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Review

Polyketides as Secondary Metabolites from the Genus *Aspergillus*

Xuelian Bai [1], Yue Sheng [1], Zhenxing Tang [2], Jingyi Pan [1], Shigui Wang [1], Bin Tang [1], Ting Zhou [1], Lu'e Shi [1] and Huawei Zhang [3,*]

[1] College of Life and Environmental Sciences, Hangzhou Normal University, Hangzhou 311121, China
[2] School of Culinary Arts, Tourism College of Zhejiang, Hangzhou 311231, China
[3] School of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, China
* Correspondence: hwzhang@zjut.edu.cn; Tel.: +86-571-8832-0613

Abstract: Polyketides are an important class of structurally diverse natural products derived from a precursor molecule consisting of a chain of alternating ketone and methylene groups. These compounds have attracted the worldwide attention of pharmaceutical researchers since they are endowed with a wide array of biological properties. As one of the most common filamentous fungi in nature, *Aspergillus* spp. is well known as an excellent producer of polyketide compounds with therapeutic potential. By extensive literature search and data analysis, this review comprehensively summarizes *Aspergillus*-derived polyketides for the first time, regarding their occurrences, chemical structures and bioactivities as well as biosynthetic logics.

Keywords: fungus; *Aspergillus*; secondary metabolite; polyketide; bioactivity; therapeutic effect

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1. Introduction

Polyketides are a highly diverse group of natural products having structurally intriguing carbon skeletons, such as polyphenols, macrolides, polyenes, enediynes, and polyethers [1]. These substances encompass an important source of pharmaceutically relevant molecules, such as antibiotics, immunosuppressants, antiparasitics, cholesterol-lowering, and antitumoral agents [2–6]. Biosynthetically, polyketide motifs are biochemically formed by acetyl-CoA units undergoing a sequence of events catalyzed by polyketide synthases (PKS), a multi-enzyme complex that is highly homologous to fatty acid synthase (FAS) [7].

As one of the ubiquitous fungi in nature, the genus *Aspergillus* has recently received much more attention owing to its great biosynthetic potential of secondary metabolites (SMs) with nutritional, agrochemical and medicinal applications [8]. By the end of 2022, over 3100 *Aspergillus*-derived SMs had been isolated and collected in the Dictionary of Natural Products (DNP) database [9]. Among these substances, as many as 343 polyketide derivatives (**1**–**343**) had been discovered and characterized from *Aspergillus* strains. To enrich our knowledge of these molecules and explore their therapeutic potentials, all aspects are well organized and comprehensively summarized in this review, including their biological sources, structural features, biological properties as well as biosynthetic logic.

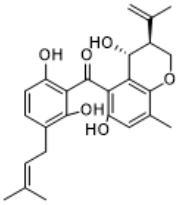
2. *Aspergillus*-Derived Polyketides as Secondary Metabolites

According to structural features, *Aspergillus*-derived polyketides are grouped into fourteen types, including benzophenone, diphenyl ether, furan and furanone, isocoumarin, lignan, naphthalene, phenolic, polyene, pyran and pyranone, quinone, steroid, meroterpenoid, xanthone and miscellaneous, which are respectively introduced below. Detailed information for these chemicals was summarized in Table S1.

2.1. Benzophenones

Benzophenone derivatives (Figure 1) are a class of ketones formed by the direct connection of one carbonyl with two phenyl groups and play an important role in medicinal

chemistry [10]. Under nitrogen-limiting culture conditions, strain *A. nidulans* FGSCA4 was found to produce a novel prenylated benzophenone pre-shamixanthone (**1**), which exerted significant inhibition against lipid accumulation in HepG2 cells without cytotoxic effect and displayed a potent reduction of total cholesterol and triglycerides [11,12]. Two new dichlorinated benzophenones **2** and **3** were purified from *A. terreus* C9408-3 [13], and the later compound is a promising immunosuppressant agent targeting the isomerase cyclophilin A (CyPA) [14]. Three benzophenone analogs (**4**–**6**) obtained from a wetland fungus *A. flavipes* PJ03-11 exhibited stronger α-glucosidase inhibitory activities than acarbose [15]. Bioassay-guided fractionation of the EtOAc extract of one marine sponge-derived strain *A. europaeus* WZXY-SX-4-1 led to the isolation of eight benzophenone derivatives (**7**–**14**), of which compounds **9**, **11**, and **12** showed potent radical scavenging activity against DPPH (2,2-diphenyl-1-picrylhydrazyl) and **8** had strong down-regulation of NF-κB in LPS-induced SW480 cells [16]. Moreover, the putative biosynthetic pathway analysis indicates that endocrocin and emodin were their precursors through consecutive oxidation and methylation (Scheme 1).



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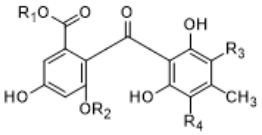
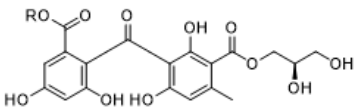


2 R_1 = H, R_2 = H, R_3 = R_4 = Cl
3 R_1 = CH_3, R_2 = H, R_3 = R_4 = Cl
4 R_1 = CH_3, R_2 = H, R_3 = R_4 = Cl
5 R_1 = CH_3, R_2 = R_3 = R_4 = H
6 R_1 = H, R_2 = CH_3, R_3 = R_4 = Cl



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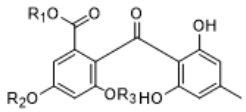
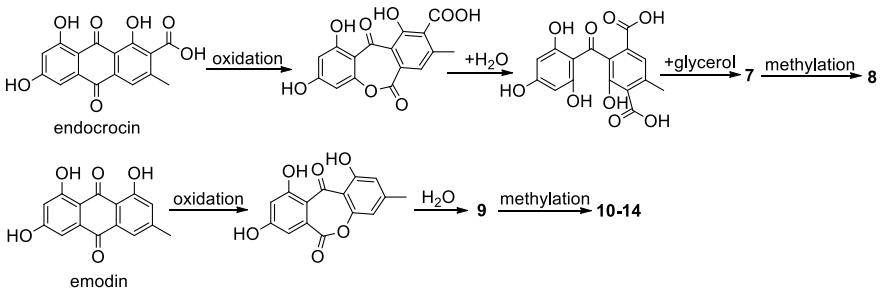


9 R_1 = R_2 = R_3 = H
10 R_1 = R_3 = H, R_2 = CH_3
11 R_1 = CH_3, R_2 = R_3 = H
12 R_1 = H, R_2 = R_3 = CH_3
13 R_1 = R_2 = CH_3, R_3 = H
14 R_1 = R_2 = R_3 = CH_3

Figure 1. *Aspergillus*-derived benzophenones (**1**–**14**).



Scheme 1. Proposal biosynthetic pathways for compounds **7**–**14**.

2.2. Diphenyl Ethers

Aspergillus-derived diphenyl ethers (**15**–**31**, Figure 2) consist of at least two phenyls connected by one or more oxygen atoms. These aromatic polyketides exhibited excellent potential for therapeutic and industrial applications [17]. Two new rare dibenzo-1,4-dioxins, gibellulins C (**15**) and D (**16**), were produced by genetically modified *A. nidulans* through the deletion of a global regulator *LaeB* [18]. F-9775A (**17**) and F-9775B (**18**), originally isolated from *Paecilomyces carneus*, were detected in the crude extract of *A. nidulans* RMS011 and acted as potent inhibitors of protease K, which could inhibit osteoporosis [19]. Tetraorcinol A (**19**) was a new orcinol tetramer isolated from the fermentation broth of the coral-associated fungus *A. versicolor* LCJ-5-4 and displayed weak DPPH radical-scavenging activity with an IC_{50} value of 67 μM [20]. Besides two chlorinated benzophenones **2** and **3**, three diphenyl ethers (**20**–**22**) were also produced by strain *A. terreus* C9408-3 [13], and

compound **20** was shown to be a new endothelin binding inhibitor [21]. Strain *A. flavipes* PJ03-11 also manufactured one new diphenyl ether, 5-hydroxymethylasterric acid (**23**), and seven known analogs (**24**–**30**), of which compound **25** exhibited a stronger inhibitory effect on α-glucosidase than acarbose [15]. Diorcinol (**31**) obtained from the fermentation culture of endophytic *A. flocculus* was found to inhibit the growth of chronic myelogenous leukemia cell line K562 at 30 μM [22].

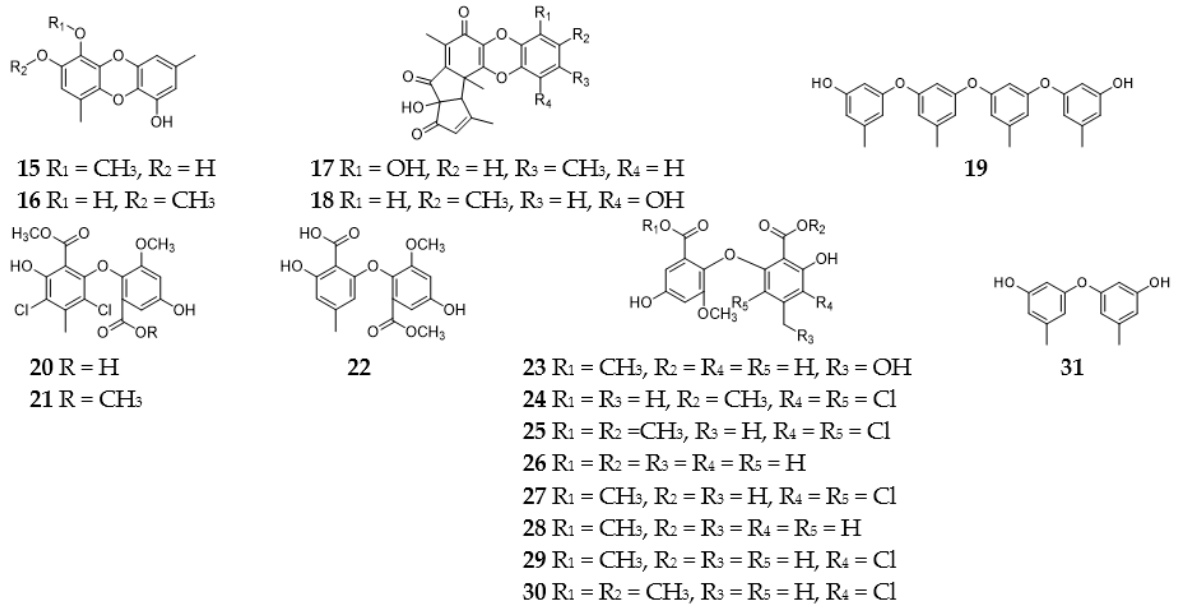


Figure 2. *Aspergillus*-derived diphenyl ethers (**15**–**31**).

2.3. Furans and Furanones

Furans and furanones are the most polyketides produced by *Aspergillus* spp. and display a broad spectrum of biological properties [23]. Structurally, these substances are classified into two major types, including furans and benzofurans (Figure 3) and furanones and benzofuranones (Figures 4–6).

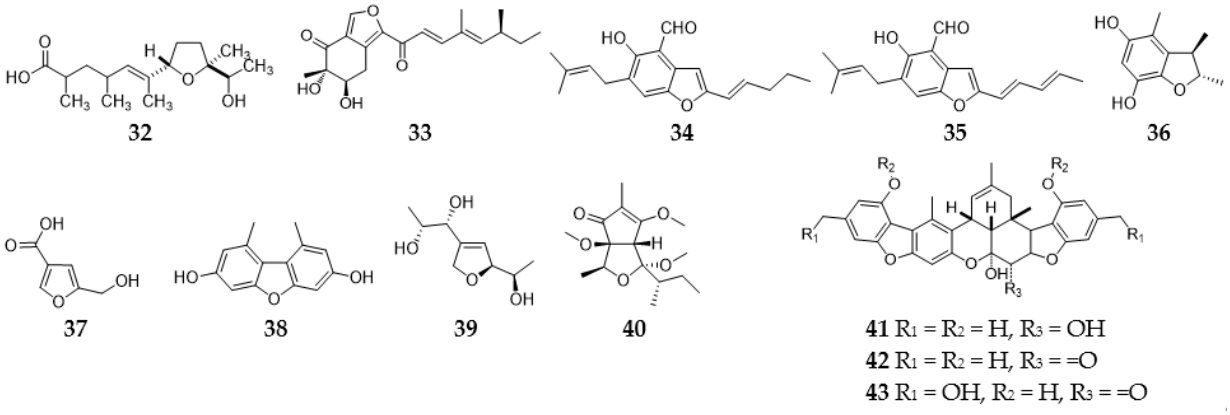


Figure 3. *Aspergillus*-derived furans and benzofurans (**32**–**43**).

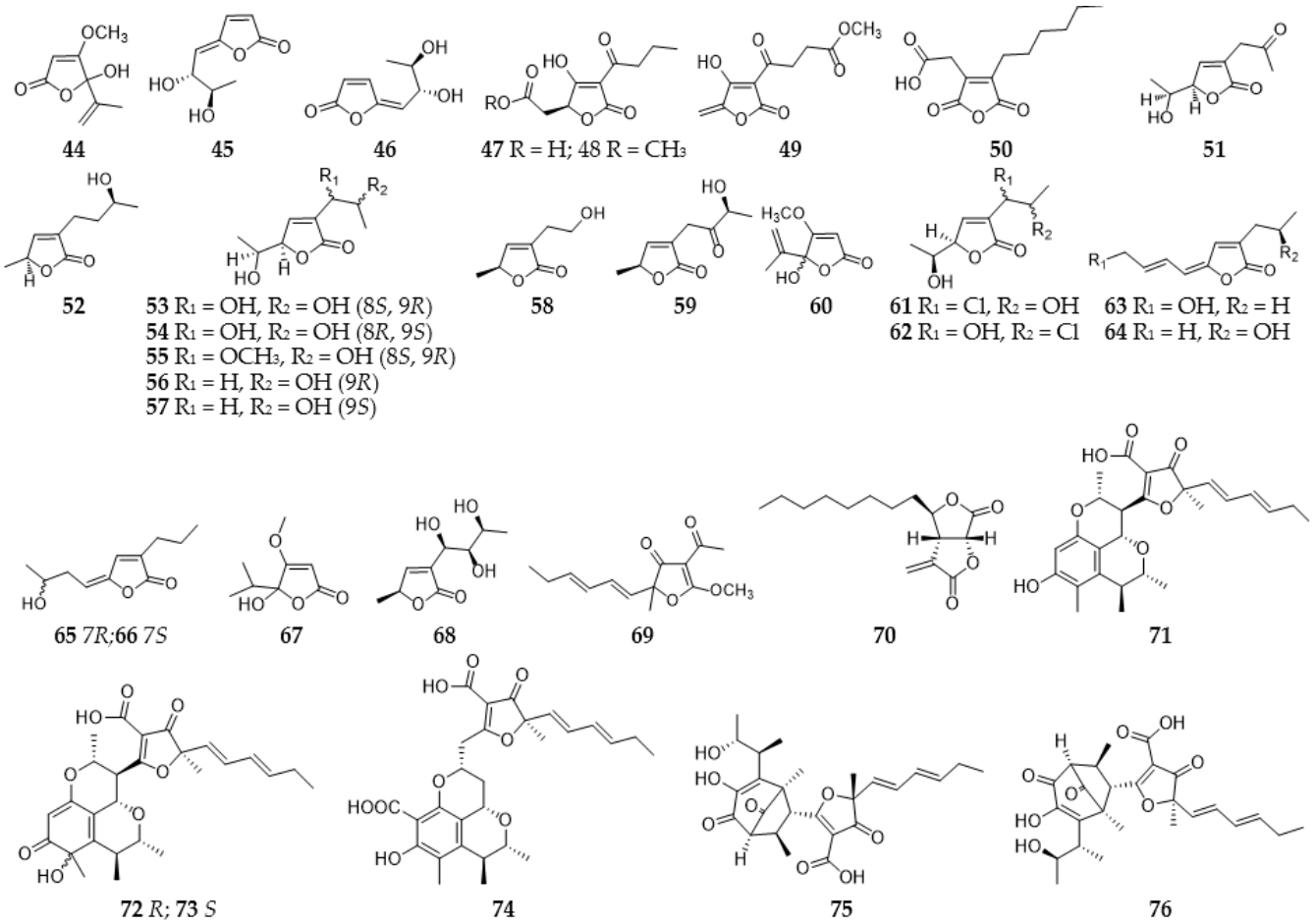


Figure 4. *Aspergillus*-derived furanones (**44**–**76**).

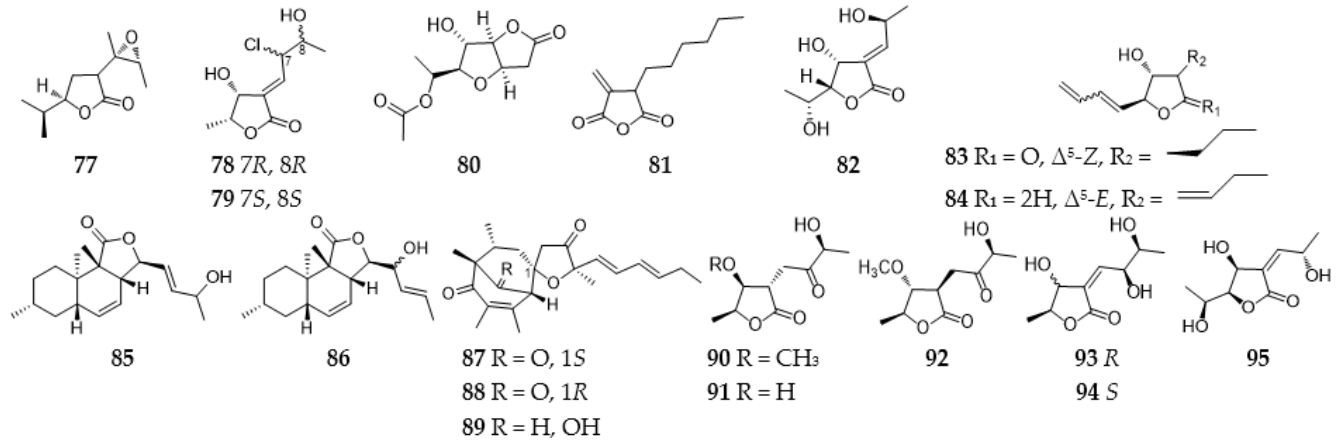


Figure 5. *Aspergillus*-derived tetrahydrofuranones (**77**–**95**).

