Journal of Coastal Life Medicine

journal homepage: www.jclmm.com

Review doi: 10.12980/JCLM.3.2015JCLM-2015-0018

An overview of the marine natural products in clinical trials and on the market

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ARTICLE INFO

Article history:
Received 17 Mar 2015
Accepted 15 Apr 2015
Available online 7 May 2015

Keywords:
Marine natural products
Marine drugs
Anticancer drugs
Antiviral drugs
Analgesic drugs
Clinical trials

ABSTRACT

The first marine natural products that served as leads or scaffolds for medicines were discovered in the middle of last century: the arabinosyl glycosides from the marine sponge *Tectitethya crypta*. Synthesis and modifications of the natural molecules generated antiviral and antileukemic drugs developed in the 1970's and in the following decades, including the first effective treatment against HIV infection.

With the improvement of techniques for the elucidation of chemical structure of the molecules, as well as chemical synthesis, especially from the 1990's, there was an increase in the number of bioactive natural products characterized from marine organisms. New chemical structures with high specificity towards molecular targets in cells allowed the development of new drugs with indication for the treatment of several illnesses, from cancer to new antibiotics, and even neurological disorders.

Currently there are at least 13 molecules derived from marine natural products on advanced clinical trials, and nine were approved to be used as medicines. Considering that in the past eight years, more than 1 000 new compounds from marine organisms were described, per year, the expectation is that many more drugs will be derived from marine natural products in a near future.

1. Introduction

The search for biologically active marine natural products started along with the beginning of marine natural products chemistry, with the pioneer work of the researchers Bergmann and Feeney in 1951[1]. When studying a Caribbean marine sponge, *Tectitethya crypta* (*Cryptotethya crypta*), they characterized two arabinosyl glycosides, named spongouridine and spongotimidine (or Ara-U and Ara-T, respectively), with bioactive properties. Once knowing that the biological systems would recognize the nucleoside base with altered sugar moieties, the chemists tried to substitute the typical pentoses by modified sugar or by acyclic entities, leading to the synthesis of several nucleoside analogues used as antitumoral or antiviral drugs, like zidovudine[2], the main antiretroviral drug used to suppress viremia in HIV-positive patients. Obtained by synthesis, cytarabine (arabinofuranosylcytidine or Ara-C, Cytosar-U®) inserts into the DNA chain, inhibiting the DNA polymerase and holding the cell cycle on phase S; it is indicated for the treatment of acute non-lymphocytic, chronic myelocytic and meningeal leukemias[3,4]. Vidarabine (arabinofuranosyladenine or Ara-A) produced by *Streptomyces antibioticus* fermentation and commercialized as Vira-A®[5], aciclovir (Zovirax®) and other related compounds are indicated for the treatment of herpes simplex and herpes zoster viruses infections[6,7]. Nowadays not only sponges but also other marine organisms (including fungi and bacteria) are being the source of natural compounds with amazing different structures and a myriad of potential activities[8].

The first marine natural product with industrial use was nereistoxin, from the polychaeta worm *Lumbrinereis* sp., and used as a prototype in the synthesis of the insecticide Cartap (Padan®)[9], developed by Takeda Chemical Ltd. (Tokyo), and exported to many countries to control insect plagues in orange plantation and other cultures such as rice and sugarcane fields[10,11]. Cartap is considered to be a highly effective, low toxicity and low residue pesticide, with very rare cases of human toxicity resulting from occupational exposure or deliberate self-harm ingestion[11,12].

Like nereistoxin, many of the most potent marine natural products will never be used as medicines, but may be of great importance as biochemical tools[13]. One example would be the palytoxin originally isolated in Hawaii from the tropical soft coral

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Foundation Project: Supported by CNPq (National Council for Scientific and Technological Development) (Grant No. 473645/2012-2), and received a postdoctoral fellowship from CAPES (Coordination for the Improvement of Higher Level -or Education- Personnel).

Palythoa sp., a zoanthid[14-16]. This substance and its analogs found in dinoflagellates from the genus *Ostreopsis* are very toxic to all mammal cells, due to the blocking of Na^+/K^+-ATPase pump, but are powerful tools to study cellular ion transport mechanisms[13,17].

