Chemical Diversity and Biological Activities of Anthraquinones Derived from Marine Fungi: A Comprehensive Update

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Abstract

Marine microorganisms took excessive attention as prolific producers of structurally unique secondary metabolites, offering a promising potential as substitutes or conjugates for the current therapeutics. Given the fact that various fungal species have the potential to produce secondary metabolites, only a small share of bioactive natural products have been identified from marine microorganisms thus far, we are confident that existing research has only scratched the surface in terms of secondary metabolites diversity and potential industrial applications. Anthraquinones derived from filamentous fungi are a distinct large group of polyketides containing compounds of the quinone family which feature a common 9,10-dioxoanthracene core. A considerable number of reported anthraquinones and their derivatives have shown tremendous biological activities as well as highly economical, commercial, and biomedical potentialities such as anticancer, antiviral, antimicrobial, antioxidant, and anti-inflammatory activities. Accordingly, and in this context, this review comprehensively covers the state-of-art over 20 years about 208 structurally diverse anthraquinones and their derivatives isolated from different species of marine-derived fungal genera along with their reported bioactivity wherever applicable. Also, in this manuscript, we will present recent insights centred on their biosynthetic routes.

Keywords: Marine fungi, anthraquinones, natural products chemistry, antimicrobial, cytotoxic, anti-inflammatory, bioactivity, biosynthesis.

1. Introduction

Throughout history, different natural sources have been used as valuable suppliers of biologically active compounds with diverse bioactivities that can be used to develop new drugs [1–6]. Marine organisms and microorganisms were among the valuable sources of new natural products [2]. Microbial secondary metabolites have been known for their chemical diversity and broad range of bioactivities [6,7]. Marine microorganisms have been considered as highly productive sources of physiologically active compounds including peptides, anthraquinones, polyketides, terpenes, and alkaloids [8–10]. Some marine-based compounds have been approved as drugs with different pharmacological uses [11,12], while several others are under different clinical trials before their approval as new drugs [11].

During the last few decades, numerous drug discovery programs focused on marine-derived microbial natural products due to their great potential for the production of structurally diverse biologically active secondary metabolites [13,14]. Among the hot microbes responsible for the production of interesting compounds, fungi, served as the primary source for mining the first reported antibiotic, penicillin, whereas they are still one of the main sources for discovering novel bioactive compounds from different niches including the marine fungi which have high biological diversifications [15,16]. Therefore, the bioactive secondary metabolites recovered from the marine-derived fungi have gained great interest as promising sources of therapeutics. Interestingly, more than a thousand compounds have been isolated from marine fungi with a wide range of bioactivities including antiviral, anticancer, and antibacterial activities [17]. Even though only one bioactive compound, cyclosporine A, has been approved for clinical use in the market. This might be attributed to problems in the optimization methods or the screening approaches of natural products discovery [18].

Studying the marine-derived fungi has been started around two centuries ago when the first fungal species, *Sphaeria posidoniae* (*Halotthia posidoniae*) was reported on a rhizome of the marine grass *Posidonia oceanica* in 1846 [19]. Marine fungi have been isolated from different habitats including algae, mobile, and sessile invertebrates, sediments, marine mammals, and driftwood from different marine locations [20]. Despite the importance of marine fungi as a promising source for novel bioactive secondary metabolites, marine fungi are still less investigated sources for natural products discovery programmes compared to other niches of fungi [18,21]. Although the estimated number of fungal species on the earth is ranging from 1.5 to 5 million species, only around 1100 species have been exclusively isolated from the marine niche [18,20].

Marine-derived fungi produce various classes of different compounds with both chemical and biological diversities [22,23]. For instance, they produce varieties of bioactive compounds such as terpenes, alkaloids, peptides, and polyketides [18]. Polyketides have been reported in many previous studies as dominant natural products from marine filamentous fungi [24,25]. They are a large group of complex chemical architectures such as anthraquinones, hydroxyanthraquinones, naphthoquinones, macrolides, flavonoids, polyenes, and tetracyclines. Around 700 anthraquinones and their derivatives have been reported from different natural sources, while anthraquinones are widely produced by marine filamentous fungi [16,26]. Chemically, anthraquinones are a group of polyketides of the quinone family with a basic cyclic scaffold of three fused benzene rings including two ketone groups on the central 9, 10-carbons with a chemical formula of $C_{14}H_8O_2$, while their derivatives are generated by the decoration of the around free protons with different functional groups. Interestingly, many reported anthraquinones exhibited potent biological activities including antitumor, antibacterial, antifungal, antioxidant, and immunomodulatory bioactivities [16].

Herein and as a part of our continuous program on pharmacologically active fungal natural products [4,27,28], we are presenting an extensive coverage over the period 2000-2020 for 208 anthraquinones and their derivatives, extensively reported from different marine-derived fungal genera such as *Nigrospora*, *Aspergillus*, *Penicillium*, *Stemphylium*, *Alternaria*, *Eurotium*, *Trichoderma*, *Halorosellinia*, and *Fusarium*. In addition, we reported here their different biological activities wherever applicable, in addition to a general overview of their proposed biogenesis pathways.

2. Anthraquinones isolated from Marine-Derived Fungi

In this manuscript, we provide extensive insights about chemical and biological investigations centered on anthraquinones derived from marine fungi. For the handling of this documentation, all isolated anthraquinones are classified according to the marine fungal genera where they have been recovered along with their recorded biological potentialities whenever applicable.

2.1. Anthraquinones isolated from *Nigrospora* sp.

Ten anthraquinones (**1-10**) were reported from the marine-derived fungus *Nigrospora* sp. Nigrodiquinone A (**1**) was isolated for the first time as a new hydroanthraquinone dimer from the zoanthid-derived fungus *Nigrospora* sp. [29]. Another four anthraquinone derivatives namely 4a-epi-9α-methoxydihydrodeoxybostrycin (**2**), 10-deoxybostrycin (**3**), 3,5,8-trihydroxy-7-methoxy-2-methylanthracene-9,10-dione (**4**), and austrocortirubin (**5**) were reported from both sea anemone-derived [30] and zoanthid-derived fungus *Nigrospora* sp. [29],

while austrocortirubin (**5**) was also recorded from the sea fan-derived fungi *Fusarium* sp. [31], and the mangrove endophytic fungi *Guignardia* sp. [32] and *Halorosellinia* sp. [32,33].

Although nigrodiquinone A (**1**) showed no antiviral or antibacterial activities [29], compounds **4**-**5** displayed mild antiviral activity with IC_{50} values of 93.7 µM against coxsackievirus (Cox-B3) and 74.0 µM against the respiratory syncytial virus (RSV), respectively.

Notably, compounds **2**-**3** showed potent antibacterial activity against both the Gram-positive bacteria (*Staphylococcus aureus* and *Micrococcus tetragenus*) and the Gram-negative bacteria (*Escherichia coli*, *Vibrio anguillarum* (*V. anguillarum*), and *V. parahemolyticus*). Compound **3** displayed MIC of equal to or less than 2.5 µM against all tested bacteria, whereas compound **2** exhibited MIC of equal to or less than 2.5 µM against all tested bacteria except *V. anguillarum* and *V. parahemolyticus* against which it showed MIC of 25.0 µM [30].

In addition, compound **3** showed potent cytotoxic activity against the human lung cancer cell line (A549) with an IC_{50} value of 4.56 µM [30], while austrocortirubin (**5)** displayed an IC_{50} value of 6.3 µM against the human breast adenocarcinoma cells (MCF-7) [31].

Further anthraquinone derivatives **6-10** were previously isolated from the sea anemone-derived fungus *Nigrospora* sp. [30]. Also, some of these anthraquinone derivatives have been isolated from other marine fungal species such as *Fusarium* sp. PSU-F14 from which compounds **6-8** and **10** were recovered [31], while compounds **7**-**8**, and **10** were also isolated from the marine-derived fungus *Aspergillus* sp. [34].

Compounds **6-10** exhibited different interesting biological activities. For instance, nigrosporin B (**6**) displayed modest anti-mycobacterial activity [35], phytotoxic activity [36], and potent antibacterial and cytotoxic activity [30]. Also, 4-deoxybostrycin (**9**) showed modest anti-mycobacterial activity [35], potent antibacterial activity [30], and moderate antitumor activity [37]. Nigrosporin B (**6**) and 4-deoxybostrycin (**9**) displayed potent antibacterial activity against both the Gram-positive bacteria, *Bacillus subtilis* (*B. subtilis*), *B. cereus*, *Staphylococcus albus* (*S. albus*), *S. aureus*, and *Micrococcus tetragenus*) and the Gram-negative bacteria (*Escherichia coli* (*E. coli*), *V. anguillarum*, and *V. parahemolyticus*) with MIC values equal to or less than 2.5 and 3.12 µM, respectively [30]. Moreover, both compounds exhibited modest anti-mycobacterial activity against several mycobacterial species including two multidrug-resistant (MDR) *Mycobacterium tuberculosis* (*M. tuberculosis*) with MIC values of less than 30 µg/mL [35].

An additional example of anthraquinones isolated from *Nigrospora* sp. with multiple bioactivities is tetrahydrobostrycin (**8**) which exhibited moderate to high antibacterial activity against the Gram-positive bacteria; *B. subtilis* and *B. cereus* (MIC value of 2.5 µM), *S. aureus*,

and *Micrococcus luteus* (MIC value of 2.5 µM) and *Micrococcus tetragenus* (MIC value of 1.25 µM) [30]. Compound **8** displayed significant antibacterial activity against the Gram-negative bacteria; *E. coli* (MIC value of 6.25 µM), *V. anguillarum* (MIC value of 1.56 µM), and *V. parahemolyticus* (MIC value of 12.5 µM) [30]. Additionally, it exhibited potent activity against *M. tuberculosis* with an MIC value of 12.50 µg/mL and was also active against *Plasmodium falciparum* with an IC_{50} value of 7.94 µg/mL [38], (Figure 1).

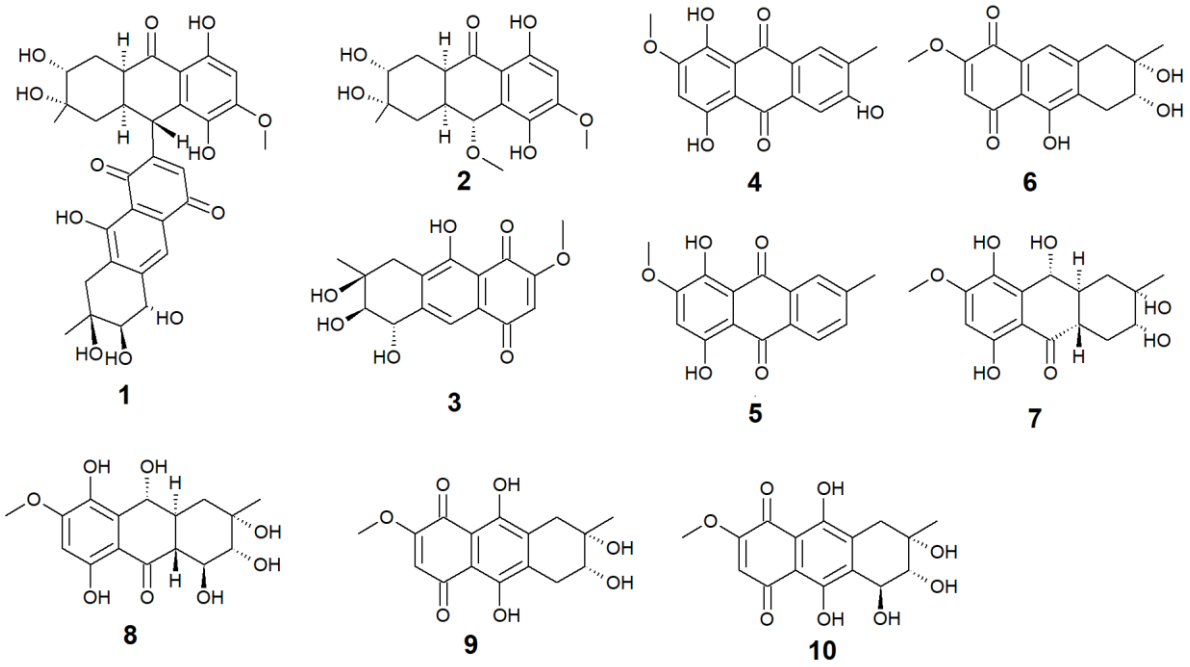

Figure 1: Chemical structures **1-10**

2.2. Anthraquinones isolated from *Aspergillus* sp.

Aspergillus was the richest source of marine anthraquinones and their derivatives among all marine-derived fungi with 73 reported compounds including the previously mentioned **7**, **8**, and **10** as well as other seventy anthraquinones (**11-80**). For instance, thirteen compounds (**11-23**) were isolated from the marine-derived fungus *Aspergillus glaucus* (*A. glaucus*) [39]. Aspergiolide A (**11**), which features a naphtho[1,2,3-de]chromene-2,7-dione skeleton was isolated as a novel anthraquinone derivative from a marine-derived fungus *A. glaucus* [40]. Aspergiolide B (**12**) was isolated from *A. glaucus* as a new analogue for aspergiolide A (**11**) [39]. Aspergiolides A-B (**11-12**) exhibited potent cytotoxic activities against both adenocarcinoma human alveolar basal epithelial cell line A-549 with IC_{50} values of 0.13 and 0.24 µM and human leukemia cell line HL-60 with IC_{50} values of 0.28 and 0.51 µM, respectively [39,40] indicating that methylation of one hydroxyl group in aspergiolide A (**11**)

to be a methoxy group in aspergiolide B (**12**) slightly affected the cytotoxicity of aspergiolide A.

Furthermore, emodin (**13**) which was reported from the marine-derived fungus *A. glaucus*, was also recovered from many other marine fungal species such as *Penicillium citrinum* (*P. citrinum*) [41], *Trichoderma aureoviride* (*T. aureoviride*) [42], *Monodictys* sp. [43], *Gliocladium* sp. [44], *Paecilomyces* sp. [45] and *Eurotium rubrum* (*Eu. rubrum*) [46] and *A. versicolor* [47]. Emodin (**13**) showed moderate antibacterial against *Pseudomonas putida* with MIC value of 25 μM [48] and significant anti-mycobacterial activity against *M. tuberculosis* with MIC value of 12.5 μg/mL and modest antifungal activity against *Candida albicans* (*C. albicans*) with an IC_{50} value of 11 μg/mL [49]. Noteworthy, it showed potent cytotoxic activity against both oral human epidermoid carcinoma cell line, KB and human breast cancer cell line, MCF7 with IC_{50} value of 0.88 and 2.8 μg/mL, respectively [49].

Physcion (**14**) was also isolated from other species of *Aspergillus* such as *A. glaucus* [39], *A. wentii* [50], and the halotolerant *A. variecolor* [51] besides the marine-derived fungus *Microsporum* sp. [52]. Physcion (**14**) displayed different biological activities including cytotoxic activity against human cervical carcinoma HeLa cells [52] and moderate antifungal activity against *Trichophyton mentagrophytes* with MIC value of 25 μg/mL and weak antifungal activity against both *C. albicans* and *Cryptococcus neoformans* with an MIC value of 50 μg/mL [53]. It also exhibited weak free radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) with an IC_{50} value of 99.4 μg/mL [50].

Further anthraquinones **17-18,** and **20** which were isolated from both *A. glaucus* [39] and the halotolerant *A. variecolor* [51], showed variable bioactivities. Questin (**17**) and catenarin (**18**) exhibited DPPH radical scavenging activity [54] and potent antibacterial activity against *Brevibacillus brevis* with MIC value of 1 μg/mL [55], respectively, while (+)-variecolorquinone A (**20**) displayed positive cytotoxicity against the human hepatocellular carcinoma cell line BEL-7402, mouse lymphoma cell line P388, human leukemia cell line HL-60, and adenocarcinoma human alveolar basal epithelial A-549 cells with IC_{50} values of 114, 266, 309, and 3.0 μM, respectively [51].

Notably, the known anthraquinone dimer (**21**), as well as two new isomers of anthraquinone dimer (**22-23**), were also isolated from *A. glaucus* [39]. However, compound **21** was not evaluated for any relevant bioactivity, the *trans* isomer of emodin-physcion bianthrone (**22**) showed good cytotoxicity against the cell lines; A-549 and HL-60 with IC_{50} values of 9.2 and 7.8 μM, respectively. On the other hand, its *cis* isomer (**23**) was less active as its IC_{50} values

were 14.2 and 44.0 μM, respectively [39], suggesting that isomerization slightly affected the cytotoxicity of the compound (**22**).

Additional thirty anthraquinones (**24-54**) have been isolated from the marine-derived fungus *A. versicolor*. Two new anthraquinone dimers (**24-25**) besides three other known closely related anthraquinone derivatives (**26-28**) were isolated from the marine-derived fungus *A. versicolor* [56]. Averantin (**26**) and its derivative 1'-*O*-methylaverantin (**27**) were isolated earlier from the marine-derived fungus *P. purpurogenum* G59 [57] and *Aspergillus* sp. SCSIO F063 [58], while averythrin (**28**) was formerly reported only from the marine-derived fungus *Aspergillus* sp. SCSIO F063 [58].

Compounds **24-25** showed selective antibacterial activity against the Gram-positive bacterium, *S. aureus* using disk diffusion method at a concentration of 30 μg/well [56], whereas the same study revealed that compound **24** had a selective cytotoxic activity against human CNS cancer cells XF-498 with IC_{50} of 22.39 μg/mL. In addition, averantin (**26**) and its derivative 1'-*O*-methylaverantin (**27**) displayed a weak antitumor activity against the bone marrow cancer cell line K562 at a concentration of 100 μg/mL [57]. Another study mentioned that compound **27** exhibited modest cytotoxic activity against human glioblastoma SF-268, human breast adenocarcinoma MCF-7 and human large-cell lung carcinoma NCI-H460 cell lines with IC_{50} value ranging from 33.59 to 44.22 μM, whilst compounds **26** and **28** displayed weak to moderate cytotoxic activity against MCF-7 with IC_{50} value of 45.47 and 29.69 μM, respectively [58]. Also, compounds **26-27** displayed potent antioxidant activity, whereas compound **28** exhibited weak antioxidant activity in terms of antioxidant capacity compared to Trolox [59] suggesting that the presence of oxygen in the side chain of the anthraquinones may play role in their antioxidant activity.

Additionally, compound **26** displayed promising antibacterial activity against different strains of the Gram-positive bacteria *Streptococcus pyogenes* (*Str. pyogenes*) and *S. aureus* with MIC values of equal to or less than 3.13 μg/mL, while its 1'-*O*-methylated derivative (**27**) showed weaker antibacterial activity as it was only active against one strain of *Str. pyogenes* with MIC values of 6.25 μg/mL with no activity against the other strain of *Str. pyogenes* or any strain of *S. aureus* up to a concentration of 12.5 μg/mL [60], indicating that *O*-methylation at position 1 greatly affected the antibacterial activity of averantin (**26**).

