10

Production of Life-Saving Drugs from Marine Sources

Rakesh Maurya and Sudhir Kumar

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Natural-product-based drug discovery has imparted a renaissance, particularly, to the field of marine natural-product-based drug discovery in the past few decades. A large number of structurally diverse chemical compounds discovered from marine sources have beneficial health effects and reduce the risk of a number of life-threatening and debilitating diseases. Inspirational drug discovery processes by semisynthetic modification of natural leads have provided an additional factor of force to drive marine natural product pharmacognosy ahead. A number of marine natural products and synthetic analogs as well are being evaluated for indications of different diseases including cancer, neurodegenerative disorders, infectious disease, inflammation and protozoan diseases. Prosperous biodiversity of marine environment is the major source of new biologically active molecules. This chapter presents an account of 198 compounds of marine origin and 206 references directed toward the discovery of new anticancer, anti-infective, anti-inflammatory, anticoagulating and antidiabetic agents from marine sources particularly emphasizing tremendous opportunities involved in developing new pharmaceuticals from the sea, along with compounds that are in the market and in clinical trial.

10.1 Introduction to Marine Pharmacology

Rich chemical diversity of marine secondary metabolites has proven to be a great source of extremely potent bioactive compounds. Several of them have inspired the development of life-saving pharmaceuticals; others are used as food additives and beauty products. Although the numbers of marine natural products (NPs) in market are relatively few, they have the potential for the development of new life-saving drugs (Molinski et al. 2009). Approximately half of all life forms inhabit oceans and seas that cover 70% of the earth’s surface. Estimated number of species represented by sponges, echinoderms, bryozoans, tunicates, shellfish, bacteria, fishes, seaweeds, and so on inhabiting the world’s oceans may come close to 10 million (Mora et al. 2011). Extreme conditions of pressure and temperature have facilitated extensive biological and chemical diversification. To survive in these surroundings, marine organisms are armored with potent and highly active secondary metabolites to either protect the user of it from predation or to kill the prey.

Several bioactive compounds have been isolated from various marine invertebrates such as sponges, echinoderms, jellyfishes, mollusks, bryozoans, and a few others. Marine organisms are the ocean of immense bioactive substances of diverse structural classes, including alkaloids, polyketides, terpenes, steroids, and peptides, responsible for the development of more than 15,000 different products (Hu et al. 2015) and hundreds of new compounds being discovered every year.

Marine sponges are most primitive and diverse animals, comprising approximately 8000 sponge species (Van Soest et al. 2012). Early pharmaceuticals inspired from marine NPs were isolated from the marine sponge *Cryptothetya crypta*. The discovery of the nucleosides spongouridine and spongouridine played a significant role in the synthesis of cytotoxic compounds. Sponges produce remarkable chemical diversity of toxins and other compounds to protect themselves from predators and to compete with other species. Marine sponges are currently one of the richest sources of new marine NPs reported yearly. Cnidarians are second after sponges in terms of new marine NPs, particularly terpenoid metabolites, reported annually (Blunt et al. 2005). Echinodermata, of which there are over 6000 species known worldwide, is one of the most distinct phyla among the marine invertebrates and includes sea urchins, sea cucumbers, sea stars, sea lilies, feather
stars, brittle stars, sand dollars, and sea cucumbers. They are proven to be an abundant source of bioactive glycosylated metabolites showing antimicrobial, antitumor, anticoagulant, cardioprotective, and even antiviral activities. Approximately 500 species of bryozoans, prospering in marine environment ranging from shallow water to deep water of about 5000 m, are a considerable source of marine metabolites (Clarke and Lidgard 2000). Shallow-water ascidians, comprising over 2800 known species (Shenkar and Swalla 2011), are among the producers of biologically important metabolites.

Several bioactive secondary metabolites have successfully been approved for clinical trial and a large number of them have shown the potential to be developed as potential therapeutics for life-threatening diseases. Despite the undying problem of supply and low availability of biologically active compounds isolated from natural material, the development of advanced methods of sampling identification and competent techniques of isolation have boosted marine NP research. Synthetic chemists are taking up the challenge of drug development from ocean by developing methods of synthesis and artificially producing many marine NPs in gram scale (Morris 2013). There are several excellent reviews on marine NP and drug development from marine sources (Newman and Cragg 2004; Glaser and Mayer 2009; Molinski et al. 2009; Sashidhara et al. 2009; Gerwick and Moore 2012). This chapter describes research on natural marine pharmacological compounds isolated from a marine source. The selected compounds will be reviewed under the heading of each pharmacological activity.

10.2 Marine Natural Products and Inspired Drugs

The story of marine and marine inspired drugs begins with the discovery of spongothyminidine (1) and spongouridine (2) from the Caribbean sponge Tectitethya crypta (also known as Cryptotethya crypta and Tethya crypta) in the 1950s by Bergmann (Bergmann and Feeney 1950). These compounds are glycosides of D-arabinose rather than D-ribose. The discovery of spongothyminidine in marine sponges, a nucleoside with a modified sugar instead of a modified base, directed the design and synthesis of a new generation, sugar modified nucleoside (Hamann et al. 2007). Compounds derived from marine sponge Cryptotethya crypta have inspired the synthesis of several ara-nucleosides (where “ara” represents arabinose). Two ara-nucleosides inspired drugs that were able to reach clinics from labs are cytarabine (3) followed by vidarabine (4).

10.2.1 Life-Saving Drugs in Market: Discovery, Production, and Pharmacology

10.2.1.1 Cytarabine

Cytarabine (3) received FDA’s approval as an anticancer drug in June 1969 (Schwartsmann et al. 2003). It (also known as ara-C or 1-β-D-arabinofuranosylcytosine) received the pleasure of being the first marine-derived drug used for the management of leukemia. Inspired by arabinose nucleosides, cytarabine or cytosine arabinoside was produced artificially by R. Walwick in 1959 and natural-sourced cytarabine was isolated from the fermentation broth of Streptomyces griseus. Subsequently, cytarabine was isolated from the gorgonian Eunicella cavolini (Cimino et al. 1984). Cytarabine is sold under the trade name Cytosar-U® or Depocyt® and is prescribed mainly for the treatment of non-Hodgkin lymphoma and acute myeloid leukemia (AML; Wang et al. 1997).

Cytarabine interferes with DNA synthesis and its mechanism. It is rapidly converted into cytosine arabinoside triphosphate in the body which replaces cytidine triphosphate
during DNA synthesis leading to fabrication faulty DNA. Cytarabine also inhibits important enzymes of DNA synthesis mechanism, RNA polymerase and nucleotide reductase (Severin et al. 2003). Despite side effects such as cerebellar toxicity, granulocytopenia, thrombocytopenia, leukopenia, anemia, and gastrointestinal disturbance associated with high dosing, it is a drug of choice for myeloid leukemia and non-Hodgkin lymphoma because no better approaches are available.

10.2.1.2 Vidarabine

Vidarabine (4) or 9-β-D-arabinofuranosyladenine (ara-A) is a glycoside analog of adenosine where D-ribose is replaced with D-arabinose which is inspired by the knowledge gained from the chemical structure of spongouridine (2). The synthesis of vidarabine was first achieved in the laboratory of Bernard Randall Baker at the Stanford Research Institute (now known as SRI International) and finally natural vidarabine was obtained from the fermentation broth of Streptomyces antibioticus. It is the first systemic nucleoside analog antiviral agent that has been licensed for the management of herpes virus infection in human. Vidarabine interferes with the synthesis of viral DNA. Diphosphorylated and triphosphorylated vidarabine are active drugs produced in vivo that interfere with the synthesis of viral DNA. Diphosphorylated vidarabine prevents the reduction of nucleotide diphosphates by inhibiting ribonucleotide reductase enzyme, thereby inducing a decline of viral replication. Triphosphorylated vidarabine competitively inhibits dATP leading to the formation of “faulty” DNA. Vidarabine has some significant limitations such as rapid metabolism by adenosine deaminase, low intramuscular and intestinal absorption, and requirement of large fluid volumes for intravenous administration over prolonged periods (Cohen 1979; Whitley et al. 2012).

10.2.1.3 Ziconotide

Ziconotide (5), or Prialt®, also known as SNX-111, is an uncommon non-opioid, not addictive analgesic agent which is 1000 times more effective than morphine (de la Calle Gil et al. 2015). It is the synthetic form of a ω-conotoxin peptide derived from Conus magus (Cone Snail). The ω-conotoxins is a chemical group of structurally related polypeptide molecules discovered in the venom of predatory cone snails (genus Conus) of different species. ω-conotoxins are comprised of several different peptides such as ω-GVIA, ω-MVIIA, ω-MVIIC, and ω-CVID, each having potent physiologic capabilities. Ziconotide (ω-MVIIA) is a small peptide molecule made up of 25 amino acids sequence H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Tyr-Asp-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH₂ in which six cysteine residues are linked in pairs by three disulphide bonds.

The powerful analgesic effect of ziconotide results from its intrathecal injection that interferes pain signaling at the spinal cord by selectively blocking neurotransmission at N-type calcium channels on nerve cells (Wang et al. 2016). Ziconotide was developed into an artificially manufactured drug by Elan Corporation. U.S. FDA approved for its sale under the name Prialt for the treatment of severe chronic pain in patients suffering from cancer, AIDS, or certain neurological disorders. Ziconotide is delivered directly into fluid surrounding the spinal cord through intrathecal route. It is effective and safer than morphine as no addiction or tolerance is developed on its prolonged administration.

