

# Bioactive Compounds from Marine Foods

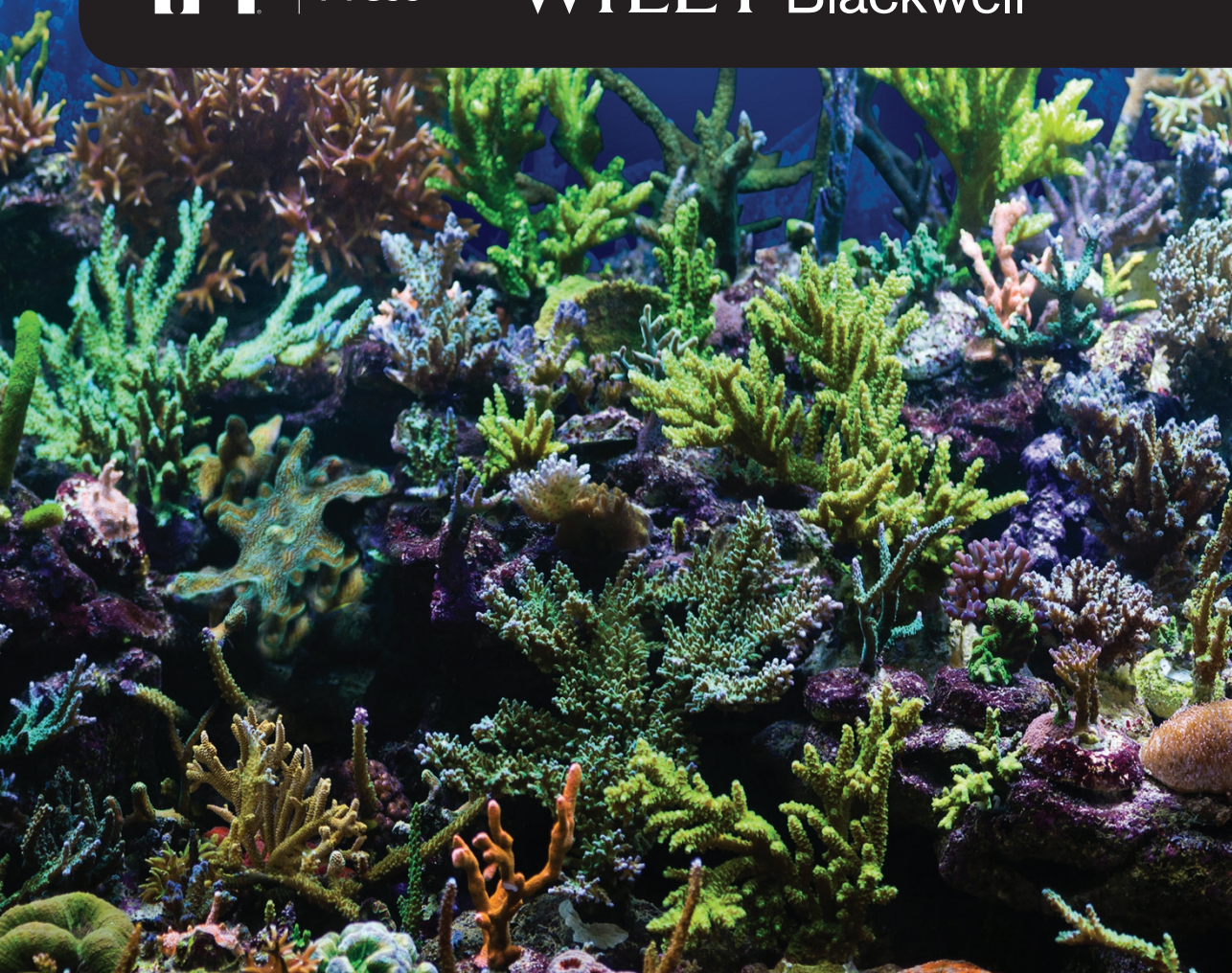
Plant and Animal Sources

Blanca Hernández-Ledesma  
and Miguel Herrero *EDITORS*



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# **Bioactive Compounds from Marine Foods**



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# Bioactive Compounds from Marine Foods

