

Natural Halogenated Polyethers, Pyrones, Coumarins and Flavones

VALERY M. DEMBITSKY¹ and GENRICH A. TOLSTIKOV²

¹Department of Pharmaceutical Chemistry and Natural Products, School of Pharmacy, The Hebrew University of Jerusalem, P.O. Box 12065, Jerusalem 91120 (Israel)

E-mail: dvalery@cc.huji.ac.il

²Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Pr. Akademika Lavrentyeva 9, Novosibirsk 630090 (Russia)

E-mail: gtolstik@nioch.nsc.ru

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Abstract

Halogenated polyethers, pyrones, coumarins and flavones compose four comparatively small but interesting groups of natural compounds. Some of these compounds are antibiotics, toxins or biologically active substances. They have been found in microorganisms, *e. g.* cyanobacteria, fungi, plants, algae and in invertebrates. Structures of about 100 compounds have been considered, and data on their biological activity presented.

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INTRODUCTION

The term *polyethers* means for a large class of natural metabolites whose molecules include oxygen-containing heterocyclic (almost exclusively saturated) fragments. The size of these fragments varies within the limits of three to eight atoms, including oxygen. Polyethers often contain spirane or transcondensed (bound) systems, and often have a macrocyclic structure [1–9]. These polyester types in their majority are toxins [1–3] or antibiotics [4–8] and often exhibit anticarcinogenic, antifungal and other kinds of activity [5–8]. For the first time, polyether antibiotics were detached into a separate class of biologically active natural com-

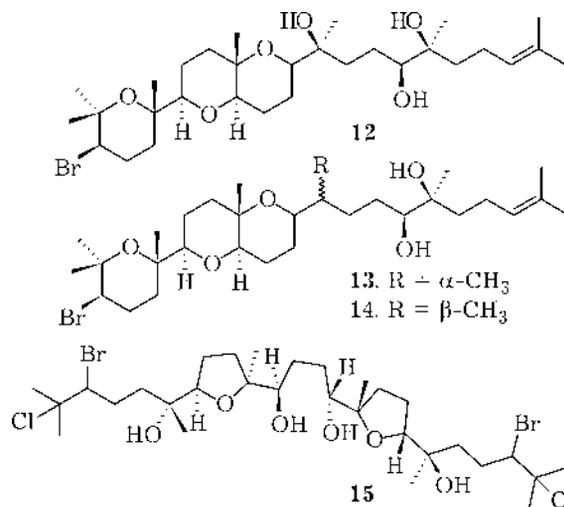
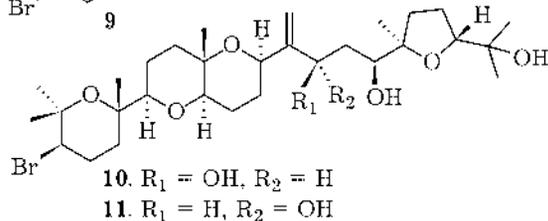
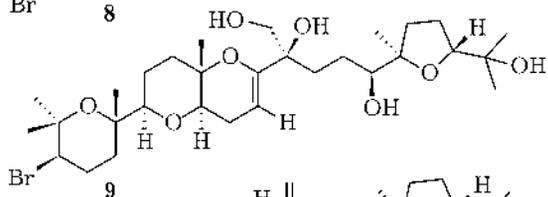
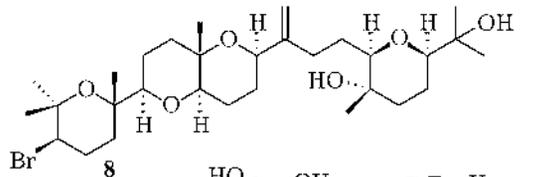
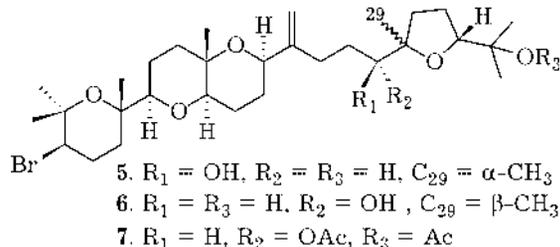
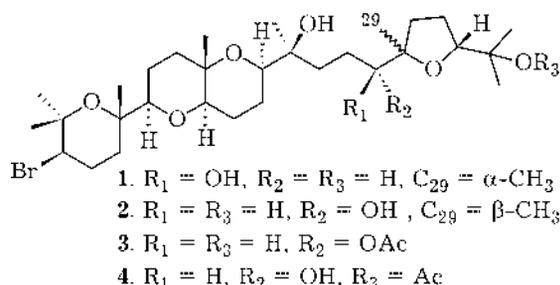
pounds in 1967 [10], when the monencine structure was established. In some cases, they display properties of carboxylic acid ionophores, and in this they differ from other compounds displaying ionophoretic activity [4, 7, 8]. The recently isolated toxins, as a rule of sea origin, have a high molecular mass and unusual structures [1–3]. The biological activity of these high-molecular compounds, their synthesis and biosynthesis provoke a great interest of chemists, pharmacologists and physicians. A comparatively small number of polyethers contain halogen atoms.

