

Natural Halogenated Mononuclear Phenol Compounds and Their Derivatives

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Abstract

Mononuclear halogenated simple phenol compounds and their derivatives formed from mono- and polyhydroxybenzenes are represented in nature by metabolites of insects, fungi, plants and microorganisms living on land and in water. The structures of a hundred compounds of phenol, quinones and cyclitol types, their metabolism and data on their biological activity are considered in the review.

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INTRODUCTION

Chlorinated phenols are manufactured on a large scale. For example, the world production of 2,4-dichlorophenol (**1**), which is used to obtain herbicides, accounts for several hundred thousand tons per year. Toxicity of chlorinated phenols caused the necessity to include these compounds in the list of strictly monitored anthropogenic pollutants [1]. Because of this, proceeding to the discussion of natural halogenated phenols, we keep in mind only the compounds synthesized in organisms *via* inherent metabolic routes. It should be specially

stressed that in this review we discuss monocyclic phenols of the benzene row, as well as quinones and cyclitols derived from them.

PHENOL COMPOUNDS IN FUNGI, PLANTS AND MICROORGANISMS

2,4-Dichlorophenol (**1**) was first isolated from soil fungus *Penicillium* sp. [2]. Its function as growth hormone in this organism was determined. Sex hormone 2,6-dichlorophenol (**2**) was discovered in some species of bloodsucking parasites belonging to the Ixodoidea family,

such as *Amblyomma americanum* [3–5], *A. maculatum* [4, 5], *A. variegatum* [6], *Rhipicephalus sanguineus* [7, 8], *Dermacentor andersoni* и *D. variabilis* [9], *D. albipictus* [13], *Hyalomma truncatum* [6], *H. dromedarii* [11], *Haemaphysalis leporispalustris* [10] and *Boophilus microplus* [8]. Berger [4] demonstrated using radioactive chlorine (^{36}Cl) that it freely gets included into sex hormones, in particular 2,6-dichlorophenol, in some species of the parasites. 2,5-Dichlorophenol (**3**) was found in secretory glands of *Romalea microptera* grasshopper. However, the authors of [12] assume that this phenol compound could be of exogenous origin. Investigation of *Drosophila subrata* fungi belonging to Basidiomycetes showed that they contain 2,3,5,6-tetrachloro-4-methoxyphenol (**4**) which was called drosophilin A [13, 14], while its methylated ether (**5**) was isolated from other fungi species: *Fomes fastuosus* [15], *F. robiniae* [16], *Phellinus yucatensis* [17], *Agaricus bisporus* [18]. *Fomes robiniae* fungus also generates nitro derivatives of chlorophenol (**6**), which are extremely rare in nature.

Amudol (**7**) which exhibits antibacterial action was isolated from the cultivated soil fungus *Penicillium martinsii* [19]. White parasitic fungi *Bjerkandera* sp. and *B. adusta*, which stimulate decomposition of wood substrate, generate chlorinated benzyl alcohol (**8**) [20]. Chlorogentizyl alcohol (**9**) was found in cultivated *Phyllosticta* sp. fungus [21, 22]. Investigation of biosynthesis of (**9**) showed that it is endogenous metabolite [23]. The *Caldariomyces fumago* fungus generates chloro- (**10**) and dichlorophenols (**11**) [24]; the authors assume that these compounds are derivatives of tyrosol and are formed under the action of chloroperoxidase [24].

Humus saprophytes, such as *Lepista diemii* (Tricholomataceae family) [25], many of which are toxic, are widely spread in Europe and generate two isomeric chlorobenzaldehydes (**12**) and (**13**). These fungi have unpleasant smell resembling that of DDT, perhaps due to the presence of chlorinated phenols. *Marasmius palmivorus* fungus, which belongs to the same family, generated metabolite (**14**) [26].

The *Everniaprunastri* lichen contains chlorophenols (**15**), (**16**) [27] and ethylhematomate (**17**) [28], which exhibited the ability to

suppress the development of larva of coelminth parasit (*Toxocaria canis*) [28]. The soil microbe *Chaetomium* sp. generates antibiotic differanisoole A (**18**) [29]. Polyacetylenide (**19**) was found in *Helichrysum coriaceum* plant (Compositae family) [30].

