Natural Halogenated Complex Phenols

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Abstract

Halogenated complex phenols comprise several small groups of natural compounds. These compounds were detected in microorganisms, cyanobacteria, algae and invertebrates. The structures of about 150 compounds are considered and the data on their biological activity are reported.

Content

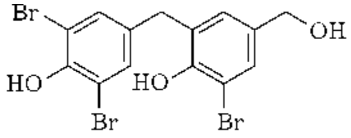
INTRODUCTION

Halogenated complex phenols are widespread in nature. They are synthesized by fungi, lichens, plants, cyanobacteria, marine and microorganisms [1–3]. The presence of bromine atom is characteristic of the complex phenols isolated from marine organisms, while the land plants and other organisms contain chlorine [1–3]. As a rule, these halogenated compounds are formed as a result of the action of enzymes, haloperoxidases in the presence of hydrogen peroxide and halide ions (Cl^-, Br^- or I^-) [4–6]. At present, large number of different haloperoxidases was isolated from plants, algae, lichens and fungi [4–10]. The structure of some peroxidases was established [11]. Haloperoxidases have recently found wide application in the synthesis of new organic compounds [5, 6, 12–14].

Previously we considered natural halogenated simple phenols [15], as well as phenol-containing metabolites of lichens and fungi [16]. This work is a continuation of previous publications.

DIPHENYLMETHANES AND RELATED COMPOUNDS

Some compounds synthesized by marine organisms are derivatives of diphenylmethane (**1**)–(**14**). Thelephenol (**1**) and metabolite (**2**), which possess antimycotic activity, are generated by segmented marine worm *Thelepus setosus* [17, 18]. Red algae *Rytiphlea tinctoria* [19] and *Rhodomela larix* [20] synthesize phe-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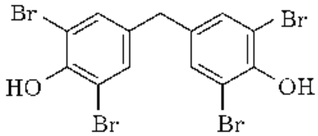
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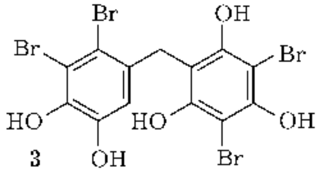
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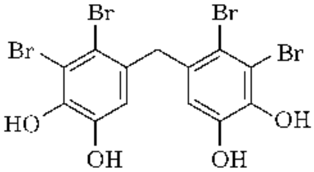
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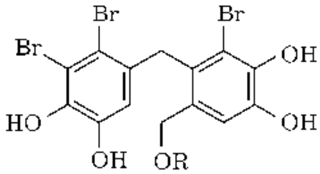
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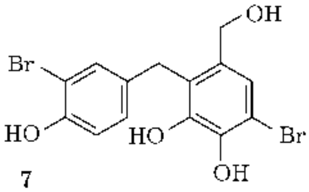
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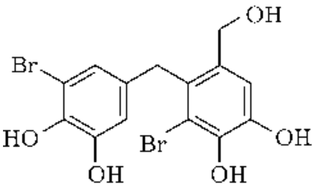
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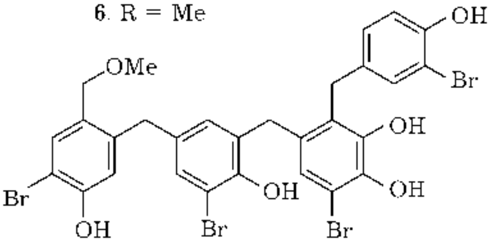
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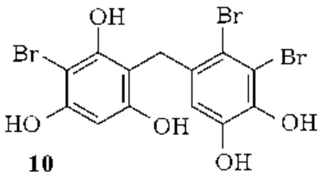
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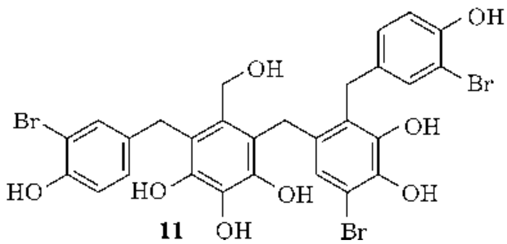
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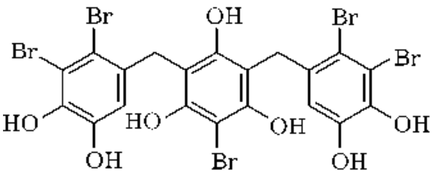
nolic metabolites (**3**) and (**4**), (**5**) and (**6**), respectively. Brominated diphenol (**6**) was also detected in red algae *Polysiphonia nigrerescens*, *Rhodomela confervoides* [21], *Polysiphonia urceolata* [22], *P. brodiaei* [23] and *Rhodomela larix* [24]. Green tropical alga *Avrainvillea longnicaulis* contains avrainvilleol (**7**) (1 % of the dry mass) which is very toxic for fish and exhibits antibacterial activity toward the marine bacterium *Vibrio anguillarum* [25]. Another green alga species *Avrainvillea nigricans* growing near the coast of Puerto Rico contains avrainvilleol (**7**) and a new metabolite 5'-hydroxyiso-avrainvilleol (**8**) [26, 27]. The *Avrainvillea rawsoni* alga collected in the western part of the Caribbean Sea generates rawsonol (**9**) and iso-rawsonol (**11**) [28]. Vidalols A (**10**) and B (**12**), which were detected in the red alga *Vidalia obtusaloba* [29] are powerful inhibitors of phospholipase A_2. Vidalol A (**10**) is toxic for fish,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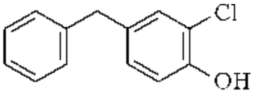
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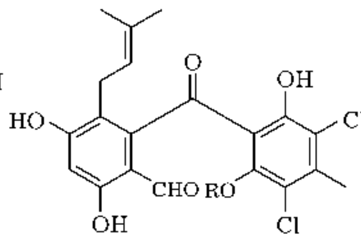
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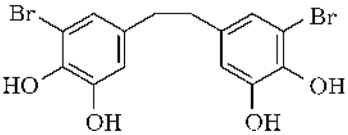
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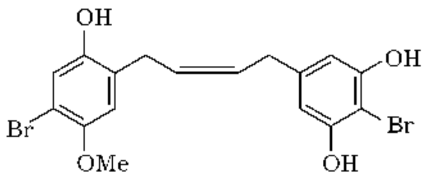
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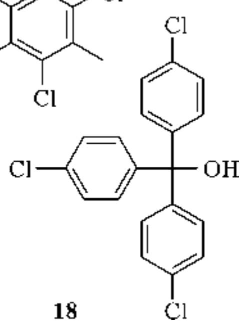
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too [29]. Marine cyanobacteria *Anacystis marina* synthesizes chlorine-containing diphenylmethane (**13**) [30].

