

MARINE ORGANISMS: AN ALTERNATIVE SOURCE OF POTENTIALLY VALUABLE NATURAL PRODUCTS

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This paper recalls the outcoming of marine natural products research and reviews a selection of marine bioactive metabolites in current use together with some promising trends in marine pharmacology.

Key words: bioactivities – algae – invertebrates – fishes

Since the High Antiquity, terrestrial plants have been the main, if not the only, source of valuable natural products. Plants and their extracts were used for a variety of applications, e.g. in leather treatment, culinary, as pigments or drugs, etc. . . Extensive use and increasing demand have resulted in insufficient plant material to satisfy market needs, and have contributed to destroy some of the natural sources. Phytochemical research has dedicated much attention to discover new sources of useful natural products. Alternatively, organic chemistry has provided synthetic stuff. However, as far as natural bioactive compounds are concerned, phytochemistry has almost systematically failed to find new abundant sources of known metabolites since popular wisdom had already done this seaving work along the centuries. On the other hand, synthetic chemistry turned out to be unable to supply chiral compounds, at low costs, or to afford new bioactive products completely different from the “me too” compounds that filled the shelves of pharmaceutical industries. This situation has deeply contributed to stimulate the increasing interest for unconventional, and thus unexplored sources of natural products. In this respect, marine organisms have focused much attention over the past 30 years. Such a tardy interest can be explained, in part, by technical problems mostly overcome by the development of the SCUBA diving equipment.

Thus, although toxic fishes and mollusks, jelly-fish induced dermatitis, ichthyotoxic red

tides, antihelminthic algae, . . . were known, in some cases for thousands of years, it was not before 1960 that a scientific meeting discussed the potential value of the seas for food and drugs supplies (Nigrelli, editor 1960). The isolation, in 1969, of high amounts of prostanooids, e.g. [1], from the sea whip *Plexaura homomalla* (Weinheimer & Spraggins, 1969), much more than any other work, alerted to the enormous potential of marine organisms as alternative sources of valuable natural products. Since then, a series of Food-Drugs from the Sea Meetings, Gordon Conferences and Marine Natural Products Symposia, *inter alii*, were held and it may be stated that these meetings played a fundamental catalytic role to promote marine natural products research.

THE SEARCH FOR MARINE NATURAL BIOACTIVE PRODUCTS

In the early years of marine chemical research, there has been an enormous interest for toxins. This resulted probably from the biotoxic experiences encountered by American troops in the Pacific during World War II (Halstead, 1965). Most of these compounds, isolated from fish, coelenterates and mollusks, were proteinaceous and/or hydrosoluble. They were, at that moment, hard to purify and their structures were uneasy to establish.

The search for marine bioactive products faced another kind of problem: the lack, in many countries, of detailed ethnopharmacological informations on most marine organisms. This induced a number of laboratories to adopt a random approach to search for bio-

active metabolites, and this attitude turned out to be equally successful. Ecological field observations and the well known fact that primitive organisms are the "best chemists" allowed to improve the selection of organisms to be studied and favoured the success in the isolation of bioactive metabolites. However, here again a serious problem hampered research: the taxonomy of marine organisms, and mainly of invertebrates, was, and still is, far than established.

Simultaneously with the starting interest for marine research, a number of new techniques were developed (DCCC, reversed phase, HPLC, resins, planetary chromatography) that allowed the chemists to purify and study about all kinds of compounds. In addition, the enormous advances in NMR spectroscopies were a quite as much contributing and decisive factor for the boom of marine natural products chemistry. As a result, an amazing number of secondary metabolites has been isolated and described during the past three decades. These belong to practically all the classes of natural products with the exception of cinnamic acid derivatives almost absent from marine environment. Most of these metabolites possess unique skeletons that have no terrestrial counterpart and that still constitute a challenge for natural products chemists.

Notwithstanding this enormous chemical work, much less significant contributions have been made, in the past, to marine pharmacology. Recently, a number of bioactive metabolites have been reported. Substances with antibiotic, antifungal, antiviral, antitumor, antimitotic, cytotoxic, neurotoxic, anti-inflammatory and cardiovascular activities have been described. A variety of metabolites have reached the clinical tests, mainly as antiviral and antitumor drugs. Marine compounds are also being tested successfully as insecticides and even for specific pest control.

