

Review

Pharmacological activities of sulphated steroids derived from marine sources

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ABSTRACT

This review is devoted to sulphated steroids that are produced by brittle star, starfish, sponges, ascidian, snails and algae. Mono sulphated steroids have the pharmacological potential on anti-hypercholesterolemic, anti-neoplastic, and anti-inflammatory activity estimated with a confidence of 88 to 92 percent. Di-sulphated steroids that produced by marine starfish are predicted as having anti-neoplastic, anti-inflammatory and anti-hypercholesterolemic activity with a confidence of 78 to 89 percent. In addition, they may have potential immunosuppressant and hepatoprotective inhibitors estimated with a confidence of 73 to 83 percent. Tri-sulphated steroids exhibit anti-inflammatory and antineoplastic activities with a confidence level of 74 to 82 percent.

Keywords: Steroids, lipids, sulphated, marine sponges, starfish, anticancer

INTRODUCTION

Sulphated compounds, including steroids are widely distributed in nature.¹⁻⁸ Sulphated steroids are found in many animals, reptiles and humans.⁹⁻¹² In addition, they are present in extracts of plants and some shrubs, are produced by fungi, and also found in many marine invertebrates such as brittle star, starfish, sponges, ascidian, snails and algae.^{1,13-15}

One of the known and studied functions of sulphated steroids is that they are like a storehouse of biologically active steroid hormones.¹⁶ As is known, sulphated steroids are biologically inactive molecules in cells and acquire activity under the action of steroid sulfatase (STS) enzyme, which removes the sulphate group in steroids.¹⁶⁻²¹ STS inhibitors are potential therapeutic drugs for the treatment of steroid-dependent cancers such as breast, prostate, endometrial cancer, as well as melanoma cells SK-MEL-28, SK-MEL-5 and RPMI-7951.^{18,22-26} Recently, various groups of scientists have shown that sulfonated steroids can perform the functions of endogenous neuro-modulators.²⁷⁻²⁹

Relationships between chemical structure and biological activity have been known for over 150 years.³⁰ This principle is widely used in pharmacology, biochemistry, bioorganic chemistry and medicine. There are different approaches and methods, but the relationships between structure and activity are constantly preserved. As one of the existing methods is the computer program PASS, which contains about one million chemical compounds and more than 8,000 biological activities. In a number of publications, this method was used and it proved to be very practical with a large degree of effectiveness.³¹⁻³⁴ The algorithm of PASS practical utilization is described in detail in several publications.³⁵⁻³⁹

This review is devoted to sulphated steroid derived from marine sources and their confirmed and predicted biological activities.

Steroid Mono sulphates

Currently, more than 150 sulphated steroids have been found in marine invertebrates and algae. We selected about a third of the steroids that are of potential interest for practical and clinical medicine.^{1,15}

Cholesterol sulphate (**1**, structure see Figure 1 and activities see Table 1) has been isolated from the starfish, *Asterias rubens*.^{40,41}

Cholesterol sulphate (**1**) and cholestanol sulphate (**2**) and were identified as the major components among the 34 different sterol sulphates of the sea cucumber *Eupentacta fraudatrix*.⁴²