Some researchers [31–34] assume that 2,4,6-trichlorophenol (**20**) is a vital product of soil microbes. It is typical that (**20**) and 2,4,6-trichloroanisole (**21**) were found in river and lake sediments, and in different soils. In addition, (**21**) was discovered in some kinds of wine and in food [35–37] (Table 1).

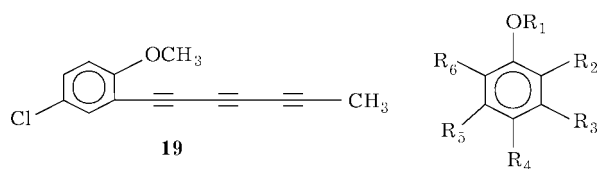
PHENOL COMPOUNDS IN SEAWEEDS AND CYANOBACTERIA

Seaweeds, similarly to marine invertebrates, generate large amounts of diverse halogenated phenols [38, 39]. Bromine-containing phenols were first discovered in red seaweeds which are widespread along the coast of France [40]. Subsequent research showed that many species of red seaweeds generate halogenated phenols [41–44]. For example, bromocatechol (**22**) was found in red seaweeds *Halopitrys incurvus*, *Polysiphonia nigra*, *P. elongata*, *P. fastigiata*, *Pterosiphonia complanata* and *Vidalia volubilis* [40–44]. In addition, recent works showed that bromocatechol (**22**) is also present in other species of red seaweeds: *Odonthalia dentata* [45], *Polysiphonia lanosa* [46, 47], *P. morrowii* [48], *P. nigrescens* [45] and *P. urceolata* [45, 47, 49–51].

Lanosol (**23**), which is a very toxic compound, is generated both by red and brown seaweeds (Fucaceae family): *Antithamnion plumula* [45], *Ceramium rubrum* [45], *Coralina officinalis* [45], *Fucus vesiculosus* (kelp), [52], *Odonthalia dentata* [45, 53], *Phycodrys rubens* [45], *Polysiphonia brodiaei* [45, 54, 57], *P. elongata* [47], *P. lanosa* [46, 47], *P. fruticulosa* [47], *P. nigra* [47], *P. nigrescens* [45] and *P. urceolata* [45], *P. thuyoides* [47], *P. violacea* [47], *Rhodomela confervoides* [45, 53, 55], *R. larix* [56, 57], *R. subfusca* [47, 58], *Rytiophlea tinctoria* [59]. Lanosol methylate (**24**) was discovered in red seaweeds: *Antithamnion plumula* [45], *Ceramium rubrum* [45], *Odonthalia corymbifera* [60], *O. dentata* [45], *O. floccosa* [61], *O. washing-*

TABLE 1

Chlorine-containing phenol compounds in fungi, plants and microorganisms



Phenol compound No.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
1	H	Cl	H	Cl	H	H
2	H	Cl	H	H	H	Cl
3	H	Cl	H	H	Cl	H
4	H	Cl	Cl	OCH ₃	Cl	Cl
5	CH ₃	Cl	Cl	OCH ₃	Cl	Cl
6	CH ₃	Cl	Cl	OCH ₃	Cl	NO ₂
7	H	Cl	H	OH	CH ₂ OH	H
8	CH ₃	Cl	H	CH ₂ OH	H	H
9	H	Cl	H	Cl	H	CH ₂ OH
10	H	Cl	H	(CH ₂) ₂ OH	H	H
11	H	Cl	H	(CH ₂) ₂ OH	H	Cl
12	CH ₃	Cl	H	CHO	H	H
13	CH ₃	Cl	H	H	CHO	H
14	H	Cl	H	CH ₂ COOH	H	H
15	CH ₃	Cl	CH ₃	H	OCH ₃	H
16	H	Cl	OCH ₃	H	CH ₃	H
17	H	Cl	CH ₃	COOEt	OH	CHO
18	CH ₃	Cl	OH	COOH	<i>n</i> -C ₃ H ₇	Cl
20	H	Cl	H	Cl	H	Cl
21	CH ₃	Cl	H	Cl	H	Cl

toniensis [61], *Phycodrys rubens* [45], *Polysiphonia brodiaei* [45], *P. nigrescens* [45] and *P. urceolata* [45], *Rhodomela confervoides* [45], *R. larix* [57, 67].

