Review

The odyssey of marine pharmaceuticals: a current pipeline perspective

Alejandro M.S. Mayer[1], Keith B. Glaser[1,2], Carmen Cuevas[3], Robert S. Jacobs[4], William Kem[5], R. Daniel Little[6], J. Michael McIntosh[7], David J. Newman[8], Barbara C. Potts[9] and Dale E. Shuster[10]

[1] Department of Pharmacology, Chicago College of Osteopathic Medicine, Midwestern University, 555 31st Street, Downers Grove, IL 60515, USA
[2] Cancer Research, R47J-AP9, Abbott Laboratories, 100 Abbott Park Rd, Abbott Park, IL 60064-6121, USA
[3] Research and Development Director, R&D PharmaMar, Avda. de los Reyes, 1 P.I. La Mina Norte, 28770 Colmenar Viejo, Madrid, Spain
[4] Ecology, Evolution and Marine Biology, University of California at Santa Barbara, Santa Barbara, CA 93106-9610, USA
[5] Department of Pharmacology and Therapeutics, University of Florida College of Medicine, P.O. Box 100267, Gainesville, FL 32610-0267, USA
[6] Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, CA 93106-9510, USA
[7] Department of Psychiatry, University of Utah, 257 S. 1400 E., Salt Lake City, UT 84112-0840, USA
[8] Natural Products Branch, National Cancer Institute, 1003 W. 7th Street, Suite 206, Frederick, MD 21701, USA
[9] Nereus Pharmaceuticals, Inc., 10480 Wateridge Circle, San Diego, CA 92121, USA
[10] Oncology, Eisai, Inc., 300 Tice Blvd., Woodcliff Lake, NJ 07677, USA

The global marine pharmaceutical pipeline consists of three Food and Drug Administration (FDA) approved drugs, one EU registered drug, 13 natural products (or derivatives thereof) in different phases of the clinical pipeline and a large number of marine chemicals in the preclinical pipeline. In the United States there are three FDA approved marine-derived drugs, namely cytarabine (Cytosar-U®, Depocyt®), vidarabine (Vira-A®) and ziconotide (Prialt®). The current clinical pipeline includes 13 marine-derived compounds that are either in Phase I, Phase II or Phase III clinical trials. Several key Phase III studies are ongoing and there are seven marine-derived compounds now in Phase II trials. The preclinical pipeline continues to supply several hundred novel marine compounds every year and those continue to feed the clinical pipeline with potentially valuable compounds. From a global perspective the marine pharmaceutical pipeline remains very active, and now has sufficient momentum to deliver several additional compounds to the marketplace in the near future; this review provides a current view of the pipeline.

Introduction

Natural products have been the mainstay of disease therapy for most of the history of man and are a major component of the modern pharmaceuticals that we use to treat human disease. The diversity of organisms in the marine environment has inspired researchers for many years to identify novel marine natural products that could eventually be developed into therapeutics. By 1974, two marine-derived natural products (cytarabine, Ara-C and vidarabine, Ara-A) were part of the pharmacopeia used to treat human disease. It has taken over 30 years for another marine-derived natural product to gain approval and become part of the pharmacopeia. Since the approval in 2004 of ziconotide (Prialt®) for the treatment of moderate to severe pain, Yondelis® has received European approval in 2007 for the treatment of soft tissue sarcoma, and in 2009 for ovarian carcinoma. Concomitantly numerous other marine natural products or derivatives thereof are in different phases of clinical trials. This review summarizes the current pipeline of marine natural products that are currently being evaluated in clinical trials and provides a view into the promise that marine natural products pose to improve the diversity of our pharmacopeia to treat a wide variety of human disease.

Marine pharmaceuticals: FDA-approved drugs

There are currently three Food and Drug Administration (FDA)-approved drugs in the US Pharmacopeia, namely cytarabine (Cytosar-U®, Depocyt®), vidarabine (Vira-A®) and ziconotide (Prialt®). Currently, trabectedin (Yondelis®) has been approved by the European Agency for the Evaluation of Medicinal Products (EMEA), and is completing key Phase III studies in the US for approval. The next section will provide details of these compounds, their discovery, mode of action and clinical application.

Approved marine-derived drugs

Cytarabine (arabinosyl cytosine or cytosine arabinoside, *Ara-C*) is a synthetic pyrimidine nucleoside (Figure 1) which was developed from spongothymidine, a nucleoside originally isolated from the Caribbean sponge *Tethya crypta* [1]. Cytarabine is an S-phase specific antimetabolite

Corresponding author: Mayer, A.M.S. (amayer@midwestern.edu).

