



Review Article

Research progress on new alkaloids of the genus *Aspergillus* from 2019 to 2024

Ming-Feng He¹, Jia-Xiang Huang¹, Shao-Yun Wang¹, Yong-Qi Tian^{1,2} (✉)

¹ College of Biological Science and Engineering, Fuzhou University, Fuzhou 350000, China

² Fujian Province-Indonesia Marine Food Joint Research and Development Center, Fuzhou 350000, China

Received: 22 September 2024 / Revised: 28 September 2024 / Accepted: 29 September 2024

Abstract: The genus *Aspergillus* is a ubiquitous and significant fungus with an increasingly pervasive role in both daily life and the food industry. This article presents a comprehensive overview of the 245 novel alkaloids identified within the *Aspergillus* genus since 2019. It offers a detailed introduction to the diverse biological activities and functional characteristics exhibited by these compounds, including antibacterial, antiviral, anti-inflammatory, and cytotoxic activity, as well as enzyme inhibition. Additionally, the article provides a detailed analysis of the structural features, publications, and countries of discovery for these alkaloids. It offers strategic guidance for the development of secondary metabolites derived from *Aspergillus* alkaloids, stimulating innovation in this field.

Keywords: *Aspergillus*; alkaloids; biological activities

Citation: He M. F., Huang J. X., Wang S. Y., et al. Research progress on new alkaloids of the genus *Aspergillus* from 2019 to 2024. *Food & Medicine Homology*, 2027, 4: 9420151. <https://doi.org/10.26599/FMH.2027.9420151>

1 Introduction

Aspergillus, a widely distributed member of the fungal genus that shares its name, occupies a prominent ecological niche due to its distinctive filamentous morphology. There are more than 340 species in the genus *Aspergillus*, including *Aspergillus terreus*, *Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus flavus* and so on^[1,2]. It is recognized as one of the most diverse and extensively distributed fungi, thriving in various extreme environments such as water, soil, air, and even moldy food and clothing. This robust environmental adaptability arises from its minimal growth requirements. Equally notable is *Aspergillus*' metabolic capability. The *Aspergillus* Secondary Metabolite Database (A2MDB) is a compilation of selected information on *Aspergillus* and its secondary metabolites. Back in 2017, the A2MDB included 807 unique and non-redundant secondary metabolites from 675 species of *Aspergillus*^[3]. The compound NPI-2350, isolated from *Aspergillus* sp. CNC-139, was chemically synthesized to yield a selective tumor vascular blocker, plinabulin (NPI-2358). The drug inhibits microtubulin polymerization by interacting with the colchicine binding site, thereby blocking the cell cycle in mitosis. Phase I clinical trials were completed in 2010, and phase III clinical trials for the treatment of non-small cell lung cancer were conducted in 2015^[4]. Among the secondary metabolites of *Aspergillus*, alkaloids, with their unique nitrogen-containing basic cyclic structures, exhibit rich chemical diversity and possess a wide range of biological activities, including antiviral, antibacterial, anti-inflammatory, and antitumor pharmacological effects, making them a hot topic in the field of medicine and food homology^[5,6].

Due to the above-mentioned activities of *Aspergillus* secondary metabolites, there is no doubt that they can be used in food products. The concept of "medicine and food homology" emphasizes the complex interrelationship between food and medicine, whereby a multitude of natural products serve dual functions as nutritional supplements in foodstuffs and as therapeutic agents. *Aspergillus* is also an important fungal genus in the fermentation and food processing industries, with nearly 60 species being utilized mainly for brewing, vinegar production, and other purposes. Citric acid and fructose syrup can often be found on the ingredient lists of food and beverages, and both of them have the contribution of *Aspergillus niger* in their manufacturing process. Some filamentous fungi of *Aspergillus* sp., synthesizing both GlcCer and GalCer, would be an amenable source to exploit glycosylceramides that widely added in cosmetics as moisturizing ingredients or health food as dietary supplements^[7]. Besides, Wen *et al.*^[8] explored the optimal conditions for quenching of *Aspergillus oryzae* strains, and at the same time investigated the sizes of saccharase and neutral protease viability produced by them, which provided a guarantee of pre-enzymatic quenching for the development of concentrated, high-color sweet noodle sauces. These properties are of significant importance for applications in the fields of medicine, food science, and even dermatology.

This article focused on the most recent developments in the scientific study of alkaloids derived from *Aspergillus*. The article provides a comprehensive and meticulous compilation and categorization of the new alkaloids isolated from various *Aspergillus* species since 2019, organized according to their biological activities. These findings not only enhance our

comprehension of *Aspergillus*' natural products but also pave the way for novel developments in the fields of medicine and food homology.

2 The structure of new alkaloids from *Aspergillus* (2019-2024) and their biological activities

2.1 Antibacterial activity

Song *et al.*^[9] investigated the antibacterial activity of the crude extract from a marine-derived *Aspergillus fumigatus* MF029 against *Bacillus subtilis*, *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), and other bacterial strains. The results showed that the crude extract possessed moderate bioactivity. Through further isolation and purification, two novel compounds 1-2 were identified. Lv *et al.*^[10] obtained two new indole-dione piperazines (3-4) from the fermentation cultures of the deep-sea fungus *Aspergillus chevalieri* MCCC M23426. Notably, compound 3 exhibited significant inhibitory effects on the growth of *Staphylococcus aureus*. Li *et al.*^[11] isolated two new indole alkaloids (5-6) from the chemical constituents of the cigar endophytic fungus *Aspergillus oryzae*, both of which showed good activity against MRSA with IZD of 22.4 ± 2.4 and 24.6 ± 2.2 mm, respectively. The *Aspergillus amoenus* Roberg strain UP197 was proven to produce antibacterial alkaloids, and Nord *et al.*^[12] characterized two new compounds 7-8 from this strain. Liu *et al.*^[13], through the study of the chemical constituents of the seawater fungus *Aspergillus sydowii* SW9, isolated and identified a new quinazoline alkaloid (9), which showed selective inhibitory activity against human pathogens including *Staphylococcus aureus* and *Escherichia coli*. Liu *et al.*^[14] isolated and characterized an unusual N-phenylmethyl malonate trimer (10) from the coral-derived fungus *Aspergillus terreus*. Although the NMR signals posed challenges for structural identification, recrystallization ultimately provided suitable crystals for X-ray single-crystal diffraction experiments, confirming the structure. Compound 10 exhibited significant antibacterial activity against seven pathogenic microorganisms with MIC values of 2–64 $\mu\text{g/mL}$. Dong *et al.*^[15] isolated and characterized two new quinazolinone piperazine alkaloids (11-12) from the deep-sea coral endophytic fungus *Aspergillus versicolor* AS-212. Among them, compound 12 showed inhibitory effects against *Vibrio harveyi* and *Vibrio parahaemolyticus* with MIC values of 9.0–18.1 μM . Yang *et al.*^[16] isolated six new prenylated indole-dione piperazine alkaloids (13-18) from the marine endophytic *Aspergillus* sp. YJ191021. Compound 18 exhibited moderate antibacterial activity against *Vibrio anguillarum* and *Xanthomonas oryzae* pv. *oryzae*. Wang *et al.*^[17] isolated three new indole alkaloids (19-21) from an endophytic fungus, *Aspergillus lentulus*. Compounds 19 and 20 showed moderate antibacterial effects against *Xanthomonas oryzae* pv. *oryzae* and *Xanthomonas oryzae* pv. *oryzicola*. Wang *et al.*^[18] isolated three new indole-dione piperazine alkaloids (22-24) from the solid cultures of an endophytic fungus, *Aspergillus cristatus*. Among them, compound 22 exhibited moderate antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* with MIC₅₀ of 8.5 and 32.2 $\mu\text{g/mL}$, respectively. Yan *et al.*^[19] isolated and identified five new metabolites (25-29) from the deep-sea sediment-derived fungus *Aspergillus fumigatus* SD-406. Compounds 25-29 all exhibited inhibitory activity against pathogenic bacteria and plant pathogenic fungi, with MIC values ranging from 4 to 64 $\mu\text{g/mL}$. Yan *et al.*^[20] discovered five novel

antibacterial indole-dione piperazine alkaloids (30-34) from the deep-sea cold seep fungus *Aspergillus chevalieri* strain, and all five compounds showed inhibitory activity against several pathogenic bacteria. Abdel-Wahab *et al.*^[21] isolated a new aflaquinolone (35) from the co-culture of the sponge-associated fungus *Aspergillus versicolor* and *Bacillus subtilis* (Fig. 1).

Lv *et al.*^[22] isolated and identified three new emestrin-type thiodiketopiperazines (36-38) from the culture extract of the fungus *Aspergillus nidulans* SD-531, which was extracted from a deep-sea cold seep sediment sample from the South China Sea. Compound 38 displayed antimicrobial activity against some tested strains. Kong *et al.*^[23] isolated two new indole alkaloids (39-40) from the endophytic fungus *Aspergillus felis* derived from cigar tobacco. Compounds 39 and 40 exhibited potential antifungal activity with inhibition rates of $72.6 \pm 5.2\%$ and $61.7 \pm 5.0\%$, respectively, at a concentration of 250 $\mu\text{g/mL}$, although the inhibition rates were lower than that of the positive control $93.2 \pm 5.5\%$. Yang *et al.*^[24] isolated three new compounds 41-43 from *Aspergillus* sp. 0338 and evaluated their anti-MRSA activity. The results indicated that compounds 41-43 showed good inhibitory effects with IZD values of 15.2 ± 1.8 , 14.6 ± 2.0 , and 13.4 ± 2.2 mm, respectively. Zhao *et al.*^[25] isolated two pairs of new dimeric diketopiperazine alkaloids, ($\pm$)-dibrevianamides Q1 and Q2 (44-47) from the marine fungus *Aspergillus* sp. Among them, Compounds 44 and 47 displayed anti-H1N1 virus activity with IC₅₀ values of 12.6 and 19.5 μM . Compound 44 showed significant activity against *Mycobacterium tuberculosis* (MIC, 10.2 $\mu\text{g/mL}$). Kong *et al.*^[26] obtained seven new alkaloids (48-54) from the marine fungus *Aspergillus* sp. HNMF114. Compounds 53 and 54 showed quorum sensing inhibitory activity against *Chromobacterium violaceum* CV026 with MIC values of 32 and 32 $\mu\text{g/well}$, respectively. Guo *et al.*^[27] isolated a zinc complex dimer (55) from the sponge-derived fungus *Aspergillus ochraceopetaliformis* SCSIO 41018, which exhibited significant antibacterial and cytotoxic activities. Wu *et al.*^[28] obtained a new sulfur-containing metabolite (56) from the mangrove endophytic fungus *Aspergillus* sp. GXNU-MA, which showed mediated activity against *Staphylococcus aureus* and *Enterobacter aerogenes* with an MIC of 12.5 $\mu\text{g/mL}$ (Fig. 2).

A total of 56 compounds with antimicrobial activity have been identified, the majority of which are indole alkaloids, comprising 35 distinct structures, including 7 quinazoline-containing indole alkaloids and 15 indole diketopiperazine alkaloids. A limited number of other classes of alkaloids, such as quinazoline alkaloids, quinolones, and piperazine alkaloids, have also been identified. It can therefore be surmised that indole alkaloids may represent one of the principal active components of the antimicrobial action of *Aspergillus* secondary metabolites. With regard to conformational relationships, the presence of quaternary ammonium ions in the structure may be a pivotal group for the antimicrobial action, as evidenced by compounds 13, 14, 15, 16, and so on. This bears resemblance to the outcomes observed with the plant-derived spectroscopic antimicrobial drug berberine^[29].