As for inclusion of halogenated pyrones, coumarins, isocoumarins, flavones and isoflavones into this review, they are rather rare in

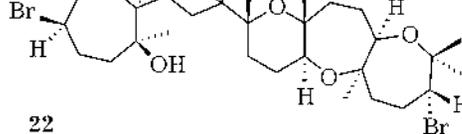
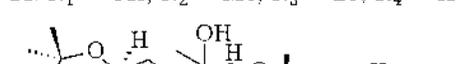
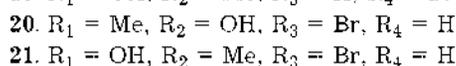
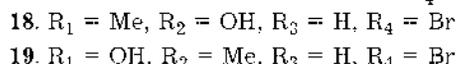
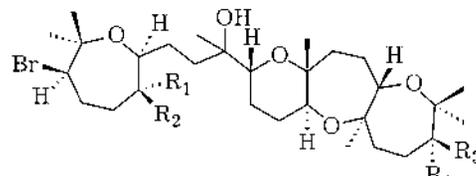
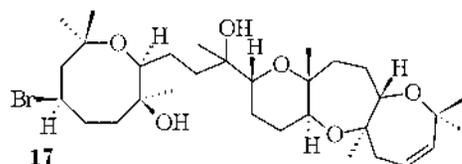
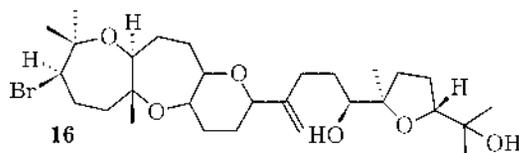
nature and have been detected in plants, fungi and lichens.

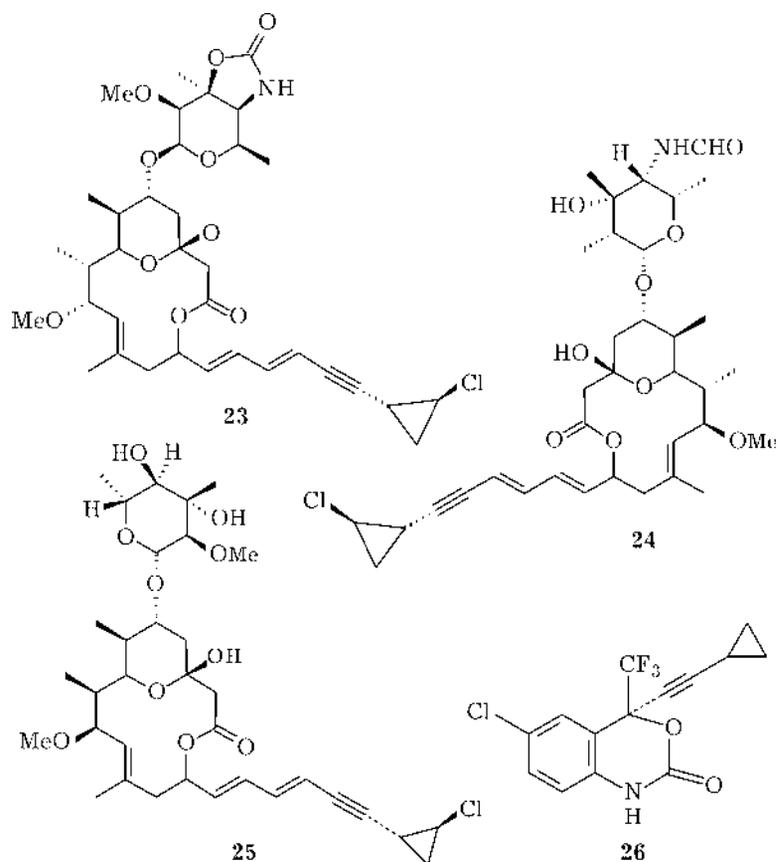
POLYETHERS

Triterpenoid polyethers with a structural squalene skeleton are synthesized by red algae, sea sponges and molluscs [11]. Regular studies of squalene metabolites started with the discovery of their representative thyrseferol (1) in 1978 by a team of Australian scientists [12]. This bromine-containing metabolite was isolated from the red alga *Laurencia thyrsefera* [12]. Thyrseferol (1) has demonstrated a high toxicity to cancer cells P-388 [13, 14]. Venustatriol (2) and its derivatives (3), (4) have been detected in the extract from the alga *L. viridis*



from the Canary Islands [15–17]. Dehydrothyrseferol (5), Dehydrovenustatriol (6), isodehydrothyrseferol (8) and thyrseferol B (9) also isolated from *L. viridis* (14) have demonstrated a still greater anticarcinogenic activity with respect to cells P-388 ($\text{IC}_{50} = 0.01 \text{ mg/ml}$) [18]. In the extract from the alga *L. viridis*, together with martiriol and pseudodehydrothyrseferol not containing any halogen atom, 16-epihydroxy-