Tetrodotoxin (TTX) and saxitoxin are guanidine neurotoxins found in many marine organisms, such as mussels and fishes, which bind to the site 1 of voltage dependent sodium channels, blocking the propagation of action potentials on muscle and nerve cells[18,19]. Okadaic acid, a lipophilic polyether originally isolated from the sponges *Halichondria okadai*, *Halichondria melanodocia* and from several dinoflagellates species[20,21], inhibits specifically cell phosphatases that regulate different cellular processes such as ion balance, neurotransmission and the cell cycle, being a well known tumor promoter[22,23].

These three toxins (TTX, saxitoxin and okadaic acid) are responsible for several cases of human poisoning, caused by the consumption of fish, clams, oysters and mussels that accumulated these toxins[24-26]. Despite that, due to its specific and reversible activity on voltage dependent sodium channels (Na_v 1.1-1.4, 1.6-1.7), two formulations containing TTX are currently under clinical trials.

In vitro cytotoxicity was the most prominent bioactivity searched in novel marine compounds for the past 30 years[27,28]. Therefore, besides cytarabine (Ara-C), many other compounds targeting cancer therapy are currently under investigation.

The Developmental Therapeutics Program of the U.S. National Cancer Institute (NCI) has a library of approximately 200 000 extracts from plants, marine organisms, bacteria and fungi. More than 13 000 marine animal specimens were processed, comprising 6 100 and 450 different species of marine animals and plants, respectively. From those, over 5 000 specimens belonged to the Phylum Porifera[29]. Results obtained from the NCI *in vitro* screening program (NCI60, the human tumor cell line assay) indicated that in late 1990's marine invertebrates were the major source of extracts with significant activity, with a probability to find an active extract near four times higher than in terrestrial animals and plants, microorganisms and marine algae. Amongst marine invertebrates, the sponges presented the strongest activity spectrum, followed by tunicates, cnidarians and bryozoans[30].

Since 1985, most novel marine bioactive compounds were isolated from invertebrates, Porifera and Cnidaria accounted for 56.89% of the total bioactive compounds[28]. Considering all articles on marine natural products published in the last 50 years, the most studied Phylum was the Porifera, although the proportion of new compounds described for sponges has diminished since the mid 1990s. Starting from this period, Ascomycota, Actinobacteria, Cyanobacteria and Cnidaria had an increase in the number of studies[8,31-33], while Rhodophyta, Ochrophyta, Echinodermata and Mollusca had a decrease in their popularity[34].

According to Hu *et al.*[28], only approximately 25% of more than 16 000 new marine natural products described since 1985 had their biological activities investigated. Additionally, the average proportion of bioactive compounds among the novel compounds is declining according to the data published in the last decade. These authors suggest that the technologies to find new compounds are more advanced than the research tools and methods for prospecting bioactivity[28]. Nonetheless, considering that more than 1 000 new molecules have been described from marine organisms yearly for the past eight years[34-41], the biotechnological and pharmaceutical potential of the sea is definitively very impressive.

In the present review we focused on the marine natural products that are under clinical trials, or that have been already approved as drugs, grouped according to the therapeutic targets. Their chemical structures, mechanisms of action and a brief history of their discovery and development are presented.

2. Antitumor

Until now, four drugs based on marine natural products entered the market for cancer treatment, while nine are promising molecules in clinical trials. Their structures are represented in the Figures 1 and 2. The investigations of their mechanisms of action have shown them to be unique, in some cases. Promising antitumor drugs targeting apoptosis and the transcription factor NF-κB among other mechanisms have been reviewed[42,43].

