Review

Marine-Derived Steroids for Cancer Treatment: Search for Potential Selective Glucocorticoid Receptor Agonists/Modulators (SEGRAM)

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Marine-Derived Steroids for Cancer Treatment: Search for Potential Selective Glucocorticoid Receptor Agonists/Modulators (SEGRAM)

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Abstract

Steroids, particularly glucocorticoids, are essential components of cancer treatment for both hematological malignancies and solid cancers. The adverse effects of standard steroid-based drugs have forced drug discovery research to develop chemotherapeutics with a more selective mechanism of action and, therefore, an improved therapeutic index. Steroids of natural origin and their analogs represent a significant source of novel molecules with a wide spectrum of biological activities. In the presented review, we aimed to analyze marine-derived steroids and their anticancer activity. Moreover, we discussed more specifically the molecules with not only anti-cancer but also anti-inflammatory activities that could potentially mimic the effects of glucocorticoids. We hypothesized that several of the reviewed compounds could reveal the affinity to glucocorticoid receptor, and, furthermore, could possess the properties of selective glucocorticoid receptor agonists/modulators with increased therapeutic activity and decreased side effects.

Keywords: marine-derived steroids; anti-cancer therapy; anti-inflammatory effects; glucocorticoid; selective glucocorticoid receptor agonists

1. Introduction

Cancer pathologies are characterized by the uncontrolled proliferation of transformed cells, replacement of normal tissues, and invasion and metastasis into adjacent and distant organs. Pleotropic mechanisms of cell transformation including cell cycle disruptions, attenuation of apoptosis, aberrant signaling, neoangiogenesis, invasion, changes in tumor epigenetics and microenvironment require multifactorial strategy of treatment [1–3]. Targeted therapy of cancer is crucially dependent on the identification of a specific biomarkers, is frequently associated with activation of alternative signaling and, consequently, with the development of pharmacological resistance [4,5]. Multitargeted therapies could be more effective alternative with the use of either drug combinations or single drug with multiple targets [6]. There are several options for multitargeted drug exploration: 1) design of novel molecules with a number of targets (i.e., low molecular weight multikinase inhibitors) [6–11]; 2) repurposing of registered and marketed drugs after detailed study of the mechanism of action and revelation of novel targets (i.e., thalidomide, rapamycin) [12–19]; and 3) using of biologically active compounds of natural origin and their secondary metabolites (i.e.,

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polyphenols, flavonoids) with usually mild and reversable but multiple effects on various targets [20–28].

Steroids can be discussed as multitargeted molecules, applied and repurposed in the various ways including cancer. Structurally steroids represent hydrophobic molecules, which are biosynthesized from cholesterol and could be also obtained from numerous terrestrial and marine sources [29–31]. Physiologically, steroid hormones are responsible for sex differentiation and reproduction (androgens, estrogens, and progestogens), metabolism and immunity (glucocorticoids, GC), homeostasis, blood volume and electrolyte maintenance (mineralocorticoids), calcium absorption (calciferols) [32,33]. In cancer therapy, the application of steroids is accounted to its binding with the specific receptors overproduced in particular tissues. Ligand-related receptor activation as transcription factor leads to regulation of the transcription of the dependent genes resulting in changes of cancer cell proliferation [34–37]. Moreover, competitive synthetic ligands of steroid hormone receptors can be designed as antagonists or selective agonists that completely or partially block receptor functions. Thus, anti-androgens are described for prostate cancer therapy, and anti-estrogens are successfully used in breast cancer treatment. GC represent significant part of blood cancer therapy as well as supportive therapy in various solid cancers [35,38–46].

Selective hormone receptor modulators may be a safer alternative to classic steroids. In particular, selective glucocorticoid receptor agonists/modulators (SEGRAM) of natural and synthetic origin are considered as anti-cancer and anti-inflammatory drugs with improved therapeutic index [22,47–60]. Several SEGRAM entered the clinical trials but to date no drug from SEGRAM class reached the pharmaceutical market [61–68]. In our previous research papers, we considered the Compound A (CpdA) or synephrine, originating from terrestrial plants, as the templates for novel SEGRAM synthesis [51,52]. Marine life demonstrates infinite biodiversity, with biologically active low-molecular weight molecules from the classes of polyketides, alkaloids, terpenoids, polyphenols, and steroids with anti-microbial, anti-cancer, anti-inflammatory and wound-healing activity [69–78]. In the presented review we aimed to follow marine sources of biologically active steroids and analyze the possibility of finding potential SEGRAM for cancer treatment.

2. Marine-Derived Steroids with Anti-Cancer Activity

To date, research on novel molecules in medical and biological chemistry has demonstrated a reverse shift to molecules of natural origin, particularly from the marine environment. Due to geographical and topographical peculiarities, the components of marine organisms are not well studied, compared to terrestrial ones but technological progress made possible the collection of organisms from deep sea water and the study of their biologically active components [79]. Marine natural products frequently show favorable pharmacokinetic profiles, multiple molecular targets as well as wide spectrum of high biological activity including anti-inflammatory, anti-microbial, anti-viral, wound healing as well as anti-cancer effects [27,28,80–83]. Moreover, marine-derived compounds are characterized by great structural diversity and may include polyketides, terpenoids, alkaloids, steroids, peptides, and others [84,85].

Marine ecosystems including microorganisms, algae, sea grass, echinoderms, chordates, cnidarians, sponges and other invertebrates and vertebrates produce many steroids with significant anti-cancer potential. Thus, novel steroids, 5a-cholesta-24-en-3b,20b-diol-23-one (1) and 5α-cholesta-9(11)-en-3β,20β-diol (**2**), are isolated from *Acanthaster planci* (crown of thorns starfish) and characterized by anti-cancer activity on MCF-7 breast cancer cells of luminal A subtypes [86]. Steroid dendrodoristerol (**3**) is found in Vietnamese nudibranch *Dendrodoris fumata* and demonstrates the cytotoxic effects on the panel of cancer cells of different origin (hepatocellular carcinoma cells HepG2, prostate cancer cells LNCaP, breast cancer cells MCF-7, lung adenocarcinoma cells SK-LU-1, epidermal carcinoma cells KB, leukemia cells HL-60) [87]. Among a number of the compounds isolated from cold-water starfish *Ctenodiscus crispatus*, cytotoxic activity of (25S)-5α-cholestane-3β,5,6β,15α,16β,26-hexaol (**4**) is demonstrated on hepatocellular carcinoma cells HepG2 and glioblastoma cells U87MG [88].

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(3E)-cholest-4-en-3,6-dione-3-oxime (**5**) from the marine sponge *Cinachyrella australiensis* also reveals the cytotoxic activity against hepatocellular carcinoma cells HepG2 [89]. Another steroid compounds from marine sponge, gracilosulphates A-G (**6-10**) from *Haliclona gracilis* species [90], sterols (**11-12**) from Echinoclathria gibbosa [91] and trihydroxysterols (13-16) from Psammoclema species [92], are demonstrated to inhibit the proliferation of prostate cancer cells 22Rv1, PC-3 and DU-145, respectively.

Two asterosaponins archasterosides A (**17**) and B (**18**), containing 3β,6α-dihydroxysteroid aglycons with a 9(11)-double bond and sulfate group at C-3, from starfish *Archaster typicus* show moderate anti-cancer activity om cervical cancer cells HeLa [93]. Another asterosaponins and glycosylated polyhydroxy steroids were founded in starfish from *Culcita novaeguineae, Linckia laevigata* and *Halityle regularis* (**19-22**), reveal significant cytotoxic effects against prostate cancer cells LNCaP [94]. Spiculiferosides A (**23**), B (**24**), and C (**25**) isolated from the starfish *Henricia leviuscula spiculifera* collected in the Sea of Okhotsk show weak cytotoxic effect in melanoma SK-MEL-28, breast cancer MDA-MB-231, and colorectal cancer HCT 116 cells but reveal the potential to induce cell cycle arrest and to suppress the colony formation via inhibition of CDK2, CDK4, cyclins and MAPK/ERK signaling [95]. Steroidal 3β,21- and 3β,22-disulfates (**26-31**), isolated from Eastern starfish *Pteraster marsippus* species are demonstrated to inhibit colony formation of breast cancer cells as well [96]. Esters of polyhydroxy steroids and long-chain fatty acids (**32-35**) from starfish *Ceramaster patagonicus* is shown not only inhibition of the proliferation of breast and colorectal cancer cells but also the suppression of their migration activity suggesting the role of these steroids in the therapy of metastatic cancers [97]. (23R)-methoxycholest-5,24-dien-3β-ol (**36**) is isolated from the marine bryozoan *Cryptosula pallasiana* and reveal cytotoxic effects in leukemia, liver and gastric cancer [98].

Three ergostane-type steroid compounds from marine-derived fungus *Penicillium levitum*, namely cerevisterol (**37**), ergosterol peroxide (**38**), and (3b,5a,22E)-ergosta-6,8(14),22-triene-3,5-diol (**39**) are characterized by antiproliferative effect *in vitro*, and (**39**) being the most potent cytotoxic against cancer cell lines Hep-G2, A549 and MCF-7 [99]. Steroids from marine algae *Tydemania expeditionis*, (E)-stigmasta-24(28)-en-3,6-dione (**40**), fucosterol (**41**) and saringosterol (**42**), demonstrate cytotoxic activity on prostate cancer cells LNCaP, DU-145 and PC-3 with IC50 values in micromolar range [80,100]. Cytotoxic and proapoptotic effects realized via ERK1/2-MAPK signaling inactivation in prostate carcinoma PC-3 are also demonstrated for steroidal constituents (**43-54**) from sea urchin *Diadema savignyi Michelin* [101].

Soft corals present the distinct class of marine biosphere and another source of steroid compounds with potential in cancer treatment. In particular, klyflaccisteroids (**55-58**) from the soft coral *Klyxum flaccidum* exhibit the cytotoxicity against colon cancer HT-29 cells, lung cancer A549 cells and murine leukemia P388 [102]. One from 12 novel steroids found in soft coral *Sinularia conferta*, ergosta-24(28)-ene-3β,5α,6β-triol-6-acetate (**59**), reveals higher cytotoxic effect in lung and cervical cancer cells in comparison with camptothecin and etoposide [29]. Component of soft coral *Dendronephthya* species extract, dendronestadione (**60**), significantly inhibits the proliferation of hepatocellular, prostate and colorectal carcinoma cells *in vitro* [103]. (22E)-4α,24-dimethyl-5α-cholesta-22,24(28)-dien-3β,8β-diol (**61**) and (22E,24R)-7β-acetoxy-24-methyl-cholesta-5,22-dien-3β,19-diol (**62**) exhibited strong cytotoxic effects on breast cancer cells MCF-7 [104].