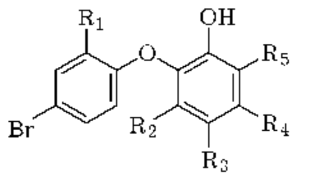
New antibiotics pestalons (**14**) and (**15**) are generated by marine fungus *Pestalotia* sp., strain CNJ-328 [31]. Pestalon (**14**) inhibits the growth of cancer cells (GI_{50} = 6 mg/ml), and exhibits activity against *Staphylococcus aureus*, *Enterococcus faecium* and other pathogenic microbes. Two metabolites, (**16**) and colpol (**17**), were isolated from extracts of red algae *Polysiphonia urceolata* [22, 32] and *Colpomenia sinuosa* [33], respectively. An interesting metabolite *tris*-(4-chlorophenyl)methanol (**18**) was discovered in some marine animals and birds [34]. The authors suppose that some species of marine organisms can generate it; however, in the majority of cases it can be considered as a product of oxidation of DDT.

DIPHENYL ETHERS AND RELATED COMPOUNDS

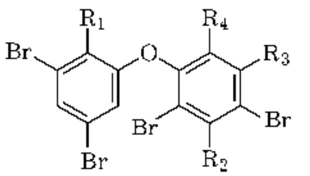
Unlike diphenylmethanes, diphenyl ethers and related compounds were detected mainly in sea sponges. The *Dysidea herbacea* sponge generates diphenyl ethers (**19**)–(**26**), (**30**), (**31**), (**35**), (**37**) [35–39]; the *Dysidea* sp. sponge inhabiting the Great Barrier Reef (Australia) contains metabolites (**27**)–(**34**) [40].

The *Dysidea chlorea* sponge contains metabolite (**21**) [38]; *D. fragilis* [41] contains metabolites (**22**), (**25**) and (**37**) [41]. The *Dysidea* sp. sponge living around the Philippines contains [25] and an antibacterial metabolite (**38**) [42]. Marine bacteria associated with the *Dysidea* sp. generate in culture metabolites (**37**) and (**39**) [43, 44]. The *Phyllospongia joliascens* sponge contains compounds (**30**), (**31**) and (**40**) [38]; the compound (24) and a new chlorine-containing metabolite (**41**) were extracted from non-identified Australian sponge species [45]. The *Tedania ignis* sponge also contains a known brominated diphenyl ether (**24**) [46].

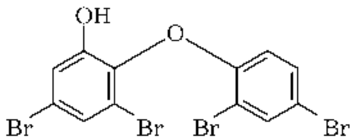
Marine green alga *Cladophora fascicularis* and mollus *Aplysia dactylomela* eating this alga contain metabolites (**21**) and (**42**) [47]. Freshwater fungus *Kirschsteiniothelia* sp. generates new chlorine-containing compounds (**43**) and (**44**) possessing antibacterial properties [48].



19. $R_1 = R_3 = R_4 = R_5 = H, R_2 = Br$
20. $R_1 = R_3 = R_5 = H, R_2 = R_4 = Br$
21. $R_1 = R_3 = R_5 = Br, R_2 = R_4 = H$
22. $R_1 = R_2 = R_3 = R_4 = Br, R_5 = H$
23. $R_1 = R_3 = R_4 = R_5 = Br, R_2 = H$
24. $R_1 = R_2 = R_4 = Br, R_3 = R_5 = H$
25. $R_1 = R_2 = Br, R_3 = R_4 = R_5 = H$
26. $R_1 = R_3 = R_4 = R_5 = Br$



27. $R_1 = OMe, R_2 = R_3 = R_4 = H$
28. $R_1 = R_4 = OMe, R_2 = R_3 = H$
29. $R_1 = R_4 = OMe, R_3 = H, R_2 = Br$
30. $R_1 = R_4 = OH, R_2 = H, R_3 = Br$
31. $R_1 = R_4 = OH, R_2 = R_3 = Br$
32. $R_1 = R_4 = OMe, R_2 = H, R_3 = Br$
33. $R_1 = R_4 = OMe, R_2 = R_3 = Br$



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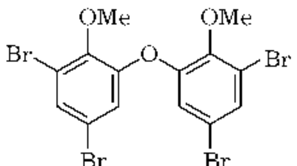

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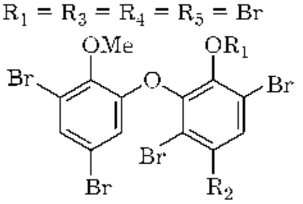

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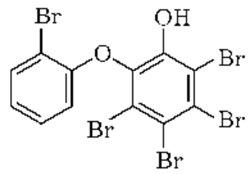
37. $R_1 = R_2 = H$



