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Drugs from the deep: marine natural products as drug candidates

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In recent years, marine natural product bioprospecting has yielded a considerable number of drug candidates. Most of these molecules are still in preclinical or early clinical development but some are already on the market, such as cytarabine, or are predicted to be approved soon, such as ET743 (Yondelis™). Research into the ecology of marine natural products has shown that many of these compounds function as chemical weapons and have evolved into highly potent inhibitors of physiological processes in the prey, predators or competitors of the marine organisms that use them. Some of the natural products isolated from marine invertebrates have been shown to be, or are suspected to be, of microbial origin and this is now thought to be the case for the majority of such molecules. Marine microorganisms, whose immense genetic and biochemical diversity is only beginning to be appreciated, look likely to become a rich source of novel chemical entities for the discovery of more effective drugs.

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▼ More than 70% of our planet's surface is covered by oceans and life on Earth has its origin in the sea. In certain marine ecosystems, such as coral reefs or the deep sea floor, experts estimate that the biological diversity is higher than in tropical rain forests. Many marine organisms are soft bodied and have a sedentary life style necessitating chemical means of defence. Therefore, they have evolved the ability to synthesize toxic compounds or to obtain them from marine microorganisms. These compounds help them deter predators, keep competitors at bay or paralyze their prey. The overwhelming biological diversity of marine microbes has so far only been explored to a very limited extent. This diversity is believed to give rise to an equally high diversity of secondary metabolites synthesized by the marine microfauna and microflora (see supplementary material at http://archive.bmn.com/supp/ddt/ddt_marine.pdf).

Natural products released into the water are rapidly diluted and, therefore, need to be highly potent to have any effect. For this reason, and because of the immense biological diversity in the sea as a whole, it is increasingly recognized that a huge number of natural products and novel chemical entities exist in the oceans, with biological activities that may be useful in the quest for finding drugs with greater efficacy and specificity for the treatment of many human diseases [1,2].

Molecules targeting ion channels

Cone snail venoms are highly potent and act as selective peptide antagonists or agonists of ligand or voltage-gated ion channels and G-protein-coupled receptors (GPCR) [3,4]. Nicotinic acetylcholine receptors (nAChR) are competitively inhibited by α- and αA-conotoxins, whereas ψ-conotoxins show noncompetitive inhibition of this family of receptors. The σ-conotoxins antagonize the related 5-HT_3 serotonin receptor and the conopressins are agonists of vasopressin receptors, a family of GPCR; ω-conotoxins are calcium-channel blockers, κ-conotoxins are potassium-channel blockers and μ-, as well as μO-conotoxins, are sodium channel blockers, to name but a few of the conotoxin families. The high potency of these toxins, which are potentially lethal to humans, may, in the future, be turned to our advantage by pharmacologists who have been investigating their potential use as adjuncts in anaesthesia, analgesics or as drugs for the treatment of conditions such as epilepsy, cardiovascular disease and psychiatric disorders [4]. The strong commercial interest in these molecules is reflected by more than 100 patents and patent applications with the word 'conotoxin(s)' in their title (for further details refer to the esp@cenet worldwide database; http://www.espacenet.com). The available conotoxin libraries are thought to contain more than 50,000 distinct molecules. The

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main players in the field of conotoxin commercialization are Cognetix, Neurex, AMRAD and Xenome. Ziconotide, previously referred to as CI1009 or SNX111, is the synthetic form of ω-conotoxin MVIIA, a neuron-specific, N-type calcium-channel blocker and the first conotoxin drug to receive an approval letter from the FDA [5 and Investigational Drugs Database at http://www.iddb3.com]. Ziconotide was developed by Neurex as an intrathecal treatment for chronic pain. Unlike morphine it does not induce the development of tolerance, constipation or respiratory suppression. Another ω-conotoxin, AM336, is in clinical development at AMRAD for the treatment of severe morphine-resistant pain. This molecule was found to be 100-fold more selective than Ziconotide for N-type over P/Q-type calcium channels with reduced adverse neurological effects, which suggests that it may be preferable to Ziconotide [Prous Science at http://www.prous.com].