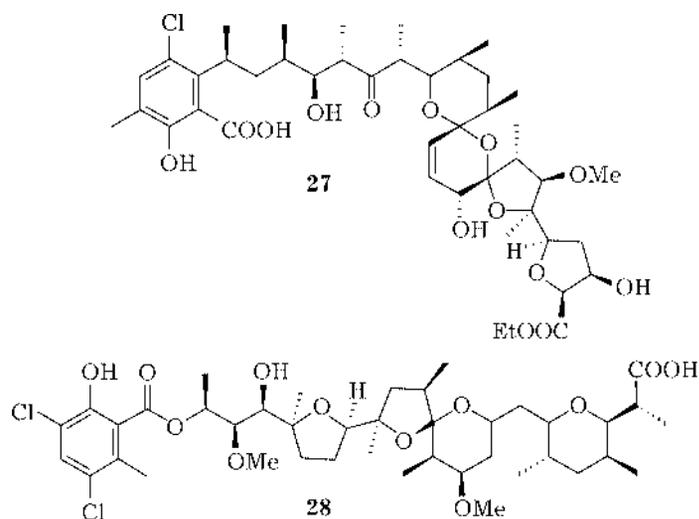


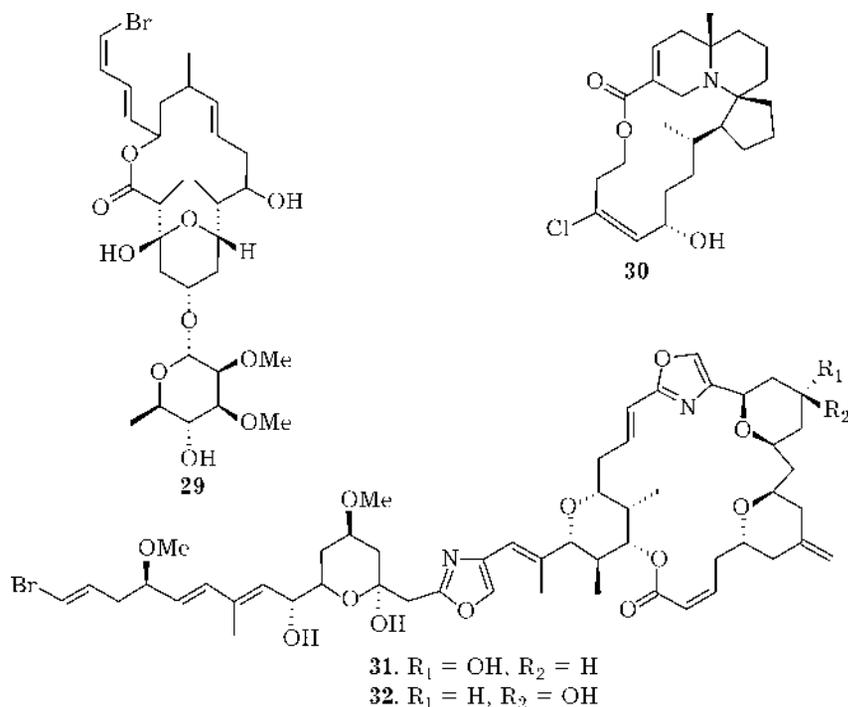
dehydrothysiferol (**10**), 16-hydroxydehydrothysiferol (**11**) and dioxepandehydrothysiferol (**16**) have been found [18]. Dehydrothysiferol (**5**) has also been found in the alga *L. pinnatifida* [19], and acetates (**3**), (**4**) and (**7**) have been detected in the alga *L. obtusa* [20].

Magireols A (**12**), B (**13**) and C (**14**) have been isolated from *L. obtusa* [21], and intricatetraol (**15**) unique with its symmetry has been found

in *L. intricata* [22]. All the magireols – A (**12**), B (**13**) and C (**14**) – inhibit the growth of cancer cells P-388.

New brominetrimeric polyethers armatols A–F (**17**)–(**22**) have been detected in the red alga *Chondria armata* (type Rhodomelaceae, section Ceramiales) growing in the Indian Ocean [23]. The biological activity of individual compounds has not been assayed, but the





extract of this alga has displayed a high antibacterial and antifungal activity [24, 25].