Summarizing this chapter, it should be noted that there are the number of marine-derived steroids with weak or moderate anti-cancer activity *in vitro* not mentioned above. Moreover, plenty of the steroids of marine origin are characterized chemically but the biological, in particular, anti-cancer activity have not been tested yet. And vice versa, many of tested steroids were studied in the form of total extracts with cytotoxic effects *in vitro* but they were not isolated and characterized as individual chemicals [105–109]. To date, none of the steroidal compounds characterized *in vitro* did not enter neither *in vivo* preclinical study or clinical trials, providing the broad field of investigation. Interestingly, hormone-dependent cancers as breast and prostate neoplasms presented as the cancer models the most frequently used for cytotoxicity evaluation and confirmation. It provides the rationale of further studies of androgen and estrogen receptor signaling as potential molecular

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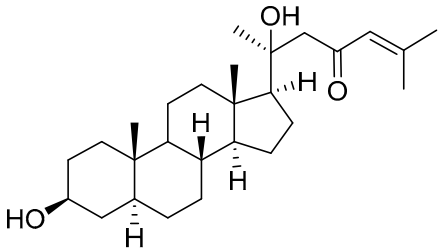
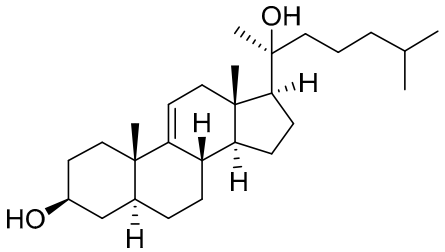
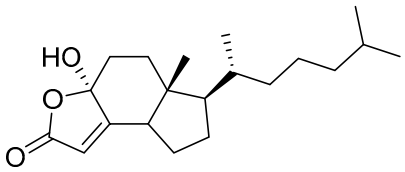
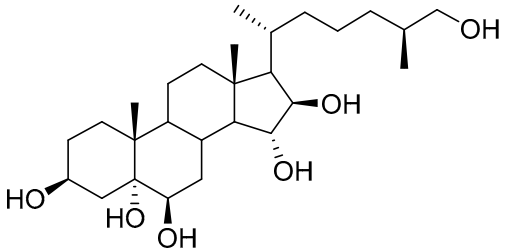
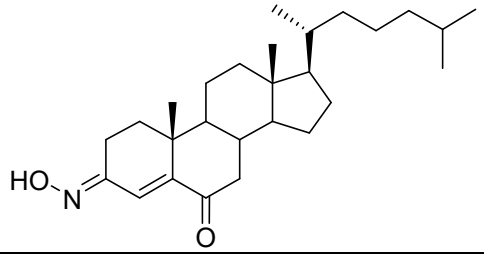
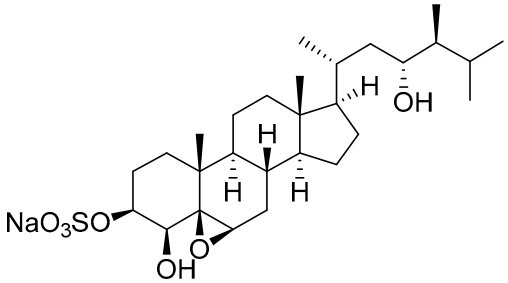
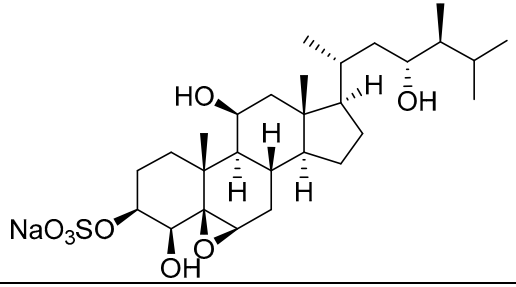
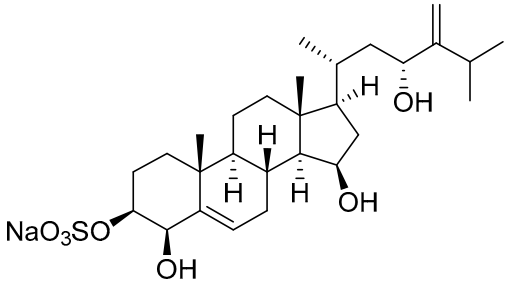
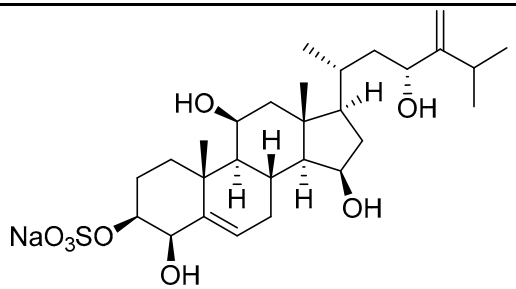
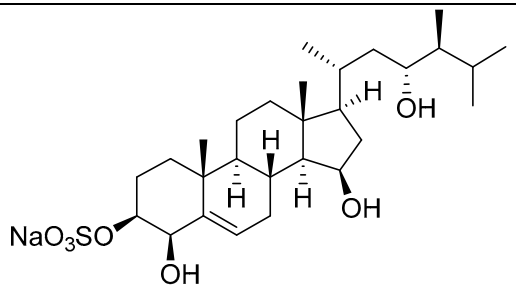
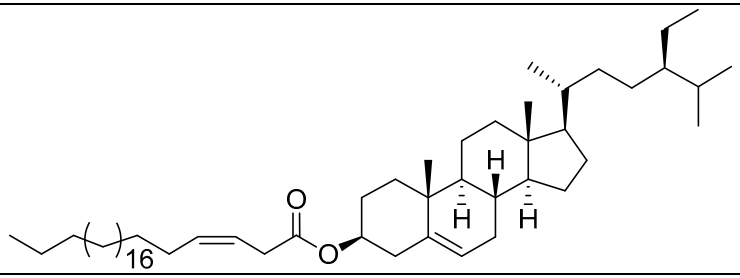
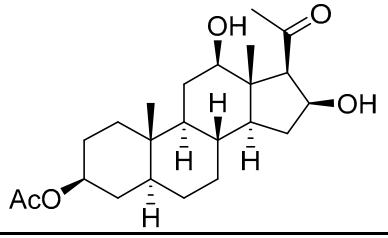
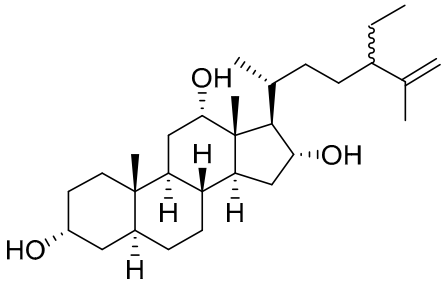
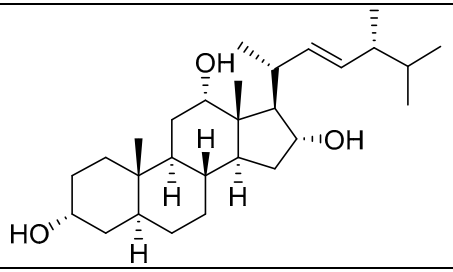
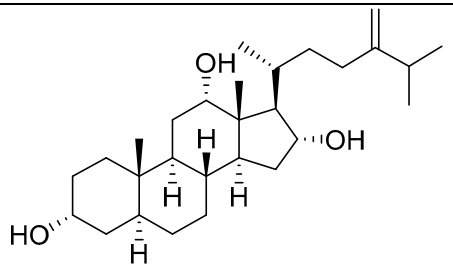
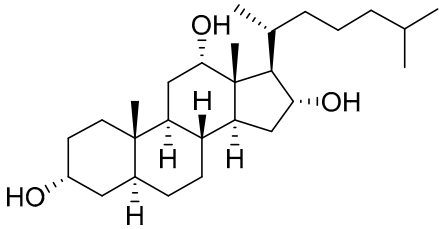
mechanisms of action of marine-derived steroids [110]. Furthermore, blood cancer cells *in vitro* were sensitive to a number of described steroidal compounds, assuming specific cytotoxic activity to lymphocytes and similarity to glucocorticoid effects in hematological malignancies. In the next chapter we discuss the possibility of the replacement of GC-based therapies by marine-derived steroids/ligands of GC receptors.

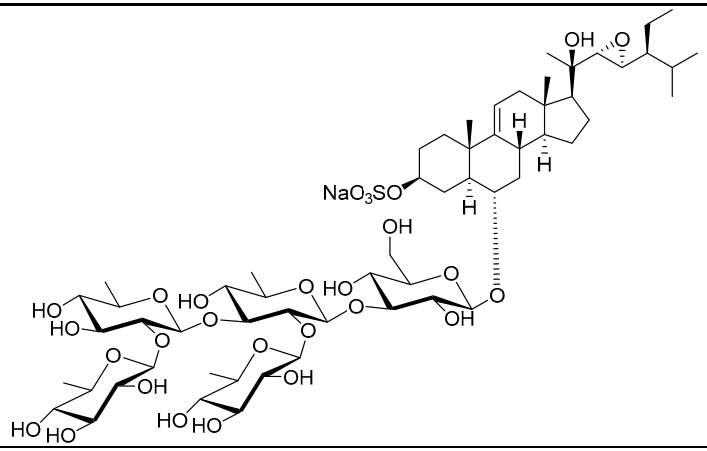
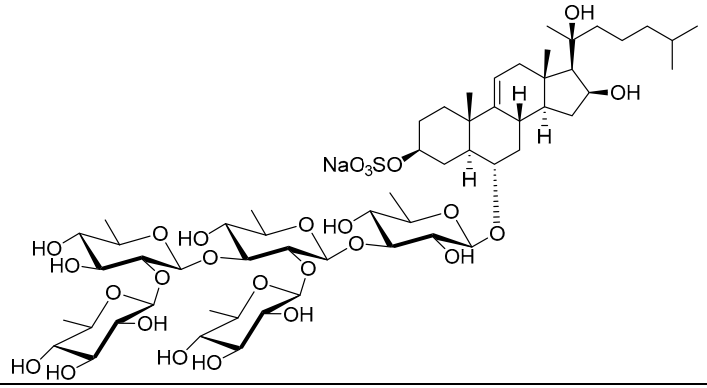
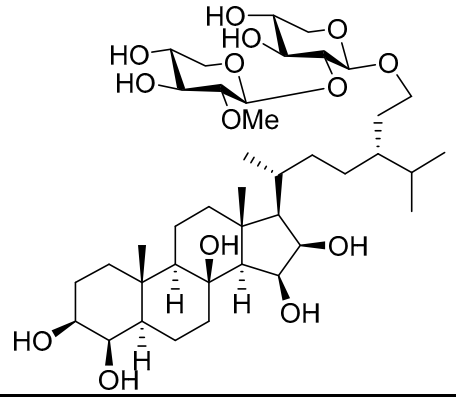
Table 1. Steroids from marine ecosystems with found anti-cancer activity.