GTS21, 3-(2,4-dimethoxybenzylidene)-anabaseine, is a selective α7 nAChR partial agonist in clinical development at Taiho to treat Alzheimer's disease and schizophrenia. GTS21 was isolated from the nemertine worm *Amphiporus lactifloreus*. The compound has been shown to improve learning performance and memory retention in passive avoidance models in nucleus basalis magnocellularis (NbM)-lesioned rats as well as in active avoidance models in aged rats. It also reduced neocortical cell loss in NbM-lesioned rats and cell death induced by β-amyloid or glutamate in cultures of neuronal cells (http://www.iddb3.com; http://www.prous.com).

Compounds targeting enzymes

Protein serine/threonine kinase inhibitors

Bryozoans are sessile animals with a life style very similar to that of corals but, owing to their unique body plan, they constitute a phylum of their own. One particular bryozoan, *Bugula neritina*, has been the source of a family of protein kinase C (PKC) inhibitors called bryostatins currently in clinical trials for cancer. Bryostatin-1 has been granted Orphan Drug status by the FDA and has been designated an Orphan Medicinal Product in Europe for oesophageal cancer in combination with paclitaxel [6,7].

Bryostatins are complex polyketides based on the bryopyran ring system. They have been studied for their cellular activity and therapeutic potential since 1968. The first isolation and structure determination of a bryostatin was performed by George Pettit in the 1980s. Bryostatins inhibit protein serine/threonine kinases of the PKC family and have antineoplastic activity. Strictly speaking, bryostatins are not inhibitors but activators of PKC. However, bryostatin-induced activation results in the downregulation of this protein kinase by proteolysis more efficiently and rapidly than that induced by 12-*O*-tetradecanoylphorbol 13-acetate (TPA). Because of the resemblance of these macrolides to certain bacterial secondary metabolites, it has long been suspected that bryostatins are actually synthesized by symbiotic bacteria. It appears that the symbiont '*Candidatus* Endobugula sertula', a so far uncultivated γ-proteobacterium, is the true source of bryostatin-1 [8]. Fermentation of this bacterium would solve the current supply problem that exists for bryostatin-1, which, until not so long ago, had to be extracted from *B. neritina* harvested from the sea. For example, it took 2 years for divers employed by the National Cancer Institute to collect 17 tons of the organism off the southern California coast where it is most abundant. However, CalBioMarine has recently been able to establish aquaculture for the bryozoan. Total synthesis of bryostatins has also been making progress. Bryostatin-2, 3 and 7 have been produced synthetically but synthesis of the commercially most interesting bryostatin-1 has not been achieved, yet [9–11].

Owing to the therapeutic potential of the molecule, the generation of bryostatin-1 analogues is an area of intensive research. Scientists at Stanford University have synthesized a series of such analogues, some of which were two to three orders of magnitude more potent against tumour cell lines. Neristatin-1, a biologically active yet structurally simpler biosynthetic precursor of bryostatin-1, was obtained at Arizona State University Cancer Research Institute.

The screening of compounds isolated from marine invertebrates for cyclin-dependent kinase (CDK) inhibition led to the discovery of hymenialdisine as a potent (IC_{50}=10–40 nM) inhibitor of the protein serine/threonine kinases glycogen synthase kinase 3β, CDK1, CDK2, CDK5, casein kinase 1 and mitogen-activated protein kinase kinase-1 [12,13]. Hymenialdisine is a sponge alkaloid named after *Hymeniacidon aldis*. The compound inhibited the *in vitro* phosphorylation of human microtubule-associated protein tau, which is implicated in the pathogenesis of Alzheimer's disease, and in Sf9 cells expressing the protein [13]. Additionally, the molecule reduced the production of interleukin-8 and prostaglandin E_2 in human cells, indicating that it may have anti-inflammatory activity [14,15].

Scytonemin is a protein serine/threonine kinase inhibitor referred to as a marine natural product [16], but the molecule was in fact isolated for structural analysis and pharmacological characterization from the cyanobacterium *Stigonema sp.* collected from Waldo Lake, Oregon. The compound is a yellow-green ultraviolet sunscreen pigment present in the extracellular sheaths of different genera of aquatic and terrestrial blue-green algae. It has a unique symmetrical dimeric ring structure (Fig. 1). The monomeric subunit is closely related to nostodione A (Fig. 1), a mitotic

