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Review

Sponging off nature for new drug leads

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ABSTRACT

Marine sponges have consistently been the richest source of new marine natural products with unprecedented chemical scaffolds and potent biological activities that have been reported in the chemical literature since the early 1970s. During the last 40 years, chemists in the Andersen laboratory at UBC, in collaboration with biologists, have discovered many novel bioactive sponge natural products. Four experimental drug candidates for treatment of inflammation and cancer, that were inspired by members of this sponge natural product collection, have progressed to phase I/II/III clinical trials. This review recounts the scientific stories behind the discovery and development of these four drug candidates; IPL576,092, HTI-286 (Taltobulin), EPI-506 (Ralaniten acetate), and AQX-1125.

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1. Introduction

Over the last forty odd years our marine natural products chemistry group at UBC working in collaboration with biologists has discovered many novel bioactive secondary metabolites in crude extracts of marine sponges [1–5] and four experimental drugs based on our sponge chemistry research have progressed to clinical trials in humans as potential new treatments for inflammation and cancer. This review will present the scientific stories behind the discovery and development of each of these marine natural product inspired drug candidates.

A widely utilized approach to modern drug discovery starts with screening libraries of structurally diverse chemical entities for a desired type of therapeutic activity using a highly predictive and robust biological assay. This discovery framework encompasses the extremely sophisticated high throughput screening campaigns found in major pharmaceutical companies and it is also the foundation of the much more modest discovery efforts found in many academic laboratories like ours. The ultimate success of this screening approach to drug discovery, regardless of the scale, is determined by several important early stage decisions that shape the outcomes. Foremost among these is identification of the unmet medical need or therapeutic area that the discovery program aims to address. Once that is settled, it defines the nature of the 'bioactivity' the screening program is looking for, which in turn leads to the choice of a screening bioassay. The final and crucial decision is selection of the chemical-diversity screening library, since that choice determines what pharmacophores will be discovered by the screening effort.

Combinatorial synthetic chemical libraries, traditional focused synthetic chemical libraries, and libraries of pure natural products or crude extracts containing natural products are the most common pools of chemical diversity that are routinely explored in drug