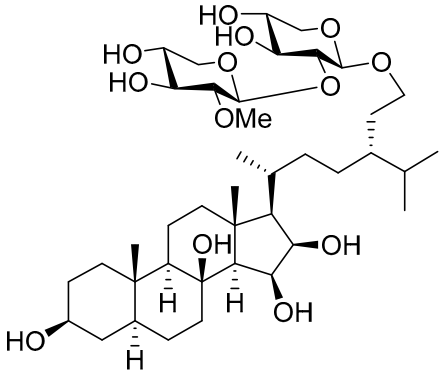
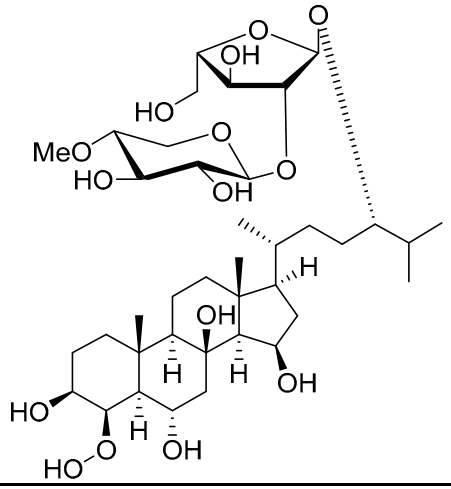
No	Name	Structure	Source	Anti-Cancer Activity	Reference
1	5*α*-cholesta-24-en-3β,20β-diol-23-one		Crown-of-thorns starfish *Acanthaster planci*	Cytotoxic activity against luminal A breast cancer cells MCF-7 in MTT assay IC50 49 ± 1.6 μg/mL	[86]
2	5*α*-cholesta-9(11)-en-3β,20β-diol		Crown-of-thorns starfish *Acanthaster planci*	Cytotoxic activity against luminal A breast cancer cells MCF-7 in MTT assay IC50 57.5 ± 1.5 μg/mL	[86]
3	Dendrodoristerol		Sea slug *Dendrodoris fumata*	Cytotoxic activity against hepatocellular carcinoma cells HepG2, prostate cancer cells LNCaP, breast cancer cells MCF-7, lung adenocarcinoma cells SK-LU-1, epidermal carcinoma cells KB, leukemia cells HL-60 in SRB assay IC50 21.63 ± 2.22, 22.22 ± 1.81, 24.53 ± 2.47, 41.19 ± 3.25, 25.34 ± 3.81, and 21.59 ± 1.38 μM	[111]
4	(25*S*)-5*α*-cholestane-3*β*,5,6*β*,15*α*,16*β*,26-hexaol		Mud star *Ctenodiscus crispatus*	Shows cytotoxic activity against hepatocellular carcinoma cells HepG2 in MTT assay	[88]

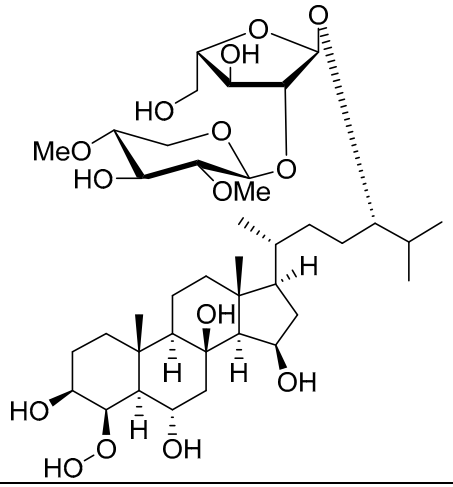
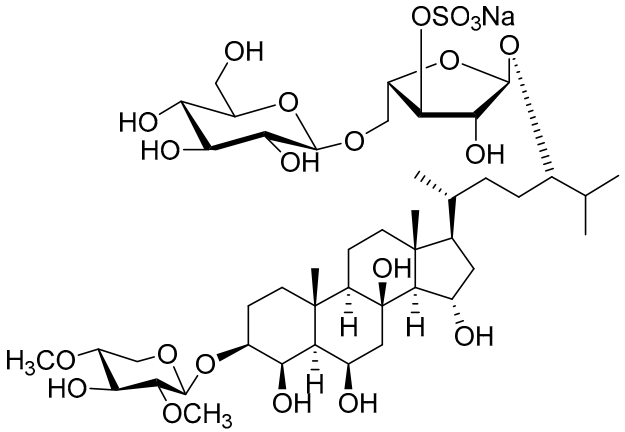
5	(3*E*)-cholest-4-en-3,6-dione-3-oxime		Sea sponge *Cinachyrella australiensis*	Cytotoxic activity against hepatocellular carcinoma cells HepG2 in MTT assay IC50 2.91 mg/mL	[89]
6	Gracilosulphate A		Sea sponge *Haliclona gracilis*	Cytotoxic activity against prostate cancer cell line 22Rv1 in MTT assay IC50 64.4 ± 14.9 μM	[90]
7	Gracilosulphate B		Sea sponge *Haliclona gracilis*	Cytotoxic activity against prostate cancer cell line 22Rv1 in MTT assay IC50 > 100 μM	[90]
8	Gracilosulphate D		Sea sponge *Haliclona gracilis*	Cytotoxic activity against prostate cancer cell line 22Rv1 in MTT assay IC50 > 100 μM	[90]

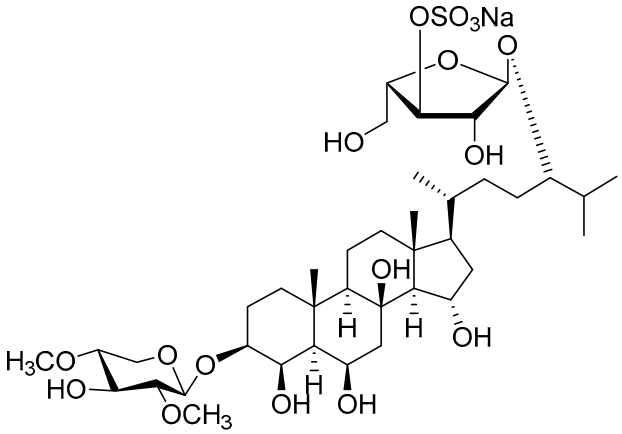
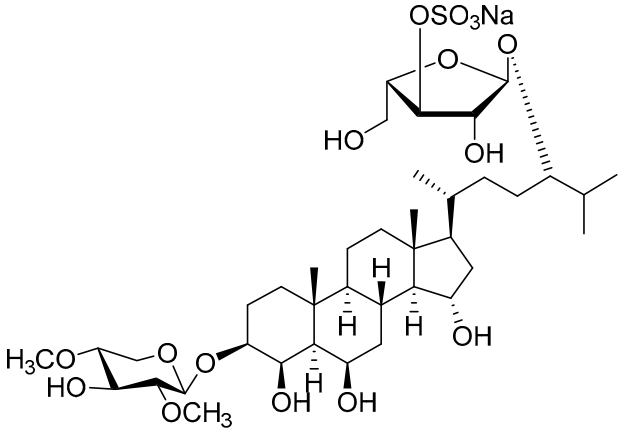
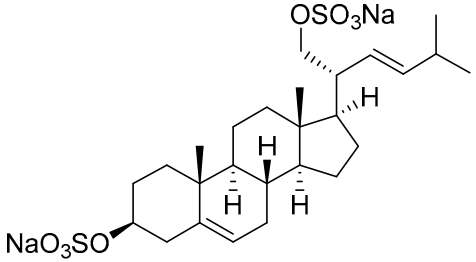
9	Gracilosulphate F		Sea sponge *Haliclona gracilis*	Cytotoxic activity against prostate cancer cell line 22Rv1 in MTT assay IC50 > 100 μM	[90]
10	Gracilosulphate G		Sea sponge *Haliclona gracilis*	Cytotoxic activity against prostate cancer cell line 22Rv1 in MTT assay IC50 > 100 μM	[90]
11	*β*-sitosterol-3-O-(3*Z*)-pentacosenoate		Sea sponge *Echinoclathria gibbosa*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 64 μM	[91]
12	5*α*-pregna-3*β*-acetoxy-12*β*,16*β*-diol-20-one		Sea sponge *Echinoclathria gibbosa*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 > 100 μM	[91]

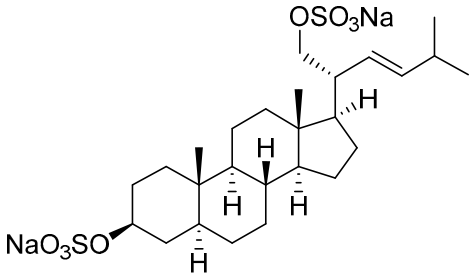
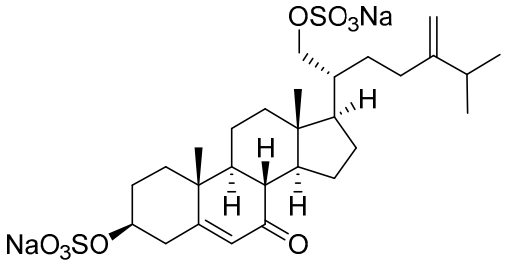
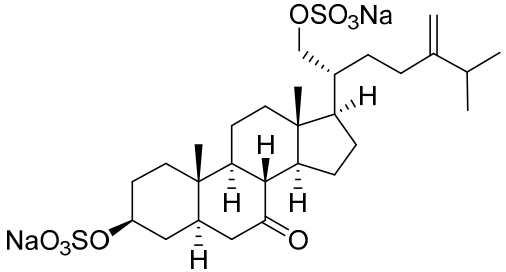
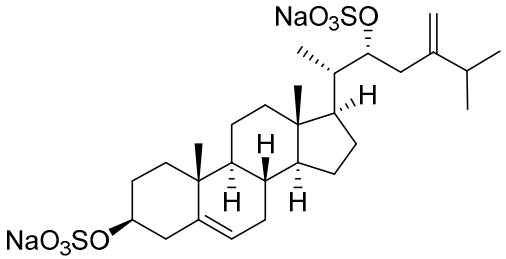
13	3α,12α,16α-trihydroxy-24ξ-ethylcholest-25-ene		Sea sponge *Psammoclema*	Cytotoxic activity against prostate cancer cells DU-145 in MTT assay GI50 13 ± 1 μM	[92]
14	3α,12α,16α-trihydroxy-24*R*-methylcholest-22*E*-ene		Sea sponge *Psammoclema*	Cytotoxic activity against prostate cancer cells DU-145 in MTT assay GI50 27 ± 1 μM	[92]
15	3α,12α,16α-trihydroxy-24-methylcholest-24(28)-ene		Sea sponge *Psammoclema*	Cytotoxic activity against prostate cancer cells DU-145 in MTT assay GI50 27 ± 1 μM	[92]
16	3α,12α,16α-trihydroxycholestane		Sea sponge *Psammoclema*	Cytotoxic activity against prostate cancer cells DU-145 in MTT assay GI50 6.7 ± 0.2 μM	[92]