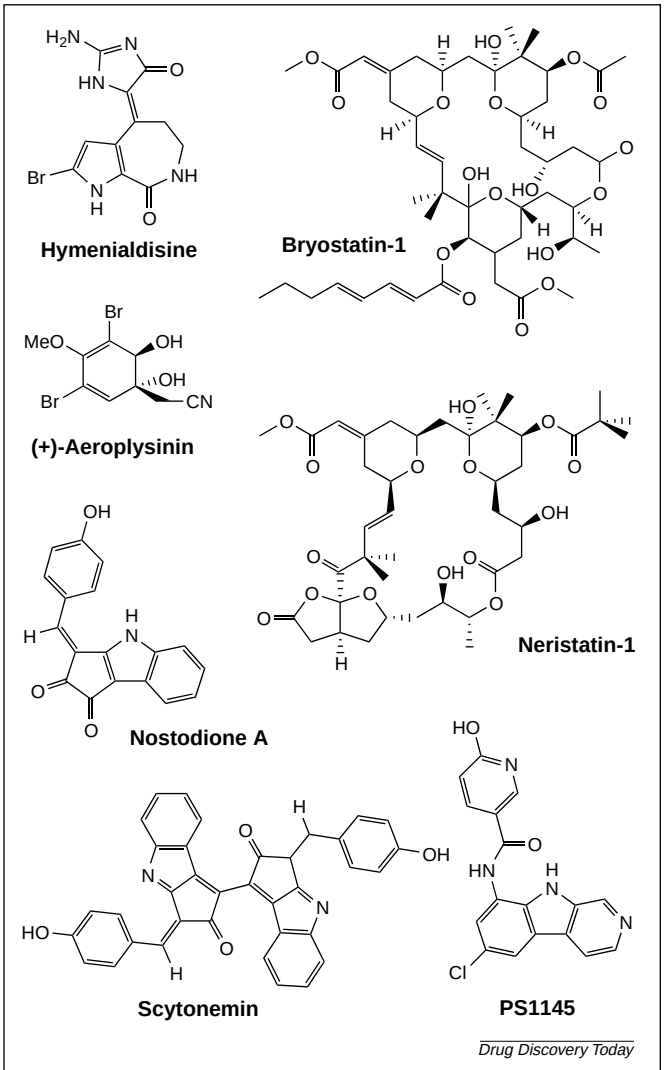

Figure 1. Marine natural product protein kinase inhibitors and similarity of Nostodione A to PS1145.

spindle poison from the terrestrial blue-green alga *Nostoc commune*. Scytonemin was found to inhibit human polo-like kinase (IC_{50}=2 μM), which has an important role in the regulation of mitotic spindle formation as well as other kinases involved in cell cycle control, including checkpoint kinase 1 and CDK1, with similar potency. Furthermore, the compound inhibits proliferation of human fibroblasts and endothelial cells in culture and reduces TPA-induced ear oedema in mice when administered topically. In this respect, it is interesting to note that nostodione A and the scytonemin monomer show a striking overall structural similiarity to PS1145, an inhibitor of the anti-inflammatory drug target IκB kinase (Fig. 1). It has been suggested that scytonemin may provide a novel pharmacophore for the development of protein kinase inhibitors as antiproliferative and anti-inflammatory drugs [17].

Protein tyrosine kinase inhibitors

Marine organisms have also been the source of several protein tyrosine kinase inhibitors. Aeroplysinin-1, a brominated tyrosine metabolite from the sponge *Verongia aerophoba*, has been found to inhibit purified epidermal growth factor (EGF) receptor protein tyrosine kinase activity, to block EGF-stimulated proliferation of cancer cell lines, to induce their apoptosis at high nanomolar concentrations and to suppress angiogenesis *in vivo* [18–20]. The polyketide halenaquinone, isolated from the Okinawan sponge *Xestospongia exigua*, has also been shown to inhibit the protein tyrosine kinase activity of the EGF receptor as well as that of the viral oncogene product v-Src [21]. The concentrations required are in the low micromolar range. The sulfated steroid derivative halistanol trisulfate, extracted from sponges of the genus *Topsentia*, has also been reported to be a v-Src inhibitor at these concentrations [22]. The brown alga *Stypopodium zonale* has yielded stypoquinonic acid and the fungus *Asochyta salicornia* has yielded ascosalipyrrolidinone A, which are two novel inhibitors of the Src-family protein tyrosine kinase Lck [23,24].