2.3.1. Furans and Benzofurans

Chemical investigation of one *A. niger* strain from the Caribbean sponge *Hyrtios proteus* led to the discovery of a new furan with a unique carbon skeleton, asperic acid (**32**) [24], which was later reisolated from the strain *A. phoenicis* collected in Saskatchewan (Canada) and exhibited potent cytotoxic activity toward the murine lymphocytic leukemia P388 with an ED_{50} value of 0.18 mug/mL and a variety of human cancer cell lines (pancreas, breast, CNS, lung, colon, and prostate) with GI_{50} values ranged from 1.7 to 2.0 µg/mL [25]. Asperfuranone (**33**) was a novel polyketide consisting of a conjugated alkene chain and

a furan subunit produced by A. nidulans by replacing the promoter of the transcription activator with the inducible alcA promoter [26]. A gene cluster containing two fungal PKSs (AN1036.3 and AN1034.3) for the biosynthesis of **33** was first characterized (Scheme 2), and its mechanism of action (MOA) showed that this compound exerted an inhibitory effect on A549 cells via blocking cell cycle progression and inducing apoptosis [27]. Two prenylated benzaldehyde derivatives (**34** and **35**) were characterized from the marine-derived fungus *A. glaucus* HB1-19 and showed strong radical-scavenging activity [28]. A new benzofuran polyketide (**36**) was produced by soil fungus *A. terreus* X3 but displayed no antimicrobial effect [29]. Flufuran (**37**) was a typical furan polyketide discovered from *A. flavus* 9643 and shown to inhibit *Phytophthora cinnamomi* at 0.2 mg/mL [30,31]. 3,7-Dihydroxy-1,9-dimethyldibenzo- furan (**38**) originally obtained from a mycobiont of the lichen Lecanora cinereocarnea was found to be produced by an endozoic fungus *A. sydowii* SCSIO 41301 from marine sponge *Phakellia fusca* [32,33]. Asperochratide H (**39**) was a new cytotoxic C_9 polyketide produced by the deep-sea-derived fungus *A. ochraceus*, and its putative biosynthetic route was proposed in Scheme 3 [34]. Asperpentenone A (**40**) possesses a rare cyclopentenone-tetrahydrofuran moiety from strain *Aspergillus* sp. SCSIO 41024 [35]. Asticolorins A–C (**41**–**43**) are toxic metabolites manufactured by strain A. versicolor MRC 638 and were characterized by the novel way in which a mevalonate-derived 3,3-dimethylallyl group was used to link two dibenzofuran moieties [36,37].

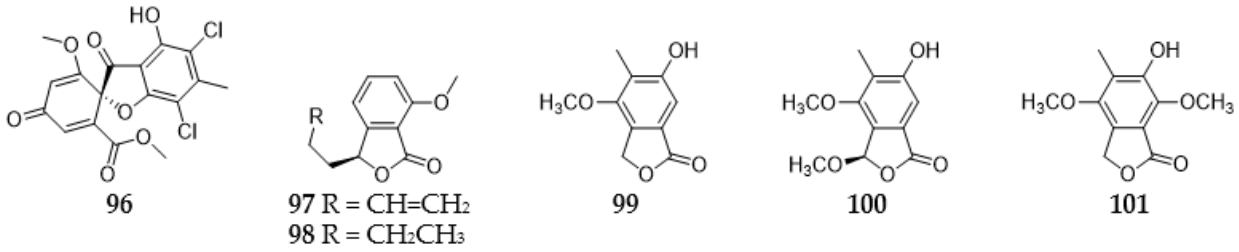
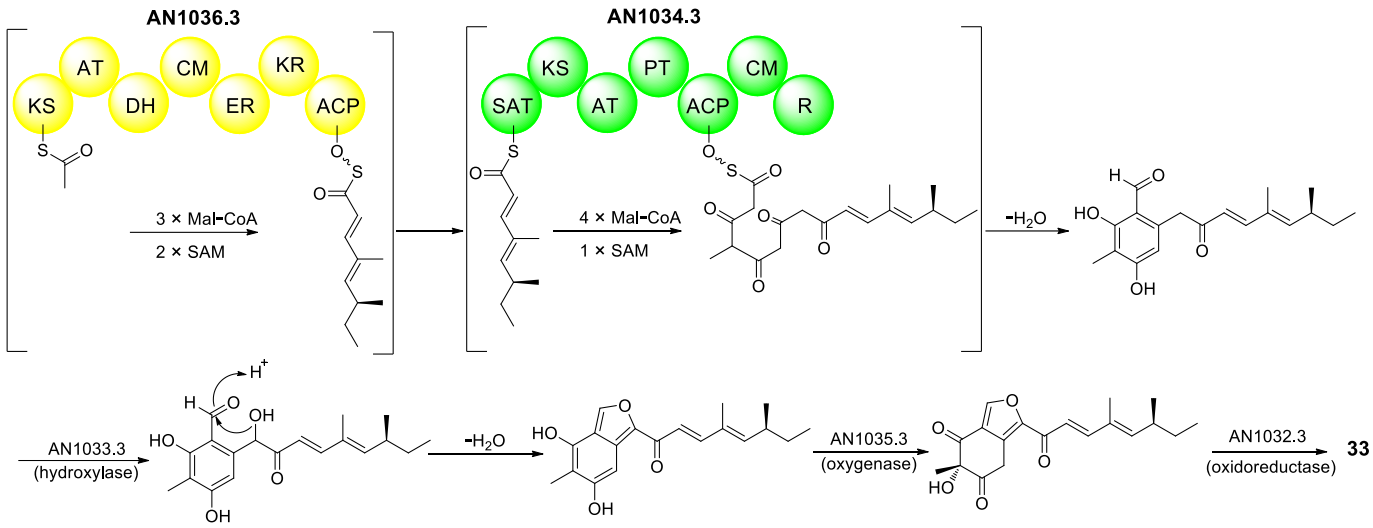
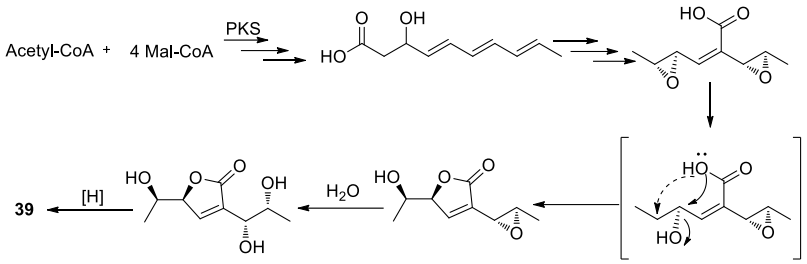


Figure 6. *Aspergillus*-derived benzofuranones (**96**–**101**).



Scheme 2. Proposal biosynthetic pathway for asperfuranone (**33**).



Scheme 3. Putative biosynthetic pathway for asperochratide H (**39**).

2.3.2. Furanones and Benzofuranones

Aspergillus-derived furanones and benzofuranones are the most commonly isolated polyketides, including furanones, dihydrofuranones, tetrahydrofuranones and benzofuranones. Interestingly, most of these compounds are aromatic and belong to α-furanone. Penicillic acid (**44**) is one of the important furanone antibiotics used to treat bacterial spot disease [38,39]. Versicolactones A (**45**) and B (**46**) were isomeric furanones produced by a coral-associated fungus *A. versicolor* LCJ-5-4, and compound **46** exhibited pronounced cytotoxicity against human pancreatic cancer cells with an IC_{50} value of 9.4 μM [20,40]. Three acyltetronic acid derivatives (**47**–**49**) were produced by strain *A. niger* ATCC1015 through the activation of the dormant PKS-NRPS gene cluster by expressing the transcription factor *CaaR* [41]. 2-Carboxymethyl-3-hexylmaleic acid anhydride (**50**) was purified from an endozoic fungus *A. tubingensis* OY907 in the Mediterranean marine sponge *Ircinia variabilis* and displayed an inhibitory effect on *Neurospora crassa* [42]. A chemical study of a marine-derived strain *Aspergillus* sp. 16-02-1 resulted in the isolation of eight dihydrofuranone analogs (**51**–**58**) with no potent cytotoxicity against human cancer K562, HL-60, HeLa and BGC-823 cell lines [43]. One new polyketide, asperochrins B (**59**), along with three derivatives (**60**–**62**), was isolated from *A. ochraceus* MA-15. Compounds **60** and **61** displayed selective antibacterial activity against *A. hydrophilia*, *V. anguillarum* and *V. harveyi* with IC_{50} values ranging from 0.5 to 32.0 μg/mL [44].

Aspergones A-D (**63**–**66**) were detected in the fermentation broth of a marine sponge-derived strain *Aspergillus* sp. OUCMDZ-1583 and compounds **63** and **64** showed an inhibitory effect on α-glucosidase with IC_{50} values of 2.36 and 1.65 mM, respectively [45]. Dihydropenicillic acid (**67**) was purified from the endophytic fungus *A. flocculus* [22] but displayed no antimicrobial or cytotoxic activity [46]. Asperochratide F (**68**) was another new C_9 polyketide from the deep-sea-derived fungus *A. ochraceus* and exerted significant cytotoxic effects on the BV-2 cell line [34]. Gregation B (**69**) was a rare β-furanone derived from *A. flavus* in food samples by a qualitative analytical method based on the identification of fungal chemical markers by HPLC-MS [30] and exhibited antibacterial activity against *E. coli* [47]. Avenaciolide (**70**) produced by strain *A. avenaceous* G. Smith displayed an inhibitory effect on the transport of glutamate in rat liver mitochondria [48,49]. Citrifurans A−D (**71**–**74**) was the first heterodimers of azaphilone and furanone from a symbiotic *Aspergillus* strain in the intestines of centipedes and displayed moderate inhibitory activities against LPS-induced NO production in RAW 264.7 macrophages [50]. One year later, two additional new β-furanones (**75** and **76**) were obtained from the same strain, and **76** showed significant NO inhibition with an IC_{50} value of 16.0 μM [51].

Asperlactone (**77**) was a new tetrahydrofuranone purified from *A. melleus* CMI 49108 and exhibited superoxide anion inhibition at 30 ± 9% at 10 μM [52,53]. Two new chlorinated polyketides, chlorocarolides A (**78**) and B (**79**), were isolated and characterized from the saltwater culture of *A. ochraceus* [50]. Protulactones A (**80**) possessing unique ring systems was discovered from the marine-derived fungus *Aspergillus* sp. SF-5044 [54]. In addition to compound **47**, tubingenoic anhydride A (**81**) was also produced by strain *A. tubingensis* OY907 and shown to inhibit *Neurospora crassa* growth at 330 μM [42]. Strain *A. ochraceus* MA-15 was found to produce a new C_9 polyketide asperochrins A (**82**), which showed inhibitory activity against aquatic pathogenic bacterial *Aeromonas hydrophila*, *Vibrio anguillarum*, and

V. harveyi [52]. Strain *Aspergillus* sp. OUCMDZ-1583-derived aspergiones E (**83**) and F (**84**) displayed α-glucosidase inhibitions [45]. Allahabadolactones A (**85**) and B (**86**) were separated from the endophytic stain *A. allahabadii* BCC45335, and compound **85** displayed moderate cytotoxicity against NCI-H187 and Vero cell lines, and 8**6** exhibited low anti-*B. cereus* effect [55]. Three spiro *β*-furanones, asperones C–E (**87**–**89**), are dimeric polyketides with two distinct skeletons from an unidentified stain *Aspergillus* sp. and compounds **87** and **88** showed significant nitric oxide (NO) inhibition in lipopolysaccharide (LPS)-induced RAW 264.7 macrophage cells with IC_{50} values of 13.2 and 6.0 μM, respectively [51]. Six new C_9 polyketides (**90**–**95**) were also produced by the marine strain *A. ochraceus*, and compound **94** exerted significant cytotoxic effects on the BV-2 cell line [34].

(+)-Geodin (**96**), originally derived from strain *P. glabrum* AJ117540 was produced by strain *A. terreus* ATCC 20542 and exhibited the activity that stimulates glucose uptake by rat adipocytes [56,57]. Asperetide (**97**) and (5)-3-butyl-7-methoxyphthalide (**98**) were purified from the medicinal plant-derived fungus *Aspergillus* sp. TJ23 [58]. In addition to gibellulins C (**15**) and D (**16**), three porriolide analogs (**99**–**101**) were manufactured by disruption of the global regulator *LaeB* in *A. nidulans* [18] and displayed an inhibitory effect on the root elongation of both lettuce and stone-leek seedlings by 53.3% and 48.5%, respectively [59,60].

2.4. Isocoumarins

Aspergillus-derived isocoumarins (Figure 7) are a class of phenolic compounds usually containing hydroxyl group(s) and display various pharmacological properties, including antimicrobial, anti-inflammatory, cytotoxic activities and inhibitory effects on serine protease and gamma-secretase [61–63]. Chemical investigation of an Indo-Pacific marine sponge-derived *A. ochraceus* afforded a new dihydroisocoumarin, (−)-(*R*)-mellein (**102**), which exhibited a broad spectrum of antifungal and antioomycetes activities [64]. One marine-derived strain *A. ochraceus* MA-15 was shown to produce four isocoumarin derivatives (**103**–**106**), of which compound **106** had inhibitory activity against aquatic pathogenic bacterial *Aeromonas hydrophila*, *Vibrio anguillarum*, and *V. harveyi* [44].

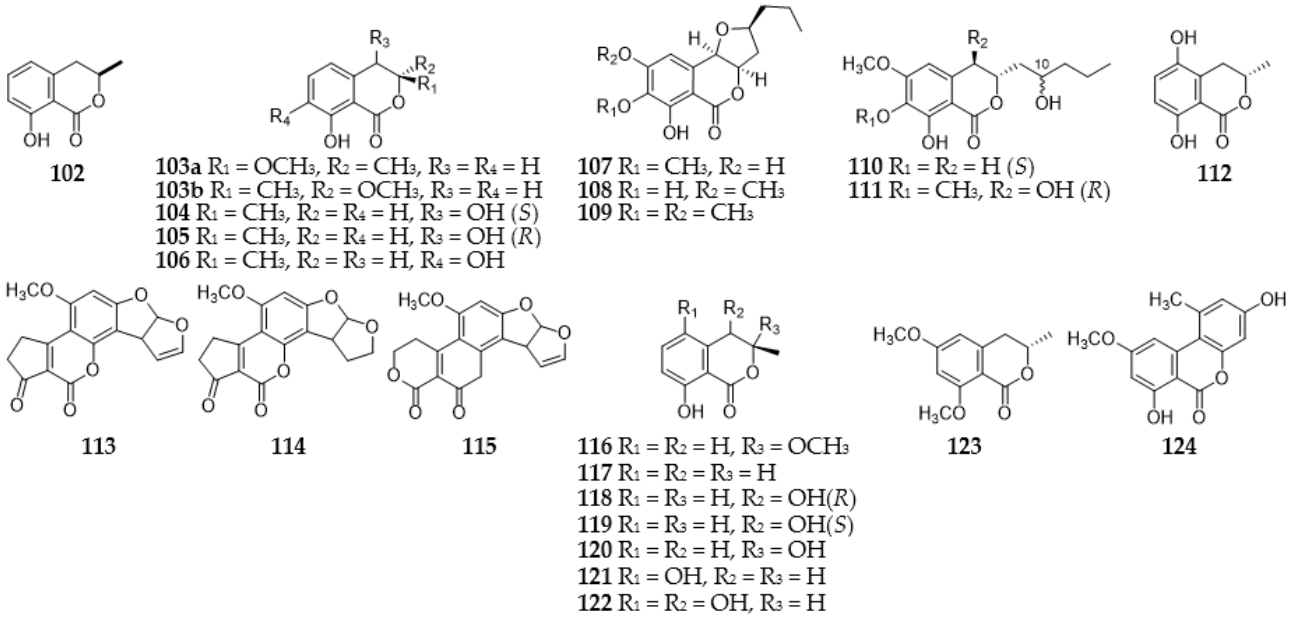


Figure 7. *Aspergillus*-derived isocoumarins (**102**–**124**).

In addition to aspergones A–D (**69**–**72**), five isocoumarins (**107**–**111**) were also obtained from the endozoic strain OUCMDZ-1583 [45], and compounds **107** and **109**–**111** showed α-glucosidase inhibitions with IC_{50} values of 0.027, 1.65, 1.19, and 1.74 mM, respectively, and **107** and **109** exhibited inhibitory activity against the influenza A (H1N1) virus. (3*S*)-5-Hydroxymellein (**112**), originally derived from *Cephalosporium* sp. AL031 was found to be

produced by the marine sponge-derived fungus *Aspergillus* sp. SCSIO XWS03F03 [65,66]. Aflatoxins B_1, B_2, and G_1 (**113**–**115**) are a kind of naturally occurring carcinogens frequently detected in secondary metabolites of *A. flavus* [30,67,68]. Compounds **116**–**123** are dihydroisocoumarin derivatives separated from the endophytic strain *A. flocculus* and the marine strain *A. terreus* SCSIO 41008 and displayed no potent cytotoxic effect on chronic myelogenous leukemia cell line K562 [22,69]. Alternariol 9-O-methyl ether (**124**) was isolated from an endophytic strain *A. fumigatus* D but exhibited no antimicrobial activity [70].

