Halogenated Phenol Compounds in Lichens and Fungi

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Abstract

The structures of hundred halogenated metabolites of phenolic nature generated by lichens and fungi are considered. The groups of depsides, depsidones, fungoid metabolites are marked out. The problems related to biological activity are discussed.

Contents

INTRODUCTION

The amount and structural variety of compounds containing phenolic structural unit is innumerable in nature. Examples of the isolation and identification of the halogenated phenolic compounds of complicated structure become more and more numerous. As one would expect, substances with extremely valuable biological activity are discovered among halogen-containing compounds of phenolic type. A very indicative example is the recent discovery of strobilurine compounds, fungoid metabolites which served as a basis fort he design of a new class of fungicides to be introduced into the agriculture [1, 2]. Many fungi synthesize chlorinated phenols, which are likely to cause various diseases in plants, leading to plant death. Lichens are symbiotic organisms composed of a photobiont, which is a microalga or a cyanobacteria, on the one hand, and a mycobiont, which is a fungus of *Ascomycetes,* on the other hand [3]. Lichens generate a number of biologically active molecules, among which a noticeable role is played by halogenated phenol compounds.

In the review, we consider typical lichen metabolites, such as depsides and depsidones, as well as complicated phenolic metabolites of fungi.

LICHEN DEPSIDES AND DEPSIDONES

Depsides are esters formed by the derivatives of *p*-oxybenzoic acid and phenols. They comprise a small group of polyketides and are generated mainly by lichens. For example, the

