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Natural Indole Alkaloids from Marine Fungi: Chemical Diversity and Biological Activities

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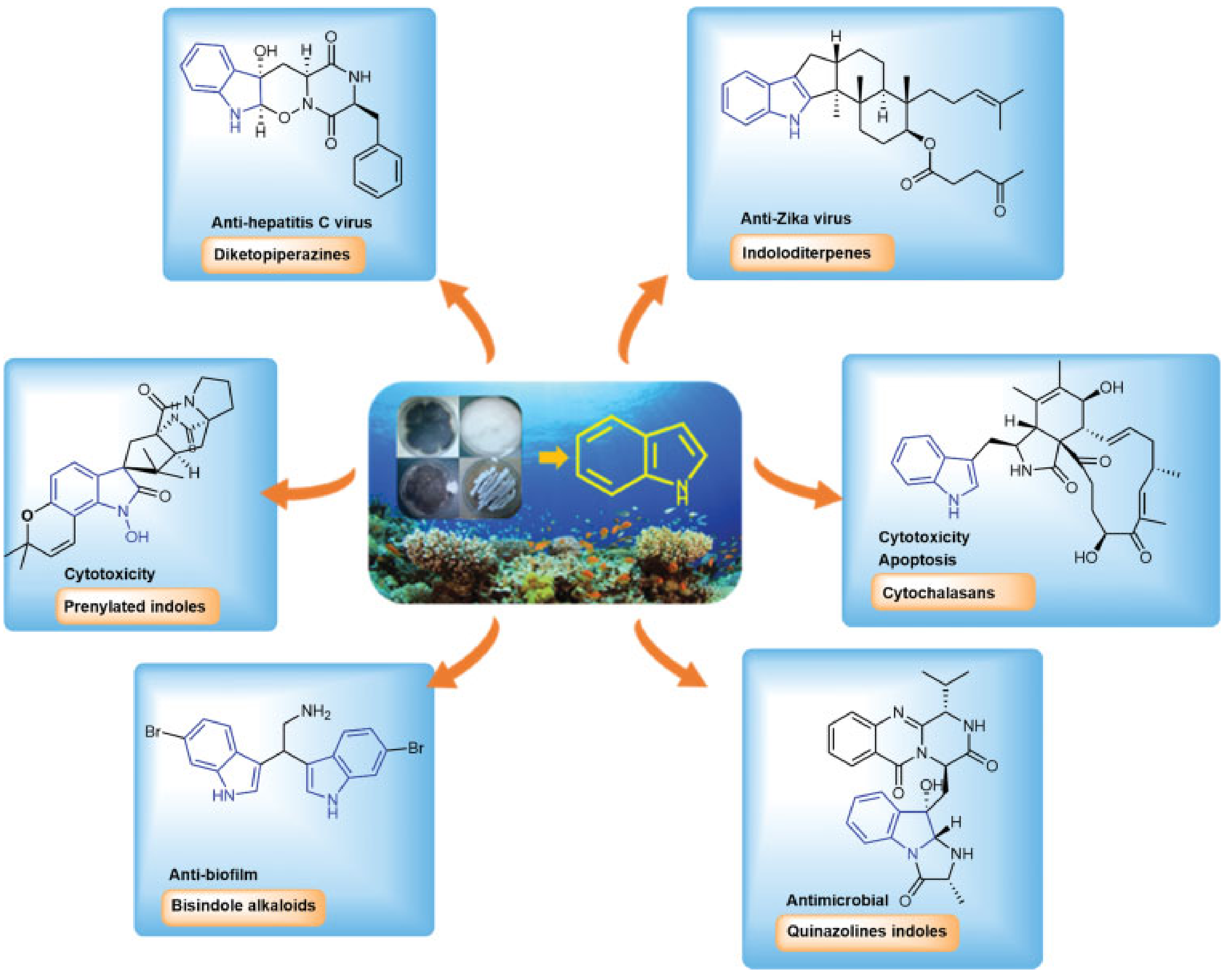

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Abstract

The indole scaffold is one of the most important heterocyclic ring systems for pharmaceutical development, and serves as an active moiety in several clinical drugs. Fungi derived from marine origin are more liable to produce novel indole-containing natural products due to their extreme living environments. The indole alkaloids from marine fungi have drawn considerable attention for their unique chemical structures and significant biological activities. This review attempts to provide a summary of the structural diversity of marine fungal indole alkaloids including prenylated indoles, diketopiperazine indoles, bisindoles or trisindoles, quinazoline-containing indoles, indole-diterpenoids, and other indoles, as well as their known biological activities, mainly focusing on cytotoxic, kinase inhibitory, antiinflammatory, antimicrobial, anti-insecticidal, and brine shrimp lethal effects. A total of 306 indole alkaloids from marine fungi have been summarized, covering the references published from 1995 to early 2021, expecting to be beneficial for drug discovery in the future.

Keywords

- ► marine fungi
- ► indole alkaloids
- ► structural diversity
- ► biological activity

Introduction

The indole fragment is a valuable unit in a wide range of clinical drugs for treating various diseases, such as sunitinib (anticancer), nintedanib (anti-idiopathic pulmonary fibrosis), reserpine (antihypertension), indomethacin (antiinflammation), amedalin (antidepression), atevirdine (anti-human immunodeficiency virus), zafirlukast (antiasthma), etc. (►**Fig. 1**).[1–7] This ring system is one of the most important heterocycles for pharmaceutical development[8,9] and widely distributed in bioactive heterocyclic natural products.[10] The marine fungi are a rich underexploited source to produce novel indole-containing secondary metabolites for drug discovery, due to their extreme marine living conditions.[11–14] Thus, the indole alkaloids from marine fungi have drawn considerable attention for their unique chemical structures and significant biological activities.[13,15,16] In the light of the increasing attention paid on the marine fungal indoles, it is necessary to give a comprehensive summary on these indoles from the specific source. Herein, we reviewed the chemical diversity and biological properties of marine fungal indole alkaloids, expecting to provide clear evidence that these metabolites possess potential of application as lead compounds in the drug innovation and discovery.

Marine Fungal Indole Alkaloids

Prenylated Indole Alkaloids

Prenylated indole alkaloids are hybrid natural products with indole rings and isoprenoid fragments derived from tryptophan and prenyl diphosphates or their precursors, displaying a high structural diversity, especially the prenylated

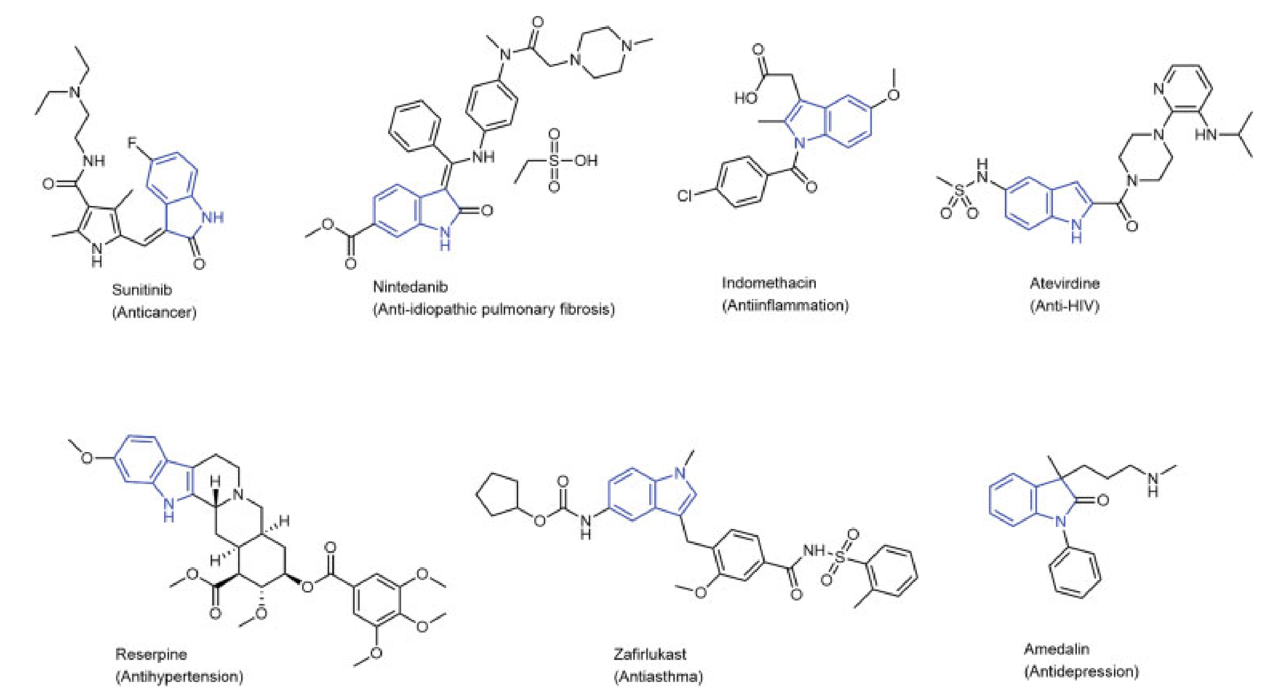

Fig. 1 Representative-approved drugs containing an indole moiety for various diseases.

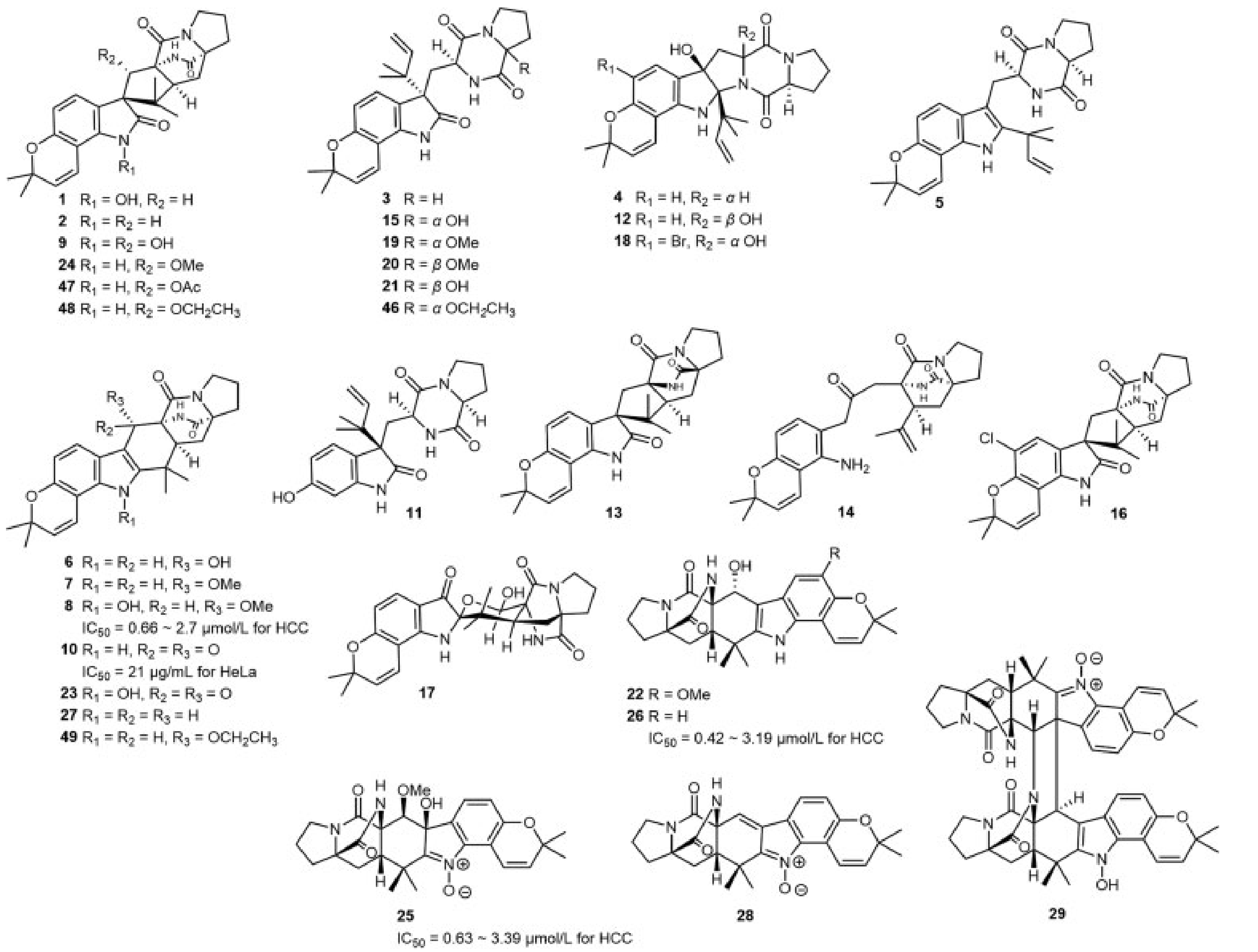

Fig. 2 Chemical structures of prenylated indole alkaloids 1–29 and 46–49.

tryptophan diketopiperazine skeleton (as shown in ►**Figs. 2–10**).[17] These alkaloids are widely discovered from terrestrial and marine fungi, mainly focusing on the spectra of *Aspergillus* and *Penicillium*, with a wide spectrum of biological and pharmacological activities such as insecticidal, antiparasitic, cytotoxic, and antimicrobial effects.[17–19]

Notoamide/stephacidin-type alkaloids with a pyranoindole ring are one of the most typical indole alkaloids. Notoamides A–D (**1**–**4**) are four new doubly prenylated indole alkaloids, first isolated from the marine fungus *Aspergillus* sp., which was derived from the common mussel *Mytilus edulis* (►**Fig. 2**). Notoamides A–C (**1**–**3**) with a dihydroxypyrano-2-oxindole ring system exhibited moderate cytotoxic effect toward HeLa and L1210 cells.[20]

Notoamide E (**5**) (►**Fig. 2**) was found in a marine-derived fungus *Aspergillus* sp., being considered as a key precursor of prenylated alkaloids in the biosynthesis process.[21,22]

One new notoamide/stephacidin-type alkaloid, 21-hydroxystephacidin (**6**) (►**Fig. 2**), was harbored from the culture of a marine fungus *Aspergillus ostianus*.[23] Notoamides F–K (**7**–**12**) (►**Fig. 2**) were harbored from a marine-derived fungus strain *Aspergillus* sp. Notoamide I (**10**) exhibited weak cytotoxic effect toward HeLa cells ($IC_{50} = 21$ μg/mL).[24,25]

Four notoamide/stephacidin-type analogues, named antipodal (−)-versicolamide B (**13**) and notoamides L–N (**14**–**16**) (►**Fig. 2**), were produced by a marine-derived *Aspergillus* sp. Compound **14** is the first prenylated indole alkaloid presenting 25 carbons. Compound **15** is probably the precursor in the biosynthesis of the bicyclo[2.2.2]diazaoctane ring system.[26]

Notoamides O–Q (**17**–**19**) (►**Fig. 2**) were isolated from a culture medium of marine-derived *Aspergillus* sp. Compound **17** contained a unique hemiacetal/hemiaminal ether moiety, which was unpresented in these groups of prenylated indole alkaloids.[27,28]

17-*Epi*-notoamides Q (**20**) and M (**21**) (►**Fig. 2**) were two new prenylated indole alkaloids, which were obtained from a marine-derived fungus *Aspergillus* sp.[29,30]

Four new notoamide-type alkaloids, notoamides W–Z (**22**–**25**), as well as seven known analogues, notoamide F (**7**), notoamide G (**8**), 19-*epi*-notoamide R (**26**), notoamide I (**10**), stephacidin A (**27**), avrainvillamide (**28**), and a dimer of notoamide-type alkaloid stephacidin B (**29**), were discovered from a coral-associated fungus *Aspergillus ochraceus* LZDX-32–15 (►**Fig. 2**). Compounds **8**, **25**, and **26** exhibited potent inhibitory activity toward a panel of HCC (hepatocellular carcinoma) cell lines with IC_{50} values in the range of 0.42 to