2.5. Lignans

Lignans mainly exist in plants and have the function of scavenging free radicals and antioxidation [71]. Interestingly, some of these substances had been isolated and characterized from microorganisms, including *Aspergillus* strains (Figure 8). Chemical investigation of the fumaroles-derived strain *A. terreus* C9408-3 afforded four lignan derivatives (**125**–**128**), which compounds **126** and **127** exhibited mild cytotoxic activity, and **128** showed antiplasmodial activity against *Plasmodium falciparum* K1 with an IC_{50} value of 7.9 μg/mL [13,72–74]. Three new butenolides (**129**–**131**) together with flavipesin B (**132**) and butyrolactone II (**133**) produced by the fungus *A. flavipes* PJ03-11 displayed stronger α-glucosidase inhibitory activity than acarbose [15]. Microperfuranone (**134**) was a biphenyl furanone polyketide purified from *A. nidulans* [21,75]. Aspergillosis (**135**) and (±)-asperteretal D (**136**) were obtained from cultures of the potato endophytic fungus *A. carneus* L03 and showed moderate antifungal activity against plant pathogens and inhibitory effect on nitric oxide production in lipopolysaccharide-stimulated RAW264.7 cells [76].

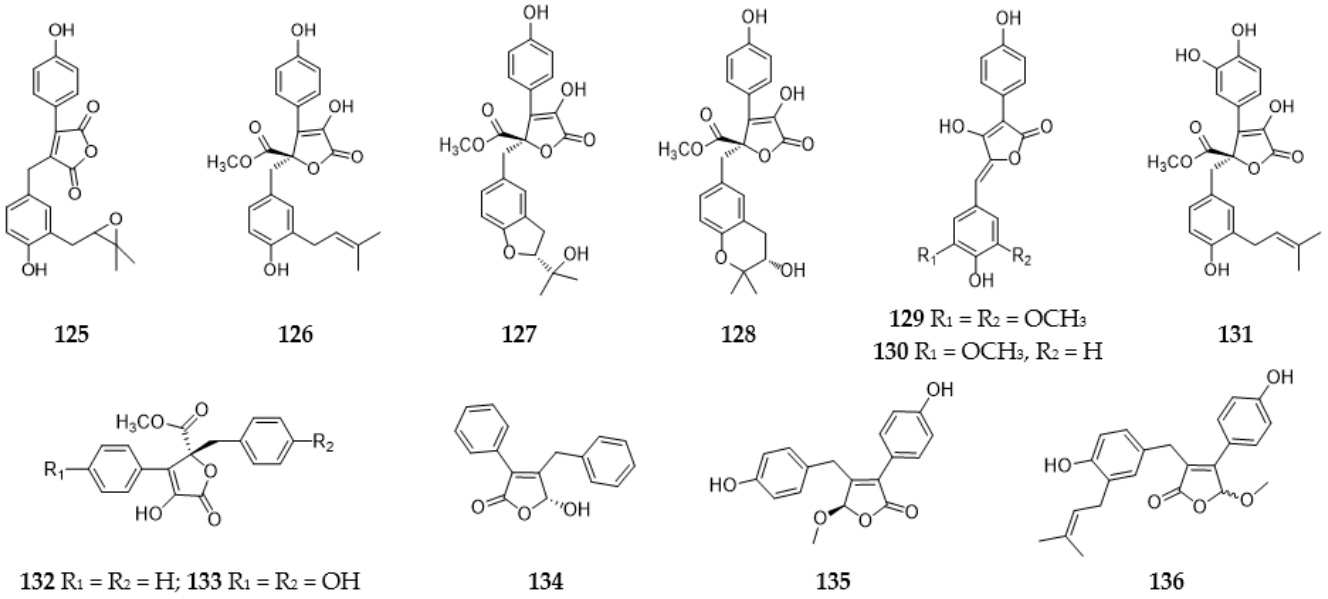


Figure 8. *Aspergillus*-derived lignans (**125**–**136**).

2.6. Naphthalenes

Naphthalenes, a kind of polycyclic aromatic hydrocarbon composed of two benzene rings sharing two adjacent carbon atoms, are toxic to the liver and nervous system and usually cause cataracts and retinal hemorrhage [77,78]. Six naphthalenes **137**–**142** (Figure 9) were separated from the marine-derived fungus *A. glaucus* but showed no cytotoxicity at 100 μM against the HL-60 and A-549 cell lines [79]. Using heterologous expression in model host *A. nidulans* RJMP1.49, three analogs neosartoricins B-D (**143**–**145**) were biosynthesized and identified [80]. Funalenone (**146**) was produced by an epigenetic regulator gene-deleted strain *A. niger* FGSC A1279 and displayed an inhibitory effect on type I collagenase activity at 170 μM [81]. Two hydroxynaphthalene-2-carboxylate (**147**,**148**) were derived from the

marine fungus *A. terreus* SCSIO 41008 and showed weak or no cytotoxic activities toward human glioma U87 cells and glutamate-induced toxicity in HT22 cells [69].

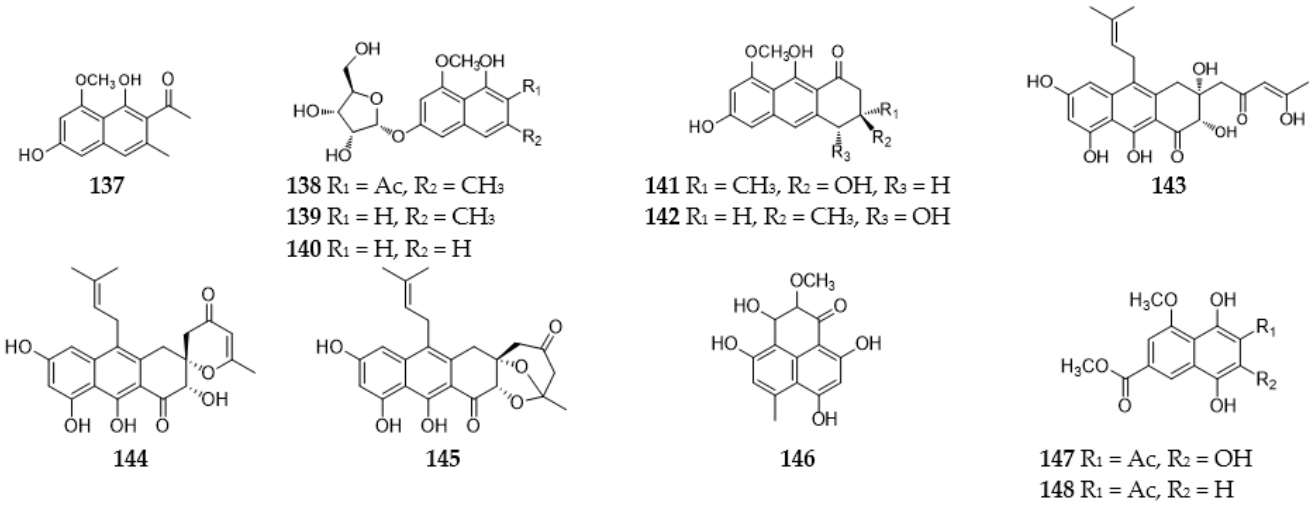


Figure 9. *Aspergillus*-derived naphthalenes (**137**–**148**).

2.7. Phenolics

Phenolics are a class of aromatic compounds containing one or more hydroxyl groups and usually act as antioxidants in a number of ways [82]. Orsellinic acid (**149**) and lecanoric acid (**150**, Figure 10) were isolated from A. nidulans RMS011 through co-cultivation with a collection of 58 soil-dwelling actinomycetes. Compound **150** was originally isolated from the lichen *Parmotrema tinctorum* and had a toxic effect on HepG2 and CCF cell lines [83,84]. Bioactivity-guided fractionation of the crude extract of the fungus A. versicolor from a marine sponge *Petrosia* sp. afforded a new aromatic polyketide (**151**), which showed no cytotoxicity against cell lines A-549, SK-OV-3, SK-MEL-2, XF498 or HCT-15 [85]. Seven phenolics (**152**–**158**) from the marine strain A. glaucus HB1-19 exhibited strong radical-scavenging activity [28]. Flavipin (**159**) produced by endophyte A. fumigatus AF3-093A from the brown alga displayed broad-spectrum antimicrobial activity [86]. Porosuphenols A−D (**160**, **161**, **162a** and **162b**) were obtained from the endophytic strain *A. porosus* and possessed a dynamic diene-dione functionality within a flexible carbon chain [87]. Hydroxysydonic acid (**163**) had been isolated from *A. flavus* 9643 and *A. sydowi* and showed NO inhibitory effects in LPS-stimulated BV2 cells [88,89]. A sponge-derived fungus *Aspergillus* sp. F40 was shown to produce a new aliphatic benzoic acid (**164**) with moderate antimicrobial activities [90,91]. Bioactivity-guided isolation and MS-based metabolomics analysis of the endophytic *A. flocculus* resulted in the discovery of three novel phenolics (**165**–**167**) [22]. Eight phenolic polyketides (**168**–**175**) were identified from the marine fungus *A. sydowii* SCSIO 41301, and **172** displayed antimicrobial activity [33,92,93]. Antioxidant agent **176** was the precursor of caffeic acid 3,4-dihydroxyphenethyl ester from the deep-sea fungus *Aspergillus* sp. SCSIO 41024 [35,94].

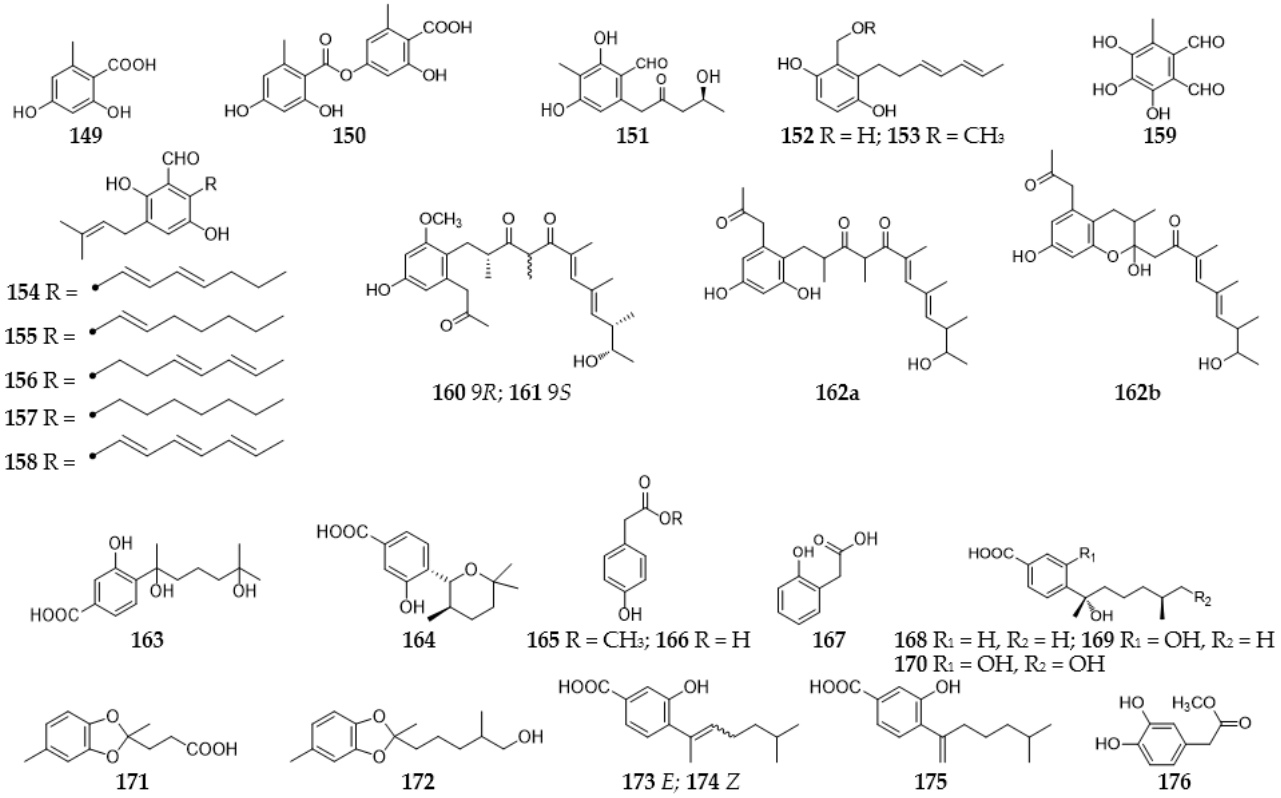


Figure 10. *Aspergillus*-derived phenolic compounds (**149**–**176**).

2.8. Polyenes

Polyene polyketides are one kind of important antibiotic which are widely used in the treatment of microbial infections [95]. Structurally, *Aspergillus*-derived polyenes are linear chain molecules (Figure 11). Fumagillin (**177**), discovered from *Aspergillus* sp. in 1949, was shown to be an antiphage agent [96]. Aspinonene (**178**) was a new multifunctional fungal metabolite isolated from the culture broth of *A. ochraceus* FH-A6692 [97]. Compounds **179**–**182** are new C_9 polyketides and exhibited a weak antitumor effect on K562, HL-60, HeLa, and BGC-823 cell lines but no anti-MRSA activity [58,98]. Aspergones I−M (**183**–**187**) were purified as new polyketides from the strain *Aspergillus* sp. OUCMDZ-1583 and compounds **184** and **185** displayed strong α-glucosidase inhibitions with IC_{50} values of 2.37 and 2.70 mM, respectively [45]. A new antibacterial polyketide (−)palitantin (**188**) was isolated from *A. fumigatiaffnis*, an endophytic fungus on the medicinal plant *Tribulus terestris* and inhibited the growth of multi-resistant clinical isolate of *Enterococcus faecalis* and *Streptococcus pneumoniae* with a MIC value of 64 μg/mL [99].

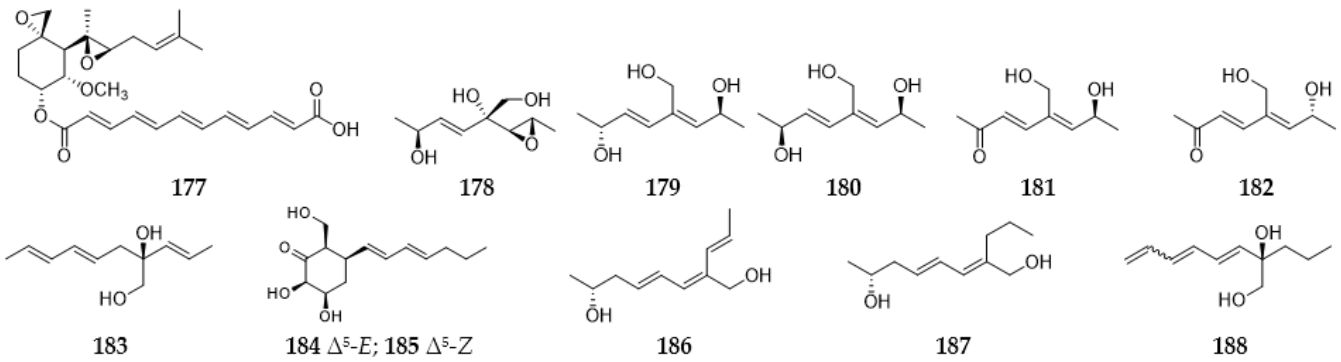


Figure 11. *Aspergillus*-derived polyenes (**177**–**188**).

2.9. Pyrans and Pyranones

2.9.1. Pyrans

Recently pyran derivatives received more and more attention due to their wide biological activities, including antibacterial and antifungal activities, and many of them have been developed as commercial antimicrobial agents, such as triadimefon, triadimenol, diniconazole, myclobutanil and bitertanol [100,101]. Azaphilones (**189**–**193**, Figure 12) are a class of highly oxygenated pyrano-quinone bicyclic chemicals from strain *A. niger* ATCC 1015 by activation of a silent PKS gene (*aza*) [102]. Moreover, their biosynthetic pathways were shown to involve the convergent actions of a highly reducing PKS and a non-reducing PKS. Citrinin (**194**) is a pyran mycotoxin produced by several strains of *Aspergillus*, *Penicillium* and *Monascus*. In addition to toxicity, this compound displayed certain anticancer and neuroprotective effects [103]. Five new benzopyran derivatives (**195**–**199**), including two pairs of enantiomers, were purified from the fermentation broth of *A. fumigatus*, an endophytic fungus associated with *Cordyceps Sinensis*. Compounds **195** and **197** exhibited a moderate inhibitory effect on the MV4-11 cell line in vitro with IC_{50} values of 23.95 μM and 32.70 μM, respectively [104]. Two new C_9 pyran polyketides, asperochratides I (**200**) and J (**201**), were isolated from the deep-sea-derived *A. ochraceus* but showed no cytotoxic, anti-food allergic, anti-H1N1 virus and anti-inflammatory activities [34].