most widespread chlorine-containing depside chloroatranorin (**1**) was discovered in more than 40 lichen species: *Evernia prunastri* [4−6], *Pseudevernia furfuracea* [7, 8], *P. intensa* [9], *Parmelia perlata* [10, 11], *P. pseudoreticulata* [11], *P. olivetorum* [12], *P. cryptochlorophaea* [13], *P. tinctorum* [9−14], *P. pseudofatiscens* [15], *P. horrescens* [15], *P. damaziana* [16], *P. furfuracea* [17], *Buellia canescens* [18, 19], *Ramalina siliquosa* [20], *R. druidarum* [9], *Lecidea carpathica* [21], *Lecidea* sp. [22], *Phiscia picta* [23], *Cetralia cetrarioides* [9], *C. japonica* [9], *Usnea canariensis* [9], *Hypogymnia physodes* [9], *H. billardieri* [24], *H. enteromorpha* [24], *H. lugubris* [24], *H. subphysodes* [9], *Anaptychia neoleucomelaena* [9−25], *Menegazzia asahinae* [26], *M. terebrata* [26], *M. dispora* [27], *Platismatia glauca* [28], *Parmotreama demethylmicrophyllinicum* [29], *P. praesorediosum* [30], *Lacanora braccha* [31], *L. epibryon* [31], *L. rupicola* [9, 32] and *L. gangaleoides* [9, 33].
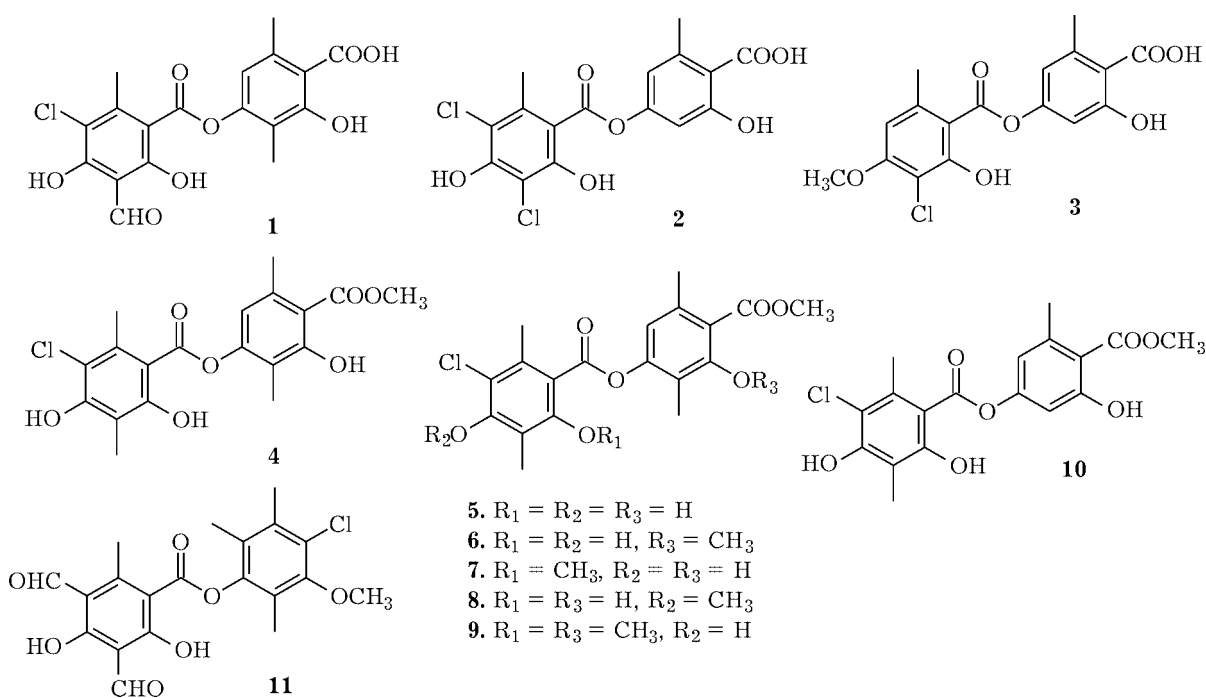
Tumidulin (**2**), a less widely spread lichen metabolite, was discovered only in *Ramalina* genus: *R. ceruchis, R. flaccescens, R. tumidula, R. inanis, R. cactacearuum, R. peruviana* and *R. chilensis* [9, 25, 33−36]. The *Erioderma wrightii* lichen generates wrightin (**3**) [37], (**4**)−(**10**) metabolites were detected in *Erioderma sp.*, and depside (**11**) was isolated from extracts of *Pseudocyphellarie pickeringii* [40]. Me-
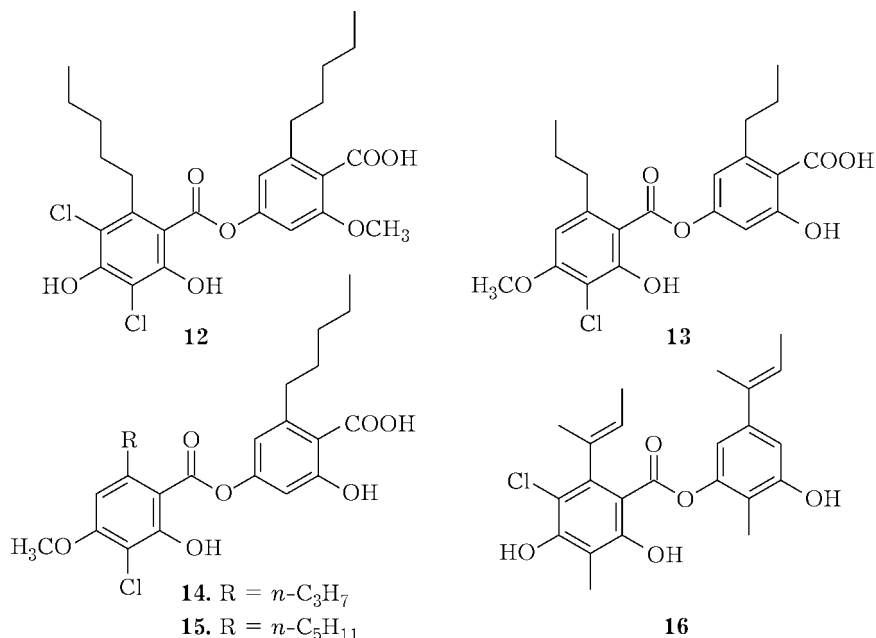
tabolite (**12**) was isolated from the extracts of *Lecanora sulphurella* lichen; its structure was confirmed by synthesis [41].

