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Biologically active marine natural products

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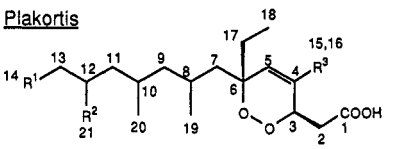
Abstract - Sponges, tunicates, and other species from shallow and deep-sea habitats yield antiviral, antitumor, antimicrobial, and antifouling compounds, as well as cytotoxic and immunomodulatory agents; our structure assignments and synthetic work are reviewed. Didemnin B, from a colonial tunicate, is in Phase II clinical trials in the United States and has been synthesized along with related compounds, including stereoisomers, whose bioactivity is compared.

The search for biologically active marine natural products has expanded horizontally (to new sites) and vertically (to deeper water). In collaboration with Harbor Branch Oceanographic Institution, Inc./SeaPharm Project we have recently undertaken an investigation of a number of sponges collected at depths of 30 to 800 meters and demonstrated in the field to give biologically active extracts (ref. 1). Some of the compounds isolated from a few of these deep-water sponges are shown in Scheme 1. While most of the pharmacological activities ascribed to the compounds have not been reported previously and the sources of the sponges as well as nearly all the sponge species themselves are novel, the compounds are generally either known or of recognized types. An example is provided by compounds isolated from a new genus (a Goreauiella species) collected at -698 m; these proved to be oroidin and odiline, previously obtained from other genera of shallow-water sponges (refs. 2-4). Similarly, the new compounds topsentin and bromotopsentin, obtained from a sponge collected in the Caribbean at -174 to -360 m, were isolated simultaneously from a shallow-water Mediterranean sponge (refs. 5,6).

Scheme 1

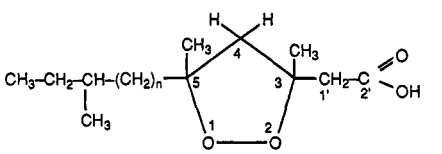
Plakortis



R^1	R^2	R^3	R^1	R^2	R^3
H	H	Et	Me	H	Et
Me	H	Me	Me	Me	Et

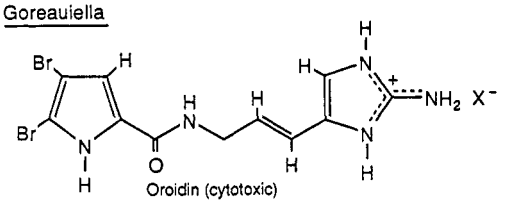
and 4,5-dihydro analogues (antimicrobial, cytotoxic)

Pachastrella



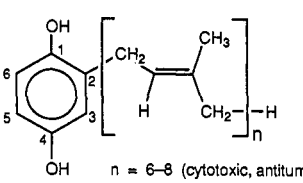
Pachastrellins: n = 9–13 (antifungal, cytotoxic)

Goreauiella



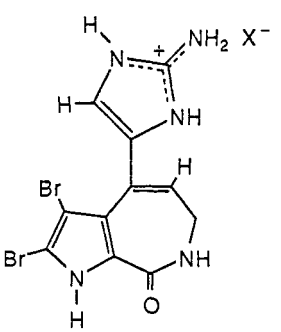
Oroidin (cytotoxic)

Ircinia

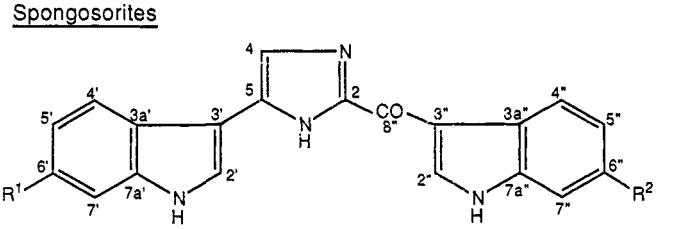


n = 6–8 (cytotoxic, antitumor)

Spongosorites



Odiline (Stevensine, cytotoxic)