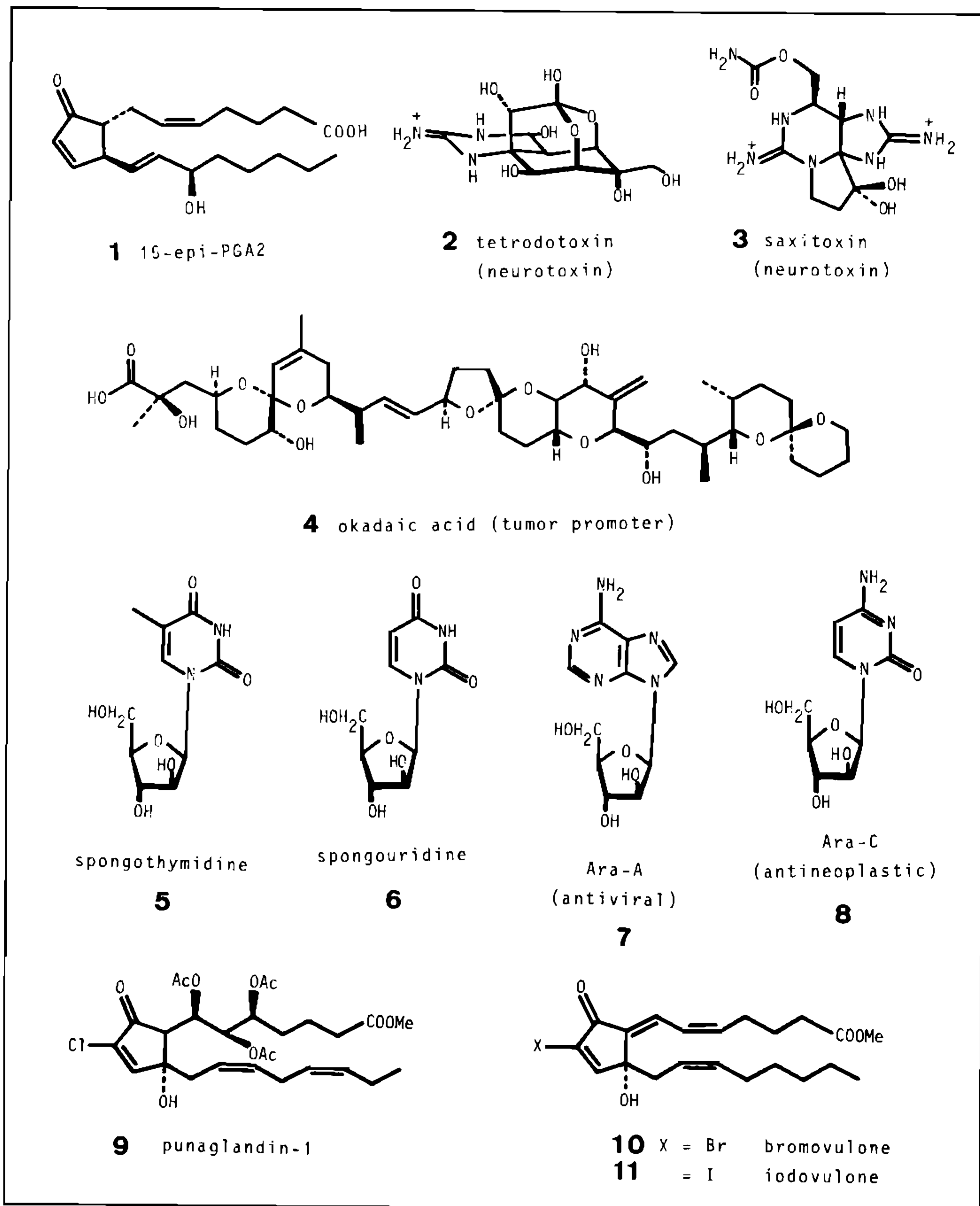
Dinoflagellates and benthic algae (the red, brown, green and blue-green ones), sponges, coelenterates, mollusks, echinoderms (sea-stars and sea cucumbers), tunicates and to a less extend fishes are among the principal sources of marine bioactive metabolites.

Some outstanding results will now be briefly reviewed with special emphasis on marine metabolites in current use. Selected promising trends are also commented.

TOXINS

Although toxins are not likely to have direct use as drugs, some marine toxins have been used in neurophysiological studies and allowed a molecular approach to neuroreceptors studies. Tetrodotoxin [TTX, 2], first isolated from ovaries of the puffer fish *Fugus rubipes rubipes* (Yokoo, 1950) but from bacterial origin (Yasumoto et al., 1989), and saxitoxin [STX, 3], first obtained from the mussel *Saxidomus giganteus* (Schuett & Rapoport, 1962) that concentrates STX from its diet the dinoflagellates *Gonyaulax* spp (Hashimoto, 1979), are two remarkable examples of non-proteinic marine neurotoxins that block specifically the sodium channels of the membranes promoting paralysis of peripheral nerves (Shimizu, 1978). The biosynthesis of these guanidine metabolites is only partly established. TTX [2] seems to be biosynthesized from arginine and a C-5 unit derived from either amino acids, isoprenoids, shikimates (less probable) or branched sugars (Shimizu & Kobayashi, 1983). STX [3] derives from two acetate units, arginine and probably S-adenosyl methionine (SAM) (Shimizu et al., 1989).

