

Natural Halogenated Furanones, Higher Terpenes and Steroids

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Abstract

Natural halogenated furanones, higher terpenes and steroids comprising three relatively small groups of natural compounds were isolated mainly from sea organisms, as well as from some plant species. The structures of about 90 compounds are considered and the data on the biological activity of some of them are presented.

Contents

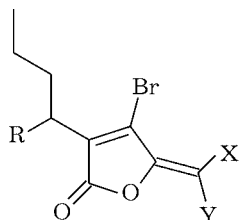
Introduction	697
Furanones of seaweeds and invertebrates	–
Furanones in natural water	699
Higher terpenes	700
Steroids of plants and sea organisms	701

INTRODUCTION

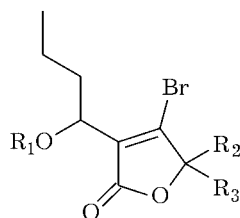
The present review provides grouping of natural metabolites allied with each other (higher terpenes and steroids), with the metabolites which represent a kind of the fragments of larger molecules, including such widespread terpenoids and steroids as oxygen-containing heterocyclic fragments of the furan and pyran series. The review is a logical continuation of the series of papers dealing with halogenated terpenoid and acetogenin metabolites [1–5].

FURANONES OF SEAWEEDS AND INVERTEBRATES

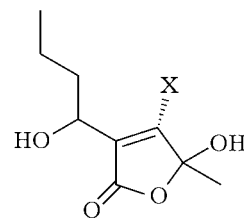
Halogenated furanones are a group of rarely occurring metabolites extracted from sea organisms. A brief description of them is presented in [6, 7]. The red alga *Delisea fimbriata* living near the north-eastern coast of Australia contains really rare set of halogenated furanones (**1**)–(**17**) [8]. Uniqueness of this alga as a generating species is connected with its ability to generate lactones the molecules of which comprise only one of three halogens (chlorine, bromine, iodine). It is typical that neither of



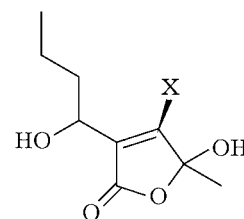
1. R = H, X = Br, Y = H
2. R = H, X = H, Y = Br
3. R = H, X = Br, Y = Br
4. R = OH, X = Br, Y = H
5. R = OH, X = H, Y = Br
6. R = OH, X = I, Y = H
7. R = OH, X = H, Y = I
8. R = OH, X = Cl, Y = H
9. R = OH, X = H, Y = Cl
10. R = OH, X = Br, Y = Br
11. R = OAc, X = Br, Y = H
12. R = OAc, X = H, Y = Br
13. R = OAc, X = H, Y = I
14. R = OAc, X = I, Y = H
15. R = OAc, X = Cl, Y = H
16. R = OAc, X = H, Y = Cl
17. R = OAc, X = Br, Y = Br



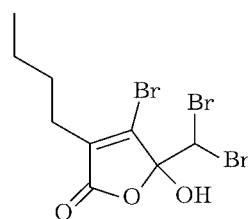
18. R₁ = Ac, R₂ = OCH₃, R₃ = CH₂I
19. R₁ = H, R₂ = OCH₃, R₃ = CH₂I
20. R₁ = H, R₂ = CH₂I, R₃ = OCH₃
21. R₁ = Ac, R₂ = CH₃, R₃ = OCH₃
22. R₁ = Ac, R₂ = OCH₃, R₃ = CH₃
23. R₁ = Ac, R₂ = CHBr₂, R₃ = OCH₃
24. R₁ = Ac, R₂ = OCH₃, R₃ = CHBr₂



26. X = Br
27. X = Cl



28. X = Br
29. X = Cl



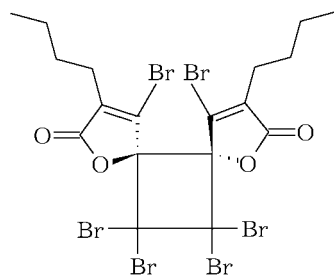
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the metabolites contains two halogens. Compounds (1)–(3) were called fimbrolides, (4)–(10) hydroxyfimbrolides, while metabolites (11)–(17) were called acetoxyfimbrolides.

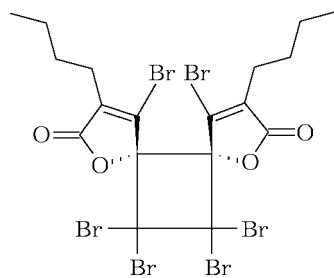
The red alga *Delisea fimbriata* living near the Antarctic ice cover synthesizes compounds (11)–(14), (16) and (17) [9].

