and a known analogue 07H239-A (**305**). All but **305** showed the activation of α-glucosidase at 0.15 μM (146%), but gradually α-glucosidase showed inhibitory activity as concentrations increased, with an IC_{50} value of 6.54 μM [113]. Metabolite **305** also showed cytotoxic activity against human breast cancer cell lines MCF-7 and MDA-MB-435, with IC_{50} values of 22.5 and 7.1 μM, respectively [153]. Tremulenolide A (**306**), a representative member of the substituted perhydroazulene tremulanes,

previously reported from the liquid cultures of the aspen (*Populus tremuloides*) rotting fungus *Phellinus tremulae* [154], was reisolated from *Flavodon flavus* PSU-MA201 endophytic to *Rhizophora apiculata* [138]. The tricyclic compound **307** was isolated for the first time as a natural product from *Acanthus ilicifolius* L. endophytic fungus *Xylaria* sp. BL321. Attempted single-crystal X-ray crystallography resulted in establishing its stereochemistry [153, 155] A previously known phytotoxin altiloxin B (**308**) isolated from culture filtrate of *Phoma asparagi* Sacc., the causal fungus of stem blight disease on asparagus [156], has also been found in our laboratory from *Pestalotiopsis* sp., an endophyte from the leaves of the Chinese mangrove plant *Rhizophora mucronata* [157]. *Aspergillus terreus* (No. GX7-3B) isolated from the branch of *Bruguiera gymnoihiza* (L.) Savigny (Guangxi, China) was the source of four sesquiterpenes, involving a new compound botryosphaerin F (**309**), together with three known compounds (13,14,15,16-tetranorlabd-7-ene-19,6b:12,17-diolide) (**310**), botryosphaerin B (**311**) and LL-Z1271b (**312**). Compound **309** was found to have strong inhibitory activity towards MCF-7 (IC_{50} 4.49 μM) and HL-60 (IC_{50} 3.43 μM), and compound **312** exhibited significant activity against HL-60 cell line with an IC_{50} value of 0.6 μM. The possible biosynthetic approach for these four sesquiterpenes is proposed in Scheme 13 [158]. A known analogue, dilation (**313**), was characterized from *Penicillium* sp. ZH58 on mangrove tree *Avicennia* (Hainan, China) [49]. Two previously known mycotoxins, 8-deoxytrichothecin (**314**) and trichodermol (**315**), were obtained from *Acremonium* sp. PSU-MA70 of *Rhizophora apiculata* [40]. It was reported that compound **314** showed selective cytotoxicity against human breast cancer (BC-1) and

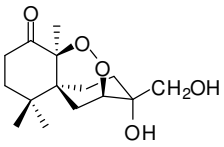
human small cell lung cancer (NCI-H187) lines with IC_{50} values of 0.88 and 1.48 μM, respectively [159]. Furthermore, **315** was shown to have antifungal activity [160].



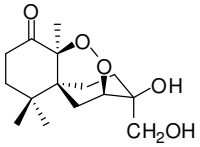
282 R = H
287 R = $COCH_3$



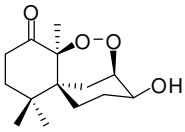
283



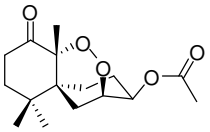
284



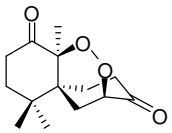
285



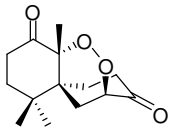
286



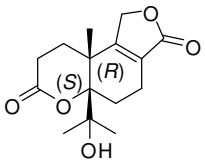
288



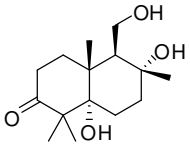
289



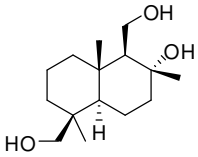
290



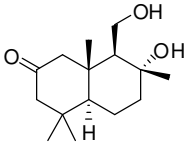
291



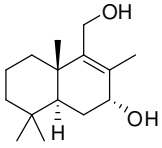
292



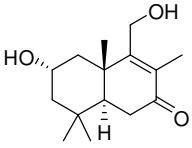
293



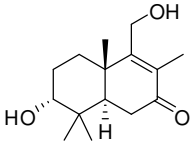
294



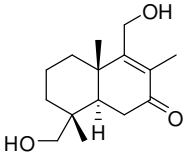
295



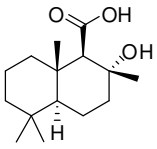
296



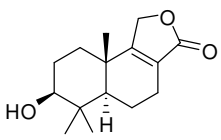
297



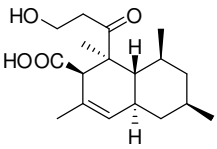
298



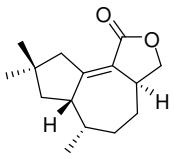
299



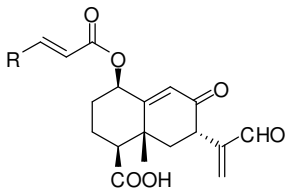
300



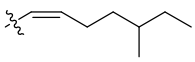
301



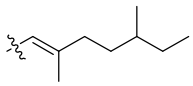
306



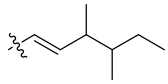
302 R =



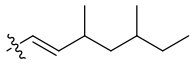
303 R =

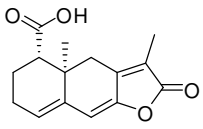


304 R =

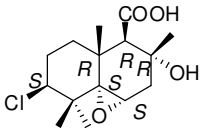


305 R =

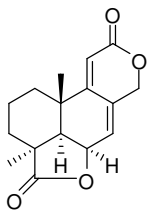




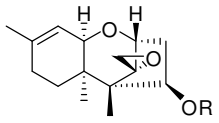
307



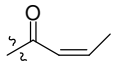
308 Altiloxin B



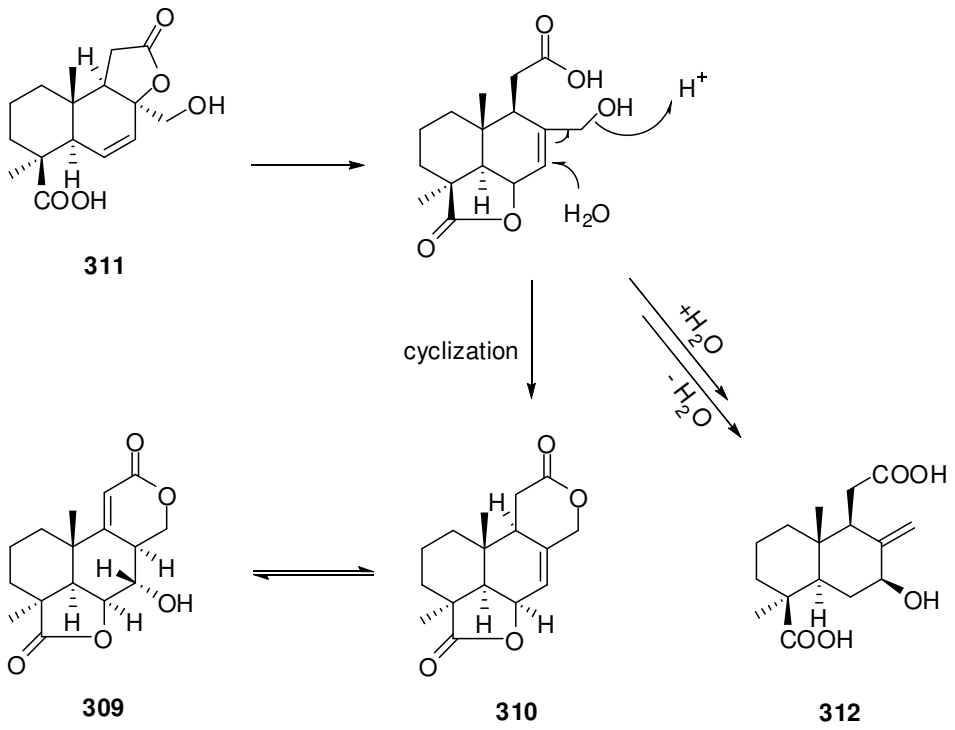
313



314 R =



315 R = H

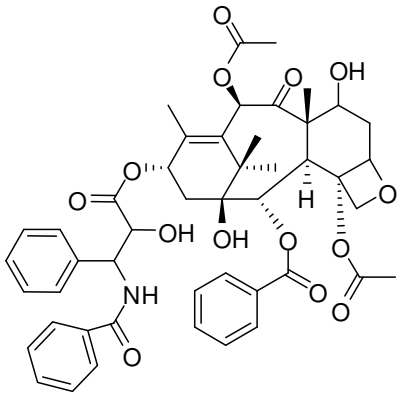


Scheme **13**. Possible biogenetic relationship between compounds **309–312.**

4.2.2 Diterpenes

The world's first billion-dollar anticancer drug, called paclitaxel (taxol), was previously reported only from the inner bark of the Pacific yew *Taxus brevifolia* [161, 162], and its production by bioengineering has still not reached a commercial scale. Paclitaxel has a complex and fascinating structure, which probably involves lengthy syntheses steps resulting in extremely low overall yields that impede the large-scale commercial preparation of this drug [163]. Alternative approaches for paclitaxel production involving the use of taxol producing fungi have made significant progress worldwide. Various genera including *Taxomyces* [164, 165], *Pestalotiopsis* [166], *Alternaria* [167], *Fusarium* [168] and *Periconia* [169] were found to have the capability to produce taxol and its derivatives. Recently, a mangrove endophytic fungus, *Fusarium oxysporum* obtained from *Rhizophora annamalayana* was verified for the production of taxol

(**316**) [170]. It would be remarkable if mangrove endophytic fungi could become a potential alternative source for the production of taxol on a commercial scale.

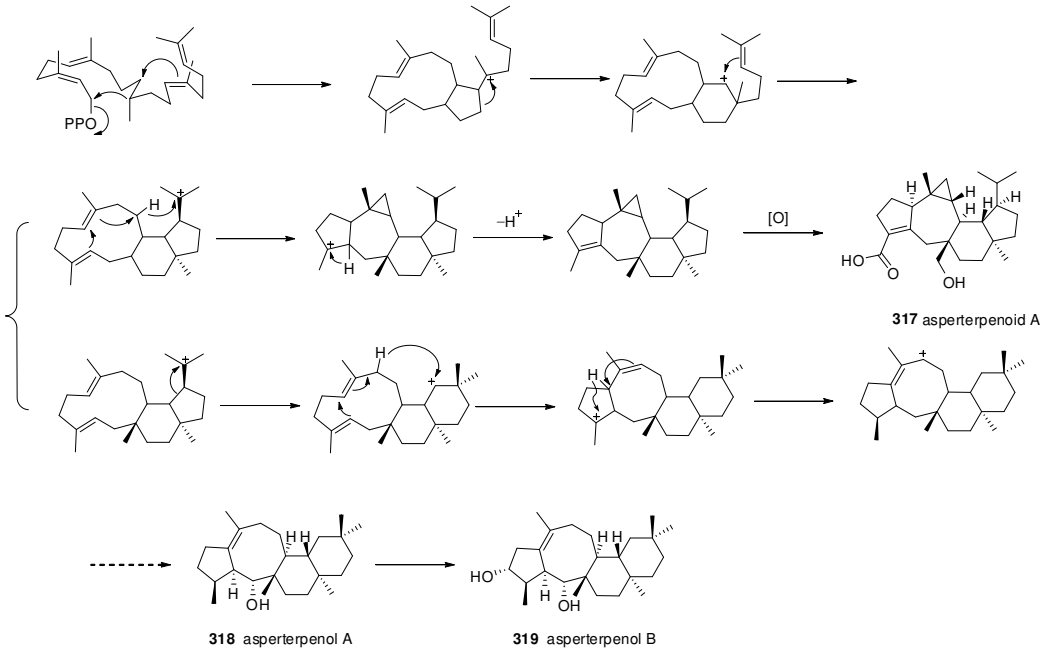


316 paclitaxel

4.2.3 Sesterterpenoids

Sesterterpenoids (C25) form the smallest class of the terpenoid family; they are rarely encountered in marine-derived fungi and no example has been reported from mangrove microbes to date [171-173]. Recently, a novel 5/7/(3)6/5 pentacyclic sesterterpenoid named asperterpenoid A (**317**) has been isolated from a *Sonneratia apetala* endophyte, which was identified from *Aspergillus* sp. 16-5c [174]. Another two novel sesterterpenoids with an unusual 5/8/6/6 tetracyclic ring skeleton, named asperterpenols A (**318**) and B (**319**) were isolated from *Acanthus ilicifolius* endophytic *Aspergillus* sp. 085242. Absolute configuration of these metabolites **317-319** were determined by single crystal X-ray diffraction analysis and was further confirmed from the proposed biosynthetic pathway. These metabolites are derivable from the same precursor geranylfarnesyl diphosphate (GFPP), through a series of cationic cyclizations, rearrangements and oxidation, as shown in Scheme **14**. An extensive bioassay disclosed strong inhibitory activity of compound **317** against

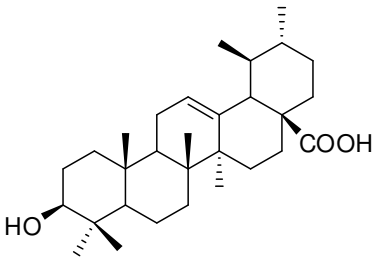
Mycobacterium tuberculosis protein tyrosine phosphatase B (mPTPB) with an IC_{50} value of 2.2 μM while compounds **318** and **319** strongly inhibited acetylcholinesterase(AChE) with IC_{50} values of 2.3 and 3.0 μM, respectively [175].



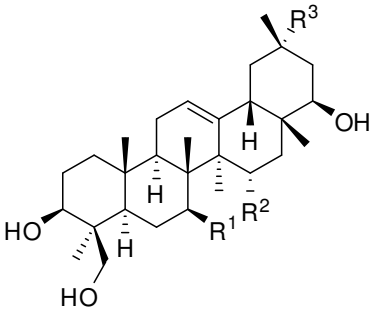
Scheme **14**. Possible biogenetic pathway for sesterterpenoids **317-319**.

4.2.4 Triterpenes

Along with ursolic acid (**320**), 3β,22β,24-trihydroxy-olean-12-ene (**321**), three new oleanane-type triterpenoids, (15α)-15-hydroxysoyasapogenol B (**322**), (7β,15α)-7,15-dihydroxysoyasapogenol B (**323**), and (7β)-7,29-dihydroxysoyasapogenol B (**324**) were isolated from the liquid culture of *Pestalotiopsis clavispora*, an endophytic fungus isolated from the Chinese mangrove plant *Bruguiera sexangula* (Dongzhai, Hainan, China) [87, 176].



320 ursolic acid



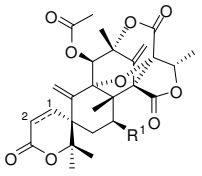
321 R^1 = H R^2 = CH_3 R^3 = CH_3
322 R^1 = H R^2 = H R^3 = CH_3
323 R^1 = OH R^2 = OH R^3 = CH_3
324 R^1 = H R^2 = CH_3 R^3 = CH_2OH

4.2.5 Meroterpenes

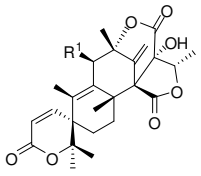
The term meroterpenoid was first applied by Cornforth, in 1968, to describe natural products of mixed biosynthetic origin, which are partially derived from terpenoids. These natural products are most often isolated from fungi and marine organisms and some have provided valuable access to novel hybrid chemotypes originating from simple compounds. These compounds comprise a prenyl unit linked to the polyketide unit to form unique architectural scaffolds, and are widely distributed in mangrove-derived fungi [177]. Austin-like metabolites represent a class of meroterpenoids mainly isolated from *Aspergillus* and *Penicillium* genera [178-181]. It was previously reported that these derivatives show notable toxicities to insects [182, 183]. Chemical investigation on the mangrove endophytic fungus *Aspergillus* sp. 085241B, led to the isolation of two new austin-like hybrid spirolactone meroterpenes, acetoxydehydroaustin B (**325**) and 1,2-dihydro-acetoxydehydroaustin B (**326**) [184]. Culture of *Emericella* sp., isolated as an endophytic fungus associated with *Aegiceras corniculatum* resulted in the purification of further members of the series such as austin (**327**), deacetylaustin (**328**) and dehydroaustin (**329**) [185]. Recently, compounds

325, **327** and **329** were shown to have a blocking action on cockroach nicotinic acetylcholine receptors [186]. A static culture of *Penicillium* sp. MA-37, which was obtained from the rhizospheric soil of the mangrove plant *Bruguiera gymnorrhiza* led to the identification three new meroterpenoid derivatives, namely 4,25-dehydrominiolutelide B (**330**), 4,25-dehydro-22-deoxyminiolutelide B (**331**), and isominiolutelide A (**332**), together with three known congeners, berkeleyacetals A and B (**333**, **334**), and 22-epoxyberkeleydione (**335**) [78]. The genus *Pestalotiopsis* has been shown to be a good source of sesquiterpenes, some of which are analogues arising from the metabolic hybrid with mero-sesquiterpenoid skeletons [187]. Two novel hybrid sesquiterpene-cyclopaldic acid metabolites with an unusual carbon skeleton, named pestalotiopens A and B (**336**, **337**), were obtained from the endophytic fungus *Pestalotiopsis* sp. JCM2A4 isolated from the leaves of the Chinese mangrove, *Rhizophora mucronata*. The absolute configurations of the new metabolites were determined by a combination of spectroscopic methods and quantum-chemical optical-rotatory dispersion (ORD) and circular dichroism (CD) calculations. A biosynthetic pathway to pestalotiopens A and B was proposed with altiloxin B (**308**) as one of the suggested precursors as illustrated in Scheme **15**. Both compounds were evaluated for their antimicrobial and antifungal activities against six bacterial strains, namely, *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia*. All compounds except **336** showed moderate antimicrobial activity against *Enterococcus faecalis* [157]. The search for new acetylcholinesterase inhibitors has led to the

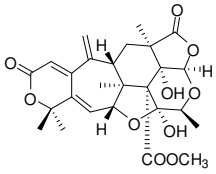
characterization of a series of potential inhibitors, **338–340,** from *Kandelia candel* endophytic *Penicillium* sp. sk5GW1L, with IC_{50} values of 0.64 ± 0.08 μM, 0.37 ± 0.11 μM, and 7.03 ± 0.20 nM, respectively. Of these, α-pyrone meroterpene arigsugacin I (**338**) is new. Low temperature (100 K), single crystal X-ray diffraction with Cu Kα radiation led to the determination of the absolute configuration as shown in compounds **338** and **339** [188].



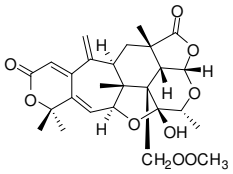
325 C(1)=C(2), R^1= $COCH_3$
326 C(1)–C(2), R^1= $COCH_3$
327 R^1= H



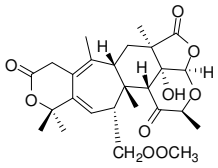
328 R^1 = $COCH_3$
329 R^1 = OH



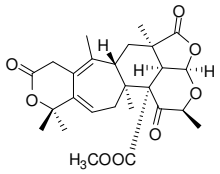
330



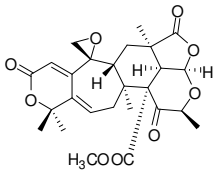
331



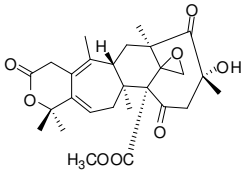
332



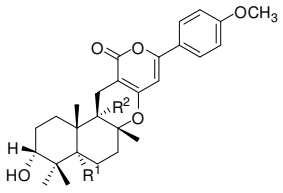
333



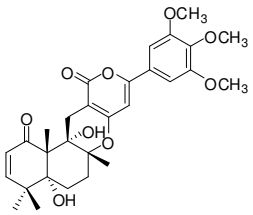
334



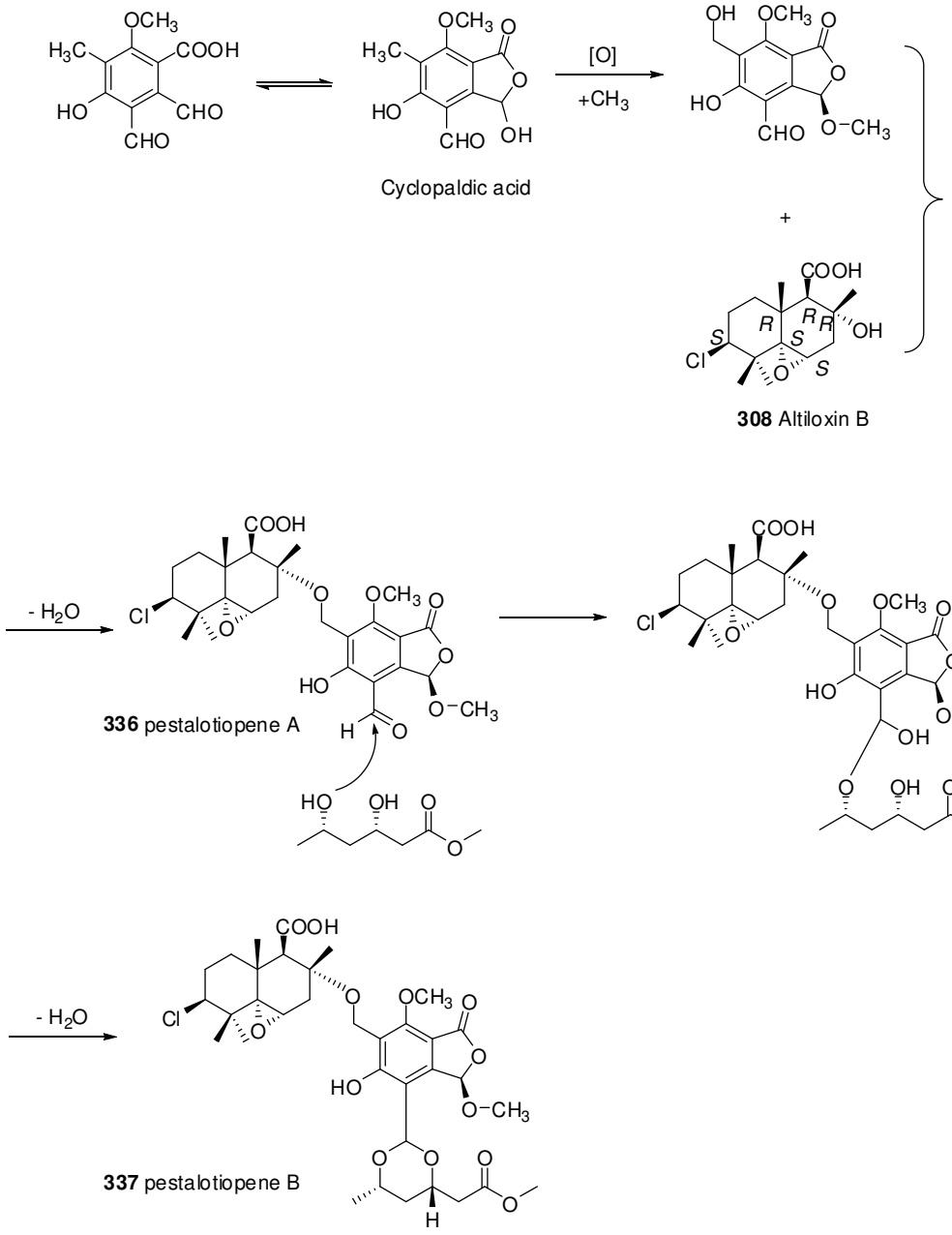
335



338 R^1= R^2= OH
339 R^1= R^2= H



340



Scheme **15**. Proposed biogenetic transformation from compound **308** to compound **336**, **337**.