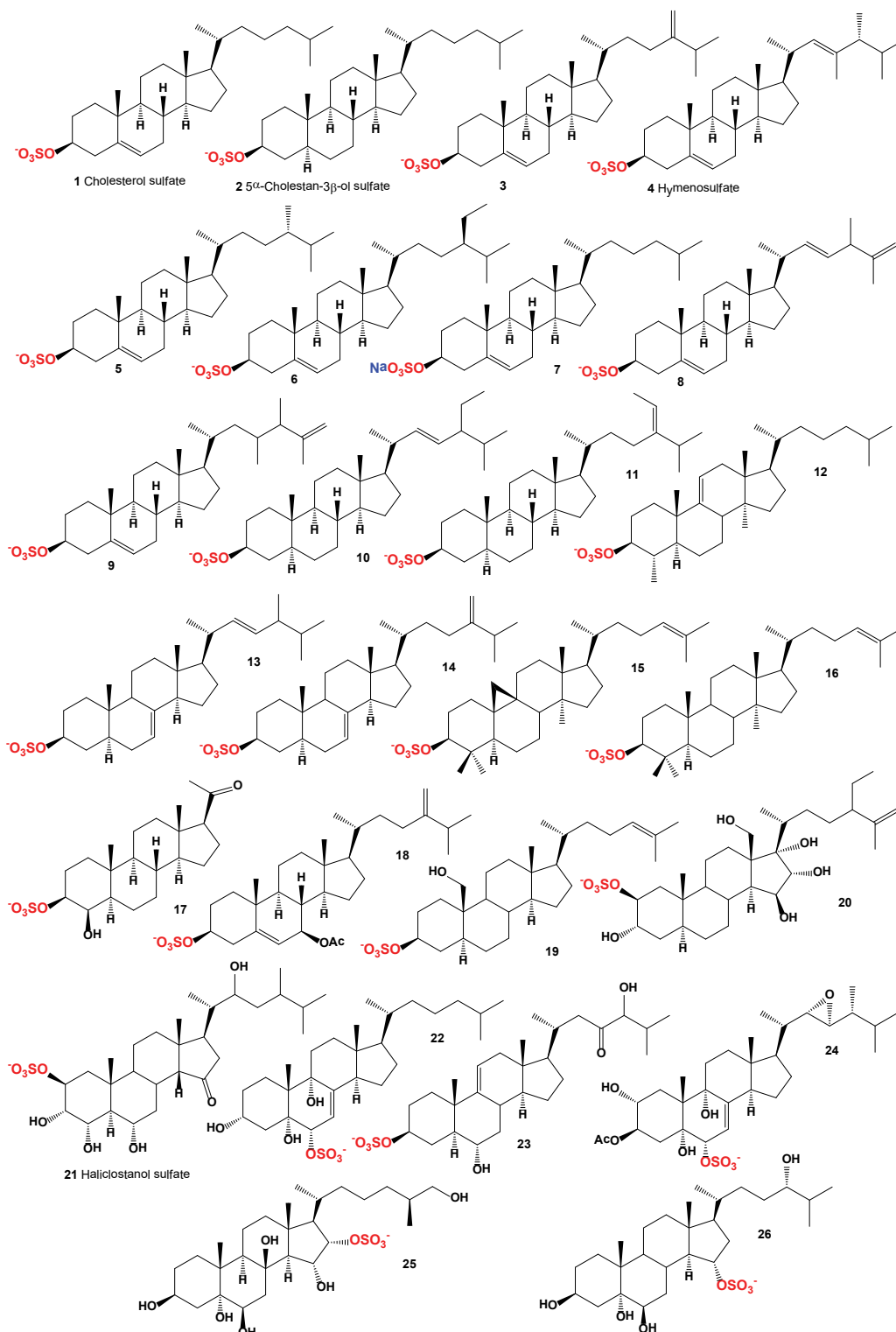


Figure 1. Bioactive steroid monosulphates derived from marine sources

No.	Predicted biological activities of mono sulphate steroids, (Pa)*
1	Wound healing agent (0,975); Antihypercholesterolemic (0,919); Biliary tract disorders treatment (0,861); Hepatoprotectant (0,851); Chemopreventive (0,828); Cholesterol synthesis inhibitor (0,803); Antineoplastic (0,798); Acute neurologic disorders treatment (0,787); Antiinflammatory (0,783); Antieczematic (0,783); Diuretic (0,773); Oxytotic (0,748); Antiosteoporotic (0,731); Antifungal (0,728); Atherosclerosis treatment (0,722); Antipruritic (0,664); Antipsoriatic (0,654); Anesthetic (0,649); Hemostatic (0,646); Antilucerative (0,640); Antibacterial (0,629)
2	Biliary tract disorders treatment (0,955); Wound healing agent (0,945); Antihypercholesterolemic (0,874); Hepatoprotectant (0,870); Antieczematic (0,810); Cholesterol synthesis inhibitor (0,789); Antineoplastic (0,780); Laxative (0,779); Chemopreventive (0,766); Antifungal (0,753); Diuretic (0,752); Antiosteoporotic (0,744); Atherosclerosis treatment (0,733); Antiinflammatory (0,733); Anesthetic (0,726); Antipruritic (0,697); Prostate disorders treatment (0,680); Antipsoriatic (0,658); Antibacterial (0,658)
3	Antihypercholesterolemic (0,907); Wound healing agent (0,846); Chemopreventive (0,841); Biliary tract disorders treatment (0,823); Cholesterol synthesis inhibitor (0,818); Hepatoprotectant (0,816); Diuretic (0,805); Antineoplastic (0,804); Antifungal (0,792); Antiinflammatory (0,786); Antieczematic (0,778); Hypolipemic (0,775); Atherosclerosis treatment (0,724); Antiosteoporotic (0,722); Oxytotic (0,686); Prostate disorders treatment (0,675); Antibacterial (0,649); Antipsoriatic (0,637); Apoptosis agonist (0,603); Hemostatic (0,584)
4	Antihypercholesterolemic (0,886); Antineoplastic (0,858); Biliary tract disorders treatment (0,801); Chemopreventive (0,797); Antiinflammatory (0,792); Wound healing agent (0,783); Hepatoprotectant (0,771); Antieczematic (0,771); Cholesterol synthesis inhibitor (0,753); Apoptosis agonist (0,719); Hemostatic (0,718); Antiosteoporotic (0,718); Atherosclerosis treatment (0,699); Prostate disorders treatment (0,697); Oxytotic (0,691); Antipsoriatic (0,686); Antifungal (0,668); Diuretic (0,644); Antibacterial (0,574)
5	Wound healing agent (0,938); Antihypercholesterolemic (0,909); Biliary tract disorders treatment (0,850); Hepatoprotectant (0,840); Cholesterol synthesis inhibitor (0,806); Antineoplastic (0,791); Antiinflammatory (0,762); Antieczematic (0,759); Antifungal (0,745); Atherosclerosis treatment (0,744); Antiosteoporotic (0,741); Diuretic (0,727); Prostate disorders treatment (0,692); Oxytotic (0,678); Antipsoriatic (0,662); Antibacterial (0,639)
6	Wound healing agent (0,952); Antihypercholesterolemic (0,940); Chemopreventive (0,887); Hepatoprotectant (0,876); Biliary tract disorders treatment (0,847); Cholesterol synthesis inhibitor (0,815); Antineoplastic (0,803); Antiinflammatory (0,790); Atherosclerosis treatment (0,760); Antieczematic (0,754); Antiosteoporotic (0,742); Diuretic (0,740); Antifungal (0,725); Prostate disorders treatment (0,685); Oxytotic (0,670); Apoptosis agonist (0,670); Antibacterial (0,646)
7	Wound healing agent (0,975); Antihypercholesterolemic (0,919); Biliary tract disorders treatment (0,861); Hepatoprotectant (0,851); Chemopreventive (0,828); Cholesterol synthesis inhibitor (0,803); Antineoplastic (0,798); Acute neurologic disorders treatment (0,787); Antiinflammatory (0,783); Antieczematic (0,783); Diuretic (0,773); Oxytotic (0,748); Antiosteoporotic (0,731); Antifungal (0,728); Atherosclerosis treatment (0,722); Antipruritic (0,664); Antipsoriatic (0,654); Anesthetic (0,649); Hemostatic (0,646); Antilucerative (0,640); Antibacterial (0,629)
8	Chemopreventive (0,934); Hemostatic (0,928); Antihypercholesterolemic (0,912); Antineoplastic (0,867); Apoptosis agonist (0,857); Antiinflammatory (0,827); Antieczematic (0,789); Atherosclerosis treatment (0,776); Antipsoriatic (0,766); Antiosteoporotic (0,765); Biliary tract disorders treatment (0,764); Cholesterol synthesis inhibitor (0,750); Hepatoprotectant (0,744); Wound healing agent (0,727); Diuretic (0,711); Prostate disorders treatment (0,701); Oxytotic (0,698); Antifungal (0,682); Antibacterial (0,640); Antilucerative (0,637)
9	Chemopreventive (0,891); Wound healing agent (0,816); Biliary tract disorders treatment (0,807); Antihypercholesterolemic (0,789); Cholesterol synthesis inhibitor (0,788); Antineoplastic (0,791); Antiinflammatory (0,790); Antieczematic (0,778); Hepatoprotectant (0,773); Apoptosis agonist (0,758); Antifungal (0,757); Diuretic (0,755); Atherosclerosis treatment (0,750); Antiosteoporotic (0,710); Oxytotic (0,686); Antibacterial (0,678); Prostate disorders treatment (0,674); Antipsoriatic (0,647); Antilucerative (0,588); Hemostatic (0,579)
10	Antihypercholesterolemic (0,926); Biliary tract disorders treatment (0,879); Hypolipemic (0,833); Antineoplastic (0,822); Chemopreventive (0,806); Atherosclerosis treatment (0,804); Hemostatic (0,801); Antieczematic (0,794); Antiosteoporotic (0,772); Antipsoriatic (0,764); Hepatoprotectant (0,764); Apoptosis agonist (0,757); Antiinflammatory (0,735); Cholesterol synthesis inhibitor (0,729); Antifungal (0,680); Prostate disorders treatment (0,675); Wound healing agent (0,599); Antibacterial (0,591); Diuretic (0,573)