Among other toxins, one should mention a series of polycondensed polyether fatty acid derivatives produced by dinoflagellates which exhibit ichthyotoxicity (the red tide brevetoxins) (Lin et al., 1981) or are the causative agents of diarrhetic shellfish poisoning (okadaic acid [4], dinophysin and pectenotoxins) (Yasumoto et al., 1985). Other potent toxins are the polyhydroxylated palytoxins (strong CV-blocking agents) (Kaul, 1981) isolated from zoanthids of the *Palythoa* genus (Moore & Scheuer, 1971), but probably from exogenous origin (Hirata, 1989), the sponge cytotoxic macrolides latrunculins (Kashman et al., 1980), the coelenterate paralyzing diterpene lophotoxin (Fenical et al., 1981), the ichthyotoxic and shark repellent steroidal glycosides from the sole fish *Pardachirus pavoninus* (Tashibana et al., 1984), the neurotoxic indole alkaloids of the surugatoxin type isolated from the edible mollusk *Babylonia japonica* (Kosuge et al., 1982) but from bacterial origin (Kosuge et al., 1985), and a series of sea stars and sea cucumbers saponins (Burnell & ApSimon, 1983). For a recent revision of this topic, see Kelecom (1986).

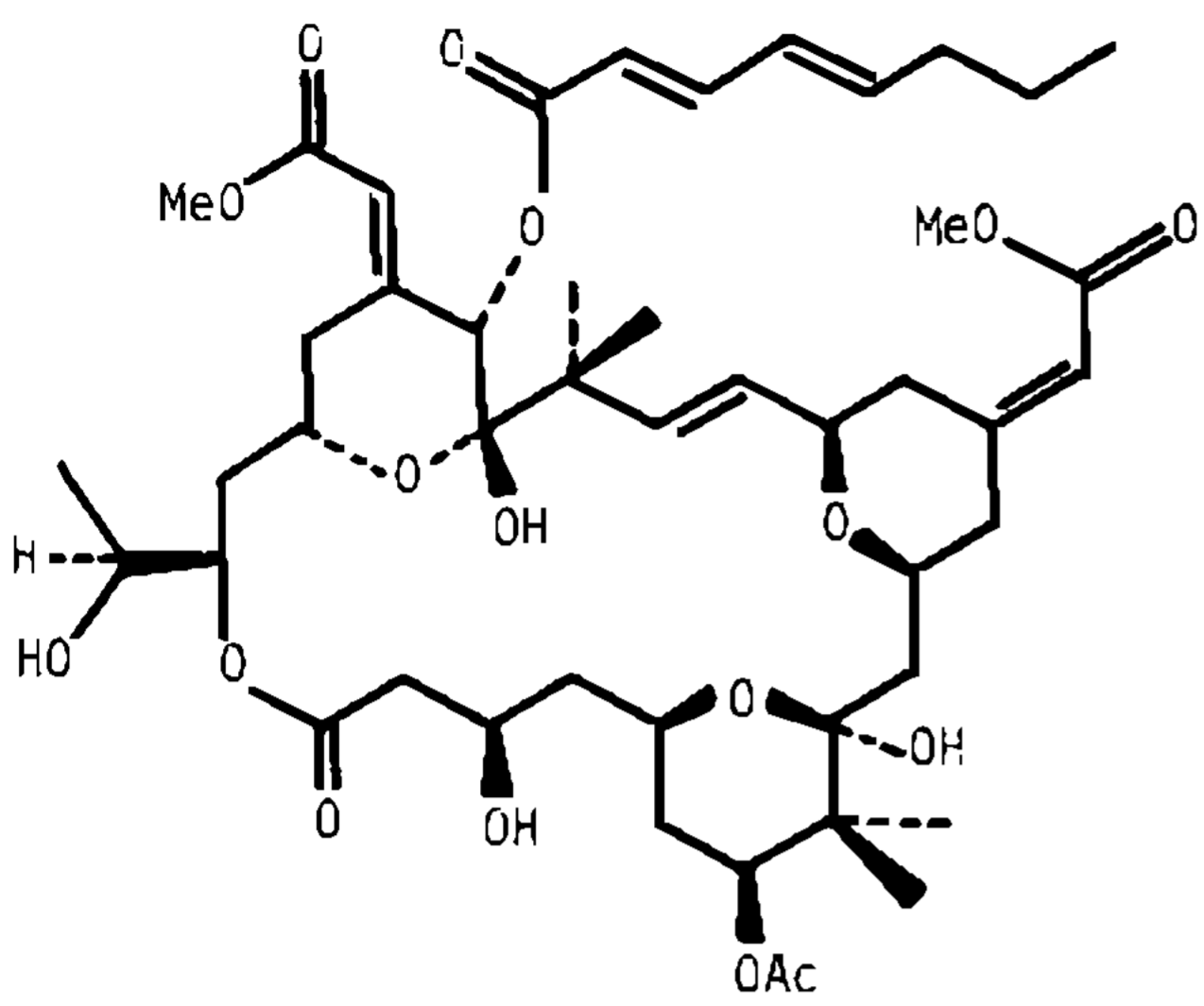


CARDIOVASCULAR ACTIVITIES

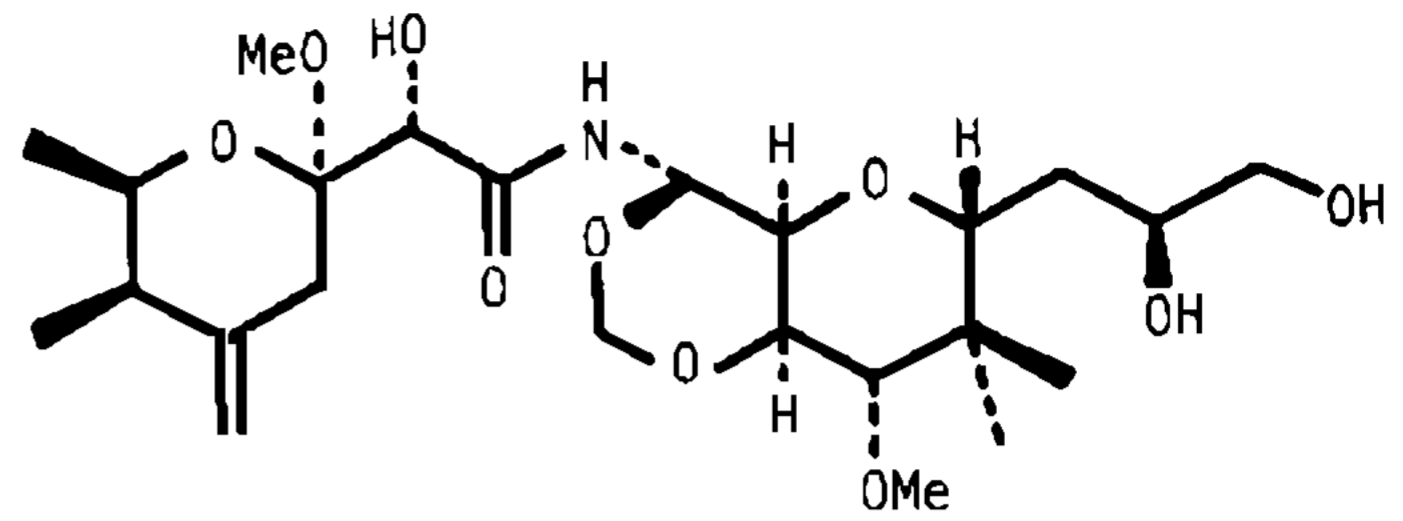
Cardiovascular diseases are, in the industrial world, among the most important *causa mortis*. It is thus not surprising that pharmaceutical industries maintain R & D programs on cardio-tonic, antihypertensive and anticoagulant drugs.

Marine sponges have furnished a large array of cardioactive metabolites. The pentacyclic

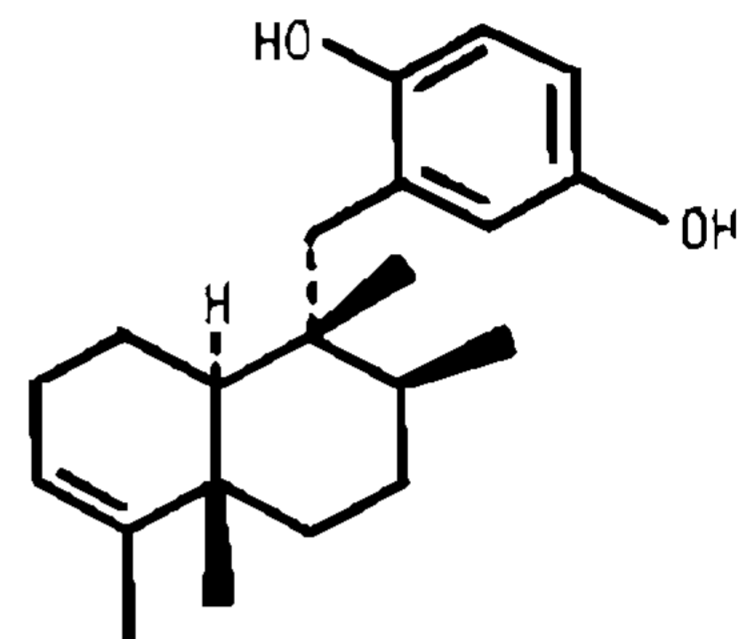
quinone xestoquinone (from *Xestospongia sapra*) possesses strong inotropic activity and inhibits the Na/K-ATPase (Nakamura et al., 1985). Vasodilatory activity is associated to a series of 1-oxa-quinolizidine alkaloids, the xestospongins (Endo et al., 1986), and to the nucleosides doridosine, isoguanosine and spongosine (Kaul, 1982). The former also showed dose-dependent hypotension and bradycardia (Quinn et al., 1980). *Hyrtios erecta* furnishes