Compound **29** which is another derivative of averantin (**26**) was isolated from another marine-derived fungus *A. versicolor* EN-7 [61]. Compound **29** showed weak antibacterial activity against only *E. coli* at a concentration of 20 μg/disk with no activity against *S. aureus* [61],

suggesting that the di-*O*-methylation of averantin (**26**) decreased its antibacterial activity against the Gram-positive bacteria.

The aflatoxin, averufin (**30**) and its *O*-methylated derivatives 6-*O*-methylaverufin (**31**) and 6,8-di-*O*-methylaverufin (**32**) were also isolated from different strains of the marine-derived fungus *A. versicolor* [60,61], whereas averufin (**30**) was also isolated from other species of *Aspergillus* such as *A. niger* [62] and *A. nidulans* [63]. Averufin (**30**) exhibited different bioactivities including potent antioxidant activity in terms of Trolox equivalent antioxidant capacity [59], weak cytotoxic activity [60], and moderate inhibitory activity against the multiplication of *Tobacco Mosaic Virus* (TMV) [62], in addition to weak antibacterial activity against the Gram-positive *Str. pyogenes* and *S. aureus* with MIC values equal to or less than 12.5 μg/mL [60]. On the other hand, neither 6-*O*-methylaverufin (**31**) nor 6,8-di-*O*-methylaverufin (**32**) showed any antimicrobial activity [61] or anti-neuroinflammatory effect [64], respectively.

Moreover, further eight bioactive compounds **33-40** were also isolated from a marine-derived fungus *A. versicolor* [59–61,65] including versicolorin B (**33**), averufanin (**35**) nidurufin (**37**), and versiconol (**39**) as well as their derivatives 1'-hydroxyversicolorin B (**34**), noraverufanin (**36**), 6,8-di-O-methylnidurufin (**38**) and 6,8-di-O-methyl versiconol (**40**), respectively. Both versicolorin B (**33**) and its hydroxyl derivative, 1'-hydroxyversicolorin B (**34**) showed potent antioxidant activity as they displayed antioxidant capacity approximately equivalent to Trolox [59], while an old study revealed that 1'-hydroxyversicolorin B (**34**) (UCT1072M1) had potent cytotoxicity against the human cervical cell adenocarcinoma HeLa S3 and the human lung giant cell carcinoma Lu-65 with IC_{50} values of 2.1 and 2.2 μM, respectively [66].

Indeed, averufanin (**35**) displayed a good antioxidant activity in terms of antioxidant capacity to Trolox [59], and weak activity against both acyl-CoA: cholesterol acyltransferase type 1 and 2 (ACAT1 and ACAT2) in the cell-based assay with IC_{50} values of 28 and 12 μM, respectively [67], whereas noraverufanin (**36**) exhibited a weak HIV latency-reversal activity with reactivation of 43.3% at 10 μM [65]. Nidurufin (**37**) which have been also isolated from the marine fungus *A. niger* [62] and marine-derived *P. purpurogenum* G59 [57], showed weak antitumor activity against the bone marrow cancer cell line K562 with an inhibition rate percentage of 25.5% at a concentration of 100 μg/mL [57] and moderate antioxidant capacity with 0.62 as Trolox equivalent as antioxidant [59].

Another previous study showed that nidurufin (**37**) had exhibited strong anticancer activity against the A-549 cells, the human ovarian cancer cells SK-OV-3, the human skin cancer cells SK-MEL-2, the human CNS cancer cells XF-498, and the human colon cancer HCT-15 with IC_{50} values of 1.83, 3.39, 3.16, 1.78 and 2.2 μg/mL beside good antibacterial activity against

different strains of the Gram-positive bacteria *Str. pyogenes* and *S. aureus* with MIC values of equal to or less than 3.13 μg/mL [60].

Compound **38**, showed weak antibacterial activity against the Gram-positive *S. aureus* as well as Gram-negative *E. coli* with inhibition zones of 7 and 6.5 mm, respectively using disk diffusion method at a concentration of 20 μg/disk [61], suggesting that the new derivatization in this compound affected the antibacterial activity of the parent metabolite, nidurufin (**37**) which showed better antibacterial activity when tested against the Gram-positive bacteria as discussed above.

Versiconol (**39**) exhibited weak anticancer activity against the A-549 cells, the SK-OV-3 cells, the SK-MEL-2 cells, the XF-498 cells, and the HCT-15 cells with IC_{50} values of 20.45, 15.29, 15.86, 23.73, and 19.2 μg/mL [60], whilst its di-*O*-methylated derivative, 6,8-di-*O*-methyl versiconol (**40**) showed selective weak antibacterial activity against *S. aureus* with inhibition zones of 6.5 mm using disk diffusion method at a concentration of 20 μg/disk when tested against both *S. aureus* and *E. coli* [61].

Other bioactive compounds isolated from the marine fungus *A. versicolor* were compounds **41**-**42**, **47**-**48**, and **50**-**54** [47,61,68]. 1-methyl emodin (**41**) which is an *O*-methylated derivative of emodin (**13**) and both were isolated from *A. versicolor* [47], exhibited better cytotoxic activity than emodin (**13**) itself against human epidermoid carcinoma cell line (KBv200) with an IC_{50} value of 190.81 μM [32], although **41** did not show any cytotoxicity against the human leukemia cell line (CCRF-CEM) and some other solid tumors (human lung H-125, human colon HCT-116, human liver Hep-G2) [68]. On the other hand, **41** showed less inhibitory activity against Hepatitis C virus (HCV) protease than its parent **13** with IC_{50} values of 40.2 and 22.5 μg/mL, respectively [68]. The same study showed that the new metabolite from *A. versicolor*; isorhodoptilometrin-1-methyl ether (**42**) displayed moderate antibacterial activity against *B. cereus*, *B. subtilis,* and *S. aureus* at a concentration of 50 μg/disk and mild selective cytotoxicity against the Hep-G2 cell line [68].

Additionally, 1-hydroxy-2-methyl anthraquinone (**47**) and its novel dimethoxy derivative; 2-(dimethoxy methyl)-1-hydroxy-9,10-anthraquinone (**48**) were evaluated for their antibacterial activity against two strains of methicillin-resistant *S. aureus* (MRSA) (CGMCC 1.12409 and ATCC 43300) and three strains of *Vibrio* (*V. rotiferianus, V. vulnificus, and V. campbellii*). Noteworthy, the dimethoxy derivative (**48**) was highly active against the MRSA strains showing MIC values of 7.8 and 3.9 μg/mL, respectively, and was moderately active against the *Vibrio* strains with MIC ranging from 15.6 to 62.5 μg/mL [47]. The same study mentioned that a molecular docking study was conducted to explain the cause behind this antimicrobial activity

revealing the least binding energy of compound **48** with both AmpC β-lactamase and topoisomerase IV [47]. On the other hand, its parent compound **47** displayed potent larvicidal activity against the larvae of *Aedes aegypti* with an IC_{50} value of 1.8 μg/mL [69].

Moreover, another anthraquinone derivative, damnacanthal (**50**) which was reported from *A. versicolor* [47] exhibited strong larvicidal activity against the larvae of *Aedes aegypti* with an IC_{50} value of 7.4 μg/mL [69] and weak antibacterial activity against some strains of MRSA and *Vibrio* with MIC values ranging from 31.3 to 125 μg/mL [47]. Similarly, xanthopurpurin (**51**) showed weak antibacterial properties against some strains of MRSA and *Vibrio* with the same MIC range of damnacanthal (**50**) [47]. Also, compound **51** previously showed strong antiplatelet aggregation activity *via* inhibition of collagen-induced aggregation [70]. In addition, a chemically related rubiadin (**52**) showed a strong inhibitory activity on the formation of advanced glycation end products (AGEs) with an IC_{50} value of 179.31 μM [71]. Notably, its hydroxylated derivative; 6-hydroxyrubiadin (**53**) displayed potent inhibitory activity on phosphatase of regenerating liver-3 (PRL-3) with an IC_{50} value of 1.3 μg/mL causing inhibition of migration of PRL-3 expressed tumor cells with no cytotoxicity [72].

Additional four derivatives (**55-58**) were isolated from the marine-derived fungus *A. wentii* [50,73]. Wentiquinone C (**55**) showed no free radical scavenging activity up to a concentration of 1000 μg/mL [50], whereas compounds **56-58** were not tested for any relevant bioactivity [73].

Further derivatives including compounds **59-64** were isolated from the halotolerant fungus *A. variecolor* [51], while compounds **65-67** were reported from *A. nidulans* [63]. Compounds **59-60** exhibited potent DPPH radical scavenging activity (antioxidant activity) with IC_{50} values of 6 and 11 μM, respectively [51] suggesting that the *O*-methylation of eurotinone, (**59**) slightly affected its antioxidant activity. Questinol (**62**) which was also isolated from the marine-derived fungi *Talaromyces stipitatus* KUFA 0207 [74] and *Eu. amstelodami* [75], displayed significant anti-inflammatory activity *via* different mechanisms including inhibition of both nitric oxide (NO) and prostaglandin E2 (PGE_2) production and, inhibition of the production of some inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α). Compound **62** also showed slight inhibitory activity against cyclooxygenase 2 (COX-2) expression at a concentration of 200 μM [75]. In addition, **62** exhibited potent anti-obesity activity with a 60% reduction in the stained lipids with an IC_{50} value of 0.95 μM, while the chemically related compound, fallacinol (**63**) showed no significant anti-obesity activity [74].

Interestingly, versicolorin C (**65**) displayed selective potent antibacterial activity against both *E. coli* and *V. parahaemolyticus* with MIC values of 1 μg/mL and, against *V. anguillarum* and *Edwardsiella ictaluri* with MIC values of 4 and 8 μg/mL, respectively, whilst the closely related congener isoversicolorin C (**66**) displayed selective potent antibacterial activity against both *V. alginolyticus* and *Edwardsiella ictaluri* with MIC values of 1 and 4 μg/mL, respectively [63].

Further, twelve anthraquinones including three non-halogenated ones **68**-**70**, seven new chlorinated anthraquinone derivatives **71**-**77**, two new brominated anthraquinone derivatives **78**-**79** were isolated from the marine-derived fungus *Aspergillus* sp. SCSIO F063 [58], in addition to compound **80** which was reported from another marine-derived fungus *Aspergillus* sp. SF-6796 [64]. Compounds **68**-**70** are chemically related to each other and are derivatives of averantin (**26**) which was isolated in the same study as a metabolite from *Aspergillus* sp. SCSIO F063 [58], while it was isolated earlier from the marine-derived fungi *A. versicolor* [56]. Averantin-1′-butyl ether (**70**) exhibited weak cytotoxicity against SF-268 and MCF-7 cell lines with IC_{50} values of 47.19 and 40.47 μM, respectively, revealing slightly better cytotoxicity than its parent; averantin (**26**) which only showed activity against the MCF-7 cell line with IC_{50} values of 45.47 μM [58], suggesting that the structural modification in **70** has improved its bioactivity. By contrast, neither compound **68** nor **69** displayed any cytotoxicity against all tested human cell lines including NCI-H460, SF-268, and MCF-7 [58] indicating that *O*-methylation of averantin (**26**) in compounds **68** and **69** may negatively influence their cytotoxicity.

It is noteworthy that the chlorinated anthraquinone derivative, **72** exhibited potent cytotoxicity against NCI-H460, SF-268, and MCF-7 cells with IC_{50} values of 7.42, 7.11, and 6.64 μM, respectively. While **71** showed weak cytotoxicity against only the MCF-7 cell line with IC_{50} values of 36.41 μM and **73** displayed better cytotoxic activity against the three cell lines; NCI-H460, SF-268, and MCF-7 with IC_{50} values of 37.19, 34.06 and 26.09 μM, respectively [58]. From the other chlorinated anthraquinones, **75** and **77** demonstrated weak to modest cytotoxic activity against only the MCF-7 cell line with IC_{50} values of 49.53 and 24.38 μM, respectively. The same study revealed that from the two isolated brominated anthraquinones, only **78** displayed modest cytotoxicity against NCI-H460, SF-268, and MCF-7 cell lines with IC_{50} values of 18.91, 24.69, and 25.62 μM, respectively [58]. Furthermore, another bioactive derivative of averantin (**26**) isolated from *Aspergillus* sp. is 6,8,1’-tri-*O*-methylaverantin (**80**) showed an anti-neuroinflammatory effect *via* different mechanisms including suppression of

the overproduction of many pro-inflammatory mediators including COX-2, PGE_2, and NO in lipopolysaccharide-activated BV2 microglial cells [64], (Figures 2 and **3**).

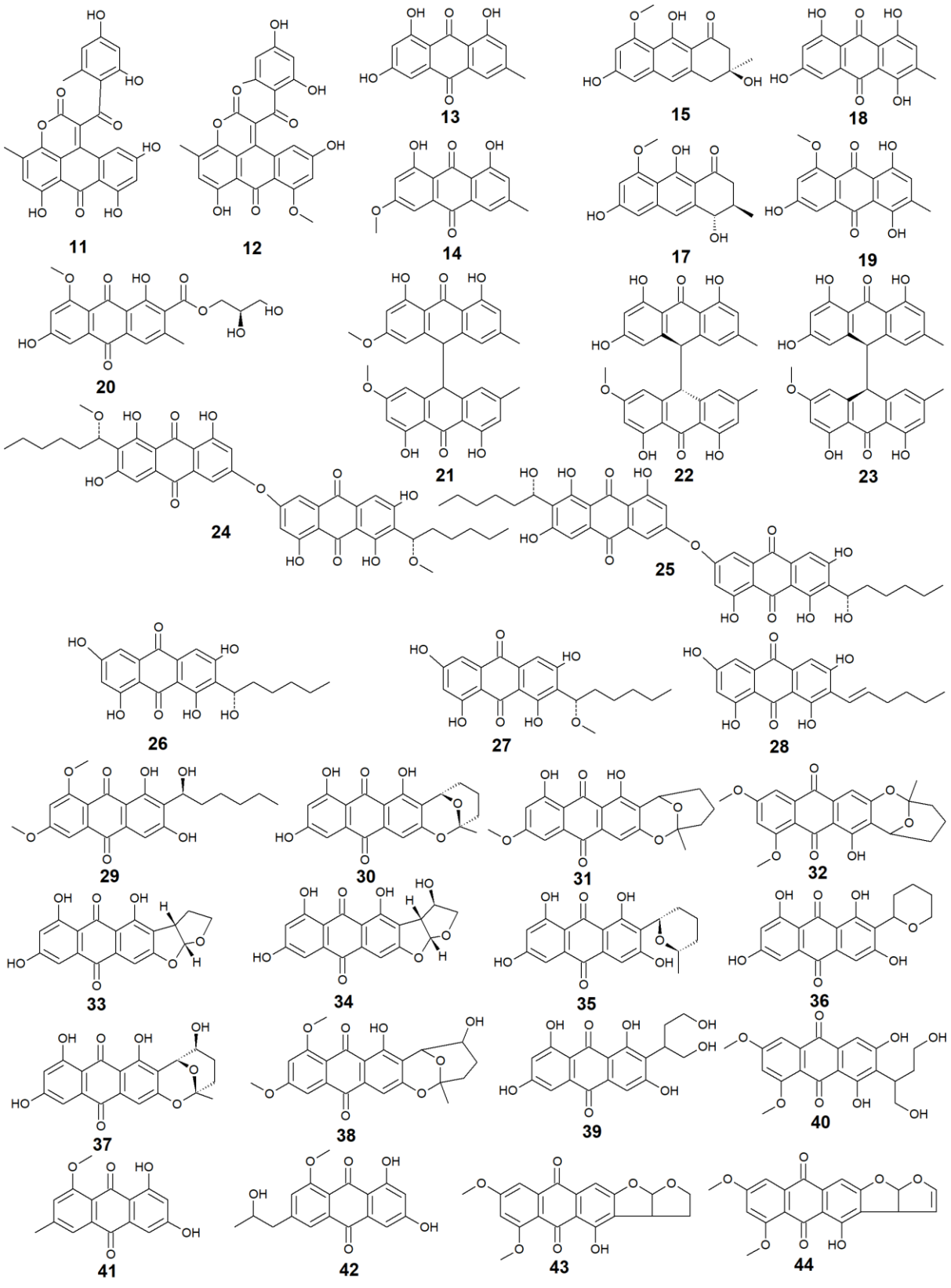

Figure 2: Chemical structures **11-44**

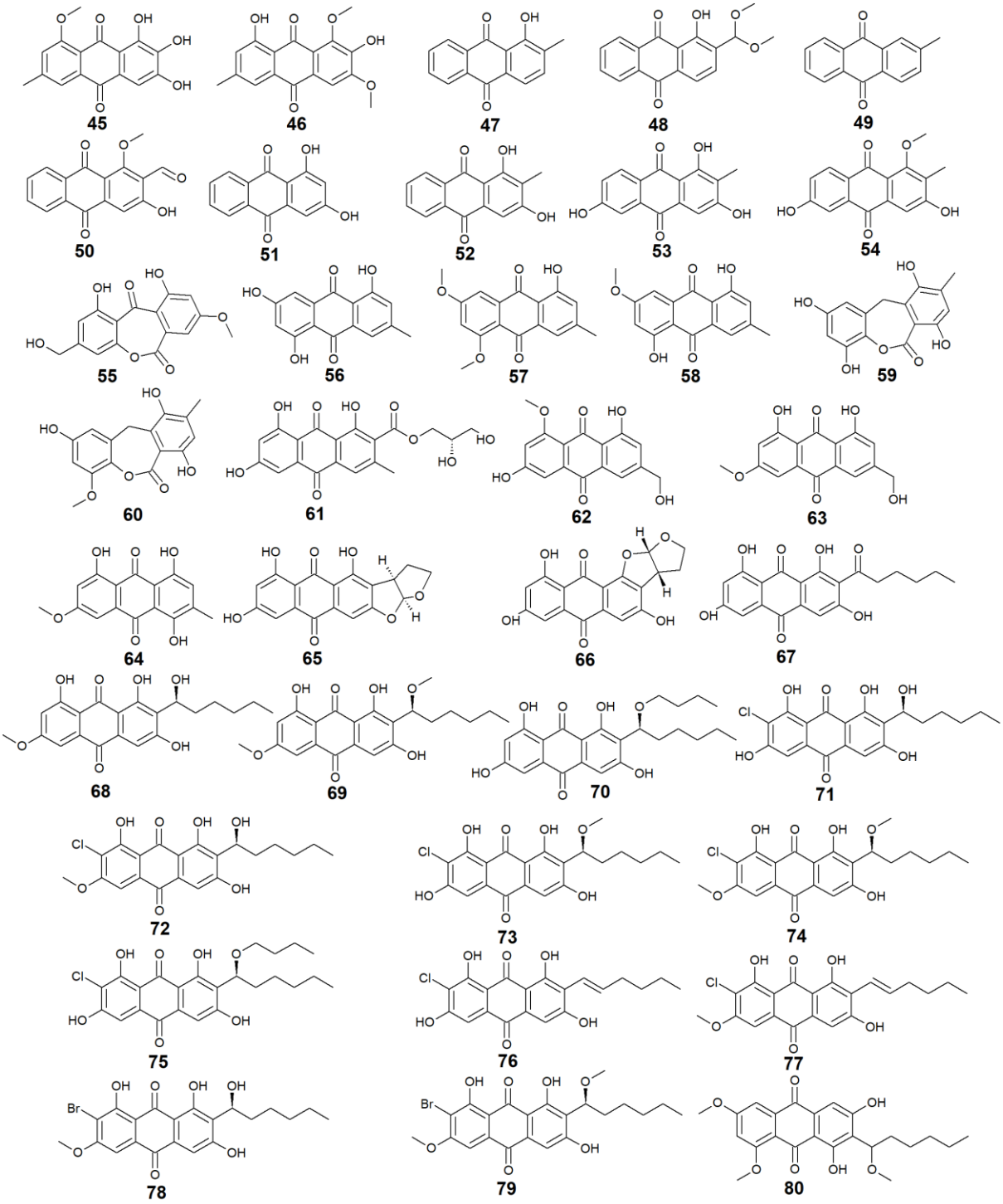

Figure 3: Chemical structures **45-80**

2.3. Anthraquinones from *Penicillium* sp.

Furthermore, eighteen compounds (**81-98**) besides the previously recorded compounds **13**, **17**, **26-27,** and **37** were isolated from different species of the marine-derived fungus *Penicillium*. Indeed, penicillanthranin A (**81**) and B (**82**) which are anthraquinone-citrinin derivatives, as well as chrysophanol (**83**) and ω-hydroxyemodin (**84**), were isolated from the marine fungus