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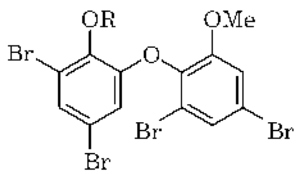

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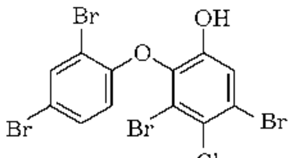
40. R = Me



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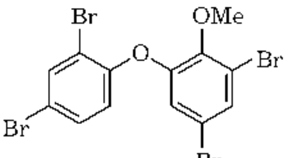

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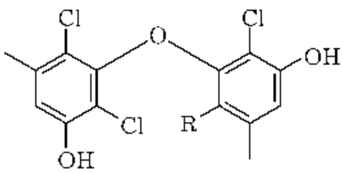

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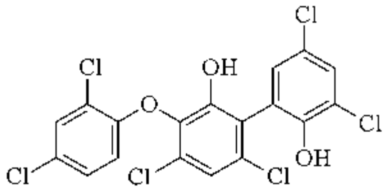
44. R = Cl



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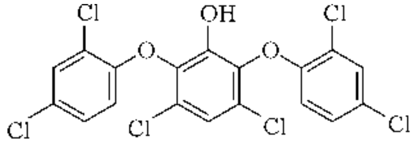

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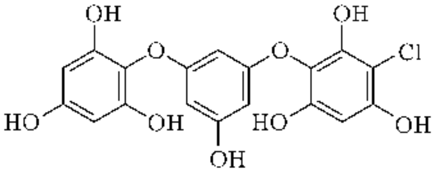

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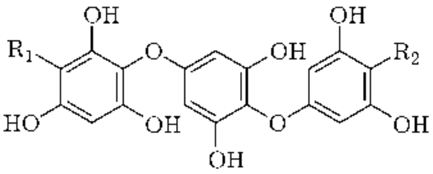
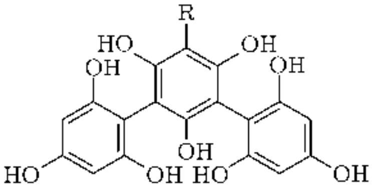


48. R_1 = H, R_2 = Br
49. R_1 = Br, R_2 = H



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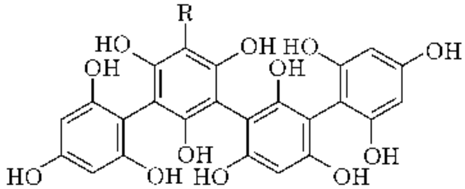
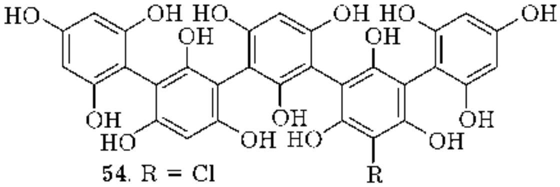
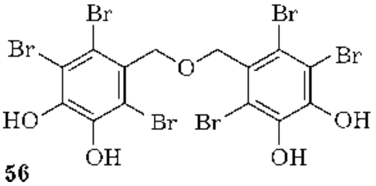
51. R = Br



52. R = Cl
53. R = Br



54. R = Cl
55. R = Br



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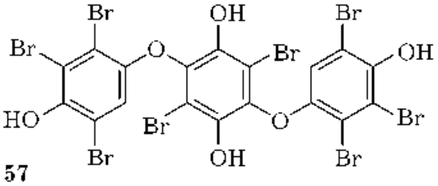

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Land cyanobacteria *Fischerella ambigna* generates biologically active polychlorinated metabolites ambigols A (**45**) and B (**46**) [49]. Both ambigol compounds exhibit antibacterial and antimycotic activity; ambigol A (**45**) additionally inhibits HIV transcriptase [49].

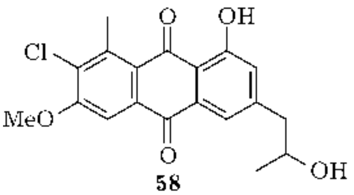
Brown algae *Laminaria ochroleuca* and *Cystophora congesta* generate metabolites (**47**) [50] and (**48**), (**49**) [51], respectively. Brown alga *Analipus japonicus* growing in the northern part of the Pacific Ocean contains halogenated diphenyl ethers (**50**)–(**55**), and red alga *Symphyocladia latiuscula* contains metabolite (**56**) [53].

The major metabolite (**57**) of sea worm *Ptychodera flava*, which is close in structure to compounds (**48**) and (**49**), exhibits antibacterial activity [54].

ANTHRAQUINONES AND RELATED COMPOUNDS

Comparatively small amount of halogenated anthraquinones was discovered in nature. For example, nalgiolaxine (**58**) and fragiline (**59**) were discovered in the cheese mould formed by the *Penicillium nalgiovensis* fungus [57]. Nalgiolaxine (**58**) was the first chlorine-containing anthraquinone discovered in nature [55].