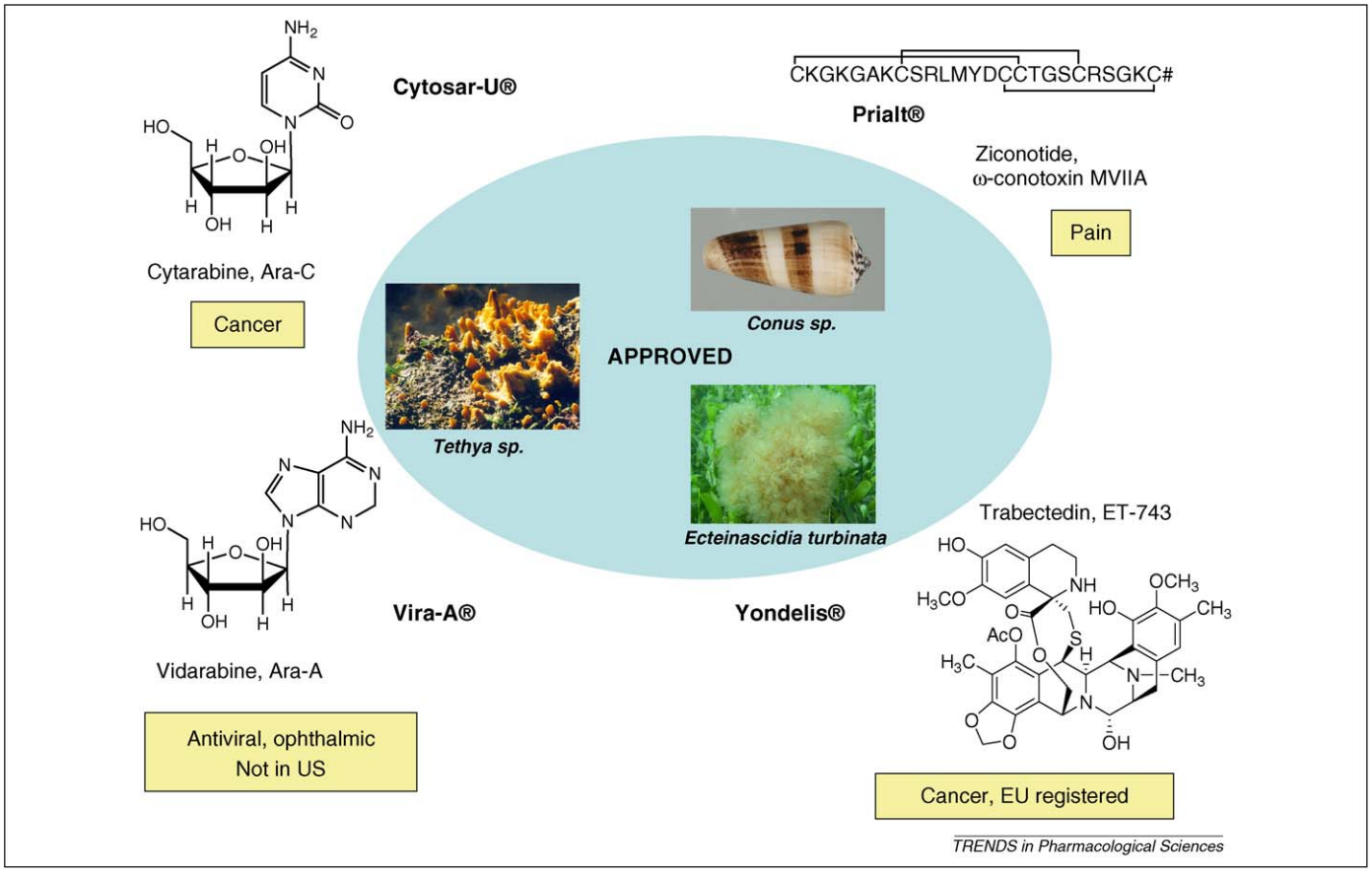

Figure 1. Marine natural products or derivatives thereof approved for use by the FDA or EMEA, their biological source, chemical structures and treatment usage. Cytarabine and ziconotide are both FDA approved drugs in the US, vidarabine is FDA approved but no longer sold in the US. Cytarabine and vidarabine are derivatives of nucleosides isolated from *Tethya sp.* Trabectedin, source organism *Ecteinascidia turbinata,* is approved by the EMEA for use in treating soft tissue sarcoma and ovarian carcinoma, and is currently in Phase III trials in the US (PharmaMar Inc., Madrid, Spain). Photograph of the source organism for ziconotide, *Conus sp.,* was created by Kerry Matz and kindly provided by B. M. Olivera (University of Utah, Salt Lake City, UT, USA).

cytotoxic agent, which when converted intracellularly to cytosine arabinoside triphosphate competes with the physiologic substrate deoxycitidine triphosphate, thus resulting in both inhibition of DNA polymerase and DNA synthesis. Cytarabine is currently available as either conventional cytarabine (Cytosar-U®) or liposomal formulations (Depocyt®) and received FDA approval in 1969. A search in PubMed (December 2009) using the search term cytarabine retrieved 13,008 publications in the peer-reviewed literature, thus revealing the significant impact cytarabine has had on preclinical and clinical cancer pharmacology. FDA-labeled indications for conventional cytarabine are treatment of acute lymphocytic leukemia, acute myelocytic leukemia and blast crisis phase of chronic myelogenous leukemia and meningeal leukemia [2,3]. Liposomal cytarabine (Depocyt®) is indicated for intrathecal treatment of lymphomatous meningitis [4]. Cytarabine (Cytosar-U®) and liposomal cytarabine (Depocyt®) are marketed by Bedford Laboratories (http://www.bedfordlabs.com/) and Enzon Pharmaceuticals (http://www.enzon.com/), respectively.

Vidarabine (arabinofuranosyladenine or adenine arabinoside, *Ara-A*) is a synthetic purine nucleoside (Figure 1) which was developed from spongouridine, a nucleoside originally isolated from the Caribbean sponge *Tethya crypta* [1], and which is currently obtained from *Streptomyces antibioticus*. Adenine arabinoside is rapidly converted into adenine arabinoside triphosphate, which inhibits viral DNA polymerase and DNA synthesis of herpes, vaccinia and varicella zoster viruses. A search in PubMed (December 2009) using the search term vidarabine retrieved 3640 publications in the peer-reviewed literature, thus highlighting the importance of vidarabine on preclinical and clinical antiviral pharmacology [5]. Although its marketing status is currently listed as discontinued by the FDA in the US market, vidarabine (Vira-A®) received FDA approval in 1976. FDA-labeled indications for conventional vidarabine (Vira-A ophthalmic ointment, 3%) are treatment of acute keratoconjunctivitis, recurrent epithelial keratitis caused by herpes simplex virus type 1 and 2, and superficial keratitis caused by herpes simplex virus that has not responded to topical idoxuridine (Herplex®) [6]. Vidarabine (Vira-A®), previously marketed by King Pharmaceuticals (http://www.kingpharm.com/) was discontinued in June of 2001 by an executive decision, possibly associated with the lower therapeutic window of vidarabine relative to newer antiviral compounds currently on the market.

Ziconotide (*Prialt®*) is the synthetic equivalent of a naturally occurring 25-amino acid peptide, ω-conotoxin MVIIA (Figure 1), originally isolated from the venom of the fish-hunting marine snail *Conus magus* [7]. Ziconotide is a potent analgesic with a completely novel mechanism of

Table 1. The odyssey of marine pharmaceuticals: a current pipeline perspective

Clinical status	Compound name	Trademark	Marine organism[b]	Chemical class	Company[a] or Institution	Disease area
Approved	Cytarabine, Ara-C	Cytosar-U®	Sponge	Nucleoside	Bedford, Enzon	Cancer
	Vidarabine, Ara-A	Vira-A®	Sponge	Nucleoside	King Pharmaceuticals	Antiviral
	Ziconotide	Prialt®	Cone snail	Peptide	Elan Corporation	Pain
	Trabectedin (ET-743) (EU Registered only)	Yondelis®	Tunicate	Alkaloid	Pharmamar	Cancer
Phase III	Eribulin Mesylate (E7389)	NA	Sponge	Macrolide	Eisai Inc.	Cancer
	Soblidotin (TZT 1027)	NA	Bacterium	Peptide	Aska Pharmaceuticals	Cancer
Phase II	DMXBA (GTS-21)	NA	Worm	Alkaloid	Comentis	Cognition Schizophrenia
	Plinabulin (NPI-2358)	NA	Fungus	Diketopiperazine	Nereus Pharmaceuticals	Cancer
	Plitidepsin	Aplidin®	Tunicate	Depsipeptide	Pharmamar	Cancer
	Elisidepsin	Irvalec®	Mollusc	Depsipeptide	Pharmamar	Cancer
	PM1004	Zalypsis®	Nudibranch	Alkaloid	Pharmamar	Cancer
	Tasidotin, Synthadotin (ILX-651)	NA	Bacterium	Peptide	Genzyme Corporation	Cancer
	Pseudopterosins	NA	Soft coral	Diterpene glycoside	NA	Wound healing
Phase I	Bryostatin 1	NA	Bryozoa	Polyketide	National Cancer Institute	Cancer
	Hemiasterlin (E7974)	NA	Sponge	Tripeptide	Eisai Inc.	Cancer
	Marizomib (Salinosporamide A; NPI-0052)	NA	Bacterium	Beta-lactone-gamma lactam	Nereus Pharmaceuticals	Cancer