P. citrinum PSU-F51 [41]. Penicillanthranin A (**81**) and chrysophanol (**83**) exhibited selective antibacterial activity against the Gram-positive *S. aureus* ATCC25923 with MIC value of 16 μg/mL and MRSA SK1 with MIC value of 16 and 64 μg/mL, respectively [41], while both compounds **82** and **84** were not screened for their antimicrobial activity in the same study. Interestingly, some earlier studies revealed that ω-hydroxyemodin (**84**) showed moderate activity against MRSA SK1 and mild activity against *S. aureus* ATCC 25923 with MIC values of 32 and 200 μg/mL, respectively [42], in addition to good anti-mycobacterial activity against *M. tuberculosis* H37Ra with MIC value of 12.5 μg/mL [49]. It also showed potent cytotoxicity against the human oral epidermoid carcinoma KB cells with an IC_{50} value of 4.5 μg/mL, and weak cytotoxic activity against both human breast cancer cells, MCF7 and human lung carcinoma cells, NCI-H187 with IC_{50} values of 22 and 39 μg/mL, respectively [49]. In contrast, penicillanthranin A (**81**) showed selective cytotoxicity to the KB cell lines with an IC_{50} value of 30 μg/mL [41].

Another bioactive metabolite, 2′-acetoxy-7-chlorocitreorosein (**85**) which was first recovered from a mangrove-derived fungus *P. citrinum* HL-5126 [76] demonstrated moderate antibacterial activity against *S. aureus* and significant activity against *V. parahaemolyticus* with MIC values of 22.8 and 10 μg/mL, respectively [76], suggesting that such modification in its structure from that of ω-hydroxyemodin (**84**) resulted in significant improvement in its antibacterial activity.

Further anthraquinone derivatives discovered from the marine fungus *P. oxalicum*, including citreorosein-3-*O*-sulphate (**86**), emodin-3-*O*-sulphate (**87**), and aloe-emodin (**88**) were not tested for any relevant activity [77]. However, other previous studies revealed that aloe-emodin (**88**) displayed modest antimalarial activity against *Plasmodium falciparum* (MRC-2) with an EC_{50} value of 22 μg/mL [78] and weak antimicrobial activity against the Gram-positive bacteria; *S. aureus, S. epidermidis, B. cereus, B. subtilis, Micrococcus kristinae*, and the Gram-negative bacteria; *E. coli, Enterobacter aerogenes, Proteus vulgaris,* and *Shigella sonnei* with MIC values ranging from 62.5 to 250 μg/mL [79].

Additional ten bioactive compounds including eight newly isolated anthraquinone−amino acid conjugates, namely emodacidamide A-H (**89-96**) along with the previously isolated anthraquinone derivatives; emodic acid (**97**) and 2-chloro-1,3,8 trihydroxy-6 (hydroxymethyl)anthracene-9,10 dione (**98**), were isolated from the marine fungus *Penicillium* sp. SCSIO sof101 [80]. Emodacidamides A-H (**89-96**) displayed immunomodulatory activity with inhibitory activity against IL-2 production from Jurkat cells [80]. Intriguingly, emodacidamides A (**89**), C (**91**), and E (**93**) showed potent IL-2 inhibitory activity with IC_{50}

values of 4.1, 5.1, and 5.4 μM, respectively [80]. Meanwhile, emodic acid (**97**) showed no remarkable inhibition of IL-2 secretion at a concentration of 20 μM, indicating that amino acid conjugation with the anthraquinone derivatives enhanced their inhibitory effect on IL-2 secretion [80].

On the other side, emodic acid (**97**) which was previously isolated from the marine endophytic fungus *Eu. rubrum* [46], evoked potent inhibition of $p56^{lck}$ tyrosine kinase with an IC_{50} value of 1.07 μg/mL [81]. In addition, compound **97** demonstrated a potent inhibitory effect on both the tyrosine kinase domain of the epidermal growth factor receptor (EGF-R) and protein tyrosine kinase $p59^{fyn}$ with IC_{50} values of 0.078 and 0.080 μg/mL, respectively without any noted cytotoxicity on human foreskin fibroblast [81], (Figure 4).

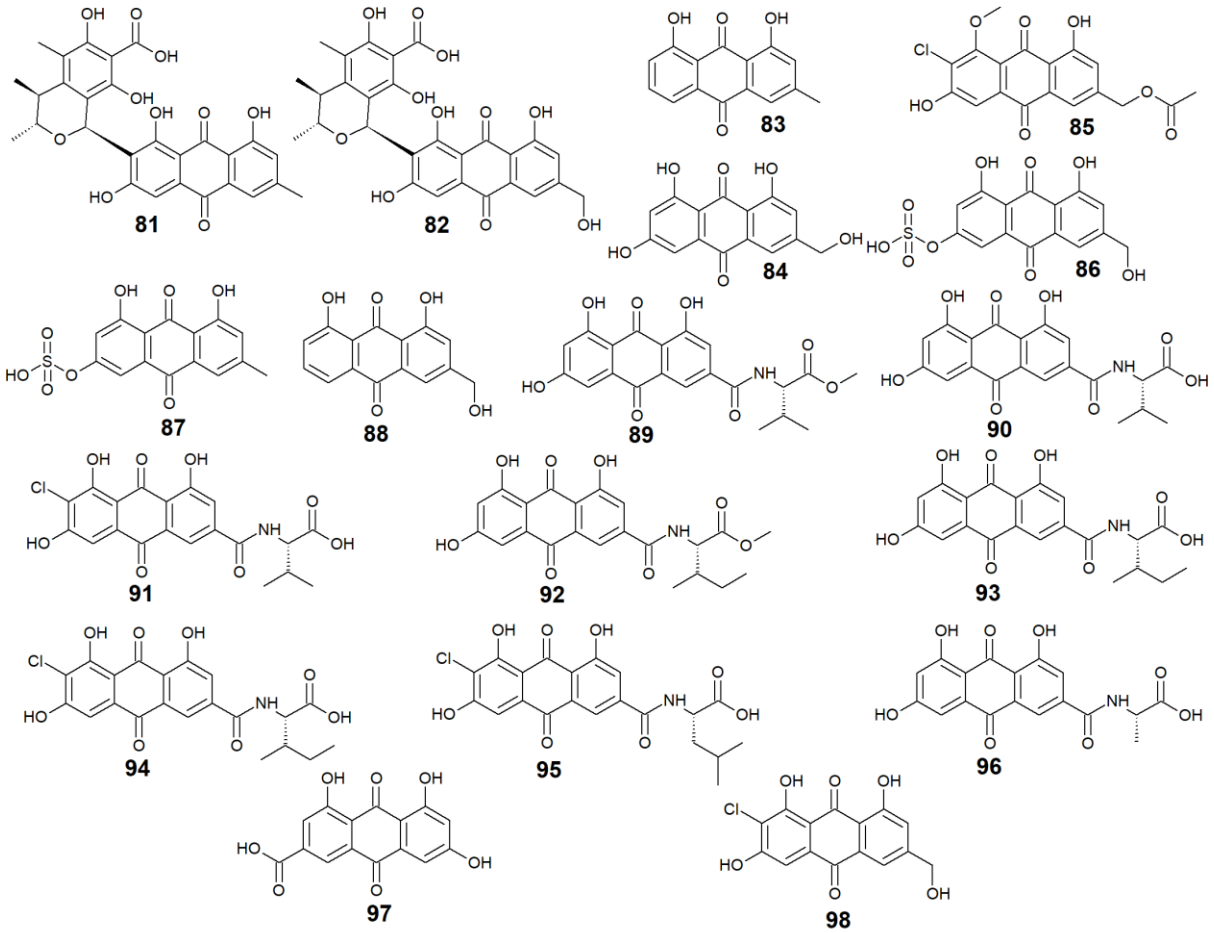

Figure 4: Chemical structures **81-98**

2.4. Anthraquinones from *Stemphylium* sp.

The marine-derived fungus *Stemphylium* is another good source of the bioactive anthraquinones with thirty -two recovered compounds (**99-130**). A group of twenty-five

anthraquinones derivatives (**99-123**) were reported from a mangrove-derived fungus *Stemphylium* sp. 33231 [82] including the bioactive altersolanol A, B, C (**99**, **101**, **104**) and L (**105**) as well as their derivatives dihydroaltersolanol A (**100**), tetrahydroaltersolanol B (**102**), 2-*O*-acetylaltersolanol B (**103**).

Altersolanol A (**99**) showed selective antimicrobial activity against *S. aureus, E. coli, B. subtilis*, and *Micrococcus tetragenus* with MIC values of 2.07, 4.1, 4.1, and 8.2 μM, respectively, whereas altersolanol B (**101**) displayed similar antibacterial activity against *S. aureus, E. coli* and *B. subtilis* as well as the Gram-positive bacterium *Kocuria rhizophila* with MIC value of 7.8 μM for all strains [82]. The same study revealed that altersolanol C (**104**) had a narrow spectrum of activity against only *B. subtilis* with an MIC value of 8.8 μM, while altersolanol L (**105**) had no antibacterial activity against the tested strains [82]. Additionally, a recent study showed that both altersolanol A (**99**) and B (**101**) had strong cytotoxicity against MCF-7 and HCT-116 cell lines with IC_{50} values of 7.21, 1.3 μM for altersolanol A (**99**) and, 9.0, 3.5 μM for altersolanol B (**101**), respectively [83]. By contrast, dihydroaltersolanol A (**100**) did not show any antibacterial or cytotoxicity when tested against various microbes and cell lines [82,84], suggesting that the derivatization of its parent altersolanol A (**99**) into dihydroaltersolanol A (**100**) lead to a significant change in its biological activities. Moreover, another recent study demonstrated that altersolanol L(**105**), had modest antifungal activity against *P. italicum* and *Rhizoctonia solani* with MIC values of 35 and 50 μg/mL, respectively [85].

Furthermore, ampelanol (**107**), macrosporin (**108**) and its sulphate derivative, macrosporin-7-*O*-sulphate (**109**), in addition to its glycosidic derivative, macrosporin 2-*O*-(6′-acetyl)-*α*-D-glucopyranoside (**110**), as well as auxarthrol C (**111**), were also recovered from the marine fungus *Stemphylium* sp. 33231 [82]. Ampelanol (**107**) displayed moderate cytotoxicity against the L5178Y murine lymphoma cell line [86], whereas macrosporin (**108**) exhibited significant antibacterial activity against *Micrococcus tetragenus, E. coli,* and *S. aureus* with MIC values of 4.6, 4.6, and 9.*2* μM, respectively [82]. On the other hand, both derivatives of macrosporin (**108**), macrosporin-7-*O*-sulphate (**109**) and macrosporin 2-*O*-(6′-acetyl)-α-D-glucopyranoside (**110**) displayed no antibacterial activity against the same indicator strains up to a concentration of 10 μM [82], indicating that these modifications in the chemical structure of macrosporin (**108**) have greatly affected its antibacterial activity. Additionally, macrosporin (**108**) was shown to have potent antifungal activity against *Fusarium oxysporum* (*F. oxysporum*) with an MIC value of 3.75 μg/mL and modest antifungal activity against *Colletotrichum musae, F. graminearum, P. italicum,* and *Colletotrichum gloeosporioides* with MIC values ranging from

30 to 60 μg/mL [85]. Noteworthy, compound **110** demonstrated remarkable brine shrimp lethality using *Artemia salina* with an LD_{50} value of 10 μM [82], while the parent compound **108**, and its derivative **109** showed no lethality in the same study [82] suggesting that brine shrimp lethality might be dependent on acetylation and/or glycosylation of this compound. Also, the same study revealed that auxarthrol C (**111**) displayed selective antibacterial against only the Gram-negative organism, *E. coli* with an MIC value of 9.8 μM with no notable cytotoxicity or brine shrimp lethal effect [82].

Moreover, other bioactive anthraquinone dimers including alterporriols B-E (**113-116**), N (**117**), Q (**118**), U (**121**), and V (**122**) were also isolated from the same fungus *Stemphylium* sp. 33231 [82]. The anthraquinone dimers, alterporriols B-E (**113-116**) displayed positive antibacterial activity, whereas alterporriol A (**112**) did not show either antibacterial or cytotoxic activity [82]. Alterporriol B (**113**) showed a narrow spectrum of antimicrobial activity against *B. cereus* with MIC values of 7.9 μM, whereas alterporriol C (**114**) showed selective antibacterial activity against *S. albus* with an MIC value of 8.9 μM. Interestingly, alterporriol D (**115**) exhibited notable antibacterial activity against both *S. aureus* and *E. coli* and with MIC values of 5.0 and 7.5 μM, respectively, while alterporriol E (**116**) displayed potent antimicrobial activity against *B. cereus* and *E. coli* with MIC values of 2.5 and 5.0 μM [82]. The same study demonstrated that alterporriol Q (**118**) and R (**119**) showed no antimicrobial activity against various tested microbes up to a concentration of 10.0 μM [82]. This finding was confirmed in another study which showed that both compounds did not display any antibacterial activity against different Gram-positive as well as *E. coli* from the Gram-negative bacteria up to a concentration of 20.0 μM [84]. However, alterporriol Q (**118**) exhibited strong antiviral activity against the porcine reproductive and respiratory syndrome virus (PRRSV) with an MIC value of 22.0 μM, whereas alterporriol R (**119**) showed no antiviral activity [84]. Also, the same study revealed that alterporriol C (**114**) had a modest antiviral activity with an MIC value of 39.0 μM [84]. In addition, the other anthraquinone dimers, alterporriol U (**121**) and V (**122**) exhibited a narrow spectrum of antibacterial bioactivity against the Gram-positive bacterium, *B. cereus* with MIC values of 8.3 and 8.1 μM, respectively [82].

Further anthraquinone dimers including alterporriol N (**117**), F (**124**), G (**125**), Z1 (**126**), Z2 (**127**), and Z3 (**128**) were also isolated recently from another marine fungus *Stemphylium* sp. FJJ006 [87]. They showed no antimicrobial activity against either Gram-positive and Gram-negative bacterial strains up to a concentration of 128.0 μg/mL or antitumor activity against a panel of cancer cell lines with an IC_{50} value higher than 20.0 μM. Also, they did not show bioactivity against the microbial enzymes, isocitrate lyase, and sortase A with an IC_{50} value of

more than 145.0 μM. However, the same study revealed that alterporriols N (**117**), F, G, Z1-Z2 (**124-127**) had anti-inflammatory activity through their capability of suppressing the lipopolysaccharide-induced nitric oxide production in the murine macrophages RAW 264.7 cells with IC_{50} values of 8.4, 9.6, 10.7, 11.6, and 16.1 μM, respectively, whereas alterporriol Z3 (**128**) did not display any anti-inflammatory activity [87]. On the other hand, another previous study demonstrated the potent cytotoxicity of alterporriol F (**124**) against the HeLa and KB human cell lines with IC_{50} values of 6.5 and 7.0 μg/mL, respectively [88]. In addition, alterporriol N (**117**) was presented in another study as a weak antimicrobial agent with a narrow spectrum of activity against only the Gram-positive bacteria, *Enterococcus faecalis*, MRSA, and *Str*. *pneumoniae* with MIC values of 15.63, 62.5, and 125 μg/mL, respectively, while alterporriol G (**125**) displayed moderate cytotoxicity against the mouse cancer cell line, L5178Y[89], (Figure 5 and 6).