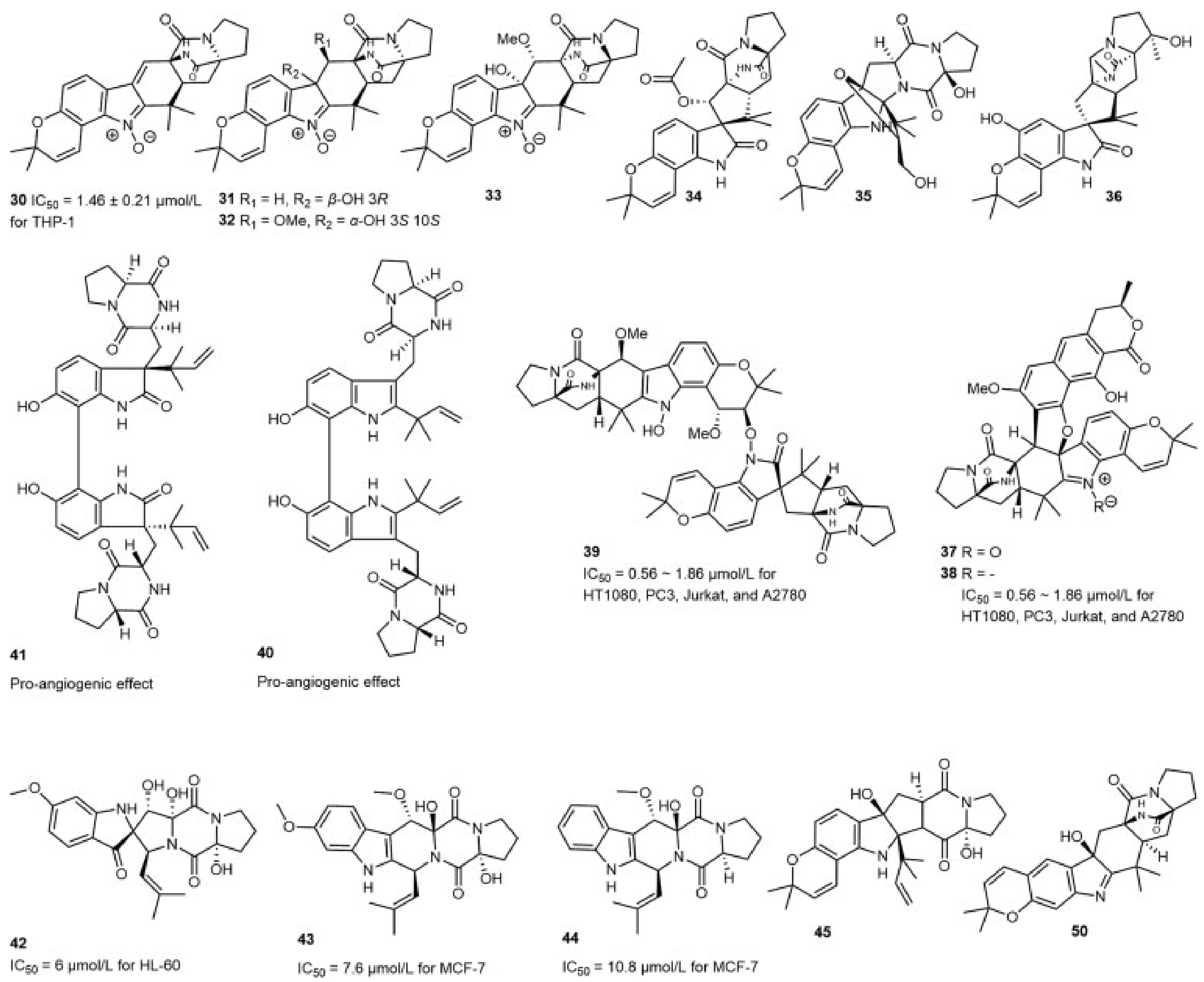

Fig. 3 Chemical structures of prenylated indole alkaloids **30–45** and **50**.

3.39 μmol/L. Notoamide G (**8**) inhibited the viability of HepG2 and Huh-7 cells via apoptosis and autophagy way through a P38/JNK signaling pathway.[31]

Six new prenylated indole alkaloids with diketopiperazine ring, asperthrins A–F (**30**–**35**), were obtained from marine fungi *Aspergillus* sp. YJ191021 (►**Fig. 3**). Asperthrin A (**30**) showed moderate inhibitory activities against three agricultural pathogenic microorganisms and significant antiinflammatory effect with IC_{50} value of 1.46 ± 0.21 μmol/L in the model of human monocyte cell line (THP-1) induced by *Propionibacterium acnes*.[32]

Paraherquamide J (**36**) (►**Fig. 3**) is a new prenylated indole alkaloid, obtained from the fungus *Penicillium janthinellum* HK1–6, which was derived from mangrove rhizosphere soil. This alkaloid showed inactive effect in the assay of topoisomerase I (topo I) inhibitory, antibacterial, and lethality against brine shrimp *Artemia salina*.[33]

Three new prenylated indole alkaloids waikikiamides A–C (**37**–**39**) (►**Fig. 3**) with a complex diketopiperazine moiety were produced by the marine fungus *Aspergillus* sp. FM242. Compounds **37** and **38** contain an unprecedented indole alkaloid skeleton featuring with a hendecacyclic ring system. Compound **39** is the first unique heterodimer of two notoamide derivatives joined by an N – O – C bridge. Compounds **37** and **39** showed significant antiproliferative activity against four cancer cell lines, HT1080, PC3, Jurkat, and A2780, with IC_{50} values in the range of 0.56 to 1.86 μmol/L.[34]

Di-6-hydroxydeoxybrevianamide E (**40**) and dinotoamide J (**41**) (►**Fig. 3**), two new homodimers, represent new examples of prenylated indole alkaloid, and were discovered from *Aspergillus austroafricanus* Y32–2. They exhibited proangiogenic effect in a zebrafish model of vascular injury induced by PTK787.[35]

Three new alkaloids, spirotryprostatin G (**42**), and cyclotryprostatins F and G (**43** and **44**) (►**Fig. 3**), were isolated from the marine-derived fungal strain *Penicillium brasilianum* HBU-136. Compound **42** exhibited potent cytotoxic effect against the HL-60 cell line ($IC_{50} = 6.0$ μmol/L). Compounds **43** and **44** showed cytotoxicity toward the MCF-7 cell line with IC_{50} values of 7.6 and 10.8 μmol/L, respectively.[36]

17-Hydroxynotoamide D (**45**), 17-*O*-ethylnotoamide M (**46**), 10-*O*-acetylsclerotiamide (**47**), 10-*O*-ethylsclerotiamide (**48**), and 10-*O*-ethylnotoamide R (**49**) (►**Figs. 1** and **3**) are five new prenylated indole alkaloids, being obtained from two marine-derived fungi *Aspergillus sulphureus* KMM 4640 and *Isaria felina* KMM 4639 by co-culture

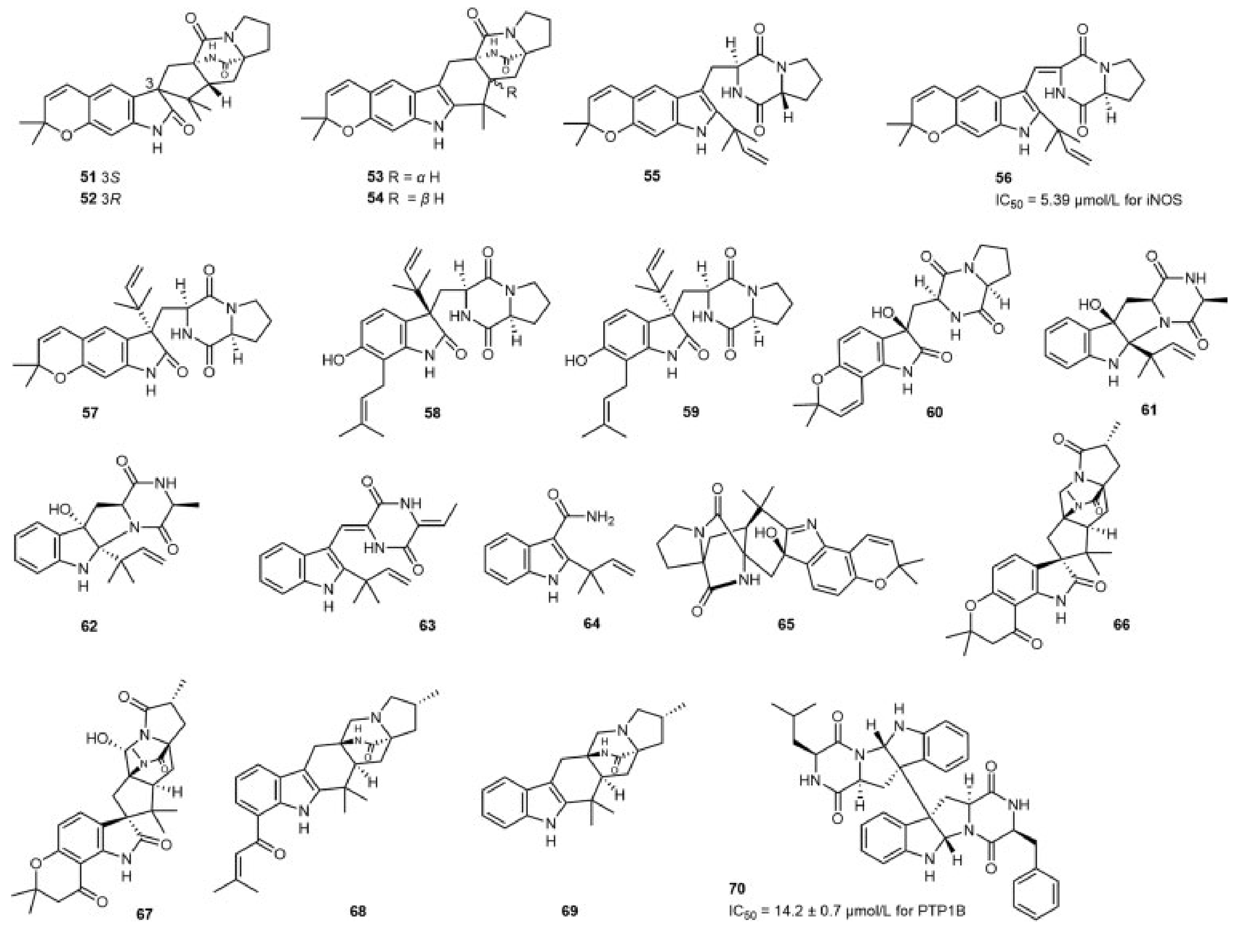

Fig. 4 Chemical structures of prenylated indole alkaloids **51–70**.

method. Compound **46** showed inhibitory effect against the human prostate cancer cells 22Rv1 at a concentration of 10 μmol/L.[37]

Asperversiamides A–H (**50**–**57**) (►**Figs. 3** and **4**), eight new linearly fused prenylated indole alkaloids with a rare pyrano[3,2-*f*]indole moiety, were found from the marine-derived fungus *Aspergillus versicolor*. Compound **56** showed potent inhibitory activity toward iNOS with an IC_{50} value of 5.39 μmol/L in the antiinflammatory test.[38]

Three new indole diketopiperazine alkaloids, asperochramides A–C (**58**–**60**) (►**Fig. 4**), were obtained from a marine fungus *A. ochraceus*. Compound **58** exhibited significant antiinflammatory effects against the lipopolysaccharide (LPS)-stimulated RAW 264.7 cells.[39]

Three new prenylated diketopiperazine indole alkaloids eurotiumins A–C (**61**–**63**) and one new prenylated indole alkaloid eurotiumin D (**64**) (►**Fig. 4**) were produced by the marine-derived fungus *Eurotium* sp. SCSIO F452. Compounds **61** and **62** are a pair of diastereomers both with a hexahydropyrrolo[2,3-*b*]indole skeleton. Compound **63** exhibited significant radical scavenging effects toward DPPH with IC_{50} values of 13 μmol/L.[40]

Taichunamide H (**65**) (►**Fig. 4**), a new indole alkaloid with a fused-imine-containing pyrrole ring, was isolated from the fungus *A. versicolor*. The resonance at 190.4 ppm was assigned as the imine carbon in the molecule by using X-ray diffraction, and the structure of taichunamide A was also revised. However, compound **65** showed no antifungal and cytotoxic activity.[41]

Mangrovamides D–G (**66**–**69**) (►**Fig. 4**) are four new prenylated indole alkaloids from the mangrove sediment-derived fungus *Penicillium* sp. SCSIO041218 with no anti-allergic effect *in vitro* assay.[42]

SF5280–415 (**70**) (►**Fig. 4**), a new bispyrrolidinoindoline diketopiperazine alkaloid, and a known analogue SF5280–451 (**71**) (►**Fig. 5**) were obtained from the marine-derived fungus *Aspergillus* sp. SF-5280. Compounds **70** and **71** displayed potent inhibitory effect toward PTP1B with IC_{50} values of 14.2 ± 0.7 and 12.9 ± 0.7 μmol/L, respectively.[43]

Two new prenylated indole derivatives brevicompanine B (**72**) and verrucofortine (**73**) (►**Fig. 5**) were found from a marine fungus *Penicillium* sp. NH-SL, and compound **73** showed potent cytotoxicity toward Hepa 1c1c7 cells.[44]

Four new indole diketopiperazine alkaloids, *N*-(40-hydroxyprenyl)-cyclo(alanyltryptophyl) (**74**), isovariecolorin I (**75**), 30-hydroxyechinulin (**76**), and 29-hydroxyechinulin (**77**) (►**Fig. 5**), were obtained from the marine-derived fungus *Eurotium cristatum* EN-220. Compound **75** exhibited lethal effect against brine shrimp with the LD_{50} value of 19.4 μg/mL.[45]

Two new prenylated indole derivatives, named penicimutamides D and E (**78** and **79**) (►**Fig. 5**), were produced by the

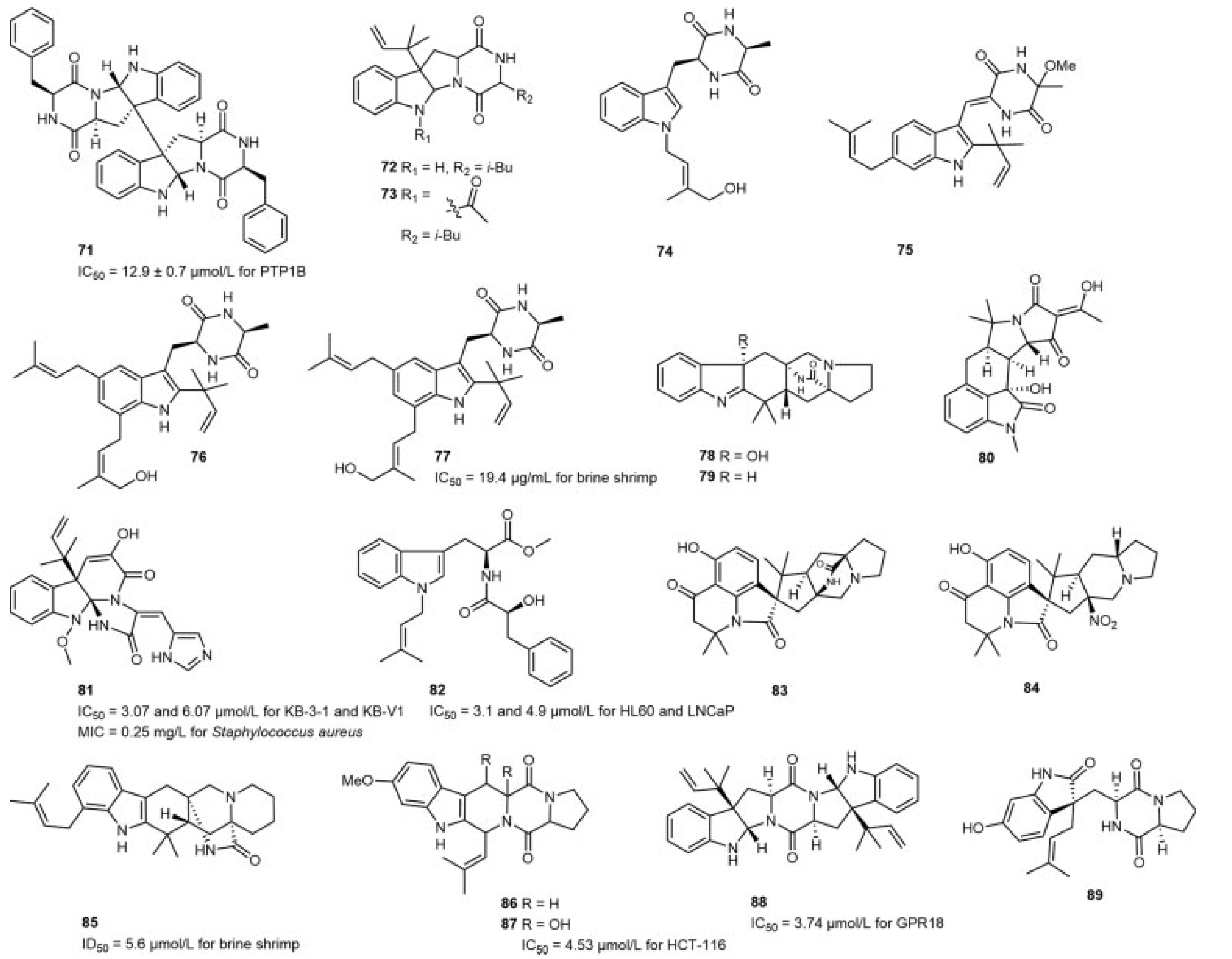

Fig. 5 Chemical structures of prenylated indole alkaloids **71–89**.