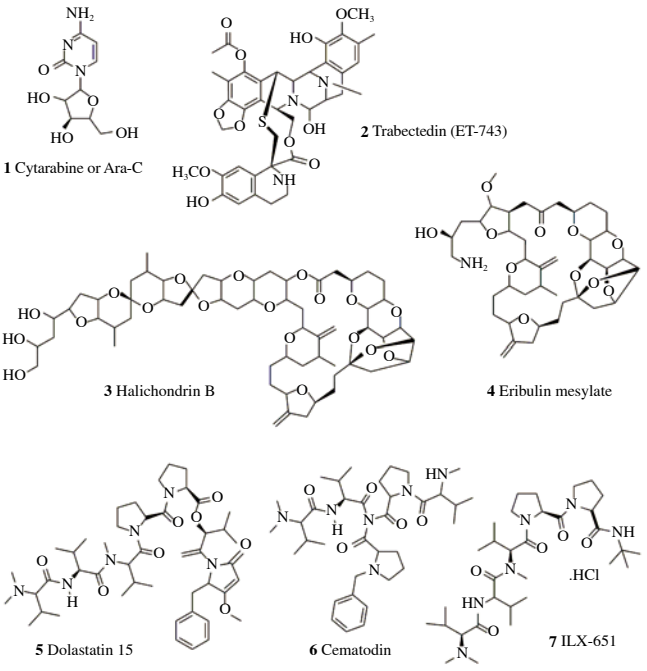


Figure 1. Marine-derived antitumoral drugs that are on the market (1-3) or in clinical trials. The sources of the natural compounds include sponges, tunicates and sea hares.

As mentioned above, the nucleosides from the Caribbean sponge *Tectitethya crypta*[1] were used as a model for the synthesis of analogs such as cytarabine or Ara-C **1**, the active substance of Cytosar-U® (Upjohn)[44]. Ara-C was approved for medicinal use in 1972, indicated for treatment of leukemia and lymphoma[4].

The marine tetrahydroisoquinoline alkaloid ecteinascidin 743 (generic name trabectedin, but also known as ET-743) **2**, produced by the tunicate *Ecteinascidia turbinata*, is a broad spectrum antitumor agent[2] first described by researchers from Illinois University (USA)[45], and licensed to PharmaMar (Spain) for pharmaceutical development. ET-743 interferes with cell division, and DNA transcription and repair mechanisms by biding in the minor groove of DNA molecules. The compound was obtained by synthesis in order to allow the sustainability of the production. From the isolation of the natural compound to the approval by Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA), it took almost 40 years[42]: Yondelis® is the trade name for the medicine developed with the semi-synthetic

drug and it was approved in 2007 for advanced or metastatic soft tissue sarcoma treatment, and in 2009 for therapy of ovarian cancer in association with pegylated liposomal doxorubicin DOXIL®)/ Caelyx® (www.pharmamar.com /yondelis.aspx). A review about trabectedin was published recently[46].

The macrocyclic polyether halichondrin B **3**[47] obtained from several species of marine sponges, such as *Halichondria okadai*, *Axinella* spp. and *Phakellia* spp., was also a model for the development of anticancer drugs[48,49]. The chemical synthesis of halichondrin B[50], enabled the discovery of the simplified analog, eribulin mesylate (E7389) **4**[51-53], approved in 2010 and commercialized as Halaven® for metastatic breast cancer chemotherapy[54]. Developed and marketed by Eisai Co (Japan), this compound affects microtubule polymerization, and therefore the mitosis (http://www.eisai.com/ir/individual/word/word_h03.html).

Dolastatins are potent antimitotic polypeptides originally isolated from the sea hare *Dolabella auricularia* (Phylum Mollusca), and also produced by Cyanobacteria[55]. Different synthetic analogs of dolastatin-15 **5** were produced[56]. Cematodin (LU-103793) **6** was developed by ABBOTT GmbH & Co. KG (Germany)[57], and concluded phase II of clinical trials for melanoma. BASF Pharma synthesized tasidotin hydrochloride (ILX-651) **7** that was licensed for development to ILEX Oncology (USA) and concluded clinical trials (phase I) against advanced solid tumors (colorectal, lung, kidneys and pancreas)[58]. Dolastatin 10 **8** reached phase II of clinical trials[59], but was withdrawn. Years later, a dolastatin 10 synthetic analog, monomethyl auristatin E **9**[60] was conjugated with an antibody and showed to be effective on cancer therapy, especially carcinoma[61]. The chimerical antibody conjugated with monomethyl auristatin E got the generic name "brentuximab vedotin" and was launched on market in 2011 by Seattle Genetics Inc. as ADCETRIS®, indicated for the treatment of lymphomas. Glembatumumab vedotin (CDX011), PSMA-ADC and ABT-414 are other antibody drug conjugates linked to the toxins monomethyl auristatin E and monomethyl auristatin F **10** that are currently in phase II of clinical trials for cancer treatment[62], under development by Celldex Therapeutics (http://www.celldex.com/pipeline/cdx-011.php), Progenics Pharmaceuticals (http://www.progenics.com/product-pipeline/psma-adc-therapeutic-technology/) and Abbvie (http://www.abbvie.com/oncology/home/pipeline.html#), respectively.

