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Medicinal Chemistry and Rational Drugs 2018: Marine bioactive natural products from coral-derived fungi collected from the South China Sea

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Abstract

Symbiotic microorganisms in corals have proven to be a rich source of structurally novel and biologically active secondary metabolites that have become interesting and significant resources for drug discovery. In recent years, during our ongoing study on bioactive natural products from the South China Sea, diverse bioactive secondary metabolites with variety structures have been isolated from coral-derived fungi, such as alkaloids, macrolides, anthraquinones, and peptides. For instance, a pair of new enantiomeric alkaloid dimers, (+)- and (−)-Pestaloxazine A, with unprecedented symmetric spiro-[oxazinanepiperazinedione] skeleton, consisting of 22 carbons and 12 heteroatoms, were isolated from a Pestalotiopsis sp. fungus derived from the soft coral Sarcophyton sp.. A series of prenylated indole alkaloids were isolated from Aspergillus sp. fungus derived from the gorgonian coral Dichotella gemmacea. Quinazoline alkaloids with heptacyclic skeleton formed via a bridging hemiaminal linkage was isolated from Scopulariopsis sp. fungus derived from gorgonian Carijoa sp. Prenylated dihydroquinolone derivatives were obtained from the fungus Aspergillus sp. cultured from gorgonian Muricella abnormalis. And a series of 14-membered resorcylic acid lactones (RALs) belonging to a family of benzannulated macrolides were obtained from a gorgonian-derived fungal strain Cochliobolus lunatus. The compounds exhibited diverse promising bioactivities, including antifouling activity against barnacle B amphitrite, antibacterial activity towards pathogenic bacteria, cytotoxicity against human tumour cell lines, and antiviral activity against human respiratory syncytial virus (RSV) and enterovirus 71 (EV 71). It could be concluded that the bioactive secondary metabolites produced by coral-derived symbiotic microorganisms should be a rich source for discovery of marine lead compounds.

The marine environment has been proven to be a rich source of new bioactive natural products for drug discovery. Coral reefs are among the most productive ecosystems and are a source of a large group of structurally unique biosynthetic products. To date, more than 40,000 marine natural products (MNPs) have been identified from various marine organisms, such as sponges, cnidarians, tunicates, molluscs, echinoderms, bryozoans, red algae, brown algae, green algae, and microorganisms (Carroll et al. 2019; Deshmukh et al. 2017; Jiménez 2018; Leal et al. 2016; Newman and Cragg 2016b). The upward trend in the discovery of new MNPs sourced from marine microorganisms continues unabated and now represents 57% of the total new MNPs reported in 2017 (Carroll et al. 2019). Based upon the putative biogenetic origins, these MNPs can be classified as polyketides, terpenoids, alkaloids, steroids, lactones, peptides, phenols, and lipids. Also, a large proportion of MNPs display interesting pharmaceutical activities, such as cytotoxic, antimicrobial, hypolipidemic, anti-inflammatory, antimalarial, analgesic, and antiasthmatic activities (According to the following websites: http://marinepharmacology.midwestern.edu; Jiménez 2018). Hence, MNPs are considered as an excellent and potentially valuable source for new chemical entities with novel structures and distinct mechanisms of action. To date, there have been 13 approved therapeutic agents that could be considered derivatives of MNPs (Altmann 2017; Jiménez 2018; Newman 2019; Pereira et al. 2019). Moreover, more than 30 MNP derivatives constitute the global marine pharmaceutical clinical pipeline in Phases III, II or I of drug development (According to the following websites: http://marinepharmacology.midwestern.edu; http://pharma.id.informa.com (accessed on August 6, 2019); Jiménez 2018; Newman 2019; Pereira et al. 2019). The significant potential for new drug development based on MNPs in all disease areas has been previously discussed (Newman and Cragg 2016a).

Marine invertebrates have proven to be a primary source of bioactive MNPs, as many serve as chemical defense tools against predators, competitors and other ecological pressures. It has been demonstrated that the true origin of most MNPs appears to be the microorganisms living in concert with invertebrates. Most invertebrates are sessile, soft-bodied and move slowly, and are thus subject to potential parasite predation and detrimental microbial colonization. Therefore, they require a complex arsenal of

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secondary metabolites produced by their symbiotic microorganisms to facilitate a form of chemical defense (Jiménez 2018; Wang et al. 2008). This is likely the reason why MNPs from marine invertebrates and their symbiotic microorganisms are a rich sources of diverse and bioactive secondary metabolites (Martins et al. 2014; Mayer et al. 2010; Newman and Cragg 2016b). The chemical ecology underlying invertebrate–microorganism interactions provides a great opportunity for natural product chemists to mine for novel drug discovery. Therefore, the invertebrates and the abundant microorganisms in their ecosystems have attracted widespread attention for producing novel structural metabolites with potential bioactive applications (Blunt et al. 2018).

In the recent decade, the China Sea, especially the South China Sea, has become a hot spot in searching for novel bioactive MNPs. The invertebrates including sponges, soft corals, gorgonians and tunicates are prolific in the coral reefs in the South China Sea, and the microorganisms associated with these invertebrates have been demonstrated as a distinctive source for new bioactive MNPs.

In recent years, we have initiated a research program to find biological active MNPs based on marine chemical ecology (Figs. 1, 2) (Hou et al. 2015, 2019a; Wang et al. 2008). A total of 709 MNPs including 307 new compounds have been obtained from marine invertebrates and their symbiotic microorganisms collected from the South China Sea. In this review, we summarize the representative 287 MNPs (Table 1) obtained by our group, highlighting multiple structural types of compounds and demonstrating discovery, diversity, compound mining, and bioactive application. The goal is to provide further inspiration for the discovery of bioactive MNPs and subsequent drugs development.