4.3. Nitrogenated compounds

4.3.1 Amines and amides

A halotolerant fungus, *Penicillium chrysogenum* PXP-55, was isolated from the root surface of *Rhizophora stylosa* (Hainan, China) and was later cultured in a hypersaline

medium. It provided five new cerebrosides, chrysogesides A-E (**341**-**345**), and two new 2-pyridone alkaloids, chrysogedones A and B (**346**, **347**). Among chrysogesides B-D (**342**-**344**) were the first cerebrosides that featured an unsaturated C19-fatty acid. Attemped application of both the CD excitation chirality and the modified Mosher method resulted in the determination of **341**-**347** as stereochemistries, of which **342** was antimicrobial against *Enterobacter aerogenes* with an MIC value of 1.72 μM [189].

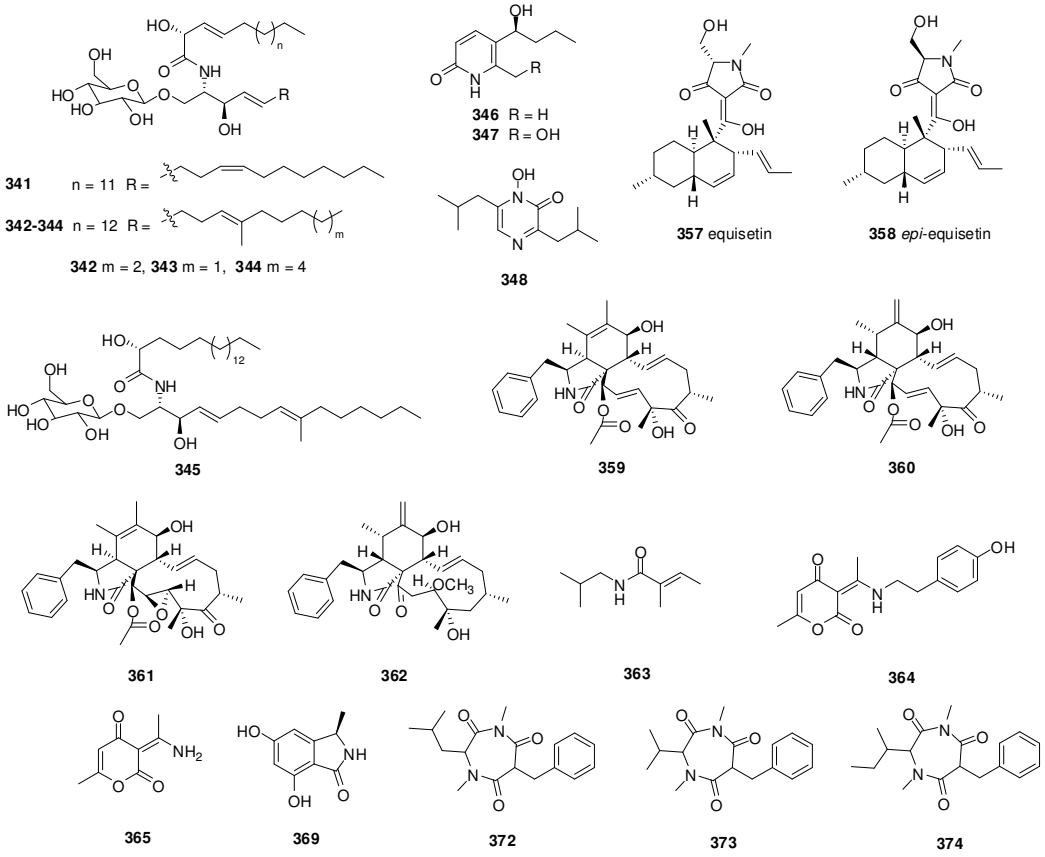
Several studies demonstrated that mangrove-derived fungi are capable of producing a number of important bioactive secondary metabolites, hitherto known in trace quantities. This is of particular significance since it highlights the potential of using these fungi as alternative and effective source for these metabolites [190]. Different *Aspergillus* strains are capable of making various hydroxypyrazine derivatives. A known antibiotic, neoaspergillic acid (**348**), originally obtained from the fungal species *Aspergillus sclerotiorum* [191] was reisolated from the mixed cultured mycelia of two mangrove *Avicennia* epiphytic *Aspergillus* sp. fungi strain FSY-01 and FSW-02. Compound **348** showed significant antibacterial activity against three Gram-positive bacteria, namely, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus subtilis* (IC_{50} 0.49-1.95 μg/mL), and three Gram-negative bacteria, *Bacillus dysenteriae*, *Bacillus proteus*, and *Escherichia coli*, (IC_{50} 7.80-15.62 μg/mL) [192]. Bioassay-guided fractionation of extracts from the endophytic fungus *Emericella* sp. (HK-ZJ) isolated from *Aegiceras corniculatum* led to the isolation of eight isoindolone derivatives, termed as emerimidines A and B (**349**, **350**) and emeriphenolicins A-D (**351**-**354**), and two previously reported compounds,

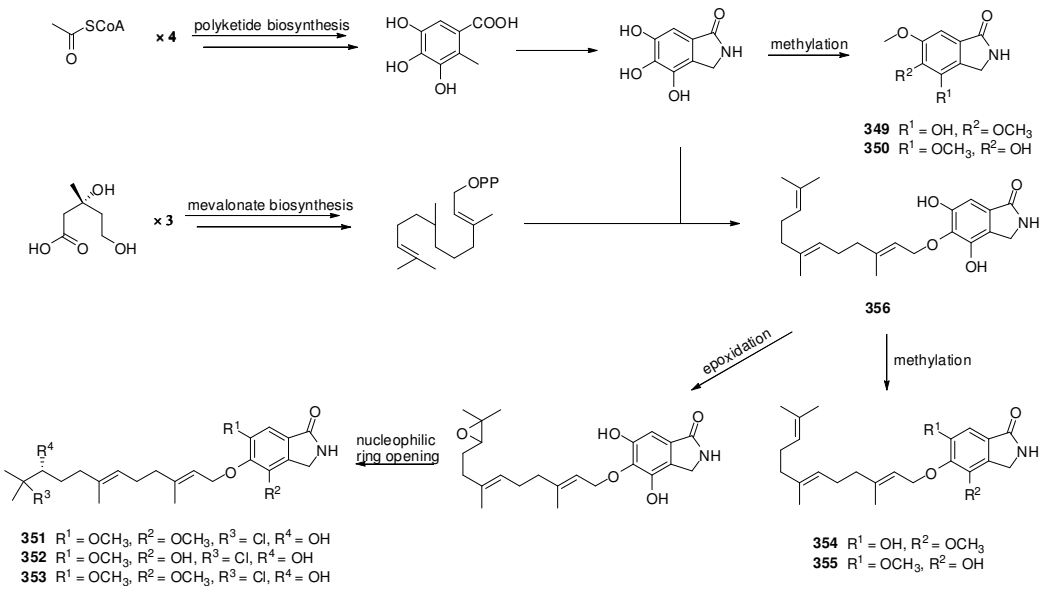
aspernidines A and B (**355**, **356**). A close biogenetic relationship probably existed among these compounds; thus, a mixed biosynthetic route involving polyketide and mevalonate pathways is proposed in Scheme **16**. All isolated metabolites were tested for *in vitro* activity against H1N1 replication in MDCK cells. However, only compounds **349** and **350** showed moderate inhibitory effects with IC_{50} values of 42.07 and 62.05 μg/mL, respectively [185]. Two previously known phytotoxins, equisetin (**357**) and *epi*-equisetin (**358**) were isolated from *Rhizophora stylosa* (Hainan, China) endophytic *Fusarium equiseti* AGR12, and showed moderate antibacterial activity [193, 194]. Equisetin was a classical antibiotic agent and showed selectivity against several strains of Gram-positive bacteria [195]. Surprisingly, it was reported to inhibit the 2, 4-dinitrophenol (DNP) stimulated ATPase activity of rat liver mitochondria and mitoplasts in a concentration-dependent manner; effectively 50% inhibition was caused by about 8 nmol equisetin/mg protein [196]. Cytochalasans are a group of substances whose structures include the presence of a hydrogenated and highly substituted bicyclic isoindolone moiety fused to a marcrocyclic ring and several have been reported to originate from mangrove fungi [8]. Studies are currently being conducted into the active constituents of the endophytic fungus *Xylaria* sp. BL321 of *Acanthus ilicifolius* L. Some of these studies have already led to the characterization of three known amides, cytochalasins C-D (**359**, **360**), and 19,20-epoxycytochalasin C (**361**) [153]. Cytochalasin IV (**362**) was found to be present in a fungal endophyte *Sporothrix* sp. (#4335) of *Kandelia candel* [41]. Compounds **359**-**361** exhibited cytotoxic activity against MCF-7 and MDA-MB-435 cell lines, with IC_{50} values of

33.0, 26.3, and 13.6 μM and 9.3, 11.1, and 6.9 μM, respectively [153]. A number of unusual alkaloids were reported from the culture broth of endophytic *Fusarium incarnatum* (HKI0504), which was isolated from the fruit of *Aegiceras corniculatum*, including *N*-2-methylpropyl-2-methylbutenamide (**363**), fusamine (**364**), and 3-(1-aminoethylidene)-6-methyl-2*H*-pyran-2,4(3*H*)-dione (**365**). Of these, the compounds **364** and **365** exhibited weak antiproliferative activity and were cytotoxic against HUVEC, K-562, and HeLa human cell lines, with IC_{50} values ranging from 9.0 to 103.6 μM [197]. The mycelium extract of a cultured, unidentified endophytic fungus (No. AMO 3-2) originated from the inner tissues of the healthy leaves from the mangrove plant *Avicennia marina,* from Oman. This afforded five farinomalein derivatives, including three new farinomaleins C-E (**366-368**), and one new isoindoline congener (**369**), together with the known farinomalein (**370**) and its methyl ester (**371**), with only **367** being moderately cytotoxic to mouse lymphoma cells L5178Y with an IC_{50} value of 4.4 μg/mL. To the best of our knowledge, only two such farinomalein derivatives are known to exert this functionality: farinomalein from entomopathogenic *Paecilomyces farinosus* [198], and pestalotiopsoid from *Rhizophora mucronata* endophytic *Pestalotiopsis* sp. [199]. A plausible biogenetic pathway of the isolated farinomaleins is proposed as shown in Scheme 17 [200].

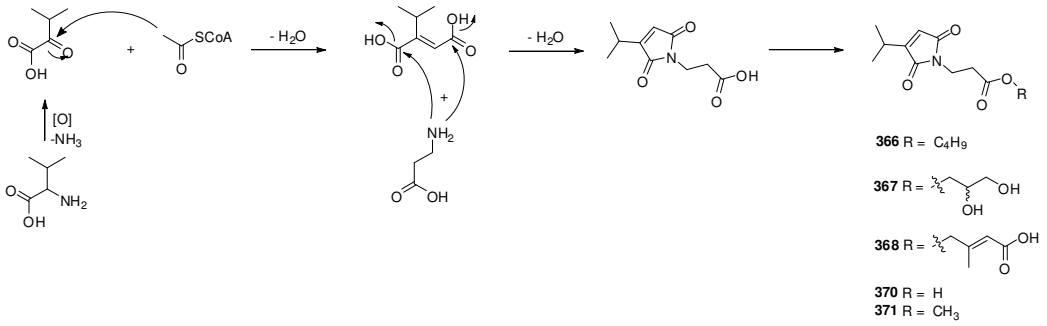
Terretrione A–C (**372–374**) were new cycloheptanetriones derived probably from the condensation of amino acids with hydrophobic side chain and phenylalanine analogue, were isolated from the culture of *Aspergillus terreus* A8-4 (sediment). Unlike the production of diketopiperazines, an additional carbonyl group was randomly inserted

between amino-nitrogen and α-carbon of phenylalanine followed by the cyclization reaction forming the so-called cycloheptanetriones skeleton, which rarely occurred in the metabolites isolated from microorganisms [105].





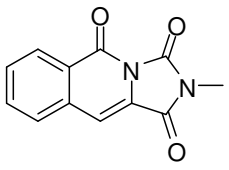
Scheme **16**. Hypothetic biosynthesis pathway of **349-356**.



Scheme **17**. Proposed biogenetic pathway of farinomaleins **366-368**, **370**, **371**.

4.3.2 Isoquinolines

During 2011–2013, only one previously unknown isoquinoline derivative, 2-methylimidazo[1,5-*b*]isoquinoline-1,3,5(2*H*)-trione (**375**), was isolated from the culture of *Hypocrea virens* obtained from the mangrove flora *Rhizophora apiculata* (Guangxi, China) [201].

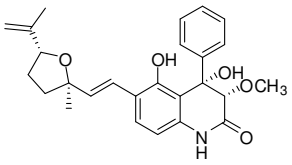


375

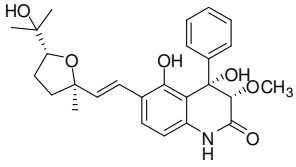
4.3.3 Quinolines

Quinoline alkaloids have been widely isolated from plants; however, very few examples of such compounds have been described from filamentous fungi [202]. Six new members of these compounds were isolated and identified from the cultures of *Aspergillus nidulans* MA-143, an endophytic fungus obtained from the fresh leaves of *Rhizophora stylosa.* These compounds incorporate a 4-phenyl-3,4-dihydroquinolin-2-one moiety, and are: aniduquinolones A–C (**376–378**), 6-deoxyaflaquinolone E (**379**), isoaflaquinolone E (**380**), and 14-hydroxyaflaquinolone F (**381**), as well as one related known compound, aflaquinolone A (**382**). X-ray analysis confirmed and established the absolute configuration of compound **376**. In bioscreening experiments, none of the isolated compounds showed potent antibacterial or cytotoxic activity. However, compounds **377**, **378**, and **382** exhibited lethality against brine shrimp (*Artemia salina*), with LD_{50} values of 7.1, 4.5, and 5.5 μM, respectively [203]. Co-cultures of two unidentified mangrove-derived endophytic fungi from the coast of the South China Sea provided marinamide (**383**) and its methyl ester (**384**), which originally had been reported as pyrrolyl 1-isoquinolone alkaloids. Their structures were alternatively revised as pyrrolyl 4-quinolone, based on the recrystallization of **384** from pyridine; this yielded the known pesticide quinolactacidewhich was treated with methyl iodide to afford *N*-methyl quinolactacide and was then identified using X-ray crystallography. Potential cytotoxicity against HepG2, 95-D, MGC832, and HeLa tumour cell lines reaching nM degree were observed for both **383** and **384**, ranging from 0.4 nM to 2.52

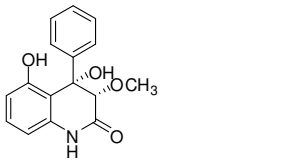
μM [204].



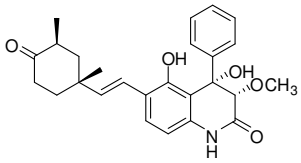
376



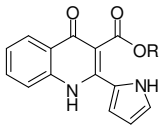
377



378 $R^1 = CH_3$, $R^2 = H$, $R^3 = OH$, R^4 = 
379 $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$
380 $R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = OH$
381 $R^1 = R^3 = R^4 = H$, $R^2 = OH$



382



383 R = H
384 R = CH_3

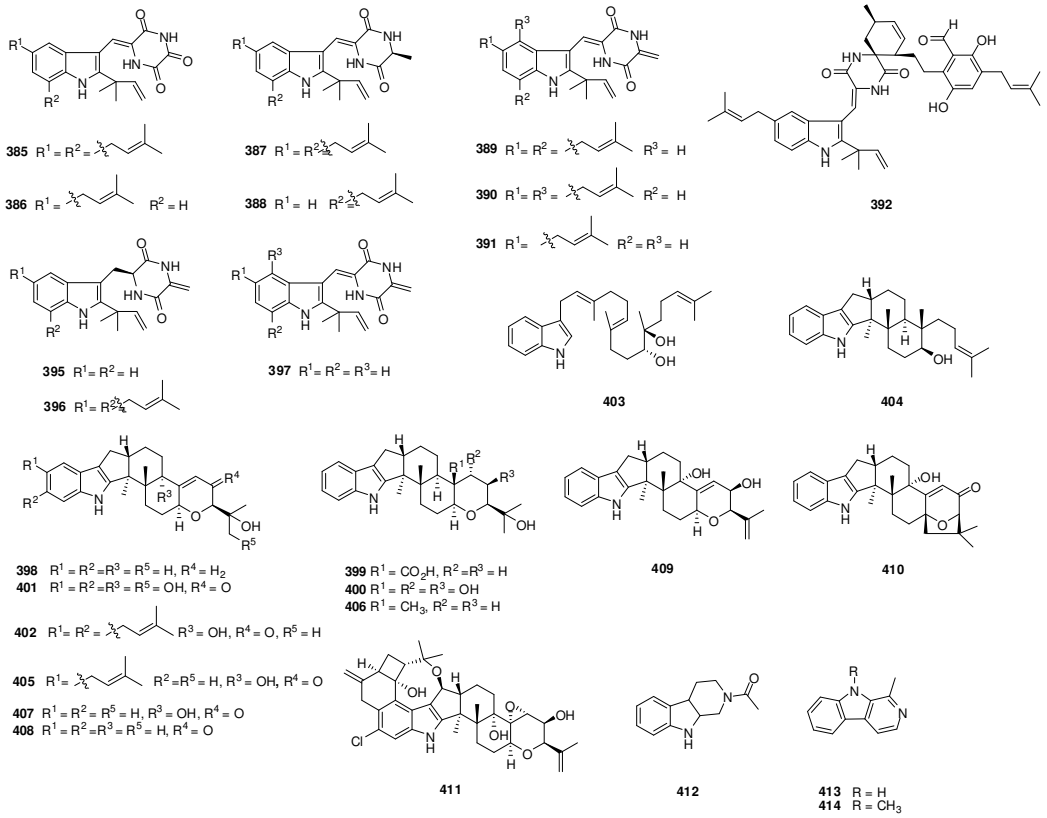
4.3.4 Indole derivatives

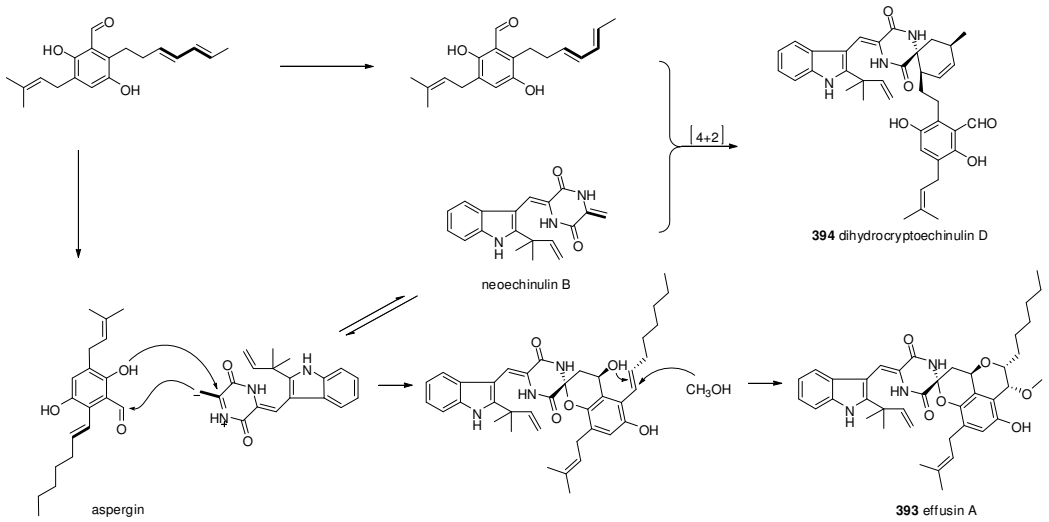
Isolation and fermentation of the fungal strain *Eurotium rubrum*, an endophyte inhabiting the inner stem tissues of *Hibiscus tiliaceus*, previously yielded several dioxopiperazines [205]. Further research on the same fungus yielded another new dioxopiperazine alkaloid, 12-demethyl-12-oxo-eurotechinulin B (**385**), together with seven related known derivatives, including variecolorin J (**386**), eurotechinulin B (**387**), variecolorin G (**388**), alkaloid E-7 (**389**), cryptoechinuline G (**390**), isoechinulin B (**391**) and 7-isopentenylcryptoechinuline D (**392**). All isolates were evaluated for their cytotoxic activity against seven tumor cell lines of MCF-7, SW1990, HepG2, NCI-H460, SMMC-7721, Hela, and Du145 and only compounds **385**, **388**, and **389** displayed moderate cytotoxic activities against one or two of these cell lines [63]. Effusin A (**393**), a spirobicyclic *N*,*O*-acetal derivative with an unprecedented 3′,3a′,5′,6′-tetrahydrospiro-[piperazine-2,2′-pyrano[2,3,4-*de*]chromene] ring system, and a spiro-polyketide-diketopiperazine hybrid dihydrocryptoechinulin D