Didemnins are a family of cyclic depsipeptides isolated from the Caribbean tunicate *Tridemnum solidum*[63]. Besides antitumor activity, they presented potent antiviral properties in assays performed *in vitro* and *in vivo*. However, despite its important antiviral activity, didemnin B **11** has low selectivity and therapeutic index: it is cytotoxic and inhibits the synthesis of proteins, DNA and RNA of cells at the same concentrations that inhibit the virus growth. Starting in 1986, didemnin B underwent clinical trials (phase I and II)[30,48], but the tests were interrupted due to substantial toxic side effects[2].

In the decade of 1990, the depsipeptide dehydrodidemnin B **12**, also known as aplidine or plitidepsin, was isolated from the

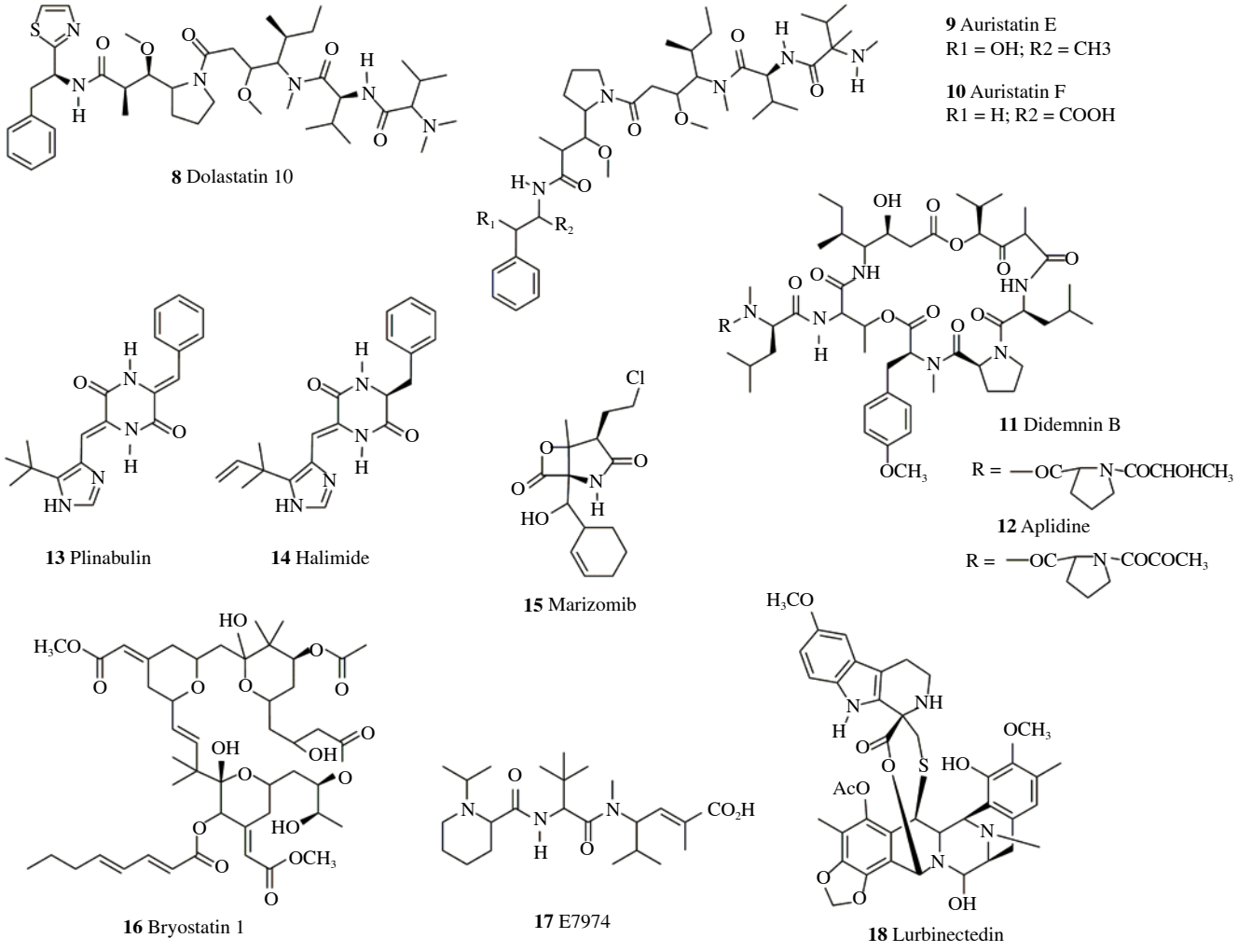


Figure 2. Structures of polypeptides, depsipeptides, diketopiperazines and other marine derived antitumoral drugs that are on the market (9) or clinical trials.

Mediterranean tunicate *Aplidium albicans*[64]. This substance has antiproliferative activity by blocking the cell cycle and inducing apoptosis, with strong activity against multiple myeloma cells[65-67]. PharmaMar is currently developing Aplidin® for the treatment of multiple myeloma (phase III of clinical trials), and for solid and hematological malignant neoplasias, like T-cell lymphoma (phase II of clinical trials) (http://www.pharmamar.com/aplidin.aspx).

Plinabulin (NPI-2358) **13**[8,68] is a synthetic analog of the diketopiperazine halimide (or phenylahistin) **14**[69], a natural product isolated from a marine fungi (*Aspergillus* sp.). Plinabulin inhibits tubulin polymerization, leading to the disruption of the vascular endothelial architecture of the tumor. This substance inhibits tumor growth through two different mechanisms: by inducing the collapse of the existing