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Review

"Marine Rule": discovery of marine natural small molecule drug leads in China in the past decade

Xinqi Chen[a,c,Δ], Xi Zhang[b,Δ], Chunmei Chen[a,c], Jianglian She[a,c], Yonghong Liu[a,*], Cuixian Zhang[d,*], Jian Cai[a,c,*], Lan Tang[b,*], Xuefeng Zhou[a,c,*]

[a] *State Key Laboratory of Tropical Oceanography/Guangdong Key Laboratory of Marine Materia Medica, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou 510301, China*

[b] *NMPA Key Laboratory for Research and Evaluation of Drug Metabolism, Guangdong Provincial Key Laboratory of New Drug Screening, School of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, China*

[c] *School of Marine Sciences, University of Chinese Academy of Sciences, Beijing 100049, China*

[d] *School of Pharmaceutical Sciences, Guangzhou University of Chinese Medicine, Guangzhou 510006, China*

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ABSTRACT

This review systematically analyzes 186 valid data points derived from 157 distinct marine natural small-molecule drug leads discovered in China in the past decade (2015–2024). These compounds have all undergone phenotypic and target studies, and certain "structure-activity-target" relationships have been established, revealing the recent progress in the basic research of marine drug discovery in China. Therapeutically, antitumor agents dominated (50.0%), while emerging candidates for Alzheimer's disease (3.8%) and osteoporosis (5.4%) demonstrated the multi-target potential of marine chemistry. Ecologically, marine fungi (45.2%) and mangrove symbionts (11.8%) have emerged as prolific sources. Strikingly, 38.2% of the compounds exceeded Lipinski's 500 Da threshold, with higher-molecular-weight agents leveraging macrocyclic architectures (e.g., polyketide-alkaloid hybrids) to enhance bioactivity. These findings challenge traditional drug-likeness criteria and propose a "Marine Rule" framework that prioritizes conformational rigidity, ecosystem-driven scaffold optimization, and the repurposing of defense molecules. This review provides critical insights into China's evolving leadership in marine natural product research and offers strategic guidance for future innovations in the discovery of small molecule leads.

1. Introduction

China has historically been among the forefront of civilizations in recognizing and utilizing the therapeutic potential of marine-derived organisms. Records of marine traditional Chinese medicine can be found in the *Rites of Zhou Dynasty*, the *Book of Songs*, and the *Classic of Mountains and Seas*. Among them, the book *Classic of Mountains and Seas* in the pre-Qin period recorded 27 species of fish and turtles, and 5 species were clearly recorded as medicinal species [1, 2]. China has a long history of using marine organisms for medicinal purposes, thus providing a foundation for modern research on Chinese marine drugs [3].

Chinese researchers have extensively explored marine natural products (MNPs) from diverse sources and extreme environments. Studies have covered marine microorganisms, plants, and animals, yielding thousands of new compounds with novel structures and bioactivities [4, 5]. Investigations have extended to extreme habitats, such as deep-sea cold seeps, hydrothermal vents, and polar regions, revealing unique metabolites with pharmaceutical potential [6, 7]. China's marine biodiversity research has significantly advanced since the 1950s, contributing to the development of fisheries, medicine, and biotechnology [8]. The exploration of MNPs continues to be a promising field for drug discovery and biotechnological applications [9].

Recent statistical analyses of annual global discoveries of marine-derived bioactive natural products have revealed a significant upward trend in China's contributions. Specifically, China's share has demonstrated a consistent escalation from 23.6% during 2014–2015 to 31.6% in 2016–2017, reaching 34.4% by 2018, and further climbing to 35.7% in the most recent reporting period (2019–2021) [10–13]. This progressive increase underscores China's expanding capacity and considerable potential for identifying pharmacologically active MNPs, particularly in the discovery of novel bioactive secondary metabolites from marine ecosystems.

Recent advances in drug discovery have diversified screening methods for bioactive compounds. Beyond conventional cellular toxicity and *in vivo* mouse models, high-throughput screening (HTS), which encompassing target-based enzyme assays and phenotypic cell-based models, has developed rapidly [14, 15]. Concurrently, chemical genetics has emerged as an effective strategy that integrates phenotypic screening with target identification,

* Corresponding author.
E-mail addresses: yonghongliu@scsio.ac.cn (Y. Liu); zhangcuixian@gzucm.edu.cn (C. Zhang); caijian19@mails.ucas.ac.cn (J. Cai); tl405@smu.edu.cn (L. Tang); xfzhou@scsio.ac.cn (X. Zhou)
[Δ] These authors contributed equally to this work.

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facilitating the discovery of novel marine natural products (MNPs) with complex structures and therapeutic potential [16, 17], while further accelerating target identification and validation, supporting rational drug design [18, 19].

Progress in MNP review is evident in authoritative annual reports (2015–2023, Natural Product Reports) that catalog novel marine compounds [20–28]. Although existing reviews cover China's MNP research, they are organized by chemical classification [29–31], biological sources [32–34], or geographical origins [35]. A systematic evaluation of pharmacologically validated marine-derived compounds-especially those with well-defined mechanisms, target engagement, and therapeutic efficacy in disease models-remains lacking.

Research on MNPs in China began later than that in Europe and the United States. Although the number of natural products discovered has made remarkable contributions since 2000, China is still in the early stages of drug lead and candidate drug discovery. In the past decade, particularly since 2020, with the rapid development of chemical biology and chemical genetics in China and the deepened collaboration between chemists, biologists, and pharmacologists, China has made outstanding progress in the discovery of marine natural small molecule drug leads.

This review summarizes and analyzes marine natural small molecule drug leads discovered in China in the past decade (2015–2024), with following characteristics. 1) They showed obvious medicinal activity through phenotypic screening, such as cells or animals models; 2) The drug targets or pharmacological mechanisms of these compounds have been studied to some extent, rather than merely virtual screening; 3) Those natural small molecules (not macromolecular such as polysaccharides and peptides), with well-defined chemical structures, are originated from marine organisms or microorganisms, excluding compounds obtained through chemical synthesis or structural modifications; 4) The research was primarily led by Chinese scholars, and the main corresponding authors of the cited papers were from Chinese universities or research institutions. Such marine natural small molecule drug leads, which have established certain "structure-activity-target" relationships, serve as the most important bridge between MNPs and small molecule new drugs.

This review aims to provide a comprehensive and systematic overview of the progress in discovering marine-derived lead compounds in China over the past decade, critically analyzing their chemical diversity, biological activities, and potential therapeutic applications, while also introducing and discussing the conceptual framework of the 'Marine Rule'. Ultimately, by critically evaluating a decade of discovery, this work aspires to transcend being a mere reference and instead serve as a foundational framework-one that not only codifies past successes but also actively shapes the future paradigm of targeted and mechanism-driven marine drug discovery, solidifying China's role as a leading force in the next wave of pharmaceutical innovation from the ocean.

2. Antitumor drug lead compounds

2.1. Sources of marine animal

Marine organisms, particularly invertebrates like corals and sponges, have emerged as crucial sources of bioactive compounds with potential antitumor properties [36, 37], the following examples serve as good illustrations (Fig. 1).

Two soft coral-derived compounds (**1**–**2**) in this subset have been isolated from taxonomically distinct species. A cembrane diterpenoid named 3-dehydroxylpresinularolide B (**1**), discovered from the soft coral *Lobophytum crissum*, significantly inhibited the proliferation, migration, and invasion of A549 and H1299 cells, stimulated reactive oxygen species (ROS) accumulation, decreased the phosphorylation of human epidermal growth factor receptor 3 (EGFR3), and downregulated the protein expression of tyrosine kinase-like orphan receptor 1, human EGFR3, non-receptor tyrosine kinase Src, and p-signal transducer and activator of transcription 3 (STAT3), which has the potential ability to treat non-small cell lung cancer (NSCLC) [38]. Sinularin (**2**) from the soft coral *Sinularia flexibilis*, can treat gastric cancer by inducing apoptosis through mitochondrial dysfunction and inactivation of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway in gastric carcinoma cells [39]. 3β,11-dihydroxy-9,11-secogorgost-5-en-9-one (**3**), discovered in the soft coral *Klyxum flaccidum*. It activated caspases, cleaved PARP, and altered expression of key PPARγ-regulated biomarkers (cyclin D1, CDK6, Bcl-2, p38, ERK). Additionally, it elevated ROS, increased H2AX phosphorylation/expression, and induced autophagy. Pre-treatment with autophagy inhibitor 3-methyladenine reversed its growth-inhibitory effects, indicating the cytotoxic activity of **3** is, in part, mediated through autophagy induction. These findings indicated its translational potential for breast cancer therapy [40].

Multiple independent studies have reported lead compounds originating from the same sponge species, suggesting that these species possess substantial potential for yielding compounds with excellent bioactivity. Aaptamines, a class of alkaloids obtained from marine sponges of the genus *Aaptos*, had attracted significant attention as a promising scaffold for the development of anticancer agents. Aaptamine (**4**), discovered from the South China Sea (SCS) marine sponge *A. suberitoides* Brøndsted (Suberitidae), can attenuate the proliferation and progression of NSCLC by retarding the proliferation and invasion of NSCLC cells by selectively targeting the pathway phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/glycogen synthase kinase 3β (GSK-3β) [41]. Aaptamine-7 (**5**), obtained from the sponge *A. aaptos*, [42] was discovered as a sensitizer to cisplatin in the treatment of multidrug-resistant NSCLC *via* checkpoint kinase 1-dependent mechanisms [43]. Another aaptamines derivative with cyclin-dependent kinases 2 inhibitory activity from the sponge *A. suberitoides* was 3-(*N*-4-methylpentanoate) aminodemethyl (oxy) aaptamine (**6**). Cyclin-dependent kinases 2 can protect cells from pronase degradation and thus acted as an antitumor agent [44]. Halenaquinone (**7**) and xestoquinone (**8**) were discovered with antileukemic effects from the sponge *Petrosia* sp.. The former could induce Molt-4 cell apoptosis *via* oxidation inhibition of histone deacetylase (HDAC) and topoisomerase [45], while the latter could inhibit the ROS-induced HSP90 [46]. Heteronemin (**9**) and 12-deacetyl-12-epi-scalaradial (**10**) were both separated from sponge *Hippospongia* sp.. Compound **9** was collected from coral reefs off the coast [47]. It can induce apoptosis in prostate LNcap cells *via* oxidative and endoplasmic reticulum (ER) stress which combined with the inhibition of DNA Topoisomerase II (TOP2) and heat shock protein 90 (HSP90) to treat prostate cancer [48]. Furtherly it induced apoptosis in leukemia Molt-4 cells through oxidative stress, mitochondrial dysfunction, and induction of Talin expression to inhibit the progression of leukemia [49], and also induced anti-proliferation in cholangiocarcinoma cells by inhibiting the transforming growth factor-β (TGF-β) pathway [50]. Compound **10** induced HeLa cell apoptosis *via* the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway, modulates orphan nuclear receptor Nur77, and can treat cervical cancer to a certain extent [51]. Jorunnamycin A (**11**) derived from a Thai blue sponge *Xestospongia* sp. [52]; and the same as renieramycin T (**12**) [53]. Compound **11** used herein was synthesized according to the literature [54], but it was indeed of natural marine origin when it was first discovered. Compound **11** can suppress muscle-invasive bladder cancer by targeting fatty acid synthase (FASN) and DNA Topoisomerase I (TOP1) [55]. Com-

pound **12** used herein was synthesised according to the literature [56]. It inhibited melanoma B16F10 cell metastasis and invasion by regulating nuclear factor erythroid 2-related factor 2 (Nrf2) and STAT3 signaling pathways to exert an anti-melanoma effect [57]. Five psammaplins reported by the same article were interesting. Psammaplin E (**13**), (*E*,*Z*)-psammaplin A (**14**), (*E*,*E*)-psammaplin K (**15**), (*E*,*E*)-psammaplin A (**16**), and bisaprasin (**17**), discovered from the sponge *Dendrilla lacunose*. Psammaplin-based HDAC inhibitors were found to differentially inhibit HDAC activity, inducing activation of hypoxia-inducible factor-1 (HIF-1) and disrupting organotropic metastatic triple negative breast cancer subclone growth, which showed new directions for anti-metastatic breast tumors [58].

Stellettin B (**18**), discovered from the SCS sponge *Jaspis stellifera*, can induce G_1 arrest, apoptosis and autophagy in human NSCLC A549 cells *via* blocking PI3K/AKT/mTOR pathway [59]. It could also induce apoptosis in human chronic myeloid leukemia cells *via* targeting PI3K and STAT5, and it was expected to be a candidate drug for the treatment of chronic myeloid leukemia [60]. While, another research group come to terms with it that it exhibited potent anti-bladder cancer activity by suppressing the fibroblast growth factor receptor 3 (FGFR3)-transforming acidic coiled-coil containing protein 3/AKT/mTOR pathway, which resulted in the activation of autophagy and subsequently activated apoptosis in a dependent manner of death associated protein kinase 2 [61]. Sokotrasterol sulfate (**19**), first discovered in the SCS sponge *Topsentia* sp.. It sensitized tumor cells to antigen-specific T-cell killing in the T cell–tumor cell coculture system and suppressed interferon (IFN)-γ-induced programmed cell death 1 ligand 1 (PD-L1) expression by inhibiting janus kinase (JAK) activity to inhibit tumors [62]. Smenospongine (**20**), discovered in a SCS sponge *Spongia pertusa* Esper, preferentially eliminated breast cancer stem-like cells *via* the p38 mitogen-activated protein kinase (p38 MAPK)/adenosine 5'-monophosphate-activated protein kinase α (AMPKα) pathway [63]. Benzosceptrin C (**21**), discovered in the marine sponge *Agelas dendromorpha* [64], induced lysosomal degradation of PD-L1 and promotes antitumor immunity by targeting DHHC3 (Asp-His-His-Cys) [65]. Phakefustatin A (**22**), a cycloheptapeptide discovered from the sponge *Phakellia fusca*, is an retinoid X receptor α modulator that inhibited cancer cell growth, and its pharmacophores were the Kyn and guanidine groups [66].

Saponin 2 (**23**), isolated from the SCS sea cucumber *Holothuria moebii*, significantly induced apoptosis in human glioblastoma U87-MG cells and reduced the expression levels of several glioma metabolic enzymes involved in glycolysis and glutaminolysis, acting as an anti-glioblastoma agent [67]. Among the multitude of sponge- and coral-derived compounds in this section, compound **23** stands as the sole representative within this cohort sourced from a sea cucumber.

2.2. Sources of marine plants (including mangrove plants)

Marine algae are highly enriched with diverse bioactive compounds. A vast number of natural compounds, such as polysaccharides, polyphenols, carotenoids, and terpenoids, have been isolated from marine algae, and some of them showing potential antitumor abilities [68–70] (Fig. 2). D-isofloridoside (**24**), isolated from the marine red algae *Laurencia undulata*, effectively inhibited the PI3K/AKT and renin-angiotensin system (Ras)/MAPK pathways, as well as HIF-1α expression and vascular endothelial growth factor (VEGF) secretion. It also effectively inhibited vascular endothelial growth factor receptor 2 (VEGFR-2) activation and the PI3K/AKT, MAPK, and nuclear factor kappa-B (NF-κB) signaling pathways, thereby inhibiting tumor angiogenesis [71]. AYP (**25**) was isolated from the marine alga *Isochrysis zhanjiangensis*, which was named after its discoverer. It potently inhibited VEGFR-2 signaling and its downstream PI3K/AKT and Ras/MAPK pathways, thereby suppressing inflammation-mediated tumor angiogenesis [72]. Fucoxanthin (**26**), discovered in many types of marine algae, inhibited two gastric cancer cell lines, SGC-7901 and BGC-82 by downregulating Mcl-1 and STAT3 [73]. The one which was discovered from the diatom *Nitzschia* sp., induced apoptosis in human glioma cells by triggering ROS-mediated oxidative damage and regulating the MAPKs and PI3K/AKT pathways [74].