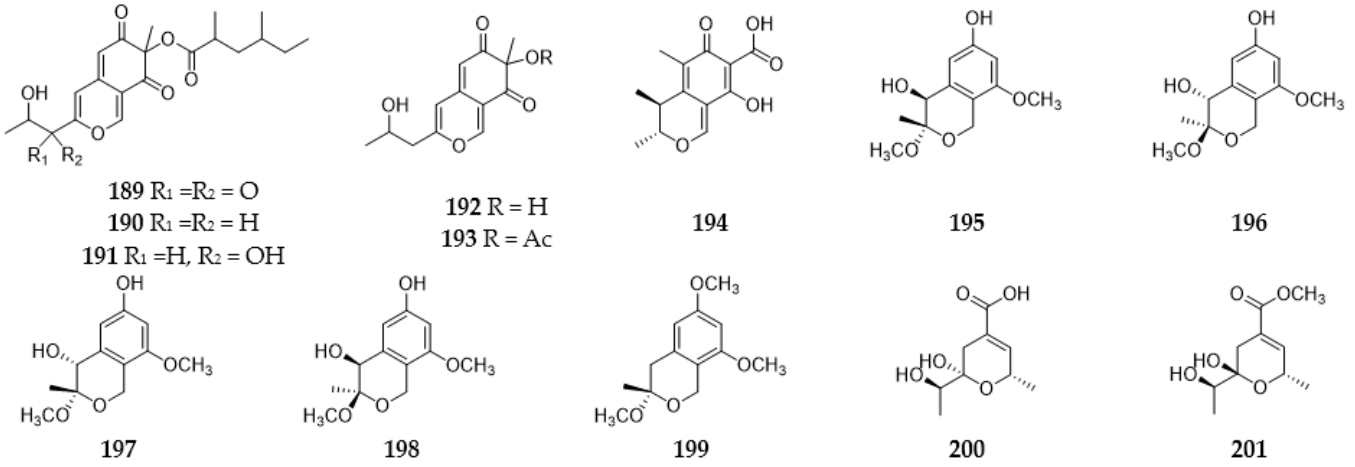


Figure 12. *Aspergillus*-derived pyrans (**189**–**201**).

2.9.2. Pyranones

Protulactone B (**202**, Figure 13) was a new α-pyranone polyketide possessing unique ring systems isolated from an EtOAc extract of the marine-derived fungus *A.* sp. SF-5044 [54]. Chaetoquadrin F (**203**) produced by strain *A.* sp. 16-02-1 showed antitumor activity against HeLa cell lines with an inhibitory rate (IR) of 13.5% at 100 μg/mL [43]. In addition to asperochrins A (**82**), five pyranone derivatives (**204**–**208**) were also obtained from strain *A. ochraceus* MA-15 and compounds **205** and **206** displayed inhibitory activity against aquatic pathogens *A. hydrophila*, *V. anguillarum*, and *V. harveyi* [44].

By the heterologous expression of the avirulence gene *ACE1* in *A. oryzae* M-2-3, two new polyenyl-α-pyranones (**209** and **210**) were produced and shown to be not responsible for the observed *ACE1*-mediated avirulence [105]. (+)-Asperlin (**211**) was discovered from an *A. nidulans* mutant, which fused the DNA-binding domain of a transcription factor associated with a silent SM gene cluster with the activation domain of a robust SM transcription factor *AfoA* [106]. Deletion of the epigenetic regulator gene, a histone acetyltransferase in the SAGA/ADA complex, resulted in the production of a novel compound, nigerpyrone (**212**) in *A. niger* FGSC A1279 [107]. Moreover, its biosynthetic pathway was disclosed via gene knockout and complementation experiments (Scheme 4). Aspopyrone A (**213**) was produced by an Okinawan plant-derived fungus, *A.* sp. TMPU1623 exhibited a strong inhibitory effect on protein tyrosine phosphatase (PTP) 1B with an IC_{50} value

of 6.7 μM [108]. Bioactivity-guided fractionation of the crude extract of an endophytic strain, *A. flocculus*, resulted in the isolation of three pyranone analogs (**214**–**216**) [22]. 4-Hydroxy-3,6-dimethyl-2-pyrone (**217**) and 4-methyl-5,6-dihydropyran-2-one (**218**) were also produced by the marine strain *A. sydowii* SCSIO 41301 [33], and phomapyrone C (**219**) together with compounds **40**, **176** and **215** was purified from strain SCSIO 41024 [35].

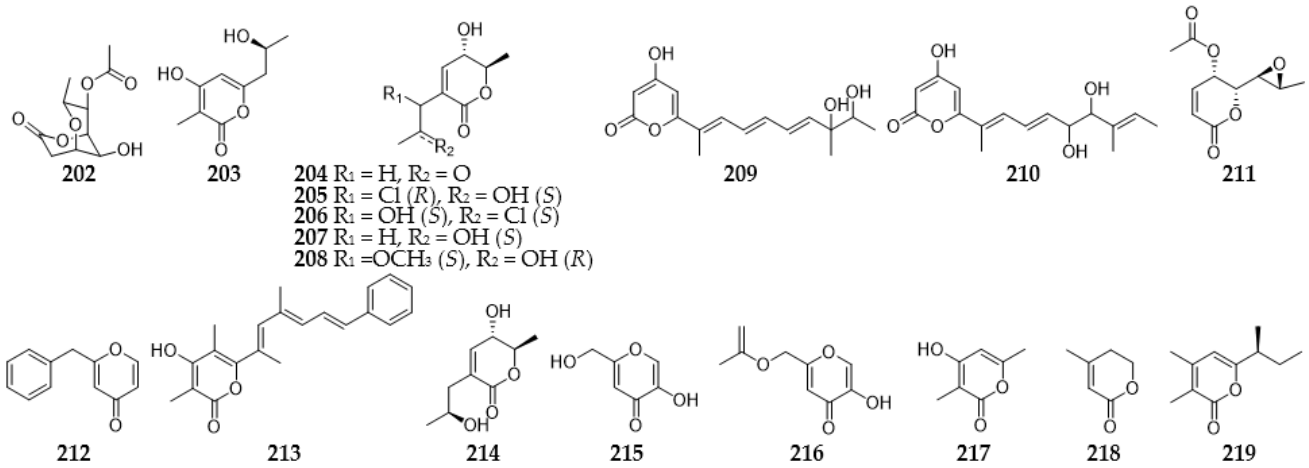
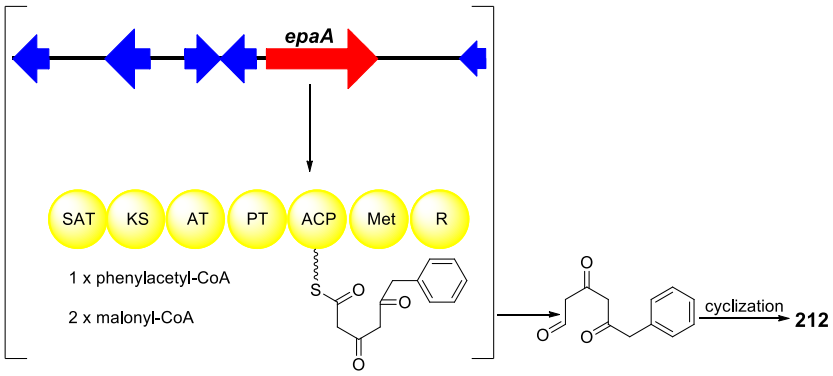


Figure 13. *Aspergillus*-derived pyranones (**202**–**219**).



Scheme 4. Biosynthetic pathway for nigerpyrone (**212**).

2.9.3. Benzopyranones and Naphthopyranones

Aspergchromones A (**220**) and B (**221**), together with noreugenin (**222**, Figure 14), were two new benzopyranones from the marine sponge-derived strain SCSIO XWS03F03 [65]. By deletion of the epigenetic regulator *gcnE* in strain *A. niger* FGSC A1279, two naphthopyranones, aurasperones A (**223**) and Fonsecinone D (**224**) were synthesized, and compound **223** showed a potent inhibitory effect on brine shrimp with an LD_{50} value of 9 ppm [107,109]. In addition to **124**, five naphthopyranone analogs (**225**–**229**) were also produced by the symbiotic strain *A. fumigatus* D but displayed no potent antimicrobial activity [70].

2.10. Quinones

Quinones constitute an important class of naturally occurring compounds containing unsaturated cyclic ketone(s) [110]. On the basis of chemical structure, *Aspergillus*-derived quinones (**230**–**277**) could be divided into three types, including anthraquinone, benzoquinone and naphthoquinone, in which the first is the major subgroup [111].

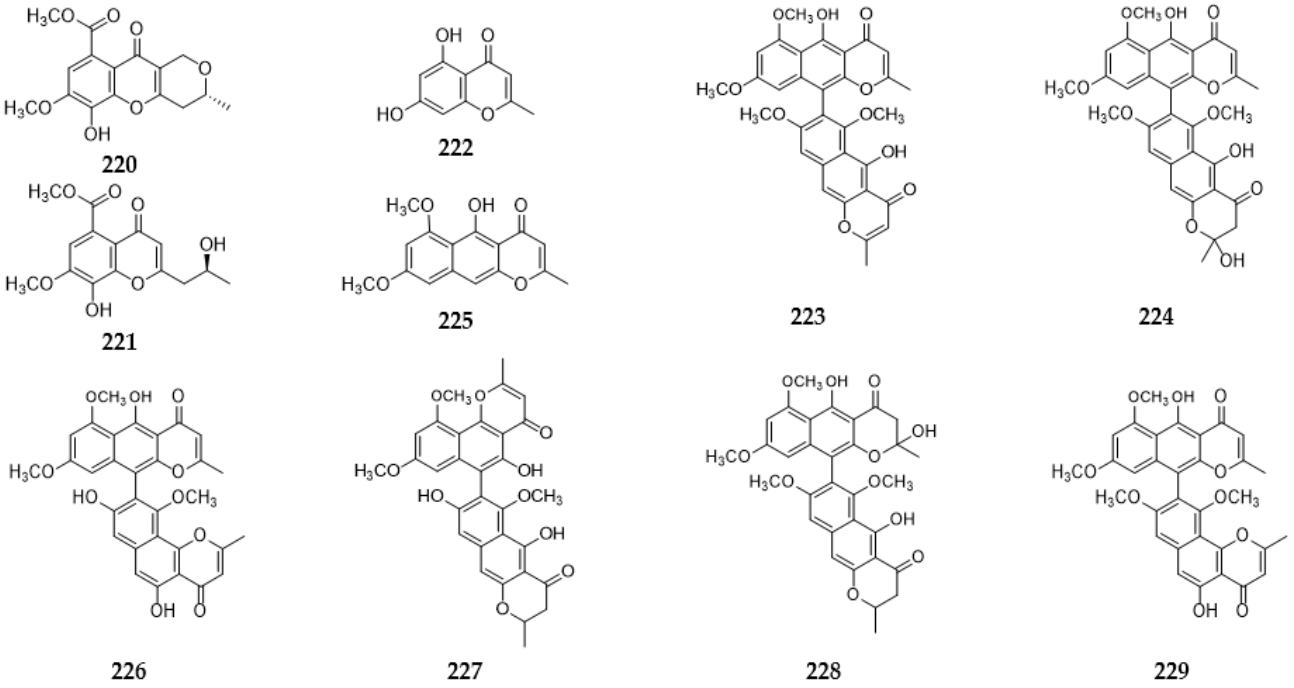


Figure 14. *Aspergillus*-derived benzopyranones (**220**–**222**) and naphthopyranones (**223**–**229**).

2.10.1. Anthraquinones

Anthraquinones are a group of structurally diverse and biologically active natural products with therapeutic effects [112,113]. Several chemical studies suggested that the marine-derived fungus *A. glaucus* HB1-19 was a versatile producer of anthraquinone polyketides (**230**–**242**, Figure 15), which compounds **230** and **231** displayed potent cytotoxicities against A-549, HL-60, BEL-7402, and P388 cell lines and **241** and **242** had strong inhibitory effects on the receptor tyrosine kinases (RTKs) c-Met, Ron, and c-Src with low-micromolar IC_{50} values [79,114,115]. In addition to the aromatic polyketide **151**, substances **243**–**247** were obtained from the marine strain *A. versicolor*, and **243**, **244**, and **246** exhibited significant cytotoxicity against five human solid tumor cell lines (A-549, SK-OV-3, SK-MEL-2, XF-498, and HCT-15) with IC_{50} values in the range of 0.41–4.61 μg/mL and **243** and **246** also showed excellent antibacterial activity against several clinical Gram-positive strains with MIC values of 0.78–6.25 μg/mL [85]. Sanghaspirodins A (**248**) and B (**249**) were two novel antiproliferative agents from strain *A. nidulans* grown in a chemostat under nitrogen limitation [116]. Two anthraquinones (**250** and **251**) were synthesized by inducing the expression of the silent PKS gene in *A. nidulans* FGSCA4 under a continuous cultivation regime [117]. Compounds **252** and **253** were produced by the fumarole-derived strain *A. terreus* C9408-3 when cultured at 40 °C for 7 days on potato dextrose agar plates [13]. Dermolutein (**254**) and methylemodin (**255**), along with compounds **240** and **256**–**258**, were purified from the EtOAc extract of *A. europaeus* WZXY-SX-4-1 and exerted remarkable down-regulation of NF-κB in LPS-induced SW480 cells [16]. By disruption of a global regulator *LaeB* in *A. nidulans*, a potent aggregation inhibitor asperthecin (**259**) was identified from a mutant by a filter trap assay and electron microscopy [118]. Versiconol B (**260**) together with three analogs (**247**, **261**, **262**) produced by strain *A.* sp. F40 showed weak antimicrobial activity against *S. aureus* and *V. parahaemolyticus* [90]. In addition to the common metabolite **234**, compounds **263**–**267** were detected in the crude extracts of two marine strains *A. sydowii* SCSIO 41301 and *A. terreus* SCSIO 41008 [33,69], and **234**, **264** and **265** exhibited broad inhibitory activities against H1N1 and H3N influenzas. Whereas strain *A. versicolor* HBU-2017-7-derived, two anthraquinones (**268**) and (**269**) showed no antibacterial or cytotoxic activity [119].

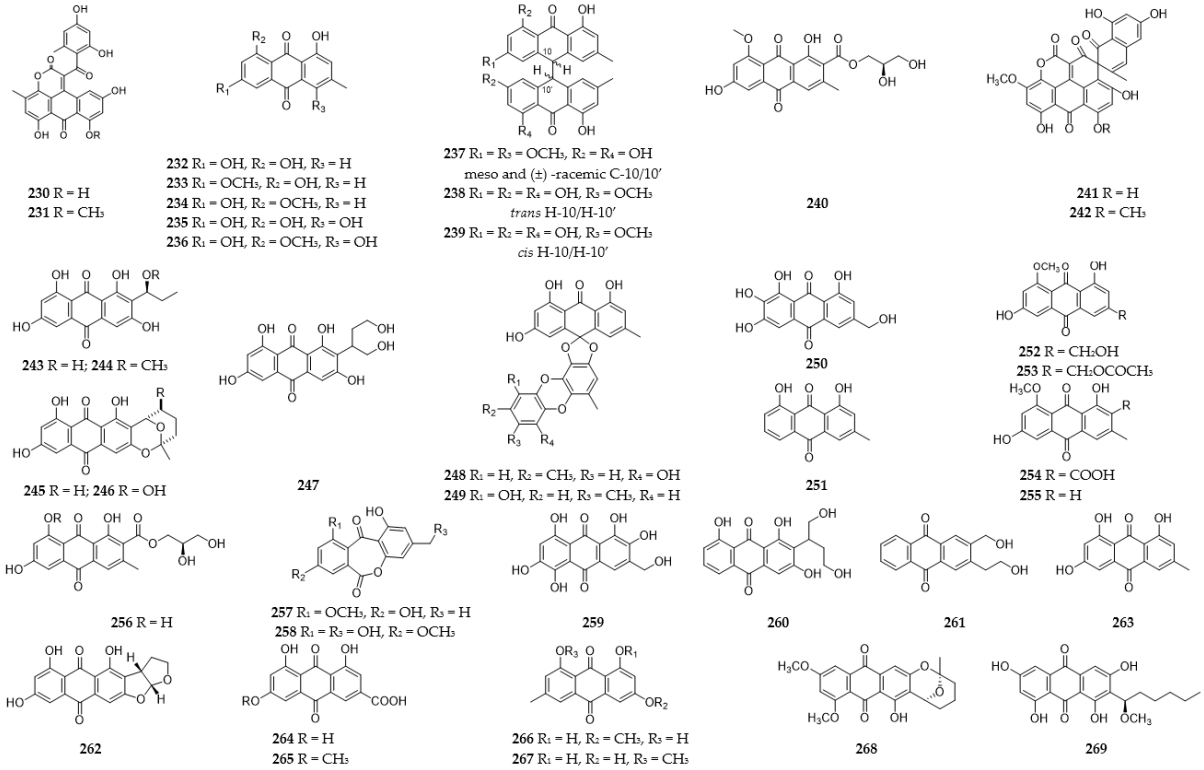


Figure 15. *Aspergillus*-derived anthraquinones (**230**–**269**).