2.2 Antiviral activity

Wu *et al.*^[30] isolated two novel alkaloids (57-58) from the endophytic fungus *Aspergillus lentulus* in cigar tobacco leaves. Compound 58 exhibited high anti-Tobacco Mosaic Virus (TMV) activity, while compound 57 showed weaker anti-TMV activity. Wang *et al.*^[31] obtained two new CPA-type indole alkaloids (59-60) from *Aspergillus versicolor*, both of which possessed potential anti-TMV activity with inhibition rates of 33.6% and 29.4%,

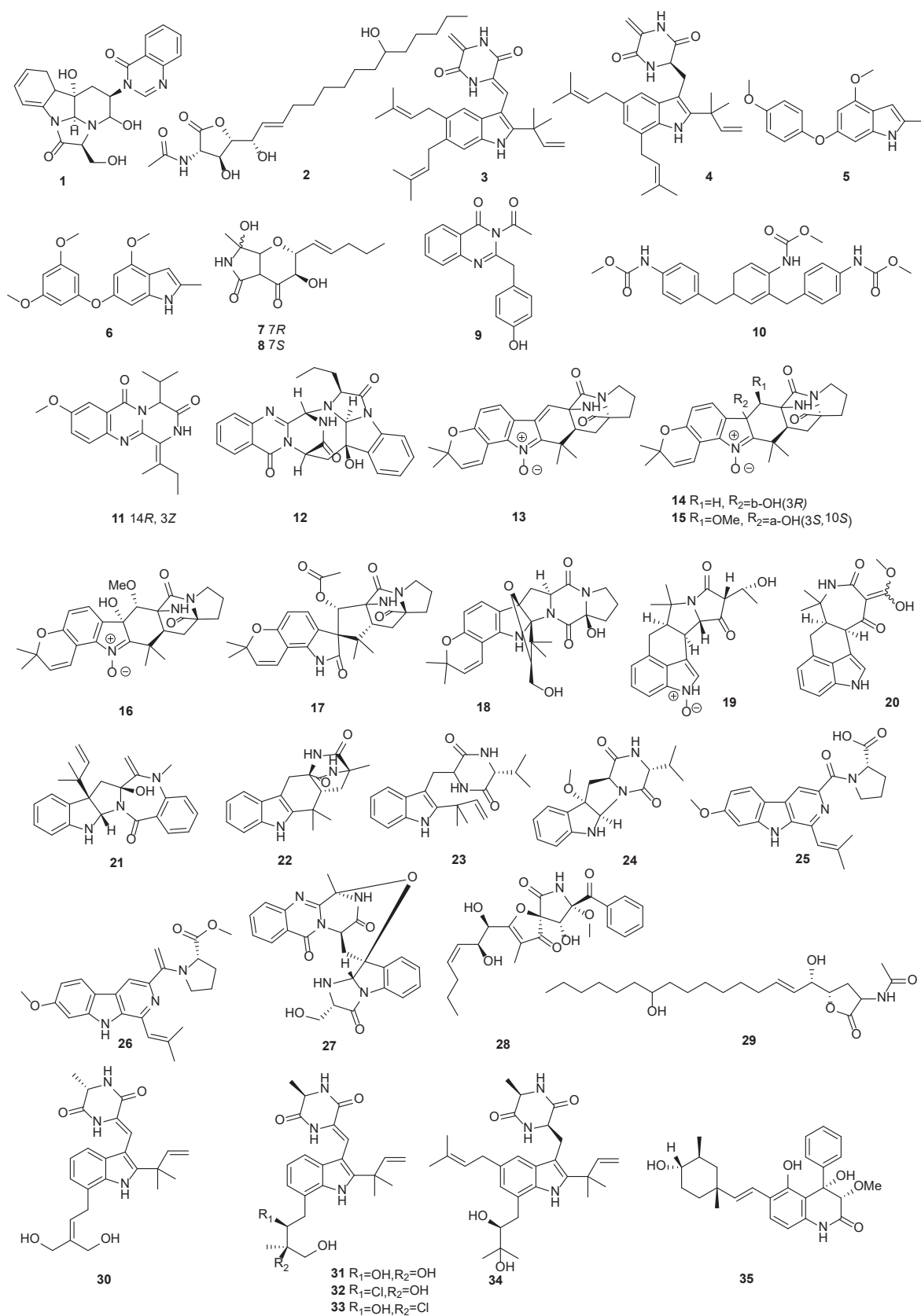


Figure 1 Structure of compounds 1-35.

respectively, at a concentration of 20 μM , close to that of the positive control. Yang *et al.*^[32] discovered five new tricyclic or tetracyclic indole alkaloids (**61-65**) from tobacco-derived *Aspergillus versicolor* YNCA0363, and some of these compounds

exhibited significant anti-TMV activity. Zhao *et al.*^[25] isolated two pairs of novel dimeric diketopiperazine alkaloids (**44-47**) from the marine fungus *Aspergillus* sp. Among them, compounds **44** and **47** displayed anti-H1N1 virus activity with IC_{50} of 12.6 and

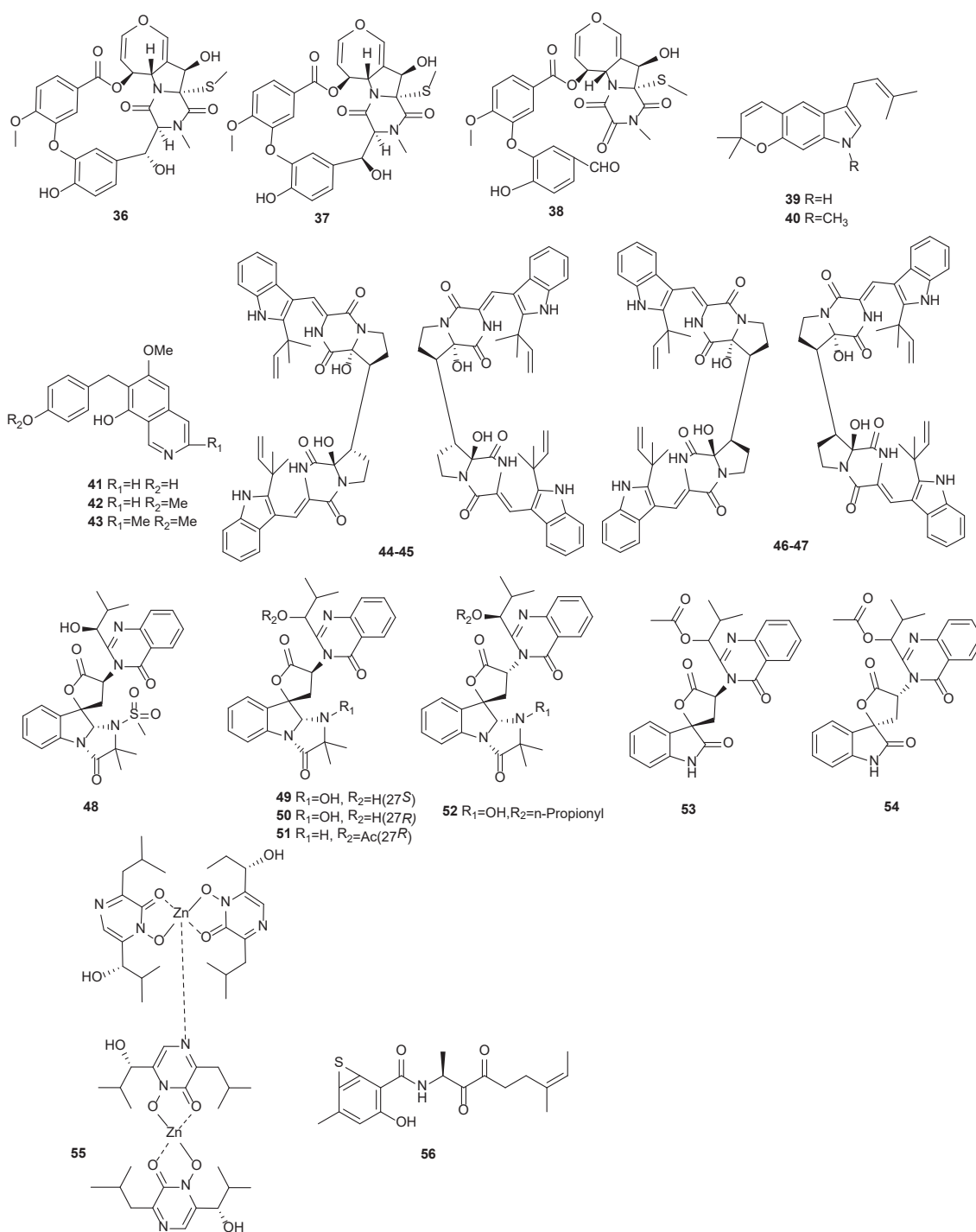


Figure 2 Structure of compounds 36-56.

19.5 μ M, respectively. Cha *et al.*^[33] separated two new β -carboline alkaloids (**66-67**) from the endophytic fungus *Aspergillus* sp. in cigar tobacco. Anti-TMV activity tests revealed that both compounds showed potential anti-TMV activity with inhibition rates of 31.8% and 35.5%, respectively. Ma *et al.*^[34] isolated two novel indole alkaloids (**68-69**) from the fermentation products of the endophytic fungus *Aspergillus fumigatus* in cigar tobacco, both of which exhibited potential anti-TMV activity with inhibition rates of 26.5% and 28.8%, respectively (Fig. 3).

Of the 17 compounds with antiviral activity previously mentioned, 9 have been specifically classified as indole alkaloids. Furthermore, the investigation of the diverse activities of indole alkaloid derivatives has revealed that tricyclic indole alkaloids and

the substituent at the N-1 hydroxyl position are crucial for their anti-TMV efficacy^[32].

2.3 Anti-inflammatory activity

Anh *et al.*^[35] purified two novel nitrogen-containing compounds **70-71** from the EtOAc extract of the deep-sea fungus *Aspergillus unguis* IV17-109. Compound **70** exhibited moderate anti-inflammatory activity with an IC₅₀ of 20.0 μ M. Yang *et al.*^[16] isolated six new prenylated indole diketopiperazine alkaloids (**13-18**) from the marine endophytic *Aspergillus* sp. YJ191021. Among them, compound **13** showed significant anti-inflammatory activity in *Propionibacterium acnes*-induced human monocyte-like cell

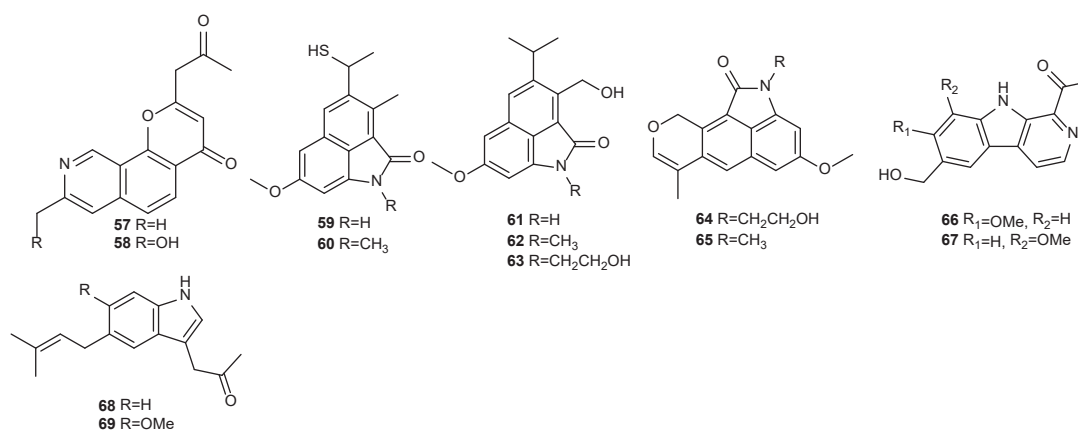


Figure 3 Structure of compounds 57-69.

line (THP-1) with an IC_{50} of $1.46 \pm 0.21 \mu M$. In tracking the *in vitro* anti-inflammatory activity of the organic extract of the sponge-derived fungus *Aspergillus tamarii* MCCF102, Niveditha *et al.*^[36] discovered two new dipyrrolylbenzoquinone compounds **72-73**. *In vitro* tests on lipopolysaccharide-stimulated RAW 264.7 mouse macrophages revealed that compounds **72** and **73** inhibited nitric oxide (NO) production in a concentration-dependent manner ($IC_{50} < 1 \mu M$), thereby exhibiting anti-inflammatory activity, without any observed cytotoxicity at the same concentrations. Huang *et al.*^[37] conducted a chemical study on the fermentation extract of the mangrove endophytic fungus *Aspergillus* sp. GXNU-A1 and discovered a pair of new enantiomers (**74-75**) that showed significant inhibitory activity against NO production in activated macrophages. Li *et al.*^[38] isolated and identified six new cytochalasins (**76-81**) from the endophytic fungus *Aspergillus* sp. of the medicinal plant *Lonicera japonica*. Compounds **76**, **78**, **80**, and **81** all exhibited inhibitory

activity against NO production, with IC_{50} all less than $40 \mu M$. Shan *et al.*^[39] isolated three new alkaloids (**82-84**) from *Aspergillus ruber* WH4-1. Compound **84** showed weak inhibitory activity against NO production in lipopolysaccharide (LPS)-stimulated RAW264.7 cells, with an inhibition rate of $53.2 \pm 3.8\%$ at $30 \mu M$ (Fig. 4).