Mangrove-derived antitumor leads frequently adopt multi-ring scaffolds (≥ 3 cyclic moieties)-a chemical signature potentially driven by evolutionary selection for bioactive stability under tidal fluctuation stress. Lyoniresinol-3*α*-*O*-*β*-rhamnopyranoside (**27**), contains three cyclic moieties and a glycosyl group, collected from Hainan mangrove stem of *Rhizophora apiculate*. In human colon cancer cells, compound **27** bound reversibly to the KR domain of FASN, preventing the reduction of saturated acyl groups during fatty acid synthesis. The effect of **27** on human colon cancer cells can be reversed by the end products of chemical reactions catalyzed by FASN, reflecting the specificity of LR for FASN. It was expected to be a lead compound for the treatment of colon cancer [75]. ZWM026 (**28**), incorporates a hexacyclic architecture equally divided between pyrrolidine ring and benzene ring, discovered in mangroves in coastal wetlands, was selective and reversible for T790M-mutated EGFR in naturally occurring NSCLC cells and constructed NIH-3T3 cells. In this way, it can exert its anti-small cell lung cancer ability [76]. Secalonic acid D (**29**), isolated from marine mangroves, possesses a hexacyclic scaffold with six six-membered rings arranged in a 3,3-symmetrical pattern and interconnected *via* a central carbon bridge. It induced cell apoptosis in both sensitive and ABCG2-overexpressing multidrug-resistant cancer cells by upregulating c-Jun expression. Thus, by inhibiting the proteasome-dependent degradation of c-Jun, it induced cancer cell death *via* the c-Jun/Src/STAT3 signaling axis [77].

2.3. Sources of marine fungi (including mangrove-associated fungi)

Mangrove-associated fungi have demonstrated significant potential in producing antitumor compounds (Fig. 3). D1952 (**30**) was first isolated from the endophytic fungus *Phoma* sp. SK3RW1M isolated from the roots of mangrove *Avicenniamarina* (Forsk.) *Vierh* collected from the SCS [78]. It can effectively target cyclin kinase 2, arrest MDA-MB-435 cells in the G_1/S phase, and promote the cleavage of poly ADP-ribose polymerase (PARP), thereby exhibiting an anti-breast cancer effect [79]. Talaketide E (**31**) was isolated from *Talaromyces* sp. SCSIO 41027 in the rhizosphere sediment of a mangrove forest. Compound **31** significantly inhibited colony formation in prostate cancer (PC)-3 cells, arrested the cell cycle in the S-phase, and ultimately induced apoptosis. These findings indicated that **31** may serve as a promising lead compound for the development of a potential treatment for prostate cancer [80]. SZ-685C (**32**), discovered from the mangrove endophytic fungus *Halorosellinia* sp. No. 1403, induced apoptosis in human non-functioning pituitary adenoma cells by inhibiting the AKT pathway *in vitro* [81]. Brefeldin A (**33**), isolated from mangrove-derived fungus *Aspergillus* sp. 9H [82]. Compound **33** synergized with docetaxel to inhibit growth in PC-3 monolayer and 3D cultures. While docetaxel was standard in late-stage prostate cancer, its efficacy was limited by toxicity and resistance. Mechanistically, the combination induced growth arrest and apoptosis, correlating with reduced B-cell lymphoma-2 (Bcl-2) levels. This suggests **33** may enhance docetaxel efficacy by targeting Bcl-2 [83]. Stemphone C (**34**), derived from the mangrove endophytic fungus *Mollisia* sp. SCSIO 41409. It reduced PC-3 cell colony formation, inducing apoptosis and blocks the cell cycle at the S-phase in a dose-dependent manner, and can be considered a potential antiproliferative agent and a promising lead

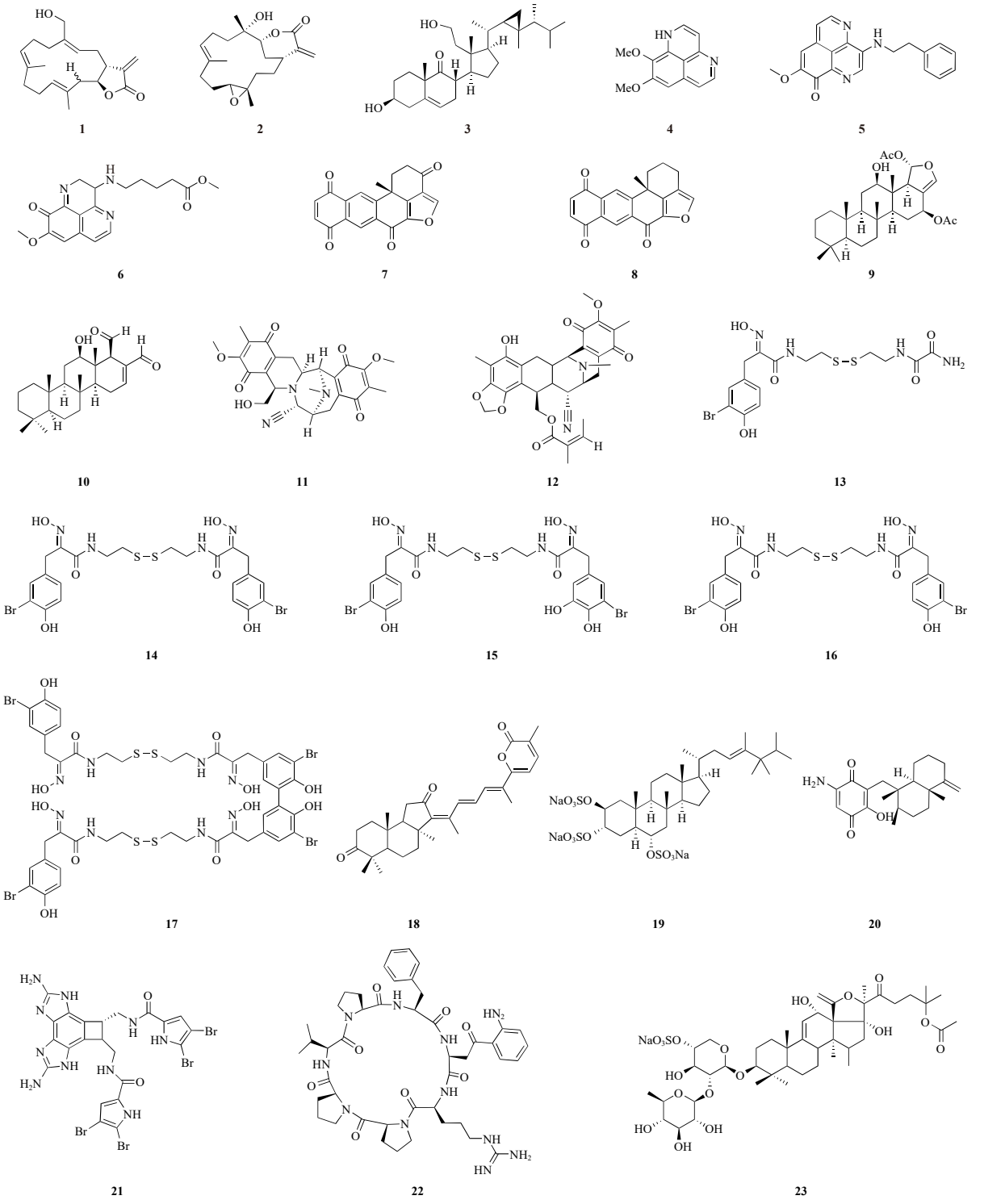


Fig. 1 Structures of compounds **1**–**23**.

compound for anti-prostate cancer therapy [84]. Versixanthone G (**35**) was discovered from the fungal strain *Aspergillus versicolor* HDN1009 [85], and was confirmed to inhibit TOP1-mediated DNA relaxation by targeting TOP1, thereby arresting the cell cycle process and inducing necrosis in cancer cells [83]. Dicerandrol C (**36**), derived from the mangrove endophytic fungus *Phomopsis asparagi* DHS-48, could decrease proliferation, clonality, migration, invasion, and also induce apoptosis of HepG2 and Hela cancer cells by inhibiting Wnt/β-catenin signaling pathway [86]. GQQ-792 (**37**), obtained from the marine compound library of the Pharmacy College, Ocean University of China, was a novel structured polythiodiketopiperazine (ETPs) compounds derived from endophytic fungi of marine mangroves [87]. Compound **37** was discovered as a non-ATP-competitive PGK1 inhibitor. Its disulfide pharmacophore bound Cys379/Cys380, occluding ATP binding. This blocked hypoxia- and EGF-induced PGK1 kinase activity, suppressing PDK1 phosphorylation at T338 in glioblastoma cells. Consequently, lactate production and glucose uptake decrease, inducing apoptosis [88].

Fungi (except mangrove fungi mentioned above), particularly *Aspergillus* and *Penicillium* species, are major producers of antitumor compounds [89]. Questiomycin A (**38**) and xanthocillin X (**39**), derived from the marine fungus *Penicillium* sp. ZZ1750, both exhibited antiproliferative activity against U87MG and U251

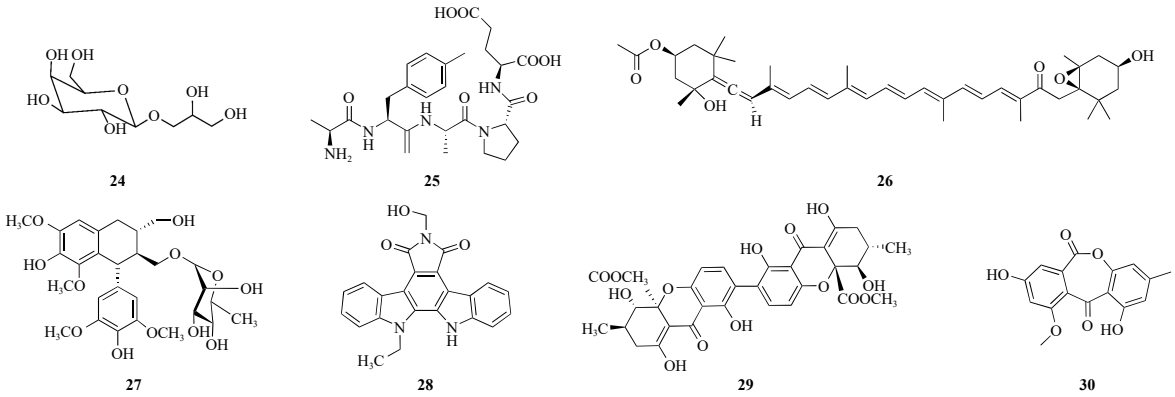


Fig. 2 Structures of compounds **24**–**30**.

cells. Their antiglioma activity may be related to the promotion of ROS production, reduction of mitochondrial membrane potential (MMP), and enhancement of caspase-3 enzyme activity [90]. 10,11-Dehydrocurvularin (**40**), obtained from the *Penicillium* sp. SF-5859 [91], showed antitumor effects against human breast cancer by suppressing STAT3 activation, and the *α*,*β*-unsaturated carbonyl moiety of **40** was essential for STAT3 inactivation [92]. Dicitrinone G (**41**), obtained from the starfish-derived fungus *Penicillium* sp. GGF16-1-2 [93, 94], exhibited stronger cytotoxic activity against human pancreatic cancer cell lines BXPC-3 and PANC-1 than the positive control drug. It induced cell apoptosis by activating caspase-3 protein, thereby exerting an antitumor effect [93]. Further study found that **41** could greatly suppress tumor growth and angiogenesis in mice, and decrease the expression of CD31 and caspase-1. *In vitro*, conditioned medium from **41**-treated BXPC-3 cells suppressed tube formation and pro-angiogenic Notch intracellular domain expression in human umbilical vein endothelial cells (HUVECs). These findings indicated **41** inhibits angiogenesis *via* the NLRP3/IL-18 pathway and may impede tumor growth [95]. Pretrichodermamide B (**42**) was derived from the from a deep-sea derived fungus *P. janthinellum* SH0301. It directly bound to STAT3 and prevented its phosphorylation, thereby inhibiting the JAK/STAT3 signaling pathway. In addition, it can induce cell cycle arrest and promote apoptosis, thereby exerting an antitumor effect [96]. Secalonic acid D (**29**), discovered from the marine fungus *P. oxalicum*, had anti-lung metastasis efficacy *via* the decrease of MMP-9 expression in the hepatoma-22 and hepatocellular carcinoma mice model [97].

14-*O*-acetylinsulicolide A (**43**), a nitrobenzoyl sesquiterpenoid obtained from the fungal strain *Aspergillus ochraceus* Jcma1F17, showed cytotoxicities against three renal carcinoma cell lines (ACHN, OS-RC-2, 786-O cells). Further studies indicated that **43** arrested the cell cycle at the G_0/G_1 phase and induced late apoptosis [98]. Gliotoxin (**44**), discovered from the marine fungus *A. fumigatus*, can induce ferroptosis by downregulating SUV39H1 expression in oesophageal cancer cells, providing a new idea for the treatment of oesophageal squamous cell carcinoma [99]. Wentilactone A (**45**), first isolated from *A. wentii* EN-48, blocked the expression of extracellular matrix protein 1 (ECM1) by inhibiting the phosphorylation of inhibitor of kappa B kinase (IKK)/inhibitor of NF-κB (IκB), thereby inhibiting the phosphorylation of NF-κB, reversing the activation of NF-κB/ECM1 induced by cisplatin, and antagonising the symptoms of cisplatin resistance. In addition, compound **45** reduced the expression of ECM1 protein through the IKK/IκB/NF-κB signaling pathway and targeted tumor cells and the tumor microenvironment to further resist or even reverse the symptoms of cisplatin resistance [100]. Aspulvinone H (**46**), derived from *A. terreus*, potently inhibited glutamic oxaloacetate transaminase 1 (GOT1) *via* competitive binding with its cofactor pyridoxal 5'-phosphate (PLP). It demonstrated significant *in vivo* antitumor efficacy in an SW1990 xenograft model and sensitized pancreatic ductal adenocarcinoma (PDAC) cells to oxidative stress by suppressing glutamine metabolism, thereby inhibiting proliferation. These findings positioned **46** as a promising lead for anti-PDAC drug development [101]. Sclerotiamide C (**47**), derived from the fungus *A. sclerotiorum* LZDX-33-4, induced apoptosis in HeLa cells by arresting the cell cycle, activating ROS production, and regulating apoptosis-related proteins in the MAPK signaling pathway, and it had potential antitumor activity [102]. Terphenyllin (**48**), obtained from coral-derived fungus *A. tritici* SP2-8-1, could induce pancreatic cancer cell apoptosis by increasing the expression levels of pro-apoptotic proteins (Bax, Bad, Puma, BimL), and decreasing the expression levels of anti-apoptotic proteins (Bcl-2, Bcl-xL) [103]. In addition, it can reduce the expression of phos-Bcl-2 and cleave and activate caspase-7 and PARP, suggesting its potential for the treatment of pancreatic cancer [104].

