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® (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® (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 (Irvalac® (Elisidepsin, PM02734) and Halaven® (Eribulin mesylate, E7389)) and (b) chemical probes (Jasplakinolide and Psammaplin 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 jasplakinolide and psammaplin 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

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® (PharmaMar), from an ascidian (EU approved 2007), and ziconotide (14), whose commercial name is Prialt® (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®) (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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound name</th>
<th>Invertebrate source</th>
<th>Biosynthetic class</th>
<th>Target</th>
<th>Therapeutics</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pseudopterosin A (1)</td>
<td>Soft coral Pseudopterogorgia elisabethae</td>
<td>Diterpene glycoside</td>
<td>Antiinflammatory; wound healing</td>
<td>First discovered in 1986, its 25 analogues are of continuing interest.</td>
<td>Estee Lauder’s Resilience® label lists P. elisabethae, source of 1, as an active ingredient.</td>
</tr>
<tr>
<td>2</td>
<td>Halichondrin B (2)</td>
<td>Sponge Lissodendoryx sp.</td>
<td>Polyketide</td>
<td>Cancer: clinical use USA</td>
<td>—</td>
<td>Reduced-complexity synthetic analogue Halaven® (Eribulin mesylate, E7389) marketed by Eisai. US FDA approved November 2010.</td>
</tr>
<tr>
<td>3</td>
<td>Fijianolide B (3)</td>
<td>Sponge Cacospongia mycotijensis</td>
<td>Polyketide–macrolide</td>
<td>Cancer</td>
<td>Many analogues evaluated to develop SAR against microtubulin target; in vivo activity shown.</td>
<td>Commercial chemical probe targeting microtubules/CAS #: 115268-43-3 (Pac Mar Bioactives).</td>
</tr>
<tr>
<td>4</td>
<td>Ecteinascidin 743 (4) (ET-743) (Yondelis®)</td>
<td>Ascidian Ecteinascidia turbinata</td>
<td>Alkaloid</td>
<td>Cancer: clinical use EU</td>
<td>Enantiopure clinical compound via semisynthesis.</td>
<td>—</td>
</tr>
</tbody>
</table>

(continued)
Table 1.1 (Continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound name</th>
<th>Invertebrate source</th>
<th>Biosynthetic class</th>
<th>Target</th>
<th>Therapeutics</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Jorumycin (7)</td>
<td>Mollusc Jorunna funebris</td>
<td>Alkaloid</td>
<td>Cancer: phase II clinical trial</td>
<td></td>
<td>Synthetic analogue Zalypsis® under development by PharmaMar.</td>
</tr>
<tr>
<td>8</td>
<td>(−)-phenylahistin (8) (NPI-2350) Halimide</td>
<td>Fungus Aspergillus ustus (derived from alga Halimeda lacrimosa)</td>
<td>Alkaloid–diketopiperzine</td>
<td>Cancer: antimicrotubule</td>
<td>Colchicine-like tubulin depolymerization agent. Potent and selective activity against HT-29 human colon cancer cell line.</td>
<td>This compound provided the stimulus to synthesis of plinabulin (NPI-2358), which is in a cancer phase II clinical trial. Dropped from clinical trials (1995).</td>
</tr>
<tr>
<td>9</td>
<td>Didemnin B (9)</td>
<td>Ascidian Trididemnum solidum</td>
<td>Depsipeptide</td>
<td>Cancer: phase I clinical trial</td>
<td>Advanced by NCI to phase I anticancer clinical trial and subsequently discontinued.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Dehydrodidemnin B (10) (Aplidin®)</td>
<td>Ascidian Aplidium albicans</td>
<td>Depsipeptide</td>
<td>Cancer: phase III clinical trial</td>
<td>Analogue replacing didemnin B under development by PharmaMar.</td>
<td>EU-approved as orphan drug.</td>
</tr>
<tr>
<td>11</td>
<td>Kahalalide F (11)</td>
<td><strong>Mollusc</strong> <em>Elysia rufescens</em>; <strong>Alga</strong> <em>Bryopsis</em> sp.</td>
<td>Depsipeptide</td>
<td>Cancer: Phase II clinical trial</td>
<td>Synthetic analogue <em>Irvalec®</em> (Elisidepsin, PM02743) under development by PharmaMar.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Latrunculin A (12)</td>
<td><strong>Sponge</strong> <em>Cacospongia mycofijiensis</em>, <em>Negombata magnifica</em></td>
<td>Polyketide–nonribosomal peptide</td>
<td>Cancer: actin inhibitor</td>
<td>Commercial chemical probe targeting actin/CAS #: 76343-93-6 (Invitrogen).</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Halovir A (13)</td>
<td><strong>Fungus</strong> <em>Scytalidium</em> sp.</td>
<td>Peptide</td>
<td>Antiviral</td>
<td>Lipophilic, linear peptide; potent <em>in vitro</em> inhibitor of herpes simplex viruses 1 and 2.</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Prialt® (14) <em>(Ziconotide)</em>; ω-conotoxin (14) <em>(MVIIA)</em></td>
<td><strong>Snail</strong> <em>Conus magus</em></td>
<td>Polypeptide</td>
<td>Analgesic: N-type calcium channel; in clinical use</td>
<td>Synthetic material developed by Elan Corp.</td>
<td></td>
</tr>
</tbody>
</table>
1.1.3.3 Alkaloid

The tunicate compound ecteinascidin 743 (4), also known as ET-743, trabectedin, and marketed as Yondelis® (PharmaMar), was the first clinically approved chemotherapeutic “based on an actual marine natural product” (Carrol & Crews 2010). This compound is currently used in the EU to treat rhabdomyosarcoma and platinum-sensitive ovarian cancers (Radjasa et al. 2011). Due to the low isolated yield of 4, the clinically used material was obtained by kilogram semisynthesis (Tsuji 1985; Cuevas et al. 2000; Cuevas & Francesch 2009).