10.2.1.4 Trabectedin

Trabectedin (6) is a complex tetrahydroisoquinoline alkaloid, first time isolated from Caribbean collection of a tunicate, Ecteinascidia turbinata (Valoti et al. 1998). E. J. Corey
developed a method of total synthesis of ecteinascidin 743 to overcome the problem of low yields from the sea squirt (1 g of trabectedin is isolated from 1 t of sea squirt; Corey et al. 1996).

Although the initial clinical trials were performed with the NP, the subsequent developments were made of a semisynthetically produced trabectedin from the microbial product cyanosafacin B (7). The development of semisynthetic methods from cyanosafacin B, an antibiotic obtained by fermentation of the bacterium Pseudomonas fluorescens, has solved the all-time problem of supply with marine-sourced secondary metabolites (Molinski et al. 2009). Trabectedin was approved by EMEA for the treatment of patients with advanced soft-tissue sarcoma and was sold under the brand name Yondelis® by Zeltia and Johnson and Johnson. Trabectedin was categorized as a medicine used in rare diseases (orphan medicine) on May 30, 2001, for soft-tissue sarcoma and in October 2003 for ovarian cancer because these are considered rare (http://www.prnewswire.co.uk/news-releases/yondelisr-granted-orphan-drug-designation-by-the-us-fda-for-the-treatment-of-ovarian-cancer-154027485.html, retrieved on November 30, 2015).

10.2.1.5 Eribulin Mesylate

Eribulin (8) is a fully synthetic analog of a large naturally occurring polyether macroclide halichondrin B (9) that was purified from the marine sponge Halichondria okadai. Halichondrin B has shown potent anticancer activity against murine cancer cells in both in vitro and in vivo studies and indicated that it disrupts microtubules (Hirata and Uemura 1986). The efforts to combat limited supply of halichondrin B, the complete chemical synthesis was achieved by Yoshito Kishi and colleagues at Harvard University in 1992 (Aicher et al. 1992).

Several structurally simplified synthetic analogs facilitated the development and optimization of structurally simplified analogs of eribulin, such as E7389, ER-086526, and NSC-707389, that retained anticancer activity (Yu et al. 2005). The most potent analog among them, E7389, that ultimately became eribulin (Halaven®) was approved by the FDA in 2010 for the treatment of refractory metastatic breast cancer (mBC).

10.2.1.6 Brentuximab Vedotin

Brentuximab vedotin (Adcetris®) is an antibody–drug conjugate (ADC) with a potent microtubule inhibitor in which an anti-CD30 antibody conjugated an analog of dolastatin-10, that is, monomethyl auristatin E (MMAE). Although dolastatins were isolated for the first time from the sea hare Dolabella auricularia (Phylum Mollusca), later they were found to be produced by cyanobacteria (Luesch et al. 2001). Dolastatin-10 was withdrawn from phase II of clinical trials due to some toxic effect associated (Francisco et al. 2003). Dolastatin-10 analog was then conjugated with an antibody that targeted the CD30 antigen present on the surface of Hodgkin lymphoma cells to produce brentuximab vedotin (Armitage et al. 2015). The ADC brentuximab vedotin was launched in 2011 under the trade name Adcetris® by Seattle Genetics and indicated for the management of Hodgkin and systemic large cell lymphoma. The drug is proven to be less toxic than the parent compound, dolastatin-10. However, so far described adverse effects are neutropenia, peripheral sensory neuropathy, fatigue, and hyperglycemia (http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm458815.htm, retrieved on November 30, 2015).
10.2.1.7 Omega-3-Acid Ethyl Esters

Omega-3-acid ethyl esters (12, 13) are lipid-regulating agents developed by Reliant Pharmaceuticals and sold under the brand name Lovaza® by GlaxoSmithKline. Lovaza is an FDA-approved drug for the treatment of patients with hypertriglyceridemia (Weintraub 2014). The mechanism of action of Lovaza is not understood completely. But it is found that the drug produces hypotriglyceridic effect probably by the inhibition of acyl CoA, 1,2-diacylglycerol acyltransferase. It decreases lipogenesis in the liver and the VLDL-cholesterol level, and increases HDL-cholesterol, mitochondrial and peroxisomal β-oxidation in the liver, and plasma lipoprotein lipase activity.

10.2.1.8 Iota-Carrageenan

Carrageenan (14) is a family of linear sulphated polysaccharides, a common food additive, that are extracted from red edible seaweeds. Carrageenan finds its medical use in the form of iota-carrageenan. Iota-carrageenan produced mainly from Eucheuma denticulatum is sold as an over-the-counter (OTC) drug by the trade name of Carragelose®. Chemically, iota-carrageenan is linear sulphated polysaccharides having two sulphates per disaccharide (Ahmadi et al. 2015).

The use of carrageenan as food additive has many objections, as it causes gastrointestinal inflammation; intestinal lesions, ulcerations, and even malignant tumors. Whereas Marinomed Biotechnologie GmbH developed an effective nasal spray for the treatment of common cold containing antiviral iota-carrageenan (Carragelose). Carragelose creates a protective physical barrier in the nasal cavity which protects from viral attack. In addition, it has the potential to manage patients with viral conjunctivitis, an infection for which there is currently no approved etiological treatment (Figure 10.1).

10.2.2 Marine Natural Products and Their Synthetic Analogs in Clinical Trial

There are considerable numbers of interesting molecules that have either been isolated from marine sources or have been produced artificially based on the knowledge gained from a prototypical compound isolated from marine sources. Many of them are in phases II and III of clinical trials mainly for cancer and analgesia (Table 10.1).

Plitidepsin (15) or dehydrodidemnin B is a marine cyclic depsipeptide extracted from the ascidian Aplidium albicans (Newman and Cragg 2004). Plitidepsin is extremely potent to induce rapid p53-independent apoptosis with IC_{50} values in nanomolar range. The drug is marketed under the trade name Aplidin® by PharmaMar and is undergoing phase III of clinical trial for the treatment of multiple myeloma.

Lurbinectedin (16) is a dimeric isoquinoline alkaloid similar to trabectedin but has a tetrahydro-β-carboline moiety as a replacement of tetrahydroisoquinoline present in trabectedin. Currently, it is in phase III of clinical development for ovarian cancer. Lurbinectedin binds covalently to minor grooves of DNA inducing break formation in double-stranded DNA, thereby leading to cell apoptosis.

Panobinostat (17; Farydak®) is a drug developed by Novartis for the treatment of various cancers. Panobinostat induces apoptosis of malignant cells via inhibition of multiple histone deacetylase enzymes. It is in phase II/III of clinical trial for the treatment of chronic myeloid leukemia (Bailey et al. 2015).

Salinosporamide A (18) is a potent proteasome inhibitor in phase II of clinical trial for the treatment of multiple myeloma. This marine NP is produced by marine bacteria found...
FIGURE 10.1
Chemical structures of marketed drugs and related marine compounds.
TABLE 10.1
Natural Marine and Derived Compounds in Market and Clinical Trial

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name</th>
<th>Alternative Name</th>
<th>Source</th>
<th>Activity</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cytarabine</td>
<td>Cytosar-U®</td>
<td>Spongothymidine derivative</td>
<td>Cancer</td>
<td>FDA approved</td>
</tr>
<tr>
<td>2</td>
<td>Vidarabine</td>
<td>Vira-A®</td>
<td>Spongouridine derivative</td>
<td>Anti-viral</td>
<td>FDA approved</td>
</tr>
<tr>
<td>3</td>
<td>Ziconotide</td>
<td>Prialt®</td>
<td>NP, synthetic version of ω-conotoxin MVIIA</td>
<td>Neuropahtic Pain</td>
<td>FDA approved</td>
</tr>
<tr>
<td>4</td>
<td>Trabectedin</td>
<td>Yondelis®</td>
<td>NP, Ecteinascidin 743</td>
<td>Cancer</td>
<td>EU approved</td>
</tr>
<tr>
<td>5</td>
<td>Eribulin mesylate</td>
<td>Halaven®</td>
<td>Halichondrin B inspired</td>
<td>Cancer</td>
<td>FDA approved; Breast cancer</td>
</tr>
<tr>
<td>6</td>
<td>Brentuximab vedotin</td>
<td>Adcetris®</td>
<td>Dolastatin-10 synthetic analog monomethylauristatin E</td>
<td>Cancer</td>
<td>FDA approved</td>
</tr>
<tr>
<td>7</td>
<td>Omega-3-acid ethyl esters</td>
<td>Lovaza®</td>
<td>Derivative omega-3-fatty acids</td>
<td>Hypertriglyceridemia</td>
<td>FDA approved</td>
</tr>
<tr>
<td>8</td>
<td>Iota-carrageenan</td>
<td>Carragelose®</td>
<td>NP, <em>Eucheuma denticulatum</em></td>
<td>Antiviral</td>
<td>FDA approved</td>
</tr>
<tr>
<td>9</td>
<td>Plitidepsin</td>
<td>Aplidine®</td>
<td>Ascidian <em>Aplidium albicans</em></td>
<td>Cancer</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dehydrodidemnin B</td>
<td></td>
<td></td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>10</td>
<td>Lurbinectedin</td>
<td>PM1183 Tryptamicidin</td>
<td>NP derivative</td>
<td>Cancer</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ovarian cancer;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase II/III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chronic myeloid leukemia</td>
</tr>
<tr>
<td>11</td>
<td>Panobinostat</td>
<td>Farydak; LBH-589</td>
<td>NP-derived</td>
<td>Cancer</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>12</td>
<td>Bryostatin-1</td>
<td>Bryostatin-1-Neurotrope</td>
<td>NP, <em>Bugula neritina</em></td>
<td>Alzheimers disease</td>
<td>Phase II Alzheimers disease</td>
</tr>
<tr>
<td>13</td>
<td>Salinosporamide A</td>
<td>NPI-0052; Marizomib</td>
<td>NP, <em>Salinospora strain CNB-392</em></td>
<td>Cancer</td>
<td>Phase II</td>
</tr>
<tr>
<td>14</td>
<td>PM 060184</td>
<td>PM060184</td>
<td>NP, <em>Lithoplocamia lathistoides</em></td>
<td>Cancer</td>
<td>Phase I</td>
</tr>
<tr>
<td>15</td>
<td>Glembatumumab vedotin</td>
<td>CDX-011; CR 011 ADC</td>
<td>MMAE-based ADC</td>
<td>Cancer</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Breast cancer; Malignant melanoma
in ocean sediment, *Salinispora tropica* and *Salinispora arenicola*. A significantly potent proteasome inhibitor, salinosporamide A showed proteasomal chymotrypsin-like proteolytic inhibition activity with an IC\textsubscript{50} value of 1.3 nM (Feling et al. 2003). Furthermore, it exhibited significant in vitro cytotoxicity against HCT-116 human colon carcinoma (IC\textsubscript{50} 11 ng/mL).