(**394**) were isolated from a mangrove rhizosphere soil derived fungus, *Aspergillus effuses* H1-1. Both isolated compounds occurred as racemates, the enantiomers of which were separated and characterized by online HPLC-ECD analysis and their absolute configurations were determined by the solution TDDFT ECD calculation approach. Compound **393** could be obtained by a domino ring-closure reaction between the substituted salicylaldehyde moiety in aspergin and the enamide moiety of the diketopiperazine unit in neoechinulin B. In contrast, an enzyme-catalyzed regiospecific [4+2] Diels–Alder reaction produces the spirobicycle of **394** as shown in Scheme 18. A similar Diels–Alder biosynthetic reaction was suggested for a few recent examples, such as yaoshanenolides and lanceolatins [206]. Notably, all of the key intermediates including neoechinulin B [207], isodihydroauroglaucin [208] and aspergin [209] were isolated from this fungus *Aspergillus* sp, which supported our biosynthetic hypothesis. Preliminarily cytotoxic effects were evaluated and compound **394** showed potent activity on P388 cells with an IC_{50} value of 1.83 μM. The target of racemic **394** was also investigated and the (12*R*,28*S*,31*S*)-**394** enantiomer showed selectivity against topoisomerase I [210]. Another new prenylated indole diketopiperazine, named dihydroneochinulin B (**395**), alongside three co-occuring known metabolites didehydroechinulin B (**396**), neoechinulin B (**397**), and spiropolyketide-diketopiperazine hybrid cryptoechinuline D were reisolated from the mangrove rhizosphere soil derived fungus, *Aspergillus effuses* H1-1. The cytotoxic effects of these compounds were preliminarily evaluated against P388, HL-60, BEL-7402 and A-549. Compound **395** showed weak activity against BEL-7402 and

A-549 cell lines while compound **397** showed significant inhibitory activity against A-549 and BEL-7402. The IC_{50} values of A-549 and BEL-7402 were 1.43 and 4.20 μM, respectively [86]. Indole-diterpenoids are known as a large and structurally diverse group of fungal secondary metabolites [211] that possess a common cyclic diterpene backbone derived from geranylgeranyl diphosphate and an indole group derived from indole-3-glycerol phosphate [212]. They are known as tremorgenic mycotoxins [213, 214] and display anti-insectan [215, 216] and antibiotic activities [217, 218]. Six new indole-diterpenoid alkaloids (**398–403**), as well as five known analogues, emindole SB (**404**), 21-isopentenylpaxilline (**405**), paspaline (**406**), paxilline (**407**), and dehydroxypaxilline (**408**) were isolated and identified from an aciduric fungal strain, *Penicillium camemberti* OUCMDZ-1492 obtained from an acidic mangrove soil and mud niche around the roots of *Rhizophora apiculata*. Compared with ribavirin (IC_{50} 113.1 μM), compounds **398–400** and **402–408** showed significant activity *in vitro* against the H1N1 virus with IC_{50} values of 28.3, 38.9, 32.2, 73.3, 34.1, 26.2, 6.6, 77.9, and 17.7 μM, respectively [219]. Another four known structure resembling congeners, penijanthine A (**409**), paspalinine (**410**), and penitrem A (**411**) were later found to be produced by the endophytic fungus *Alternaria tenuissima* EN-192. This fungus was isolated from the stem bark of *Rhizophora stylosa* [60]. Carboline derivatives constitute an important group of natural products that possess various biological activities such as antiviral (e.g., euditomins, from tunicates) [221], and cytotoxic and antimicrobial (e.g., manzamines, from sponges) activities [222]. Although most tetrahydrocarbolines were previously believed to solely originate from marine animals, recent findings indicate

that microorganisms are also capable of producing carbolines such as oxopropaline [223, 224], bauerine [225], and *β*-carboline-1-propionic acid. The known synthetic compound 2-acetyl-1,2,3,4-tetrahydro-*β*-carboline (**412**) was isolated from a natural source for the first time from *Fusarium incarnatum* (HKI0504) isolated from *Aegiceras corniculatum.* However, it showed weak antiproliferative and cytotoxic activity against HUVEC, K-562, and HeLa human cell lines [197]. Other carboline members such as harman (1-methyl-*β*-carboline) (**413**) and *N*9-methyl-1-methyl-*β*-carboline (**414**), were isolated from a culture of *Penicillium* sp. ZH58 of *Avicennia*, suggesting yet another possible method to produce these compounds [45]. This was the first time that such metabolites had been reported from mangrove microbes.



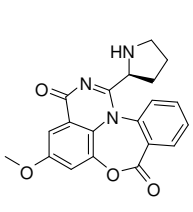


Scheme **18**. Plausible biosynthetic pathway to **393** and **394**.

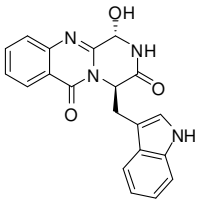
4.3.5 Quinazoline derivatives

A new moderate antibacterial agent, designated as aspergicin (**415**), was discovered from the mixed cultures of epiphytic *Aspergillus* sp. strain FSY-01 and FSW-02 occurring in *Avicennia* [192]. Five new glyantrypine derivatives, including 3-hydroxyglyantrypine (**416**), oxoglyantrypine (**417**a, **417**b), cladoquinazoline (**418**), epi-cladoquinazoline (**419**), and a new pyrazinoquinazoline derivative norquinadoline A (**420**) and eight known alkaloids (**421–428**) were isolated from the culture of the mangrove soil fungus *Cladosporium* sp. PJX-41 (Guangzhou, China). The absolute configurations of compounds **416–424** were established on the basis of CD, NOESY data, and single crystal X-ray diffraction analysis. Compounds **417**b, **420**, **422**-**424**, and **426** showed significant activities against the influenza virus A (H1N1) with IC_{50} values of 82–89 μM [225]. A series of quinazolinones, namely, aniquinazolines A-D (**429**-**432**) were isolated and identified from the culture of *Aspergillus nidulans* MA-143, an endophytic fungus obtained from the leaves of marine mangrove plant

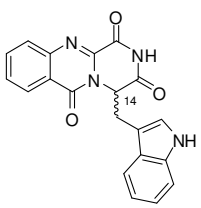
Rhizophora stylosa. As with some other classes of metabolites, these compounds showed potent lethality against brine shrimp with LD_{50} values of 1.27, 2.11, 4.95 and 3.42 μM, respectively, which were stronger than that of the positive control colchicine (with LD_{50} value of 88.4 μM). However, none of these displayed any antitumor (BEL-7402, MDA-MB-231, HL-60, and K562) or antibacterial (*Escherichia coli* and *Staphylococcus aureus*) activity [226].



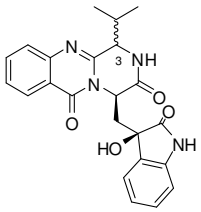
415 aspergicin



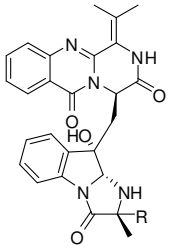
416



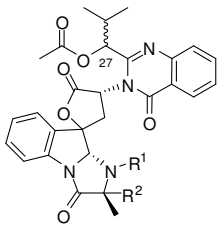
417a 14*R*
417b 14*S*



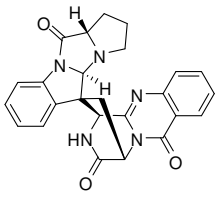
418 3*R*
419 3*S*



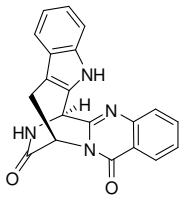
420 R = H
421 R = CH_3



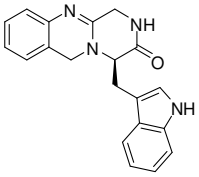
422 $R^1 = R^2$ =H, 27S
423 R^1 = H, R^2 = CH_3, 27S
424 R^1 = OH, R^2 = CH_3, 27S
425 R^1 = OH, R^2 = CH_3, 27R



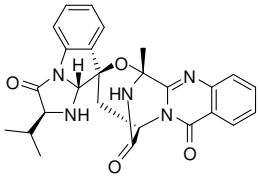
426



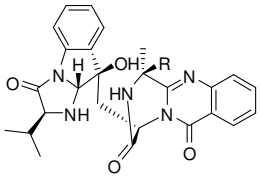
427



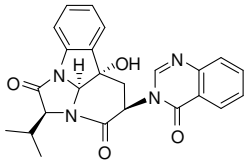
428



429



430 R = H
431 R = OH



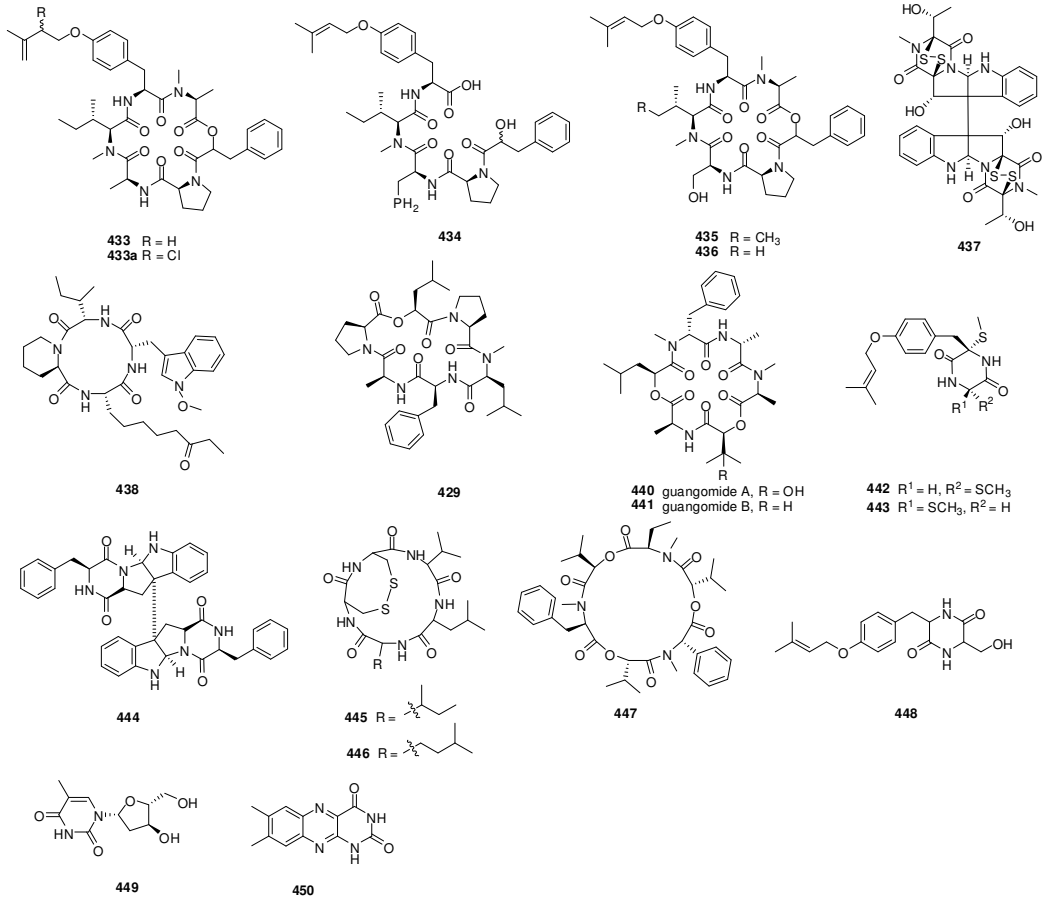
432

4.3.6 Peptides

Culture of *Bionectria ochroleuca*, endogenous to the inner leaf tissues of *Sonneratia caseolaris* (Sonneratiaceae), yielded two new peptides designated pullularins E (**433**) and F (**434**) and two known congeners pullularins A (**435**) and C (**436**). In addition to the above mentioned compounds, the fungal

epipolythiodioxopiperazine metabolite verticillin D (**437**) was also obtained from the *Bionectria* culture. All compounds were evaluated for cytotoxicity against the mouse lymphoma cells (L5178Y). Compounds **433**, **435** and **436** showed moderate activity with EC_{50} value ranging between 2.6 and 6.7 μg/mL. Interestingly, compound **437** showed pronounced activity against the mouse lymphoma cells with EC_{50} value less than 0.1 μg/mL [227]. Known pharmacological peptides were also isolated. A known cyclic tetrapeptide apicidin (**438**), previously characterized from *Fusarium pallidoroseum*, was reisolated from the culture of an unidentified endophytic fungus No. ZSU-H16 obtained from *Avicennia*. It was reported as a potent inhibitor of apicomplexan histone deacetylase (IC_{50} 1-2 nM), a broad spectrum antiparasitic agent *in vitro* inhibits the activity of apicomplexan parasites and has shown *in vivo* efficacy against *Plasmodium berghei* malaria [65, 228]. Exumolide A (**439**), which can accelerate the growth of subintestinal vessel plexus (SIV) branches markedly, was identified from *Phomopsis* sp. (No. ZH-111) from sediment [35]. Furthermore, two cyclic depsipeptides, guangomides A (**440**) and B (**441**) in addition to two diketopiperazines, Sch 54794 (**442**) and Sch 54796 (**443**) were purified from *Acremonium* sp. PSU-MA70 that were endophytes of *Rhizophora apiculata* [40]. Compounds **440** and B **441** showed weak antibacterial activity against *Staphylococcus epidermidis* and *Enterococcus durans* [229] while compound **442** exhibited inhibitory activity in the platelet activating factor (PAF) assay [230]. A new diketopiperazine dimer, WIN 64821 (**444**) was isolated from the culture of *Penicillium expansum* 091006 associated with *Excoecaria agallocha* [80]. Dimer **444** was described as a competitive antagonist to

substance P (SP) at the human NK1 receptor with an inhibitor affinity constant of 230±30 nM against [^{125}I]SPin human astrocytoma cells [231]. Two known cyclopentapeptides, malformins A1 and C (**445** and **446**) were identified from *Aspergillus niger* MA-132 isolated from *Avicennia marina*. Both compounds showed weak antibacterial activities against *Staphylococcus aureus* [232]. More recently, a known insecticidal agent beauvericin (**447**) isolated from an *Aspergillus terreus* (No. GX7-3B) colonizing in *Bruguiera gymnoihiza*, displayed remarkable inhibition against α-acetylcholinesterase (AChE) with IC_{50} value 3.09 μM and strong cytotoxic activity against MCF-7 (IC_{50} 2.02 μM), A549 (IC_{50} 0.82 μM), Hela (IC_{50} 1.14 μM) and KB (IC_{50} 1.10 μM) cell lines [61]. Six other common compounds of this type, 3-(hydroxymethyl)-6-[4-(3-methylbut-2-enyloxy)benzyl]piperazine-2,5-dione (**448**), thymidine (**449**), and lumichrome (**450**), were first reported from different mangrove endophytes, *Avicennia* endophytic *Penicillium* sp. ZH58 [49], *Penicillium chrysogenum* PXP-55 of *Rhizophora stylosa* [189], and *Pestalotiopsis clavispora* of *Bruguiera sexangula* [87].

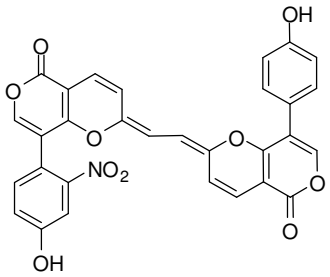


4.3.7 Miscellaneous nitrogenated derivatives

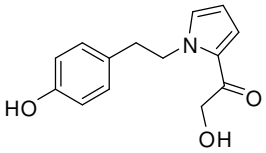
Phomopsis-H76 C (**451**) from a *Phomopsis* sp. (#zsu-H76) originated from *Excoecaria agallocha*, featuring an unprecedented pyrano [4,3-*b*]pyran-5(2*H*)-one ring system. Primary bioassays showed that this metabolite inhibited subintestinal vessel plexus (SIV) branch growth [44]. An unusual pyrrole fusarine (**452**) was characterized from endogenous *Fusarium incarnatum* (HKI0504) in *Aegiceras corniculatum* [197]. *Phomopsis* sp. PSU-MA214 of *Rhizophora apiculata* yielded a known phenylethyl alcohol phomonitroester (**453**) previously described from another species *Phomopsis* PSU-D15 isolated from *Garcinia dulcis* [59, 71]. A previously known 8-*O*-methylbostrycoidin (**454**) has been isolated from *Aspergillus terreus* (No.

GX7-3B) inhabitated in *Bruguiera gymnoihiza* as a strong inhibitor of α-acetylcholinesterase (AChE) with IC_{50} values 6.71 μM [61].

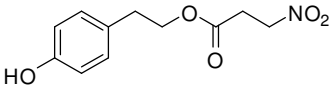
The mycelium extract of a cultured *Fusarium* sp. from the bark of *Kandelia candel* (L.) Druce (Hainan, China) yielded fusaric acid (**455**) as the predominant constituent responsible for the antimycobacterial activity. A variety of metal complexes of fusaric acid were prepared. Antimycobacterial assays showed that Cadmium (II) and Copper (II) complexes exhibited potent inhibitory activity against the *Mycobacterium bovis* BCG (MIC = 4 μg/mL) and the *M. tuberculosis* H37Rv (MIC = 10 μg/mL). This is the first report of the antimycobacterial activity of a mangrove *Fusarium* metabolite and its coordinating metal complexes [233].



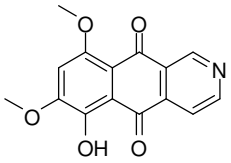
451



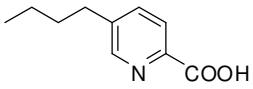
452



453



454



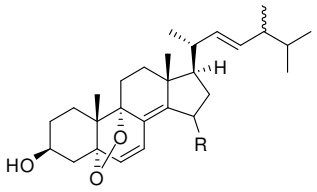
455

4.4. Steroids

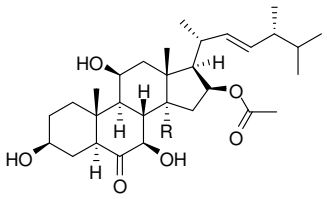
Sterols with a 5,8-epidioxy moiety are well-known metabolites from marine organisms, such as corals, sponges, and mangrove-derived fungi, as well as terrestrial macrofungi [234-238]. In contrast, sterols with the 5,9-epidioxy motif have been rarely

reported. So far, only five 5,9-epidioxy-sterols have been isolated from several edible mushrooms; however, none of them were extracted from mangrove organisms. Nigerasterols A and B (**456**, **457**) representing the first 5,9-epidioxy-sterols of mangrove origin were characterized from *Aspergillus niger* MA-132 isolated from *Avicennia marina*. Both **456** and **457** displayed potent activity against tumor cell lines HL60 (IC_{50} 0.30/1.50 μM) and A549 (IC_{50} 1.82/5.41 μM) in a preliminary bioassay. The absolute configuration of compound **456** was determined by the application of a modified version of Mosher's method [232]. Apart from a known neuritogenic compound NGA0187 (**458**), compounds 3β,5α-dihydroxy-(22*E*,24*R*)-ergosta-7,22-dien-6-one (**459**), 3β,5α,14α-trihydroxy-(22*E*,24*R*)-ergosta-7, 22-dien-6-one (**460**) were also purified from the culture of *Aspergillus terreus* (No. GX7-3B) obtained from *Brugnieria gymnoihiza*. Metabolite **458** induced significant neurite outgrowth in PC12 cells and was found to show potent inhibitory activity against MCF-7, A549, HL-60 and KB cell lines. MCF-7, A549, HL-60 and KB cell lines had IC_{50} values of 4.98, 1.95, 0.68, 1.50 μM, respectively [61, 239, 240]. The 3β-hydroxy sterols and their oxygenated analogues include a large group of metabolites found in lower terrestrial organisms, marine organisms, lichens and fungi [241]. Several ubiquitous microbial secondary metabolites such as ergosta-4,6,8(14),22-tetraen-3-one (**461**) were isolated from *Pestalotiopsis clavispora* from the stem of *Bruguiera sexangula* [87]. The sterol 7,22-(*E*)-diene-3β,5α,6β-triol-ergosta (**462**) was discovered using a mixed fermentation technique on unidentified mangrove endophytic fungal strains *Kandelia*

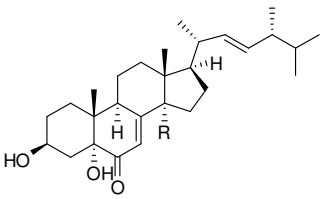
candel endophytic K38 and *Eucheuma muricatum* endophytic E33 [37].