Phospholipase A_2 inhibitors

In humans, secreted type IIA phospholipase A_2 (PLA_2) is involved in the pathogenesis of a variety of inflammatory diseases via the production of arachidonic acid, the precursor of prostaglandins and leukotrienes. Secreted PLA_2 is, therefore, seen as a promising target for the development of anti-inflammatory drugs and a considerable research effort has been focused on this family of enzymes [25,26].

The first natural marine human synovial PLA_2 inhibitor, the sesterterpene manoalide (IC_{50}=3.9 μM) (Fig. 2), was isolated from the Palauan sponge *Luffariella variabilis* and was found to have analgesic and anti-inflammatory activity [27]. This compound was taken into phase I clinical trials by Allergan but its development was later discontinued. Other marine sponge terpenoid PLA_2 inhibitors are the sesterterpenes variabilin from *Ircinia variabilis*, cacospongionolide B from *Fasciospongia cavernosa* and petrosaspongiolide M from *Petrospongia nigra*, as well as the sesquiterpene bolinaquinone from *Dysidea sp.* (Fig. 2). Variabilin inhibits human synovial PLA_2 (IC_{50}=6.9 μM) but not 5-lipoxygenase or cyclooxygenases 1 and 2 *in vitro* [28]. These sesquiterpenes were found to inhibit human neutrophil degranulation, superoxide generation, leukotriene B_4 (LTB_4) production (variabilin), TPA-induced ear oedema (variabilin, bolinaquinone, topically) as well as carrageenan-induced paw oedema (variabilin, petrosaspongiolide M and bolinaquinone, p.o.) in mice [29–32].

The long-known anti-inflammatory sponge PLA_2 inhibitors are the scalaranes, sesterterpenes, named after

scalaradial isolated from *Cacospongia mollior*, and the pseudopterosins [33], diterpene-pentoseglycosides, which also have analgesic properties and are used as additives in certain skin-care products. One compound in this family, the semisynthetic methopterosin (OAS1000) (Fig. 2), has entered clinical development for the promotion of wound healing. OAS1000 has also shown anti-inflammatory activity in animal models, which is thought to be due to its inhibition of LTB_4 synthesis in neutrophils.

Microtubule-interfering agents

The development of resistance in tumours to the microtubule-stabilizing taxanes has prompted the search for novel microtubule-interfering agents in the hope of finding a way to circumvent this problem. Marine organisms have yielded the largest number of such compounds [34]:

- discodermolide, a polyketide, purified from the sponge *Discodermia dissolute*;
- eleutherobin, a diterpenoid, from the soft coral *Eleutherobia* sp;
- sarcodictyins, diterpenoids, from the Mediterranean coral *Sarcodictyon roseum*;
- dolastatins, short peptides containing unique amino acids, from the sea hare *Dolabella auricularia* [35], a nudibranch snail and, later, from marine cyanobacteria [36];
- halichondrin B (Fig. 3), a polyether macrolide from the sponge *Halichondria okadai* [37];
- laulimalide, as well as its rearrangement product isolaulimalide, which are 18-membered macrocyclic lactones, from the sponge *Cacospongia mycofijiensis [*38];
- peloruside A, related to bryostatin 1, from the sponge *Mycale* sp. [39];
- hemiasterlins, tripeptides from the sponges *Auletta* sp. and *Siphonochalina* sp. [40];
- vitilevuamide (Fig. 3), a bicyclic marine peptide, from the ascidians *Didemnum cuculiferum* and *Polysyncraton lithostrotum* [41].

All of these compounds have been reported to have general cytotoxic activity and to kill cancer cells *in vitro* but only dolastatin 10, the dolastatin 15 analogues ILX651 and cemadotin, discodermolide and the hemiasterlin analogue HTI286 have so far reached clinical development. Halichondrin B analogues are in preclinical development at Eisai. The laulimalides and discodermolide are of special interest to anticancer drug discovery researchers because they have been shown to remain active in cells overexpressing multidrug-resistant P-glycoprotein [38,42].