A series of new furanones (18)–(24) was isolated from the red alga *Delisea pulchra* (cf. *Fimbriata*) living near the Australian coast [10].

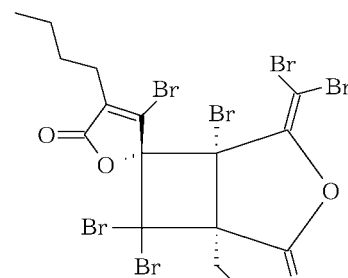
A new tribrominated fimbrolide (25) was discovered in the extract from the red alga *Delisea elegans* which is widely spread near the coast of New Zealand [11]. The red alga



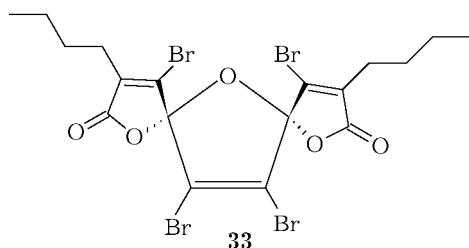
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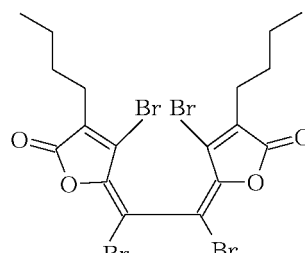
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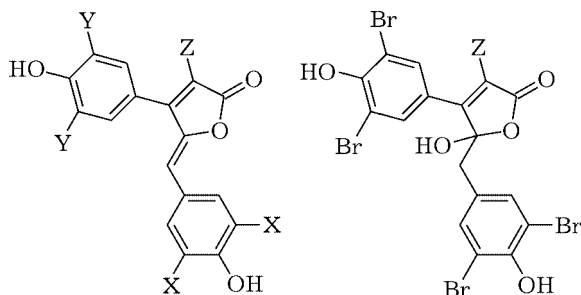
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35. X = Br, Y = Br, Z = H

36. X = Br, Y = Br, Z = Cl

37. X = Br, Y = H, Z = H

38. X = H, Y = Br, Z = H

39. Z = H

40. Z = Cl

Beckerella subcostatum generates bromine-containing beckerelides (**26**), (**28**) and chlorine-containing (**27**), (**28**) ones [12].

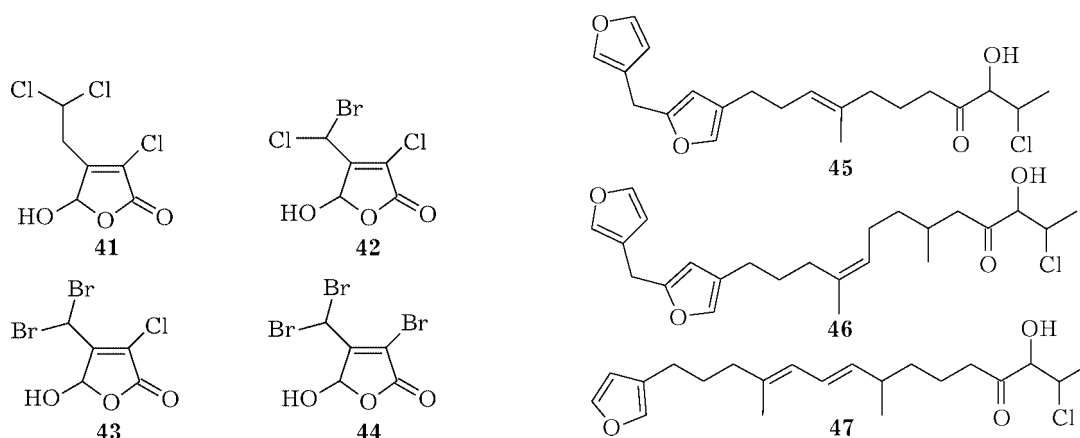
The products of transformations of dibromomethylene furanones are generated by the red alga *Delisea elegans* collected near the coast of New Zealand [11]. For instance, metabolites (**30**), (**31**) can be considered as a result of [2+2] cycloaddition of dibromomethylene lactone (**3**) proceeding with the formation of stereo isomers. Metabolite (**32**) was formed by cycloaddition with the participation of dibromomethylene group and the double bond of the cycle. Metabolites (**33**), (**34**) can be easily represented as the derivatives of cyclic adduct (**31**).