Libertellenone H (**49**), obtained from Arctic fungus *Eutypella* sp. D-1, could induce apoptosis by accumulating ROS. It simultaneously reduced intracellular glutathione levels and activated the downstream apoptosis signal regulating kinase 1/c-Jun N-terminal kinase (JNK) signaling pathway, and was a Trx system inhibitor and a promising anticancer candidate [105]. Scoparasin B (**50**), obtained from marine fungus *Eutypella* sp. F0219, inhibited tumor angiogenesis and vasculogenic mimicry by reducing VEGF-A levels and inhibiting VEGF-A/VEGFR-2 signaling, thereby demonstrating its antitumor effects [106]. Acremochlorins A (**51**) and M (**52**), discovered from the coral endophytic fungus *Acremonium sclerotigenum* GXIMD 02501, both significantly inhibited the growth of triple-negative breast cancer cells and induced apoptosis by inhibiting human dihydrolactic acid bacteria dehydrogenase [107]. Nigrosporins B (**53**), isolated from a sponge-associated fungus *Nigrospora* sp. ZJ-2010006 [108], was a potential anticervical cancer agent because of its inducing apoptosis and protective autophagy abilities in human cervical cancer Ca Ski cells, which mediated by the PI3K/AKT/mTOR signaling pathway [109]. 5'-Epiequisetin (**54**), from the marine sponge-derived fungus *Fusarium equiseti* SCSIO 41019 [110], showed an anti-prostate cancer effect by inducing apoptosis and inhibiting cell proliferation and migration both *in vitro* and *in vivo*, suggesting it as a promising lead compound for the pharmacotherapy of prostate cancer [111]. Arthpyrone M (**55**), isolated from the marine sponge endophytic fungus *Arthrinium arundinis*, inhibited the growth and metastasis of gastric cancer by targeting the mTORC1 signaling pathway [112]. *N*-(3,7-dimethyl-2,6-octadienyl)-2-aza-2-deoxychaetoviridin A (**56**), derived from fungus *Chaetomium globosum* MP4-S01-7 in abyssal water [113], effectively inhibited STAT3 and its downstream genes, MYC and SLC39A10. Therefore, it may be an effective lead compound for the treatment of STAT3-activated gastric cancer [114]. Trichodimerol (**57**), derived from the marine

fungus *Trichothecium* sp., induced apoptosis in A375-S2 human melanoma cells by modulating ERK and p38 activities mediated by ROS, demonstrating its potential in combating melanoma [115]. FGFC1 (**58**) was isolated from the fungus *Stachybotrys longispora* FG216, which was collected from seawater and seafloor mud from Taohua Bay of Zhoushan Island in the East China Sea [116, 117]. Compound **58** can inhibit erlotinib-resistant NSCLC *via* the elevation of ROS mediated by the EGFR/PI3K/AKT/mTOR pathway [118]. Terphenyllin (**48**), obtained from coral-derived marine fungus, inhibited the phosphorylation and activation of STAT3 and decreased the protein levels of STAT3-dependent target genes, including c-Myc and Cyclin D1, indicating its ability to suppress the growth and metastasis of gastric cancer by inhibiting the STAT3 signaling pathway [119]. Surprisingly, four serial lead compounds

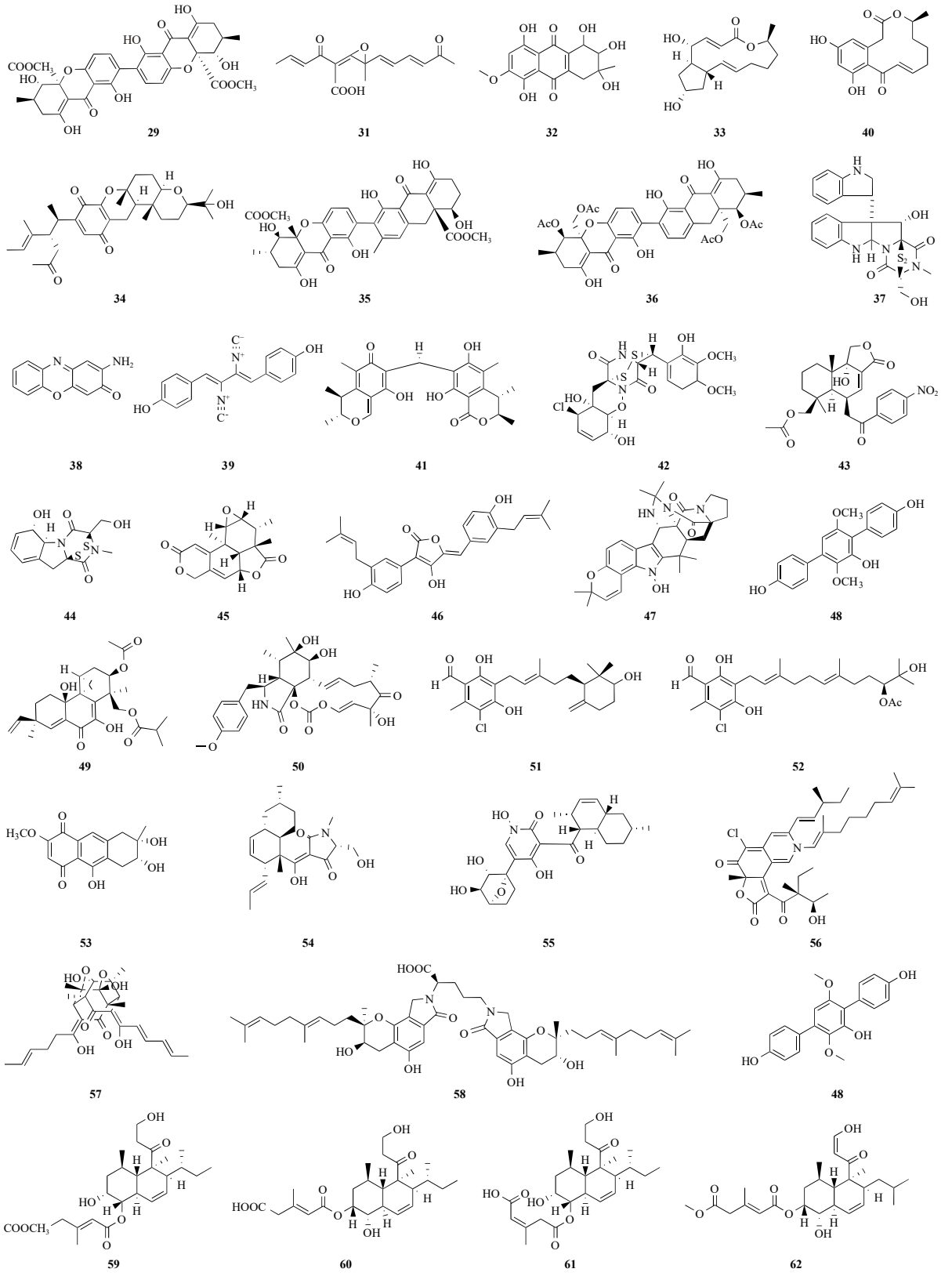


Fig. 3 Structures of compounds **29** and **31**–**62**.

identified from marine organisms including tandyukisin B (**59**), trichoharzin (**60**), tandyukisin C (**61**), and tandyukisin (**62**) in this study, which were firstly isolated from marine imperfect fungus *Trichoderma harzianum* [120–122]. These marine compounds potently inhibited EGFR-critical for BC growth-overcoming resistance-conferring mutations. They induced early apoptosis *via* Caspase-3 activation. Furthermore, compounds **60** and **62** bound distinct EGFR sites, and their combination enhances BC cell apoptosis, supporting development of novel marine-derived EGFR inhibitors to address drug resistance [123].

2.4. Sources of marine actinomycetes (including mangrove-associated actinomycetes)

Actinomycetes, ubiquitous bacteria found in various environments including marine ecosystems and mangrove sediments, have significant potential for producing antitumor compounds [124, 125]. In recent years, many species of actinomycetes have produced a number of lead compounds with anti-tumor activities (Fig. 4). Piericidin A (**63**) and glucopiericidin A (**64**) were isolated from *Streptomyces psammoticus* SCSIO NS126 in mangrove sediment collected from the Pearl River Estuary. Peroxiredoxin 1 (PRDX1) was a potential target of **63** and **64**. Both agents promoted apoptosis in ACHN cells by upregulating PRDX1 mRNA/protein, thereby reducing ROS levels. They demonstrated potent antitumor efficacy in ACHN xenograft models, correlating with elevated tumor PRDX1 expression. Critically, PRDX1 nuclear translocation induced by these compounds represents a key anti-renal cell carcinoma mechanism [126]. This novel PRDX1-targeting strategy may address limitations of current renal cancer targeted therapies. Malaymycin (**65**), derived from *S. malaysiensis* SCSIO 41397, it induced G_0/G_1 phase arrest and cell shrinkage in C42B cells, while dose-dependently suppressing androgen receptor expression at mRNA and protein levels. It also potently inhibited androgen receptor target genes KLK2/KLK3 in C42B and 22RV1 models, demonstrating potential as a lead candidate for castration-resistant prostate cancer therapy [127]. Grincamycin B (**66**), as an angucycline glycoside isolated from actinomycete *S. lusitanus* SCSIO LR32 [128], selectively induced human acute promyelocytic leukemia NB4 cell line, enhanced endoplasmic reticulum stress and intracellular ROS accumulation, and induced NB4 cell death by targeting isocitrate dehydrogenase 1 through a ROS-mediated mechanism [129]. Gincamycin B (**67**), discovered in the same actinomycete LR32, functions as a potent inhibitor of glioblastoma stem cells by targeting ras homolog family member A and PI3K/AKT [128]. Azalomycin F4a (**68**), discovered in the marine actinomycete *S. solisilvae* HNM30702, directly bound autophagy protease ATG4B with high affinity. It effectively suppressed advanced gastric cancer autophagy *via* ATG4B inhibition *in vitro* and *in vivo*, concurrently inhibiting tumor growth, migration, and invasion. Compound **68** also sensitized tumors to chemotherapy. As a confirmed ATG4B inhibitor, this natural product warrants development for advanced gastric cancer therapy [130].

Although the specific species of *Streptomyces* has not been identified in some studies of actinomycetes metabolites, many excellent products have been obtained from them. Streptoglutarimide H (**69**), discovered from the *Streptomyces* sp. ZZ741, downregulated cell cycle- and nucleotide synthesis-related proteins to block the cell cycle at the G_0/G_1 phase, reduced the expression levels of glycolytic metabolic enzymes to inhibit glycolysis, and downregulates the important cancer transcription factor c-Myc and the therapeutic target deubiquitinase USP28 [131]. Gephyromycin C (**70**), isolated from the *Streptomyces* sp. SS13I, was a novel small molecule inhibitor of heat shock protein HSP90. It induced G_2/M cell cycle arrest and apoptosis in PC3 cells *in vitro*, thereby treating human prostate cancer [132]. Resistomycin (**71**), isolated from a *Streptomyces* sp. in marine sediment samples, inhibited Wnt/β-catenin signaling to induce apoptotic death in human colorectal cancer cells [133]. Antimycin A2c (**72**), discovered from the *Streptomyces* sp. THS-55, suppressed HeLa cells *via* disrupting mitochondrial function and depleting human papilloma virus oncoproteins E6/E7, can play a role in the treatment of cervical cancer [134]. RK-286C (**73**), isolated from the sponge-associated *Streptomyces* sp. NBU3142 [135, 136], inhibited migration, induced apoptosis, arrested cell cycle progression, and promoted senescence in both parental and paclitaxel-resistant MDA-MB-231 cells. Mechanistically, compound **73** targeted mitogen-activated protein kinase kinase kinase 11-validating its role in breast tumorigenesis through proliferation, migration, and cell cycle regulation [137]. 7-Oxostaurosporine (**74**) was a marine-derived compound isolated from *Streptomyces* sp. SS-13G, TZ-A47, DT-A61. Compound **74** was a potent dual protein kinase C θ/δ inhibitor that can efficiently inhibited tumor growth in pancreatic cancer by inducing cellular apoptosis and suppressing the NF-κB/p-P65 pathway [138]. Chrysomycin A (**75**), derived from the marine sediment-derived *Streptomyces* sp. 891 [139], could inhibit the proliferation, migration and invasion of glioblastoma cells through the Akt/GSK-3β/β-catenin signaling pathway [140]. Subsequent studies revealed **75** significantly inhibited glioblastoma progression in xenograft models. Mechanistically, compound **75** enhanced apoptosis in U251/U87-MG cells by elevating caspase-3/7 activity, shifting the Bax/Bcl-2 ratio to trigger caspase cascades. It also downregulated p-Akt and p-GSK-3β, furtherly suggesting that **75** may contribute to glioblastoma regression modulating in the Akt/GSK-3β signaling pathway to promote apoptosis of neuroglioma cells *in vivo* and *in vitro* [141]. Therefore, compound **75** was a lead compound for glioblastoma treating because of its strongly therapeutic effect on glioblastoma.

Five serial compounds including 24-lumooligomycin B (**76**), 4-lumooligomycin B (**77**), 6-lumooligomycin B (**78**), 40-homooligomycin B (**79**) and 15-hydroxy-oligomycin B (**80**), were isolated from the marine sediment-derived *Streptomyces* sp. FXY-T5. The oligomycins mentioned above induced significant G1-phase cell cycle arrest in cancer cells and significantly attenuated their Cyclin D1 and proliferating cell nuclear antigen expression through the β-catenin signaling pathway [142].

2.5. Sources of marine bacteria (including mangrove-associated bacteria) and other sources

Many bacteria possess the potential to produce lead compounds with antitumor activity (Fig. 5). Prodigiosin (**81**), discovered from the marine sediment bacteria *Vibrio* sp. C1-TDSG02-1, can induce autophagic cell death and cell cycle arrest in oral squamous cell carcinoma cells OECM1 and SAS cells *via* the microtubule-associated protein 1 light chain 3 (LC3)-mediated P62/LC3-I/LC3-II pathway. These findings showed that prodigiosin may target the autophagic cell death pathways as a potential agent in cancer therapeutics [143]. Pseurotin A (**82**), isolated from the marine *Bacillus sp*. FS8D, downregulated glycolytic enzymes PKM2 and LDH5 while upregulating PDHB, ATP5B, and cytochrome c-key regulators of TCA cycle and oxidative phosphorylation. This multi-enzyme targeting underlined its anti-glioma mechanism [144]. Chromopeptide A (**83**) was discovered in marine bacteria *Chromobacterium* sp. HS-13-94. It selectively inhibited HDAC activity *via* substrate non-competitive binding, dose-dependently suppressing prostate cancer proliferation. Compound **83** could also induce G_2/M arrest, apoptosis, and inhibit PC3 migration. *In vivo*, tumor growth suppression correlated with elevated Ac-H3 and p21 expression. As a novel class I HDAC inhibitor, compound **83** represented a therapeutic strategy for prostate cancer [145]. Microcolin H (**84**), discovered in a marine cyanobacteria *Moorea producens*, can induce autophagic death of tumor cells by directly acting on phosphatidylinositol transporter α/β,