Plant and Animal Sources

Edited by

**Blanca Hernández-Ledesma and Miguel Herrero**

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# 1 An Update on the Biomedical Prospects of Marine-derived Small Molecules with Fascinating Atom and Stereochemical Diversity

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## 1.1 INTRODUCTION

In this chapter we discuss a selection of structurally diverse marine-derived small molecules (MDSMs) with potent and/or specific bioactivity and analyze their biomedical applications. The compounds included have been isolated either from marine macroorganisms, including sponges, ascidians (tunicates), bryozoans, and molluscs, or from microorganisms, such as bacteria and fungi. Our inquiry begins with a look back in time at a selection of important marine natural products, with particular focus on compounds in the clinical pipeline. The chapter continues with an analysis of a biosynthetically diverse assortment of 22 MDSMs and their structural elements of atom and stereochemical diversity. Entries have been divided into five biosynthetic classes: terpene, polyketide, alkaloid, depsipeptide, and polyketide–peptide. Enormous structural variety is represented by the marine natural products treated herein. The compounds selected can be considered to represent case examples of significant biomolecules with positivity and, in some cases, potent bioactivity accompanied by an unusual mechanism of action.

### 1.1.1 Overview of known compounds, highlighting molecules of significance

The ocean covers more than 70% of the earth's surface and is home to exceptional biodiversity: more than one million marine species and an estimated one billion different kinds of marine microbe (Census of Marine Life Press Release 2010). We and others firmly believe that MDSMs represent a continuing resource for tools important in cell biology research and in the design of the next-generation leads for drug discovery and development. The record to date firmly illustrates that the structures of natural products continue to be invaluable in expanding pharmacophore structural space. For example, Newman and Cragg recently provided a detailed analysis of the last 30 years of natural products in drug discovery, wherein they contended that, "Nature's 'treasure trove of small molecules' remains to be explored, particularly from the marine and microbial environments" (Newman & Cragg 2012).

It is appropriate to return to a theme expressed in the past based on ecology and natural history. Simply stated, marine-derived biosynthetic products must have unprecedented chemodiversity (National Research Council 2002) in comparison to those from the terrestrial realm, due to the difference in biosynthetic machinery that must exist between the macroorganisms abundant in these different environments. The structures shown in this review will provide the reader with up-to-date information related to these results. On the horizon is the demonstration that stunning natural products will be discovered from marine-derived strains isolated and re-cultured grown under saline conditions (Imhoff *et al.* 2011). Thus, many of the molecules discussed in this chapter have been chosen to illustrate the headway being made in this direction.