As previously stated, a total of 21 alkaloids have been subjected to rigorous scientific testing and have been demonstrated to possess potent anti-inflammatory properties. Hu *et al.* postulated that indole alkaloids containing aziridine may serve as crucial determinants of anti-inflammatory activity. The anti-inflammatory efficacy of these compounds is primarily attributed to their ability to inhibit the production of nitric oxide (NO)^[40].

2.4 Cytotoxic activity

Niu *et al.*^[41] isolated a novel acremolin-type alkaloid (**85**) from the deep-sea fungus *Aspergillus sydowii* MCCC 3A00324 through

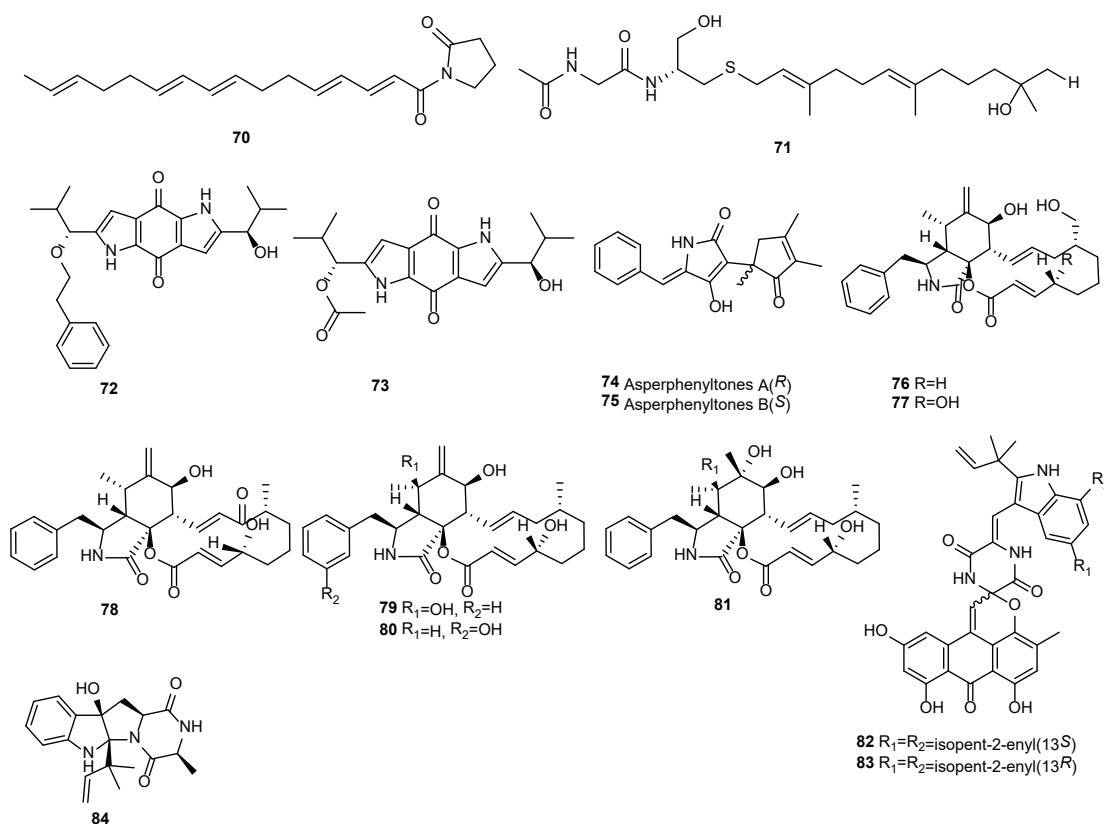


Figure 4 Structure of compounds 70-84.

chemical investigation. This compound exhibited inhibitory effects on the proliferation of A549, HeLaS3, HepG2, and K562 cell lines at a concentration of 20 μM . Wu *et al.*^[42] separated a new paraherquamide (**86**) from the EtOAc extract of *Aspergillus aculeatinus* WHF0198 culture medium, which displayed cytotoxicity against Bel-7402 cells with an IC_{50} of 3.3 μM . Wang *et al.*^[43] isolated heterocyclic fused cytochalasin homodimers (**87-88**) from the endophytic fungus *Aspergillus flavipes*. Compound **87** exhibited cytotoxic activity against five cancer cell lines (HL-60, SMMC-7721, A549, MCF-7, and SW-480) with IC_{50} of 4.45–22.99 μM . Compounds **89-93** are five novel cytochalasin heterotrimers isolated from *Aspergillus micronesiensis*. Among them, compounds **89-93** exhibited potent cytotoxic activity against six human cancer cell lines, with IC_{50} of 4.36–5.69 μM against HL-60^[44]. Wang *et al.*^[17] obtained three new indole alkaloids (**19-21**) from the endophytic fungus *Aspergillus lentulus*. Compounds **20** and **21** showed moderate cytotoxicity against the A549 cell line. Xu *et al.*^[45] targeted the marine deep-sea fungus *Aspergillus flavipes* DS720 and isolated two new indole alkaloids (**94-95**) through activity-guided fractionation. Compound **94** demonstrated broad-spectrum cytotoxicity against HeLa, 5637, CAL62, PTU8988T, A375, and A673 cell lines. Fan *et al.*^[46] separated four new conjugate dimers (**96-99**) from the fermentation broth of the coral-associated fungus *Aspergillus ochraceus* LCJ11-102. Compound **96** exhibited cytotoxic activity against ten human cancer cell lines, while compounds **97** and **99** selectively inhibited U251, and compound **98** was active against A673 and U87. Compounds **100-102** are three novel cytochalasin heterotrimers isolated from *Aspergillus micronesiensis* PG-1. Compounds **100** and **101** possessed an unprecedented 5/6/11/5/5/6/6/5/11/6/5 eleven-membered ring skeleton, while **102** contains a twelve-membered furan ring. In addition, **100** and **101** exhibited potent cytotoxic activities through apoptosis induction mediated by caspase-3 activation and PARP degradation, and their IC_{50} against HL-60 cells were 1.71 and 3.74 μM , respectively^[47]. Wei *et al.*^[48] isolated three new indole-dione-piperazine alkaloids (**103-105**) from the soft coral-associated fungus *Aspergillus* sp. EGF 15-0-3 and preliminarily evaluated the cytotoxic activity of all isolated compounds against the gefitinib-resistant cell line NCI-H1975 (NCI-H1975/GR) using the MTT method. Li *et al.*^[49] isolated four emestrin hybrid polymers (**106-109**) from the fungus *Aspergillus nidulans*. Compound **107** showed moderate cytotoxicity against cancer cell lines (SU-DHL-2, HepG2, and HL-60). Gu *et al.*^[50] isolated a novel asymmetric diketopiperazine dimer (**110**) from the fungus *Aspergillus versicolor* 16F-11. Compound **110** exhibited moderate cytotoxicity against A375 with an IC_{50} of $10.29 \pm 2.37 \mu\text{M}$. Orfali *et al.* obtained a novel cytochalasin (**111**) from the marine fungus *Aspergillus oryzae* derived from sediments of the Red Sea near Jeddah, Saudi Arabia. Compound **111** possessed an unprecedented 6/6/11 tricyclic skeleton and exhibited moderate antiproliferative activity against three human cancer cell lines, including A549, HepG2, and MCF-7, without toxicity to zebrafish embryos^[51] (Fig. 5).

Wei *et al.*^[52] isolated a new 5/7/8 tricyclic heterocyclic skeleton, a new diketomorpholine (DKM), two new diketomorpholine derivatives, a new indole isoquinoline alkaloid, and three new indole alkaloids from the culture of the fungus *Aspergillus terreus* CXX-158-20, numbered as compounds (**112-119**). Compound **119** had a cytotoxicity of 3.96 μM against the A549 cell line and exhibited cytotoxic activity against Namalwa and U266 with IC_{50} of 12.36 μM and 12.48 μM , respectively. Luo *et al.*^[53] characterized

ten new diketopiperazine alkaloids (**120-129**) from the marine sponge-derived fungus *Aspergillus versicolor* SCSIO 41016, and some of these compounds exhibited weak cytotoxic activity against ACHN, OS-RC-2, and 786-O cells. Compound **125** showed a synergistic effect with adriamycin against MCF-7 cells. Li *et al.*^[54] isolated five new alkaloids (**130-134**) from the endophytic fungus *Aspergillus versicolor* F210, which showed moderate cytotoxicity against HL-60 cells with IC_{50} of 5.6 μM . El-Kashef *et al.*^[55] isolated a novel prenylated indole diketopiperazine alkaloid (**135**) from the fermentation culture of the marine sediment-derived fungus *Aspergillus chevalieri* collected from 15 meters deep near the Dahab lighthouse in the Red Sea, Egypt. Compound **135** exhibited cytotoxic activity against PANC-1 with an IC_{50} of 25.8 μM . Chen *et al.*^[56] isolated a new bicyclo[2.2.2]diazaoctane ring prenylated indole alkaloid (**136**) from the endophytic fungus *Aspergillus taichungensis* 299 of the marine red alga *Gelidium amansii*. *In vitro* cytotoxicity assays showed that compound **136** had selective cytotoxic activity against five human tumor cell lines (A549, HeLa, HepG2, HCT-116, and AGS) with IC_{50} of 1.7–48.5 μM . Compound **136** reduced the viability of AGS cells in a concentration-dependent manner with an IC_{50} of 1.7 μM . Further studies indicated that **136** might induce programmed cell death in AGS cells through the apoptotic pathway. Huang *et al.*^[57] isolated three new compounds **137-139** from the culture of the deep-sea fungus *Aspergillus terreus* MCCC M28183. The activity results showed that compound **137** had moderate inhibitory activity against the human gastric cancer cell MKN28. Al-Khdhairawi *et al.* isolated four previously undescribed alkaloids (**140-143**) from the PDA culture of *Aspergillus* sp. HAB10R12. Compounds **140-143** did not exhibit antiproliferative activity against HepG2 and A549 cancer cell lines^[58]. Guo *et al.*^[59] isolated six new alkaloid compounds **144-149** from the marine gorgonian-derived fungus *Aspergillus sclerotiorum* LZDX-33-4 through activity-guided isolation combined with LC-MS and NMR detection. Among them, compound **144** induced apoptosis in HeLa cells by blocking cell cycle activation of ROS production and regulating apoptosis-related proteins in the MAPK signaling pathway (Fig. 6).

Li *et al.*^[60] isolated two previously unreported prenylated quinolinone alkaloids (**150-151**) and three novel prenylated isoindolinone alkaloids (**152-154**) from *Aspergillus nidulans*. They evaluated the cytotoxicity of these compounds against five human cancer cell lines and found that compounds **152** and **154** exhibited strong inhibitory activity against A549 and SW-480 cells, with IC_{50} of 3.50 and 4.77 μM , respectively. Zhang *et al.*^[61] isolated three novel cytochalasin heterotetramers (**155-157**), one unusual cytochalasin monomer (**158**), and four additional novel cytochalasin monomers (**159-162**) from the fermentation cultures of the fungus *Aspergillus micronesiensis*. Compounds **155-157** and **159-162** demonstrated moderate cytotoxicity against four human cancer cell lines, while compound **158** induced apoptosis in HL-60 cells. Bo *et al.*^[62] obtained a novel benzoquinone (**163**) from the mangrove-derived fungus *Aspergillus* sp. GXNU QG1a, which displayed significant cytotoxicity against selected tumor cells. Kang *et al.*^[63] isolated three new alkaloids (**164-166**) from *Aspergillus iizukae* cultures, with compound **164** exhibiting cytotoxicity against HL-60 and A549 cell lines, with IC_{50} of 3.8 and 7.2 μM , respectively. Wang *et al.*^[64] separated three structurally complex diketopiperazine derivatives (**167-169**) from *Aspergillus* sp. FM242. Compounds **167** and **169** showed antiproliferative activity with IC_{50} ranging from 0.56 to 1.86 μM . Kwon *et al.* isolated six novel spiroindole alkaloids (**170-175**) from the ethyl

