Indian Journal of Geo-Marine Sciences
Vol. 41(1), February 2012, pp. 27-39

Marine natural products: A lead for Anti-cancer

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Received 21 August 2010; revised 7 January 2011

Various active anticancer agents are derived from plants and terrestrial microorganisms. Isolation of C-nucleosides from the Caribbean sponge, Cryptotheca crypta, four decades ago, provided the basis for the synthesis of cytarabine, the first marine derived anticancer agent to be developed for clinical use. Cytarabine is currently used in the routine treatment of patients with leukaemia and lymphoma. Gemcitabine, one of its fluorinated derivatives, has also been approved for use in patients with pancreatic, breast, bladder, and non-small-cell lung cancer. Over the past decade, several new experimental anticancer agents derived from marine sources have entered preclinical and clinical trials. Present study address anticancer drug discovery from an evolutionary perspective and present a series of case studies that demonstrate that the rate of anticancer drug discovery can be increased greatly by targeted screening of natural compounds from marine sources.

[Keywords: Marine natural products, didemnin B, Dolastatin, Bryostatin1,Kahalalide F**]**

Introduction

Marine environment is an exceptional reservoir of bioactive natural products, many of which exhibit structural/chemical features not found in terrestrial natural products[1]. Marine organisms have evolved biochemical and physiological mechanisms that include the production of bioactive compounds for such purposes as reproduction, communication, and protection against predation, infection and competition[2]. Because of the physical and chemical conditions in the marine environment, almost every class of marine organism exhibits a variety of molecules with unique structural features. The oceans covers over 70% of the earth's surface and 95% of its tropical biosphere represents 34 of the 36 phyla contain an extraordinary diversity of life[3-6]. Our interest in understanding the function of marine ecosystems has been accelerated in recent years with growing recognition of their importance in human life[7-9]. Cancer is a growing public problem whose estimated worldwide new incidence is about 6 million cases per year.

A large number of plant, marine, and microbial sources have been tested as leads, and many compounds have survived the potential leads[10]. Marine organisms comprise approximately half of the total biodiversity on the earth and the marine ecosystem is the greatest source to discover useful therapeutics[4,11-12] Sessile marine invertebrates such as sponges, bryozoans, tunicates, mostly lacking morphological defence structures have developed the largest number of marine-derived secondary metabolites including some of the most interesting drug candidates[13-16]. In recent years, a significant number of novel metabolites with potent pharmacological properties have been discovered from the marine organisms. Although there are only few marine-derived products currently in the market, several marine natural products are now in the clinical pipeline, with more undergoing development[17-18]. The development of molecular biology field and recent progress of new technologies such as genetic engineering and bioactivity screening offer a unique opportunity to establish marine natural products as drug leads[19-21].

There are several examples of recent advances in the application of above technologies to the discovery and development of novel drugs from marine origin. In this review we have focused on the pharmacologically active marine natural products that have been shown to have biological activity, including cytotoxic, anti-cancer activity and

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antitopoisomerase-I activity, along with *in vivo* activity when available.

Marine natural products and drug discovery

Unlike the long-standing historical medical uses of terrestrial plants, marine organisms have a shorter history of utilization in the treatment and/or prevention of human disease.

Among the first bioactive compounds from marine sources, spongouridine and spongothymidine from the Caribbean sponge (*Cryptotheca crypta*), were isolated serendipitously in the early 1950s[22]. They were approved as an anticancer drug (cytosine arabinoside, Ara-C) and an antiviral drug (adenine arabinoside, Ara-A), respectively, 15 years later[23]. However, it was only in middle of the 20th century that scientists began to systematically probe oceans for medicines. So far, more than 10,000 bioactive molecules have been discovered from marine sources, with hundreds of new compounds still being discovered every year[24]. However, in marine environment, this leading position is taken by invertebrates such as sponges, molluscs, bryozoans, tunicates, etc. They not only produce a great number of marine natural products currently known but also show the largest chemical diversity of natural products, including alkaloids, peptides, terpenes, polyketides, etc. Interestingly, out of 13 marine natural products (or analogues derived from them) that are currently in clinical trials as new drug candidates, 12 are derived from invertebrates[25]. Consider the fact that many marine organisms have soft bodies and lead a sedentary lifestyle, making a chemical system of defense almost essential for survival. Marine organisms have evolved the ability to synthesize such toxic compounds or extract or convert pertinent compounds from other marine microorganisms. Natural products from marine organisms are released into the water and therefore are rapidly diluted; accordingly they must be very potent materials to have the desired end effect. The richly available marine biodiversity that is available to us has to this point only been explored to an extremely limited extent. Furthermore, the primary chemical diversity available from marine organisms is most likely capable of delivering an even greater abundance of secondary metabolites for research use. Drug discovery research from marine organisms has been accelerating and now involves interdisciplinary research including biochemistry, biology, ecology, organic chemistry, and pharmacology[26-27]. For all of these reasons it is believed that the natural products that are available from the seas and oceans provide a tremendous opportunity for the discovery of novel therapeutic agents[28].

