16

Biologically active compounds from marine organisms

G. Blunden

INTRODUCTION

When compared to land plants and animals, the use of marine organisms in folk medicine is very restricted, particularly outside Asia. Much use has been made of marine plants and animals for food but, probably because of their inaccessibility, serious consideration of these organisms as sources of biologically active compounds has been confined to the last 40 years or so. There are several well-known marine products that have been in use for many years, such as cod and halibut liver oils, spermaceti, protamine sulphate and the seaweed polysaccharides agar, carrageenan and alginic acid; all of these are covered elsewhere in this book.

Marine macroalgae, or seaweeds as they are more generally known, have been used as crude drugs in the treatment of iodine deficiency states, such as goitre, Basedow's disease and hypothyroidism. Some seaweeds have also been utilized as sources of additional vitamins and in the treatment of anaemia during pregnancy. They have also been taken for the treatment of various intestinal disorders, as vermifuges, and as hypocholesterolaemic and hypoglycaemic agents. This last property has been claimed for the seaweeds *Cystoseira barbata*, *Sargassum confusum* and *Jania rubens*, but the mechanisms involved in lowering blood sugar levels by the use of these algae are not known.

Seaweeds have been employed as dressings, ointments and in gynaecology. For example, *Porphyra atropurpurea* has been used in Hawaii to dress wounds and burns and *Durvillaea antarctica* was used by the Maoris of New Zealand to treat scabies. Prepared, sterilized stipes of *Laminaria digitata* have been utilized, in conjunction with prostaglandins, to dilate the cervix, as the stipes swell to several times their original diameter when moistened (B. Rubin, *Econ. Bot.*, 1977, **31**, 66).

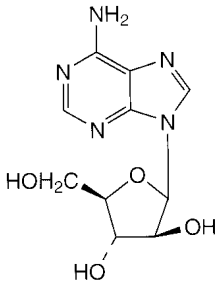
During the past 40 years, numerous novel compounds have been isolated from marine organisms and many of these substances have been demonstrated to possess interesting biological activities. To appreciate the range of compounds reported, the reviews by Faulkner should be consulted (*Nat. Prod. Rep. (R. Chem. Soc.)*, **16**, 113 and earlier reviews cited therein). However, much of this work has been motivated by an interest in the chemistry of the novel metabolites rather than in their biological activities. Often the compounds have been isolated in small amounts, which restricts the range of pharmacological evaluation. In some cases a much more extensive range of activities may have been tested for than those published, but because of their potential economic value, the data have not been reported.

CLASSES OF ACTIVE COMPOUNDS

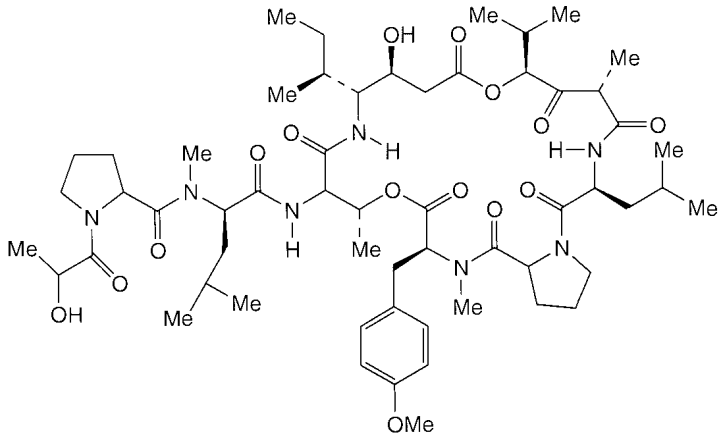
It is the intention in this chapter to illustrate the range of metabolites isolated from marine organisms, but concentrating on compounds of medical, biomedical, pharmaceutical and agricultural interest. The numbers in parentheses following the names of the compounds refer to the relevant chemical structures in Fig. 16.1.

ANTIVIRAL SUBSTANCES

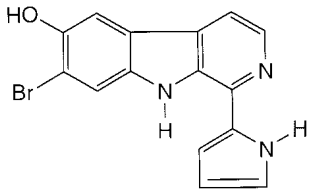
Drugs active against human viruses are in great demand and pharmaceutical companies, research institutes and academic groups have set up screening procedures in the search for such drugs. This work has been highlighted in the popular press by the worldwide AIDS epidemic. Not surprisingly, many marine organisms have been screened for the presence of compounds with antiviral activity, but the search has been disappointing and, to date, only one compound has been shown to



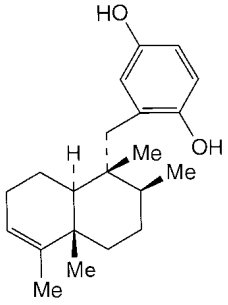
ARA-A (1)



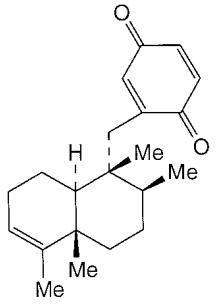
Didemnin B (2)