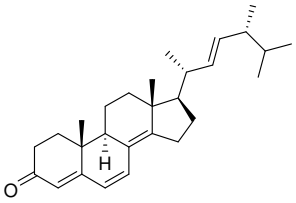
456 nigerasterols A, R = α–OH
457 nigerasterols B, R = β–OH



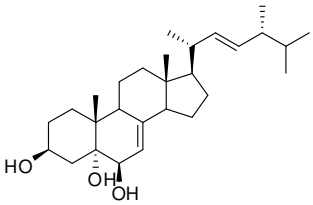
458



459 R = H
460 R = CH_3



461



462

Table 2. Fungal metabolites

fungal species	host(s)	natural product(s)	biological activity	ref
Acremonium sp. PSU-MA70	*Rhizophora apiculata*	acremonone B (**34**)		40
		acremonone C (**35**)		
		acremonone D (**36**)		
		acremonone E (**37**)		
		acremonone F (**38**)		
		acremonone G (**39**)		
		acremonone H (**40**)		
		acremonide (**216**)		
		acremonone A (**217**)		
		(+)-brefeldin A (**218**)	strong protein secretion inhibitor	
		5,7-dimethoxy-3,4-dimethyl-3-hydroxyphthalide (**219**)		
		4-methyl-1-phenyl-2,3-hexanediol (**272**)		
		(2*R*,3*R*)-4-methyl-1-phenyl-2,3-pentanediol (**273**)		
		8-deoxytrichothecin (**314**)	selectively cytotoxic	
		trichodermol (**315**)	antifungal	
		guangomide A (**440**)	weak antibacterial	
		guangomide B (**441**)	weak antibacterial	
		Sch 54794 (**442**)	PAF inhibitor	
		Sch 54796 (**443**)		

Alternaria tenuissima EN-192	*Rhizophora stylosa*	tricycloalternarene 3a (**87**) tricycloalternarene 1b (**88**) tricycloalternarene 2b (**89**) paspaline (**406**) penijanthine A (**409**) paspalinine (**410**) penitrem A (**411**) djalonensone alternariol	moderate antibacterial	60
Alternaria sp. ZJ9-6B	*Aegiceras corniculatum*	alterporriol K (**70**) alterporriol L (**71**) alterporriol M (**72**) anthraquinones (**73-76**)	moderate cytotoxic moderate cytotoxic	52
Aspergillus effuses H1-1	rhizosphere soil	effusin A (**393**) dihydrocryptoechinulin D (**394**) auroglaucin (**166**) dihydroneochinulin B (**395**) didehydroechinulin B (**396**) neoechinulin B (**397**) cryptoechinuline D	strong cytotoxic; selectivity topoisomerase I inhibitor weak cytotoxic strong cytotoxic	86, 210
Aspergillus nidulans MA-143	*Rhizophora stylosa*	aniduquinolone A (**376**) aniduquinolone B (**377**) aniduquinolone C (**378**) 6-deoxyaflaquinolone E (**339**) isoaflaquinolone E (**380**) 14-hydroxyaflaquinolone F (**381**) aflaquinolone A (**382**) aniquinazoline A (**429**) aniquinazoline B (**430**) aniquinazoline C (**431**) aniquinazoline D (**432**)	brine shrimp lethality brine shrimp lethality brine shrimp lethality strong brine shrimp lethality strong brine shrimp lethality strong brine shrimp lethality strong brine shrimp lethality	203, 226
Aspergillus niger MA-132	*Avicennia marina*	nigerapyrone A (**187**) nigerapyrone B (**188**) nigerapyrone C (**189**) nigerapyrone D (**190**) nigerapyrone E (**191**)	selective cytotoxic weak cytotoxic cytotoxic	103

		nigerapyrone F (**192**)		
		nigerapyrone G (**193**)		
		nigerapyrone H (**194**)		
		asnipyrone A (**195**)		
		asnipyrone B (**196**)	selective cytotoxic	
		nigerasterol A (**456**)	strong cytotoxic	232
		nigerasterol B (**457**)		
		malformin A1 (**445**)	weak antibacterial	
		malformin C (**446**)	weak antibacterial	
Aspergillus taichungensis ZHN-7-07	*Acrostichum aureum*	prenylterphenyllin A (**130**)	moderate cytotoxic	76
		prenylterphenyllin B (**131**)		
		prenylterphenyllin C (**132**)		
		prenylcandidusin A (**133**)		
		prenylcandidusin A (**134**)	moderate cytotoxic	
		prenylcandidusin C (**135**)		
		4″-dehydro-3-hydroxyterphenyllin (**136**)	moderate cytotoxic	
		prenylterphenyllin (**137**)	moderate cytotoxic	
		terprenin (**138**)		
		deoxyterhenyllin (**139**)		
		3-hydroxyterphenyllin (**140**)		
		terphenyllin(**141**)		
		3,3′-dihydroxyterphenyllin (**142**)		
		candidusin A (**143**)		
		candidusin C (**144**)		
Aspergillus terreus Gwq-48	rhizosphere soil	isoaspulvinone E (**232**)	significant anti-influenza A H1N1; significant H1N1 neuraminidase inhibitor	122
		aspulvinone E (**233**)	significant anti-influenza A H1N1	
		pulvic acid (**234**)	significant anti-influenza A H1N1	
Aspergillus terreus A8-4	sediment	7″-hydroxybutyrolactone Ⅲ(**197**)	weak cytotoxic	105
		butyrolactone I (**198**)	weak cytotoxic; eukaryotic CDK inhibitor	
		terretrione A (**372**)		
		terretrione B (**373**)		
		terretrione C (**374**)		
		cyclo(Leu-Pro)		
		cyclo(Val-Pro)		
		cyclo(Ile-Pro)		
		cyclo(Phe-Pro)		

Aspergillus terreus (No. GX7-3B)	*Bruguiera gymnoihiza*	8-hydroxy-2-[1-hydroxyethyl]-5,7-dimethoxynaphtho[2,3-*b*] thiophene-4,9-dione (**90**)		61. 158
		anhydrojavanicin (**91**)	remarkable AChE inhibitor	
		8-*O*-methyljavanicin (**92**)		
		botryosphaerone D (**93**)		
		6-ethyl-5-hydroxy-3,7-dimethoxynaphthoquinone (**94**)		
		beauvericin (**447**)	insecticidal	
		8-*O*-methylbostrycoidin (**454**)		
		NGA0187 (**458**)	neuritogenic	
		3β,5α-dihydroxy-(22*E*,24*R*)-ergosta-7,22-dien-6-one (**459**)		
		3β,5α,14α-trihydroxy-(22*E*,24*R*)-ergosta-7, 22-dien-6-one (**460**)		
		botryosphaerin F (**309**)	strong cytotoxic	
		(13,14,15,16-tetranorlabd-7-ene-19,6b:12,17-diolide) (**310**)		
		botryosphaerin B (**311**)		
		LL-Z1271b (**312**)	significant cytotoxic	
Aspergillus tubingensis (GX1-5E)	*Pongamia pinnata*	rubasperone A (**47**)		46, 47
		rubasperone B (**48**)		
		rubasperone C (**49**)		
		rubasperone D (**50**)	mild cytotoxic	
		rubasperone E (**51**)		
		rubasperone F (**52**)		
		rubasperone G (**53**)		
		rubrofusarin (**54**)	moderate tyrosinase inhibitor	
		rubrofusarin B (**55**)	mild α-glucosidase inhibitor; mild cytotoxic	
		TMC 256 A1 (**56**)	cytotoxic	
		fonsecin (**57**)		
		flavasperone (**58**)	mild cytotoxic	
Aspergillus sp. strain FSY-01 and FSW-02	*Avicennia*	neoaspergillic acid (**348**)	significant antibacterial	192
		aspergicin (**415**)	moderate antibacterial	
		ergosterol		
Aspergillus sp. 16-5c	*Sonneratia apetala*	asperterpenoid A (**317**)	strong mPTPB inhibitor	164
Aspergillus sp. 085241B		acetoxydehydroaustin B (**325**)		184
		1,2-dihydro-acetoxydehydroaustin B (**326**)		
Aspergillus sp. 085242	*Acanthus ilicifolius*	asperterpenol A (**318**)	strong AChE inhibitor	174
		asperterpenol B (**319**)	strong AChE inhibitor	
Aspergillus sp.	*Bruguiera gymnorrhiza*	aspergillumarin A (**32**)	weak antibacterial	39
		aspergillumarin B (**33**)	weak antibacterial	
Bionectria	*Sonneratia*	pullularin E (**434**)	moderate cytotoxic	227

ochroleuca	*caseolaris*	pullularin F (**434**)		
		pullularin A (**435**)	moderate cytotoxic	
		pullularin C (**436**)	moderate cytotoxic	
		verticillin D (**437**)	pronounced cytotoxic	
Cladosporium sp. PJX-41	soil	3-hydroxyglyantrypine (**416**)		189
		oxoglyantrypine (**417**a, **417**b)	compound **417**b significant anti-H1N1	
		cladoquinazoline(**418**)		
		epi-cladoquinazoline (**419**)		
		norquinadoline A (**420**)	significant anti-H1N1	
		quinadoline A (**421**)		
		deoxynortryptoquivaline (**422**)	significant anti-H1N1	
		deoxytryptoquivaline (**423**)	significant anti-H1N1	
		tryptoquivaline (**424**)	significant anti-H1N1	
		CS-C (**425**)		
		quinadoline B (**426**)		
		prelapatin B (**427**)		
		glyantrypine (**428**)		
Corynespora cassiicola	*Laguncularia racemosa*	2,5,7-trihydroxy-3-methoxynaphthalene-1,4-dione (**99**)		62, 106
		6-(3′-hydroxybutyl)-7-*O*-methylspinochrome B (**99**)		
		xestodecalactone D (**199**)		
		xestodecalactone E (**200**)		
		xestodecalactone F (**201**)		
		corynesidone C(**202**)		
		corynesidone A (**203**)		
		corynesidone B (**204**)	protein kinase inhibitor	
		coryoctalactone A (**205**)		
		coryoctalactone B (**206**)		
		coryoctalactone C (**207**)		
		coryoctalactone D (**208**)		
		coryoctalactone E (**209**)		
Deuteromycete sp.	drift wood	deuteromycol A (**123**)		73
		deuteromycol B (**124**)		
Diaporthe phaseolorum	*Laguncularia racemosa*	3-hydroxypropionic acid (3-HPA) (**267**)	antibacterial	139
Diaporthe sp.	*Rhizophora stylosa*	diaporol A (**291**)		150
		diaporol B (**292**)		
		diaporol C (**293**)		
		diaporol D (**294**)		
		diaporol E (**295**)		
		diaporol F (**296**)		
		diaporol G(**297**)		
		diaporol H (**298**)		

		diaporol I (**299**)		
		3β-hydroxyconfertifolin (**300**)		
		diplodiatoxin (**301**)		
Emericella sp.	*Aegiceras corniculatum*	acetoxydehydroaustin B (**325**)		185
		austin (**327**)	nAChR antagonist	
		deacetylaustin (**328**)		
		dehydroaustin (**329**)	nAChR antagonist	
		emerimidine A (**349**)	moderate anti-H1N1	
		emerimidine B (**350**)	moderate anti-H1N1	
		emeriphenolicin A (**351**)		
		emeriphenolicin B (**352**)		
		emeriphenolicin C (**353**)		
		emeriphenolicin D (**354**)		
		aspernidine A (**355**)		
		aspernidine B (**356**)		
Eurotium rubrum	*Hibiscus tiliaceus*	emodic acid (**99**)		63
		9-dehydroxyeurotinone (**210**)	weak antibacterial	
		2-*O*-methyl-9-dehydroxyeurotinone (**211**)		
		12-demethyl-12-oxo-eurotechinulin B (**384**)	moderate cytotoxic	
		variecolorin J (**386**)		
		eurotechinulin B (**387**)		
		variecolorin G (**388**)	moderate cytotoxic	
		alkaloid E-7 (**389**)	moderate cytotoxic	
		cryptoechinuline G (**390**)		
		isoechinulin B (**391**)		
		7-isopentenylcryptoechinuline D (**392**)		
		emodin		
Flavodon flavus PSU-MA201	*Rhizophora apiculata*	flavodonfuran (**266**)	mild antibacterial and antifungal	138
		tremulenolide A (**306**)	mild antibacterial and antifungal	
Fusarium equiseti AGR12	*Rhizophora stylosa*	equisetin (**357**)	phytotoxic; moderate antibacterial	193
		epi-equisetin (**358**)	phytotoxic; moderate antibacterial	
		ergosterol		
Fusarium incarnatum (HKI0504	*Aegiceras corniculatum*	*N*-2-methylpropyl-2-methylbutenamide (**363**)		197
		fusamine (**364**)	weak cytotoxic	
		3-(1-aminoethylidene)-6-methyl-2*H*-pyran-2,4(3*H*)-dione (**365**)	weak cytotoxic	
		2-acetyl-1,2,3,4-tetrahydro-β-carboline (**412**)	weak cytotoxic	
		fusarine (**452**)		
Fusarium	*Rhizophora*	taxol (**316**)	clinical antitumor	170

oxysporum	*annamalayana*		medicine	
Fusarium sp.	*Kandelia candel*	fusaric acid (**455**)	antimycobacterial	233
Fusarium sp. ZZF60	*Kandelia candel*	5-hydroxy-7-methoxy-4′-*O*-(3-methylbut-2-enyl) isoflavone (**66**) eriodictyol (**67**) 3,6,7-trihydroxy-1-methoxyxanthone (**111**) 1,3,6-trihydroxy-8-methylxanthone (**112**) vittarin-B (**167**) cyclo (Phe–Tyr)		50
Hypocrea virens	*Rhizophora apiculata*	2-methylimidazo[1,5-*b*]isoquinoline-1,3,5(2*H*)-trione (**375**)		201
Leucostoma persoonii	*Rhizophora mangle*	cytosporone R (**150**) cytosporone E (**220**) cytosporones B cytosporones C	anti-infective; antimicrobial	79
Nigrospora sp. No.1403	*Kandelia candel*	deoxybostrycin (**77**) methyl 3-chloro-6-hydroxy-2-(4-hydroxy-2-methoxy-6-methylphenoxy)-4-methoxybenzoate (**145**) (2*S*,5′*R*,*E*)-7-hydroxy-4,6-dimethoxy-2-(1-methoxy-3-oxo-5-methylhex-1-enyl)-benzofuran-3(2*H*)-one (**251**) dechlorogriseofulvin (**254**) griseofulvin bostrycin	strong antitumor; strong antimicrobial; strong antimycobacteria phytotoxic; antibacterial;strong antitumor; strong antimicrobial	56, 57
Nigrospora sp. No. MA75	*Pongamia pinnata*	2,3-didehydro-19α-hydroxy-14-epicochlioquinone B (**78**) 4-deoxytetrahydrobostrycin (**79**) 3,8-dihydroxy-6-methoxy-1-methylxanthone (**108**) 3,6,8-trihydroxy-1-methylxanthone (**109**) griseophenone C (**110**) 6-*O*-desmethyldechlorogriseofulvin (**252**) 6′-hydroxygriseofulvin (**253**) dechlorogriseofulvin (**254**) griseofulvin tetrahydrobostrycin	strong cytotoxic moderate antimicrobial antibacterial	58
Paecilomyces sp.		paeciloxocins A (**179**)	strong cytotoxic; mildly antimicrobial	89

		paeciloxocin B (**180**)		
Penicillium camemberti OUCMDZ-1492	mangrove soil and mud	(2*S*,4b*R*,6a*S*,12b*S*,12c*S*,14a*S*)-3-deoxo-4b-deoxypaxilline (**398**)	significant anti-H1N1	219
		(2*S*,4a*R*,4b*R*,6a*S*,12b*S*,12c*S*,14a*S*)-4a-demethylpaspaline-4a-carboxylic acid (**399**)	significant anti-H1N1	
		(2*S*,3R,4*R*,4a*S*,4b*R*,6a*S*,12b*S*,12c*S*,14a*S*)-4a-demethylpaspaline-3,4,4a-triol (**400**)	significant anti-H1N1	
		(2*R*,4b*S*,6a*S*,12b*S*,12c*R*,14a*S*)-2′-hydroxypaxilline (**401**)		
		(2*R*,4b*S*,6a*S*,12b*S*,12c*R*,14a*S*)-9,10-diisopentenylpaxilline (**402**)	significant anti-H1N1	
		(6*S*,7*R*,10*E*,14*E*)-16-(1*H*-indol-3-yl)-2,6,10,14-tetramethylhexadeca-2,10,14-triene-6,7-diol (**403**)	significant anti-H1N1	
		emindole SB (**404**)	significant anti-H1N1	
		21-isopentenylpaxilline (**405**)	significant anti-H1N1	
		paspaline (**406**)	significant anti-H1N1	
		paxilline (**407**)	significant anti-H1N1	
		dehydroxypaxilline (**408**)		
Penicillium chermesinum (ZH4-E2)	*Kandelia candel*	6′-*O*-desmethylterphenyllin (**125**)	strong α-glucosidase inhibitor	53
		3-hydroxy-6′-*O*-desmethylterphenyllin(**126**)	strong α-glucosidase inhibitor	
		3″-deoxy-6′-*O*-desmethylcandidusin B (**127**)	strong α-glucosidase inhibitor	
		3,3″-dihydroxy-6′-*O*-desmethylterphenyllin (**128**, **129**)	acetylcholinesterase inhibitor	
		6′-*O*-desmethylcandidusin B		
		chermesinone B (**185**)		
		chermesinone C (**186**)		
		Chermesinone A (**259**)	mild *R*-glucosidase inhibitor	
Penicillium chrysogenum PXP-55	*Rhizophora stylosa*	chrysogeside A (**341**)		189
		chrysogeside B (**342**)	antimicrobial	
		chrysogeside C (**343**)		
		chrysogeside D (**344**)		
		chrysogeside E (**345**)		
		chrysogedone A (**346**)		
		chrysogedone B (**347**)		
Penicillium expansum 091006	*Excoecaria agallocha*	expansol C (**151**)	weak cytotoxic	80
		expansol D (**152**)		
		expansol E (**153**)	weak cytotoxic	
		expansolF (**154**)		
		3-*O*-methyldiorcinol (**155**)		
		(+)-(7*S*)-7-*O*-methylsydonic acid (**156**)		

		3,7-dihydroxy-1,9-dimethyldibenzofuran (**157**)		
		orcinol (**158**)		
		2,4-dimethoxyphenol (**159**)		
		4-hydroxybenzoic acid (**160**)		
		butyrolactone I (**198**)	weak cytotoxic; eukaryotic CDK inhibitor	
		butyrolactone V (**231**)	moderate antimalarial	
		WIN 64821 (**444**)		
		expansol A		
		expansol B		
		diorcinol		
		S-(+)-sydonic acid		
Penicillium sumatrense MA-92	*Lumnitzera racemosa*	sumalarin A (**240**)	strong cytotoxic	130
		sumalarin B (**241**)	strong cytotoxic	
		sumalarin C (**242**)	strong cytotoxic	
		curvularin (**239**)		
		dehydrocurvularin (**243**)	strong cytotoxic	
		curvularin-7-*O*-*β*-D-glucopyranoside(**244**)		
Penicillium sp. MA-37	*Bruguiera gymnorrhiza*	7-*O*-acetylsecopenicillide C (**146**)		78
		hydroxytenellic acid B (**147**)		
		6-[2-hydroxy-6-(hydroxymethyl)-4-methylphenoxy]-2-methoxy-3-(1-methoxy-3-methylbutyl)benzoic acid (**148**)		
		secopenicillide C (**149**)		
		$\Delta^{1',3'}$-1′-dehydroxypenicillide (**212**)		
		penicillide (**213**)	brine shrimp lethality	
		dehydroisopenicillide (**214**)	brine shrimp lethality	
		3′-*O*-methyldehydroisopenicillide (**215**)		
		4,25-dehydrominiolutelide B (**330**)		
		4,25-dehydro-22-deoxyminiolutelide B (**331**)		
		isominiolutelide A (**332**)		
		berkeleyacetals A (**333**)		
		berkeleyacetal B (**334**)		
		22-epoxyberkeleydione (**335**)		
Penicillium sp. sk5GW1L	*Kandelia candel*	arigsugacin I (**338**)	potential AChE inhibitor	188
		arigsugacins F (**339**)	potential AChE inhibitor	
		territrem B (**340**)	potential AChE inhibitor	
Penicillium sp. ZH16	*Avicennia*	5-methyl-8-(3-methylbut-2-enyl) furanocoumarin (**23**)	modest cytotoxic	33
		bergapten (**24**)		
		scopoletin (**25**)		

		umbelliferone (**26**)		
		sterequinone C (**80**)		
		1,7-dihydroxyxanthone (**113**)		
		3,5-dimethoxybiphenyl (**168**)		
		cyclo(6,7-en-Pro-L-Phe)		
Penicillium sp. ZH58	*Avicennia*	5-hydroxy-3-hydroxymethyl-7-methoxy-2-methyl-4H-1-benzopyran-4-one (**63**)	antibiotic	49
		4-(methoxymethyl)-7-methoxy-6-methyl-1(3*H*)-isobenzofuranone (**238**)		
		curvularin (**239**)		
		5,5′-oxy-dimethylene-*bis*(2-furaldehyde) (**281**)		
		dilation (**313**)		
		harman (1-methyl-*β*-carboline) (**413**)		
		*N*9-methyl-1methyl-*β*-carboline (**414**)		
		lumichrome (**450**)		
Pestalotiopsis clavispora	*Bruguiera sexangula*	3-hydroxy-4-methoxystyrene (**169**)		86
		3,4-dihydroxyphenylethanol (**170**)		
		p-tyrosol (**171**)		
		diisobutyl phthalate (**271**)		
		ursolic acid (**319**)		
		3*β*,22*β*,24-trihydroxy-olean-12-ene (**320**)		
		thymidine (**449**)		
		ergosta-4,6,8(14),22-tetraen-3-one (**461**)		
		3 *β*-hydroxy-5 *α*,8 *α*-epidioxyergosta-6,22-diene		
		(15α)-15-hydroxysoyasapogenol B (**322**)		176
		(7*β*,15α)-7,15-dihydroxysoyasapogenol B (**323**)		
		(7*β*)-7,29-dihydroxysoyasapogenol B (**324**)		
Pestalotiopsis foedan	*Bruguiera sexangula*	(−)-(4*S*, 8*S*)-foedanolide (**236**)	modest cytotoxic	124
		(+)-(4*R*, 8*R*)-foedanolide (**237**)	modest cytotoxic	
Pestalotiopsis heterocornis (L421)	*Bruguiera gymnorrhiza*	7-hydroxy-5-methoxy-4,6-dimethyl-7-*O*-a-L-rhamnosyl-phthalide (**182**)		90
		7-hydroxy-5-methoxy-4,6-dimethyl-7-*O*-b-D-glucopyranosyl-phthalide (**183**)		
		7-hydroxy-5-methoxy-4,6-dimethylphthalide (**184**)		
Pestalotiopsis virgatul	*Sonneratia caseolaris*	pestalotiopyrone I (**245**)		131
		pestalotiopyrone J (**246**)		
		pestalotiopyrone K (**247**)		
		pestalotiopyrone L (**248**)		
		(6*S*,10*S*,20*S*)-hydroxypestalotin (**249**)		
Pestalotiopsis JCM2A4	*Rhizophora mucronata*	*n*-hexadecanoic acid (**264**)		137
		elaidic acid (**265**)		
		altiloxin B (**308**)		157
		pestalotiopen A (**336**)	moderate antimicrobial	

		pestalotiopen B (**337**)		
Pestalotiopsis sp. PSU-MA69	*Rhizophora apiculata*	pestalochromone A (**60**) pestalochromone B (**61**) pestalochromone C (**62**) asperpentyn (**100**) siccayne (**101**) pestaloxanthone (**115**) pestalotethers A (**161**) pestalotethers B (**162**) pestalotethers C (**163**) pestalotetherD (**164**) pestalolide (**228**) seiridin (**229**) (*S*)-penipratynolene (**276**) anofinic acid (**277**)	weak antifungal DNA-damaging active	48
Pestalotiopsis sp. PSU-MA92/*Pestalotiopsis* sp. PSU-MA119	*Rhizophora apiculata*/*Rhizophora mucronata*	pestalotiopyrone A (**221**) pestalotiopyrone B (**222**) pestalotiopyrone C (**223**) pestalotioprolide A (**224**) pestalotioprolide B (**225**) seiricuprolide (**226**) 2´-hydroxy-30,40-didehydropenicillide (**227**)		111
Phoma herbarum VB7		dibutylphthalate (**269**) mono (2-ethylhexyl) phthalate (**270**)		140
Phoma sp. SK3RW1M	*Avicennia marina*	1-hydroxy-8-(hydroxymethyl)-6-methoxy-3-methyl-9H-xanthen-9-one (**105**) 1-hydroxy-8-(hydroxymethyl)-3-methoxy-6-methyl-9H-xanthen-9-one (**106**) 1,8-dihydroxy-10-methoxy-3-methyldibenzo[*b*,*e*]oxepine-6,11-dione (**178**)		66
Phomopsis sp. IM 41-1	*Rhizhopora mucronata*	phomoxanthone A (**121**) 12-*O*-deacetyl-phomoxanthone A (**122**)	moderate antimicrobial moderate antimicrobial	156
Phomopsis sp. (No. SK7RN3G1)	sediment	2,6-dihydroxy-3-methyl-9-oxoxanthene-8-carboxylic acid methyl ester (**117**) lichenxanthone (**118**) griseoxanthone C (**119**) 1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (**120**)	modest cytotoxic	69
Phomopsis sp. (ZH76)	*Excoecaria agallocha*	3-*O*-(6-*O*-*α*-L-arabinopyranosyl)-*β*-D-glucopyranosyl-1,4-dimethoxyxanthone (**116**) phomapyrone D (**235**) 2-methoxy-3,4-methylenedioxybenzophenone *cyclo*(D-6-Hyp-L-Phe)	modest cytotoxic	68
Phomopsis sp.	sediment	(3*R*,	strong SIV accelerator;	35