Marine organism derived anticancer agents

In the past 30-40 years, marine plants and animals have been the focus of a worldwide effort to define the natural products of the marine environment. A small number of marine plants, animals, and microbes have already yielded more than 12000 novel chemicals, with hundreds of new compounds still being discovered every year. These discovery efforts have yielded several bioactive metabolites that have been successfully developed by the pharmaceutical industry[28-29]. Several clinically useful drugs, investigational drug candidates, and pharmacological tools have already resulted from these marine-product discovery programmes. One of the marine natural products that is currently under clinical investigation as a potential new anticancer agents is the marine alkaloid ecteinascidin-743, isolated from the tunicate *Ecteinascidia turbinate*. Ecteinascidin is a broad-spectrum antitumour agent and is among the most advanced compounds with clinical applications[30]. Nature has been a relevant resource for the discovery of anticancer entities. Today, more than 60% of the anticancer drugs commercially available are of naturally origin[31-35], naturally derived antiproliferative drugs such as doxorubicin, daunomicin, bleomycin, mytomicin C, vincristine and vinblastine play an important role in curative cancer chemotherapy in a number of solid tumors and haematological malignancies and the most important recent incorporations to the clinical armamentarium in oncology, taxanes and campthothecins, are also naturally derived compounds[36-40]. The marine environment is a rich source of both biological and chemical diversity. This diversity has been the source of unique chemical compounds with the potential for industrial development as pharmaceuticals, cosmetics, nutritional supplements, molecular probes, fine chemicals and agrochemicals[41]. Marine organisms are a rich source for natural products and many compounds that are derived from these organisms have generated interest both as challenging problems for structure elucidation and synthesis and for their cytotoxicities Table 1. The new classes of anticancer drugs that have been isolated from marine organisms have been shown to possess cytotoxic activity against

Table 1—Marine Natural Products with established mechanism of action

Organism	Compound	Chemistry	Mechanism of action	References
Sponge	Aaptamine	Alkaloid	Induction of p21 gene and G2/M cell cycle arrest	104
Sponge	Agosterol A	Steroid	Azido agosterol A binding to MRP1 abolished by ICL5 and ICL7 domain mutations	105
Sponge	Alkylpyridinim salts	Alkaloid	Induction of apoptosis and reduced cell adhesion	106
Ascidian	Ascididemin	Alkaloid	Enhanced binding to telomeric DNA quadruplex	107
Sea hare	Aplyronine A	Macrolide	Binding to hydrophobic cleft in actin molecule involving trimethylserine moiety	108
Ascidian	Aplidine	Depsipeptide	Oxidation and inactivation of low molecular weight-protein tyrosine phosphatase activity	109
Bryozoan	Bryostatin-1	Macrolide	Apoptosis induction enhanced by PKCe overexpression	110
Sponge	Bastadin 6	Alkaloid	Inhibition of angiogenesis in vitro and in vivo involves apoptosis	111
Ascidian	Bistramide A	Polyketide	Depolymerisation of F-actin, inhibition of G-actin polymerisation, binding to actin subdomains 1 and 3	112, 113
Soft coral	Bromovulone III	Prostanoid	Apoptosis and endoplasmic reticulum stress, activation of caspase-12	114
Tube worm	Cephalostatin 1	Steroid	Bcl-2 hyperphosphorylation independent of M-phase arrest and DNA damage	115
Sponge	Cortistatin A	Alkaloid	Selective inhibition of angiogenesis	116
Sponge	Dictyostatin-1	Macrolide	Tubulin binding, taxoid site binding and antiproliferative effects comparable to discodermolide	117
Sponge	Discodermolide	Polyketide	Binding to amino acid residues 305-359 in the S9-S10 loop in b-tubulin	118
Ascidian	Ecteinascidin-743	Isoquinoline alkaloid	Cell cycle promoters are selectively affected	119
Ascidian	Fucoxanthinol	Carotenoid	Induction of apoptosis and decrease in Bcl-2 protein	120
Mollusk	Kahalalide F	Depsipeptide	ErbB3 protein and PI3K-Akt pathway involved in necrosis induction	121, 122
Sponge	Onnamide A	Polyketide	Protein synthesis inhibition, activation of stress-activated protein kinases and apoptosis	123, 124
Sponge	Peloruside A	Macrolide	Synergistic effect with taxoid site drugs but not with laulimalide	125

multiple tumor types[42-44]. Most of these compounds were identified during the 1980s following great improvements in deep-sea sample collection and in technologies that allowed the production of drugs on a large scale through aquaculture and synthesis[45]. Overall, more than 3000 new substances have been identified from marine organisms during the past three decades, demonstrating the great potential of the sea as a source of novel chemical classes[46-48]. To date, researchers have isolated approximately 7000 marine natural products, 25 percent of which are from algae, 33 percent from sponges, 18 percent from coelenterates (sea whips, sea fans and soft corals), and 24 percent from representatives of other invertebrate phyla such as ascidians (also called tunicates), opisthobranch molluscs (nudibranchs, sea hares etc), echinoderms (starfish, sea cucumbers *etc*) and bryozoans (moss animals). A simplistic analysis of these data reveals that as the search for "Drugs from the Sea" progresses at the rate of a 10 percent increase in new compounds per year, researchers are concentrating their efforts on slow-moving or sessile invertebrate phyla that have soft bodies, and lack of spines or a shell, *i.e.* animals that require a chemical defence mechanism[40,49-51]. The first anticancer product derived from marine sources to enter clinical trials was didemnin B, a cyclic depsipeptide isolated from the tunicate *Tridemnum solidum*[46].