Fraginine (**59**) was later isolated from various lichen species: *Byssoloma tricholomum* [58], *Caloplaca arenaria*, *C. percrocata* [59], *Caloplaca* spp. [60, 61], *Sphaerophorus coralloides*, *S. fragilis*, *S. globutus* [57], *S. melanocarpus* [62] and *Nephroma laevigatum* [63]. 7-Chloremodine (**60**) is also widespread in fungi (*Aspergillus fumigatus* [64], *Penicillium sp.* [62] and *Valsaria rubricosa* [65]) and in lichens (*Anaptychia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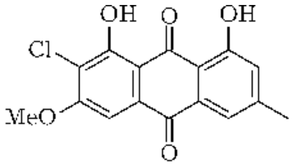
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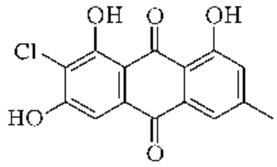
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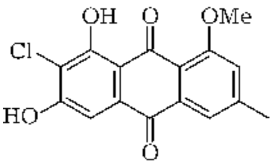
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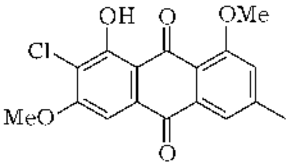
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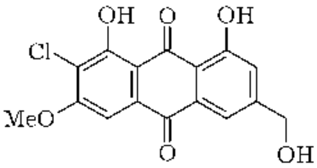
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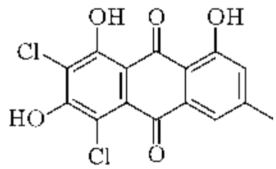
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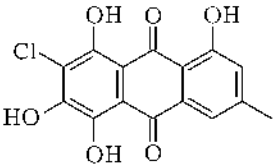
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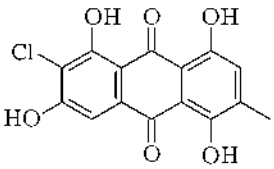
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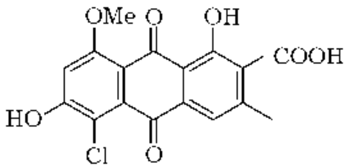
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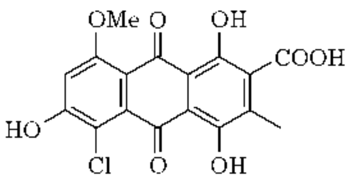
obscurata [66], *Byssoloma tricholomum* [58], *Caloplaca arenaria, C. percrocata* [59], *Caloplaca* spp. [60, 61], *Heterodermia obscurata* [62], *Nephroma laevigatum* [63], *Lasallia papulosa* [67, 68] and *Ledidea quernea* [69]). Metabolites (**61**) and (**62**) were isolated from *Nephroma laevigatum* lichen [63], (**61**) was also detected in *Phialophora alba* fungus [70], and (**62**) in *Caloplaca* spp. lichen [60]. Pathogenic fungus *Aspergillus fumigatus* generates metabolite (**63**) [64], while *Valsaria rubricosa* fungus contains metabolites 5,7-dichloremodin (**64**), valsarin (**65**) [65, 68] and (**66**) [68]. Valsarin (**65**) and (**66**) were also discovered in *Lasallia papulosa* lichen [67, 68].

The majority of lethally poisonous fungi belonging to the Cortinariaceae family (sub-genus *Cermocybe*) generate toxic anthraquinones – 5-chlorodermolutein (**67**) and 5-chlorodermorubin (**68**) [71]. These fungi include *Dermocybe* spp., *D. alnophila, D. malicoria, D. phoenica, D. sanguinea, D. sanguinea* var. *vitiosa, D. soommerfeltii* (the species containing metabolite (**67**)) [72], *D. phoenica, Dermocybe spp.* [71, 73], *D. crocea, D. marylandensis, D. phoenica* var. *occidentalis, D. punicea, D. sanguinea, D. sanguinea* var. *sierraensis, D. sanguinea* var. *vitiosa, D. soommerfeltii, D. uliginosa, D. semisanguinea* (the species containing metabolite (**68**)) [72]. 5-Chlorodermorubin (**68**) is also generated by poisonous fungus *Cortinarius subcroceofolius* belonging to the same family [72].

Lichens *Caloplaca* sp., for example *Caloplaca xanthapsis*, synthesize metabolites (**69**) [60] and (**70**) [61]. Wood fungus *Phialophora alba*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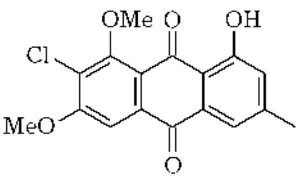
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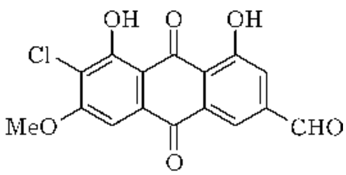
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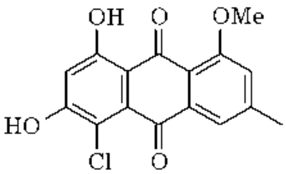
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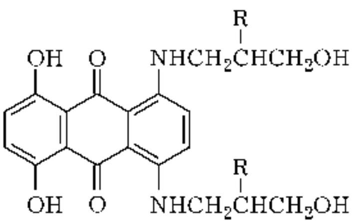
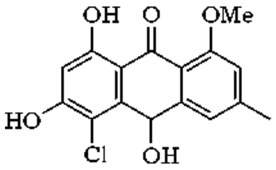

72. R = Cl
73. R = Br



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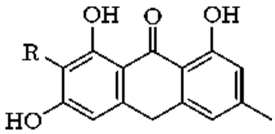
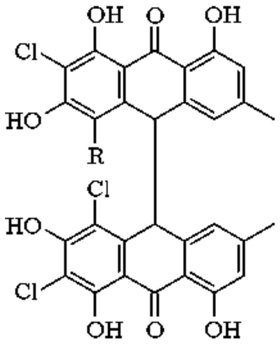
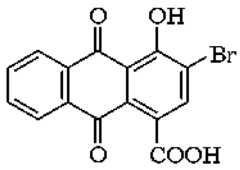


75. R = Cl
76. R = Br



77. R = H
78. R = Cl



79

(Deuteromycetes class) generates metabolite (**71**) [70].