2.10.2. Benzoquinones and Naphthoquinones

By HPLC-MS analysis, a toxic benzoquinone spinulosin (**270**, Figure 16) was detected in the SMs of several *A. flavus* strains and displayed effective nematicidal activity against *B. xylophilus* without any plant growth inhibition [30,120,121]. Terreic acid (**271**) produced by strain *A. terreus* ATCC 20542 was a potential anticancer agent with an inhibitory effect on Bruton's tyrosine kinase [56,122]. Phomaligol A (**272**) and phomaligol A1 (**273**) were two new isomeric benzoquinones discovered from the fermentation culture of *A. flocculus*, and the later possessed a moderate anti-trypanosome activity against *T. brucei* with an MIC of 25 μg/mL [22]. Csypyrone B1 (**274**) was identified as a *csyB* gene product by overexpression under the control of α-amylase promoter in *A. oryzae* M-2-3 [123]. A new naphthoquinone derivative, aspergiodiquinone (**275**), was obtained from a marine-derived *A. glaucus* HB1-19 [28]. From the solid rice medium of marine strain SCSIO XWS03F03, (4*S*)-6-hydroxyisosclerone (**276**) and (-)-regiolone (**277**) were discovered, while the later was shown to be a phytotoxin [65,124].

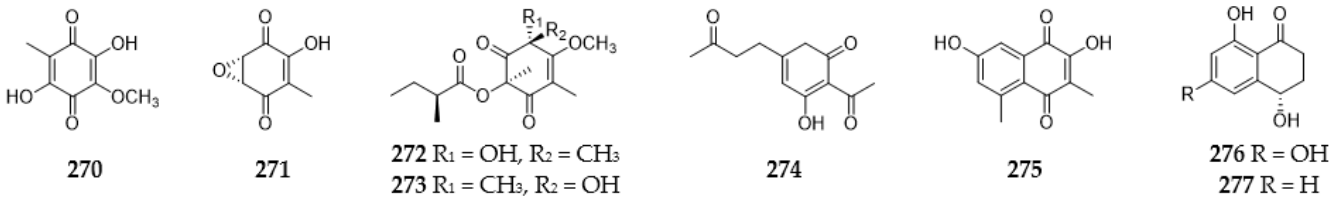


Figure 16. *Aspergillus*-derived benzoquinones (**270**–**274)** and naphthoquinones (**275**–**277**).

2.11. Steroids

Steroids are cyclopentane polyhydrophenanthrenes and play an important role in life activities [125,126]. Ergosterol (**278**, Figure 17) was isolated and identified from an endophytic strain *A.* sp. TJ23 and exhibited anticancer activities against cell lines B16, MDA-MB-231, 4Tl, HepG2 and LLC with IC_{50} values ranging from 5.13 to 12.3 μM [63]. An ergosterol peroxide (**279**) and campesterol (**280**) were obtained from the fermentation

culture of an oyster-derived *A. flocculus* by using modern metabolomics technology [22], and the former displayed an inhibitory effect on the migration of MDA-MB-231 cells at <20 μM [127,128]. An epoxide steroid (**281**) was discovered from the deep-sea strain *A.* sp. SCSIO 41017 was shown to possess moderate activity against cancer cell lines SF-268, MCF-7, HepG-2 and A549 with IC_{50} values of 13.5–18.0 μM [129].

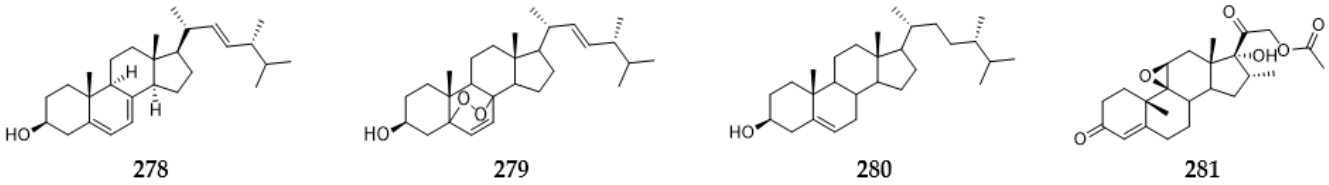


Figure 17. *Aspergillus*-derived steroids (**278**–**281**).

2.12. Meroterpenoids

Meroterpenoids as polyketide-terpenoid hybrids are a family of fungal metabolites possessing significant biological activities [130]. However, only a small group of meroterpenoids (**282**–**292**, Figure 18) had been isolated and characterized from *Aspergillus* strains. Terretonin (**282**), produced by a strain of *A. terreus*, had a novel, heavily oxidized 25-carbon skeleton and was presumably derived from the degradation of a triterpene precursor [131]. Co-cultivation of a strain of *A. fumigatus* with the actinomycete *Streptomyces rapamycinicus* afforded the production of two new prenylated polyketides (**283** and **284**) [132]. Parasiticolide A (**285**) was the common SM of two strains of *A. flavus* and *A. parasiticus* IFO 4082 [30,133]. Spiroaspertrione A (**286**) was a novel terpene-polyketide hybrid bearing a unique spiro[bicyclo[3.2.2]nonane-2,1′-cyclohexane] carbocyclic skeleton produced by strain *Aspergillus* TJ23 and performed as an effective potentiator for oxacillin in suppressing MRSA growth by reducing the oxacillin MIC up to 32-fold [134].

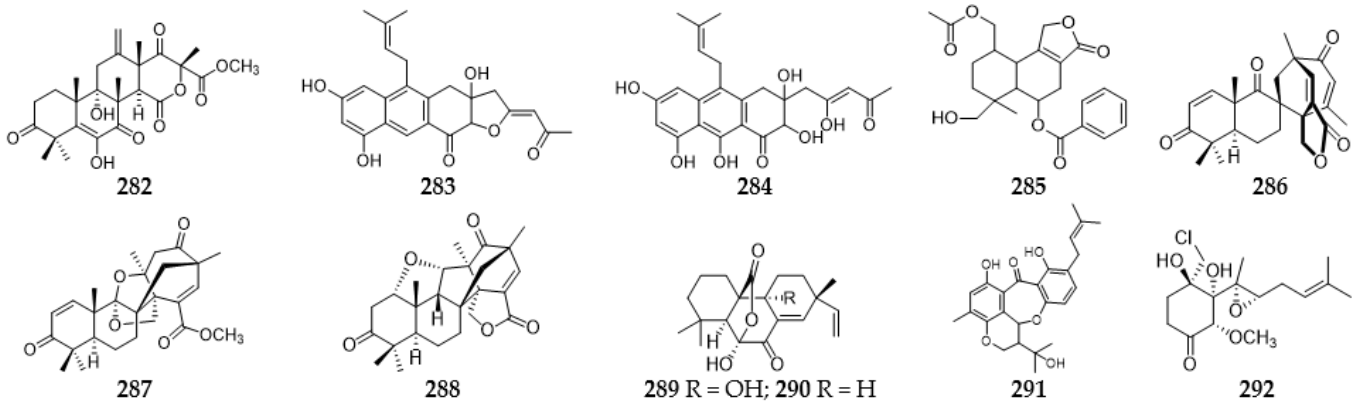


Figure 18. *Aspergillus*-derived meroterpenoids (**282**–**292**).

Additionally, chemical analysis of the liquid cultures of strain TJ23 resulted in the discovery of two novel terpene-polyketide hybrids (**287** and **288**), of which compound **287** was a potential inhibitor of PBP2a and worked synergistically with the *β*-lactam antibiotics oxacillin and piperacillin against MRSA [135]. Sphaeropsidin A (**289**), along with aspergiloid E (**290**), was obtained from an endophytic fungus *A. porosus* [87] and recently gained interest as a cytotoxic agent, showing selectivity toward melanoma and kidney cancer cell lines with a unique mechanism of action targeting regulatory volume increase [136]. Arugosin C (**291**) was a novel prenylated polyketide produced by a marine-derived fungus, *A. versicolor* HBU-2017-7, but exhibited no inhibitory activity against HCV protease [119,137]. Chlovalicin (**292**) was determined as a new chlorinated meroterpenoid from strain *A. niger* BRF-074 and displayed no cytotoxicity towards the HCT-116 cell line [138].

2.13. Xanthones

Xanthones are a class of natural products with hetero-tricyclic structures possessing a variety of biological activities, including antihypertensive, anticonvulsant, antithrombotic, antitumor and so on [139–143]. Two new xanthones (**293** and **294**, Figure 19) were purified from a marine sponge-derived fungus *A. versicolor* [85], and compound **293**, along with its derivative (**295**), was also obtained from strain *A. versicolor* HBU-2017-7 and shown to have significant cytotoxicity [119]. By continuous cultivation for activating silent polyketide BGCs in strain *A. nidulans* FGSCA4, a new prenylated cytotoxic xanthone (**296**) was discovered in its chemostat cultures [144]. Two xanthone dimers (**297** and **298**) originally produced by *A. aculeatus* in 1977 were rediscovered from strains *A.* sp. SCSIO XWS03F03 and *A. aculeatus* IBT 21030 [65,145]. Bioassay-guided fractionation of the crude extract of a soil fungus *A. terreus* X3 resulted in the isolation of penicitrinones A and B (**299** and **300**), which the former showed moderate activity against *B. megaterium* with a MIC value of 1.60 μM [29]. Four prenylated xanthones (**301**–**304**) were separated from the rice medium of the endophytic strain *A.* sp. TJ23 exhibited weak inhibitory activities against the growth of B16, HepG2, and LLC cancer cell lines [58]. Chemical analysis of a marine sponge-derived strain *A. europaeus* WZXY-SX-4-1 afforded six xanthone polyketides (**305**–**310**), of which compounds **305** and **310** exerted excellent down-regulation of NF-κB in LPS-induced SW480 cells [16]. Oxisterigmatocystin I (**311**), along with four analogs (**293**, **312**–**314**), were purified from the culture of a sponge-derived strain *A.* sp. F40 and showed weak antimicrobial activity against *S. aureus* [90]. When cultured under static conditions, strain *A. sydowii* SCSIO 41301 was found to produce two new xanthones (**315** and **316**), which exhibited obvious selective inhibitory activity against H1N1 influenza [33].

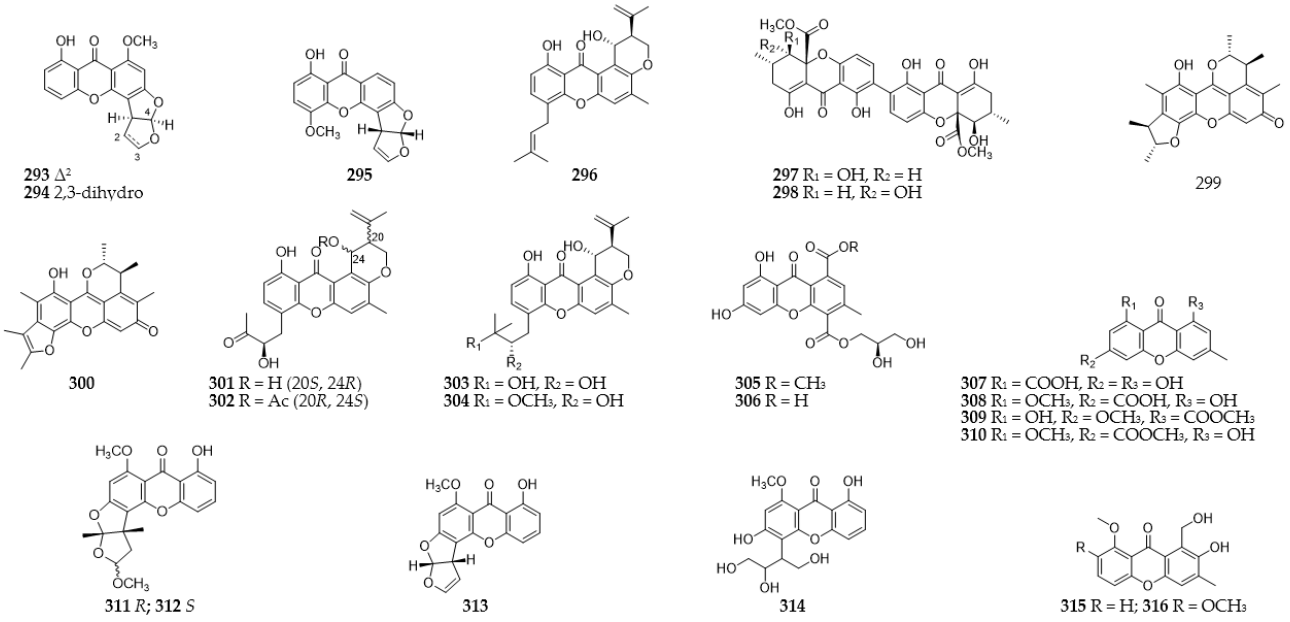


Figure 19. *Aspergillus*-derived xanthones (**293**–**316**).

2.14. Miscellaneous

A number of other bioactive polyketides had been discovered and identified from *Aspergillus* strains. Mevinolin (**317**, Figure 20), along with its analog **318**, was obtained from strain *A. terreus* ATCC 20542 and exhibited a potent competitive inhibitory effect on hydroxymethylglutaryl coenzyme A (HMG CoA) reductase [146]. Aspermytin A (**319**) was a new neurotrophic agent produced by a mussel-derived strain of *Aspergillus* [147]. Three decaline derivatives (**320**–**322**) showed significant cytotoxicity against melanoma cell lines [148,149]. Calbistrin A (**323**), together with its analog (**324**) derived from strain *A. aculeatus* IBT 21030, acted as an excellent antifungal agent, a promoter of nerve growth factor

(NGF) production and a cholesterol-lowering substance [150,151]. Two lovastatin analogs (**325** and **326**) were detected in the solid culture of *A. versicolor* SC0156 [152]. Aspergones N-Q (**327**–**330**), along with epoxyquinol (**331**) were separated from the fermentation broth of *A.* sp. OUCMDZ-1583 and displayed strong α-glucosidase inhibitory effects [45]. Salimyxin B (**332**) produced by the endophytic strain *A.* sp. TJ23 showed inhibitory activities against HepG2 with an IC_{50} value of 9.87 μM [58]. Hexylitaconic acid (**333**) was a binary fatty acid originally derived from a marine-derived fungus *Arthrinium* sp., was also produced by the strain of *A. niger* and showed potent antibacterial and antioxidant activities as well as good inhibitory effect on acetylcholinesterase and p53–HDM2 interaction [41,153,154].

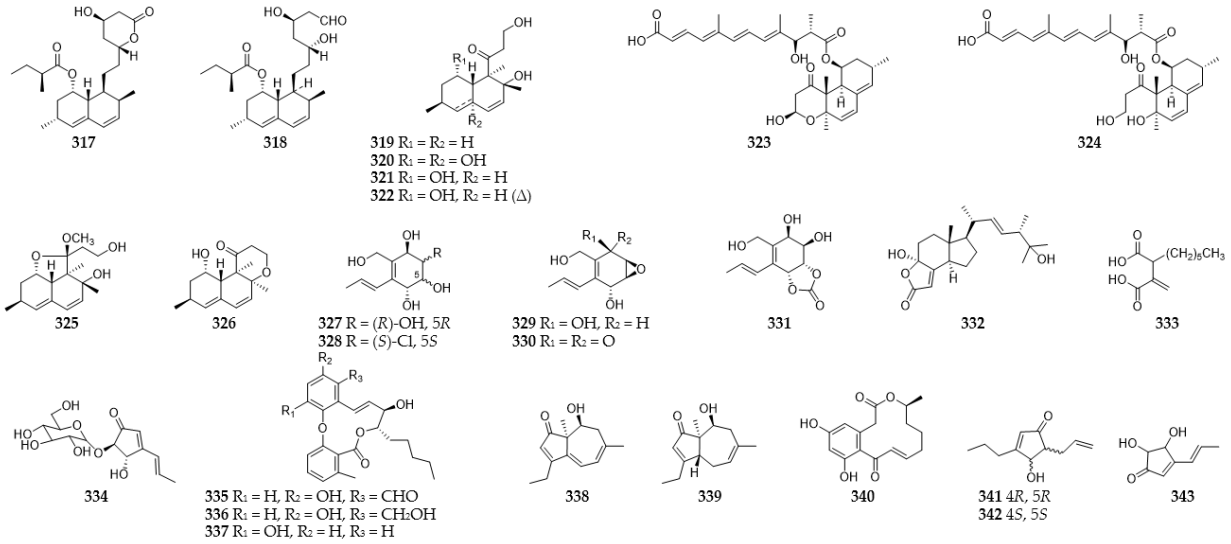


Figure 20. *Aspergillus*-derived miscellaneous compounds (**317**–**343**).

A terrein glucoside (**334**) was a new angiogenin secretion inhibitor produced by strain *A.* sp. PF1381 [155]. Bioassay-guided isolation of an extract of *A.* sp. MF6215 led to the discovery of three novel 11-membered macrocyclic biphenyl ether lactones (**335**–**337**), in which compound **335** inhibited the IgE binding to its receptor by an IC_{50} value of 200 μM [156]. By UHPLC-DAD-HRMS and dereplication, aculenes C and D (**338** and **339**) were isolated from a strain of *A. aculeatus* but showed weak antifungal activity [150]. Dehydrocurvularin (**340**) was a new lactone polyketide from strain *A. terreus* ATCC 20542 and acted as a prevalent fungal phytotoxin with heat shock response and immune-modulatory activities and a broad-spectrum inhibitor of various cancer cell lines in vitro [61,157,158]. Aspergones G and H (**341** and **342**) produced by the strain *A.* sp. OUCMDZ-1583 displayed no cytotoxic activity [45]. *A. flavus*-derived terrein (**343**) was a novel suppressor of ABCG2-expressing breast cancer cells MCF-7 cells [13,30].