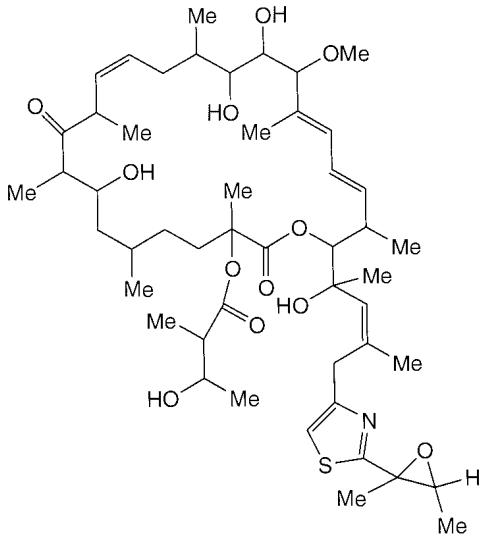
Eudistomin A (3)



Avarol (4)



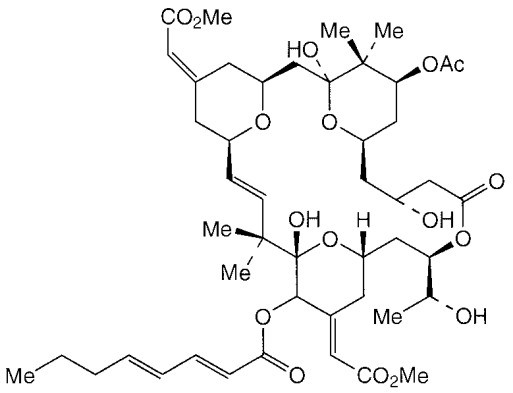
Avarone (5)



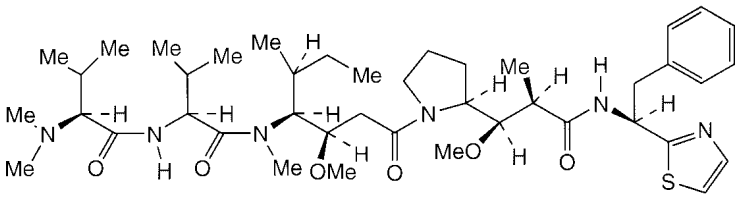
Patellazole B (6)

Fig. 16.1 Chemical structures of biologically active compounds from marine organisms.

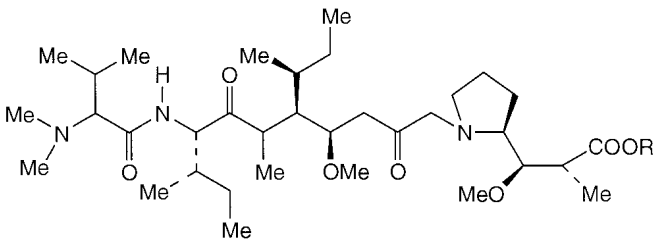
Fig. 16.1 (continued)

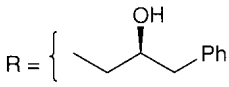


Bryostatin-1 (7)

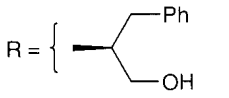


Dolastatin-10 (8)

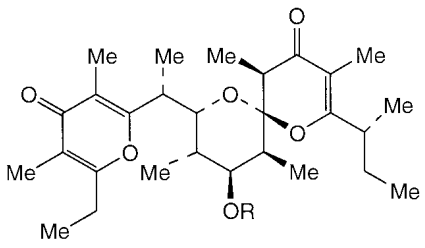




= Dolastatin-H (9)



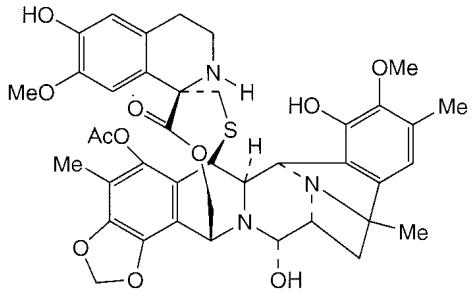
= Isodolastatin-H (10)



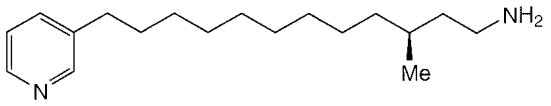
R = $COCH_2CHMe_2$ = Auripyrone-A (11)

R = COCH(Me)Et = Auripyrone-B (12)

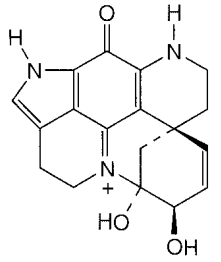
Fig. 16.1 (continued)



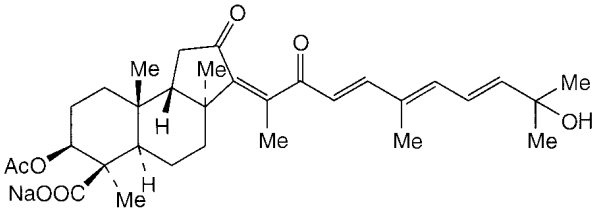
Ecteinascidin 743 (13)



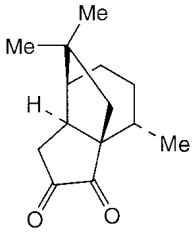
Niphatesine D (14)



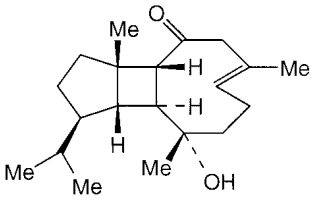
Epinardin A (15)



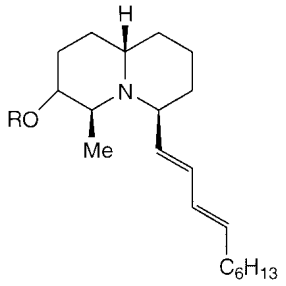
Globostellatic Acid A(16)