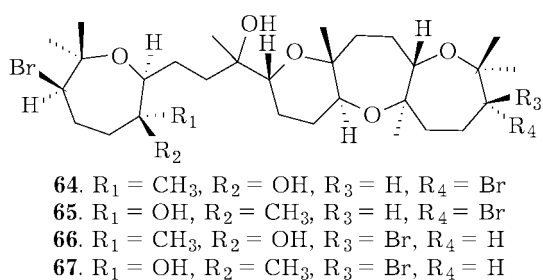
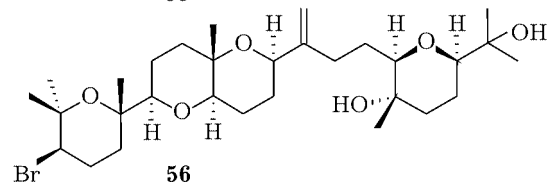
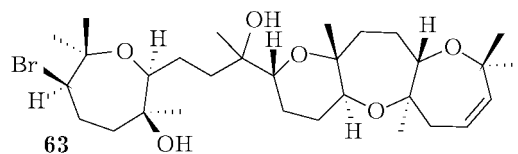
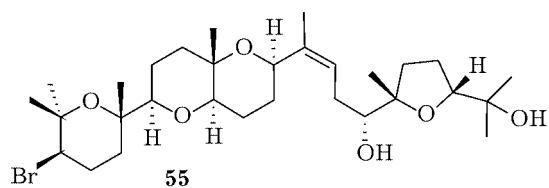
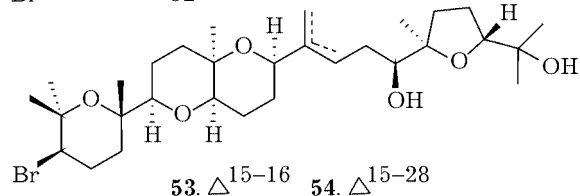
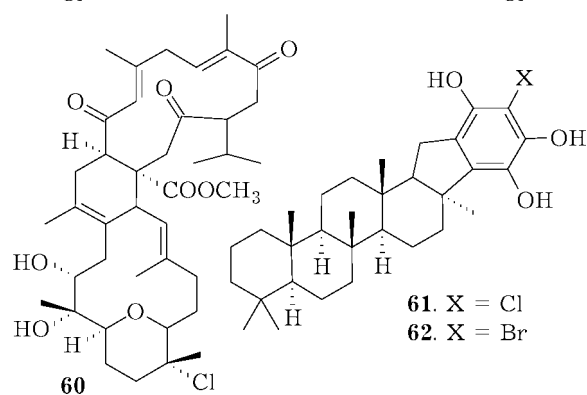
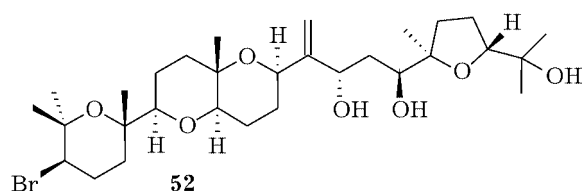
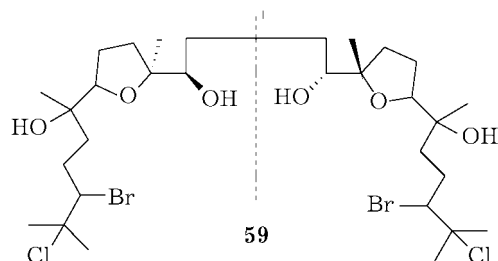
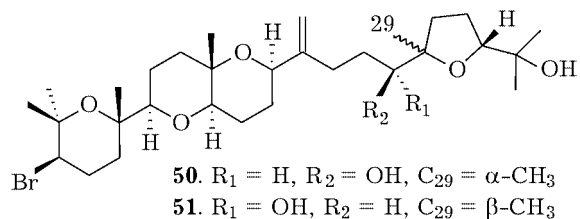
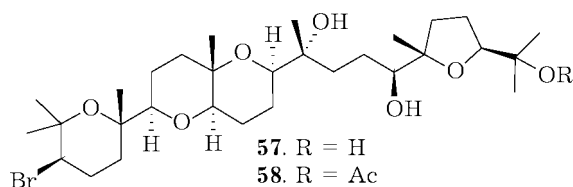
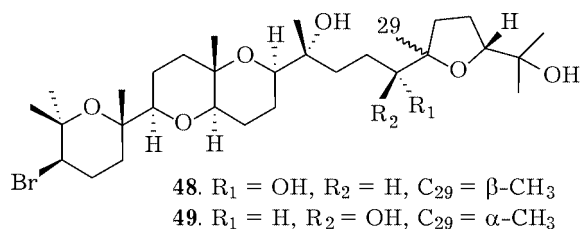
Several furanones were discovered in the extracts of sea invertebrates. For example, filtering invertebrates, *i.e.*, colonial sea ascidia *Ritterella rubra* with their immobile mode of living attached to a solid substrate synthesize diarylfuranones called rubrolides A (**35**), B (**36**), C (**37**), D (**38**), G (**39**) and H (**40**) [13]. These compounds are strong antibacterial