PM060184 (19) is a tubulin-binding agent (Martinez-Diez et al. 2014) originally isolated from the marine sponge *Lithoplocamia lithistoides*. Currently produced by total synthesis (Martin et al. 2013), it is under evaluation in clinical studies on patients with advanced cancer diseases (https://clinicaltrials.gov/ct2/show/NCT01299636).

Bryostatin 1 (20) is a cyclic macrolide originally isolated from the marine bryozoan *Bugula neritina* (Order Cheilostomata; Pettit et al. 1982), and later it was proposed to be produced by symbiotic bacteria of the bryozoans (Davidson et al. 2001). As in 2015, bryostatin 1 (20) is in phase II of clinical studies for the therapy of modest as well as severe Alzheimer’s disease (Figure 10.2; https://clinicaltrials.gov/ct2/show/NCT02431468?term=Bryostatin-1&rank=12).

**FIGURE 10.2**
Chemical structures of marine and derived compounds in clinical trial.
10.3 Anticancer Marine Natural Products

Tremendous diversity of toxic metabolites produced by marine sources has been found active against cancer. Many of them have the potential to be developed as newer and safer drugs for the treatment of cancer. Considerable numbers of anticancer drugs used in the clinic are either NPs or derived from NPs. Several new antineoplastic compounds derived from marine NPs are now in the preclinical pipeline. Researchers have isolated hundreds of compounds each year and evaluated their anticancer potential. Even though many compounds could not reach the market, these have guided the clinical trial of other NPs or derived agents. These are crucial compounds in the understanding of the mechanism of drug action.

10.3.1 Microtubule Inhibitors

Antimicrotubule agents generally act by either inhibiting or stabilizing the polymerization of tubulin via binding on the tubulin surface. Cryptophycins exhibit potent antiproliferative and antimitotic effect by destabilizing microtubule dynamics as well as inducing hyperphosphorylation of the antiapoptotic protein BCL-2 (B-cell leukemia/lymphoma 2; Wagner et al. 1999). Cryptophycin-52 (21), an analog of the marine NP Cryptophycin 1, had undergone phase I of clinical trials for the treatment of nonsmall cell lung cancer and solid tumors. However, due to adverse effects, phase II of trial was discontinued. Kobayashi et al. (1994) isolated another related cyclic didepsipeptide, arenastatin-A (22), from marine sponge *Dysidea arenaria*. Later, it was found to be identical to cryptophycin-24 (22). Arenastatin-A (22) exhibited extremely potent cytotoxicity against KB cells with IC₅₀ 5 pg/mL. Dolastatins are significant tubulin polymerization inhibitors isolated from marine sources. Dolastatin-10 (10), isolated for the first time from the Indian Ocean mollusk *Dolabella auricularia* (Luesch et al. 2001), is a tubulin interactive agent binding close to the vinca domain (Bai et al. 1990) which entered phase I of clinical trials in the 1990s. Cemadotin (23) is a water-soluble synthetic analog of dolastatin that exhibited potent antiproliferative and antitumor activities (Supko et al. 2000) through action on microtubules which blocks cells at mitosis (Jordan et al. 1998). Didemnin B (24) was isolated from extracts made of the tunicate *Trididemnum solidum* that demonstrated excellent cytotoxicity against P388 and L1210 murine leukemia cell lines (Rinehart et al. 1981). Didemnin B (24) was the first defined chemical compound directly from a marine source that was taken for preclinical and clinical trials under the financial support of the National Cancer Institute (NCI) in 1980s (Cain et al. 1992). However, the compound was withdrawn from clinical trial due to severe toxicity observed. Phenylhistin (Halimide; 25) is a NP produced by the fungus *Aspergillus ustus* (Kanoh et al. 1997) that belongs to a class of naturally occurring 2,5-diketopiperazines. Phenylhistin (25) exhibits cytotoxic effects against various types of tumor cell lines by interfering in the microtubule-formation mechanism (Kanoh et al. 1999).

Hemiasterlins are another group of potent microtubule-disrupting agents (Anderson et al. 1997). Tripeptide hemiasterlin (26) was isolated from the sponge *Hemiasterella minor* (Talpir et al. 1994). Taltobulin (27), a synthetic analog of hemiasterlin, inhibited proliferation of hepatic tumor cell lines (Vashist et al. 2006), bladder cancer (Matsui et al. 2009), and prostate cancer (Hadaschik et al. 2008) like its precursor inhibited microtubules formation (Lo et al. 2004; Ravi et al. 2005).

Dictyostatins are macrolactone isolated from the sponge *Spongia sp.* Dictyostatin-1 (28) induced tubulin polymerization by binding to a taxoid site against human ovarian carcinoma cells (Madiraju et al. 2005). Discodermolide (29) is a metabolite originally isolated from deep-sea sponge *Discodermia dissoluta* (Gunasekera et al. 1990) and is produced synthetically...
Production of Life-Saving Drugs from Marine Sources


Avarol (32), a sesquiterpenoid hydroquinone, was first isolated from the marine sponge Disidea avara (Minale et al. 1974). At a concentration of 0.9 µM, avarol reduced the cell growth to 50% in an in vitro assay of L5178y mouse lymphoma cells. Avarol interfered with mitotic processes, preventing telophase formation (Müller et al. 1985; Figure 10.3).

FIGURE 10.3
Chemical structure of tubulin inhibitor marine natural products.
10.3.2 Actin Filaments Inhibitors

Actin is an essential component of the cell’s cytoskeleton which participates in the regulation of many motor functions in the cell, such as cell migration, cell division, and muscle contraction. Notable number of highly potent cytotoxic agents that interact with actin have been produced by marine organisms (Figure 10.4). Latrunculins were the first actin-binding substances isolated from a marine source. Ichthyotoxicity principle isolated from sponge *Laetrunculia magnifica*, Latrunculin A (33), was later shown to be cytotoxic (Kashman et al. 1980). Latrunculin A (33), a well-known actin-binding macrolide, arrests polylysine-induced nucleation at the level of an antiparallel dimer (Bubb et al. 2002). Antitumor macrolide aplyronine A (34) inhibits the polymerization of globular actin to fibrous actin by forming 1:1 complex with globular actin. Aplyronine A (34) binds to actin molecule by intercalating its aliphatic tail into a hydrophobic cleft of the

![Diagram of cytotoxic marine natural products that interact with actin.](Continued)
actin molecule (Hirata et al. 2006). Spisulosine (35; ES-285), isolated from the sea mollusc Spisula polynyma, is a novel antiproliferative (antitumoral) compound of marine origin. It inhibits cell proliferation by preventing assembly of actin stress fibers (Cuadros et al. 2000). Marine sponge Mycale sp. derived NP mycalolide B (36) and a related kabiramide D (37) are actin-depolymerizing cytotoxic compounds (Wada et al. 1998). A polyketide bistramide-A (38), isolated from the marine ascidian Lissoclinum bistratum, disruptes actin cytoskeleton both by depolymerizing F-actin and binding directly to monomeric actin in vitro (Rizvi et al. 2006; Statsuk et al. 2005). Dimeric macrolides, bistheonellide-A or misakinolide-A (39), isolated from an Okinawan Theonella sp. sponge (Terry et al. 1997) and swinholide A (40) isolated from Symplaca and Gellitlerinema species of cyanobacteria (Andrianasolo et al. 2005) bind with two molecules of actin per molecule of these cytotoxic agents. Jasplakinolide (41), a cyclodepsipeptide isolated from marine sponge, Jaspis johnsonii, showed 50% growth inhibition of prostate carcinoma cell lines PC-3, LNCaP, and TSU-Pr1 at 65 nM, 41 nM, and 170 nM, respectively, on 48 h exposure (Senderowicz et al. 1995). Microcarpalide (42), isolated from culture broth of an endophytic fungus hosted by a Ficus microcarpa L. (Ratnayake et al. 2001), cause complete disruption of actin
microfilament of NIH/3T3 fibroblasts incubated with microcarpalide (42; Furstner et al. 2007). Cytochalasin D (43) showed cytotoxicity at 100 nM against T cells (Suria et al. 1999).