Suberosenone (17)

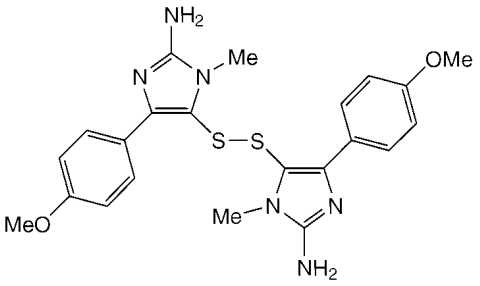


Sarcoglane (18)

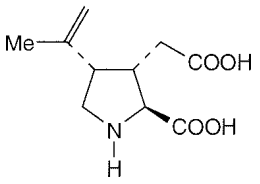


R = Ac, Clavepictine-A (19)

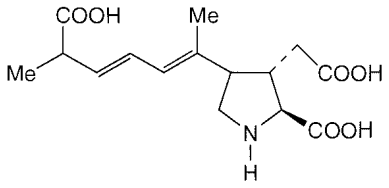
R = H, Clavepictine-B (20)



Polycarpine (21)

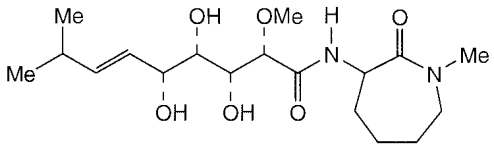


α-Kainic acid (22)

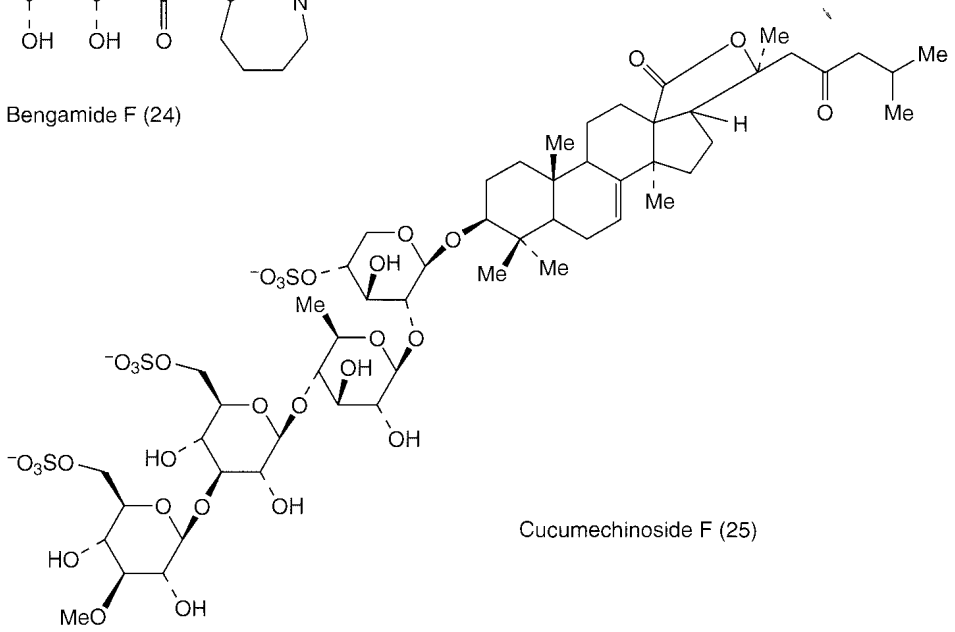


Domoic acid (23)

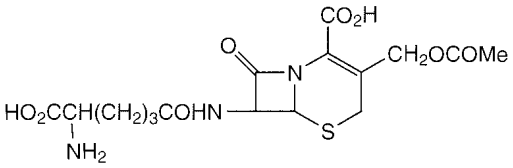
Fig. 16.1 (continued)



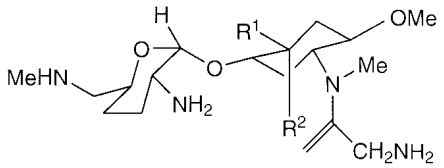
Bengamide F (24)



Cucumechinoside F (25)

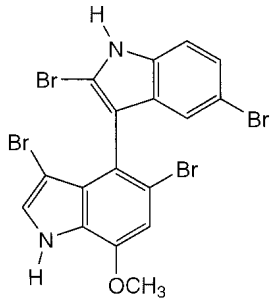


Cephalosporin C (26)

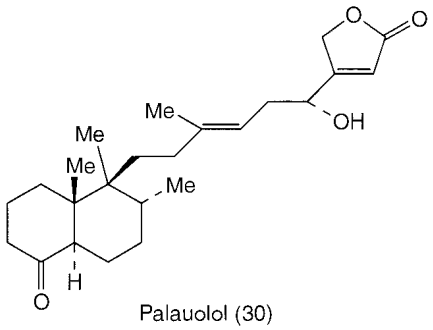


Istamycin A $R^1 = H$, $R^2 = NH_2$ (27)

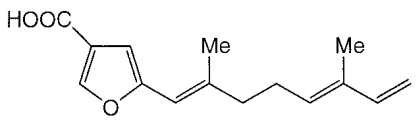
Istamycin B $R^1 = NH_2$, $R^2 = H$ (28)



(+)-7'-Methoxy-2,3,5,5'-tetra-bromo-3,4'-bi-1H-indole (29)

