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·Review·

Recent advances in isolation, synthesis, and evaluation of bioactivities of bispyrroloquinone alkaloids of marine origin

NIJAMPATNAM Bhavitavya, DUTTA Shilpa, VELU Sadanandan E.*

Department of Chemistry, University of Alabama at Birmingham, Birmingham, AL 35294, USA

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[ABSTRACT] The ocean continues to provide a plethora of unique scaffolds capable of remarkable biological applications. A large number of pyrroloiminoquinone alkaloids, including discorhabdins, epinardins, batzellines, makaluvamines, and veiutamine, have been isolated from various marine organisms. A class of pyrroloiminoquinone-related alkaloids, known as bispyrroloquinones, is the focus of this review article. This family of marine alkaloids, which contain an aryl substituted bispyrroloquinone ring system, includes three subclasses of alkaloids namely, wakayin, tsitsikammamines A-B, and zyzzyanones A-D. Both wakayin and the tsitsikammamines contain a tetracyclic fused bispyrroloiminoquinone ring system, while zyzzyanones contain a fused tricyclic bispyrroloquinone ring system. The unique chemical structures of these marine natural products and their diverse biological properties, including antifungal and antimicrobial activity, as well as the potent, albeit generally nonspecific and universal cytotoxicities, have attracted great interest of synthetic chemists over the past three decades. Tsitsikammamines, wakayin, and several of their analogs show inhibition of topoisomerases. One additional possible mechanism of anticancer activity of tsitsikammamines analogs that has been discovered recently is through the inhibition of indoleamine 2, 3-dioxygenase, an enzyme involved in tumoral immune resistance. This review discusses the isolation, synthesis, and evaluation of bioactivities of bispyrroloquinone alkaloids and their analogs.

[KEY WORDS] Bispyrroloquinones; Tsitsikammamines; Wakayin; Zyzzyanones; Topoisomerase; Anticancer; Antimicrobial

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Introduction

Since the olden ages, humanity has relied on nature to provide therapeutics for a plethora of deadly diseases [1]. Nearly fifty percent of new drugs introduced in the past four decades have been natural products, their mimics, or their synthetic derivatives [2]. Of these compounds, those that are derived from marine sources are believed to be superior to terrestrial natural products in terms of their chemical novelty and their ability to induce potent bioactivities. A contributing factor for this observation stems from the fact that greater than 70% of earth's surface is covered by oceans and thus marine ecosystems exhibit a higher degree of biological diversity [3-6]. Moreover, the sedentary lifestyle adopted by majority of the marine organisms has necessitated the evolution of highly efficient chemical agents for their defense mechanisms.

These chemical substances, which are produced within their system, are called 'marine natural products'. Usually existing as secondary metabolites in marine invertebrates such as sponges, bryozoans, tunicates, and ascidians, marine natural products help these organisms by deterring their predators or paralyzing their prey [7-8]. Upon the release of these compounds into their surroundings, they are usually rapidly diluted by water. Hence, in order to be effective against their predators or prey, the compounds need to exhibit high potency. For this reason, marine natural products usually demonstrate extremely potent biological activities and continue to be a rich source of a vast array of such medicinally valuable compounds [7, 9-13].

As a result of the potential for new drug discovery scaffolds, marine natural products have attracted the attention of scientists from various disciplines, including organic chemistry, bioorganic chemistry, medicinal chemistry, pharmacology, and biology. With the improvement in the deep-sea sample