11	Antihypercholesterolemic (0,929); Biliary tract disorders treatment (0,910); Hepatoprotectant (0,876); Hypolipemic (0,839); Antineoplastic (0,781); Chemopreventive (0,780); Antifungal (0,778); Antieczematic (0,777); Cholesterol synthesis inhibitor (0,762); Antiinflammatory (0,725); Wound healing agent (0,712); Atherosclerosis treatment (0,682); Antiosteoporotic (0,676); Antibacterial (0,666); Diuretic (0,631); Prostate disorders treatment (0,628); Antipsoriatic (0,619); Apoptosis agonist (0,593); Hemostatic (0,539)
12	Wound healing agent (0,895); Hepatoprotectant (0,888); Chemopreventive (0,837); Antifungal (0,815); Acute neurologic disorders treatment (0,808); Antineoplastic (0,777); Antiinflammatory (0,770); Cholesterol synthesis inhibitor (0,719); Antieczematic (0,719); Atherosclerosis treatment (0,701); Biliary tract disorders treatment (0,688); Antilucerative (0,686); Apoptosis agonist (0,673); Diuretic (0,611); Antibacterial (0,602); Antipsoriatic (0,592); Prostate disorders treatment (0,588); Antiosteoporotic (0,587); Antihypercholesterolemic (0,520)
13	Antihypercholesterolemic (0,931); Chemopreventive (0,902); Apoptosis agonist (0,894); Antineoplastic (0,866); Hemostatic (0,847); Biliary tract disorders treatment (0,844); Hepatic disorders treatment (0,818); Antiosteoporotic (0,808); Atherosclerosis treatment (0,807); Antipsoriatic (0,783); Antieczematic (0,771); Cholesterol synthesis inhibitor (0,732); Antiinflammatory (0,701); Prostate disorders treatment (0,686); Antifungal (0,652); Contraceptive (0,628); Spasmolytic (0,563); Wound healing agent (0,556); Antibacterial (0,551)
14	Antihypercholesterolemic (0,897); Hepatoprotectant (0,879); Biliary tract disorders treatment (0,866); Chemopreventive (0,850); Cholesterol synthesis inhibitor (0,819); Antifungal (0,807); Antieczematic (0,778); Antineoplastic (0,777); Atherosclerosis treatment (0,731); Diuretic (0,728); Antiosteoporotic (0,702); Apoptosis agonist (0,696); Antiinflammatory (0,695); Wound healing agent (0,663); Antibacterial (0,650); Prostate disorders treatment (0,645); Antipsoriatic (0,631); Antilucerative (0,584)
15	Chemopreventive (0,944); Hepatoprotectant (0,872); Antifungal (0,831); Antiinflammatory (0,823); Antieczematic (0,809); Apoptosis agonist (0,808); Antineoplastic (0,795); Cholesterol synthesis inhibitor (0,714); Atherosclerosis treatment (0,708); Immunosuppressant (0,708); Biliary tract disorders treatment (0,702); Wound healing agent (0,677); Antibacterial (0,651); Antipsoriatic (0,628); Antilucerative (0,611)
16	Wound healing agent (0,965); Hepatoprotectant (0,933); Chemopreventive (0,913); Antieczematic (0,825); Antilucerative (0,810); Antiinflammatory (0,809); Antifungal (0,806); Antineoplastic (0,796); Biliary tract disorders treatment (0,791); Apoptosis agonist (0,790); Cholesterol synthesis inhibitor (0,762); Antihypercholesterolemic (0,726); Atherosclerosis treatment (0,717); Diuretic (0,713); Antipsoriatic (0,678); Antibacterial (0,650); Antiosteoporotic (0,638)
17	Hepatoprotectant (0,893); Erythropoiesis stimulant (0,789); Antineoplastic (0,772); Alopecia treatment (0,771); Diuretic (0,759); Immunosuppressant (0,737); Chemopreventive (0,715); Antiinflammatory (0,713); Antieczematic (0,691); Biliary tract disorders treatment (0,684); Prostate disorders treatment (0,677); Atherosclerosis treatment (0,611); Antifungal (0,589); Anesthetic (0,584); Menopausal disorders treatment (0,560); Antibacterial (0,554); Cholesterol synthesis inhibitor (0,550)
18	Antihypercholesterolemic (0,906); Chemopreventive (0,882); Biliary tract disorders treatment (0,847); Cholesterol synthesis inhibitor (0,823); Hepatoprotectant (0,812); Antineoplastic (0,803); Antifungal (0,796); Antieczematic (0,766); Antiinflammatory (0,760); Antibacterial (0,734); Diuretic (0,719); Atherosclerosis treatment (0,705); Apoptosis agonist (0,656); Antiosteoporotic (0,653); Antipsoriatic (0,620); Hemostatic (0,614); Prostate disorders treatment (0,584); Antimycobacterial (0,531)
19	Hepatoprotectant (0,933); Biliary tract disorders treatment (0,895); Antihypercholesterolemic (0,895); Wound healing agent (0,885); Antineoplastic (0,845); Antieczematic (0,838); Chemopreventive (0,834); Apoptosis agonist (0,826); Antifungal (0,788); Diuretic (0,784); Acute neurologic disorders treatment (0,779); Cholesterol synthesis inhibitor (0,776); Antiinflammatory (0,745); Atherosclerosis treatment (0,712); Antiosteoporotic (0,696); Antibacterial (0,690)
20	Hepatoprotectant (0,859); Antiinflammatory (0,832); Chemopreventive (0,821); Antineoplastic (0,805); Antifungal (0,799); Apoptosis agonist (0,730); Cholesterol synthesis inhibitor (0,667); Diuretic (0,666); Antibacterial (0,628); Biliary tract disorders treatment (0,599); Allergic conjunctivitis treatment (0,595); Antieczematic (0,595); Atherosclerosis treatment (0,561); Wound healing agent (0,536); Antiarthritic (0,534); Antiosteoporotic (0,529)