vasculature of the tumor, and promoting apoptosis. Phases I and II of clinical trials against solid tumors and lymphomas were conducted by the extinct Nereus Pharmaceuticals. Now, BeyondSpring Pharmaceuticals is developing plinabulin, and announced the start of phase III clinical trials in patients with non-small cell lung cancer for the first quarter of 2015 (http://www.beyondspringpharma.com/press-release-plinabulin-phase-3-trial/).

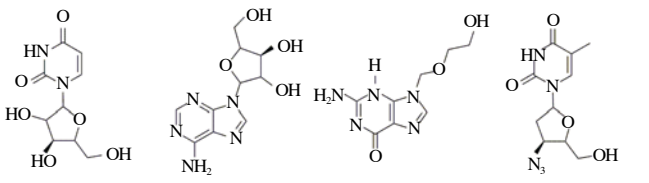
Triphase Accelerator Corporation is currently developing a medicine that contains marizomib (NPI-0052 or salinosporamide A) **15**, which is a natural product from the marine actinomycete *Salinispora tropica*[70], and a novel, highly potent proteasome inhibitor that irreversibly targets and inhibits all three proteasome subunits; it is active against cells resistant to proteasome inhibitor bortezomib[42]. Marizomib is on phase I of clinical trials against multiple myeloma, lymphomas, leukemias and solid tumors (http://triphaseco.com/pipeline/).

Other substances that have ongoing phase I clinical trials are: bryostatin 1 **16**, from the bryozoan *Bugula neritina*[71]; E7974 **17**, an analog of the tripeptide hemiasterlin isolated from the sponges *Auletta* sp. and *Siphonochalina* sp., that inhibits microtubules polymerization[72,73]; and lurbinectedin or PM01183 **18**, an alkaloid related to the eictinascidins 2 that binds to certain DNA sequences, inducing apoptosis[74] (http://www.pharmamar.com/pm01183-en.aspx).

3. Antiviral

Marine natural products also played a very important role in the development of antiviral drugs. In a general way, there are more anticancer drugs (and a higher diversity of mechanisms of action) in the market than antiviral drugs. Nevertheless, the number of approved drugs of marine origin is similar in both classes.