Microbes and/or microbial associations offer the promise of a renewable and sustainable source of significant MDSMs, especially as new culturing strategies emerge (Radjasa et al. 2011). An encouraging example is given by manzamine A (5), which has reportedly been produced by the culture of Micromonospora M42 (Peraud 2006). A second remarkable example is the proteosome-inhibitor salinosporamide A (6) (NPI-0052) (marizomib), which was isolated from a salt obligate actinomycete, Salinispora tropica, presently under phase I clinical investigation for anticancer therapeutic development by Nereus Pharmaceuticals (USA; www.nereuspharm.com) (Fenical et al. 2009).

Organic synthesis has reliably resolved this resupply problem, providing entry to material for clinical evaluation. The mollusc Jorunna funebris-derived alkaloid jorumycin (7) served as the scaffold for the synthetic compound Zalypsis® (PharmaMar), an anticancer agent presently in phase II cancer clinical trials (Mayer et al. 2010). (−)-phenylahistin (8) (halimide) (NPI-2350) is the MDSM structural basis of the synthetic clinical candidate plinabulin (NPI-2358) (Nereus Pharm.) (Mita et al. 2010).

1.1.3.4 Depsipeptide

The potent antiproliferative didemnin B (9) was the first marine natural product to be investigated in phase I human cancer clinical trials; despite later being dropped, this was a milestone for MDSMs. Dehydrodidemnin B, aplidine (10), is a redesigned analogue replacing didemnin B and is presently under development by PharmaMar and marketed as Aplidin® (Lee et al. 2012). Phase III cancer trials of 10 in combination therapy for multiple myeloma are underway at this time, with organic synthesis affording the clinical material (ClinicalTrials.gov 2012; Lee et al. 2012). Aplidin® is presently in clinical use in the EU (EU approved 2003) under an orphan drug status as a therapy for acute lymphoblastic leukemia. As previously alluded to, the mollusc Elysia rufescens kahalalide F (11) is the structural scaffold of the clinically used synthetic anticancer agent Irvalec® (PharmaMar) (Figure 1.1a).

1.1.3.5 Polyketide–peptide

The marine macrolide latrunculin (12) is an important chemical probe whose biological target is actin inhibition (Radjasa et al. 2011). A further discussion of the identification of the biological targets of 12 will be presented in Section 1.4. An example of a linear peptide is given by the lipophilic marine fungal metabolite halovir A (13), from Scytalidium strain CNL240 (Rowley et al. 2003). This peptide is a potent in vitro inhibitor of herpes simplex viruses 1 and 2 and was the subject of a coupled synthesis–SAR investigation in which the pharmacophore was identified for optimal therapeutic activity (Rowley et al. 2004).

The polypeptide snail-derived toxin ziconotide (14), also known as ω-conotoxin, MVIIA, SNX-111, or ziconotide acetate, marketed as Prialt®, is another striking example of a marine-derived drug that has successfully overcome the resupply challenge (Radjasa et al. 2011). Clinically used as an analgesic in both the USA (Elan Corporation) and the EU (Eisai), Prialt® is obtained by synthesis to afford a drug identical to the snail toxin (Mayer et al. 2010).

1.1.4 New insights and lessons that address supply challenges

The collection of MDSMs in Table 1.1 and Figure 1.2 provides illustrative examples of various strategies employed by researchers to overcome the resupply challenges in the development of MDSM-inspired
clinical therapeutics (Radjasa et al. 2011). Another compelling example of a similar achievement is given by the recent disclosure by Xu et al. (2012) of an elegant investigation of didemnin B (9) biosynthesis. Throughout the preclinical and early clinical development of the antiproliferative 9, the low isolation yield of the ascidian–MDSM posed a significant challenge. A similar resupply challenge was encountered in the development of analogue 10. Remarkably, Xu et al. (2012) identified didemnins as bacterial secondary metabolites of α-proteobacterial Tistrella mobilis and Tistrella bauzanensis. Via the complete genome sequence and annotation of T. mobilis strain, two significant findings were achieved: (1) identification of the putative biosynthetic didemnin (did) cluster, and (2) identification of a post-synthetase maturation process in the biosynthesis of didemnin B. This extraordinary contribution will undoubtedly pave the way for future genetic bioengineering studies and provide access to didemnin analogues, both of which will function as an enduring solution to the resupply challenge.

1.2 A VIEW BASED ON ATOM DIVERSITY

Eleven structures are presented in Table 1.2 and Figure 1.4 to illustrate the outstanding atom diversity of MDSMs, compiled according to biosynthetic classes. The MDSMs included in Table 1.2 are derived from three of the most prolific groups: sponges, fungi, and bacteria. The marine natural products in this section represent tremendous chemical diversity and highlight the biosynthetic richness within the different structural classes. Each product’s molecular formula and unsaturation number (UN) are given as a measure of atom diversity, and comments are provided to direct the reader to additional information.