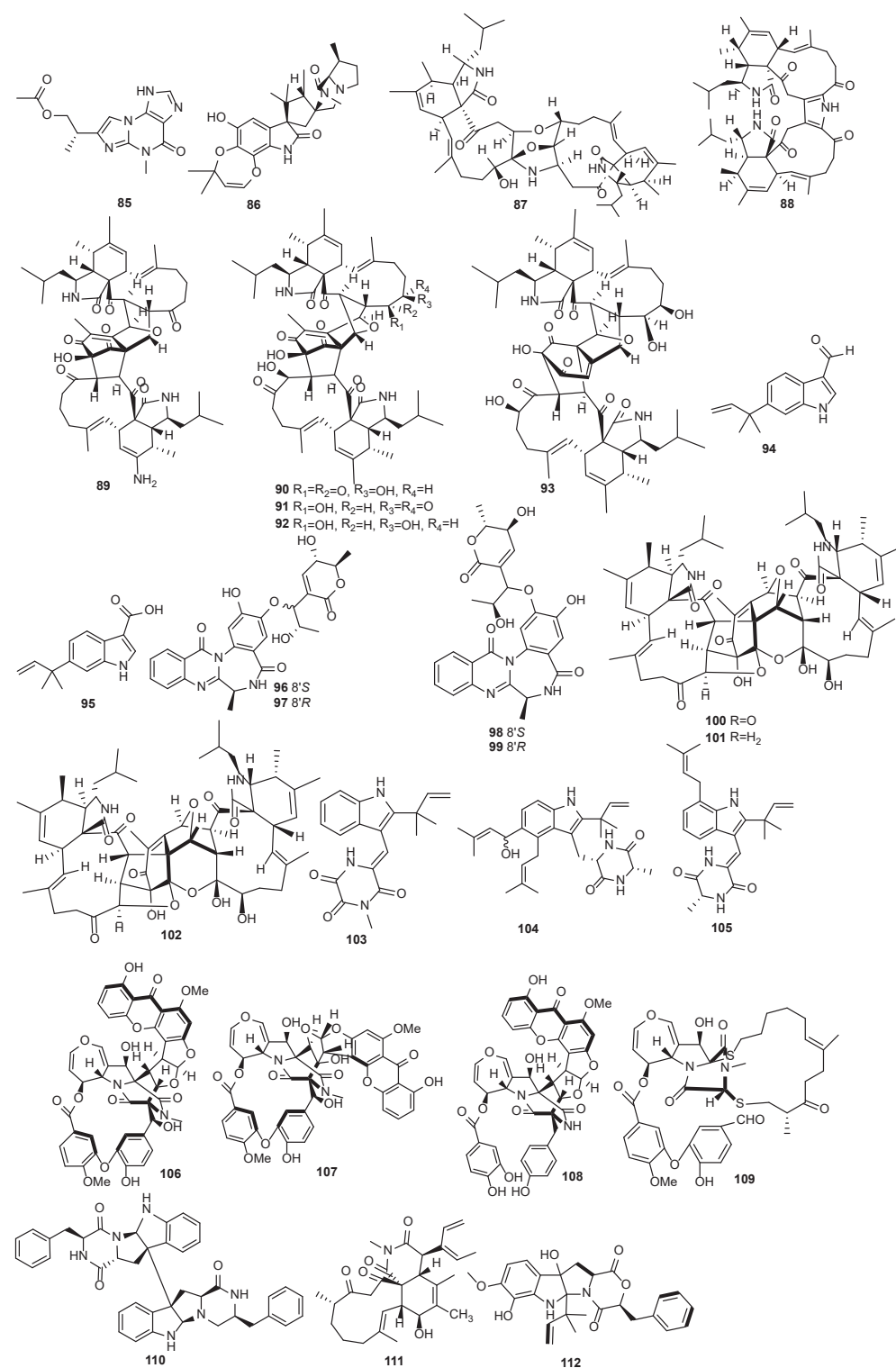


Figure 5 Structure of compounds 85-112.

acetate extract of *Aspergillus duricaulis*. The inhibitory activities of all isolated compounds against β -amyloid ($A\beta$) aggregation-induced PC12 cytotoxicity and $A\beta$ aggregation were evaluated. Compounds **174** and **175** showed moderate inhibition of $A\beta$ aggregation but failed to protect cells from $A\beta$ aggregation-induced toxicity^[65]. Compound **176**, the first reported indoleketopiperazine alkaloid with a tricyclic 5/6/5 skeleton isolated from the fungus *Aspergillus fumigatus*, exhibited moderate cytotoxicity with an IC_{50} of $14.6 \mu M$ ^[66]. Wang *et al.*^[67] separated

three novel cytochalasin homodimers (**177-179**) from the endophytic fungus *Aspergillus flavipes*. Among them, compound **179** inhibited human T-cells proliferation with an IC_{50} of $15.8 \mu M$ while maintaining low cytotoxicity to T-cells. Wu *et al.*^[68] isolated eight undescribed aspochalains (**180-187**) from the solid cultures of *Aspergillus micronesiensis*. Compounds **181** and **182** possessed an aschachalasin with a 5/6/6/8 tetracyclic skeleton, while compounds **183** and **184** were diastereomers of aschachalains I and J, respectively. Compounds **185** and **186** were the first

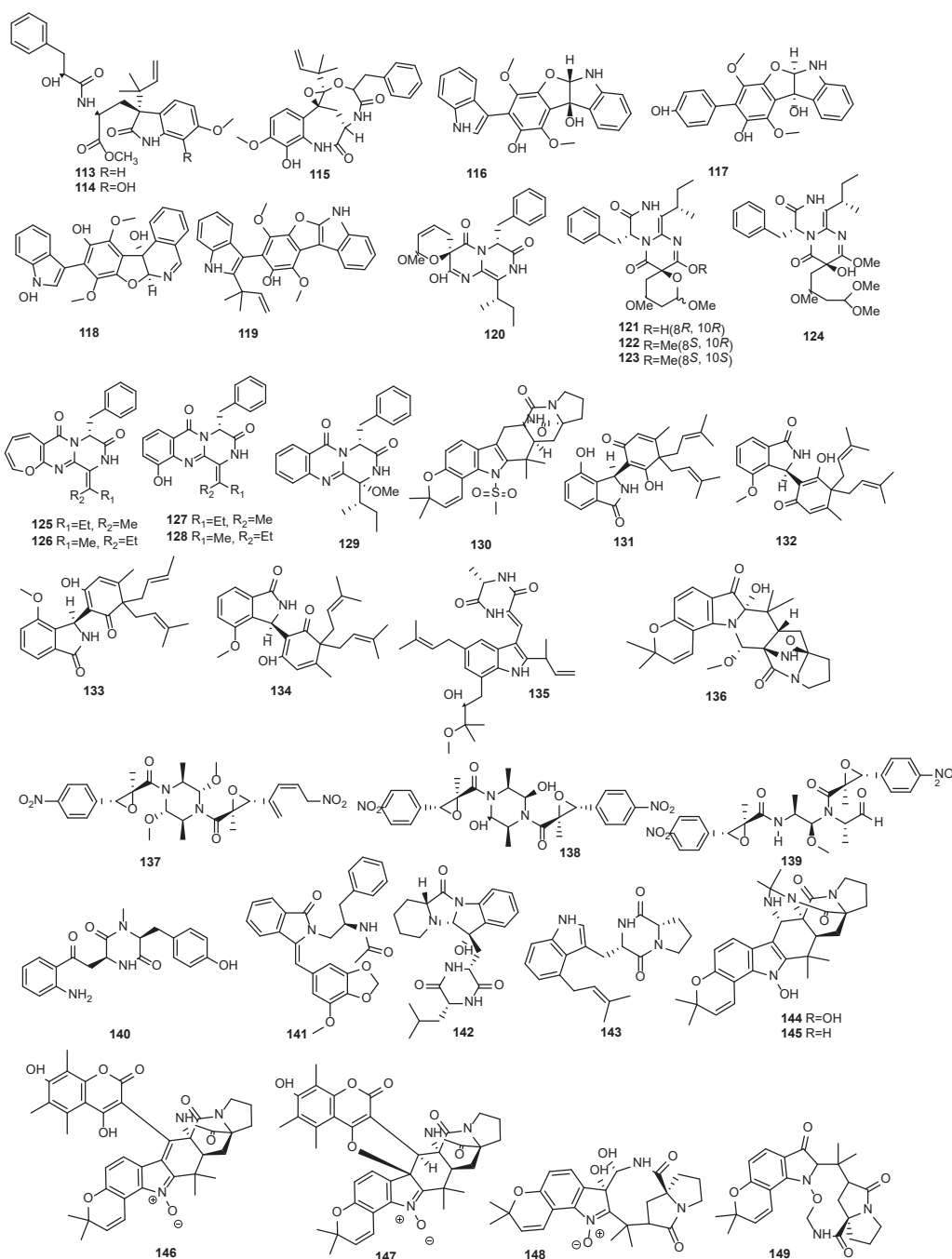


Figure 6 Structure of compounds 113-149.

cytochalasins with a long-chain open structure. Additionally, the cytotoxicity and antibacterial effects of all compounds were evaluated, revealing that compounds **183** and **184** had moderate cytotoxicity (Fig. 7).

Of the 103 compounds with cytotoxic activity, 31 are indole alkaloids, 15 are piperazine alkaloids, and the remainder are other alkaloids, including quinolone. As evidenced by the findings presented in this paper, the majority of the compounds under review demonstrate notable cytotoxic activity, suggesting that *Aspergillus*-derived alkaloids represent a crucial element in the development of antitumor pharmaceuticals. With regard to the issue of cytotoxic activity, it has been established that the presence of amide groups in the compounds in question serves to enhance the antitumor activity of the target compounds. Furthermore, the

presence of disulfide bonds markedly enhances the cytotoxicity of the compounds^[69,70].

2.5 Enzyme inhibitory activity

Huo *et al.*^[71] obtained six novel azaphenanthrene compounds **188-193** from the solid cultures of the wild fungus *Aspergillus deflectus* NCC0415. All six compounds exhibited strong or moderate inhibitory effects on SHP2 and PTP1B. He *et al.*^[72] identified three new alkaloids (**194-196**) from the diversity-enhanced extract of the endophytic fungus *Aspergillus flavus* GZWMJZ-288 isolated from bamboo shoots, where compound **194** showed α -glucosidase inhibitory activity with an IC₅₀ of $41.97 \pm 0.97 \mu\text{M}$. Wang *et al.*^[73] isolated two novel spiro alkaloids (**197-198**) from the marine fungus *Aspergillus ruber* TX-M4-1, of

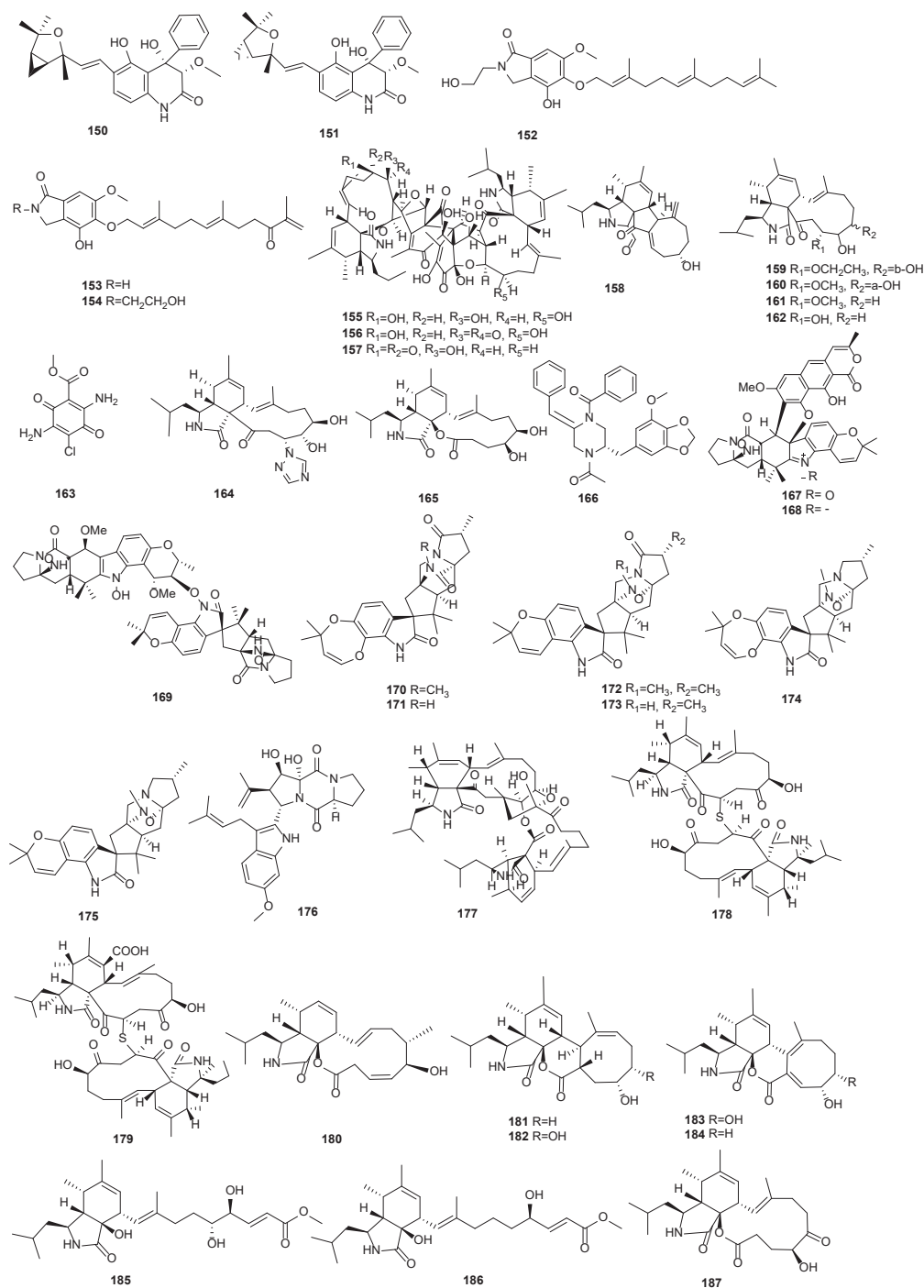


Figure 7 Structure of compounds 150-187.