mutant fungus strain of *Penicillium purpurogenum* G59 derived from marine through the stimulation of diethyl sulfate. These two derivatives displayed weak suppressive effect toward cancer cell lines.[46]

4,3-Hydroxysperadine A (**80**) (►**Fig. 5**), a new cyclopiazonic acid congener, was isolated from a marine sponge-associated fungus *Aspergillus oryzae* HMP-F28 by a bioassay-guided separation.[47]

A known alkaloid, meleagrin (**81**) (►**Fig. 5**), was rediscovered from a marine-derived fungus *Emericella dentata* Nq45. Its absolute structure was determined by the single-crystal X-ray diffraction method. This compound exhibited potent cytotoxic activity toward KB-3–1 cell line (the human cervix carcinoma) and KB-V1, a multidrug resistant subclone of KB-3–1, with the IC_{50} values of 3.07 and 6.07 μmol/L, respectively. It also showed potent antibacterial effect against *Staphylococcus aureus* (minimum inhibitory concentration [MIC] = 0.25 mg/mL).[48]

Misszrtine A (**82**) (►**Fig. 5**) is a novel prenylated indole alkaloid possessing a *N*-isopentenyl fragment, which was the first example of tryptophan methyl ester in this kind of alkaloids. This molecule, obtained from a marine sponge-derived fungus *Aspergillus* sp. SCSIO XWS03F03, displayed a significant antagonistic effect against HL60 and LNCaP cell lines, with the IC_{50} values of 3.1 and 4.9 μmol/L, respectively.[49]

Cycloexpansamines A (**83**) and B (**84**) (►**Fig. 5**), two novel prenylated alkaloids with a spiroindolinone moiety, were produced by a marine fungus strain *Penicillium* sp. SF-5292.[50]

Penioxamide A (**85**) (►**Fig. 5**), a new prenylated indole congener with a piperidine moiety and a unique antirelative configuration of the bicyclo[2.2.2]diazaoctane ring system, was afforded from the culture medium of fungus *Penicillium oxalicum* EN-201. Compound **85** exhibited pronounced lethality effect against brine shrimp (LD_{50} = 5.6 μmol/L).[51]

Two diketopiperazine indole alkaloids, named fumitremorgin C (**86**) and 12,13-dihydroxy-fumitremorgin C (**87**) (►**Fig. 5**), were obtained from the culture of a fungus *Aspergillus* sp. BRF 030, displaying cytotoxic activity toward the HCT-116 cell line (IC_{50} = 15.17 and 4.53 μmol/L, respectively).[52]

A new diketopiperazine indole derivative, amauromine (**88**) (►**Fig. 5**), was isolated from the marine fungus *Auxarthron reticulatum* derived from marine sponge. This compound was considered to be a remarkable lead molecule for

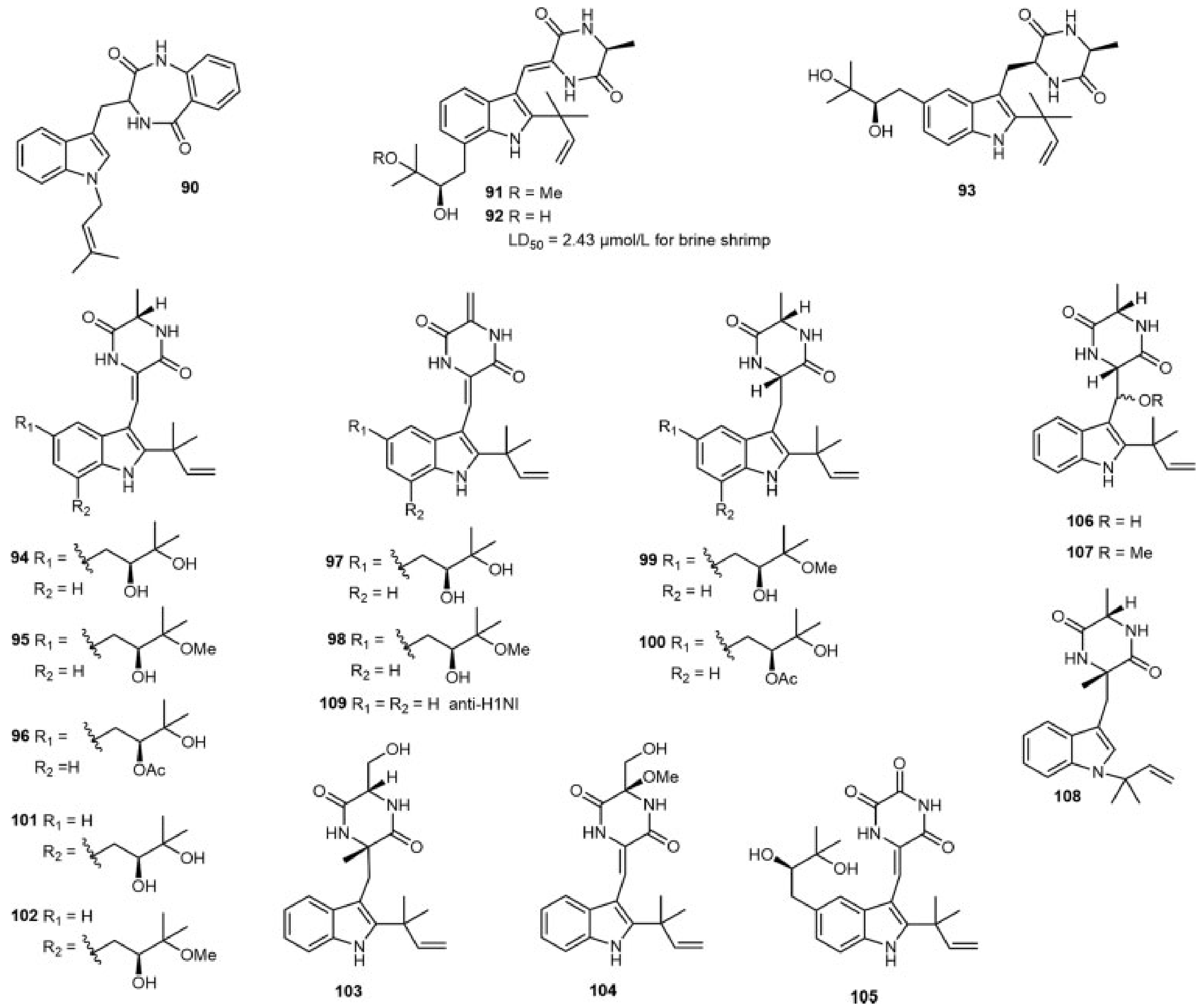

Fig. 6 Chemical structures of prenylated indole alkaloids **90–105**.

the research of selective antagonists of GPR18, for its potent suppressive effect toward GPR18 with the IC_{50} value of 3.74 µmol/L.[53]

Spirotryprostatin K (**89**) (►**Fig. 5**) is a new diketopiperazine alkaloid, obtained from an extract of the marine fungus *Aspergillus fumigatus*.[54]

A new prenylated natural alkaloid takakiamide (**90**) (►**Fig. 6**) was obtained from the culture medium of the algicolous-derived fungus *Neosartorya takakii* KUFC 7898. However, this compound showed no antibacterial effect and no quorum sensing inhibitory activity.[55]

Rubrumazines A–C (**91**–**93**) (►**Fig. 6**) are three new iso-echinulin-type indole diketopiperazine alkaloids bearing an oxygenated prenyl ether segment and produced by a mangrove-derived fungus *Eurotium rubrum* MA-150. Compounds **92** exhibited remarkable lethality toward brine shrimp with the LD_{50} values of 2.43 µmol/L.[56]

Rubrumlines A–O (**94** – **108**) as well as its known analogue neoechinulin B (**109**) are a series of indole diketopiperazine alkaloids obtained from the extract of the culture of the marine fungus *E. rubrum* (►**Fig. 6**). Neoechinulin B (**109**) showed significant inhibitory activity toward H1N1 virus in MDCK cells, and a class of influenza virus strains comprising amantadine- and oseltamivir-resistant ones, which were isolated from clinical samples.[57]

Dihydrocarneamide A (**110**) and iso-notoamide B (**111**) (►**Fig. 7**), two new prenylated indole analogues with the rare fused dimethyldihydropyran ring in the indole moiety by C-5 prenylation, are produced by the culture of the marine fungus *Paecilomyces variotii* EN-291. However, these two alkaloids represent weak cytotoxic effect toward the NCI-H460 cell line.[58]

Cladosporin A (**112)** and cladosporin B (**113**) (►**Fig. 7**), two new sulfur-containing diketopiperazine indole derivatives, are harbored from a culture of fungus *Cladosporium* sp. derived from marine. These two compounds show moderate cytotoxicity against HepG2 cell line ($IC_{50} = 21$ and 48 µg/mL).[59]

Penipalines A and B (**114** and **115**), two new *β*-carbolines, and penipaline C (**116**), one new indole carbaldehyde congener, were afforded from the culture of the deep-sea-sediment fungus *Penicillium paneum* SD-44 (►**Fig. 7**). Compounds **115** and **116** exhibited significant cytotoxicity on A-549 and HCT-116 cell lines.[60]

One new diketomorpholine derivative shornephine A (**117**) and a new prenylated indole 15b-*β*-methoxy-5-*N*-

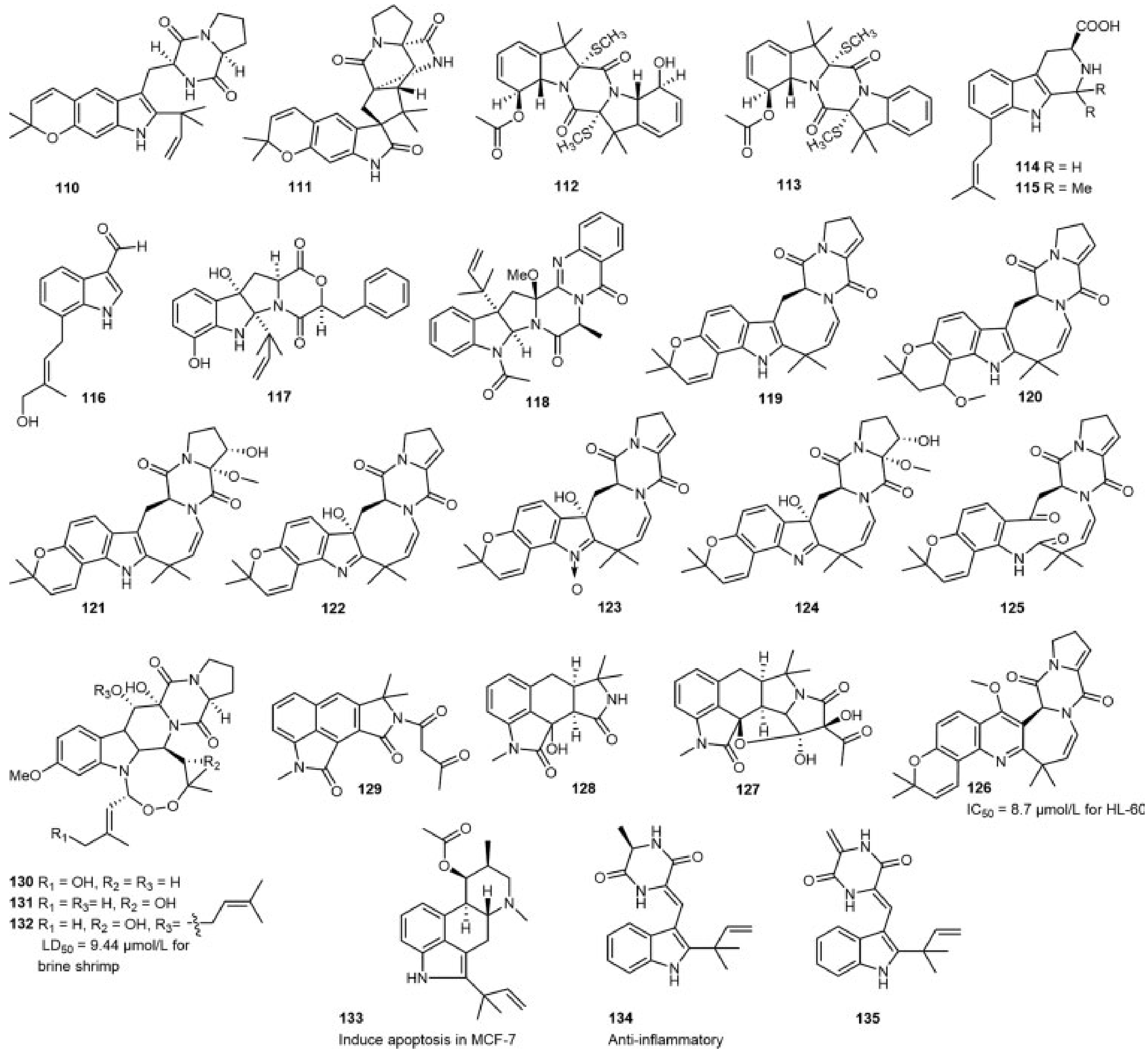

Fig. 7 Chemical structures of prenylated indole alkaloids **110–135**.

acetyladreemin (**118**) were yielded from a marine sediment-derived *Aspergillus* sp. CMB-M081F (►**Fig. 7**). Compound **117** exhibited significant inhibitory activity against drug efflux mediated by P-glycoprotein in human multidrug-resistant colon cancer cells at the concentration of 20 μmol/L.[61]

Versicamides A–H (**119**–**126**) (►**Fig. 7**), eight new prenylated alkaloids, were produced by the marine fungus *A. versicolor* HDN08–60. Compound **126** presented moderate suppressive effect on HL-60 cells ($IC_{50} = 8.7$ μmol/L), and it showed selective inhibitory function to PTK by further research of target screening.[62]

Speradine F (**127**), a new alkaloid with a rare hexacyclic oxindole ring system, and two new alkaloids bearing a tetracyclic oxindole moiety, speradines G (**128**) and H (**129**), were obtained from a strain of the marine fungus *A. oryzae* (►**Fig. 7**). Unfortunately, these compounds displayed weak cytotoxic function toward the HeLa, HL-60, and K562 cell lines.[63]