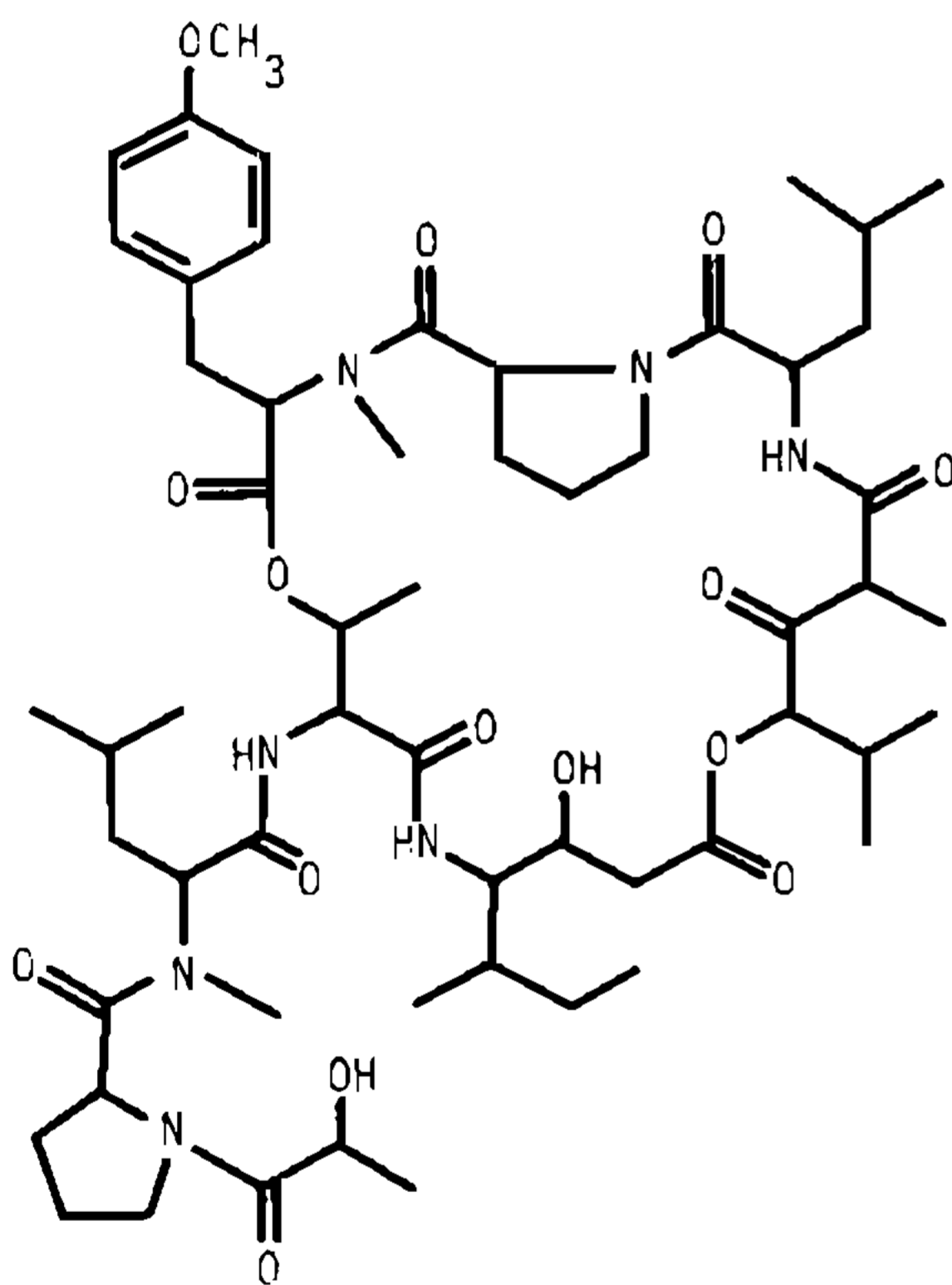
12 bryostatin-1
(anti-tumor)