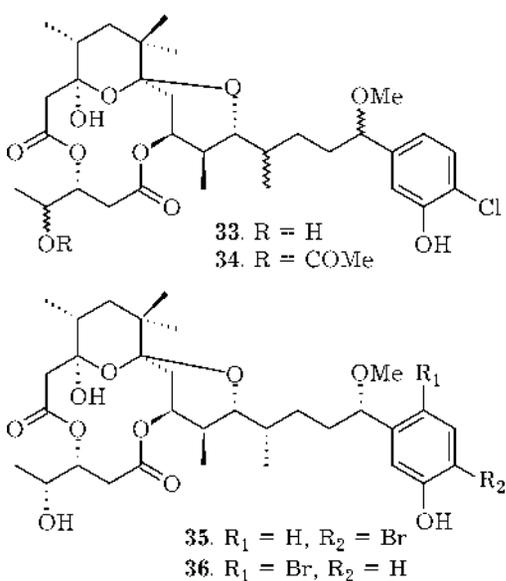
Three new chlorine-containing glycoside metabolites – callipeltosides A (**23**), B (**24**) and C (**25**) – with a high anti-HIV activity have been found in the extract from the sea sponge *Callipelta* sp. (fam. Lithisida) inhabiting the waters about the New Caledonia Islands [26, 27]. Extracts from this sponge have also displayed an activity against cancer cells KB and P-388. It is noteworthy that such a structural fragment as cyclopropylethynyl contained in polyether molecules (**23**)–(**25**) is progressively often taken into consideration in the design of synthetic molecules. One of fresh examples is the preparation Evaviron Z (**26**) recently introduced into the treatment of HIV infection [28].

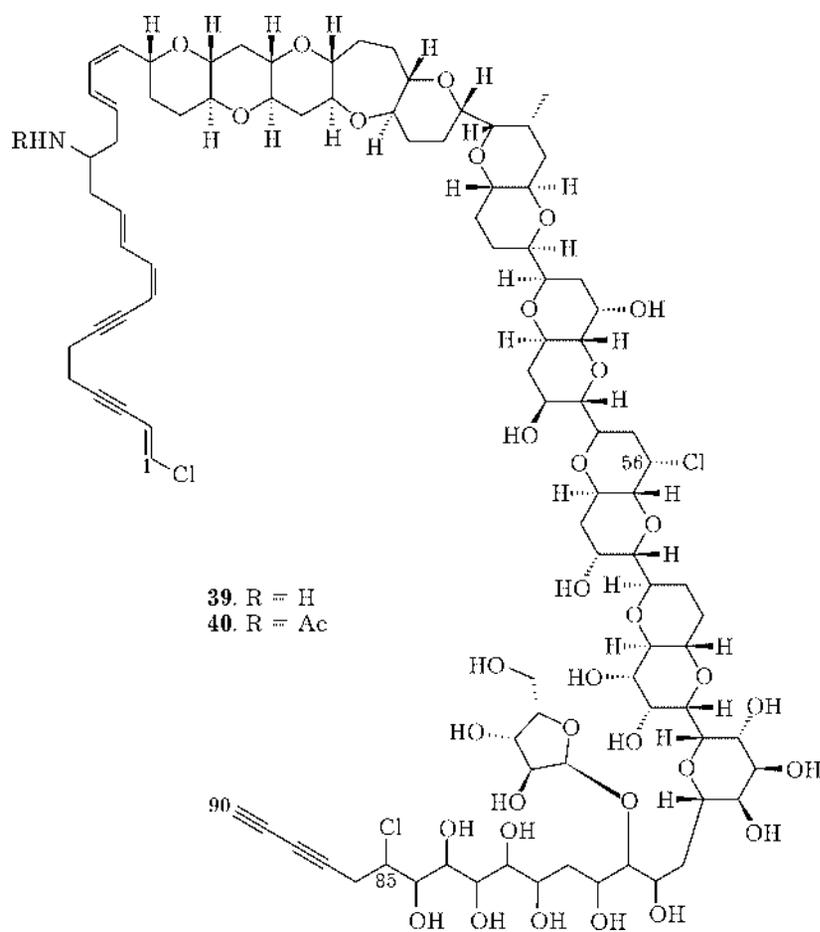
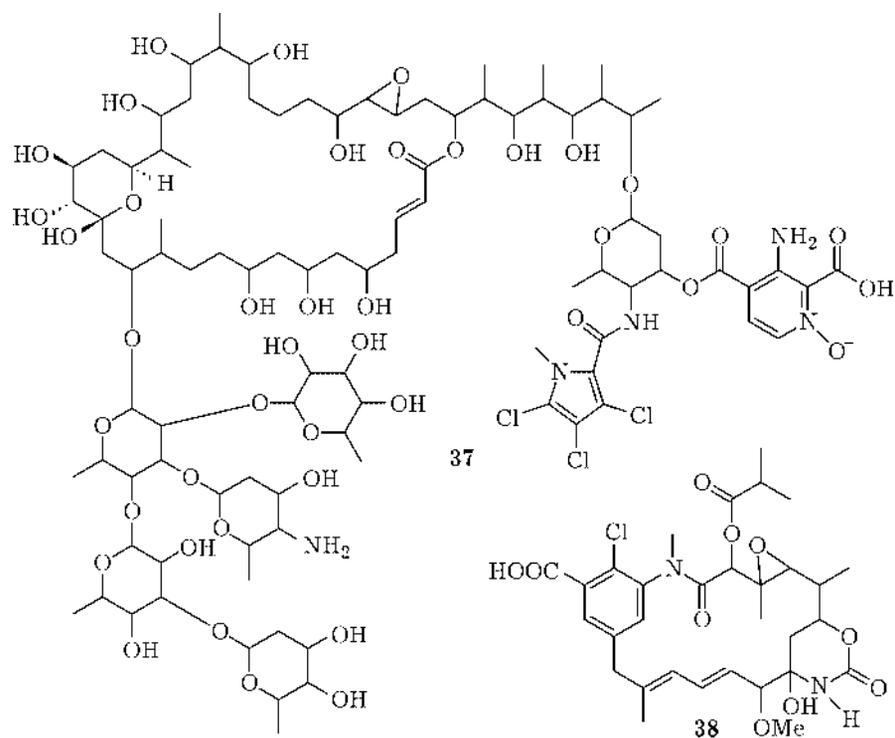
The polyether chlorine-containing phenol X-14766A (**27**) is produced by a microorganism *Streptomyces malachitofuscus* subsp. *downeyi* [29, 30]. This metabolite is the first from the series of halogenated polyether antibiotics that include a phenol type fragment. Another similar antibiotic (**28**) has been detected in the culture of *Actinomadura routienii* [31, 32].

