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REVIEW

Biologically Active Compounds from Marine Organisms†

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TOXINS

During the past 30 to 40 years, numerous novel compounds have been isolated from marine organisms and many of these have been reported to have biological activities, some of which are of interest from the point of view of potential drug development. On the other hand, some of the compounds pose potential risks to human health. In this latter category are the paralytic, diarrhetic and amnesic shellfish toxins.

From time to time, large concentrations of dinoflagellates occur in the sea, which because of their pigmentation, give the water a rusty-brown to red colouration. Such phenomena are known as 'red tides'. Some of the dinoflagellate species produce toxins, which concentrate in the flesh of filter feeders, such as shellfish, when they consume the dinoflagellates. In turn, when the shellfish are eaten by humans, severe toxic effects can result. The toxins are referred to as either paralytic or diarrhetic shellfish poisons. The former can prove fatal, but the latter, although producing very unpleasant effects, are not fatal.

The most well-known paralytic shellfish toxin is saxitoxin (Fig. 1), although other related compounds have been reported, such as neosaxitoxin, the 11-α and 11-β-*O*-sulphates of saxitoxin and neosaxitoxin, and carbonyl-*N*-sulphate derivatives of saxitoxin and neosaxitoxin (Faulkner, 1986). These compounds are produced from certain species of *Alexandrium* and *Gymnodinium. Ptychodiscus brevis* produces another class of paralytic shellfish toxins known as brevetoxins, the most potent of which is brevetoxin A (Fig.1). Of the diarrhetic shellfish toxins, the best known are the dinophysistoxins, for example dinophysistoxin 1 (Fig. 1), which are produced by *Dinophysis* species, such as *D. fortii* (Yasumoto *et al.*, 1985). Other compounds producing diarrhetic shellfish toxicity are the pectenotoxins (Fig. 1) (Lee *et al.*, 1989).

Because of the potential health hazards of paralytic and diarrhetic shellfish poisoning, monitoring programmes on shellfish toxicity have been introduced in many countries. For paralytic shellfish poisons, the methods include mouse tests as well as HPLC procedures (Nagashima *et al.*, 1989; Oshima *et al.*, 1989). For diarrhetic shellfish toxins, methods include bioassays, immunoassays and physicochemical methods (Fremy *et al.*, 1999).

Whereas both paralytic and diarrhetic shellfish toxins are produced by dinoflagellates, amnesic shellfish poisoning results from the ingestion of shellfish contaminated with diatoms. In 1987, over 100 cases of poisoning, including three fatalities, were recorded for eastern Canada as a result of people eating infected mussels. The toxic compound was shown to be domoic acid (Fig. 1), produced by the diatom *Pseudonitzschia pungens* forma *multiseries*. The effects of domoic acid poisoning include gastrointestinal symptoms such as nausea, vomiting, anorexia, gastric bleeding, diarrhoea and abdominal cramps, followed by neurological disorders such as confusion, disorientation, loss of short-term memory, coma and death (Lundholm *et al.*, 1994).

The ingestion of other marine organisms can also lead to serious poisoning. Well known examples include the potent neurotoxin tetrodotoxin, resulting from eating pufferfish, and ciguatoxin, associated with ingestion of tropical fish which have fed on the dinoflagellate, *Gambierdiscus toxicus*.

MARINE ORGANISMS AS POTENTIAL SOURCES OF DRUGS

Despite the very many compounds isolated from marine organisms and the biological activities attributed to many of them, those that have either been marketed or are under development are very few. An early candidate, contemplated for the production of prostaglandins, was the soft coral, *Plexaura homomalla*, which is a rich source of 15-*epi*-PGA_2 and its acetate, methyl ester derivative. These can be converted into PGE_2 and PGF_{2a} (Fig. 2), which at the time were the compounds in demand for prostaglandin research (Schneider *et al.*, 1973). However, subsequent synthetic routes to the desired prostaglandins thankfully rendered the widespread collection of *Plexaura* unnecessary.

