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Chemical constituents of *Haliclona*: An overview

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Abstract

Marine sponges (Porifera) are rich sources of bioactive compounds. Marine sponge of the family Haliclونidae have proved to be a rich source of nitrogen containing metabolites with various biological activities. E.g. halitoxin, xestospongins, sarains, papuamines and haliclونadamine. Sponges of the genus *Haliclona* are well known for producing a variety of secondary metabolites, most commonly bioactive alkaloids. The genus *Haliclona* has a history of providing diverse structures. The present review article compiles the different classes of compounds isolated from the genus *Haliclona* and their bioactivities. A wide range of bioactivities like antimicrobial, hemolytic, hemagglutination, antibacterial, antioxidant, anti-inflammatory and anticancer activities have reported from *Haliclona*.

Keywords: *Haliclona*, sponge, chemical constituents, bioactivities

Introduction

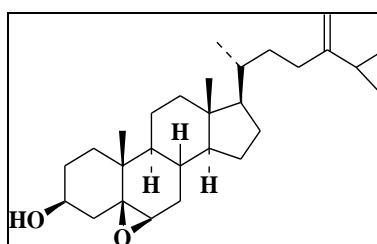
Approximately 10,000 sponges have been described in the world and most of them live in marine waters. A range of bioactive metabolites has been found in about 11 sponge genera. Three of these genera (*Haliclona*, *Petrosia* and *Discodermia*) produce powerful anti-cancer, anti-inflammatory agents [1]. Marine sponges (Porifera) are rich sources of bioactive compounds. It has also been well known that they harbor bacteria in their tissues [2]. Moreover, numbers of marine natural products obtained from sponges have been found to show structural similarities to the metabolites of marine and terrestrial microorganisms.

Marine sponge of the family Haliclونidae have proved to be a rich source of nitrogen containing metabolites with various biological activities. E.g. halitoxin, xestospongins, sarains, papuamines, and haliclونadamine [3]. Sponges of the genus *Haliclona* are well known for producing a variety of secondary metabolites, most commonly bioactive alkaloids. Few bis-1-oxaquinolizidine alkaloids and one furano sesquiterpene herbacin from this species (*Haliclona exigua*) were reported in the literature. Other species of *Haliclona* are well known to contain chemically diverse secondary metabolites with interesting biological activities such as cytotoxic, antifungal, antibacterial, antiviral, antimalarial, anti-inflammatory, neurotogenic and hemolytic activities. Some believe that sponges may provide the richest source of sterol diversity in the entire animal kingdom [4].

The genus *Haliclona* has a history of providing diverse structures including polycyclic amines [5], sesquiterpenoids quinols [6], glycosphingolipids [7], resorcinols [8] and tetrahydropyranone [9]. The different classes of compounds isolated from the sponges of the genus *Haliclona* are described as follows:

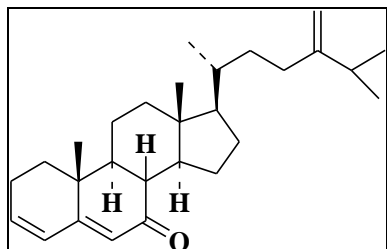
Sterols

Chemical studies on sponges have shown that they often are a source of novel sterols of biogenetic interest [10]. The methanolic extract of *H. oculata* showed the presence of substantial amounts of compounds more polar than the monohydroxylated sterols [11]. Purification of more polar sterols was achieved by a combination of column chromatography, prep. T.L.C. and HPLC on silica gel and reversed phase systems. In some cases it was necessary to separate mixtures after acetylation. The sterol having epoxide ring (1) and dienone (2) functionality group were also purified [11].