Starting from the chemical structure of the nucleoside spongouridine **19**[1], semi synthetic modifications originated the antiviral drugs vidarabine or Ara-A/Vira A **20**, aciclovir **21**, and zidovudine [azidothymidine or AZT] **22**[2,75], that are shown in Figure 3.



19 Spongouridine **20** Vidarabine or Ara-A **21** Aciclovir **22** Zidovudine or AZT

Figure 3. The marine nucleoside spongouridine and their synthetic analogues used therapeutically as antiviral drugs.

Vidarabine, after being obtained by synthesis[76], has been produced by *Streptomyces antibioticus* fermentation to be marketed as Vira-A® since 1976. Vidarabine inhibits the DNA polymerases of herpes, vaccinia and varicella-zoster viruses[77]. It is also prescribed for the treatment of herpes virus related conjunctivitis[5]. Aciclovir (Zovirax®) is a guanosine analog indicated to treat infections caused by herpes simplex, zoster and varicella viruses[78], and is currently the first line drug for herpes simplex infections. In the market there are also some prodrugs of aciclovir, as valaciclovir[79].

AZT was first synthesized in 1964 by Jerome P. Horwitz as a potential anticancer compound. More than twenty years later the drug was found to be a potent antiretroviral drug by inhibiting the reverse transcriptase of HIV (RT-HIV)[80]. AZT was the first treatment available for HIV infected patients, prescribed under the trade name Retrovir®, and launched in 1987. The time lapse for the development of Retrovir® by Burroughs Wellcome (now GlaxoSmithKline), from the confirmation of its *in vitro* efficacy against HIV to its approval by the United States FDA, was only a little longer than two years (http://www.fda.gov/ForPatients/Illness/HIVAIDS/History/ucm151074.htm). Based on its efficacy and safety, several other nucleoside analogues were developed as RT-HIV inhibitors, like lamivudine (3TC), abacavir (ABC), *etc*. These substances still have a role as components of the antiretroviral therapy[81].

4. Analgesic

Some analgesic formulations derived from marine toxins were developed for the treatment of neuropathic and chronic pain, especially in morphine-unresponsive patients. One natural compound is already on the market (ziconotide) and another is on clinical trials (tetrodotoxin). Their structures are represented in Figure 4.

Neurex Corporation (Menlo Park, Califórnia, EUA) and Cognetix Inc. (Salt Lake City, Utah, EUA) synthesized the peptide ziconotide (ω-conotoxin MVIIA) **23**, obtained from the venom of the mussel *Conus magnus*. It is an N-type calcium channel blocker that reduces chronic and neuropathic pain[82,83]. This peptide (and others from *Conus* venom) was characterized by professors Baldomero Olivera (Utah University) and George Miljanich (California University), and it promotes the decrease of upper and lower limbs reflexes, thus reducing the spasticity caused by spinal cord injury[84]. Prialt® (Ziconotide) was launched in 2004 by Elan Pharmaceuticals as a new therapy for chronic pain due to its significant antinociceptive action even in morphine-unresponsive patients. It must be administered by intrathecal route, and therefore its use is restricted to hospitals[85-87]. Figure 4 presents the sequence of aminoacids and the disulfide bridges in its structure.

The guanidine alkaloid tetrodotoxin (TTX) **24**, a blocker of voltage dependent sodium channels isolated from fish, algae and bacteria[88], has shown therapeutic efficacy as analgesic in cancer patients. Two formulations are currently under evaluation in phases II and III of clinical trials by the Canadian WEX Pharmaceuticals Inc.: the first formulation is on phase III, indicated for the treatment of neuropathic pain in cancer patients, by intramuscular and subcutaneous administration; the second one is on phase II of clinical trials, for peripheral pain and cancer-related pain (http://www.wextech.ca/clinical_trials.asp?m=1&s=0&p=0; http://www.clinicaltrials.gov). A review on tetrodotoxin chemistry and toxicity