(No. ZH-111)		4*S*)-3,4-dihydro-4,5,8-trihydroxy-3-methylisocoumarin (**27**)	weak cytotoxic	
		4-(hydroxymethyl)-7-methoxy-6-methyl-1(3*H*)-isobenzofuranone (**181**)	SIV inhibitor	
		exumolide A (**439**)	strong SIV accelerator	
Phomopsis sp. PSU-MA214	*Rhizophora apiculata*	(2*R*,3*S*)-7-ethyl-1,2,3,4-tetrahydro-2,3,8-trihydroxy-6-methoxy-3-methyl-9,10-anthracenedione (**81**)	weak cytotoxic	59
		tetrahydroaltersolanol B (**82**)		
		tetrahydroaltersolanol C (**83**)		
		ampelanol (**84**)		
		macrosporin (**85**)		
		1-hydroxy-3-methoxy-6-methylanthraquinone (**86**)		
		phenethyl alcohol hydracrylate (**274**)		
		butanamide (**275**)		
		phomonitroester (**453**)		
Phomopsis sp. ZSU-H26	*Excoecaria agallocha*	5-hydroxy-6,8-dimethoxy-2-benzyl-4*H*-naphtho[2,3-*b*]-pyran-4-one (**43**)	cytotoxic	43
		5,7-dihydroxy-2-methylbenzopyran-4-one (**44**)		
		3,5-dihydroxy-2,7-dimethylbenzopyran-4-one (**45**)		
		cyclo(Tyr-Tyr)		
Phomopsis sp. (#zsu-H76)	*Excoecaria agallocha*	phomopsis-H76 A (**46**)	strong SIV accelerator	44
		phomopsis-H76 B (**177**)		
		phomopsis-H76 C (**450**)	SIV inhibitor	
Sporothrix sp. (No. 4335)	*Kandelia candel*	7-chloro-2′,5,6-trimethoxy-6′-methylspiro(benzofuran-2(3*H*),1′-(2) cyclohexene)-3,4′-dione (**250**)		134
		2-acetyl-7-methoxybenzofuran (**256**)		
		diaporthin (**42**)		41
		5-hydroxy-2-methylchromanone (**64**)		
		5-methoxy-2-methylchromone (**65**)		
		1,8-dihydroxy-4-methylanthraquinone (**102**)		
		1,8-dihydroxy-5-methoxy-3-methyl-9*H*-xanthen-9-one (**114**)		
		3-methoxy-6-methyl-1,2-benzenediol (**173**)		
		4-methoxypyrocatechol (**174**)		
		3,5-dimethylphenol (**175**)		
		1-hydroxy-8-methoxynaphthalene (**176**)		
		7-chloro-2′,5,6-trimethoxy-6′-methylspiro[benzofuran-2(3*H*),1′-(2)cyclohexene]-3,4′-dione (**255**)		
		1,8-dimethoxynaphthalene (**279**)		
		methyl 7-methylbenzofuran-2-carboxylate (**280**)		
		cytochalasin IV (**361**)		
		sporothrin A		
		sporothrin B		

		sporothrin C		
		1,8-dihydroxy-5-methoxy-3-methyl-9*H*-xanthen-9-one		
		5-carboxymellein		
		peroxyergosterol		
		cyclo(L-Leu-L-Pro)		
		cyclo-L-phenylalanyl-L-alanine		
		2,4-dihydroxypyrimidine		
Talaromyces flavus	*Sonneratia apetala*	talaperoxide A (**287**)		149
		talaperoxide B (**288**)	cytotoxic	
		talaperoxide C (**289**)		
		talaperoxide D(**290**)	cytotoxic	
		merulin A (steperoxide B) (**282**)		
Talaromyces sp. ZH-154	*Kandelia candel*	7-epiaustdiol (**257**)	moderate cytotoxic; significant antimicrobial	135
		8-*O*-methylepiaustdiol (**258**)	moderate cytotoxic	
		stemphyperylenol		
		skyrin		
		secalonic acid A		
		emodin		
		norlichexanthone		
Xylaria cubensis PSU-MA34	*Bruguiera parviflora*	(*R*)-(−)-5-carboxymellein(**29**)		38
		(*R*)-(−)-5-methoxycarbonylmellein (**30**)		
		(*R*)-(−)-mellein methyl ester (**31**)		
		2-chloro-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (**95**)		
		isosclerone (**96**)		
		xylacinic acid A (**260**)		
		xylacinic acid B (**261**)		
		2-hexylidene-3-methyl succinic acid 4-methyl ester (**262**)		
		cytochalasin D (**359**)		
Xylaria sp. BL321	*Acanthus ilicifolius*	isocoumarin (**41**)		113, 153
		lactone (**230**)		
		07H239-A (**305**)	cytotoxic; concentration dependent *α*-glucosidase activator and inhibitor	
		tricyclic lactone (**307**)		
		cytochalasin C (**359**)		
		cytochalasin D (**359**)		
		19,20-epoxycytochalasin C (**360**)		
		three new eremophilane sesquiterpenes (**302**–**304**)		
unidentified	*Scyphiphora*	*R*-3-hydroxyundecanoic acid methyl	modest antimicrobial	136

fungus A1	*hydrophyllacea*	ester-3-*O*-α-L-rhamnopyranoside (**263**)		
unidentified fungus No. AMO 3-2	*Avicennia marina*	farinomalein C (**366**) farinomalein D (**367**) farinomalein E (**368**) farinomalein (**369**) farinomalein methyl ester (**370**) (3*R*)-5,7-dihydroxy-3-methylisoindolin-1-one (**371**)		197
unidentified fungal strains K38 and E33	*Kandelia candel*/ *Eucheuma muricatum*	8-hydroxy-3-methyl-9-oxo-9H-xanthene-1-carboxylic acid methyl ether (**107**) 6, 8-dihydroxy-4-acetylisocoumarin (**28**) 2, 5-hydroxy-6, 8-dimethoxy-2, 3-dimethyl-4*H*-naphtho-[2，3-*b*]-pyran-4-one (**59**) 2-formyl-3,5-dihydroxy-4-methyl-benzoic acid (**172**) allitol (**268**) 7,22-(*E*)-Diene-3*β*,5*α*,6*β*-triol-ergosta (**463**)	antifungal	37, 67
unidentified fungus XG8D	*Xylocarpus granatum*	merulin A (**282**) merulin B (**283**) merulin C (**284**)	significant cytotoxic significant cytotoxic; promising antiangiogenic	147
		merulin D (**285**) steperoxide A (**286**)		148
unidentified fungus Zh6-B1	*Sonneratia apetala*	3,4-dihydro-4,8-dihydroxy-7-(2-hydroxyethyl)-6-methoxy-1(2*H*)-naphthalen-1-one (**68**) 10-norparvulenone (**69**) 3*R*,5*R*-sonnerlactone 3*R*,5*S*-sonnerlactone	 anti-influenza cytotoxic	51
unidentified fungus No. ZSU-H16	*Avicennia*	3,5,8-trihydroxy-2,2-dimethyl-3,4,4-trihydro-2H,6H-pyrano[3,2-b]-xanthen-6-one (**103**) 5,8-dihydroxy-2,2-dimethyl-2*H*,6*H*-pyrano[3,2-b]xanthen-6-one (**104**) cyclo-(*N*-*O*-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) (**439**) *cyclo*-(Phe-Tyr)		65
Unidentified fungi Nos. K38 and E33		ethyl 5-ethoxy-2-formyl-3-hydroxy-4-methylbenzoate (**165**)	weak antifungal	84
unidentified two co-cultured fungi		marinamide (**383**) marinamide methyl ester (**384**)	potent cytotoxic potent cytotoxic	204

5. Concluding remarks

Mangrove-associated microbes continue to be the focus for much of natural products research that has been well documented. In this review, we systematically summarized the new findings regarding the chemistry and bioactivities of most natural products found in mangrove microbial ecosystems during the last three years. These include 464 naturally occurring small-biomolecules. The rate at which these metabolites have been discovered within the past three years has increased sharply (33%). Furthermore, they have contributed to increasing chemical diversity in the compounds discovered over the past twenty years. This increase is largely due to improvements in isolation procedures and structural analysis. These trends are shown graphically in Figure 1, which compares outputs for 1989 through to Nov. 2010 with those for the recent three years. The compounds are shown according to their structural classification.

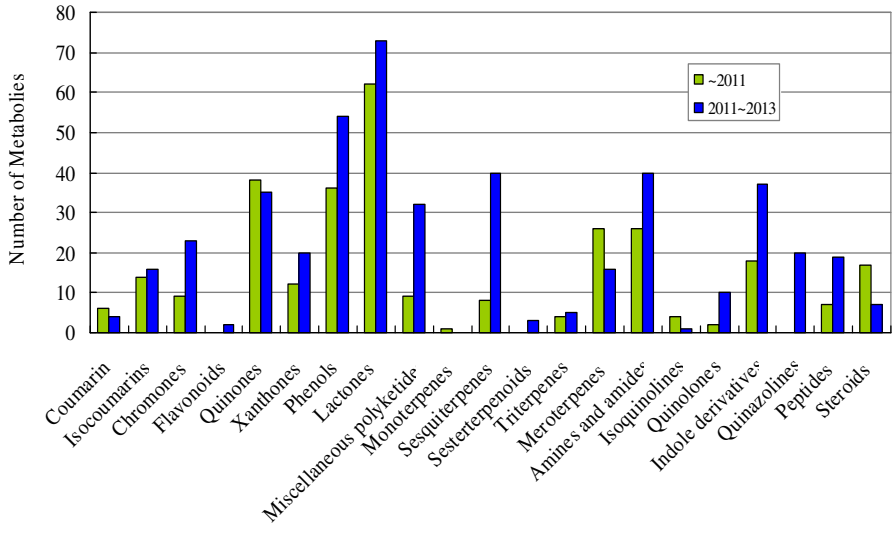


Fig. 1. Comparison of Mangrove-Associated Microbial Metabolites Distribution by Backbone.

At the domain level, <5% of the species examined originated from the actinomyces or bacteria while the majority (>95%) originated from fungi. Actinomycetes are of special interests (4%) as they are known to produce chemically diverse compounds with an extraordinarily high proportion (60%) of their metabolites showing a wide range of biological activities. The endophytic fungi have been found to produce a significant number of interesting metabolites (>83%) with biologically active substances. The endophytic fungi have been found to produce a significant number of interesting metabolites >83% with 32% biologically active substances, occur in considerably higher numbers than those produced by rhizosphere soil or sediments microorganisms <12% but of 38% of bioactive substances. The high rate of inactive metabolite discovery in previous studies was probably because of bias in the screening programmes and limitations in analytical technology. It is noteworthy that *Aspergillus*, *Penicillium*, and *Pestalotiopsis* are predominant as producers of promising chemical diversity. Furthermore, they constitute 46% of the compounds reported, and if five other prolific genera such as *Streptomyces*, *Acremonium*, *Phomopsis*, *Sporothrix*, and *Xylaria* are considered, they account for nearly 68% of all of the metabolites. The remaining 26% are scattered across another 17 genera, and less than 6% of the metabolites are from unidentified microorganisms. *Rhizophora apiculata*(14%), rhizosphere soil and sediment(11%), *Kandelia candel* (10%), *Bruguiera gymnoihiza* (8%) and *Rhizophora stylosa* (6%) were considered to be the main sources of metabolic microbes. The emergence of plants native to China and Thailand as significant sources of new compounds may be of particular significance.

Our last review discussed the problem of ambiguously described microorganisms; however, since then the ratio of ambiguous microbes and sources reported in the ensuing three years have declined dramatically, and most microbes are properly documented and characterized (Tables 1 and 2).

Some compounds intrigue the natural product researchers because of their unusual structures including the unusual 5/8/6/6 tetracyclic ring or 5/7/(3)6/5 pentacyclic sesterterpenoids asperterpenoid A (**317**), asperterpenols A (**318**) and B (**319**) from *Aspergillus* sp.. Some metabolites have provided valuable access to novel hybrid chemotypes derived from different biosynthetic routes. These include NRPS, terpene, shikimate and polyketide mixed biosynthetic tetrasubstituted benzothiazole erythrazoles A (**21**) and B (**22**) from *Erythrobacter* sp., hybrid sesquiterpene-polyketide metabolites pestalotiopens A and B (**336**, **337**) from *Pestalotiopsis* sp. JCM2A4. Among the 130 or so bioactive components presented in this review, several have fascinating bioactivities comparable to those of modern pharmacological products. These include the antitumor agents paeciloxocin A (**179**), sumalarins A–C (**240–242**), and merulin A and C (**287**, **289**). Paeciloxocin A from *Paecilomyces* sp. exhibited strong cytotoxicity effects against the growth of hepG2 cell line at 1 μg/mL. Sumalarins A–C (**240–242**) from *Penicillium sumatrense* MA-92 showed potent cytotoxicity against some of the tested tumor cell lines, whereas merulin A and C (**282**, **284**) were identified from an unidentified fungus XG8D isolated from the leaves of *Xylocarpus granatum,* which displayed significant cytotoxicity against human breast cancer line (BT474) with IC_{50} values of 4.98 and

1.57 μg/mL, respectively. Merulin C **284**displayed promising activity in a rat aortic ring sprouting (*ex vivo*) and a mouse Matrigel (*in vivo*) assay. Anti-H1N1 agents such as isoaspulvinone E (**232**) from *Aspergillus terreus* Gwq-48 showed significant anti-influenza A H1N1 virus activities with IC_{50} value of 32.3 μg/mL and exhibited effective inhibitory activity against H1N1 viral neuraminidase (NA). Indole-diterpenoid alkaloids **398–400** and **402–408** from *Penicillium camemberti* OUCMDZ-1492 exhibited significant *in vitro* anti-H1N1 with IC_{50} values of 6.6-89 μM, respectively. The compounds **417**b, **420**, **422**-**424**, and **426** from *Cladosporium* sp. PJX-41 showed significant activities against the influenza virus A (H1N1) with IC_{50} values of 82–89 μM, which is much more effective than ribavirin (IC_{50} 113.1 μM). Anti-enzyme agents such as *p*-terphenyls **125-127** showed strong inhibitory effects against *R*-glucosidase with IC_{50} values of 0.9, 4.9, and 2.5 μM, respectively. The compound **317** displayed strong inhibitory activity against *Mycobacterium tuberculosis* protein tyrosine phosphatase B (mPTPB) with an IC_{50} value of 2.2 μM while compounds **318** and **319** strongly inhibited acetylcholinesterase (AChE) with IC_{50} values of 2.3 and 3.0 μM, respectively. Arigsugacin I (**338**) from *Penicillium* sp. sk5GW1L showed potential anti-AChE activity with IC_{50} values of 0.64 ± 0.08 μM. Compounds, **27**, **46** and **439** from *Phomopsis* sp. were demonstrated to accelerate the growth of subintestinal vessel plexus (SIV) markedly, whereas phomopsis-H76 C (**451**) was shown to be a subintestinal vessel plexus (SIV) branch growth inhibitor. Strong brine shrimp lethality was detected by aniquinazolines A-D (**429**-**432**) from *Aspergillus nidulans*. MA-143 showed potent lethality with LD_{50} values of 1.27, 2.11,

4.95 and 3.42 μM, respectively, which were over 40 times stronger than that of the positive control colchicines. This makes many of these compounds suitable candidates for drug discovery and will trigger groundbreaking synthesis studies of these compounds in the coming years.

Biogenetic hypotheses have become increasingly valuable in the screening of structurally related missing precursors/intermediates/products. Metabolites are biologically compatible with many living systems and often possess unique and useful biological activities, largely because their scaffolds are the result of evolutionarily significant selective pressures. Activation of these attenuated or silenced genes of biosynthetic pathways to obtain either improved titers of known compounds or new ones altogether has been the subject of particular interest. "One Strain Many Compounds" (OSMAC) approach has been popular towards the discovery of new metabolites. Consequently, the manipulation of biosynthetic pathways, epigenetic modifications (cytosporone R **150** from concomitant supplementation of *Leucostoma persoonii*), varying culture conditions (compounds **47-58** from *Aspergillus tubingensis*) and co-culturing two organisms together (compounds **221-227** from *Pestalotiopsis* sp. PSU-MA92/ PSU-MA119) have been applied to stimulate the production of new compounds.

The anticancer drug taxol (**316**) was purified from *Fusarium oxysporum* of *Rhizophora annamalayana*. This drug implicated mangrove endophytes as a sustainable, economically feasible and alternative source of therapeutic compounds. The production of bioactive substances by mangrove microbes is directly related to

the independent evolution of these microorganisms, which may have incorporated genetic information from their biotope and carry out certain functions. For example, austin-like derivatives **325-329** represent a class of compounds (identified from *Emericella* sp.) that are toxic to insects and play crucial ecological roles such as the capacity to protect its host plant against insect invaders. Thus, they contribute to a range of defense substances secreted by plants that can be further investigated. Interesting biotopes such as the mangrove microbial communities are especially productive since they accumulate a diverse array of bioactive compounds with novel scaffolds. As yet, the potential of this area remains virtually untapped. Substantial evidence now exists showing that in the long-term maintenance of the biodiversity profile, mangrove ecosystems can provide a valuable function in wave and storm surge attenuation, and erosion reduction,. However, nowadays approximately one-third of the global cover of these ecosystems has been lost; this is particularly true in Southeast Asia. The most challenging goals concerning secondary metabolites are the elucidation of their true function in their native mangrove habitats and, closely associated with this, the identification of the physiological and ecological conditions that have led to the activation of secondary metabolism gene clusters. Many of the extensive areas of mangrove restoration throughout the world have cited expected ecosystem protection benefits, which will also support the continued provision of functional, diverse, inhabitated microbes. Multidisciplinary research and collaborative endeavors amongst biotechnologists, microbiologists, chemists and pharmacologists would result in the isolation of unusual or rare microorganisms that produce

structurally interesting and biologically active molecules with potential use in medicinal and agricultural applications.

Acknowledgements

Co-Financed by grants of National Natural Science Foundation of China for Young Scholar (No. 81202456), Hainan Provincial Natural Science Foundation (No. 814285), Special Foundation for Modernization of Traditional Chinese Medicine of Hainan (ZY201429) and the programs for New Century Excellent Talents in University (NCET-13-0760) are gratefully acknowledged.

6 References

1. Feller, I. C.; Lovelock, C. E.; Berger, U.; McKee, K. L.; Joye, S. B.; Ball, M. C. Biocomplexity in mangrove ecosystems. *Annu. Rev. Mar. Sci.*, **2010**, *2*, 395-417.

2. Thatoi, H.; Behera, B. C.; Mishra, R. R.; Dutta, S. K. Biodiversity and biotechnological potential of microorganisms from mangrove ecosystems: a review. *Ann. Microbiol.*, **2013**, *63*, 1-19.

3. Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H.; Prinsep, M. R. Marine natural products. *Nat. Prod. Rep.*, **2013**, *30*, 237-323.

4. Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H.; Prinsep, M. R. Marine natural products. *Nat. Prod. Rep.*, **2014**, *31*, 160-258.

5. Wang, X.; Mao, Z. G.; Song, B. B.; Chen, C. H.; Xiao, W. W.; Hu, B.; Wang, J. W.; Jiang, X. B.; Zhu, Y. H.; Wang, H. J. Advances in the study of the structures and bioactivities of metabolites isolated from mangrove-derived fungi in the South China Sea. *Mar. Drugs* **2013**, *11*, 3601-3616.

6. Debbab, A.; Aly, A. H.; Proksch, P. Bioactive secondary metabolites from endophytes and associated marine derived fungi. *Fungal Divers.*, **2011**, *49*, 1-12.

7. Debbab, A.; Aly, A. H.; Proksch, P. Mangrove derived fungal endophytes-a chemical and biological perception. *Fungal Divers.*, **2013**, *61*, 1-27.

8. Xu, J. Biomolecules produced by mangrove-associated microbes. *Curr. Med. Chem.*, **2011**, *18*, 5224-5266.

9. Subramani, R.; Aalbersberg, W. Culturable rare *Actinomycetes*: diversity, isolation and marine natural product discovery. *Appl. Microbiol. Biotechnol.*, **2013**, *97*, 9291-9321.

10. Brown, G. D. The biosynthesis of artemisinin (Qinghaosu) and the phytochemistry of *Artemisia annua L.* (Qinghao). *Molecules*, **2010**, *15*, 7603-7698.

11. Gong, H. Q.; Wu, Q. X.; Liu, L. L.; Yang, J. L.; Wang, R.; Shi, Y. P. Sesquiterpenoids from the aerial parts of *Inula japonica*. *Helv. Chim. Acta.*, **2011**, *94*, 1269-1276.

12. Shirota, O.; Oribello, J. M.; Sekita, S.; Satake, M. Sesquiterpenes from *Blumea balsamifera*. *J. Nat. Prod.*, **2011**, *74*, 470-476.

13. Garcez, F. R.; Garcez, W. S.; Hamerski, L.; Miranda, A. C. d. M. Eudesmane and rearranged eudesmane sesquiterpenes from *Nectandra cissiflora*. *Qùim. Nova*, **2010**, *33*, 1739-1742.

14. Wu, S. J.; Fotso, S.; Li, F.; Qin, S.; Kelter, G.; Fiebig, H. H.; Laatsch, H. *N*-Carboxamido staurosporine and selina-4(14), 7(11)-diene-8, 9-diol, new metabolites from a marine *Streptomyces* sp. *J. Antibiot.*, **2006**, *59*, 331-337.