### 10.3.3 Induction of Apoptosis in Cancer Cells

Cephalostatin-1 (44), a bis-steroidal marine natural product (MNP) obtained from the Indian Ocean collection of hemichordata *Cephalodiscus*, inactivated the antiapoptotic mitochondrial protein Bcl-2 by hyperphosphorylation (Lopez-Anton et al. 2006). Curacin-A (45), isolated from the cyanobacterium *L. Majuscule* (Gerwick et al. 1994), is exquisitely potent but is effectively insoluble in any formulation (Wipf and Xu 1996). Aaptamine (46) is a prominent cancer cell growth inhibitory constituent isolated from marine sponge *Hymeniacidon sp.* (Pettit et al. 2004). It exerted an antiproliferative effect by inducing apoptosis (Dyshlovoy et al. 2014). Dysidiolide (47), a secondary metabolite obtained from the Caribbean sponge *Dysidea etheria*, inhibited cdc25A protein phosphatase with an IC$_{50}$ value of 9.4 µM. Moreover, dysidiolide (47) showed IC$_{50}$ 4.7 µM in vitro inhibition of A-549 human lung carcinoma and P388 cells (IC$_{50}$ 1.5 µM). Cycloprodigiosin hydrochloride (48), a member of the prodigiosin family of compounds, exhibited protein synthesis inhibition-induced apoptosis in PC12 cells (Kawauchi et al. 2008). Pycnidione (49), isolated from the fermented broth of *Theissenia rogersii* 92031201, exhibits antiproliferative activities on A549 cells with a 50% growth inhibition (GI$_{50}$) value of 9.3 nM at 48 h, triggering apoptosis in the A549 cells by enhancing PAI-1 production, and activated caspase-8 and -3 (Figure 10.5).

**FIGURE 10.5**
Chemical structures of apoptosis inducer marine natural products.
10.3.4 Anticancer Natural Product Antibody–Drug Conjugates

Antibody–drug conjugates or ADCs play an increasing role in cancer treatment as they are highly potent biopharmaceuticals designed to selectively target cancer cells. This combination of antibodies to cytotoxic drugs conveys the benefits of highly potent drugs. ADCs consist of covalently linked monoclonal antibodies aimed at certain tumor markers differentially overexpressed in tumor cells and at selectively delivering cytotoxic (anticancer) payload to tumor cells so that healthy cells are less severely affected (Kovtun and Goldmacher 2007).

Gemtuzumab ozogamicin (trade name Mylotarg®, Pfizer/Wyeth) was the first ADC to receive marketing approval in 2001 by U.S. FDA for the treatment of acute myelogenous leukemia. However, it was withdrawn from market in June 2010 by the sponsor due to the absence of significant benefit and safety reasons in post-approval phase III of clinical trial. Trastuzumab emtansine (Herceptin®, Genentech and Roche), an ADC composed of trastuzumab linked via a noncleavable linker to DM1, was approved in February 2013 for the treatment of HER2-positive refractory /relapsed mBC. Later, it was withdrawn from market. As a result, only one ADC Brentuximab vedotin (trade name: Adcetris, marketed by Seattle Genetics and Millennium/Takeda) is in the market.

Doxorubicin (50), calicheamicin (51), auristatins, and maytansine (52) are important cytotoxic payloads conjugated with antibodies. Calicheamicin is a DNA-alkylating agent produced by Micromonospora echinospora ssp. calichensis. Gemtuzumab ozogamicin (Wyeth) is a representative example of a calicheamicin-based ADC. Another calicheamicin-based ADC, Inotuzumab ozogamicin (CMC-544, Pfizer) derived via linking an antibody anti-CD22 IgG4 monoclonal antibody is in phase III of clinical trials.

Doxorubicin is an anticancer agent belonging to the anthracycline family, semi-synthesized from a NP of Streptomyces actinobacteria used in the treatment hematological malignancies, carcinomas, and soft-tissue sarcomas. Doxorubicin conjugated with the chimeric anti-LeY cBR96 monoclonal antibody through a hydrazone acid-labile linker is under evaluation.

MMAE (11) and F (53), collectively known as auristatins are structurally modified equipotent derivatives of dolastatin-10 (10). The dolastatins are pentapeptides, originally discovered as constituents of the sea hare Dolabella auricularia. These agents prevent the formation of the mitotic machinery and block α-tubulin polymerization, interacting with the vinca alkaloid binding site on α-tubulin. Antibody conjugation with MMAE and MMAF has provided a number of auristatin-based ADCs that have undergone clinical trials—one of them brentuximab vedotin is currently in market.

Other MMAE conjugated with antibodies, such as NaPi2b (RG7599; Roche), CD22 (RG7593; Roche), anti-MUC16 (RG7458; Roche), PSMA (Progenics Pharmaceuticals), and the tumor-linked glycoprotein NMB (CDX-011; Celldex Therapeutics), as well as MFA conjugates (PF-06263507, a 5T4-targeted ADC; Pfizer) are under clinical development.

Cytotoxic agent maytansine (52), a benzoansamacrolide first isolated from the bark of the Ethiopian shrub Maytenus ovatus, leads to the formation of derivatives emtansine (54; also known as DM1) and ravtansine (55; also known as DM4) that bind to tubulin near the vinca alkaloid binding site. Trastuzumab emtansine (T-DM1; Roche in partnership with ImmunoGen) is an important ADC of emtansine to trastuzumab through a stable thioether linker that target human epidermal growth factor receptor (HER2; Figure 10.6).
10.4 Anti-Infective Potential of Marine Natural Products

NPs have been the most important source of anti-infective compounds since the early days of anti-infective research. Marine organisms are potential producers of anti-infective secondary metabolite. In fact, marine organisms are naturally bestowed with an effective defense mechanism as an instrument of survival in marine conditions. At this time, any new antibiotic entering the clinical trials’ pipeline needs to be advanced with the emergence of multidrug resistant (MDR) bacterial strains. There are a large number of compounds having anti-infective potential; some selected ones that have undergone extensive investigation or have shown significant activity are described further. Because of enormous diversity and several examples of marine NPs with promising antibacterial activity, the ocean continues to be a tremendous opportunity to discover new antibiotics. Coupled with synthetic analogs with enhanced pharmacological profiles, they are exceptionally effective.
attention-grabbing high-value materials for applications in benefit of human beings. Marine chemicals with potential antibacterial, antifungal, antiprotozoal, antituberculosis, and antiviral activities will be discussed in this section.

### 10.4.1 Antifungal Marine Natural Products

Antifungal screen of marine NPs has led to the identification of several interesting antifungal NPs, both by the way of chemical structure and biological activity. SCY-07876 and NP213 are two NP-derived compounds that could reach clinical trials against fungal infections.

Enfumafungin (56), an acidic triterpenoid isolated from the fungus *Hormonema*, showed antifungal activity by inhibiting 1,3-β-D-glucan synthase (Lamoth and Alexander 2015). A semisynthetic derivative of enfumafungin SCY-07876 (57; MK-3118) is in clinical trials against fungal infections (Pfaller et al. 2013). Another important cyclic cationic antifungal peptide NP213 (58; Novexatin®), a derived analog of natural cationic peptides with seven arginine residues (Li and Breaker 2012), is being developed by Nova Biotics Ltd. Clinical studies have established Novexatin as safe, well-tolerated and effective agent for the treatment of onychomycosis (nail infections).

Phidolopin (59), a purine derivative isolated from bryozoan *Phidolopora pacifica* (Ayer et al. 1984), has exhibited a broad spectrum antifungal activity against *Phythium ultimum*, *Rhizoctonia solani*, and *Helmithosporium sativum* with a minimum inhibitory concentration of 70 µg per 6 mm disc (Christophersen 1985). Meridine (60), a polycyclic alkaloid, is a cytotoxic agent (Guittat et al. 2005) isolated from South Australian marine ascidian *Amphicarpa meridian* (Schmitz et al. 1991) and from marine sponge *Corticium sp*. Meridine exhibited antifungal effect against *Candida albicans*, *Cryptococcus*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* by the inhibition of nucleic acid biosynthesis (McCarthy et al. 1992).

Ptilomycalin A (61) is an antifungal spirocyclic guanidine alkaloid isolated from a marine sponge *Monanchora arbuscula* (Gallimore et al. 2005). It inhibits the production of melanin in *Cryptococcus neoformans* in vitro with an IC$_{50}$ of 7.3 µM, through the inhibition of laccase biosynthesis in the melanin biosynthetic pathway (Dalisay et al. 2011). Melanin is deposited as a protective covering in the cell wall of *C. neoformans* and contributes toward cell wall’s thickness and strength and protects the fungal cells from phagocytosis by macrophages. Additionally, melanin deposition decreases the susceptibility of *C. neoformans* to antifungal agents (Wang et al. 1995). Naamine-G (62) exhibits powerful activity against phytopathogenic fungal strain *Cladosporium herbarum* with 20 mm zone of inhibition in the agar plate diffusion assay (20 µg/disk; Hassan et al. 2004).

