ACCSCIENCE PUBLISHING

Tumor Discovery

REVIEW ARTICLE

Boronosteroids as potential antitumor drugs: A review

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Abstract

Boron's unique chemical properties have long fascinated scientists, particularly its ability to form stable five- or six-membered spiroborate compounds. Among these, tetracoordinate compounds, where boron is bonded to four oxygen atoms, stand out for their versatility and significance across various fields. Over the past few decades, these compounds have demonstrated remarkable pharmacological properties and biological activity, establishing them as a cornerstone of modern boron chemistry. The reaction between boric acid and *cis*-1,2- and 1,3-diol groups has been known for more than a century, providing the basis for analytical chemistry and adsorption techniques. Building upon this knowledge, the interaction between boric acid and steroids opens new horizons in lipid chemistry. These boron-steroid complexes, though largely unexplored, hold great promise for future biomedical applications. The steroids that form boron complexes exhibit enhanced solubility in an aqueous solution, which in turn augments the antitumor efficacy of these steroids. The data presented show that 58% of steroids exhibit strong antineoplastic and related activities, 31% display moderate activity, and <11% show weak antineoplastic activity and varying levels of activity in other biological mechanisms.

Keywords: Antitumor activity; Boronosteroids; Bacteria; Invertebrates; Fungi; Plants

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1. Introduction

Steroids are lipid molecules of animal or plant origin that exhibit high biological activity due to a sterane framework within their composition.[1] They are naturally formed from isoprenoid precursors and have four sequentially linked hydrocarbon atoms in their structure.[2-4] Steroids play a crucial role in the regulation of metabolism and physiological functions in many living organisms, including humans.[5,6] Depending on their chemical structure, steroids can exhibit a wide range of biological activities, such as antitumor activity.[7,8]

Steroids containing *cis*-1,2- and/or 1,3-diol groups can form stable five- and/or six-membered spiroborate complexes, which have demonstrated exceptional pharmacological properties and selective biological activity. These complexes are the basis of modern boron chemistry, and boric acid interactions with steroids open up new opportunities in steroid chemistry.[9-12]

Scorei *et al.*[13] conducted a study on the effectiveness of sugar-borate esters in preventing prostate cancer. They discovered that these esters act as boron transporters, increasing the concentration of borate in cancer cells compared to normal cells. This increase in intracellular borate concentration activates borate transporters, leading to growth inhibition and apoptosis. Among the most effective classes of sugar-borate esters for anticancer therapy are trigonal *cis*-diol boron monoesters. There is a negative correlation between borate intake and the risk of prostate cancer, as cancer cells overexpress sugar transporters. Therefore, these sugar-borate esters may serve as potential chemopreventive agents for both primary and recurrent prostate cancer. Moreover, boron complexes with steroids could potentially enhance the antitumor properties of steroids.

Boric acid is a weak acid that does not dissociate into ions in aqueous solution like other Brønsted acids. Instead, it behaves as a Lewis acid, attracting a hydroxyl ion and forming the tetrahydroxyborate ion, as demonstrated using Raman spectroscopy.[14]

In natural aqueous systems, the dominant inorganic boron species are in mononuclear forms such as boric acid ($B[OH]_3$) and borate ion ($B[OH]_4^{-1}$). The distribution of these species depends on the dissociation constant of boric acid and the pH of the solution. As the pH increases, more boric acid molecules bind with hydroxyl groups to form the anionic tetrahydroxyborate complex (Figure 1).[15] The pKa value for the borate anion has been measured to be 9.24 at 25°C in freshwater, indicating that it is more stable in alkaline conditions. This B-anion can form complexes with metals and other ions, playing an essential role in geochemical processes.

This article explores the fascinating world of boronosteroids, which are derived from plants and other natural sources. We delve into the biological activities of these unique compounds, which feature vicinal *cis*-1,2- and/or 1,3-diol groups in their molecular structures. We also discuss the antitumor properties of certain boron-containing steroid complexes.

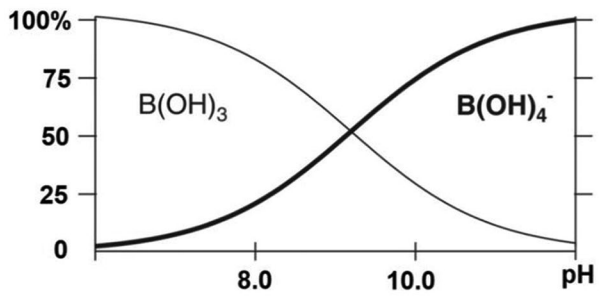

Figure 1. When boron-containing minerals dissolve in water, they exist mainly in the form of boric acid or borates. Boric acid is a weak acid with a pKa between 8.68 and 9.25, depending on the salinity and temperature of the solution. This pKa refers to the equilibrium between the boric acid molecule (H_3BO_3) and its associated monoborate ion ($B[OH]_4^{-1}$). At low pH values (<9), boric acid predominates, while at higher pH values (>9) and in more dilute solutions, the monoborate form becomes dominant. Image created by the authors using MGI PhotoSuite.

2. Ouabain and its boron complexes

Antitumor agent, ouabain (1, Figure 2), also known as strophanthin, is a natural cardiac glycoside that can be found in plants such as *Strophanthus gratus*.[16] It has been used as an arrow poison in the past, but it can be used to treat heart conditions and low blood pressure in lower doses. Ouabain works by inhibiting the sodium-potassium pump in cell membranes, which can increase the force of the heart's contraction. This makes it a valuable drug for treating heart problems. Although ouabain has a rapid onset of action and short duration, it does not accumulate in the body. It was found to induce apoptosis in androgen-independent prostate cancer cells *in vitro*.[17]

Aqueous leaf extracts from *Strophanthus* have been shown to have similar effects. An aqueous-ethanol extract from *S. gratus* has shown a remarkable ability to prolong the clotting time of blood treated with viper (*Echis carinatus*) venom. The venom causes rapid intra-arterial blood clotting, leading to death.[18,19]

S. gratus is a climbing plant that can grow up to 25 m in height. It produces a transparent or translucent latex. This plant is native to West and Central Africa, from Senegal to Congo. It is cultivated for its medicinal and toxic properties in Nigeria, Cameroon, and Gabon. The plant thrives in primary and secondary forests, often near forest edges or along riverbanks, at altitudes ranging from sea level to 650 m.[20] In Sierra Leone, the leaves of this plant are used alone or in combination with other plants to treat gonorrhea.[21] In Côte d'Ivoire, a decoction of the leaves and twigs is taken orally to treat neonatal conjunctivitis and fever.[22] In Ghana, the sap from the leaves is applied to wounds, and the leaves are used to make a poultice for treating guinea worm sores.[23] Moreover, in Sierra Leone, the leaves are used as an antidote against the venom of the black-headed cobra (*Naja nigricollis*).[24] In Congo, the sap from the fresh bark of *S. gratus* is mixed with the sap of *Parquetina nigrescens* to create a poison for arrows. The bark of the root is employed as a remedy for food poisoning,[22] while decoctions of the root and stem bark are used as a cough suppressant and syphilis treatment.[25]

The seeds of the plant are used to effectively treat rheumatoid arthritis. In ancient times, the juice and fruits of this plant were used to prepare poisons for arrows. In addition, the juice from the fresh bark of the plant, when mixed with *Omphalognus caliphyllus*, has also been used