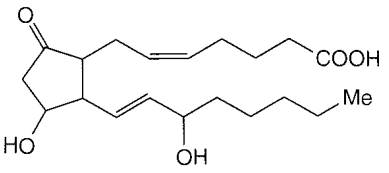


Palauolol (30)

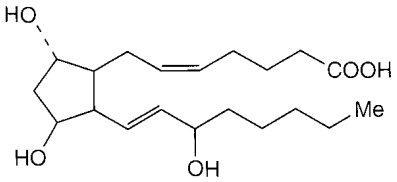


Sesquiterpene furan (31)

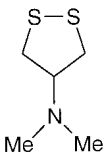
Fig. 16.1 (continued)



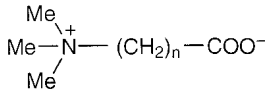
Prostaglandin E_2 (PGE_2) (32)



Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (33)



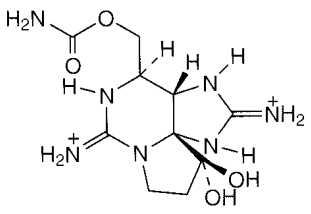
Nereistoxin (34)



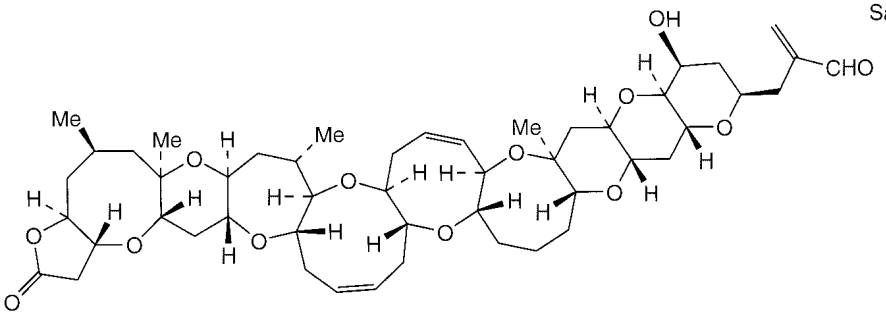
n = 1 = glycinebetaine (35)

n = 2 = γ-aminobutyric acid betaine (36)

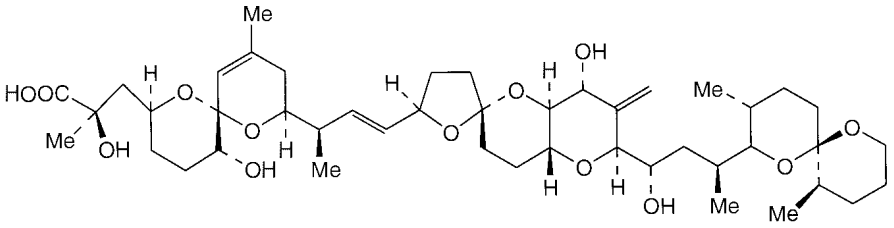
n = 3 = δ-aminovaleric acid betaine (37)



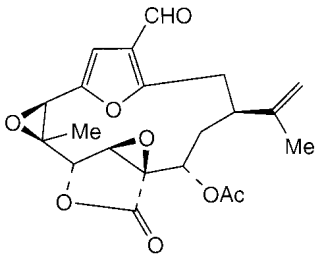
Saxitoxin (38)



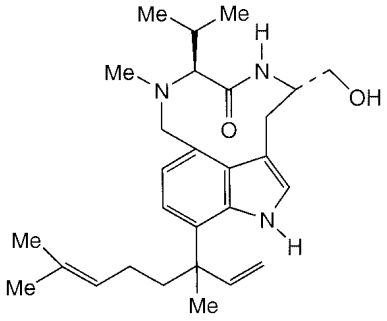
Brevetoxin A (39)



Dinophysistoxin-1 (40)

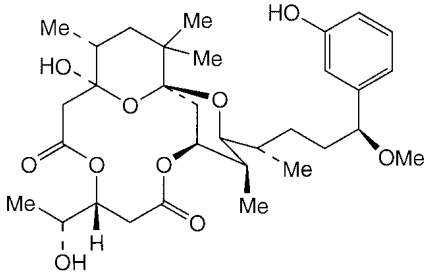


Lophotoxin (41)

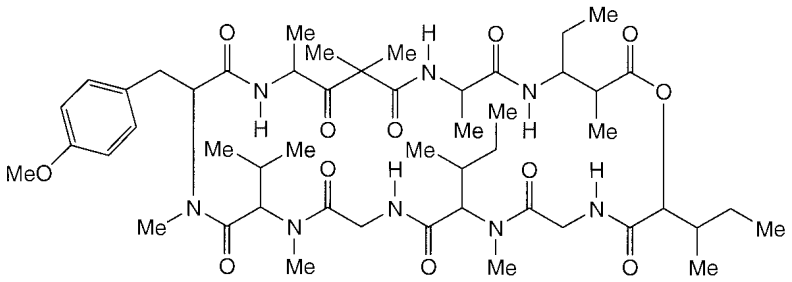


Lyngbyatoxin (42)

Fig. 16.1 (continued)



Debromoaplysiatoxin (43)



Majusculamide (44)

have significant therapeutic activity. This is ara-A (**1**), which is a semi-synthetic substance based on the arabinosyl nucleosides isolated from the sponge *Tethya crypta*. Several compounds isolated from marine organisms have been shown to have pronounced *in vitro* activity, but only the didemnins (**2**) have produced activity *in vivo*; these are cyclic depsipeptides isolated from *Tridemnum* species (tunicates). In addition to antiviral properties, some of the didemnins exhibit antitumour activity.