* Only activities with Pa > 0.5 are shown

Table 1. Predicted biological activities of mono sulphate steroids

The 24-methylidene-cholesterol sulphate (**3**) was found in the diatomic microalga *Nitzschia alba* more than 50 years ago,⁴³ and other derivative of cholesterol sulfate called hymenosulfate (**4**) with an unusual side chain was found in the haptophytic microalga *Hymenomonas* sp.⁴⁴ Three sulphated sterols, cholesterol sulphate (**1**), 24-methylcholest-5-en-3 β ol sulphate (**5**) and 5-sitosten-3 β -ol sulphate (**6**) produced by the diatom *Skeletonema*

marinoi.⁴⁵ The cholest-5-ene-3 β -sulfate sodium (**7**) was isolated from the methanol extract of the sea urchin *Diadema savignyi*.⁴⁶ Two derivatives of cholesterol sulphate (**8** and **9**) were isolated from the tropical marine cucumber *Holothuria* sp.,⁴⁷ and two derivatives of cholestanol sulphate (**10** and **11**), and minor sterols (**12-16**) were detected in the Far Eastern holothurian *Eupentacta fraudatrix*.⁴²

An Australian marine sponge *Stilopus australis* produced sulphated steroid with the pregnane skeleton (**17**).⁴⁸ An annasterol sulphate (**18**) was isolated from the Pacific deep-water sponge *Poecilastra laminaris*, and this compound showed a β -1,3-glucanase inhibitor.⁴⁹ Polyhydroxysteroid monosulphate (**19**) was found in extract of the sponge *Toxadocia zumi*.⁵⁰ Rare steroid monosulphate with the sulfate group in 2 β -position (**20**) was isolated from sponge *Echinoclathria suhispidia* collected from the Japan Sea near the coast of Japan.⁵¹ The Malaysian sponge *Haliclona* sp. from an Indo-Pacific has yielded haliclostanone sulphate (**21**).⁵² The unique cytotoxic steroid (**22**) containing a sulphate group in 6 α -position was found in the sponge *Dysidea fragilis* collected from the lagoon of Venice, Italy.⁵³ Sulphated steroid called apheloketotriol (**23**) was isolated from a Far Eastern sponge *Aphelasterias japonica*,⁵⁴ and acanthosterol E (**24**) was found in the sponge *Acanthodendrilla* sp. contain sulphate group in 6-position.⁵⁵