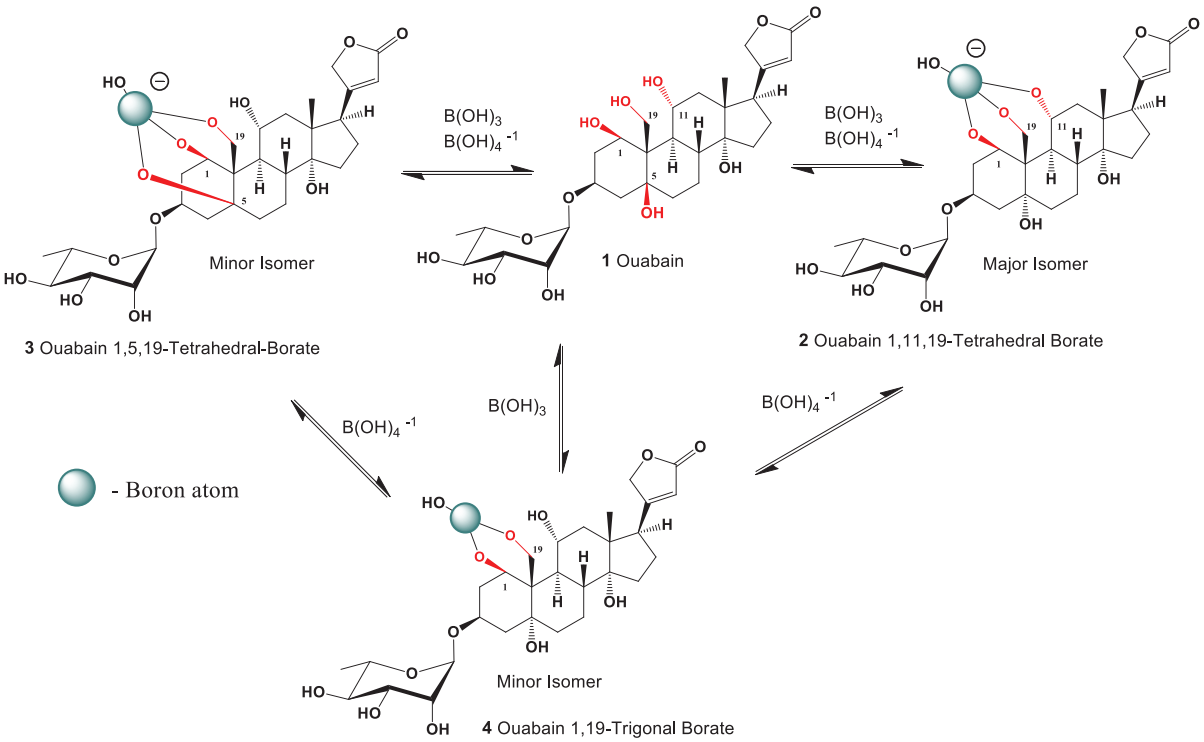

Figure 2. The general scheme for the formation of boron complexes with ouabain. Borax, which, when dissolved in water, forms boric acid and boron anion, reacts with ouabain and forms tetrahedral- and trigonal-borate complexes.[30-32] Highlighted in red are hydroxyl groups that interact with boric acid or boron anion to form cycloborates. Image created by the authors using ChemDraw Ultra version 12.0.2.

for similar purposes. The seeds contain strophanthin, and its aqueous extract is a potent poison. An antidote for this poison is the external application of *Erythrophleum guineense* bark powder, as well as the internal use of *Alstonia congensis* spp.[23] The plant is also used to treat certain heart conditions in some West African countries. In several West African nations, a leaf paste is applied to sores, including those caused by guinea worms. In Nigeria, a tea made from the leaves is taken to relieve constipation and applied to the body to reduce fever. A decoction of the roots is said to have aphrodisiac properties. In West Africa, the plant is believed to bring good luck.[20]

Among the steroid hormones, endogenous ouabain (EO, Figure 2) and its boron complexes are among the most extensively researched. EO was first detected in human plasma approximately 30 years ago.[26,27] The presence of EO in humans and other mammals has been confirmed through physical and chemical methods. Through the use of multistage mass spectrometry, researchers have studied the effects of pregnancy and central angiotensin II infusion on EO levels in rat plasma, leading to the discovery of two isomers of EO. Isomer 2 has a product ion spectrum that is identical to that of EO, although it is more polarized and binds to an antibody for radioimmunoassay. Isomer 3 is less polarized and has a clear mass spectrum.

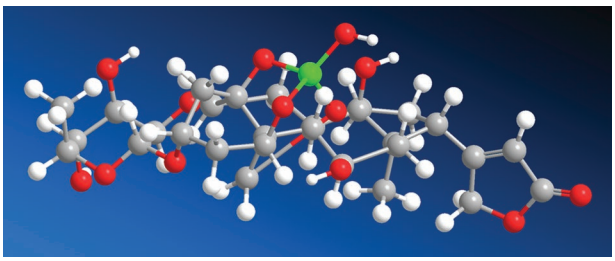

Figure 3. Three-dimensional graph of the complex of the major isomer of ouabain 1,11,19-tetrahedral borate. The boron atom is highlighted in green, and oxygen is highlighted in red. Image created by the authors using ChemDraw Ultra version 12.02.

It also demonstrates weak cross-reactivity in the radioimmunoassay method.

The primary structural difference between EO and these isomers may be related to the steroid nucleus. It is noteworthy that neither of these isomers has been previously described nor has been found in plant-derived ouabain.[28,29]

The reaction between EO and borate in borosilicate glassware leads to the creation of two isomeric boron complexes: the major isomer is 1,11,19-tetrahedral borate (2, Figure 3), while the minor isomers are 1,5,15-tetrahedral borate (3, Figure 4) and 1,19-trigonal borate. In addition,

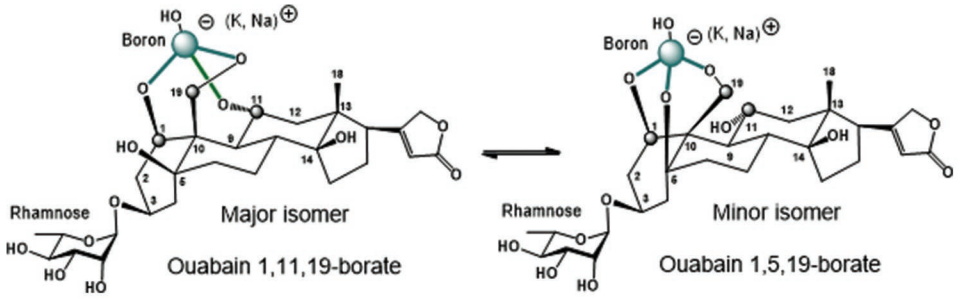

Figure 4. Three-dimensional structures of two coordination isomers of tetrahedral ouabain borates. The chemical nature of the transition from the major to the minor isomer has not been established. It is assumed that this may occur due to the position of the hydroxyl groups, changes in pH, or other factors. Image created by the authors using ChemDraw Ultra 12.02.

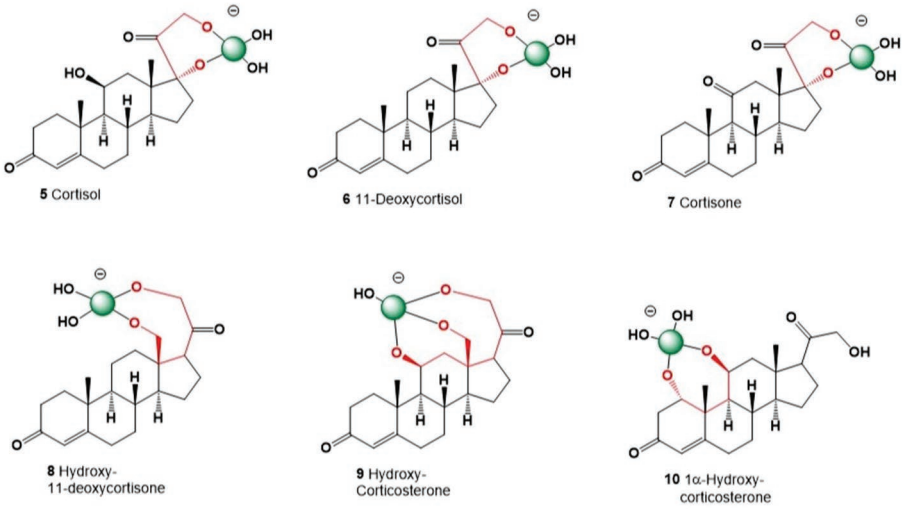

Figure 5. The samples of boron-based complexes of corticosteroids prepared for separation by means of capillary electrophoresis.[40,41] Image created by the authors using ChemDraw Ultra 12.02.

the trigonal-borate complex (4) can transform into tetrahedral-borate complexes (2 and 3) when there is an excess of boron anion and the pH is alkaline.[30,31]

The similarity between the isosteric carbon and boron centers, including the bond distances, angles, and the slightly larger boron radius, makes the formation of borate esters follow well-established reaction pathways commonly employed in the synthesis of steroid analogs.