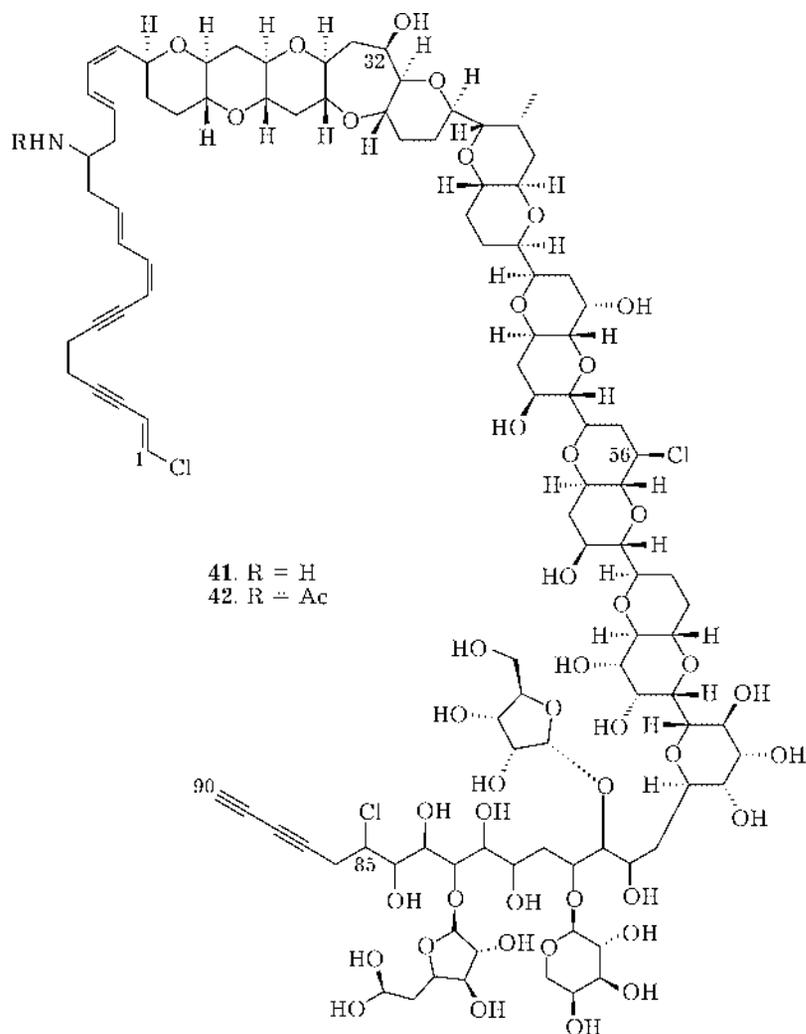
The glycoside lyngbyalocide (**29**) is synthesized by cyanobacterium *Lyngbya bouillonii* collected from the depth of 10 m

off the shores of the Ling Island (Papua New Guinea) [33]. New polyether metabolites phorboxazoles A (**30**) and B (**31**) inhibiting the growth of cancer cells HCT-116 and HT-29 have been isolated from the extracts of a sea sponge *Phorbas* sp. [34, 35].