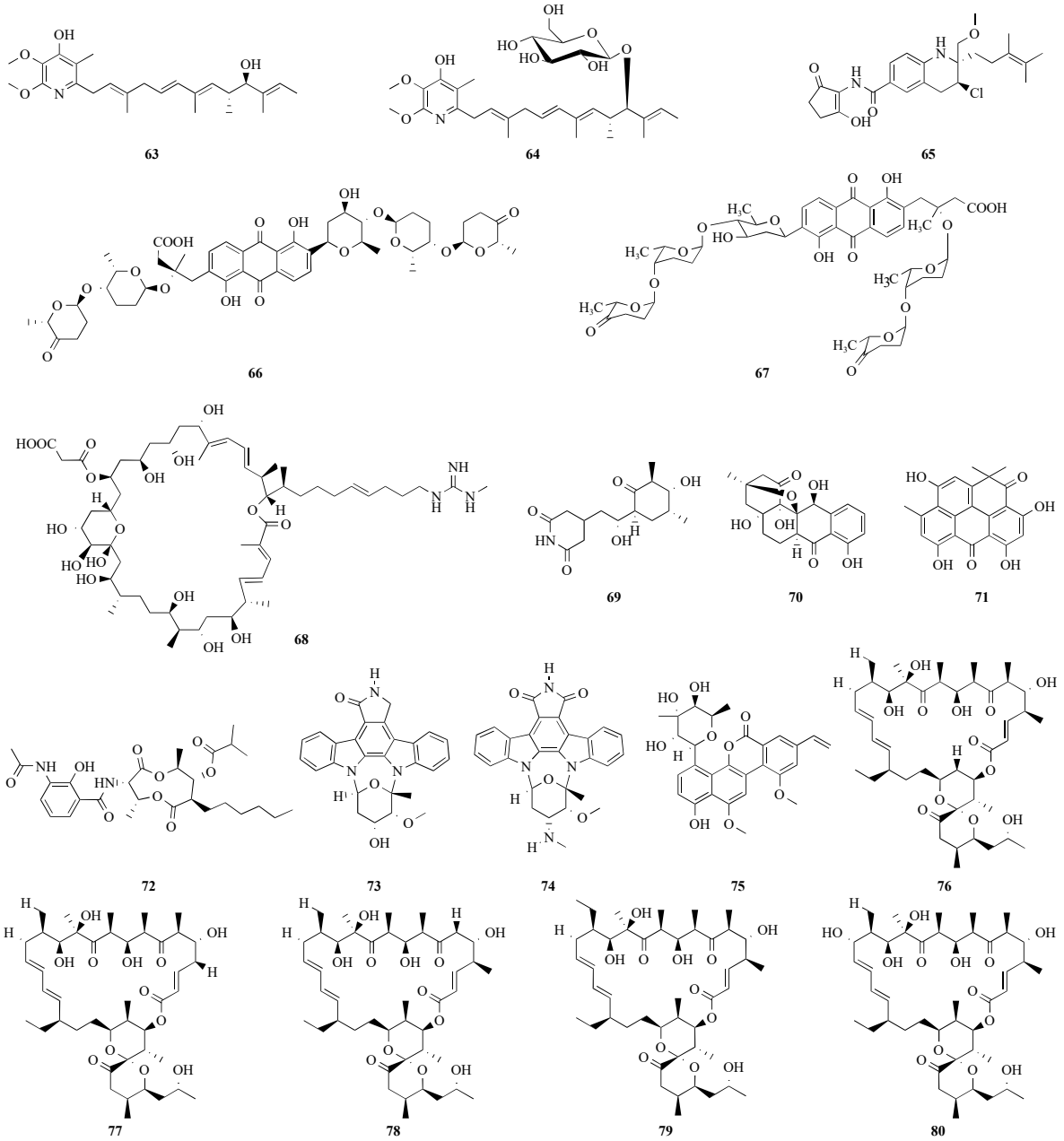


Fig. 4 Structures of compounds **63–80**.

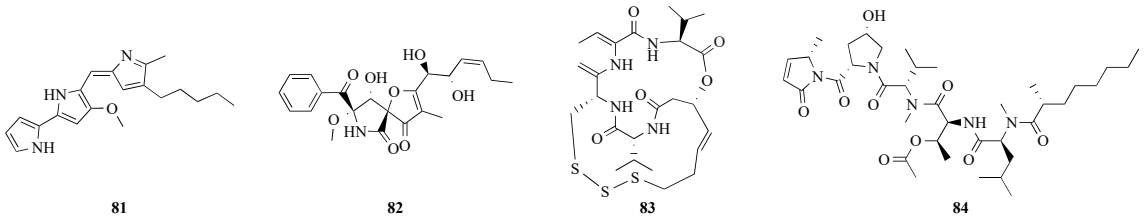


Fig. 5 Structures of compounds **81–84**.

thereby exerting its powerful antitumor activity [146].

3. Anti-inflammatory drug lead compounds

3.1. Sources of marine animal

Dysidea genus sponges are an important source of anti-inflammatory substances. Arenarialins D (**85**), isolated from the sponge *D. arenaria,* showed inhibitory activity on the production of inflammatory cytokines tumor necrosis factor alpha (TNF-α) and IL-6 in lipopolysaccharides (LPS)-induced RAW264.7 macrophages and regulated the NF-κB/MAPK signaling pathway, indicating its potential as an anti-inflammatory drug lead compound [147]. Dysambiol (**86**), obtained from a sponge *Dysidea* sp., exhibited remarkable anti-inflammatory activity by regulating the

inhibitor kappa B alpha (IκBα) protein and MAPK signaling pathway [148]. Septosone A (**87**), isolated from the *D. septosa*, exhibited anti-inflammatory activity in $CusO_4$-induced transgenic fluorescent zebrafish, possibly by inactivating the NF-κB signaling pathway [149].

4,14-Dioxatricyclo[11.3.2.0^{3,5}]octadec-8-en-15-one,12-(acetyloxy)-5,9,13-trimethyl-16-methylene-(1*R*,3*S*,5*S*,8*E*,12*R*,13*R*)-(9CI, ACI) (**88**) and 11-Dehydrosinulariolide (**89**) were discovered from soft coral *Sinularia pedunculata* [150, 151]. Compounds **88** and **89** exhibited anti-inflammatory activity by inhibiting nitric oxide (NO) production. SAR analysis revealed their suppression of NF-κB/MAPK pathways and inflammatory cytokines. In DSS-induced colitis mice, they ameliorated inflammation, repaired colonic epithelium, and demonstrate cembranolides' potential as ulcerative colitis therapeutics [152].

Astaxanthin (**90**) is a well-known natural carotenoid, which can be extracted from multiple crustaceans [153–155]. In a severe burn rat model, astaxanthin ameliorated renal injury, reducing serum creatinine and NGAL levels while relieving oxidative stress and tubular apoptosis. It increased p-AKT/p-Bad phosphorylation and suppressed downstream pro-apoptotic proteins (cytochrome C, caspase-3/9) dose-dependently. These effects-reversed by PI3K inhibitor LY294002-demonstrate astaxanthin protects against burn-induced acute kidney injury by modulating the mitochondrial AKT/Bad/caspase pathway [156]. Years later, the same research team made new discoveries. In burn-injured rats, astaxanthin dose-dependently suppressed renal inflammatory mediators and inhibited the TLR4/MyD88/NF-κB axis. TLR4 antagonist Resatorvid and NF-κB inhibitor PDTC (pyrrolidinedithiocarbamate ammonium) enhanced astaxanthin's anti-inflammatory effects, while LPS reversed them. Astaxanthin also upregulated heme oxygenase-1 (HO-1) dose-dependently, indicating its renal protection involves TLR4/MyD88/NF-κB suppression and HO-1 induction [157]. These discoveries showed that astaxanthin played an anti-inflammatory role, ultimately preventing early acute kidney injury following severe burns.

The structures of compounds **85–90** are illustrated below (Fig. 6).

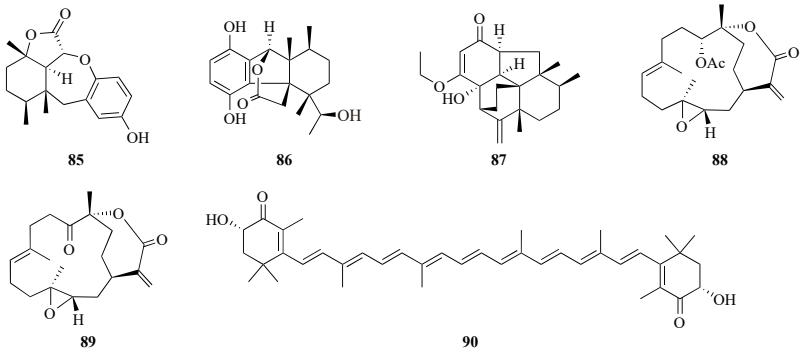


Fig. 6 Structures of compounds **85–90**.

3.2. Sources of marine plants

Vomifoliol (**91**), isolated from the mangrove plant *Ceriops tagal*, could significantly inhibited calcineurin with low cytotoxicity. It suppressed PMA/ionomycin-induced Jurkat cell activation, blocking NFAT1 dephosphorylation and reducing IL-2 expression. So, compound **91** was revealed as a calcineurin-targeting inhibitor of NFAT signaling with low-toxicity, which is potential to be an immunosuppressant for inflammatory conditions [158]. Sargasilol A (**92**), isolated from a brown alga *Sargassum siliquastrum*, inhibited LPS-induced NO production in BV-2 microglial cells. It was established as an anti-neuroinflammatory agent by targeting the IKK/IκB/NF-κB signaling pathway [159] (Fig. 7).

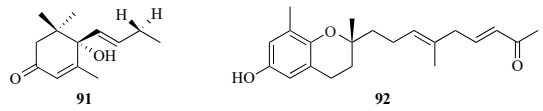


Fig. 7 Structures of compounds **91–92**.

3.3. Sources of marine fungi (including mangrove-associated fungi)

Spiromaterpene E (**93**), obtained from the deep-sea derived fungus *Spiromastix* sp. MCCC 3A00308, significantly suppressed NO production in LPS-stimulated BV2 microglia. SAR indicated a 2(*R*),11-diol unit enhances activity. It abolished LPS-induced NF-κB nuclear translocation and dose-dependently reduced pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), iNOS, and COX-2 at mRNA/protein levels [160]. Varioxepine B (**94**), obtained from the soft coral derived fungus *Aspergillus terreus*, suppressed Con A-induced murine splenocyte proliferation *in vitro* [161]. Pretreatment of **94** reduced proinflammatory cytokines and ameliorated liver injury in Con A-challenged mice. It also inhibited anti-CD3/CD28-stimulated proliferation in murine/human T cells and suppressed Th1/Th2 cytokine production [162]. So, compound **94** has potential therapeutic activity against hepatitis.

While above situation, a several numbers of others exhibited higher molecular weights. Gymnoasin A (**95**) was discovered in an Antarctic fungus *Pseudogymnoascus* sp. HDN17-895. It can inhibit the activation of caspase-1 and the secretion of the pro-inflammatory cytokines IL-1β and IL-18 in response to various NLRP3 stimuli but does not affect the activation of other inflammasomes, such as NLRC4 and AIM2. It is suggested to be a potent and selective inhibitor of NLRP3 inflammasomes [163]. Pseudoviridinutan F (**96**) was obtained from fungus *Aspergillus pseudoviridinutans* TW58-5, which was isolated from a hydrothermal vent sediment. Compound **96** inhibits the production of NO in LPS-induced murine macrophage RAW264.7 cells by regulating the expression levels of NLRP3 and iNOS, demonstrating its anti-inflammatory ability [164]. Isaridin E (**97**), derived from the ascidian-derived fungal strain *Amphichorda felina* SYSU-MS7908, could improve survival and mitigated lung injury, thrombocytopenia, endothelial hyperpermeability, and vascular inflammation in septic mice. It suppressed von willebrand factor (vWF) release by downregulating VAMP8/SNAP23 in activated platelets. Furthermore, compound **97** inhibited platelet-endothelial adhesion in LPS-stimulated HUVECs, reducing vWF secretion and endothelial permeability. Cilengitide inhibition studies confirmed **97** blocked vWF binding to integrin *αvβ3*, thereby suppressing the *αvβ3*-focal adhesion kinases (FAK)/Src pathway underlying sepsis-induced endothelial dysfunction. Collectively, compound **97** protected against sepsis by inhibiting platelet-endothelial interactions and endothelial hyperpermeability [165] (Fig. 8).

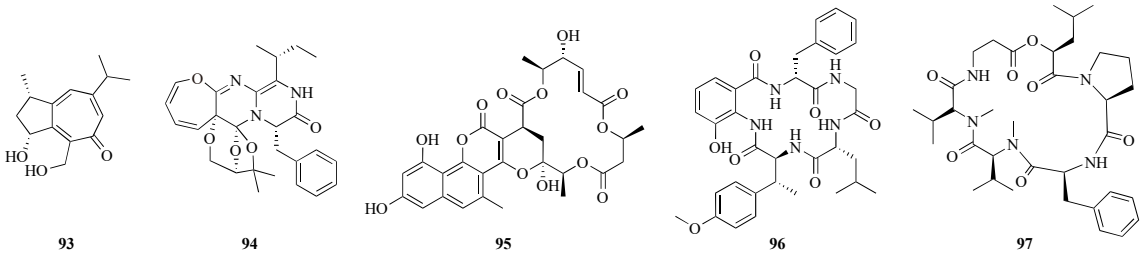


Fig. 8 Structures of compounds **93–97**.

3.4. Sources of marine actinomycetes

In the discovery of anti-inflammatory lead compounds, a substantial proportion of actinomycetes-derived products have demonstrated significant bioactivity, accounting for nearly half of the total (48.1%) (Fig. 9).

Saccharothrixin F (**98**), obtained from the actinomycete *Saccharothrix* sp. D09 [166], revealed anti-inflammatory activity by inhibiting the production of NO [167]. Deoxynyboquinone (**99**) was a natural small molecule isolated from an ocean aerobic actinomycete *Pseudonocardia antitumoralis* sp. nov SCSIO 01299 [168, 169]. Compound **99** could activate the Nrf2/ARE pathway, exerting potent anti-inflammatory effects *in vitro* and *in vivo*. It directly targeted Keap1, alkylating Cys489 in its Kelch domain to trigger Keap1 ubiquitination and degradation. This Nrf2 activation was mediated by DNQ's *α,β*-unsaturated amide group, positioning Keap1-Cys489 alkylators as promising anti-inflammatory therapeutics [170].

Eleven oleanane-type triterpenoids, soyasapogenol B1-B3 (**100–102**), B5–B11 (**103–109**), and B4 (**110**), were obtained from the sponge-derived actinomycete *Nonomuraea* sp. MYH-522 [171]. These compounds alleviated 5,6-dimethylxanthenone-4-acetic acid-induced inflammation in Raw264.7 cells *via* the stimulator of IFN/TANK-binding kinase 1/NF-κB signaling pathway [172].

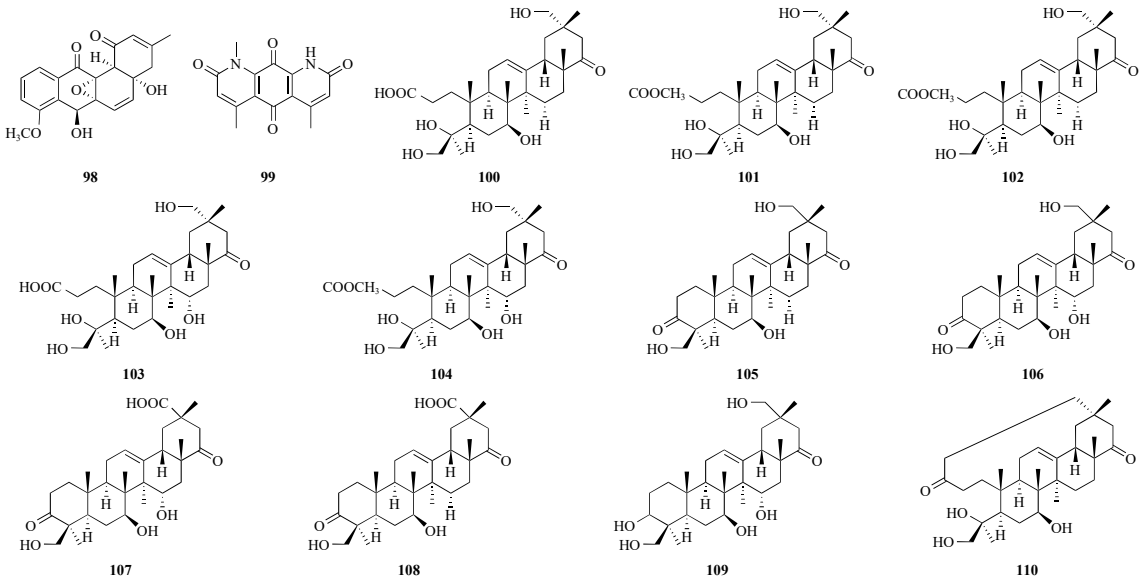


Fig. 9 Structures of compounds **98–110**.