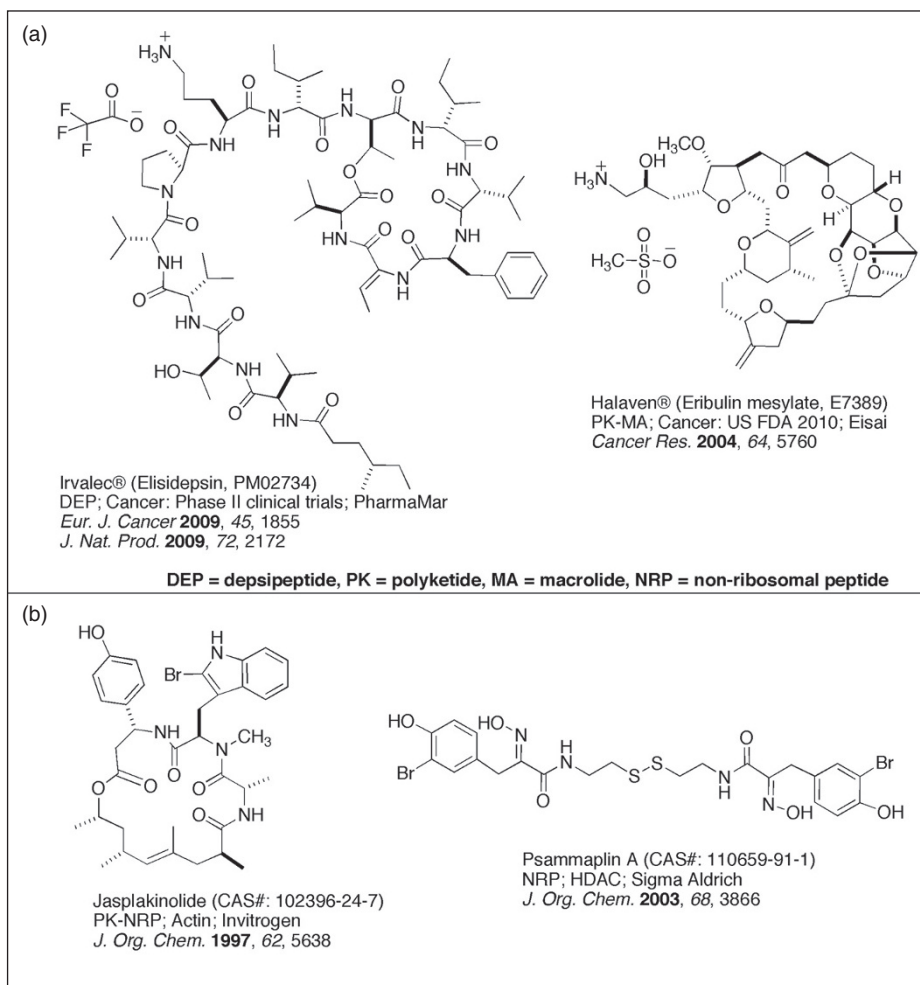
This treatise extends to recent annual reviews in the literature, which focus on several important issues. At the top of the list are discussions of marine natural products in biomedical investigations, and there is a steady stream of such comprehensive papers (Hughes & Fenical 2010a; Radjasa *et al.* 2011; Gerwick & Moore 2012). The dynamic pipeline of MDSMs into “marine pharmaceuticals” has been well documented by reviews in the peer-reviewed literature (Newman & Cragg 2004, 2012; Fenical 2006; Molinski *et al.* 2009; Mayer *et al.* 2010; Montaser & Luesch 2011). It is also important to be aware of accounts of marine natural products structural revisions (Suyama *et al.* 2011). Central to efforts to confirm structure assignment and absolute stereochemistry has been the interplay between total syntheses and reexamination of the spectroscopic data (Suyama *et al.* 2011). Lastly, a further indication of the importance of MDSMs in biomedical discovery is a recent in-depth review dedicated to aspects surrounding the organic synthesis of biologically active marine natural products (Morris & Phillips 2011).

### 1.1.1.1 *Clinical candidates and MDSM chemical probes*

Marine macro- and microorganisms are sources of tremendous chemodiversity and offer new scaffolds for biomedical exploration. The connection between an MDSM's structure, biological activity, and biological target for mechanism of action is at the crux of collaborative investigations by the marine natural products, synthetic, and chemical biology communities. Illustrated in Figure 1.1 is a selection of four important marine-derived natural products which summarize those molecules that are (a) presently used as synthetic clinical therapeutics and (b) employed as chemical probes in chemical biology, biochemistry, and molecular genetics to further our understanding of biological function. The biosynthetic classes, biological targets, and commercial sources, if available, are given below the structures, as is additional citation information useful in further current-awareness searches.

There are two complex structures in Figure 1.1, either of which can be considered a poster child for exotic yet exceedingly important scaffolds. Both possess a blizzard of chiral centers and a density of functionalization. But the pathways to their respective developments as preclinical or clinical agents were slightly different. The former possesses a virtually identical synthetic scaffold to the natural product. Here is a brief outline. Irvalec<sup>®</sup> (panel A1), under development by PharmaMar (Spain; www.pharmamar.com), is an unnatural salt of isokahalalide F, a natural product congener co-isolated with kahalalide F (**11** in Figure 1.2) (Gao *et al.* 2009). Alternatively, eribulin mesylate (E7389) represents a reduced-complexity analogue of a very complex natural product. This compound is marketed as Halaven<sup>®</sup> (Eisai, Japan; www.eisai.com) and gained US Food and Drug Administration (FDA) approval in November 2010 for treatment of metastatic breast cancer unresponsive to other drug treatments (Jefferson 2010). A combined synthetic—structure—activity relationship (SAR) investigation found that the entire western portion of halichondrin B (**2**) could be truncated without a deleterious effect on the therapeutic activity (Qi & Ma 2011).