3. Conclusions and Perspectives

In summary, the genus *Aspergillus* is a prolific source of polyketides with diverse chemical structures and a variety of biological activities. Many of these substances or derivatives have therapeutic effects, such as the immunosuppressant agent (**3**), the antioxidant benzaldehydes (**34**,**35**), the α-glucosidase inhibitors (**327**–**330**), etc. Furthermore, the potential to discover novel polyketides from *Aspergillus* strains is still immense since a great number of their BGCs are shown to be inactive or unawakened under traditional culture conditions [159]. With the development and application of bioinformative tools and analytical techniques, more and more *Aspergillus* genomes, as well as functional genes, will be sequenced and annotated. These silent BGCs responsible for the biosynthesis of novel polyketides are being disclosed and activated using new strategies, such as the one strain many compounds (OSMAC) approach and genome mining combined with metabolic engineering [8,160,161]. In addition, the biosynthesis of polyketides from acyl-CoA thioesters

is catalyzed by various PKSs, which structures of initiation and condensation domains provide valuable insights into the molecular factors governing starter unit selectivity and chain-length control. A detailed understanding of these PKS structural features controlling polyketide biosynthesis and modification offers a powerful tool for the controlled and rational design of novel polyketides through enzyme engineering. Therefore, more efforts should be made to employ biosynthetic engineering approaches to improve the efficient discovery of novel polyketides from the genus *Aspergillus*.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jof9020261/s1. Detailed information for *Aspergillus*-derived polyketides (**1**–**343**) is available in Table S1: Detail information for *Aspergillus*-derived polyketides.

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References

1. Alberti, F.; Foster, G.D.; Bailey, A.M. Natural products from filamentous fungi and production by heterologous expression. *Appl. Microbiol. Biotechnol.* **2016**, *101*, 493–500. [CrossRef] [PubMed]
2. Bills, G.F.; Gloer, J.B. Biologically active secondary metabolites from the fungi. *Microbiol. Spectr.* **2016**, *4*, 1087–1119. [CrossRef] [PubMed]
3. Theobald, S.; Vesth, T.C.; Rendsvig, J.K.; Nielsen, K.F.; Riley, R.; de Abreu, L.M.; Salamov, A.; Frisvad, J.C.; Larsen, T.O.; Andersen, M.R.; et al. Uncovering secondary metabolite evolution and biosynthesis using gene cluster networks and genetic dereplication. *Sci. Rep.* **2018**, *8*, 17957. [CrossRef] [PubMed]
4. Xiong, Z.; Cao, X.H.; Wen, Q.Y.; Chen, Z.T.; Cheng, Z.X.; Huang, X.Y.; Zhang, Y.X.; Long, C.N.; Zhang, Y.; Huang, Z. An overview of the bioactivity of monacolin K/lovastatin. *Food Chem. Toxicol.* **2019**, *131*, 110585. [CrossRef] [PubMed]
5. Aubel-Sadron, G.; Londos-Gagliardi, D. Daunorubicin and doxorubicin, anthracycline antibiotics, a physicochemical and biological review. *Biochimie* **1984**, *66*, 333–352. [CrossRef] [PubMed]
6. Hawkyard, C.V.; Koerner, R.J. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: Benefits versus risks. *J. Antimicrob. Chemother.* **2007**, *59*, 347–358. [CrossRef]
7. Chooi, Y.-H.; Tang, Y. Navigating the fungal polyketide chemical space: From genes to molecules. *J. Org. Chem.* **2012**, *77*, 9933–9953. [CrossRef]
8. Yu, R.; Liu, J.; Wang, Y.; Wang, H.; Zhang, H. *Aspergillus niger* as a Secondary Metabolite Factory. *Front. Chem.* **2021**, *9*, 701022. [CrossRef]
9. Dictionary of Natural Products. Available online: https://dnp.chemnetbase.com/faces/chemical/ChemicalSearch.xhtml (accessed on 31 December 2022).
10. Mihai, D.M.; Hall, S.; Deng, H.; Welch, C.J.; Kawamura, A. Benzophenone and its analogs bind to human glyoxalase 1. *Bioorganic Med. Chem. Lett.* **2015**, *25*, 5349–5351. [CrossRef]
11. Sarkara, A.; Funka, A.N.; Scherlach, K.; Horn, F.; Schroeckh, V.; Chankhamjon, P.; Westermann, M.; Roth, M.; Brakhage, A.A.; Hertweck, C.; et al. Differential expression of silent polyketide biosynthesis gene clusters in chemostat cultures of *As-pergillus* nidulans. *J. Biotechnol.* **2012**, *160*, 64–71. [CrossRef]
12. Wu, Q.; Wu, C.M.; Long, H.L.; Chen, R.; Liu, D.; Proksch, P.; Guo, P.; Lin, W.H. Varioxiranols A-G and 19-o-methyl-22-methoxypreshamixanthone, PKS and hybrid PKS-derived metabolites from a sponge-associated *Emericella variecolor fungus*. *J. Nat. Prod.* **2015**, *78*, 2461–2470. [CrossRef] [PubMed]
13. Liao, W.-Y.; Shen, C.-N.; Lin, L.-H.; Yang, Y.-L.; Han, H.-Y.; Chen, J.-W.; Kuo, S.-C.; Wu, S.-H.; Liaw, C.-C. Asperjinone, a nor-neolignan, and terrein, a suppressor of ABCG2-expressing breast cancer cells, from thermophilic *Aspergillus terreus*. *J. Nat. Prod.* **2012**, *75*, 630–635. [CrossRef] [PubMed]

14. Hamed, A.; Ismail, M.; Shaaban, M. X-ray, structural assignment and molecular docking study of dihydrogeodin from As-pergillus terreus TM8. *Nat. Prod. Res.* **2019**, *33*, 117–121. [CrossRef] [PubMed]
15. Zhang, L.-H.; Feng, B.-M.; Zhao, Y.-Q.; Sun, Y.; Liu, B.; Liu, F.; Chen, G.; Bai, J.; Hua, H.-M.; Wang, H.-F.; et al. Polyketide butenolide, diphenyl ether, and benzophenone derivatives from the fungus *Aspergillus flavipes* PJ03-11. *Bioorganic Med. Chem. Lett.* **2016**, *26*, 346–350. [CrossRef] [PubMed]
16. Du, X.; Liu, D.; Huang, J.; Zhang, C.; Proksch, P.; Lin, W. Polyketide derivatives from the sponge associated fungus *Aspergillus europaeus* with antioxidant and no inhibitory activities. *Fitoterapia* **2018**, *130*, 190–197. [CrossRef] [PubMed]
17. Kini, S.G.; Rathi, E.; Kumar, A.; Bhat, V. Potentials of diphenyl ether scaffold as a therapeutic agent: A review. *Mini Rev. Med. Chem.* **2019**, *19*, 1392–1406. [CrossRef]
18. Lin, H.; Lyu, H.N.; Zhou, S.; Yu, J.W.; Keller, N.P.; Chen, L.; Yin, W.B. Deletion of a global regulator LaeB leads to the discovery of novel polyketides in *Aspergillus nidulans*. *Org. Biomol. Chem.* **2018**, *16*, 4973–4976. [CrossRef]
19. Schroeckh, V.; Scherlach, K.; Nützmann, H.-W.; Shelest, E.; Schmidt-Heck, W.; Schuemann, J.; Martin, K.; Hertweck, C.; Brakhage, A.A. Intimate bacterial–fungal interaction triggers biosynthesis of archetypal polyketides in *Aspergillus nidulans*. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 14558–14563. [CrossRef]
20. Zhuang, Y.B.; Teng, X.C.; Wang, Y.; Liu, P.P.; Wang, H.; Li, J.; Li, G.Q.; Zhu, W.M. Cyclopeptides and polyketides from coral-associated fungus, *Aspergillus versicolor* LCJ-5-4. *Tetrahedron* **2011**, *67*, 7085–7089. [CrossRef]
21. Ohashi, H.; Akiyama, H.; Nishikori, K.; Mochizuki, J.-I. Asterric acid, a new endothelin binding inhibitor. *J. Antibiot.* **1992**, *45*, 1684–1685. [CrossRef]
22. Tawfike, A.F.; Romli, M.; Clements, C.; Abbott, G.; Young, L.; Schumacher, M.; Diederich, M.; Farag, M.; Edrada-Ebel, R. Isolation of anticancer and anti-trypanosome secondary metabolites from the endophytic fungus *Aspergillus flocculus* via bioactivity guided isolation and MS based metabolomics. *J. Chromatogr. B* **2019**, *1106–1107*, 71–83. [CrossRef] [PubMed]
23. Mohanlall, V.; Odhav, B. Furans and furanones with antimycotoxigenic activity isolated from *Warburgia salutaris (Canel-laceae)*. *J. Med. Plants Res.* **2009**, *3*, 231–240. [CrossRef]
24. Varoglu, M.; Crews, P. Biosynthetically diverse compounds from a saltwater culture of sponge-derived *Aspergillus niger*. *J. Nat. Prod.* **1999**, *63*, 41–43. [CrossRef] [PubMed]
25. Pettit, G.R.; Du, J.; Pettit, R.K.; Knight, J.C.; Doubek, D.L. Antineoplastic agents. 575. The Fungus *Aspergillus phoenicis*. *Heterocycles* **2009**, *79*, 909. [CrossRef]
26. Chiang, Y.-M.; Szewczyk, E.; Davidson, A.D.; Keller, N.; Oakley, B.R.; Wang, C.C.C. A gene cluster containing two fungal polyketide synthases encodes the biosynthetic pathway for a polyketide, asperfuranone, in *Aspergillus nidulans*. *J. Am. Chem. Soc.* **2009**, *131*, 2965–2970. [CrossRef]
27. Wang, C.C.C.; Chiang, Y.-M.; Praseuth, M.B.; Kuo, P.-L.; Liang, H.-L.; Hsu, Y.-L. Asperfuranone from *Aspergillus nidulans* inhibits proliferation of human non-small cell lung cancer A549 cells via blocking cell cycle progression and inducing apoptosis. *Basic Clin. Pharmacol. Toxicol.* **2010**, *107*, 583–589. [CrossRef]
28. 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. [CrossRef]
29. Xu, L.-L.; Cao, F.; Tian, S.-S.; Zhu, H.-J. Alkaloids and polyketides from the soil fungus *Aspergillus terreus* and their antibacterial activities. *Chem. Nat. Compd.* **2017**, *53*, 1212–1215. [CrossRef]
30. Saldan, N.C.; Almeida, R.T.R.; Avíncola, A.; Porto, C.; Galuch, M.B.; Magon, T.F.S.; Pilau, E.J.; Svidzinski, T.I.E.; Oliveira, C.C. Development of an analytical method for identification of *Aspergillus flavus* based on chemical markers using HPLC-MS. *Food Chem.* **2018**, *241*, 113. [CrossRef]
31. Evidente, A.; Cristinzio, G.; Punzo, B.; Andolfi, A.; Testa, A.; Melck, D. ChemInform abstract: Flufuran, an antifungal 3,5-Disubstituted furan produced by *Aspergillus flavus* link. *Chem. Biodivers.* **2009**, *6*, 328–334. [CrossRef]
32. Tanahashi, T.; Takenaka, Y.; Nagakura, N.; Hamada, N. Dibenzofurans from the cultured lichen mycobionts of *Lecanora cinereocarnea*. *Phytochemistry* **2001**, *58*, 1129–1134. [CrossRef] [PubMed]
33. Liu, N.; Peng, S.; Yang, J.; Cong, Z.; Lin, X.; Liao, S.; Yang, B.; Zhou, X.; Zhou, X.; Liu, Y.; et al. Structurally diverse sesquiterpenoids and polyketides from a sponge-associated fungus *Aspergillus sydowii* SCSIO41301. *Fitoterapia* **2019**, *135*, 27–32. [CrossRef] [PubMed]
34. Zou, Z.-B.; Zhang, G.; Li, S.-M.; He, Z.-H.; Yan, Q.-X.; Lin, Y.-K.; Xie, C.-L.; Xia, J.-M.; Luo, Z.-H.; Luo, L.-Z.; et al. Asperochratides A–J, ten new polyketides from the deep-sea-derived *Aspergillus ochraceus*. *Bioorganic Chem.* **2020**, *105*, 104349. [CrossRef] [PubMed]
35. Chen, W.; Liu, H.; Long, J.; Tao, H.; Lin, X.; Liao, S.; Yang, B.; Zhou, X.; Liu, Y.; Wang, J. Asperpentenone A, a novel polyketide isolated from the deep-sea derived fungus *Aspergillus* sp. SCSIO 41024. *Phytochem. Lett.* **2019**, *35*, 99–102. [CrossRef]
36. Steyn, P.S.; Vleggaar, R.; Simpson, T.J. Stable isotope labelling studies on the biosynthesis of asticolorin C by *Aspergillus multicolor*. Evidence for a symmetrical intermediate. *J. Chem. Soc. Chem. Commun.* **1984**, *12*, 765–767. [CrossRef]
37. Rabie, C.J.; Simpson, T.J.; Steyn, P.S.; van Rooyen, P.H.; Vleggaar, R. Structure and absolute configuration of the asticolorins, toxic metabolites from *Aspergillus multicolor*. *J. Chem. Soc. Chem. Commun.* **1984**, *12*, 764–765. [CrossRef]
38. Abrell, L.M.; Borgeson, B.; Crews, P. Chloro polyketides from the cultured fungus (*Aspergillus*) separated from a marine sponge. *Tetrahedron Lett.* **1996**, *37*, 2331–2334. [CrossRef]
39. Nguyen, H.; Yu, N.; Jeon, S.; Lee, H.; Bae, C.-H.; Yeo, J.; Kim, I.-S.; Park, H.; Kim, J.-C. Antibacterial activities of penicillic acid isolated from *Aspergillus persii* against various plant pathogenic bacteria. *Lett. Appl. Microbiol.* **2016**, *62*, 488–493. [CrossRef]