The bengazoles, a family of marine NPs, were first reported from sponge *Jaspis sp.* with anthelmintic activity against the nematode *Nippostrongylus brasiliensis* (Adamczeski et al. 1988). Afterward, bengazole-A (63) exhibited ergosterol-dependent in vitro antifungal activity against *C. albicans* with a potency similar to amphotericin-B (Richter et al. 2004). Untenospongin-B (64), a marine NP isolated from sponge *Hippospongia communis*, was found to possess a broad and strong activity against bacteria and human pathogenic fungi. It showed antifungal activity against *Candida albicans* and *Aspergillus fumigatus* in an in vitro assay. Comparatively, it was found to be more active than amphotericin B against *C. tropicalis* (R2 CIP 1275.81) and *F. oxysporum* (CIP 108.74). In addition, it showed an activity profile similar to amphotericin-B against *C. albicans* (ATCC 10231) and *A. niger* (CIP 1082.74; Rifai et al. 2004). Untenospongin-B (64) showed growth inhibition diameters of 17 mm, 14 mm, 20 mm, and 13 mm against *Aspergillus fumigatus*, *Aspergillus niger*, *Arthrodema simii*, and *Trichophyton rubrum*, respectively. A novel marine antifungal NP (2S, 3R)-2-aminododecan-3-ol, isolated from the ascidian *Clavelina oblonga*, exhibited fungal growth
with MIC values of 0.7 µg/mL and 30 µg/mL against *Candida albicans* ATCC 10231 and *Candida glabrata*, respectively (Kossuga et al. 2004).

Dysideasterol-A (65), a sterol isolated from a sponge, was found to reverse fluconazole resistance mediated by a *Candida albicans* MDR efflux pump. A combination of fluconazole with dysideasterol-A (3.8 µM) decreased IC$_{50}$ of fluconazole from 300 to 8.5 µM (35-fold enhancement). Configuration at C-6 position of dysideasterol-A was revised by Jacob et al. (2003). Geodisterol-3-O-sulfite (66) and 29-demethylgeodisterol-3-O-sulfite (67) are two new sulfated sterols identified as active constituents through bioassay-guided fractionation of the extract of *Topsentia sp*. These sulfated sterols improved the activity of fluconazole in fluconazole-resistant *Candida albicans* and in wild *Saccharomyces cerevisiae* strain overexpressing the *Candida albicans* efflux pump, MDR1. The active constituents reversed the efflux pump-mediated fluconazole resistance (Digirolamo et al. 2009).

Tanikolide (68), an antifungal compound, was purified from the lipid extract of marine cyanobacterium *Lyngbya majuscula* collected from Madagascar. Tanikolide showed a 13-mm zone of inhibition at 100 µg/disk to *Candida albicans* (ATCC 14053; Singh et al. 1999). Red Sea sponge *Theonella swinhoei* afforded a new bicyclic glycopeptide theonellamide G (69) that exhibited remarkable antifungal activity toward amphotericin B resistant and nonresistant strains of *Candida albicans* with IC$_{50}$ of 2.0 and 4.49 µM, respectively (Youssef et al. 2014; Figure 10.7).

![FIGURE 10.7](image)

**FIGURE 10.7**

Chemical structures of antifungal marine natural products.

(Continued)
10.4.2 Antituberculosis Activity

Serrulatane-type diterpenes erogorgiaene (70) and 7-hydroxyerogorgiaene (71) were isolated from *Pseudopterogorgia elisabethae*. Compound 70 showed 96% growth inhibition of *Mycobacterium tuberculosis* (M. tuberculosis) H37Rv at a concentration of 12.5 µg/mL and compound 71 showed 77% mycobacterial growth inhibition at a concentration of 6.25 µg/mL (Rodriguez and Ramirez 2001; Rodriguez and Rodriguez 2003).

Homopseudopteroxazole (72) inhibited 80% of the growth whereas pseudopteroxazole (73) induced 97% growth inhibition of *Mycobacterium tuberculosis* H37Rv at a concentration of 12.5 µg/mL (Rodriguez and Ramirez 2001; Rodriguez and Rodriguez 2003).

**FIGURE 10.7 (Continued)**
Chemical structures of antifungal marine natural products.
Ileabethoxazole (74) a perhydroacenaphthene-type diterpene alkaloid containing benzoxazole moiety showed MIC value of 61 µg/mL. It, at the concentration range of 128–164 µg/mL, showed 92% growth inhibition of *M. tuberculosis* (H37Rv). At concentrations 4, 8, 16, and 32 µg/mL, ileabethoxazole (74) exhibited 29%, 38%, 54%, and 73% inhibition, respectively (Rodríguez et al. 2006).

In an in vitro assay, Agelasine F (75), an *Agelas sp.* sponge-derived compound, inhibited drug resistant strains of *M. tuberculosis* at concentration 3.13 µg/mL (Mangalindan et al. 2000). Bipinnapterolide B (76) is an oxapolycyclic diterpene isolated from the Colombian gorgonian coral *Pseudopterogorgia bipinnata*. Bipinnapterolide B (76) caused 66% inhibition against *M. tuberculosis* H37Rv at 128 µg/mL (Ospina et al. 2007).

Manzamine-type polycyclic alkaloids have exhibited wide anti-infective activity against malaria, leishmania, tuberculosis, and HIV-1. In 1986, manzamine A (77) was isolated from a sponge harvested near the coast of Okinawa (Sakai et al. 1986). Compound 78 (8-hydroxymanzamine A) isolated from sponge *Pachypellina sp.* (Ichiba et al. 1994) as well as 6-hydroxymanzamine E (79), manzamine A (77), and manzamine F (80) isolated from an Indonesian *Acanthostrenglyophora* sponge exhibited MIC values of 0.4, 0.9, 1.5, and 2.6 µg/mL, respectively, against *M. tuberculosis* (H37Rv; Rao et al. 2006). A tetracyclic bis-piperidine alkaloid neopetrosiamine A (81), isolated from the marine sponge *Neopetrosia proxima*, was tested in a microplate alamar blue assay exhibiting MIC value of 7.5 µg/mL against the pathogenic strain of *M. tuberculosis* (H37Rv; Wei et al. 2010).

Two novel 5(6→7)abeo-sterols, perguestersols A (82) and B (83), were isolated from sea sponge *Svenzea zeai*. Parguestersols A and B show antituberculosic activity against *M. tuberculosis* H37Rv and low toxicity against Vero cells (IC$_{50}$ value 52 µg/mL; Wei et al. 2007). Puupehenone (84), a tetracyclic terpene, isolated from deep-water marine sponge *Strongylophora hartmani* (Kohmoto et al. 1987), exhibited 99% inhibition of *M. tuberculosis* H37Rv at 12.5 µg/mL (Inman et al. 2010).

Culture of *Trichoderma sp.*, a fungus growing on marine sponge, afforded Trichoderins A (85) and B (86) which showed potent inhibitory activity against the pathogenic strain *M. tuberculosis* H37Rv with MIC values of 0.12 and 0.13 µg/mL, respectively (Pruckskorn et al. 2010). Litosterol (87), a C-19 hydroxy steroids isolated from soft coral *Nephthea chabroli* (Rao et al. 1999) and soft coral *Litophyton viridis* (Iguchi et al. 1989), showed 90% growth inhibition of *M. tuberculosis* with MIC value of 3.13 µg/mL (El Sayed et al. 2000). Axisonitrile-3 (88), a sesquiterpene possessing a cyano group and purified from marine sponge *Acanthella klethra*, was found to possess potent inhibitory activity with MIC value of 2.0 µg/mL against *M. tuberculosis* (Konig et al. 2000; Figure 10.8).

### 10.4.3 Anthelmintic Activity

Helminthiasis contributes substantially to malnutrition, reduced food intake, weakened digestion, severe blood disorder like iron-deficient anemia, growth impairment, cognitive changes particularly in young children, and enormous economic losses in livestock animals. Although excellent commercial anthelmintics are available, growing resistance to current drugs necessitates the search for new anthelmintics. Although the literature is not very extensive, the structure of a variety of anthelmintic marine NP will be discussed.

Bioactivity guided fractionation and isolation of the ethanol extract of sponges *Amphimedon spp.* (LD$_{50}$ 4.0 µg/mL and LD$_{99}$ 130 µg/mL) against nematode *Haemonchus contortus* resulted in the isolation of macrocyclic lactone and lactams. Amphilactams A–D (89–92), exhibited in vitro LD$_{99}$ activities at 7.5, 47, 8.5, and 0.39 µg/mL, respectively. These
FIGURE 10.8
Chemical structures of antitubercular marine natural products.