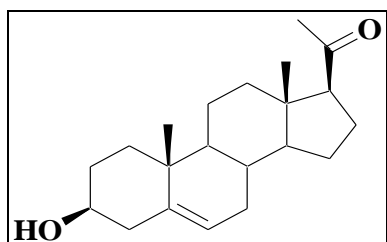
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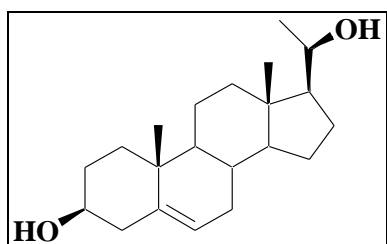


(2)

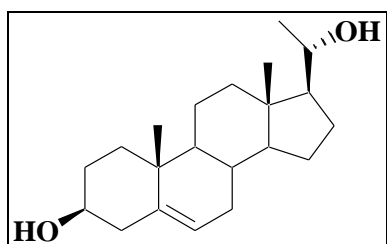
A number of pregnane derivatives in the sterol mixture were isolated from a sponge *H. rubens* [12]. This animal has been found to contain 3 β -hydroxy-17 β -pregn-5-en-20-one (3), 3 β , 20 β -dihydroxy-17 β -pregn-5-ene (4), 3 β , 20 α -dihydroxy-17 β -pregn-5-ene (5) ketosterols. The sterol fraction was crystallized from methanol and examined by GC-MS techniques. A very complex sterol G.L.C profile was observed [12].



(3)

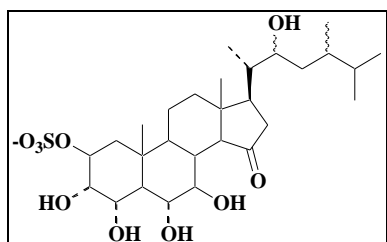


(4)

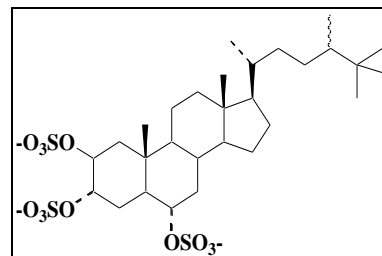


(5)

Two steroids haliclostano sulfate (6) and halistanol sulfate (7) were isolated from a *Haliclona* sp. [13]. Compound (6) is unique, and member of a rare class of naturally occurring sterols sharing a Cis C/D ring junction, 14 β proton and a C-15 ketone.



(6)



(7)

Cholesterol was shown to be a main sterol in the free sterol fraction from *Haliclona* sp. It was reported [14] to contain Δ^5 -sterols and stanols. Bioactive polyhydroxylated sterols have been isolated from the marine sponge *Haliclona crassiloba* and their antimicrobial activities have been studied [15]. Brominated Polyunsaturated Lipids and Steroids were reported [16] from the South China Sea Sponge *Haliclona subarmigera*. Cytotoxic constituents [17] were reported from Vietnamese Marine Sponge *Haliclona oculata* (Linnaeus, 1759). Five sterols and two brominated lipids 3 β -hydroxy-5-cholenic acid methyl ester, stigmasta-5, 24(28)-dien-3 β , 29-diol, 24-methylenecholest-4-en-3 β , 6 β -diol, cholest-5-en-3 β , 7 β -diol, 24-vinylcholest-5-en-3 β , 24-diol, and xestospongiene A, and xestospongiene J, respectively, were isolated from the methanol extract of Vietnamese marine sponge *Haliclona oculata* (Linnaeus, 1759).

Alkaloidal Compounds

A literature survey revealed that the genus *Haliclona* produces complex macrocyclic alkaloids including the β -carboline derived oncolytic alkaloids manzamines A, B, and C [18] and the pentacyclic alkaloids papuamines [19] halitoxin [20], xestospongins [21], sarains [22] and haliclonadiazine [23] which have antifungal and antimicrobial properties. Alkylpyridines [24, 25] from different *Haliclona* sp. have been reported. Bioassay guided purification of the acetone extract of the marine sponge, *Haliclona exigua*, (Gulf of Mannar, India) yielded a fraction rich in bis-1-oxaquinolizidine alkaloids, active against seven strains of fouling bacteria. The major alkaloids in the mixture have been tentatively identified as nor-Araguspongine C (33.76%), Araguspongine C (6.49%), dihydroxy Araguspongine (36.36%), methyl & dimethyl derivatives of the latter (12.98 & 10.38% respectively) from HRMS studies. Antifouling activity exhibited by secondary metabolites including bis-1-oxaquinolizidine alkaloids, of the marine sponge, *Haliclona exigua* (Kirkpatrick) was determined [26]. Cyclic Bis-1, 3-dialkylpyridiniums were isolated [27] from the Sponge *Haliclona* sp.