Didemnin B (Fig. 1)

Our first compound is a didemnins are cyclic depsipeptide compounds isolated from a tunicate (sea-squirt) of the genus *Tridemnum* (family of Didemnidæ) that were collected in the Caribbean Sea[52,53]. They were first isolated in 1978 at the University of Illinois Fig. 1. Although more than nine didemnins (Didemnins A-E, G, X and Y) have been isolated from the extract of *Tridemnum solidum*, Didemnin B is the one that possesses the most potent biological activities[54]. Mechanistically, didemnin B

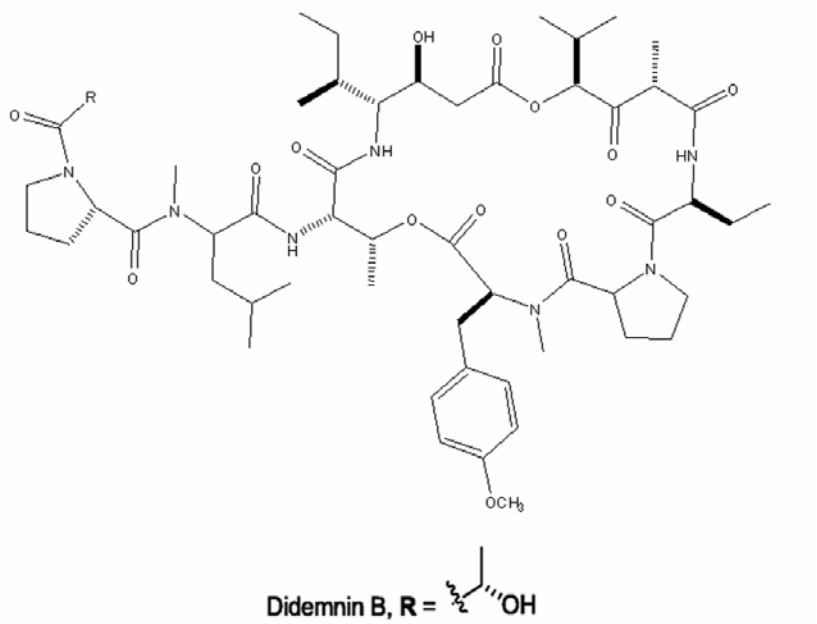

Fig. 1–Chemical structure of didemnin B

acts at the GTP-binding protein elongation factor[55]. This compound, though, is too toxic to be useful as antiviral or immunosuppressive agent; it has been in Phase I clinical trials as an anticancer agent. Phase II clinical trials are underway[56-57]. A close relative of didemnin B-dehydrodidemnin B, isolated from a Mediterranean tunicate *Aplidium albicans*, is currently in Phase II studies in the United States and Europe, to determine its anticancer properties[50].

Dolastatins (Fig. 2)

Dolastatins are peptides isolated from the Indian Ocean sea hare, *Dolabella auricularia*. Among the dolastatin family, the linear peptide dolastatin 10 and the desipeptide dolastatin 15 exhibit the most promising antiproliferative actions[58]. Dolastatin 10 is a pentapeptide with four of the residues being structurally unique (dolavaline, dolaisoleucine, dolaproline, and dolaphenine, in addition to valine) Fig. 2. Interestingly, at the time of its discovery, it was the most potent antiproliferative agent. Dolastatin 10 is in Phase I clinical trials as anticancer agent for use in the treatment of breast and liver cancers, solid tumours and leukemia[59]. Dolastatins 10 and 15 are small peptides; dolastatin 10 was selected for clinical trials because of its more favourable preclinical profile[60-61]. It inhibits microtubule assembly, causing cells to accumulate in metaphase and is extremely potent *in vitro*[62-63]. Dolastatin 10 caused bone-marrow toxicity in initial clinical trials, as well as local irritation at the injection site and mild peripheral neuropathy[64-65]. Dolastatin 15, a seven-subunit depsipeptide derived from Dolabella auricularia, is a potent antimitotic agent structurally related to the antitubulin agent dolastatin 10, a five-subunit peptide isolated from extracts of the Indian Ocean sea hare D. auricularia. Indeed, numerous dolastatin 15-related peptides have been isolated from diverse marine cyanobacteria[65]. Its linear depsipeptide sequence is composed of seven amino acid or hydroxyl acid residues.