An unusual sulphate of bromine-containing phenol was discovered in red seaweeds belonging to the *Polysiphonia* genus: *P. brodiaei*, *P. elongata* [47, 62], *P. lanosa* [63], *P. fruticulosa*, *P. nigra*, *P. nigrescens*, *P. urceolata*, *P. violacea* [47, 62], *Rhodomela subfusca*, *R. larix* [56–68]. Cyanobacteria *Calothrix brevissima* synthesized lanosol (**23**) and bromine-containing phenol (**26**) [64].

A red pigment floridorubin, which is present in red seaweed *Lenormandia prolifera*, hydrolyzes to form (**23**) and (**26**) among other phenols [68]. The functions of these bromophenols are unclear, however, they are antibiotics and suppress the development of some

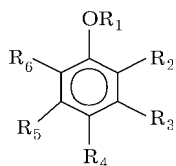
marine bacteria [66]. Brown seaweed *Fucus vesiculosus* [52], as well as red macrophyte seaweed *Polysiphonia brodiaei* [45, 47], *P. lanosa* [47], *P. nigrescens* [45, 47, 55], *P. urceolata* [47, 49–51], *Rhodomela confervoides* [45, 53, 55], *R. larix* [58] contain metabolite (**26**). Metabolite (**27**) was found in red seaweed species *Polysiphonia urceolata* [50] and *Rhodomela larix* [58].

Benzaldehyde (**28**) is generated in red seaweeds: *Cystoclonium purpureum* [45], *Odonthalia dentata* [45], *Polysiphonia elongata* [45, 54], *P. fruticulosa* [47], *P. brodiaei* [45], *P. lanosa* [46, 47], *P. nigrescens* [47], *P. urceolata* [45], *P. violacea* [47], *Rhodomela confervoides* [45], *R. larix* [57, 67], *R. subfusca* [47].

Two dibromophenols (**29**) and (**30**) were found only in one red seaweed species: *Halopytis incurvus* [68]. Bromophenol (**31**) is

TABLE 2

Phenol compounds in seaweeds and cyanobacteria



Phenol compound No.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
22	H	Br	H	CHO	Cl	OH
23	H	Br	Br	CH ₂ OH	H	OH
24	H	Br	Br	CH ₂ OCH ₃	H	OH
25	SO ₃ K	Br	Br	CH ₂ OSO ₃ K	H	OH
26	H	Br	H	CH ₂ OH	H	Br
27	H	Br	H	CHO	H	Br
28	H	Br	Br	CHO	H	OH
29	H	Br	H	CH ₂ COOH	H	Br
30	H	Br	H	CH ₂ COCOOH	H	Br
31	H	Br	H	CH ₂ OH	H	OH
32	H	Br	Br	CH ₂ OH	Br	OH
33	H	Br	Br	CH ₂ OC ₃ H ₇	H	OH
34	H	Br	H	CH ₂ OH	H	H
35	H	Br	OH	Br	OH	H
36	H	Br	H	Cl	H	Cl
37	H	Br	H	CHO	H	H
38	SO ₃ Na	Br	Br	CH ₂ OSO ₃ Na	Br	OH
39	H	Br	CH ₂ COOH	Br	OH	H
40	H	Br	OH	H	OH	Cl
41	H	Br	OH	Br	OH	Br
42	H	Br	OH	Cl	OH	Br
43	H	Br	OH	H	OH	H
44	H	Cl	OH	H	OH	H
45	H	Br	Br	CH ₂ OH	H	Br
46	H	Br	Br	CHO	H	Br
47	Ac	Br	OAc	H	OAc	H
48	Ac	I	OAc	H	OAc	H
49	H	Br	H	H	H	H
50	H	H	H	Br	H	H
51	H	Br	H	Br	H	H
52	H	Br	H	Br	H	Br