There are probably several reasons why so few compounds originating from marine plants and animals have been developed as drugs. There is no doubt that much of the work undertaken in the 1960s, 1970s and probably the early 1980s was driven by an interest in the chemistry of new compounds rather than in their biological activities; many of the scientists involved would have scorned the thought of working on applied aspects of the subject. However, in order to maintain research funding, it became more and more necessary to link the chemistry of the new compounds with their

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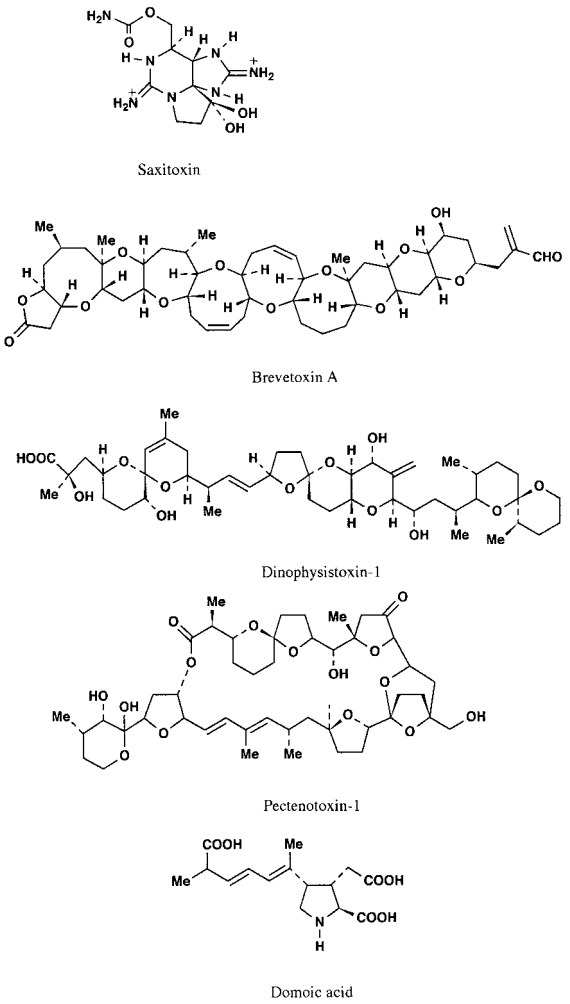

Figure 1. Examples of paralytic, diarrhetic and amnesic shellfish toxins.

biological properties. Much of the earlier work limited the biological testing to antimicrobial activity, but this was often extended later to testing for cytotoxic properties, which may provide useful leads for anticancer drugs. This latter area is the one that most of the compounds in various stages of clinical trials are located. Screening for other activities has, of course, also been undertaken, for example for antiviral, antiinflammatory, anticoagulant and antiparasitic compounds.

Many of the compounds shown to have promising biological properties have complicated chemical structures, the synthesis of which would be hard and expensive. The pharmaceutical industry is unlikely to consider development of a complex compound extracted from a marine organism, which is probably obtainable in comparatively small quantities and often from a relatively remote area. These organisms are valuable as sources of new biologically active chemical structures, but unless either the compounds or a derivative of them can be readily synthesized, they are of little commercial interest to the pharmaceutical industry.

In this review, the examples given of pharmacologically active compounds have been chosen to illustrate the range of structures reported and also the variety of marine animals and plants from which they have been isolated. It would be impossible in a limited survey to include all the