Ouabain has shown strong inhibitory effects on cell proliferation and caused significant morphological changes in melanoma cells. In addition, ouabain induced apoptosis in A375 cells but not in SK-Mel-28 cells, through the upregulation of B-cell lymphoma 2-associated X protein expression and the downregulation of B-cell lymphoma 2 expression. Ouabain treatment induced cell cycle arrest in the G2/M phase in both A375 and SK-Mel-28 cells through upregulation of cyclin B1 expression and downregulation of *CDC2* and *CDC25C* expression.[32] As we have recently shown, boron forms complexes with salicylic acid and organic acids, thereby increasing the solubility of the latter and significantly increasing the activity of the resulting biomolecules, including steroids.[33] Thus, ouabain in the form of a boron complex gains additional solubility in the bloodstream and delivers this steroid to tumor cells, which increases its cytotoxicity.

3. Corticosteroids and their boron complexes

Corticosteroids are a type of steroid hormone produced exclusively by the adrenal cortex. They are different from the hormones produced by the sex glands and lack progestogenic, androgenic, and estrogenic activity. However, they have varying degrees of glucocorticoid and mineralocorticoid activity.[34,35]

Glucocorticoids, a subgroup of corticosteroids, are anti-inflammatory medications used to treat various

conditions such as rheumatoid arthritis, asthma, leukemia, and other inflammatory diseases. They can also be used for the treatment and prevention of shocks. These drugs play a crucial role in preventing organ and tissue rejection in transplantation by suppressing the immune system. They are also effective in managing autoimmune diseases.[36-39]

Corticosteroids readily form complexes with boron (Figure 5), a phenomenon well documented in scientific literature. For example, the efficient separation of endogenous 17- or 18-hydroxylated corticosteroids (from the 21-hydroxylated 4-pregnene series) as charged boron complexes has been achieved in capillary electrophoresis at pH 9. The borate ion $B(OH)_4^{-1}$ has been identified as a crucial buffer component through boron-11 nuclear magnetic resonance spectroscopy. Corticosteroids bind to borate through their proximal hydroxyl groups, specifically the 17- or 18-hydroxyl in conjunction with the hydroxyl at the 21-position. This binding is reversible, and the strength of the resulting complex—rather than the charge-to-mass ratio—primarily determines the mobility of the charged complex in capillary electrophoresis.[40,41]

4. Steroids derived from natural sources

Various steroid analogs (Figure 6) have been obtained from different natural sources, demonstrating promising pharmacological effects. Specifically, eurypongiols 11 and 12 are epimeric 3α-hydroxy secosteroids with antihistamine properties, isolated from the marine sponge *Eurypongia* spp. These highly oxygenated secosteroids from marine sponges, including eurypongiols A1-A5, differ in their side chain structure, and the eurypongiols, B1-B5, which are 3α-epimers of the A series, exhibit potent inhibition of histamine release from mast cells. This suggests that these compounds could potentially serve as anti-asthmatic and anti-allergic drugs.[42,43] Stelletasterenol

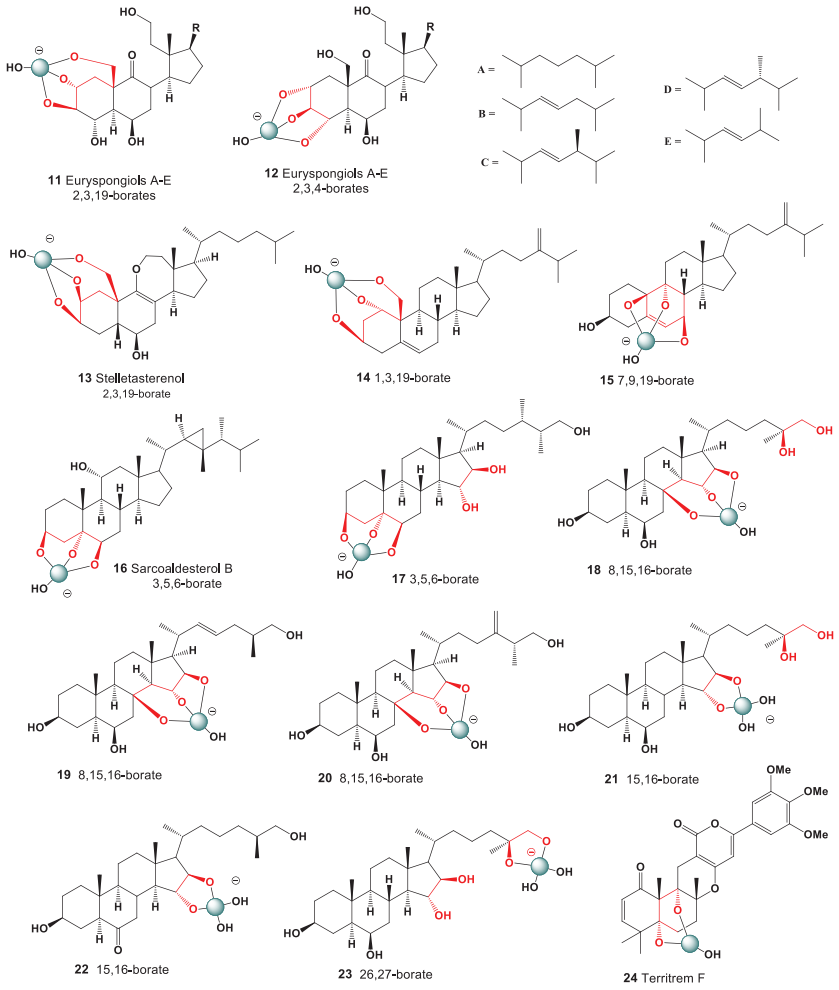

Figure 6. The natural steroids and meroterpenoids derived from nature, along with their boron complexes. Highlighted in red are hydroxyl groups that interact with boric acid or boron anion to form cycloborates. Image created by the authors (Created with ChemDraw Ultra 12.02. PerkinElmer.com).

(13) is a unique cyclic 9(11)-secosterenol obtained from *Euryspongia arenaria*, containing an oxygen atom between C(9) and C(11). It acts as a platelet-activating factor agonist.[44]

The compounds 24-melenic cholestene-1α,3β,19-triols (14) and 24-methene cholestene 3β, 7β,19α-tetraols (15) were isolated from *Nepthea chabroly*.[45] Sarcoaldosterol B (16) with hydroxyl groups at positions 7, 9, and 19 was extracted from *Sarcophyton* species and has the potential for forming boron complexes.[46]

Polyhydroxysteroids (17–20) were identified in *Luidaster dawson*i and a starfish of the Antarctic Echinaster family (18–21).[47,48] *Ctenodiscus crispatus* from the Atlantic, Panama, and Japan contained another polyhydroxysteroid (22). Additional compounds (23 and 24) were also found in Echinasterids.[48]

Drimane borate, territrem F (24), and its diol precursor territrem B were isolated from an associated spore-forming mold fungus (*Alternaria* species). These compounds feature a unique boron ring system and exhibit significant inhibitory activity against synchronized Ca^{2+} oscillations and epileptic discharges caused by 4-aminopyridines.[49]

5. Bioactive steroids derived from the soft coral steroids

Soft corals are a group of organisms belonging to the order *Alcyonacea*, which is part of the class *Octocorallia*, *Anthozoa*, and *Cnidaria*. They are also known as gorgonians and can