1.2.1 Terpene

Alotaketal A (15), isolated from the marine sponge Hamigera sp., collected in Papua New Guinea, is an unusual sesterterpenoid, having a molecular formula of C_{25}H_{34}O_{4} and nine sites of unsaturation (Forestieri et al. 2009). Sponge–metabolite 15 has two unusual structural features of note: (1) an unprecedented spiroketal substructure and (2) an appended monocyclic regular sesterterpenoid carbon skeleton. Equally impressive is that 15 is a potent agonist of second messenger cAMP cell-signaling pathway, with a half-maximal effective concentration (EC_{50}) of 18 nM, at which it increases intracellular cAMP levels 170 times more effectively than the commercially available chemical probe forskolin (EC_{50} = 3 μM) (Forestieri et al. 2009). Support for the biomedical promise of 15 comes in the form of the recent enantioselective total synthesis of the MDSM 15 (Huang et al. 2012). Chemical probes have also been employed to evaluate the agonistic cAMP signaling of 15, in order to facilitate SAR studies.

1.2.2 Polyketide

Sponge-derived enigmazole A (16) is a novel phosphate polyketide–alkaloid isolated from Cinachyrella enigmatica, a Papua New Guinea marine sponge (Oku et al. 2010). Enigmazole A has the molecular formula C_{29}H_{46}NO_{10}P and nine sites of unsaturation, at which the phosphate functionality is unprecedented in marine macrolides. It is an excellent example of significant atom diversity. Inspection of 16 reveals extensive methylation and hydroxylation, both of which provide support for polyketide biosynthesis, whereas the appended oxazole moiety is the result of alkaloid biosynthesis (Oku et al. 2010). The phosphomacrolide 16 displays impressive cytotoxicity in the National Cancer Institute (NCI) 60-cell-line screen, yielding a required concentration to achieve 50% growth inhibition (GI_{50}) average of 1.7 μM however, 16 lacks tumor cell selectivity. Further, sponge–metabolite 16 displays promising inhibitory activity against the receptor tyrosine kinase proto-oncogene c-Kit, whereby mutations of this molecular target are implicated in certain cancers (Lennartson & Ronnstrand 2006). The enantioselective total synthesis of 16 was reported in a back-to-back isolation–synthesis disclosure in the same issue (June 2010) and was achieved in 22 steps with an overall 0.41% yield (Skepper et al. 2010), providing a route to 16 for further biomedical investigation.
Table 1.2  A selection of 11 marine-derived natural products, illustrating interesting atom and/or functional group diversity.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Natural product</th>
<th>Organism source</th>
<th>Biosynthetic class</th>
<th>Molecular formula</th>
<th>UN</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alotaketal A (15)</td>
<td>Sponge Hamigera sp.</td>
<td>Sesterterpenoid</td>
<td>C_{25}H_{34}O_{4}</td>
<td>9</td>
<td>Fascinating spirocyclic framework. Potent agonist of cAMP cell-signaling pathway.</td>
</tr>
<tr>
<td>2</td>
<td>Enigmazole A (16)</td>
<td>Sponge Cinachyrella enigmatica</td>
<td>Phosphate polyketide–alkaloid</td>
<td>C_{29}H_{46}NO_{10}P</td>
<td>9</td>
<td>First marine-derived phosphomacrolide from a marine source. Structure confirmed by total synthesis.</td>
</tr>
<tr>
<td>3</td>
<td>Zamamidine A (17)</td>
<td>Sponge Amphimedon sp.</td>
<td>Alkaloid</td>
<td>C_{49}H_{60}N_{6}O</td>
<td>23</td>
<td>In vitro cytotoxicity against P388 murine leukemia.</td>
</tr>
<tr>
<td>4</td>
<td>Neopetrosiamine A (18)</td>
<td>Sponge Neopetrosia proxima.</td>
<td>Alkaloid</td>
<td>C_{30}H_{52}N_{2}</td>
<td>6</td>
<td>In vitro inhibition against Mycobacterium tuberculosis and Plasmodium falciparum, without significant cytotoxicity.</td>
</tr>
<tr>
<td>5</td>
<td>Splenocin A (19)</td>
<td>Bacterium Streptomyces sp.</td>
<td>Alkaloid</td>
<td>C_{26}H_{28}N_{2}O_{9}</td>
<td>14</td>
<td>Potent inhibitor of pro-inflammatory cytokine production in splenocyte cytokine assay; antiasthma activity.</td>
</tr>
<tr>
<td>6</td>
<td>Plectosphaeroic Acid A (20)</td>
<td>Fungus Plectosphaerella cucumerina</td>
<td>Alkaloid–diketopiperzine</td>
<td>C_{39}H_{32}N_{6}O_{10}S_{2}</td>
<td>27</td>
<td>In vitro inhibition of indoleamine 2,3-dioxygenase (IDO).</td>
</tr>
<tr>
<td>7</td>
<td>(E,Z)-bastadin 19 (21)</td>
<td>Sponge Ianthella cf. reticulata</td>
<td>Brominated–alkaloid</td>
<td>C_{34}H_{27}Br_{5}N_{4}O_{8}</td>
<td>21</td>
<td>First report of bastadin class (Z)-oximo amide configuration.</td>
</tr>
<tr>
<td>8</td>
<td>Ammosamide A (22)</td>
<td>Bacterium Streptomyces sp.</td>
<td>Chlorinated-alkaloid</td>
<td>C_{12}H_{10}ClN_{5}OS</td>
<td>10</td>
<td>Awesome structural challenge: core ratio H/C &lt; 1. X-ray data analysis used to solve structure.</td>
</tr>
<tr>
<td>9</td>
<td>Largazole (23)</td>
<td>Cyanobacterium Symploca sp.</td>
<td>Depsipeptide</td>
<td>C_{29}H_{42}N_{4}O_{5}S_{3}</td>
<td>11</td>
<td>Nanomolar antiproliferative activity identified as histone deacetylase inhibitor.</td>
</tr>
<tr>
<td>10</td>
<td>Carmaphycin A (24)</td>
<td>Cyanobacterium Symploca sp.</td>
<td>Peptide</td>
<td>C_{25}H_{45}N_{3}O_{6}S</td>
<td>5</td>
<td>Cytotoxic and cytostatic through inhibition of the 20S proteasome.</td>
</tr>
<tr>
<td>11</td>
<td>Bisebromoamide (25)</td>
<td>Cyanobacterium Symploca sp.</td>
<td>Brominated-peptide</td>
<td>C_{51}H_{72}BrN_{2}O_{8}S</td>
<td>19</td>
<td>Protein kinase inhibitor and actin filament stabilizer. Structure revised following total synthesis.</td>
</tr>
</tbody>
</table>