agents and provide selective inhibition of phosphatase [13].

FURANONES IN NATURAL WATER

The major part of lakes, rivers and reservoirs are the source of fresh water in many countries. Water chlorination for the purpose of its disinfection is accompanied by the formation of chlorinated products, such as chloroform and trichloromethanes, which were discovered more than 20 years ago [14, 15]. In 1986, a strong mutagenic product was isolated: 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (**41**), which was called MX [16]. The presence of MX in drinking water was detected in many countries [17]. The mutagenic activity of MX is comparable with that of the known toxin aflatoxin [18]. Extremely high mutagenic activity of MX toward human B-lymphoblastoid cells was demonstrated in recent works [19]. MX is also a strong carcinogenic agent and causes cancer in rats [20]. The World Health Organization (WHO) included MX into a list of compounds especially dangerous for human health [21]. Recently, MX was detected in the water of the Taikhu lake (China) [22]. Examination of the samples of drinking water from Japan revealed three brominated furanones along with the known MX (**41**); they were called BMX-1 (**42**), BMX-2 (**43**) and BMX-44 [23]. New brominated furanones were present in concentrations comparable with that of MX [23]. It is assumed that all the halogenated furanones are of natural origin [7].



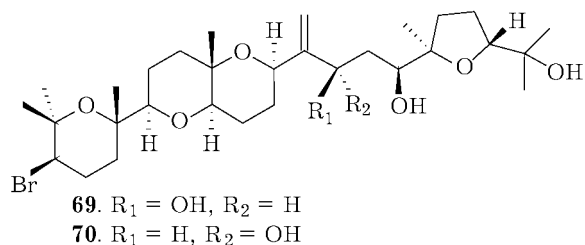
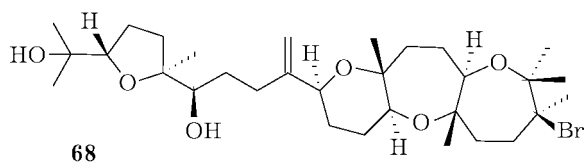