The authors of [74] demonstrated that the enzymes isolated from the homogenate of *Nephroma leavigatum* lichen in the presence of H_2O_2 and Cl^- ions (KCl solution) chlorinate anthraquinone into positions 5 and 7 for 64 h. However, these enzymes are less selective than the enzymes isolated from lichen mycobionts (fungoid symbionts). This is confirmed by the fact that mycobionts in lichens generate haloperoxidases which are the main enzymes synthesizing halogenated metabolites.

Halohydrines with chlorine (**72**) and bromine (**73**) atom, isolated from higher plants, exhibited high antineoplastic activity, which is substantially higher than that of similar compounds containing no halogen atoms [75].

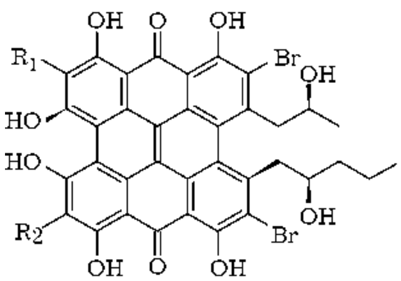
Several chlorine-containing metabolites of anthraquinone type were discovered in nature. For example, wood fungus *Phialophora alba* protects wood from the parasitic wood-destroying fungus *Phellinus tremulae* by generating 7-chloranthrone (**75**), as well as metabolites (**61**) and (**71**) [70]. 5-Chloranthrone (**74**) was isolated from the culture of *Aspergillus fimugatus* fungus. A bromine-containing analog (**76**) is generated by the fungus in the presence of bromide ions [64]. New *bis*-anthrones flavoobscurines A (**77**) and B (**78**) were discovered in *Anaptychia obscurate* lichen [76]. Metabolite (**79**) is released by the stone coral *Tubastraea micrantha* to protect itself from the Crown Pluck starfish *Acanthaster planci* [77]. It is known that this starfish destroys the coral polyps at the Great Barrier Reef [77].

A deepwater organism *Gymnocrinus richeri* living at the depth of more than 500 m contains new condensed anthraquinones gymnochromeses A–D (**80**)–(**83**) and isogymnochrome D (**84**) [78]. Metabolites (**83**)–(**84**) are esters of sulphuric acid, which is typical for many marine metabolites.

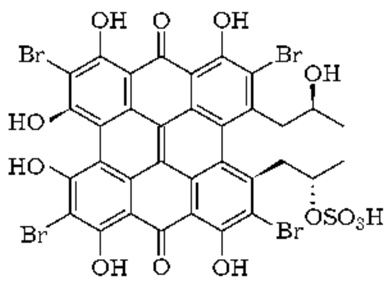
A chlorine-containing metabolite (**85**), which is similar in structure with gymnochromeses A–D (**80**)–(**83**) was detected in *Nephroma laevigatum* lichen.

GRISEOFULVINS AND RELATED COMPOUNDS

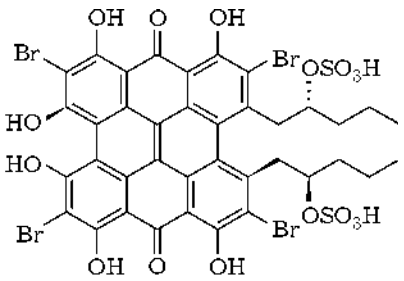
Griseofulvins comprise a rarely occurring group of natural compounds synthesized mainly by parasitic fungi; they are widely used as antimycotic preparations [80]. Geodine (**86**) and erdine (**87**) were isolated from the cultures of *Aspergillus terreus* [81–83] and *Penicillium* sp. fungi [84]. Griseofulvin (**88**) was first isolated from *Penicillium griseofulvum* fungus in 1939 [85]; thus other related compounds were named. Later on, griseofulvin (**88**) was discovered in



80. $R_1 = R_2 = Br$
81. $R_1 = H, R_2 = Br$
82. $R_1 = Br, R_2 = H$



83



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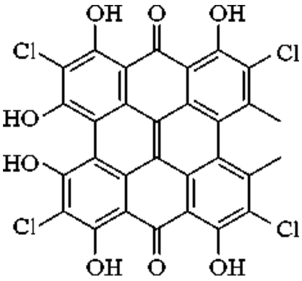


85

many other fungi species belonging to the *Penicillium* genus [86–89]. Dehydrogriseofulvin (**89**) and dihydrogriseofulvin (**90**) were detected in *Penicillium martinsii* [89] and *Penisillium patulum* [90]. Geodoxin (**91**) and gillusdine (**92**) are generated by *Aspergillus terreus* fungus [91, 92]. These fungi also synthesize precursors of griseophenons A (**93**), B (**94**), dihydrogeodine (**95**) and metabolites (**96**, **97**) [88, 90, 93–95]. Only one of the representatives of griseofulvins was detected in sea invertebrates. The sea worm *Thelepus setosus* contains thelerine (**98**) possessing high antimycotic activity [17, 18].

DERIVATIVES OF COMPLEX PHENOLS OF MIXED TYPES

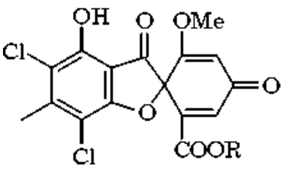
Freshwater cyanobacterium *Scytonema hofmanni* generates three chlorine-containing metabolites (**99**)–(**101**) [96, 97], while cyanobacterium *Nostoc* sp. (lichen phytobiont) isolated from *Peltigera canina* lichen contained two new metabolites nostoclide-1 (**102**) and nostoclie-2 (**103**) [98].

The *Pulveroboletus auriflammeus* fungus (the family of white fungi Boletas) generates methyl esters of pulvinic acid (**104**) and (**105**) [99].