Bryostatin 1 (Fig. 3)

The Bryostatins are macrocyclic lactones isolated from the marine bryozoan *Bugula neritina* (Bugulidae) and found to possess both antineoplastic and immunopotentiating properties. Bryostatin 1 is one of the most abundant and best studied compounds of this series[40,66]. It was originally described on the basis of inhibiting growth in murine P388 lymphocytic leukemia cells at subnanomolar concentrations. A range of properties have subsequently been described including activation of T-cells, immunomodulation and stimulation of haematopoietic progenitor cells. However, only many years after its discovery was the molecular site of action of this compound identified. Bryostatin 1 was found to bind to protein kinase C with high affinity, which may be the mechanistic basis for both observed anticancer and immunostimulating properties Fig. 3.

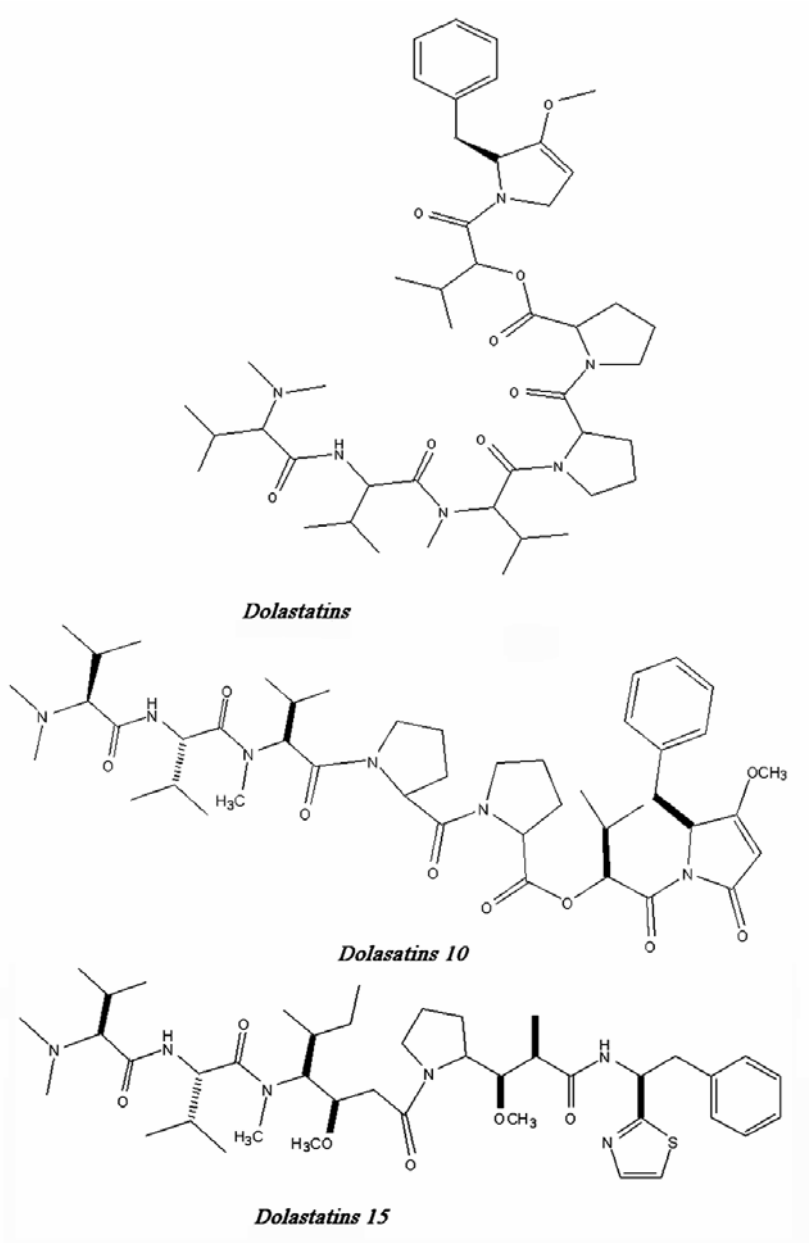

Fig. 2–Chemical structures of dolastatin, dolasatins 10 and dolastatins 15

Bryostatin 1 may be used in tandem with cancer treatments that respond to taxol, such as breast, ovarian and lung cancers. It modulates the activity of protein kinase C (PKC), lacks tumour-promoting activity and shows differentiationinducing effects in various *in vitro* and *in vivo* models[57,67-68]. It also has immunomodulatory properties, including the induction of cytokine release and expansion of tumourspecific lymphocyte populations[69-70]. Bryostatin 1 has shown antitumour activity in phase I trials in patients with malignant melanoma, lymphoma, and ovarian carcinoma and is undergoing broad phase II evaluation. The main toxic effects in initial clinical trials were myalgia, local phlebitis, fatigue, nausea and vomiting, and thrombocytopenia. Bryostatin 1 showed no significant objective antitumour activity in phase I and II trials in patients with advanced solid tumours, including renal-cell and non-small-cell lung cancer, and malignant melanoma[46,72-75]. However, it was shown to induce cell differentiation in patients with refractory chronic lymphocytic leukaemia.

