Halogenated (Cl, Br and I) marine steroids and their biological activities: A brief review

Natalia V Zhukova, Tatyana A Gloriozova, Vladimir V Poroikov and Valery M Dembitsky

Abstract

The present review describes the biological activities of natural halogenated (Cl, Br and I) marine steroids. More than twenty biologically active steroids have shown confirmed anti-tumour, antibacterial, antiviral and other activities. The structures and reported and predicted activities of natural halogenated steroids are available. With the computer programme PASS and based on structure-activity relationships (SAR), some additional activities are also predicted, which point towards new possible applications of these lipids. This review emphasizes the role of natural halogenated steroids as an important source and potential leads for drug discovery and they are of great interest to chemists, physicians, biologists, pharmacologists and the pharmaceutical industry.

Keywords: Steroids, marine, lipids, halogenated, activities, SAR, PASS

1. Introduction

Halogenated steroids represent a small group of natural lipid molecules and are found in plants, algae and marine invertebrates. Through the 1960s, halogenated natural products were thought to be infrequent and poisonous products that have since increased dramatically to nearly 5,000 [1-4]. This is thankfully due to excellent reviews and books by Gribble [1, 5-8], who for a quarter of a century devoted his work to the study of halogenated natural metabolites. Previously, we devoted two books [9, 10] and several reviews to halogenated alkaloids [2, 11], fatty acids [3], alkanes and cycloalkanes [12], and other natural halogenated metabolites [13-16]. As already proved by numerous works, there is a relationship between structure and activity, and this principle is called SAR (Structure-Activity-Relationship). We used the computer program PASS, containing about one million chemical compounds and more than 8,000 biological activities, and calculated the biological activity of different natural and/or synthetic compounds [17-20]. PASS predictions are based on SAR analysis of the training set consisting of more than one million drugs, drug candidates and lead compounds. The algorithm of PASS practical utilization is described in detail in several publications [21-23]. This review is devoted to an interesting topic, i.e., natural halogenated steroids, which are found in algae and marine invertebrates.

2. Halogenated Marine Steroids

A significant amount of the halogenated steroids was found in marine sponges, corals, stars, and seaweeds. Interestingly, marine organisms produce steroids containing chlorine, bromine or iodine atoms in the skeleton core [1, 2, 5, 8, 9, 16]. Strong cytotoxic chlorinated steroids, which are called clionastatins A (17) and B (18), have been isolated from the burrowing sponge Cliona nigricans, and these unique molecules contain tri- and tetrachlorinated androstane derivatives, respectively, and they represent the first polyhalogenated steroids found in a living organism, either marine or terrestrial, and the first examples of halogenated androstanes in nature [24]. The chlorinated steroid, aragusterol C (19), was isolated from an Okinawan marine sponge of the genus Xestospongia sp. This isolated steroid strongly inhibited the proliferation of KB cells in vitro and showed potent in vivo antitumour activity against L1210 cells in mice [25]. Aragusteroketal C (20) which is a steroid having a dimethylketal structure was isolated from the same sponge. This chlorinated steroid showed cytotoxic activity against the tumour KB cell line (IC₅₀ = 4 ng/mL) [26].
Cytotoxic chloro ketosteroids, which are called kiheistriones C (21), D (22) and E (23), were present in the extracts of marine sponge *Strongylacedon* sp. from Maui [27]. Unique pentacyclic saturated sesterpene condensed with hydroxyhydroquinone moiety, which are called 6'-chlorodisidein (24) and 6'-bromoisidein (25), respectively, have been isolated from the marine sponge *Disidea pallescens* as disulfate sodium calcium salt [28].

The chlorinated sterol disulfate, chalinulasterol (26), was isolated from the Caribbean sponge *Chalinula molitha* [29]. Two related C-nor-D-homosteroids, nakiterpiosinone (27) and nakiterpiosin (28), were isolated from the sponge *Terpios hoshinota*. Both compounds may be useful as an anticancer agent in tumours resistant to existing antimitotic agents and dependent on Hedgehog pathway responses for growth [30, 31]. Chlorine-containing steroid sulfate (29) and the first natural iodinated steroid (30) have been isolated from the marine sponge *Topsentia* sp. Chlorinated steroid (29) proved to be an effective inhibitor of endo-1,3-β-D-glucanase from the marine mollusc *Spisula sachalinensis* [32].

Chlorinated styptriol triacetate (31) was isolated from the dichloromethane extract of the brown alga *Stypopodium flabelliforme* [33]. The (3β,5α,22R,23S)-22-Chlorocholest-8,14-diene-3,23-diol (32) was isolated from starfish *Echinarachnius parma* [34].

Two unique chloro-pregnane steroids (33 and 34) have been isolated from the eastern Pacific octocoral *Carijoa multiflora* [35]. Three chlorinated steroids, yonarasterols G (35), H (36) and I (37), were isolated from the Okinawan soft coral, *Clavularia viridis* [36]. The structures of marine steroids are presented in Fig. 1, and the biological activities of plant steroids are presented in Table 1.