which **197** inhibited thioredoxin reductase (TrxR) activity with an IC₅₀ of 6.2 μmol/L. Ye *et al.*^[74] obtained six new alkaloids (**199-204**) from the mangrove-derived endophytic fungus *Aspergillus* sp. 16-5c. Compound **201** demonstrated moderate α-glucosidase inhibitory activity, while compounds **199-204** did not exhibit significant PTP1B enzyme inhibitory activity. Ohte *et al.*^[75] isolated a novel compound **205** from the crude extract of the marine fungus *Aspergillus* sp., which inhibited bone morphogenetic protein (BMP)-induced alkaline phosphatase activity with an IC₅₀ of 4.7 μM. Among the five novel tricyclic or tetracyclic indole alkaloids (**61-65**) discovered by Yang *et al.*^[32] from the tobacco-derived *Aspergillus versicolor* YNCA0363, some compounds also exhibited enhanced activities of two reactive oxygen species-

scavenging enzymes: peroxidase and superoxide dismutase. Li *et al.*^[76] isolated three new diketopiperazine alkaloids (**206-208**) from the marine red alga-derived fungus *Aspergillus creber* EN-602. Compounds **206** and **207** showed inhibitory activity against angiotensin-converting enzyme (ACE) with IC₅₀ of 11.2 and 16.0 μM, respectively. Fukuda *et al.*^[77] separated a pair of novel piperazine derivatives (**209-210**), enantiomers, from the culture broth of *Aspergillus nidulans* BF-0142. In Chinese hamster ovary (CHO) cells expressing SOAT1 and SOAT2, compounds **209** and **210** showed some inhibitory effects on both SOAT1 and SOAT2 (Fig. 8).

A total of 28 compounds have been identified with enzyme inhibitory activity. These compounds contain 4 cyclic peptide

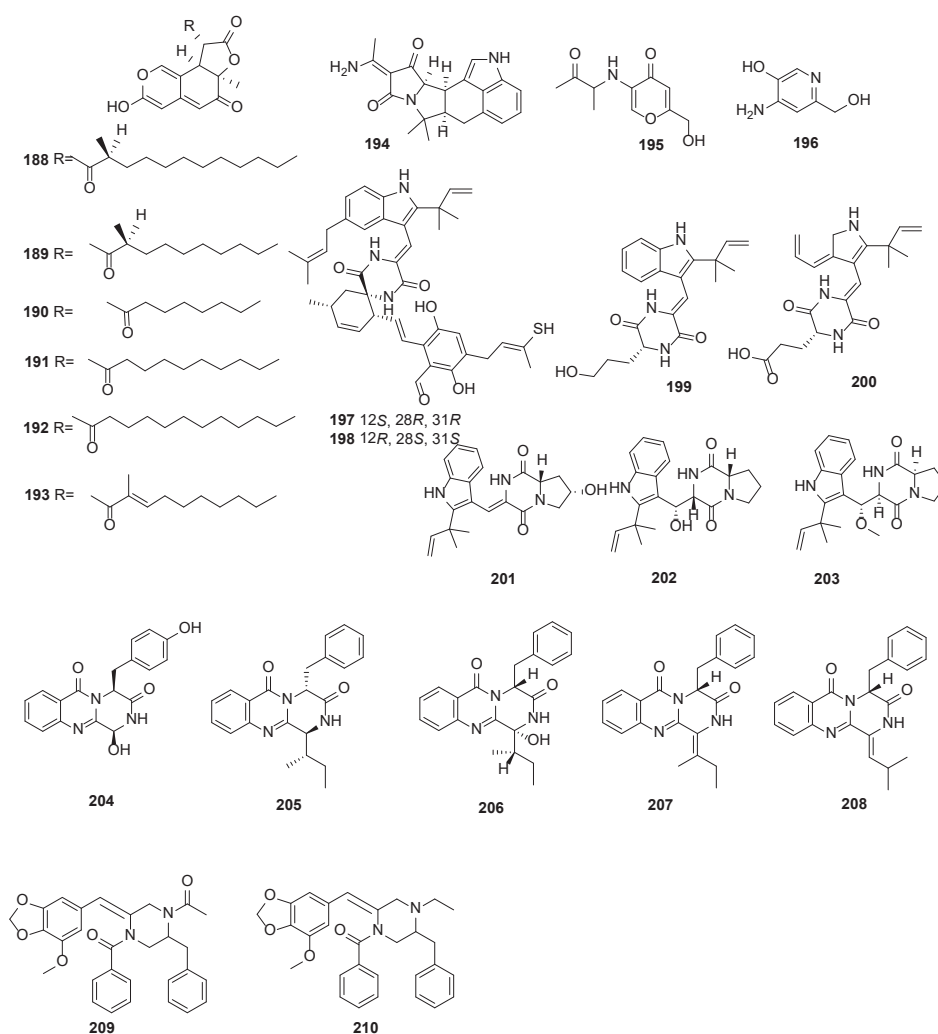


Figure 8 Structure of compounds 188-210.

alkaloids, in addition to a number of other alkaloids. The three novel compounds extracted from *Aspergillus flavus* GZWMJZ-288 associated with *Garcinia multiflora* mentioned in this paper, compounds **194** with a rare 1,3,4,5-tetrahydro-1-azaacenaphtho[3,4-c]pyrrolizidine skeleton, showed α -glucosidase inhibitory activity, indicating that the 5R-configuration of CPAs is good for α -glucosidase inhibition and the diversity-oriented synthesis was an effective approach for obtaining bioactive natural product-like compounds. This finding supports the notion that diversity-oriented synthesis represents an efficacious approach for the synthesis of bioactive natural product analogues^[72].

2.6 Other activities

Hu *et al.*^[78] isolated two novel alkaloid compounds (**211-212**) from *Aspergillus ochraceus*, both exhibiting potential anti-Parkinson's disease activity with EC_{50} values of 2.30 and 2.45 μ M, respectively. Ding *et al.*^[79] obtained four novel indole alkaloid compounds and two novel diketopiperazine compounds, numbered (**213-218**), from the solid cultures of the marine crab-derived endophytic fungus *Aspergillus versicolor*. All isolated compounds were virtually screened against the coronavirus 3-chymotrypsin-like protease (Mpro) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), among which compounds **213**, **214**, **217**, and **218** scored the highest in docking, potentially contributing to COVID-19 treatment upon further research. He *et al.*^[80] isolated two new indole

dimethylpiperazines (**219-220**) from the solid cultures of *Aspergillus* sp. GZWMJZ-258, which selectively inhibited the human FLT3-ITD mutant acute myeloid leukemia MV4-11 cell line with IC_{50} of 7.2 and 10.0 μ M, respectively. Bai *et al.*^[81] discovered a new piperazine diketone derivative (**221**) from the mangrove-derived fungus *Aspergillus niger* JX-5. Compound **221** exhibited inhibitory activity against *Helicoverpa armigera* with an IC_{50} of 200 μ g/mL. Cai *et al.*^[82] isolated a pair of novel enantiomeric alkaloid dimers (**222-223**) from mangrove-derived endophytic *Aspergillus* sp. These enantiomeric dimers were separated by chiral HPLC columns, and compound **222** showed antifouling activity against the barnacle *Balanus reticulatus*. Yan *et al.* obtained two indole alkaloid piperazine alkaloids (**224-225**) from the fermentation products of the deep-sea cold seep fungus *Aspergillus chevalieri* CS-122. Compounds **224** and **225** exhibited significant angiogenesis-promoting activity in transgenic zebrafish^[83]. Li *et al.*^[84] through chemical investigation of the secondary metabolites of the marine-derived fungus *Aspergillus austroafricanus* Y32-2, isolated two new prenylated indole alkaloid homodimers (**226-227**) and a novel pteridine alkaloid asperpteridine A (**228**). Among them, compound **227** demonstrated concentration-dependent angiogenesis-promoting activity in a PTK787-induced vascular injury zebrafish model. Wang *et al.*^[85] isolated a novel oxygenated tricyclic CPA-type alkaloid (**229**) from coral-associated *Aspergillus flavus* GXIMD 02503, which strongly inhibited lipopolysaccharide (LPS)-induced NF- κ B. Wang *et al.*^[86] purified two new alkaloids (**230-231**) from

the fungal strain *Aspergillus felis* FM324 isolated from Hawaiian beach soil samples, with compound **240** inhibiting nuclear factor NF- κ B with an IC_{50} of 30.9 μ M. Hu *et al.*^[87] purified two novel indole-dione-piperazine alkaloids (**232-233**) from the soft coral-associated endophytic fungus *Aspergillus versicolor* CGF 9-1-2. Molecular docking results indicated that both compounds exhibited good binding affinities towards TDP1, TDP2, TOP1, TOP2, Ache, NLRP3, EGFR, EGFR L858R, EGFR T790M, and EGFR T790/L858. Liang *et al.*^[88] obtained eight new diketopiperazine alkaloids (**234-241**) from the fermentation products of the deep-sea fungus *Aspergillus puniceus* SCSIO z021,

including four oxetane-containing diketopiperazine alkaloids and four 4-quinazoline alkaloids. Compounds **234-241** demonstrated significant transcriptional activation of liver X receptor alpha (LXR α) with EC_{50} of 1.7–50 μ M, with **240** and **241** being the most potent agonists. Hong *et al.*^[89] isolated four new diketopiperazine alkaloids from the extract of the marine-derived fungus *Aspergillus pingueus* FAHY0085, including one oxepin-containing diketopiperazine alkaloid (**242**) and three 4-quinazolinone alkaloids (**243-245**). Compound **244** showed notable transcriptional activation of LXR α with an EC_{50} value of 2–50 μ M (Fig. 9).