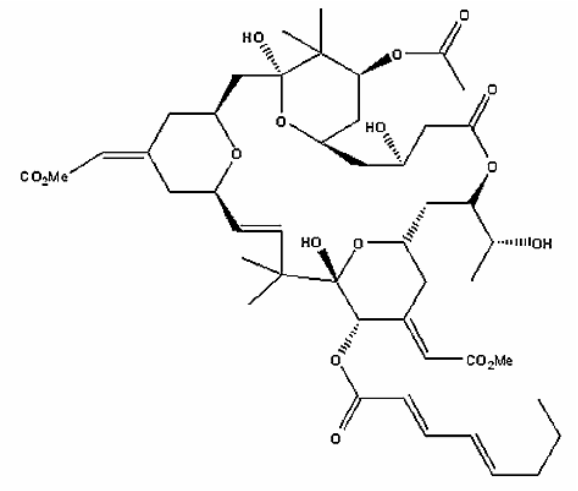

Fig. 3–Chemical structure of bryostatin 1

Khalalide F (Fig. 4)

Kahalalide F (KF) is one of a family of dehydroaminobutyric acid-containing peptides derived from the marine mollusc Elysia rufescens., a marine mollusc found in Hawaii. This mollusc is able to sequester chloroplasts from an alga to participate in the synthesis of secondary metabolites[76-79]. The green algae *Bryopsis* sp. also produces some of Kahalalide peptides in smaller yields. The structure of KF (Fig. 4) contains a lateral chain and a cycled region with the molecular formula $C_{75}H_{124}N_{14}O_{16}$. KF is the largest and most active of the seven natural compounds isolated from *E. rufescens*. Six cyclic (peptides A-F) and one acyclic analogue (peptide G) are known[80]. KF displays both *in vitro* and *in vivo* antitumor activity in various solid tumor models, including colon, breast, non–small cell lung, and in particular prostate cancer[81]. Studies to determine the mechanism of action of Kahalaide F showed that, in certain experimental systems, it caused a disruption of lysosomal membranes and consequently the formation of large vacuoles. This mechanism is unique among anticancer agents and may cause increasing acidification of the intra-cellular space, a stimulatory event that initiates a pathway for apoptosis[79]. In addition, Kahalaide F leads to an inhibition of *erb* 2 transmembrane tyrosine kinase activity and inhibits TGF-a gene expression. The pattern of Kahalaide F cytotoxicity was distinct from any of the other standard chemotherapeutic agents. Kahalaide F showed *in vitro* and *in vivo* selectivity for prostate-derived cell lines and tumours. It is further selective for hormone-independent prostate tumour cells, which generally represent the more aggressive and harder to

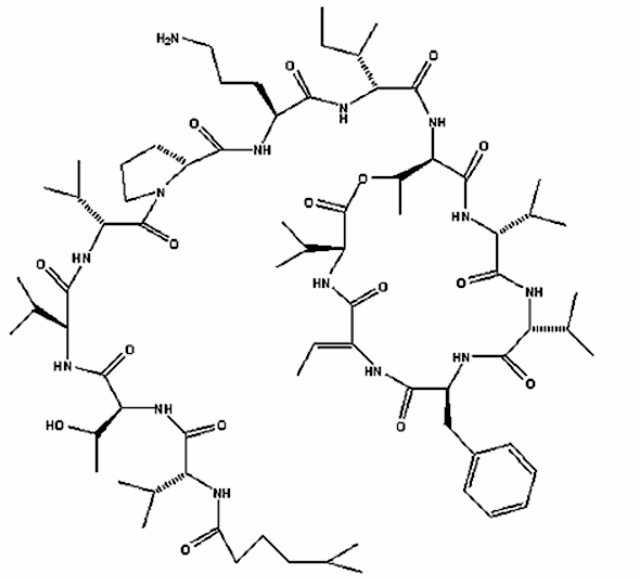

Fig. 4–Chemical structure of khalalide F

treat type of prostate cancer. Phase-I clinical trials in patients with androgen-independent prostate cancer have begun.

Manzamine (Fig. 5)

Manzamine A, a beta-carboline alkaloid present in several marine sponge species, has potent anti-inflammatory activity, antifungal, anti-HIV-I activities with moderate antitumour activity[80-81] Fig. 5. Manzamine also exhibited insecticidal activity towards neonate larvae of the polyphagouspset insects *Spodopteralittoralis* with an Ed_{50} 35 ppm in a chronic feeding bioassay. It was also found to be active against the Gram-positive bacteria *Bacillus subtillis* and *Staphylococcus aureus*. The anti-malarial effect of manzamine A was due to inhibition of the growth of the rodent malaria parasite *Plasmodium berghei in vivo*[82]. Several new derivatives of manzamine A have been isolated from indo-pacific sponges with similar or improved biological activity[83-84]. Oral and intravenous pharmacokinetic studies of manzamine A derivatives in rats indicated that they have low metabolic clearance, a reasonably long pharmacokinetic half life, and good absolute oral bioavailability which make them as potential leads for preclinical assessment. In addition, 8-hydroxymanzamine A, isolated from an undescribed sponge, Pachypellina species exhibited moderate antitumour and anti HSV-II activity. Further (-) 8-hydroxymanzamine A was also found to be a promosing new anti-malarial agent[85].