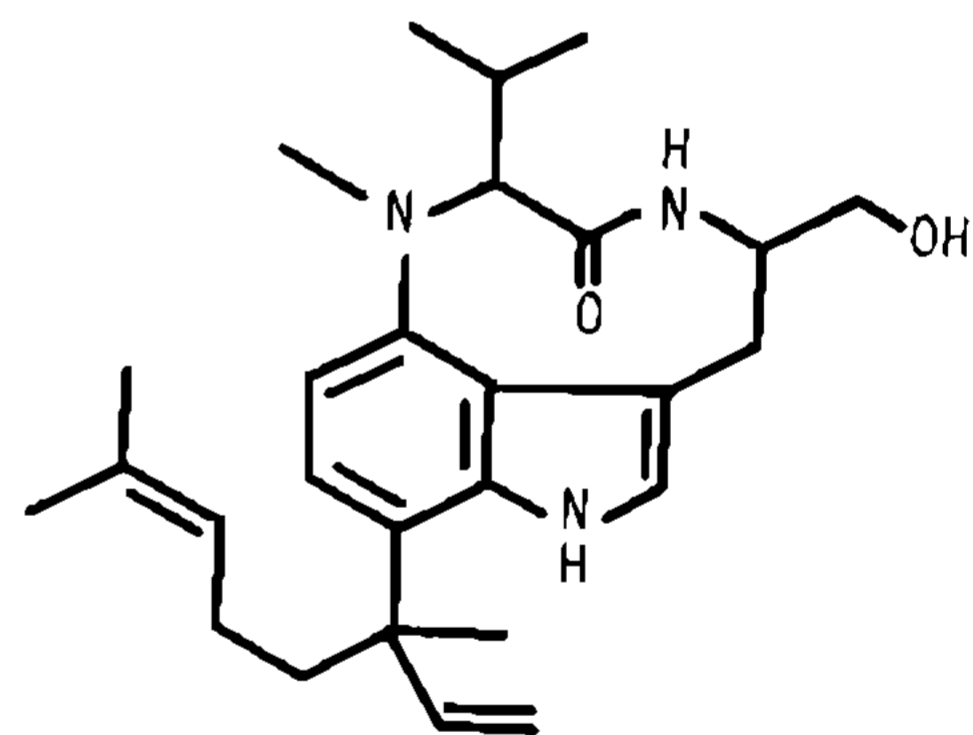
15 mycalamida-A
(anti-viral)



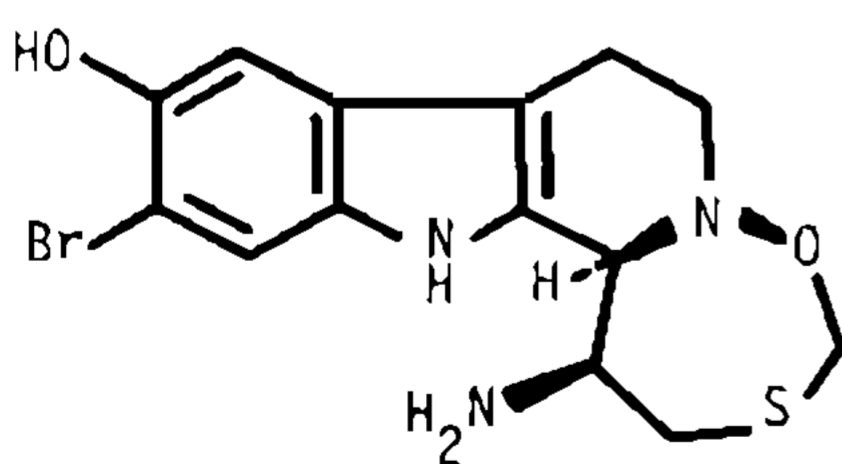
16 avarol
(cytostatic)



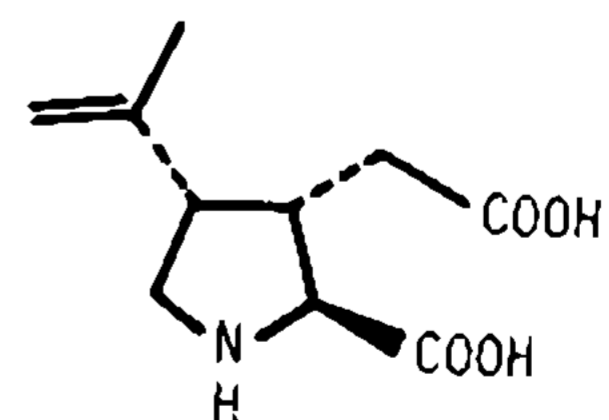
13 didemnin-B
(anti-tumor)



17 lyngbyatoxin-A



14 eudistomin-C
(anti-viral)



18 kainic acid
(anti-helminthic)

a sesterterpene, 12- ϵ -scalaradial, endowed of antihypertensive activity (Endo et al., 1986).

Sea-anemones are rich sources of cardiotoxic polypeptides. The best studied one, anthopleurine-A, from *Anthopleura elegantissima*, contains 49 amino acids and presents a very potent positive inotropic effect without chronotropic action (Kaul & Daftari, 1986). These cardiotoxics are about 35-fold more active than digoxine, but showed undesirable antigenic activity. Other coelenterates also produce cardiotoxic compounds such as palytoxins (Kaul, 1981) and subergorgic acid a sesquiterpene isolated from the gorgonian *Subergorgia suberosa* (Groweiss et al., 1985).

Finally, the endecapeptide eledoisin, from the octopus *Eledone* spp, is strongly hypotensive and vasodilatatory, but its major activity is observed on the smooth muscles, being of clinical use (Anastasi & Erspamer, 1963). Further information on marine cardioactive metabolites is found in Kelecom (1988).