Two additional compounds are shown in Figure 1.1b, which represent commercially available MDSM chemical probes. We have adopted the definition of a “chemical probe” set forth in an editorial in *Nature Chemical Biology* (Editorial 2010) and elaborated on in a commentary by Frye (2010): “Potent, selective and cell-permeable small molecules that perturb a biological target in a dose-dependent manner [and] can be used to dynamically ‘probe’ the role of the target in biology.” Terrestrial and marine natural-product chemical probes were recently reviewed by Carlson (2010), and the reader is

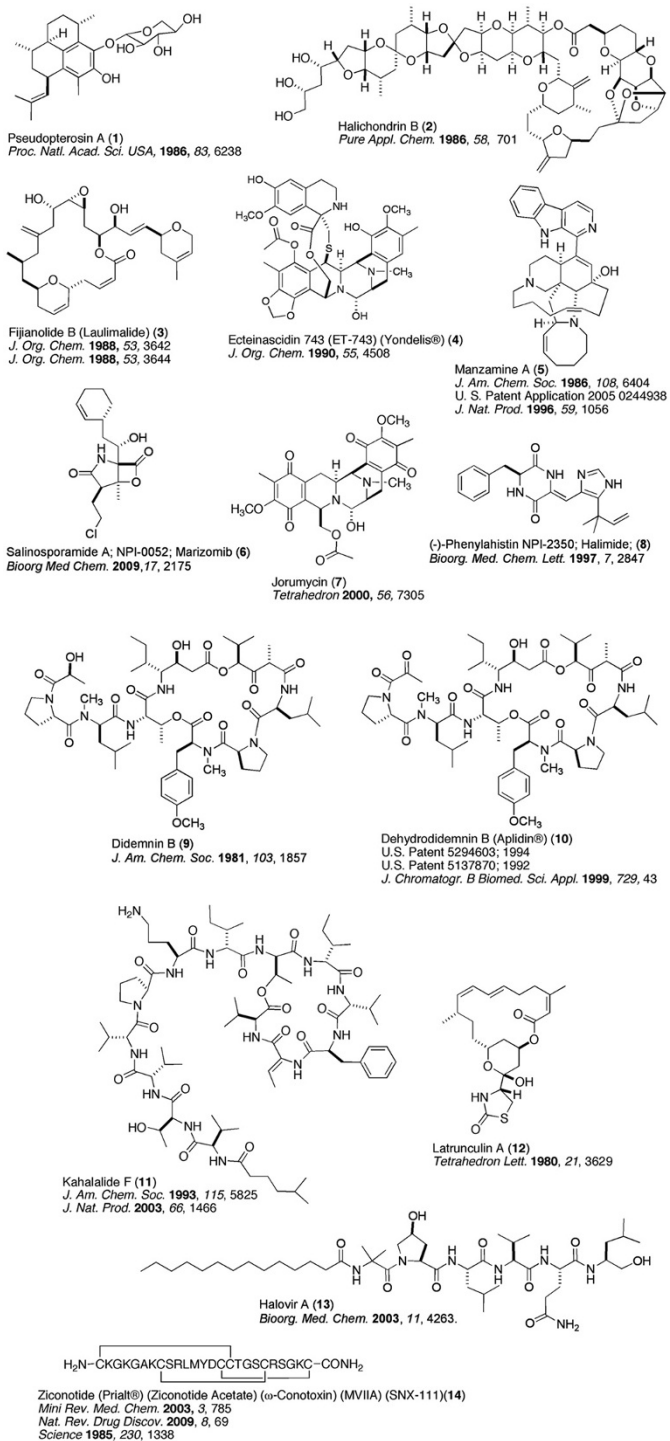


**Figure 1.1** A snapshot of marine-derived natural products highlighting (a) clinical therapeutics (Irvalec® (Elisidepsin, PM02734) and Halaven® (Eribulin mesylate, E7389)) and (b) chemical probes (Jaspilkinolide and Psammoplina A).