Future prospects of marine natural products as anti-cancer

In the future, marine natural products will remain as important sources of new drugs and lead structures. Nature has supplied several active anticancer agents (eg the vinca alkaloids-vincristine, vinblastine, anthracyclines, epipodophyllotoxins, and taxanes), which have significantly improved the management of many types of human cancers[86-90.] These marine-derived compounds are extremely potent in culture, with inhibitory concentrations generally in the nanogram range[67]. Traditionally, among the first options to be explored for the supply of marine-derived small molecules is chemical synthesis. Unfortunately, the structural complexity of marine molecules Figs 6 & 7, which suggests novel mechanisms of action and high selectivity, has also resulted in few economically feasible strategies for total chemical synthesis. The successful example of the synthetic production of a marine-product drug in unlimited quantities is the conus toxin ziconotide, because of its peptide nature[91-92]. The aquaculture of the source organisms, including sponges, tunicates, and bryozoans, with the aim of securing a steady supply of drug product, has progressed notably in cancer applications, although in most cases the biomass currently generated is still far short of those required should a marine-based drug finally enter the market[93]. Furthermore, the cultivation of invertebrates in their natural environment is subject to several uncertainties, such as destruction by storms or disease. An intriguing strategy has been to identify the true producers of bioactive compounds to find out whether or not they are of microbial origin, based on the fact that most if not all of the marine invertebrates harbour large communities of microorganisms, including bacteria, cyanobacteria, and fungi within their tissues[94]. Many studies have successfully provided data to support the involvement of

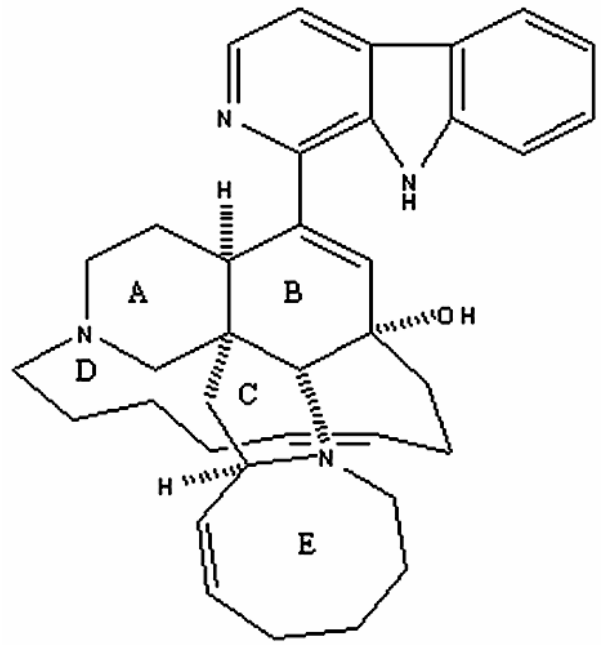

Fig. 5–Chemical structure of manzamine-A

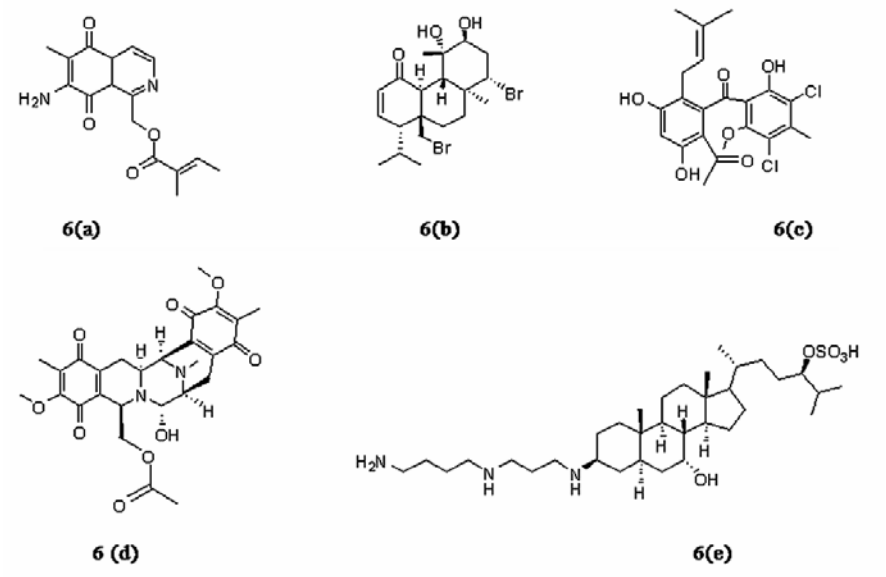

Fig. 6–Chemical structures of some marine natural products with antibacterial properties. (a) Bromosphaerone (b) Cribrostatin 3 (c) Pestalone (d) Jorumycin (e) Squalamine.