ANTITUMORS, TUMOR PROMOTERS, CYTOTOXICS AND ANTIVIRALS

The impact of massive funding for cancer research, the lack of efficient treatment against herpes and the AIDS problem explosion during the last decade have overwhelmingly contributed to the enormous number of marine metabolites reported to show the title activities. We will very briefly present here some of the major results. For a complete review of the subject, see Kelecom (1990).

The nucleosides spongothymidine [5] and spongouridine [6] are among the first marine metabolites that have been described (Bergmann & Burke, 1955). Isolated in the early fifties from sponges, these nucleosides served as model for the synthesis of Ara-A [7], an antiviral agent, and Ara-C [8], an antineoplastic agent (Cohen, 1963). The former is commercially used against the human eye-herpes infection (Scheuer, 1989). The octocorals *Telesto riisei* and *Clavularia inflata* produce halogenated prostanoids (the punaglandins [9], clavulones, bromo- [10] and iodovulones [11]) that showed strong antiproliferative activity against leukemia HL-60 (Baker et al., 1985; Iguchi et al., 1986). The macrolide bryostatin-1 [12] is effective against leukemia P-388 (Pettit

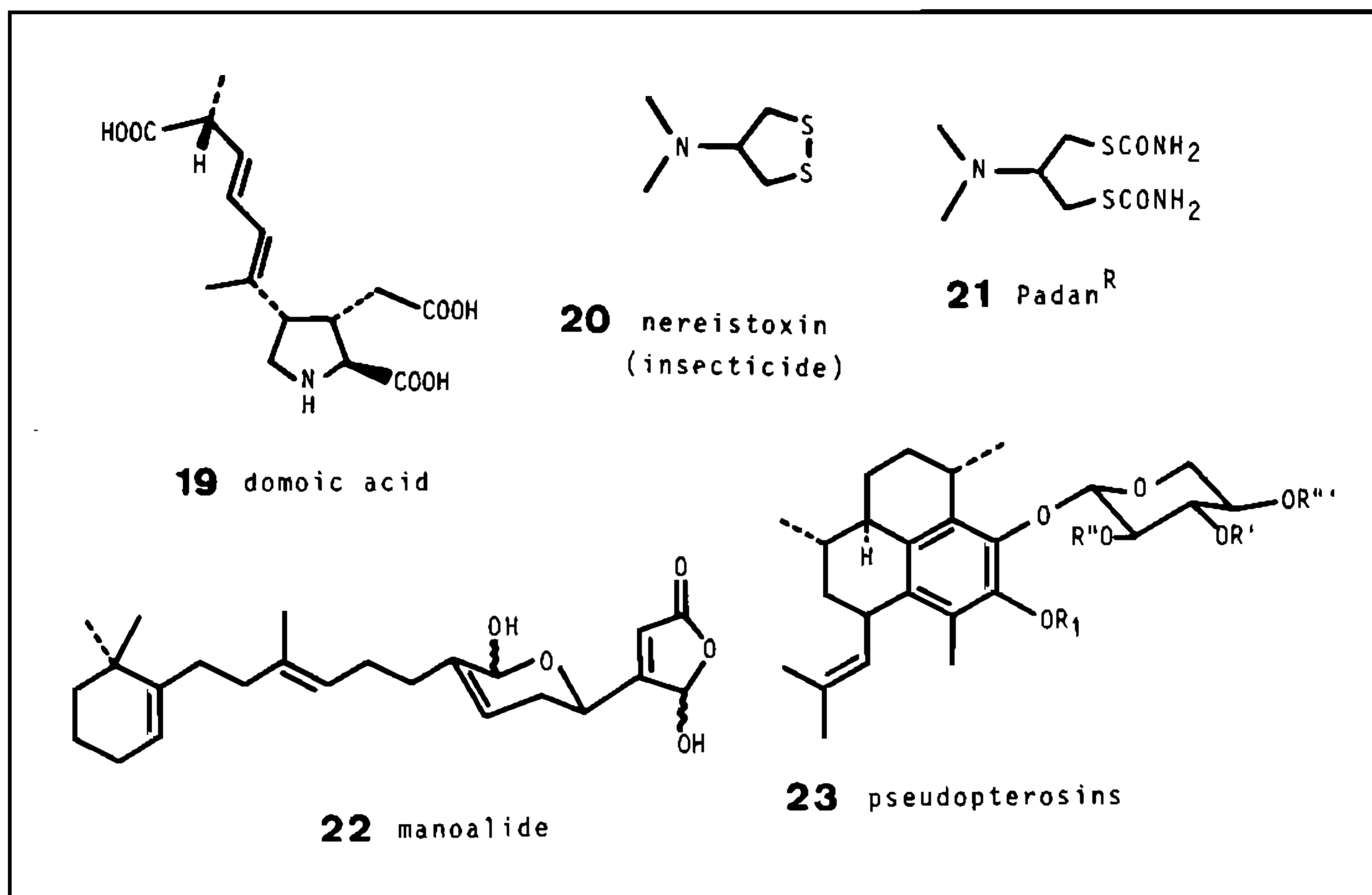
et al., 1982) and has reached phase-2 of clinical tests. It was first isolated, in extremely low yield, from the bryozoarian *Bugula neritina* that grows on ship hulls (Pettit et al., 1982) and is now available by synthesis (Masamune, 1989). Also in phase-2 of clinical tests is the cyclic depsipeptide didemnin-B [13] isolated from the tunicate *Trididemnum solidum* (Rinehart et al., 1981). Besides its *in vivo* antitumor activity (P-388 leukemia, B-16 melanoma), didemnin-B also possesses strong antiviral and cytotoxic actions and shows immunosuppressive properties (Rinehart, 1989).