15. Yang, Z.; Yang, Y.; Yang, X.; Zhang, Y.; Zhao, L.; Xu, L.; Ding, Z. Sesquiterpenes from the secondary metabolites of *Streptomyces* sp. (YIM 56130). *Chem. Pharm. Bull.*, **2011**, *59*, 1430-1433

16. Ding, L.; Maier, A.; Fiebig, H. H.; Lin, W. H.; Peschel, G.; Hertweck, C. Kandenols A-E, eudesmenes from an endophytic *Streptomyces* sp. of the mangrove tree *Kandelia candel*. *J. Nat. Prod.*, **2012**, *75*, 2223-2227.

17. Ding, L.; Münch, J.; Goerls, H.; Maier, A.; Fiebig, H. H.; Lin, W. H.; Hertweck, C. Xiamycin, a pentacyclic indolosesquiterpene with selective anti-HIV activity from a bacterial mangrove endophyte. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 6685-6687.

18. Ding, L.; Maier, A.; Fiebig, H. H.; Lin, W. H.; Hertweck, C. A family of multicyclic indolosesquiterpenes from a bacterial endophyte. *Org. Biomol. Chem.*, **2011**, *9*, 4029-4031.

19. Xu, Z. L.; Baunach, M.; Ding, L.; Hertweck, C. Bacterial synthesis of diverse indole terpene alkaloids by an unparalleled cyclization sequence. *Angew. Chem. Int. Ed.* **2012**, *51*, 10293-10297.

20. Li, X. L.; Xu, M. J.; Zhao, Y. L.; Xu, J. A novel benzo[f][1,7]naphthyridine produced by *Streptomyces Albogriseolus* from mangrove sediments. *Molecules*, **2010**, *15*, 9298-9307.

21. Xu, M. J.; Liu, X. J.; Zhao, Y. L.; Liu, D.; Xu, Z. H.; Lang, X. M.; Ao, P.; Lin, W. H.; Yang, S. L.; Zhang, Z. G.; Xu, J. Identification and characterization of an anti-fibrotic benzopyran compound isolated from mangrove-derived *Streptomyces xiamenensis*. *Mar. Drugs*, **2012**, *10*, 639-654.

22. Tian, C.; Jiao, X.; Liu, X.; Li, R.; Dong, L.; Liu, X.; Zhang, Z. G.; Xu, J.; Xu, M. J.; Xie, P. First total synthesis and determination of the absolute configuration of 1-*N*-methyl-3-methylamino-[*N*-butanoicacid-3-(9-methyl-8-propen-7-one)-amide]-benzo[*f*][1,7]naphthyridine-2-one, a novel benzonaphthyridine alkaloid. *Tetrahedron Lett.*, **2012**, *53*, 4892-4895.

23. Chen, G. D.; Gao, H.; Tang, J. S.; Huang, Y. F.; Chen, Y.; Wang, Y.; Zhao, H. N.; Lin, H. P.; Xie, Q. Y.; Hong, K.; Li, J.; Yao, X. S. Benzamides and quinazolines from a mangrove actinomycetes *Streptomyces* sp. (No. 061316) and their inhibiting caspase-3 catalytic activity *in vitro*. *Chem. Pharm. Bull.*, **2011**, *59*, 447-451.

24. Ueki, M.; Ueno, K.; Miyadoh, S.; Abe, K.; Shibata, K.;Taniguchi, M.; Oi, S. UK-1, a novel cytotoxic metabolite from *Streptomyces* sp. 517-02. I. Taxonomy, fermentation, isolation, physico-chemical and biological properties. *J. Antibiot.*, **1993**, *46*, 1089-1094.

25. Sommer, P. S.; Almeida, C.; Schneider, K.; Beil, W.; Süssmuth, R. D.; Fiedler, H. P. Nataxazole, a new benzoxazole derivative with antitumor activity produced by *Streptomyces* sp. Tü 6176. *J. Antibiot.*, **2008**, *61*, 683-686.

26. Michel, K. H.; Boeck, L. D.; Hoehn, M. M.; Jones, N. D.; Chaney, M. O. The discovery, fermentation, isolation, and structure of antibiotic A33853 and its tetraacetyl derivative. *J. Antibiot.*, **1984**, *37*, 441-445.

27. Hohmann, C.; Schneider, K.; Bruntner, C.; Irran, E.; Nicholson, G.; Bull, A. T.; Fiedler, H. P. Caboxamycin, a new antibiotic of the benzoxazole family produced by the deep-sea strain *Streptomyces* sp. NTK 937*. *J. Antibiot.*, **2009**, *62*, 99-104.

28. Chu, Y. W.; Li, J. J., Wang, L.; Yu, R. Antifungal antibiotic CAl189 produced by a mangrove endophyte *Streptomyces* sp. A1626. *Chin. J. Antibiot.*, **2011**, *36*, 14-17, 47.

29. Neumann, C. S.; Fujimori, D. G.; Walsh, C. T. Halogenation strategies in natural product biosynthesis. *Chem. Biol.*, **2008**, *15*, 99-109.

30. Li, X. G.; Tang, X. M.; Xiao, J.; Ma, G. H.; Xu, L.; Xie, S. J.; Xu, M. J.; Xiao, X.; Xu J. Harnessing the potential of halogenated natural product biosynthesis by mangrove-derived actinomycetes. *Mar. Drugs*, **2013**, *11*, 3875-3890.

31. Higashide, E; Hatano, K; Shibata, M; Nakazawa, K. Enduracidin, a new antibiotic. I. *Streptomyces fungicidicus* No. B5477, an enduracidin producing organism. *J. Antibiot.*, **1968**, *21*, 126-137.

32. Hu, Y.; MacMillan, J. B. Erythrazoles A-B, cytotoxic benzothiazoles from a marine-derived *Erythrobacter* sp. *Org. Lett.*, **2011**, *13*, 6580-6583.

33. Huang, Z.; Yang, J.; Cai, X.; She, Z.; Lin, Y. A new furanocoumarin from the mangrove endophytic fungus Penicillium sp.(ZH16). *Nat. Prod. Res.*, **2012**, *26*, 1291-1295.

34. Thongbai, B.; Surup, F.; Mohr, K.; Kuhnert, E.; Hyde, K. D.; Stadler, M. Gymnopalynes A and B, chloropropynyl-isocoumarin antibiotics from cultures of the basidiomycete *Gymnopus* sp. *J. Nat. Prod.*, **2013**, *76*, 2141-2144.

35. Yang, J. X.; Chen, Y.; Huang, C.; She, Z.; Lin, Y. A new isochroman derivative from the marine fungus *Phomopsis* sp.(No. ZH-111). *Chem. Nat. Comp.*, **2011**, *47*, 13-16.

36. Pettit, R. K. Mixed fermentation for natural product drug discovery. *Appl. Microbiol. Biotechnol.*, **2009**, *83*,19-25.

37. Li, C. Y.; Zhang, J.; Zhong, J. S.; He, B. J.; Li, R. T.; Liang, Y. C.; Lin, Y. C.; Zhou, S. N. Isolation and identification of the metabolites from the mixed fermentation broth of two mangrove endophytic fungi. *J. South China Agr. Univ.*,

2011, *32*, 117-119, 123.

38. Klaiklay, S.; Rukachaisirikul, V.; Sukpondma, Y.; Phongpaichit, S.; Buatong, J.; Bussaban, B. Metabolites from the mangrove-derived fungus *Xylaria cubensis* PSU-MA34. *Arch. Pharm. Res.*, **2012**, *35*, 1127-1131.

39. Li, S.; Wei, M.; Chen, G.; Lin, Y. Two new dihydroisocoumarins from the endophytic fungus *Aspergillus* sp. collected from the south china sea. *Chem. Nat. Comp.*, **2012**, *48*, 371-373.

40. Rukachaisirikul, V.; Rodglin, A.; Sukpondma, Y.; Phongpaichit, S.; Buatong, J.; Sakayaroj, J. Phthalide and isocoumarin derivatives produced by an *Acremonium* sp. isolated from a mangrove *Rhizophora apiculata*. *J. Nat. Prod.*, **2012**, *75*, 853-858.

41. Wen, L.; Wei, Q.; Chen, G.; Cai, J.; She, Z. Chemical constituents from the mangrove endophytic fungus *Sporothrix* sp. *Chem. Nat. Comp.*, **2013**, *49*, 137-149.

42. Barrow, R. A.; McCulloch, M. W. B. Linear naphtha-γ-pyrones: A naturally occurring scaffold of biological importance. *Mini-Rev. Med. Chem.*, **2009**, *9*, 273-292.

43. Huang. Z.; Yang, R.; Guo, Z.; She, Z. G.; Lin, Y. C. A new naphtho-pyrone from mangrove endophytic fungus ZSU-H26. *Chem. Nat. Comp.*, **2010**, *46*, 15-18.

44. Yang, J.; Xu, F.; Huang, C. ; Li, J.; She, Z.; Pei, Z. ; Lin, Y. Metabolites from the mangrove endophytic fungus *Phomopsis* sp.(# zsu-H76). *Eur. J. Org. Chem.*, **2010**, *19*, 3692-3695.

45. Lin, Z.; Zhu, T.; Wei, H.; Zhang, G.; Wang, H.; Gu, Q. Spicochalasin A and new aspochalasins from the marine-derived fungus *Spicaria elegans*. *Eur. J. Org.*

Chem., **2009**, *18*, 3045-3051.

46. Huang, H. B.; Feng, X. J.; Liu, L.; Chen, B.; Lu, Y. J.; Ma, L.; She, Z. G.; Lin, Y. C. Three dimeric naphtho-γ-pyrones from the mangrove endophytic fungus *Aspergillus tubingensis* isolated from *Pongamia pinnata*. *Planta Med.*, **2010**, *76*, 1888-1891.

47. Huang, H. B.; Xiao, Z. E.; Feng, X. J.; Huang, C. H.; Zhu, X.; Ju, J. H.; Li, M. F.; Lin, Y. C.; Liu, L.; She, Z. G. Cytotoxic naphtho-γ-pyrones from the mangrove endophytic fungus *Aspergillus tubingensis* (GX1-5E). *Helv. Chim. Acta.*, **2011**, *94*, 1732-1740.

48. Klaiklay, S.; Rukachaisirikul, V.; Tadpetch, K.; Sukpondma, Y.; Phongpaichit, S.; Buatong, J.; Sakayaroj, J. Chlorinated chromone and diphenyl ether derivatives from the mangrove-derived fungus *Pestalotiopsis* sp. PSU-MA69. *Tetrahedron*, **2012**, *68*, 2299-2305.

49. Yang, J.; Huang, R.; Qiu, S. X.; She, Z.; Lin, Y. A new isobenzofuranone from the mangrove endophytic fungus *Penicillium* sp.(ZH58). *Nat. Prod. Res.*, **2013**, *27*, 1902-1905.

50. Huang, Z.; Yang, J.; She, Z.; Lin, Y. A new isoflavone from the mangrove endophytic fungus *Fusarium* sp.(ZZF60). *Nat. Prod. Res.*, **2012**, *26*, 11-15.

51. Li, K. K. ; Lu, Y. J.; Song, X. H., She, Z. G. ; Wu, X. W.; An, L. K.; Ye, C. X.; Lin, Y. C. The metabolites of mangrove endophytic fungus Zh6-B1 from the South China Sea. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 3326-3328.

52. Huang, C. H.; Pan, J. H.; Chen, B.; Yu, M.; Huang, H. B.; Zhu, X.; Lu, Y. J.;

She, Z. G.; Lin, Y. C. Three bianthraquinone derivatives from the mangrove endophytic fungus *Alternaria* sp. ZJ9-6B from the South China Sea. *Mar. Drugs*, **2011**, *9*, 832-843.

53. Huang, C.; Jin, H.; Song, B.; Zhu, X.; Zhao, H.; Cai, J.; Lu, Y. J.; Chen, B.; Lin, Y. The cytotoxicity and anticancer mechanisms of alterporriol L, a marine bianthraquinone, against MCF-7 human breast cancer cells. *Appl. Microbial. Biotechnol.*, **2012**, *93*,777-785.

54. Xia, X. K.; Huang, H. R.; She, Z. G.; Shao, C. L.; Liu, F.; Cai, X. L.; Vrijmoed, L. L. P.; Lin, Y. C. ^{1}H and ^{13}C NMR assignments for five anthraquinones from the mangrove endophytic fungus *Halorosellinia* sp. (No. 1403). *Magn. Reson. Chem.*, **2007**, *45*, 1006-1009.

55. Chen, H.; Zhu, X.; Zhong, L. L.; Yang, B.; Li, J.; Wu, J. H.; Chen, S. P.; Lin, Y. C.; Long, Y. H.; She, Z. G. Synthesis and antitumor activities of derivatives of the marine mangrove fungal metabolite deoxybostrycin. *Mar. Drugs*, **2012**, *10*, 2715-2728.

56. Xia, X. K.; Li, Q.; Li, J.; Shao, C. L.; Zhang, J. Y.; Zhang, Y. G.; Liu, X.; Lin, Y. C.; Liu, C. H.; She, Z. G. Two new derivatives of griseofulvin from the mangrove endophytic fungus *Nigrospora* sp.(Strain No. 1403) from *Kandelia candel* (L.) Druce. *Planta Med.*, **2011**, *77*, 1735-1738.

57. Wang, C.; Wang, J.; Huang, Y. H.; Chen, H.; Li, Y.; Zhong, L. L.; Chen, Y.; Chen, S. P.; Wang, J.; Kang, J. L.; Peng, Y.; Yang, B.; Lin, Y. C.; She, Z. G.; Lai, X. M. Anti-mycobacterial activity of marine fungus-derived 4-deoxybostrycin and

nigrosporin. *Molecules*, **2013**, *18*, 1728-1740.

58. Shang, Z.; Li, X. M.; Li, C. S.; Wang, B. G. Diverse secondary metabolites produced by marine-derived fungus *Nigrospora* sp. MA75 on various culture media. *Chem. Biodivers.*, **2012**, *9*, 1338-1348.

59. Klaiklay, S.; Rukachaisirikul, V.,; Phongpaichit, S.; Pakawatchai, C.; Saithong, S.; Buatong, J.; Preedanon, S.; Sakayaroj, J. Anthraquinone derivatives from the mangrove-derived fungus *Phomopsis* sp. PSU-MA214. *Phytochem. Lett.*, **2012**, *5*, 738-742.

60. Sun, H.; Gao, S.; Li, X.; Li, C.; Wang, B. Chemical constituents of marine mangrove-derived endophytic fungus *Alternaria tenuissima* EN-192. *Chinese J. Oceanol. Limnol.*, **2013**, *31*, 464-470.

61. Deng, C. M.; Liu, S. X.; Huang, C. H.; Pang, J. Y.; Lin, Y. C. Secondary metabolites of a mangrove endophytic fungus *Aspergillus terreus* (No. GX7-3B) from the South China Sea. *Mar. Drugs*, **2013**, *11*, 2616-2624.

62. Ebrahim, W.; Aly, A. H.; Mándi, A.; Totzke, F.; Kubbutat, M. H.; Wray, V.; Lin, W. H.; Dai, H. F.; Proksch, P.; Kurtán, T.; Debbab, A. Decalactone derivatives from *Corynespora cassiicola*, an endophytic fungus of the mangrove plant *Laguncularia racemosa*. *Eur. J. Org. Chem.*, **2012**, *2012*, 3476-3484.

63. Yan, H. J.; Li, X. M.; Li, C. S.; Wang, B. G. Alkaloid and anthraquinone derivatives produced by the marine-derived endophytic fungus *Eurotium rubrum*. *Helv. Chim. Acta.*, **2012**, *95*, 163-168.

64. Masters, K. S., Bräse, S. Xanthones from fungi, lichens, and bacteria: The natural products and their synthesis. *Chem. Rev.*, **2012**, *112*, 3717-3776.

65. Huang. Z.; Yang, R.; Guo, Z.; She, Z. G.; Lin, Y. C. A new xanthone derivative from mangrove endophytic fungus No. ZSU-H16. *Chem. Nat. Comp.*, **2010**, *46*, 348-351.

66. Pan, J. H.; Deng, J. J.; Chen, Y. G.; Gao, J. P.; Lin, Y. C.; She, Z. G.; Gu, Y. C. New lactone and xanthone derivatives produced by a mangrove endophytic fungus *Phoma* sp. SK3RW1M from the South China Sea. *Helv. Chim. Acta.*, **2010**, *93*, 1369-1374.

67. Li, C. Y.; Zhang, J.; Shao, C. L.; Ding, W. J.; She, Z.G.; Lin, Y. C. A new xanthone derivative from the co-culture broth of two marine fungi (strain No. E33 and K38). *Chem. Nat. Comp.*, **2011**, 47, 382-384.

68. Huang, Z.; Yang, J.; Lei, F.; She, Z.;Lin, Y. A New Xanthone *O*-glycoside from the mangrove endophytic fungus *Phomopsis* sp. *Chem. Nat. Comp.*, **2013**, *49*, 27-30.

69. Yang, J. X.; Qiu, S. X.; She, Z. G.; Lin, Y. C. A new xanthone derivative from the marine fungus *Phomopsis* sp.(No. SK7RN3G1). *Chem. Nat. Comp.*, **2013**, *49*, 246-248.

70. Isaka, M.; Jaturapat, A.; Rukseree, K.; Danwisetkanjana, K.; Tanticharoen, M.; Thebtaranonth, Y. Phomoxanthones A and B, novel xanthone dimers from the endophytic fungus *Phomopsis* species. *J. Nat. Prod.*, **2001**, *64*, 1015-1018.

71. Rukachaisirikul, V.; Sommart, U.; Phongpaichit, S.; Sakayaroj, J.; Kirtikara, K.

Metabolites from the endophytic fungus *Phomopsis* sp. PSU-D15. *Phytochemistry*, **2008**, *69*, 783-787.

72. Shionoa, Y.; Sasakia, T.; Shibuyaa, F.; Yasudaa, Y.; Kosekia, T.; Supratman, U. Isolation of a phomoxanthone a derivative, a new metabolite of tetrahydroxanthone, from a *Phomopsis* sp isolated from the mangrove, *Rhizhopora mucronata*. *Nat. Prod. Commun.*, **2013**, *8*, 1735-1737.

73. Nawwar, M.; Hussein, S.; Ayoub, N. A.; Hashim, A.; Mernitz, G.; Cuypers, B.; Linscheid, M.; Lindequist, U. Deuteromycols A and B, two benzofuranoids from a Red Sea marine-derived *Deuteromycete* sp. *Arch. Pharm. Res.*, **2010**, *33*, 1729-1733.

74. Cali, V.; Spatafora, C.; Tringali, C. Polyhydroxy-*p*-terphenyls and related *p*-terphenylquinones from fungi: Overview and biological properties. *Stud. Nat. Prod. Chem.*, **2003**, *29*, 263-307.

75. Wei, H.; Inada, H.; Hayashi, A.; Higashimoto, K.; Pruksakorn, P.; Kamada, S.; Arai, M.; Ishida, S.; Kobayashi, M. Prenylterphenyllin and its dehydroxyl analogs, new cytotoxic substances from a marine-derived fungus *Aspergillus candidus* IF10. *J. Antibiot.*, **2007**, *60*, 586-590.

76. Cai, S.; Sun, S.; Zhou, H.; Kong, X.; Zhu, T.; Li, D.; Gu, Q. Prenylated polyhydroxy-*p*-terphenyls from *Aspergillus taichungensis* ZHN-7-07. *J. Nat. Prod.*, **2011**, *74*, 1106-1110.

77. Paul, C.; Pohnert, G. Production and role of volatile halogenated compounds from marine algae. *Nat. Prod. Rep.*, **2011**, *28*, 186-195.

78. Zhang, Y.; Li, X. M.; Shang, Z.; Li, C. S.; Ji, N. Y.; Wang, B. G. Meroterpenoid and diphenyl ether derivatives from *Penicillium* sp. MA-37, a fungus isolated from marine mangrove rhizospheric soil. *J. Nat. Prod.*, **2012**, *75*, 1888-1895.

79. Beau, J.; Mahid, N.; Burda, W. N.; Harrington, L.; Shaw, L. N.; Mutka, T.; Kyle, D. E.; Barisic, B.; Olphen, A.; Baker, B. J. Epigenetic tailoring for the production of anti-infective cytosporones from the marine fungus *Leucostoma persoonii*. *Mar. Drugs*, **2012**, *10*, 762-774.

80. Wang, J.; Lu, Z.; Liu, P.; Wang, Y.; Li, J., Hong, K.,; Zhu, W. Cytotoxic Polyphenols from the fungus *Penicillium expansum* 091006 endogenous with the mangrove plant *Excoecaria agallocha*. *Planta Med.*, **2012**, *78*, 1861-1866.

81. Teuten, E. L.; Xu, L.; Reddy, C. M. Two abundant bioaccumulated halogenated compounds are natural products. *Science*, **2005**, *307*, 917-920.

82. Shimada, A.; Takahashi, I.; Kawano, T.; Kimura, Y. Z. Chloroisosulochrin, chloroisosulochrin dehydrate, and pestheic acid, plant growth regulators, produced by *Pestalotiopsis theae*. *Naturforsch*, **2001**, *56b*, 797-803.

83. Li, J. Y, Strobel, G. A. Jesterone and hydroxy-jesterone antioomycete cyclohexenone epoxides from the endophytic fungus *Pestalotiopsis jesteri*. *Phytochemistry*, **2001**, *57*, 261-265.

84. Wang, J.; Ding, W.; Li, C.; Huang, S.; She, Z.; Lin, Y. A new polysubstituted benzaldehyde from the co-culture broth of two marine fungi (Strains Nos. E33 and K38). *Chem. Nat. Comp.*, **2013**, *49*, 799-802.

85. Gould, B. S.; Raistrick, H. Studies in the biochemistry of micro-organisms: The

crystalline pigments of species in the *Aspergillus glaucus* series. *Biochemical J.*, **1934**, *28*, 1640-1656.

86. Gao, H.; Zhu, T.; Li, D.; Gu, Q.; Liu, W. Prenylated indole diketopiperazine alkaloids from a mangrove rhizosphere soil derived fungus Aspergillus effuses H1-1. *Arch. Pharm. Res.*, **2013**, *36*, 952-956.

87. Deng, H. Y.; Xing, J. G.; Luo, D. Q. Metabolites of endophytic fungus *Pestalotiopsis clavispora* isolated from the stem of *Bruguiera sexangula*. *Mycosystema*, **2011**, *30*, 263–267.

88. Ahmed, S. A.; Bardshiri, E.; McIntyre, C. R.; Simpson, T. J. Biosynthetic-studies on tajixanthone and shamixanthone, polyketide hemiterpenoid metabolites of *Aspergillus variecolor*. *Aust. J. Chem.*, **1992**, *45*, 249-274.