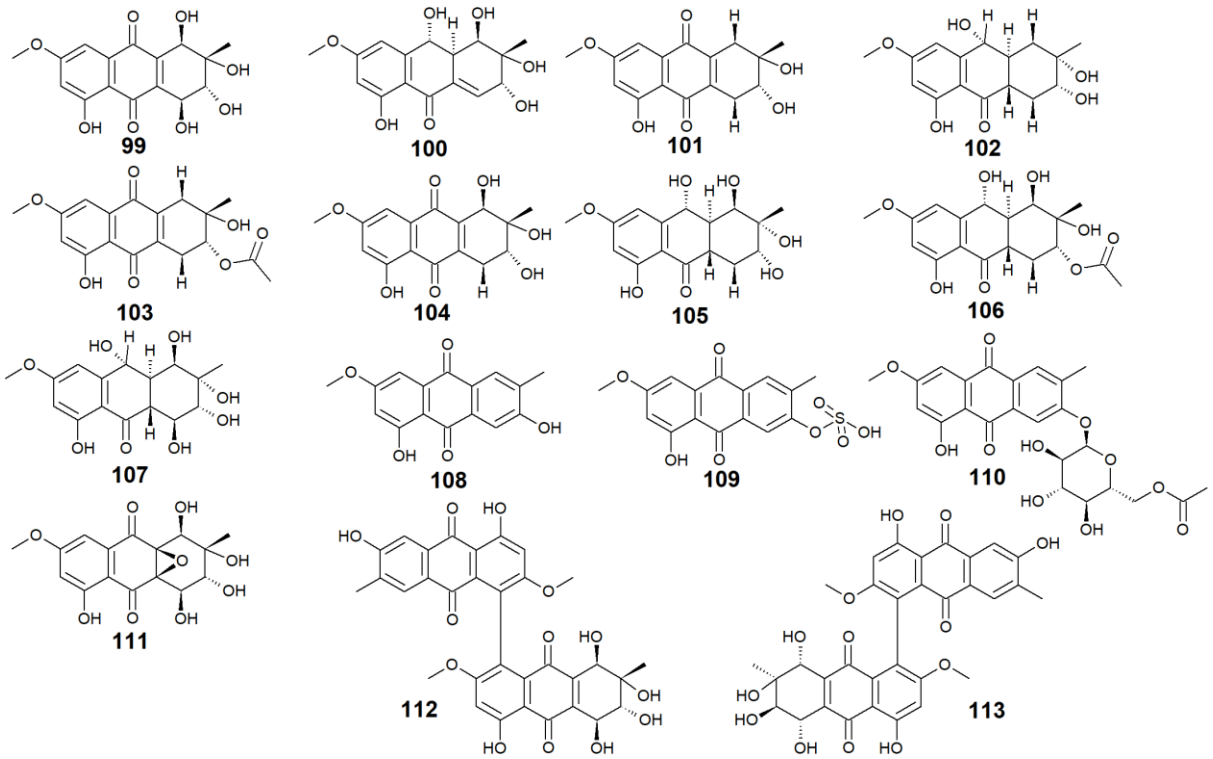

Figure 5: Chemical structures **99-113**

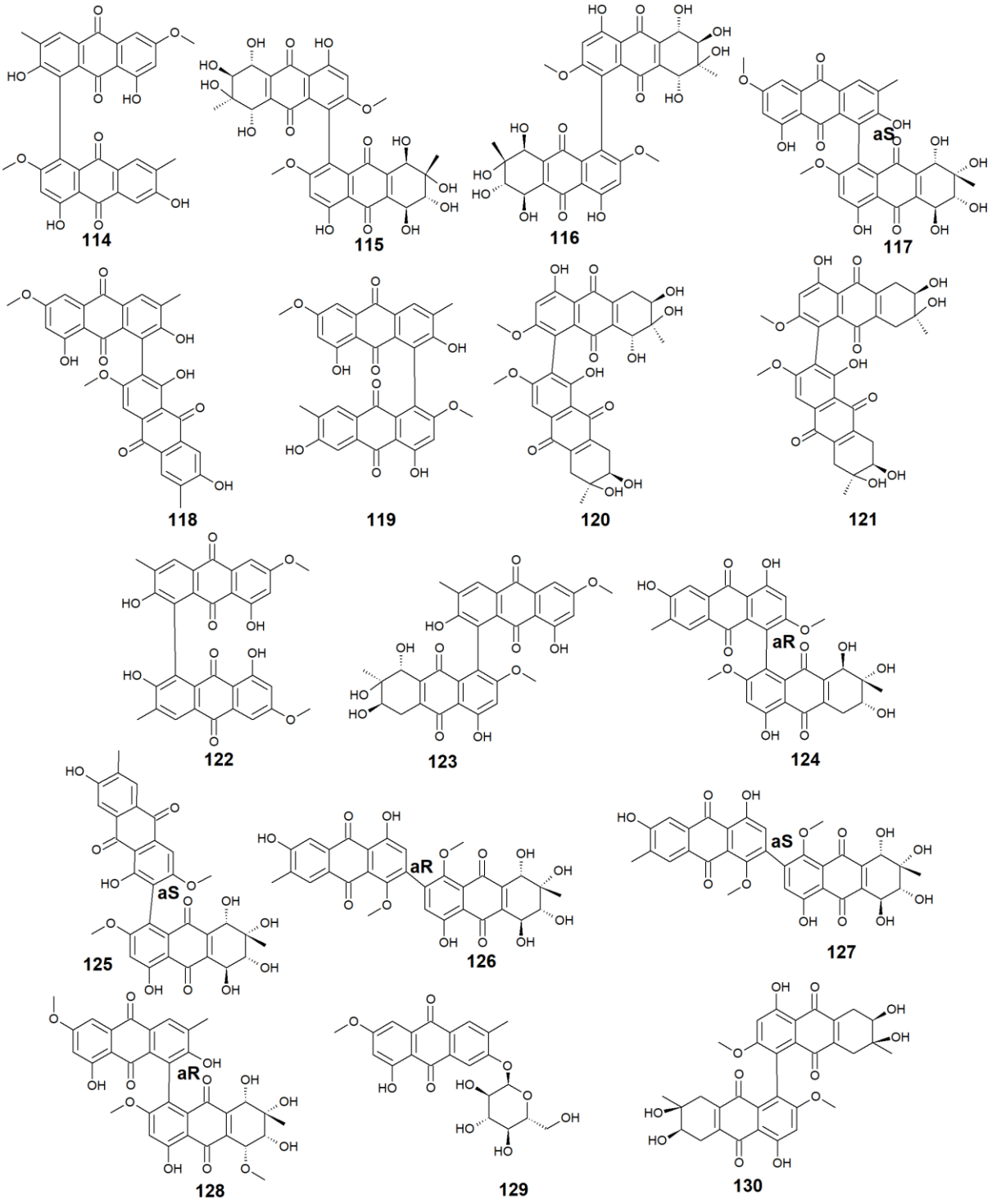

Figure 6: Chemical structures **114-130**

2.5. Anthraquinones from *Alternaria* sp.

A list of twenty anthraquinones was isolated earlier from different species of *Alternaria* including the previously mentioned compounds (**100-102**, **104**, **105**, **107**, **108,** and **114**) as well as twelve anthraquinone derivatives, **131-142**. Two bioactive bi-anthraquinones, named alterporriol K (**131**) and L (**132**) were isolated from marine endophytic fungus *Alternaria* sp.

ZJ9-6B [90] and displayed moderate cytotoxic activity against the human breast cells, MCF-7 and MDA-MB-435 with IC_{50} values of 29.11, 26.97 μM respectively, while alterporriol M (**133**) was not evaluated for any biological activity in this study [90].

Further compounds including alterporriol O (**134**) and P (**135**) were isolated from the marine-derived *Aspergillus* sp. ZJ-2008003. Only alterporriol P (**135**) exhibited significant cytotoxicity against the human prostate cancer cell line, PC3, colon cancer cell line, HCT-116, liver hepatoma cell lines, Hep-G2 and Hep-3B in addition to the breast cancer cell line, MCF-7/ADR with IC_{50} value of 6.4, 8.6, 20.0, 21.0, and 23.0 μM, respectively. Unlikely, alterporriol O (**134**) did not demonstrate any bioactivity when it was evaluated for its cytotoxicity, antibacterial activity, and antiviral activities [84].

Additional anthraquinones, tetrahydroaltersolanols C-F (**136-139**) were also isolated from the marine-derived *Alternaria* sp. ZJ-2008003 [84]. Tetrahydroaltersolanol C (**136**) displayed moderate antiviral activity against the PRRSV with an IC_{50} value of 65.0 μM [84].

More anthraquinone derivatives (**140-142**) were reported recently from the marine fungus *Alternaria tenuissima* DFFSCS013 [91]. Anthrininone A (**140**) demonstrated selective protein tyrosine phosphatase inhibitory effect on indoleamine 2,3 dioxygenase 1 enzyme (IDO1) with IC_{50} value of 32.3 μM as well as the stimulatory effect on the intracellular levels of calcium in HEK293 cells at a concentration of 10.0 μM [91]. It is noteworthy that 6-*O*-methylalaternin (**141**) displayed a wide range of anti-protein tyrosine phosphatases activity including activity against TCPTP, SHP1, SHP2, and PTP-MEG2 enzymes with potent bioactivity against both IDO1 and PTP1B with IC_{50} values of 1.7 and 2.1 μM, respectively. On the other hand, **141** did not show a noticeable stimulatory effect on the intracellular levels of calcium in HEK293 cells at a concentration of 10.0 μM [91], (Figure 7).

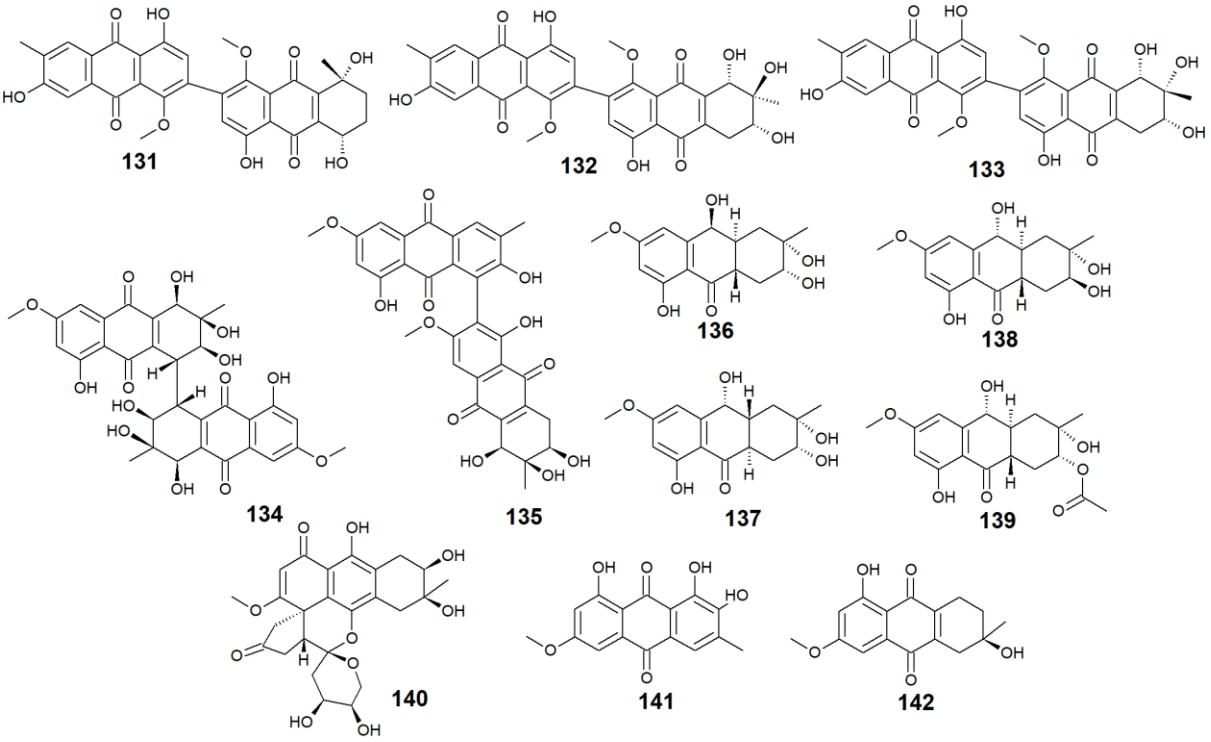

Figure 7: Chemical structures **131-142**

2.6. Anthraquinones from *Trichoderma* sp.

Trichoderma sp. is another prolific anthraquinones' producer from which the previously discussed compounds, **13**, **83,** and **84** were isolated as well as the anthraquinone derivatives, **143-155**. Harzianumnones A-B (**143-144**) were reported earlier as new hydroxyanthraquinones from the marine fungus *T. harzianum* XS-20090075. They showed neither DNA topoisomerase I (Topo I) inhibitory activity nor anti-acetylcholinesterase activity [92]. The same study revealed that phomarin (**145**), ω-hydroxydigitoemodin (**146**), pachybasin (**147**), and (+)-2'*S*-isorhodoptilometrin (**148**) isolated also from *T. harzianum* XS-20090075, displayed a weak anti-acetylcholinesterase activity at a concentration of 100 μM [92]. Interestingly, pachybasin (**147**) also demonstrated potent cytotoxic activity against the human cancer cell lines, KB and KBv200 with IC_{50} values of 3.17 and 3.21 μM, respectively [32]. In addition, its derivative, ω-hydroxypachybasin (**149**) as well as (+)-2'*S*-isorhodoptilometrin (**148**) exhibited significant cytotoxic activity against Hep-G2 and HeLa cancer cell lines showing IC_{50} value of 9.39, 22.6 μM, respectively [92]. Also, compounds **148** and **149** revealed moderate DNA Topo I inhibitory activity with an IC_{50} value of 100.0, 50.0 μM, respectively, in addition to significant selective antibacterial activity against the Gram-positive bacterium, *S. aureus* showing MIC value of 25.0, 25.0 μM, respectively [92].

Moreover, another study demonstrated that **148** isolated from marine-derived fungus *T. aureoviride* PSU-F95 showed strong antibacterial activity against MRSA with an MIC value of 16 μg/mL[42]. Similarly, coniothranthraquinone 1 (**150**) displayed strong antibacterial activity against MRSA and *S. aureus* with MIC values of 8 and 16 μg/mL, respectively [42]. In the contrast, trichodermaquinone (**151**) was also isolated from the marine fungus *T. aureoviride* PSU-F95 and demonstrated weak antibacterial activity against MRSA with an MIC value of 200 μg/mL [42]. However, compounds **152** and **153** which were recovered also from the marine fungus *T. aureoviride* PSU-F95, both were not evaluated for any bioactivity in this study [42]. Additionally, coniothyrinone A (**154**) and lentisone (**155**) were previously isolated from another marine fungus, *Trichoderma* sp., and exhibited potent antibacterial activity against the Gram-negative bacteria, *V. parahaemolyticus*, *V. anguillarum*, and *Pseudomonas putida* with MIC values of [6.25, 1.56, 3.13 μM] for coniothyrinone A (**154**) and [12.5, 1.56, 6.25 μM] for lentisone (**155**), respectively [48] (Figure 8).

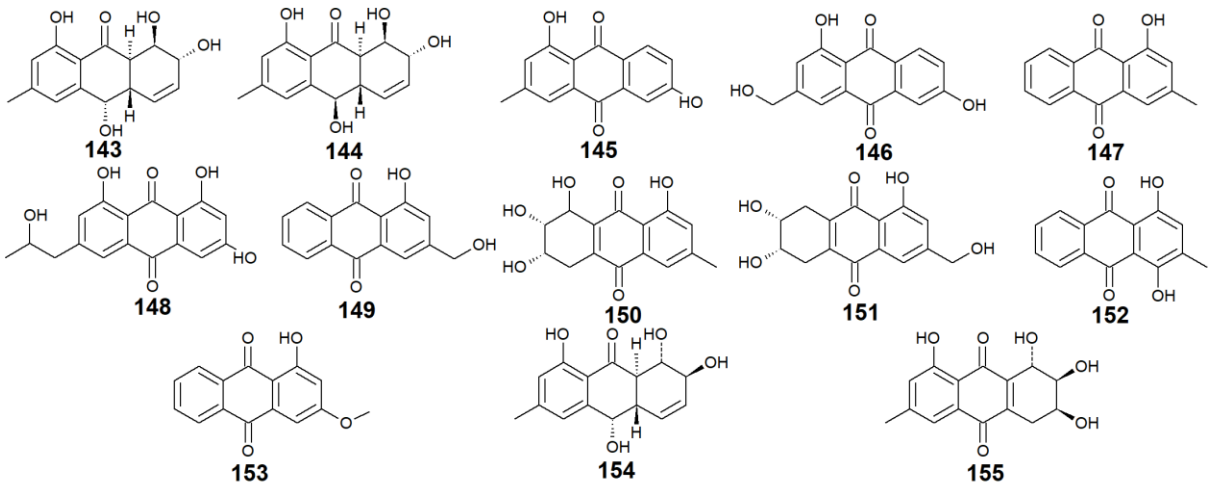

Figure 8: Chemical structures **143-155**

2.7. Anthraquinones from *Eurotium* sp.

Seventeen anthraquinones and their derivatives were reported from species of the marine fungus *Eurotium*, including the previously mentioned compounds, **13**, **15**, **18-20**, **60**, **62**, **97**, and **154** in addition to other eight congeners, **156-163**. Compound 9-dehydroxyeurotinone (**156**) and its *O*-methyl derivative, 2-*O*-methyl-9-dehydroxyeurotinone (**157**) as well as its glycosidic derivative, 2-*O*-methyl-4-*O*-(α-D-ribofuranosyl)-9-dehydroxyeurotinone (**158**) were isolated from marine-derived fungus *Eu. rubrum* [46,54]. The parent compound, 9-dehydroxyeurotinone (**156**) exhibited weak antibacterial activity against the Gram-negative

bacterium, *E. coli* showing a 7-mm zone of inhibition using 100 µg/disk. Also, it displayed selective cytotoxic activity against the human cholangiocarcinoma cells, SW1990 with an IC_{50} value of 25.0 µg/mL [46]. Another study revealed that compounds **157-159** had positive antioxidant activity through free radical scavenging activity against DPPH [54].

Furthermore, the same study showed that eurorubrin (**160**) demonstrated a potent free radical scavenging activity with an IC_{50} value of 44.0 µM with better antioxidant activity than the standard antioxidant, butylated hydroxytoluene which had an IC_{50} value of 82.6 µM [54]. Interestingly, 3-*O*-(α-D-ribofuranosyl)-questin (**159**) and eurorubrin (**160**) were re-isolated also from the marine endophytic fungus *Eu. cristatum* EN 220. They displayed modest antibacterial activity against the Gram-negative bacterium, *E. coli* with MIC values of 32.0 and 64.0 µg/mL, respectively [93]. Notably, 3-*O*-(α-D-ribofuranosyl)questinol (**161**) which is an alcoholic derivative of the bioactive compound, 3-*O*-(α-D-ribofuranosyl)questin (**159**) showed no antibacterial activity against *E. coli* suggesting that this hydroxylation leads to loss of the antimicrobial activity [93]. Furthermore, asperflavin ribofuranoside (**162**) which was isolated earlier from the marine fungus *Eu. cristatum* EN 220 [93] and the marine-derived fungus *Microsporum* sp. [94], was reported as a potent free radical scavenging agent with an IC_{50} value of 14.2 µM with better antioxidant activity than the standard antioxidant, ascorbic acid which had an IC_{50} value of 20.0 µM [94]. Also, it exhibited modest antibacterial activity against both MRSA and MDR *S. aureus* with MIC values of 50.0, 50.0 µg/mL, respectively[94]. Moreover, rubrumol (**163**) was reported as a new anthraquinone derivative from the saline-alkali endophytic fungus *Eu. rubrum* with relaxation activity on Topo I with an IC_{50} value of 23.0 µM [95], (Figure 9).