Eight novel cyclic bis-1, 3-dialkylpyridiniums, as well as two known compounds from the cyclostelletamine class, were isolated [27] from the sponge *Haliclona* sp. from Korea. Structures of these novel compounds were determined using combined NMR and FAB-MS/MS analyses. Several of these compounds exhibited moderate cytotoxic and antibacterial activities against A549 cell-line and Gram-positive strains, respectively. A new macrocyclic diamide named Haliclonin A was also isolated [28] from the genus *Haliclona*. The isolation and occurrence of, 1-(1H-indol-3-yloxy) propan-2-ol (1), with the previously synthesized pyrrolidine alkaloid, (2R, 3S, 4R, 5R) pyrrolidine-(1-hydroxyethyl)-3, 4-diol hydrochloride (4), isolated from a natural source Red Sea *Haliclona* sp. for the first time was reported in 2016 [29]. Halitoxin, toxic complex of several marine sponges of the genus *Haliclona* [20] were

reported. Manzamine A-D, isolated from *Haliclona* sp. exhibited prominent antitumour and cytotoxic properties [30, 18]. Haliclonamides C, D and E [31] were reported from *Haliclona* sp. In samples of *Haliclona viscosa* [32], which were collected between 1999 and 2003, several new secondary metabolites-viscosaline, haliclamines C-F, the known cyclostelletamine C, a cyclic monomer and the trimer viscosamin were isolated and identified by NMR and MS methods. The cytotoxic alkaloids Haliclamines A & B were isolated [33] from *Haliclona* sp. (Japanese location). These alkaloids consisted of two tetrahydropyridines linked through C₉ & C₁₂ alkyl chains. New Haliclamines E and F were reported from the Arctic Sponge *Haliclona viscosa* [34]. Cyclic 3-alkyl pyridinium alkaloid monomers were reported from a new Zealand *Haliclona* sp. [35]. The new compounds, dehydrohalicyclins C and F, are the first reported examples of cyclic 3-APA monomers with unsaturation in the alkyl chain. The known compound halicyclin C was also isolated. *Haliclona exigua* (Kirkpatrick) contained bis-1-oxaquinolizidine alkaloids (Xestospongine-D and Araguspogin_C), having vasodilatory activity. A new isoquinoline alkaloid, which was established as 1-hydroxymethyl-7-methoxy isoquinoline 6-ol and the known compound mimosamycin [36].

Renieramycins [37] are very labile compounds, readily decomposing to monomeric renierone, mimosamycin and their analogs. The monomeric alkaloids O-demethyl renierone and mimosamycin are found in *H. cribricutis* and *Reniera* sp. Biologists are of the opinion that the names *Reniera* & *Haliclona* denote one & the same genus.

The novel metabolites, named Halipeptin A & B [38] were isolated from *Haliclona* sp. and showed a very strong anti-inflammatory activity *in vivo*. Chemically both halipeptins A & B are mixed biogenesis metabolites consisting of a peptidic portion connected to a polyketide framework and characterized by the presence of unusual residues along with conventional proteinogenic amino acid units.