DNA-interactive agents

Several established anticancer drugs are DNA-interactive agents. These compounds, including the platinum drugs cisplatin and carboplatin, are characterized by strong cytotoxic activity, but they also show a total lack of specificity for cancer versus normal cells. The question of whether DNA can be a suitable target for the development of more specific, second-generation anticancer drugs has, therefore, been raised [43]. Support for the idea that DNA is still a target worth aiming at has come from clinical trials with a marine natural product, ET743 (Yondelis™) (Fig. 4); for a summary of the results see PharmaMar Fact Sheets (http://www.pharmamar.es/en/prosci/facts_001.cfm). ET743 is one of a family of tunicate-derived antitumour compounds originally identified in 1988 by Kenneth Rinehart's team at the University of Illinois, Urbana-Champaign [44] and licenced to PharmaMar in 1994. These ecteinascidins, named after *Ecteinascidia turbinata*, a colonial ascidian from which they were isolated, are not the only class of marine DNA-interactive compounds active in cytotoxicity screens. Others include dercitin, an acridine alkaloid isolated from a sponge of the genus *Dercitus* [45], and the topsentins, a class of sponge-derived

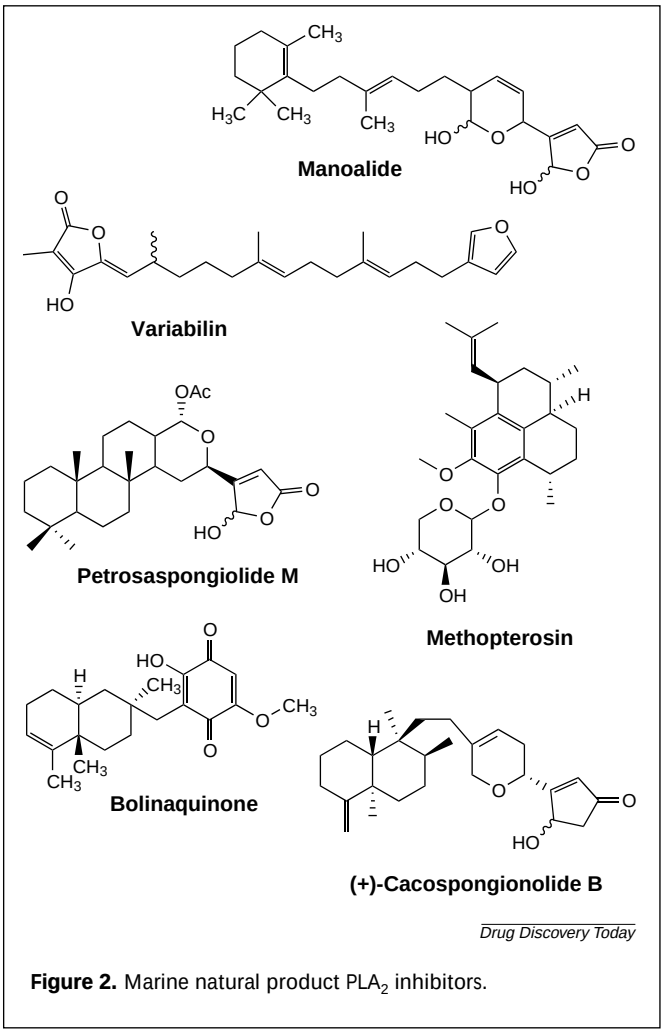

Figure 2. Marine natural product PLA_2 inhibitors.

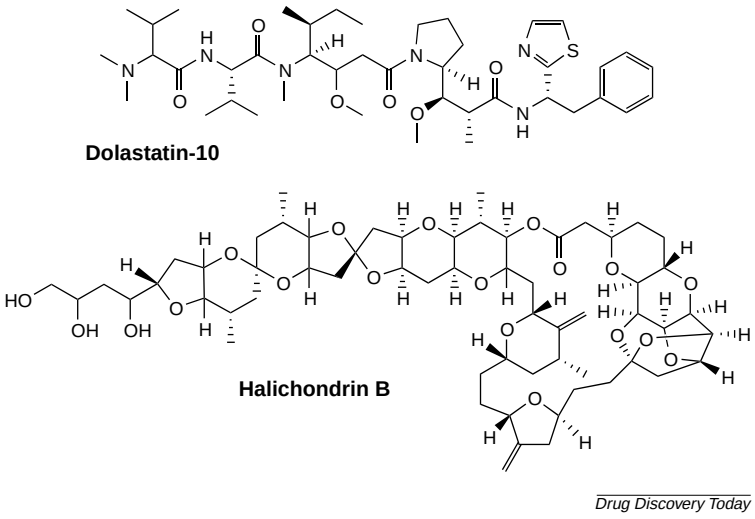

Figure 3. Microtubule-interfering agents from marine sources. The structures of discodermolide, eleutherobin, sarcodictyins, laulimalide and isolaulimalide are shown in a previous *Drug Discovery Today* article [34].

bisindole alkaloids [46], but ET743 is so far the only compound that has gone into clinical development.