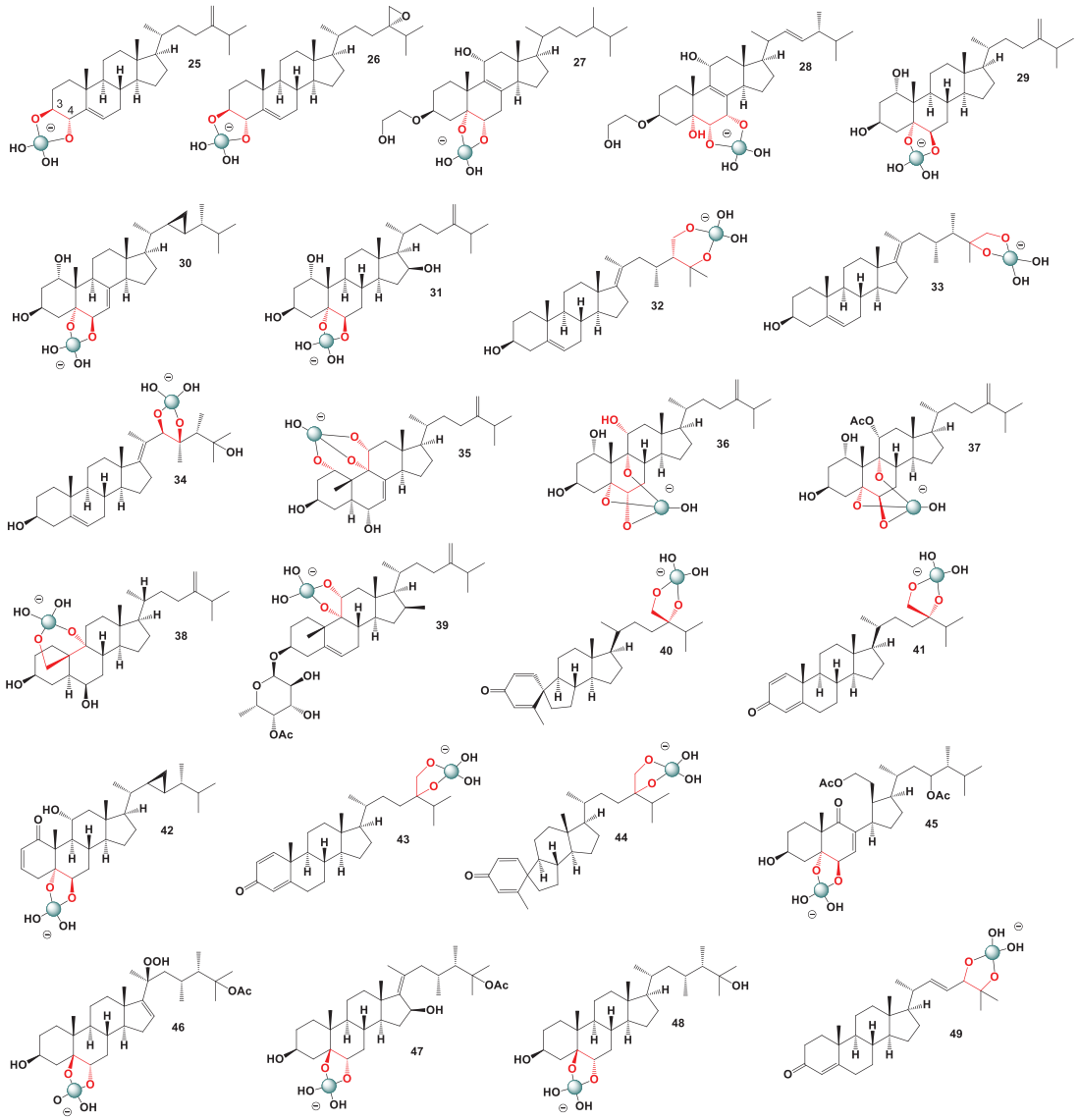

Figure 7. Chemical diversity of bioactive steroids derived from the soft corals. Image created by the authors using ChemDraw Ultra 12.02.

be found in all the oceans of the world, particularly in the tropical and subtropical regions. Some soft coral steroids contain fragments of *cis*-1,2- and 1,3-diol and can react with boron anions or boric acid, which are abundant in seawater.[50]

A methanol extract of the soft coral *Sinularia nanolobata* from Vietnamese sea waters contained a pair of bioactive steroids (25 and 26, Figure 7). Thus, steroid (26) showed moderate cytotoxicity against acute leukemia cells (HL-60) and a small effect on colon adenocarcinoma (SW480) and hepatoma cancer cells (HepG2).[51]

Rare steroids, (27) and (28), were discovered in the South China Sea gorgonians *Subergorgia suberosa*,[52] and a minor sterol (29) was identified in the *Sinularia numerosa*.[53] Kobayashi and colleagues conducted research on the soft coral *Sinularia mayi*, *Sinularia gibberosa*, *Sinularia dissecta*, and *Sinularia* spp., collected from the coast of Japan. They identified a series of steroids (30 and 31).[54-58] The same researchers investigated the same soft corals collected from the shores of Japan. They discovered a range of steroids (32 to 37), but the biological effects of the isolated steroids were not assessed.[54-58] A 3,6,9,19-tetraol-steroid (38) was obtained from *S. inexplicita*.[59] A water-methanol solution containing several soft corals, *Sinularia crispa*,[60] *Sinularia* spp.,[61] and *S. gibberosa*,[62] was found to contain the same cytotoxic steroid glycoside (39).

The cytotoxic steroids 40 and 41 were obtained from methanol and the acetone extracts of the soft coral *Nephthea erecta*.[63] Chabrolosteroid C (40), a steroid with a spiro-ring A, B system, was detected in an organic extract of the Taiwanese soft coral *Nephthea chabrolii*,[64] and stoloniferone J (42), which exhibited cytotoxic activity, was found in the Okinawan soft coral *Clavularia viridis*.[65]

The cytotoxic steroid, erectasteroid H (43), showed activity against P-388 (leukemia) and human colorectal adenocarcinoma cells (HT-2966), and the bioactive spirosteroid (44) was found in an extract of the Formosan soft coral *N. erecta*.[66-68] The coral *Pinnigorgia* spp. produces a 9,11-secosteroid, pinnisteroid C (45), which inhibited superoxide anion formation and elastase release in human neutrophils.[69]

The coral *Lobophytum michaelae*, a rich source of secondary metabolites found in Taiwanese waters and a producer of cytotoxic polyoxygenated steroids, is known for its compounds michosterol A–C (46–48).[70] Another coral, *Leptogorgia* spp., from the South China Sea is a producer of dihydroxyketosteroid (49).[71] The chemical formulas of these steroids (25–49) are shown in Figure 7, and their potential biological activities are shown in Table 1.

Table 1. Antitumor and related activity of soft coral steroids

Compound	Reported biological effect	Activity rank
25	Antineoplastic	Moderate
	Chemopreventive	Weak
	Proliferative diseases treatment	Weak
	Antimetastatic	Weak
	Anticarcinogenic	Weak
26	Antineoplastic	Moderate
	Chemopreventive	Weak
	Proliferative diseases treatment	Weak
	Antimetastatic	Weak
27	Antineoplastic	Moderate
	Apoptosis agonist	Weak
28	Antineoplastic	Moderate
	Apoptosis agonist	Weak
	Chemopreventive	Weak
29	Apoptosis agonist	Moderate
	Antineoplastic	Moderate
	Proliferative diseases treatment	Weak
30	Antineoplastic	Moderate
31	[a]Antineoplastic	Strong
	Apoptosis agonist	Moderate
	Proliferative diseases treatment	Weak
32	[a]Antineoplastic	Strong
	Proliferative diseases treatment	Weak
33	[a]Antineoplastic	Strong
	Proliferative diseases treatment	Weak
34	[a]Antineoplastic	Strong
	Proliferative diseases treatment	Weak
35	Apoptosis agonist	Moderate
	Antineoplastic	Moderate
	Proliferative diseases treatment	Weak
36	Apoptosis agonist	Moderate
	Antineoplastic	Moderate
37	Apoptosis agonist	Moderate
	Antineoplastic	Moderate
38	Antineoplastic	Moderate
	Apoptosis agonist	Weak
	Proliferative diseases treatment	Weak
39	[a]Chemopreventive	Strong
	[a]Proliferative diseases treatment	Strong
	Antineoplastic	Moderate
40	Antineoplastic	Weak
	Proliferative diseases treatment	Weak

(Cont'd...)