Three new indole diketopiperazine peroxides, 24-hydroxyverruculogen (**130**), 26-hydroxyverruculogen (**131**), and 13-*O*-prenyl-26-hydroxyverruculogen (**132**), were produced by the fungus *Penicillium brefeldianum* SD-273 isolated from marine sediment (►**Fig. 7**). Compound **132** exhibited remarkable brine shrimp lethal effect toward *A. salina* ($LD_{50} = 9.44$ μmol/L).[64]

A prenylated indole, fumigaclavine C (**133**) (►**Fig. 7**), was obtained from a marine-derived fungus *A. fumigatus*. This compound induced apoptosis in MCF-7 cells via PI3/Akt and NF-κB signaling, resulting in activating the mitochondrial cell death pathway.[65]

Neoechinulins A (**134**) and B (**135**) (►**Fig. 7**) are two diketopiperazine indole alkaloids which were discovered and identified from the marine fungus *Eurotium* sp. SF-5989. Compounds **134** exhibited antiinflammatory activity by inhibiting the NF-κB and p38 MAPK pathways in LPS-stimulated RAW264.7 macrophages.[66]

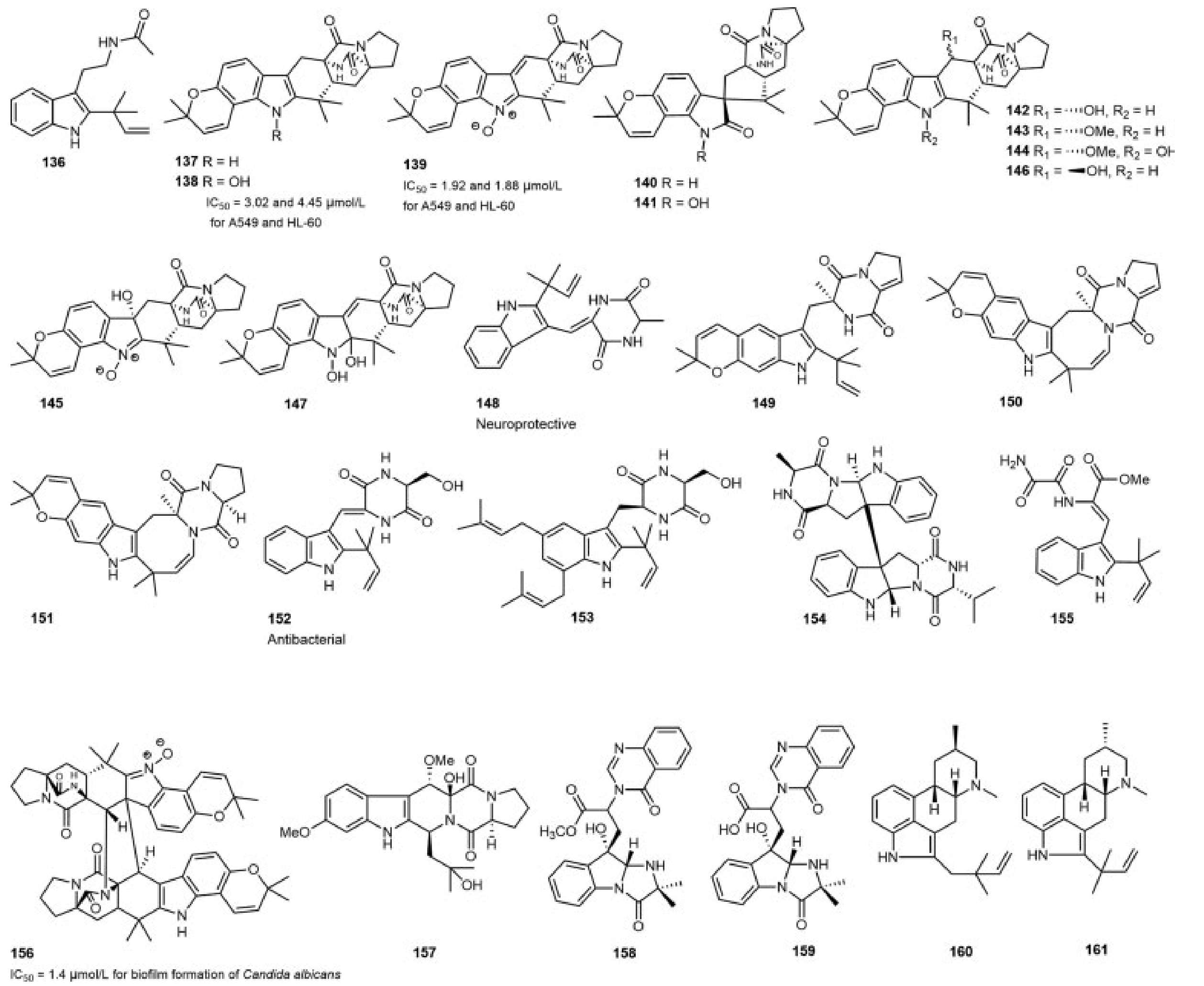

Fig. 8 Chemical structures of prenylated indole alkaloids 136–161.

Brocaeloid C (**136**) (►**Fig. 8**), a new indole alkaloid possessing a C-2 reversed prenylated segment, was harbored from the cultures of *Penicillium brocae* MA-192, a marine fungus isolated from the fresh leaves of the mangrove *Avicennia marina*.[67]

6-*Epi*-stephacidin A (**137**), *N*-hydroxy-6-*epi*-stephacidin A (**138**), and 6-*epi*-avrainvillamide (**139**) (►**Fig. 8**), prenylated alkaloids bearing a unique anti-bi cyclo-[2.2.2]diazaoctane core structure, were obtained from the cultures of marine fungus *Aspergillus taichungensis*. (+)-Versicolamides B and C (**140** and **141**) with a spiro-center, as well as six derivatives (**142** – **147**), were harbored as conversion products of compound **138** through a photo-induced reaction (►**Fig. 8**). Compounds **138** and **139** displayed remarkable cytotoxic effect toward two cell lines, with IC_{50} values of 3.02 and 1.92 μmol/L against A549 cells, 4.45 and 1.88 μmol/L against HL-60 cells, respectively.[68]

An indole alkaloid, named neoechinulin A (**148**) (►**Fig. 8**), which was produced by a marine fungus *Microsporum* sp., exhibited inhibitory effect toward the microglia activation induced by amyloid-*β* oligomer, and the protection of inflammation-mediated toxicity in PC-12 cells, suggesting its potential to be developed as a protective agent for neuroinflammation associated with Alzheimer's disease. Compound **148** also showed an effect of inducing apoptosis in HeLa cells in another biotest.[69,70]

Carneamides A–C (**149**–**151**) (►**Fig. 8**) are three prenylated indole alkaloids that are afforded from the fungus *Aspergillus carneus* KMM 4638 derived from marine environment. However, these compounds showed no *in vitro* antimicrobial and cytotoxic effects.[71]

Cristatumins A–D (**152**–**155**) (►**Fig. 8**), four new indole analogues, were obtained and identified from the culture of the marine alga endophytic fungus *E. cristatum* EN-220. Compound **152** produced antibacterial effect both toward *Escherichia coli* and *S. aureus*.[72]

Waikialoid A (**156**) (►**Fig. 8**), a new dimer of prenylated indole derivative, is produced by a strain of marine fungus *Aspergillus* sp. This molecule exhibits potent inhibitory activity against the biofilm formation of *Candida albicans* (IC_{50} = 1.4 μmol/L). And waikialoid A (**156**) displayed the potential to be developed as a promising lead for the biofilm

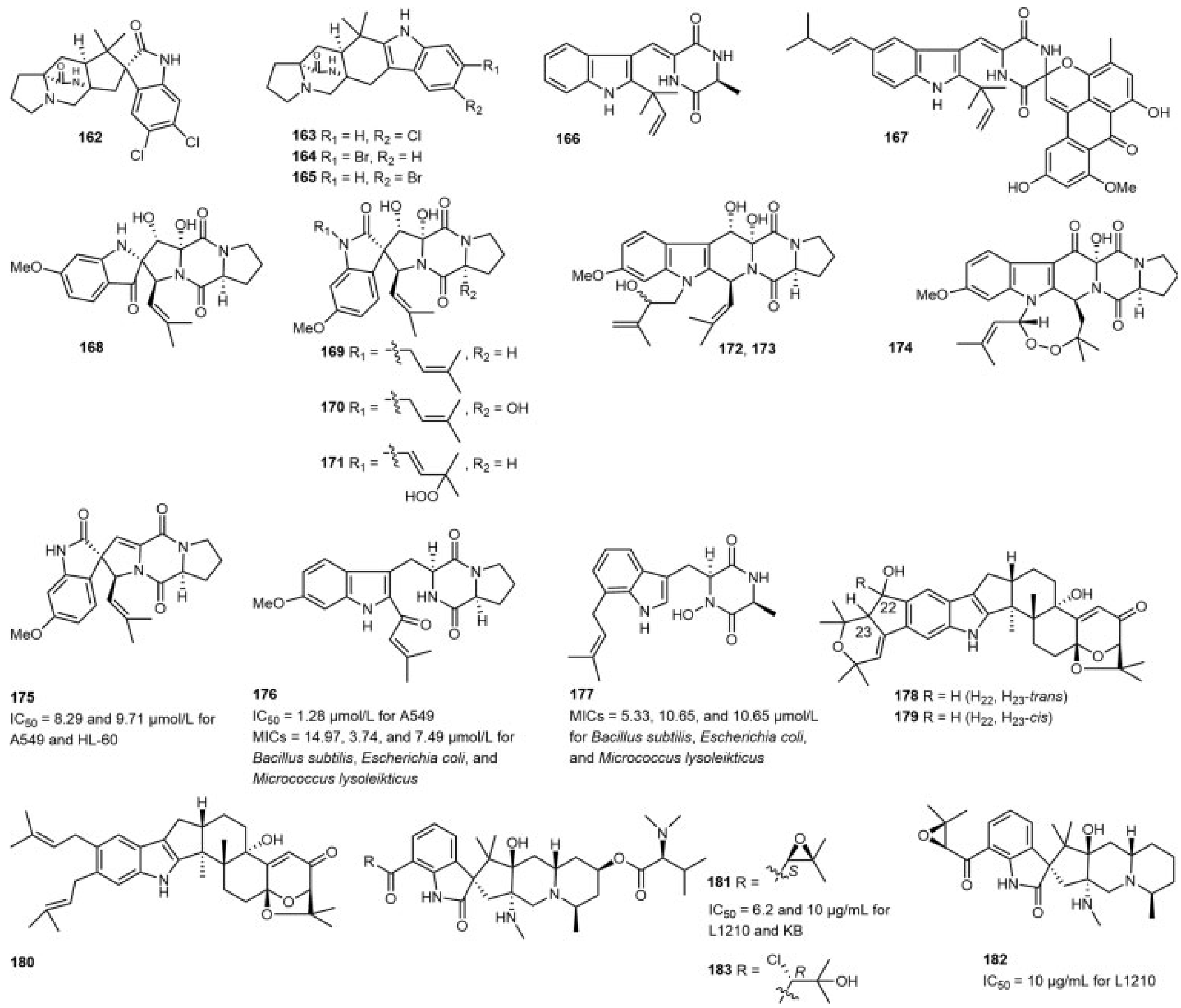

Fig. 9 Chemical structures of prenylated indole alkaloids **162–183**.

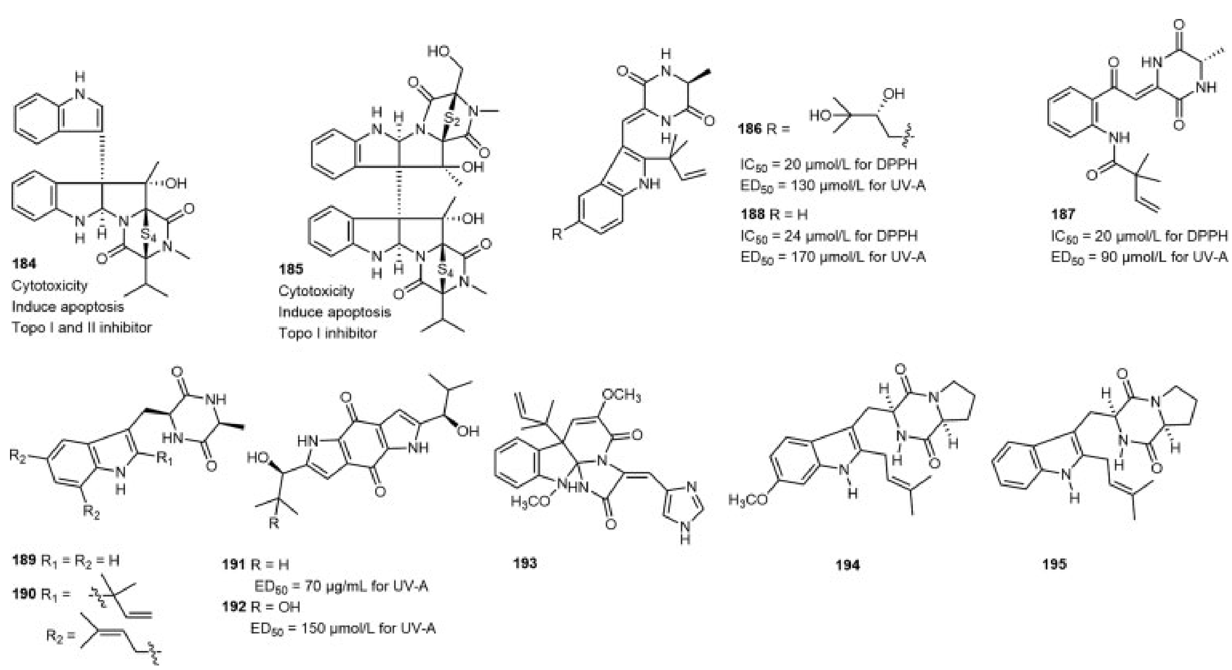

Fig. 10 Chemical structures of prenylated indole alkaloids **184–195**.

inhibitors in combination with antibiotics for this metabolite, and showed no cytotoxicity toward fungi or human cells (200 μmol/L).[73]

Cyclotryprostatin E (**157**) (►**Fig. 8**), a new indole diketopiperazine alkaloid, was discovered from the strain of marine fungus *Aspergillus sydowii* SCSIO 00305, which was separated from a healthy tissue of gorgonian coral *Verrucella umbraculum*.[74]

Tryptoquivalines P and Q (**158** and **159**) (►**Fig. 8**) are two new indole alkaloids which were produced by a marine-derived fungal strain *Neosartorya* sp. HN-M-3.[75]

Two new prenylated indole alkaloids, identified as 2-(3,3-dimethylprop-1-ene)-costaclavine (**160**) and 2-(3,3-dimethylprop-1-ene)-epicostaclavine (**161**) (►**Fig. 8**), had been obtained from the culture of marine fungal strain *A. fumigatus*. Compounds **160** and **161** exhibited weak cytotoxicity against P388 cell lines.[76]

Two novel chlorinated prenylated indole alkaloids, (−)-spiromalbramide (**162**) and (+)-isomalbrancheamide B (**163**), and two new brominated derivatives, (+)-malbrancheamide C (**164**) and (+)-isomalbrancheamide C (**165**) (►**Fig. 9**), were discovered from an invertebrate-derived fungal strain *Malbranchea graminicola* assisted by a direct analysis in real time mass spectrometry technique.[77]

A prenylated indole alkaloid, neoechinulin A (**166**) (►**Fig. 9**), was produced by a marine fungus, and exhibited a protected effect toward PC12 cells against the cytotoxicity of 1-methyl-4-phenylpyridinium (MPP^+) and rotenone, two neurotoxins inducing Parkinsonian.[78]

7-*O*-Methylvariecolortide A (**167**) (►**Fig. 9**), a new alkaloid with spirocyclic diketopiperazine ring, was produced by the cultures of fungal strain *E. rubrum* derived from the stems of mangrove *Hibiscus tiliaceus*.[79]