ET743 is an isoquinoline compound consisting of three tetrahydroisoquinoline rings. The first total synthesis of the molecule was achieved in 1996 by David Gin in Elias Corey's team at Harvard University [47]. Owing to its extreme potency (picomolar to low nanomolar IC_{50} values for the inhibition of growth in sensitive human tumour cell lines), extraction of the drug is a viable strategy for obtaining adequate amounts for clinical trials even though more than half a ton of the sea squirt needs to be harvested to obtain 1 g of the compound. Nevertheless, a hemisynthetic process starting from Safracin B, an antibiotic obtained by fermentation of the bacterium *Pseudomonas fluorescens*, has been developed at PharmaMar and successfully used to synthesize ET743 in sufficient quantities for further commercial development [48]. Corey and his student Eduardo Martinez designed a structurally simpler, easier to synthesize and more stable analogue of ET743 named phthalascidin (PT650) (Fig. 4). PT650 and ET743 show undiminished potency in cell lines resistant to the topoisomerase inhibitors camptothecin and etoposide [49].

Structural modelling has suggested that two of the tetrahydroisoquinoline rings of ET743 bind to the minor grove of DNA resulting in DNA adduct formation with a guanine residue [50]. The binding of ET743 to the minor groove results in bending of the DNA towards the major groove, induction of a conformational change that appears to be unique to ET743. The protruding third ring is predicted to interact with so far unknown DNA-binding proteins that are believed to be responsible for the pharmacodynamic properties of the compound. ET743 was shown to cause a prolonged cell cycle blockade in G_2/M and to inhibit induced gene transcription of several genes including HSP70 and p21 while having little effect on basal gene expression [51,52]. Moreover, ET743 can enhance the activities of other chemotherapeutic agents by inhibiting multidrug resistant MDR1 gene expression upon co-administration [53]. Cells in the G_1 phase of the cell cycle, and of these soft-tissue sarcoma cells in particular, are extremely sensitive to ET743-induced cell killing. Other cancer cells that have shown sensitivity towards ET743 are cell lines and xenografts derived from tumours of the breast, kidney, lung, ovaries and prostate as well as from glioblastomas and melanomas [54]. The cytotoxic effects of ET743 are entirely dependent on the presence of functional transcription-coupled nucleotide excision repair (TC-NER) in the treated cells but independent of wild-type p53 tumour suppressor protein function [55]. Interference with this DNA repair pathway is, therefore, thought to be at the heart of the unique mode of action of ET743. Loss of TC-NER renders cancer cells exquisitely sensitive to cisplatin [56]. This effect may open up new avenues for combination chemotherapy because it should be feasible to stop the outgrowth of ET743-resistant tumour cell populations by simultaneous treatment with cisplatin. This approach is currently being tested by PharmaMar in a phase I clinical trial. ET743 has also been found to act synergistically with doxorubicin or paclitaxel in soft-tissue sarcoma cell lines, suggesting that a combination of the drug with anthracyclins or taxanes may also result in increased therapeutic benefit [57].

ET743 has completed clinical trials for soft-tissue sarcoma and is currently under regulatory review in Europe for the treatment of this type of cancer for which it was granted Orphan Medicinal Product designation by The European Agency for the Evaluation of Medicinal Products in 2001. In the same year, Zeltia, the parent company of PharmaMar, announced a licensing agreement with Ortho Biotech, a Johnson and Johnson subsidiary, to develop and market ET743. A comprehensive development programme to study the potential use of ET743 for the treatment of other forms of cancer was agreed. So far, promising results have been released from phase II clinical trials for ovarian and breast cancer. The efficacy of ET743 in endometrial and non-small cell lung cancer is also being investigated in phase II trials. To date, more than 1,600 patients have been treated with ET743 [58].