present in *Polysiphonia urceolata* seaweed growing in many regions of oceans from the coast of Japan to the southern coast of France [45, 47, 49–51]. In addition, (**31**) was found in seaweeds: *Halopytis incurvus* [47], *Odonthalia dentata* [45], *Polysiphonia lanosa* [46, 47] and *P. nigrescens* [47]. Tribromophenol (**32**) is present in extracts from *Polysiphonia lanosa*, *P. nigrescens*

[47], as well as in two species of *Phodomela* genus: *R. confervoides* [55] and *R. subfusca* [47]. Bromine-containing metabolite (**33**) was found in *Polysiphonia lanosa* and *P. nigrescens* algae [47].

Bromobenzyl alcohol (**34**) was isolated from aqueous extracts of *Halopytis incurvus* [47], *Odonthalia dentata* [45], *Polysiphonia brodi-*

aei, *P. nigra* [47], *P. urceolata* [47, 51] and *Rhodomela larix* algae [58]. 2,4-Dibromophloroglucinol (**35**) was discovered in a rarely occurring species of red seaweeds *Rhabdonia verticillata* [69] and *Rytiphlea tinctoria* [59].

Phenol (**36**) which contains chlorine and bromine occupying unknown positions was isolated from *Polysiphonia nigrescens* and *Rhodomela confervoides* algae [55]. 2-Bromo-3-hydroxybenzaldehyde (**37**) was found only in *Rhodomela larix* [58]. Sulphate of bromated protocathechuic alcohol (**38**) is generated in red seaweed *Symphyclocladia latiuscula* [70]; dibromine-substituted resorcinol (**39**) is generated by *Halopitys incurvus* [71].

Five chlorine- and bromine-containing derivatives of phloroglucinol (**40**)–(**44**) were discovered in addition to phenol (**35**) described earlier in red alga *Rhabdonia verticillata* [69]. Tribromides of *p*-oxybenzyl alcohol and *p*-oxybenzaldehyde (**45**) and (**46**) are generated by cyanobacteria *Calothrix bressime* [64]. It was established that, in addition to red algae synthesizing mainly various halogenated phenol compounds, green seaweeds of tropical seas *Avrainvillea nigricans* and *A. rawsonii* generate also phenol (**31**) [72, 73].

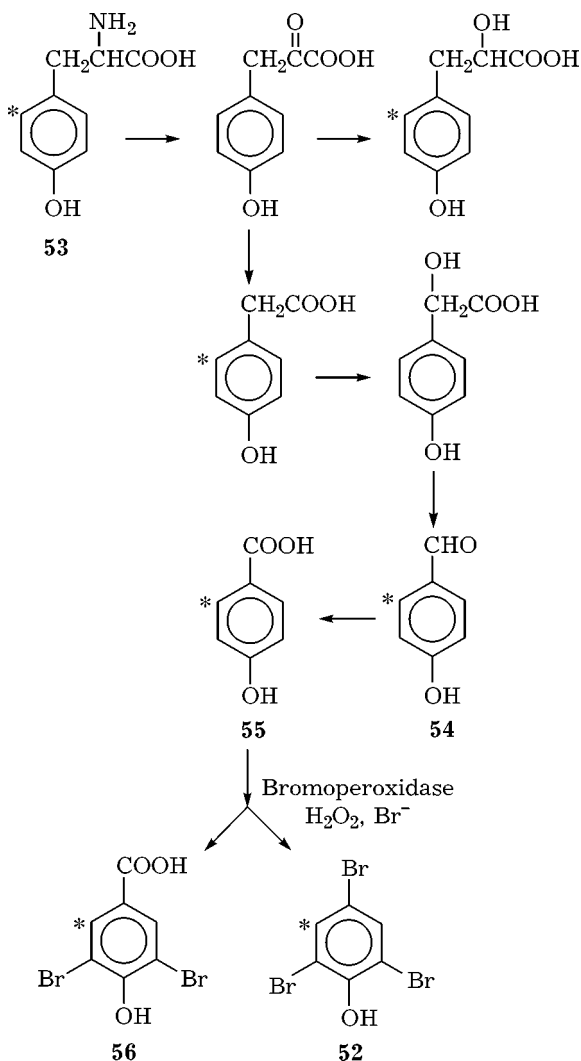
Brown algae *Ascophyllum nodosum* [74] and *Eisenia arborea* [75] contain halogenated phenols (**23**), (**26**), as well as bromide (**47**) and iodide (**48**) of phloroglucinol triacetate (Table 2).