Compound (**168**), spirotryprostatins C–E (**169**–**171**), fumitremorgin B derivatives **172** and **173**, and 13-oxoverruculogen (**174**) (►**Fig. 9**) were seven new prenylated indole diketopiperazine alkaloids, which were obtained and identified from the marine fungus *A. fumigatus* isolated from holothurian. Compounds **171**–**173** exhibited better selectivity toward MOLT-4, HL-60, and A549 than toward other compounds.[80]

Three new prenylated indole alkaloids with an oxaspiro [4.4]lactam core ring system, 6-methoxyspirotryprostatin B (**175**), 18-oxotryprostatin A (**176**), and 14-hydroxyterezine D (**177**), were discovered from the cultures of a marine-derived fungus *A. sydowii* PFW1–13 (►**Fig. 9**). Compounds **175**–**177** showed significant cytotoxic effect toward the A549 cell line (IC_{50} = 8.29, 1.28, and 7.31 μmol/L, respectively). Compound **175** also exhibited weak inhibitory function to HL-60 cells (IC_{50} = 9.71 μmol/L). Compounds **176** and **177** produced potent antimicrobial effect toward *Bacillus subtilis*, *E. coli*, and *Micrococcus lysodeikticus* (MICs = 14.97, 3.74, and 7.49 μmol/L for **176**; MICs = 5.33, 10.65, and 10.65 μmol/L for **177**).[81]

Shearinines D – F (**178**–**180**) (►**Fig. 9**), three new prenylated indole alkaloids, were yielded from the culture of marine fungal strain *P. janthinellum* Biourge. Compounds **178** and **179** could induce apoptosis in HL-60 cells, and **179** also exhibited inhibitory activity against EGF-induced malignant transformation in JB6 P+ Cl 41 cells.[82]

Two new pentacyclic indolinone alkaloids, named citrinadins A and B (**181** and **182**), as well as **181**'s known derivative compound **183** (►**Fig. 9**), were obtained from the marine red alga-derived fungal strain of *Penicillium citrinum*. Compound **181** exhibited growth-inhibitory effect against L1210 and KB cells (IC_{50} = 6.2 and 10 μg/mL); compound **182** displayed modest cytotoxic activity toward L1210 cells (IC_{50} =10 μg/mL).[83,84] Lep F (**184**) and Lep C (**185**) (►**Fig. 10**), two prenylated bisindole alkaloids produced by marine fungal strain of *Leptoshaeria* species, exhibited potent growth suppressive effect toward RPMI8402 and 293 tumor cell lines. And these two compounds also induced apoptosis through suppressing the survival pathway by inactivation of Akt/protein kinase B. What's more, they were remarkable topoisomerase catalytic inhibitors. Compound **185** targets topo I both *in vitro* and *in vivo* and **184** targets both topo I and II *in vitro*.[85,86]

A class of isoechinulin-type indole alkaloids, dihydroxyisoechinulin A (**186**), golmaenone (**187**), neoechinulin A (**188**), *L*-alanyl-*L*-tryptophan anhydride (**189**), and echinulin (**190**) (►**Fig. 10**), bearing isoprenic chains in the indole ring, were obtained from the cultures of marine fungal strain *Aspergillus* sp. Compounds **186** and **188** displayed potent radical scavenging effect toward 1,1-diphenyl-2-picrylhydrazyl (DPPH) (IC_{50} = 20, 20, and 24 μmol/L, respectively), similar to ascorbic acid (positive control, IC_{50} = 20 μmol/L). They also displayed significant ultraviolet (UA)-A protective activity (ED_{50} = 130, 90, and 170 μmol/L, respectively), more potent than oxybenzone (a currently used sunscreen agent, ED_{50} = 350 μmol/L).[87,88]

A new chiral dipyrrolobenzoquinone alkaloid, terreusinone (**191**), was found from the marine algicolous fungus *Aspergillus terreus*. Another new analogue terreusinol (**192**) was produced by biotransformation of terreusinone (**191**) in the co-culture of terreusinone and *Streptomyces* sp. (►**Fig. 10**). These two compounds showed potent UV-A protecting activity (ED_{50} = 70 μg/mL for **191**, and 150 μmol/L for **192**), which were more active than positive control oxybenzone (ED_{50} = 350 μmol/L).[89,90]

Indolyl alkaloids with a prenylated chain, oxaline (**193**) (►**Fig. 10**), was isolated from the extract of the culture of an unidentified fungal strain derived from the marine red alga *Gracilaria verrucosa*.[91]

Tryprostatins A and B (**194** and **195**) (►**Fig. 10**), two new prenylated indole alkaloids, were isolated from a marine fungal strain *A. fumigatus* BM939, which was collected from a sea sediment sample. These two metabolites showed mammalian cell-cycle inhibitory activity.[92]

Diketopiperazine Indole Alkaloids

The diketopiperazine indole alkaloids without a prenylated fragment were included in this section (►**Fig. 11**). The 2,5-diketopiperazine ring is usually a cyclodipeptide that is condensed by two amino acids. In the diketopiperazine indoles, the condensed six-membered ring is formed by tryptophan and another amino acid.[18]

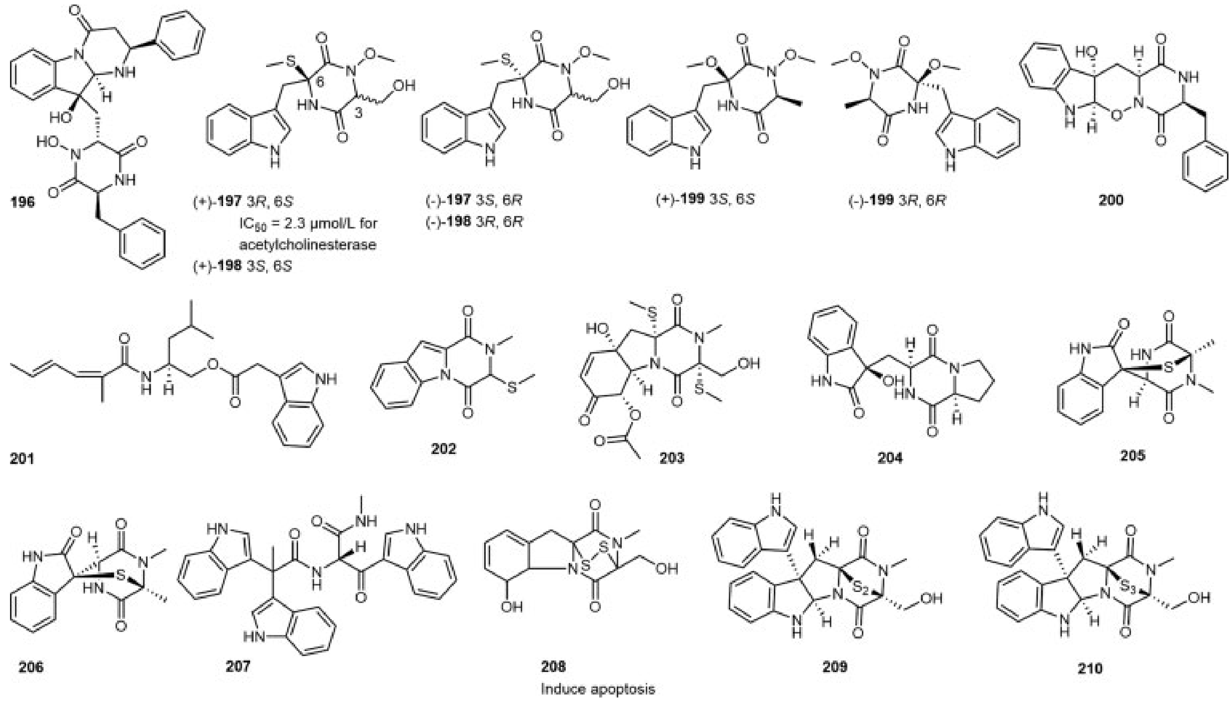

Fig. 11 Chemical structures of diketopiperazine indole alkaloids **196–210**.

Haenamindole (**196**) (►**Fig. 11**) is a diketopiperazine alkaloid with benzyl-hydroxypiperazindione and phenyl-pyrimidoindole fragments, discovered from the marine-derived fungus *Penicillium* sp. KCB12F005. However, this compound displayed no significant cytotoxic and antimicrobial activity.[93]

Three pairs of enantiomers (±)-acrozines A–C ((±)-**197** to (±)-**199**) (►**Fig. 11**) with a novel *N*-methoxy diketopiperazine ring system, were afforded from the marine green alga-derived fungus *Acrostalagmus luteoalbus* TK-43. (+)-Acrozines A ((+)-**197**) displayed better inhibitory activity toward acetylcholinesterase ($IC_{50} = 2.3$ μmol/L) than that of (−)-acrozines A ((−)-**197**) and (±)-**197**.[94]

A new indole diketopiperazine alkaloid, raistrickindole A (**200**) (►**Fig. 11**), bearing a unique pyrazino[1′,2′:2,3]-[1,2]oxazino[6,5-b]indole tetraheterocyclic core ring, was produced by the marine fungal strain of *Penicillium raistrickii* IMB17–034. Compound **200** exhibited inhibitory effects toward the hepatitis C virus.[95]

Dichotomocej D (**201**), a new aliphatic amide, and dichocerazines A and B (**202** and **203**) (►**Fig. 11**), two diketopiperazines, were isolated from the culture of a marine fungal strain of *Dichotomomyces cejpii* F31–1.[96]

A new indole diketopiperazine alkaloid, asperochramide D (**204**) (►**Fig. 11**), was afforded from the culture extract of marine-derived fungus *A. ochraceus*. Compound **204** represents a rare example of indole diketopiperazines possessing a 3-hydroxyl-2-indolone ring system.[39]

A pair of bridged irregularly epimonothiodiketopiperazine diastereomers, pseudellones A and B (**205** and **206**) (►**Fig. 11**), containing a unique 3-indolylglycine and alanine segments, and a new alkaloid pseudellone C (**207**), bearing an unusual nucleus, were obtained from the culture medium of marine fungus *Pseudallescheria ellipsoidea* F42–3.[97]

An indole diketopiperazine alkaloid, gliotoxin (**208**) (►**Fig. 11**), discovered from the marine-derived fungus *Aspergillus* sp., produced apoptosis via the mitochondrial pathway in HeLa and SW1353 cells, resulting in an apoptotic type of cell death.[98]

Luteoalbusins A and B (**209** and **210**) (►**Fig. 11**), two new indole diketopiperazine alkaloids, were yielded from the deep-sea sediment-derived fungus *A. luteoalbus* SCSIO F457. Compounds **209** and **210** exhibited potent cytotoxic activity toward SF-268, MCF-7, NCI-H460, and HepG-2 cell lines.[99]

Quinazoline-Containing Indole Alkaloids

Aspertoryadins A–G (**211**–**217**) are seven new quinazoline-containing indole alkaloids (►**Fig. 12**), produced by the mollusk-derived marine fungus *Aspergillus* sp. HNMF114. Aspertoryadin A (**211**) bears a unique aminosulfonyl group in the molecule, an exceedingly rare moiety in nature. Aspertoryadins F and G (**216** and **217**) were found to have quorum-sensing inhibitory effect to *Chromobacterium violaceum* CV026, both with MIC values of 32 μg/well.[100]

Chaetominine (CHA) (**218**) (►**Fig. 12**), a quinazolinone alkaloid produced by marine crab-derived fungus *A. fumigatus* CY018, showed potent growth-inhibitory activity toward K562 and SW1116 cell lines.[101]

Neofiscalin A (**219**) and fiscalin C (**220**) (►**Fig. 12**) were two quinazolinone alkaloids obtained from *Neosartorya siamensis* KUFA 0017, a marine sponge-associated fungus. They exhibited potential for the development as new leads of anti-Gram-positive bacterial infectious agents especially in multidrug-resistant strains.[102]

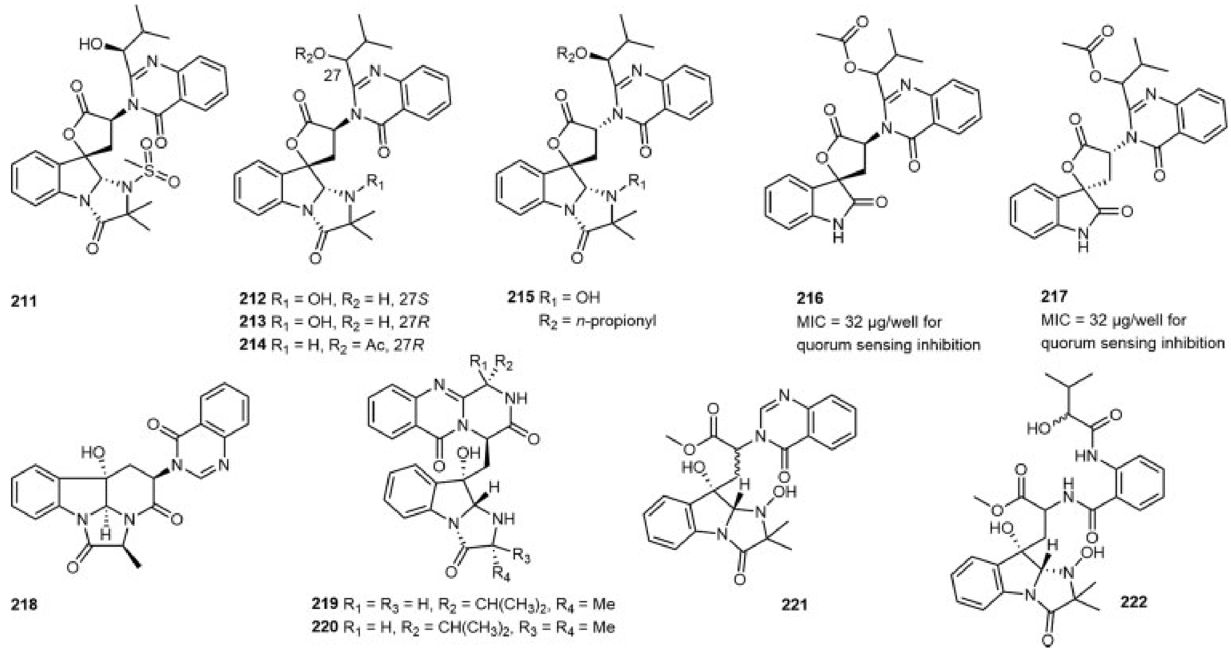

Fig. 12 Chemical structures of quinazoline-containing indole alkaloids **211–222**.