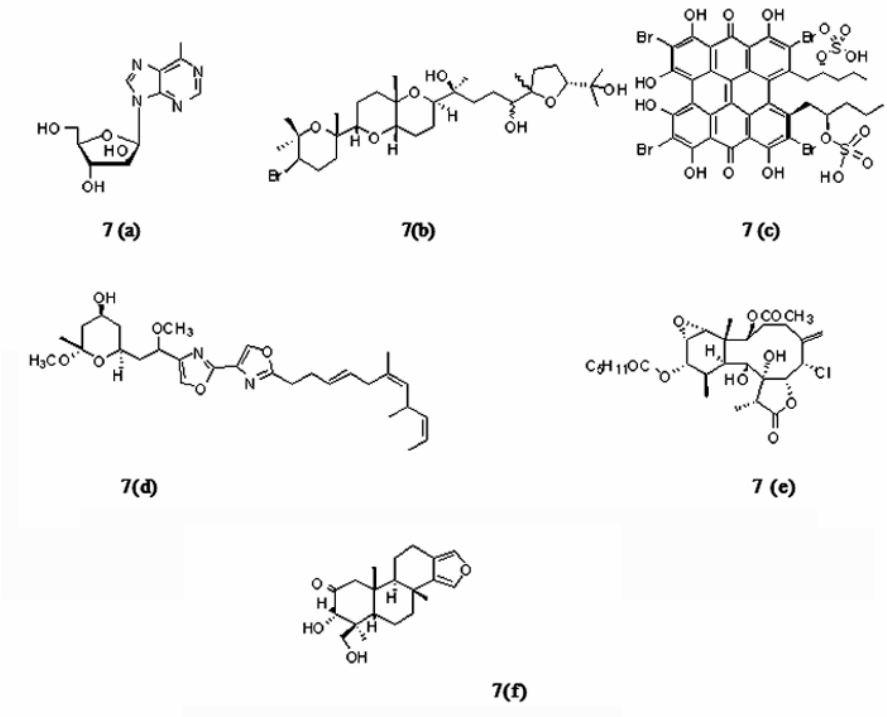

Fig. 7–Chemical structure of some marine natural products with antiviral properties. (a) Ara- A, (b) Thyrsiferol 7 18S, 19R, (c) Gymnochrome D, (d) Hennoxazole A, (e) Solenolide A, (f) Spongiadiol.

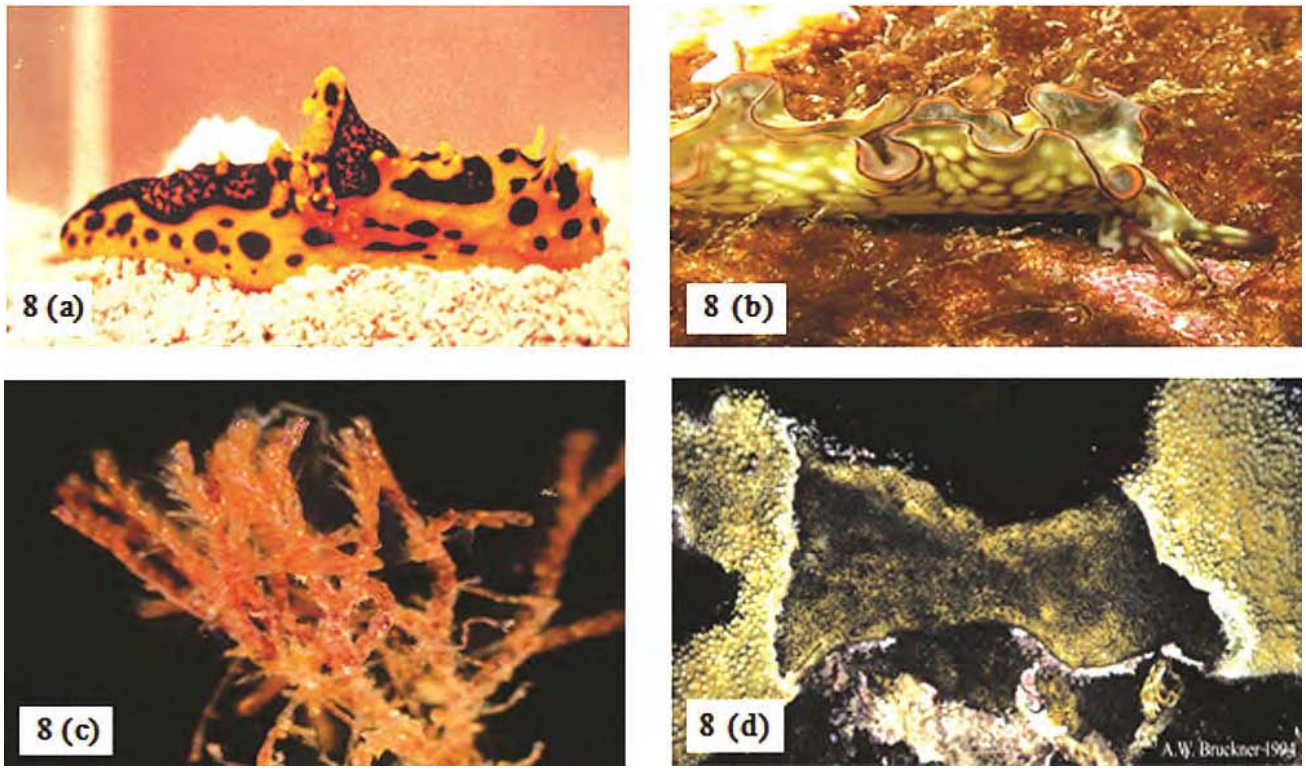

Fig. 8–Marine species producing anti-cancer drugs. (a) *Dolabella auricularia* (b) Elysia rufescens (c) *Bugula neritina* (d) *Trididemnum solidum*