[a]Bedford Laboratories: http://www.bedfordlabs.com/; Enzon Pharmaceuticals: http://www.enzon.com/; King Pharmaceuticals: http://www.kingpharm.com/; Elan Corporation: http://www.elan.com/; Pharmamar: http://www.pharmamar.com/Default.aspx; Eisai Inc.: http://www.eisai.com/pipeline; Aska Pharmaceutical Co., Ltd.: http://www.aska-pharma.co.jp; Comentis: http://www.athenagen.com/; Nereus Pharmaceuticals, Inc.: http://www.nereuspharm.com/; Genzyme Corporation: http://www.genzymeoncology.com/; NA: not applicable.
[b]The marine pharmaceuticals pipeline consists of natural products, analogs or derivatives of compounds produced by this marine organism.

action [8,9]. Various subtypes of voltage-gated calcium channels have been identified in the nervous system. Ziconotide reversibly blocks N-type calcium channels located on primary nociceptive afferent nerves in the superficial layers of the dorsal horn of the spinal cord. Binding of ziconotide to presynaptic N-type calcium channels reduces the release of excitatory neurotransmitter release from the primary afferent nerve terminals [10,11]. Tolerance to drug effects is a major limiting factor in opiate-based therapies; unlike opiates, ziconotide does not produce tolerance [12]. A recent search in PubMed (December 2009) using the search terms ω-conotoxin MVIIA, SNX-111, ziconotide or Prialt® retrieved 261 publications in the peer-reviewed literature. Ziconotide does not readily cross the blood–brain barrier and is therefore delivered intrathecally via an implantable pump or temporarily by an external microinfusion device [11,13,14]. Ziconotide received FDA approval in December 2004 and is currently labeled for the management of severe chronic pain in patients with cancer or AIDS [14,15] for whom intrathecal (IT) therapy is warranted, and who are intolerant of or refractory to other treatments, such as systemic analgesics, adjunctive therapies or IT morphine. Prialt® is marketed by Elan Corporation, PLC (http://www.elan.com/therapies/products/prialt.asp). Ziconotide has also been approved by the EMEA [16].

Trabectedin (*Yondelis®*, *ET-743*) is a marine natural product isolated from *Ecteinascidia turbinata*, a tunicate found in the Caribbean and Mediterranean sea [17,18]. Trabectedin is a tetrahydroisoquinoline alkaloid (Figure 1) and has been the first marine anticancer agent approved in the European Union for patients with soft tissue sarcoma (STS) [19] and patients with relapsed platinum-sensitive ovarian cancer [20]. The chemical structure of trabectedin is formed by three fused tetrahydroisoquinoline rings through a 10-member lactone bridge and it is obtained by chemical synthesis starting from safracin B cyano [21]. Although the mechanism of action is not fully elucidated, it is well known that trabectedin binds by a covalent reversible bond to the DNA minor groove [22] and interacts with different binding proteins of the Nucleotide Excision Repair (NER) system [23–25]. Thus, although other known DNA-interacting agents require a deficient NER mechanism to exert their activity, trabectedin needs a proficient NER system to exert its cytotoxic activity. Cell cycle studies on tumor cells reveal that trabectedin arrests at G2/M [26] and the apoptotic response is independent of p53. Based on *in vitro* and *in vivo* results, trabectedin has been developed and approved for STS and ovarian cancer. Currently, the product is being developed in Phase II trials in breast, lung, prostate and pediatric cancer, and Phase III trials for first-line therapy in STS. Regarding its safety profile [27], the most frequent adverse event appears to be neutropenia, which is reversible and transaminase elevations which were also transient. No mucositis, alopecia, neurotoxicity, cardiotoxicity or cumulative toxicities have been observed. Yondelis® is being developed and marketed by Pharmamar (http://www.pharmamar.com/products.aspx).

Marine pharmaceuticals: clinical pipeline

As shown in Table 1, there are currently 13 marine-derived compounds in clinical development. The marine natural products that are currently in Phase III trials are shown in Figure 2 and include eribulin mesylate (E7389), soblidotin (TZT-1027) and trabectedin (Yondelis® for US approval), and the following section will provide a more detailed status update on eribulin mesylate and soblidotin.

Marine-derived compounds in Phase III trials

Eribulin mesylate (*E7389*) Halichondrin B (HB), a polyether macrolide natural product originally isolated from