Tryptoquivalines *R* and *S* (**221** and **222**) (►**Fig. 12**) are two new indole quinazolinone alkaloids harbored from the organic extract of a marine fungal strain *Neosartorya* sp. HN-M-3.[103]

Bisindoles

Two new bisindole alkaloids, fusariumindoles A and B (**223** and **224**) (►**Fig. 13**), were yielded from the marine fungus *Fusarium* sp. L1 stimulated by *L*-tryptophan supplementation.[104]

Asterriquinone F (**225**) (►**Fig. 13**), a new bisindole quinone alkaloid, was obtained from the culture of *A. terreus* LM.1.5.[105]

(±)-Fusaspoid A (**226a**/**226b**) (►**Fig. 13**), obtained as a pair of new bisindole alkaloid enantiomers, were produced by the marine fungal strain of *Fusarium* sp. XBB-9. Compounds **226a**/**226b** were inactive in the cytotoxic assay in HCT-15 and RKO cell lines.[106]

Chaetoindolone A (**227**) and chaetoindolone C (**228**) (►**Fig. 13**), two new indole alkaloids, were produced by

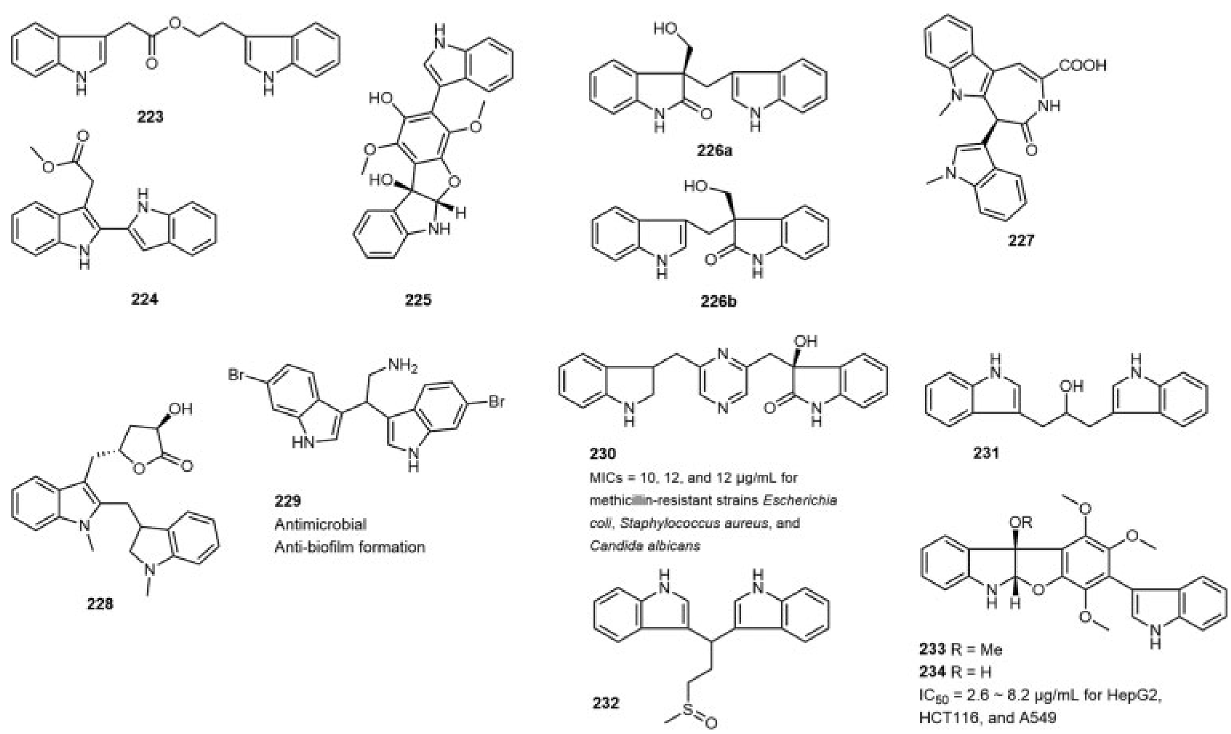

Fig. 13 Chemical structures of bisindole alkaloids **223–234**.

the strain of *Chaetomium globosum* 1C51 through biotransformation, a fungus collected from a marine fish sample. Compound **227** was confirmed to suppress the growth of the rice-pathogenic bacteria *Xanthomonas oryzae* pv. *oryzae (xoo)*.[107]

2,2-Bis(6-bromo-3-indolyl)ethylamine (**229**) (►**Fig. 13**), a bisindole alkaloid derived from a strain of marine fungus, was confirmed to have the potential to be developed as an antibiofilm lead compound for its greatest antimicrobial and biofilm formation inhibitory activity.[108]

A new bisindole alkaloid indolepyrazine A (**230**) (►**Fig. 13**) containing an unpresented indole–pyrazine–oxindole skeleton was obtained from the marine fungal strain of *Acinetobacter* sp. ZZ1275. Compound **230** exhibited significant antimicrobial effects toward methicillin-resistant strains *E. coli*, *S. aureus*, and *C. albicans* (MIC values, 10, 12, and 12 μg/mL, respectively).[109]

Pseudboindoles A and B (**231** and **232**) (►**Fig. 13**), two new bisindole alkaloids, were yielded from the cultures of marine fungus *Pseudallescheria boydii* F44–1 through adding amino acids to the culture medium.[110]

Varioloids C and D (**233** and **234**) (►**Fig. 13**), two indolyl-6,10*b*-dihydro-5*aH*-[1]benzofuro[2,3-*b*]indole alkaloids, were isolated from the strain of *P. variotii* EN-291, a marine alga-derived fungus. Both compounds **233** and **234** displayed cytotoxic activity toward HepG2, HCT116, and A549 cell lines (IC_{50} = 2.6–8.2 μg/mL).[111,112]

Indoloditerpenes

Indoloditerpenes are a series of structurally diverse meroterpenoids featuring with an indole ring connected with a cyclic diterpene backbone, distributed widely both in terrestrial and marine fungi, exhibiting great potential of drug research as lead compounds for their potent insecticidal, antivirus, cytotoxic, and antimicrobial effects.[17,104,113]

Fusaindoterpenes A and B (**235** and **236**) (►**Fig. 14**), two new indoloditerpenes or their derivatives, were afforded from a marine-derived fungal strain of *Fusarium* sp. L1 by adding *L*-tryptophan in culture supplementation. Compound **235** possesses a unique 6/9/6/6/5 heterocyclic ring system. And compound **236** exhibited significant effect toward Zika virus (EC_{50} = 7.5 μmol/L).[104]

Compound **237** (►**Fig. 14**), a new indoloditerpene, was obtained from a culture of marine fungal strain of *A. versicolor* ZZ761. This compound displayed antimicrobial effects against *E. coli* and *C. albicans* (MIC = 20.6 and 22.8 μmol/L, respectively).[113]

Anthcolorin G and H (**238** and **239**) (►**Fig. 14**), two new oxoindoloditerpene epimers, were yielded from the cultures of *A. versicolor*, a mangrove endophytic fungus. Compound **239** produced weak cytotoxicity toward HeLa cells.[114]

Penicindopene A (**240**) (►**Fig. 14**), a new indoloditerpene possessing a rare 3-hydroxyl-2-indolone fragment, was obtained from the strain of *Penicillium* sp. YPCMAC1, a deep-sea-derived fungus. Compound **240** showed moderate

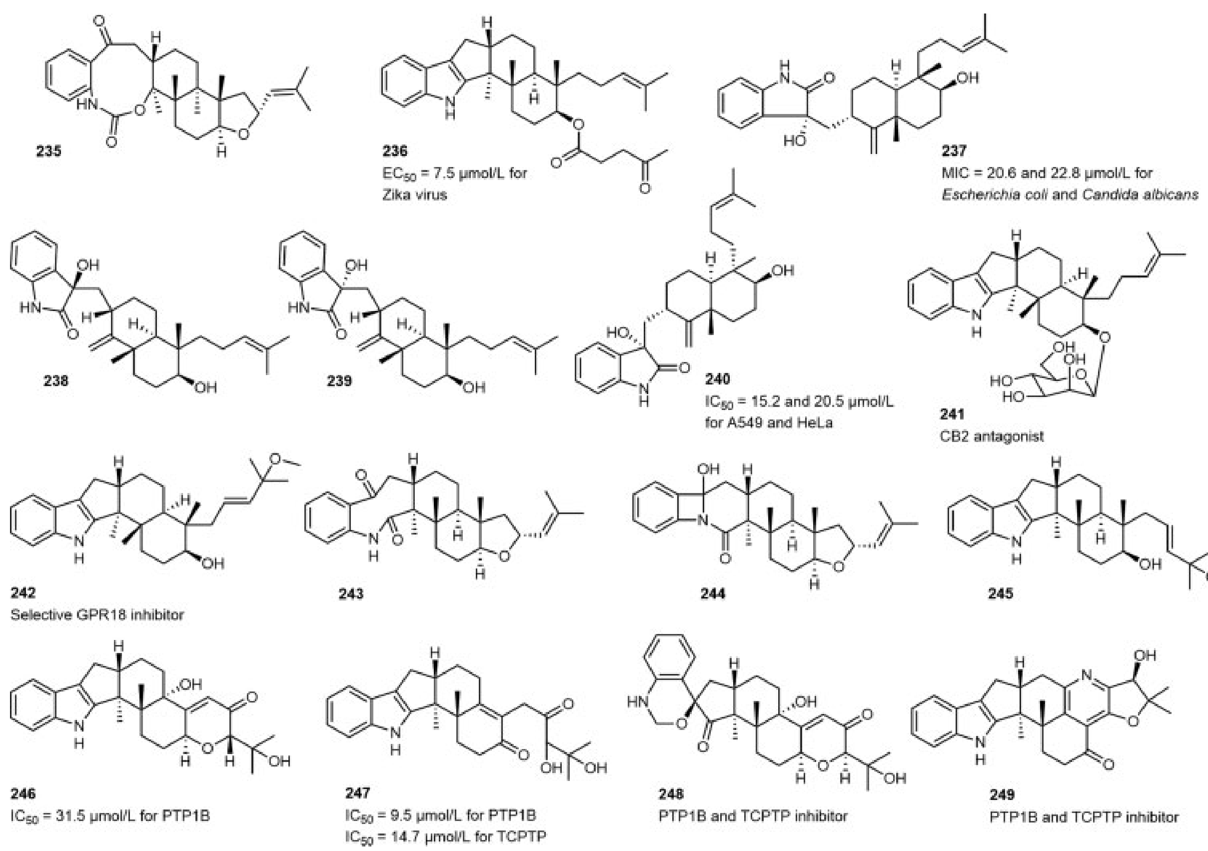

Fig. 14 Chemical structures of indoloditerpenes 235–249.

cytotoxic activity against A549 and HeLa cell lines (IC_{50} = 15.2 and 20.5 μmol/L).[115]

Emindole SB *β*-mannoside (**241**) and 27-*O*-methylasporyzin C (**242**) (►**Fig. 14**), two new indoloditerpenes, were produced by a marine-derived strain of *D. cejpii*. Compound **241** was confirmed to be a CB2 antagonist, and compound **242** was found to be the first indole derivative possessing selective GPR18 inhibitory activity. These two indole derivatives may be investigated as lead molecules for the research of GPR18- and CB receptor-blocking drugs.[116]

Asporyzins A–C (**243**–**245**) (►**Fig. 14**), three new indolo-diterpene derivatives, were found from the cultures of *A. oryzae*, an endophytic fungus derived from the marine red alga *Heterosiphonia japonica*. Compound **245** showed potent inhibitory effect toward *E. coli*.[117]

Epipaxilline (**246**) and penerpene J (**247**) (►**Fig. 14**), two new indoloditerpenes, were obtained from the organic extract of the cultures of marine fungus *Penicillium* sp. KFD28. They displayed inhibitory effects toward PTP1B (IC_{50} = 31.5 and 9.5 μmol/L) and compound **247** also presented suppressive effects against TCPTP (IC_{50} = 14.7 μmol/L).[118]

Penerpenes A–D (**248**–**251**) (►**Figs. 14** and **15**), four unique indoleterpenoids, were obtained and identified from the marine fungal strain of *Penicillium* sp. KFD28. Compounds **248** and **249** exhibited significant inhibitory effect against protein tyrosine phosphatases (PTP1B and TCPTP).[119]

Penerpenes E–I (**252**–**256**) (►**Fig. 15**), five new indoleterpenoids, were obtained from *Penicillium* sp. KFD28, a marine fungus isolated from a bivalve mollusk *Meretrix lusoria*. Compound **252** possesses a rare 6/5/5/6/6/5/5 heptacyclic moiety. Compound **253** is a new carbon skeleton of indolediterpenoid derived from paxilline. Compound **254** contains a unique 6/5/5/6/6/7 hexacyclic skeleton bearing a 1,3-dioxepane ring. Compounds **252**, **253**, and **256** displayed inhibitory effects toward protein tyrosine phosphatase 1B (PTP1B) (IC_{50} = 14, 27, and 23 μmol/L, respectively).[120]

Penijanthines C and D (**257** and **258**) (►**Fig. 15**), two new indolediterpenoid derivatives, were obtained from the cultures of a marine-derived fungal strain *P. janthinellum*. These two compounds exhibited potent antivibrio effect toward three pathogenic *Vibrio* spp. (MIC = 3.1–50.0 μmol/L).[121]

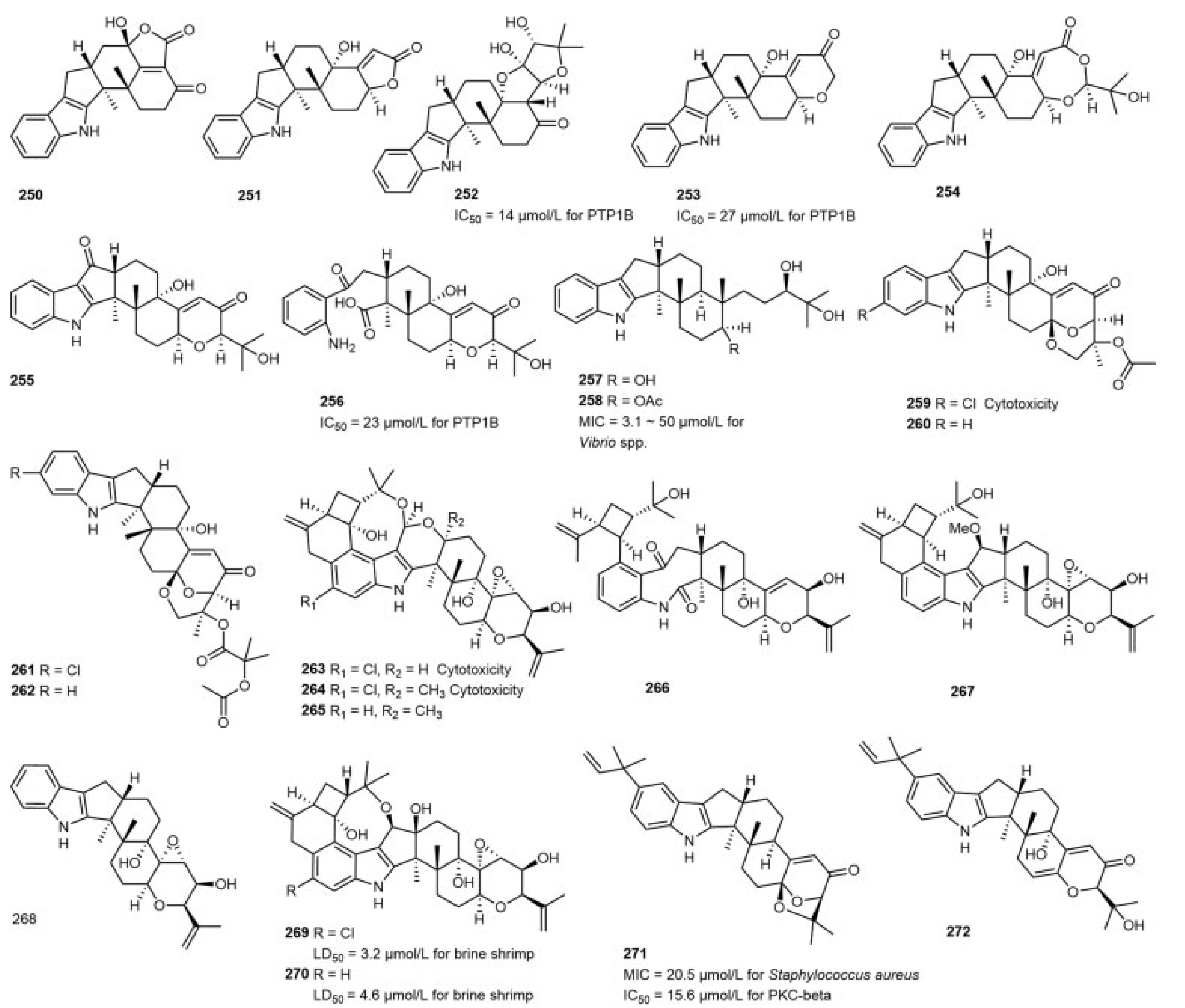

Fig. 15 Chemical structures of indoloditerpenes **250**–**272**.