89. Wen, L.; Chen, G.; She, Z.; Yan, C.; Cai, J.; Mu, L. Two new paeciloxocins from a mangrove endophytic fungus *Paecilomyces* sp. *Russ. Chem. Bull.*, **2010**, *59*, 1656-1659.

90. Xing, J. G.; Deng, H. Y.; Luo, D. Q. Two new compounds from an endophytic fungus *Pestalotiopsis heterocornis*. *J. Asian Nat. Prod. Res.*, **2011**, *13*, 1069-1073.

91. Yoshida, E.; Fujimoto, H.;Yamazaki, M. Isolation of three new azaphilones, luteusins C, D, and E, from an ascomycete, talaromyces luteus. *Chem. Pharm. Bull.*, **1996**, *44*, 284-287.

92. Matsuzaki, K.; Tahara, H.; Inokoshi, J.; Tanaka, H.; Masuma, R.; Omura, S. New brominated and halogen-less derivatives and structure-activity relationship of azaphilones inhibiting gp120-CD4 binding. *J. Antibiot.*, **1998**, *51*, 1004-1011.

93. Nam, J. Y.; Kim, H. K.; Kwon, J. Y.; Han, M. Y.; Son, K. H.; Lee, U. C.; Choi, J. D.; Kwon, B. M. 8-*O*-Methylsclerotiorinamine, antagonist of the Grb2-SH2 domain, isolated from *Penicillium multicolor*. *J. Nat. Prod.*, **2000**, *63*, 1303.

94. Clark, R. C.; Lee, S. Y.; Searcey, M.; Boger, D. L. The isolation, total synthesis and structure elucidation of chlorofusin, a natural product inhibitor of the p53-MDM2 protein-protein interaction. *Nat. Prod. Rep.*, **2009**, *26*, 465-477.

95. Musso, L.; Dallavalle, S.; Merlini, L.; Bava, A.; Nasini, G.; Penco, S.; Giannini, G.; Giommarelli, C.; De Cesare, A.; Zuco, V.; Vesci, L.; Pisano, C.; Dal Piaz, F.; De Tommasi, N.; Zunino, F. Natural and semisynthetic azaphilones as a new scaffold for Hsp90 inhibitors. *Bioorg. Med. Chem.*, **2010**, *18*, 6031-6043.

96. Osmanova, N.; Schultze, W.;Ayoub, N. Azaphilones: a class of fungal metabolites with diverse biological activities. *Phytochem. Rev.*, **2010**, *9*, 315-342.

97. Gao, J. M.; Yang, S. X.; Qin, J. C. Azaphilones: chemistry and biology. *Chem. Rev.*, **2013**, *113*, 4755-4811.

98. Chong, R.; King, R. R.; Whalley, W. B. The chemistry of fungi. Part LXI. The synthesis of (±)-sclerotiorin, of (±)-4,6-dimethylocta-*trans*-2,*trans*-4-dienoic acid, and of an analogue of rotiorin. *J. Chem. Soc. C*, **1971**, 3566-3571.

99. Zhu, J.; Germain, A. R.; Porco, J. A. Synthesis of azaphilones and related molecules by employing cycloisomerization of *O*-alkynylbenzaldehydes. *Angew. Chem.*, **2004**, *116*, 1259-1263.

100. Marsini, M. A.; Gowin, K. M.; Pettus, T. R. Total synthesis of (±)-mitorubrinic acid. *Org. Lett.*, **2006**, *8*, 3481-3483.

101. Germain, A. R.; Bruggemeyer, D. M.; Zhu, J.; Genet, C.; O'Brien, P.; Porco Jr, J. A. Synthesis of the azaphilones (+)-sclerotiorin and (+)-8-*O*-methylsclerotiorinamine utilizing (+)-sparteine surrogates in copper-mediated oxidative dearomatization. *J. Org. Chem.*, **2011**, *76*, 2577-2584.

102. Huang, H. B.; Feng, X. J.; Xiao, Z. E.; Liu, L.; Li, H. X.; Ma, L.; Liu, Y. J.; Ju, J. H.; She, Z. G.; Lin, Y. C. Azaphilones and *p*-terphenyls from the mangrove endophytic fungus *Penicillium chermesinum* (ZH4-E2) isolated from the South China Sea. *J. Nat. Prod.*, **2011**, *74*, 997-1002.

103. Liu, D.; Li, X. M.; Meng, L.; Li, C. S.; Gao, S. S.; Shang, Z.; Proksch, P.; Huang, C. G.; Wang, B. G. Nigerapyrones A-H, α-pyrone derivatives from the marine mangrove-derived endophytic fungus *Aspergillus niger* MA-132. *J. Nat. Prod.*, **2011**, *74*, 1787-1791.

104. Kitagawa, M.; Okabe, T.; Ogino, H.; Matsumoto, H.; Suzuki-Takahashi, I.; Kokubo, T.; Higashi, H.; Saitoh, S.; Taya, Y.;Yasuda, H.; Ohba, Y.; Nishimura, S.; Tanaka, N.; Okuyama, A. Butyrolactone I, a selective inhibitor of cdk2 and cdc2 kinase. *Oncogene*, **1993**, *8*, 2425-2432.

105. Shen, Y.; Zou, J.; Xie, D.; Ge, H.; Cao, X.; Dai, J. Butyrolactone and cycloheptanetrione from mangrove-associated fungus *Aspergillus terreus*. *Chem. Pharm. Bull.*, **2012**, *60*, 1437-1441.

106. Ebrahim, W.; Aly, A. H.; Wray, V.; Proksch, P.; Debbab, A. Unusual octalactones from *Corynespora cassiicola*, an endophyte of *Laguncularia racemosa*. *Tetrahedron Lett.*, **2013**, *54*, 6611-6614.

107. Helms, J. B.; Rothman, J. E. Inhibition by brefeldin A of a Golgi membrane enzyme that catalyses exchange of guanine nucleotide bound to ARF. *Nature*, **1992**, *360*, 352-354.

108. Brady, S. F.; Wagenaar, M. M.; Singh, M. P.; Janso, J. E.; Clardy, J. The cytosporones, new octaketide antibiotics isolated from an endophytic fungus. *Org. Lett.*, **2000**, *2*, 4043-4046.

109. Hall, J. D.; Duncan-Gould, N. W.; Siddiqi, N. A.; Kelly, J. N.; Hoeferlin, L. A.; Morrison, S. J.; Wyatt, J. K. Cytosporone E: racemic synthesis and preliminary antibacterial testing. *Bioorg. Med. Chem.*, **2005**, *13*, 1409-1413.

110. Ohzeki, T.; Mori, K. Synthetic racemate and enantiomers of cytosporone E, a metabolite of an endophytic fungus, show indistinguishably weak antimicrobial activity. *Biosci. Biotechnol. Biochem.*, **2003**, *67*, 2584-2590.

111. Rukachaisirikul, V.; Rodglin, A.; Phongpaichit, S.; Buatong, J.; Sakayaroj, J. α-Pyrone and seiricuprolide derivatives from the mangrove-derived fungi *Pestalotiopsis* spp. PSU-MA92 and PSU-MA119. *Phytochem. Lett.*, **2012**, *5*, 13-17.

112. Xu, J.; Aly, A. H.; Wray, V.; Proksch, P. Polyketide Derivatives of Endophytic Fungus *Pestalotiopsis* sp. Isolated from the Chinese Mangrove Plant *Rhizophora mucronata*. *Tetrahedron Lett.*, **2011**, *52*, 21-25.

113. Song, Y.; Wang, J.; Huang, H.; Ma, L.; Wang, J.; Gu, Y.; Liu, L; Lin, Y. Four eremophilane sesquiterpenes from the mangrove endophytic fungus *Xylaria* sp. BL321. *Mar. Drugs*, **2012**, *10*, 340-348.

114. Kiriyama, N.; Nitta, K.; Sakacuchi, Y.; Taguchi, Y.; Yamamoto, Y.

Studies on the metabolic products of Aspergillus terreus. III. Metabolites of the strain IFO 8835. (1). *Chem. Pharm. Bull.*, **1977**, *25*, 2593-2601.

115. Haritakun, R.; Rachtawee, P.; Chanthaket, R.; Boonyuen, N.; Isaka, M. Butyrolactones from the fungus *Aspergillus terreus* BCC 4651. *Chem. Pharm. Bull.*, **2010**, *58*, 1545-1548.

116. Nishio, K.; Ishida, T.; Arioka, H.; Kurokawa, H.; Fukuoka, K.; Nomoto, T.; Fukumoto, H.; Yokote, H.; Saijo, N. Antitumor effects of butyrolactone I, a selective cdc2 kinase inhibitor, on human lung cancer cell lines. *Anticancer Res.*, **1995**, *16*, 3387-3395.

117. Schimmel, T. G.; Coffman, A. D.; Parsons, J. Effect of butyrolactone I on the producing fungus, *Aspergillus terreus*. *Appl. Environ. Microbiol.*, **1998**, *64*, 3707-3712.

118. Ojima, N.; Takenaka, S.; Seto, S. New butenolides from *Aspergillus terreus*. *Phytochemistry*, **1973**, *12*, 2527-2529.

119. Caufield, C. E.; Antane, S. A.; Morris, K. M.; Naughton, S. M.; Quagliato, D. A.; Andrae, P. M.; Enos, A.; Chiarello, J. F. *PCT Int. Appl.*, **2005**, WO 2005019196, 118.

120. Cruz, P. G.; Auld, D. S.; Schultz, P. J.; Lovell, S.; Battaile, K. P.; MacArthur, R.; Shen, M.; Tamayo-Castillo, G.; Inglese, J.; Sherman, D. H. Titration-based screening for evaluation of natural product extracts: identification of an aspulvinone family of luciferase inhibitors. *Chem. Biol.*, **2011**, *18*, 1442-1452.

121. Vertesy, L.; Burger, H. J.; Kenja, J.; Knauf, M.; Kogler, H.; Paulus, E. F.;

Ramakrishna, N. V.; Swamy, K. H.; Vijayakumar, E. K.; Hammann, P. Kodaistatins, novel inhibitors of glucose-6-phosphate translocase T1 from *Aspergillus terreus* thom DSM 11247: Isolation and structural elucidation. *J. Antibiot.*, **2000**, *53*, 677-686.

122. Gao, H.; Guo, W.; Wang, Q.; Zhang, L.; Zhu, M. ; Zhu, T. ; Gu, Q.; Li, D. Aspulvinones from a mangrove rhizosphere soil-derived Fungus *Aspergillus terreus* Gwq-48 with anti-influenza A viral (H1N1) activity. *Bioorg. Med. Chem. Lett.*, **2013**, *23*, 1776-1778.

123. C Pedras, M. S.; Chumala, P. B. Phomapyrones from blackleg causing phytopathogenic fungi: isolation, structure determination, biosyntheses and biological activity. *Phytochemistry*, **2005**, *66*, 81-87.

124. Yang, X. L.; Li, Z. Z. New spiral γ-lactone enantiomers from the plant endophytic fungus *Pestalotiopsis foedan*. *Molecules*, **2013**, *18*, 2236-2242.

125. Dai, J.; Krohn, K.; Flörke, U.; Pescitelli, G.; Kerti, G.; Papp, T.; Kövér, K. E.; Bényei, A. C.; Draeger, S.; Schulz, B.; Kurtán, T. Curvularin-type metabolites from the fungus *Curvularia* sp. isolated from a marine alga. *Eur. J. Org. Chem.*, **2011**, *36*, 6928-6937.

126. Rudolph, K.; Serwe, A.; Erkel, G. Inhibition of TGF-β signaling by the fungal lactones (*S*)-curvularin, dehydrocurvularin, oxacyclododecindione and galiellalactone. *Cytokine*, **2013**, *61*, 285-296.

127. Aly, A. H.; Edrada-Ebel, R.; Wray, V.; Proksch, P. Antitrypanosomal metabolites from an endophytic *Penicillium* sp. isolated from *Limonium tubiflorum*.

Planta Med., **2010**, *76*, 402.

128. Schmidt, N.; Art, J.; Forsch, I.; Werner, A.; Erkel, G.; Jung, M.; Horke, S.; Kleinert, H.; Pautz, A. The Anti-Inflammatory fungal compound (*S*)-curvularin reduces proinflammatory gene expression in an *in vivo* model of rheumatoid arthritis. *J. Pharmacol. Exp. Ther.*, **2012**, *343*, 106-114.

129. Xu, Y.; Espinosa-Artiles, P.; Schubert, V.; Xu, Y. M.; Zhang, W.; Lin, M.; Gunatilaka, A. A. L.; Süssmuth, R.; Molnár, I. Characterization of the biosynthetic genes for 10, 11-dehydrocurvularin, a heat shock response-modulating anticancer fungal polyketide from *Aspergillus terreus*. *Appl. Environ. Microb.*, **2013**, *79*, 2038-2047.

130. Meng, L. H.; Li, X. M.; Lv, C. T.; Li, C. S.; Xu, G. M.; Huang, C. G.; Wang, B. G. Sulfur-containing cytotoxic curvularin macrolides from *Penicillium sumatrense* MA-92, a fungus obtained from the rhizosphere of the mangrove *Lumnitzera racemosa*. *J. Nat. Prod.*, **2013**, *76*, 2145-2149.

131. Rönsberg, D.; Debbab, A.; Mándi, A.; Wray, V.; Dai, H. F.; Kurtán, T.; Proksch, P.; Aly, A. H. Secondary metabolites from the endophytic fungus *Pestalotiopsis virgatula* isolated from the mangrove plant *Sonneratia caseolaris*. *Tetrahedron Lett.*, **2013**, *54*, 3256-3259.

132. Jiang, G. C.; Lin, Y. C.; Zhou, S. N.; Vrijmoed, L. L. P.; Jones, E. D. G. Studies on the secondary metabolites of mangrove fungus No. 1403 from the South China Sea. *Acta Sci. Nat. Univ. Sunyatseni*, **2000**, *39*, 68-72.

133. Rønnest, M. H.; Rebacz, B.; Markworth, L.; Terp, A. H.; Larsen, T. O.;

Kräimer, A.; Clausen, M. H. Synthesis and structure-activity relationship of griseofulvin analogues as Inhibitors of centrosomal clustering in cancer cells. *J. Med. Chem.*, **2009**, *52*, 3342-3347.

134. Wen, L.; Guo, Z.; Li, Q.; Zhang, D.; She, Z.; Vrijmoed, L. L. A new griseofulvin derivative from the mangrove endophytic fungus *Sporothrix* sp. *Chem. Nat. Comp.*, **2010**, *46*, 363-365.

135. Liu, F.; Cai, X. L.; Yang, H.; Xia, X. K.; Guo, Z. Y.; Yuan, J.; Li, M. F.; She, Z. G.; Lin, Y. C. The bioactive metabolites of the mangrove endophytic fungus *Talaromyces* sp. ZH-154 isolated from *Kandelia candel* (L.) Druce. *Planta Med.*, **2010**, *76*, 185-189.

136. Zeng, Y. B.; Wang, H.; Zuo, W. J.; Zheng, B.;Yang, T.; Dai, H. F.; Mei, W. L. A fatty acid glycoside from a marine-derived fungus isolated from mangrove plant *Scyphiphora hydrophyllacea*. *Mar. Drugs*, **2012**, *10*, 598-603.

137. Li, D. H.; Liang, Z. Y.; Guo, M. F.; Zhou, J.; Yang, X. B.; Xu**,** J. Study on the chemical composition and extraction technology optimization of essential oil from *Wedelia trilobata* (L.) Hitchc. *Afri. J. Biotechnol.* **2012**, *11*(20), 4513-4517.

138. Klaiklay, S.; Rukachaisirikul, V.; Phongpaichit, S.; Buatong, J.; Preedanon, S.; Sakayaroj, J. Flavodonfuran: a new difuranylmethane derivative from the mangrove endophytic fungus *Flavodon flavus* PSU-MA201. *Nat. Prod. Res.*, **2012**, 1-5.

139. Sebastianes, F. L.; Cabedo, N.; El Aouad, N.; Valente, A. M.; Lacava, P. T.; Azevedo, J. L.; Pizzirani-Kleiner, A. A.; Cortes, D. 3-Hydroxypropionic acid as an antibacterial agent from endophytic fungi *Diaporthe phaseolorum*. *Curr.*

Microbiol., **2012**, *65*, 622-632.

140. Bhimba, B. V.; Pushpam, A. C.; Arumugam, P.; Prakash, S. Phthalate derivatives from the marine fungi *Phoma herbarum* VB7. *Int. J. Biol. Pharma. Res.*, **2012**, *3*, 507-512.

141. Nakahara, S.; Kusano, M.; Fujioka, S.; Shimada, A.; Kimura, Y. Penipratynolene, a novel nematicide from *Penicillium bilaiae* Chalabuda. *Biosci. Biotechnol. Biochem.*, **2004**, *68*, 257-259.

142. Baldoqui, D. C.; Kato, M. J.; Cavalheiro, A. J.; Bolzani, V. D. S.; Young, M. C. M.; Furlan, M. A chromene and prenylated benzoic acid from *Piper aduncum*. *Phytochemistry*, **1999**, *51*, 899-902.

143. Casteel, D. A. Peroxy natural products. *Nat. Prod. Rep.*, **1999**, *16*, 55-73.

144. Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. V. Natural peroxy anticancer agents. *Mini-Rev. Med. Chem.*, **2007**, *7*, 571-589.

145. Dembitsky, V. M. Bioactive peroxides as potential therapeutic agents. *Eur. J. Med. Chem.*, **2008**, *43*, 223-251.

146. Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. Artemisinin and the antimalarial endoperoxides: from herbal remedy to targeted chemotherapy. *Microbiol. Rev.*, **1996**, *60*, 301-315.

147. Chokpaiboon, S.; Sommit, D.; Teerawatananond, T.; Muangsin, N.; Bunyapaiboonsri, T.; Pudhom, K. Cytotoxic nor-chamigrane and chamigrane endoperoxides from a basidiomycetous fungus. *J. Nat. Prod.*, **2010**, *73*, 1005-1007.

148. Chokpaiboon, S.; Sommit, D.; Bunyapaiboonsri, T.; Matsubara, K.; Pudhom,

K. Antiangiogenic effect of chamigrane endoperoxides from a Thai mangrove-derived fungus. *J. Nat. Prod.*, **2011**, *74*, 2290-2294.

149. Li, H.; Huang, H.; Shao, C.; Huang, H.; Jiang, J.; Zhu, X.; Liu, Y.; Liu, L.; Lu, Y. J.; Li, M. F.; Lin, Y. C.; She, Z. Cytotoxic norsesquiterpene peroxides from the endophytic fungus *Talaromyces flavus* isolated from the mangrove plant *Sonneratia apetala*. *J. Nat. Prod.*, **2011**, *74*, 1230-1235

150. Zang, L. Y.; Wei, W.; Guo, Y.; Wang, T.; Jiao, R. H.; Ng, S. W.; Tan, R. X.; Ge, H. M. Sesquiterpenoids from the mangrove-derived endophytic fungus *Diaporthe* sp. *J. Nat. Prod.*, **2012**, *75*, 1744-1749.

151. Fraga, B. M. Natural sesquiterpenoids. *Nat. Prod. Rep.*, **2011**, *28*, 1580-1610.

152. Fraga, B. M. Natural sesquiterpenoids. *Nat. Prod. Rep.*, **2013**, *30*, 1226-1264.

153. Song, Y. X.; Wang, J.; Li, S. W.; Li, S. W.; Cheng, B.; Li, L.; Chen, B.; Liu, L.; Lin, Y. C.; Gu, Y. C. Metabolites of the mangrove fungus *Xylaria* sp. BL321 from the south China sea. *Planta Med.*, **2012**, *78*, 172-176.

154. Ayer, W. A.; Cruz, E. R. The tremulanes, a new group of sesquiterpenes from the aspen rotting fungus *Phellinus tremulae*. *J. Org. Chem.*, **1993**, *58*, 7529-7534.

155. Singh, S. B.; Felock, P.; Hazuda, D. J. Chemical and enzymatic modifications of integric acid and HIV-1 integrase inhibitory activity. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 235-238.

156. Ichihara, A.; Sawamura, S.; Sakamura, S. Structures of altiloxins A and B, phytotoxins from *Phoma asparagi* sacc. *Tetrahedron Lett.*, **1984**, *25*, 3209-3212.

157. Hemberger, Y.;[†] Xu, J.;[†] Wray, V.; Proksch, P.; Wu J.; Bringmann, G.

Pestalotiopens A and B: Stereochemically challenging flexible sesquiterpene-cyclopaldic acid hybrids from *Pestalotiopsis* sp. *Chem. Eur. J.*, **2013**, *19*, 15556-15564.

158. Deng, C. M.; Huang, C. H.; Wu, Q. L.; Pang, J. Y.; Lin, Y. C. A new sesquiterpene from the mangrove endophytic fungus *Aspergillus terreus* (No. GX7-3B). *Nat. Prod. Res.*, **2013**, *27*, 1882-1887.

159. Chinworrungsee, M.; Wiyakrutta, S.; Sriubolmas, N.; Chuailua, P.; Suksamrarn, A. Cytotoxic activities of trichothecenes isolated from an endophytic fungus belonging to order *Hypocreales*. *Arch. Pharm. Res.*, **2008**, *31*, 611-616.

160. Ayer, W. A.; Miao, S. Secondary metabolites of the aspen fungus *Stachybotrys cylindrospora*. *Can. J. Chem.*, **1993b**, *71*, 487-493.

161. Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. Taxine. Part IV. The constitution of taxine-I. *J. Chem. Soc. (C)*, **1966**, 1933-1945.

162. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. Plant antitumor agents. VI. Isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. *J. Am. Chem. Soc.*, **1971**, *93*, 2325-2327.

163. Wang, Y. F.; Shi, Q. W.; Dong, M.; Kiyota, H.; Gu, Y. C.; Cong, B. Natural taxanes: developments since 1828. *Chem. Rev.*, **2011**, *111*, 7652-7709.

164. Stierle, A.; Strobel, G.; Stierle, D. Taxol and taxane production by *Taxomyces andreanae*. *Science*, **1993**, *260*, 214-216.

165. Stierle, A.; Strobel, G.; Stierle, D.; Grothaus, P.; Bignami, G. The search for taxol producing microorganisms among the endophytic fungi of the Pacific yew,

Taxus brevifolia. *J. Nat. Prod.*, **1995**, *58*, 1315-1324.