Polyacetylenic Compounds

Polyacetylenic long chain fatty acids and fatty alcohols are the distinct lipid composition of the *Haliclona* sp. that possesses significant biological activities [39]. Some polyacetylenic compounds which are isolated from *Haliclona* sp., are osirisynes, haliclonyne [40], lembhynes [41] and chlorinated acetylenes [42]. Many isomers of the chlorinated acetylenes were isolated from *Haliclona lunisimilis* (San Diego). E.g. (1E, 3E, 9Z)-1-chlorohexadeca-5, 7-diyne-1, 3, 9-triene-15-ol and (1Z, 3E, 9Z)-1-chlorohexadeca-5, 7-diyne-1, 3, 9-triene-14-ol. Haliclonyne possesses a diacetylenic carbinol and a 2-yne-4, 5, 6-trihydroxy carboxylic acid group as structural features, making it structurally related to osirisynes A-F previously isolated from the sponge [43].

Sphingosine Derivatives

Ceramides are amides of fatty acids with long-chain di- or trihydroxy bases, the commonest in animals being sphingosine and in plants phytosphingosine. *Haliclona* sp. was found to halicerebroside a [44]. New ceramide from marine sponge *Haliclona koremella* and related compounds as antifouling substances against macroalgae. Various cerebrosides have been isolated from *Haliclona* sp. [45].

Miscellaneous Compounds

Haliclona species have led to the isolation of peptides e.g. hexapeptide waiakeamide [46], tetrahydropyrans [47], hemiketal

[48], sesquiterpenoids [49], heterocyclic sesquiterpene, macrocyclic lactones [50], aminoalcohols [51], long chain acetylene alcohols [52], halipeptins [53], protein, halipeptine (depsipeptides), cyclic peptide, lectin, from *Haliclona* sp. A new pentacyclic sulfated hydroquinone [54] from the marine sponge *Haliclona* sp. Nucleosides are also reported from the Marine Sponge *Haliclona* sp. Three known nucleosides [55] were isolated from the sponge *Haliclona* sp. The structures were established on the basis of NMR data and comparison with those reported, and chemotaxonomic relationships of the sponge nucleosides were discussed. A new compound maleimide-5-oxime was isolated, together with 3, 4-dihydroxybenzoic acid, tetillapyrone, from the ethyl acetate extract of the marine sponge *Haliclona baeri* while tetillapyrone, nortetillapyrone, p-hydroxybenzaldehyde and phenylacetic acid were isolated from the ethyl acetate extract of *Haliclona cymaeformis* collected from the Gulf of Thailand [56]. Venkateshwar *et al.* isolated two fenverolate isomer 4, 5. (S)- α -cyano-3-phenoxy benzyl (S)-2-(4-chlorophenyl)-isovalarate or (S) (S)-fenvalarate and (R) α -cyano-3-phenoxy benzyl (S)-2-(4-chlorophenyl)-isovalarate or (R)(S)-fenvalarate [57].

Biological Activities

Antimicrobial [23], hemolytic, and hemagglutination activities [58] have been studied by comparing natural and cultured sponges and types of solvent used. This study was aimed to extract and to characterize the secondary metabolite from sponges originated from Indonesia (*Haliclona molitba* and *Stylotella aurantium*). *H. exigua* showed potent antibacterial, antioxidant, anti-inflammatory and anticancer activities [59, 60]. Antioxidant activity determination showed that the hexane, dichloromethane and ethyl acetate extracts of marine sponge *Haliclona* sp. showed antioxidant and cytotoxic activities of the marine sponges may be attributed to the zoochemicals present. *Haliclona viscosa* are active against phytopathogenic fungi studied [61]. Nortetillapyrone showed antifungal activity [56], with a preponderance on the dermatophytic filamentous fungi. Some of the nonpolar compounds have shown to have some antibacterial activities [62]. Other activities reported are antifouling [46], neurotogenic [52], hemagglutinating [63], anti HIV [54], anti-inflammatory [38], inhibitor of kinesin family [64], antimicrobial, antimalarial [65] & antitumor [7], anticancer [50], toxicity activity [66], haemolytic [20, 69] & ichthyotoxic [67] and cytotoxic [68] activities.

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