BIOSYNTHESIS OF HALOGENATED PHENOL COMPOUNDS

Red algae are the main source of halogenated phenol compounds, as indicated above. Recent research carried out by Australian scientists showed that the green seaweeds can also synthesize simple halogenated phenols. For example, green seaweed *Ulva lactuca* inhabiting the western coast of Australia generates 2-bromo- (**49**), 4-bromo- (**50**), 2,4-dibromo- (**51**) and 2,4,6-tribromophenols (**52**) [76]. Concentrations of bromated phenol compounds can vary substantially depending on season. Only the concentration of 2,4,6-tribromophenol (**52**) remains rather high all year round [77]. Till recently, the mechanism of formation and precursors of simple halogenated phenol compounds in algae were unknown; it was only

successfully established that 4-hydroxybenzoic acid is a precursor for the synthesis of 2,4,6-tribromophenol (**52**) [78].

The assumed mechanism of biosynthesis of 2,4,6-tribromophenol (**52**) in *Ulva lactuca* alga is shown in scheme 1 [78]. L-Tyrosine (**53**) was used as one of the possible precursors for the synthesis of 4-hydroxybenzoic acid (**55**). This route of biosynthesis was previously investigated by the authors of [79]. Compounds found in the extract of *Ulva lactuca* alga [79] are marked with asterisk. To bromate 4-hydroxybenzoic acid (**55**) which is formed by oxidation of 4-hydroxybenzaldehyde (**54**), bromoperoxidase isolated from *Ulva lactuca* was used. Two products were formed in this process: 3,5-dibromo-4-hydroxybenzoic acid (**56**) and 2,4,6-



Scheme 1.

tribromophenol (**52**). The authors of [52] assume that bromated phenol compounds synthesized by red or brown algae can be formed *via* a similar mechanism; however, bromation stage can differ from that included in the proposed scheme, and other compounds can be formed, for instance, (**29**), (**31**), (**34**) or (**37**).

PHENOL COMPOUNDS IN MARINE INVERTEBRATES

Marine invertebrates synthesize simple halogenated phenols to a less extent than seaweeds do. One cannot exclude that some of these phenol compounds can get into the organisms of invertebrates which use seaweeds in dietary intake.

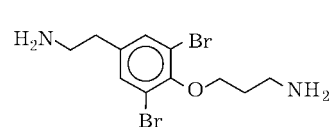
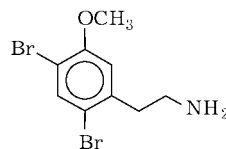
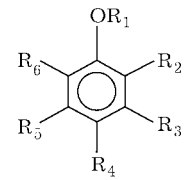
2,6-Dibromophenol (**57**) was found in sea acorn *Balanoglossus biminiensis*. Its concentration can reach 15 mg per one individual [80].