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[*Corresponding author] Tel: (205) 975-2478, Fax: (205) 934-2543, Email: svelu@uab.edu
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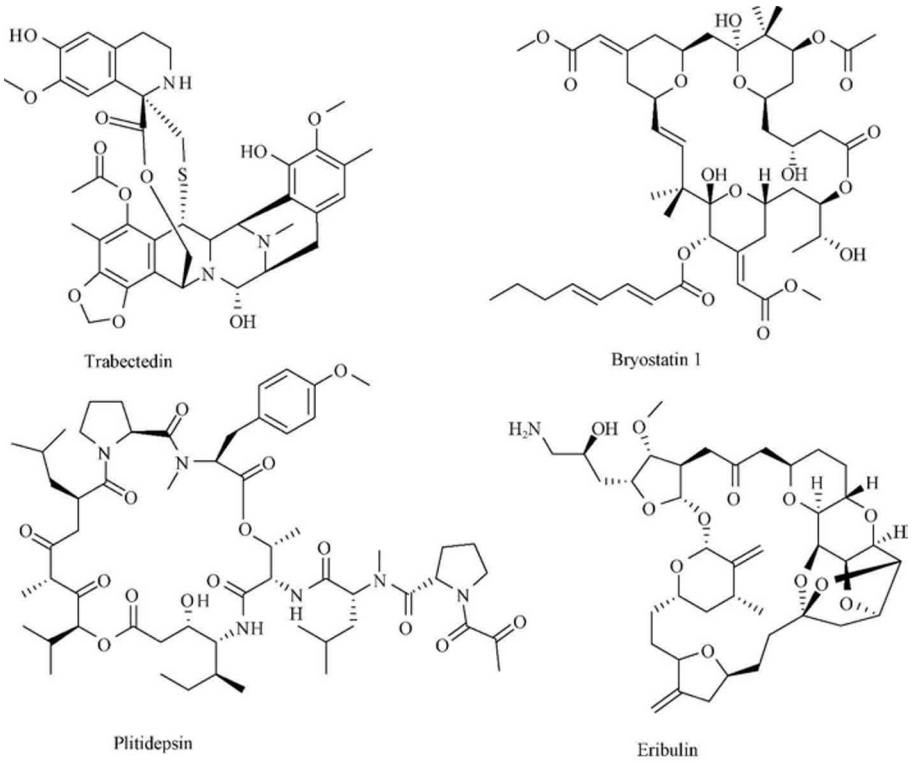

Fig. 1 Marine derived drugs

collection technology and the large scale drug production through aqua culture, there has been an increase in the number of biologically active natural products isolated from marine sources in the last decade [14].

Marine derived drugs

More than a dozen of these marine alkaloids are currently undergoing various phases of human clinical trials for treatment of different types of cancers. Compounds such as trabectedin, bryostatins, plitidepsin, and eribulin shown in Fig. 1 capture the pharmacological value of marine natural products.

Trabectedin (ET-743, Yondelis®) was originally isolated from the Caribbean sea squirt, *Ecteinascidia turbinate*. It is the first anticancer marine-derived drug that was approved by the European Union for the treatment of patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide. Trabectedin is also in phase II trials for prostate, breast and pediatric cancer [15-17].

Bryostatins represent an important group of pharmaceutically promising substances that are produced by commensal microorganisms naturally occurring in marine invertebrates [18]. So far, twenty bryostatins have been discovered, which elicit a remarkable range of biological activities, including antineoplastic activity, synergistic chemotherapeutic activity, and cognition memory enhancement [19]. The most extensively studied compound, bryostatin 1, selectively modulates the function of various individual protein kinase C isozymes. It has been proposed for phase I and phase II clinical trials for the treatment against Alzheimer's disease [18, 20-21].

Similarly, plitidepsin was originally isolated from the marine tunicate *Plitidepsin*. This compound exhibits antitumor, antiviral, and immunosuppressive activities and has especially shown promise in shrinking tumors in pancreatic, stomach, bladder, and prostate cancers [22]. It was granted orphan drug status by the European Medicines Agency for treating acute lymphoblastic leukemia. It is currently in phase II clinical trials for solid and hematological malignant neoplasias like T cell lymphoma and in phase III clinical trials for multiple myeloma [23].

Finally, eribulin is a U.S. Food and Drug Administration approved anticancer drug under the trade name Halaven, which is used to treat patients with metastatic breast cancer who have received at least two prior chemotherapy regimens for late-stage disease [24-25]. Eribulin is also being investigated by Eisai Co. for use in a variety of other solid tumors, including non-small cell lung cancer, prostate cancer, and sarcoma.

Marine sponges

Of the various sources of marine natural products, marine sponges are a particularly fertile field for the discovery of bioactive scaffolds. Several reviews concerning the sponge-derived bioactive marine alkaloids with future pharmaceutical applications have been published in the last few decades [3, 26-31]. Sponges produce a plethora of chemical compounds with widely varying carbon skeletons. Most bioactive compounds from sponges which have been isolated in sufficient quantities exhibited a variety of activities such as anti-inflammatory, antitumor, immunosuppressive, neurosup-