UN, unsaturation number.
1.2.3 Alkaloid

Given the molecular formula of $C_{49}H_{60}N_6O$, the manzamine alkaloid zamamidine A (17) has 23 sites of unsaturation (Takahashi et al. 2009). Structure assignment of zamamidine A has revealed an $N$-2 ethylene bound $\beta$-carboline ring. Impressive cytotoxicity against P388 murine leukemia, with a half-maximal inhibitory concentration (IC$_{50}$) of 13.8 $\mu$g/ml, is promising, despite the lack of in vitro cytotoxicity against KB human epidermoid carcinoma cells.
Structurally related to the manzamine alkaloids is the tetracyclic bis-piperidine alkaloid neopetrosiamine A (18) (Wei et al. 2010). On the basis of its molecular formula, C_{26}H_{28}N_{2}O_{9}, 18 has six sites of unsaturation. Neopetrosiamine A displays strong in vitro cytotoxicity against NCI’s panel of 60 human tumor cell lines, with IC_{50} values of 1.5, 2.0, and 3.5 μM for MALME-3M melanoma cancer, CCRFCEM leukemia, and MCF7 breast cancer, respectively (Wei et al. 2010). Adding to the biomedical promise of 18 is its in vitro inhibitory activity against the pathogenic microbes *Mycobacterium tuberculosis* and *Plasmodium falciparum* (Wei et al. 2010).

The marine actinomycete *Streptomyces* alkaloid splenocin A (19), isolated by Strangman et al. (2009), is a potent inhibitor of the cytokine production implicated in asthma. With a molecular formula of C_{25}H_{45}N_{3}O_{6}S, splenocin A has 14 degrees of unsaturation. The cyclic bis-lactone 19 is a potent inhibitor of pro-inflammatory cytokine production (IC_{50} = 3 nM) and has a biological profile comparable to that of the corticosteroid dexamethasone (IC_{50} = 5 nM) (Strangman et al. 2009). From the perspective of drug development, 19 is marked by exceptional biomedical promise as an antiasthma lead compound.

Plectosphaeroic acid A (20) is an alkaloid–diketopiperazine cultured from the fungus *Plectosphaerella cucumerina*, obtained from marine sediments collected in Barkley Sound, British Columbia (Carr et al. 2009). With a molecular formula of C_{25}H_{36}N_{3}O_{9}, MDSM 19 has 27 sites of unsaturation. The plectosphaeroic acid family is biosynthetically derived from four equivalents of tryptophan and one equivalent of either alanine or serine, followed by subsequent modification to yield the various analogues (Carr et al. 2009). Having inhibitory activity against the molecular target of indoleamine 2,3-dioxygenase (IDO), 20 is a promising lead compound for anticancer agents that modify the ability of tumor cells to evade the T-lymphocyte-based immune response ( Muller & Prendergast 2005).

The brominated-alcohol (E,E)-bastadin 19 (21) was isolated from a marine sponge, *Lanthella cf. reticulata* (Calcul et al. 2010), and is the diasteromer of known (E,E)-bastadin 19 (Mack et al. 1994). The molecular formula of 21 has been established as C_{34}H_{27}Br_{3}N_{4}O_{8}, with 21 degrees of unsaturation and a core ratio H/C < 1. The presence of 2-hydroxyimino-N-alkylamide functionality is characteristic of bastadin metabolites, whereby the configuration about the oximo amide bonds is the basis of the diastereomeric relationship of 21. (E,Z)-bastadin 19 is the first reported (Z)-oximo amide bastadin. The inherent instability of the Z-oximo amide configuration readily leads to isomerization of functionality to the thermodynamically more stable E-isomer, which fact has been recently supported by molecular modeling of macrocycle 21 (Inman & Crews 2011). The bastadins display an impressive bioactivity, including Ca^{2+} channel modulation (Inman & Crews 2011).