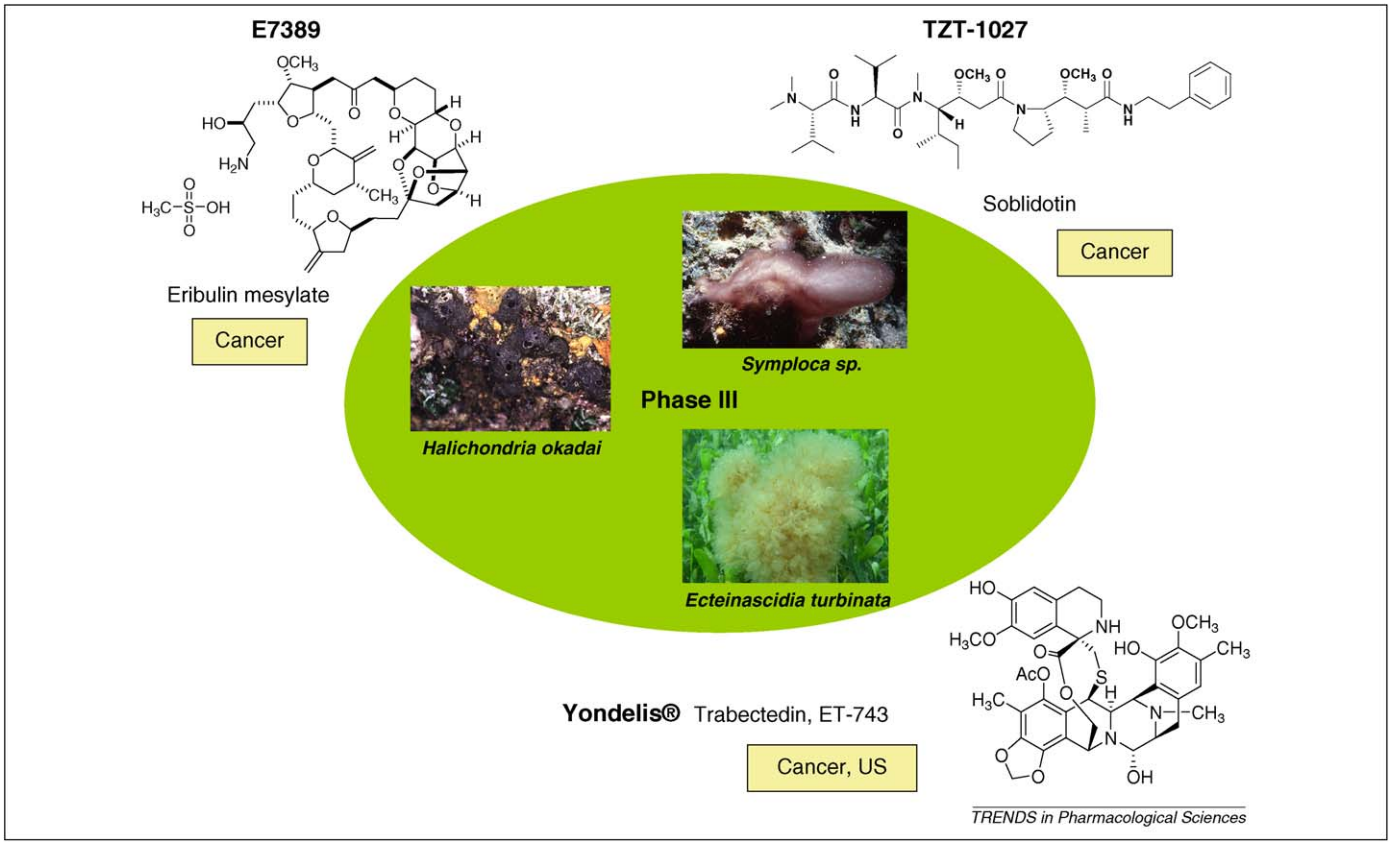

Figure 2. Marine natural products or derivatives thereof in Phase III clinical trials, their biological source, chemical structures and treatment usage. Photograph of the E7389 source organism, *Halichondria okadai*, was reproduced with kind permission from Professor Yasunori Saito. Photograph of the source organism for TZT-1027, *Symploca sp.*, was courtesy of Raphael Ritson-Williams (Smithsonian Institute, Ft. Pierce, FL, USA). Photograph of the trabectedin source organism, *Ecteinascidia turbinata*, was provided by PharmaMar, Inc., Madrid, Spain.

marine sponges [28], shows potent anticancer activity in preclinical animal models [29]. This activity is retained in structurally simplified macrocyclic ketone analogs [30], and the development candidate, eribulin mesylate (Figure 2), retains the promising biological properties of the natural product as well as favorable pharmaceutical attributes including water solubility and chemical stability [31]. Like the widely used taxane and vinca alkaloid chemotherapeutics, eribulin and HB are tubulin-targeted agents. However, eribulin and HB inhibit microtubule dynamics through a unique mechanism distinct from those of the taxanes and vincas [32,33]. Against cancer cells, eribulin exerts potent and irreversible antimitotic effects leading to cell death by apoptosis [34]. In Phase I studies, the maximum tolerated dose of eribulin mesylate given intravenously was 1–2 mg/m^2 depending upon the regimen; dose-limiting toxicities included neutropenia, febrile neutropenia and fatigue [35,36]. Pharmacokinetics was dose proportional with a terminal elimination half-life of 1.5–2 days. Phase II studies in patients with advanced disease were completed in multiple tumor types. Against breast cancer, the most studied tumor, the response rate was 9.3–11.5% in heavily pretreated patients, with responses occurring in patients refractory to taxanes or other agents [37,38]. Common Grade 3/4 adverse events reported as treatment-related were neutropenia, leukopenia and fatigue. Two Phase III studies are evaluating eribulin versus capecitabine (NCT00337103) and eribulin versus treatment of physician's choice (NCT00388726). Preliminary results of the latter study show statistically significant improvement in overall survival, the primary endpoint, with a safety profile similar to Phase II results (Eisai Inc., 2009). Eribulin mesylate (E7389) is being developed by Eisai Inc. (http://www.eisai.com/pipeline.asp?ID=173).

Soblidotin (*Auristatin PE*; *TZT-1027*) As with tasidotin (see below), this compound is a synthetic derivative of the dolastatin backbone (Figure 2), but this time from dolastatin 10. Of interest is that the compound is also a vascular disrupting agent (VDA), causing the vasculature inside the tumor to collapse [39,40], in addition to its tubulin inhibitory activity. TZT-1027 entered Phase I clinical trials in Europe, Japan and the USA under the auspices of either Teikoku Hormone, the originator or the licensee, Daiichi Pharmaceuticals. It has had an interesting development path, as after Phase I and Phase II clinical trials [41] the licensing agreement with Daiichi was terminated, and currently it is under the auspices of Aska Pharmaceuticals (http://www.aska-pharma.co.jp/english/corporate/work1.html), a recently formed company composed of Teikoku Hormone and Grellan Pharmaceuticals that has licensed the compound to Yakult for world-wide development. However, in addition to the potential work by Yakult, it is in three clinical trials (Phases I, II and III) with different companies using it as a "warhead" linked via modified peptides to specific Seattle Genetics-sourced monoclonal antibodies under the code numbers of SGN-75 (Phase I), CR-011 (Phase II) and SGN-35 (Phase III) [41].

Marine-derived compounds in Phase II trials

The marine natural products that are currently in Phase II trials are shown in Figures 3 and 4, and include DMXBA (GTS-21), Plinabulin (NPI-2358), Plitidepsin (Aplidin®), Elisidepsin (Irvalec®, PM02734), PM00104 (Zalypsis®), ILX-651 (Tasidotin or Synthadotin) and the pseudopterosins. Their discovery, stage of development and clinical effects are provided in more detail below.

DMXBA [3-(2,4-dimethoxybenzylidene)-anabaseine; *GTS-21*], is a synthetic derivative of anabaseine, an alkaloid present in several species of marine worms (Phylum Nemertea). GTS-21 [42] (Figure 3) selectively stimulates α7 nicotinic acetylcholine receptors [43], which are expressed on CNS neurons and astrocytes, and on peripheral macrophages. A search in PubMed (December 2009) revealed 124 peer-reviewed publications concerning anabaseine and its derivatives. DMXBA improves cognition [44] and deficient sensory gating [45] in a variety of animal models. DMXBA and other related arylidene–anabaseines have also been demonstrated to be neuroprotective *in vitro* as well as *in vivo* [46,47]. DMXBA counteracted the deleterious effects of beta-amyloid in primary cultures of cerebral cortex neurons [48]. GTS-21 displays anti-inflammatory activities in animal models that are mediated through its effects on macrophage α7 receptors [49,50]. It was recently found to improve survival of rats undergoing experimental hemorrhage [51,52]. Phase I clinical trials have demonstrated significant improvements in cognition of healthy young males [53] and schizophrenics [54]. A recent, academic Phase II trial with schizophrenics showed improvements in cognitive function [55]. GTS-21 is currently licensed by Comentis Inc. (http://www.comentis.com/), a company developing treatments for Alzheimer's disease.