The red alga *Gracilaria coronopifolia* growing in shallow waters near the Hawaiian Islands (USA) produces toxins manaulealides A (**32**), B (**34**), C (**33**) and aplisiatoxins (**35**), (**36**) [36]. Cases







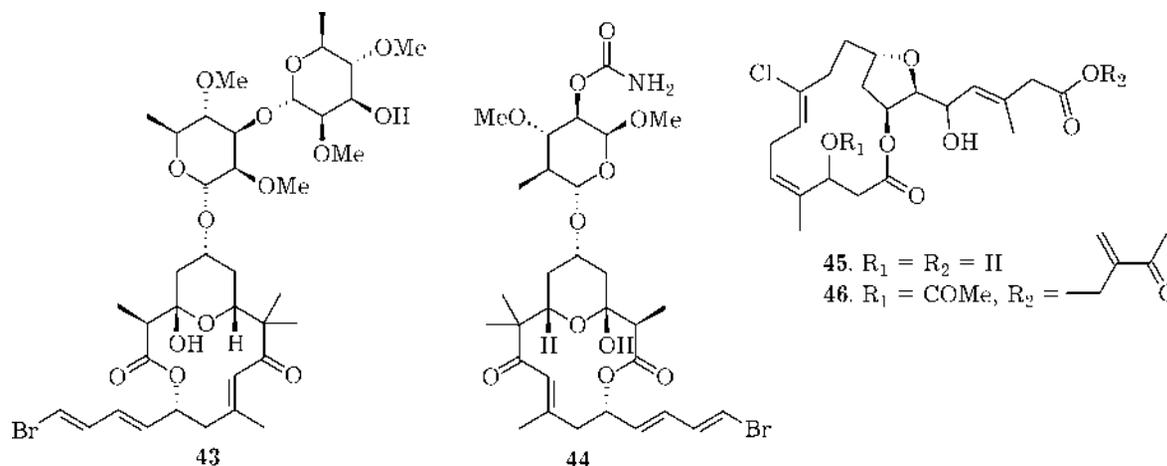
of death have been recorded when these toxins got into the human organism [37].

A new 34-membered polyether antibiotic colubricidin A (**37**) with the molecular mass of 2153.9 has been found in a new strain *Streptomyces* LL-C13122 [38]. This antibiotic has displayed a very high activity against Gram-positive bacteria *Caenorhabditis elegans* and *Trichostrongylus colubriformis* [38]. Another chlorine-containing antibiotic – ansamitocin (**38**) whose biosynthesis was studied in [39] is produced by the culture of *Streptomyces* TU-1892.

New ichthyotoxins of unusual structure prymnesin-1 (**39**) and its acetate (**40**), and prymnesin-2 (**41**) and its acetate (**42**) are synthesized by phytoflagellates (sea microalgae) *Prymnesium parvum* (fam. Haptophytes) [40, 41]. In 1940 “blooming” of water provoked by the reproduction of the alga *Primnesia parvum* inflicted a serious damage to the fishery of

Palestine due to the mass death of fishes [42]. The “red blooming” of water noted in Norway fjords was also caused by the reproduction of the mentioned alga. As a result, hundreds thousand tons of red salmon died due to the action of toxins (**39**) and (**41**) [43]. More than 40 years were spent for the study of biological properties and structure of prymnesin-1 (**39**) and prymnesin-2 (**41**), and it is only in 1996 that Japanese scientists completed this complicated work [40, 41].

The studies of biological activity of the new class of polyether metabolites have demonstrated that these compounds in very small amounts (up to 3 nmoles) are perilous to fishes, in particular *Tanichthys albonubes*. The presence of three chlorine atoms in positions 1, 56 and 85 of prymnesins (**39**)–(**42**) increases their toxicity by more than 1000 times as compared with the known toxin brechotoxin B which does



not contain any chlorine, and the toxicity with respect to fishes exceeds that of vegetable saponins by more than 5000 times [1, 40].

New 14-membered polyether glycosides auriside A (**43**) and auriside B (**44**) have been isolated from methanol extracts of sea mollusc *Dolabella auricularia* [45]. Both of these metabolites have displayed an activity against cancer cells HeLa S_3 ($IC_{50} = 0.17$ and $1.2 \mu\text{g/ml}$, respectively). The soil bacterium *Serratia plymuthica* produces haterumalide A (**45**) [46], and the ascidium *Lissoclinum* sp. living near the Okinawa Island (Japanese Sea) produces two haloid-free cytotoxic metabolites and haterumalide B (**46**) [47]. Haterumalides A (**45**) and B (**46**) have demonstrated a high cytotoxic activity [46, 47].