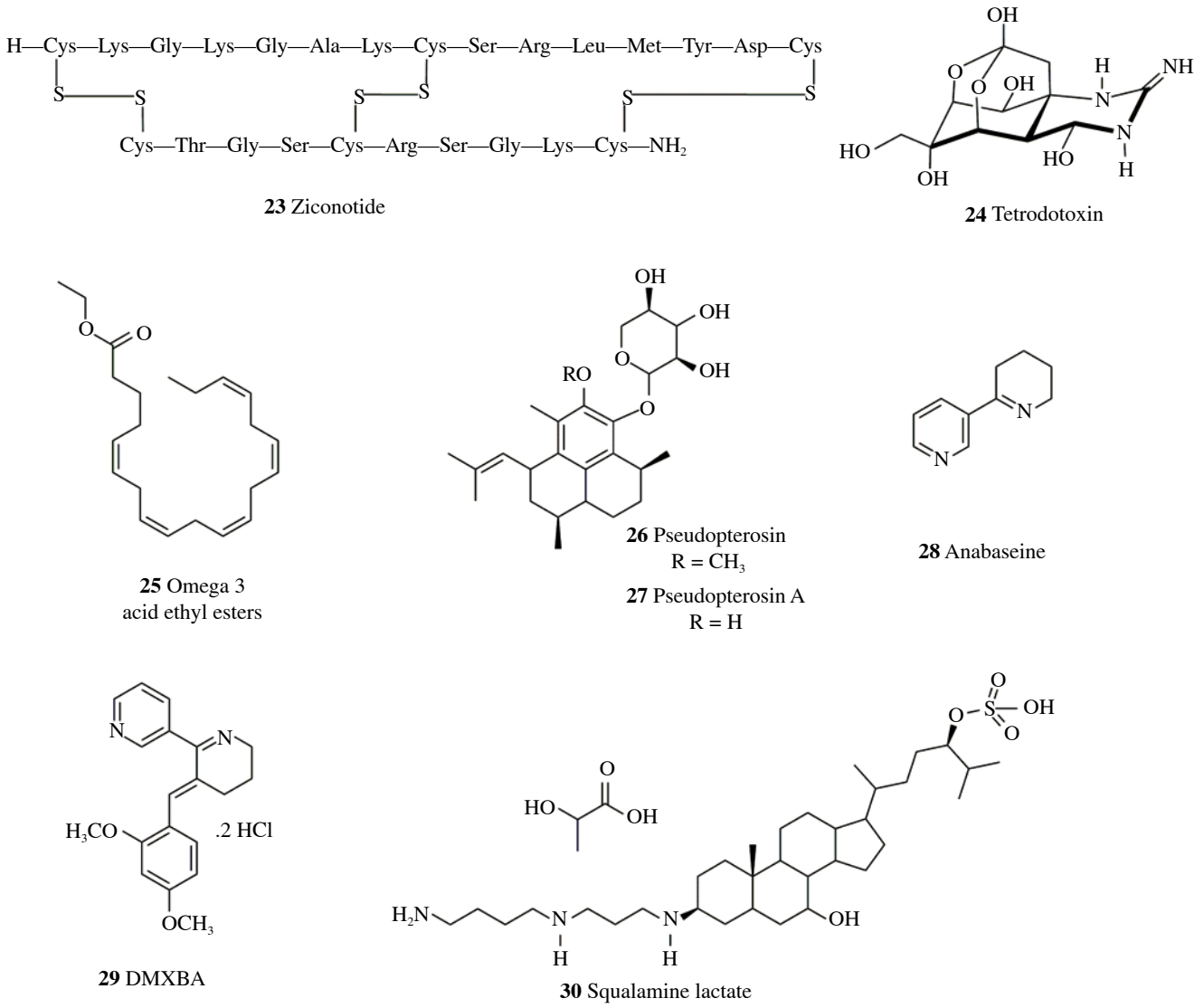


Figure 4. Marine natural products that are being commercialized as analgesic, for treatment of hypertriglyceridemia and marine derived drugs that are on clinical trials for other therapeutic uses.

was published recently[89].

5. Other applications

One marine derived drug was approved by the FDA to treat a metabolic disease, while three others are under clinical trials for miscellaneous applications. Their structures are represented on Figure 4.