Plitidepsin (*Aplidin®*) is a marine natural depsipeptide isolated from *Aplidium albicans*, a tunicate found in the Mediterranean Sea that currently is obtained by total synthesis (Figure 3). The macrocycle is made of six subunits: (S)-Leu, (S)-Pro, (1S,2R)-Thr, (S)-N(Me)-O(Me)-Tyr, (3S,4R,5S)-isostatin and (2S,4S)-3-oxo-4-hydroxy-2,5-dimethylhexanoic acid. The side chain consists of three amino acids: (R)-N-Me-Leu linked to the Thr and piruvil-(L)-Pro. Plitidepsin is an extremely potent inducer of apoptosis with IC_{50} values in the low nanomolar range. It depletes GSH and triggers Rac 1 activation, together with MPK-1 downregulation, and sustained JNK activation [56,57]. Ongoing efforts seek to identify the primary cellular target. Preclinical studies with different tumor types, both *in vitro* and *in vivo*, were the basis for the selection and design of the Phase I and Phase II programs. Clinically, plitidepsin has demonstrated preliminary efficacy in two different Phase II clinical trials in relapsing and refractory multiple myeloma and T cell lymphoma [58]. The encouraging results gathered from these clinical trials support further clinical research, particularly in combination with other active agents. The main toxicity

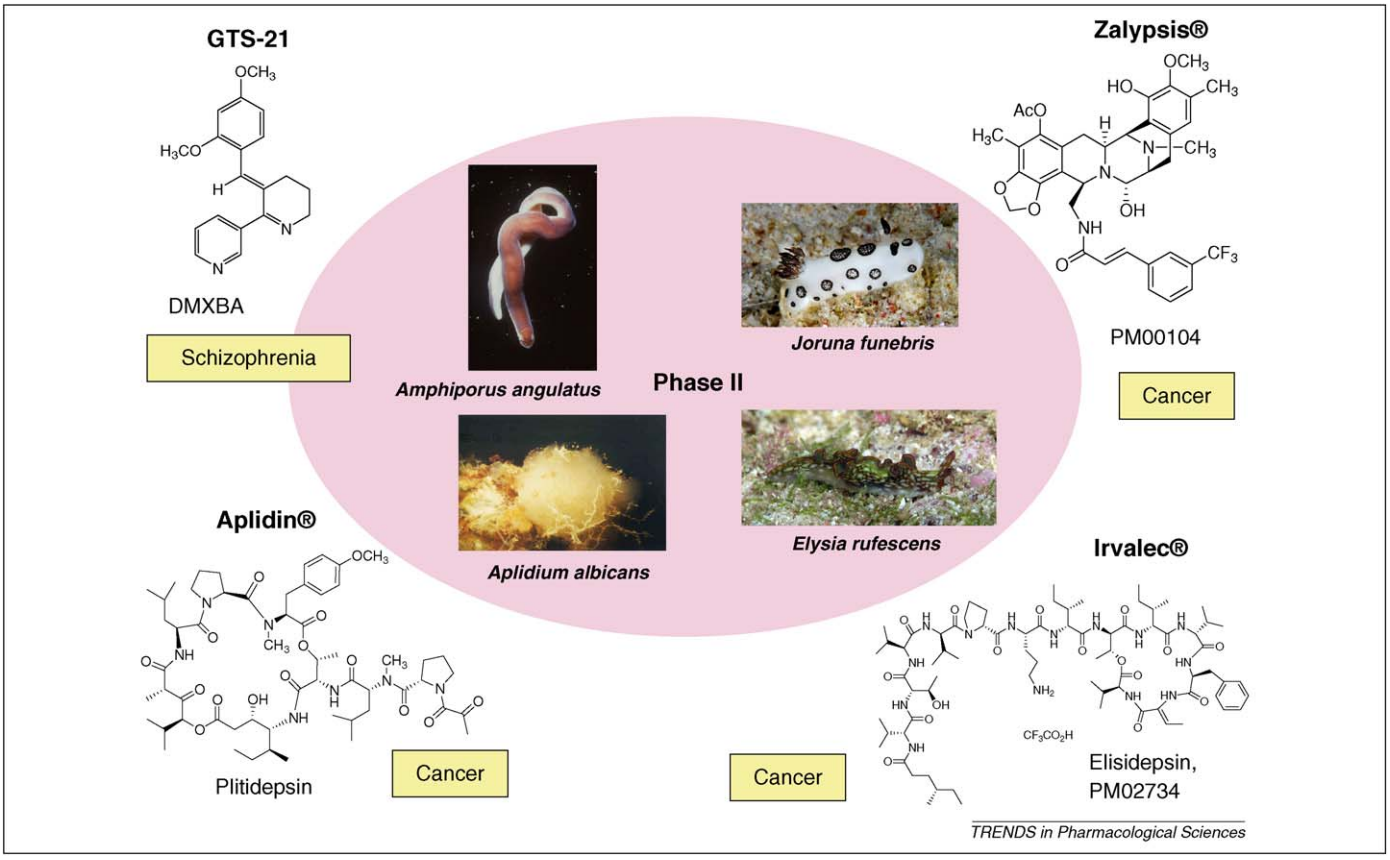

Figure 3. Marine natural products or derivatives thereof currently in Phase II clinical trials, their biological source, chemical structures and treatment usage. GTS-21 is a synthetic derivative of the marine toxin anabaseine, an alkaloid present in several hoplonemertine worms including *Amphiporus angulatus* (Kem, W.R., Scott, K.N., and Duncan, J.H. 1976 Hoplonemertine worms – a new source of pyridine neurotoxins. *Experientia* 32, 684–686). Photograph of the source organisms for Zalypsis® (*Joruna funebris*), Aplidin® (*Aplidium albicans*) and Irvalec® (*Elysia rufescens*) were provided by PharmaMar Inc. Madrid, Spain.