Table 1. ***(Continued)***

Compound	Reported biological effect	Activity rank
41	[a]Chemopreventive	Strong
	Antineoplastic	Moderate
	Proliferative diseases treatment	Weak
42	Antineoplastic	Moderate
	Alzheimer's disease treatment	Weak
43	[a]Chemopreventive	Strong
	Antineoplastic	Moderate
	Apoptosis agonist	Weak
44	Chemopreventive	Weak
	Antineoplastic	Weak
45	Antineoplastic	Moderate
	Apoptosis agonist	Weak
	Chemopreventive	Weak
46	Antineoplastic	Weak
47	Antineoplastic	Weak
	Prostate disorders treatment	Weak
48	Apoptosis agonist	Weak
	Antineoplastic	Weak
49	[a]Antineoplastic	Strong
	Apoptosis agonist	Moderate
	Proliferative diseases treatment	Weak

Note: The compounds correspond to those in Figure 7. [a]Steroids that demonstrated strong antineoplastic and related activities.

6. Antitumor profile of carbon-bridged steroids and triterpenoids

The sea sponge *Stylissa* spp., found in the waters off the coast of Okinawa, has become the subject of research into bioactive molecules. Analysis of the extract obtained from this sponge has revealed the presence of a steroid known as hatomasterol (50). This particular steroid exhibits remarkable activity against the immortal HeLa cell line when tested *in vitro*.[72] Figure 8 shows the compound's structure, and Table 2 shows its activity.

Okinawa is a famous Japanese island located in the East China Sea. The city of Naha on the island is home to the beautiful Shuri Castle and its ornate Shureimon gate. Surrounding the island is the Sea of Japan, which is home to a variety of marine life, including the *Xestospongia* marine sponge. This sponge produces two compounds, 26,27-cyclosterols and aragusterols B (51) and C (52), both of which have been shown to have cytotoxic properties.[73,74] This species of marine sponge is known for its richness in dimethyl acetal-structured marine steroids, such as aragusteroketal C (53), which exhibit cytotoxic

Table 2. Antitumor and related activity of marine steroids

Compound	Reported biological effect	Activity rank
50	[a]Antineoplastic	Strong
	Apoptosis agonist	Moderate
	Antineoplastic (liver cancer)	Moderate
	Chemopreventive	Weak
	Cytoprotectant	Weak
	Prostate cancer treatment	Weak
	Antimetastatic	Weak
51	Antineoplastic	Moderate
	Proliferative diseases treatment	Weak
	Cytoprotectant	Weak
	Chemopreventive	Weak
	Apoptosis agonist	Weak
	Antineoplastic (sarcoma)	Weak
	Antimetastatic	Weak
52	[a]Antineoplastic	Strong
	Proliferative diseases treatment	Weak
	Prostate cancer treatment	Weak
	Antineoplastic (sarcoma)	Weak
	Cytoprotectant	Weak
	Antineoplastic (renal cancer)	Weak
	Apoptosis agonist	Weak
53	[a]Antineoplastic	Strong
	Prostate disorders treatment	Weak
	Proliferative diseases treatment	Weak
	Antineoplastic (sarcoma)	Weak
54	Antineoplastic	Moderate
	Cytoprotectant	Weak
	Proliferative diseases treatment	Weak
	Chemopreventive	Weak
	Antineoplastic (sarcoma)	Weak
	Prostatic (benign) hyperplasia treatment	Weak
55	Antineoplastic	Moderate
	Cytoprotectant	Weak
	Antineoplastic (sarcoma)	Weak
	Antimetastatic	Weak
	Antineoplastic (renal cancer)	Weak
	Prostate disorders treatment	Weak
	Proliferative diseases treatment	Weak
	Apoptosis agonist	Weak
	Antineoplastic (pancreatic cancer)	Weak
	Chemopreventive	Weak
	Antineoplastic (genitourinary cancer)	Weak

(Cont'd...)

Table 2. ***(Continued)***

Compound	Reported biological effect	Activity rank
56	Antineoplastic	Weak
	Apoptosis agonist	Weak
	Prostate disorders treatment	Weak
57	Antineoplastic	Weak
	Apoptosis agonist	Weak
58	Antineoplastic	Moderate
	Apoptosis agonist	Weak
	Prostate disorders treatment	Weak
	Antineoplastic (sarcoma)	Weak
	Antineoplastic (pancreatic cancer)	Weak
59	Antineoplastic	Moderate
	Prostate disorders treatment	Weak

Note: The compounds correspond to those in Figure 8. [a]Steroids that demonstrated strong antineoplastic and related activities.

properties.[74] The Similan Islands, an archipelago located in the Andaman Sea and part of Phang Nga Province in southern Thailand, attract scientists to study the sponges of the genus *Petrosia*. These sponges are known for their ability to produce sterol (54).[75]

One of the species of starfish found in the Similan Islands is the *Hippasteria phrygiana*. This starfish feeds on other echinoderms and bivalves and has a life span of 20–400 years. The extract of this starfish contains a hydroxy sterol with a cyclopropane ring called phrygiasterol (55).[76]

The three well-known species of soft corals—*C. viridis*, *S. dissecta*, and *Pseudopterogorgia* spp.—produce a compound known as norsteroid (56), which was isolated from their extracts.[77] In a methanol extract of the soft coral *Klyxum flaccidum*, a steroid called klyflaccisteroid L (57) was discovered. This steroid exhibits moderate cytotoxic activity against various types of cancer cells, but it is particularly noteworthy due to its unconventional 11-nortriene backbone.[78]

Xestobergsterol B (58), which is a unique pentacyclic polyhydroxylated sterol, was found in the extract of *Xestospongia bergquistia*,[79] and its derivative compound xestobergsterol C (59) was found in the Okinawan sponge *Ircinia* spp.[80]

Phytopathogenic fungus *Glomerella fusarioides* (syn. *Fusarium graminearum* and its teleomorph *Gibberella zeae*), which causes fusarium head blight in cereal crops, transforms cycloartenol into 24,25-dihydroxycycloarten-3-one (60, Figure 9 and Table 3),[81] and shengmaxide C (61), has been isolated from an ethanol extract of the roots of *Cimicifuga simplex*.[82] Steroid, named ailanthusin D (62),

Table 3. Antitumor and related activity of terrestrial steroids

Compound	Reported biological effect	Activity rank
60	[a]Chemopreventive	Strong
	Antineoplastic	Moderate
	Apoptosis agonist	Weak
	Cytoprotectant	Weak
	Antineoplastic (pancreatic cancer)	Weak
	Antineoplastic enhancer	Weak
	Antimetastatic	Weak
61	[a]Chemopreventive	Strong
	Antineoplastic	Moderate
	Apoptosis agonist	Moderate
	Anticarcinogenic	Weak
	Antineoplastic (sarcoma)	Weak
	Antineoplastic (pancreatic cancer)	Weak
62	Antineoplastic	Moderate
	Apoptosis agonist	Weak
63	Antineoplastic	Weak
	Chemopreventive	Weak
	Apoptosis agonist	Weak
	Antineoplastic (sarcoma)	Weak
	Antineoplastic (renal cancer)	Weak
64	Antineoplastic	Moderate
	Apoptosis agonist	Weak
	Chemopreventive	Weak
	Antineoplastic (myeloid leukemia)	Weak
65	[a]Chemopreventive	Strong
	Antineoplastic	Moderate
	Proliferative diseases treatment	Weak
	Anticarcinogenic	Weak
	Apoptosis agonist	Weak
	Antimetastatic	Weak
	Antineoplastic (myeloid leukemia)	Weak
	Antineoplastic (pancreatic cancer)	Weak
66	[a]Chemopreventive	Strong
	Antineoplastic	Moderate
	Anticarcinogenic	Weak
	Apoptosis agonist	Weak
	Proliferative diseases treatment	Weak
	Antimetastatic	Weak
	Antineoplastic (myeloid leukemia)	Weak
	Antineoplastic (lymphocytic leukemia)	Weak
67	[a]Chemopreventive	Strong
	Antineoplastic	Moderate

(Cont'd...)