4. Treating metabolic diseases drug lead compounds

At present, there are still relatively few marine derived lead compounds can be used to treat metabolic diseases. The representative lead compounds have only been discovered in marine plants and fungi.

4.1. Sources of marine plants

In marine plants, the versatile compound fucoxanthin has re-emerged as a noteworthy entity (Fig. 10). Fucoxanthin (**26**) was found in many types of seaweed, especially brown algae [173]. Fucoxanthin reduced ROS generation and ECM accumulation in high glucose (HG)-stimulated glomerular mesangial cells. It rescued HG-induced silent information regulator 1 (SIRT1) suppression and AKT activation-which promote FoxO3α nuclear exclusion-by enhancing FoxO3α nuclear translocation and transcriptional activity. Consequently, compound **26** upregulated manganese superoxide dismutase (MnSOD) expression, quenching ROS and suppressing collagen production. These findings indicated fucoxanthin alleviates HG-induced oxidative stress and fibrosis *via* AKT/SIRT1/FoxO3α signaling, supporting its potential for diabetic nephropathy therapy [174]. In addition, compound **26** could reduce palmitic acid-induced hepatic lipid deposition and obesity-associated steatosis in *ob/ob* mice. Mechanistically, it activated AMPK, stimulating both the KEAP1/Nrf2/ARE pathway to combat oxidative stress and the PGC-1α/NRF1 axis to enhance mitochondrial biogenesis. These findings supported fucoxanthin's therapeutic potential for metabolic-associated fatty liver disease (MAFLD) [175].

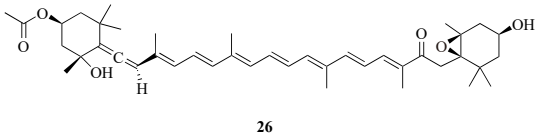


Fig. 10 Structure of compound **26**.

4.2. Sources of marine fungi (including mangrove-associated fungi)

Within this section, firstly two lead compounds HN-001 (**111**) and xyloketal B (**112**), demonstrate exceptional structural and functional profiles (Fig. 11).

A *p*-terphenyl derivate named as HN-001 (**111**), discovered in the fungus *Aspergillus* sp. c1, was revealed with the effects attenuating palmitic acid-induced hepatocyte death. This activity was mediated by IRE-1*α*-dependent inhibition of X-box binding protein 1 (XBP-1) splicing, blocking XBP-1s nuclear translocation and transcriptional activity. Crucially, ER stress relief required phospholipase A2 (PLA2), as PLA2 overexpression exacerbated lipotoxicity and attenuated **111**'s protection. *In vivo*, chronic **111** administration alleviated MAFLD manifestations-steatosis, injury, inflammation, and fibrosis-correlating with PLA2/IRE-1α/XBP-1s axis and JNK suppression, supporting **111** as a promising MAFLD therapeutic candidate targeting lipotoxicity [176]. Further study showed that, compound **111** dose/time-dependently activated heat shock factor 1 (HSF1), inducing its nuclear translocation and enhanced binding to PGC1α. *In vivo*, compound **111** alleviated diet-induced obesity and metabolic disorders. Treated mice showed enhanced UCP1 expression and mitochondrial biogenesis in white/brown adipose tissues. It is confirmed that **111** is a potential therapeutic candidacy for obesity-related diseases through HSF1/PGC1α-mediated energy expenditure enhancement [177].

Xyloketal B (**112**) was first obtained from the mangrove fungus *Xylaria* sp. no.2508, which was isolated from the seeds of mangrove in Hong Kong, and other coast of the SCS [178, 179]. Compound **112** could reduce atherosclerotic plaque area in aortic sinus and aorta of high-fat-fed apo$E^{-/-}$ mice dose-dependently. It was demonstrated that **112** have anti-atherosclerotic effects *in vivo* through antioxidant activity and endothelial function restoration [180]. Compound **112** improved hepatic histology and reduced blood lipids/glucose in high fat diet (HFD)/high-fructose-fed mice while attenuating hepatic steatosis. The results confirmed **112** exerts lipid-lowering effects *via* SREBP-1c pathway inhibition, positioning it as a promising NAFLD therapeutic [181]. Another research team found that **112** reduced systolic and diastolic blood pressure, and they demonstrated **112**'s dual antihypertensive mechanism: endothelial NO-sGC-cGMP signaling and smooth muscle Ca^{2+} regulation (VDCCs/SOCE), supporting its therapeutic potential for hypertension [182]. In addition, compound **112** ameliorated hepatic steatosis in HFD mice and upregulated PPARα/PGC1α expression. In MCD-induced NASH/fibrosis models, it exerted PPARα-mediated anti-inflammatory and antifibrotic effects: improving histology while reducing inflammatory factors, adhesion molecules, and fibrosis markers. These findings demonstrated **112** activated PPARα/PGC1α signaling to ameliorate multiple NAFLD stages, supporting its development as a novel NAFLD therapeutic strategy [183].

Two fumitremorgin derivatives, 12*R*,13*S*-dihydroxyfumitremorgin C (**113**) and tryprostatin A (**114**), isolated from the sponge-derived fungus *Aspergillus* sp. SCSIO 41420, reversed hepatic steatosis *in vitro* and reduced liver damage/blood cholesterol in high-cholesterol diet-fed mice. Critically, these effects were abolished in LXRα$^{-/-}$ mice. They outperformed conventional LXRα agonists by suppressing SREBP-1 expression, mitigating lipotoxicity. This demonstrated their potential as anti-hypercholesterolemic agents targeting LXRα [184].

Equisetin (**115**), derived from the deep-sea fungus *Fusarium equiseti* 10-33 [185], exerted anti-obesity activity by targeting adipose tissue, inhibiting adipogenesis *in vitro* and reducing HFD-induced obesity in mice. Its primary mechanism involved potent inhibition of 11*β*-hydroxysteroid dehydrogenase type 1 (11β-HSD1), an established therapeutic target in adipose tissue. Compound **115** directly bound 11*β*-HSD1 protein and demonstrated superior inhibitory intensity and anti-obesity efficacy compared to known 11*β*-HSD1 inhibitors [186]. Diaporisoindole B (**116**) was obtained from the fungal strain *Diaporthe* sp. SYSU-HQ3, isolated from the branches of the mangrove plant *Excoecaria agallocha* [187, 188]. Compound **116** reduced lipid accumulation in THP-1 macrophage cells by reducing lipid intake and promoting lipid efflux. It also promoted the reverse cholesterol transport mechanism by upregulating scavenger receptor class B type 1 and low-density lipoprotein receptor in HepG2 cells and has the potential to treat atherosclerosis [189]. Scequinadoline D (**117**), obtained from the soft coral derived fungus *Scedosporium apiospermum* F41-1, enhanced triglyceride accumulation in 3T3-L1 cells. It upregulated mRNA expression of PPARγ, AMPKα, C/EBPα, LXRα, SCD-1, and FABP4. Collectively, compound **117** acted as a PPARγ-targeting insulin sensitizer in adipocytes, holding therapeutic potential for type 2 diabetes mellitus [190].

Furanone (**118**) was isolated from the sponge-derived fungus *Setosphaeria* sp. SCSIO 41009, with a simple architecture [191]. It exhibited powerful lowering effects to total cholesterol and triglyceride, most likely by targeting LXRα and peroxisome proliferator-activated receptor α (PPARα), with weak cytotoxicity [192]. Dihydrotrichodimerol (**119**), derived from *Acremonium citrinum* isolated from mangrove sediments, attenuated hepatic lipid accumulation in oleic acid-induced NAFLD cellular and HFD-induced murine models. Furthermore, it potently inhibited hepatic steatosis in a choline-deficient, amino acid-defined diet-induced NAFLD mouse model, acting PPARα-dependently. Mechanistically, compound **119** PPARα-dependently upregulated SIRT1 expression, activating AMPK and inactivating acetyl-CoA carboxylase. Collectively, compound **119** represented a structurally distinct dual PPARα/γ ligand with therapeutic efficacy against NAFLD, offering a promising candidate for this unmet clinical need [193].

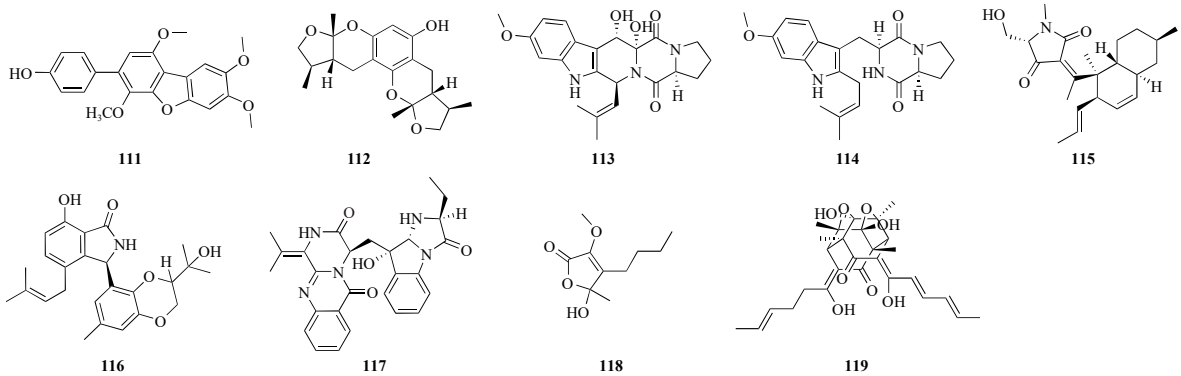


Fig. 11 Structures of compounds **111–119**.

5. Antimicrobial drug lead compounds

5.1. Sources of marine animal

Pyropheophorbide A (**120**) was isolated from seafood *Musculus senhousei*, bought from a seafood market in Guangzhou, China. Compound **120** was revealed with broad anti-influenza A activity *in vitro* against multiple strains. It acted early in infection by binding the virion lipid bilayer, disrupting membrane function and blocking viral entry. Treated mice exhibited prolonged survival rates and mean survival times versus untreated controls following influenza A infection [194] (Fig. 12).

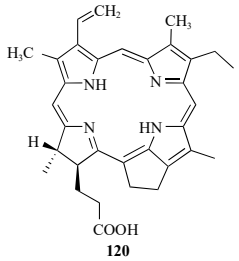


Fig. 12 Structure of compound **120**.

5.2. Sources of marine fungi

Quinolactacin H (**121**), obtained from *Penicillium* sp. ENP701 which was isolated from the water sample from the East China Sea, has been chemically fully synthesized for further research and development. Both (*R*) and (*S*)-quinolactacin H showed a strong inhibition and dispersion of *Pseudomonas aeruginosa* PAO1 biofilms, and it could be proposed and developed as a natural anti-biofilm agent [195]. Neoechinulin B (**122**), obtained from deep-sea sediment derived fungus *Eurotium rubrum* F33, potently inhibited H1N1 infection in MDCK cells and a panel of influenza strains, including amantadine- and oseltamivir-resistant clinical isolates. It bound influenza haemagglutinin, disrupting haemagglutinin-sialic acid receptor interaction and viral attachment, and maintained inhibitory efficacy against influenza A/WSN/33 virus through five serial passages. This potent, broad-spectrum activity with low resistance development establishes **122** as a promising lead for novel influenza inhibitors [196]. Equisetin (**115**), from the deep-sea sponge derived fungus *Fusarium equiseti* 33-10, could act synergistically against *Staphylococcus aureus* with colistin [197]. Low-level equisetin-resistant *Staphylococcus aureus* displayed collateral sensitivity to multiple classes of existing antibiotics with decreased capacity to produce biofilms [185]. Subsequently, compound **115** eradicated intracellular *Staphylococcus aureus* by enhancing host autophagy and inducing mitochondrial ROS generation. Its significant anti-infective efficacy was confirmed in a murine peritonitis model. Compound **115** employed a unique dual mechanism-modulating host-pathogen interactions-to clear intracellular bacteria, establishing it as a promising host-directed agent against intracellular pathogens [198].

Marine fungus derived quinolone alkaloid (**123**), inhibited influenza A virus (IAV) replication by targeting the viral nucleoprotein (NP), blocking viral RNA (vRNA) nuclear export. It disrupted CRM1 binding to NP's nuclear export signal 3, inhibiting NP/vRNP nuclear export, and interfered with NP-RNA binding (but not oligomerization), impairing vRNP assembly. Key residues (Arg305, Phe488–Gly490) mediate quinolone-NP interaction, defining a promising anti-IAV target. Orally administered **123** outperformed oseltamivir in protecting mice against IAV-induced mortality and weight loss [199]. Peniterphenyl A (**124**), obtained from a deep-sea-derived *Penicillium* sp. SCSIO 41030, inhibited herpes simplex virus (HSV)-1/2 in Vero cells with low cytotoxicity, outperforming acyclovir. Its mechanism involved blocking viral entry *via* direct interaction with glycoprotein D, disrupting viral adsorption and membrane fusion-distinct from nucleoside analogues like acyclovir [200].

Harzianopyridone (**125**), obtained from the sponge derived fungus *Trichoderma* sp. SMU 410205, can inhibit Zika virus (ZIKV) replication without showing obvious cytotoxicity in multiple cellular models. It reduced the expression of viral proteins and protected cells from viral infection. More importantly, compound **125** directly bound to ZIKV RNA-dependent RNA polymerase and suppressed its polymerase activity. Collectively, these findings suggested that **125** was a promising candidate for the development of anti-ZIKV drugs [201]. Spirostaphylotrichin X (**126**), obtained from the marine alga derived fungus *Cochliobolus lunatus* SCSIO 41401, potently inhibited multiple influenza strains by suppressing viral polymerase activity and progeny vRNA production. It directly bound the conserved cap-binding domain of PB2, and has been suggested to be a novel PB2-targeting lead compound for anti-influenza therapeutics [202] (Fig. 13).

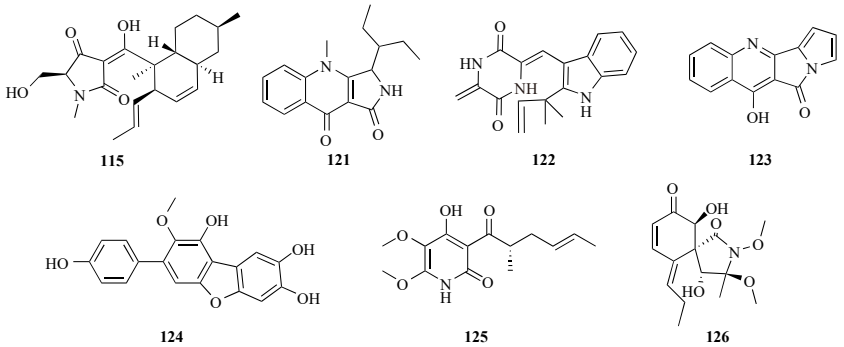


Fig. 13 Structures of compounds **115** and **121–126**.

5.3. Sources of marine actinomycetes

Three natural colletotryptins metabolites (Fig. 14), (−)colletotryptin B (**127**), (+)colletotryptin B (**128**), and 2-[(1*R*)-3-hydroxy-1-(1*H*-indol-3-yl)-2-methoxypropyl]-1*H*-indole-3-acetic acid (**129**), have been obtained from the marine sponge derived actinomycete strain *Rubrobacter radiotolerans* 05039. All of three metabolites suppressed chlamydial growth in a concentration-dependent manner *in vitro*, they seemed to target the mid-stage of the chlamydial developmental cycle by interfering with reticular body replication, but not directly inactivating the infectious elementary body [203].