Significant antiviral activity was observed for a series of tunicate indole alkaloids, eudistomin-C [14] being the most effective agent against herpes simplex virus (Rinehart, 1989; Munro et al., 1989). Eudistomins are also fairly good antitumor agents (Munro et al., 1989). Mycalamide-A [15], isolated from the sponge *Mycale* sp (Perry et al., 1988), is active *in vivo* against leukemia P-388, *Herpes simplex* and polio virus type I. It is also strongly active, *in vivo*, against RNA virus, *Coronavirus A-59* and acts inhibiting protein synthesis (Munro et al., 1989). Another potential anti-AIDS drug that is being tested is avarol [16], a sesquiterpene of mixed biogenetic origin, isolated from the sponge *Dysidea avara* (Minale et al., 1974) and that shows strong cytotoxic activity (Mueller et al., 1985).

Tumor promoters have been described such as the dinoflagellate polyether okadaic acid [4] (Suganuma et al., 1988) and lyngbyatoxin-A [17], an indole alkaloid produced by the blue-green alga *Lyngbya majuscula* (Cardinella et al., 1979). This metabolite binds to the same receptor as phorbol ester (Scheuer, 1989). It is worth while noting that cited alga has been implicated in the swimmer itch outbreaks, a sporadic dermatitis reported from Hawaii and Japan (Moore, 1982).

MISCELLANEOUS

The proline derivatives kainic acid [18] and domoic acid [19], both isolated first from red algae (Murakami et al., 1953; Takemoto et al., 1966), possess anti-helminthic activity. The first is used as a drug since the antique Chinese dynasties, and is still commercially used in Japan. Kainic acid, in addition, mimics Huntington's disease and could thus be a useful tool for neurophysiological studies of this



disorder (Scheuer, 1989). Recently, mussel intoxication in Canada caused two deaths that could be associated, after a 5-days of very intense research, to the presence of domoic acid (Wright et al., 1989). This metabolite is a potent glutamate agonist inducing neurological symptoms, such as amnesia (Hockin, 1989).

Another nitrogenated metabolite, nereistoxin [20], from the worm *Lumbriconereis heteropoda* (Okaichi & Hashimoto, 1962), is a potent insecticide that served as model for the synthesis of Padan [21] used, since 1967, in pest control (Konishi, K., 1971).

New anti-inflammatory agents have also been observed. The sesterterpene manoalide [22], from the sponge *Luffariella variabilis* (de Silva & Scheuer, 1980), inhibits the writhing syndrome induced by phenylquinone (Jacobs et al., 1985). This agent is more potent than indomethacin but less than hydrocortisone, and acts inhibiting irreversibly the enzyme phospholipase-A₂ (de Freitas et al., 1984). Similarly, the pseudopterosins [23], a series of diterpene glycosides from the gorgonian *Pseudoptero-gorgia elisabethae* (Look et al., 1986), exhibit potent analgesic and anti-inflammatory activities (Fenical, 1987). Both manoalide and pseudo-

pterosins constitute completely new kinds of anti-inflammatory agents that might have promising future.

Finally, the blood of the horseshoe crab *Limulus polyphemus* clots in the presence of Gram-negative endotoxins (Cohen, 1968). This observation has led to the development of a very efficient test that is now largely used in clinical and pharmaceutical control and also by food industries (Scheuer, 1989). Unfortunately, this industrial interest is strongly contributing to the extinction of cited invertebrate.

CONCLUSIONS

The few examples commented here testify the enormous potential of marine organisms as sources of valuable natural bioactive metabolites. The diversity of structural and chemical types is amazing, much more than the array of detected activities. This probably reflects the lack of suitable pharmacological tests and the need for new and novel screening strategies and techniques adapted to such different molecular patterns.

Marine natural products chemistry is a rapidly moving field. New trends are firming,

such as marine chemical ecology. It may be predicted that the major contributions in the future will result from studies of associated marine microorganisms, and that biotechnology, and more specifically genetic engineering, will contribute to bring to reality the potential of the oceans.

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