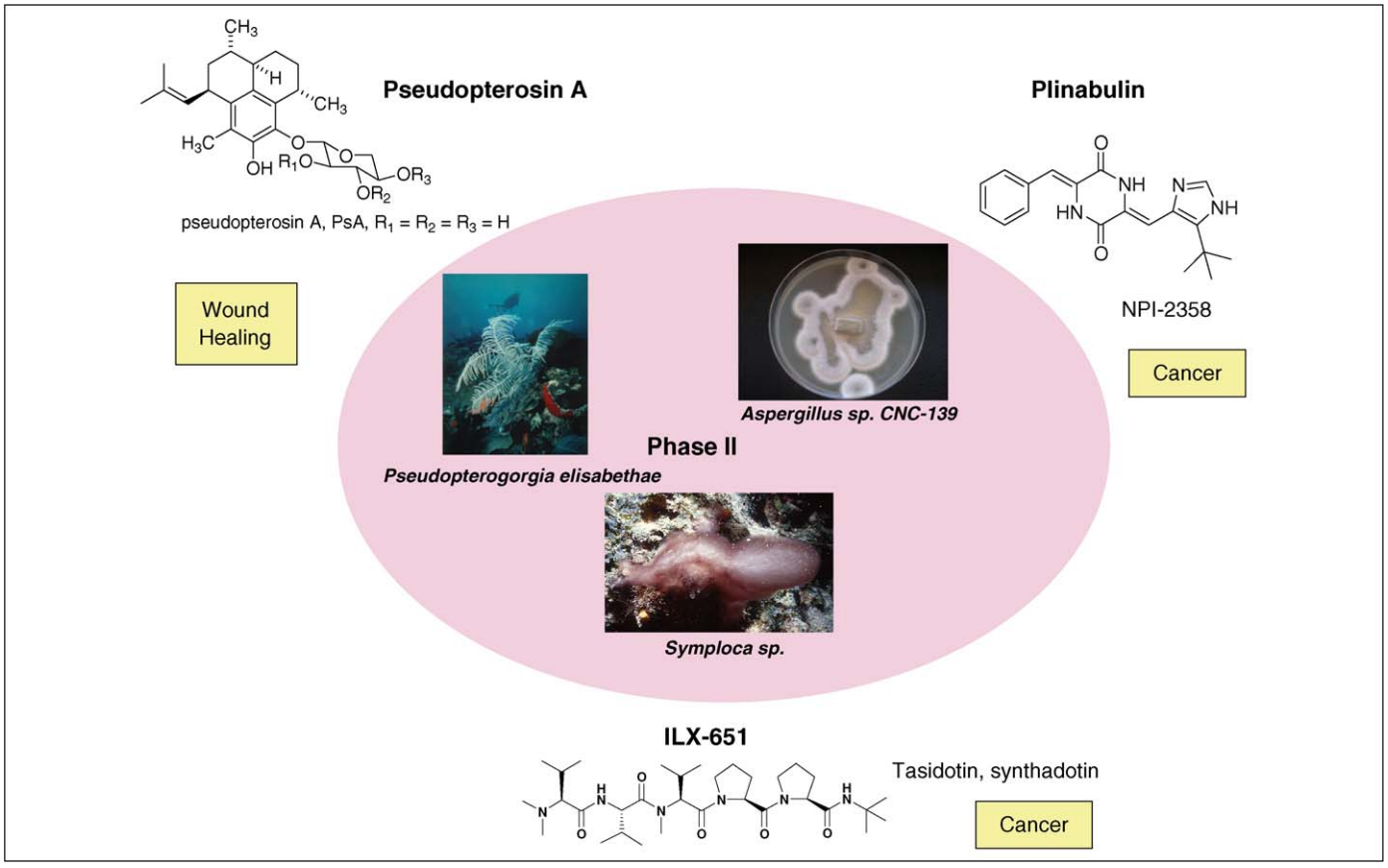

Figure 4. Marine natural products or derivatives thereof in Phase II clinical trials, continued, their biological source, chemical structures and treatment usage. Plinabulin is a fully synthetic analog of halimide, which was isolated from *Aspergillus* sp. CNC-139 (photograph courtesy of Paul Jensen, University of California, San Diego, CA, USA). Photograph of the source organism for ILX-651, *Symploca sp.*, was courtesy of Raphael Ritson-Williams (Smithsonian Institute, Ft. Pierce, FL, USA). Photograph of the source organism for pseudopterosin A, *Pseudopterogorgia elisabethae*, was originally created by Valerie Paul, Smithsonian Institution, and provided by Drs. R.S. Jacobs and R. Daniel Little (University of California at Santa Barbara, CA, USA).

[59], found with most schedules, included muscular toxicity, transient increase of transaminases (in many cases related with liver metastasis and biochemical abnormalities at baseline), fatigue, diarrhea and cutaneous rash. Plitidepsin showed no severe bone marrow toxicity. Plitidepsin (Aplidin®) is being developed by Pharmamar (http://www.pharmamar.com/products.aspx).

Elisidepsin (*Irvalec®*, *PM02734*) is a novel marine-derived cyclic peptide belonging to the Kahalalide family of compounds [60,61], currently under Phase II development with preliminary evidence of antitumor activity and a favorable therapeutic index [62] (Figure 3). It has potent cytotoxic activity *in vitro* against a variety of human tumor cell lines. Although little is known about its mechanism of action, it has been reported that the compound induces oncolytic rather than apoptotic cell death. Elisidepsin (Irvalec®, PM02734) is being developed by Pharmamar (http://www.pharmamar.com/products.aspx).

PM00104 (*Zalypsis®*) is a new DNA-binding alkaloid related to jorumycin isolated from the skin and mucus of the Pacific nudibranch *Joruna funebris* and *renieramiycins* isolated from sponges and tunicates [63] (Figure 3). Zalypsis binds to guanines in selected DNA triplets, DNA adducts eventually give rise to double-strand breaks, S-phase arrest and apoptosis in cancer cells. Cell lines with mutant p53 or lacking p53 are more sensitive to the treatment with Zalypsis than cell lines with wild type p53 [64]. Preclinical *in vivo* studies have demonstrated strong antitumor activity in breast, prostate and renal cancer and a moderate antitumor profile against colon cancer. The main toxicity observed during Phase I trials has been hematological disorders or liver enzyme increases, mostly reversible. Currently Zalypsis is in Phase II trials. Zalypsis® is being developed by Pharmamar (http://www.pharmamar.com/products.aspx).