Other marine natural product drug candidates in clinical development

APL (dehydrodidemnin B, Aplidin™) a cyclic depsipeptide derived from *Aplidium albicans*, is another tunicate marine natural product discovered by Rinehart and coworkers [43] and licensed to PharmaMar. The compound triggers rapid and persistent activation of the apoptotic process as a consequence of the induction of oxidative stress and the sustained activation of the protein kinases Jun N-terminal kinase, p38 stress-activated protein kinase, EGF receptor and Src [59,60]. At present, more than 200 patients have been treated with APL in phase I clinical trials for cancer.

Kahalalide F is a third marine natural product anticancer drug candidate in clinical development at PharmaMar [61]. This cyclic depsipeptide was isolated from the sea slug *Elysia rufescens* but is most probably derived from *Bryopsis sp.*, its green algal diet. The compound has shown antitumour activity, probably by interfering with lysosome function in prostate, colorectal and lung cancer cell lines as well as in animal models of lung and breast cancer. It is currently in phase I trials for prostate cancer and other solid tumours.

Kirin Brewery is developing KRN7000, a novel α-galactosylceramide derived from agelasphin-9b, which, in turn, was isolated from the sponge *Agelas mauritianus*, for the potential treatment of cancer and other diseases [62]. KRN7000 has been shown to have immunostimulatory and antimetastatic activity possibly by enhancing antigen-presenting cell function. Phase I clinical trials for solid tumours showed no drug-related toxicity, no signs of accumulation or saturation and an increase in interferon-γ, interleukin-4, interleukin-12 and granulocyte macrophage colony-stimulating factor levels, as well as natural killer cell activity at least in some of the patients.

Squalamine lactate, a novel antiangiogenic aminosteroid from the dogfish shark *Squalus acanthias* is currently in phase II clinical trials for ovarian and non-small cell lung cancer at Genaera and was granted Orphan Drug status for the treatment of ovarian cancer by the FDA. Reported objective response rates were around 30% for one or more cycles of treatment in combination with standard chemotherapy. The compound is thought to act by sequestration of calmodulin [63], resulting in the inhibition of a sodium/proton antiport regulating intracellular pH and, consequently, in reduced cell proliferation in endothelial cells.

IPL512602, a synthetic analogue of the steroid contignasterol isolated from the sponge *Petrosia contignata* [64], is in phase II clinical trials as a leukocyte-suppressing anti-inflammatory drug for the treatment of asthma.

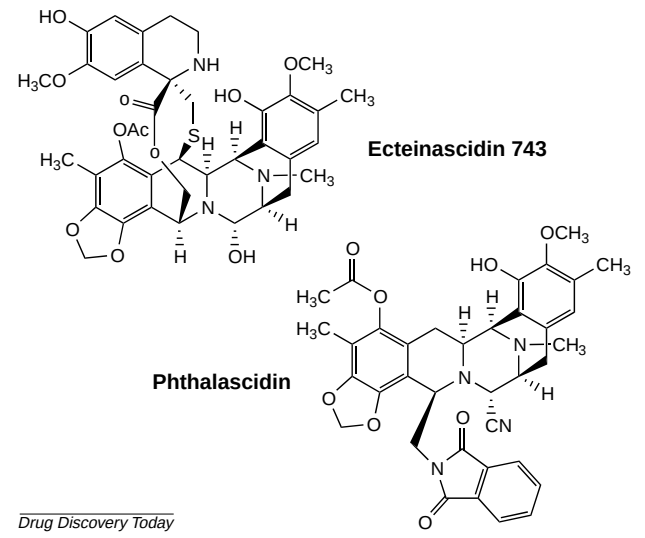

Figure 4. ET743 and its synthetic analogue PT650.

LAF389 is an easier to synthesize and more water-soluble synthetic analogue of bengamide B, a heterocyclic amino acid derivative from the sponge *Jaspis digonoxea* [65]. LAF389 induces cell cycle arrest by inhibition of methionine aminopeptidase.

A promising future for marine natural products in drug discovery?