Other interesting compounds have been isolated, particularly from tunicates, sponges and gorgonians. The eudistomins (**3**), first isolated from *Eudistoma olivaceum* (family Polycitoridae), form a second family of compounds from tunicates with potent antiviral activity; these are β-carbolines.

The two compounds, avarol (**4**) and avarone (**5**), extracted from the sponge *Disidea avara*, have been reported to inhibit immunodeficiency virus, have high therapeutic indices and the ability to cross the blood–brain barrier. These compounds were thus proposed as having potential use in the treatment of AIDS (P. S. L. Sarin *et al.*, *J. Natl. Cancer Inst.*, 1987, **78**, 663).

Very potent *in vitro* activity against herpes simplex viruses was displayed by patellazole B (**6**), isolated from the tunicate *Lissoclinum patella*. A review of the range of antiviral substances reported from marine organisms has been published by K. L. Rinehart *et al.* (in *Marine Biotechnology*, 1993, Vol. 1, *Pharmaceutical and Bioactive Natural Products* (eds D. H. Attaway and O. R. Zaborsky), New York: Plenum Press, p. 309).

CYTOTOXIC COMPOUNDS

Not surprisingly, many marine organisms have been tested for cytotoxicity in the search for compounds active against cancer and numerous substances have been shown to possess such properties. It would not be appropriate to review this work here, but a few selected compounds have been chosen to illustrate the range of materials reported. (For reviews see M. H. G. Munro, R. T. Luibrand and J. W. Blunt, in *Bioorganic Marine Chemistry*, 1987, Vol. 1 (ed. P. J. Scheur), New York: Springer-Verlag, p. 93, and F. J. Schmitz, B. F. Bowden and S. I. Toth, in *Marine Biotechnology*, Vol. 1, *Pharmaceutical and Bioactive Natural Products*, 1993 (eds D. H. Attaway and O. R. Zaborsky), New York: Plenum Press, p. 197).

Probably the best known of the compounds are the group of macrolides known as bryostatins, which have been isolated primarily from the bryozoan *Bugula neritina*, although some have also been extracted from collections of sponges and tunicates. Many bryostatins have been isolated and characterized and shown to possess pronounced biological activity. The potential use of bryostatins for treating neoplastic bone-marrow-failure states has been suggested as a result of the compounds stimulating human haemopoietic cells. Bryostatin-1 (**7**) 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 (PKC) and arachidonic acid metabolite release. Both bryostatin-1 and -2 enhance the efficiency of interleukin-2 in initiating 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.

Cell growth inhibitory activity *in vitro* has been demonstrated by a group of cyclic and linear peptides and depsipeptides known collectively as dolastatins. These were first isolated from the sea hare *Dolabella auricularia*. At the time of publication, dolastatin-10 (**8**) was reported to be the most active antineoplastic substance known (G. R. Pettit *et al.*, *J. Am. Chem. Soc.*, 1987, **109**, 6883). More recently, other dolastatins have been isolated and both dolastatin-H (**9**) and isodolastatin-H (**10**) have been shown to be highly cytotoxic (H. Sone

et al., *J. Am. Chem. Soc*, 1996, **118**, 1874). Also cytotoxic are the polypropionates, auripyrone-A (**11**) and -B(**12**), which have also been isolated from *D. auricularia* (K. Suenaga, H. Kigoshi and K. Yamada, *Tetrahedron Lett.*, 1996, **37**, 5151).

Extracts of the tunicate *Ecteinascidia turbinata* were shown to increase dramatically the life-span of mice inoculated with P388 cells. The active compounds were characterized as a group of complicated alkaloids, which were called ecteinascidins. Ecteinascidin 743 (**13**) has undergone phase 1 clinical trials as an anticancer agent.

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 (**14**), which was extracted from a *Niphates* species (J. Kobayashi *et al.*, *J. Chem. Soc., Perkin Trans*, 1, 1990, 3301); the epinardins (**15**), isolated from an unidentified species (M. D'Ambrosio *et al.*, *Tetrahedron*, 1996, **52**, 8899); and the globostellatic acids (**16**), which are isomalabaracane triterpene constituents of *Stelletta globostellata* (G. Ryu, S. Matsunaga and N. Fusetani, *J. Nat. Prod.*, 1996, **59**, 512).

Cytotoxic compounds isolated from coelenterates include the sesquiterpene, suberosenone (**17**), extracted from *Subergorgia suberosa* (H. R. Bokesch *et al.*, *Tetrahedron Lett.*, 1996, **37** 3259), the diterpene sarcoglane (**18**), from *Sarcophyton glaucum* (E. Fridkovsky *et al.*, *Tetrahedron Lett.*, 1996, **37**, 6909) and the cembranoids from *Simularia gibberosa* (C-Y Duh and R-S Hou, *J. Nat. Prod.*, 1996, **59**, 595). Examples of active compounds from tunicates are the alkaloids clavepictine-A (**19**) and -B (**20**) isolated from *Clavelina picta* (M. F. Raub *et al.*, *J. Am. Chem. Soc.*, 1991, **113**, 3178) and the dimeric disulphide alkaloid polycarpine (**21**) from *Polycarpa clavata* (H. Kang and W. Fenical, *Tetrahedron Lett.*, 1996, **37**, 2369).