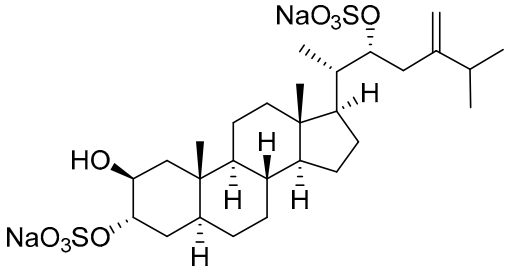
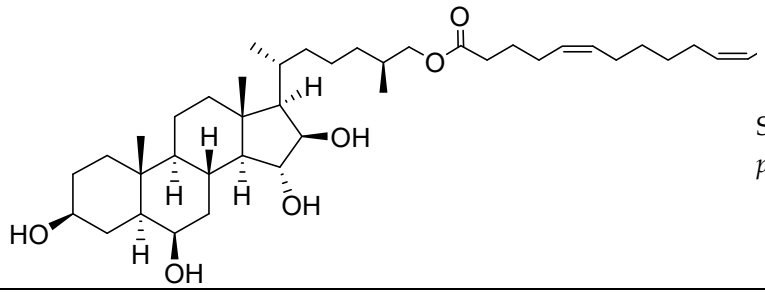
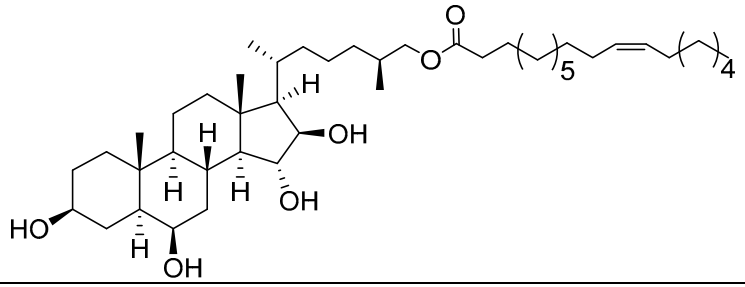
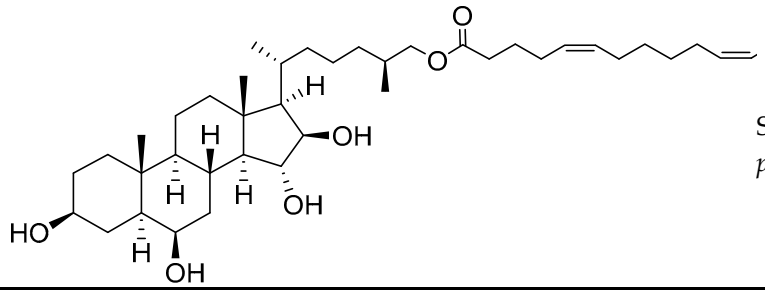
17	Archasteroside A				[93]
18	Archasteroside B				[93]
19	Halityloside A		Starfish *Culcita novaeguineae*	Cytotoxic activity against prostate cancer cells LNCaP in SRB assay IC50 48.59 ± 2.30 μM	[94]

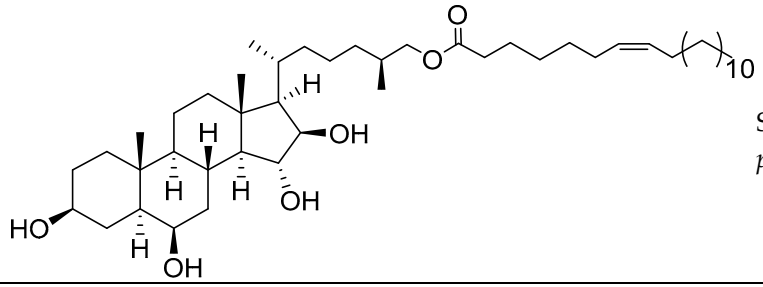
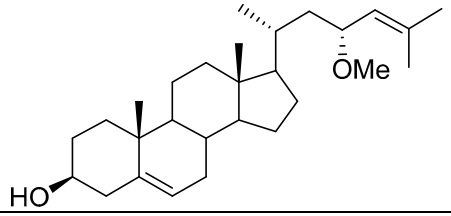
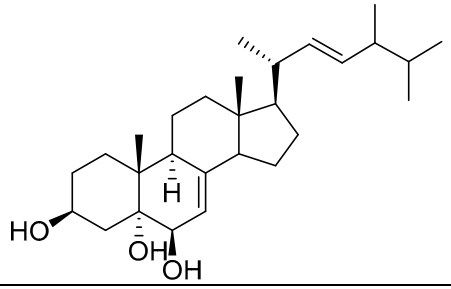
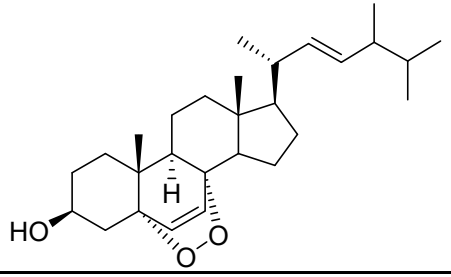
20	Halityloside B		Starfish *Culcita novaeguineae*	Cytotoxic activity against prostate cancer cells LNCaP in SRB assay IC50 39.68 ± 2.65 μM [94]
21	Culcitoside C_5		Starfish *Culcita novaeguineae*	Cytotoxic activity against prostate cancer cells LNCaP in SRB assay IC50 57.08 ± 1.81 μM [94]

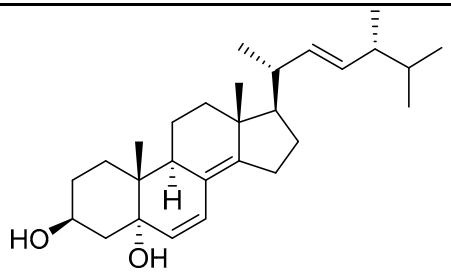
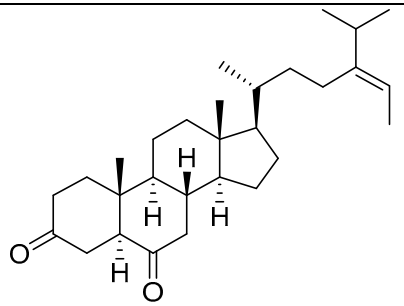
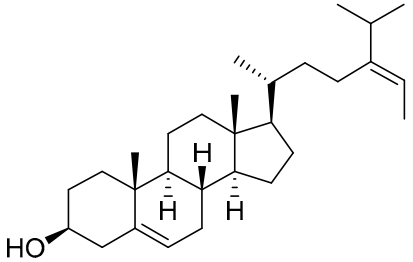
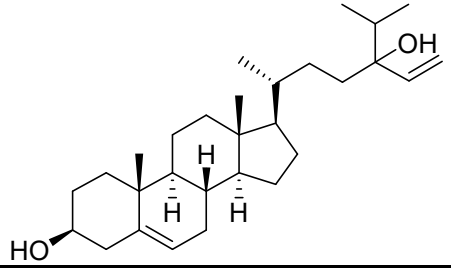
22	Halityloside D		Starfish *Culcita novaeguineae*	Cytotoxic activity against prostate cancer cells LNCaP in SRB assay IC50 31.80 ± 1.59 μM	[94]
23	Spiculiferosides A		Starfish *Henricia leviuscula spiculifera*	Inhibition of colony formation colorectal carcinoma cells HCT 116 at concentration 40 μM was 65%	[95]

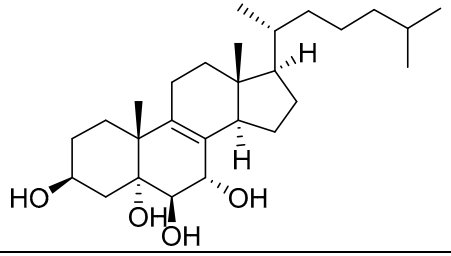
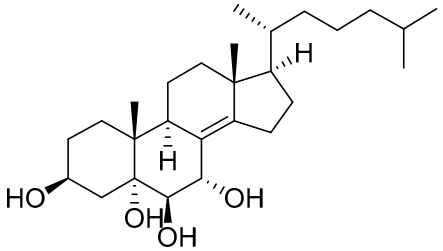
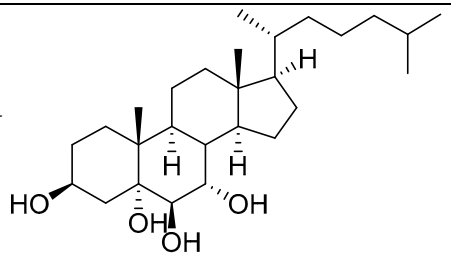
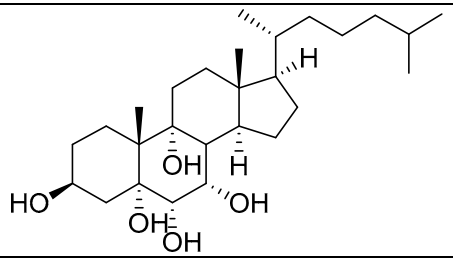
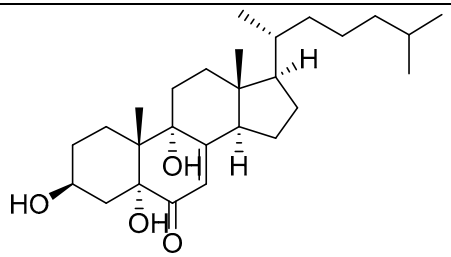
24	Spiculiferosides B		Starfish *Henricia leviuscula spiculifera*	Inhibition of colony formation colorectal carcinoma cells HCT 116 at concentration 40 μM was 81%	[95]
25	Spiculiferosides C		Starfish *Henricia leviuscula spiculifera*	Cytotoxic activity against colorectal carcinoma cells HCT 116 in MTS assay IC50 87.6 μM; Inhibition of colony formation colorectal carcinoma cells HCT 116 at concentration 40 μM was 87%	[95]
26	(20*R*,22*E*)-24-norcholesta-5,22-diene-3β,21-diol 3,21-disulfate disodium salt		Starfish *Pteraster marsippus*	Inhibition of colony formation breast cancer cells T-47D at concentration 50 μM was 76%	[112]

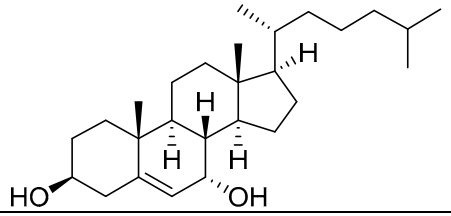
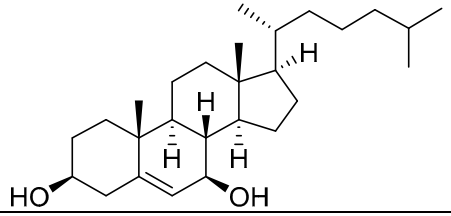
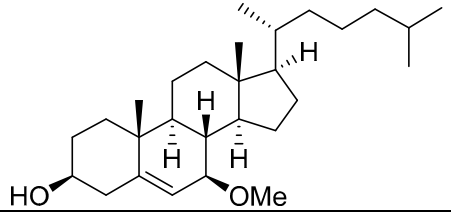
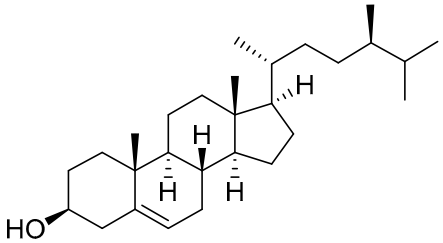
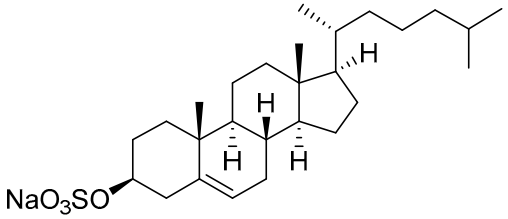
27	(20*R*,22*E*)-24-nor-5α-cholest-22-ene-3β,21-diol 3,21-disulfate disodium salt		Starfish *Pteraster marsippus*	Inhibition of colony formation breast cancer cells T-47D at concentration 50 μM was 86% [112]
28	(20*R*)-7-oxo-24-methylcholesta-5,24(28)-diene-3β,21-diyl disulfate disodium salt		Starfish *Pteraster marsippus*	Cytotoxic activity of the mixture of 28 and 29 against human breast carcinoma cells ZR-75-1 in MTS assay IC50 90.4 μM [96]
29	(20*R*)-7-oxo-24-methyl-5α-cholest-24(28)-ene-3β,21-diyl disulfate disodium salt		Starfish *Pteraster marsippus*	Cytotoxic activity of the mixture of 28 and 29 against human breast carcinoma cells ZR-75-1 in MTS assay IC50 90.4 μM [96]
30	(20*S*,22*R*)-24-metylcholesta-5,24-diene-3β,22-diol 3,22-disulfate disodium salt		Starfish *Pteraster marsippus*	Inhibition of colony formation breast cancer cells T-47D at concentration 50 μM was 71% [112]