Plinabulin (*NPI-2358*) is a fully synthetic analog of the natural product known as halimide [65] from marine *Aspergillus* sp. CNC-139 (cultured from the alga *Halimeda lacrimosa* collected in the Bahamas) and phenylahistin [66] (from *Aspergillus ustus*) (Figure 4). Plinabulin binds at a boundary region between α- and β-tubulin near the colchicine binding site and inhibits tubulin polymerization [67,68], leading to destabilization of tumor vascular endothelial architecture. Thus, plinabulin functions as a VDA that induces selective collapse of established tumor vascular, in addition to its direct apoptotic effect on tumor cells [67]. In 2006, Nereus Pharmaceuticals initiated a Phase I clinical trial in patients with solid tumors or lymphomas. Disruption of tumor blood flow measured using dynamic contrast-enhanced magnetic resonance imaging indicated that plinabulin had a measurable effect on tumor vasculature at doses $\geq$13.5 mg/m^2 and was well tolerated up to 30 mg/m^2 [69]. These findings, together with indications that VDAs can complement or synergize

with chemotherapeutics and antiangiogenesis agents, led to initiation of the ADVANCE (Assessment of Docetaxel and Vascular Disruption in Non-Small Cell Lung Cancer) Phase I/II trial in 2009. Plinabulin (NPI-2358) is being developed by Nereus Pharmaceuticals, Inc. (http://www.nereuspharm.com/) for cancer.

ILX-651 (*Tasidotin or Synthadotin*) ILX-651 is a synthetic dolastatin-15 derivative and has had an interesting development path as companies were bought and sold (Figure 4). Although ILX-651 is known to be an inhibitor of tubulin assembly, further refinements on its mechanism of action have been reported recently [70,71] where the "active version" is probably the pentapeptide produced by hydrolysis of the C-terminal amide bond. ILX-651 is orally active and has advanced to Phase II trials in a variety of cancers initially under Ilex Pharmaceuticals, and then under Genzyme Corporation following the purchase of Ilex. Those trials were completed [41] and recently (mid-2008) (http://www.genzymeoncology.com/onc/research/onc_p_tasidotinHydrochloride.asp) Genzyme reported that ILX-651 was well tolerated but that efficacy was not such that further single agent trials were warranted at that time. Subsequently, ILX-651 has re-entered preclinical studies to better define routes and targets including advanced refractory neoplasms.

The *pseudopterosins* constitute a class of diterpene glycosides isolated from the marine octocoral *Pseudopterogorgia elisabethae* [72,73,74] (Figure 4). Structurally, they consist of a tricarbocyclic core possessing four stereocenters, and a sugar that is appended at either C-9 or C-10 of a catechol subunit that constitutes one of the three rings. Pseudopterosins A–D were the first of a series that now numbers 26 members. A search in PubMed (December 2009) indicated that 24 peer-reviewed publications have appeared since their discovery in 1986. Pseudopterosin A (PsA), a potent inhibitor of phorbol myristate acetate, induces topical inflammation in mice [75], stabilizes cell membranes [76], prevents the release of prostaglandins and leukotrienes from zymosan-stimulated murine macrophages [77] and inhibits degranulation of human polymorphonuclear leukocytes and phagosome formation in *Tetrahymena* cells [78]. Treatment with pertussis toxin prior to pseudopterosin administration blocked the ability of PsA to inhibit phagocytosis, prompting an investigation of the role of the pseudopterosins to act upon G-protein-coupled receptors of the adenosine variety [79,80]. The C-10 O-methyl ether of PsA displays potent anti-inflammatory and wound healing properties [81]. Extensive preclinical studies revealed accelerated wound healing and reepithelialization activity in partial and full thickness wounds in several animal models including the diabetic mouse, the Yorkshire and Harford miniature pigs. The methyl ether also showed efficacy in healing dichloronitrobenzene induced full thickness wounds in Hartley guinea pigs. In Phase II clinical trials, a double-blind study revealed increased

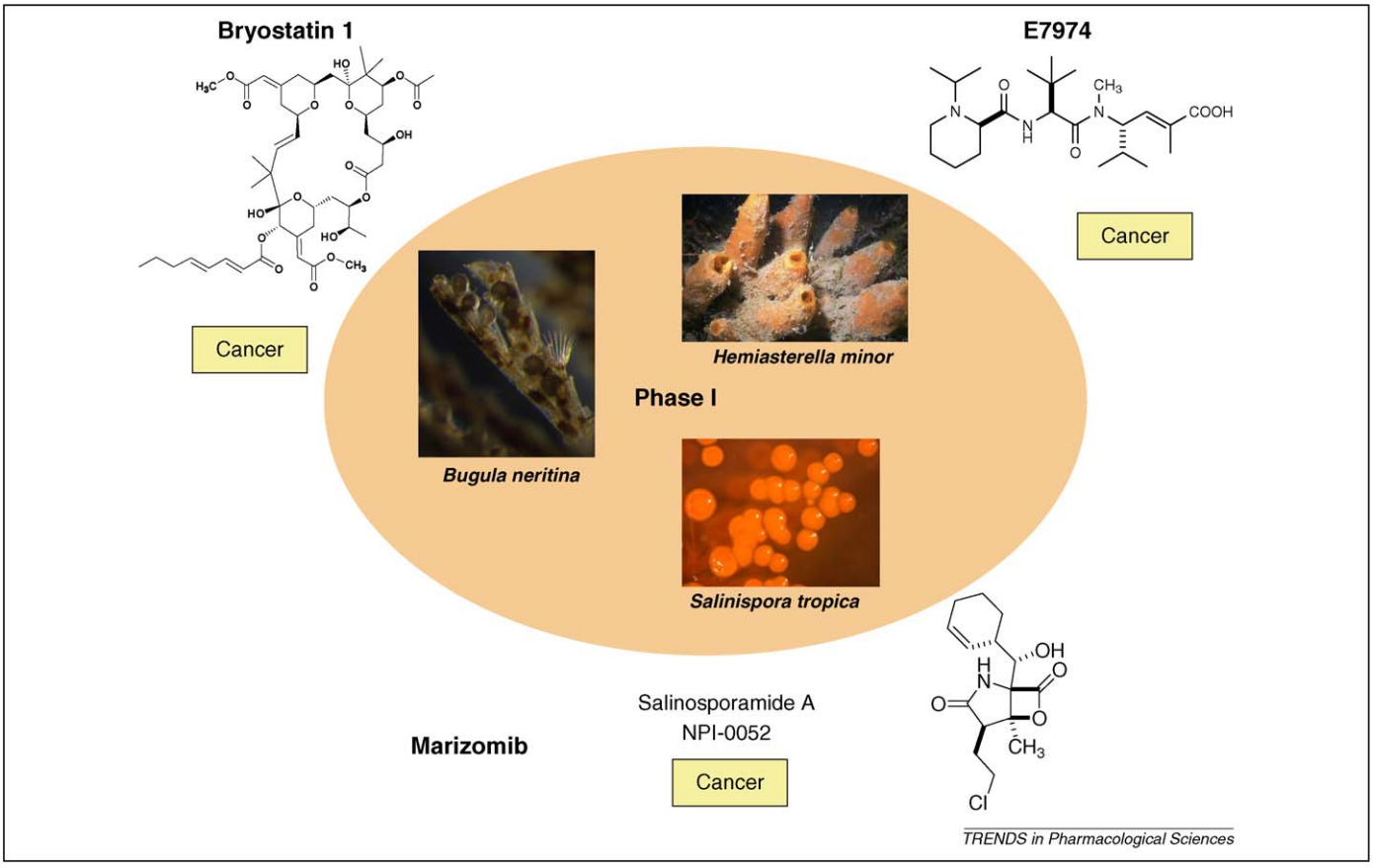

Figure 5. Marine natural products or derivatives thereof in Phase I clinical trials, their biological source, chemical structures and treatment usage. Photograph of the source organism for Bryostatin 1, *Bugula neritina*, was courtesy of Koty Sharp, (Ocean Genome Legacy, Ipswich, MA, USA). Photograph of the source organism of E7974, *Hemiasterella minor*, was reproduced with kind permission from Y. Benayahu and S. Perkol-Finkel. Photograph of the source organism of marizomib, *Salinispora tropica*, was courtesy of Sy Teisan (Nereus Pharmaceuticals, Inc., San Diego, CA, USA).