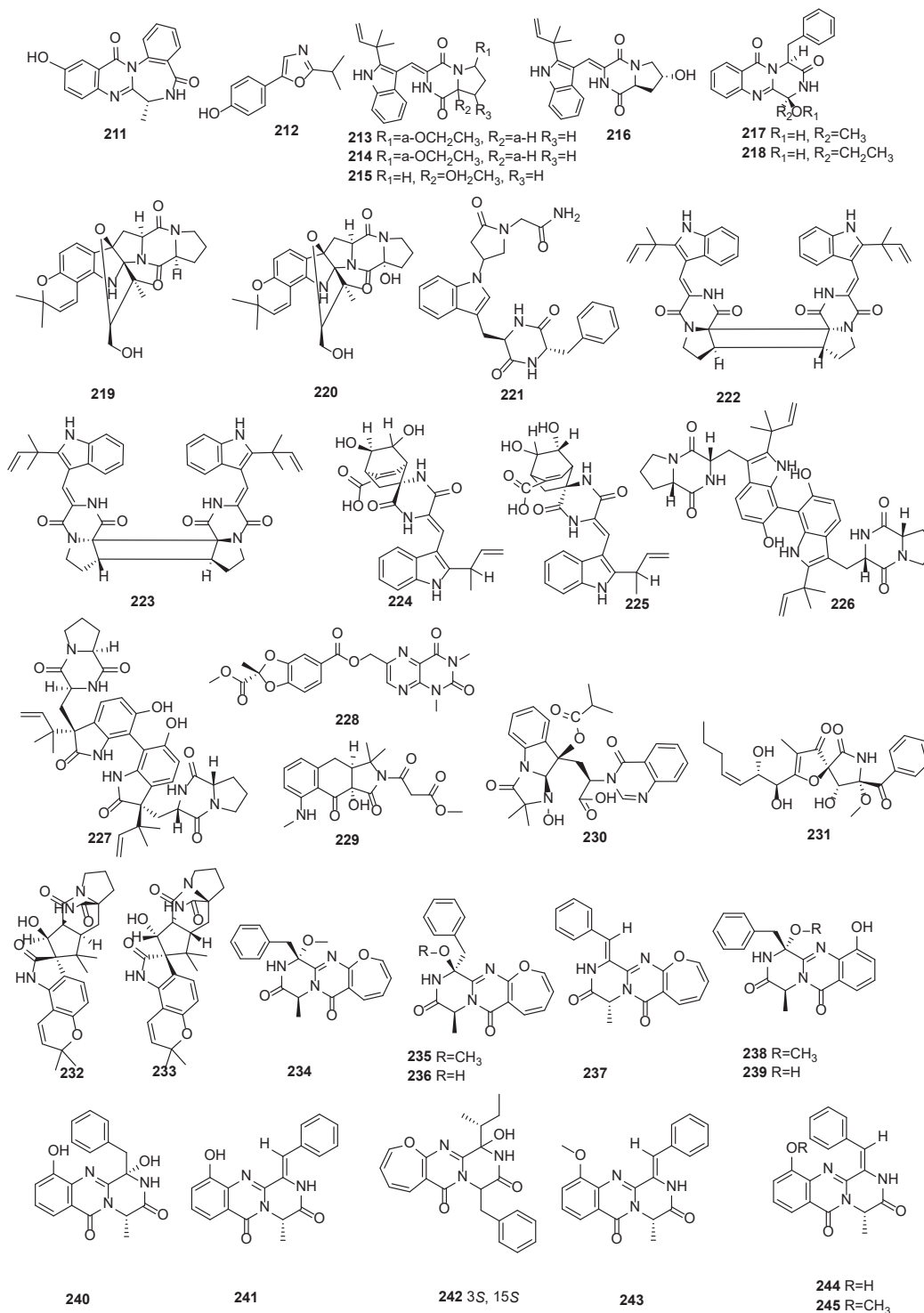


Figure 9 Structure of compounds 211-245.

3 Summaries and classifications

This review comprehensively delved into the recent advancements in the realm of natural alkaloid products sourced from *Aspergillus* species, encompassing discoveries made since 2019. It meticulously summarized a comprehensive list of 245 novel compounds, with an impressive 69.3% (170 compounds) having biological activities confirmed, while the remainder await further exploration. The structural diversity of these compounds is striking, with indole alkaloids dominating at 34.7%, closely followed by piperazine alkaloids at 18.4%, and notable mentions including quinoline alkaloids (4.9%), cyclic peptide alkaloids (1.6%), pyranone and pyrrolidine alkaloids (each at 0.8%), cytochalasins (12.2%), and a diverse assortment of other alkaloids accounting for 26.5% (Fig. 10A). Among the compounds with verified activities, a diverse array of biological effects emerges: 69

(40.8%) demonstrated cytotoxic activity, 35 (20.7%) displayed antibacterial activity, 14 (8.3%) inhibited enzyme function, 11 (6.5%) possessed anti-inflammatory capabilities, 7 (4.1%) exhibited multiple biological activities, 9 (5.3%) exhibited antiviral properties, and 24 (14.2%) possessed other, less common types of activity (Fig. 10B). Additionally, the review offered an insightful overview of the publication landscape, highlighting the journals that have significantly contributed to this field. Notably, *Journal of Nature Products*, *Organic Letters*, *Phytochemistry*, *Chemistry of Natural Compounds*, *Natural Product Research* and *Marine Drugs* stand out, accounting for 6.6%, 7.9%, 7.9%, 7.9%, 9.2%, and 14.5% of the total publications (Fig. 10C). Furthermore, it underscored the substantial contribution of Chinese scholars to the realm of marine microbial natural products, who have authored an impressive 89.5% of the academic papers in this domain since 2019 (Fig. 10D).

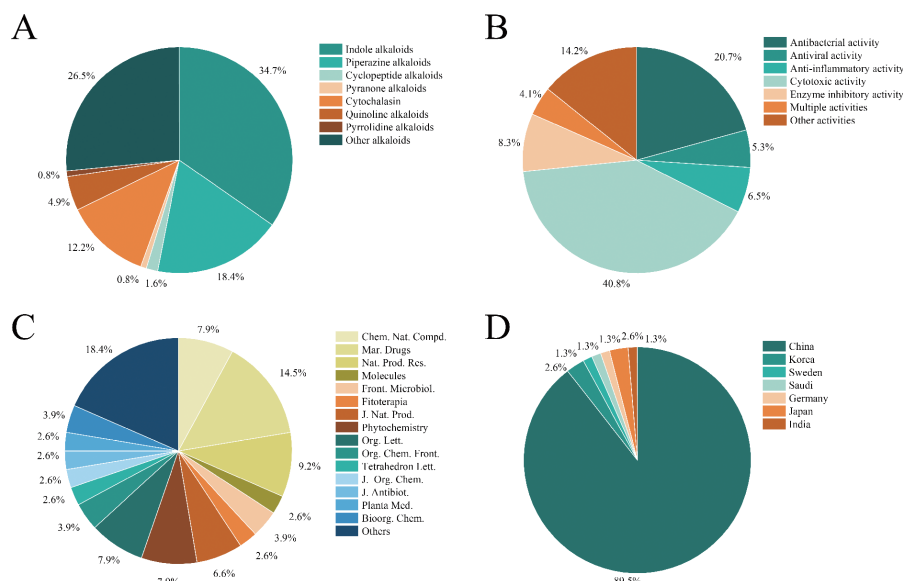


Figure 10 Classification of new alkaloids from secondary metabolites of *Aspergillus*. (A) Structural classification, (B) Activity classification, (C) reporting journal and (D) Country of discovery.

4 Conclusion and prospect

This article presents a comprehensive overview of the 245 novel alkaloids identified within the *Aspergillus* genus since 2019. Furthermore, a summary of their structure, activity, journal of publication, and the nationality of the discoverer is provided. *Aspergillus*-derived alkaloids, which possess intricate activities and unique structures, including antibacterial, antiviral, anti-inflammatory, anthelmintic, and enzyme inhibitory properties, have broad application prospects in the fields of food, disease treatment, insecticide, and skincare^[7,90]. In the food industry, modified alkaloids have the potential to serve as natural preservatives, thereby enhancing shelf life and food safety, or as flavor enhancers for the development of healthier food products. In the field of medicine, the exploitation of their bioactivity facilitates the creation of innovative therapeutic agents, including anticancer drugs, anti-infectives, and neuroprotectants. For example, Liu *et al.*^[91] summarized the potential roles of several common alkaloids in the prevention and treatment of HCC by revising the preclinical studies, highlighting the potential applications of alkaloids when they function as a therapeutic choice for HCC treatment, and integrating them into clinical practices. Some alkaloids, such as berberine, have been

demonstrated to possess notable antimicrobial activity, capable of inhibiting the growth of a diverse array of bacteria and fungi.

In conclusion, the investigation of the conformational relationship of alkaloids is of paramount importance in elucidating the mechanism of their biological activities and directing the development of novel drugs. In the future, with the ongoing advancement and deepening of research technology, we anticipate the discovery of additional alkaloids and their derivatives with potential medicinal value, thereby making significant contributions to human health.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 42006094), by the Fujian Natural Science Foundation (No. 2022J01561), and by the Fujian Province-Indonesia Marine Food Joint Research and Development Center Open-Ended Foundation (No. Y1-KF2201).