Table 3. *(Continued)*

Compound	Reported biological effect	Activity rank
	Proliferative diseases treatment	Weak
	Apoptosis agonist	Weak
	Anticarcinogenic	Weak
	Antineoplastic (pancreatic cancer)	Weak
	Antimetastatic	Weak
	Antineoplastic (sarcoma)	Weak
68	Chemopreventive	Weak
	Antineoplastic	Weak
69	Antineoplastic	Weak
70	Antineoplastic	Weak
	Chemopreventive	Weak
71	Antineoplastic	Weak
	Chemopreventive	Weak
72	Antineoplastic	Weak
73	Antineoplastic	Moderate
	Proliferative diseases treatment	Weak
	Chemopreventive	Weak
	Anticarcinogenic	Weak
	Apoptosis agonist	Weak
	Antineoplastic (sarcoma)	Weak
	Antimetastatic	Weak
74	Antineoplastic	Moderate
	Chemopreventive	Weak
	Apoptosis agonist	Weak
	Antineoplastic (sarcoma)	Weak
	Proliferative diseases treatment	Weak
	Antineoplastic (lymphocytic leukemia)	Weak
	Prostate disorders treatment	Weak
	Cytostatic	Weak
	Anticarcinogenic	Weak
	Antineoplastic (pancreatic cancer)	Weak
	Antineoplastic (breast cancer)	Weak
	Antimetastatic	Weak
75	Antineoplastic	Weak
	Antineoplastic (renal cancer)	Weak
76	Antineoplastic	Moderate
	Apoptosis agonist	Weak
	Chemopreventive	Weak
	Cytoprotectant	Weak
	Proliferative diseases treatment	Weak
	Prostate cancer treatment	Weak

(Cont'd...)

Table 3. *(Continued)*

Compound	Reported biological effect	Activity rank
	Antineoplastic (pancreatic cancer)	Weak
77	[a]Antineoplastic	Strong
	Chemopreventive	Moderate
	Apoptosis agonist	Moderate
	Cytoprotectant	Weak
	Antimetastatic	Weak
	Antineoplastic (pancreatic cancer)	Weak
78	Antineoplastic	Moderate
	Apoptosis agonist	Weak
79	Antineoplastic	Moderate
	Apoptosis agonist	Weak
80	Apoptosis agonist	Weak
81	[a]Antineoplastic	Strong
82	Antineoplastic	Weak
83	[a]Apoptosis agonist	Strong
	Antineoplastic	Moderate
	Antineoplastic (genitourinary cancer)	Weak
84	[a]Antineoplastic	Strong
	Apoptosis agonist	Moderate
	Antineoplastic (genitourinary cancer)	Weak
	Antimetastatic	Weak
85	[a]Antineoplastic	Strong
	Apoptosis agonist	Weak
	Antimetastatic	Weak
86	[a]Chemopreventive	Strong
	Apoptosis agonist	Moderate
	T cell inhibitor	Weak

Note: The compounds correspond to those in Figure 9. [a]Steroids that demonstrated strong antineoplastic and related activities.

has been found and isolated from the dichloroethane extract of the Thailand rainforest tree *Ailanthus triphysa*.[83]

Didymocheton muelleri, the red bean or Miva mahogany, is a tree in the Meliaceae family that grows in tropical forests, and a dichloromethane extract of the air-dried leaves contained a triterpenoid (63).[84]

Aglaia crassinervia, a plant of the Meliaceae family found in Brunei, India, Indonesia, Malaysia, Myanmar, the Philippines, and Thailand, contained cytotoxic triterpenoids, aglaiaglabretol C (64), and antitumor triterpene glucosides, which were named cumingianosides A (65), D (66), and M (67).[85] Cumingianoside M (67) was found to be particularly effective, exhibiting significant cytotoxicity at concentrations below 4 mM.[86,87] A hexane

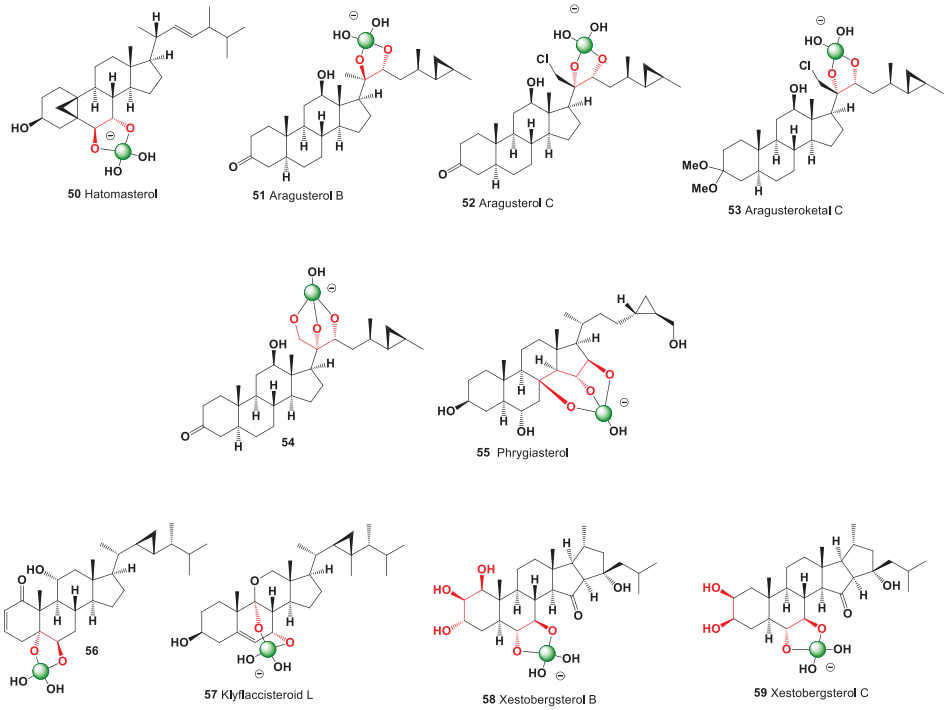

Figure 8. Bioactive steroids derived from marine sources. Highlighted in red are hydroxyl groups that interact with boric acid or boron anion to form cycloborates. Image created by the authors (Created with ChemDraw Ultra 12.02. PerkinElmer.com).

extract of the wood of *Dysoxylum muelleri* has yielded a triterpenoid called dysoxin 3B (68).[88,89]

Dichapetalum madagascariense, a plant species originally found in Madagascar but now widespread in mainland tropical Africa, produces active triterpenoids, with roots containing the cytotoxic dichapetalin C (69).[90,91] In Taiwan and the Philippines, *Dysoxylum cumingianum* of the mahogany family (Meliaceae) grows, and a methyl extract of the leaves of this tree showed significantly enhanced cytotoxicity in the presence of colchicine, as triterpenoids were found in the extract (70 and 71).[92] In addition, the compound, 14-deoxy-14,18-cyclo-20-hydroxyecdysone (72) was isolated and obtained by photochemical transformation of 20-hydroxyecdysone.[93]