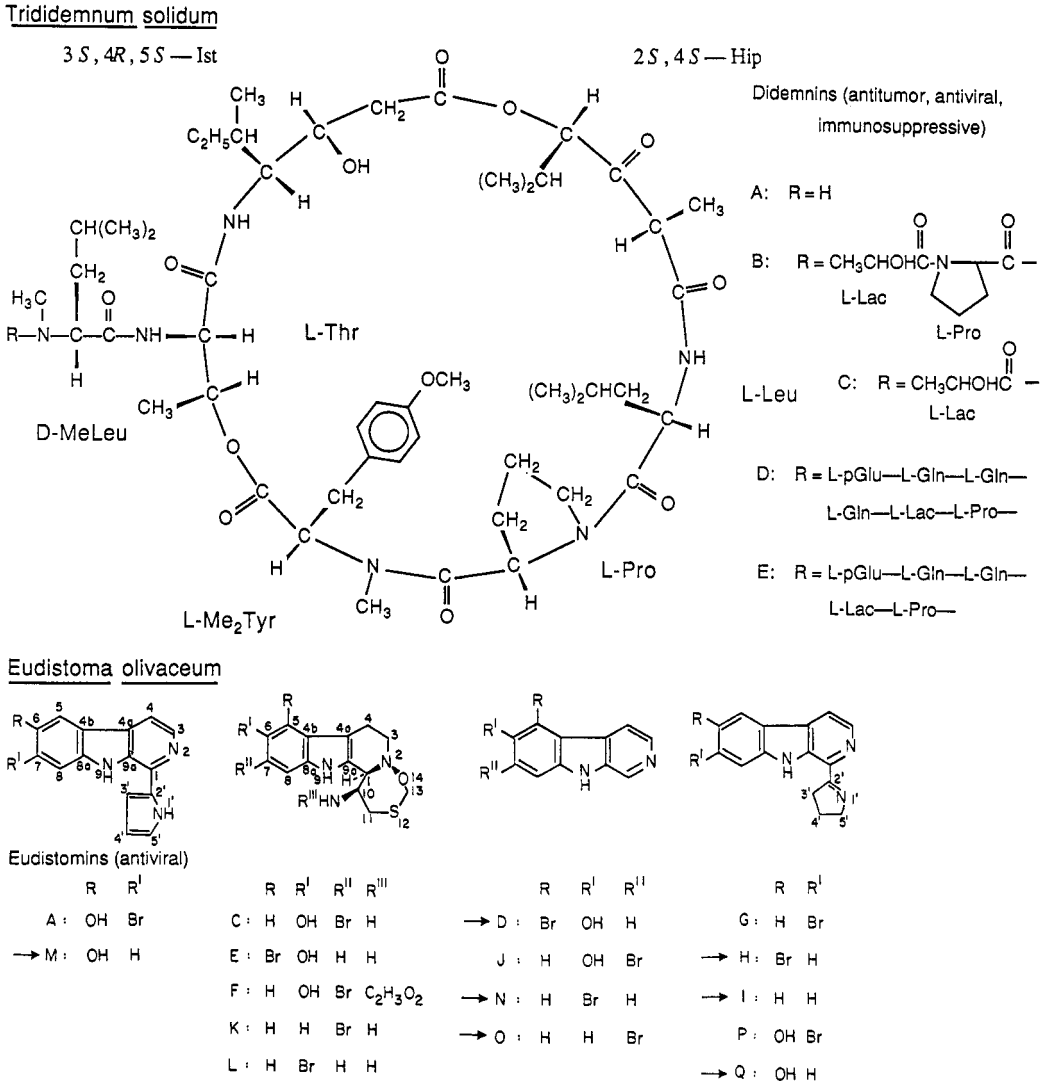
R^1 = H, R^2 = OH (Topsentin)

R^1 = Br, R^2 = OH (Bromotopsentin)

and 4,5-Dihydro-6"-deoxybromotopsentin

(antitumor, antiviral)

Scheme 2



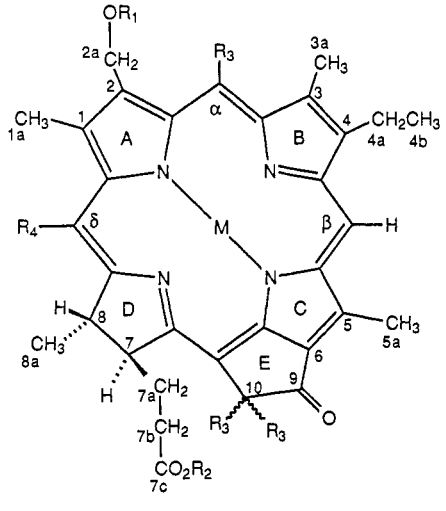
Earlier University of Illinois expeditions (ref. 7) have also been bioassay-directed in the field and have provided a number of promising new drug candidates (Scheme 2). Among these are the ecteinascidins (from the tunicate Ecteinascidia turbinata) (refs. 8-10), isolated by employing countercurrent chromatography (CCC, Ito coil) and by following separations with tissue culture bioautography. The most active of the six isolated ecteinascidins have ID_{50} 0.0004 μg/mL vs. L1210 leukemia cells and T/C 214 at 0.0038 mg/kg for P388 leukemia in mice. Among the most active antiviral agents are eudistomins C and E, isolated from the tunicate Eudistoma olivaceum, highly active at 25 ng/12.7-mm disk vs. Herpes simplex virus, type 2 (refs. 11,12). A number of the other eudistomins have been synthesized (those indicated by arrows) but are less active. The didemnins (from another tunicate, Tridídemnum solidum) are extremely potent antiviral and immunosuppressive agents and are currently in Phase II clinical trials as anticancer agents (refs. 13-15). We recently synthesized three of the less polar didemnins, including didemnin B (ref. 16), and structure-activity relationship studies indicate strong dependence on substitution pattern and stereochemistry.