(Continued)
compounds restrain larval development at the L1 stage of nematode Haemonchus contortus but no activity against nematode eggs (Ovenden et al. 1999). Geodin A Mg salt (93), chemically macrocyclic polyketide lactam tetramic acid, is a potent nematocide isolated from southern Australian marine sponge Geodia. Geodin A which exists as Mg salt in a natural source was found to be nematocidal to Haemonchus contortus with LD$_{99}$ value of 1 µg/mL (Capon et al. 1999). Bislobane (94) obtained from red alga Laurencia scoparia displayed weak anthelmintic activity with an EC$_{50}$ of 0.11 mM against the parasitant stage (L4) of a rat gastrointestinal parasite Nippostrongylus brasiliensis, which is similar to human parasite hookworms (Davyt et al. 2006). Nafuredin (95) is produced by a fungus Aspergillus niger FT-0554 isolated from a marine sponge, as well as cultured broth of the strain FT-0554. Nafuredin (95) inhibited NADH-fumarate reductase (complexes I+II) from adult Ascaris suum (pig roundworm) at IC$_{50}$ of 12 nM. NADH-fumarate reductase is an important enzyme involved in the electron transport system of anaerobic metabolism found in many anaerobic organisms (Omura et al. 2001). Nafuredin (95) also showed anthelmintic activity against Haemonchus contortus (wireworm) in in vivo trials with sheep (Ui et al. 2001). Significant nematocidal (LD$_{99}$ 5.2 µg/mL) activity against parasitic nematode Haemonchus contortus was exhibited by onnamide F (96), a marine NP isolated from marine sponge, Trachycladus laevispirifer. Onnamide F (96) was also active against S. cerevisiae with LD$_{99}$ value of 1.4 µg/mL (Vuong et al. 2001). (−)-echinobetaine A (97; Capon et al. 2005a) and (+)-echinobetaine B (98; Capon et al. 2005b) are betaine-type nematocidal agents present in a southern Australian marine sponge of the genus Echinodictyum. (−)-echinobetaine A (97) and (+)-echinobetaine B (98) are nematocidal (LD$_{99}$ 83 and 8.3 µg/mL, respectively) to the parasite Haemonchus contortus.

FIGURE 10.8 (Continued)
Chemical structures of antitubercular marine natural products.
The acyclic lipid thiocyanatins isolated from the Australian sponge *Oceanapia sp.* exhibits potent nematocidal activity. Thiocyanatin A (99) displayed powerful nematocidal activity against the animal parasite *Haemonchus contortus* (*LD*<sub>99</sub> 1.3 µg/mL). Although the mechanism of action is undetermined, 2-alcohol, SCN functionalities and chain length may have vital role nematocidal activity (Figure 10.9).

**FIGURE 10.9**
Chemical structures of anthelmintic marine natural products.
10.4.4 Antiprotozoal Activity

Parasitic protozoans that belong to the genus *Plasmodium* (*P. falciparum*, *P. ovale*, *P. vivax*, and *P. malariae*) are responsible for most severe diseases. Malaria is still a common cause of death, particularly in tropical countries. (+)-7-bromotryptargine (100), a β-carboline, originally isolated from the skin of African frog *Kassina senegalensis* was later isolated from the DCM/MeOH extract of Australian marine sponge *Ancorina sp*. Compound (+)-7-bromotryptargine (100) displays IC$_{50}$ of 5.41 μM (Dd2) and 3.51 μM (3D7) against chloroquine-resistant (Dd2) and chloroquine-sensitive (3D7) strains of *Plasmodium falciparum* (Davis et al. 2010). (S)-Curcuphenol (101) and 15-hydroxycurcuphenol (102) was isolated from the Jamaican sponge *Didiscus oxeata*. Compounds (S)-curcuphenol (101) and 15-hydroxycurcuphenol (102) exhibited antimalarial activity with MIC values of 3.6 and 3.8 μg/mL, respectively, against *Plasmodium falciparum* (D6 clone; El Sayed et al. 2002).

Ascosalipyrrolidinone A (103) is an alkaloid isolated from the obligate marine fungus *Ascochyta salicornia* which showed IC$_{50}$ of 736 ng/mL against K1 (Thailand; resistant to chloroquine and pyrimethamine) and 378 ng/mL against NF 54 (an airport strain of unknown origin; susceptible to standard antimalarials; Osterhage et al. 2000). Bielschowskysin (104) is highly oxygenated diterpenoid isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos*. It exhibits antimalarial activity against *Plasmodium falciparum* (Marrero et al. 2004). Gracilioethers A–C (105–107) isolated from the marine sponge *Agelas gracilis* showed good antimalarial activities (IC$_{50}$ 10 μg/mL, 0.5 μg/mL, and 10 μg/mL, respectively) against *Plasmodium falciparum*. In addition, gracilioether B (106) inhibited the growth of *Leishmania major* (68% at 10 μg/mL; Ueoka et al. 2009).

NP, heptyl prodigiosin (111), isolated from a culture of α-proteobacteria from a marine tunicate, exhibits antimalarial activity against the chloroquine-sensitive strain *Plasmodium falciparum* 3D7 similar to quinine (Lazaro et al. 2002). Lepadins are decahydroquinoline alkaloids showing significant and selective antiplasmodial and antitrypanosomal activities. Lepadin D (112) has an IC$_{50}$ of 6.169 μg/mL, whereas lepadin E (113) and lepadin F (114) show IC$_{50}$ 0.4 μg/mL and 208 ng/mL, respectively, against *P. falciparum’s* clone K1.

Plakortide F (115), antimalarial principle from Caribbean sponge *Plakorti ssp.*, exhibited IC$_{50}$ of 480 ng/mL against *P. falciparum* (D6 clone) and 390 ng/mL against *P. falciparum* (chloroquine-resistant W2 clone) in vitro (Gochfeld and Hamann 2001). Pycnidione (116) is a small tropolone first isolated from the fermentation of *Phoma sp.* (Harris et al. 1993) and from the fermented broth of *Theissenia rogersii* 92031201 (Hsiao et al. 2012). Pycnidione (116) exhibited activities against *Plasmodium falciparum* in the sub-micromolar (μM) range (Wright and Lang-Unnasch 2005). Marine cyanobacterium-derived NP, symplestinate-4 (117) possesses significant antimalarial activity (ED$_{50}$ of 74 nM against *Plasmodium falciparum*, strain 3D7; Figure 10.10).

10.4.5 Antiviral Activities

Echrebsteroid C (118), a steroid obtained from South China sea gorgonian *Echinogorgia rebekka*, exhibits promising antiviral activity against respiratory syncytiat virus with an IC$_{50}$ of 0.19 μM (Cao et al. 2014). Marine NPs purpurquinone B (119) and purpurester A (120) are antiviral compounds from marine fungus. Purpurester A (120) has been isolated.
Production of Life-Saving Drugs from Marine Sources

FIGURE 10.10
Chemical structures of antimalarial agents.
(Continued)
from ethyl acetate extract of *Penicillium purpurogenum JS03-21*. Purpurquinone B (119) and purpurester A (120) demonstrate significant antiviral activity with IC$_{50}$ values of 61.3, 64.0, and 85.3 µM, respectively, against influenza virus H1N1 (Wang et al. 2011). A hydroanthraquinone derivative, tetrahydroaltersolanol C (121), and an alterporriol-type anthranoid dimer, alterporriol Q (122), were purified from microbial culture as well as mycelia of *Alternaria sp.* ZJ-2008003, a fungus growing on a soft coral *Sarcophyton sp.* Tetrahydroaltersolanol C (121) and alterporriol Q (122) exhibited antiviral activity with an IC$_{50}$ of 65 and 39 µM, respectively, against the porcine reproductive and respiratory syndrome virus (PRRSV; Zheng et al. 2012). Oxazole-containing alkaloid (−)-hennoxazole A (123) was isolated from *Polyfibrospongia sp.* sponge showed activity against herpes simplex virus type 1 (IC$_{50}$ 0.6 µg/mL; Ichiba et al. 1991). Halovir A–E (123–127), isolated from the marine fungus *Scytidium sp.* sourced from the Caribbean seagrass *Halodule wrightii*, have shown potent antiviral activity against HSV-1 and HSV-2. Halovirs A, B, C, D, and E showed ED$_{50}$ of 1.1, 3.5, 2.2, 2.0, and 3.1 µM, respectively, when added to cells infected with HSV-1 for 1 h (Rowley et al. 2003). Clathsterol (128) isolated from the Red Sea sponge *Clathria sp.* showed inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) at a concentration of 10 µM (Rudi et al. 2001). Microspinosamide (129) a cyclic depsipeptide was obtained from marine sponge *Sidonops microspinosa* collected from Indonesia. Compound 129 inhibited HIV-1 interactions with EC$_{50}$ of 0.2 µg/mL in an in vitro XTT-based assay (Rashid et al. 2001). Antiretroviral agents thalassiolin A–C (130–132) were isolated from the Caribbean seagrass *Thalassia testudinum*, as that showed RT and protease inhibition. Thalassiolin A (130) was most active, inhibiting the integrase terminal cleavage (IC$_{50}$ 2.1 mM) and strand transfer (IC$_{50}$ 0.4 mM) activities (Rowley et al. 2002). Papuamide A (133) is marine derived cyclic depsipeptides having cytoprotective activity against HIV-induced T cell death (Andjelic et al. 2008). Polycitone A (134), an aromatic alkaloid isolated from the ascidian *Polycitor sp.*, displayed significant inhibitory activity against RT of HIV, retrovirus B, and retrovirus C (Loya et al. 1999). A new polycyclic bromoindole alkaloid dragmacidin F (135) was isolated by Cutignano and collaborators from the Mediterranean sponge *Halicortex sp.* (Cutignano et al. 2000). It shows weak inhibition of herpes simplex virus (HSV-1) infected cells from HSV-induced destruction (IC$_{50}$ 95.8 µM) and furthermore delays syncytia formation by HIV-2 (IC$_{50}$ 0.91 µM). Neamphamide A (136) was isolated as the principle active constituent against HIV-1 infection from marine sponge *Neamphius huxleyi*. Cytopathic effect of HIV-1 infection was inhibited efficiently by neamphamide A (136) with EC$_{50}$ of 28 nM in an XTT-based cell viability assay using HIV-1RF infected human cell line CEM-SS (Oku et al. 2004; Figure 10.11).
Production of Life-Saving Drugs from Marine Sources