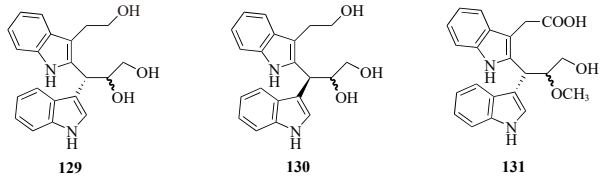


Fig. 14 Structures of compounds **127**–**129**.

6. Other pharmacologically active lead compounds

6.1. Sources of marine animal

There are two sea cucumber saponins, echinoside A (**130**) and holothurin A (**131**), obtained from *Pearsonothuria graeffei* from the Philippines [204]. In ovariectomized osteoporotic mice, 90-day oral **130** and **131** suppressed high bone turnover by reducing serum osteogenesis markers (ALP, collagen I, osteocalcin) and resorption markers (MMP-9, cathepsin K, TRAP), while increasing bone mineral density, apposition rate, and restoring trabecular/marrow stroma (echinoside A superior). Both saponins stimulated CB1 and mitogen-activated protein kinase phosphatase-1, downregulating PI3K/AKT/β-catenin signaling to alleviate osteogenesis; they also suppressed osteoclastogenesis by downregulating IKK, NF-κB, and phosphorylated NF-κB p65 *via* the OPG/RANKL/NF-κB pathway, reducing c-fos and NFATc1 expression [205].

Aaptamine (**4**), obtained from the marine sponge *Aaptos suberitoides* Brøndsted (Suberitidae), acted as a mixed-type inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), targeting key anionic sites. *In vivo*, it enhanced dyskinesia recovery, albeit marginally lower than donepezil. This dual AChE/BuChE inhibition underlied compound **4**'s anti-Alzheimer potential, identifying it as a novel structural scaffold for drug development [206]. (2*R*,11*S*,12*S*)-isosarcophytoxide (**132**), isolated from the soft coral *Sinularia scabra*, selectively inhibited B-cell proliferation (IC_{50} 4.4 μmol·L^{-1}, SI = 10.9). Further studies revealed suppression of cytokine production, abnormal activation, antigen presentation, and plasma cell formation, indicating therapeutic potential of **132** for autoimmune diseases [207]. 7-Dehydroerectasteroid F (**133**), obtained from the soft coral *Dendronephthya gigantea*, was showed potent protection against H_2O_2-induced oxidative damage in neuron-like PC12 cells by promoting nuclear translocation of Nrf2 and enhancing the expression of HO-1. Compound **133** represents the first steroid-type antioxidant from marine organisms, with the potential to be an antioxidant drug lead [208]. Astaxanthin (**90**) originates from many kinds of seafood, such as microalgae, trout, yeast, salmon, and krill [153, 209]. The research showed that **90** suppressed NO, ROS, and lipid peroxidation (LPO) in LPS-induced dendritic cells (DCs) and mice while elevating reduced glutathione (GSH) levels and GSH/oxidized glutathione ratio, enhancing cellular reductive status. It upregulated glutathione peroxidase, catalase, and superoxide dismutase activities, inhibited IL-1β/IL-17/TGF-β secretion, and activated the HO-1/Nrf2 pathway, confirming its antioxidant mechanism in DC-related inflammation for potential sepsis treatment [210] (Fig. 15).

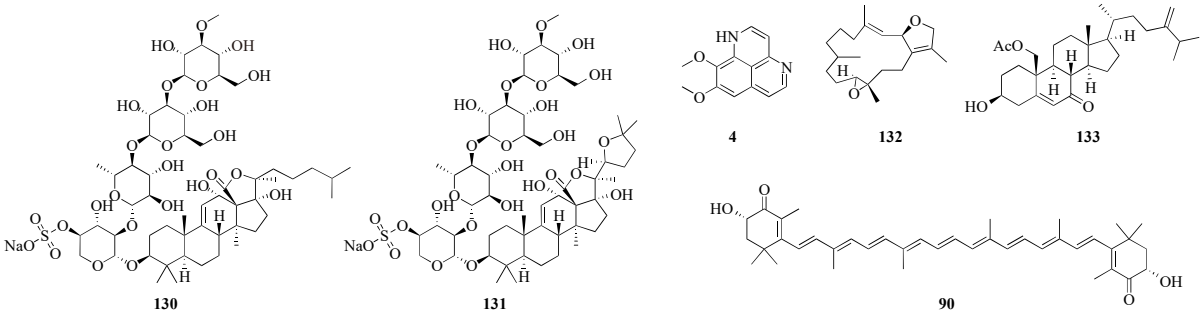


Fig. 15 Structures of compounds **4**, **90** and **130**–**133**.

6.2. Sources of marine plants (including mangrove plants)

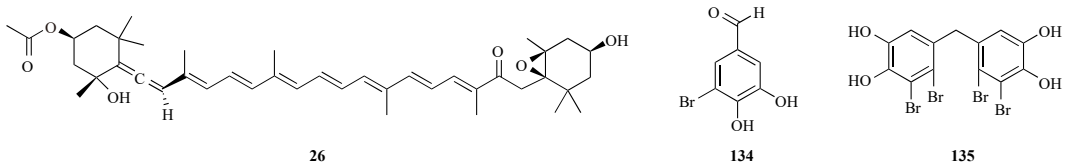
3-Bromo-4,5-dihydroxybenzaldehyde (**134**), a natural bromophenol isolated from marine red algae, such as *Polysiphonia morrowii*, *Rhodomela confervoides*, and *Polysiphonia urceolata* [211–213], dose-dependently attenuated oxygen and glucose deprivation (OGD)-induced cytotoxicity in cardiomyocytes, reducing apoptosis and Caspase-3 cleavage. It countered OGD-triggered oxidative stress (suppressed ROS/lipid peroxidation) and mitochondrial dysfunction (blocked cytochrome c release, restored ATP synthesis), while enhancing mitochondrial antioxidant enzymes (IDH2, GSH-Px, MnSOD). The compound upregulated p-AKT, silent information regulator 3 (SIRT3), and PGC1α expression; its cardioprotection was partially reversed by AKT inhibition or PGC1α downregulation. *In vivo*, it attenuated myocardial contractile dysfunction and activated the AKT-PGC1α-SIRT3 pathway, confirming this pathway's role in protection against myocardial IR injury [214]. Bis-(2,3-dibromo-4,5-dihydroxy-phenyl)-methane (**135**) was first isolated from the red alga *Odonthalia corymbifera* [215], and also chemical synthesized [216]. Compound **135** potently inhibited angiogenesis *in vitro* by suppressing endothelial sprouting, migration, proliferation, and tube formation. It acted as a selective multi-target RTK inhibitor, blocking FGFR2&3, VEGFR-2, and PDGFRα (IC_{50} 10 μmol·L^{-1}). Dose-dependent reductions in AKT/eNOS phosphorylation and NO production were observed, supporting its potential as an anti-angiogenic lead compound for novel multi-target RTK inhibitors [217].

The functions and the activities of seaweed derived fucoxanthin (**26**) were diverse. It was reported that **26** dose-dependently upregulated antioxidant enzymes (HO-1, GCLM, GCLC) in PC12 cells and improved swimming distance/brain tissue integrity in 6-OHDA-exposed zebrafish, confirming its neuroprotective potential against neurodegenerative diseases through Keap1 targeting [218]. In addition, compound **26** reversed scopolamine-induced AChE hyperactivity and brain-derived neurotrophic factor (BDNF)/ChAT suppression in mice, directly inhibiting AChE *via* non-competitive binding to its peripheral anionic site-demonstrating multi-target therapeutic potential for Alzheimer's disease through AChE inhibition and BDNF upregulation [219]. Compound **26** concentration-dependently blocked amyloid-β oligomers (AβOs)-induced neuronal apoptosis and intracellular ROS in SH-SY5Y cells, and prevented AβOs-induced PI3K/AKT/ERK dysregulation [220]. Further study showed that **26** inhibits β-amyloid (Aβ) fibril/oligomer formation and reduces AβOs neurotoxicity *in vitro* by blocking Aβ conformational transition *via* hydrophobic binding. It attenuates cognitive deficits in AβOs-injected

mice while suppressing oxidative stress, enhancing brain-derived neurotrophic factor (BDNF), and increasing hippocampal choline acetyltransferase-positive regions. These findings supported fucoxanthin's Alzheimer's therapeutic potential through Aβ assembly inhibition and neurotoxicity attenuation [221].

In summary, the team's previous research on fucoxanthin in the treatment of Alzheimer's found that although it exhibited anti-Alzheimer's disease neuroprotective effects *in vitro* and *in vivo*, it suffered from low bioavailability in the central nervous system (CNS). To overcame fucoxanthin's low CNS bioavailability, PLGA-PEG-Fuc nanoparticles (about 200 nm, negative charge) were developed for sustained CNS delivery. These nanoparticles inhibited Aβ fibril/oligomer formation, reduced AβOs-induced neurotoxicity *via* neuronal/microglial internalization *in vitro*, and surpassed free fucoxanthin in alleviating cognitive deficits in Alzheimer's mice upon IV administration-potentially through Nrf2/NF-κB modulation. PLGA-PEG nanoparticles thus enhanced fucoxanthin bioavailability and efficacy for Alzheimer's therapy [222].

Fucoxanthin has undoubtedly emerged as a prominent compound. Over the past decade, extensive research has been conducted both domestically and internationally. In addition to its remarkable bioactivities, its accessibility and high extraction yield serve as crucial prerequisites for comprehensive investigation. Among the compounds synthesized by algae, fucoxanthin is the most abundant of about 700 natural carotenoids, accounting for more than 10% of their aggregate mass [223]. The compound exhibits anti-obesity and anti-diabetic effects, particularly relevant given the global increase in metabolic syndrome. Metabolic syndrome is highly prevalent worldwide , with global prevalence ranging from 12.5% to 31.4% , and is significantly higher in certain regions and with increased country income (based on a meta-analysis of 1129 prevalence data from 28 million participant). [224] Although research attention has somewhat declined in recent years, fucoxanthin undoubtedly retains significant potential for treating metabolism-related diseases (Fig. 16).



26 134 135

Fig. 16 Structures of compounds **26** and **134**–**135**.

6.3. Sources of marine fungi (including mangrove-associated fungi)

Bioactive natural products from chordate-associated symbiotic microbial communities have received considerable attention (Fig. 17). Aspermeroterpene B (**136**) was obtained from the fungal strain *Aspergillus terreus* GZU-31-1 which was isolated from *Onchidium struma* collected from the SCS. Compound **136** exhibited a potent inhibitory effect on the activation of hepatic stellate cells by targeting Nrf2 signaling pathway [225]. Isaridin E (**97**), was isolated from the fungus *Amphichorda felina* sp. SYSU-MS7908, collected from an ascidian *Styela plicata* from the North Atoll of the Xisha Islands in the SCS [226]. Compound **97** concentration-dependently inhibited adenosine diphosphate(ADP)-induced platelet aggregation, activation, and secretion *in vitro*. It reduced $FeCl_3$-induced thrombosis dose-dependently without prolonging bleeding time. Mechanistically, it suppressed ADP-mediated PI3K/AKT phosphorylation. These results demonstrated its bleeding-sparing antithrombotic effect *via* selective ADP/PI3K/AKT inhibition, supporting its potential as a lead compound for arterial occlusive diseases [227].

A subset of lead compounds with excellent bioactivity exhibits relatively straightforward structural architectures. Tetrahydroauroglaucin (**137**), obtained from the sponge-derived fungus *Aspergillus ruber* TX-M4-1, attenuated MPTP/MPP^+-induced neurotoxicity by rectifying lipid metabolism disorders in Parkinson's models [228]. It suppressed lipid droplets (LDs) accumulation *via* RUBCN downregulation and enhanced autophagic flux. Conditional Rubcn knockdown abolished tetrahydroauroglaucin's neuroprotection and LD reduction, confirming its action through the RUBCN-autophagy pathway as a novel Parkinson's therapeutic strategy [229]. Penicisteck acid F (**138**), obtained from the mangrove-associated fungus *Penicillium steckii* SCSIO 41025, potently inhibited NF-κB and osteoclastogenesis *in vitro* by blocking RANKL-induced IκBα degradation, NF-κB p65 nuclear translocation, and NFATc1 activation/nuclear translocation [230, 231]. *In vivo*, it reduced osteoclast numbers and alleviated ovariectomy-induced osteoporosis, establishing this novel inhibitor as a promising antiosteoporosis lead [232]. Another mangrove-associated fungus derived compound, eupenicisirenin C (**139**), inhibited NF-κB and suppressed the cGAS-STING pathway, blocking RANKL-induced osteoclast differentiation in bone marrow macrophages. It attenuated prednisolone-induced osteoporosis in zebrafish, with transcriptome analysis implicating extracellular matrix receptor interaction pathways [233]. Steckwaic acid F (**140**), obtained from the algae-derived *Penicillium steckii* SCSIO 41040, suppressed RANKL-induced osteoclast differentiation by inhibiting LPS-induced NF-κB [234]. Sponge-associated fungus derived alternapyrone G (**141**) [235] not only suppressed M1 polarisation in LPS-stimulated BV2 microglia but also stimulated dendrite regeneration and neuronal survival after Aβ treatment, suggesting that it may be utilized as a privileged scaffold for Alzheimer's disease drug discovery [236].

Alternariol monomethyl ether (**142**) from the fungus *Alternaria* sp., attenuated food allergy symptoms and serum histamine release in mice while reducing splenic/mesenteric lymph node mast cells. It inhibited *β*-hexosaminidase/histamine release and suppressed mast cell activation *via* MAPK/NF-κB pathway modulation, corroborated by transcriptomic regulation of mast cell genes [237]. Irpetone A (**143**), obtained from the sponge-derived fungus *Irpex* sp. NBUF088, inhibited receptor activator of NF-κB ligand-induced osteoclastogenesis in bone marrow monocytes without causing notable cytotoxicity. It was also determined that **143** inhibited the phosphorylation of ERK1/2-JNK1/2-p38 MAPKs and the nuclear translocation of NF-κB, consequently suppressing the activation of MAPK and NF-κB signaling pathways [238]. Nodulisporenones A (**144**) and pestanoid A (**145**), obtained from the sponge-derived fungus *Pestalotiopsis* sp. NBUF-145, inhibited bone marrow monocyte osteoclastogenesis and their mechanism was the same as that of **143** [239]. Penicilliumin B (**146**), obtained from the deep-sea fungus *Penicillium* sp. F00-120 [240], inhibited renal fibrogenesis *in vitro* by disrupting oxidative stress in RMC cells, demonstrating potential as a natural renoprotective agent for diabetic nephropathy fibrosis [241]. Compound **146** protected against cisplatin-induced apoptosis in renal cells and mice by preserving mitochondrial morphology, suppressing mtROS, and activating AMPK. This AMPK activation triggered autophagy and mitochondrial biogenesis, establishing its potential for acute kidney injury treatment [242]. Talaroterphenyl A

(**147**), obtained from the mangrove-associated fungus *Talaromyces* sp. SCSIO 41412, inhibited phosphodiesterase 4 (PDE4), suppressed LPS-induced inflammation in RAW264.7 cells, and downregulated FN1/COL1/α-SMA in TGF-β1-induced pulmonary fibrosis-demonstrating potential as a marine-derived PDE4-targeting antifibrotic agent [243]. Butyrolactone I (**148**) was obtained from *Aspergillus* sp. isolated from a hydrothermal sulfide deposit in the southwest Indian Ocean. Deep-sea-derived **148** suppressed ovalbumin (OVA)-induced anaphylaxis in mice by reducing histamine/mMCP-1 levels, OVA-IgE, and splenic/mesenteric mast cells; downregulated c-KIT in BMMCs; and bound inhibitory receptor FcγRIIB-demonstrating mast cell-targeted anti-food allergy efficacy [244]. Another deep-sea fungus derived anti-food allergy agent, viridicatol (**149**) [245], was also discovered and revealed with the mechanism of suppressing Ca^{2+} accumulation [246].