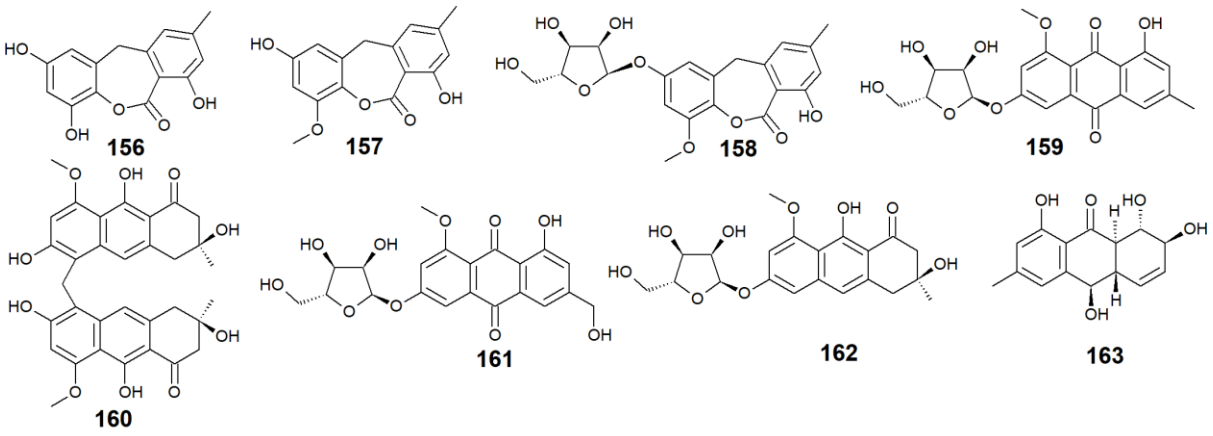

Figure 9: Chemical structures **156-163**

2.8. Anthraquinones from *Fusarium* sp.

Twelve anthraquinone derivatives were isolated earlier from different species of the marine-derived fungus *Fusarium* sp. including the previously discussed compounds, **5-8** and **10** along with other structurally related compounds **164-170**. Although both nigrosporin A (**164**) and fusaranthraquinone (**165**) were recovered from the marine-derived fungus *Fusarium* sp. PSU-F14 [31], only nigrosporin A (**164**) displayed promising inhibitory activity against photosynthesis and weak antibacterial activity against *B. subtilis* showing an inhibition zone of 14 mm at 200 ppm [36], whereas fusaranthraquinone (**165**) did not demonstrate any antibacterial activity when it was tested against both *S. aureus* and MRSA [31]. Interestingly, additional bioactive fusaquinons A-C (**166-168**) were reported from the marine fungus *Fusarium* sp. ZH-210 and displayed weak cytotoxic activity against MCF-7, KB, and KBv200 cell lines with IC_{50} values of more than 50 μM [96].

It is noteworthy that nigrosporin A (**164**) and fusaquinon A (**166**) were also evaluated in another study for their antimalarial, anti-mycobacterial, antibacterial, and cytotoxic activity. Both compounds showed no antimalarial, antibacterial, or anti-mycobacterial activity, whereas they showed selective cytotoxicity [97]. Nigrosporin A (**164**) displayed weak cytotoxic activity against the MCF-7 cell line with an IC_{50} value of 110.36 μM and good cytotoxicity against NCI-H187 cell line with IC_{50} value of 13.69 μM, while fusaquinon A (**166**) exhibited weak cytotoxicity against both human cancer cells, MCF-7, and monkey kidney cells, Vero cells with IC_{50} value of 84.38 and 44.46 μM, respectively. Also, fusaquinon A (**166**) displayed potent cytotoxicity against the NCI-H187 cell line with an IC_{50} value of 7.32 μM [97]. Another bioactive anthraquinone derivative isolated from mangrove-derived fungus *Fusarium* sp. ZZF60 was 6,8-dimethoxy-1-methyl-2-(3-oxobutyl)anthracene-9,10-dione (**169**) [98]. Notably, it demonstrated moderate cytotoxicity against Hep2 and Hep-G2 cells with IC_{50} values of 16.00 and 23.00, respectively, (Figure 10).

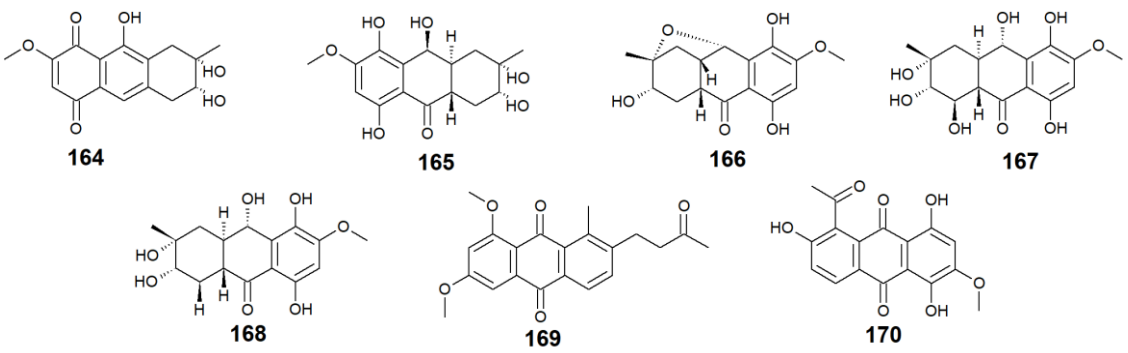

Figure 10: Chemical structures **164-170**

2.9. Anthraquinones from *Engyodontium album*

Six compounds (**171-176**) out of seven anthraquinone derivatives (**171-177**) isolated from the marine-derived fungus *Engyodontium album* LF069 were bioactive, while the anthraquinone derivative, Engyodontochone D (**177**) was not tested for any relevant biological activity [23]. It is noteworthy that compounds (**171-173**) exhibited diverse bioactivities including antibacterial, antifungal, and cytotoxic activity. They demonstrated better antibacterial activity against *S. epidermidis* and MRSA than chloramphenicol with an IC_{50} value of 0.19, 0.17 μM for engyodontochone A (**171**), 0.21, 0.25 μM for JBIR-99 (**172**), and 0.22, 0.24 μM for engyodontochone B (**173**), respectively. On the other hand, they displayed weak to modest antifungal activity against the fungi, *C. albicans*, and *T. rubrum* with IC_{50} values ranging from 4.3 to 13.5 μM. Additionally, compounds **171-173** exhibited modest cytotoxicity against the mouse fibroblasts cell line, NIH-3T3 with IC_{50} values of 11.0, 13.2, and 14.4 μM, respectively [23]. Also, engyodontochone C (**174**) showed good selective bioactivity against *S. epidermidis* and MRSA with IC_{50} values of 1.80 and 2.39 μM, respectively. In addition, it displayed weak cytotoxic activity against the cell line, NIH-3T3 with an IC_{50} value of 34.3 μM, whereas it did not show any antifungal activity against either, *C. albicans* or *T. rubrum* up to a concentration of 100 μM [23].

Similarly, engyodontochone F (**175**) demonstrated promising selective antibacterial activity against both *S. epidermidis* and MRSA with IC_{50} values of 3.41 and 3.13 μM, respectively although it exhibited weak selective antifungal activity against *T. rubrum* with an IC_{50} value of 73.4 μM. In the contrast, engyodontochone E (**176**) has only showed potent antibacterial activity against *S. epidermidis* and MRSA with IC_{50} values of 6.77 and 6.74 μM, respectively with no antifungal or cytotoxic activity up to a concentration of 100.0 and 50.0 μM, respectively [23], (Figure 11).

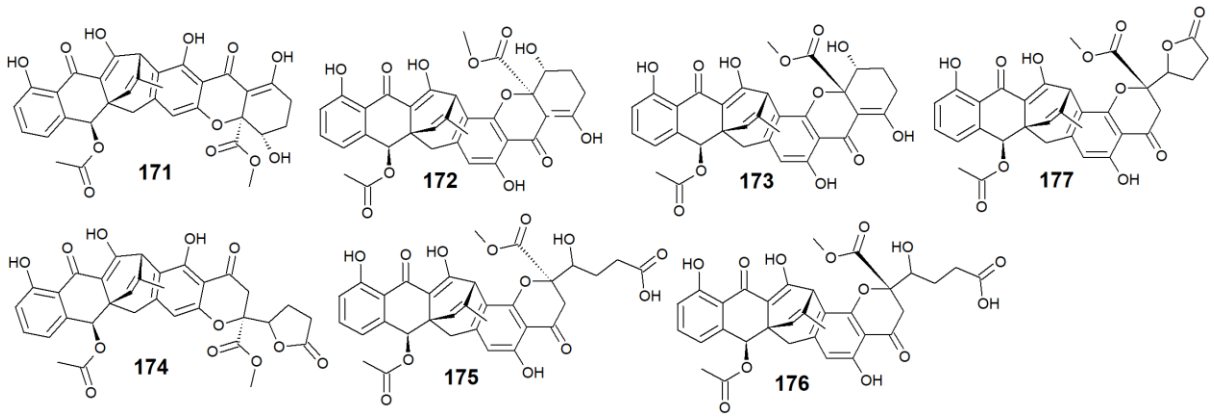

Figure 11: Chemical structures **171-177**

2.10. Anthraquinones from *Sporendonema casei*

Seven bioactive anthraquinones named 4-dehydroxyaltersolanol A (**178**) and auxarthrols D-H (**179-183**) along with the previously discussed altersolanol B (**101**) were recovered from the marine fungus, *Sporendonema casei* HDN16-802 [99]. This group of anthraquinone derivatives (**178-183**) were evaluated for their antibacterial activity against *M. phlei*, *B. subtilis*, *V. parahaemolyticus*, *E. coli*, *Pseudomonas aeruginosa,* and *Proteus* sp. and for their antifungal activity against *C. albicans*. Interestingly, 4-dehydroxyaltersolanol A (**178**) exhibited the best antibacterial activity among this group of anthraquinones against *M. phlei*, *B. subtilis*, *Pseudomonas aeruginosa*, *V. parahaemolyticus,* and *Proteus* sp. with MIC value ranging from 25.0 to 50.0 μM [99]. However, its parent altersolanol A (**99**) demonstrated potent antibacterial activity against *S. aureus*, *E. coli*, *B. subtilis*, and *Micrococcus tetragenus* with MIC values of 2.07, 4.1, 4.1, and 8.2 μM [82]. suggesting that its dehydroxylation might lead to a decrease in its antimicrobial activity. Auxarthrol E (**180**) and H (**183**) showed no antimicrobial activity against different indicator strains. However, auxarthrol F (**181**) only displayed very weak activity against *M. phlei*, *B. subtilis*, *Pseudomonas aeruginosa*, and *Proteus* sp. with an MIC value of 200 μM. Both auxarthrol D (**179**) and G (**182**) demonstrated a broad spectrum of antibacterial activity against *M. phlei*, *B. subtilis*, *Pseudomonas aeruginosa*, *V. parahaemolyticus,* and *Proteus* sp. with MIC value ranging from 25.0 to 100.0 μM, whereas **182** displayed very weak antifungal activity against *C. albicans* with MIC value of 200.0 μM [99].

Moreover, only **179** and **181** were evaluated for their cytotoxicity against different cancer cell lines in the same study revealing modest cytotoxic activity against several cell lines. Compound **179** exhibited a selective cytotoxic effect on seven cell lines including HL-60, HCT-116, MGC-803, MDA-MB-231, SH-SY5Y, PC-3, and BEL-7402 with IC_{50} value ranging from 7.5 to 22.9 μM. In the contrast, compound **181** displayed a broad spectrum of cytotoxicity against the eleven tested cancer cell lines in this study with IC_{50} values ranging from 4.5 to 22.2 μM [99]. In addition, all compounds (**178-183**) showed significant anticoagulant activity, meanwhile, they did not show any anti-mycobacterial activity [99], (Figure 12).

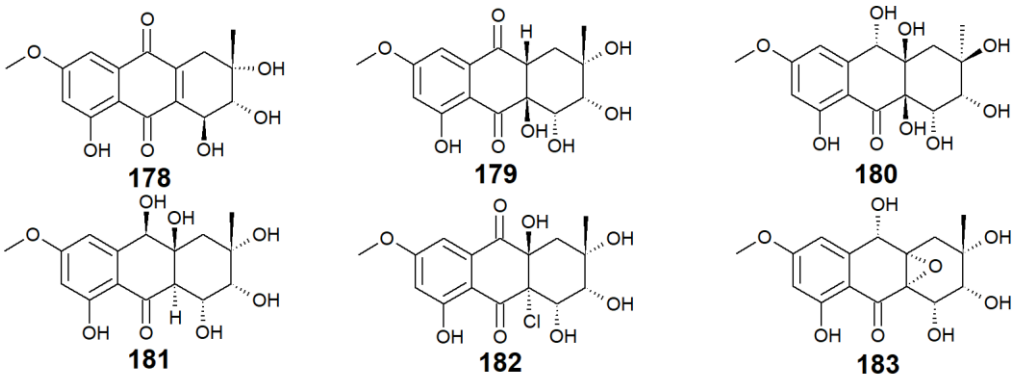

Figure 12: Chemical structures **178-183**

2.11. Anthraquinones from other marine fungi

A considerable number of anthraquinones and their derivatives were isolated from other marine-derived fungi including compounds **184-208**. Compounds **184-192, as well as previously discussed anthraquinone derivatives, 5, 41, 83, and 147,** were reported from the mangrove endophytes, *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382 [32]. Eight compounds from them, **184-191** showed weak cytotoxic activity, while **192** displayed no cytotoxicity up to a concentration of 500.0 μM [32]. It is noteworthy that compounds **184-188** exhibited weak cytotoxicity against both tested cancer cell lines, KB and KBv200 with IC_{50} value ranging from 34.64 to 243.69 μM, whereas compounds **189-191** demonstrated a narrow spectrum of activity against only KBv200 cell line with IC_{50} value of 72.60, 185.68 and 301.47 μM, respectively. The best cytotoxicity was recorded for 1,3-dihydroxy-6-methoxy-8-methylanthracene-9,10-dione (**187**) which displayed activity against both KB and KBv200 cells lines with IC_{50} values of 38.05 and 34.64 μM, respectively [32].

Interestingly, SZ-685C (**193**) was isolated as a novel anthraquinone derivative from the marine endophytic fungus *Halorosellinia* sp. No. 1403 with anticancer potential [100–102]. It was demonstrated that SZ-685C (**193**) had anticancer activity against the rat pituitary adenoma MMQ and human non-functioning pituitary adenoma (NFPA) cell lines with IC_{50} value of 14.51 and 18.76 μM, respectively, while it had an IC_{50} value of 56.09 μM against the normal cell line, rat pituitary cells (RPC) [100]. Another study revealed similar results of its cytotoxic activity against the MMQ and RPC cell lines with IC_{50} values of 13.2 and 49.1 μM, respectively [102]. Also, it showed good cytotoxicity against both human MCF-7 and MCF-7/ADR cancer cell lines with IC_{50} values of 7.38 and 4.17 μM, respectively [101].

Additional anthraquinone derivatives, phomopsanthraquinone (**194**), and 1-hydroxy-3-methoxy-6-methyl anthraquinone (**195**) were isolated from the marine-derived fungus,

Phomopsis sp. PSU-MA214, besides the previously mentioned compounds, **102**, **107**-**108**, and **136** [103]. Phomopsanthraquinone (**194**) demonstrated cytotoxicity against MCF-7 and KB cancer cell lines with an IC_{50} value of 27.0 μM for both cell lines. Also, it exhibited moderate antibacterial activity against both MRSA and *S. aureus* with MIC values of 64.0 and 128.0 μg/mL, respectively. In the contrast, 1-hydroxy-3-methoxy-6-methyl anthraquinone (**195**) neither showed antibacterial activity nor cytotoxicity [103].

Further three anthraquinones, tetrahydroxyanthraquinone (**196**), methoxy-tetrahydroxyanthraquinone (**197**) and 1,2,3,6,8-pentahydroxy-7-[(1R)-1-methoxyethyl]-9,10-anthraquinone (**198**) along with previously mentioned noraverufanin (**36**), were recorded from the sponge-associated fungus *Microsphaeropsis* sp. [104]. All those anthraquinones showed a broad spectrum of protein kinases' inhibitory activity against cyclin-dependent kinase 4 in complex with its activator cyclin D1 (CDK4/cyclin D1), protein kinase C (PKC), and EGF-R with IC_{50} value ranging from 18.5 to 54.0 μM [104].

Moreover, the anthraquinone, lunatin (**199**), and the anthraquinone dimer, cytoskyrin A (**200**) were reported earlier from the sponge-associated fungi *Curvularia lunata* with positive antibacterial activity [105]. Both compounds exhibited antibacterial activity against *B. subtilis*, *S. aureus*, and *E. coli* using the disk diffusion method at a concentration of 5 μg/disk. Meanwhile, they showed no antifungal activity against *C. albicans* up to a concentration of 10 μg/disk [105].

Furthermore, rheoemodin (**201**), 2, 2′-bis-(7-methyl-1,4,5-trihydroxy-anthracene-9,10-dione) (**202**) as well as the previously discussed compounds, **62**, **63,** and **84** were isolated earlier from another sponge-associated fungus *Talaromyces stipitatus* KUFA 0207 [74]. Rheoemodin (**201**) displayed no significant anti-obesity activity, whereas 2, 2′-bis-(7-methyl-1,4,5-trihydroxy-anthracene-9,10-dione) (**202**) was not tested for any relevant activity [74].

Additional two anthraquinones, 7-methoxymacrosporin (**203**) and 7-(γ,γ)-dimethylallyloxymacrosporin (**204**) along with previously discussed compounds, **102**, **105**, **107**-**108**, were isolated from the mangrove fungus, *Phoma* sp. L28 [85]. 7-methoxymacrosporin (**203**) displayed weak antifungal activity against *F. graminearum*, *F. oxysporum*, *P. italicum*, *Rhizoctonia solani*, and *Colletotrichum gloeosporioides* with MIC values of 100.0, 100.0, 100.0, 150.0, and 200.0 μg/mL, respectively. Also, 7-(γ,γ)-dimethylallyloxymacrosporin (**204**) demonstrated weak selective antifungal activity against *F. graminearum*, *Rhizoctonia solani*, and *Colletotrichum gloeosporioides* with MIC value of 80.0, 150.0, and 200.0 μg/mL, respectively [85]. By comparing this weak antifungal of **203** and **204** to their parent macrosporin (**108**) which displayed potent antifungal activity against *F.*

oxysporum and modest antifungal activity against *Colletotrichum musae*, *F. graminearum*, *P. italicum*, and *Colletotrichum gloeosporioides* [85], we can conclude that the structural modifications in both **203** and **204** have greatly affected their bioactivity.

Four additional bioactive anthraquinone derivatives were reported from the marine-derived fungus *Monodictys* sp. including the previously discussed compounds, **13**, **83,** and **147** as well as monodictyquinone A (**205**). Compound **205** displayed promising antimicrobial activity against *B. subtilis*, *E. coli*, and *C. albicans* showing zones of inhibition with a diameter of 15.0, 15.0, and 11.0 mm, respectively at a concentration of 10 μg/disk [43].