The chlorinated-alcohol ammosamide A (22) belongs to the pyrroloiminoquinone class of natural products and displays extraordinary atom diversity. It possesses a molecular formula of C_{12}H_{10}ClN_{5}O_{5}S and 10 sites of unsaturation (Hughes et al. 2009b). MDSM 22 was cultured from a marine-derived actinomycete, *Streptomyces* strain CNR-698, obtained from deepwater sediments in the Bahamas Islands (Hughes et al. 2009b). As 22 has a core ratio of H/C < 1, it presents an awesome structural challenge, which is further compounded by the dense arrangement of the heteroatoms (N, O, S) and the relative lack of hydrogen atoms. Thus, x-ray crystal analysis was ultimately responsible for the structure assignment of 22 and led to the identification of the unusual thio-γ-lactam ring. Ammosamide A is an encouraging MDSM, possessing potent in vitro cytotoxicity against HCT-116 colon carcinoma (IC_{50} = 320 nM), and has as its molecular target the myosin family (Hughes et al. 2009a). The total synthesis of ammosamide A and B was completed shortly after initial structure disclosure (Hughes & Fenical 2010b). A short review highlighting ammosamide MDSMs as modulators of the cell cycle had already been published (Zurwerra et al. 2010).

### 1.2.4 Depsipeptide

The cyclic depsipeptide largazole (23), isolated from a marine cyanobacterium, *Symploca* sp., collected from Key Largo, Florida Keys, has a molecular formula of C_{29}H_{42}N_{2}O_{3}S_{3} and 11 sites of unsaturation (Taori et al. 2008). Largazole possesses significant atom and functional group diversity: substituted
4-methylthiazoline linearly fused to thiazole and thioester functionality. Cyanobacteria metabolite 23 is a potent and selective cytotoxic agent, with nanomolar activity against various epithelial and fibroblastic cancer cell lines (Taori et al. 2008). Its structural complexity and biological activity have made it an attractive candidate for total synthesis. Just a few months after the initial disclosure, the total synthesis of 23 was completed and its molecular target was identified (Ying et al. 2008). Remarkably, the therapeutic profile of 23 is attributed to the selective molecular inhibition of class I histone deacetylases (HDACs) overexpressed in cancer cells (Hong & Luesch 2012). Additional analysis and discussion of 23 as a chemical probe will be given in Section 1.4.

1.2.5 Polyketide–peptide

A culture of the marine cyanobacterium *Symploca* sp. led to the isolation of a new class of proteasome inhibitors, represented by carmaphycin A (24) (Pereira et al. 2012). Having a molecular formula of C_{25}H_{45}N_{3}O_{6}S and five sites of unsaturation, 24 displays an appreciable degree of chemical diversity. Its consists of two unusual structural elements: an α,β-epoxyketone “warhead” and methionine sulfoxide functionality (1 : 1; R-S-sulfoxide diastereomers). The cyanobacterial peptide 24 inhibits extracellular signal-regulated protein kinase (ERK) phosphorylation of the β5 subunit of *Saccharomyces cerevisiae* 20S proteasome with “chymotrypsin-like activity” (Groll et al. 2000). Pereira et al. (2012) speculate that the sulfoxide is the structural element responsible for the observed bioactivity.

The thiazole-containing brominated–peptide bisebromoamide (25) displays a striking degree of atom diversity, with a molecular formula of C_{51}H_{72}BrN_{7}O_{8}S and 19 sites of unsaturation (Teruya et al. 2009). Like the cyanobacterial metabolites, 25 possesses a combination of D-amino acid and N-methylated residues, along with nonribosomal derived moieties (Teruya et al. 2009). Having potent cytotoxicity against 39 human cancer cell lines (JFCR39 panel at the Japanese Foundation for Cancer Research), yielding an average GI_{50} of 40 nM across the tested strains, bisebromoamide is a compelling MDSM ideally suited for total synthesis and biological exploration. Gao et al. (2010) disclosed its first total synthesis and stereochemical reassignment. Later, Sumiya et al. (2011) reported a method for cell morphological profiling of natural product libraries, whereby 25 was identified as an actin filament stabilizer.

1.3 A VIEW BASED ON STEREOCHEMICAL DIVERSITY

Eleven structures are presented in Table 1.3 and Figure 1.5 to illustrate the outstanding stereochemical diversity of MDSMs, compiled according to biosynthetic classes. The structures included in Table 1.3 are derived from the two most prolific groups: sponges and bacteria. To highlight the stereochemical diversity between the structural classes represented in Table 1.3, the number of defined stereocenters and E,Z-olefins has been included. Comments are given to provide additional perspective and direct the reader to salient features of this group of MDSMs.