Rare monosulphate (**25**) containing sulfate group in 16-position was found in starfish *Luidia clathrata* (family Luidiidae)⁵⁶ although the other 3-monosulfate (**26**) was isolated from Far Eastern starfish *Luidia quinaria* (Japan Sea).⁵⁷

Three sulfated steroidal glycosides (**27-29**, structure see Figure 2 and activities see Table 2) were isolated from the visceral extract of the cone snail *Conus pulicarius*. The three new compounds exhibited significant *in vitro* cytotoxicity (GI₅₀ values down to 0.49 μ M) against the K562 human leukemia cell line.⁵⁸

Three sulfated steroid monoglycosides, leptaochotensosides A–C (**30-32**), and a sulphated polyhydroxylated steroid (**33**) were isolated from the alcoholic extract of the Far Eastern starfish *Leptasterias ochotensis*.⁵⁹ Leptaochotensoside A (**30**) demonstrated inhibition of T-47D cell colony formation in a soft agar clonogenic assay at nontoxic doses. In addition, this compound decreased the epidermal growth factor (EGF)-induced colony formation of mouse epidermal JB6 Cl41 cells. The cancer preventive action of (**30**) is realized through regulation of mitogen-activated protein kinase (MAPK) signaling pathway.

A rare sulphated steroid at position 5, named phallusiasterol A (**34**) was isolated from the Mediterranean ascidian *Phallusia fumigata*.⁶⁰ Polyhydroxylated sterol called asterosaponin P2 (**35**), with the sulfate group only in the side chain, isolated from the Far-Eastern starfish *Patiria (Asterina) pectinifera*,⁶¹ exhibited activity against HSV-1, with MIC values of 0.07 μ M.⁶²

A series of sulphated steroid-containing amide fragment (**36-41**) were isolated from marine invertebrates. So starfish, *Styracaster caroli* which was collected at a depth of 2000 m between the islands of Thio and Lifou (New Caledonia) contained unique polyhydroxylated steroids in water-acetone extract (**36** and **37**).⁶³ The same steroids (**36-39** and **41**) were found in the sponge *Polymastia boletiformis*.^{64,65}

Sulphated steroid xyloside, minutosides B (**40**) has been isolated from the brine shrimp active fraction of the ethanolic extract of

the starfish *Anasterias minuta*. This xyloside exhibited antifungal activity against *Cladosporium cucumerinum* and *Aspergillus flavus*.⁶⁶

Di- and tri-sulphate steroids

Di- and trisulphates of steroids represent a fairly rare group of lipids. Their total content in marine organisms is two to three times less than that of steroids containing one sulphate group.^{1,15} The antiviral orthoesterol B (**42**, structure see Fig. 3 and activities see Table 3) showed antiviral activity was found in the marine sponge *Petrosia weinbergi*.⁶⁷ Weinbersterol B (**43**), sulphated tetrahydroxy steroid with an unprecedented cyclopropane-containing side chain, was isolated from the sponge *Petrosia weinbergi*. This compound is active *in vitro* against feline leukemia virus, and active *in vitro* against HIV.⁶⁸

A series of steroid disulphates were found in starfishes and ophiuroids. Thus compound (**44**) was isolated from the starfish *Tremaster novaecaledonia*⁶³ and from *Aphelasterias japonica*.⁶⁹ Brittle stars are echinoderms and belong to the class Ophiuroidea produce a large number of active metabolites including lipids, fatty acids and steroids.⁷⁰⁻⁷⁴ Sulphated stanols are widely distributed in various representatives in more than 30 species of Ophiuroidea.^{1,13} Disulphate stanol (**45**) was first discovered in brittle star *Ophioderma longicaudum*⁷⁵ and another steroid (**46**) containing an additional hydroxy group at C12 was isolated from the ophiuroids *Ophioderma longicaudum* from the Mediterranean Sea.^{1,15,76} The disulphated steroid (**47**) containing three functional groups in the ring A was isolated from the antarctic brittle star *Ophioparte gigas*,⁷⁷ the same steroid also was found in *Astroclades exiguus* and *Amphiophiura ponderosa*.⁷⁸ Rare sulphated steroid (**49**) containing sulphate groups in 2 β - and 21 α -positions, was detected in extracts from the starfishes of the starfish *Pteraster tessellatus*.⁷⁹

Trisulfated polyhydroxysteroids are rare and typical metabolites which produced by marine sponges and echinoderms.^{1,15,80} Halistanol sulphate sodium (**50**), the most widespread sponge steroid sulphate, was discovered from the sponge *Halichondria moori* by Fusetani and co-workers more than 35 years ago.⁸¹ Analogue of compound (**50**), halistanol sulfate I sodium (**51**) was isolated from a marine sponge *Halichondria* sp. collected at Hachijo-jima Island. Obtained steroid showed inhibitory activity against SIRT 1-3 with IC₅₀ of 45.9, 18.9 and 21.8 μ M respectively.⁸²

Polyhydroxylated sterol derivatives called topsensterol B (**52**) has been isolated from a marine sponge *Topsentia* sp. collected from the South China Sea. Isolated compound exhibited cytotoxicity against human gastric carcinoma cell line SGC-7901 with an IC₅₀ value of 8.0 μ M,⁸³ and topsentiasterol sulphate E (**53**) was found in the sponge *Sphaciospongia* sp., collected in the Philippines. This compound inhibited PKCzeta with IC₅₀ value of 1.21 μ M, and in a cell-based assay, also inhibited NF-kappa B activation with EC₅₀ value of 12 μ M.⁸⁴