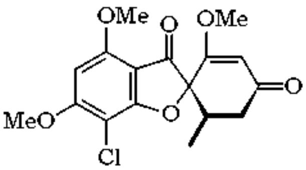
Dimeric polybrominated benzofuranes yatherane A (**106**), its acetate (**107**) and iatherane B (**108**) were isolated from the Australian sea sponge *Ianthella* sp. [100]. These metabolites inhibit the action of Na,K-ATR phase enzyme.

Chlorine-containing antibiotic napiradiomycine-B4 (**109**) is generated by *Chainia rubra* microorganism [1], while naphthaquinone derivatives bromine-containing antibiotics marinone (**110**) and isomarinone (**111**) with high cytotoxic activity were discovered in marine bacteria belonging to *Actinomycetales* (strain CNH-009) [101]. A new chlorine-containing antibiotic of coumarin type chlorobiocine (**112**) exhibiting antibacterial action was obtained from novobiocine using the enzymes isolated from *Escherichia coli* [102].

New chlorine-containing glycosides of the naphthalene row (**113**) and (**114**) were isolated from the methanol extract of the roots of *Rumex patientia* herb (Polygonaceae family) which is widely used in dietary intake in Tur-



86. R = Me
87. R = H



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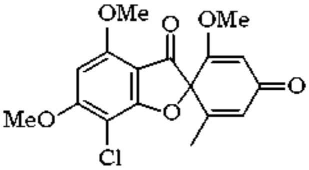

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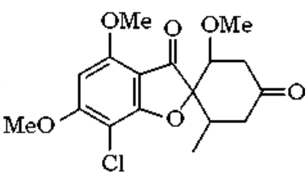

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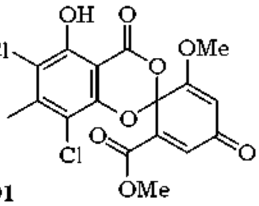

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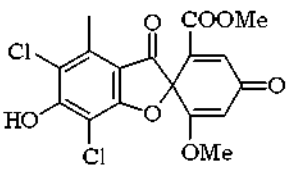

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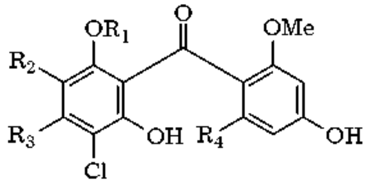
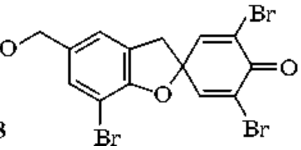
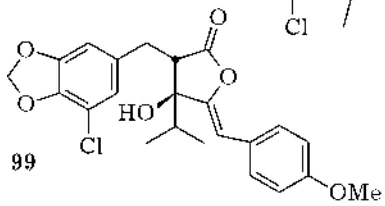


93. $R_1 = R_4 = Me, R_2 = H, R_3 = OMe$
94. $R_1 = R_2 = H, R_3 = OMe, R_4 = Me$
95. $R_1 = H, R_2 = Cl, R_3 = Me, R_4 = COOMe$
96. $R_1 = R_2 = H, R_3 = Me, R_4 = COOMe$
97. $R_1 = R_3 = R_4 = Me, R_2 = H$



98



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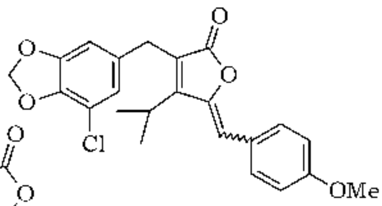
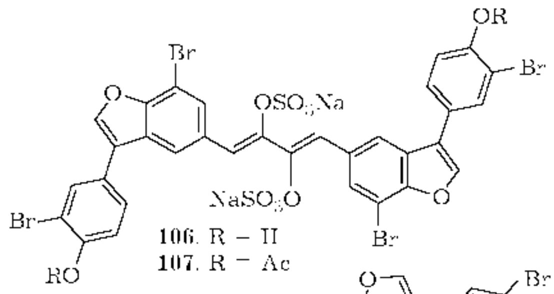
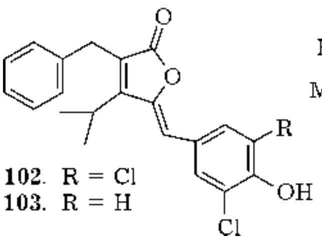