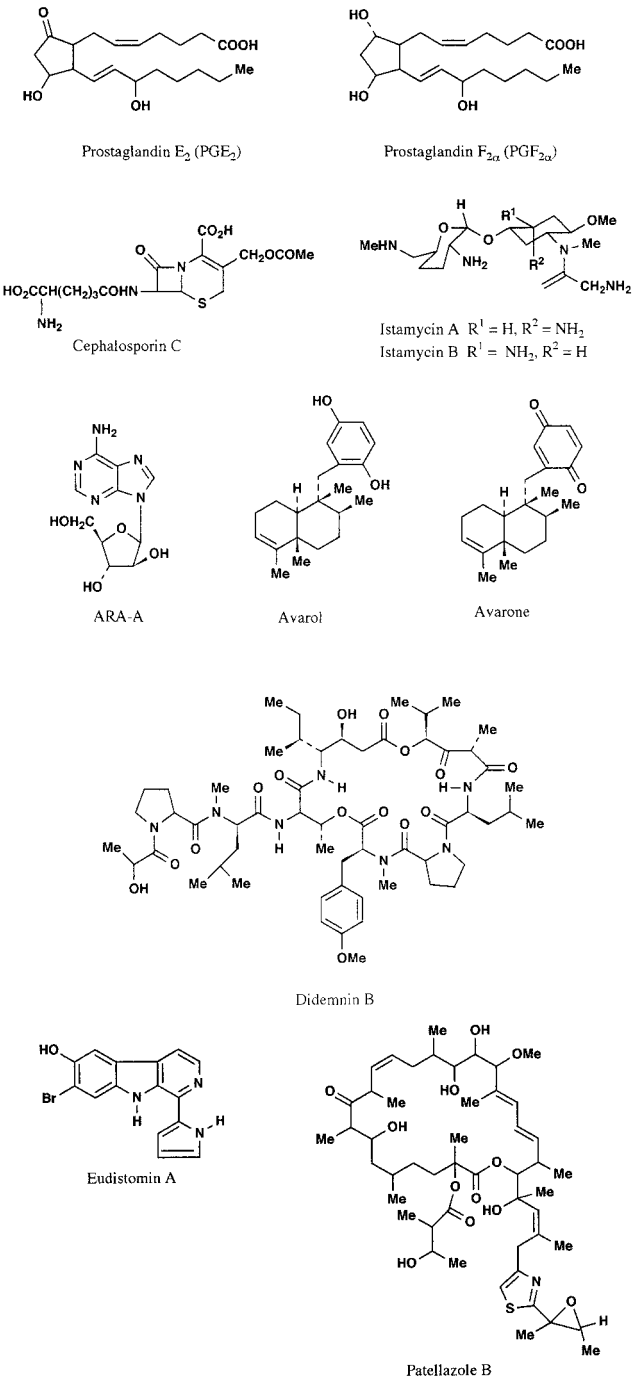

Figure 2. Prostaglandins; antimicrobial and antiviral compounds from marine organisms.

compounds considered to have significant biological activity. For detailed reviews see Faulkner (1998 and his previous reviews in this series).

ANTIMICROBIAL COMPOUNDS

The cephalosporins are good examples of drugs which owe their origin to a marine source. From the marine fungus, *Cephalosporium acremonium*, cephalosporin C (Fig. 2) was isolated. A semi-synthetic derivative of this, cephalothin sodium, has been widely used as an antibiotic drug.