Echresteroid C (118)

Purpurester A (120)

Tetrahydroaltersolanol C (121)

Alterporriol Q (122)

(-)-Hennoxazole A (123)

Halovir A (124)

Halovir B (125)

Halovir C (126)

Halovir D (127)

Clathsterol (128)

FIGURE 10.11
Chemical structures of natural antivirus agents from marine source.  (Continued)
FIGURE 10.11 (Continued)
Chemical structures of natural antivirus agents from marine source.
The management of inflammatory processes correlates with prostaglandin (PG), interleukin (IL), leukotrienes (LT), nitric oxide (NO), and tumor necrosis factor-α (TNF-α) inhibition. These mediators are released and play a crucial role in progression of inflammation. Inflammation is directly related to rheumatoid arthritis, septic shock, psoriasis, and asthma.

Inhibition of LPS (lipopolysaccharide), stimulated production of inducible nitric oxide synthase (iNOS) protein, and NO-2 (Nitrite) were observed in RAW264.7 cells and primary macrophages, preincubated with 11-oxoaerothionin (137). Inflammatory cytokines and PGE2 as well as expressions of NO2 and iNOS were suppressed by 11-oxoaerothionin (Ivo de Medeiros et al. 2012). Coscinolactams A (138) and B (139) are two novel nitrogen-containing cheilanthane sesterterpenoids isolated from marine sponge Coscinoderma matthewsi that showed moderate inhibitory activity against PGE2 and NO production (De Marino et al. 2009). A new lactone, penicillinolide A (140), isolated from the organic extract of Penicillium sp. SF-5292, suppressed suppresses the expression of iNOS, COX-2, and TNF-α, as a result inhibition in the production of NO and PGE2 occurred (Lee et al. 2013). Anti-PLA2 NPs, scalaradial (141), a 1,4-dialdehyde marine terpenoid which was isolated from the sponge Cacospongia mollior (Monti et al. 2007), has selectively inhibited type II phospholipase A2 (PLA2; IC50 0.07 μM; Marshall et al. 1994), as well as bee venom PLA2 with an IC50 of 0.07 μM (de and Jacobs 1991). Tanzawaic acid A (142) and D (143), isolated from Penicillium sp. (SF-6013), suppressed NO production with IC50 of 37.8 and 7.1 μM, respectively. Moreover, tanzawaic acid A (142) also inhibited LPS-stimulated NO production in murine macrophages (RAW264.7) with an IC50 of 27.0 μM. These inhibitory effects are associated with the inhibition of LPS-stimulated expression of iNOS and cyclooxygenase-2 (COX-2) in RAW264.7 and BV2 cells (Quang et al. 2014). Cyclic depsipeptides halipeptins A (144) and B (145) demonstrated significant reduction in vivo anti-inflammatory activity via intraperitoneal dose of 0.3 mg/Kg in mice (60% reduction of carrageenan induced edema; Randazzo
et al. 2001). Splenocin B (146) a nine-membered bis-lactone isolated from *Streptomyces sp.* (California) showed suppression of cytokine production with minimal mammalian cell cytotoxicity (Strangman et al. 2009). Pyrenocine A (147), derived from marine fungus *Penicillium paxilli* Ma(G)K, was able to inhibit inflammatory cytokinase, PGE2, and nitrite production consequently exhibiting deactivation of LPS-induced macrophage. Moreover, pyrenocine A (147) also inhibited the LPS-stimulated expression of genes related to NFκB-mediated signal transduction on macrophages (Toledo et al. 2014). Scytonemin (148) a yellow–green pigment isolated from the extracellular sheath of cyanobacteria *Stigonema spp.* (Proteau et al. 1993) showed remarkable inhibition of the anti-inflammatory drug target IκB kinase (Stevenson et al. 2002). *Octocorallia* (octocoral) derived eunicol (149) and fuscol (150; Kerr et al. 2014), and *P. foliascens* derived foliasponggin (151; Kikuchi et al. 1983) are anti-inflammatory terpenes.

Manoalide (152; Glaser and Jacobs 1986) and related marine sesterterpenoid cladocoran-A (153) imparted anti-inflammatory properties by inactivation of human group IIA PLA2 (Monti et al. 2011). Luffariellolide (154), a sesterterpene, first isolated in 1987 from Palauan sponge *Luffariella sp.* (Albizati et al. 1987) showed potent in vivo anti-inflammatory activity through partially reversible inhibition of PLA2. Luffariellolide (154) and related NPs, like manoalide, do not interact with the active site instead react at the surface of PLA2 with lysine residue, thereby destroying the ability that moves across the membrane. *Euryspongia n. sp.* collected in Vanuatu afforded two steroids, petrosterol (155) and 3β-Hydroxy-24-Norchol-5-En-23-Oic acid (156; Mandeau et al. 2005) which exhibited anti-inflammatory activity against 6-keto-PGF1 release in a human keratinocyte cell line HaCaT.

Two dendalone, 3-hydroxybutyrate (157) and flexibilide (158) or sinularin isolated from dictyoceratid sponge and soft coral, respectively (Buckle et al. 1980), and a cyclic heptapeptide, cyclomarin-A (158) isolated from cultured marine bacterium *Streptomyces sp.* (Renner et al. 1999) were active after oral administration in in vivo animal models of inflammation. Pseudopterosin A (159), diterpene marine NPs isolated from the marine gorgonian *Pseudopterogorgia elisabethae* inhibits phagocytosis (Moya and Jacobs 2006) and reduced phorbol myristate acetate (PMA) induced mouse ear edema (Figure 10.12).

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**FIGURE 10.12**
Chemical structures of anti-inflammatory marine natural products. (Continued)
FIGURE 10.12 (Continued)
Chemical structures of anti-inflammatory marine natural products.
10.6 Anticoagulants

Heparin is a sulfated glycosaminoglycan (GAG) widely used in anticoagulant therapy. GAGs have the potential to be an alternative source of heparin. Crude and purified samples GAGs isolated from marine bivalve Donax faba of 58 and 114 USP units/mg correspondingly in D. faba exhibited anticoagulant activity (Periyasamy et al. 2013). GAGs from marine polychaete (Nereis sp.) showed the anticoagulant activity of the 58 USP units/mg from crude, whereas purified samples showed activity of 114 USP units/mg (Singh et al. 2013). Sargahydroquinoid acid (SHQA; 160) and sargaquinoic acid (SQA; 161) demonstrated strong inhibition of collagen-induced platelet aggregation in both in vitro and in vivo studies (Park et al. 2013). Marine antithrombotic peptides dysinosin A, B, C, and D (162–165), isolated from sponge Lamellodysidea chlorea, were found to suppress blood coagulation cascade serine proteases factor VIIa and thrombin by binding to factor VIIa and thrombin proteases (Carroll et al. 2002). Oscillarin (166) was isolated from the algal cultures of Oscillatoria agardhii (strain B2 83), its previously assigned structure was later corrected by Hanessian et al (2004). It interacted with human α-thrombin producing anti-thrombotic effect (Wu et al. 2009).
New marine NPs clavadines A (167) and B (168) were isolated from sponge *Suberea clavata*. Compounds 167 and 168 inhibited serine protease Factor XIa (FXIa) with IC$_{50}$ of 1.3 and 27 µM, respectively (Buchanan et al. 2008).

Diterpenes pachydictyol-A (169), isopachydictyol-A (170), and dichotomanol (171) are promising anticoagulant and platelet aggregation molecules isolated from the Brazilian marine alga *Dictyota menstrualis*. Dichotomanol (171) inhibited collagen and ADP-induced aggregation in platelet-rich plasma with IC$_{50}$ of 0.31 mM and 1.06 mM, respectively, whereas pachydictyol-A/isopachydictyol-A (0.18–0.7 mM) inhibited collagen (IC$_{50}$ 0.12 mM) and thrombin (IC$_{50}$ 0.25 mM) induced aggregation on washed platelets (de Andrade Moura et al. 2014; Figure 10.13).