1.3.1 Terpene

Monamphilectine A (26) is an unusual diterpenoid alkaloid isolated from a marine sponge, *Hymeniacidon* sp., obtained from Mona Island, of the Puerto Rican archipelago (Avilés & Rodríguez 2010). MDSM 26 exhibits a rare marine-derived β-lactam moiety (Anthoni et al. 1987), in combination with an amphilectane-base carbon framework. Semisynthesis has been used to confirm the structure assignment and absolute configuration of 26, which possesses seven chiral centers in very close proximity. A remarkable, facile, one-pot, multiple-component synthesis has been developed (Dömling & Ugi 2000). The unusual sponge metabolite 26 displays potent antimalarial activity. Its biomedical prospects will undoubtedly benefit from the effective one-pot synthesis, which addresses the supply challenge.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Natural product</th>
<th>Organism source</th>
<th>Biosynthetic class</th>
<th>Stereocenters/E,Z-olefins</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Marinomycin A (27)</td>
<td>Bacterium Marinispora sp.</td>
<td>Polyketide</td>
<td>10/10</td>
<td>Potent cytotoxicity against melanoma cancer cell lines. Significant antimicrobial activity against drug-resistant bacteria.</td>
</tr>
<tr>
<td>3</td>
<td>Indoxamycin A (28)</td>
<td>Bacterium Streptomyces sp.</td>
<td>Polyketide</td>
<td>6/4</td>
<td>Significant growth inhibition (&lt;50% of growth) at concentrations between 0.3 and 3 μM relative to control.</td>
</tr>
<tr>
<td>4</td>
<td>Spongistatin 1 (29a) &lt;br&gt; Altohyrtin (29b) &lt;br&gt; Cinachyrolide A (29c)</td>
<td>Sponge (10a) Spongia sp., Spirastrella spinispirulifera; (10b) Hyrtios alatum, Haliclona sp.; (10c) Cinachyra sp.</td>
<td>Polyketide–macrolide</td>
<td>24/2</td>
<td>Isolated in low yields, 0.003–0.17 mg/Kg from five different sponges possessing nM in vitro activity vs. cancer cells. Synthesis: 29a = 29b.</td>
</tr>
<tr>
<td>7</td>
<td>Muironolide A (32)</td>
<td>Sponge Phorbas sp.</td>
<td>Polyketide–chlorinated-alkaloid</td>
<td>8/3</td>
<td>Microscale structure elucidation (0.09 mg).</td>
</tr>
<tr>
<td>9</td>
<td>Marinopyrrole B (34)</td>
<td>Bacterium Streptomyces sp.</td>
<td>Halogenated-alkaloid</td>
<td>0/0</td>
<td>Axially chiral compound biosynthetically produced in atropselective enzymatic catalysis.</td>
</tr>
<tr>
<td>11</td>
<td>Paltolide A (36)</td>
<td>Sponge Theonella swinhoei</td>
<td>Peptide</td>
<td>6/0</td>
<td></td>
</tr>
</tbody>
</table>
1.3.2 Polyketide

A novel of marine actinomycetes *Marinispora* strain CNQ-140 led to the isolation of marinomycin A (27), which exhibits unusual polyene–polyol functionalities (Kwon *et al.* 2006). Polyketide 27 exhibits a high degree of stereochemical diversity, possessing 10 stereocenters and 10 E,Z-olefins, and is among the first class of marine natural products to possess the unusual polyene–polyol structure. Owing to the hydroxylated and conjugated structural architecture, 27 exhibits atypical chiroptical properties.
Coplanar and opposing conformations of the polyene–polyol chains in 27 have been ascribed to conformational interactions, with this observation supported by reports of chirality in the absence of chiral carbons, as observed for certain polyolefinic systems (Kwon et al. 2006). Marinomycin A displays potent antimicrobial activity against antibiotic-resistant strains of methicillin-resistant Staphylococcus aureus (MRSA), with minimum inhibitory concentration required to inhibit growth of 90% of organisms (MIC90) of 0.13 μM, and against vancomycin-resistant Enterococcus faecium (MIC90 = 0.13 μM). For comparison, the gold-standard antibiotic vancomycin has a MIC90 of 0.95–0.391 μg/ml, while penicillin G has a MIC90 of 6.25–12.5 μg/ml (Kwon et al. 2006).

From the standpoint of addressing the resupply challenge of MDSMs, the total synthesis of marinomycin A has been reported (Nicolaou et al. 2006, 2007). Recently, a convergent total synthesis of 27 was disclosed, which featured the chemoselective construction of the macrodiolide dimerization (Evans et al. 2012). The differing synthetic methodologies offer entry to material 27 for future antibacterial drug development.

Indoxamycin A (28) is an unusual polyketide isolated from the novel marine actinomycete strain NPS-643, from Kochi Harbor, Japan. It possesses low homology (96%) to Streptomyces sp. (Sato et al. 2009). Belonging to a class of novel tricyclic polyprenopiones, 28 exhibits tremendous stereochemical diversity: an impressive collection of six consecutive and highly congested chiral carbons and four E/Z-olefins. The unusual incorporation of propionates is noteworthy, and Sato et al. (2009) hypothesize the biosynthesis of 28 to be an adaptation of NPS-643 to the marine habitat. Possessing cytotoxicity against the human colon adenocarcinoma HT-29 cell line (IC50 = 0.59 μM), 28 is an inspiring MDSM with biological promise and significant stereochemical diversity. The total synthesis and stereochemical reassignment of (±)-indoxamycin B has recently been reported by Jeker & Carreira (2012).

Spongistatin 1 (29a) ≈ altohyrtin (29b) ≈ cinachryolide A (29c) is a highly oxygenated polyketide–macrolide isolated in low yield from a collection of diverse marine sponges (Pietruszka 1998; Radjasa et al. 2011). With 24 stereocenters and two E,Z-olefins, spongistatin 1 displays tremendous stereochemical complexity. Polyketide–macrolide 29a has nanomolar in vitro activity in the screen of the NCI panel of 60 cancer cells and remains an inspirational case of an MDSM with potent cytotoxicity. Given the therapeutic profile of 29a, synthetic efforts have addressed its resupply challenge, and highlights from these strategies have been reviewed in the literature (Dalby & Paterson 2010; Qi & Ma 2011).