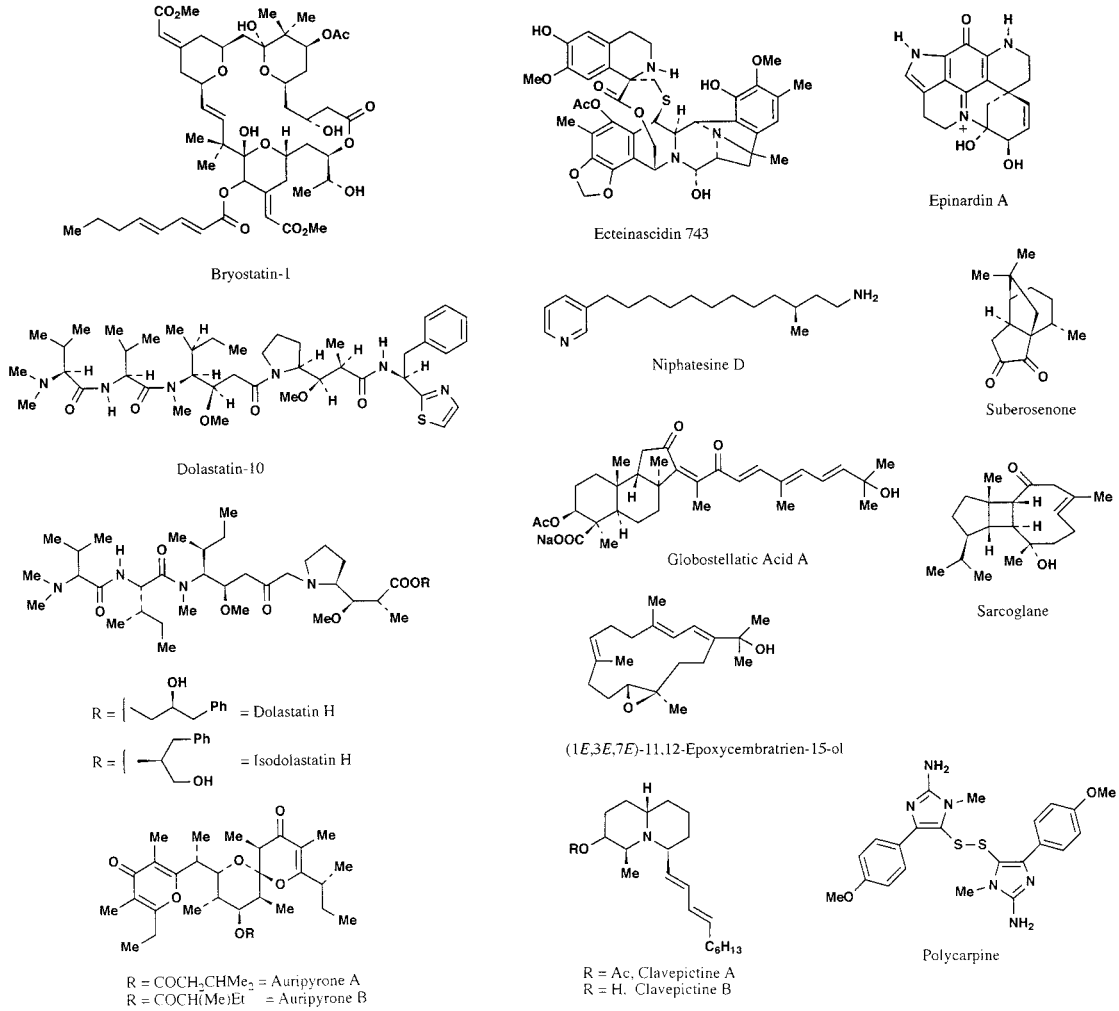

Figure 3. Cytotoxic compounds from marine organisms.

Marine microorganisms which can be grown in culture to yield valuable compounds would be of interest to the pharmaceutical industry. Examples of compounds which have been obtained by fermentation are the istamycins (Fig. 2), produced by the marine actinomycete *Streptomyces tenjimariensis* SS-939. These compounds were reported to have *in vitro* activity against both Gram-negative and Gram-positive bacteria, including those with known resistance to the aminoglycoside antibiotics (Okami *et al*., 1979).

ANTIVIRAL COMPOUNDS

Many papers have been published which give the results of the screening of marine organisms for antiviral activity and a wide range of active compounds has been isolated and characterized (Rinehart *et al.*, 1993). However, the only compound reported to have significant therapeutic activity is ara-A (Fig. 2), which is a semi-synthetic substance based on the arabinosyl nucleosides isolated from the sponge *Tethya crypta*.

Compounds reported to have antiviral properties include the didemnins, which are cyclic depsipeptides isolated from *Tridemnum* species (tunicates). Didemnin B (Fig. 2), as well as being antiviral, also shows pronounced antitumour activity.

Other antiviral compounds include avarol and avarone (Fig. 2), isolated from a sponge, *Disidea avara*. These compounds inhibit the immunodeficiency virus, have high therapeutic indices and the ability to cross the blood–brain barrier (Sarin *et al.*, 1987). Patellazole B (Fig. 2), isolated from the tunicate, *Lissoclinum patella* (Zabriskie *et al.*, 1988), has very potent *in vitro* activity against herpes simplex viruses. Another example of an antiviral compound isolated from a tunicate is eudistomin A (Fig. 2), which, along with related β-carbolines, was first isolated from *Eudistoma olivaceum* (Rinehart *et al.*, 1993).