The didemnins, mentioned earlier under antiviral substances, have also been demonstrated to have pronounced antitumour properties and didemnin B has undergone clinical trials.

ANTIPARASITIC COMPOUNDS

The red alga, *Digenia simplex*, has been used as a vermifuge for hundreds of years. The active substance is α-kainic acid (**22**), which has been marketed for many years as a broad spectrum anthelmintic. It is effective against the parasitic round worm, the whip worm and the tape worm. Takeda Pharmaceutical Industries markets various preparations of the compound. A chemically related compound, domoic acid (**23**), also has anthelmintic properties; this has been isolated from the red algae *Chondria armata* and *Alsidium corallimum*.

Studies of marine animals as a source of antiparasitic agents led to the isolation and characterization of anthelmintic compounds from sponges, a nudibranch and a zoanthid. Interesting substances include bengamide F (**24**), which has been demonstrated to be effective *in vitro*. Another is cucumechinoside (**25**), isolated from a sea cucumber, which has antiprotozoal activity. For more information on these agents from marine animals see the review by P. Crews and L. M. Hunter in *Marine Biotechnology*, 1993, Vol. 1, *Pharmaceutical and Bioactive Natural Products* (eds D. H. Attaway and O. R. Zaborsky), New York: Plenum Press, p. 343.

ANTICOAGULANTS

Anticoagulant activity associated with polysaccharides from marine algae has been known for many years. The earliest report is from 1936 when an anticoagulant effect of a sulphated galactan from *Iridaea laminarioides* was recorded. Similar effects were demonstrated with carrageenans from *Chondrus crispus*, *Euchema spinosum* and *Polyides rotundus*. It was later shown that carrageenans had a direct effect on the *in vitro* inactivation of thrombin.

The anticoagulant effects of isolated fractions from the brown alga *Fucus vesiculosus* have been studied and an antithrombin effect was attributed to fucoidan. Evidence has been provided that the antithrombin effect of fucoidan is mediated through heparin cofactor II. Antithrombin activity associated with an unknown plasma factor has been reported for crude, aqueous extracts of the green alga *Codium fragile* ssp. *tomentosoides*. Another subspecies of *C. fragile* (ssp. *atlanticum*) yielded high molecular weight proteoglycans which possessed anticoagulant activity.

ANTIMICROBIAL AGENTS

Marine microorganisms have been studied as a source of biologically active substances and several compounds have been isolated and characterized which have been shown to possess antimicrobial activity. Of particular note is the fungus *Cephalosporium acremonium*, from which cephalosporin C (**26**) was isolated, a semi-synthetic derivative of which, cephalothin sodium, is widely used as an antibiotic drug. Other examples of antimicrobial compounds isolated from marine microorganisms are istamycins A (**27**) and B (**28**), which were produced by fermentation of the marine streptomycete, *Streptomyces tenjimariensis* SS-939. *In vitro* activity is observed against Gram-negative and Gram-positive bacteria, including those with known resistance to the aminoglycoside antibiotics.

A feature of many metabolites of marine organisms is the occurrence of halogens, in particular bromine. Many of these compounds exhibit antimicrobial activity, but are either not sufficiently potent or are too toxic, or both, to render them of clinical value.

ANTI-INFLAMMATORY COMPOUNDS

The sulphated polysaccharide carrageenan is used in several tests devised for the screening of anti-inflammatory drugs. The carrageenan-induced, non-immune inflammatory response, rat paw oedema assay is a standard model system for this purpose. Other test systems involving the use of carrageenan have been developed, including the infusion of the polysaccharide into the lungs of either mice or rats to produce a pleurisy-like reaction. Potential anti-inflammatory drugs are used in this system to determine the extent to which they alleviate the condition. Carrageenan has also been injected into the synovial fluid of animals to produce an arthritis-like model which can be used to test arthritis-specific anti-inflammatory drugs.

A series of novel bi-indoles was isolated from the marine cyanobacterium, *Rivularia firma*. One of the major compounds was (+)-7′-methoxy-2, 3, 5, 5′-tetrabromo-3, 4′-bi-1H-indole (**29**), which is active in both the carrageenan-induced rat paw oedema and kaolin rat paw oedema tests and also in central nervous system tests. There was promise in the isolated compound for development as a medicinally-useful product, but the company that was responsible for this work did not proceed with this compound.

In more recent years, other compounds with anti-inflammatory activity have been reported for marine organisms. Examples are the sesterterpene palauolol (**30**), from the sponge *Fascaplysinopsis* sp. (E. W. Schmidt and D. J. Faulkner, *Tetrahedron Lett.*, 1996, **37**, 3951) and a sesquiterpene furan (**31**) from the coelenterate, *Sinularia* sp.; this has subsequently been synthesized.

PROSTAGLANDINS

Prostaglandins constitute a group of biologically potent substances of wide spectrum activity. Although first recognized in the 1930s, they remained of little interest until the structures of two of them were determined in 1962. Structurally, all the compounds are based on prostanoic acid, which is itself inactive. Six series (A–E) arise by modification of the cyclopentane ring and these are now available as synthetic products. However, prior to synthetic compounds being available, research on prostaglandins was restricted by inadequate supplies of the two active compounds, PGE_2 (**32**) and PGF_{2a} (**33**). The discovery that the soft coral, *Plexaura homomalla*, was a rich source of 15-*epi*-PGA_2 and its acetate, methyl ester derivative, was a major breakthrough as the Upjohn Company developed a synthetic pathway to convert these inactive compounds into the required active ones. The synthetic routes to the required compounds saved the possible widespread collection of *Plexaura*.