40. Qi, C.; Gao, W.; Guan, D.; Wang, J.; Liu, M.; Chen, C.; Zhu, H.; Zhou, Y.; Lai, Y.; Hu, Z.; et al. Butenolides from a marine-derived fungus *Aspergillus terreus* with antitumor activities against pancreatic ductal adenocarcinoma cells. *Bioorganic Med. Chem.* **2018**, *26*, 5903–5910. [CrossRef]
41. Yang, X.-L.; Awakawa, T.; Wakimoto, T.; Abe, I. Three acyltetronic acid derivatives: Noncanonical cryptic polyketides from *Aspergillus niger* identified by genome mining. *ChemBioChem* **2014**, *15*, 1578–1583. [CrossRef]
42. Koch, L.; Lodin, A.; Herold, I.; Ilan, M.; Carmeli, S.; Yarden, O. Sensitivity of *Neurospora crassa* to a marine-derived *Aspergillus tubingensis* anhydride exhibiting antifungal activity that is mediated by the mas1 protein. *Mar. Drugs* **2014**, *12*, 4713–4731. [CrossRef] [PubMed]
43. Chen, X.-W.; Li, C.-W.; Cui, C.-B.; Hua, W.; Zhu, T.-J.; Gu, Q.-Q. Nine new and five known polyketides derived from a deep sea-sourced *Aspergillus* sp. 16-02-1. *Mar. Drugs* **2014**, *12*, 3116–3137. [CrossRef] [PubMed]
44. Liu, Y.; Li, X.-M.; Meng, L.-H.; Wang, B.-G. Polyketides from the marine mangrove-derived fungus *Aspergillus ochraceus* MA-15 and their activity against aquatic pathogenic bacteria. *Phytochem. Lett.* **2015**, *12*, 232–236. [CrossRef]
45. Kong, F.D.; Zhao, C.Y.; Hao, J.J.; Wang, C.; Wang, W.; Huang, X.L.; Zhu, W.M. New α-glucosidase inhibitors from a marine sponge-derived fungus, *Aspergillus* sp. OUCMDZ-1583. *RSC Adv.* **2015**, *5*, 68852–68863. [CrossRef]
46. Phainuphong, P.; Rukachaisirikul, V.; Tadpetch, K.; Sukpondma, Y.; Saithong, S.; Phongpaichit, S.; Preedanon, S.; Sakayaroj, J. Gamma-butenolide and furanone derivatives from the soil-derived fungus *Aspergillus sclerotiorum* PSU-RSPG178. *Phytochemistry* **2017**, *137*, 165–173. [CrossRef]
47. Wijeratne, E.M.K.; Xu, Y.M.; Arnold, A.E.; Gunatilaka, A.A.L. Pulvinulin A, graminin C, and cis-gregatin B—new natural furanones from *Pulvinula* sp. 11120, a fungal endophyte of cupressus arizonica. *Nat. Prod. Commun.* **2015**, *10*, 107–111. [CrossRef]
48. Brookes, D.; Tidd, B.K.; Turne, W.B. Avenaciolide, an antifuingal lactone from *Aspergillus avenaceus*. *J. Chem. Soc.* **1963**, *68*, 5385–5391. [CrossRef]
49. Castelo-branco, P.A.; Rubinger, M.M.M.; Alves, L.D.C.; de Barros, P.M.; Pereira, S.G.; de Melo, V.J.; Pilo-Veloso, D.; Zambolim, L. Synthesis and antifungal activity of aromatic bis-gamma-lactones analogous to avenaciolide. *Chem. Biodivers.* **2007**, *4*, 2745–2754. [CrossRef]
50. Yin, G.P.; Wu, Y.R.; Yang, M.H.; Li, T.X.; Wang, X.B.; Zhou, M.M.; Lei, J.L.; Kong, L.Y. Citrifurans A-D, four dimeric aromatic polyketides with new carbon skeletons from the fungus *Aspergillus* sp. *Org. Lett.* **2017**, *19*, 4058–4061. [CrossRef]
51. Yin, G.P.; Wu, Y.R.; Han, C.; Wang, X.B.; Gao, H.L.; Yin, Y.; Kong, L.Y.; Yang, M.H. Asperones A–E, five dimeric polyketides with new carbon skeletons from the fungus *Aspergillus* sp AWG 1–15. *Org. Chem. Front.* **2018**, *5*, 2432–2436. [CrossRef]
52. Garson, M.J.; Staunton, J.; Jones, P.G. New polyketide metabolites from *Aspergillus melleus*: Structural and stereochemical studies. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1021–1026. [CrossRef]
53. Sakhri, A.; Chaouche, N.K.; Catania, M.R.; Ritieni, A.; Santini, A. Chemical composition of *Aspergillus creber* extract and evaluation of its antimicrobial and antioxidant activities. *Pol. J. Microbiol.* **2019**, *68*, 309–316. [CrossRef] [PubMed]
54. Sohn, J.-H.; Oh, H.-C. Protulactones A and B: Two new polyketides from the marine-derived fungus *Aspergillus* sp. SF-5044. *Bull. Korean Chem. Soc.* **2010**, *31*, 1695–1698. [CrossRef]
55. Sadorn, K.; Saepua, S.; Boonyuen, N.; Laksanacharoen, P.; Rachtawee, P.; Prabpai, S.; Kongsaeree, P.; Pittayakhajonwut, P. Allahabadolactones A and B from the endophytic fungus, *Aspergillus allahabadii* BCC45335. *Tetrahedron* **2016**, *72*, 489–495. [CrossRef]
56. Boruta, T.; Bizukojc, M. Culture-based and sequence-based insights into biosynthesis of secondary metabolites by *Aspergillus terreus* ATCC 20542. *J. Biotechnol.* **2014**, *175*, 53–62. [CrossRef]
57. Sato, S.; Okusa, N.; Ogawa, A.; Ikenoue, T.; Seki, T.; Tsuji, T. Identification and preliminary SAR studies of (+)-geodin as a glucose uptake stimulator for rat adipocytes. *J. Antibiot.* **2005**, *58*, 583–589. [CrossRef]
58. Qiao, Y.B.; Tu, K.; Feng, W.Y.; Liu, J.J.; Xu, Q.Q.; Tao, L.; Zhu, H.C.; Chen, C.M.; Wang, J.P.; Xue, Y.B.; et al. Polyketide and prenylxanthone derivatives from the endophytic fungus *Aspergillus* sp. TJ23. *Chem. Biodivers.* **2018**, *15*, e1800395. [CrossRef]
59. Suemitsu, R.; Ohnishi, K.; Horiuchi, M.; Morikawa, Y.; Sakaki, Y.; Matsumoto, Y. Structure of porriolide, a new metabolite from *Alternaria porri*. *Biosci. Biotech. Biochem.* **1993**, *57*, 334–335. [CrossRef]
60. Yang, X.-L.; Zhang, S.; Hu, Q.-B.; Luo, D.-Q.; Zhang, Y. Phthalide derivatives with antifungal activities against the plant pathogens isolated from the liquid culture of *Pestalotiopsis photiniae*. *J. Antibiot.* **2011**, *64*, 723–727. [CrossRef]
61. Frédérick, R.; Masereel, B. Coumarin and isocoumarin as serine protease inhibitors. *Curr. Pharm. Des.* **2004**, *10*, 3781–3796. [CrossRef]
62. Frederic, C.; Costa Cristine, A.; Erwan, A.; David, A.; Cecile, D.; Michael, F.; Jean-Francois, H.; Martinez, J.; Solveig, L.J.; Philippe, M.; et al. JLK inhibitors: Isocoumarin compounds as putative probes to selectively target the gamma-secretase pathway. *Curr. Alzheimer Res.* **2005**, *2*, 327–334. [CrossRef] [PubMed]
63. Hussain, H.; Green, I.R. A patent review of two fruitful decades (1997–2016) of isocoumarin research. *Expert Opin. Ther. Pat.* **2017**, *27*, 1267–1275. [CrossRef] [PubMed]
64. Cimmino, A.; Maddau, L.; Masi, M.; Linaldeddu, B.T.; Evidente, A. Secondary metabolites produced by *Sardiniella urbana*, a new emerging pathogen on European hackberry. *Nat. Prod. Res.* **2019**, *33*, 1862–1869. [CrossRef] [PubMed]
65. Wang, Y.; Lin, X.P.; Ju, Z.R.; Liao, X.J.; Huang, X.J.; Zhang, C.; Zhao, B.X.; Xu, S.H. Aspergchromones A and B, two new polyketides from the marine sponge-associated fungus *Aspergillus* sp. SCSIO XWS03F03. *J. Asian Nat. Prod. Res.* **2017**, *19*, 684–690. [CrossRef]

66. Bi, Y.-M.; Bi, X.-B.; Zhao, Q.-R.; Fang, A.; Chen, Y.-G. Dihydroisocoumarins from the Fungus *Cephalosporium* sp. AL031. *Pol. J. Chem.* **2006**, *80*, 397–401. [CrossRef]
67. Chang, S.B.; Abdel Kader, M.M.; Wick, E.L.; Wogan, G.N. Aflatoxin B2: Chemical identity and biological activity. *Science* **1963**, *142*, 1191–1192. [CrossRef]
68. Klich, M.A. *Aspergillus flavus*: The major producer of aflatoxin. *Mol. Plant Pathol.* **2007**, *8*, 713–722. [CrossRef]
69. Luo, X.-W.; Lin, Y.; Lu, Y.-J.; Zhou, X.F.; Liu, Y.H. Peptides and polyketides isolated from the marine sponge-derived fungus *Aspergillus terreus* SCSIO 41008. *Chin. J. Nat. Med.* **2019**, *17*, 149–154. [CrossRef]
70. Hua, Y.; Pan, R.; Bai, X.L.; Wei, B.; Chen, J.W.; Wang, H.; Zhang, H.W. Aromatic polyketides from a symbiotic strain *Asper-gillus fumigatus* D and characterization of their biosynthetic gene D8.t287. *Mar. Drugs* **2020**, *18*, 324. [CrossRef]
71. Runeberg, P.A.; Brusentsev, Y.; Rendon, S.M.K.; Eklund, P.C. Oxidative transformations of lignans. *Molecules* **2019**, *24*, 300. [CrossRef]
72. Rao, K.V.; Sadhukhan, A.K.; Veerender, M.; Ravikumar, V.; Mohan, E.V.S.; Dhanvantri, S.D.; Sitaramkumar, M.; Babu, J.M.; Vyas, K.; Reddy, G.O. Butyrolactones from *Aspergillus terreus*. *Chem. Pharm. Bull.* **2000**, *48*, 559–562. [CrossRef] [PubMed]
73. Lin, T.; Lu, C.; Shen, Y. Secondary metabolites of *Aspergillus sp.* F1, a commensal fungal strain of *Trewia nudiflora*. *Nat. Prod. Res.* **2009**, *23*, 77–85. [CrossRef]
74. 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. [CrossRef] [PubMed]
75. Furukawa, T.; Fukuda, T.; Nagai, K.; Uchida, R.; Tomoda, H. Helvafuranone produced by the fungus *Aspergillus nidulans* BF0142 isolated from hot spring-derived soil. *Nat. Prod. Commun.* **2016**, *11*, 1001–1003. [CrossRef]
76. Zhang, X.; Zhang, F.-L.; Wu, X.; Ye, K.; Lv, X.; Ai, H.-L.; Liu, J.-K. Bioactive polyketides from the potato endophytic fungus *Aspergillus carneus*. *Nat. Prod. Commun.* **2020**, *15*, 1–5. [CrossRef]
77. A Schreiner, C. Genetic toxicity of naphthalene: A review. *J. Toxicol. Environ. Heal. Part B* **2003**, *6*, 161–183. [CrossRef] [PubMed]
78. Preuss, R.; Drexler, H. Naphthalene—An environmental and occupational toxicant. *Int. Arch. Occup. Environ. Heal.* **2003**, *76*, 556–576. [CrossRef] [PubMed]
79. Du, L.; Zhu, T.; Liu, H.; Fang, Y.; Zhu, W.; Gu, Q. Cytotoxic polyketides from a marine-derived fungus *Aspergillus glaucus*. *J. Nat. Prod.* **2008**, *71*, 1837–1842. [CrossRef]
80. Yin, W.-B.; Chooi, Y.H.; Smith, A.R.; Cacho, R.A.; Hu, Y.; White, T.C.; Tang, Y. Discovery of cryptic polyketide metabolites from dermatophytes using heterologous expression in *Aspergillus nidulans*. *ACS Synth. Biol.* **2013**, *2*, 629–634. [CrossRef]
81. Inokoshi, J.; Shiomi, K.; Masuma, R.; Tanaka, H.; Yamada, H.; Omura, S. ChemInform abstract: Funalenone, a novel collagenase inhibitor produced by *Aspergillus Niger*. *J. Antibiot.* **1999**, *52*, 1095–1100. [CrossRef]
82. Machrafi, Y.; Prévost, D.; Beauchamp, C.J. Toxicity of phenolic compounds extracted from bark residues of different ages. *J. Chem. Ecol.* **2006**, *32*, 2595–2615. [CrossRef] [PubMed]
83. Lünne, F.; Niehaus, E.-M.; Lipinski, S.; Kunigkeit, J.; Kalinina, S.A.; Humpf, H.-U. Identification of the polyketide synthase PKS7 responsible for the production of lecanoric acid and ethyl lecanorate in *Claviceps purpurea*. *Fungal Genet. Biol.* **2020**, *145*, 103481. [CrossRef] [PubMed]
84. Bogo, D.; Matos, M.D.C.; Honda, N.K.; Pontes, E.C.; Oguma, P.M.; Santos, E.C.D.; de Carvalho, J.E.; Nomizo, A. In vitro an-titumour activity of orsellinates. *Z. Nat. C* **2010**, *65*, 43–48. [CrossRef]
85. Lee, Y.M.; Li, H.; Hong, J.; Cho, H.Y.; Bae, K.S.; Kim, M.A.; Kim, D.-K.; Jung, J.H. Bioactive metabolites from the sponge-derived fungus *Aspergillus versicolor*. *Arch. Pharmacal Res.* **2010**, *33*, 231–235. [CrossRef] [PubMed]
86. Flewelling, A.J.; Bishop, A.L.; Johnson, J.A.; Gray, C.A. Polyketides from an endophytic *Aspergillus fumigatus* Isolate inhibit the growth *of Mycobacterium tuberculosis* and MRSA. *Nat. Prod. Commun.* **2015**, *10*, 1661–1662. [CrossRef]
87. Neuhaus, G.F.; Adpressa, D.A.; Bruhn, T.; Loesgen, S. Polyketides from marine-derived *Aspergillus porosus*: Challenges and opportunities for determining absolute configuration. *J. Nat. Prod.* **2019**, *82*, 2780–2789. [CrossRef]
88. Hamasaki, T.; Nagayama, K.; Hatsuda, Y. Two new metabolites, sydonic acid and hydroxysydonic acid, from *Aspergillus sydowi*. *Agri. Biol. Chem.* **1978**, *42*, 37–40. [CrossRef]
89. Quang, T.H.; Phong, N.V.; Hanh, T.T.H.; Cuong, N.X.; Ngan, N.T.T.; Oh, H.; Nam, N.H.; Minh, C.V. Cytotoxic and im-munomodulatory phenol derivatives from a marine sponge-derived fungus *Ascomycota sp*. VK12. *Nat. Prod. Res.* **2021**, *35*, 5153–5159. [CrossRef]
90. Tian, Y.-Q.; Lin, S.-T.; Kumaravel, K.; Zhou, H.; Wang, S.-Y.; Liu, Y.-H. Polyketide-derived metabolites from the sponge-derived fungus *Aspergillus sp*. F40. *Phytochem. Lett.* **2018**, *27*, 74–77. [CrossRef]
91. Hu, J.S.; Li, Z.; Gao, J.Y.; He, H.T.; Dai, H.Q.; Xia, X.K.; Liu, C.H.; Zhang, L.X.; Song, F.H. New diketopiperazines from a ma-rine-derived fungus strain *Aspergillus versicolor* MF180151. *Mar. Drugs* **2019**, *17*, 262. [CrossRef]
92. Kudo, S.; Murakami, T.; Miyanishi, J.; Tanaka, K.; Takada, N.; Hashimoto, M. Isolation and absolute stereochemistry of op-tically active sydonic acid from *Glonium* sp. (Hysteriales, Ascomycota). *Biosci. Biotechnol. Biochem.* **2009**, *73*, 203–204. [CrossRef] [PubMed]
93. Wei, M.Y.; Wang, C.Y.; Liu, Q.A.; Shao, C.L.; She, Z.G.; Lin, Y.C. Five sesquiterpenoids from a marine-derived fungus *Asper-Gillus* sp. isolated from a gorgonian *Dichotella gemmacea*. *Mar. Drugs* **2010**, *8*, 941–949. [CrossRef] [PubMed]
94. Zhang, Z.; Xiao, B.; Chen, Q.; Lian, X.-Y. Synthesis and biological evaluation of caffeic acid 3,4-dihydroxyphenethyl ester. *J. Nat. Prod.* **2010**, *73*, 252–254. [CrossRef] [PubMed]

95. Lakhani, P.; Patil, A.; Majumdar, S. Challenges in the polyene- and azole-based pharmacotherapy of ocular fungal infections. *J. Ocul. Pharmacol. Ther.* **2019**, *35*, 6–22. [CrossRef]
96. Hanson, F.R.; Eble, T.E. AN antiphage agent isolated from *Aspergillus* sp. *J. Bacteriol.* **1949**, *58*, 527–529. [CrossRef]
97. Fuchser, J.; Grabley, S.; Noltemeyer, M.; Philipps, S.; Thiericke, R.; Zeeck, A. Secondary metabolites by chemical-screening, 28. Aspinonene, a new multifunctional fungal metabolite. *Liebigs Ann. Der Chem.* **1994**, *8*, 831–835. [CrossRef]
98. Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. Pentaketides relating to aspinonene and dihydroaspyrone from a marine-derived fungus, *Aspergillus ostianus*. *J. Nat. Prod.* **2007**, *70*, 2022–2025. [CrossRef]
99. Ola, A.R.B.; Tawo, B.D.; Belli, H.L.L.; Proksch, P.; Tommy, D.; Hakim, E.H. A new antibacterial polyketide from the endophytic fungi *Aspergillus fumigatiaffinis*. *Nat. Prod. Commun.* **2018**, *13*, 1573–1574. [CrossRef]
100. Su, S.; Yin, P.; Li, J.; Chen, G.; Wang, Y.; Qu, D.; Li, Z.; Xue, X.; Luo, X.; Li, M. In vitro and in vivo anti-biofilm activity of pyran derivative against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. *J. Infect. Public Heal.* **2019**, *13*, 791–799. [CrossRef]
101. McDonald, B.R.; Scheidt, K.A. Pyranone Natural products as inspirations for catalytic reaction discovery and development. *Acc. Chem. Res.* **2015**, *48*, 1172–1183. [CrossRef]
102. Zabala, A.O.; Xu, W.; Chooi, Y.-H.; Tang, Y. Characterization of a silent azaphilone gene cluster from *Aspergillus niger* ATCC 1015 reveals a hydroxylation-mediated pyran-ring formation. *Chem. Biol.* **2012**, *19*, 1049–1059. [CrossRef] [PubMed]
103. Filho, J.W.G.D.O.; Islam, M.T.; Ali, E.S.; Uddin, S.J.; Santos, J.V.D.O.; de Alencar, M.V.O.B.; Júnior, A.L.G.; Paz, M.F.C.J.; Brito, M.D.R.M.D.; Sousa, J.M.D.C.E.; et al. A comprehensive review on biological properties of citrinin. *Food Chem. Toxicol.* **2017**, *110*, 130–141. [CrossRef] [PubMed]
104. Guy, M.; Mathieu, M.; Anastopoulos, I.P.; Martínez, M.G.; Rousseau, F.; Dotto, G.L.; de Oliveira, H.P.; Lima, E.C.; Thyrel, M.; Larsson, S.H.; et al. Process parameters optimization, characterization, and application of KOH-activated norway spruce bark graphitic biochars for efficient azo dye adsorption. *Molecules* **2022**, *27*, 456. [CrossRef] [PubMed]
105. Song, Z.; Bakeer, W.; Marshall, J.W.; Yakasai, A.A.; Khalid, R.M.; Collemare, J.; Skellam, E.; Tharreau, D.; Lebrun, M.-H.; Lazarus, C.M.; et al. Heterologous expression of the avirulence gene ACE1 from the fungal rice pathogen *Magnaporthe oryzae*. *Chem. Sci.* **2015**, *6*, 4837–4845. [CrossRef]
106. Grau, M.F.; Entwistle, R.; Chiang, Y.-M.; Ahuja, M.; Oakley, C.E.; Akashi, T.; Wang, C.C.C.; Todd, R.B.; Oakley, B.R. Hybrid transcription factor engineering activates the silent secondary metabolite gene cluster for (+)-asperlin in *Aspergillus nidulans*. *ACS Chem. Biol.* **2018**, *13*, 3193–3205. [CrossRef]
107. Wang, B.; Li, X.; Yu, D.; Chen, X.; Tabudravu, J.; Deng, H.; Pan, L. Deletion of the epigenetic regulator GcnE in *Aspergillus niger* FGSC A1279 activates the production of multiple polyketide metabolites. *Microbiol. Res.* **2018**, *217*, 101–107. [CrossRef]
108. Yamazaki, H.; Takahashi, K.; Iwakura, N.; Abe, T.; Akaishi, M.; Chiba, S.; Namikoshi, M.; Uchida, R. A new protein tyrosine phosphatase 1B inhibitory α-pyrone-type polyketide from Okinawan plant-associated *Aspergillus* sp. TMPU1623. *J. Antibiot.* **2018**, *71*, 745–748. [CrossRef]
109. Siriwardane, A.M.; Kumar, N.S.; Jayasinghe, L.; Fujimoto, Y. Chemical investigation of metabolites produced by an endo-phytic *Aspergillus* sp. isolated from *Limonia acidissima*. *Nat. Prod. Res.* **2015**, *29*, 1384–1387. [CrossRef]
110. Monks, T.J.; Jones, D.C. The metabolism and toxicity of quinones, quinonimines, quinone methides, and quinone-thioethers. *Curr. Drug Metab.* **2002**, *3*, 425–438. [CrossRef]
111. Espinosa-Bustos, C.; Vázquez, K.; Varela, J.; Cerecetto, H.; Paulino, M.; Segura, R.; Pizarro, J.; Vera, B.; González, M.; Zarate, A.M.; et al. New aryloxy-quinone derivatives with promising activity on *Trypanosoma cruzi*. *Arch. Pharm.* **2019**, *353*, e1900213. [CrossRef]
112. Li, J.L.; Jiang, X.; Liu, X.; He, C.; Di, Y.; Lu, S.; Huang, H.; Lin, B.; Wang, D.; Fan, B. Antibacterial anthraquinone dimers from marine derived fungus *Aspergillus* sp. *Fitoterapia* **2018**, *133*, 1–4. [CrossRef] [PubMed]
113. Malik, E.M.; Müller, C.E. Anthraquinones as pharmacological tools and drugs. *Med. Res. Rev.* **2016**, *36*, 705–748. [CrossRef]
114. Du, L.; Zhu, T.; Fang, Y.; Liu, H.; Gu, Q.; Zhu, W. Aspergiolide A, a novel anthraquinone derivative with naphtho[1,2,3-de]chromene-2,7-dione skeleton isolated from a marine-derived fungus *Aspergillus glaucus*. *Tetrahedron* **2007**, *63*, 1085–1088. [CrossRef]
115. Du, L.; Ai, J.; Li, D.; Zhu, T.; Wang, Y.; Knauer, M.; Bruhn, T.; Liu, H.; Geng, M.; Gu, Q.; et al. Aspergiolides C and D: Spirocyclic aromatic polyketides with potent protein kinase c-met inhibitory effects. *Chem. A Eur. J.* **2010**, *17*, 1319–1326. [CrossRef] [PubMed]
116. Scherlach, K.; Sarkar, A.; Schroeckh, V.; Dahse, H.-M.; Roth, M.; Brakhage, A.A.; Horn, U.; Hertweck, C. Two Induced fungal polyketide pathways converge into antiproliferative spiroanthrones. *Chembiochem* **2011**, *12*, 1836–1839. [CrossRef]
117. Xie, L.; Tang, H.; Song, J.; Long, J.; Zhang, L.; Li, X. Chrysophanol: A review of its pharmacology, toxicity and pharmacokinetics. *J. Pharm. Pharmacol.* **2019**, *71*, 1475–1487. [CrossRef]
118. Paranjape, S.R.; Chiang, Y.M.; Sanchez, J.F.; Entwistle, R.; Wang, C.C.C.; Oakley, B.R.; Gamblin, T.C. Inhibition of tau ag-gregation by three *Aspergillus nidulans* secondary metabolites: 2,omega-dihydroxyemodin, asperthecin, and asperbenzal -dehyde. *Planta Med.* **2014**, *80*, 77–85. [CrossRef]
119. Zhang, S.S.; Zhu, A.O.; Bai, X.; Zhu, H.J.; Cao, F. Alkaloids and polyketides from the marine-derived fungus *Aspergillus ver-sicolor*. *Chem. Nat. Compd.* **2020**, *56*, 964–967. [CrossRef]
120. Frisvad, J.C.; Larsen, T.O. Extrolites of *Aspergillus fumigatus* and Other Pathogenic Species in *Aspergillus* section fumigati. *Front. Microbiol.* **2016**, *6*, 1485. [CrossRef]