Two nitrobenzoyl sesquiterpenoids, 6*β*,9*α*-dihydroxy-14-*p*-nitrobenzoylcinnamolide (**150**) and insulicolide A (**151**), were obtained from the marine alga-derived fungal strain *Aspergillus ochraceus* Jcma1F17 [98]. Compound **150** suppressed RANKL-induced osteoclastogenesis and bone resorption, by blocking IκBa phosphorylation, nuclear translocation of NF-κB p65/RelB, and NFATc1 activation while reducing DC-STAMP (but not c-Fos) expression *in vitro*, and ameliorated LPS-induced osteolysis *in vivo* [247]. Compound **151** inhibited osteoclastogenesis *in vitro* by blocking c-Fos/NFATc1 nuclear translocation and suppressing osteoclast-related genes/*DC-STAMP* (but not *NF-κB/MAPKs*), and protected against LPS-induced osteolysis *in vivo*, demonstrating therapeutic potential for osteoclast-related diseases [248].

A recurring star compound xyloketal B (**112**), obtained from the mangrove fungus *Xylaria* sp. [178, 179], significantly reduced infarct volume and neurological deficits in transient middle cerebral artery occlusion (tMCAO) mice with pre/post-treatment, without hemodynamic effects. It suppressed ROS overproduction, increased MnSOD, and inhibited TLR4/NF-κB/iNOS proteins while downregulating *IL-1β/TNF-α/IL-6/IFN-γ* mRNA and protecting blood-brain barrier integrity. Administered within 2-h post-stroke, it protected against cerebral ischemia *via* ROS/TLR4/NF-κB pathway suppression, demonstrating stroke therapeutic potential [249]. Circumdatin D (**152**), obtained from the fungus *Aspergillus ochraceus* LZDX32-15, delayed paralysis in Alzheimer's nematode models (CL4176) by suppressing AChE and inflammation-related genes. It reduced pro-inflammatory cytokines in LPS-stimulated microglia (BV-2/primary) and modulated TLR4-mediated NF-κB/MAPKs/JAK-STAT pathways, protecting neurons from LPS neurotoxicity [250]. Quinadoline B (**153**), obtained from the sponge-derived fungus *Aspergillus clavulus* LZD32-24, suppressed angiogenesis by inhibiting vascular outgrowth in zebrafish. It disrupted actin cytoskeleton *via* suppressing ROCK/MYPT1/MLC2/cofilin and FAK/Src pathways, and inhibited B16F10 melanoma lung metastasis in mice [251].

In addition to the activities mentioned above, the star compound xyloketal B has been extensively studied worldwide. A review in 2024 by Sreelekshmi Puthuvalnikarthil Udayan et al., systematically summarizes the multifaceted bioactivities of xyloketal B. It specifically identifies xyloketal B as one of the most potent variants with extensive and robust biological activities, including free radical scavenging capability, inhibition of cell proliferation, reduction of neonatal hypoxic-ischemic brain damage, antioxidant activity, acetylcholinesterase inhibition, and L-type calcium channel blockade, among others [252].

Concurrently, a significant synthetic chemistry breakthrough was achieved in 2023 by Evan O. Romero et al., who reported the first asymmetric total synthesis of xyloketal B. Their research employed a chemoenzymatic strategy, utilizing a biocatalytic phenyl hydroxylation reaction to obtain an ortho-quinone methide intermediate. This intermediate then underwent a cycloaddition reaction to stereoselectively generate the crucial cyclic ketal framework. The study utilized MicroED technology to rapidly confirm the relative configuration of the intermediate, culminating in the stereoselective synthesis of (+)-xyloketal B [253].

These recent publications confirm the multi-target therapeutic potential of xyloketal B, particularly for conditions such as Alzheimer's disease and atherosclerosis [252]. However, its complex stereochemistry remains a critical bottleneck for its synthesis and development as a drug. In summary, while recent research affirms the promising bioactivities of xyloketal B and marks important advances in synthetic methodology, significant challenges remain in advancing this lead compound into clinical investigation.

Additionally, a notable compound distinctively incorporates both polycyclic frameworks and extended aliphatic chains, demonstrating a substantial molecular weight. FGFC1 (**58**), first isolated from the metabolites of the deep-sea fungus *Starchbotrys longispora* (or *S. microspora*) FG216, was an isoindolone alkaloid [254]. Compound **58** protected hCMEC/D3 barrier integrity against H_2O_2-induced damage by inhibiting transendothelial electrical resistance (tcTEER) decline, upregulating claudin-5 (CLDN-5), and preventing VE-cadherin (VE-cad) downregulation at the transcriptional level. Molecular docking confirmed direct binding to CLDN-5/VE-cad, revealing FGFC1's novel dual role in thrombolysis and barrier protection to reduce hemorrhagic risk in cerebral thrombosis therapy [255].

6.4. Sources of marine actinomycetes (including mangrove-associated actinomycetes)

All lead compounds derived from marine actinomycetes in this subset exhibit high molecular weights exceeding 500 Da (Fig. 18). Two piericidin glycosides, 13-hydroxyglucopiericidin A (**154**) and 13-hydroxypiericidin A 10-*O*-*α*-*D*-glucose (1→6)-*β*-*D*-glucoside (**155**), were discovered from the strain *Streptomyces psammoticus* SCSIO NS126 which was isolated from a mangrove sediment [126]. Compound **154** bound Cys83 of PRDX1, augmenting its peroxidase activity to alleviate kidney injury in Prdx1-overexpressing mice. It promoted PRDX1 nuclear translocation and activates Nrf2/HO-1/NQO1 pathway to inhibit ROS. To overcome poor bioavailability (2.6%) and renal distribution, a pH-sensitive kidney-targeting dodecanamine-chitosan nanoparticle was developed, enhancing therapeutic efficiency *via* reduced metabolic elimination and UGT-mediated biotransformation modulation, advancing marine-derived AKI drug development [256]. Compound **155** bound protein tyrosine phosphatase nonreceptor type 22 (PTPN22) with high affinity, inhibiting osteogenic responses and mitochondrial stress in human aortic valve interstitial cells. It alleviated aortic valve lesions in injured mice, validating PTPN22 inhibition as a novel strategy for anti-calcific aortic valve disease drug development [257].

Chrexanthomycins C (**156**) and F (**157**), obtained from the marine actinomycete strain *Streptomyces chrestomyceticus*, exhibited potent transient receptor potential vanilloid-1 (TRPV1) inhibition. Both compounds suppressed capsaicin-induced pain in mice comparably to capsazepine and SAR analysis indicated functional group-dependent activity. These findings underscored the therapeutic potential of chrexanthomycins and paved the way for further investigations into marine-derived TRPV1 modulators for pain management [258].

7. Conclusions and perspectives

7.1. The marine characteristics and marine rules of drug leads

This review systematically analyzes 186 valid data points derived from 157 distinct marine natural small-molecule drug leads

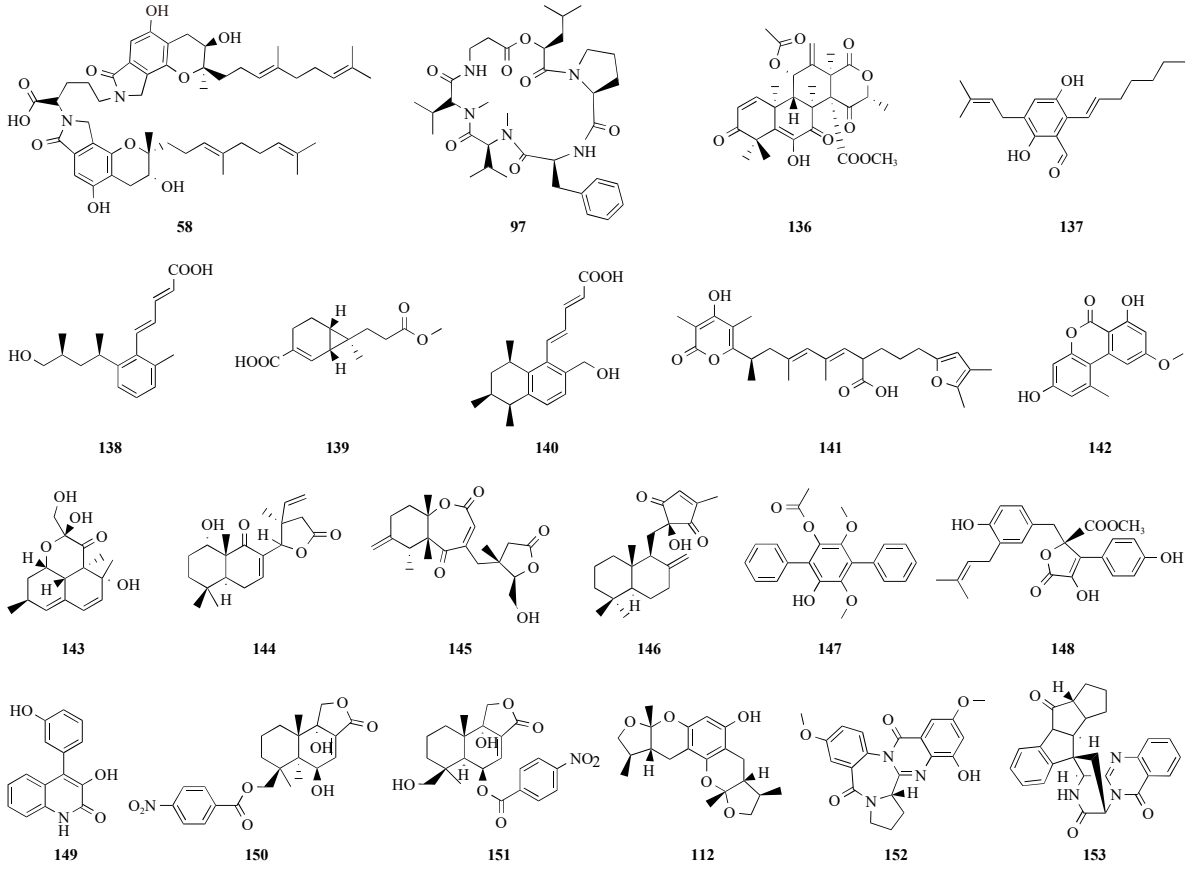


Fig. 17 Structures of compounds **58**, **97** and **136–153**.

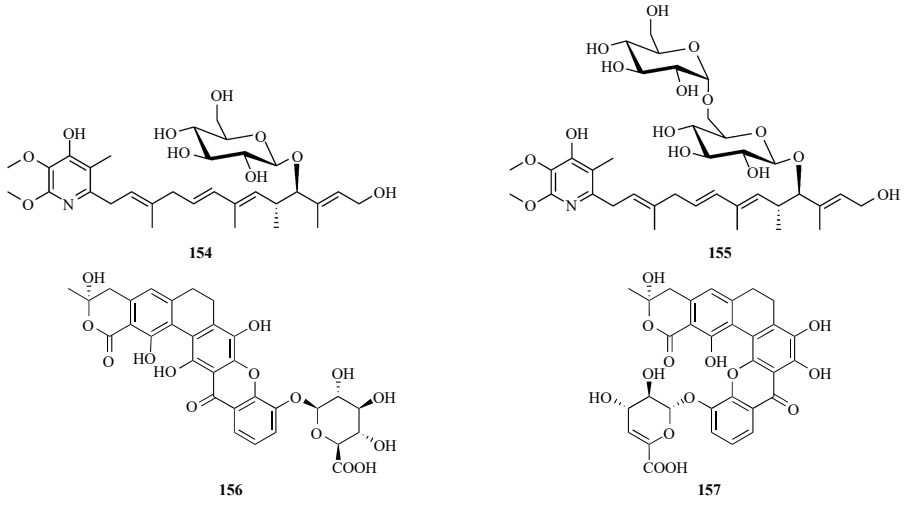


Fig. 18 Structures of compounds **154–157**.

discovered in China between 2015 and 2024. Subsequent statistical analyses of these 186 valid data points will be conducted across four key dimensions: the annual number of lead compounds discovered, the diseases targeted, the sources, and the molecular weights.

7.1.1. The temporal trends in marine-derived lead compounds discovery

The chronological distribution of 186 valid data points exhibited a biphasic growth pattern with critical inflection points (Fig. 19).

Annual discovery counts remained low (lowest 2.2%–highest 9.7%) from 2015 to 2019, followed by a sustained surge post-2020, peaking at 19.9% in 2024. Three key drivers likely contributed to this trajectory.

Technological Convergence: The 2017–2018 growth phase (8.6%–9.7%) aligns with the widespread adoption of single-cell metabolomics in marine microbiology. Subsequent declines in 2019 (3.2%) reflect the transitional challenges in integrating clustered regularly interspaced short palindromic repeats (CRISPR)-based genome mining with traditional activity-guided isolation. Post-2021 stabilisation corresponds to AI-driven virtual screening platforms (e.g., MarinePharmDB 2.0) achieved > 40% hit-rate improvements.

COVID-19 Pandemic Catalyzed Innovation (2020–2021): The 2.7 folds year-on-year increase from 2019 (3.2%) to 2020

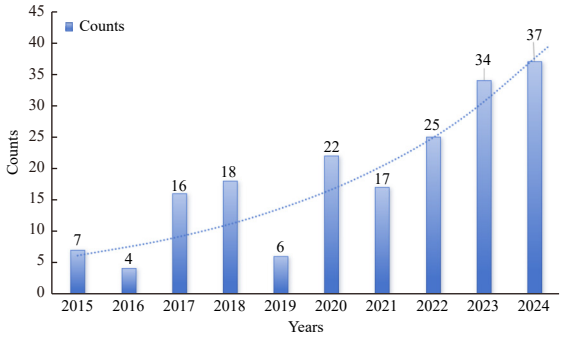


Fig. 19 Number of lead compounds discovered annual.

(11.8%) coincided with global shifts toward antiviral drug discovery [259, 260]. Marine organisms have become prioritized screening targets because of their evolutionary advantages in producing immunomodulatory compounds (e.g., nucleoside analogues from sponges) [261]. China's "Blue Drug Bank" initiative (launched in 2020) specifically allocated $220M USD toward marine antiviral research, accelerating the high-throughput screening of archived deep-sea samples.

Policy-Driven Expansion (2021–2024): The 14th Five-Year Plan (2021–2025) established marine biomedicine as a national strategic focus, correlating with compound discovery rates doubling from 2021 (9.1%) to 2024 (19.9%). The implementation of the "Deep Sea and Polar Key Technology" national special project (2022–2030) has enabled the systematic sampling of previously inaccessible ecosystems. A total of 78% of the 2022–2024 compounds originated from hadal trenches (> 6000 m) and Antarctic ice shelf communities.

7.1.2. The therapeutic abilities distribution in marine-derived lead compounds

The pharmacological activity spectrum of 186 valid data points demonstrate a pronounced focus on oncology, with antitumor agents constituting 50.0% of the total (n = 93), followed by anti-inflammatory (14.5%, n = 27) and treatment of metabolic disease (8.1%, n = 15) activities. Notably, the "Other" category (21.0%, n = 39) reveals emerging therapeutic priorities, including compounds targeting osteoporosis (5.4%, n = 10) and targeting Alzheimer's disease (3.8%, n = 7), suggesting paradigm shifts in marine drug discovery (Fig. 20).