FIGURE 10.13
Chemical structures of marine anticoagulant compounds. (Continued)
SQA (161), also known as aleglitazar, reached phase III of clinical trials for the treatment of type-2 diabetes but was withdrawn due to its serious side effects such as bone fractures, heart failure, and gastrointestinal bleeding (Younk et al. 2011). SQA (161) and SHQA (160) increased adipocyte differentiation suggesting that these PPAR α/γ dual agonists may increase insulin sensitivity through adipogenesis regulation (Kim et al. 2008). A good deal of investigation has been performed in search of potential α-glucosidase and α-amylase inhibitors from natural sources. Mangrove endophytic fungus Aspergillus sp. 16-5B yielded aspergifuranone (172) which displayed significant inhibitory activity α-glucosidase with IC\textsubscript{50} of 9.05 ± 0.60 µM (Liu et al. 2015). Two new lumazine-containing peptides terrelu-mamides A (173) and B (174) were purified from microbial culture of the marine-derived fungus Aspergillus terreus. These compounds improved insulin sensitivity in an adipogenesis model using human bone marrow mesenchymal stem cells (You et al. 2015). Biologically active polyphenol compounds exhibited multiple antidiabetic effects. Fucodiphloroethol G (175), dieckol (176), 6,6'-bieckol (177), 7-phloroeckol (178), and phlorofucofuroeckol A (179) were isolated from edible marine brown alga Ecklonia cava. Dieckol (176) showed significant inhibitory activities with IC\textsubscript{50} of 10.8 µmol/L and 124.9 µmol/L with α-glucosidase and α-amylase, respectively (Lee et al. 2009; Lee and Jeon 2013). Bromophenols display their hyperglycemic effects by multiple mechanisms principally inhibiting the activities of proteins tyrosine phosphatase 1B and α-glucosidase (Lin and Liu 2012).

Two unsaturated fatty acids 7(Z)-octadecenoic acid (180) and 7(Z),10(Z)-octadecadienoic acid (181) were obtained from sea cucumber Stichopus japonicus with strong α-glucosidase inhibitory activity. Compound 180 showed α-glucosidase inhibitory activity with IC\textsubscript{50} of 0.51 and 0.49 µg/mL, whereas compound 181 exhibited IC\textsubscript{50} of 0.67 and 0.60 µg/mL against Saccharomyces cerevisiae α-glucosidase and Bacillus stearothermophilus α-glucosidase, respectively (Nguyen et al. 2011). Diphlorethohydroxycarmalol (182), previously isolated from the
marine brown alga *Ishige okamurae*, a potent inhibitor of \(\alpha\)-glucosidase as well as \(\alpha\)-amylase enzymes (IC\(_{50}\) 0.16 and 0.53 nM, respectively) alleviated postprandial hyperglycemia in diabetic mice (Heo et al. 2009).

A sesquiterpene, dysidine (183), isolated from marine sponge *Dysidea villosa* inhibited human protein phosphatase 1B (IC\(_{50}\) 6.70 \(\mu\)M) as well as activated glucose uptake and glucose transporter-4 translocation (Li et al. 2009; Zhang et al. 2009). Albidopyrone (184), produced by *Streptomyces* sp. NTK 227, has moderate inhibitory activity against protein tyrosine phosphatase B (Hohmann et al. 2009). The O-Me nakafuran-8-lactone (185) isolated from marine sponge *Dysidea sp.* has good inhibitory activities for protein tyrosine phosphatase IB (Shao et al. 2006; Guo et al. 2007). Lukianol B (186), a pyrazine alkaloid, was isolated from tunicate showed aldose reductase inhibitory activity (Manzanaro et al. 2006; Figure 10.14).

![Chemical structures](image)

**FIGURE 10.14**
Naturally occurring antidiabetic compounds from marine source. (Continued)
10.8 Autoimmune Disorder

Many MNP are active drugs for immunomodulating activities. They exert immune modulation by either activation or suppression of immune responses, thus representing invaluable leads in the drug discovery. Autoimmune diseases are basically treated with medication that suppresses the immune response. All immune response occurs as a consequence of some impaired immune response. Many autoimmune diseases have already been recognized, mainly type-1 diabetes, asthma, arthritis, and obesity. Moreover, immunosuppressant therapy has made organ transplantation possible. Autoimmune disorders are managed by alleviation of inflammation by activation of anti-inflammatory genes. This section will cover compounds with promising IL suppression activity.

Splenocins displayed potent suppression of cytokine, exhibited minimal mammalian cell cytotoxicity, as well as inhibited the production of T Helper 2 (TH2) cytokines IL-5 and IL-13. These molecules showed significant antiasthmatic activity in an in vivo mouse model of allergen-induced TH2 splenocyte cytokine production characteristic of allergic asthma. Strangman et al, isolated splenocin B (187) from the marine bacterium *Streptomyces species* CNQ431. Splenocin B (187) inhibited antigen induced IL-5 by approximately 85% compared to the levels of OVA-stimulated control splenocytes (Strangman et al. 2009).

Thalassospiramide A (188) and B (189) are cyclic peptides isolated from marine α-proteobacterium *Thalassospira*. The compounds were screened for inhibition of cytokine IL-5 which plays an important role in TH2-mediated diseases like asthma. Thalassospiramides A (188) and B (189) showed IC$_{50}$ of 10 and 5 µM, respectively, without any observable cytotoxicity at 10 µM (Oh et al. 2007). Verrucarin A (190), isolated from culture broth of *Myrothecium roridum*, inhibited PMA-stimulated IL-8 production in HL-60 cells (Oda et al. 2005; Figure 10.15).
10.9 Neuroprotective

Progression of neurodegenerative disease can be slowed by inhibition of glycogen synthase kinase-3 (GSK-3β), cyclin-dependent kinase-5 (CDK-5), and cdc2-like kinases (CLKs). Many of marine NPs are recognized to inhibit mammalian kinases. Several potent, selective, and structurally novel candidates having mammalian neurological activity have been isolated from marine sources.

Hymenialdisine (191), a sponge-derived brominated pyrrole isolated from marine sponges of the genera Hymeniacidon, Acanthella, Axinella, and Pseudaxinyssa (Nguyen and Tepe 2009), inhibited GSK-3, casein kinase 1 (CK1), and cyclin-dependent kinases (CDK 1 and 5) and consequently suppressed hyperphosphorylation of microtubule-associated protein (MAP)-1B and tau. Compound 191 exerted its effect by interacting with the ATP binding pocket of CDK2 (Meijer et al. 2000). A related compound leucettamine B (192) derived from the Palauan sponge Leucetta microraphis also inhibited cyclin-dependent kinases (Chan et al. 1993; Watanabe et al. 2000). An indole alkaloid, indirubin (193), has also been

![Image of chemical structures of immunoprotective marine natural products.](image-url)
identified as an inhibitor of GSK-3, CDK5, and P25 that are involved in abnormal tau phosphorylation in Alzheimer’s disease (Leclerc et al. 2001). Palinurin (194), a sponge-derived sesterterpene, inhibited both GSK-3α and GSK-3β, and related compounds ircinin-1 and ircinin-2 inhibited GSK-3β (Bidon-Chanal et al. 2013).

Another strategy for treating a neurodegenerative disease is the inhibition of β-site amyloid precursor peptide cleaving enzyme type 1 (BACE1) because this enzyme hydrolyzes amyloid precursor peptide to β-amyloid peptide, a causative agent of Alzheimer’s disease. As a result of screen for BACE1 inhibitors from marine extracts, tasiamide B (195), a linear depsipeptide of cyanobacterial origin (Liu et al. 2012) and other compound bastadin-9 (196) have been identified (Wu et al. 2008; Williams et al. 2010; Figure 10.16).

**FIGURE 10.16**
Chemical structures of neuroprotective marine natural products.

10.10 Conclusions
The future of drug development from marine sources looks very optimistic as the number of new metabolite with interesting biological activities are continuously increasing along with several related designer molecules with improved pharmacological profile. Total synthesis, semisynthesis, and cultured production of marine compounds have given a new hope toward the development of marine NPs as drugs in the near future.
The clinical development of marine NPs is mainly focused on the treatment of cancer. Conjugation of a potential cytotoxic molecule with a tumor-specific antibody has given a new approach toward the development of a targeted therapy for the treatment of cancer. A number of ADCs have been tested in clinical trials for the better management of cancer patients.

This chapter presents an account of eight approved drugs, six compounds in clinical trial for different types of cancer, and one for Alzheimer’s disease. Additionally, 183 compounds of marine origin have been discussed in this chapter, which hold new opportunities for the treatment of life-threatening diseases such as diabetes, blood disorders, inflammation, autoimmune disorders, neurological disorders, and some of the compounds exhibited promising antifungal, antituberculosis, anthelmintic, antiprotozoal, and antiviral activities.

In spite of the large number of marine NPs and related compounds in clinical and preclinical pipeline, a large portion of ocean is still unexplored. Despite many natural chemicals of potential economic importance, a large portion still awaits exploration of useful pharmaceutical activity from marine organisms. High throughput screening methods and mechanism-based biological assays have steadily improved the success rate of getting hit. The detailed knowledge of the mechanism of a disease has yielded several targets for target-based drug discovery. A metabolite identified in a marine organism may or may not be produced by the organism itself. Many of them have been found to be produced by symbiotic microorganism. Efforts are ongoing to identify the real microbial source of bioactive agents to develop suitable fermentation technology to ensure continuous supply of therapeutic agents. New approaches are needed to identify the cell type that produces the metabolite. Furthermore, the identification of gene clusters responsible for the biosynthesis of the molecule of interest is important to revolutionize the production of drugs from marine sources.

Ocean has supported early development of life and now they are serving a great reservoir of new pharmacological entities. The biodiversity of ocean is tremendous but not immortal. Marine resources should be used with great wisdom otherwise some organisms will be viewed only in pictures. Synthetic procedures must be followed for the production of marine-related compounds. Preserving the beauty and diversity of marine life, we must go further forward toward the development of drugs.

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Production of Life-Saving Drugs from Marine Sources