121. Hayashi, A.; Fujioka, S.; Nukina, M.; Kawano, T.; Shimada, A.; Kimura, Y. Fumiquinones A and B, nematicidal quinones produced by *Aspergillus fumigatus*. *Biosci. Biotechnol. Biochem.* **2007**, *71*, 1697–1702. [CrossRef]
122. Kong, C.; Huang, H.; Xue, Y.; Liu, Y.; Peng, Q.; Liu, Q.; Xu, Q.; Zhu, Q.; Yin, Y.; Zhou, X.; et al. Heterologous pathway assembly reveals molecular steps of fungal terreic acid biosynthesis. *Sci. Rep.* **2018**, *8*, 2116. [CrossRef] [PubMed]
123. Seshime, Y.; Juvvadi, P.R.; Kitamoto, K.; Ebizuka, Y.; Fujii, I. Identification of csypyrone B1 as the novel product of *Aspergillus oryzae* type III polyketide synthase CsyB. *Bioorganic Med. Chem.* **2010**, *18*, 4542–4546. [CrossRef] [PubMed]
124. Xu, Z.; Xiong, B.; Xu, J. Chemical investigation of secondary metabolites produced by mangrove endophytic fungus phyl-losticta capitalensis. *Nat. Prod. Res.* **2021**, *35*, 1561–1565. [CrossRef] [PubMed]
125. Marcos, J.; Pozo, J.O. Current LC-MS methods and procedures applied to the identification of new steroid metabolites. *J. Steroid Biochem. Mol. Biol.* **2016**, *162*, 41–56. [CrossRef] [PubMed]
126. Salmi, C.; Brunel, J.M. Therapeutic potential of cationic steroid antibacterials. *Expert Opin. Investig. Drugs* **2007**, *16*, 1143–1157. [CrossRef]
127. Chobot, V.; Opletal, L.; Jahodar, L.; Patel, A.V.; Dacke, C.G.; Blunden, G. Ergosta-4,6,8,22-tetraen-3-one from the edible fungus, *Pleurotus ostreatus* (oyster fungus). *Phytochemistry* **1997**, *45*, 1669–1671. [CrossRef]
128. Lee, D.Y.; Lee, S.J.; Kwak, H.Y.; Jung, L.K.; Heo, J.; Hong, S.; Kim, G.W.; Baek, N.I. Sterols isolated from nuruk (rhizopus oryzae KSD-815) inhibit the migration of cancer cells. *J. Microbiol. Biotechnol.* **2009**, *19*, 1328–1332. [CrossRef]
129. Salendra, L.; Lin, X.; Chen, W.; Pang, X.; Luo, X.; Long, J.; Liao, S.; Wang, J.; Zhou, X.; Liu, Y.; et al. Cytotoxicity of polyketides and steroids isolated from the sponge-associated fungus *Penicillium citrinum* SCSIO 41017. *Nat. Prod. Res.* **2019**, *35*, 900–908. [CrossRef]
130. Nazir, M.; Saleem, M.; Tousif, M.I.; Anwar, M.A.; Surup, F.; Ali, I.; Wang, D.; Mamadalieva, N.Z.; Alshammari, E.; Ashour, M.L.; et al. Meroterpenoids: A comprehensive ipdate insight on structural di-versity and biology. *Biomolecules* **2021**, *11*, 957. [CrossRef]
131. Springer, J.P.; Dorner, J.W.; Cole, R.J.; Cox, R.H. Terretonin, a toxic compound from *Aspergillus terreus*. *J. Org. Chem.* **1979**, *44*, 4852–4854. [CrossRef]
132. König, C.C.; Scherlach, K.; Schroeckh, V.; Horn, F.; Nietzsche, S.; Brakhage, A.A.; Hertweck, C. Bacterium induces cryptic meroterpenoid pathway in the pathogenic fungus *Aspergillus fumigatus*. *Chembiochem* **2013**, *14*, 938–942. [CrossRef] [PubMed]
133. Hamasaki, T.; Kuwano, H.; Isono, K.; Hatsuda, Y.; Fukuyama, K.; Tsukihara, T.; Katsube, Y. A new metabolite, parasiticolide A, from *Aspergillus parasiticus*. *Agric. Biol. Chem.* **2014**, *39*, 749–751. [CrossRef]
134. Hu, Z.X.; Sun, W.G.; Li, Q.; Li, X.N.; Zhu, H.C.; Huang, J.F.; Liu, J.J.; Wang, J.P.; Xue, Y.B.; Zhang, Y.H. Spiroaspertrione A, a bridged spirocyclic meroterpenoid, as a potent potentiator of oxacillin against methicillin-resistant staphylococcus aureus from *Aspergillus sp*. TJ23. *J. Org. Chem.* **2017**, *82*, 3125–3131. [CrossRef]
135. Qiao, Y.; Zhang, X.; He, Y.; Sun, W.; Feng, W.; Liu, J.; Hu, Z.; Xu, Q.; Zhu, H.; Zhang, J.; et al. Aspermerodione, a novel fungal metabolite with an unusual 2,6-dioxabicyclo[2.2.1]heptane skeleton, as an inhibitor of penicillin-binding protein 2a. *Sci. Rep.* **2018**, *8*, 5454. [CrossRef] [PubMed]
136. Yan, T.; Guo, Z.K.; Jiang, R.; Wei, W.; Wang, T.; Guo, Y.; Song, Y.C.; Jiao, R.H.; Tan, R.X.; Ge, H.M. New flavonol and diterpenoids from the endophytic fungus *Aspergillus* sp. YXf3. *Planta Med.* **2013**, *79*, 348–352. [CrossRef] [PubMed]
137. Hawas, U.W.; El-Beih, A.A.; El-Halawany, A.M. Bioactive anthraquinones from endophytic fungus *Aspergillus versicolor* iso-lated from red sea algae. *Arch. Pharm. Res.* **2012**, *35*, 1749–1756. [CrossRef]
138. Uchoa, P.K.S.; Pimenta, A.T.A.; Braz-Filho, R.; de Oliveira, M.D.C.F.; Saraiva, N.N.; Rodrigues, B.S.F.; Pfenning, L.H.; Abreu, L.M.; Wilke, D.V.; Florêncio, K.G.D.; et al. New cytotoxic furan from the marine sediment-derived fungi *Aspergillus niger*. *Nat. Prod. Res.* **2017**, *31*, 2599–2603. [CrossRef]
139. Yoiprommarat, S.; Kongthong, S.; Choowong, W.; Boonyuen, N.; Isaka, M.; Bunyapaiboonsri, T. Xanthones from a lignicolous freshwater fungus (BCC 28210). *Nat. Prod. Res.* **2019**, *34*, 1233–1237. [CrossRef]
140. Wu, Z.-H.; Liu, D.; Xu, Y.; Chen, J.-L.; Lin, W.-H. Antioxidant xanthones and anthraquinones isolated from a marine-derived fungus Aspergillus versicolor. *Chin. J. Nat. Med.* **2018**, *16*, 219–224. [CrossRef]
141. Khattab, A.R.; Farag, M.A. Current status and perspectives of xanthones production using cultured plant biocatalyst models aided by in-silico tools for its optimization. *Crit. Rev. Biotechnol.* **2020**, *40*, 415–431. [CrossRef]
142. Malik, A.; Ardalani, H.; Anam, S.; McNair, L.M.; Kromphardt, K.J.; Frandsen, R.J.N.; Franzyk, H.; Staerk, D.; Kongstad, K.T. Antidiabetic xanthones with α-glucosidase inhibitory activities from an endophytic penicillium canescens. *Fitoterapia* **2020**, *142*, 104522. [CrossRef] [PubMed]
143. Masters, K.-S.; Bräse, S. Xanthones from fungi, lichens, and bacteria: The natural products and their synthesis. *Chem. Rev.* **2012**, *112*, 3717–3776. [CrossRef] [PubMed]
144. Pornpakakul, S.; Liangsakul, J.; Ngamrojanavanich, N.; Roengsumran, S.; Silhanonth, P.; Piapukiew, J.; Sangvichien, E.; Puthong, S.; Petsom, A. Cytotoxic activity of four xanthones from *Emericella variecolor*, an endophytic fungus isolated from Croton oblongifolius. *Arch. Pharm. Res.* **2006**, *29*, 140–144. [CrossRef] [PubMed]
145. Andersen, R.; Buechi, G.; Kobbe, B.; Demain, A.L. Secalonic acids D and F are toxic metabolites of *Aspergillus aculeatus*. *J. Org. Chem.* **1977**, *42*, 352–353. [CrossRef] [PubMed]
146. Alberts, A.W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; et al. Mevinolin: A highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 3957–3961. [CrossRef]

147. Tsukamoto, S.; Miura, S.; Yamashita, Y.; Ohta, T. Aspermytin A: A New neurotrophic polyketide isolated from a marine-derived fungus of the genus *Aspergillus*. *Bioorganic Med. Chem. Lett.* **2004**, *35*, 417–420. [CrossRef]
148. Zhuravleva, O.I.; Afiyatullov, S.S.; Vishchuk, O.M.; Denisenko, V.A.; Slinkina, N.N.; Smetanina, O.F. Decumbenone C, a new cytotoxic decaline derivative from the marine fungus *Aspergillus sulphureus* KMM 4640. *Arch. Pharmacal Res.* **2012**, *35*, 1757–1762. [CrossRef]
149. Zhuravleva, O.I.; Kirichuk, N.N.; Denisenko, V.A.; Dmitrenok, P.S.; Pivkin, M.V.; Afiyatullov, S.S. New kipukasin from marine isolate of the fungus *Aspergillus flavus*. *Chem. Nat. Compd.* **2016**, *52*, 266–268. [CrossRef]
150. Petersen, L.M.; Hoeck, C.; Frisvad, J.C.; Gotfredsen, C.H.; Larsen, T.O. Dereplication guided discovery of secondary metabo-lites of mixed biosynthetic origin from *Aspergillus aculeatus*. *Molecules* **2014**, *19*, 10898–10921. [CrossRef]
151. Jackson, M.; Karwowski, J.P.; Humphrey, P.E.; Kohl, W.L.; Barlow, G.J.; Tanaka, S.K. Calbistrins, novel antifungal agents produced by *Penicillium restrictum*. I. Production, taxonomy of the producing organism and biological activity. *J. Antibiot.* **1993**, *46*, 34–38. [CrossRef]
152. Fu, Y.; Wu, P.; Xue, J.H.; Wei, X.Y.; Li, H.X. Versicorin, a new lovastatin analogue from the fungus *Aspergillus versicolor* SC0156. *Nat. Prod. Res.* **2015**, *29*, 1363–1368. [CrossRef] [PubMed]
153. Tsukamoto, S.; Yoshida, T.; Hosono, H.; Ohta, T.; Yokosawa, H. Hexylitaconic acid: A new inhibitor of p53-HDM2 interaction isolated from a marine-derived fungus, *Arthrinium* sp. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 69–71. [CrossRef] [PubMed]
154. Kaaniche, F.; Hamed, A.; Abdel-Razek, A.S.; Wibberg, D.; Abdissa, N.; El Euch, I.Z.; Allouche, N.; Mellouli, L.; Shaaban, M.; Sewald, N. Bioactive secondary metabolites from new endophytic fungus *Curvularia* sp. isolated from *Rauwolfia macrophylla*. *PLoS ONE* **2019**, *14*, e0217627. [CrossRef] [PubMed]
155. Arakawa, M.; Someno, T.; Kawada, M.; Ikeda, D. A New Terrein Glucoside, a Novel Inhibitor of Angiogenin Secretion in Tumor Angiogenesis. *J. Antibiot.* **2008**, *61*, 442–448. [CrossRef] [PubMed]
156. Singh, S.B.; Jayasuriya, H.; Zink, D.L.; Polishook, J.D.; Dombrowski, A.W.; Zweerink, H. Aspercyclide A–C, three novel fungal metabolites from *Aspergillus sp.* as inhibitors of high-affinity IgE receptor. *Tetrahedron Lett.* **2004**, *45*, 7605–7608. [CrossRef]
157. Xu, Y.Q.; Espinosa-Artiles, P.; Schubert, V.; Xu, Y.M.; Zhang, W.; Lin, M.; Gunatilaka, A.A.L.; Sussmuth, R.; Molnar, 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. [CrossRef]
158. Santagata, S.; Xu, Y.-M.; Wijeratne, E.M.K.; Kontnik, R.; Rooney, C.; Perley, C.C.; Kwon, H.; Clardy, J.; Kesari, S.; Whitesell, L.; et al. Using the heat-shock response to discover anticancer compounds that target protein homeostasis. *ACS Chem. Biol.* **2011**, *7*, 340–349. [CrossRef]
159. Park, H.-S.; Jun, S.-C.; Han, K.-H.; Hong, S.-B.; Yu, J.-H. Diversity, application, and synthetic biology of industrially important *Aspergillus* fungi. *Adv. Appl. Microbiol.* **2017**, *100*, 161–202. [CrossRef]
160. Pfannenstiel, B.T.; Greco, C.; Sukowaty, A.T.; Keller, N.P. The epigenetic reader SntB regulates secondary metabolism, development and global histone modifications in *Aspergillus flavus*. *Fung. Genet. Biol.* **2018**, *120*, 9–18. [CrossRef]
161. Tang, S.; Zhang, W.; Li, Z.; Li, H.; Geng, C.; Huang, X.; Lu, X. Discovery and characterization of a PKS–NRPS hybrid in *Aspergillus terreus* by genome mining. *J. Nat. Prod.* **2020**, *83*, 473–480. [CrossRef]