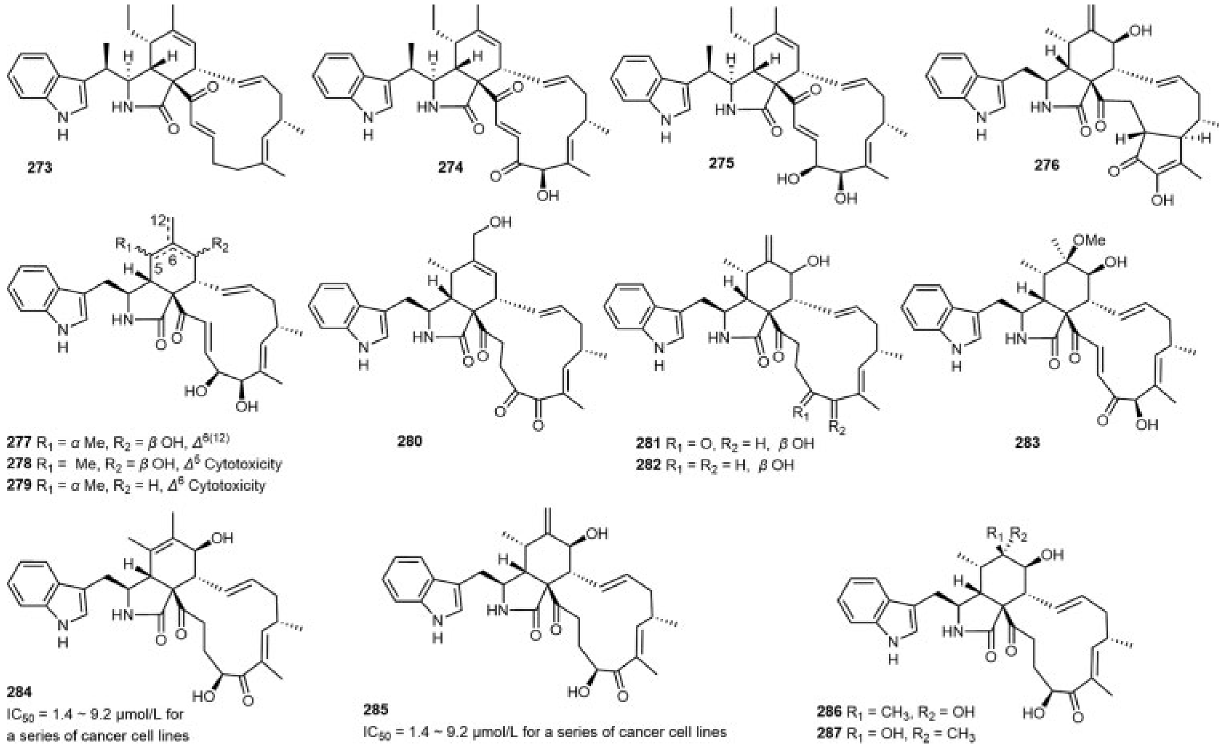

Fig. 16 Chemical structures of cytochalasans **273–287**.

Asperindoles A–D (**259**–**262**) (►**Fig. 15**), four new indolediterpene alkaloids, were produced by the cultures of a marine ascidian-derived fungal strain *Aspergillus* sp. Asperindoles C and D (**261** and **262**) bear an unusual 2-hydroxyisobutyric acid (2-HIBA) moiety, which is very rare in natural products. Compound **259** showed cytotoxic effect toward PC-3 and 22Rv1 cells that are resistant to hormone therapy, as well as human prostate cancer cells that are sensitive to hormone therapy, and apoptosis-induced activity in the above-mentioned cells.[122]

Rhizovarins A–F (**263**–**268**) (►**Fig. 15**), six new indolediterpenes, were discovered by a genome-mining method from the strain of *Mucor irregularis* QEN-189, a marine fungus derived from the mangrove plant *Rhizophora stylosa*. Among these molecules, compounds **263**–**265** contain the most complex and unique structure of the indolediterpenes, with a rare acetal linked to a hemiketal or a ketal forming a novel 4,6,6,8,5,6,6,6,6-fused indole–diterpene skeleton. Compounds **263** and **264** displayed inhibitory effect toward A-549 and HL-60 cancer cell lines.[123]

19-Hydroxypenitrem A (**269**) and 19-hydroxypenitrem E (**270**) (►**Fig. 15**), two new chlorinated indole-diterpenoids, were yielded from the marine strain of *Aspergillus nidulans* EN-330, which was isolated from red alga *Polysiphonia scopulorum* var. *villum*. Compounds **269** and **270** showed cytotoxicity toward brine shrimp (LD_{50} = 3.2 and 4.6 μmol/L). In addition, compound **269** displayed moderate antimicrobial function against four pathogens *Edwardsiella tarda*, *Vibrio anguillarum*, *E. coli*, and *S. aureus*.[124]

Compounds **271** and **272** (►**Fig. 15**), two new indolediterpenoids, were harbored from the cultures of the marine-derived fungal strain of *Aspergillus flavus* OUCMDZ-2205. Compound **271** presented antibacterial effect toward *S. aureus* (MIC = 20.5 μmol/L). And both compounds could arrest the cell cycle in the S phase at 10 μmol/L in A549 cell lines. Compound **271** exhibited PKC-β inhibitory activity (IC_{50} = 15.6 μmol/L).[125]

Cytochalasans

Chaetoglobosin-510 (**273**), -540 (**274**), and -542 (**275**), three cytochalasin-type alkaloids (►**Fig. 16**), were obtained from the cultures of the marine fungal strain of *Phomopsis asparagi*. Chaetoglobosin-542 (**275**) produced antimicrofilament effect and cytotoxic activity against leukemia cancer and murine colon cell lines.[126]

Cytoglobosins A–G (**276**–**282**) (►**Fig. 16**), seven new cytochalasin-type alkaloids, were obtained from the cultures of marine green alga-derived fungus *C. globosum* QEN-14. Compounds **278** and **279** exhibited cytotoxicity toward the A549 tumor cell line.[127]

A new cytochalasans derivative, 6-*O*-methyl-chaetoglobosin Q (**283**), along with several known analogues, was produced by a coral-associated fungus *C. globosum* C2F17. The known congeners chaetoglobosins E (**284**) and Fex (**285**) (►**Fig. 16**), exhibited significant antiproliferative activity toward a series of cancer cell lines (IC_{50} = 1.4–9.2 μmol/L).[128]

Cytoglobosins H and I (**286** and **287**) (►**Fig. 16**), two new cytochalasans derivatives, as well as several known congeners, were obtained from a deep-sea sediment-derived marine fungal strain of *C. globosum*. The known compound chaetoglobosin E (**284**) displayed potent growth-inhibitory effect against LNCaP and B16F10 cell lines (IC_{50} = 0.62 and 2.78 μmol/L, respectively). Besides, compound **284** suppressed the growth of LNCaP cells via inducing apoptosis.[129]

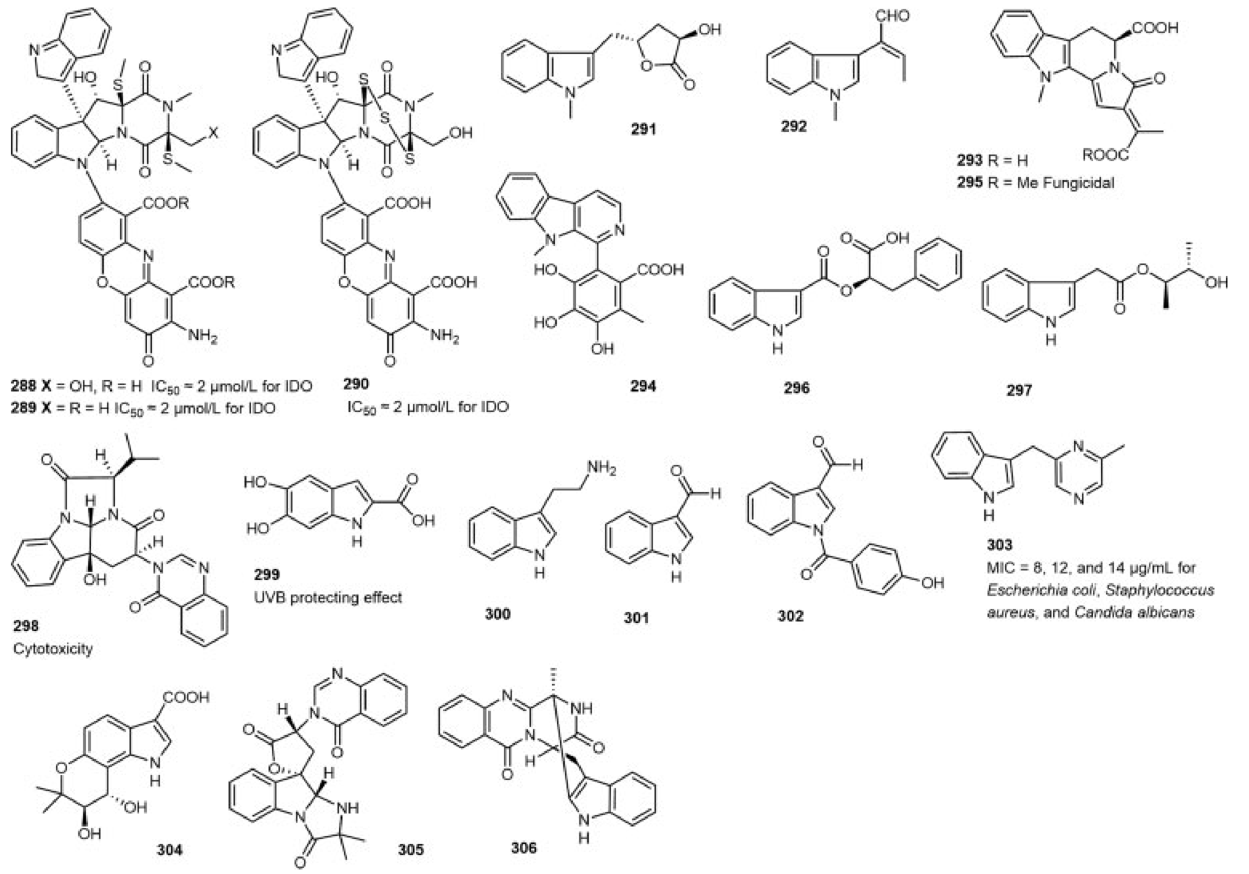

Fig. 17 Chemical structures of other indole alkaloids 288–306.

Other Indole Alkaloids

Plectosphaeroic acids A–C (**288**–**290**) (►**Fig. 17**), three new plectosphaeroic acid derivatives, were obtained from the laboratory cultures of the fungus *Plectosphaerella cucumerina* collected from marine sediments. They were evaluated and presented significant inhibitory activity against indoleamine-2,3-dioxygenase (IDO), with IC_{50} values of 2 μmol/L.[130]

Chaetoindolone B (**291**), chaetoindolone D (**292**), 19-*O*-demethylchaetogline A (**293**), 20-*O*-demethylchaetogline F (**294**), and chaetogline A (**295**) (►**Fig. 17**) are five new indole alkaloids obtained from the marine fungus *C. globosum* 1C51, through biotransformation induced by 1-methyl-*L*-tryptophan (1-MT) supplemented in the culture medium. Chaetogline A (**295**) showed fungicidal effect toward a pathogenic fungus *Sclerotinia sclerotiorum*, the cause of rape sclerotinia rot, indicating the potential agrochemical significance of indole alkaloids.[107]

Two new indole alkaloids, Fusariumindoles C (**296**) and (±)-isoalternatine A (**297**) (►**Fig. 17**), were produced by the marine fungus *Fusarium* sp. L1, induced by the *L*-tryptophan added in the culture condition. However, they exhibited no significant effect against Zika virus.[104]

A known marine indole alkaloid derivative isolated from a fungal strain of *Neosartorya pseudofischeri*, isochaetominine C (**298**) (►**Fig. 17**), displayed potent cytotoxic activity toward the Sf9 cells.[52]

5,6-Dihydroxyindole-2-carboxylic acid (DHICA) (**299**) was yielded from the cultures of marine fungus *A. nidulans* (►**Fig. 17**). The simple indole alkaloid **299** showed remarkable UV-B protecting effect both *in vivo* and *in vitro* assays, presenting the potential as a sun-protective agent added to sunscreen cream.[131]

Two simple indole alkaloids, tryptamine (**300**) and indole-3-carbaldehyde (**301**) (►**Fig. 17**), were expressed by the marine-derived fungus *Penicillium* species. Compound **301** showed modest antimicrobial activity.[132]

1-(4-Hydroxybenzoyl)indole-3-carbaldehyde (**302**) (►**Fig. 17**), a new indole alkaloid with an aldehyde group, was isolated from a strain of marine fungus *Engyodontium album* IVB1b. It was inactive both in cytotoxic and antimicrobial tests.[133]

Indolepyrazine B (**303**) (►**Fig. 17**), a new indole alkaloid, was harbored from the culture medium of marine-derived fungus *Acinetobacter* sp. ZZ1275. It displayed antimicrobial effect against *E. coli*, *S. aureus*, and *C. albicans*, three methicillin-resistant pathogenic strains, with MIC values of 8, 12, and 14 μg/mL, respectively.[109]

A new indole carboxylic acid, nigrospin A (**304**) (►**Fig. 17**), was obtained from the cultures of the marine fungal strain *Nigrospora oryzae* SCSGAF 0111.[134]

Compound **305** (►**Fig. 17**) was a new tryptoquivaline derivative isolated from the marine alga-derived fungus *N.*

takakii KUFC 7898. In the antimicrobial biotests, it exhibited no significant activity.[55]

Fumiquinazoline K (**306**) (►**Fig. 17**), a new indole alkaloid, had been obtained from a strain of marine fungus *A. fumigatus* KMM 4631, which was derived from the soft coral *Sinularia* sp.[135]

Conclusion

In this review, we have investigated and summarized comprehensively the chemical diversity and biological activity of marine fungal indole alkaloids from 1995 to early 2021, covering a total of 306 indole derivatives. The chemical types of these marine fungal indole alkaloids can be mainly classified to prenylated indoles, diketopiperazine indoles, bisindoles, quinazoline-containing indoles, indole-diterpenoids, and others. As shown in ►**Fig. 18**, the prenylated indoles represent the predominant marine fungal alkaloids (63.5%) exhibiting high structural diversity, especially the prenylated tryptophan diketopiperazine skeleton. As for the sources, the species of *Aspergillus* (41.2%) and *Penicillium* (19.2%) are the two main producing strains of marine fungal indoles. As shown in ►**Table 1**, the natural indole metabolites from marine fungi displayed excellent cytotoxic, antimicrobial, sun-protective, antiinflammatory, antivirus, neuroprotective, kinase inhibitory, crop-protective, and brine shrimp lethal activities. They presented great potential of research as new lead structures for the development of new drugs, especially GPR18-selective antagonist **88**, biofilm inhibitor **156**, anti-multidrug-resistant bacterial molecules **219** and **220**, and GPR18- and CB antagonists **241** and **242**.

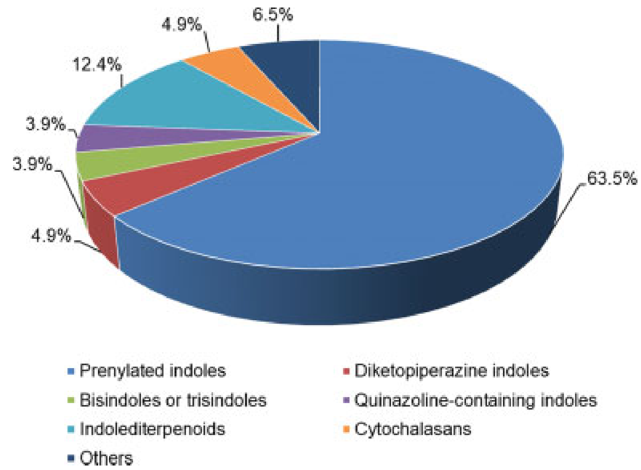

Fig. 18 Percentage of structural types of marine fungal indole alkaloids.