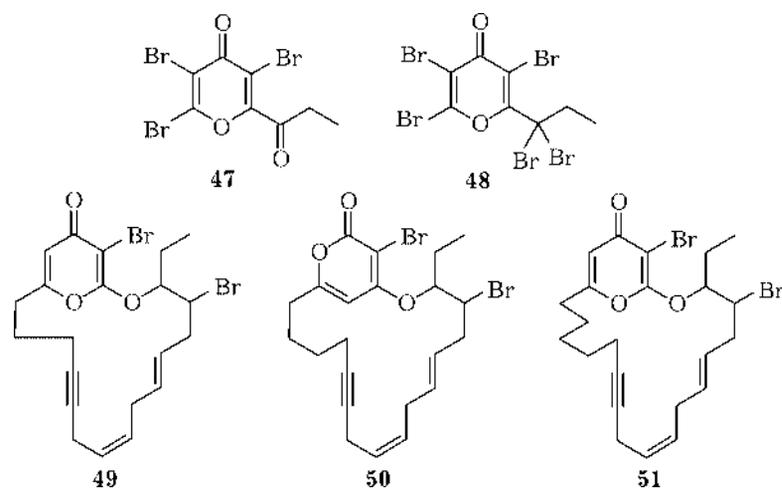
PYRONES

In natural objects, four representatives of halogenated γ -pyrone and one compound

belonging to the class of α -pyrone have been found. The red alga *Ptilonia australasica* produces two derivatives of γ -pyrone – (**47**) and (**48**) [48], and the red alga *Phacelocarpus labillardieri* growing off the shores of Australia contains new macrocyclic pyrones (**49**)–(**51**) [49–51].

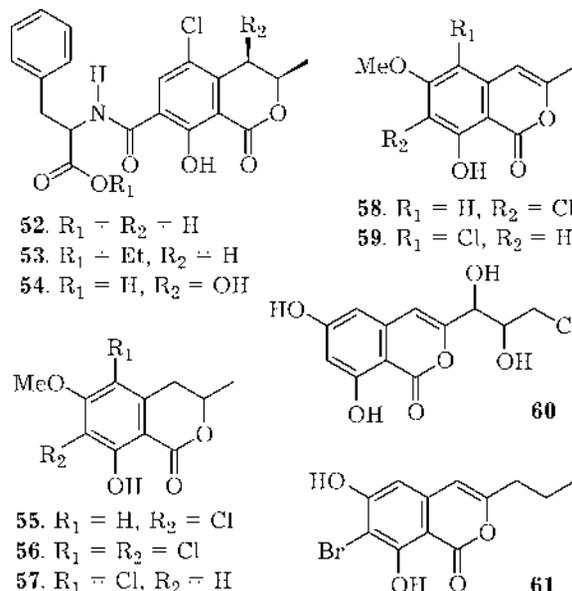
COUMARINS AND ISOCOUMARINS

One of the most widespread fungal toxins ochratoxin (**52**) is a derivative of isocoumarins and was first isolated from the pathogenic fungus *Aspergillus ochraceus* [52, 53]. Later on, this toxin was found in many species of fungi – *Penicillium viridicatum* [54], *P. cyclopium*, *P. commune*, *P. variabile*, *P. purpureus* [55–58], *Aspergillus melleus* and *A. sulphureus* [59]. The ochratoxin C (**53**) and 4-hydroxyochratoxin A (**54**) similar in their structure are produced by *Aspergillus ochraceus* [60] and *Penicillium*