Two other anthraquinone derivatives, 1,3,6-trihydroxy-7-(1-hydroxyethyl) anthracene-9,10-dione (**206**) and phaseolorin I (**207**) were isolated earlier from the marine-derived fungi, *Cladosporium* sp. HNWSW-1 [106] and *Diaporthe phaseolorum* FS431 [107], respectively. Phaseolorin I (**207**) was inactive when it was tested for its cytotoxicity against the cell lines, MCF-7, Hep-G2, A549, and SF-268 [107], whereas **206** did not demonstrate cytotoxicity against the cell lines, BEL-7042, HeLa, and K562 as well as the human papillomavirus-related endocervical adenocarcinoma SGC-7901 cell line [106]. However, **206** exhibited α-glycosidase inhibitory activity with an IC_{50} value of 49.3 μM compared to the standard agent, acarbose which had an IC_{50} value of 275.7 μM [106].

Finally, 6,8-di-*O*-methyl averufanin (**208**) which is a derivative of the bioactive anthraquinone derivative, averufanin (**35**) was previously reported from the unidentified marine endophytic fungus ZSUH-36 as well as the previously mentioned compounds, **27**, **30**, **32-33**, **40**, **43**, and **80** [108]. Compound **208** demonstrated weak antifungal activity against the phytopathogenic fungi, *Botrytis cinerea* and *Magnaporthe oryzae* with MIC values of 50.0 and 100.0 μM, respectively [109]. Also, it displayed good phytotoxicity on the hypocotyls of radish seedlings at a concentration of 100 μM with an inhibition rate of 30.6% compared to 28.1% for the standard, glyphosate [109], (Figure 13).

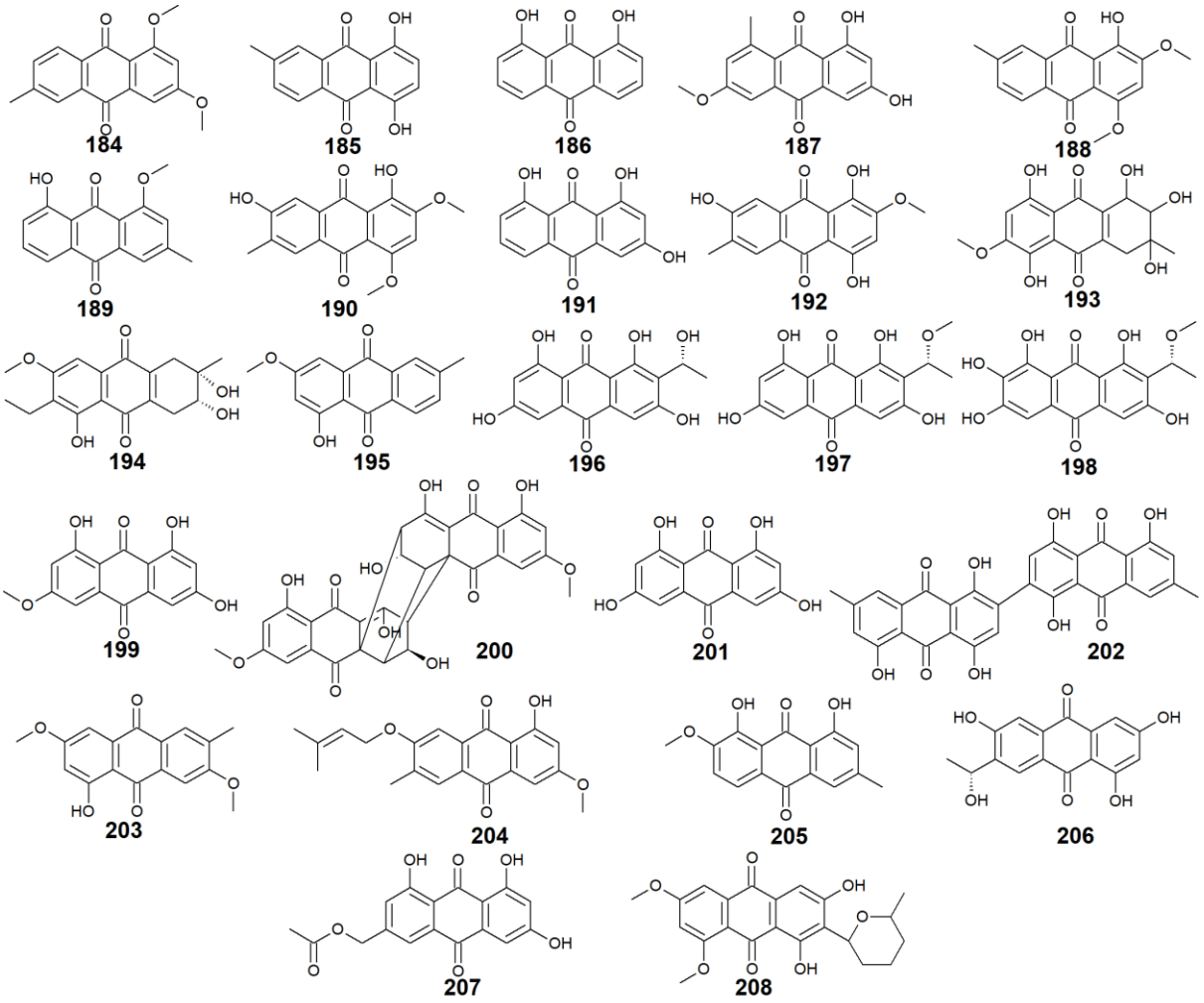

Figure 13: Chemical structures **184-208**

Table 1: Anthraquinones and their derivatives isolated from different species of marine-derived fungi with their sources and biological activities. MF = Molecular formula.

Compound	MF	Name	Bioactivity	Source	Reference
1	$C_{31}H_{32}O_{12}$	Nigrodiquinone A	Displayed no antibacterial or antiviral activity	Zoanthid-derived fungus *Nigrospora* sp.	[29]
2	$C_{17}H_{22}O_7$	4a-epi-9-methoxydihydrodeoxybostrycin	Antibacterial activity	Zoanthid-derived fungus *Nigrospora* sp. and sea anemone-derived fungus *Nigrospora* sp.	[29,30]
3	$C_{16}H_{16}O_7$	10-deoxybostrycin	Antibacterial and cytotoxic activities	Zoanthid-derived fungus *Nigrospora* sp. and sea anemone-derived fungus *Nigrospora* sp.	[29,30]
4	$C_{16}H_{12}O_6$	3,5,8-trihydroxy-7-methoxy-2-methylanthracene-9,10-dione	Antiviral activity	Zoanthid-derived fungus *Nigrospora* sp. and sea anemone-derived fungus *Nigrospora* sp	[29,30]
5	$C_{16}H_{12}O_5$	Austrocortirubin	Antiviral and cytotoxic activities	Zoanthid-derived fungus *Nigrospora* sp., mangrove endophytic fungi *Halorosellinia* sp. (No. 1403), and *Guignardia* sp. (No. 4382), sea anemone-derived fungus *Nigrospora* sp., and sea fan-derived fungi *Fusarium* sp. PSU-F14	[29–33]
6	$C_{16}H_{16}O_6$	Nigrosporin B	Antibacterial, anti-mycobacterial, cytotoxic, and phytotoxic activities	Sea anemone-derived fungus *Nigrospora* sp. and sea fan-derived fungi *Fusarium* sp. PSU-F14	[30,31,35,36]
7	$C_{16}H_{20}O_7$	1-deoxytetrahydrobostrycin	Antibacterial and cytotoxic activities	Sea anemone-derived fungus *Nigrospora* sp., sea fan-derived fungi *Fusarium* sp. PSU-F14 and marine-derived fungus *Aspergillus* sp.	[30,31,34]

8	$C_{16}H_{20}O_8$	Tetrahydrobostrycin	Antibacterial, antimalarial, anti-mycobacterial, and cytotoxic activities	Sea anemone-derived fungus *Nigrospora* sp, sea fan-derived fungi *Fusarium* sp. PSU-F14, and marine-derived fungus *Aspergillus* sp.	[30,31,34,38]
9	$C_{16}H_{16}O_7$	4-deoxybostrycin	Antibacterial, anti-mycobacterial, and cytotoxic activities	Sea anemone-derived fungus *Nigrospora* sp.	[30,35,37]
10	$C_{16}H_{16}O_8$	Bostrycin	Antibacterial, antimalarial, and cytotoxic activities	Sea anemone-derived fungus *Nigrospora* sp., marine-derived fungus *Aspergillus* sp., and sea fan-derived fungi *Fusarium* sp. PSU-F14	[30,31,34,37]
11	$C_{25}H_{16}O_9$	Aspergiolide A	Cytotoxic activity	Marine-derived fungus *A. glaucus*	[39,40]
12	$C_{26}H_{18}O_9$	Aspergiolide B	Cytotoxic activity	Marine-derived fungus *A. glaucus*	[39]
13	$C_{15}H_{10}O_5$	Emodin	Antibacterial, antifungal, anti-HCV protease, anti-mycobacterial, and cytotoxic activities	Sea fan-derived fungus *P. citrinum* PSU-F51, marine-derived fungi *T. aureoviride* PSU-F95, *Trichoderma* sp., *A. glaucus*, and halotolerant *A. variecolor*, marine lichen-derived fungus *Gliocladium* sp. T31, sea urchin-derived fungus *Monodictys* sp., marine mangrove fungus *Paecilomyces* sp., and marine-derived endophytic fungus *Eu. rubrum*	[32,39,41–49,51,55]
14	$C_{16}H_{12}O_5$	Physcion	Antifungal, antioxidant, and cytotoxic activities	Marine-derived fungi *Microsporum* sp., *A. glaucus*, and halotolerant *A. variecolor*, and marine algae-derived fungus *A. wentii* EN-48	[39,50–53]
15	$C_{16}H_{16}O_5$	Asperflavin	Antioxidant activity	Marine-derived fungus *A. glaucus* and marine algae-derived endophytic fungus *Eu. Cristatum* EN-220	[39,54,93]
16	$C_{16}H_{16}O_5$	Isoasperflavin	Displayed no cytotoxic activity	Marine-derived fungus *A. glaucus*	[39]

17	$C_{16}H_{12}O_5$	Questin	Antioxidant activity	Marine-derived fungi *A. glaucus* and halotolerant *A. variecolor*, and mangrove-derived fungus *P. citrinum* HL-5126	[39,51,54,76]
18	$C_{15}H_{10}O_6$	Catenarin	Antibacterial activity	Marine-derived fungi *A. glaucus*, *Eu. Rubrum*, and halotolerant *A. variecolor*	[39,51,55,95]
19	$C_{16}H_{12}O_6$	Rubrocristin	Displayed no antibacterial activity	Marine-derived fungi *A. glaucus*, *Eu. Rubrum*, and halotolerant *A. variecolor*	[39,51,55,95]
20	$C_{20}H_{18}O_{10}$	(+)-Variecolorquinone A	Cytotoxic activity	Marine-derived fungi *A. glaucus* and halotolerant *A. variecolor*, and marine algae-derived endophytic fungus *Eu. cristatum* EN-220	[39,51,93]
21	$C_{32}H_{26}O_8$	Physcion-10,10'-bianthrone	Was not evaluated for any relevant bioactivity	Marine-derived fungus *A. glaucus*	[39]
22	$C_{31}H_{24}O_8$	(*trans*)-Emodin-physcion bianthrone	Cytotoxic activity	Marine-derived fungus *A. glaucus*	[39]
23	$C_{31}H_{24}O_8$	(*cis*)-Emodin-physcion bianthrone	Cytotoxic activity	Marine-derived fungus *A. glaucus*	[39]
24	$C_{42}H_{42}O_{13}$	6,6′-oxybis(1,3,8-trihydroxy-2-((S)-1-methoxyhexyl)anthracene-9,10-dione)	Antibacterial and cytotoxic activities	Marine-derived fungus *A. versicolor*	[56]
25	$C_{40}H_{38}O_{13}$	6,6′-oxybis(1,3,8-trihydroxy-2-((S)-1-hydroxyhexyl) anthracene-9,10-dione)	Antibacterial activity	Marine-derived fungus *A. versicolor*	[56]

26	$C_{20}H_{20}O_7$	Averantin	Antibacterial, antioxidant, and cytotoxic activities	Marine-derived fungi *A. versicolor* and *P. purpurogenum* G59	[56,57,59,60,110]
27	$C_{21}H_{22}O_7$	1'-*O*-methylaverantin	Antibacterial, antioxidant, and cytotoxic activities	Marine-derived fungi *A. versicolor* and *P. purpurogenum* G59, and the mangrove endophytic fungus (ZSUH-36)	[56,57,59,60,108]
28	$C_{20}H_{18}O_6$	Averythrin	Antioxidant and cytotoxic activities	Marine-derived fungi *A. versicolor* and *Aspergillus* sp. SCSIO F063	[56,58,59]
29	$C_{22}H_{24}O_7$	6,8-di-*O*-methylaverantin	Antibacterial activity	Marine-derived fungus *A. versicolor* EN-7	[61]
30	$C_{20}H_{16}O_7$	Averufin	Antibacterial, antioxidant, antiviral, and cytotoxic activities	Marine-derived fungi *A. versicolor* and *A. niger* (MF-16), mangrove endophytic fungi ZSUH-36 and (isolate 1850), and mangrove-derived endophytic fungus *A. nidulans* MA-143	[59,60,62,63,108,111]
31	$C_{21}H_{18}O_7$	6-*O*-methylaverufin	Displayed no antimicrobial activity	Marine-derived fungus *A. versicolor* EN-7	[61]
32	$C_{22}H_{20}O_7$	6,8-di-*O*-methylaverufin	Displayed no anti-neuroinflammatory activity	Marine-derived fungi *Aspergillus* sp. SF-6796 and *A. versicolor* EN-7, and the mangrove endophytic fungus (ZSUH-36)	[61,64,108]
33	$C_{18}H_{12}O_7$	Versicolorin B	Antioxidant activity	Marine-derived fungus *A. versicolor* and mangrove endophytic fungus ZSUH-36	[59]
34	$C_{18}H_{12}O_8$	1'-hydroxyversicolorin B	Antioxidant and cytotoxic activities	Marine-derived fungus *A. versicolor*	[59,66]
35	$C_{20}H_{18}O_7$	Averufanin	Antioxidant activity and inhibitory activity of acyl-CoA: cholesterol acyltransferase	Marine-derived fungus *A. versicolor* and mangrove-derived endophytic fungus *A. nidulans* MA-143	[59,67]

36	$C_{19}H_{16}O_7$	Noraverufanin	Anti-HIV activity	Sponge-associated fungi *Microsphaeropsis* sp. and *A. versicolor* SCSIO 41016	[65,104]
37	$C_{20}H_{16}O_8$	Nidurufin	Antibacterial, antioxidant, antiviral, and cytotoxic activities	Marine-derived fungi *A. versicolor*, *A. niger* (MF-16), and *P. purpurogenum* G59, and marine-derived mangrove endophytic fungus (isolate 1850)	[57,59,60,62,111]
38	$C_{22}H_{20}O_8$	6,8-di-*O*-methylnidurufin	Antibacterial activity	Marine-derived fungus *A. versicolor* EN-7	[61]
39	$C_{18}H_{16}O_8$	Versiconol	Cytotoxic activity	Marine-derived fungus *A. versicolor*	[60]
40	$C_{20}H_{20}O_8$	6,8-di-*O*-methyl versiconol	Antibacterial activity	Mangrove endophytic fungus (ZSUH-36) and marine-derived fungus *A. versicolor* EN-7	[61,112]
41	$C_{16}H_{12}O_5$	1-methyl emodin	Anti-HCV protease and cytotoxic activities	Mangrove endophytic fungi *Halorosellinia* sp. (No. 1403) and *Guignardia* sp. (No. 4382), and Red Sea endophytic fungus *A. versicolor*	[32,68]
42	$C_{18}H_{16}O_6$	Isorhodoptilometrin-1-methyl ether	Antibacterial and cytotoxic activities	Red Sea endophytic fungus *A. versicolor*	[68]
43	$C_{20}H_{16}O_7$	Aversin	Displayed no antimicrobial activity	Mangrove endophytic fungus (ZSUH-36) and marine-derived fungus *A. versicolor* EN-7	[61,112]
44	$C_{20}H_{14}O_7$	6,8-di-*O*-methylversicolorin A	Displayed no antimicrobial activity	Marine-derived fungus *A. versicolor* EN-7	[61]
45	$C_{16}H_{12}O_6$	Evariquinone	Was not evaluated for any relevant bioactivity	Red Sea endophytic fungus *A. versicolor*	[68]
46	$C_{17}H_{14}O_6$	7-hydroxyemodin 6,8-methyl ether	Was not evaluated for any relevant bioactivity	Red Sea endophytic fungus *A. versicolor*	[68]
47	$C_{15}H_{10}O_3$	1-hydroxy-2-methyl anthraquinone	Anti-mosquito activity	Marine-derived fungus *A. versicolor*	[47,69]

48	$C_{17}H_{14}O_5$	2-(dimethoxy methyl)-1-hydroxy-9,10-anthraquinone	Antibacterial activity	Marine-derived fungus *A. versicolor*	[47]
49	$C_{15}H_{10}O_2$	Tectoquinone	Was not evaluated for any relevant bioactivity	Marine-derived fungus *A. versicolor*	[47]
50	$C_{16}H_{10}O_5$	Damnacanthal	Antibacterial and anti-mosquito activities	Marine-derived fungus *A. versicolor*	[47,69]
51	$C_{14}H_8O_4$	Xanthopurpurin	Antibacterial and anti-platelets aggregation activities	Marine-derived fungus *A. versicolor*	[47,70]
52	$C_{15}H_{10}O_4$	Rubiadin	Inhibitory activity on formation of advanced glycation end products	Marine-derived fungus *A. versicolor*	[47,71]
53	$C_{15}H_{10}O_5$	6-hydroxyrubiadin	Inhibitory effects on the release of β-hexosaminidase and inhibitory activity on phosphatase of regenerating liver-3	Marine-derived fungus *A. versicolor*	[47,72]
54	$C_{16}H_{12}O_5$	Rubianthraquinone	Anti-inflammatory activity	Marine-derived fungus *A. versicolor*	[47,113]
55	$C_{16}H_{12}O_7$	Wentiquinone C	Displayed no antioxidant activity	Marine algae-derived fungus *A. wentii* EN-48	[50]
56	$C_{15}H_{10}O_5$	Alatinone	Was not evaluated for any relevant bioactivity	Marine-derived endophytic fungus *A. wentii* pt-1	[73]
57	$C_{17}H_{14}O_5$	5-hydroxy-1,3-dimethoxy-7-methyl anthraquinone	Was not evaluated for any relevant bioactivity	Marine-derived endophytic fungus *A. wentii* pt-1	[73]
58	$C_{16}H_{12}O_5$	1,5-dihydroxy-3-methoxy-7-methyl anthraquinone	Was not evaluated for any relevant bioactivity	Marine-derived endophytic fungus *A. wentii* pt-1	[73]