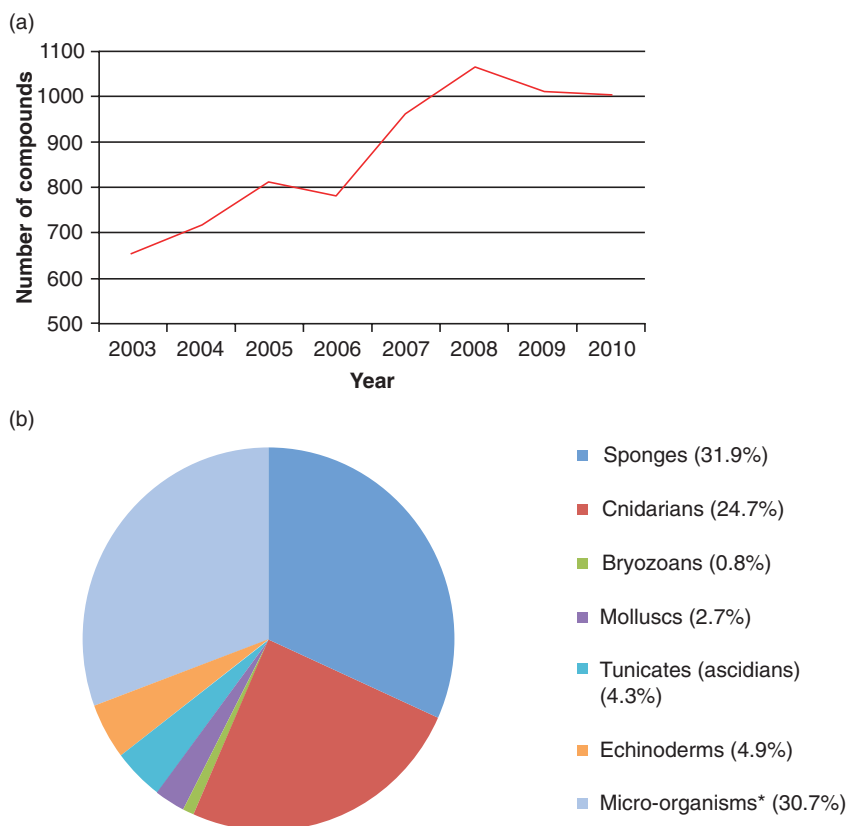
encouraged to refer to the literature for additional perspective. The notion that natural products have evolved for specificity towards biological macromolecules, particularly proteins and genes, is supported by the community (Clardy & Walsh 2004; Piggott & Karuso 2004; Carlson 2010). The sponge-derived probes jaspilkinolide and psammoplina A are both important MDSM chemical probes and the reader is directed to recent literature surrounding their biological function (Boulant *et al.* 2011; Baud *et al.* 2012).

### 1.1.2 Selected important marine sources of MDSMs

The annual review “Marine Natural Products” by Blunt *et al.* (2005, 2006, 2007, 2008, 2010, 2011, 2012) in *Natural Products Reports (NPR)* provides a detailed perspective on the publication record



**Figure 1.2** A glimpse into the past via a selection of 14 invertebrate- and microorganism-derived natural products in clinical use or of therapeutic potential.



**Figure 1.3** A recent snapshot of MDSMs in the literature, highlighting (a) a histogram of the number of compounds reported between 2003 and 2010, and (b) an expanded view of MDSM sources reported between 2008 and 2010. (Adapted from Blunt *et al.* 2005, 2006; 2007, 2008, 2010, 2011, 2012). \*Microorganisms: fungi, bacteria, phytoplankton, and brown, green, and red algae. (For a color version of this figure, please see the color plate section.)

of peer-reviewed compounds, with an emphasis on new compounds and their biological activities. Marine natural products are also entered and tabulated in MarinLit, a database of the marine natural products literature produced and maintained by the Department of Chemistry, University of Canterbury, New Zealand (<http://www.chem.canterbury.ac.nz/marinlit/marinlit.shtml>). Figure 1.3a is a histogram of the number of marine natural products reported in the literature between 2003 and 2010. It shows an upward trend, with the number of new compounds reported annually increasing for the years examined.