microorganisms in the biosynthesis of natural products isolated from invertebrates. The challenge of identifying new anticancer agents Fig. 8 in the oceans has been taken up by a group of scientists who have formed a worldwide collaboration to investigate the organisms found on coral reefs and in deep ocean thermal vents. This field is also expanding thanks to advances in deep-sea collection techniques, aquaculture, and the technology needed to extract nucleic acids from biological materials. The manipulation of microbial biosynthetic pathways through genetic engineering has also led to the production of interesting new molecules. These living organisms represent a rich reservoir of genetic and metabolic diversity, which is ready to be exploited and which will certainly make anticancer drug discovery from marine sources[67].

Conclusions

The medical treatment of cancer has made substantial improvements since the early years of modern anti-tumour drug research. A selected number of human malignancies (e.g. childhood lymphoblastic leukemia, lymphomas and testicular cancer) can be cured with the today's therapies and prolonged survival has been obtained in several others[95-96]. The identification and development of marine natural compounds and their derivatives have greatly contributed to this progress and many of these compounds are now being used in clinical practice. Marine is still today a rich source of active principles against cancer cells. Marine natural compounds comprise either classical cytotoxic moieties targeting nonspecific macromolecules expressed by cancer cells and to a lesser extent by normal proliferating cells (e.g. DNA, enzymes, microtubules) or new compounds targeting macromolecules specifically expressed on cancer cells (e.g. oncogenic signal transduction pathways). Another relevant field of application of marine natural compounds is cancer chemoprevention since these compounds may inhibit specific processes involved in cancerogenesis[97]. In conclusion, the application of natural compounds in the treatment of cancer, the very common "plague" of our modern times, has resulted in increased therapeutic efficacy. Research results both testify to the evolution of knowledge coming from marine pharmacognosy and its historical roots in marine medicine, as well as to the great possibilities of future progress by means of a rational, marine natural product-based drug discovery approach[98]. The above examples illustrate the intense excitement which surrounds the past decade's achievements in the area of new anticancer leads from marine organisms. The combination of novel structures and for some, novel mechanisms of action, is translating into new methods by which to treat cancer, and ultimately, improved outcomes, particularly for patients with solid tumors of the lung, breast, colon or prostate[60,99]. The last decade has seen an ever evolving strategy for the screening and discovery of new anticancer leads from nature, and this is proving effective. From former times of evaluation of crude extracts by *in vivo* screens to current evaluation of peak or prefractionated libraries in mechanism-based assays, the level of sophistication and success has steadily improved[100]. Screening strategies are continuing to evolve, probing new ideas and knowledge of cancer, introducing high throughput screening and new analytic methodologies. In part, the need for this continuing evolution has been stimulated by a desire to develop novel and less toxic therapies for cancer treatment. High throughput screening methods have both enabled more sophisticated mechanism based screening, and subsequently required the move to prefractionation and peak library generation. These "prior-to-screening" purifications have the consequence of reducing the complexity of screening materials, increasing the titer of low abundance components, segregating nuisance substances into discrete fractions, and generally speeding up the time line from detection of a primary screening hit to identification of a molecular structure for the active substance[101-102]. It can generally be concluded that contemporary screening protocols in natural products chemistry are using chromatographic purification steps, sometimes producing pure compounds, before biological or enzymatic bioassay. Coupled to these more effective paradigms for screening are new assays that evaluate natural products in more detailed, refined, and novel ways. For example, detailed knowledge of the cellular mechanisms controlling proliferation has yielded numerous targets for mechanism-based anticancer screens. The productivity of the past decade in terms of discovery of new clinical anticancer leads from diverse marine life should translate into a number of new treatments for cancer in the decade to come. In turn, these successes should rekindle serious efforts to evaluate marine life for useful leads with anticancer properties.

Approaches in the past which have largely screened crude extracts for biological activity have allowed a rich harvest of "low hanging fruit." With effective prefractionation strategies broadly in utilization, a rich repertoire of diverse biological assays now available, highly effective nuclear magnetic resonance and mass spectrometry methods well suited to solving complex structures on vanishingly small quantities of a compound, and synthetic methods able to approach and be commercially tenable for exceedingly complex natural products and their derivatives, we can expect the next decade to yield an even more bountiful crop of new clinical agents from the sea[103].

Acknowledgement

Authors are thankful to Dr. K.F.H. Nazeer Ahamed, Assistant Professor, Department of Pharmacology, Vel's College of Pharmacy, Chennai, for his unprecedented support and encouragement.

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