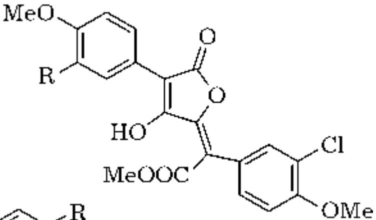
100. *E*-isomer
101. *Z*-isomer



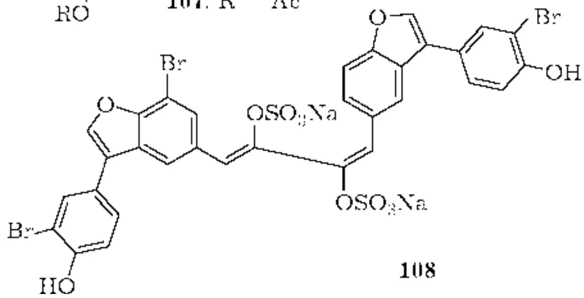
106. R = H
107. R = Ac



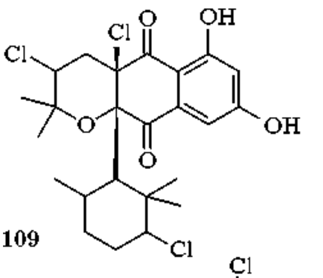
102. R = Cl
103. R = H



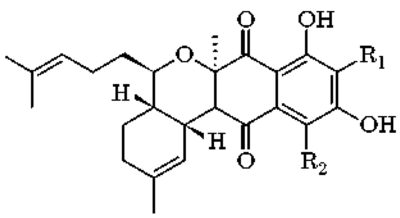
104. R = H
105. R = OMe



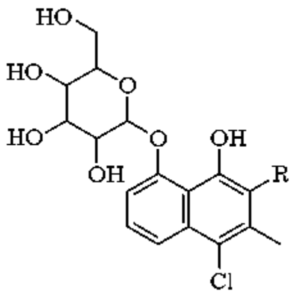
108



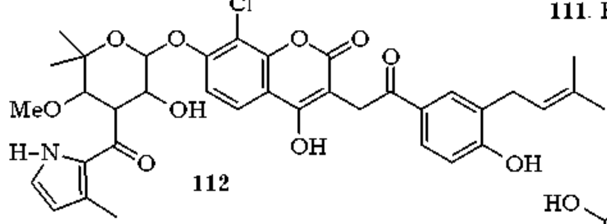
109



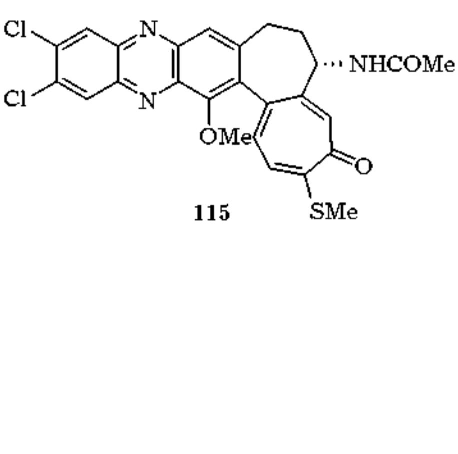
110. R_1 = Br, R_2 = H
111. R_1 = H, R_2 = Br



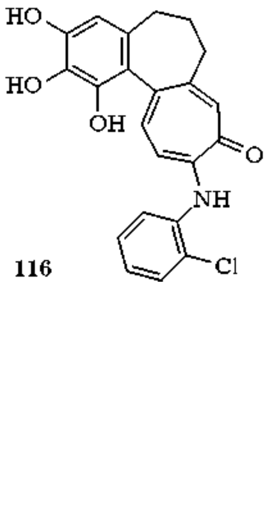
113. R = COMe
114. R = Cl



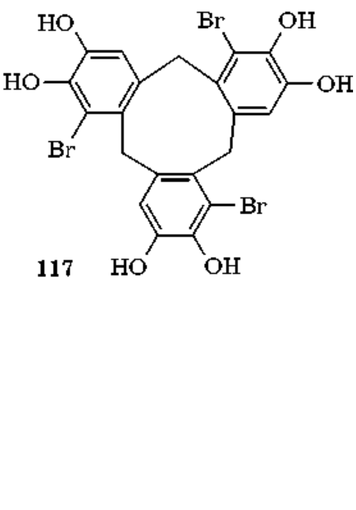
112



115



116



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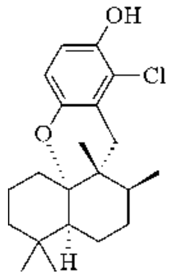

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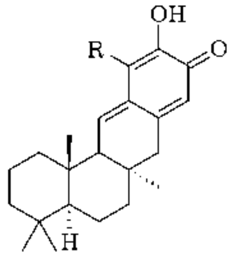
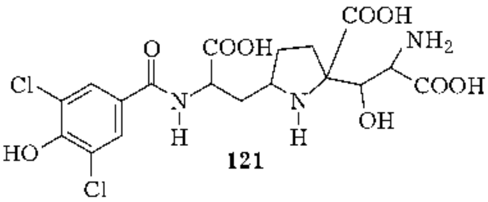
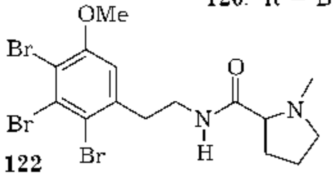


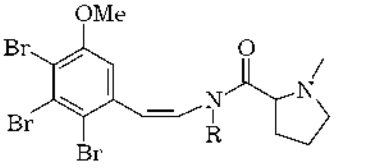
119. R = Cl
120. R = Br



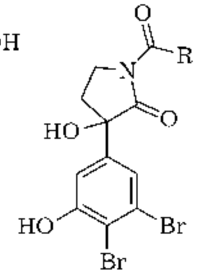
121



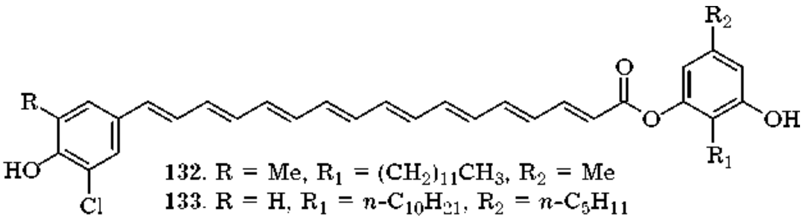
122



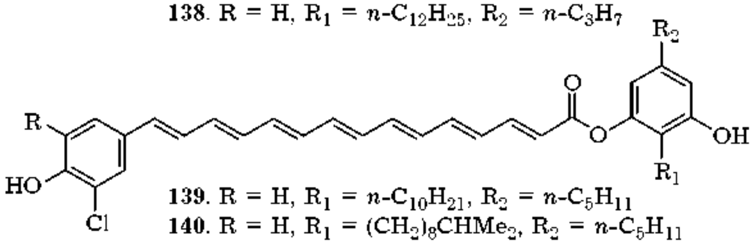
123. R = Me (*E*-isomer)
124. R = H(*E*-isomer)
125. R = H(*Z*-isomer)