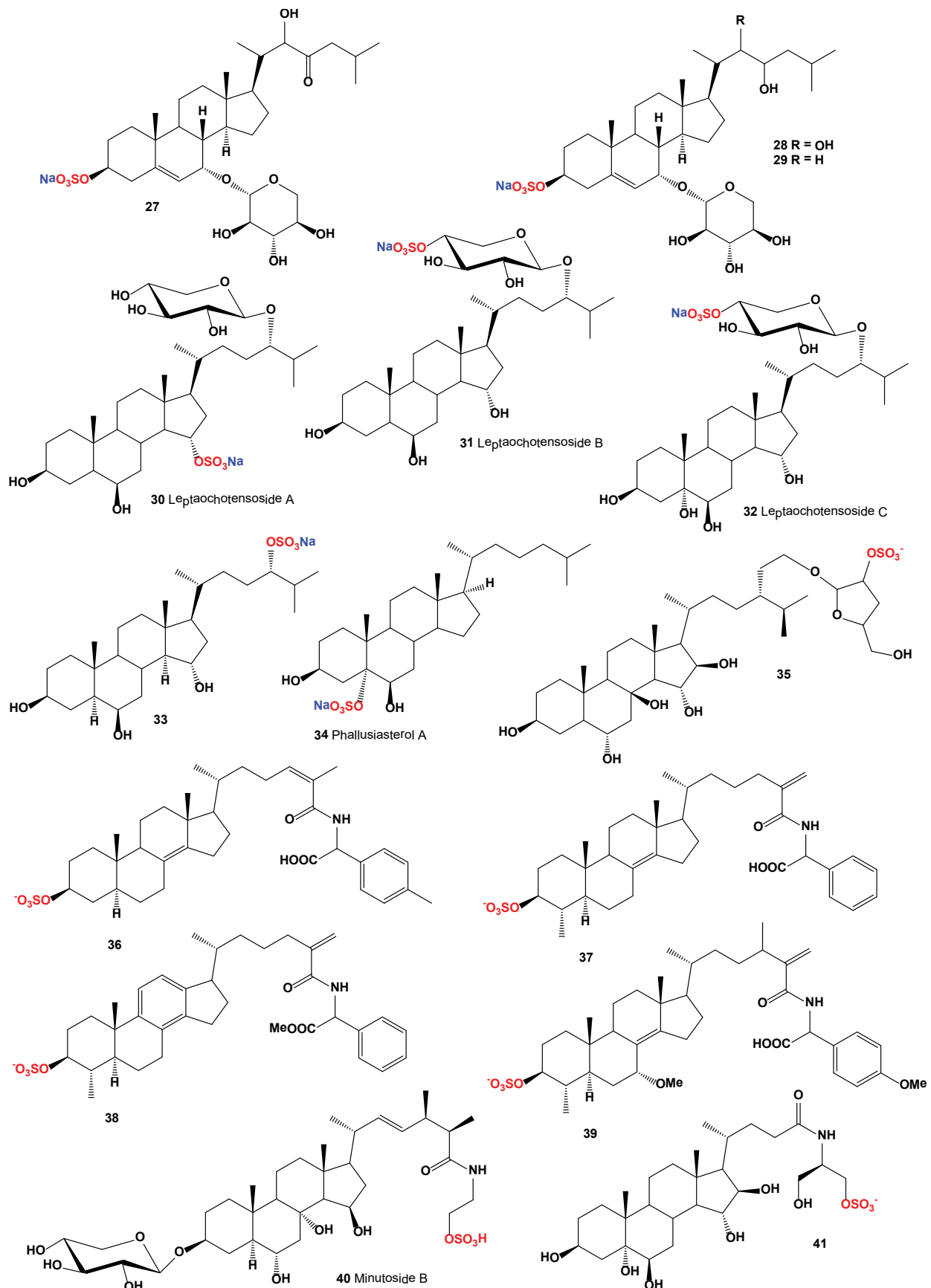


Figure 2: Bioactive steroid monosulphates derived from marine sources

No.	Predicted biological activities of mono sulphate steroids, (Pa)*
21	Hepatoprotectant (0,968); Antineoplastic (0,830); Antiinflammatory (0,817); Apoptosis agonist (0,792); Chemopreventive (0,783); Antifungal (0,767); Biliary tract disorders treatment (0,704); Antipsoriatic (0,694); Atherosclerosis treatment (0,691) Cholesterol synthesis inhibitor (0,682); Antieczematiac (0,676); Antibacterial (0,626); Rhinitis treatment (0,617); Prostate disorders treatment (0,606) Wound healing agent (0,592); Diuretic (0,552); Antiestoporotic (0,542)
22	Antischematic, cerebral (0,850); Antiestoporotic (0,814); Antifungal (0,807); Chemopreventive (0,777); Antineoplastic (0,779) Hepatoprotectant (0,774); Antieczematiac (0,768); Antihypercholesterolemic (0,748); Antipsoriatic (0,739); Biliary tract disorders treatment (0,728) Cholesterol synthesis inhibitor (0,717); Atherosclerosis treatment (0,712); Antiinflammatory (0,710); Apoptosis agonist (0,680) Laxative (0,631); Cardiotoxic (0,599); Wound healing agent (0,595); Anesthetic (0,593); Antibacterial (0,555)
23	Hepatoprotectant (0,844); Biliary tract disorders treatment (0,833); Chemopreventive (0,821); Wound healing agent (0,794); Antifungal (0,774) Antineoplastic (0,765); Diuretic (0,749); Antieczematiac (0,728); Cholesterol synthesis inhibitor (0,727); Antiinflammatory (0,697) Acute neurologic disorders treatment (0,687); Antihypercholesterolemic (0,671); Atherosclerosis treatment (0,669); Antiestoporotic (0,653) Prostate disorders treatment (0,640); Antibacterial (0,628); Antipsoriatic (0,570)
24	Antifungal (0,860); Antineoplastic (0,829); Antischematic, cerebral (0,785); Hepatic disorders treatment (0,771); Antieczematiac (0,771) Antipsoriatic (0,717); Antiinflammatory (0,707); Chemopreventive (0,691); Antibacterial (0,682); Antiestoporotic (0,654) Angiogenesis inhibitor (0,629); Cholesterol synthesis inhibitor (0,618); Cardiotoxic (0,583); Apoptosis agonist (0,570); Atherosclerosis treatment (0,543); Antiarthritic (0,523)
25	Antineoplastic (0,813); Antifungal (0,714); Antiestoporotic (0,699); Antiinflammatory (0,689); Chemopreventive (0,677) Biliary tract disorders treatment (0,639); Atherosclerosis treatment (0,629); Apoptosis agonist (0,629); Hepatoprotectant (0,625) Antieczematiac (0,612); Cholesterol synthesis inhibitor (0,593); Antipsoriatic (0,582); Allergic conjunctivitis treatment (0,542); Antibacterial (0,535)
26	Biliary tract disorders treatment (0,931); Antiinflammatory (0,824); Antineoplastic (0,823); Antifungal (0,808); Hepatic disorders treatment (0,794) Antiestoporotic (0,782); Antieczematiac (0,771); Apoptosis agonist (0,759); Chemopreventive (0,753); Antipruritic (0,743) Atherosclerosis treatment (0,715); Cholesterol synthesis inhibitor (0,673); Antipsoriatic (0,665); Antibacterial (0,650); Diuretic (0,636) Wound healing agent (0,627); Anesthetic (0,625); Prostate disorders treatment (0,607)
27	Wound healing agent (0,953); Antihypercholesterolemic (0,926); Hepatoprotectant (0,925); Chemopreventive (0,924); Antineoplastic (0,837) Antifungal (0,826); Antiinflammatory (0,800); Biliary tract disorders treatment (0,777); Antibacterial (0,766); Diuretic (0,739) Atherosclerosis treatment (0,671); Cholesterol synthesis inhibitor (0,670); Antieczematiac (0,648); Apoptosis agonist (0,628); Acute neurologic disorders treatment (0,593); Antipruritic (0,567); Antipsoriatic (0,546); Hemostatic (0,536); Prostate disorders treatment (0,536)
28	Wound healing agent (0,963); Hepatoprotectant (0,915); Antihypercholesterolemic (0,902); Antiinflammatory (0,859); Antineoplastic (0,854) Diuretic (0,800); Apoptosis agonist (0,790); Antifungal (0,787); Biliary tract disorders treatment (0,776); Antibacterial (0,708) Atherosclerosis treatment (0,675); Antieczematiac (0,649); Cholesterol synthesis inhibitor (0,639); Proliferative diseases treatment (0,608) Hemostatic (0,601); Antipsoriatic (0,553); Prostate disorders treatment (0,532)
29	Wound healing agent (0,975); Antihypercholesterolemic (0,942); Chemopreventive (0,918); Hepatoprotectant (0,915); Antifungal (0,831) Biliary tract disorders treatment (0,807); Antineoplastic (0,806); Diuretic (0,794); Antiinflammatory (0,763); Antibacterial (0,743) Cholesterol synthesis inhibitor (0,712); Antipruritic (0,698); Atherosclerosis treatment (0,693); Antieczematiac (0,649); Hemostatic (0,601) Antipsoriatic (0,585); Prostate disorders treatment (0,545); Antiestoporotic (0,544); Antiulcerative (0,550); Antidiabetic (0,531)
30	Wound healing agent (0,980); Hepatoprotectant (0,972); Biliary tract disorders treatment (0,958); Chemopreventive (0,935) Antihypercholesterolemic (0,901); Antifungal (0,844); Antiinflammatory (0,827); Antineoplastic (0,818); Antipruritic (0,779); Laxative (0,758) Antibacterial (0,751); Antieczematiac (0,702); Atherosclerosis treatment (0,685); Antipsoriatic (0,654); Diuretic (0,638) Antiestoporotic (0,621); Prostate disorders treatment (0,618)