In 2004 the FDA approved fish omega 3 acid ethyl esters (Lovaza®) **25** to treat hypertriglyceridemia[90,91], a very important risk factor for coronary heart disease. Lovaza® inhibits the triglyceride synthesizing enzymes, thus resulting in decreased synthesis and serum levels of triacylglycerols. These omega 3 esters, also commercialized outside USA as Omacor®, were developed by Reliant Pharmaceuticals, which was acquired by GlaxoSmithKline in 2007[92].

Pseudopterosin A methyl ether **26** (also known as VM301), a hemi synthetic derivative of pseudopterosin A **27**, a diterpene glycoside isolated from the soft coral *Pseudopterogorgia elizabethae*[93], presented anti-inflammatory and cicatrizing properties[49]. In double blind phase II clinical trials pseudopterosin increased reepithelization, and accelerated the wound healing process[5]. There are several reports of total synthesis of pseudopterosin analogues[94-96], so one might expect new derivatives of pseudopterosin to be developed in the next years.

Anabaseine **28**[97] is a toxic alkaloid from several nemertinean species, such as *Paranemertes peregrine* and *Amphiporus lactifloreus*[98], that seems to play ecological roles paralyzing preys, and as a feed-deterrent. Its synthetic derivative, DMXBA (3-(2,4-dimethoxybenzylidene)-anabaseine, also known as GTS-21 **29**, has the same mechanism as the natural compound: it stimulates the α7 nicotinic acetylcholine receptors expressed in neurons and astrocytes in central nervous system, and in the peripheral macrophages[99,100]. DMXBA improved cognition and sensory deficit in several animal models, and has shown neuroprotective effect *in vitro* and *in vivo*. Furthermore, presented anti-inflammatory activity mediated by α7 receptor in animal models. DMXBA (GTS-21) was licensed to Comentis Inc., which is developing drugs for treatment for Alzheimer's disease and schizophrenia on their clinical pipeline (http://comentis.com/). Phases I and II of clinical trials studies showed a significant cognitive improvement in healthy young adults and in schizophrenic patients[5]. Additional clinical trials (phases I and II) for schizophrenia therapy and other psychotic disorders are now under recruitment (https://clinicaltrials.gov/ct2/results?term=DMXBA&Search=Search).

Squalamine lactate (MSI-1256F) **30** is an amino sterol with antibiotic activity isolated from the stomach of the shark *Squalus acanthias*[101]. Squalamine is also a potent angiogenesis inhibitor, and thus was evaluated in several human clinical trials for cancer (https://clinicaltrials.gov/ct2/results?term=Squalamine+lactate+&Search=Search). OHR Pharmaceutical Inc. is currently developing MSI-1256F for ophthalmologic wet age-related macular degeneration (wet AMD), with ongoing clinical trials of phases II and III (http://www.ohrpharmaceutical.com/research/squalamine). Its potential in other ophthalmic problems involving pathological angiogenesis in the eye is also being evaluated[102].

6. Concluding remarks

The examples above illustrate briefly the history of marine natural products that originated medicines, or are in advanced clinical development. To date, clinical development of marine drugs focused mainly in cancer treatment[42,103], with at least nine derivatives currently under advanced clinical trials, and four already marketed. Most of the drugs presented in this review were first discovered as toxins, exerting ecological roles to the organisms that produce or accumulate them. Characterization of the mechanisms of action and the molecular targets of these compounds pointed them towards a possible pharmaceutical application. In general, in order to go further in the pharmaceutical industry pipeline these molecules must have low molecular weight, and their chemical synthesis elucidation and/or fermentation production are essential to guarantee the supply in adequate amount, since the harvesting of natural sources is usually scarce. In the last 25 years there was an increase in the number of bioactive natural products characterized from marine organisms, raising the expectation that many more medicines will be derived from marine natural products in the near future.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

The authors wish to thank Tauana Wanke for assistance with the figures.

Marisa Rangel is supported by CNPq (National Council for Scientific and Technological Development) (Grant 473645/2012-2), and received a postdoctoral fellowship from CAPES (Coordination for the Improvement of Higher Level -or Education- Personnel).

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