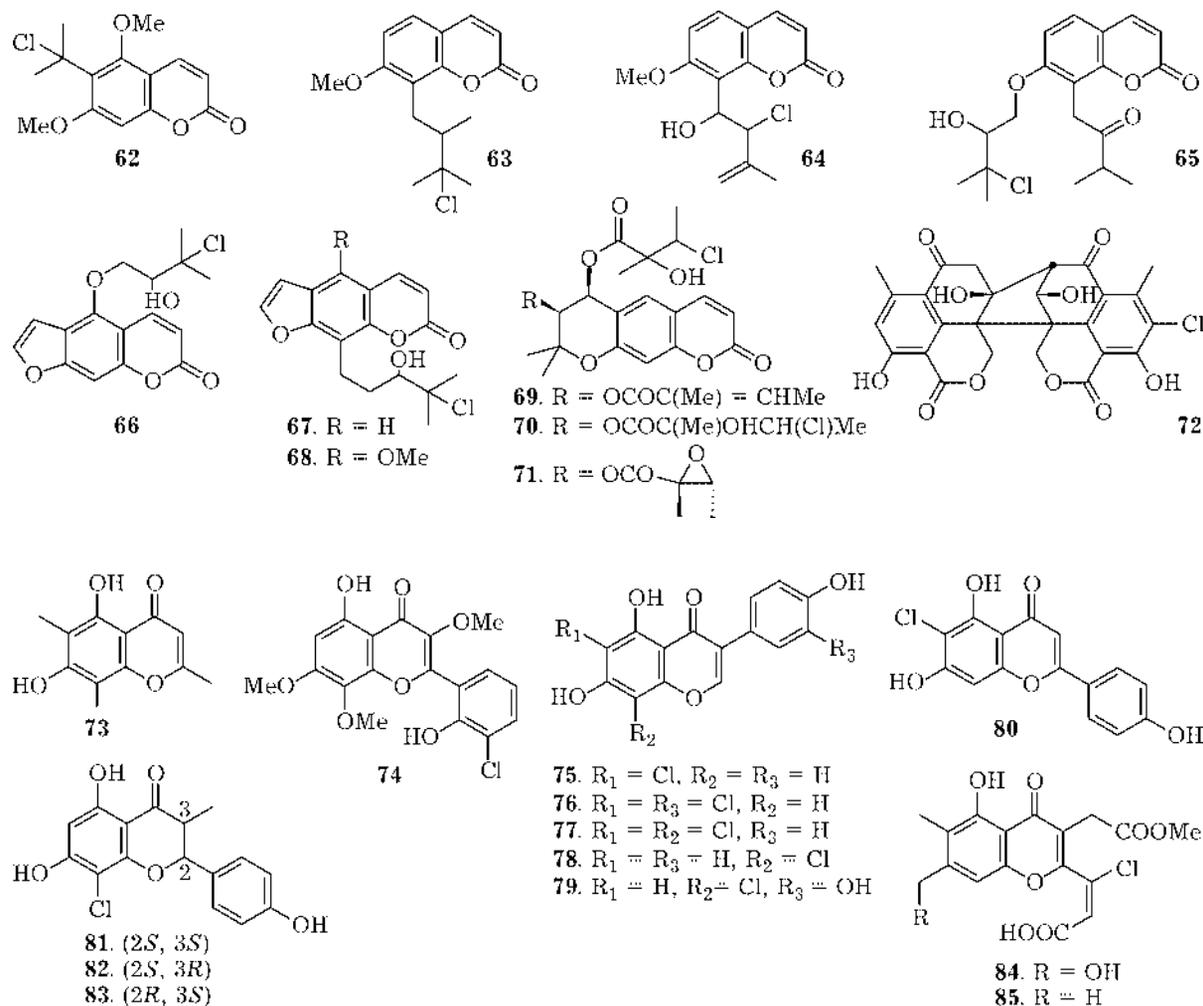


veridicatum [61], respectively. The pathogenic fungus *Sporormia affinis* affecting the carrot contains isocoumarins (55) and (56) [62], and the fungus *Periconia macrospinosa* contains the metabolite (57) [63]. The Brazilian plant *Swartzia laevicarpa* (fam. Leguminosae) synthesizes isocoumarins (58) and (59) [64], and another species of the plant from Brazil - *Tovomita brasiliensis* (fam. Guttiferae) - contains the compound (58) [65]. A fungus conditionally designated as LL-Z1640-5 is a source of the toxic isocoumaran (60) [66], and the metabolite hiburipyranone (61) is produced by the sea sponge *Mycale adhaerens* [67].

Chlorocoumarin (62) has been isolated from the extract of Indian plant *Toddalia asiatica* [68], chloroticol (63) extracted from the plant *Murraya exotica* [70]. All the plants belong to the family Rutaceae [68, 69]. The plant *Triphasia triphasia* belonging to the same family contains chlorinated coumarin (65) [71].



Several chlorine-containing furocoumarins (psoralens) have been detected in the roots or seeds of plants. Thus, saxalin (66) has been



isolated from roots of the plants *Angelica saxatilis* [72] and *Cachrys pubescens* [73], and also from seeds of the Texas plant *Ammi majus* [74] and parsley *Petroselinium sativum* [75]. Psoralens (**67**) and (**68**) were found in two species – *Heracleum granatense* [76] and *H. pyrenaicum* [77], respectively. Later on, psoralen (**68**) was isolated from leaves of the Indian population of the plant *Prangos pabularia* [78]. The roots of the plant *Peucedanum arenarium* (fam. Umbelliferae) contain peuchlorin (**69**), peuchlorinin (**70**) and peuchloridin (**71**) [79]. A metabolite of a new structural type gilmaniellin (**72**) having a symmetric structure is present in extracts from the plant *Gilmaniella humicola* [80].

FLAVONES AND ISOFLAVONES

Only a few halogenated flavones found in nature are known. The lichens belonging to the genus *Lecanora* (*L. sordida* [81], *L. rupicola* [82–84] and *L. carpineae* [4]) contained sordinone (**73**). Chloroflavovin (**74**) is produced by the fungus *Aspurgillus candidus* [85–87]. The culture of the microorganism *Streptomyces griseus* produces chlorogenisteins (**75**)–(**79**) [88, 89], and *Streptomyces* sp. contains the metabolite (**79**) [90]. 6-Chloropigenin (**80**) has been found in the horse parasite *Equisetum arvense* (fam. Equisetaceae) [91]. The culture of *Streptomyces graminofaciens* produces inhibitors of estrogen receptors BE-14348D (**81**), BE-14348E (**82**) and BE-14348E (**83**) [92]. The fungus *Monilinia fructicola* contains chloromonilic acids A (**84**) and B (**85**) [93].

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