1.3.3 Alkaloid

Neopeltolide (30) was isolated from the deepwater marine sponge Daedalopeleta sollass in 2007 (Wright et al. 2007). It possesses stereochemical complexity, which was not trivial to assign correctly, with nanomolar activity and specificity against cancer cell lines (A-549 human lung adenocarcinoma, NCI-ADR-RES human ovarian sarcoma, and P388 murine leukemia cell lines, with reported IC50 values of 1.2, 5.1, and 0.56 nM, respectively) (Qi & Ma 2011). The compelling antiproliferative activity of 30 necessitated total synthesis in order to address the resupply challenge. The first total synthesis of 30 was accompanied by a structural revision and was reported by Custar et al. (2008). Shortly thereafter, the efficient coupled synthesis–SAR investigation of 30 was disclosed (Custar et al. 2009), and since then a multitude of other investigations have been published; these have been recently reviewed (Qi & Ma 2011).

The potent and selective cytotoxic tausalarin C (31) was isolated from a Madagascar sponge, Fascaplysinopsis sp., by Bishara et al. (2009). The polyketide–alkaloid tausalarin C is structurally intriguing and demonstrates a high degree of stereochemical diversity: nine stereocenters and six E,Z-olefins. Biosynthetically, 31 is derived from the metabolites salarin A and taumycin A, which are also isolated from Fascaplysinopsis marine sponge (Bishara et al. 2008). Bishara and colleagues suggest that the variability in chemical constitution and relative yield of Fascaplysinopsis metabolites, as well as the structural similarity to other microorganism metabolites, intimates microbial associations from the host sponge (Bishara et al. 2009; Radjasa et al. 2011).

A remarkable case of a polyketide–chlorinated-alkaloid is muironolide A (32), isolated from the marine sponge Phorbas sp. by Dalisay et al. (2009). Muironolide A is a striking example of the
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Chemodiversity of macrolides from Phorbas sp. and demonstrates the successful isolation and structure elucidation of an MDSM on nanomole scale. Muironolide A possesses high stereochemical diversity, with eight stereocenters and three E,Z-olefins, which collectively make up the novel carbon framework, which includes a unique trichloro-carbinol ester, trans-chlorocyclopropane, and hexahydro-1H-isoinodolone-triketide ring. Structure elucidation of 32 proceeded on 90 µg (152 nmol) of sample, employing microprobe nuclear magnetic resonance (NMR) spectroscopy (Dalisay & Molinski 2009). Dalisay et al. (2009) suggest that 32 might in fact be the biosynthetic product of microbial association with the host Phorbas sponge. The low-yield isolation of 32 necessitates total synthesis in order to address the resupply challenge and allow for further biomedical investigation. Flores & Molinski (2011) have recently reported the synthesis of the isoinodinone core of 32, and further investigations are underway.

The brominated-alkaloid dictazole A (33) was extracted from freeze-dried Panamanian marine sponge, Smenospongia cerebriformis, by Dai et al. (2010). The milligram isolation of 33 complements an already-known class of sponge metabolites, the dictazolines (Dai et al. 2008). Dictazole A has three stereocenters tightly congested about the cyclobutyl core, and Dai et al. (2010) thus propose it to be the biosynthetic precursor of the constitutional isomer dictazoline C by way of a vinyl cyclobutane rearrangement (Dai et al. 2010). Dictazole A is therapeutically relevant towards Alzheimer’s disease, where it inhibits the aspartic acid protease β-secretase 1 BACE1 (memapsin 2), implicating the neurodegenerative disease (Hardy 2006). The 2-iminoimidazolidinone of 33 is the presumed pharmacophore responsible for BACE1 (Hills & Vacca 2007). Taken together, 33 displays tremendous biomedical potential and warrants further investigation.

Marinopyrrole B (34) was cultured from a sediment-derived salt obligate marine actinomycete, Streptomyces sp. strain CNQ-418, obtained from La Jolla, California (Hughes et al. 2008). Having a molecular formula of C_{22}H_{11}BrCl_{4}N_{2}O_{4} and 16 degrees of unsaturation, MDSM 34 presented a significant structural challenge due to a core ratio of H/C < 1. Ultimately, the structure assignment of marinopyrrole B was established on the basis of x-ray crystallography data. Of interest to the present discussion is that marinopyrrole B is axially chiral and was isolated as a single atrop-enantiomer, which was assigned M-configuration on the basis of x-ray Flack parameter (Hughes et al. 2008). MDSM 34 displays antibacterial activity against MRSA (MIC_{90} < 2 µM) (Hughes et al. 2009c, 2010; Haste et al. 2011). Nicolaou et al. (2011) disclosed the total synthesis of the structurally related marinopyrrole A and the accompanying biological evaluation of marinopyrrole analogues.

A striking feature of marinopyrrole B is the presence of an unprecedented bispyrrole structure (Hughes et al. 2008). Yamanaka et al. (2012) recently reported an elegant study encompassing characterization of the flavoenzyme responsible for catalysis of the atrop-selective N,C2-bipyrrrole homocoupling in the biosynthesis marinopyroles. Two flavin-dependent halogenases were identified on a molecular basis as being responsible for the biosynthetic atrop-selective N,C-bipyrrrole homocoupling in the novel class 1,3′-bipyrrrole 34.