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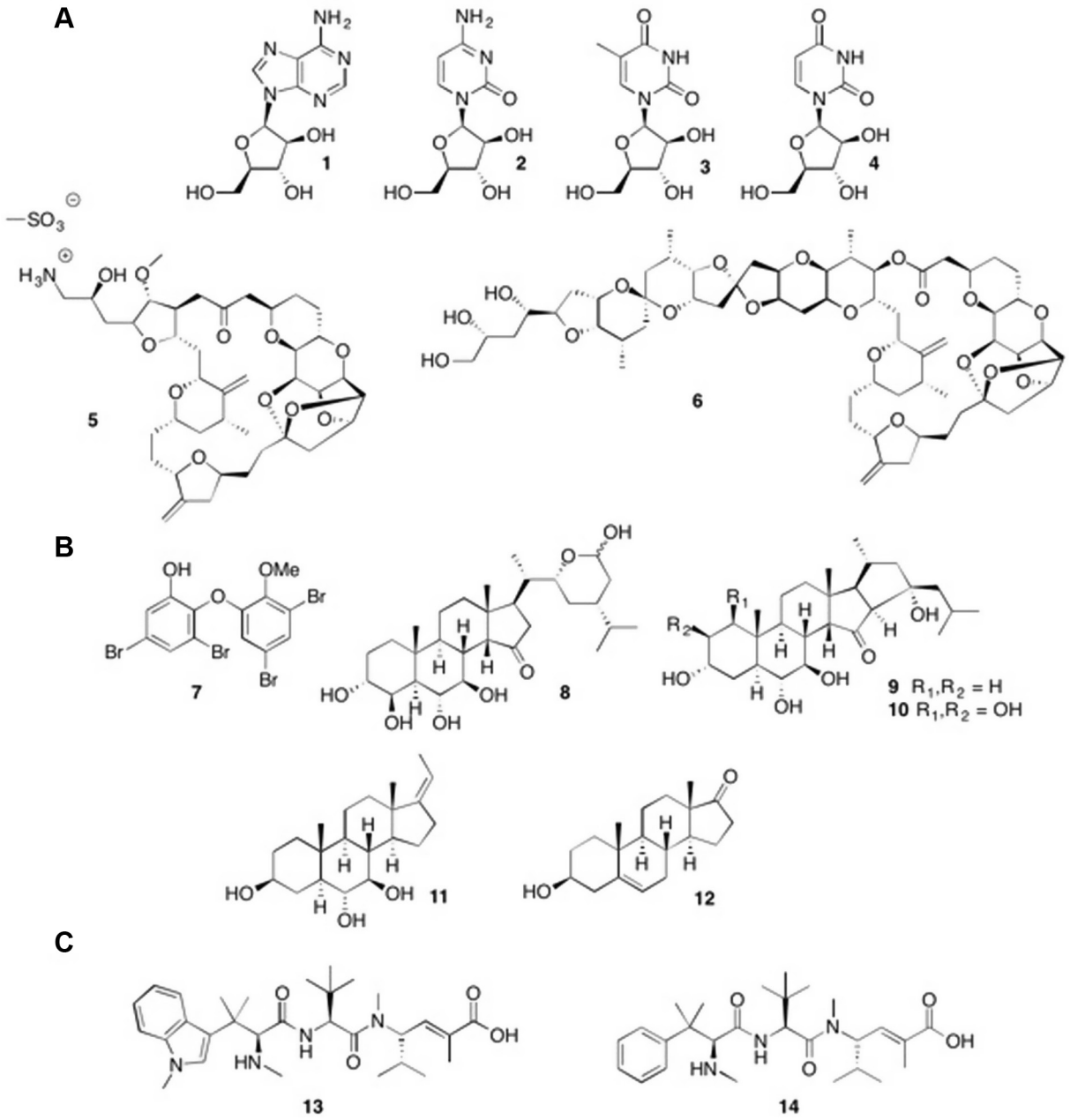

Fig. 1. A) Chemical structures of Ara A (**1**) and ara C (**2**), the first two marine-natural product-inspired drugs to enter clinical use and the natural products spongouridine (**3**) and spongothymidine (**4**) isolated from the marine sponge Crypto*tethya crypta*. Chemical structures of the approved anticancer drug erubulin mesolate (Halaven) (**5**) and the marine natural product halichondrin B (**6**) isolated from extracts of marine sponges in the genus *Halichondria*. **B)** Chemical structures of diphenyl ether **7**, contignasterol (**8**), xestobergsterols A (**9**) and B (**10**), IPL576,092 (**11**), and 5-androsten-3b-ol-17-one (**12**). **C)** Chemical structures of hemiasterlin (**13**) and HTI-286 (**14**).

discovery screening, and each of these diversity pools has its own merits [6–9]. A major focus of our drug discovery and chemical biology screening programs has been on the chemical diversity found in crude extracts of marine sponges (Phylum Porifera). Sponges are primitive invertebrate metazoans that are found in all parts of the world's oceans. They have consistently been the richest source of new natural products reported in the marine natural products literature since the early 1970s [10,11], and the majority of the novel natural product chemotypes reported from sponges have no close analogs in terrestrial plant and microbial natural products or in natural products isolated from other marine organisms.

Ara A (**1**) and ara C (**2**), the first two marine-natural-product-inspired drugs to enter clinical use, are synthetic analogs of the D-arabinose-containing natural products spongouridine (**3**) and spongothymidine (**4**) isolated from the marine sponge Crypto*tethya crypta* in the 1950s (Fig. 1A) [12]. They are still in clinical use today as antiviral and anticancer agents. More recently, erubulin mesolate (Halaven) (**5**), a synthetic analog of the complex antimitotic marine natural product halichondrin B (**6**) isolated from extracts of marine sponges in the genus *Halichondria* [13], has been approved by the FDA as a new anticancer agent for treating inoperable liposarcoma [14]. Several other sponge natural product inspired experimental drugs are currently in clinical trials and