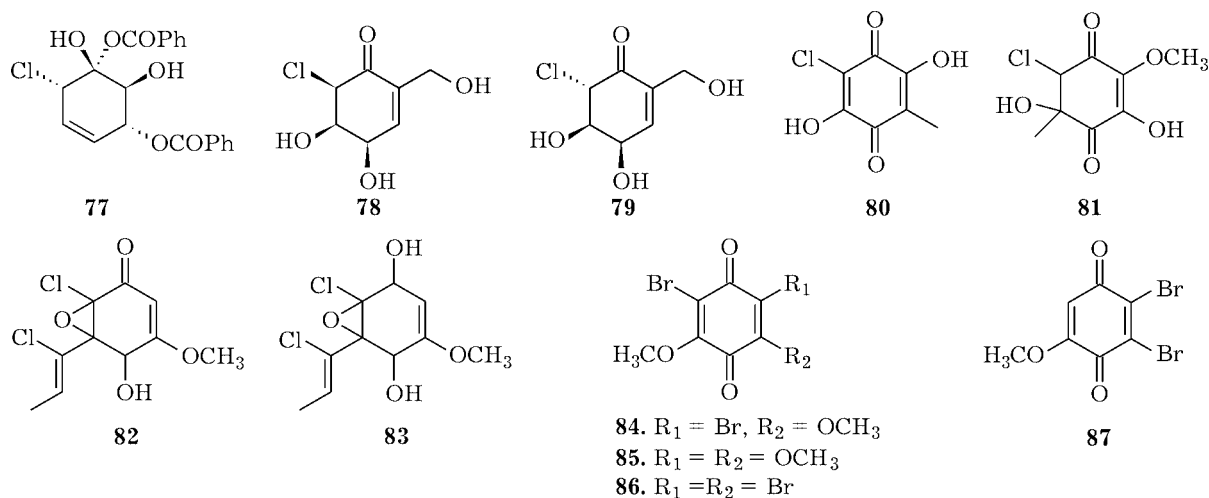
Other species of sea acorns, such as *Phoronopsis viridis* [81], *Saccoglossus kowalewskii* and *Nereis succinea* [82, 83], contain tri- and dibromophenols (**58**) and (**59**). It is assumed that sea acorns use these halogenated phenols as chemical protection from starfish and/or fish, and as antibacterial agents as well [80–82]. Segmented sea worm *Thelepus setosus* generates phenol compounds (**26**) and (**27**) [84, 85], and *Ptychodera flava* worm synthesizes metabolites (**58**) and (**60**) [86]. Sea balanus *Glossobalanus* sp., *Balanoglossus carbosus* and *B. misakiensis* generate phenol compounds (**58**)–(**63**) [86]. Deep-sea acorn *Ptychodera* sp. inhabiting the sea near the coast of Florida synthesizes phenols (**58**), (**59**) and (**63**)–(**70**) [87]. Sea polychetus *Lanice conchilega* contains phenols (**58**) and (**71**) [88].

Sea sponge *Aplysina aerophoba* living near the Canaries contains dibromide (**72**) [89]; sponge belonging to the *Verongida* genus gene-

TABLE 3

Phenol compounds of sea invertebrates

 74  76 						
Phenol compound No.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
57	H	Br	H	H	H	Br
58	H	Br	H	Br	H	Br
59	H	Br	H	OH	H	Br
60	H	Br	Br	OH	H	Br
61	H	Br	OH	Br	H	H
62	H	Br	H	Br	H	H
63	H	Br	H	OH	H	H
64	H	Br	H	OH	H	OAc
65	H	Br	H	OH	H	Cl
66	H	OH	Br	H	Br	H
67	H	Br	H	OAc	H	Br
68	H	Br	H	Cl	H	Br
69	H	Br	H	Cl	H	Cl
70	H	H	Cl	Cl	H	H
71	H	Br	H	CH ₃	H	Br
72	CH ₃	Br	H	OH	H	Br
73	CH ₃	Br	H	OH	OH	CHO
75	H	Br	H	CH ₂ CN	H	H



rates bromocatechol (**73**), miltamine (**74**) [90] and bromotyrosine (**75**) [91].

Sea bryosoa *Amathia wilsoni* living near the island of Tasmania (Australia) generates β -phenylethylamine (**76**) which is a precursor of amatamides and alkaloids [92] (Table 3).