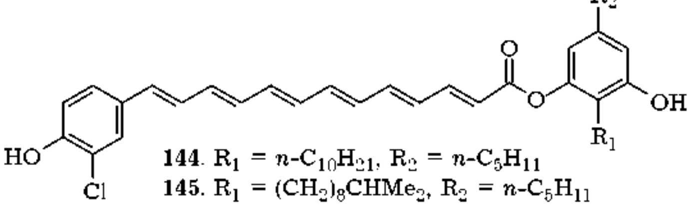
126. R = n-$C_{13}H_{27}$
127. R = $(CH_2)_7CH{=}CH(CH_2)_5CH_3$
128. R = n-$C_{15}H_{31}$
129. R = $(CH_2)_7CH{=}CH(CH_2)_7CH_3$
130. R = n-$C_{17}H_{35}$
131. R = $(CH_2)_6CH{=}CH(CH_2)_{10}CH$



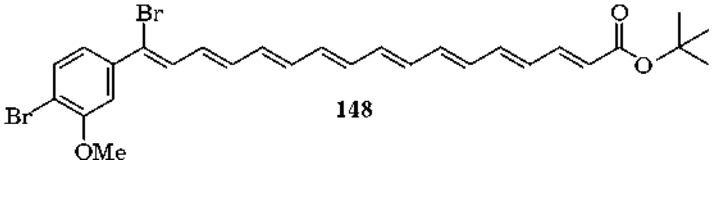
132. R = Me, R_1 = $(CH_2)_{11}CH_3$, R_2 = Me
133. R = H, R_1 = n-$C_{10}H_{21}$, R_2 = n-C_5H_{11}
134. R = H, R_1 = $(CH_2)_8CHMe_2$, R_2 = n-C_5H_{11}
135. R = H, R_1 = n-$C_{10}H_{21}$, R_2 = $(CH_2)_3CHMe_2$
136. R = H, R_1 = $(CH_2)_8CHMe_2$, R_2 = $(CH_2)_3CHMe_2$
137. R = H, R_1 = n-$C_{12}H_{25}$, R_2 = CH_2CHMe_2
138. R = H, R_1 = n-$C_{12}H_{25}$, R_2 = n-C_3H_7



139. R = H, R_1 = n-$C_{10}H_{21}$, R_2 = n-C_5H_{11}
140. R = H, R_1 = $(CH_2)_8CHMe_2$, R_2 = n-C_5H_{11}
141. R = H, R_1 = n-$C_{10}H_{21}$, R_2 = $(CH_2)_3CHMe_2$
142. R = H, R_1 = $(CH_2)_8CHMe_2$, R_2 = $(CH_2)_3CHMe_2$
143. R = Cl, R_1 = $(CH_2)_8CHMe_2$, R_2 = $(CH_2)_3CHMe_2$



144. R_1 = n-$C_{10}H_{21}$, R_2 = n-C_5H_{11}
145. R_1 = $(CH_2)_8CHMe_2$, R_2 = n-C_5H_{11}
146. R_1 = n-$C_{10}H_{21}$, R_2 = $(CH_2)_3CHMe_2$
147. R_1 = $(CH_2)_8CHMe_2$, R_2 = $(CH_2)_5CHMe_2$



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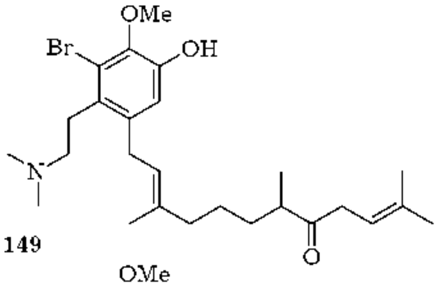

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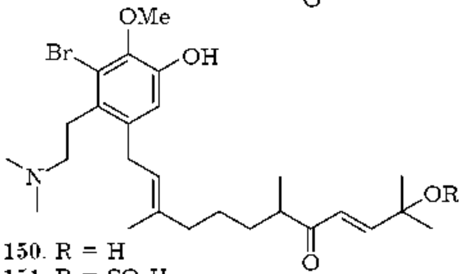

150. R = H
151. R = SO_3H

key and is known under the names of Labada and Develik [103]. Two antineoplastic metabolites – 2,3-demethylcolchicine (**115**) and colchicines derivative (**116**) – were detected in the extracts of higher plants [75]. Cyclotribromoveratrilene (**117**) is generated by the sea red alga *Halopytis pinastroides* [104].

Three halogenated metabolites, phenol derivatives (**119**) and chloro- (**119**) and bromopuupequinones (**120**) belonging to the new class of terpenophenols, were discovered in the sea sponge *Smenospongia aurea* [105] and in non-identified yellow-coloured sponge [106].

Complex phenols of pyrrolidine derivatives (**121**)–(**131**) were discovered in some species of bacteria, cyanobacteria and invertebrates. For instance, kaytacephaline (**121**) was isolated from the *Eupenicillium shearri* microorganism [107]. This metabolite exhibited the ability to protect the human cerebral neuroglia cells from ischemia. Amathamides D–F (**122**)–(**125**) are synthesized by the sea bryozoa *Amanthia wilsoni* [108], while convolutamides A–F (**126**)–(**131**) are generated by *Amathia convoluta* [109] living near the coast of Florida.

5-Chlorofexirubine (**132**) and phenol-containing pigments (**133**)–(**147**) were discovered in the cultures of bacteria *Flexibacter elegans* [109], *Cytophaga* sp. [110], *C. johnsonae* [111] and *Flavobacterium* sp. [110–114]; xanthomonadine-1 (**148**) was isolated from gram-negative bacteria *Xanthomonas juglandis* [115–117].

Mollusk *Aplysia kurodai* contains aplaminone (**149**), neoaplominone (**150**) and its sulphate (**151**) [118].

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