Table 1 The indole alkaloids from marine fungus covering from 1995 to the early 2021

Compounds	Sources	Bioactivities	Ref.
Notoamides A–D (**1–4**)	*Aspergillus* sp.	Cytotoxicity (**1–3**)	20
Notoamide E (**5**)	*Aspergillus* sp.		21,22
21-Hydroxystephacidin (**6**)	*Aspergillus ostianus*		23
Notoamides F–K (**7–12**)	*Aspergillus* sp.	Cytotoxicity (**10**)	24,25
(−)-Versicolamide B (**13**) and notoamides L–N (**14–16**)	*Aspergillus* sp.		26
Notoamides O–Q (**17–19**)	*Aspergillus* sp.		27,28
17-*Epi*-notoamides Q (**20**) and M (**21**)	*Aspergillus* sp.		29,30
Notoamides W–Z (**22–25**), 19-*epi*-notoamide R (**26**), stephacidin A (**27**), avrainvillamide (**28**), stephacidin B (**29**)	*Aspergillus ochraceus*	Cytotoxicity (**8**, **25**, **26**)	31
Asperthrins A–F (**30–35**)	*Aspergillus* sp. YJ191021	Cytotoxicity (**30**)	32
Paraherquamide J (**36**)	*Penicillium janthinellum* HK1–6	Inactive	33
Waikikiamides A–C (**37–39**)	*Aspergillus* sp. FM242	Cytotoxicity (**37**, **39**)	34
Di-6-hydroxydeoxybrevianamide E (**40**) and dinotoamide J (**41**)	*Aspergillus austroafricanus* Y32–2	Proangiogenic effect (**40** and **41**)	35
Spirotryprostatin G (**42**), cyclotryprostatins F and G (**43** and **44**)	*Penicillium brasilianum* HBU-136	Cytotoxicity (**42–44**)	36
17-Hydroxynotoamide D (**45**), 17-*O*-ethylnotoamide M (**46**), 10-*O*-acetylsclerotiamide (**47**), 10-*O*-ethylsclerotiamide (**48**), 10-*O*-ethylnotoamide R (**49**)	*Aspergillus sulphureus* KMM 4640 and *Isaria felina* KMM 4639	Cytotoxicity (**46**)	37
Asperversiamides A–H (**50–57**)	*Aspergillus versicolor*	Antiinflammatory (**56**)	38

Table 1 (*Continued*)

Compounds	Sources	Bioactivities	Ref.
Asperochramides A–C (**58–60**)	*Aspergillus ochraceus*	Antiinflammatory (**58**)	39
Eurotiumins A–D (**61–64**)	*Eurotium* sp. SCSIO F452	Radical scavenging (**63**)	40
Taichunamide H (**65**)	*Aspergillus versicolor*	No activity	41
Mangrovamides D–G (**66–69**)	*Penicillium* sp. SCSIO041218	No antiallergic effect	42
SF5280–415 (**70**), SF5280–451 (**71**)	*Aspergillus* sp. SF-5280	PTP1B inhibition	43
Brevicompanine B (**72**) and verrucofortine (**73**)	*Penicillium* sp. NH-SL	Cytotoxicity (**73**)	44
N-(40-hydroxyprenyl)-cyclo(alanyltryptophyl) (**74**), isovariecolorin I (**75**), 30-hydroxyechinulin (**76**), 29-hydroxyechinulin (**77**)	*Eurotium cristatum* EN-220	Brine shrimp lethality (**75**)	45
Penicimutamides D and E (**78** and **79**)	*Penicillium purpurogenum* G59	Cytotoxicity	46
4,3-Hydroxysperadine A (**80**)	*Aspergillus oryzae* HMP-F28		47
Meleagrin (**81**)	*Emericella dentata* Nq45	Cytotoxicity, antibacterial	48
Misszrtine A (**82**)	*Aspergillus* sp. SCSIO XWS03F03	Cytotoxicity	49
Cycloexpansamines A (**83**) and B (**84**)	*Penicillium* sp. SF-5292		50
Penioxamide A (**85**)	*Penicillium oxalicum* EN-201	Brine shrimp lethality	51
Fumitremorgin C (**86**), 12,13-dihydroxy-fumitremorgin C (**87**)	*Aspergillus* sp. BRF 030	Cytotoxicity	52
Amauromine (**88**)	*Auxarthron reticulatum*	Antagonists of GPR18	53
Spirotryprostatin K (**89**)	*Aspergillus fumigatus*		54
Takakiamide (**90**)	*Neosartorya takakii* KUFC 7898	No antibacterial effect	55
Rubrumazines A–C (**91–93**)	*Eurotium rubrum* MA-150	Brine shrimp lethality (**92**)	56
Rubrumlines A–O (**94–108**), neoechinulin B (**109**)	*Eurotium rubrum*	Anti-influenza virus (**109**)	57
Dihydrocarneamide A (**110**) and iso-notoamide B (**111**)	*Paecilomyces variotii* EN-291	Cytotoxicity	58
Cladosporin A (**112**), cladosporin B (**113**)	*Cladosporium* sp.	Cytotoxicity	59
Penipalines A–C (**114–116**)	*Penicillium paneum* SD-44	Cytotoxicity	60
Shornephine A (**117**) and 15b-*β*-methoxy-5-*N*-acetyladreemin (**118**)	*Aspergillus* sp. CMB-M081F	Inhibitory against drug efflux	61
Versicamides A–H (**119** – **126**)	*Aspergillus versicolor* HDN08–60	Cytotoxicity	62
Speradines F–H (**127** – **129**)	*Aspergillus oryzae*	Cytotoxicity	63
24-Hydroxyverruculogen (**130**), 26-hydroxyverruculogen (**131**), and 13-*O*-prenyl-26-hydroxyverruculogen (**132**)	*Penicillium brefeldianum* SD-273	Brine shrimp lethality (**132**)	64
Fumigaclavine C (**133**)	*Aspergillus fumigatus*	Apoptosis	65
Neoechinulins A (**134**) and B (**135**)	*Eurotium* sp. SF-5989	Antiinflammatory (**134**)	66
Brocaeloid C (**136**)	*Penicillium brocae* MA-192		67
6-*Epi*-stephacidin A (**137**), *N*-hydroxy-6-*epi*-stephacidin A (**138**), 6-*epi*-avrainvillamide (**139**), (+)-versicolamides B and C (**140** and **141**), compounds **142–147**	*Aspergillus taichungensis*	Cytotoxicity (**138** and **139**)	68
Neoechinulin A (**148**)	*Microsporum* sp.	Apoptosis, neuroinflammatory modulation	69,70

(*Continued*)

Table 1 (*Continued*)

Compounds	Sources	Bioactivities	Ref.
Carneamides A–C (**149–151**)	*Aspergillus carneus* KMM 4638	No effects	71
Cristatumins A–D (**152–155**)	*Eurotium cristatum* EN-220	Antibacterial effect (**152**)	72
Waikialoid A (**156**)	*Aspergillus* sp.	Biofilm inhibitors	73
Cyclotryprostatin E (**157**)	*Aspergillus sydowii* SCSIO 00305		74
Tryptoquivalines P and Q (**158** and **159**)	*Neosartorya* sp.HN-M-3		75
2-(3,3-Dimethylprop-1-ene)-costaclavine (**160**) and 2-(3,3-dimethylprop-1-ene)-epicostaclavine (**161**)	*Aspergillus fumigatus*	Cytotoxicity	76
(−)-Spiromalbramide (**162**), (+)-isomalbrancheamide B (**163**), (+)-malbrancheamide C (**164**), (+)-isomalbrancheamide C (**165**)	*Malbranchea graminicola*		77
Neoechinulin A (**166**)		Neuroprotection	78
7-*O*-Methylvariecolortide A (**167**)	*Eurotium rubrum*		79
Compound (**168**), spirotryprostatins C–E (**169–171**), fumitremorgin B derivatives **172** and **173**, and 13-oxoverruculogen (**174**)	*Aspergillus fumigatus*	Cytotoxicity (**171–173**)	80
6-Methoxyspirotryprostatin B (**175**), 18-oxotryprostatin A (**176**), and 14-hydroxyterezine D (**177**)	*Aspergillus sydowii* PFW1–13	Cytotoxicity (**175–177**) Antimicrobial effect (**176** and **177**)	81
Shearinines D–F (**178–180**)	*Penicillium janthinellum* Biourge	Antimalignant transformation	82
Citrinadins A, B (**181** and **182**) and derivative **183**	*Penicillium citrinum*	Cytotoxicity	83,84
Lep F (**184**) and Lep C (**185**)	*Leptoshaeria* sp.	Topo inhibitioncytotoxicity	85,86
Dihydroxyisoechinulin A (**186**), golmaenone (**187**), neoechinulin A (**188**), L-alanyl-L-tryptophan anhydride (**189**), and echinulin (**190**)	*Aspergillus* sp.	Ultraviolet-A protective activityradical scavenging effect	87,88
Terreusinone (**191**), terreusinol (**192**)	*Aspergillus terreus* (**191**) *Streptomyces sp.* (**192**)	UV-A protective activity	89,90
Oxaline (**193**)	Unidentified fungal strain		91
Tryprostatins A and B (**194** and **195**)	*Aspergillus fumigatus* BM939	Cell cycle inhibitory activity	92
Haenamindole (**196**)	*Penicillium* sp. KCB12F005	No cytotoxic and antimicrobial activity	93
(±)-Acrozines A-C ((±)-**197**–(±)-**199**)	*Acrostalagmus luteoalbus* TK-43	Acetylcholinesterase inhibition ((+)-**197**)	94
Raistrickindole A (**200**)	*Penicillium raistrickii* IMB17–034	Anti-hepatitis C virus	95
Dichotomocej D (**201**), dichocerazines A and B (**202** and **203**)	*Dichotomomyces cejpii* F31–1		96
Asperochramides D (**204**)	*Aspergillus ochraceus*		39
Pseudellones A–C (**205–207**)	*Pseudallescheria ellipsoidea*		97
Gliotoxin (**208**)	*Aspergillus* sp.	Apoptosis	96
Luteoalbusins A and B (**209** and **210**)	*Acrostalagmus luteoalbus* SCSIO F457	Cytotoxicity	99
Aspertoryadins A–G (**211–217**)	*Aspergillus* sp. HNMF114	Antibacterial activity (**216** and **217**)	100

Table 1 (*Continued*)

Compounds	Sources	Bioactivities	Ref.
Chaetominine (CHA) (**218**)	*Aspergillus fumigatus* CY018	Cytotoxicity	101
Neofiscalin A (**219**) and fiscalin C (**220**)	*Neosartorya siamensis* KUFA 0017	Antibacterial activity	102
Tryptoquivalines *R* and *S* (**221** and **222**)	*Neosartorya* sp. HN-M-3		103
Fusariumindoles A and B (**223** and **224**)	*Fusarium* sp. L1		104
Asterriquinone F (**225**)	*Aspergillus terreus* LM.1.5		105
(±)-Fusaspoid A (**226a**/**226b**)	*Fusarium* sp. XBB-9	Inactive	106
Chaetoindolone A (**227**) and chaetoindolone C (**228**)	*Chaetomium globosum* 1C51	Antibacterial activity	107
2,2-Bis(6-bromo-3-indolyl) ethylamine (**229**)		Antibiofilm formation	108
Indolepyrazines A (**230**)	*Acinetobacter* sp. ZZ1275	Antimicrobial effect	109
Pseudboindoles A and B (**231** and **232**)	*Pseudallescheria boydii* F44–1		110
Varioloids C and D (**233** and **234**)	*Paecilomyces variotii* EN-291	Cytotoxicity	111,112
Fusaindoterpenes A and B (**235** and **236**)	*Fusarium* sp. L1	Anti-Zika virus	104
Compound **237**	*Aspergillus versicolor* ZZ761	Antimicrobial effect	113
Anthcolorin G and H (**238** and **239**)	*Aspergillus versicolor*	Cytotoxicity	114
Penicindopene A (**240**)	*Penicillium* sp. YPCMAC1	Cytotoxicity	115
Emindole SB *β*-mannoside (**241**) and 27-*O*-methylasporyzin C (**242**)	*Dichotomomyces cejpii*	CB2 antagonist (**241**) GPR18 antagonist (**242**)	116
Asporyzins A–C (**243–245**)	*Aspergillus oryzae*	Antimicrobial effect (**245**)	117
Epipaxilline (**246**) and penerpene J (**247**)	*Penicillium* sp. KFD28	PTP1B inhibition (**246** and **247**) TCPTP inhibition (**247**)	118
Penerpenes A–D (**248–251**)	*Penicillium* sp. KFD28	PTP1B and TCPTP inhibition (**248** and **249**)	119
Penerpenes E–I (**252–256**)	*Penicillium* sp. KFD28	PTP1B inhibition (**252**, **253**, and **256**)	120
Penijanthines C and D (**257** and **258**)	*Penicillium janthinellum*	Antivibrio effect	121
Asperindoles A–D (**259–262**)	*Aspergillus* sp.	Cytotoxicity and apoptosis (**259**)	122
Rhizovarins A–F (**263–268**)	*Mucor irregularis* QEN-189	Cytotoxicity (**263** and **264**)	123
19-Hydroxypenitrem A (**269**) and 19-hydroxypenitrem E (**270**)	*Aspergillus nidulans* EN-330	Brine shrimp lethality (**269** and **270**) Antimicrobial activity (**269**)	124
Compounds **271** and **272**	*Aspergillus flavus* OUCMDZ-2205	Antibacterial effect (**271**) PKC-*β* inhibitory activity (**271**)	125
Chaetoglobosin-510 (**273**), -540 (**274**), and -542 (**275**)	*Phomopsis asparagi*	Antimicrofilament effect (**275**) Cytotoxicity (**275**)	126
Cytoglobosins A–G (**276–282**)	*Chaetomium globosum* QEN-14	Cytotoxicity (**278** and **279**)	127
6-*O*-Methyl-chaetoglobosin Q (**283**), chaetoglobosins E (**284**) and Fex (**285**)	*Chaetomium globosum* C2F17	Cytotoxicity (**284** and **285)**	128
Cytoglobosins H and I (**286** and **287**), chaetoglobosin E (284)	*Chaetomium globosum*	Cytotoxicity and apoptosis (**284)**	129
Plectosphaeroic acids A–C (**288–290**)	*Plectosphaerella cucumerina*	IDO inhibition	130
	Chaetomium globosum 1C51	Fungicidal effect (**295**)	107

(*Continued*)

Table 1 (*Continued*)

Compounds	Sources	Bioactivities	Ref.
Chaetoindolone B (**291**), chaetoindolone D (**292**), 19-*O*-demethylchaetogline A (**293**), 20-*O*-demethylchaetogline F (**294**), and chaetogline A (**295**)			
Fusariumindoles C (**296**) and (±)-isoalternatine A (**297**)	*Fusarium* sp. L1	Inactive against Zika virus	104
Isochaetominine C (**298**)	*Neosartorya pseudofischeri*	Cytotoxicity	52
5,6-Dihydroxyindole-2-carboxylic acid (DHICA) (**299**)	*Aspergillus nidulans*	UVB protecting effect	131
Tryptamine (**230**) and indole-3-carbaldehyde (**231**)	*Penicillium* sp.	Antimicrobial activity (**231**)	132
1-(4-Hydroxybenzoyl)indole-3-carbaldehyde (**302**)	*Engyodontium album* IVB1b		133
Indolepyrazines B (**303**)	*Acinetobacter* sp. ZZ1275	Antimicrobial effect	109
Nigrospin A (**304**)	*Nigrospora oryzae* SCSGAF 0111		134
Compound **305**	*Neosartorya takakii* KUFC 7898		55
Fumiquinazoline K (**306**)	*Aspergillus fumigatus* KMM 4631		135

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Conflict of Interest

The authors declare no conflict of interest.

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