59	$C_{15}H_{12}O_6$	Eurotinone	Antioxidant activity and kinase insert domain receptor inhibitory activity	Marine-derived halotolerant fungus *A. variecolor*	[51,114]
60	$C_{16}H_{14}O_6$	2-*O*-methyleurotinone	Antioxidant activity	Marine mangrove-derived endophytic fungus *Eu. rubrum* and marine-derived halotolerant fungus *A. variecolor*	[51,54]
61	$C_{19}H_{16}O_9$	(2S)-2,3-dihydroxypropyl 1,6,8-trihydroxy-3-methyl-9,10-dioxo-9,10-dihydro-2-anthracenecarboxylate	Was not evaluated for any relevant bioactivity	Marine-derived halotolerant fungus *A. variecolor*	[51]
62	$C_{16}H_{12}O_6$	Questinol	Anti-inflammatory and anti-obesity activities	Marine-derived halotolerant fungus *A. variecolor* and marine-derived fungi *Eu. amstelodami* and *Talaromyces stipitatus* KUFA 0207	[51,74,75]
63	$C_{16}H_{12}O_6$	Fallacinol	Displayed no significant anti-obesity activity	Marine-derived halotolerant fungus *A. variecolor* and marine algae-derived fungus *Talaromyces stipitatus* KUFA 0207	[51,74]
64	$C_{16}H_{12}O_6$	Erythroglaucin	Displayed no antibacterial activity	Marine-derived halotolerant fungus *A. variecolor*	[51,55]
65	$C_{18}H_{12}O_7$	Versicolorin C	Antibacterial activity	Marine-derived mangrove endophytic fungus (isolate 1850) and mangrove-derived endophytic fungus *A. nidulans* MA-143	[63,111]
66	$C_{18}H_{12}O_7$	Isoversicolorin C	Antibacterial activity	Mangrove-derived endophytic fungus *A. nidulans* MA-143	[63]
67	$C_{20}H_{18}O_7$	Norsolorinic acid	Was not evaluated for any relevant bioactivity	Mangrove-derived endophytic fungus *A. nidulans* MA-143	[63]

68	$C_{21}H_{22}O_7$	(1′S) 6-*O*-methylaverantin	Displayed no cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
69	$C_{22}H_{24}O_7$	(1′S) 6,1′-*O, O*-dimethylaverantin	Displayed no cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
70	$C_{24}H_{28}O_7$	Averantin-1′-butyl ether	Cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
71	$C_{20}H_{19}ClO_7$	(1′S)-7-chloroaverantin	Cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
72	$C_{21}H_{21}ClO_7$	(1′S) 6-*O*-methyl-7-chloroaverantin	Cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
73	$C_{21}H_{21}ClO_7$	(1′S) 1′-*O*-methyl-7-chloroaverantin	Cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
74	$C_{22}H_{23}ClO_7$	(1′S) 6,1′- *O, O*-dimethyl-7-chloroaverantin	Displayed no cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
75	$C_{24}H_{27}ClO_7$	(1′S) 7-chloroaverantin-1′-butyl ether	Cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
76	$C_{20}H_{17}ClO_6$	7-chloroaverythrin	Displayed no cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
77	$C_{21}H_{19}ClO_6$	6-*O*-methyl-7-chloroaverythrin	Cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
78	$C_{21}H_{21}ClO_6$	(1′S) 6-*O*-methyl-7-bromoaverantin	Cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
79	$C_{22}H_{23}BrO_7$	(1′S) 6,1′-*O, O*-dimethyl-7-bromoaverantin	Displayed no cytotoxic activity	Marine-derived fungus *Aspergillus* sp. SCSIO F063	[58]
80	$C_{23}H_{26}O_7$	6,8,1’-tri-*O*-methylaverantin	Anti-inflammatory activity	Marine-derived fungus *Aspergillus* sp. SF-6796 and mangrove endophytic fungus ZSUH-36	[64,108]

81	$C_{28}H_{24}O_{10}$	Penicillanthranin A	Antibacterial and cytotoxic activities	Sea fan-derived fungus *P. citrinum* PSU-F51	[41]
82	$C_{28}H_{24}O_{11}$	Penicillanthranin B	Displayed no cytotoxic activity	Sea fan-derived fungus *P. citrinum* PSU-F51	[41]
83	$C_{15}H_{10}O_4$	Chrysophanol	Anti-acetylcholinesterase, antibacterial, and cytotoxic activities	Sea fan-derived fungus *P. citrinum* PSU-F51, marine-derived fungi *T. aureoviride* PSU-F95 and *Trichoderma* sp., mangrove endophytic fungi *Halorosellinia* sp. (No. 1403) and *Guignardia* sp. (No. 4382), sea urchin-derived fungus *Monodictys* sp., and marine mangrove fungus *Paecilomyces* sp.	[32,41–43,45,92]
84	$C_{15}H_{10}O_6$	ω-hydroxyemodin	Antibacterial, anti-mycobacterial, anti-obesity, and cytotoxic activities	Sea fan-derived fungus *P. citrinum* PSU-F51, mangrove-derived fungus *P. citrinum* HL-5126, marine-derived fungi *T. aureoviride* PSU-F95, and *Talaromyces stipitatus* KUFA 0207, and marine lichen-derived fungus *Gliocladium* sp. T31	[41,42,44,49,74,76]
85	$C_{18}H_{13}ClO_7$	2′-acetoxy-7-chlorocitreorosein	Antibacterial activity	Mangrove-derived fungus *P. citrinum* HL-5126	[76]
86	$C_{15}H_{10}O_9S$	Citreorosein-3-*O*-sulphate	Was not evaluated for any relevant bioactivity	Marine-derived fungus *P. oxalicum* 2HL-M-6	[77]
87	$C_{15}H_{10}O_8S$	Emodin-3-*O*-sulphate	Was not evaluated for any relevant bioactivity	Marine-derived fungus *P. oxalicum* 2HL-M-6	[77]
88	$C_{15}H_{10}O_5$	Aloe-emodin	Antibacterial and antimalarial activities	Marine-derived fungus *P. oxalicum* 2HL-M-6	[77–79]
89	$C_{21}H_{19}NO_8$	Emodacidamide A	Immunomodulatory activity	Marine-derived fungus *Penicillium* sp. SCSIO sof101	[80]

90	$C_{20}H_{17}NO_8$	Emodacidamide B	Immunomodulatory activity	Marine-derived fungus *Penicillium* sp. SCSIO sof101	[80]
91	$C_{20}H_{16}ClNO_8$	Emodacidamide C	Immunomodulatory activity	Marine-derived fungus *Penicillium* sp. SCSIO sof101	[80]
92	$C_{22}H_{21}NO_8$	Emodacidamide D	Immunomodulatory activity	Marine-derived fungus *Penicillium* sp. SCSIO sof101	[80]
93	$C_{21}H_{19}NO_8$	Emodacidamide E	Immunomodulatory activity	Marine-derived fungus *Penicillium* sp. SCSIO sof101	[80]
94	$C_{21}H_{18}ClNO_8$	Emodacidamide F	Immunomodulatory activity	Marine-derived fungus *Penicillium* sp. SCSIO sof101	[80]
95	$C_{21}H_{18}ClNO_8$	Emodacidamide G	Immunomodulatory activity	Marine-derived fungus *Penicillium* sp. SCSIO sof101	[80]
96	$C_{18}H_{13}NO_8$	Emodacidamide H	Immunomodulatory activity	Marine-derived fungus *Penicillium* sp. SCSIO sof101	[80]
97	$C_{15}H_8O_7$	Emodic acid	Inhibitory activity on tyrosine kinase proteins	Marine-derived endophytic fungus *Eu. rubrum* and marine-derived fungus *Penicillium* sp. SCSIO sof101	[46,80,81]
98	$C_{15}H_9ClO_6$	2-chloro-1,3,8 trihydroxy-6 (hydroxymethyl)anthracene-9,10 dione	Immunomodulatory activity	Marine-derived fungus *Penicillium* sp. SCSIO sof101	[80]
99	$C_{16}H_{16}O_8$	Altersolanol A	Antibacterial and cytotoxic activities, as well as protein kinase inhibitory activity	Mangrove-derived fungus *Stemphylium* sp. 33231 and coral-associated fungus *Stemphylium lycopersici*	[82,83,86]

100	$C_{16}H_{18}O_7$	Dihydroaltersolanol A	Displayed no antibacterial or cytotoxic activity	Mangrove-derived fungus *Stemphylium* sp. 33231, deep-sea-derived fungus *Alternaria tenuissima* DFFSCS013, and soft coral-derived *Alternaria* sp. ZJ-2008003	[82,84,91]
101	$C_{16}H_{16}O_6$	Altersolanol B	Antibacterial, anticoagulant, anti-mycobacterial, and cytotoxic activities	Mangrove-derived fungus *Stemphylium* sp. 33231, mangrove endophytic fungus *Alternaria* sp. ZJ9-6B, coral-associated fungus *Stemphylium lycopersici* and *Alternaria* sp. ZJ-2008003, deep sea-derived fungus *Alternaria tenuissima* DFFSCS013 and marine-derived fungus *Sporendonema casei* HDN16-802	[82–84,90,91,99]
102	$C_{16}H_{20}O_6$	Tetrahydroaltersolanol B	Antibacterial and antifungal activities	Mangrove-derived fungi *Phomopsis* sp. PSU-MA214, *Stemphylium* sp. 33231, and *Phoma* sp. L28, mangrove endophytic fungus *Alternaria* sp. ZJ9-6B, and soft coral-derived *Alternaria* sp. ZJ-2008003	[82,84,85,90,103]
103	$C_{18}H_{18}O_7$	2-*O*-acetylaltersolanol B	Antibacterial activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82]
104	$C_{16}H_{16}O_7$	Altersolanol C	Antibacterial activity	Mangrove-derived fungus *Stemphylium* sp. 33231 and soft coral-derived *Alternaria* sp. ZJ-2008003	[82,84]
105	$C_{16}H_{20}O_7$	Altersolanol L	Antifungal and cytotoxic activities	Mangrove-derived fungi *Stemphylium* sp. 33231 and *Phoma* sp. L28, and deep-sea derived fungus *Alternaria tenuissima* DFFSCS013 and soft coral-derived *Alternaria* sp. ZJ-2008003	[82,84,85,91,115]

106	$C_{18}H_{22}O_8$	2-*O*-acetylaltersolanol L	Displayed no antibacterial or cytotoxic activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82]
107	$C_{16}H_{20}O_8$	Ampelanol	Cytotoxic activity	Mangrove-derived fungi *Phomopsis* sp. PSU-MA214, *Stemphylium* sp. 33231, and *Phoma* sp. L28, coral-associated fungus *Stemphylium lycopersici* and *Alternaria* sp. ZJ-2008003 and, deep-sea derived fungus *Alternaria tenuissima* DFFSCS013	[82–86,91,103]
108	$C_{16}H_{12}O_5$	Macrosporin	Antibacterial, antifungal, and cytotoxic activities as well as protein kinases' inhibitory activity	Mangrove-derived fungi *Phomopsis* sp. PSU-MA214, *Stemphylium* sp. 33231, *Alternaria* sp. ZJ9-6B and *Phoma* sp. L28 and coral-associated fungus *Stemphylium lycopersici* and *Alternaria* sp. ZJ-2008003	[82–86,90,103, 115]
109	$C_{16}H_{12}O_8S$	Macrosporin-7-*O*-sulphate	Cytotoxic activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82,86]
110	$C_{24}H_{24}O_{11}$	Macrosporin 2-*O*-(6′-acetyl)-α-D-glucopyranoside	Brine shrimp lethality	Mangrove-derived fungus *Stemphylium* sp. 33231	[82]
111	$C_{16}H_{16}O_9$	Auxarthrol C	Antibacterial activity	Mangrove-derived fungus *Stemphylium* sp. 33231 and coral-associated fungus *Stemphylium lycopersici*	[82,83]
112	$C_{32}H_{26}O_{13}$	Alterporriol A	Displayed no antibacterial or cytotoxic activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82]
113	$C_{32}H_{26}O_{13}$	Alterporriol B	Antibacterial activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82]

114	$C_{32}H_{22}O_{10}$	Alterporriol C	Antibacterial and antiviral activities	Mangrove-derived fungus *Stemphylium* sp. 33231 and soft coral-derived *Alternaria* sp. ZJ-2008003	[82,84]
115	$C_{32}H_{30}O_{16}$	Alterporriol D	Antibacterial and cytotoxic activities	Mangrove-derived fungus *Stemphylium* sp. 33231	[82,86]
116	$C_{32}H_{22}O_{10}$	Alterporriol E	Antibacterial and cytotoxic activities	Mangrove-derived fungus *Stemphylium* sp. 33231	[82,86]
117	$C_{32}H_{26}O_{13}$	Alterporriol N	Antibacterial and anti-inflammatory activities	Marine-derived fungus *Stemphylium* sp. FJJ006 and mangrove-derived fungus *Stemphylium* sp. 33231	[82,87,89]
118	$C_{32}H_{22}O_{10}$	Alterporriol Q	Antiviral activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82,84]
119	$C_{32}H_{22}O_{10}$	Alterporriol R	Displayed no antiviral, antibacterial or cytotoxic activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82,84]
120	$C_{32}H_{30}O_{13}$	Alterporriol T	Displayed no antibacterial activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82]
121	$C_{32}H_{30}O_{12}$	Alterporriol U	Antibacterial activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82]
122	$C_{32}H_{22}O_{10}$	Alterporriol V	Antibacterial activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82]
123	$C_{32}H_{26}O_{12}$	Alterporriol W	Displayed no antibacterial or cytotoxic activity	Mangrove-derived fungus *Stemphylium* sp. 33231	[82]
124	$C_{32}H_{26}O_{12}$	Alterporriol F	Anti-inflammatory and cytotoxic activities	Marine-derived fungus *Stemphylium* sp. FJJ006	[87,88]

125	$C_{32}H_{26}O_{13}$	Alterporriol G	Antibacterial, anti-inflammatory, and cytotoxic activities as well as protein kinase inhibitory activity	Marine-derived fungus *Stemphylium* sp. FJJ006	[87,89,115]
126	$C_{32}H_{26}O_{13}$	Alterporriol Z1	Anti-inflammatory activity	Marine-derived fungus *Stemphylium* sp. FJJ006	[87]
127	$C_{32}H_{26}O_{13}$	Alterporriol Z2	Anti-inflammatory activity	Marine-derived fungus *Stemphylium* sp. FJJ006	[87]
128	$C_{33}H_{28}O_{13}$	Alterporriol Z3	Displayed no antibacterial or cytotoxic activity	Marine-derived fungus *Stemphylium* sp. FJJ006	[87]
129	$C_{22}H_{22}O_{10}$	Macrosporin 2-*O*-α-D-glucopyranoside	Displayed no cytotoxic activity	Coral associated fungus *Stemphylium lycopersici*	[83]
130	$C_{32}H_{30}O_{12}$	Alterporriol Y	Displayed no cytotoxic activity	Coral associated fungus *Stemphylium lycopersici*	[83]
131	$C_{32}H_{26}O_{11}$	Alterporriol K	Cytotoxic activity	Mangrove endophytic fungus *Alternaria* sp. ZJ9-6B	[90]
132	$C_{32}H_{26}O_{12}$	Alterporriol L	Cytotoxic activity	Mangrove endophytic fungus *Alternaria* sp. ZJ9-6B	[90]
133	$C_{32}H_{26}O_{12}$	Alterporriol M	Was not evaluated for any relevant bioactivity	Mangrove endophytic fungus *Alternaria* sp. ZJ9-6B	[90]
134	$C_{32}H_{30}O_{14}$	Alterporriol O	Displayed no antibacterial, antiviral, or cytotoxic activity	Soft coral derived *Alternaria* sp. ZJ-2008003	[84]
135	$C_{32}H_{26}O_{12}$	Alterporriol P	Cytotoxic activity	Soft coral derived *Alternaria* sp. ZJ-2008003	[84]
136	$C_{16}H_{20}O_6$	Tetrahydroaltersolanol C	Antiviral activity	Mangrove-derived fungus *Phomopsis* sp. PSU-MA214 and soft coral-derived fungus *Alternaria* sp. ZJ-2008003	[84,103]
137	$C_{16}H_{20}O_6$	Tetrahydroaltersolanol D	Displayed no antibacterial, antiviral, or cytotoxic activity	Soft coral derived *Alternaria* sp. ZJ-2008003	[84]

138	$C_{16}H_{20}O_6$	Tetrahydroaltersolanol E	Displayed no antibacterial, antiviral, or cytotoxic activity	Soft coral derived *Alternaria* sp. ZJ-2008003	[84]
139	$C_{18}H_{22}O_7$	Tetrahydroaltersolanol F	Displayed no antibacterial, antiviral, or cytotoxic activity	Soft coral derived *Alternaria* sp. ZJ-2008003	[84]
140	$C_{25}H_{28}O_{10}$	Anthrininone A	Inhibitory activity on protein tyrosine phosphatases and stimulatory effect on intracellular calcium levels	Deep-sea derived fungus *Alternaria tenuissima* DFFSCS013	[91]
141	$C_{16}H_{12}O_6$	6-*O*-methylalaternin	Inhibitory activity on protein tyrosine phosphatases	Deep-sea derived fungus *Alternaria tenuissima* DFFSCS013	[91]
142	$C_{16}H_{16}O_5$	(3R)-1-deoxyaustrocortilutein	Displayed no stimulation of intracellular calcium level	Deep-sea derived fungus *Alternaria tenuissima* DFFSCS013	[91]
143	$C_{15}H_{16}O_5$	Harzianumnone A	Displayed no anti-acetylcholinesterase or DNA Topo I inhibitory activities	Coral-derived fungus *T. harzianum* XS-20090075	[92]
144	$C_{15}H_{16}O_5$	Harzianumnone B	Displayed no anti-acetylcholinesterase or DNA Topo I inhibitory activities	Coral-derived fungus *T. harzianum* XS-20090075	[92]
145	$C_{15}H_{10}O_4$	Phomarin	Anti-acetylcholinesterase activity	Coral-derived fungus *T. harzianum* XS-20090075	[92]
146	$C_{15}H_{10}O_5$	ω-hydroxydigitoemodin	Anti-acetylcholinesterase activity	Coral-derived fungus *T. harzianum* XS-20090075	[92]