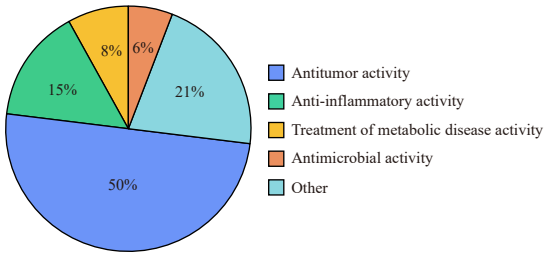


Fig. 20 Pharmacological activity of lead compounds.

Here are some conjectures of the key drivers of distribution patterns:

Oncology Dominance: The high proportion of antitumor compounds aligns with the evolutionary strategies of marine organisms to produce cytotoxic secondary metabolites (e.g., microtubule-disrupting dolastatins). China's National Cancer Centre prioritized marine antitumor drug development in its 2016–2025 plan, funding 63% of tumor-related marine studies through the National Key Research and Development Program.

Neurodegenerative Disease Breakthroughs: Alzheimer's disease-targeting compounds frequently derive from brain-penetrant marine alkaloids (e.g., homoisoprenoid scaffolds from Red Sea sponges) that inhibit Aβ42 aggregation (IC_{50} < 1 μmol·L^{-1}) while crossing the blood-brain barrier, a dual-action rarity in terrestrial molecules. The 2021 "Brain Science and Brain-Like Intelligence" national project accelerated these discoveries.

Osteoporosis Innovation: Marine osteogenic agents (e.g., sulfated polysaccharides from Sargassum) upregulate BMP-2/Runx2 pathways with 3–5 × greater efficacy than bisphosphonates. This correlates with China's aging population strategy (2020–2035), which allocated ¥850M to musculoskeletal disorder research.

7.1.3. The biological origins of marine-derived lead compounds

The taxonomic distribution of 186 valid data points were divided into five parts: sources of marine animals, sources of marine plants (including mangrove plants), sources of marine fungi (including mangrove fungi), sources of marine actinomycetes (including mangrove actinomycetes), sources of marine bacteria (including mangrove bacteria), and other sources. The results revealed a distinctive ecological stratification, with marine fungi emerging as the predominant source (45.2%, n = 84), followed by marine animals (22.0%, n = 41) and actinomycetes (21.0%, n = 39) (Fig. 21). This highlights the exceptional pharmaceutical potential of mangrove ecosystems, with 22 structurally novel compounds (11.8%) originating exclusively from this transitional coastal biome.

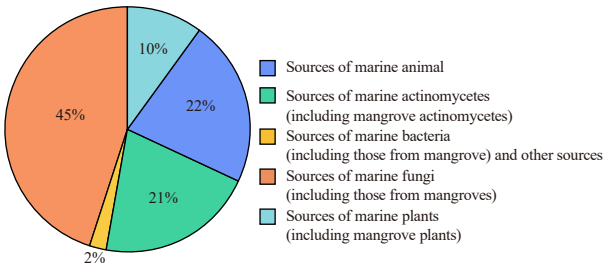


Fig. 21 Sources of lead compounds.

This pattern highlights three critical drivers of marine bioprospecting strategies:

Fungal Dominance in Chemical Diversity: Marine microorganisms, especially fungi and bacteria, are a valuable source of diverse bioactive natural products with potential applications. Fungi are prolific producers of diverse secondary metabolites, offering a rich source of chemical diversity for drug discovery with various pharmacological activities [21, 262]. These findings highlight the potential of marine fungi as valuable resources for novel bioactive compounds with pharmaceutical applications.

Actinomycete Renaissance: Actinomycetes, particularly those from marine environments, have emerged as a promising source of novel bioactive compounds for drug development [263, 264]. These microorganisms produce a diverse array of secondary metabolites with potential therapeutic applications, including antibiotics [265]. Recent advancements in isolation techniques, high-throughput fermentation, genome mining, and combinatorial biosynthesis have facilitated the discovery of novel compounds from actinomycetes [264, 266]. As antibiotic resistance continues to pose a global health threat, the exploration of actinomycetes as a source of novel bioactive compounds remains crucial for developing new therapeutic agents [265].

Special habitat of mangroves: Mangrove ecosystems, despite their limited geographical distribution, are emerging as hotspots for novel bioactive compounds with pharmaceutical potential [267]. The unique environmental conditions of mangroves, characterized by periodic flooding and high salinity, contribute to the production of structurally unprecedented bioactive natural prod-

ucts [268]. These compounds exhibit a wide range of biological activities, including antiviral, anticancer, and enzyme-inhibitory effects [269]. As of 2022, 519 natural products have been isolated from mangrove sediment-derived microbes [270]. This disproportionate chemical yield from mangrove-associated organisms underscores their immense potential as sources of novel drug candidates and warrants further exploration of this important ecological niche.

7.1.4. The molecular weight distribution in marine-derived lead compounds with Lipinski's rule implications

"Rule of Five" predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight (*Mr*) is greater than 500 and the calculated Log *P* (CLog *P*) is greater than 5 (or Mlog *P* > 4.15) [271, 272].

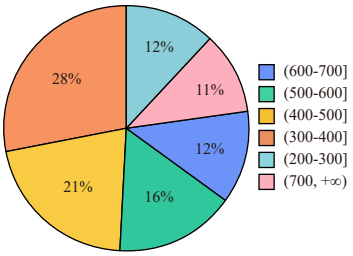


Fig. 22 Relative molecular weight of lead compounds.

The molecular weight distribution analysis of 186 valid data points revealed a striking deviation from Lipinski's "Rule of Five" criteria, where only 40.3% (*n* = 75) of compounds fell within the conventional drug-like molecular weight range (200–400 Da) [273, 274], and 20.8% (*n* = 40) in the 400–500 Da range. Notably, 38.2% of compounds exceeded 500 Da, with significant populations in the 500–600 Da (15.1%, *n* = 29), 600–700 Da (11.5%, *n* = 22), and > 700 Da (12.5%, *n* = 20) ranges (Fig. 22). This distribution pattern challenges the traditional small molecule drug paradigm (*Mr* < 500 Da) and highlights three distinctive marine pharmacological characteristics:

Structural Complexity-Enabled Bioactivity: Marine organisms frequently produce macrocyclic polyketides (e.g., bryostatins), glycosylated alkaloids, and peptide-polyketide hybrids (e.g., dolastatins) with *Mr* > 600 Da. These architectures enable multitarget engagement through extended binding interfaces, as exemplified by 843 Da ecteinascidin 743 (trabectedin), an FDA-approved anticancer agent that interacts with DNA minor grooves while maintaining cell permeability [275–277].

Enhanced Target Affinity Compensation: Despite exceeding the traditional "rule of 5" guidelines for oral bioavailability, many high-molecular-weight compounds (> 500 Da) have successfully become drugs, often utilizing intramolecular hydrogen bonding and macrocyclization to enhance their properties. High-MW marine compounds (> 500 Da) frequently achieve sub-nanomolar potency through optimized hydrogen bonding networks and hydrophobic complementarity, effectively compensating for potential bioavailability limitations [278]. The 724 Da ziconotide (ω-conotoxin MVIIA) demonstrates this principle through selective Ca^{2+} channel blockade with a 1000-fold higher affinity than small molecule alternatives [276, 279].

Alternative Administration Paradigms: The prevalence of MW > 500 Da compounds (39.1%) aligns with modern therapeutic strategies utilizing intravenous/nanoparticle delivery systems, as seen in antibody-drug conjugates (ADCs) incorporating marine payloads. ADCs have emerged as a promising therapeutic approach, particularly in cancer treatment, by combining the targeting specificity of antibodies with potent cytotoxins [280]. Marine-derived payloads, such as monomethyl auristatin E (MMAE, 718 Da), are increasingly utilized in ADCs because of their impressive structural diversity and biological properties [281, 282]. This shifts the focus from oral bioavailability to the targeted tissue distribution.

These findings suggest that marine drug discovery may require an expanded "Marine Rule" framework, where higher MW thresholds (up to 800 Da) are acceptable when accompanied by:

- Conformational rigidity reducing entropy penalty;
- Amphipathic domains enhancing membrane interaction;
- Endogenous transport mechanisms (e.g., LAT1 amino acid transporter recognition).

These data reinforce marine organisms as sources of "beyond Rule of Five" (bRo5) therapeutics, potentially establishing a new drug discovery paradigm that prioritises functional complexity over strict molecular weight compliance.

7.2. The discovery of marine natural small molecule drug leads is of great significance to the development of new drugs

7.2.1. MNPs offer infinite possibilities for discovering marine natural small molecule drug leads.

The biodiversity and ecological pressures of the marine environment have driven the evolution of unique metabolic pathways, resulting in compounds with complex structures and specific biological targets that are not commonly found in terrestrial sources [29, 33, 283–285]. The past decade has seen a surge in MNPs discovery, with over a thousand new structures reported annually [286]. Despite challenges such as limited supply and environmental concerns, MNPs continue to provide valuable leads for drug development [287].

7.2.2. Expanding the target and mechanism of drug action.

The discovery of marine natural small molecule drug leads offer promising avenues for drug discovery, revealing new therapeutic targets and biological mechanisms. These small molecules partly easily penetrate cells and target intracellular proteins [288], and also have the abilities to interact with previously unknown proteins or biomolecules, revealing potential treatment pathways [289]. This approach has expanded the scope of drug targets beyond traditional DNA replication and mitotic processes to include signaling pathways, cell surface receptors, and extracellular ligands [289]. At the same time, novel target discovery methods have improved efficiency and reduced costs in drug development [290, 291]. These discoveries can lead to innovative treatments for diseases with limited current options, including rare and complex conditions [292, 293].

7.2.3. Enriching pharmacochemical diversity to meet medical needs

The chemical diversity of leading compounds provides medicinal chemists with ample opportunities for modification and optimization to improve pharmacokinetic properties, enhance activity, increase selectivity, and reduce toxicity, thereby accelerating drug development [294–297].

This offer promising potential for drug discovery, particularly in addressing diseases with limited treatment options, such as cancer, neurodegenerative disorders, and antibiotic-resistant infections [298, 299]. Several marine-derived drugs including cytarabine and trabectedin, have already reached the market or are in clinical trials, primarily for cancer treatment, demonstrating their therapeutic value [29, 300, 301], offering hope for novel therapies to address global health challenges.

7.2.4. Promoting interdisciplinary research and collaboration.

The discovery of marine lead compounds processes involve interdisciplinary collaboration among marine biologists, chemists, and pharmacologists [299]. Interdisciplinary collaboration and

advanced technologies have accelerated the identification and characterization of bioactive marine substances [302]. For example metabolomics [303]; pharmacological approaches [304]; analytical technologies [302, 305, 306]; metagenomics and synthetic biology and so on [299, 307], are accelerating the discovery and development of marine-derived drugs, which could help accelerate the translation of marine natural small molecule drugs from discovery to clinical application.

7.3. A deeper understanding of the challenges and future perspectives of lead compounds is paramount for the advancement of the field

Marine natural product drug discovery represents both tremendous opportunity and significant challenges that require innovative solutions across multiple domains.

7.3.1. Current challenges and limitations

The field faces several persistent obstacles that limit the translation of promising marine compounds into therapeutic agents. Supply problems remain a critical bottleneck, as marine organisms often produce bioactive compounds in extremely low quantities [308, 309]. The structural complexity of marine natural products creates additional hurdles, making chemical synthesis challenging and expensive [310, 311]. Many marine-derived compounds also exhibit poor pharmacokinetic properties, including low oral bioavailability, which limits their therapeutic utility [308].

7.3.2. Technological and biotechnological solutions

Recent innovations are systematically addressing these limitations. Advanced analytical techniques, including nanoscale NMR and computational chemistry, now enable structure determination from minimal sample quantities [305, 312]. Sampling strategies have expanded to include organisms from extreme ocean environments, broadening the chemical diversity available for drug discovery [312].

Synthetic biology and metabolic engineering offer particularly promising approaches for sustainable production. Microbial cell factories can potentially provide scalable, environmentally sustainable alternatives to marine source extraction [308]. Genetic engineering and re-engineering of biosynthetic gene clusters are yielding novel agents with enhanced pharmaceutical properties compared to natural products [310].

Artificial intelligence and machine learning are increasingly integrated into marine natural product research, accelerating both discovery and development processes [299, 313]. These technologies enable more efficient screening, structure-activity relationship prediction, and optimization of lead compounds.

7.3.3. Clinical success and pipeline

Despite challenges, the field has achieved notable successes, with several marine-derived drugs receiving regulatory approval, particularly for cancer and pain treatment [310, 314]. The clinical pipeline remains robust, with numerous marine compounds in various stages of development [308].

7.3.4. Future perspectives

The convergence of interdisciplinary approaches which combining marine biology, chemistry, pharmacology, and computational sciences is accelerating progress [299]. Metagenomics approaches are expanding access to previously unculturable marine microorganisms, potentially unlocking vast new chemical diversity [299]. Advanced target identification technologies are enabling earlier mechanism-of-action determination, which can motivate investment in challenging synthetic approaches [305]. The field's evolution toward sustainable practices, combined with technological innovations, suggests that marine natural products will continue yielding "first-in-class" therapeutic agents while addressing environmental and supply concerns [299, 310].

8. Conclusion

This systematic review analyzes 186 valid data points derived from 157 distinct marine natural small-molecule drug leads discovered by Chinese research teams between 2015–2024, revealing transformative shifts in marine drug discovery paradigms. Temporally, annual discovery rates surged 5.2-fold from 2015 (3.8%) to 2024 (19.9%). Therapeutically, while antitumor agents predominated (50.0%), emerging candidates for Alzheimer's disease (n = 7, 3.8%) and osteoporosis (n = 10, 5.4%) highlighted marine chemistry's capacity to address complex pathophysiology through multi-target mechanisms. Ecologically, marine fungi emerged as dominant sources (45.2%), and it is worth mentioning that the mangrove symbiont source rate reached 11.8%, showing its potential discoverable abilities. Key findings demonstrate that 38.2% of compounds exceed Lipinski's 500 Da threshold, with higher-molecular-weight (> 500 Da) agents exhibiting enhanced multi-target engagement through macrocyclic architectures (e.g., polyketide-alkaloid hybrids). These findings collectively challenge conventional drug-likeness criteria and propose a "Marine Rule" framework emphasizing: 1) Conformational rigidity to offset high *Mr* bioavailability limitations, 2) Ecosystem-driven chemical evolution as a scaffold optimization strategy, and 3) Therapeutic repurposing of chemical defense molecules. China's leadership is evidenced by three paradigm-shifting contributions: deep-sea sampling robotics enabling > 6,000 m hadal zone bioprospecting, AI-accelerated virtual screening platforms improving hit rates by 40%, and national policies converting ecological conservation (e.g., 2023 Mangrove Protection Act) into drug discovery pipelines. This synthesis establishes MNPs as essential components of next-generation therapeutics for refractory diseases while redefining molecular guidelines for oceanic drug space exploration. Thus, this review is of significant importance for understanding the current state of marine drug research in China. The statistical and analytical results may contribute to innovative work in the field of marine natural small molecule drug lead discovery.

It is important to note that the 157 lead compounds systematically analyzed herein by no means represent an exhaustive list of all discoveries in this field within China over the past decade. Nonetheless, we sincerely hope that the collated data and preliminary analyses provided in this review may serve as a useful reference for researchers in the community.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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