Prostaglandins have also been isolated from red algae belonging to the genus *Gracilaria*.

PROTEINS

The detection of endotoxins in, for example, pharmaceutical preparations and water, is based on the clotting of amoebocyte lysate obtained from the horseshoe crab, *Limulus polyphemus*, in the presence of the endotoxins. Endotoxins are complex lipopolysaccharides, found on the outer cell wall of Gram-negative bacteria, which are relatively heat-stable.

The group of proteins known as lectins has received a good deal of attention in recent years. Lectins are carbohydrate-binding proteins and are found in a wide variety of life forms, including marine organisms. Probably the best known lectins from a marine source are the potent haemagglutinins obtained from the haemolymph of *L. polyphemus*. One of the lectins, limulin, has been isolated and shown to be a large, 18-subunit protein with a molecular mass of 350 kDa. Limulin shows specificity for binding to sialic acid, although other structures are recognized. Another lectin that shows specificity to sialic acid is that obtained from the haemolymph of the lobster, *Homarus americanus*.

Marine algae have been studied extensively as a source of lectins in recent years and several are now marketed. Much of this work has been conducted by Rogers and co-workers. They showed that the red alga, *Ptilota plumosa*, contained a lectin which reacts specifically with the α-(1,3)-linked-D-galactose unit and hence preferentially agglutinates group B human erythrocytes. Extracts of another red alga, *Solieria chordalis*, have anti-sialic acid specificity, and those from the green alga *Codium fragile* ssp. *atlanticum* react preferentially with N-acetyl-D-galactosamine. The lectins from all three species have been partially characterized. The occurrence and properties of lectins from marine algae were reviewed in 1991 (D. J. Rogers and B. C. Fish in *Lectin Reviews*, 1991 (eds E. van Driessche and T. C. Bøg-Hansen), St Louis: Sigma Chemical Company, p. 129).

AGROCHEMICAL USAGE

The marine annelid, *Lumbriconeris heteropoda*, has long been known to be toxic to insects. This activity was shown to be due to nereistoxin (**34**), which has rapid anaesthetic properties on insects and is toxic to fish and mammals, affecting the nervous system and heart. Studies on this compound led to the introduction of the synthetic pesticide Padan.

Both extracts and suspensions of brown algae are used in agriculture and horticulture. The former products are prepared by extraction of the dried plant material with either water or aqueous alkali, whereas the suspensions are produced from fresh algae. The most widely used species in the preparation of the products are *Ascophyllum nodosum*, *Ecklonia maxima* and *Durvillaea potatorum*. Many different effects have been reported as a result of the usage of these seaweed extracts and suspensions, including increased crop yields, increased resistance of treated plants to stress conditions, increased uptake of nutrients from the soil, reduced storage losses of fruit and vegetables, and improved seed germination. The active compounds present in the products have not been fully elucidated, but cytokinins and betaines have been implicated (see G. Blunden in *Seaweed resources in Europe: uses and potential*, 1991 (eds M. D. Guiry and G. Blunden), Chichester: John Wiley & Sons, p. 65). In recent years several publications have appeared showing that seaweed extract treated plants have increased resistance to pathogen attack. In particular, significantly reduced levels of infestation by root-knot nematodes (*Meloidogyne* species) has been demonstrated and the role of the betaines contained in the extracts in bringing about these effects has been clearly demonstrated. In the extracts prepared from *Ascophyllum nodosum*, glycinebetaine (**35**), γ-aminobutyric acid betaine (**36**), and δ-aminovaleric acid betaine (**37**) have been isolated.

Betaines are not restricted to the seaweed species used in the preparation of these extracts, but either betaines or a tertiary sulphonium analogue have been found in all marine algae, except one, tested for these compounds to date.

DINOFLAGELLATE- AND DIATOM-DERIVED SHELLFISH POISONING

Large concentrations of dinoflagellates occur periodically in the sea which, because of their pigmentation, give the water a brown to red coloration. The 'blooms' are known as red tides. Certain dinoflagellate species contain toxins which, when consumed by filter feeders, such as shellfish, are concentrated in the flesh of the animals. When blooms of dinoflagellates occur they can prove hazardous to human health because consumption of contaminated bivalves by man can result in severe toxic effects, including death. The toxins are usually classified as either paralytic shellfish poisons or diarrhetic shellfish poisons. The former can prove fatal, but the latter, although they can produce highly unpleasant effects, are not fatal.

The best known paralytic shellfish toxin is saxitoxin (**38**), although other related compounds have been reported, such as neosaxitoxin, the 11-α and 11-β-*O*-sulphates of saxitoxin and neosaxitoxin, and carbamoyl derivatives of saxitoxin and neosaxitoxin. Another group of paralytic shellfish toxins are known as brevetoxins, the most potent of which is brevetoxin A (**39**). The name is derived from *Gymnodinium breve* (now *Ptychodiscus brevis*), which is responsible for the red tides of Florida and the Gulf of Mexico.

The best known of the diarrhetic shellfish toxins are the dinophysistoxins, such as dinophysistoxin-1 (**40**), which are produced by species of *Dinophysis*. Other important diarrhetic shellfish toxins are the pectenotoxins.