The didemnins are accompanied by a blue-green pigment and the tunicate itself by a commensal cyanobacterium. We recently identified the blue-green pigment as tunichlorin (Scheme 3), the first nickel-containing chlorin reported from a living organism, and have synthesized the compound, starting from chlorophyll a (refs. 15,17).

The sponges Agelas coniferin and A. cf. mauritiana both contain a number of putative dimers of oroidin analogues, including the previously reported sceptrin (ref. 18), its debromo, dibromo, and oxygenated analogues (not previously reported), and corresponding ageliferins

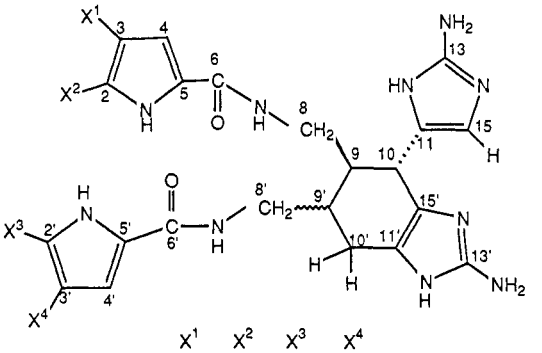
Scheme 3

Trididemnum solidum



	R_1	R_2	R_3	R_4	M
tunichlorin:	H	H	H	H	Ni

Agelas coniferin



	X^1	X^2	X^3	X^4
ageliferin:	Br	H	H	Br
bromoageliferin:	Br	H*	Br*	Br
dibromoageliferin:	Br	Br	Br	Br

(antiviral, antifouling)

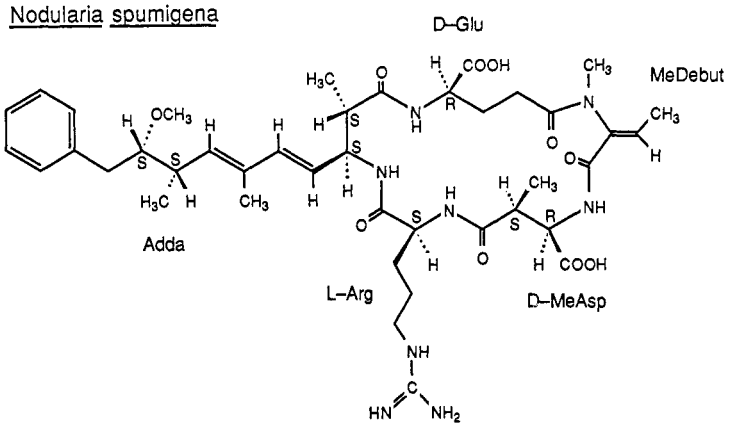
(Scheme 3) resulting from putative 4π + 2π (Diels-Alder) cyclization, which contrasts with the apparent 2π + 2π cyclization involved in sceptrin formation (refs. 19-21). Structure studies of these compounds involved both FABMS/MS and LC/FABMS techniques (ref. 22). The sceptrins and ageliferins all show antiviral activity and influence barnacle settling.

Considerably more potent antifouling activity has been demonstrated for the renillafoulins from Renilla reniformis, a sea pansy (Scheme 4). Discovered at the Duke University Marine Laboratory, these compounds were purified and assigned structures in Illinois (ref. 23).

A compound with potent (though non-therapeutic) biological activity recently studied in our laboratory is the hepatotoxin nodularin (Scheme 4) from the cyanobacterium Nodularia spumigena. This study involved collaboration with the University of Canterbury, the University of Illinois College of Veterinary Medicine, and Wright State University (ref. 24). The structure assignment required extensive use of HRFABMS and FABMS/MS. The characteristic C_{20} amino acid unit Adda also occurs in the microcystins (cyanoginosins) (refs. 25,26). In connection with our study of nodularin we assigned the absolute stereochemistry of Adda as 2S,3S,8S,9S (ref. 24) and synthesized the parent molecule and protected derivatives.

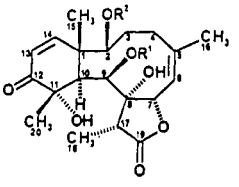
Scheme 4

Nodularia spumigena



Nodularin (hepatotoxin)

Renilla reniformis



Renillafoulins A, B, C

(antifouling)

$R^1 = R^2 = Ac$-

$R^1 = Ac$, $R^2 = C_2H_5CO$-

$R^1 = Ac$, $R^2 = n$-C_3H_7CO-

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