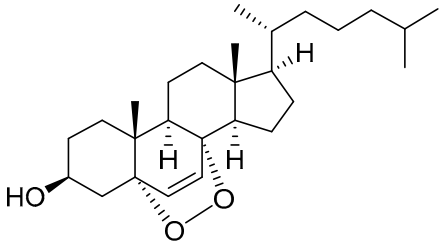
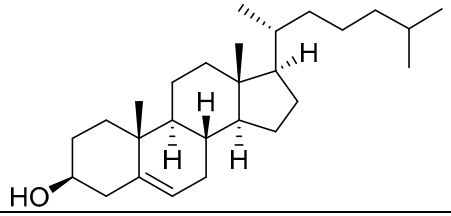
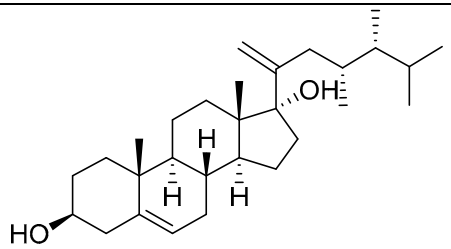
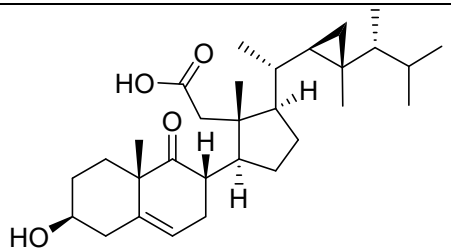
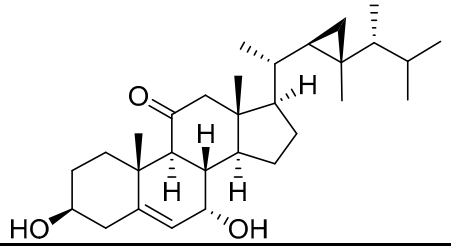
31	(20*S*,22*R*)-24-metyl-5α-cholest-24-ene-2β,3α,22-triol 3,22-disulfate disodium salt		Starfish *Pteraster marsippus*	Inhibition of colony formation breast cancer cells T-47D at concentration 50 μM was 79%	[112]
32	(25*S*)-5α-cholestane-3β,6β,15α,16β-tetraol-26-yl 5′*Z*,11′*Z*-octadecadienoate		Starfish *Ceramaster patagonicus*	Inhibitory activity against migration of colorectal carcinoma cells HCT 116 was 36%	[97]
33	(25*S*)-5α-cholestane-3β,6β,15α,16β-tetraol-26-yl 11'*Z*-octadecenoate		Starfish *Ceramaster patagonicus*	Inhibitory activity against migration of colorectal carcinoma cells HCT 116 was 73%	[97]
34	(25*S*)-5α-cholestane-3β,6β,15α,16β-tetraol-26-yl 5'*Z*,11'*Z*-eicosadienoate		Starfish *Ceramaster patagonicus*	Inhibitory activity against migration of colorectal carcinoma cells HCT 116 was 30%	[97]

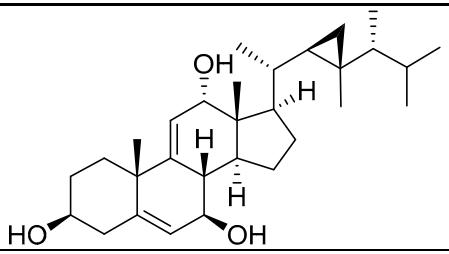
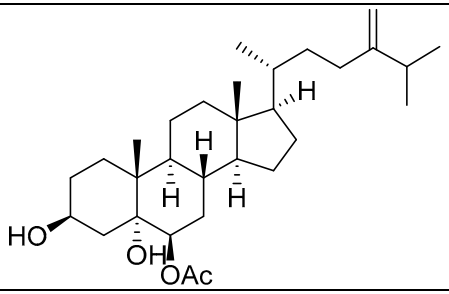
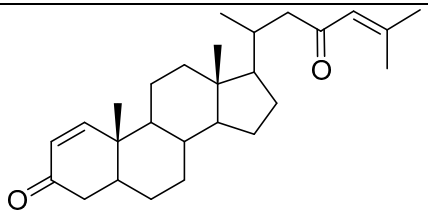
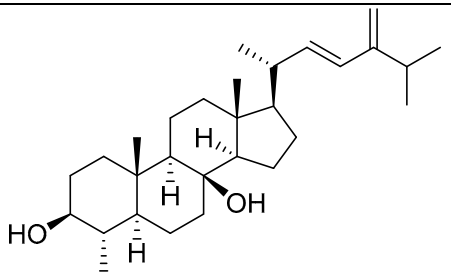
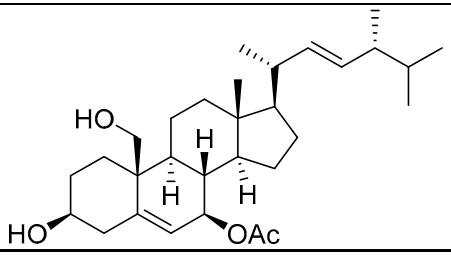
35	(25*S*)-5α-cholestane-3β,6β,15α,16β-tetraol-26-yl 7'Z-eicosenoate		Starfish *Ceramaster patagonicus*	Inhibitory activity against migration of colorectal carcinoma cells HCT 116 was 24%	[97]
36	(23*R*)-methoxycholest-5,24-dien-3β-ol		Colonial bryozoan *Cryptosula pallasiana*	Cytotoxic activity against hepatocellular carcinoma cells HepG2, gastric carcinoma SGC-7901 and leukemia cells HL-60 in MTT assay IC50 12.34 ± 0.12, 18.37 ± 0.17 and 17.64 ± 0.32 μM	[98]
37	Cerevisterol		Marine fungus *Penicillium levitum*	Cytotoxic activity against hepatocellular carcinoma cells HepG2, lung carcinoma cells A549 and breast cancer cells MCF-7 in MTT assay was not detected	[99]
38	Ergosterol peroxide		Marine fungus *Penicillium levitum*	Cytotoxic activity against hepatocellular carcinoma cells HepG2, lung carcinoma cells A549 and breast cancer cells MCF-7 in MTT assay IC50 16.22, 22.48 and 27.11 μM	[99]

39	(3β,5α,22*E*)-ergosta-6,8(14),22-triene-3,5-diol		Marine fungus *Penicillium levitum*	Cytotoxic activity against hepatocellular carcinoma cells HepG2, lung carcinoma cells A549 and breast cancer cells MCF-7 in MTT assay IC50 2.89, 18.51 and 16.47 μM	[99]
40	(24*E*)-stigmasta-24(28)-en-3,6-dione		Green algae *Tydemania expeditionis*	Cytotoxic activity against prostate cancer cells DU-145, prostate cancer cells PC-3 and prostate cancer cells LNCaP in MTT assay IC50 31.27 ± 1.50, 40.59 ± 3.10 and 19.80 ± 3.84 μM	[100]
41	Fucosterol		Green algae *Tydemania expeditionis*	Cytotoxic activity against prostate cancer cells DU-145, prostate cancer cells PC-3 and prostate cancer cells LNCaP in MTT assay IC50 12.38 ± 2.47, 2.14 ± 0.33 and 1.38 ± 0.07 μM	[100]
42	Saringosterol		Green algae *Tydemania expeditionis*	Cytotoxic activity against prostate cancer cells DU-145, prostate cancer cells PC-3 and prostate cancer cells LNCaP in MTT assay IC50 >50, >50 and 41.60 ± 4.26 μM	[100]

43	Cholest-8-ene-3*β*,5*α*,6*β*,7*α*-tetraol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 40.43 ± 1.45 μM	[101]
44	Cholest-8(14)-ene-3*β*,5*α*,6*β*,7*α*-tetraol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 5.49 ± 0.22 μM	[101]
45	Cholest-7-ene-3*β*,5*α*,6*β*-triol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 74.06 ± 3.46 μM	[101]
46	Cholest-7-ene-3*β*,5*α*,6*α*,9*α*-tetraol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 27.41 ± 0.50 μM	[101]
47	Cholest-7-ene-6-one-3*β*,5*α*,9*α*-triol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 24.40 ± 0.46 μM	[101]

48	Cholest-5-ene-3β,7α-diol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 29.22 ± 0.17 μM	[101]
49	Cholest-5-ene-3β,7β-diol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 27.94 ± 0.63 μM	[101]
50	Cholest-5-ene-7β-methoxy-3β-ol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 9.22 ± 0.67 μM	[101]
51	Campesterol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 22.26 ± 0.59 μM	[101]
52	Cholest-5-ene-3β-sulfate sodium solt		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 68.87 ± 6.08 μM	[101]

53	Cholest-6-ene-5α,8α-epidioxy-3β-ol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay IC50 6.99 ± 0.28 μM	[101]
54	Cholest-5-ene-3β-ol		Sea urchin *Diadema savignyi*	Cytotoxic activity against prostate cancer cells PC-3 in MTT assay was not detected	[101]
55	Klyflaccisteroid A		Soft coral *Klyxum flaccidum*	Cytotoxic activity against colon cancer cells HT-29, lung cancer cells A549 and murine leukemia cells P388 in Alamar Blue assay ED50 >20, 7.7 and >20 μg mL^{-1}	**10.1039/c4ra13977a**
56	Klyflaccisteroid F		Soft coral *Klyxum flaccidum*	Cytotoxic activity against colon cancer cells HT-29, lung cancer cells A549 and murine leukemia cells P388 in Alamar Blue assay ED50 >20, 14.5 and 17.9 μg mL^{-1}	[102]
57	Klyflaccisteroid C		Soft coral *Klyxum flaccidum*	Cytotoxic activity against colon cancer cells HT-29, lung cancer cells A549 and murine leukemia cells P388 in Alamar Blue assay ED50 8.2, 6.1 and 10.8 μg mL^{-1}	[102]