31	Wound healing agent (0,977); Hepatoprotectant (0,965); Chemopreventive (0,922); Antihypercholesterolemic (0,887) Biliary tract disorders treatment (0,855); Antineoplastic (0,841); Antifungal (0,834); Antiinflammatory (0,820); Laxative (0,788); Antipruritic (0,767) Antibacterial (0,746); Antieczematiac (0,713); Respiratory analeptic (0,692); Atherosclerosis treatment (0,679); Antipsoriatic (0,663); Antiestoporotic (0,628)
32	Chemopreventive (0,931); Hepatoprotectant (0,893); Wound healing agent (0,887); Antineoplastic (0,861); Antifungal (0,842) Antiinflammatory (0,837); Biliary tract disorders treatment (0,817); Apoptosis agonist (0,748); Antipruritic (0,719); Antihypercholesterolemic (0,716) Antibacterial (0,715); Atherosclerosis treatment (0,704); Antiestoporotic (0,700); Laxative (0,692); Antieczematiac (0,668); Analeptic (0,661) Antipsoriatic (0,640); Diuretic (0,609)
33	Wound healing agent (0,888); Hair growth stimulant (0,858); Antineoplastic (0,831); Hepatoprotectant (0,818); Antifungal (0,812) Antiinflammatory (0,812); Antieczematiac (0,811); Biliary tract disorders treatment (0,801); Antihypercholesterolemic (0,782); Antipruritic (0,775) Anesthetic (0,773); Angiogenesis inhibitor (0,754); Analeptic (0,743); Antipsoriatic (0,720); Atherosclerosis treatment (0,717) Antiestoporotic (0,708); Antibacterial (0,708); Prostate disorders treatment (0,665)
34	Wound healing agent (0,861); Chemopreventive (0,860); Antihypercholesterolemic (0,850); Anesthetic (0,833); Hepatoprotectant (0,817) Antineoplastic (0,813); Antieczematiac (0,802); Antifungal (0,802); Antifungal (0,788); Biliary tract disorders treatment (0,788); Antiinflammatory (0,777) Antiestoporotic (0,774); Laxative (0,769); Diuretic (0,747); Cholesterol synthesis inhibitor (0,742); Apoptosis agonist (0,707) Analeptic (0,701); Atherosclerosis treatment (0,685); Antipruritic (0,682); Antipsoriatic (0,668)
35	Hepatoprotectant (0,924); Chemopreventive (0,913); Antifungal (0,860); Antineoplastic (0,844); Antihypercholesterolemic (0,825) Antibacterial (0,797); Antiinflammatory (0,731); Biliary tract disorders treatment (0,727); Laxative (0,702); Cholesterol synthesis inhibitor (0,678) Wound healing agent (0,662); Atherosclerosis treatment (0,661); Apoptosis agonist (0,614); Genital warts treatment (0,605); Antipsoriatic (0,592); Antiestoporotic (0,542)
36	Antihypercholesterolemic (0,865); Biliary tract disorders treatment (0,794); Antieczematiac (0,745); Antineoplastic (0,716) Hepatic disorders treatment (0,692); Antifungal (0,682); Antiinflammatory (0,668); Atherosclerosis treatment (0,657); Antibacterial (0,656) Antipsoriatic (0,592); Diuretic (0,585); Cholesterol synthesis inhibitor (0,582); Autoimmune disorders treatment (0,573) Antiestoporotic (0,563); Prostate disorders treatment (0,560); Apoptosis agonist (0,535); Wound healing agent (0,526)
37	Antifungal (0,727); Antieczematiac (0,722); Antineoplastic (0,686); Antihypercholesterolemic (0,679); Hepatoprotectant (0,653) Atherosclerosis treatment (0,638); Antiinflammatory (0,607); Antibacterial (0,599); Biliary tract disorders treatment (0,592); Antipsoriatic (0,588) Acute neurologic disorders treatment (0,552); Antiestoporotic (0,537); Prostate disorders treatment (0,537)
38	Cholesterol antagonist (0,820); Antineoplastic (0,626); Antiinflammatory (0,614); Immunosuppressant (0,592); Atherosclerosis treatment (0,591) Hypolipemic (0,580); Antifungal (0,571); Antieczematiac (0,566); Antibacterial (0,544); Antiinfertility, female (0,535)
39	Cholesterol antagonist (0,934); Antifungal (0,696); Antieczematiac (0,695); Antineoplastic (0,691); Immunosuppressant (0,678) Hepatoprotectant (0,644); Antibacterial (0,627); Antihypercholesterolemic (0,608); Hypolipemic (0,606); Biliary tract disorders treatment (0,561) Antiinflammatory (0,551); Atherosclerosis treatment (0,534)
40	Antineoplastic (0,874); Chemopreventive (0,829); Antiinflammatory (0,718); Hepatoprotectant (0,699); Antihypercholesterolemic (0,697) Antifungal (0,690); Apoptosis agonist (0,685); Wound healing agent (0,681); Antipsoriatic (0,673); Spasmolytic (0,672) Atherosclerosis treatment (0,647); Antibacterial (0,634); Antieczematiac (0,621); Proliferative diseases treatment (0,534); Antiestoporotic (0,524)
41	Antineoplastic (0,849); Antiinflammatory (0,777); Atherosclerosis treatment (0,748); Antiestoporotic (0,703); Apoptosis agonist (0,692); Antifungal (0,673); Hepatoprotectant (0,618); Antibacterial (0,590); Antipsoriatic (0,581); Biliary tract disorders treatment (0,567); Antipruritic, allergic (0,534); Prostate disorders treatment (0,531)