reepithelialization and qualitative improvement during early wound repair [82].

Marine-derived compounds in Phase I trials

The marine natural products that are currently in Phase I trials are shown in Figure 5 and include bryostatin 1, E7974 (hemiasterlin) and marizomib (NPI-0052, salinosporamide A). The current status of these compounds is discussed further in the following section.

Bryostatin 1 G.R. Pettit at Arizona State University identified the *in vivo* bioactive agent bryostatin 3 (one of now 20 variations) from the bryozoan *Bugula neritina* (Figure 5). Subsequent research by the National Cancer Institute at NCI-Frederick gave 18 g of cGMP quality bryostatin 1 from a 13- ton collection in Californian waters [83]. Bryostatin 1(and other derivatives) were shown to bind to the protein kinase C (PKC) isozymes (as do the tumor-promoting phorbol esters) but without tumor promoting activity [83]. To date, bryostatin 1 has been in 80+ clinical trials for cancer [41], mainly as a single agent (http://www.clinicaltrials.gov/ct2/results?term=bryostatin). From late 2007 there were four Phase I and eight Phase II trials, all combination studies with biologicals or cytotoxins against multiple carcinomas [41]. Currently, bryostatin is in two Phase I trials and is being assessed as an anti-Alzheimer's drug (Phase I trial approved) [41]. Supply remains an issue as synthesis is difficult in the extreme. Of significance is the identification by Sudek *et al.* of the gene cluster that would produce the "hypothetical precursor, bryostatin 0" [84]. If this cluster can be expressed in a heterologous host (currently the source is an uncultured symbiont *Candidatus endobugula sertula*), then production of significant quantities of base structural material could be possible.

Hemiasterlin (*E7974*) Hemiasterlin is a cytotoxic tripeptide originally isolated from marine sponges [85]. Studies of structure–activity relationships established that substitutions to the NH_2-terminal amino acid yielded analogs with high *in vitro* potency, resistance to p-glycoprotein-mediated efflux and favorable pharmaceutical properties [86]. The optimal analog was considered to be the *N*-isopropyl-D-pipecolic acid derivative E7974 (Figure 5). The antimitotic activity of E7974 is mediated via a tubulin-based mechanism that leads to tumor cell apoptosis [87]. Unlike other tubulin-targeted agents such as taxanes, vinca alkaloids and eribulin, which bind predominantly to β-tubulin, E7974 preferentially binds to α-tubulin [87]. In Phase I studies, dose-limiting toxicities were neutropenia or febrile neutropenia, with other adverse events including fatigue, constipation, nausea and vomiting [88,89,90]. Stable disease was observed in several tumor types, with a partial response in a patient with esophageal cancer and a PSA response in a patient with prostate cancer. Hemiasterlin (E7974) is being developed by Eisai Inc. (http://www.eisai.com/pipeline.asp?ID=173) for cancer.

Marizomib (*NPI-0052, Salinosporamide A*) is a natural product of the marine actinomycete *Salinispora tropica* [91,92] (Figure 5). A search in PubMed (December 2009) using the search term NPI-0052 or salinosporamide A revealed 68 or 60 publications, respectively. Marizomib exhibits potent and selective inhibition of the proteasome [91–95], a multicatalytic enzyme complex that is responsible for non-lysosomal protein degradation in cells and represents a validated target for the treatment of cancer. Proteasome inhibition occurs via a novel mechanism involving acylation of the *N*-terminal catalytic Thr1O$^{\gamma}$ residue followed by displacement of chloride [93], resulting in prolonged proteasome inhibition *in vitro* and *in vivo* [92–95]. Translational biology studies clearly demonstrated single agent activity against solid tumor and hematologic malignancies, including multiple myeloma; further studies confirmed the potential for using marizomib in combination with biologics and/or chemotherapeutics [92,94–96]. These findings provided the basis for Nereus Pharmaceuticals to initiate several concurrent Phase I clinical trials in patients with multiple myeloma, lymphomas, leukemias and solid tumors. In an important demonstration of industrial marine microbiology, clinical trial supplies of marizomib drug substance are being manufactured through a robust saline fermentation process using *S. tropica* strain NPS21184 [92,95]. Marizomib (NPI-0052, salinosporamide A) is being developed by Nereus Pharmaceuticals, Inc. (http://www.nereuspharm.com/) for cancer.

Marine pharmaceuticals: the preclinical pipeline

During the period 1998–2006, the global marine preclinical pipeline included 592 marine compounds that showed antitumor and cytotoxic activity, and 666 additional chemicals which demonstrated a variety of pharmacological activities (i.e. antibacterial, anticoagulant, anti-inflammatory, antifungal, anthelmintic, antiplatelet, antiprotozoal and antiviral activities; actions on the cardiovascular, endocrine, immune and nervous systems; and other miscellaneous mechanisms of action). The marine preclinical pipeline (http://marinepharmacology.midwestern.edu/) has been systematically reviewed [97,98], and its significance has been discussed by leaders in marine natural products chemistry and pharmacology in a recent commentary [99].

The robustness of the marine pharmaceuticals pipeline is evident by three compounds (E7389, TZT-1027 and Yondelis) in Phase III trials, seven compounds in Phase II trials and three compounds in Phase I trials with numerous marine natural products being investigated preclinically as the next possible clinical candidates [97,98]. Opinions from leaders in the field of marine natural products all agree that the potential of these compounds to significantly contribute to the pharmacopeia is still on the horizon [99]. With the eminent development of more marine natural products from those in the current pipeline, the contribution of marine natural products to the future pharmacopeia seems to be promising. New technologies and efficient collaborations between academic and industrial scientists will be essential to ensure the future success of marine natural products as new and novel therapeutic entities that can make a significant contribution to the treatment of human disease.

Disclaimer statement

The content of this review is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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