1.3.4 Depsipeptide

The cyclic depsipeptide coibamide A (35) was isolated from a marine-derived cyanobacterium, Leptolyngya sp., from Panama, by Medina et al. (2008). Depsipeptide 35 has a total of 13 stereocenters and an appreciable degree of stereochemical diversity. Substantial N- and O-methylation of 35 is consistent with its being of cyanobacterial origin. Coibamide A displays potent and selective cytotoxicity when tested in a panel of NCI 60 cell lines, with a pattern of activity for breast, central nervous system (CNS), colon, and ovarian tumor cells. Significant cytotoxicity (50% lethal concentration (LC_{50}) < 23 nM) has been observed for NCI-H460 human lung tumor cells and mouse neuro-2a cells. The therapeutic profile of coibamide A is inspirational from the perspective of further biomedical investigation. Also promising is the extensive N-methylation present in 35, which may benefit from improved pharmacological properties and drugability as compared to standard peptides (Morishita & Peppas 2006).
1.3.5 Polyketide–peptide

The cyclic hexapeptide paltolide A (36) was isolated from a deepwater specimen of the marine sponge *Theonella swinhoei*, from Palau, by Plaza et al. (2010). MDSM 36 is characterized by a C-terminal tryptophan moiety linked to the ε-amine of a D-lysine, which is consistent with a rare subgroup of the sponge-derived anabaenopeptins (Grach-Pogrebinsky & Carmeli 2008). Paltolide A has six chiral centers, in which the presence of a distribution of D- and L-amino acids is suggestive of cyanobacterial origin. Further support for this notion is the fact that anabaenopeptins have been isolated from both sponges and cyanobacteria (Fisch et al. 2009; Christiansen et al. 2011).

1.4 CASE STUDIES OF CHEMICAL PROBES AND CHEMICAL PROBES IN THE THERAPEUTIC DISCOVERY PIPELINE

This section develops on the earlier discussion of MDSMs as chemical probes. Analysis of the peer-reviewed publication record using SciFinder® (http://www.cas.org/products/scifinder) provides the basis for the case studies and allows a perspective to be developed on the biomedical prospects of these select MDSMs as chemical probes. Three illustrative examples of MDSM classes have been selected: (1) the actin-binding marine macrolide latrunculin A (12); (2) the proteasome inhibitor salinosporamide A (6); and (3) the histone deacetylase inhibitor largazole (23). The MDSM chemical probes discussed in this section are introduced in chronological order of first isolation.

Figure 1.6 shows a histogram of peer-reviewed publications on latrunculin A, salinosporamide A, and largazole classes of MDSMs, from the year of isolation to 2011.

The story of the sponge metabolite latrunculin A begins in the early 1970s, when sponge juices from *Negombata magnifica* and *Cacospongia mycofijiensis* were identified as cytotoxic (N`eeman et al. 1975). Isolation of the sponge extracts identified latrunculin A as the active agent and eventually led to realization of the molecular target (Groweiss et al. 1983). Concurrent in vitro investigations revealed that latrunculin A interferes with mammalian actin microfilament organization (Spector et al. 1983). A significant finding was reported in 1997, when 12 was shown to effectively interfere with *Saccharomyces cerevisiae* actin cytoskeleton in under 5 minutes (Ayscough et al. 1997). Around

![Figure 1.6](image-url)
this same time, latrunculin A became commercially available as a chemical probe, which has since contributed to the upward trend in the number of peer-reviewed publications surrounding it.

A second example of an inspirational MDSM chemical probe is represented by the proteasome inhibitor salinosporamide A class. Salinosporamide A is among the drug candidates from the Actinomycetales order with the most potential and is presently in phase I evaluation as an anticancer agent (Fenical et al. 2009; Lechner et al. 2011). Like latrunculin A, salinosporamide A is commercially available as a chemical probe, used to target biological proteosome function and inhibition (Kim & Crews 2008; Kale et al. 2011). The plot of Figure 1.6 shows the steady increase in the number of peer-reviewed publications on the salinosporamide A class.

The histogram of largazole suggests that exploration of this MDSM is in its infancy, but it is nevertheless a popular subject of synthetic inquiry and biological investigation (Taori et al. 2008). Largazole has benefitted from a nearly simultaneous isolation/total synthesis (four months between publications) by the Luesch group (Ying et al. 2008), providing it with a larger than average number of peer-reviewed publications in its first year (17 publications reported in 2008). Although 23 is not commercially available at this time, its compelling biological activity as an HDAC inhibitor has captured the interest of the synthetic community and has contributed to a high incident of publication (Bowers et al. 2008, 2009). Hong & Luesch (2012) recently reviewed the literature surrounding the synthesis and development of largazole as a broad-spectrum agent. What remains most inspiring is the isoform selectivity of largazole for class 1 HDAC inhibition. Present efforts in the chemical biology community are largely directed at defining the molecular basis of largazole isoform-selective HDAC inhibition, with future research predicted to be directed at designing additional largazole analogues that possess the same, if not improved, selectivity profile (Hong & Luesch 2012).

1.5 CONCLUSION

The MDSMs highlighted in this account reinforce the biomedical promise and importance of marine-derived secondary metabolites and demonstrate an astounding chemical and functional diversity. A significant case for future exploration of underexplored taxa, particularly marine microorganisms, is greatly supported by this account. The resupply challenge has been effectively addressed for many of the MDSMs presented here, although others continue to wait for similar success. The interplay between total synthesis and structural reassignment alluded to has added further value to organic synthesis efforts, beyond purely allowing entry to material for clinical investigation and/or development. MDSMs are employed as powerful chemical probes used to understand biological function, and they will be especially useful once the resupply challenge is overcome and they achieve commercial availability. Microbial associations and/or marine-invertebrate associations offer powerful direction for future investigations, especially by way of collaborative and interdisciplinary interactions between the marine natural products, marine microbiology, synthetic, and biomolecular engineering communities.

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