CYTOTOXIC COMPOUNDS

Many of the compounds isolated from marine organisms have been tested for cytotoxicity in the search for drugs active against cancer. In this short account it is only possible to select a very few examples to illustrate the wide range of active substances. Detailed reviews have been published by Munro *et al.* (1987) and Schmitz *et al.* (1993).

Probably the best known of the compounds with

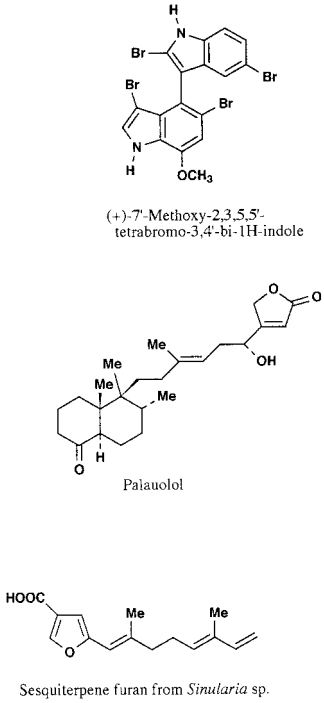

Figure 4. Antiinflammatory compounds from marine organisms.

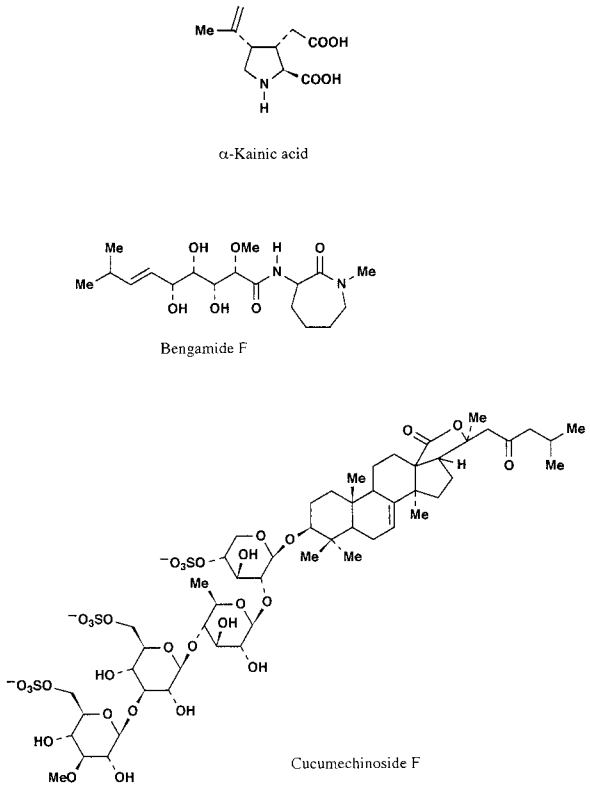

Figure 5. Antiparasitic compounds from marine organisms.

potential as anticancer drugs are the macrolides known as bryostatins, isolated primarily from the bryozoan, *Bugula neritina*, although some have been extracted from sponges and tunicates. Bryostatin-1 (Fig. 3) triggers activation and differentiation of peripheral blood cells from lymphocytic leukaemia patients. It also displays other activities such as the activation of protein kinase C and arachidonic acid metabolite release. Both bryostatin-1 and -2 enhance the efficiency of interleukin-2 in initiating the development of *in vivo* primed cytotoxic T-lymphocytes. Bryostatin-1 has undergone phase 2 clinical trials. Many other bryostatins have been isolated and bryostatins- 16, -17 and -18 have been reported to have antileukaemic activity (Petitte *et al.*, 1996).

A family of cyclic and linear peptides and depsipeptides known as dolastatins have been isolated from the sea hare, *Dolabella auricularia*. Dolastatin-10 (Fig. 3), when first reported, was claimed to be the most active neoplastic substance known (Pettit *et al.*, 1987). More recently, other dolastatins have been isolated and both dolastatin-H and isodolastatin-H (Fig. 3) have been shown to be highly cytotoxic (Sone *et al.*, 1996). Also cytotoxic are the polypropionates, auripyrone-A and -B (Fig. 3), which have also been extracted from *D. auricularia* (Suenaga *et al.*, 1996).