Pentacyclic steroids with a 3α,5α-cyclopregnane skeleton were first discovered in the 1940s and are rare norsteroids, many of which exhibit cytotoxic properties. The plant, *Vladimiria muliensis*, is specifically a member of the genus Vladimiria, which is part of the Compositae (Asteraceae) family. Its rhizomes contain a pair of highly active vladimuliecins A (73) and B (74). Testing of these steroids has shown that they exhibit cytotoxicity against cancer cell lines, including human hepatoma cells (SMMC-7721), human leukemia cells (HL-60), and human cervical carcinoma cells (HeLa).[94]

Glycoside, known as physacoztolide F (75), was found in the chloroform-methanol extract of the leaves of *Physalis coztomatl*,[95] and two steroids with a withanolide-type structure, cilistol P (76) and PM (77), have been detected in water-ethanol solution of the leaves of *Solanum cilistum*.[96]

Chukrasia tabularis var. *velutina* is a variety of *C. tabularis*, a tree known for its medicinal properties, native to tropical Asia, including India and southern China. The plant is known for its phragmalin-type limonoids, which are being studied for their potential medicinal properties. One of these, velutabularin F (78), was found in the stem bark of this plant.[97] Protolimonoid capulin (79), another limonoid, was isolated from an aqueous ethanol extract of the stem barks of *Capuronianthus mahafalensis*, endemic to Madagascar.[98] *A. triphysa*, an evergreen tree found in tropical forests of Asia and Australia, contains an unusual triterpene malabaricane type (80).[99]

Hainan is an island and province of China, located at the southernmost point of the country. It is known for its tropical climate and forested mountainous areas where the shrub *Phyllanthus hainanensis* grows. This plant has many medicinal properties, and in particular, a decoction is used to treat diabetes and prevent cancer. In addition, it is employed in preventing and managing chronic hepatitis B viral infection.[100,101] In the extracts of *P. hainanensis*, several highly modified triterpenoids have been identified, characterized by their unique

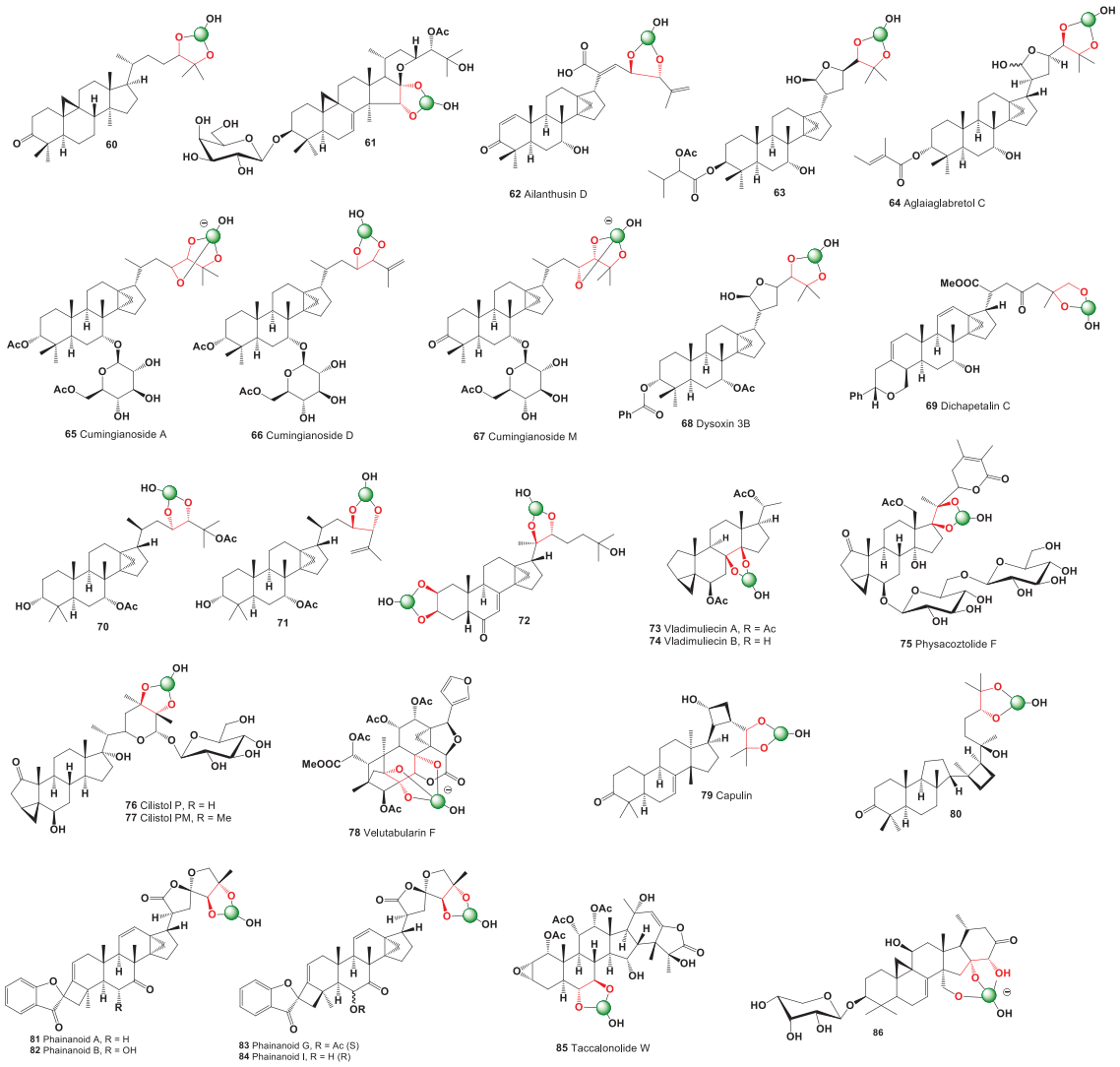

Figure 9. Bioactive carbon-bridged steroids derived from plant species. Image created by the authors (Created with ChemDraw Ultra 12.02. PerkinElmer.com).

carbon skeletons that incorporate two distinct motifs: a 4,5- and 5,5-spirocyclic system, containing cyclopropane and cyclobutene fragments. These compounds (81–84), designated as phainanoids A, B, G, and I, exhibit exceptional immunosuppressive activity *in vitro*, effectively inhibiting the proliferation of both T and B lymphocytes.[102,103] The most potent compound, phainanoid F, demonstrated remarkable activity against the proliferation of T cells, with an IC_{50} value of 2 nM, surpassing the positive control cyclosporin A by a factor of approximately 7. In contrast, its activity against B cells was even more pronounced, with an IC_{50} value below 1.6 nM, exceeding cyclosporin A by an impressive margin of approximately 221.

Taccalonolides are a class of microtubule-stabilizing steroids found in plants belonging to the genus *Tacca*. These steroids have anticancer activity and are widely used in medical practice.[104] *Tacca* species contains highly oxygenated steroid compounds with an additional carbon-carbon bond, forming a ring between C-16 and C-24. Taccalonolide A (85) is the first example of this compound.[105] A similar to taccalonolide was isolated from several plants, including *Tacca plantaginea* and *Tacca subflaellata*. The Vietnamese plant *Tacca paxiana* also yielded this compound.[106-110] In China, black cohosh (*Cimicifuga foetida*), which grows in Siberia, is used for medicinal purposes, and the roots of this plant contain trinor-cycloartane glycoside 28-hydroxy-foetidinol-3-O-β-D-xylopyranoside (86).[111]

7. Bioactive neurosteroids derived from natural sources

Neurosteroids constitute a minuscule class of lipids produced by yeasts and fungi and are also present in various

plant parts.[112] In recent times, with the advancement of steroid analytical techniques, their presence has been identified in seaweeds, demosponges, anemones, and holothurians.[9,112] The common bean (*Phaseolus vulgaris*), a large genus of annual legumes native to Central and South America, contains the unique steroid of 5α–cholestan–6–one (87, Figure 10 and Table 4).[113-117]

Brassinosteroids are a class of phytohormones that play a key role in regulating various aspects of plant growth, development, and maturation. Their structures are similar to animal steroids and are present in all plant organs, including roots, stems, leaves, flowers, and seeds.[118-120]

The seeds of the common bean (*P. vulgaris*) are edible and serve as a primary food source worldwide, consumed both as green beans (immature pods) and as dry, shelled beans. These beans contain bioactive neurosteroids (88–95).[118-120]

Lolium perenne, common name perennial ryegrass, or English ryegrass, in the pollen of which a neurosteroid was found (93),[121] and *Arabidopsis thaliana*, or cress, a plant of the cruciferous family, produces two neurosteroids (96 and 97).[122,123]

8. Mechanism of action of boron-containing steroids on cancer cells

The mechanism of action of boron-containing steroids on cancer cells includes:[124-128]

(a) Proteasome inhibition: Boron's ability to form strong bonds with hydroxyl groups allows it to inhibit proteasomes, which play a key role in protein breakdown in cells. This inhibition can lead to cell cycle arrest, and the accumulation of cell cycle-regulating proteins can halt cell cycle progression.