CYCLITOLS AND BENZOQUINONES

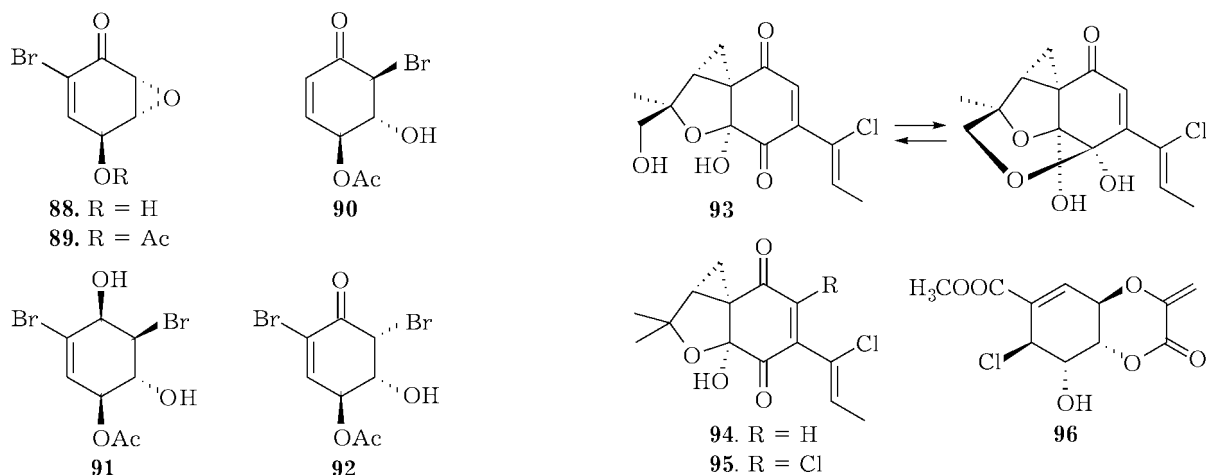
1,4-Benzoquinones and cyclitols, which are the derivatives of cyclohexene, occur in nature as the products of transformation of phenols. Halogenated cyclitols and benzoquinones were found in some species of plants, fungi and marine invertebrates. For example, cyclitol (**77**) is present in plants of *Piper* genus cultivated in India: *P. hookeri* [93], *P. nigrum* [94], *P. attenuatum* [95].

The cultivated pathogenous fungus *Phyllosticta* sp. generates stereoisomeric chlorohydrins (**78**) and (**79**) [21, 22], as well as chlorogentisilic

alcohol (**9**) [23]. Other pathogenous fungi *Aspergillus terreus* [96] and *A. fumigatus* [97] synthesize benzoquinone (**80**) and fumigatin (**81**). Two chlorine-containing cyclitols lachnumone (**82**) and lachnumone A (**83**) are present in the products of metabolism in *Lachnum papuraceum* fungus (Ascomycetes) [98, 99]. These compounds exhibit high antimicrobial and cytotoxic activity.

Bromine-containing benzoquinones (**84**)–(**87**) were found in the tissues of primitive sea worms *Ptychodera flava laysanica* (Hemichordate, Metazoa) [100]. Other worm species of *Ptychodera* genus inhabiting a deep cave Maya contain bromocyclohexenes (**88**)–(**92**) [101]. Epoxide (**89**) exhibits strong cytotoxic action against P388 cancer cells *in vitro*. Epoxides (**88**) and (**89**) were also found in *Ptychodera bahamensis* worms (*Balanoglossus* sp. after specification) inhabiting the sea near the coast of Florida (USA) [87].

The metabolite (**93**) isolated from two species of actinomycetes can be considered as a product of cyclization of the pyruvate of me-



thyl ester of 6 β -chloro-3b,4a,5a-trihydroxycyclohexenecarboxylic acid [102]. Interesting derivatives of prenylated 1,4-benzoquinone (**93**)–(**95**) are generated by some fungi. For example, microlin (**93**) is present in *Gilmaniella humicola* [103, 104], mycorrhizin A (**94**) and chloromycorrhizin A (**95**) were found in *Monotropa hypopitys* fungus [105, 106] and in *Lachnum papyraceum* actinomycete [98, 99]. According to [107], metabolite (**96**) is also generated in *Gilmaniella humicola* fungus.

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