147	$C_{15}H_{10}O_3$	Pachybasin	Anti-acetylcholinesterase and cytotoxic activities	Marine-derived fungus *T. aureoviride* PSU-F95 and mangrove endophytic fungi *Halorosellinia* sp. (No. 1403) and *Guignardia* sp. (No. 4382), and sea urchin-derived fungus *Monodictys* sp.	[32,33,42,43,92]
148	$C_{17}H_{14}O_6$	(+)-2'*S*-isorhodoptilometrin	Anti-acetylcholinesterase, antibacterial, and cytotoxic activities, as well as DNA Topo I inhibitory activity	Coral-derived fungus *T. harzianum* XS-20090075, marine lichen-derived fungus *Gliocladium* sp. T31, and marine-derived fungus *T. aureoviride* PSU-F95	[42,44,92]
149	$C_{15}H_{10}O_4$	ω-hydroxypachybasin	Antibacterial, and cytotoxic activities, as well as DNA Topo I inhibitory activity	Marine-derived fungus *T. aureoviride* PSU-F95 and coral-derived fungus *T. harzianum* XS-20090075	[42,92]
150	$C_{15}H_{14}O_5$	Coniothranthraquinone 1	Antibacterial activity	Marine-derived fungus *T. aureoviride* PSU-F95	[42]
151	$C_{15}H_{14}O_6$	Trichodermaquinone	Antibacterial activity	Marine-derived fungus *T. aureoviride* PSU-F95	[42]
152	$C_{15}H_{10}O_4$	2-methylquinizarin	Was not evaluated for any relevant bioactivity	Marine-derived fungus *T. aureoviride* PSU-F95	[42]
153	$C_{15}H_{10}O_4$	1-hydroxy-3-methoxyanthraquinone	Was not evaluated for any relevant bioactivity	Marine-derived fungus *T. aureoviride* PSU-F95	[42]
154	$C_{15}H_{16}O_5$	Coniothyrinone A	Antibacterial and antiangiogenetic activities	Marine-derived fungus *Trichoderma* sp. and saline-alkali plant endophytic fungus *Eu. rubrum*	[48,95]
155	$C_{15}H_{14}O_6$	Lentisone	Antibacterial and antiangiogenetic activities	Marine-derived fungus *Trichoderma* sp.	[48]
156	$C_{15}H_{12}O_5$	9-dehydroxyeurotinone	Antibacterial and cytotoxic activities	Marine-derived endophytic fungus *Eu. rubrum*	[46]

157	$C_{16}H_{14}O_5$	2-*O*-methyl-9-dehydroxyeurotinone	Antioxidant activity	Marine-derived endophytic fungus *Eu. rubrum* and marine mangrove-derived endophytic fungus *Eu. rubrum*	[46,54]
158	$C_{21}H_{22}O_9$	2-*O*-methyl-4-*O*-(α-D-ribofuranosyl)-9-dehydroxyeurotinone	Antioxidant activity	Marine mangrove-derived endophytic fungus *Eu. rubrum*	[54]
159	$C_{21}H_{20}O_9$	3-*O*-(α-D-ribofuranosyl)-questin	Antibacterial and antioxidant activities	Marine mangrove-derived endophytic fungus *Eu. rubrum* and marine algae-derived endophytic fungus *Eu. cristatum* EN-220	[54,93]
160	$C_{33}H_{32}O_{10}$	Eurorubrin	Antibacterial and antioxidant activities as well as brine shrimp lethality	Marine mangrove-derived endophytic fungus *Eu. rubrum* and marine algae-derived endophytic fungus *Eu. cristatum* EN-220	[54,93]
161	$C_{21}H_{20}O_{10}$	3-*O*-(α-D-ribofuranosyl)questinol	Displayed no antibacterial activity or brine shrimp lethality	Marine algae-derived endophytic fungus *Eu. cristatum* EN-220	[93]
162	$C_{21}H_{24}O_9$	Asperflavin ribofuranoside	Antibacterial and antioxidant activities	Marine algae-derived endophytic fungus *Eu. cristatum* EN-220 and marine-derived algicolous fungus *Microsporum* sp.	[93,94]
163	$C_{15}H_{14}O_5$	Rubrumol	Relaxation activity on Topo I enzyme	Saline-alkali plant endophytic fungus *Eu. rubrum*	[95]
164	$C_{16}H_{16}O_6$	Nigrosporin A	Antibacterial, cytotoxic, and phytotoxic activities	Sea fan-derived fungus *Fusarium* sp. PSU-F14	[31,36]
165	$C_{16}H_{20}O_7$	Fusaranthraquinone	Displayed no antibacterial activity	Sea fan-derived fungus *Fusarium* sp. PSU-F14	[31]
166	$C_{16}H_{18}O_6$	Fusaquinon A	Cytotoxic activity	Marine-derived fungus *Fusarium* sp. ZH-210	[96,97]
167	$C_{16}H_{20}O_8$	Fusaquinon B	Cytotoxic activity	Marine-derived fungus *Fusarium* sp. ZH-210	[96]
168	$C_{16}H_{20}O_7$	Fusaquinon C	Cytotoxic activity	Marine-derived fungus *Fusarium* sp. ZH-210	[96]

169	$C_{21}H_{20}O_5$	6,8-dimethoxy-1-methyl-2-(3-oxobutyl)anthracene-9,10-dione	Cytotoxic activity	Mangrove endophytic fungus *Fusarium* sp. ZZF60	[98]
170	$C_{17}H_{12}O_7$	5-acetyl-2-methoxy-1,4,6-trihydroxy-anthraquinone	Was not evaluated for any relevant bioactivity	Marine endophytic fungus *Fusarium* sp. b77	[116]
171	$C_{33}H_{28}O_{12}$	Engyodontochone A	Antibacterial, antifungal, and cytotoxic activities	Marine-derived fungus *Engyodontium album* strain LF069	[23]
172	$C_{33}H_{28}O_{12}$	JBIR-99	Antibacterial, antifungal, and cytotoxic activities	Marine-derived fungus *Engyodontium album* strain LF069	[23]
173	$C_{33}H_{28}O_{12}$	Engyodontochone B	Antibacterial, antifungal, and cytotoxic activities	Marine-derived fungus *Engyodontium album* strain LF069	[23]
174	$C_{33}H_{28}O_{12}$	Engyodontochone C	Antibacterial and cytotoxic activities	Marine-derived fungus *Engyodontium album* strain LF069	[23]
175	$C_{33}H_{30}O_{13}$	Engyodontochone F	Antibacterial and antifungal activities	Marine-derived fungus *Engyodontium album* strain LF069	[23]
176	$C_{33}H_{30}O_{13}$	Engyodontochone E	Antibacterial activity	Marine-derived fungus *Engyodontium album* strain LF069	[23]
177	$C_{33}H_{28}O_{12}$	Engyodontochone D	Was not evaluated for any relevant bioactivity	Marine-derived fungus *Engyodontium album* strain LF069	[23]
178	$C_{16}H_{16}O_7$	4-dehydroxyaltersolanol A	Antibacterial and anticoagulant activities	Marine-derived fungus *Sporendonema casei* HDN16-802	[99]
179	$C_{16}H_{18}O_8$	Auxarthrol D	Antibacterial, anticoagulant, and cytotoxic activities	Marine-derived fungus *Sporendonema casei* HDN16-802	[99]
180	$C_{16}H_{20}O_9$	Auxarthrol E	Anticoagulant activity	Marine-derived fungus *Sporendonema casei* HDN16-802	[99]

181	$C_{16}H_{20}O_8$	Auxarthrol F	Antibacterial, anticoagulant, and cytotoxic activities	Marine-derived fungus *Sporendonema casei* HDN16-802	[99]
182	$C_{16}H_{17}ClO_8$	Auxarthrol G	Antibacterial, anticoagulant, and antifungal activities	Marine-derived fungus *Sporendonema casei* HDN16-802	[99]
183	$C_{16}H_{18}O_8$	Auxarthrol H	Anticoagulant activity	Marine-derived fungus *Sporendonema casei* HDN16-802	[99]
184	$C_{17}H_{14}O_4$	1,3-dimethoxy-6-methylanthracene-9,10-dione	Cytotoxic activity	Mangrove endophytic fungi *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382	[32]
185	$C_{15}H_{10}O_4$	Demethoxyaustrocortirubin	Cytotoxic activity	Mangrove endophytic fungi *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382	[32,33]
186	$C_{14}H_8O_4$	Dantron	Cytotoxic activity	Mangrove endophytic fungi *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382	[32]
187	$C_{16}H_{12}O_5$	1,3-dihydroxy-6-methoxy-8-methylanthracene-9,10-dione	Cytotoxic activity	Mangrove endophytic fungi *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382	[32]
188	$C_{17}H_{14}O_5$	1-hydroxy-2,4-dimethoxy-7-methylanthracene-9,10-dione	Cytotoxic activity	Mangrove endophytic fungi *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382	[32]
189	$C_{16}H_{12}O_4$	8-hydroxy-1-methoxy-3-methyl-9,10-anthraquinone	Cytotoxic activity	Mangrove endophytic fungi *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382	[32]
190	$C_{17}H_{14}O_6$	1,7-dihydroxy-2,4-dimethoxy-6-methylanthracene-9,10-dione	Cytotoxic activity	Mangrove endophytic fungi *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382	[32]

191	$C_{14}H_8O_5$	1,3,8-trihydroxyanthraquinone	Cytotoxic activity	Mangrove endophytic fungi *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382	[32]
192	$C_{16}H_{12}O_6$	1,4,7-trihydroxy-2-methoxy-6-methyl-9,10-anthraquinone	Displayed no cytotoxic activity	Mangrove endophytic fungi *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382	[32]
193	$C_{16}H_{16}O_8$	SZ-685C	Cytotoxic activity	Mangrove endophytic fungus *Halorosellinia* sp. No. 1403	[100–102]
194	$C_{18}H_{20}O_6$	Phomopsanthraquinone	Antibacterial and cytotoxic activities	Mangrove-derived fungus *Phomopsis* sp. PSU-MA214	[103]
195	$C_{16}H_{12}O_4$	1-hydroxy-3-methoxy-6-methyl anthraquinone	Displayed no antibacterial or cytotoxic activity	Mangrove-derived fungus *Phomopsis* sp. PSU-MA214	[103]
196	$C_{16}H_{12}O_7$	Tetrahydroxyanthraquinone	Protein kinases' inhibitory activity	Sponge-associated fungus *Microsphaeropsis* sp.	[104]
197	$C_{17}H_{14}O_7$	Methoxyl-tetrahydroxyanthraquinone	Protein kinases' inhibitory activity	Sponge-associated fungus *Microsphaeropsis* sp.	[104]
198	$C_{17}H_{14}O_8$	1,2,3,6,8-pentahydroxy-7-[(1R)-1-methoxyethyl]-9,10-anthraquinone	Protein kinases' inhibitory activity	Sponge-associated fungus *Microsphaeropsis* sp.	[104]
199	$C_{15}H_{10}O_6$	Lunatin	Antibacterial activity	Sponge-derived fungus *Curvularia lunata*	[105]
200	$C_{30}H_{22}O_{12}$	Cytoskyrin A	Antibacterial activity	Sponge-derived fungus *Curvularia lunata*	[105]
201	$C_{14}H_8O_6$	Rheoemodin	Displayed no significant anti-obesity activity	Marine sponge-associated fungus *Talaromyces stipitatus* KUFA 0207	[74]
202	$C_{30}H_{18}O_{10}$	2, 2′-*bis*-(7-methyl-1,4,5-trihydroxy-anthracene-9,10-dione)	Was not evaluated for any relevant activity	Marine sponge-associated fungus *Talaromyces stipitatus* KUFA 0207	[74]
203	$C_{17}H_{14}O_5$	7-methoxymacrosporin	Antifungal activity	Mangrove-derived fungus *Phoma* sp. L28	[85]

204	$C_{21}H_{20}O_5$	7-(γ,γ)-dimethylallyloxymacrosporin	Antifungal activity	Mangrove-derived fungus *Phoma* sp. L28	[85]
205	$C_{16}H_{12}O_5$	Monodictyquinone A	Antibacterial and antifungal activities	Sea urchin-derived fungus *Monodictys* sp.	[43]
206	$C_{16}H_{12}O_6$	1,3,6-trihydroxy-7-(1-hydroxyethyl) anthracene-9,10-dione	Inhibitory activity against α-glycosidase	Mangrove-derived fungus *Cladosporium* sp. HNWSW-1	[106]
207	$C_{17}H_{12}O_7$	Phaseolorin I	Displayed no cytotoxic activity	Deep-sea sediment-derived fungus *Diaporthe phaseolorum* FS431	[107]
208	$C_{22}H_{22}O_7$	6,8-di-*O*-methyl averufanin	Antifungal and phytotoxic activities, as well as brine shrimp lethality	Mangrove endophytic fungus ZSUH-36	[108,109]

Conclusions and future prospective

The marine phoma is representing the most, the greatest and most diverse ecological structure on the planet. Over seven decades, marine natural products (MNPs) have owned credits and been privileged as a robust and sustainable supplier for pharmacologically active compounds that meet a huge interest in pharmaceutical and economical applications. Marine-derived fungi are valuable sources of structurally diverse MNPs due to their various habitats that range from the warm to the colder areas, and even at extreme temperature and pressure like in hydrothermal outlets. One of the fascinating classes of fungal derived natural products is the anthraquinones. Herein, we presented a comprehensive literature review centered on marine-derived anthraquinones as a unique group of fungal polyketides over the period 2000-2020 from twenty marine fungal genera. A list of 208 anthraquinones that have been reported from different marine fungi that feature a myriad of structural and biological diversities. Investigating such chemo-biological data has implied two remarkable points. First, it was clear that the marine fungi of the three genera *Aspergillus* sp., *Stemphylium* sp., and *Penicillium* sp., are the most creative fungal genera in terms of producing anthraquinones. Secondly, the most investigated bioactivity was cytotoxicity, where a notable number of seventy-two compounds have been evaluated for their cytotoxic activity against planes of carcinoma cell lines, whilst the anthraquinones with antibacterial activity were the second on the list with sixty-nine compounds demonstrated bioactivity against a wide range of microorganisms. Meanwhile, an enormous spectrum of further biomedical potentialities exhibited by these compounds as (antioxidant, antiviral, antifungal, immunomodulatory, anti-inflammatory, …….etc.) have been documented. Such a massive connection between chemical spaces and bioactivities highlights the huge capacity of marine-derived fungi as an attractive biological source that is worth further exploitations with distinguished anticipations for the global pharmaceuticals industries. Additionally, recent advances on the level of sampling techniques, fermentation, synthetic biology, genetic engineering, genome mining, and total chemical synthesis, all are crucial to the success of fungal MNPs as future drug leads (Figures 14 and 15).

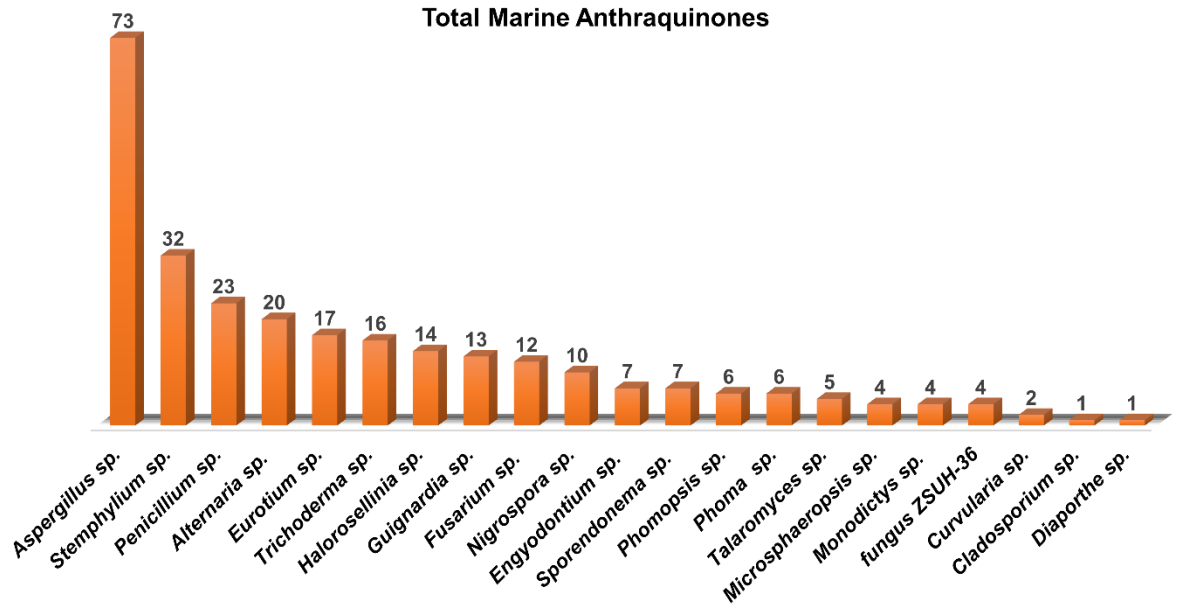

Figure 14: Distribution and total anthraquinones and their derivatives isolated from different species of marine-derived fungi.

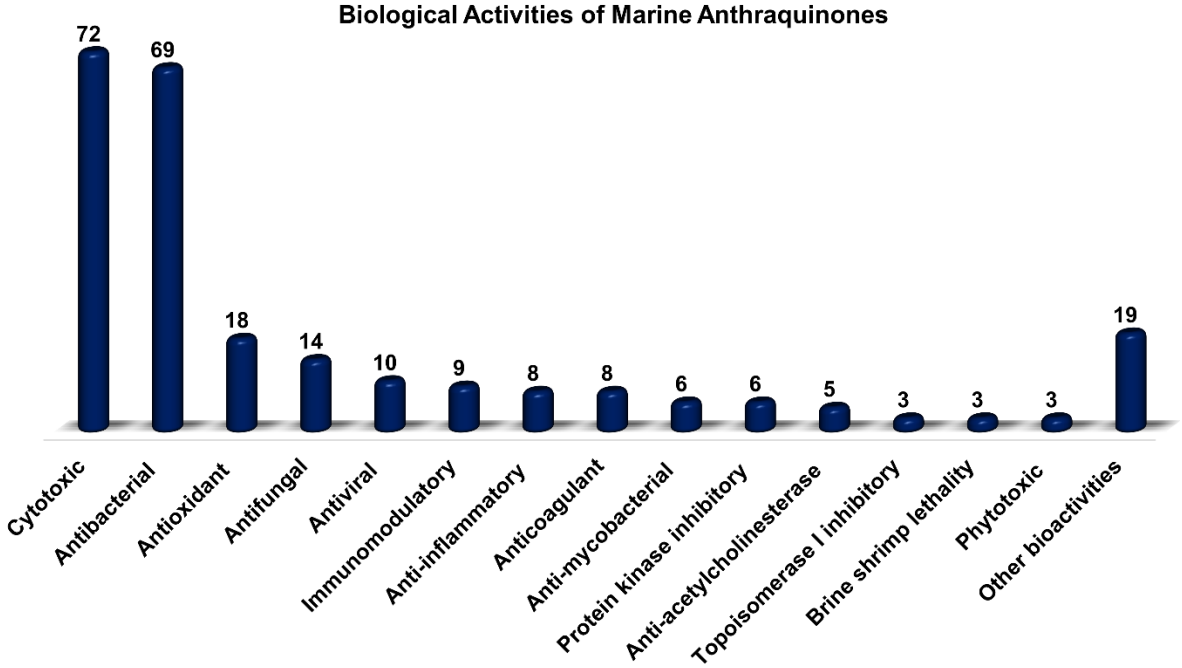

Figure 15: Total biological activities of various anthraquinones and their derivatives isolated from different species of marine-derived fungi.

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