(b) Apoptosis induction: Disruption of cellular pathways caused by proteasome inhibition can

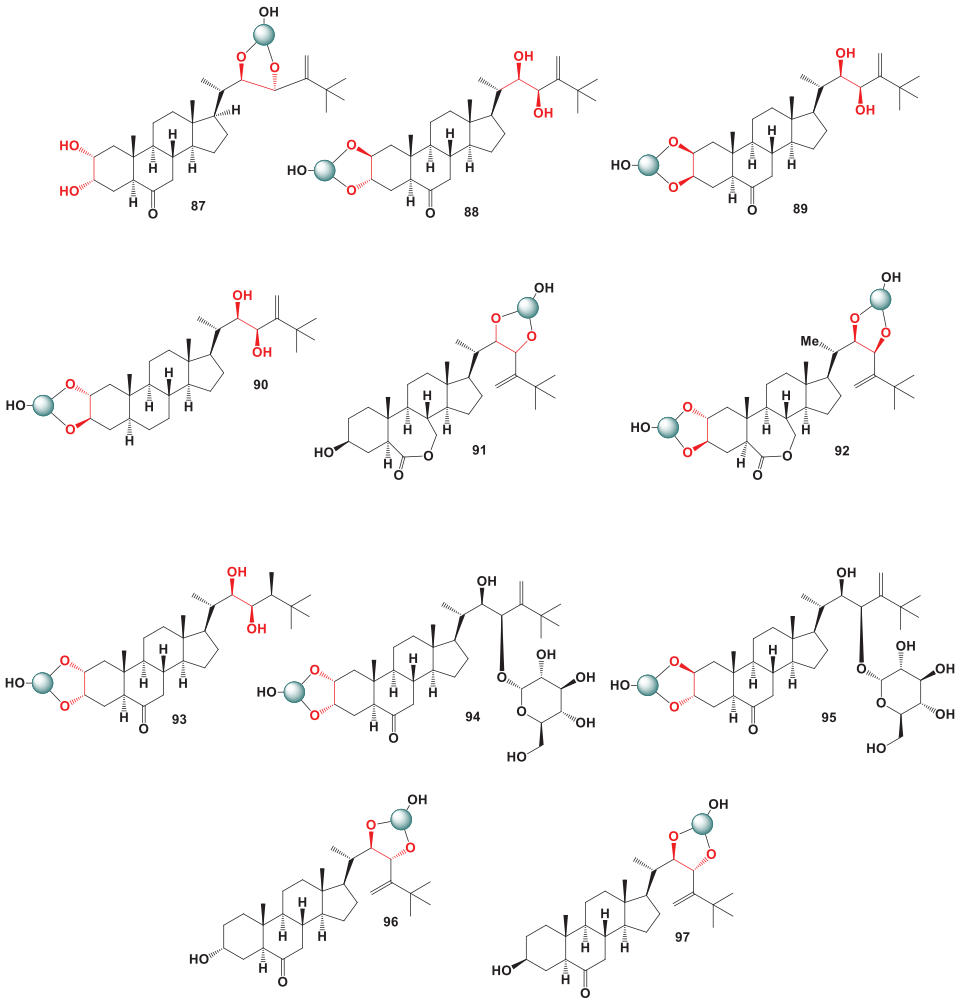

Figure 10. Bioactive neostrogens derived from natural sources. Highlighted in red are hydroxyl groups that interact with boric acid or boron anion to form cycloborates. Image created by the authors (MGI Software Corp. https://mgi-photosuite.software.informer.com).

Table 4. Antitumor and related activity of neurosteroids

Compound	Reported biological effect	Activity rank
87	[a]Antineoplastic	Strong
	Chemopreventive	Moderate
	Proliferative diseases treatment	Weak
	Antimetastatic	Weak
	Anticarcinogenic	Weak
88	Antineoplastic	Moderate
	Apoptosis agonist	Weak
89	Antineoplastic	Moderate
	Apoptosis agonist	Weak
	Proliferative diseases treatment	Weak
90	[a]Antineoplastic	Strong
91	Apoptosis agonist	Weak
	Antineoplastic	Weak
92	[a]Antineoplastic	Strong
	Proliferative diseases treatment	Weak
93	[a]Antineoplastic	Strong
94	[a]Antineoplastic	Strong
	Proliferative diseases treatment	Moderate
	Apoptosis agonist	Weak
	Anticarcinogenic	Weak
95	[a]Antineoplastic	Strong
	Proliferative diseases treatment	Moderate
	Antimetastatic	Weak
96	Antineoplastic	Weak
97	[a]Antineoplastic	Strong
	Proliferative diseases treatment	Weak
	Prostate cancer treatment	Weak

Note: The compounds correspond to those in Figure 10. [a]Steroids that demonstrated strong antineoplastic and related activities.

trigger programmed cell death (apoptosis). Steroid receptor modulation: Boron-containing compounds can interact with steroid receptors.

(c) ER-β activation: Some boron compounds can selectively bind to and activate the estrogen receptor beta (ER-β), which has a beneficial effect on reducing cancer cell proliferation.

(d) ER-α inhibition: Conversely, ER-α activation is associated with abnormal proliferation and inflammation, so its inhibition may also contribute to the anticancer effect. Interruption of Steroid Hormone Transport: Boron can interfere with the interaction of steroid hormones with their binding proteins in the bloodstream.

(e) Increased free hormone levels: This disruption of interaction may lead to increased levels of free active steroid hormones in the plasma, which may alter signaling and influence cancer cell behavior.

(f) Other potential mechanisms: Boron compounds can also inhibit other enzymes, such as steroid sulfatase, and affect signaling pathways such as hypoxia-inducible factor-1α, further enhancing their anticancer effects.

9. Conclusion

Borosteroids are a type of lipid containing a boron atom that forms a complex with a steroid. Boric acid or boron anion readily reacts with 1,2- or 1,3-diol moieties of a steroid. Steroids perform a dual function: They exhibit antitumor properties and, by forming complexes with boron, act as carriers of boron atoms to cancer cells. By forming complexes with boron, steroids reduce their toxicity in the body and increase their mobility by enhancing their hydrophilicity. Its combination with boron enhances the antitumor properties of a steroid molecule. Here, we have presented evidence that steroids with antitumor activity have been isolated from plants, fungi, or marine invertebrates. This review not only highlights their antitumor activity but also explores related activities, which are of great interest to pharmacologists, chemists, and health professionals. A comprehensive study of boron-steroid complexes in clinical settings will improve treatment guidelines for various types of cancer and provide a better understanding of the mechanism of action of these complexes. Thus, it has been shown that 58% of steroids exhibit strong antineoplastic and related activities, 31% display moderate activity, and <11% show weak antineoplastic activity and varying levels of activity in other biological mechanisms.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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Writing–original draft: Alexander O. Terent'ev, Valery M Dembitsky
Writing–review & editing: Alexander O. Terent'ev, Valery M Dembitsky

Ethics approval and consent to participate

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Consent for publication

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Availability of data

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