166. Strobel, G.; Yang, X. S.; Sears, J.; Kramer, R.; Sidhu, R. S.; Hess, W. M. Taxol from *Pestalotiopsis microspora*, an endophytic fungus of *Taxus wallachiana*. *Microbiology*, **1996**, *142*, 435-440.

167. Chen, J.; Qiu, X.; Wang, R.; Duan, L.; Chen, S.; Luo, J.; Kong, L. Inhibition of human gastric carcinoma cell growth in vitro and in vivo by cladosporol isolated from the paclitaxel-producing strain *Alternaria alternata* var. monosporus. *Biol. Pharm. Bull.*, **2009**, *32*, 2072-2074.

168. Xu, F.; Tao, W.; Cheng, L.; Guo, L. Strain improvement and optimization of the media of taxol-producing fungus *Fusarium maire*. *Biochem. Eng. J.*, **2006**, *31*, 67-73.

169. Li, J. Y.; Sidhu, R. S.; Ford, E. J.; Long, D. M.; Hess, W. M.; Strobel, G. A. The induction of taxol production in the endophytic fungus—*Periconia* sp from *Torreya grandifolia*. *J. Ind. Microbiol. Biot.*, **1998**, *20*, 259-264.

170. Elavarasi, A.; Rathna, G. S.; Kalaiselvam, M. Taxol producing mangrove endophytic fungi *Fusarium oxysporum* from *Rhizophora annamalayana*. *Asian Pac. J. Trop. Biomed.*, **2012**, *2*, S1081-S1085.

171. Ebel, R. Terpenes from marine-derived fungi. *Mar. Drugs*, **2010**, *8*, 2340-2368.

172. Cueto, M.; Jensen, P. R.; Fenical, W. Aspergilloxide, a novel sesterterpene epoxide from a marine-derived fungus of the genus *Aspergillus*. *Org. Lett.*, **2002**, *4*, 1583-1585.

173. Renner, M. K.; Jensen, P. R.; Fenical, W. Mangicols: Structures and biosynthesis of a new class of sesterterpene polyols from a marine fungus of the genus *Fusarium*. *J. Org. Chem.*, **2000**, 65, 4843-4852.

174. Huang, X. S.; Huang, H. B.; Li, H. X.; Sun, X. F.; Huang, H. R.; Lu, Y. J.; Lin, Y. C.; Long, Y. H.; She, Z. G. Asperterpenoid A, a new sesterterpenoid as an inhibitor of *Mycobacterium tuberculosis* protein tyrosine phosphatase B from the culture of *Aspergillus* sp. 16-5c. *Org. Lett.*, **2013**, *15*, 721-723.

175. Xiao, Z. E.; Huang, H. R.; Shao, C. L.; Xia, X. K.; Ma, L.; Huang, X. S.; Lu, Y. J.; Lin, Y. C.; She, Z. G. Asperterpenols A and B, new sesterterpenoids isolated from a mangrove endophytic fungus *Aspergillus* sp. 085242. *Org. Lett.*, **2013**, *15*, 2522-2525.

176. Luo, D. Q.; Deng, H. Y.; Yang, X. L.; Shi B. Z.; Zhang J. Z. Oleanane-type triterpenoids from the endophytic fungus *Pestalotiopsis clavispora* isolated from the Chinese mangrove plant *Bruguiera sexangula*. *Helv. Chim. Acta.*, **2011**, *94*, 1041-1047.

177. Menna, M.; Imperatore, C.; D'Aniello, F.; Aiello, A. Meroterpenes from Marine invertebrates: Structures, occurrence, and ecological implications. *Mar. Drugs*, **2013**, *11*, 1602-1643.

178. Schurmann, B. T. M.; Sallum, W. S. T.; Takahashi, J. A. Austin, dehydroaustin and other metabolites from *Penicillium brasilianum*. *Quim. Nova*, **2010**, *33*, 1044-1046.

179. Geris dos Santos, R.M.; Rodrigues-Filho, E. Meroterpenes from *Penicillium* sp.

found in associating with *Melia azedarach*. *Phytochemistry*, **2002**, *61*, 907-912.

180. Geris dos Santos, R.M.; Rodrigues-Filho, E. Structures of meroterpenes produced by *Penicillium* sp., an endophytic fungus found associated with *Melia azedarach*. *J. Braz. Chem. Soc.*, **2003**, *14*, 722-727.

181. Chexal, K. K.; Springer, J. P.; Clardy, J.; Cole, R. J.; Kirksey, J. W.; Domer, J. W.; Cutler, H. G.; Sterawter, B. J. Austin, a novel polyisoprenoid mycotoxin from *Aspergillus ustus*. *J. Am. Chem. Soc.*, **1976**, *98*, 6748-6750.

182. Geris, R.; Rodrigues-Fo, E.; Garcia da Silva, H. H.; Garcia da Silva, I. Larvicidal effects of fungal meroterpenoids in the control of *Aedes aegypti* L., the main vector of dengue and yellow fever. *Chem. Biodivers.*, **2008**, *5*, 341-345.

183. Hayashi, H.; Mukaihara, M.; Murao, S.; Arai, M.; Lee, A. Y.; Clardy, J. Acetoxydehydroaustin, a new bioactive compound, and related compound neoaustin from *Penicillium* sp. MG-11. *Biosci. Biotechnol. Biochem.*, **1994**, *58*, 334-338.

184. Song, Y. X.; Qiao, L. T.; Wang, J. J.; Zeng, H. M.; She, Z. G.; Miao, C. D.; Hong, K.; Gu, Y. C.; Liu, L; Lin, Y. C. Two new meroterpenes from the mangrove endophytic fungus *Aspergillus* sp. 085241B. *Helv. Chim. Acta.*, **2011**, *94*, 1875-1880.

185. Zhang, G. J.; Sun, S. W.; Zhu, T. J.; Lin, Z. J.; Gu, J. Y.; Li, D. H.; Gu, Q. Q. Antiviral isoindolone derivatives from an endophytic fungus *Emericella* sp. associated with *Aegiceras corniculatum*. *Phytochemistry*, **2011**, *72*, 1436-1442.

186. Kataoka, S.; Furutani, S.; Hirata, K.; Hayashi, H.; Matsuda, K. Three Austin

family compounds from *Penicillium brasilianum* exhibit selective blocking action on cockroach nicotinic acetylcholine receptors. *Neuro Toxicol.*, **2011**, *32*, 123-129.

187. Xu, J.;Ebada. S. S.; Proksch, P. Chemistry and bioactivity of natural products from the fungal genus *Pestalotiopsis*. *Fungal Divers.*, **2010**, *44*, 15-31.

188. Huang, X.; Sun, X.; Ding, B.; Lin, M.; Liu, L.; Huang, H.; She, Z. A New anti-acetylcholinesterase α-pyrone meroterpene, arigsugacin I, from mangrove endophytic fungus *Penicillium* sp. sk5GW1L of *Kandelia candel*. *Planta Med.*, **2013**, *79*, 1572-1575.

189. Peng, X.; Wang, Y.; Sun, K.; Liu, P.; Yin, X.; Zhu, W. Cerebrosides and 2-pyridone alkaloids from the halotolerant fungus *Penicillium chrysogenum* grown in a hypersaline medium. *J. Nat. Prod.*, **2011**, *74*, 1298-1302.

190. Aly, A. H.; Debbab, A.;Proksch, P. Fungal endophytes: unique plant inhabitants with great promises. *Appl. Microbiol. Biotechnol.*, **2011**, *90*, 1829-1845.

191. Micetich, R. G.; MacDonald, J. C. Metabolites of *Aspergillus sclerotiorum* Huber. *J. Chem. Soc.*, **1964**, 1507-1510.

192. Zhu, F.; Chen, G.; Chen, X.; Huang, M.; Wan, X. Aspergicin, a new antibacterial alkaloid produced by mixed fermentation of two marine-derived mangrove epiphytic fungi. *Chem. Nat. Comp.*, **2011**, *47*, 767-769.

193. Wang, J.; Wang, L.; Chang, M.; He, R. F.; Zhang, Q. H.; Ye, B. P. The endophytic fungus AGR12 in the stem of *Rhizophora stylosa* Grif and its antibacterial metabolite. *Chin. J. Antibiot.*, **2011**, *36*, 102-106.

194. Wheeler, M. H.; Stipanovic, R. D.; Puckhaber, L. S. Phytotoxicity of equisetin

and *epi*-equisetin isolated from *Fusarium equiseti* and *F. pallidoroseum*. *Mycol. Res.*, **1999**, *103*, 967-973.

195. Burmeister, H. R.; Bennett, G. A.; Vesonder, R. F.; Hesseltine, C. W. Antibiotic produced by *Fusarium equiseti* NRRL 5537. *Antimicrob. Agents Chemother.*, **1974**, *5*, 634-639.

196. König, T.; Kapus, A.; Sarkadi, B. Effects of equisetin on rat liver mitochondria: evidence for inhibition of substrate anion carriers of the inner membrane. *J. Bioenerg. Biomembr.*, **1993**, *25*, 537-545.

197. Ding, L.; Dahse, H. M.; Hertweck, C. Cytotoxic alkaloids from *Fusarium incarnatum* associated with the mangrove tree *Aegiceras corniculatum*. *J. Nat. Prod.*, **2012**, *75*, 617-621.

198. Putri, S. P.; Kinoshita, H.; Ihara, F.; Igarashi, Y.; Nihira, T. Farinomalein, a maleimide-bearing compound from the entomopathogenic fungus *Paecilomyces farinosus*. *J. Nat. Prod.*, **2009**, *72*, 1544-1546.

199. Xu, J.; Kjer, J.; Sendker, J.; Wray, V.; Guan, H. S.; Edrada, R. A.; Müller, W. E. G.; Bayer, M.; Lin, W. H.; Wu, J.; Proksch, P. Cytosporones, coumarins, and an alkaloid from the endophytic fungus *Pestalotiopsis* sp. isolated from the Chinese mangrove plant *Rhizophora mucronata*. *Bioorg. Med. Chem.*, **2009**, *17*, 7362-7367.

200. El Amrani, M.; Debbab, A.; Aly, A. H.; Wray, V.; Dobretsov, S.; Müller, W. E.; Lin, W. H.; Lai, D. W.; Proksch, P. Farinomalein derivatives from an unidentified endophytic fungus isolated from the mangrove plant *Avicennia marina*. *Tetrahedron Lett.*, **2012**, *53*, 6721-6724.

201. Scherlach, K.; Hertweck, C. Discovery of aspoquinolones A-D, prenylated quinoline-2-one alkaloids from *Aspergillus nidulans*, motivated by genome mining. *Org. Biomol. Chem.*, **2006**, *4*, 3517-3520.

202. Liu, T.; Li, Z. L.; Wang, Y.; Tian, L.; Pei, Y. H.; Hua, H. M. A new alkaloid from the marine-derived fungus *Hypocrea virens*. *Nat. Prod. Res.*, **2011**, *25*, 1596-1599.

203. An, C. Y.**;** Li, X. M.**;** Luo, H.**;** Li, C. S.**;** Wang, M. H.**;** Xu, G. M.**;** Wang, B. G. 4-Phenyl-3, 4-dihydroquinolone derivatives from *Aspergillus nidulans* MA-143, an endophytic fungus isolated from the mangrove plant *Rhizophora stylosa*. *J. Nat. Prod.*, **2013a**, *76*, 1896-1901.

204. Zhu, F.; Chen, G.; Wu, J.; Pan, J. Structure revision and cytotoxic activity of marinamide and its methyl ester, novel alkaloids produced by co-cultures of two marine-derived mangrove endophytic fungi. *Nat. Prod. Res.*, **2013**, 27, 1960-1964.

205. Li, D. L.; Li, X. M.; Li, T. G.; Dang, H. Y.; Wang, B. G. Dioxopiperazine alkaloids produced by the marine mangrove derived endophytic fungus *Eurotium rubrum*. *Helv. Chim. Acta.*, **2008**, *91*, 1888-1893.

206. Liu, M. T.; Lin, S.; Gan, M. L.; Chen, M. H.; Li, L.; Wang, S. J.; Zi, J. C.; Fan, X. N.; Liu, Y.; Si, Y. K.; Yang, Y. C.; Chen X. G.; Shi, J. G. Yaoshanenolides A and B: New spirolactones from the bark of *Machilus yaoshansis*. *Org. Lett.*, **2012**, *14*, 1004-1007.

207. Dossena, A.; Marchelli, R.; Pochini, A. New metabolites of *Aspergillus amstelodami* related to the biogenesis of neoechinulin. *J. Chem. Soc., Chem.*

Commun., **1974**, 771-772.

208. Sun, S. W.; Ji, C. Z.; Gu, Q. Q.; Li, D. H.; Zhu, T. J. Three new polyketides from marine-derived fungus *Aspergillus glaucus* HB1-19. *J. Asian Nat. Prod. Res.*, **2013**, *15*, 956-961

209. Sokolov, L. B.; Alekseeva, L. E.; Kul'bakh, V. O.; Kuznetsova, N. A.; Nyn, V. S. Study of the chemical composition of aspergin--a metabolite from *Aspergillus* sp. *Antibiotiki*, **1971**, *16*, 504-510.

210. Gao, H.; Liu, W.; Zhu, T.; Mo, X.; Mándi, A.; Kurtán, T.; Li, J.; Ai, J.; Gu, Q. Q.; Li, D. Diketopiperazine alkaloids from a mangrove rhizosphere soil derived fungus *Aspergillus effuses* H1-1. *Org. Biomol. Chem.*, **2012**, *10*, 9501-9506.

211. Saikia, S.; Nicholson, M. J.; Young, C.; Parker, E. J.; Scott, B. The genetic basis for indole-diterpene chemical diversity in filamentous fungi. *Mycol. Res.*, **2008**, *112*, 184-199.

212. Byrne, K. M.; Smith, S. K.; Ondeyka, J. G. Biosynthesis of nodulisporic acid A: precursor studies. *J. Am. Chem. Soc.*, **2002**, *124*, 7055-7060.

213. Li, C.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. Thiersinines A and B: novel antiinsectan indole diterpenoids from a new fungicolous *Penicillium* species (NRRL 28147). *Org. Lett.*, **2002**, *18*, 3095-3098.

214. Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Singh, S. B. Nodulisporic acid A, a novel and potent insecticide from a *Nodulisporium* sp. Isolation, structure determination,

and chemical transformations. *J. Am. Chem. Soc.*, **1997**, *119*, 8809-8816.

215. Hensens, O. D.; Ondeyka, J. G.; Dombrowski, A. W.; Ostlind, D. A.; Zink, D. L. Isolation and structure of nodulisporic acid A_1 and A_2, novel insecticides from a *Nodulisporium* sp. *Tetrahedron Lett.*, **1999**, *40*, 5455-5458.

216. Knaus, H. G.; Eberhart, A.; Glossmann, H.; Munujos, P.; Kaczorowski, G. J.; McManus, O. B.; Lee, S. H.; Schmalhofer, W. A.; Garcia-Calvo, M.; Helms, L. M. H.; Sanchez, M.; Giangiacomo, K.; Reuben, J. P.; Smith, A. B.; Kaczorowshi, G.; Garcia, M. L. Tremorgenic indole alkaloids potently inhibit smooth muscle high-conductance calcium-activated potassium channels. *Biochemistry*, **1994**, *33*, 5819-5828.

217. Qiao, M. F.; Ji, N. Y.; Liu, X. H.; Li, K.; Zhu, Q. M.; Xue, Q. Z. Indoloditerpenes from an algicolous isolate of *Aspergillus oryzae*. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 5677-5680.

218. Ding, L.; Maier, A.; Fiebig, H. H.; Görls, H.; Lin, W. H.; Peschel, G.; Hertweck, C. Divergolides A-D from a Mangrove endophyte reveal an unparalleled plasticity in ansa-macrolide biosynthesis. *Angew. Chem. Int. Ed.* **2011**, *50*, 1630-1634.

219. Fan, Y.; Wang, Y.; Liu, P.; Fu, P.; Zhu, T.; Wang, W.; Zhu, W. Indole-diterpenoids with anti-H1N1 activity from the aciduric fungus *Penicillium camemberti* OUCMDZ-1492. *J. Nat. Prod.*, **2013**, *76*, 1328-1336.

220. Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Rinehart, K. L. Eudistomins A, D, G, H, I, J, M, N, O, P, and Q, bromo-, hydroxyl-, pyrrolyl-, and

1-pyrrolinyl-β-carbolines from the antiviral caribbean tunicate *Eudistoma olivaceum*. *J. Am. Chem. Soc.*, **1984**, *106*, 1526-1528.

221. Nakamura, H.; Deng, S.; Kobayashi, J. I.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T.; Hirata, Y. Keramamine-A and -B, novel antimicrobial alkaloids from the Okinawan marine sponge *Pellina* sp. *Tetrahedron Lett.*, **1987**, *28*, 621-624.

222. Abe, N.; Nakakita, Y.; Nakamura, T.; Enoki, N.; Uchida, H.; Takeo, S.; Munekata, M. Novel cytocidal compounds, oxopropalines from *Streptomyces* sp. G324 producing lavendamycin. I. Taxonomy of the producing organism, fermentation, isolation and biological activities. *J. Antibiot.*, **1993a**, *46*, 1672-1677.

223. Abe, N.; Enoki, N.; Nakakita, Y.; Uchida, H.; Nakamura, T.; Munekata, M. Novel cytocidal compounds, oxopropalines from *Streptomyces* sp. G324 producing lavendamycin. II. Physico-chemical properties and structure elucidations. *J. Antibiot.*, **1993**, *46*, 1678-1686.

224. Larsen, L. K.; Moore, R. E.; Patterson, G. M. β-Carbolines from the blue-green alga *Dichothrix baueriana*. *J. Nat. Prod.*, **1994**, *57*, 419-421.

225. Peng, J.; Lin, T.; Wang, W.; Xin, Z.; Zhu, T.; Gu, Q.; Li, D. Antiviral alkaloids produced by the mangrove-derived fungus *Cladosporium* sp. PJX-41. *J. Nat. Prod.*, **2013**, *76*, 1133-1140.

226. An, C. Y.; Li, X. M.; Li, C. S.; Wang, M. H.; Xu, G. M.; Wang, B. G. Aniquinazolines A-D, four new quinazolinone alkaloids from marine-derived endophytic fungus *Aspergillus nidulans*. *Mar. Drugs*, **2013**, *11*, 2682-2694.

227. Ebrahim, W.; Kjer, J.; El Amrani, M.; Wray, V.; Lin, W.; Ebel, R.; Lai, D. W.; Proksch, P. Pullularins E and F, two new peptides from the endophytic fungus *Bionectria ochroleuca* isolated from the mangrove plant *Sonneratia caseolaris*. *Mar. Drugs*, **2012**, *10*, 1081-1091.

228. Singh, S. B.; Zink, D. L.; Polishook, J. D.; Dombrowski, A. W.; Darkin-Rattray, S. J.; Schmatz, D. M.; Goetz, M. A. Apicidins: novel cyclic tetrapeptides as coccidiostats and antimalarial agents from *Fusarium pallidoroseum*. *Tetrahedron Lett.*, **1996**, *37*, 8077-8080.

229. Amagata, T**.;** Morinaka, B. I**.;** Amagata, A**.;** Tenney, K**.;** Valeriote, F. A**.;** Lobkovsky, E**.;** Clardy, J.; Crews, P. A chemical study of cyclic depsipeptides produced by a sponge-derived fungus. *J. Nat. Prod.*, **2006**, *69*, 1560-1565.

230. Chu, M.; Mierzwa, R.; Truumees, I.; Gentile, F.; Patel, M.; Gullo, V.; Chan, T.-M.; Puar, M. S. Two novel diketopiperazines isolated from the fungus *Tolypocladium* sp. *Tetrahedron Lett.*, **1993**, *34*, 7537-7540.

231. Barrow, C. J.; Cai, P.; Snyder, J. K.; Sedlock, D. M.; Sun, H. H.; Cooper, R. WIN 64821, a new competitive antagonist to substance P, isolated from an Aspergillus species: structure determination and solution conformation. *J. Org. Chem.*, **1993**, *58*, 6016-6021.

232. Liu, D., Li, X. M., Li, C. S., & Wang, B. G. Nigerasterols A and B, Antiproliferative sterols from the mangrove-derived endophytic fungus *Aspergillus niger* MA-132. *Helv. Chim. Acta.*, **2013**, *96*, 1055-1061.

233. Pan, J. H.; Chen, Y.; Huang, Y. H.; Tao, Y. W.; Wang, J., Li, Y.; Dong, T.;

Lai, X. M.; Lin, Y. C. Antimycobacterial activity of fusaric acid from a mangrove endophyte and its metal complexes. *Arch. Pharm. Res.*, **2011**, *34*, 1177-1181.

234. Yaoita, Y.; Amemiya, K.; Ohnuma, H.; Furumura, K.; Masaki, A;. Matsuki, T.; Kikuchi, M. Sterol constituents from five edible mushrooms. *Chem. Pharm. Bull.*, **1998**, *46*, 944-950.

235. Yaoita, Y.; Matsuki, K.; Iijima, T.; Nakano, S.; Kakuda, R.; Machida, K.; Kikuchi, M. New sterols and triterpenoids from four edible mushrooms. *Chem. Pharm. Bull.*, **2001**, *49*, 589-594.

236. Sera, Y.; Adachi, K.; Shizuri, Y. A new epidioxy sterol as an antifouling substance from a Palauan marine sponge, *Lendenfeldia chondrodes*. *J. Nat. Prod.*, **1999**, *62*, 152-154.

237. Yu, S.; Deng, Z.; van Ofwegen, L.; Proksch, P.; Lin, W. 5,8-Epidioxysterols and related derivatives from a Chinese soft coral *Sinularia flexibilis*. *Steroids*, **2006**, *71*, 955-959.

238. Rateb, M. E.; Ebel, R. Secondary metabolites of fungi from marine habitats. *Nat. Prod. Rep.*, **2011**, *28*, 290-344.

239. Nozawa, Y.; Sakai, N.; Matsumoto, K.; Mizoue, K. A novel neuritogenic compound, NGA0187. *J. Antibiot.*, **2002**, *55*, 629-634.

240. Hua, Z.; Carcache, D. A.; Tian, Y.; Li, Y. M.; Danishefsky, S. J. The synthesis and preliminary biological evaluation of a novel steroid with neurotrophic activity: NGA0187. *J. Org. Chem.*, **2005**, 70, 9849-9856.

241. Gunatilaka, A. A. L.; Gopichand, Y.; Schmitz, F. J.; Djerassi, C. Minor and trace sterols in marine invertebrates. 26. Isolation and structure elucidation of nine new 5α, 8α-epidoxy sterols from four marine organisms. *J. Org. Chem.*, **1981**, *46*, 3860-3866.