Paralytic and diarrhetic shellfish poisonings represent potential health hazards and, as a result, monitoring programmes on shellfish toxicity have been introduced in many countries. For paralytic shellfish poisons, the methods include mice tests as well as high performance liquid chromatographic procedures, and for diarrhetic shellfish toxins the methods include bioassays, immunoassays and physicochemical methods.

In addition to dinoflagellate-derived shellfish poisoning, severe toxic effects can result from the ingestion of shellfish contaminated with diatoms. The earliest reported incident occurred in 1987 when

over 11 cases of poisoning were recorded in eastern Canada as a result of eating infected mussels. Three fatalities resulted. The toxic component was identified as domoic acid (**23**), previously isolated from species of red algae (see section on Antiparasitic compounds earlier in this chapter). The organism responsible for this compound was the diatom *Pseudonitzschia pungens* forma *multiseries*. The toxic effects produced are known as amnesic shellfish poisoning. In 1991, many brown pelicans and cormorants died as a result of domoic acid poisoning caused by *P. australis*. Since then, domoic acid has been isolated from other *Pseudonitzschia* species, including *P. seriata* from Danish waters.

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 and coma. In view of these severe effects, the need to monitor seafood for the presence of domoic acid is self evident (N. Lundholm, J. Skov, R. Pocklington and O. Moestrup, *Phycologia*, 1994, **33**, 475).

TOXINS

Many compounds isolated from marine organisms pose potential hazards to human health. Examples of these substances are the dinoflagellate toxins, responsible for paralytic and diarrhetic shellfish poisoning, and domoic acid, responsible for amnesic shellfish poisoning, all of which have been covered in this chapter. Another example is the potent neurotoxin, tetrodotoxin which, until recently, was thought to be produced by the pufferfish (family Tetraodontidae). In Japan, this fish is considered to be a great delicacy, which necessitates great care in its preparation for culinary use. Tetrodotoxin has also been isolated from other animals including crabs, and thus the origin of the toxin became a matter of considerable debate. The idea that the toxin has a microbial source was proposed and many marine bacteria have been subsequently shown to produce this dangerous toxin. Recent work also strongly suggests that the paralytic shellfish toxin, saxitoxin, is produced by bacteria and not by dinoflagellates.

Ciguatoxin is a toxin responsible for ciguatera fish poisoning, which is perhaps the biggest single problem associated with the utilization of tropical fish resources. The toxin has been isolated and characterized and shown to originate from the dinoflagellate *Gambierdiscus toxicus*. Ciguatoxin is inotropic and depolarizes excitable membranes. However, the many symptoms resulting from ciguatoxin ingestion, including neurological symptoms, suggest that other active sites are involved. *G. toxicus* is also the source of maitotoxin, a powerful calcium channel activator. Numerous pharmacological effects are produced by maitotoxin in concentrations in the pico- to nano-molar range.

The predatory cone shells of the genus *Conus* contain small, pharmacologically-active peptides, which are targeted to various ion channels and receptors. Because of their ability to select from closely related receptor subtypes, the conotoxins have become valuable for use in neuroscience research.

Another interesting toxin is lophotoxin (**41**), a diterpene lactone, isolated from the gorgonian corals of the genus *Lophogorgia*. Lophotoxin produces an irreversible postsynaptic blockage at neuromuscular junctions.

The contact dermatitis known as 'swimmers' itch' was shown to be caused by the indole alkaloid, lyngbyatoxin (**42**), produced by the marine cyanobacterium *Lyngbia majuscula*. This species is of interest because its constituents vary considerably depending on the place of collection. A totally unrelated skin irritant was isolated from a different collection of *L. majuscula*, the compound responsible being debromoaplysiatoxin (**43**); this compound has also been reported to have antineoplastic activity. Majusculamide C (**44**) was isolated from a deep water variety of the same species. This compound, a depsipeptide, inhibits the growth of fungal pathogens.

Phloroglucinol and its derivatives have a widespread distribution in the brown algae; many of these compounds have large molecular weights. These polyphenols can cause considerable problems when investigating biological activity of brown algae. For example, the compounds bind to proteins and thus inhibit enzyme activity. When brown algae are processed and used in animal feeds, the ability of the polyphenols to form insoluble complexes with protein make the latter unavailable for dietary use. Several potentially interesting biological activities recorded for extracts of brown algae have been shown, on further investigation, to be due to the non-specific properties of polyphenols. For example, extracts of certain species of brown algae, when mixed with human erythrocytes, caused agglutination. Extracts treated with polyvinylpyrrolidone did not produce this effect and it was thus considered that the activity was the result of polyphenols present in the original extracts. The active compounds were isolated and proved to be polyphenools.

CONCLUSIONS

During the past 40 years, numerous novel compounds have been isolated from marine organisms and many of these substances have been shown to have pronounced biological activity. In this chapter, examples have been given to illustrate the array of chemical structures and activities recorded; many others could easily have been included. However, the conclusion has to be drawn that, despite the large effort invested in marine natural products research, the impact on the pharmaceutical industry, at least to date, is very limited, although a few of the cytotoxic compounds have undergone clinical trials as potential anticancer drugs. Moreover, the difficulties encountered in the collection and culture of large quantities of marine organisms would discourage pharmaceutical companies developing a drug that was dependent on these natural products unless the compound could be obtained readily and economically by a synthetic route. Because of this, biologically active substances from the sea should perhaps be seen as valuable new 'lead' compounds which, if appropriate, can then be synthesized and modified to produce the desired material at an economic price.