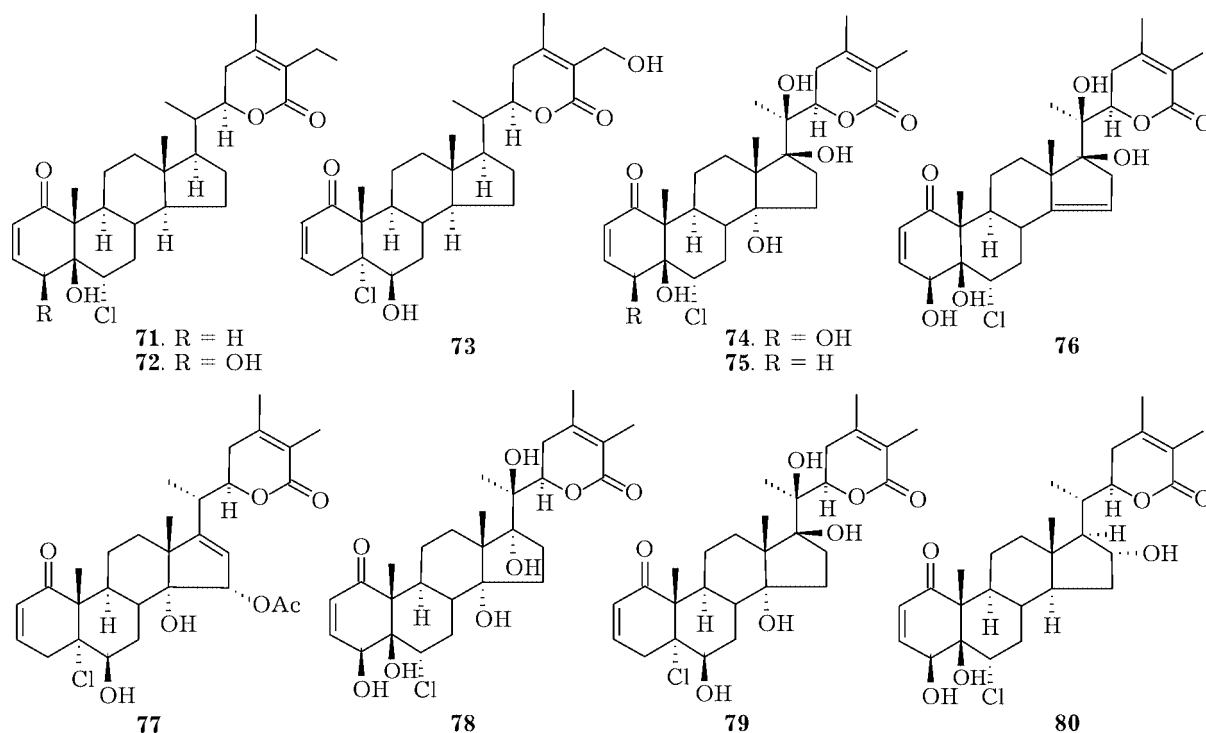
HIGHER TERPENES

In comparison with other terpenoids, relatively small number of halogenated triterpenes and other polyterpenes has been discovered till present.

Sea sponge *Ircina oros* living in inhabiting the North-Adriatic sea generates two chlorine-containing norsesiterterpenes (45) and (46) [24]. Structurally similar metabolite konachine (47) was isolated from a non-identified sponge living near the coast of Senegal [25].

A series of brominated triterpenoid polyethers (48)–(56) with the carbon structure of





squalene was extracted from the red alga *Laurencia viridis* (Ceramiales family) inhabiting near the Canary Islands [26]. This alga usually grows in the lower tidal zone in winter and in spring disappearing almost completely by the end of summer. Venustatriol (**48**) exhibiting antiviral activity was also discovered in another species, *Laurencia venusta* [27]. Compounds (**49**)–(**56**) exhibit the cytotoxic action [28].

The *Laurencia thyrsefera* generates thyrseferol (**57**) [29], and *Lausencia obtusa* produces its acetate (**58**) [30]. The structure of both compounds was confirmed by the authors of [27, 31]. Intricatetraol (**59**) of symmetrical structure was extracted from the alga *Laurencia intricate* [32].

Soft coral *Sarcophyton glaucum* generates several tetraterpenes one of which contains chlorine and was called methylchlorosarcophytoate (**60**) [33]. Two chlorine- and bromine-containing terpenoids (**61**) and (**62**) were discovered in *Disidea pallescens* sponge [34]; their structure was confirmed by halogenation of disidein (X = H).

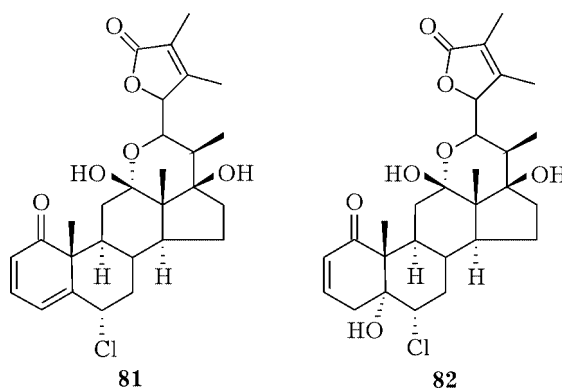
Six bromine-containing triterpenic polyethers (**63**)–(**67**) were isolated from the red seaweed *Chondria armata* living near the coast of India [35]. Extract from this seaweed exhibi-