Extracts of the tunicate *Ecteinascidia turbinata* have been shown to increase dramatically the life span of mice inoculated with P 388 cells. The active compounds are complicated alkaloids called ecteinascidins. Ecteinascidin 743 (Fig. 3) has undergone phase 1 clinical trials as an anticancer agent (Faulkner, 1998).

Sponges have been a rich source of cytotoxic compounds. As well as the bryostatins, many of the other active compounds are macrolides. Examples of other cytotoxic compounds reported for sponges are the antineoplastic alkaloid niphatesine D (Fig. 3), which was extracted from a *Niphates* species (Kobayashi *et al.*, 1990); the epinardins (Fig. 3), isolated from an unidentified species (D'Ambrosio *et al.*, 1996); and the globostellatic acids A (Fig. 3) to D, which are isomalabaracane triterpene constituents of *Stelletta globostellata* (Ryu *et al.*, 1996).

Cytotoxic compounds isolated from coelenterates include the sesquiterpene, suberosenone (Fig. 3), extracted from *Subergorgia suberosa* (Bokesch *et al.*, 1996); the cembranoids from *Sinularia gibberosa* [(1 *E*, 3 *E*, 7 *E*)-11, 12-epoxycembratrien-15-ol is shown in Fig. 3] (Duh and Hou, 1996); and the diterpene, sarcoglane, from *Sarcophyton glaucum* (Fig. 3) (Fridkovsky *et al.*, 1996).

Examples of active compounds from tunicates are the cytotoxic alkaloids clavepictine-A and -B (Fig. 3), reported for *Clavelina picta* (Raub *et al.*, 1991) and the cytotoxic dimeric disulphide alkaloid polycarpine (Fig. 3), isolated from *Polycarpa clavata* (Kang and Fenical, 1996).

ANTIINFLAMMATORY COMPOUNDS

From the marine cyanobacterium, *Rivularia firma*, a series of bi-indoles was isolated, one of which (Fig. 4) was active in both the carrageenan-induced rat-paw oedema and kaolin rat-paw oedema tests. Unfortunately, the compound also displayed central nervous system activity. The alkaloid showed potential as a lead compound for the development of antiinflammatory drugs, but for various reasons, work ceased on the compound (Baker, 1984).

In more recent years, other interesting antiinflamma-

tories have been isolated from marine animals. Examples are the sesterterpene, palaulol (Fig. 4), from the sponge *Fascaplysinopsis* sp. (Schmidt and Faulkner, 1996) and a sesquiterpene furan (Fig. 4) from the coelenterate, *Sinularia* sp.; this has subsequently been synthesized (Williams and Faulkner, 1996).

ANTIPARASITIC COMPOUNDS

Digenia simplex, a red alga, has been used as a vermifuge for very many years. Its active component, α-kainic acid (Fig. 5), is marketed for the treatment of parasitic round worm, whip worm and tape worm. Marine animals have been tested as sources of antiparasitic compounds and this work has led to the isolation and characterization of, for example, bengamide F (Fig. 5) which has anthelmintic properties and cucumechinoside F (Fig. 5), from a sea cucumber (Miyamoto *et al.*, 1990) which has antiprotozoal activity. A review of this work has been published by Crews and Hunter (1993).

CONCLUSIONS

Although large numbers of novel compounds have been isolated from marine organisms and many of these substances have pronounced biological activity, only very few have been marketed as pharmaceutical products. A few have also been valuable as 'lead' compounds, which have led to derivatives of them being marketed. Some compounds with cytotoxic properties either have been or are undergoing various phases of clinical trial and thus have the prospect of being new pharmaceutical products. However, on balance, despite the major contributions to natural products chemistry, the wide array of compounds extracted from marine organisms has been disappointing as far as the development of new medicinal agents is concerned.

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