Marine natural products included in the annual *NPR* review consist of published MDSMs isolated from both macroorganisms, such as sponges, cnidarians, bryozoans, molluscs, tunicates, and echinoderms, and microorganisms, such as fungi, bacteria, phytoplankton, green algae, brown algae, and red algae. Figure 1.3b shows an expanded view of MDSMs reported in the literature between 2008 and 2010 by Blunt *et al.* (2010, 2011, 2012). The approximate percentages are as follows: sponges, 31.9%; microorganisms, 30.7%; cnidarians, 24.7%; tunicates (ascidians), 4.3%; bryozoans, 0.8%. It is interesting to note that the three top producers of marine natural products are sponges, microorganisms, and cnidarians. Consistently, the majority of the MDSMs in this chapter are from sponge and microorganism (fungus and bacterium) sources.

### 1.1.2.1 *Macroorganisms: an analysis of their critical role*

The marine invertebrate groups of interest in the isolation of MDSMs include phyla such as Porifera, Coelenterata, Mollusca, Tunicata, and Annelida. A recent analysis by Leal *et al.* (2012) examined new MDSMs from invertebrates that appeared over the last 20 years. Marine macroorganisms are valuable producers of biomedically relevant MDSMs, many of which serve as therapeutic lead compounds, such that future conservation efforts are imperative in preserving marine invertebrates and the bionetworks that support them (Kingston 2011). Reef-invertebrate marine natural products have previously been reviewed in the literature, and the reader is directed to other references for further discussion and perspective (Fenical 2006; Carrol & Crews 2010; Mayer *et al.* 2010; Radjasa *et al.* 2011).

### 1.1.2.2 *Microorganisms: questions about their being the actual source*

Marine microorganisms are increasingly the focus of marine natural products isolation efforts, as they have proven to be prolific producers of chemodiverse MDSMs (Zhu *et al.* 2011). The advancement of biomolecular technology, particularly genomic and metagenomic techniques and analysis, offers the advantage of allowing sustainable investigation of MDSMs from renewable sources (Imhoff *et al.* 2011). Representative groups from the kingdoms Fungi and Bacteria will be considered in this chapter (Gerwick & Moore 2012; Zotchev 2012). Advancements in seawater isolation and fermentation techniques have facilitated investigation of marine-derived fungal and bacterial strains and have led to the isolation of novel secondary metabolites (Radjasa *et al.* 2011).

## 1.1.3 Highlights of MDSMs of therapeutic potential

Table 1.1 and Figure 1.2 present 14 examples of MDSMs in clinical use or of therapeutic potential, most of which have been the subjects of extensive reviews (Mayer *et al.* 2010; Montaser & Luesch 2011; Radjasa *et al.* 2011; Gerwick & Moore 2012; Newman & Cragg 2012). The compounds in Table 1.1 illustrate the chemodiversity of secondary metabolites from marine invertebrate and microorganism sources. Ecteinascidin 743 (**4**), commercially known as Yondelis<sup>®</sup> (PharmaMar), from an ascidian (EU approved 2007), and ziconotide (**14**), whose commercial name is Prialt<sup>®</sup> (Elan Corp., Ireland; www.elan.com), from a cone shell (US approved 2004), are two flagship, clinically used compounds based precisely on a marine natural product (Radjasa *et al.* 2011). For many of the MDSMs in Table 1.1, the supply problem has been addressed by either total synthesis of the MDSM or synthetic redesign of a simplified analogue. The table also includes comments providing further points of reference.

### 1.1.3.1 *Terpene*

The diterpene–glycoside pseudopterosin (**1**) is a significant potent antiinflammatory agent and the basis of the Estée Lauder cosmetic cream Resilience (Kerr 2000). Additional analogues of this compound have been evaluated as wound-healing agents (Haimes & Jimenez 1997; Hoarau *et al.* 2008). Discovered in the 1980s, it still represents a landmark and useful development; its privileged chemical structure continues to inspire many researchers.

### 1.1.3.2 *Polyketide*

An exceedingly important entry here is represented by the structure of sponge-derived halichondrin B (**2**). After decades of study, a monumental synthesis campaign uncovered a reduced complexity substructure with exquisite antitumor activity. As already noted, the clinically approved analogue, derived by total synthesis, is eribulin mesylate, E7389 (Halaven<sup>®</sup>) (Figure 1.1a). A second example in this biosynthetic class is fijianolide B (**3**) (laulimalide), a cytotoxic agent with microtubule stabilizing activity similar to that of paclitaxel (Qi & Ma 2011).