References

- [1] Zhao, W. Y., Yi, J., Chang, Y. B., et al. Recent studies on terpenoids in *Aspergillus* fungi: chemical diversity, biosynthesis, and bioactivity. *Phytochemistry*, **2022**, 193: 113011. <https://doi.org/10.1016/j.phytochem.2021.113011>
- [2] Zhu, J., Song, L., Shen, S., et al. Bioactive alkaloids as secondary metabolites from plant endophytic *Aspergillus* genus. *Molecules*, **2023**, 28: 7789. <https://doi.org/10.3390/molecules28237789>
- [3] Vadlapudi, V., Borah, N., Yellusani, K. R., et al. *Aspergillus* secondary metabolite database, a resource to understand the secondary metabolome of *Aspergillus* genus. *Scientific Reports*, **2017**, 7: 7325. <https://doi.org/10.1038/s41598-017-07436-w>
- [4] Jimenez, P. C., Wilke, D. V., Branco, P. C., et al. Enriching cancer pharmacology with drugs of marine origin. *British Journal of Pharmacology*, **2020**, 177: 3–27. <https://doi.org/10.1111/bph.14876>
- [5] Frisvad, J. C., Larsen, T. O. Chemodiversity in the genus *Aspergillus*. *Applied Microbiology and Biotechnology*, **2015**, 99: 7859–7877. <https://doi.org/10.1007/s00253-015-6839-z>
- [6] Visagie, C. M., Houbraken, J. Updating the taxonomy of *Aspergillus* in South Africa. *Studies in Mycology*, **2020**, 95: 253–292. <https://doi.org/10.1016/j.simyco.2020.02.003>
- [7] Jiang, C., Ge, J., He, B., et al. Glycosphingolipids in filamentous fungi: biological roles and potential applications in cosmetics and health foods. *Frontiers in Microbiology*, **2021**, 12: 690211. <https://doi.org/10.3389/fmicb.2021.690211>
- [8] Wen, Y. P., Xiao, L. Q., Zhou, L., et al. Study on koji-making conditions and enzyme activity of *Aspergillus oryzae* insweet soybean paste based on meat seasonings. *China Condiment*, **2023**, 48: 41–46. <https://doi.org/10.3969/j.issn.1000-9973.2023.06.007>
- [9] Song, Z. J., Liu, Y., Gao, J. Y., et al. Antitubercular metabolites from the marine-derived fungus strain *Aspergillus fumigatus* MF029. *Natural Product Research*, **2019**, 35: 2647–2654. <https://doi.org/10.1080/14786419.2019.1660331>
- [10] Lv, D. L., Xia, J. M., Guan, X. Q., et al. Indole diketopiperazine alkaloids isolated from the marine-derived fungus *Aspergillus chevalieri* MCCC M23426. *Frontiers in Microbiology*, **2022**, 13: 950857. <https://doi.org/10.3389/fmicb.2022.950857>
- [11] Li, M. F., Xiao, D., Zhu, L. C., et al. Indole alkaloids from the Cigar Tobacco-derived endophytic fungus *Aspergillus oryzae* and their antibacterial activity. *Chemistry of Natural Compounds*, **2022**, 58: 1093–1097. <https://doi.org/10.1007/s10600-022-03872-x>
- [12] Nord, C., Levenfors, J. J., Bjerketorp, J., et al. Tetramic acid based alkaloids from *Aspergillus amoenus* Roberg strain UP197 – antibiotic properties and new pyranterreones. *Natural Product Research*, **2020**, 36: 967–973. <https://doi.org/10.1080/14786419.2020.1855643>
- [13] Liu, Y. J., Zhang, J. L., Li, C., et al. Antimicrobial secondary metabolites from the seawater-derived fungus *Aspergillus sydowii* SW9. *Molecules*, **2019**, 24: 4596. <https://doi.org/10.3390/molecules24244596>
- [14] Liu, M. T., He, Y., Shen, L., et al. Asperteramide A, an unusual N-phenyl-carbamic acid methyl ester trimer isolated from the Coral-derived fungus *Aspergillus Terreus*. *European Journal of Organic Chemistry*, **2019**, 2019: 2928–2932. <https://doi.org/10.1002/ejoc.201900383>
- [15] Dong, Y. L., Li, X. M., Shi, X. S., et al. Diketopiperazine alkaloids and bisabolene sesquiterpenoids from *Aspergillus versicolor* AS-212, an endozoic fungus associated with deep-sea coral of magellan seamounts. *Marine Drugs*, **2023**, 21: 293. <https://doi.org/10.3390/md21050293>
- [16] Yang, J., Gong, L. Z., Guo, M. M., et al. Bioactive indole diketopiperazine alkaloids from the marine endophytic fungus *Aspergillus* sp. YJ191021. *Marine Drugs*, **2021**, 19: 157. <https://doi.org/10.3390/md19030157>
- [17] Wang, Z. J., Jiang, Y., Xin, X. J., et al. Bioactive indole alkaloids from insect derived endophytic *Aspergillus lentulus*. *Fitoterapia*, **2021**, 153: 104973. <https://doi.org/10.1016/j.fitote.2021.104973>
- [18] Wang, M. L., Chen, R., Sun, F. J., et al. Three alkaloids and one polyketide from *Aspergillus cristatus* harbored in *Pinellia ternate* tubers. *Tetrahedron Letters*, **2021**, 68: 152914. <https://doi.org/10.1016/j.tetlet.2021.152914>
- [19] Yan, L. H., Li, X. M., Chi, L. P., et al. Six new antimicrobial metabolites from the deep-sea sediment-derived fungus *Aspergillus fumigatus* SD-406. *Marine Drugs*, **2021**, 20: 4. <https://doi.org/10.3390/md20010004>
- [20] Yan, L. H., Du, F. Y., Li, X. M., et al. Antibacterial Indole Diketopiperazine Alkaloids from the Deep-Sea Cold Seep-Derived Fungus *Aspergillus chevalieri*. *Marine Drugs*, **2023**, 21: 195. <https://doi.org/10.3390/md21030195>
- [21] Abdel-Wahab, N., Scharf, S., Özkaya, F., et al. Induction of secondarymetabolites from the marine-derivedfungus *Aspergillus versicolor* through co-cultivation with *Bacillus subtilis*. *Planta Medica*, **2019**, 85: 503–512. <https://doi.org/10.1055/a-0835-2332>
- [22] Lv, F. Y., Mándi, A., Li, X. M., et al. Emestrin-type thiodiketopiperazines from *Aspergillus nidulans* SD-531, a fungus obtained from the deep-sea sediment of cold seep in the South China Sea. *Deep Sea Research Part I: Oceanographic Research Papers*, **2023**, 195: 104004. <https://doi.org/10.1016/j.dsr.2023.104004>
- [23] Kong, L. W., Qiu, W. Y., Chen, M. S., et al. Two new antifungal indole alkaloids from an endophytic fungi *Aspergillus felis* obtained from Cigar Tobacco. *Chemistry of Natural Compounds*, **2023**, 59: 1132–1136. <https://doi.org/10.1007/s10600-023-04210-5>
- [24] Yang, M., Dong, M., Wu, Q. Y., et al. Three new isoquinoline alkaloids from the fermentation of *Aspergillus* sp.0338 and their anti-MRSA activities. *Natural Product Research*, **2023**, 39: 1–7. <https://doi.org/10.1080/14786419.2023.2254455>
- [25] Zhao, Y. J., Li, L., Zhang, Y. H., et al. (±)-Dibrevianamides Q1 and Q2, the key precursors of asperginulin A from a marine-derived fungus. *Applied Microbiology and Biotechnology*, **2023**, 107: 6459–6467. <https://doi.org/10.1007/s00253-023-12739-2>
- [26] Kong, F. D., Zhang, S. L., Zhou, S. Q., et al. Quinazoline-containing indole alkaloids from the marine-derived fungus *Aspergillus* sp. HNMF114. *Journal of Natural Products*, **2019**, 82: 3456–3463. <https://doi.org/10.1021/acs.jnatprod.9b00845>
- [27] Guo, C., Wang, P., Pang, X. Y., et al. Discovery of a dimeric zinc complex and five cyclopentenone derivatives from the sponge-associated fungus *Aspergillus ochraceopetaliformis*. *ACS Omega*, **2021**, 6: 8942–8949. <https://doi.org/10.1021/acsomega.0c06218>
- [28] Wu, F. R., Zhang, W. X., Bo, X. L., et al. A new sulphur-containing metabolite from a mangrove endophytic fungus *Aspergillus* sp. GXNU-MA. *Natural Product Research*, **2023**, 36: 1–6. <https://doi.org/10.1080/14786419.2023.2288685>
- [29] Wang, S. G., Xu, Z., Cai, B. C., et al. Berberine as a potential multi-target agent for metabolic diseases: a review of investigations for berberine. *Endocr Metab Immune Disord Drug Targets*, **2021**, 21: 971–979. <https://doi.org/10.2174/1871530320666200910105612>
- [30] Wu, Y. P., Zhao, G. K., Liu, Z. Y., et al. Antiviral chromone alkaloids from the Cigar Tobacco leaves derived endophyticfungus *Aspergillus lentulus*. *Chemistry of Natural Compounds*, **2023**, 59: 721–725. <https://doi.org/10.1007/s10600-023-04096-3>
- [31] Wang, H. S., Zhang, L. F., Liu, M. X., et al. Two new CPA-type indole alkaloids from the Tobacco-derived fungus *Aspergillus versicolor* and the anti-TMV activity. *Chemistry of Natural Compounds*, **2022**, 58: 888–891. <https://doi.org/10.1007/s10600-022-03822-7>
- [32] Yang, F. X., Liu, H. Y., Li, Z. J., et al. Anti-Tobacco Mosaic Virus Indole Alkaloids from the *Nicotiana tabacum*-Derived Fungus *Aspergillus versicolor*. *ACS Agricultural Science & Technology*, **2022**, 3: 131–139. <https://doi.org/10.1021/acscagstech.2c00256>
- [33] Cha, X. J., Pu, G., Xiong, R. F., et al. Carboline alkaloids from the Cigar Tobacco-derived fungi *Aspergillus* sp. and their anti-TMV activity. *Chemistry of Natural Compounds*, **2023**, 59: 881–885. <https://doi.org/10.1007/s10600-023-04140-2>
- [34] Ma, Y. Y., Xiong, W., Shen, S. Y., et al. Bioactive indole alkaloids from the Tobacco-derived endophytic fungus *Aspergillus fumigatus*.

- Chemistry of Natural Compounds*, **2023**, 59: 524–528. <https://doi.org/10.1007/s10600-023-04041-4>
- [35] Anh, C. V., Yoon, Y. D., Kang, J. S., et al. Nitrogen-containing secondary metabolites from a deep-sea fungus *Aspergillus unguis* and their anti-inflammatory activity. *Marine Drugs*, **2022**, 20: 217. <https://doi.org/10.3390/md20030217>
- [36] Niveditha, L., Fu, P., Leao, T. F., et al. Targeted isolation of two new anti-inflammatory and UV-A protective dipyrroloquinones from the sponge-associated fungus *Aspergillus tamarii* MCCF102. *Planta Medica*, **2022**, 88: 774–782. <https://doi.org/10.1055/a-1769-8480>
- [37] Huang, J. G., Bo, X. L., Wu, F. R., et al. Asperphenyltones A and B: new phenylfuropyridinone skeleton from an endophytic *Aspergillus* sp. GXNU-A1. *Molecules*, **2022**, 27: 8160. <https://doi.org/10.3390/molecules27238160>
- [38] Li, Y. C., Yang, J., Zhao, Y. Z., et al. Cytochalasins from the endophytic fungus *Aspergillus* sp. LE2: Their structures, antibacterial and NO production inhibitory activities. *Journal of Fungi*, **2023**, 9: 374. <https://doi.org/10.3390/jof9030374>
- [39] Shan, T. Z., Jiang, W., Liu, X., et al. Alkaloids including two rare varicicolortides from the fungus *Aspergillus ruber*. *Tetrahedron*, **2020**, 76: 131258. <https://doi.org/10.1016/j.tet.2020.131258>
- [40] Hu, B. Y., Zhao, Y. L., Zhou, Z. S., et al. Significant anti-inflammatory aziridine-containing indole alkaloids from the Chinese medicinal plant *Alstonia scholaris*. *Chemical Communications*, **2023**, 59: 2271–2274. <https://doi.org/10.1039/d2cc07029d>
- [41] Niu, S. W., Chen, Z. M., Pei, S. X., et al. Acremolin D, a new acremolin alkaloid from the deep-sea sediment derived *Aspergillus sydowii* fungus. *Natural Product Research*, **2021**, 36: 4936–4942. <https://doi.org/10.1080/14786419.2021.1913587>
- [42] Wu, J., Wang, F. Q., He, L. M., et al. Aculeaquamide A, cytotoxic paraherquamide from the marine fungus *Aspergillus aculeatinus* WHUF0198. *Natural Product Research*, **2021**, 36: 4382–4387. <https://doi.org/10.1080/14786419.2021.1998047>
- [43] Wang, L., Yu, Z. Y., Guo, X. W., et al. Bisaspochalasins D and E: two heterocycle-fused cytochalasan homodimers from an endophytic *Aspergillus flavipes*. *The Journal of Organic Chemistry*, **2021**, 86: 11198–11205. <https://doi.org/10.1021/acs.joc.1c00425>
- [44] Wu, Z. D., Zhang, X. T., Li, Q., et al. Amichalasin F–J: cytochalasan heterotrimers with mirror-imaged core structures from *Aspergillus micronesiensis*. *Organic Chemistry Frontiers*, **2023**, 10: 3530–3536. <https://doi.org/10.1039/d3qo00565h>
- [45] Xu, A., Xu, X. N., Zhang, M., et al. Cytotoxic indole alkaloids and polyketides produced by a marine-derived fungus *Aspergillus flavipes* DS720. *Frontiers in Microbiology*, **2022**, 13: 959754. <https://doi.org/10.3389/fmicb.2022.959754>
- [46] Fan, Y. Q., Zhou, Y. L., Du, Y. Q., et al. Circumdatin-aspyrone conjugates from the coral-associated *Aspergillus ochraceus* LCJ11-102. *Marine Drugs*, **2019**, 17: 400. <https://doi.org/10.3390/md17070400>
- [47] Wu, Z. D., Tong, Q. Y., Zhang, X. T., et al. Amichalasin A–C: Three cytochalasan heterotrimers from *Aspergillus micronesiensis* PG-1. *Organic Letters*, **2019**, 21: 1026–1030. <https://doi.org/10.1021/acs.orglett.8b04066>
- [48] Wei, X., Feng, C., Wang, S. Y., et al. New indole diketopiperazine alkaloids from soft coral-associated epiphytic fungus *Aspergillus* sp. EGF 15-0-3. *Chemistry & Biodiversity*, **2020**, 17: e2000106. <https://doi.org/10.1002/cbdv.202000106>
- [49] Li, Q., Fu, A. M., Wei, M. S., et al. Asperemestrins A–D, emestrin hybrid polymers with bridged skeletons from the endophytic fungus *Aspergillus nidulans*. *Organic Letters*, **2022**, 24: 6800–6804. <https://doi.org/10.1021/acs.orglett.2c02701>
- [50] Gu, B. B., Gui, Y. H., Liu, L., et al. A new asymmetric diketopiperazine dimer from the sponge-associated fungus *Aspergillus versicolor* 16F-11. *Magnetic Resonance in Chemistry*, **2018**, 57: 49–54. <https://doi.org/10.1002/mrc.4780>
- [51] Orfali, R., Perveen, S., Khan, M. F., et al. Asporychalasin, a bioactive cytochalasan with an unprecedented 6/6/11 skeleton from the Red Sea sediment *Aspergillus oryzae*. *Phytochemistry*, **2021**, 192: 112952. <https://doi.org/10.1016/j.phytochem.2021.112952>
- [52] Wei, J. H., Chen, X. X., Ge, Y. C., et al. Cytotoxic shornephines and asterresins from the hydrothermal vent associated fungus *Aspergillus terreus* CXX-158-20. *Phytochemistry*, **2023**, 205: 113479. <https://doi.org/10.1016/j.phytochem.2022.113479>
- [53] Luo, X. W., Chen, C. M., Tao, H. M., et al. Structurally diverse diketopiperazine alkaloids from the marine-derived fungus *Aspergillus versicolor* SCSIO 41016. *Organic Chemistry Frontiers*, **2019**, 6: 736–740. <https://doi.org/10.1039/c8qo01147h>
- [54] Li, H. Q., Xu, Q. Q., Sun, W. G., et al. 21-Epi-taichunamide D and (±)-versicaline A, three unusual alkaloids from the endophytic *Aspergillus versicolor* F210. *Tetrahedron Letters*, **2020**, 61: 152219. <https://doi.org/10.1016/j.tetlet.2020.152219>
- [55] El-Kashef, D. H., Obidake, D. D., Schiedlauske, K., et al. Indole siketopiperazine alkaloids from the marine sediment-derived fungus *Aspergillus chevalieri* against pancreatic ductal adenocarcinoma. *Marine Drugs*, **2023**, 22: 5. <https://doi.org/10.3390/md22010005>
- [56] Chen, Y., Wang, S. P., Xu, L. C., et al. Asperitaichamide a, a novel cytotoxic prenylated indole alkaloid possessing a bicyclo[2.2.2]diazoctane framework from a marine algal-derived endophytic fungus *aspergillus taichungensis* 299. *Fitoterapia*, **2024**, 172: 105763. <https://doi.org/10.1016/j.fitote.2023.105763>
- [57] Huang, X. M., Wang, Y. C., Li, G. Y., et al. Secondary metabolites from the deep-sea derived fungus *Aspergillus terreus* MCCC M28183. *Frontiers in Microbiology*, **2024**, 15: 1361550. <https://doi.org/10.3389/fmicb.2024.1361550>
- [58] Al-Khdhairawi, A. A. Q., Loo, J. S. E., Abd Mutalib, N., et al. Diketopiperazine and isoindolinone alkaloids from the endophytic fungus *Aspergillus* sp. HAB10R12. *Phytochemistry*, **2023**, 211: 113685. <https://doi.org/10.1016/j.phytochem.2023.113685>
- [59] Guo, X., Meng, Q. Y., Liu, J., et al. Sclerotiamides C–H, notoamides from a marine gorgonian-derived fungus with cytotoxic activities. *Journal of Natural Products*, **2022**, 85: 1067–1078. <https://doi.org/10.1021/acs.jnatprod.1c01194>
- [60] Li, Q., Chen, C. M., He, Y., et al. Prenylated quinolinone alkaloids and prenylated isoindolinone alkaloids from the fungus *Aspergillus nidulans*. *Phytochemistry*, **2020**, 169: 112177. <https://doi.org/10.1016/j.phytochem.2019.112177>
- [61] Zhang, X. T., Wu, Z. D., Bao, A., et al. Asperflavipines C–E and aspermichalasin A: Three cytochalasan heterotetramers and an unusual cytochalasan monomer from *Aspergillus micronesiensis*. *Organic Chemistry Frontiers*, **2022**, 9: 2585–2592. <https://doi.org/10.1039/d2qo00309k>
- [62] Bo, X. L., Zhao, Y. F., Qin, F., et al. Cytotoxic metabolites from the mangrove endophytic fungus *Aspergillus* sp. GXNU QG1a. *Natural Product Research*, **2024**, 39: 2572–2579. <https://doi.org/10.1080/14786419.2024.2303601>
- [63] Kang, H. H., Zhong, M. J., Ma, L. Y., et al. Iizukines C–E from a saline soil fungus *Aspergillus iizukae*. *Bioorganic Chemistry*, **2019**, 91: 103167. <https://doi.org/10.1016/j.bioorg.2019.103167>
- [64] Wang, F. Q., Sarotti, A. M., Jiang, G. D., et al. Waikikiamides A–C: complex diketopiperazine dimer and diketopiperazine–polyketide hybrids from a Hawaiian marine fungal strain *Aspergillus* sp. FM242. *Organic Letters*, **2020**, 22: 4408–4412. <https://doi.org/10.1021/acs.orglett.0c01411>
- [65] Kwon, J. Y., Seo, Y. H., Lee, J. E., et al. Spiroindole alkaloids and spiroditerpenoids from *Aspergillus duricaulis* and their potential neuroprotective effects. *Journal of Natural Products*, **2015**, 78: 2572–2579. <https://doi.org/10.1021/acs.jnatprod.5b00508>
- [66] Jiang, Y. Q., Chen, C. M., Zhu, H. C., et al. An indole diketopiperazine alkaloid and a bisabolane sesquiterpenoid with unprecedented skeletons from *Aspergillus fumigatus*. *Organic & Biomolecular Chemistry*, **2023**, 21: 2236–2242. <https://doi.org/10.1039/d2ob02220f>
- [67] Wang, L., Yang, J., Huang, J. P., et al. Bisaspochalasins A–C: Three cytochalasan homodimers with highly fused ring system from an endophytic *Aspergillus flavipes*. *Organic Letters*, **2020**, 22: 7930–7935. <https://doi.org/10.1021/acs.orglett.0c02860>