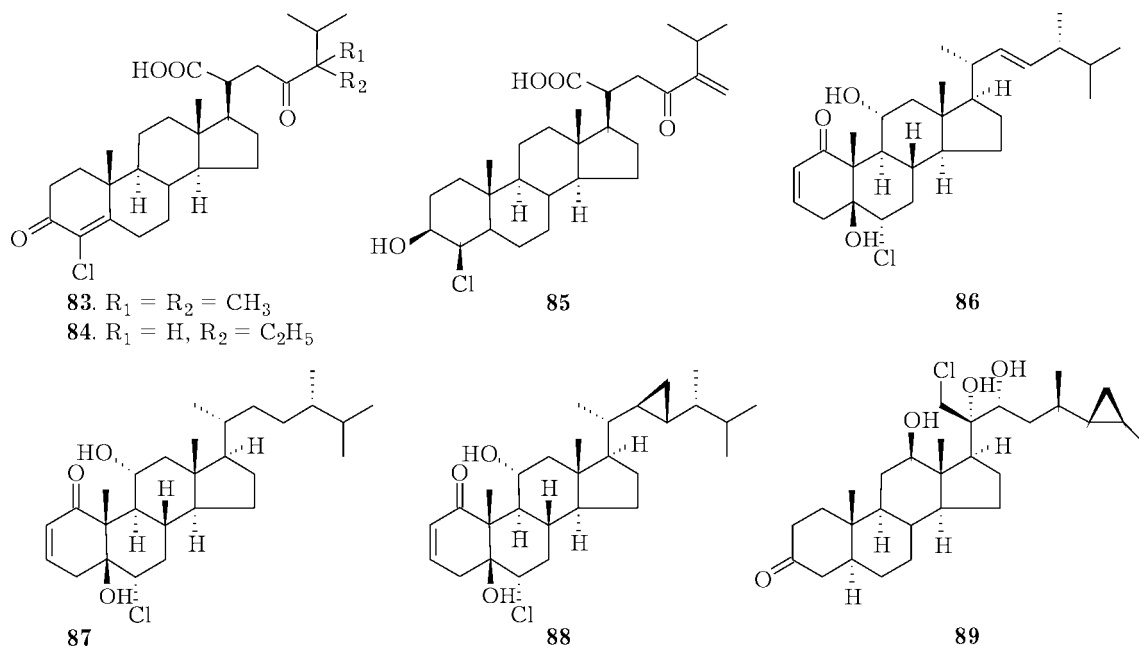
ted high antiviral, antibacterial and antifungal activity [36, 37] which is due to the presence of metabolites (**63**)–(**67**) in it.

New derivatives of dehydrothyrseferol (**68**)–(**70**) along with the known ones (**48**), (**56**) were isolated from the red alga *Laurencia viridis* [38]. These metabolites exhibited high cytotoxic activity toward P-388 cells.

STEROIDS OF PLANTS AND SEA ORGANISMS

Unlike halogenated terpenes which are mainly synthesized in seaweeds and sea invertebrates, halogenated steroids were discovered not only in sea organisms but also in higher plants.





The first chlorine-containing steroids jaborosalaltones C (**71**) and jaborosalaltones E (**73**) were isolated from the leaves of *Jaborosa integrifolia* plant (Solanaceae family) [39, 40]. Steroid with similar structure, such as withanolide (**72**), were isolated from *Withania frutescens* (Solanaceae family) [41], and physalolactone C (**76**) [44] from *Physalis peruviana* (also belonging to the Solanaceae family). Physaguline B (**77**) was discovered in *Physalis angulata* [45]. Chlorohydrin withanolide D (**78**), as well as (**75**) and (**78**), was discovered in *Withania somnifera* and *Acnistus breviflorus* plants [46, 47], respectively. The *Acnistus breviflorus* plant also synthesizes steroids (**72**) and (**73**) [48–50] which possess cytostatic activity [51]. Further research showed that *Withania somnifera* generates withanolide C (**79**), (**75**) and (**80**) [52]. Steroid (**80**) is also present in *Dunalia tubulosa* related to the mentioned family [53].

Steroids of a new structural type jaborochlorodiols (**81**) and jaborochlorotriols (**82**) were discovered in the extracts from *Jaborosa magellanica* [54].

Steroids of sea organisms are rather well investigated [55, 56], however, halogenated steroids are very rare. Halogenated steroids kichesterones C (**83**), E (**84**) and D (**85**) were isolated for the first time from the *Strongylacidon* sp. sponge in 1993 [57].

Three chlorine-containing steroids ionaras-terols G, H, I (**86**)–(**88**) were isolated from the soft coral *Clavularia viridis* living near the Okinawa island (the Japanese Sea) [58]. These steroids exhibited high cytotoxic activity toward human adenocarcinoma cells, as well as toward T-lymphocyte leukemia cells.

Aragusterol A (**89**) isolated from the *Xestospongia* sp. exhibits high antineoplastic activity [59].

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