* Only activities with Pa > 0.5 are shown

Table 2. Predicted biological activities of mono sulphate steroids

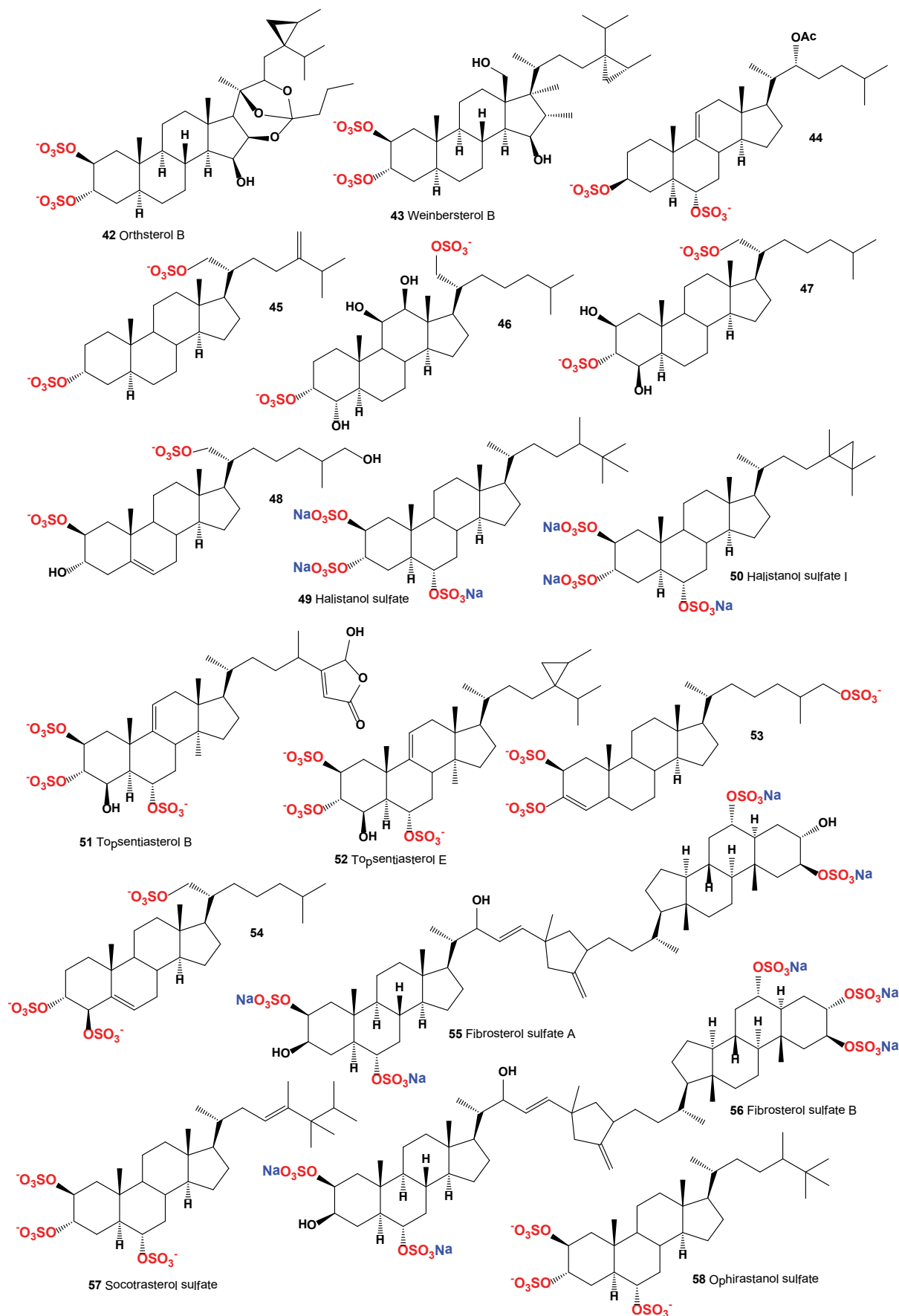


Figure 3: Bioactive steroid di- and trisulphates derived from marine sources

No.	Predicted biological activities of di- and trisulphate steroids, (Pa)*
42	Angiogenesis inhibitor (0,926); Antineoplastic (0,869); Antiinflammatory (0,781); Autoimmune disorders treatment (0,762) Immunosuppressant (0,692); Antidiabetic symptomatic (0,661); Hepatoprotectant (0,608); Antibacterial (0,573); Antifungal (0,547) Allergic conjunctivitis treatment (0,535); Antimetastatic (0,534); Biliary tract disorders treatment (0,507)
43	Hepatoprotectant (0,852); Antiinflammatory (0,811); Antineoplastic (0,796); Immunosuppressant (0,732); Atherosclerosis treatment (0,646) Allergic conjunctivitis treatment (0,603); Biliary tract disorders treatment (0,599); Antiarthritic (0,594); Prostate disorders treatment (0,570) Antieczematic (0,568); Cholesterol synthesis inhibitor (0,563); Antibacterial (0,558); Antifungal (0,552); Acute neurologic disorders treatment (0,546)
44	Biliary tract disorders treatment (0,928); Hepatic disorders treatment (0,889); Wound healing agent (0,888); Antineoplastic (0,836) Acute neurologic disorders treatment (0,832); Antiinflammatory (0,831); Antifungal (0,732); Antieczematic (0,714); Chemopreventive (0,712) Atherosclerosis treatment (0,684); Cholesterol synthesis inhibitor (0,656); Apoptosis agonist (0,649); Antipsoriatic (0,641); Prostate disorders treatment (0,624); Antihypercholesterolemic (0,617); Antibacterial (0,570); Antiosteoporotic (0,555)
45	Biliary tract disorders treatment (0,843); Antineoplastic (0,788); Immunosuppressant (0,758); Cholesterol synthesis inhibitor (0,755) Antisecretoric (0,751); Antieczematic (0,751); Antifungal (0,736); Hepatoprotectant (0,731); Antiinflammatory (0,696); Atherosclerosis treatment (0,693); Antibacterial (0,635); Chemopreventive (0,631); Prostate disorders treatment (0,603); Antiosteoporotic (0,598) Antihypercholesterolemic (0,580); Wound healing agent (0,539); Antidiabetic (0,538); Antipsoriatic (0,532)
46	Antisecretoric (0,820); Antineoplastic (0,793); Hepatic disorders treatment (0,785); Immunosuppressant (0,774); Acute neurologic disorders treatment (0,770); Antiinflammatory (0,755); Angiogenesis inhibitor (0,747); Biliary tract disorders treatment (0,713); Antieczematic (0,682) Atherosclerosis treatment (0,636); Wound healing agent (0,606); Antibacterial (0,606); Antifungal (0,605); Cholesterol synthesis inhibitor (0,587) Antiosteoporotic (0,571); Prostate disorders treatment (0,543)
47	Wound healing agent (0,933); Hepatoprotectant (0,813); Antieczematic (0,806); Acute neurologic disorders treatment (0,786); Antineoplastic (0,782) Antiinflammatory (0,781); Antifungal (0,718); Biliary tract disorders treatment (0,693); Angiogenesis inhibitor (0,681); Cholesterol synthesis inhibitor (0,671); Atherosclerosis treatment (0,647); Chemopreventive (0,641); Antibacterial (0,629); Prostate disorders treatment (0,607); Antiosteoporotic (0,606); Antipsoriatic (0,604)
48	Wound healing agent (0,942); Antisecretoric (0,836); Antineoplastic (0,820); Hepatoprotectant (0,811); Antiinflammatory (0,797) Antieczematic (0,771); Acute neurologic disorders treatment (0,765); Chemopreventive (0,755); Cholesterol synthesis inhibitor (0,734) Diuretic (0,710); Antifungal (0,692); Prostate disorders treatment (0,677); Antihypercholesterolemic (0,635); Antipsoriatic (0,626) Atherosclerosis treatment (0,623); Antiosteoporotic (0,595); Biliary tract disorders treatment (0,586); Antibacterial (0,559); Oxytocic (0,550)
49	Biliary tract disorders treatment (0,963); Hepatic disorders treatment (0,934); Wound healing agent (0,789); Antieczematic (0,737) Immunosuppressant (0,731); Antineoplastic (0,711); Cholesterol synthesis inhibitor (0,696); Antiinflammatory (0,689); Antiosteoporotic (0,668) Atherosclerosis treatment (0,665); Prostate disorders treatment (0,637); Antipsoriatic (0,632); Antifungal (0,626); Chemopreventive (0,601) Antihypercholesterolemic (0,527); Antibacterial (0,518)
50	Biliary tract disorders treatment (0,957); Hepatic disorders treatment (0,929); Antieczematic (0,797); Antineoplastic (0,764) Antiinflammatory (0,723); Antiosteoporotic (0,711); Immunosuppressant (0,705); Atherosclerosis treatment (0,684); Hypolipemic (0,681) Chemopreventive (0,670); Prostate disorders treatment (0,666); Cholesterol synthesis inhibitor (0,637); Antipsoriatic (0,629); Wound healing agent (0,590)
51	Chemopreventive (0,948); Hepatoprotectant (0,915); Antiinflammatory (0,889); Wound healing agent (0,868); Antifungal (0,811) Immunosuppressant (0,806); Antineoplastic (0,770); Antipsoriatic (0,764); Apoptosis agonist (0,746); Antitumor (0,709); Antibacterial (0,630) Antieczematic (0,615); Antiosteoporotic (0,584); Cholesterol synthesis inhibitor (0,562); Antiarthritic (0,553); Hypolipemic (0,529)
52	Hepatic disorders treatment (0,884); Biliary tract disorders treatment (0,835); Antiinflammatory (0,788); Immunosuppressant (0,735) Antineoplastic (0,729); Chemopreventive (0,723); Antifungal (0,666); Antieczematic (0,632); Antipsoriatic (0,630); Antiarthritic (0,574) Cholesterol synthesis inhibitor (0,572); Atherosclerosis treatment (0,558); Prostate disorders treatment (0,543); Apoptosis agonist (0,528)
53	Antiinflammatory (0,821); Immunosuppressant (0,758); Hepatoprotectant (0,747); Biliary tract disorders treatment (0,725); Antieczematic (0,734) Antineoplastic (0,734); Wound healing agent (0,717); Antifungal (0,687); Cholesterol synthesis inhibitor (0,661); Prostate disorders treatment (0,659) Antiosteoporotic (0,648); Antibacterial (0,623); Antipsoriatic (0,617); Acute neurologic disorders treatment (0,594); Chemopreventive (0,592) Atherosclerosis treatment (0,590); Rheumatoid arthritis treatment (0,538)
54	Antisecretoric (0,824); Wound healing agent (0,812); Antineoplastic (0,790); Immunosuppressant (0,765); Hepatoprotectant (0,750) Antieczematic (0,727); Acute neurologic disorders treatment (0,691); Antiinflammatory (0,685); Cholesterol synthesis inhibitor (0,655) Biliary tract disorders treatment (0,648); Prostate disorders treatment (0,639); Angiogenesis inhibitor (0,621); Atherosclerosis treatment (0,596) Antifungal (0,589); Antihypercholesterolemic (0,579); Antiosteoporotic (0,563); Chemopreventive (0,546); Antipsoriatic (0,525)
55	Hepatoprotectant (0,918); Antineoplastic (0,868); Antieczematic (0,864); Antiinflammatory (0,833); Biliary tract disorders treatment (0,824) Immunosuppressant (0,766); Apoptosis agonist (0,738); Antifungal (0,702); Chemopreventive (0,688); Antiosteoporotic (0,686) Antipsoriatic (0,680); Antibacterial (0,679); Prostate disorders treatment (0,659); Atherosclerosis treatment (0,645) Cholesterol synthesis inhibitor (0,606); Wound healing agent (0,601); Hypolipemic (0,592)
56	Hepatoprotectant (0,918); Antineoplastic (0,868); Antieczematic (0,864); Antiinflammatory (0,833); Biliary tract disorders treatment (0,824) Immunosuppressant (0,766); Apoptosis agonist (0,738); Antifungal (0,702); Chemopreventive (0,688); Antiosteoporotic (0,686); Antipsoriatic (0,680); Antibacterial (0,679); Prostate disorders treatment (0,659); Atherosclerosis treatment (0,645); Cholesterol synthesis inhibitor (0,606); Wound healing agent (0,601); Hypolipemic (0,592)
57	Biliary tract disorders treatment (0,943); Hepatic disorders treatment (0,934); Antineoplastic (0,748); Antieczematic (0,741) Immunosuppressant (0,738); Antiinflammatory (0,731); Hypolipemic (0,713); Wound healing agent (0,709); Chemopreventive (0,692) Cholesterol synthesis inhibitor (0,688); Atherosclerosis treatment (0,664); Antipsoriatic (0,659); Antiosteoporotic (0,653) Prostate disorders treatment (0,645); Antihypercholesterolemic (0,622); Antifungal (0,612); Antimetastatic (0,511)
58	Biliary tract disorders treatment (0,963); Hepatic disorders treatment (0,934); Wound healing agent (0,789); Antieczematic (0,737) Immunosuppressant (0,731); Antineoplastic (0,711); Cholesterol synthesis inhibitor (0,696); Antiinflammatory (0,689); Antiosteoporotic (0,668) Hypolipemic (0,667); Atherosclerosis treatment (0,665); Prostate disorders treatment (0,637); Antipsoriatic (0,632); Antifungal (0,626) Chemopreventive (0,601); Antihypercholesterolemic (0,527)

* Only activities with Pa > 0.5 are shown

Table 3. Predicted biological activities of di- and trisulphate steroids

Representatives of ophiuroids contain very interesting lipid molecules, such plasmalogenous polar lipids and fatty aldehydes.⁷² In addition, two trisulphated steroids have also been found in various types of ophiuroids, so the steroid (**54**) is isolated from *Ophiura sarsi*, and another steroid (**57**) is isolated from *Ophiurachna incrassata*.⁸⁵

Socotrasterol sulphate (**58**) was isolated from different sponge species⁸⁶ and ophirapsterol sulphate (**55**) was found in *Topsentia ophiraphidites*.⁸⁷ Rare sulphated sterol dimers called fibrosterol sulphates A (**55**) and B (**56**) were isolated from a *Lis-sodendoryx (Acanthodoryx) fibrosa* sponge from Coron Island Palawan, Philippines.⁸⁴ Both compounds have inhibited PKC ζ with IC₅₀ values of 16.4 and 5.6 μ M, respectively.⁸⁸

CONCLUSION

The sulphated steroids found in the lipid extracts of various marine organisms are an interesting group of biologically active metabolites. As shown by numerous studies in recent years, many of these compounds show anti-cancer and antiviral properties. The data in this review show that sulphated steroids can be used as potential drugs for pre-clinical use and have good chances in the future for use in cancer patients.

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CONFLICT OF INTEREST DISCLOSURES

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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