![Fig 1: Halogenated (Cl, Br and I) marine steroids](image-url)
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| Page | Not studied | Antiinflammatory (0.760)  
Hepatic disorders treatment (0.743)  
Hypolipemic (0.684)  
Antiarthritic (0.677)  
Apoptosis agonist (0.676)  
Prostate disorders treatment (0.588)  
Antiseborrheic (0.587)  
Acute neurologic disorders treatment (0.580)  
Dermatologic (0.575)  
Antifungal (0.556)  |
|---|---|---|
| 9 | Antineoplastic (0.805)  
Apoptosis agonist (0.744)  
Cytoprotectant (0.590)  
Prostate disorders treatment (0.581)  
Dermatologic (0.550)  
Antiviral (Influenza) (0.538)  
Antibacterial (0.536)  
Antiiinflammatory (0.536)  
Antifungal (0.528)  
Dementia treatment (0.519)  |
| 10 | Not studied | Antineoplastic (0.851)  
Biliary tract disorders treatment (0.841)  
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Hepatic disorders treatment (0.828)  
Antisecretorice (0.826)  
Anesthetic general (0.812)  
Aneleptic (0.796)  
Hepatoprotectant (0.790)  
Immunosuppressant (0.770)  
Anticarcinogenic (0.754)  
Antieczematic (0.751)  
Antiiinflammatory (0.744)  
Bone diseases treatment (0.725)  
Antifungal (0.723)  
Atherosclerosis treatment (0.679)  
Prostate disorders treatment (0.673)  |
| 11 | Anticancer | Antineoplastic (0.782)  
Cytostatic (0.593)  |
| 12 | Anticancer | Antineoplastic (0.822)  
Cytostatic (0.582)  |
| 13 | Inhibitor D-glucanase | Glucan endo-1,3-beta-D-glucosidase inhibitor (0.533)  |
| 14 | Inhibitor D-glucanase | Glucan endo-1,3-beta-D-glucosidase inhibitor (0.590)  |
| 15 | Not studied | Antiinflammatory (0.829)  
Hypolipemic (0.737)  
Antineoplastic (0.684)  |

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|      |             | Apoptosis agonist (0.563)  
|      |             | Antieczematic (0.551)  
|      |             | Antipruritic (0.549)  
|      |             | Prostate disorders treatment (0.520)  |
| 17   |             | Antihypercholesterolemic (0.937)  
|      |             | Respiratory analeptic (0.878)  
|      |             | Antiinfectivity, female (0.833)  
|      |             | Anesthetic (0.789)  
|      |             | Immunosuppressant (0.770)  
|      |             | Antieczematic (0.754)  
|      |             | Antineoplastic (0.751)  
|      |             | Antipruritic (0.747)  
|      |             | Antifungal (0.739)  
|      |             | Prostate disorders treatment (0.673)  
|      |             | Antiinflammatory (0.669)  
|      |             | Hair growth stimulant (0.639)  
|      |             | Atherosclerosis treatment (0.631)  |
| 18   |             | Respiratory analeptic (0.894)  
|      |             | Antineoplastic (0.832)  
|      |             | Antihypercholesterolemic (0.789)  
|      |             | Antieczematic (0.787)  
|      |             | Antipruritic (0.778)  
|      |             | Erythropoiesis stimulant (0.776)  
|      |             | Cytoprotectant (0.764)  
|      |             | Antiseborrheic (0.741)  
|      |             | Dermatologic (0.738)  
|      |             | Immunosuppressant (0.735)  
|      |             | Antiinflammatory (0.730)  
|      |             | Antisporic (0.693)  
|      |             | Ovulation inhibitor (0.684)  
|      |             | Prostate disorders treatment (0.667)  |
| 19   |             | Antihypercholesterolemic (0.911)  
|      |             | Myocardial infarction treatment (0.900)  
|      |             | Apoptosis agonist (0.862)  
|      |             | Antineoplastic (0.846)  
|      |             | Antiinflammatory (0.808)  
|      |             | Immunosuppressant (0.799)  
|      |             | Dermatologic (0.787)  
|      |             | Antipruritic (0.779)  
|      |             | Antisporic (0.774)  
|      |             | Hypopilemic (0.751)  
|      |             | Respiratory analeptic (0.742)  
|      |             | Antosteoporotic (0.730)  
|      |             | Prostate disorders treatment (0.623)  
|      |             | Anti diabetic (type 2) (0.617)  
|      |             | Atherosclerosis treatment (0.611)  |
| 20   |             | Respiratory analeptic (0.911)  
|      |             | Myocardial infarction treatment (0.906)  
|      |             | Antihypercholesterolemic (0.845)  
|      |             | Antipruritic (0.810)  
|      |             | Antiinflammatory (0.781)  
|      |             | Immunosuppressant (0.774)  
|      |             | Antineoplastic (0.738)  
|      |             | Antieczematic (0.731)  
|      |             | Antifungal (0.711)  
|      |             | Hepatoprotectant (0.677)  |
3. Conclusion
In this review, we present the structures and biological activities of marine halogenated steroids. The most characteristic biological activities for steroids were antineoplastic, antifungal, anticancer activities, and antibacterial. The biological activity for almost all of the marine steroids is anticancer activity, which is both confirmed and predicted ones.

4. Acknowledgement
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5. Conflict of interest statement
Authors have declared that no competing interests exist.

6. References