**Table 1.1** A glimpse into the past via a selection of 14 invertebrate- and microorganism-derived natural products in clinical use or of therapeutic potential (adapted from Radjasa *et al.* 2011).

Entry	Compound name	Invertebrate source	Biosynthetic class	Target	Comments	
					Therapeutics	Use
1	Pseudopterosin A (1)	<b>Soft coral</b> <i>Pseudopterogorgia elisabethae</i>	Diterpene glycoside	Antiinflammatory; wound healing	First discovered in 1986, its 25 analogues are of continuing interest.	Estee Lauder's Resilience® label lists <i>P. elisabethae</i> , source of <b>1</b> , as an active ingredient.
2	Halichondrin B (2)	<b>Sponge</b> <i>Lissodendoryx</i> sp.	Polyketide	Cancer: clinical use USA	—	Reduced-complexity synthetic analogue Halaven® [Eribulin mesylate, E7389] marketed by Eisai. US FDA approved November 2010. Commercial chemical probe targeting microtubules/ CAS #: 115268-43-3 (Pac Mar Bioactives).
3	Fijianolide B (3) (Laulimalide)	<b>Sponge</b> <i>Cacospongia mycolijiensis</i>	Polyketide–macrolide	Cancer	Many analogues evaluated to develop SAR against microtubulin target; <i>in vivo</i> activity shown.	Commercial chemical probe targeting microtubules/ CAS #: 115268-43-3 (Pac Mar Bioactives).
4	Ecteinascidin 743 (4) (ET-743) (Yondelis®)	<b>Ascidian</b> <i>Ecteinascidia turbinata</i>	Alkaloid	Cancer: clinical use EU	Enantiopure clinical compound via semisynthesis.	—
5	Manzamine A (5)	<b>Sponge</b> <i>Haliclona</i> sp.; <i>Pellina</i> sp.; <i>Pachybellina</i> sp.; <i>Xestospongia</i> sp.; <i>Ircinia</i> sp.; <i>Amphimedon</i> sp.	Alkaloid	Antimalaria: assay positive control	Isolation from diverse sponges and a marine-derived bacterium providing a means of sustainable supply.	Commercial chemical probe targeting GSK-3B/CAS #: 104196-68-1 (Santa Cruz Biotech).

(continued)

Table 1.1 (Continued)

Entry	Compound name	Invertebrate source	Biosynthetic class	Target	Comments	
					Therapeutics	Use
6	Salinosporamide A (6) (NPI-0052) (Marizomib)	<b>Bacterium</b> <i>Salinispora tropica</i>	Alkaloid	Cancer: phase I clinical trials; proteasome inhibitor	Proteasome inhibitor with potent and selective activity against HCT-116 human colon cancer cell line and proteasome.	Commercial chemical probe for proteasome/CAS #: 437742-342 (APAC Pharmaceutical).
7	Jorumycin (7)	<b>Mollusc</b> <i>Jorunna funebris</i>	Alkaloid	Cancer: phase II clinical trial	—	Synthetic analogue Zalypsis® under development by PharmaMar.
8	(-)-phenylalanistin (8) (NPI-2350) Halimide	<b>Fungus</b> <i>Aspergillus ustus</i> (derived from alga <i>Halimeda lacrimosa</i> )	Alkaloid–diketopiperazine	Cancer: antimicrotubule	Colchicine-like tubulin depolymerization agent. Potent and selective activity against HT-29 human colon cancer cell line.	This compound provided the stimulus to synthesis of plinabulin (NPI-2358), which is in a cancer phase II clinical trial.
9	Didemnin B (9)	<b>Ascidian</b> <i>Trididemnum solidum</i>	Depsipeptide	Cancer: phase I clinical trial	Advanced by NCI to phase I anticancer clinical trial and subsequently discontinued.	Dropped from clinical trials (1995).
10	Dehydrodidemnin B (10) (Aplidin®)	<b>Ascidian</b> <i>Aplidium albicans</i>	Depsipeptide	Cancer: phase III clinical trial	Analogue replacing didemnin B under development by PharmaMar.	EU-approved as orphan drug.