- [68] Wu, Z. D., Zhang, X. T., Al Anbari, W. H., et al. Amiaspochalasin A–H, undescribed aspochalasins with a C-21 ester carbonyl from *Aspergillus micronesiensis*. *The Journal of Organic Chemistry*, **2019**, 84: 5483–5491. <https://doi.org/10.1021/acs.joc.9b00440>
- [69] Zhang, Z., Sun, Y., Li, Y., et al. The potential of marine-derived piperazine alkaloids: Sources, structures and bioactivities. *European Journal of Medicinal Chemistry*, **2024**, 265: 116081. <https://doi.org/10.1016/j.ejmech.2023.116081>
- [70] Daniel, P., Antonio, M., Christian, A. O., et al. Synthesis and structure-activity relationship study of potent cytotoxic analogues of the marine alkaloid Lamellarin D. *Journal of Medicinal Chemistry*, **2006**, 49: 3257–3268. <https://doi.org/10.1016/j.bmcl.2021.128009>
- [71] Huo, C. H., Lu, X. H., Zheng, Z. H., et al. Azaphilones with protein tyrosine phosphatase inhibitory activity isolated from the fungus *Aspergillus deflectus*. *Phytochemistry*, **2020**, 170: 112224. <https://doi.org/10.1016/j.phytochem.2019.112224>
- [72] He, W. W., Xu, Y. C., Wu, D., et al. New alkaloids from the diversity-enhanced extracts of an endophytic fungus *Aspergillus flavus* GZWMJZ-288. *Bioorganic Chemistry*, **2021**, 107: 104623. <https://doi.org/10.1016/j.bioorg.2020.104623>
- [73] Wang, C., Wang, Y. F., Sun, J., et al. A pair of new spirocyclic alkaloid enantiomers with TrxR inhibitory activities were isolated from marine-derived *Aspergillus ruber* TX-M4-1. *Journal of Ocean University of China*, **2023**, 22: 1677–1682. <https://doi.org/10.1007/s11802-023-5607-4>
- [74] Ye, G. T., Huang, C. Y., Li, J. L., et al. Isolation, structural characterization and antidiabetic activity of new diketopiperazine alkaloids from mangrove endophytic fungus *Aspergillus* sp. 16-5c. *Marine Drugs*, **2021**, 19. <https://doi.org/10.3390/md19070402>
- [75] Ohte, S., Shiokawa, T., Koyama, N., et al. A new diketopiperazine-like inhibitor of bone morphogenetic protein-induced osteoblastic differentiation produced by marine-derived *Aspergillus* sp. BFM-0085. *The Journal of Antibiotics*, **2020**, 73: 554–558. <https://doi.org/10.1038/s41429-020-0316-3>
- [76] Li, H. L., Yang, S. Q., Li, X. M., et al. Structurally diverse alkaloids produced by *Aspergillus creber* EN-602, an endophytic fungus obtained from the marine red alga *Rhodomela confervoides*. *Bioorganic Chemistry*, **2021**, 110. <https://doi.org/10.1016/j.bioorg.2021.104822>
- [77] Fukuda, T., Furukawa, T., Kobayashi, K., et al. Helvamide, a new inhibitor of sterol *O*-acyltransferase produced by the fungus *Aspergillus nidulans* BF-0142. *The Journal of Antibiotics*, **2018**, 72: 8–14. <https://doi.org/10.1038/s41429-018-0101-8>
- [78] Hu, L. Z., Tian, S. Y., Wu, R. R., et al. Identification of anti-parkinson's disease lead compounds from *Aspergillus ochraceus* targeting adenosin receptors A2A. *ChemistryOpen*, **2021**, 10: 630–638. <https://doi.org/10.1002/open.202100022>
- [79] Ding, Y., Zhu, X. J., Hao, L. L., et al. Bioactive indolyl diketopiperazines from the marine derived endophytic *Aspergillus versicolor* DY180635. *Marine Drugs*, **2020**, 18. <https://doi.org/10.3390/md18070338>
- [80] He, W. W., Xu, Y. C., Fu, P., et al. Cytotoxic indolyl diketopiperazines from the *Aspergillus* sp. GZWMJZ-258, endophytic with the medicinal and edible plant *Garcinia Multiflora*. *Journal of Agricultural and Food Chemistry*, **2019**, 67: 10660–10666. <https://doi.org/10.1021/acs.jafc.9b04254>
- [81] Bai, M., Wang, Y., Liu, T., et al. One new piperazinedione isolated from a mangrove-derived fungus *Aspergillus niger* JX-5. *Natural Product Research*, **2020**, 36: 2277–2283. <https://doi.org/10.1080/14786419.2020.1828407>
- [82] Cai, R. L., Jiang, H. M., Xiao, Z., et al. (–)- and (+)-Asperginulin A, a pair of indole diketopiperazine alkaloid dimers with a 6/5/4/5/6 pentacyclic skeleton from the mangrove endophytic fungus *Aspergillus* sp. SK-28. *Organic Letters*, **2019**, 21: 9633–9636. <https://doi.org/10.1021/acs.orglett.9b03796>
- [83] Yan, L. H., Li, P. H., Li, X. M., et al. Chevalinulins A and B, proangiogenic alkaloids with a spiro[bicyclo[2.2.2]octane-diketopiperazine] skeleton from deep-sea cold-seep-derived fungus *Aspergillus chevalieri* CS-122. *Organic Letters*, **2022**, 24: 2684–2688. <https://doi.org/10.1021/acs.orglett.2c00781>
- [84] Li, P. H., Zhang, M. Q., Li, H. N., et al. New prenylated indole homodimeric and pteridine alkaloids from the marine-derived fungus *Aspergillus austroafricanus* Y32-2. *Marine Drugs*, **2021**, 19: 98. <https://doi.org/10.3390/md19020098>
- [85] Wang, J. M., Li, Z. C., Zhang, Y. T., et al. A New α -cyclopiazonic acid alkaloid identified from the Weizhou island coral-derived fungus *Aspergillus flavus* GXIMD 02503. *Journal of Ocean University of China*, **2022**, 21: 1307–1312. <https://doi.org/10.1007/s11802-022-4959-5>
- [86] Wang, C., Sarotti, A. M., Zaman, K. H., et al. New alkaloids from a Hawaiian fungal strain *Aspergillus felis* FM324. *Frontiers in Chemistry*, **2021**, 9: 724617. <https://doi.org/10.3389/fchem.2021.724617>
- [87] Hu, J. S., He, Y. P., Zhou, F. G., et al. New indole diketopiperazine alkaloids from soft coral-associated epiphytic fungus *Aspergillus versicolor* CGF 9-1-2. *Chemistry & Biodiversity*, **2023**, 20: e202300301. <https://doi.org/10.1002/cbdv.202300301>
- [88] Liang, X., Zhang, X. L., Lu, X. H., et al. Diketopiperazine-type alkaloids from a deep-sea-derived *Aspergillus puniceus* fungus and their effects on liver X receptor α . *Journal of Natural Products*, **2019**, 82: 1558–1564. <https://doi.org/10.1021/acs.jnatprod.9b00055>
- [89] Hong, Q., Guo, M. M., Yang, J., et al. Four previously undescribed diketopiperazines from marine fungus *Aspergillus puniceus* FAHY0085 and their effects on liver X receptor α . *Phytochemistry*, **2023**, 214: 113816. <https://doi.org/10.1016/j.phytochem.2023.113816>
- [90] Rodrigues, A. P., Farias, L. H., Carvalho, A. S., et al. A novel function for kojic acid, a secondary metabolite from *Aspergillus* fungi, as antileishmanial agent. *PLOS One*, **2014**, 9: e91259. <https://doi.org/10.1371/journal.pone.0091259>
- [91] Liu, C. Y., Yang, S. S., Wang, K. L., et al. Alkaloids from Traditional Chinese Medicine against hepatocellular carcinoma. *Biomed Pharmacother*, **2019**, 120: 109543. <https://doi.org/10.1016/j.biopha.2019.109543>