58	Klyflaccisteroid E		Soft coral *Klyxum flaccidum*	Cytotoxic activity against colon cancer cells HT-29 and murine leukemia cells P388 in Alamar Blue assay ED50 6.9 and 3.7 μg mL^{-1}	[102]
59	Ergosta-24(28)-ene-3β,5α,6β-triol-6-acetate		Soft coral *Sinularia conferta*	Cytotoxic activity against lung cancer cells A549, cervical adenocarcinoma cells HeLa and pancreatic epithelioid carcinoma cells PANC-1 in MTT assay IC 50 3.64 ± 0.18, 19.34 ± 0.42 and 1.78 ± 0.69 μM	[113]
60	Dendronestadione		Soft coral *Dendronephthya*	Cytotoxic activity against hepatocellular carcinoma cells HepG2, colon cancer cells HT-29 and prostate cancer cells PC-3 in MTT assay IC50 19.1 ± 1.81, 32.4 ± 2.84 and 7.8 ± 0.80 μM	[114]
61	(22*E*)-4α,24-dimethyl-5α-cholesta-22,24(28)-dien-3β,8β-diol		Soft coral *Litophyton mollis*	Cytotoxic activity against hepatocellular carcinoma cells HepG2, breast cancer cells MCF-7 and lung carcinoma cells NCI-H1299 in SRB assay IC_{50} > 50 μM in all cases	[104]
62	(22*E*,24*R*)-7β-acetoxy-24-methylcholesta-5,22-dien-3β,19-diol		Soft coral *Litophyton mollis*	Cytotoxic activity against hepatocellular carcinoma cells HepG2, breast cancer cells MCF-7 and lung carcinoma cells NCI-H1299 in SRB assay IC_{50} 32.5, 8.4 and 15.1 μM	[104]

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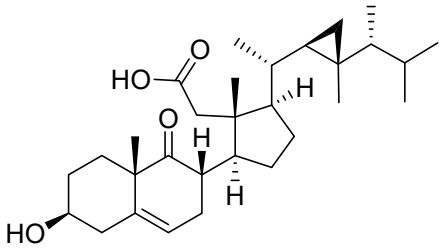
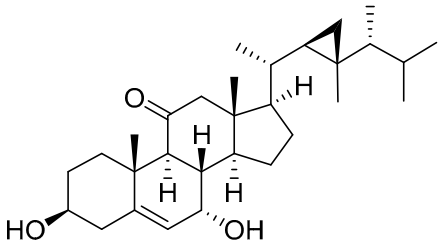
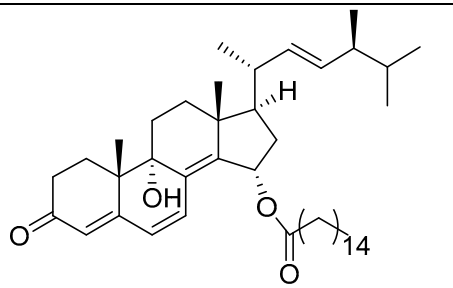
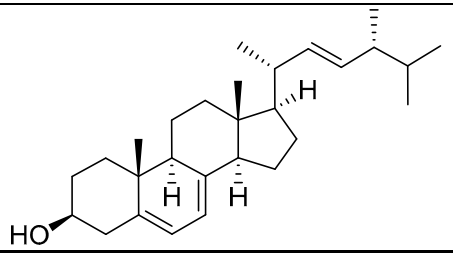
3. Potential Glucocorticoid Receptor Modulators from Marine Natural Products

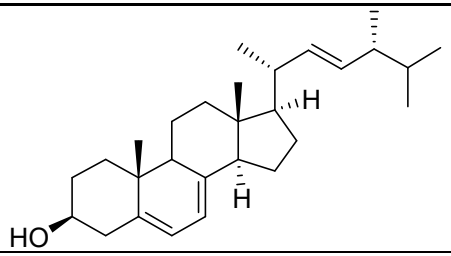
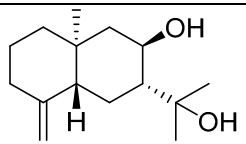
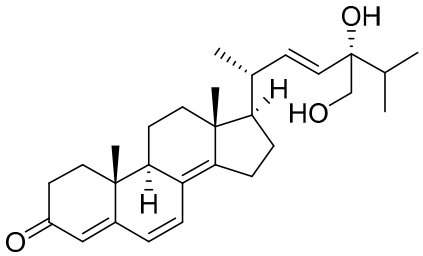
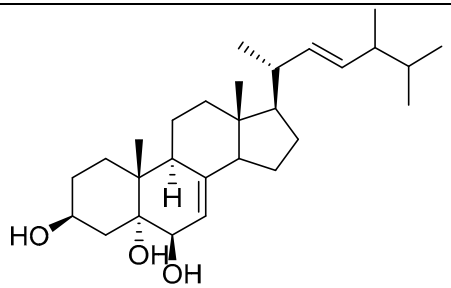
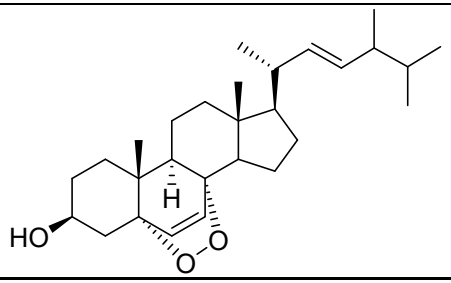
Discussing GC role in cancer therapy, the signaling of glucocorticoid receptor (GR), well-known transcription factor (TF) and mediator of GC biological effects in cells and tissues, should be briefly explained. Binding of GC with inactive GR in cytoplasm leads to receptor activation, homodimerization and translocation to nucleus. GR-GR homodimer binds to GC-responsive elements (GRE) in DNA resulting in induction or inhibition of the transcription of different gene subsets. Protein-protein interaction of GR monomers with other TFs followed by suppression of TF activity [115,116]. GR-dependent inhibition of pro-proliferative and anti-apoptotic TF activity or suppression of gene transcription (transrepression, TR) mediated therapeutic effects of GC. Induction of GR-dependent gene transcription (transactivation, TA) is mainly associated with metabolic and atrophic GC-related complications [117,118]. Therefore, the development of GC analogues of synthetic or natural origin with improved therapeutic index and attenuated side effects is of interest nowadays [50,119–121].

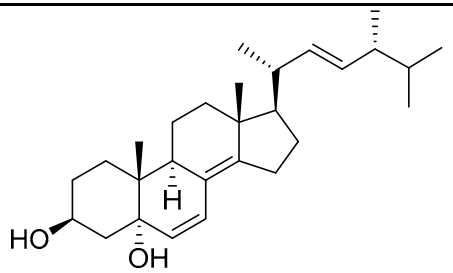
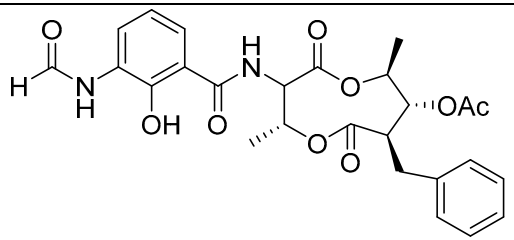
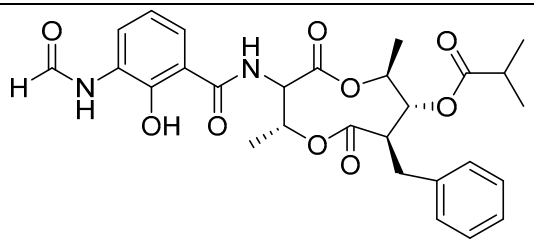
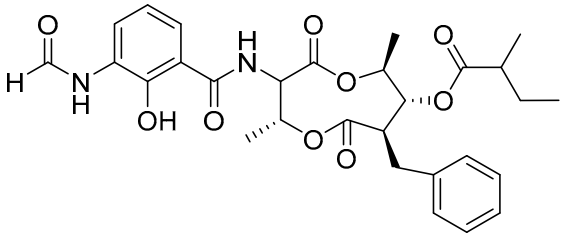
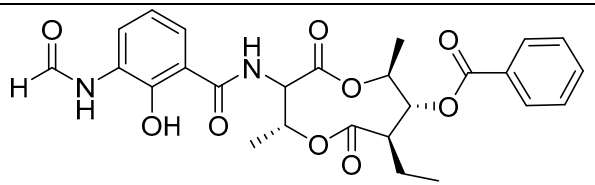
GR is the member of nuclear receptor superfamily, which also includes estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), mineralocorticoid receptor (MR), vitamin D receptor (VDR), and thyroid hormone receptor (ThR). Steroid receptors have a highly conserved DNA-binding domain (DBD), which allows them to bind to responsive elements of other family members [122,123]. It could mediate glucocorticoid-alike activity of potential ER, PR or AR ligands, and vice versa. Thus, GR could form heterodimer with AR modulating its activity [124–127]. Homology of GR and PR DBDs is 90% allowing to share the responsive elements and regulate the expression of immunophilins, oncogenes and TFs [128,129]. Cross-talk of GR and ER is realized via protein-protein interaction of receptor monomers followed by binding of heterodimer to estrogen responsive elements (ERE) as well as direct suppression of ER activity. This interaction could explain anti-proliferative activity of GC in ER-positive breast cancer cells [130–133]. However, it should be noted that ER-GR interaction may lead to breast cancer progression and metastasis in case of ER-negative cancer subtype [134–137].

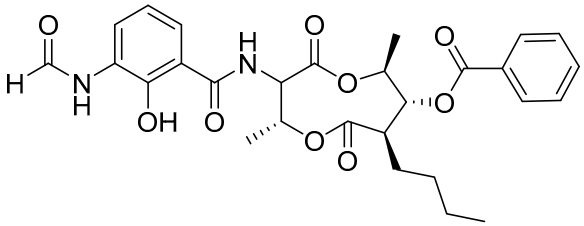
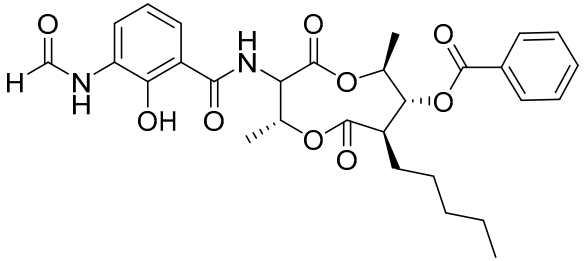
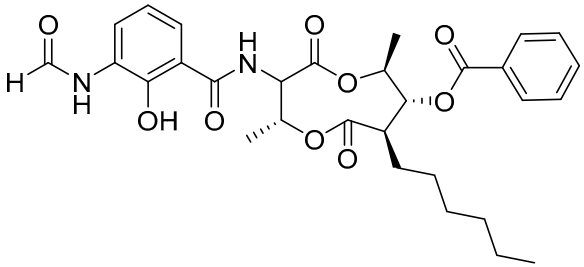
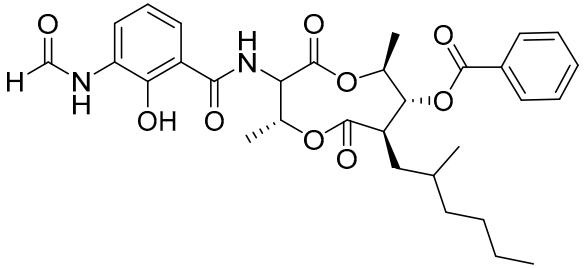
To date little is known of GR-dependent anti-cancer activity of marine-derived steroids. Gene expression profiles in GC anti-inflammatory and anti-cancer effects significantly intersects, which allow to consider marine-derived steroids with anti-inflammatory properties as an option for cancer cure. Thus, klyflaccisteroids from soft corals **(56, 57)** with cytotoxic potential also reveal strong anti-inflammatory effects *in vitro*, specifically, the inhibition of superoxide anion generation and elastase release in human neutrophils [102]. The fungus *Penicillium oxalicum* associated with soft coral *Sinularia gaweli*, produce ergostane-type sterol ester **(63)**. This sterol ester demonstrates anti-inflammatory activity in RAW264.7 macrophage cells evaluated by inhibition of expression of pro-inflammatory cytokines TNF-α and INF-β1 [138]. (22E,24R)-ergosta-5,7,22-trien-3β-ol **(64)** isolated from the mangrove *Avicennia*-associated marina fungus, *Amorosia* sp. suppresses LPS-induced NO production of NO and pro-inflammatory factors IL-6, TNF-α, MCP-1. Unfortunately, no cytotoxic activity was detected [139]. Ergosterol **(65)** found in deep-sea fungus *Samsoniella hepiali* inhibits NO production in LPS-activated microglia cells [140]. The similar inhibitory effects on inflammation markers iNOS, TNF-α, IL-6, and IL-1β, at both the mRNA and protein level *in vitro* were described for sesquiterpenoid **(66)** isolated from marine-derived fungus *Eutypella* sp [141], persteroid **(67)** isolated from marine-derived fungus *Penicillium* sp. ZYX-Z-143 [142] and ergostane-type steroid components **(37-39)** from marine-derived fungus *Penicillium levitum* with cytotoxic potential on breast, lung and liver cancer cells [99]. Non-steroidal components of marine-derived actinomycete strain, identified as a *Streptomyces* sp ten new 9-membered *bis*-lactones, splenocins A-J **(68-77)** with anti-inflammatory activity compared to GC dexamethasone in splenocyte cytokine assay were also described in the literature [143].