It has recently been argued that biodiversity prospecting is not necessary because structural diversity is of less importance than functional diversity as potent natural inhibitors for any given biological target can be found virtually in front of one's doorstep, their number greatly exceeding that of all potential drug targets encoded by the human genome [66]. However, in drug discovery it is frequently observed that a certain series of compounds that yielded the most potent inhibitors *in vitro* turned out not to be the ideal drug candidate *in vivo*. Moreover, it is likely that for every compound that does make it to the market, a better drug with distinct chemistry, improved bioavailability and less unwanted side effects can be found either in chemical libraries or among the much larger number and diversity of natural products. This has been pointed out in a reply by natural product researchers Gordon Cragg and David Newman of the National Cancer Institute [67], to which the authors of the article responded by saying, among other things, that '… the world's oceans are likely to harbour the largest biodiversity … but … can it not be argued that land, the natural environment in which mankind evolved, is more likely to contain compounds with relevant mechanisms of action?' [68]. This argument does not take into consideration the

Table 1. Marine natural products and derivatives in clinical development.

Compound name	Source	Chemical class	Company	Disease area	Status
Compounds targeting ion channels					
Ziconotide	Cone snail	Peptide	Neurex	Chronic pain	Phase III
AM336	Cone snail	Peptide	AMRAD	Chronic pain	Phase I/II
GTS21	Nemertine worm	Anabaseine-derivative	Taiho	Alzheimer's disease Schizophrenia	Phase I/II
Compounds targeting enzymes					
Methionine aminopeptidase inhibitors					
LAF389	Sponge	Amino acid derivative	Novartis	Cancer	Phase I
Protein kinase inhibitors					
Bryostatin-1	Bryozoan	Polyketide	GPC Biotech	Cancer	Phase II
PLA_2 inhibitors					
OAS1000	Soft coral	Diterpene-pentoseglycoside	OsteoArthritis Sciences	Wound healing Inflammation	Phase I/II
Microtubule-interfering agents					
Dolastatin-10	Sea slug	Peptide	NCI/Knoll	Cancer	Phase II
ILX651	Sea slug	Peptide	Ilex Oncology	Cancer	Phase I
Cemadotin	Sea slug	Peptide	Knoll	Cancer	Phase II
Discodermolide	Sponge	Polyketide	Novartis	Cancer	Phase I
HTI286	Sponge	Tripeptide	Wyeth	Cancer	Phase I
DNA-interactive agents					
Yondelis™	Sea squirt	Isoquinolone	PharmaMar/Johnson and Johnson	Cancer	Phase II/III
Oxidative stress inducers					
Aplidin™	Sea squirt	Cyclic depsipeptide	PharmaMar	Cancer	Phase II
Lysosomotropic compounds					
Kahalalide F	Sea slug/alga	Cyclic depsipeptide	PharmaMar	Cancer	Phase I
Immunostimulatory agents					
KRN7000	Sponge	α-galactosylceramide	Kirin	Cancer	Phase I
Calcium-binding protein antagonists					
Squalamine lactate	Shark	Aminosteroid	Genaera	Cancer	Phase II
Compounds with unknown mechanism of action					
IPL512602	Sponge	Steroid	Inflazyme/Aventis	Inflammation Asthma	Phase II

fact that the molecular physiology of eukaryotic cells evolved in our early marine ancestors and that it is highly conserved molecular mechanisms that are targeted by many novel drug candidates. However, the point the authors of the article make, that it is not always necessary to travel to far away, exotic places to find a specific natural product, is a fair one considering, for example, the case of scytonemin. Moreover, pharmaceutical companies do not have to bioprospect for natural products, marine or terrestrial, to benefit from the diversity of small, pharmacologically interesting molecules that exist in nature. They may just use structural scaffolds of published compounds as templates for the identification of similar molecules in their own chemical libraries, which they can use as starting points for chemical modification [69] as was done for the development of acyclovir, for example.

With three drugs from the deep, the cephalosporins, cytarabine (Ara-C) and vidarabine (Ara-A), already well-established on the market [70], the granting of Orphan Drug status to bryostatin-1, squalamine and ET743 in the past 2 years, and more than a dozen further marine compounds or derivatives currently in clinical trials (Table 1), the answer to the question of whether marine natural products will have a promising future in drug development looks

likely to be 'aye!'. Given that marine natural product bioprospecting has only begun relatively recently but has already yielded several thousand novel molecules, that deep sea biodiversity research is still in its infancy, that affordable technology for the exploration of the abyss is currently being developed, and that the total number of species and, therefore, most likely biochemical diversity in the oceans is higher than on land, there is good reason to believe that approval of the above-mentioned drugs will only be the beginning of the arrival in our pharmacies of a larger number of marine natural products, or compounds derived from them, for the improved treatment of human illnesses.

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