RECENT MARINE NITROGEN-CONTAINING METABOLITES

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Abstract
A large variety of nitrogen-containing marine natural products (M.N.P.s) were isolated from marine organisms, mainly sponges and tunicates. Many of these compounds possess interesting biological activities. A variety of M.N.P.s isolated by the Tel Aviv group from red Sea and Indo-Pacific organions are reported, including examples of the isolations, structure elucidations and details on their bioactivities.

Key-words: Tunicata, porifera, natural products

Nitrogen-containing secondary metabolites which were quite rare when the research of marine natural products (M.N.P.) began in the seventies, are now well known and a spectacular array of novel and unique compounds has been unveiled (1, 2). Many of these compounds possess useful biological or pharmaceutical properties. The most important of these compounds were obtained from sessile marine organisms such as sponges and ascidians and to a lesser extent soft corals, gorgonoins. Until recently, our research of M.N.P. concentrated primarily on Red Sea organisms. In the last few years, Indo-Pacific ocean organisms have been added to our research.

Nitrogen-containing M.N.P. may be divided into three groups : **a** acyclic and non-aromatic cyclic compounds, **b**. linear and cyclic peptides and depsipeptides and **c**. heterocyclic compounds.

This paper details nitrogen-containing M.N.P.s from Red Sea and Indo-Pacific ocean sponges, tunicates and soft corals, isolated and characterized by the Tel Aviv group over the last few years. All isolations of the M.N.P. described below were guided by NMR spectra and bioactivity tests in a variety of different systems. Each separation started with freeze-drying of the organisms followed by selective extractions, solvent partitions and chromotographies on Sephadex LH-20, silicagel and RP-18 columns. The structure elucidation of the purified compounds was achieved mainly by NMR and MS experiments and was assisted in certain cases by chemical transformation and X-ray diffraction analyses.

Examples of acyclic and non-aromatic cyclic N-containing M.N.P.s

Latrunculins (Fig. 1) are macrolides isolated from the Red Sea sponge *Latrunculia magnifica* (3). *In vivo*, they alter cell-shape, disrupt microfilament organization and inhibit the microfilament-mediated processes of fertilization and early development (4, 5). *In vitro*, latrunculin A was recently found to affect the polymerization of pure actin in a manner consistent with the formation of a 1:1 molar complex with G-actin. These *in vitro* effects, as well as previous indications that the latrunculins are more potent than the cytochalasins, suggest differences in the *in vivo* mode of action of the two classes of drugs (5). The latrunculin-induced changes are strikingly different from those induced by cytochalasin D. Latrunculins A and B were isolated from the sponge by a Sephadex LH-20 purification guided by ichthiotoxcity and their structures were determined by MS and various NMR experiments and confirmed (for latrunculin B methyl acetal) by X-ray diffraction analysis (3). Due to the potent interaction of the latrunculins with G-actin, they became a valuable tool in cell biology for the investigation of processes in which actin is involved. Most recently, latrunculin A, for example, was shown to be a very potent inhibitor of immunological phagocytosis by normal and activated macrophages (obtained from mice injected i.p. with LPS), as well as by polymorphonuclear leukocytes (6). This toxin blocks the interiorization of the immune complexes but does not interfere with their binding to the phagocyte (recognition phase); activated macrophages were more susceptible to this inhibition than normal macrophages and polymorphonuclear leukocytes.

A second example of category **a** are the *Erylus* metabolites. Fusetani, in his screening for IL-6 antagonists from Japanese marine invertebrates, has found the extract of the sponge *Erylus placenta* to be very potent (7). Interleukin-6 (IL-6) is a multifunctional cytokine which exhibits its function through binding with its specific receptor. Abnormal production of IL-6 causes development of an autoimmune state such as rheumatoid arthritis or inflammation, whereas it constitutive production results in disease states of HTLV-1 or HIV infections. Therefore, inhibitors of IL-6 may be of potential therapeutical importance. This activity was traced to a complex mixture of related metabolites from which the active erylusamines A-C were isolated (7). From another *Erylus* sp., namely *Erylus* cf. *Lendenfeldi*, collected from Dahlak archipelago, Eritrea, we have isolated three series of compounds (8). The first group, erylusamine TA, is closely related to erylusamines A-C, while the other two, erylusine and erylusidine differ not only in the sugar portion but also in the nitrogens containing long chain (Fig. 1).

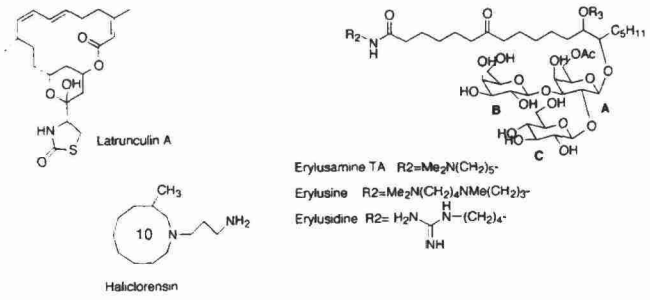

Figure 1.

The final example in this group is haliclorensin. A novel diamino alkaloid, isolated from the sponge Haliclona tulearensis and possessing an azacyclodecane ring (Fig. 1), which has been found to be cytotoxic against P388 mouse leukemia cells (IC_{50} = 0.1 μg/mL) (9). The structure of haliclorensin was established by HREIMS (*m/z* 212, $C_{13}H_{28}N_2$) and 1D and 2D NMR experiments.

Linear and cyclic peptides and depsipeptides

We isolated several linear and cyclic peptides from marine sponges (1, 10). Sponges are targets for extensive studies which seek to isolate new substances. Indeed, a large variety of new compounds have been isolated from this primitive source. Sponges are actually simple cell aggregates which are usually referred to as "the most underdeveloped multicellular animals". Therefore, sponges provide lodging for many macro organisms, bacteria, blue-green algae and dinoflagellates. Occasionally the weight of these guests reaches 50% of the biomass of the sponge. Hence, certain classes of compounds, isolated from sponges, are structurally identical or similar to those of microorganisms from other sources. As a result, similar (or the same) secondary metabolites can be isolated from completely different sponges. On the other hand, it is often impossible to re-isolate the same compounds from different collections of the same sponge (11). Sponge peptides are also suspected to be of microbial origin due to the presence of both D amino acids and other unusual amino acids, in addition to the L amino acids.

The sponge *Hemiasterella minor* (Kirkpatrick) (class, Demospongiae; order, Hadromerida; family, Hemiasterellidae), collected in Sodwana Bay, north of Durban, South Africa, was found to contain a variety of bioactive compounds (11). The major metabolite in four examined specimens was found, on the basis of its spectral data, to be the earlier reported (12) bioactive cyclic depsipeptide jaspamide (jasplkinolide) isolated from *Jaspis* sp. (order, Astrophoride (Choristida)) (0.2%, dry wt). Two of the sponge samples studied contained minute amounts of a second peptide, hemiasterlin and one specimen, a third