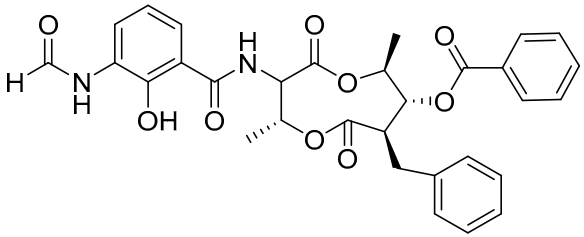
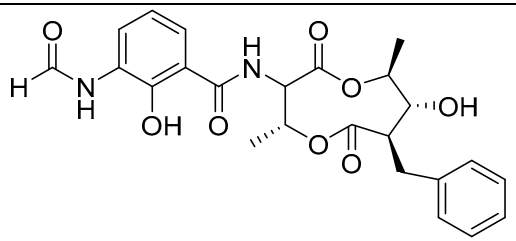
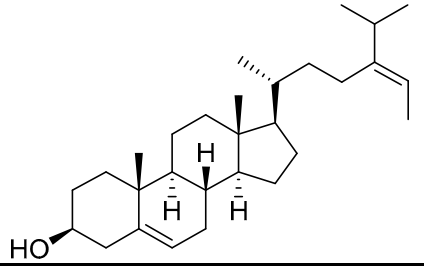
Table 2. Anti-inflammatory marine-derived steroids.

No	Name	Structure	Source	Anti-Inflammatory Effects	Reference
56	Klyflaccisteroid F		Soft coral *Klyxum flaccidum*	Activity in inhibiting the superoxide anion generation 88.26 ±35.86 % at 10 μM and activity in inhibiting against elastase release 104.22 ± 6.55 % at 10 μM in N-formyl-methionyl-leucyl-phenylalanine/ cytochalasin B (fMLP/CB)-induced neutrophils.	[102]
57	Klyflaccisteroid C		Soft coral *Klyxum flaccidum*	Activity in inhibiting the superoxide anion generation 76.24 ± 5.64 % at 10 μM and activity in inhibiting against elastase release 88.38 ± 1.19 % at 10 μM in N-formyl-methionyl-leucyl-phenylalanine/ cytochalasin B (fMLP/CB)-induced neutrophils.	[102]
63	(22*E*,24*S*)-9*a*,15*a*-dihydroxyergosta-4,6,8(14),22-tetraen-3-one 15-palmitate		Marine fungus *Penicillium oxalicum* HL-44	Inhibition of expression of pro-inflammatory cytokines TNF-α and INF-β1 on DMXAA-stimulated Raw264.7 cells by 68% and 94% at 20 μM	[138]
64	(22*E*, 24*R*)-ergosta-5,7,22-trien-3β-ol		Mangrove fungus *Amorosia* sp.	Inhibition of expression of pro-inflammatory cytokines TNF-α, IL-6 and MCP-1 on LPS-activated RAW264.7 M1-type cells by 55%, 50% and 50% at 10 μM	[139]

65	Ergosterol		Marine fungus *Samsoniella hepiali* W7	Inhibition of NO production in LPS-activated BV-2-microglia cells by 32.9 ± 1.6 % at 1 μM	[140]
66	Arctiol		Marine fungus *Eutypella* sp. F0219	Inhibition of NO production in LPS- treated BV-2-microglia cells by 71% at 20 μM	[141]
67	Persteroid		Marine fungus *Penicillium* sp. ZYX-Z-143	NO half-maximal inhibitory concentration on LPS-stimulated RAW 264.7 cells IC50 25.81 ± 0.92 μM	[142]
37	Cerevisterol		Marine fungus *Penicillium levitum*	NO half-maximal inhibitory concentration on LPS-stimulated RAW 264.7 cells IC50 25.45 μg/mL	[99]
38	Ergosterol peroxide		Marine fungus *Penicillium levitum*	NO half-maximal inhibitory concentration on LPS-stimulated RAW 264.7 cells IC50 2.85 μg/mL	[99]

39	(3β,5α,22*E*)-ergosta-6,8(14),22-triene-3,5-diol		Marine fungus *Penicillium levitum*	NO half-maximal inhibitory concentration on LPS-stimulated RAW 264.7 cells IC50 2.79 μg/mL	[99]
68	Splenocin A		Marine bacterium *Streptomyces* sp.	Inhibition of expression of pro-inflammatory cytokines IL-5 on $T_{H}2$ cells (helper T lymphocytes) IC50 3.1 ± 1.2 nM	[143]
69	Splenocin B		Marine bacterium *Streptomyces* sp.	Inhibition of expression of pro-inflammatory cytokines IL-5 and IL-13 on $T_{H}2$ cells (helper T lymphocytes) IC50 1.8 ± 0.2 and 1.6 ± 0.02 nM	[143]
70	Splenocin C		Marine bacterium *Streptomyces* sp.	Inhibition of expression of pro-inflammatory cytokines IL-5 and IL-13 on $T_{H}2$ cells (helper T lymphocytes) IC50 6.7 ± 0.2 and 7.3 ± 4.2 nM	[143]
71	Splenocin D		Marine bacterium *Streptomyces* sp.	Inhibition of expression of pro-inflammatory cytokines IL-5 and IL-13 on $T_{H}2$ cells (helper T lymphocytes) IC50 47.9 ± 2.9 and 43.7 ± 3.5 nM	[143]

72	Splenocin E		Marine bacterium *Streptomyces* sp.	Inhibition of expression of pro-inflammatory cytokines IL-5 and IL-13 on T_H^2 cells (helper T lymphocytes) IC50 16.6 ± 1.8 and 15.9 ± 1.1 nM [143]
73	Splenocin F		Marine bacterium *Streptomyces* sp.	Inhibition of expression of pro-inflammatory cytokines IL-5 and IL-13 on T_H^2 cells (helper T lymphocytes) IC50 9.4 ± 2.8 and 6.8 ± 0.3 nM [143]
74	Splenocin G		Marine bacterium *Streptomyces* sp.	Inhibition of expression of pro-inflammatory cytokines IL-5 and IL-13 on T_H^2 cells (helper T lymphocytes) IC50 5 ± 0.4 and 5.2 ± 0.1 nM [143]
75	Splenocin H		Marine bacterium *Streptomyces* sp.	Inhibition of expression of pro-inflammatory cytokines IL-5 and IL-13 on T_H^2 cells (helper T lymphocytes) IC50 4.3 ± 0.5 and 5.1 ± 0.1 nM [143]

76	Splenocin I		Marine bacterium *Streptomyces* sp.	Inhibition of expression of pro-inflammatory cytokines IL-5 and IL-13 on T_H^2 cells (helper T lymphocytes) IC50 15.8 ± 1.0 and 15.2 ± 1.3 nM [143]
77	Splenocin J		Marine bacterium *Streptomyces* sp.	Inhibition of expression of pro-inflammatory cytokines IL-5 and IL-13 on T_H^2 cells (helper T lymphocytes) IC50 1022.7 ± 52.3 and 826.3 ± 187.6 nM [143]
41	Fucosterol		Green algae *Tydemania expeditionis*	Hydrophobic interaction with GR via Leu563, Phe623, Leu608, and Met604 (molecular docking analysis) [144]

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The most intriguing case in the reviewed subsets of marine-derived steroids is fucosterol **(41)** with reported anti-cancer activity *in vitro* in prostate and breast cancer cells. Molecular docking of fucosterol on LXR-β, GR, TrkB, TLR2/4, BACE1, and AChE demonstrated that fucosterol formed several hydrophobic interactions with GR via Met604, Leu608, and Phe623. The reported molecular docking data on fucosterol GR binding affinity also suggest its anti-inflammatory action [144]. Following the observation that fucosterol decrease the angiotensin converting enzyme (ACE) levels on the endothelial cells by inhibiting GR synthesis involved in ACE regulation [145], interaction mode of fucosterol with GR could be considered as antagonism but needs further studies.

Thus, the possibility of interaction with GR has been described only for one marine steroid, despite the fact that more than 1000 marine steroids are currently known, including those isolated from marine fungi and sponges. We calculated *in silico* the GR interaction with some marine sponge- and fungal-derived steroidal compounds, which were previously investigated by one of us, to propose their GR-binding (Table 3). The molecular docking evaluation is described in detail in [146], the structure of the GR (PDB ID 1P93) is obtained from the RCSB Protein Data Bank (https://www.rcsb.org).

3β,15β-Dihydroxy-(22*E*, 24*R*)-ergosta-5,8(14),22-trien-7-one (**78**) has been isolated from Vietnamese marine fungus *Penicillium chermesinum* 2104NT-1.3 and reported as cardioprotective agent [110]. Molecular docking calculations showed that **78** did not interact with the ligand-binding domain (LBD) of GR. The number of new oxygenated sterol derivatives has been isolated from marine sponge *Inflatella* sp, collected from the Sea of Okhotsk [147]. 24-Methylcholesta-5,24(28)-diene-3β,4α-diol (**79**) was not active against 6-hydroxydopamine (6-OHDA) toxicity and 24-*nor*-cholesta-5,22-diene-3β,7α-diol (**80**) increased the 6-OHDA-treated Neuro-2a cell viability. Moreover, **(80)** enhanced formazan production in the MTT assay. The results indicated that **(79)** can interact with Arg611 and **(80)** can interact with Met604, Leu566, Tyr735, Phe623, and Cys736, which formed LBD-GR.

Moreover, we attempted to determine whether marine non-steroidal compounds may be of interest in this regard. The library of secondary metabolites isolated at various times from the fungal strains of the Collection of Marine Microorganisms of the PIBOC FEB RAS (https://kmm644.ru) was analyzed from the point of view of structural similarity with dexamethasone using the PubChem Score Matrix Service to calculated substructure key-based 2D Tanimoto similarity (https://pubchem.ncbi.nlm.nih.gov/docs/score-matrix-service access date 30.08.2025). In total, 202 compounds were analyzed, and the highest Tanimoto indexes of 69 were calculated for decumbenone C (**81**) from *Aspergillus sulphureus* KMM 4640 [148] and conidiogenone F (**82**) from *Penicillium antarcticum* KMM 4670 [149]. The list of compounds and full PubChem Score Matrix calculations are presented in the Supplementary file 1.

Molecular docking calculations for these compounds were also performed (Figure 1, Table 3), and they showed a good possibility of binding to LBD-GR. Decumbenone C (**81**) formed a complex with ΔG of -8.23 kcal/mol and interacted with Arg611, Gly567, Trp600, Met604, Met601, Met646, Phe623, and Met560. Two complexes were calculated for conidiogenone F (**82**). The first complex with ΔG of -8.46 kcal/mol included hydrophobic interactions with Gly567, Met604, Met601, Trp600, Cys736, Tyr735, Met560, Met646, and Phe623 in the LBD-GR. The second complex with ΔG of -7.91 kcal/mol included hydrogen binding with Gln642 and hydrophobic interactions with Met560, Gly567, Met604, Met646, and Cys736 in the LBD-GR. Figure 1 illustrates the compounds with the highest affinity.

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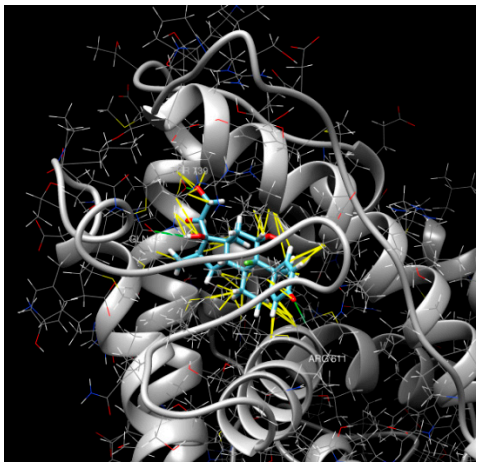
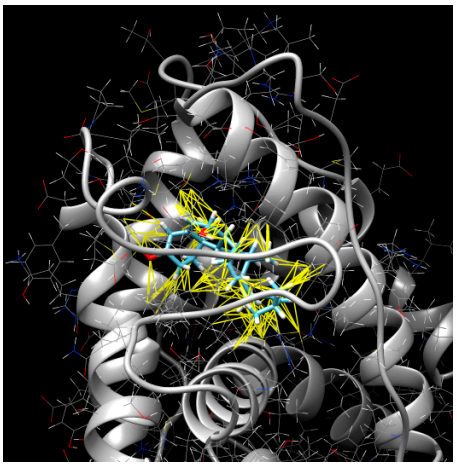
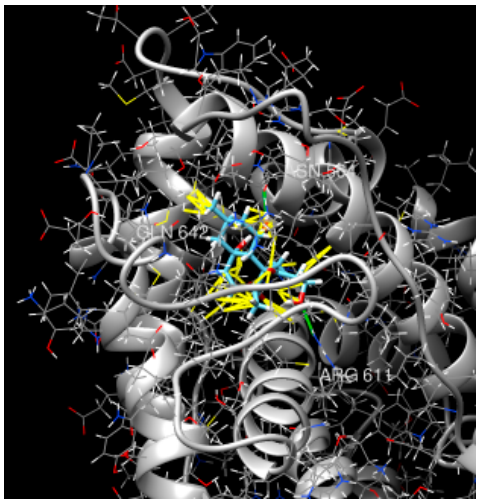


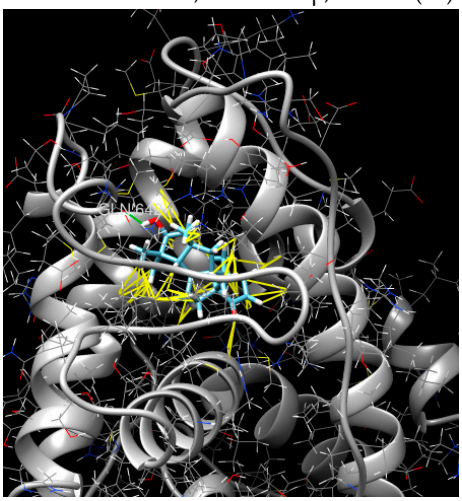
Dexamethasone



24-*nor*-Cholesta-5,22-diene-3β,7α-diol (**80**)



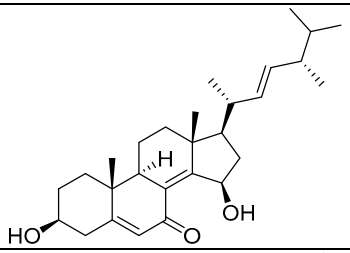
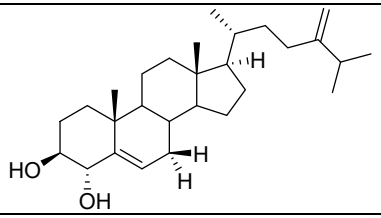
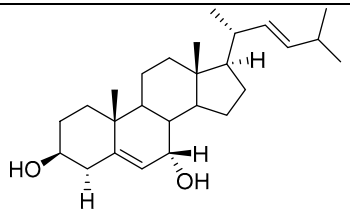
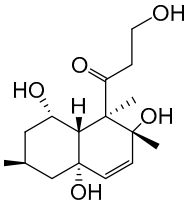
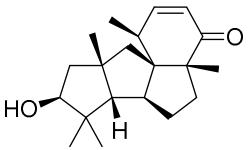
Decumbenone C (**81**)

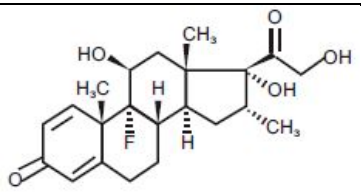


Conidiogenone F (**82**)

Figure 1. Molecular docking of the compounds with GR (PDB ID 1P93). Green lines show hydrogenic bonds, yellow lines show hydrophobic interactions.

Table 3. Molecular docking calculations of marine natural compounds with GR (PDB ID 1P93).

No	Compound	Chemical Structure	ΔG, kcal/mol	FF Score, kcal/mol	H-Binding	Hydrophobic Interactions
78	3β,15β-Dihydroxy-(22*E*, 24*R*)-ergosta-5,8(14),22-trien-7-one		-7.23	-1226.71	-	Val538, ILe539, Lys576, Ala573, Leu544, Trp577
79	24-Methylcholesta-5,24(28)-diene-3β,4α-diol		-7.40	-1204.67	H29 … **Arg611** 2.607	Val543, Trp610, Tyr660,
80	24-*nor*-Cholesta-5,22-diene-3β,7α-diol		-6.37	-1165.36	-	**Met604**, **Leu566**, Leu732, Asn630, Leu563, **Tyr735**, **Phe623**, Leu608, **Cys736**
81	Decumbenone C		-8.23	-1298.75	**Arg611** … O 2.666 H24 … Asn564 1.682	**Gly567**, **Trp600**, **Met604**, **Met601**, Leu732, **Met646**, **Phe623**, Leu563, **Met560**
82	Conidiogenone F		-8.46	-1229.36	-	**Gly567**, **Met604**, **Met601**, Leu732, **Trp600**, **Cys736**, **Tyr735**, **Met560**, Leu563, **Met646**, **Phe623**
			-7.91	-1211.54	H29 … **Gln642** 2.103	**Met560**, Leu563, Leu753, **Gly567**, **Met604**, **Met646**, Leu732, **Cys736**

Dexamethasone		-10.19	-1206.31	Arg611 … O 2.146 Met560, Leu566, Gly567, Trp600, H27 … Gln642 2.351 Met601, Met604, Phe623, Met646, H26 … Thr739 2.115 Tyr735, Cys736, Thr739, Ile747

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Interestingly, the decaline polyketide decumbenone C (**81**) showed potent cytotoxic activity against SK-MEL-5 human melanoma cells, with an IC50 of 0.9 μM, and inhibited colony formation at 0.25 μM [148]. Cyclopiane diterpene conidiogenone F (**82**) exhibited weak antimicrobial activity and was non-toxic to H9c2 cardiomyocytes [149]. However, its bioactivity has not been studied in detail because of difficulties in the isolation it from fungal extracts.

Structural similarity analysis involves the study of the presence of substructural key elements, the distance between pharmacophores or functional groups in compounds, at the same time, the detailed structure and biogenetic origin are not taken into account. This allowed us to select decalin polyketide (**81)** and diterpene derivative (**82)** as structurally similar to dexamethasone, and modular docking confirmed their prospects as GR ligands. Moreover, 10 marine fungal metabolites had Tanimoto indexes in the range from 52 to 66 and 30 compounds had Tanimoto indexes in the range from 41 to 49 (Supplementary file 1), and these 40 compounds may be also promising as GR ligands. Probably, the structural similarity of non-steroidal compounds to steroids may ensure their biological activity but reduce steroid-dependent side effects. This obviously requires additional in-depth research.

4. Conclusions

In conclusion it should be mentioned that marine ecosystems represent a significant source of natural steroid with the potential use in anti-cancer and anti-inflammatory therapies. More specifically, ligands of glucocorticoids receptors and putative selective glucocorticoid receptor agonists/modulators could be found among the marine-derived compounds, could be characterized by chemical structure as well as by biological activity. Evaluation of the affinity to glucocorticoid receptor and the assessment of the expression of marker genes specific for glucocorticoid receptor activity could be the useful set of methods for the screening of biological activity.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Abbreviations

The following abbreviations are used in this manuscript:

ACE - Angiotensin Converting Enzyme
AChE - Acetyl Cholinesterase
AR – Androgen Receptor
BACE1 - Beta-secretase 1
CDK – Cyclin Dependent Kinase
CpdA – Compound A
DBD – DNA Binding Domain
ER – Estrogen Receptor
ERE – Estrogen Responsive Elements

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ERK - Extracellular Regulated Kinase
GC – Glucocorticoids
GR – Glucocorticoid Receptor
GRE – Glucocorticoid Responsive Elements
IL – Interleukin
INF – Interferon
iNOS - Inducible Nitric Oxide Synthase
LPS – Lipopolysaccharides
LXR-β – Liver X receptor beta
MAPK - Mitogen-Activated Protein Kinase
MCP-1 - Monocyte Chemoattractant Protein-1
MR – Mineralocorticoid Receptor
PR – Progesterone Receptor
SEGRAM -Selective Glucocorticoid Receptor Agonists/Modulators
TA – Transactivation
TF – Transcription Factor
ThR - Thyroid Hormone Receptor
TLR – Toll-Like Receptor
TNF-α – Tumor Necrosis Factor alpha
TR – Transrepression
TrkB - Tropomyosin Receptor Kinase B
VDR – Vitamin D Receptor

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