3-Chlorodivaricatinic acid (**13**), 3-chlorostenosporic (**14**) and 3-chloroperlatolic (**15**) acids were discovered in *Thelomma mammosum* [42] and *Dimelaena sp.* lichens [43]. Guisinol (**16**) was discovered in isolates from marine fungus *Emericella unguis* (known also as *Aspergillus unguis*) [44]. This is the first and sole representative of depsides detected not in lichens; it exhibits high antibacterial activity [44].

Depsidones are the derivatives of diphenyloxide containing the heterocyclic system of 1,4-dioxacycloheptanone-7 as a result of the formation of itramolecular ester bond. The first representative of depsidones, namely, diploicin (**17**), was isolated in 1904 by Zopf from a lichen of undetermined species [45]. Subsequent research showed that (**17**) is present in *Buellia canescens* [18, 19, 46, 47] and *Lecidea cargaleoides* [21] lichens.

Though gangaleoidin (**18**) was discovered more than 65 years ago in *Lecanora gangaleoides* lichen [48, 49], its structure was confirmed only after 30 years [50]. Pannarin (**19**) was initially isolated from the lichens of *Pannaria* genus: *P. lanuginosa, P. fulvescens*, and *P. lurida* [51], *P. pityrea, P. rubiginosa*, and later from *Lecanora hercynica, Bombyliospora*

5. $R_1 = R_2 = R_3 = H$
6. $R_1 = R_2 = H, R_3 = CH_3$
7. $R_1 = CH_3, R_2 = R_3 = H$
8. $R_1 = R_3 = H, R_2 = CH_3$
9. $R_1 = R_3 = CH_3, R_2 = H$

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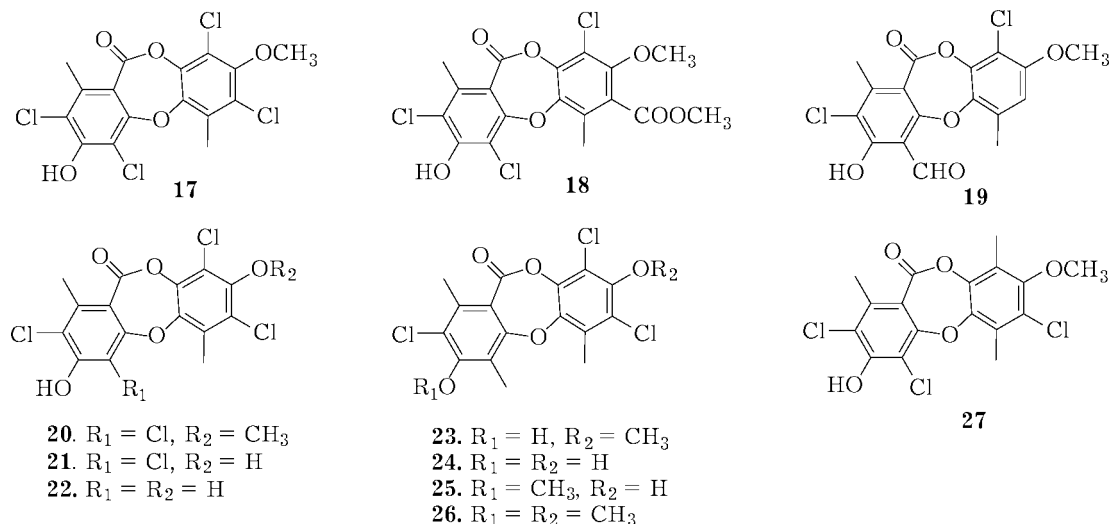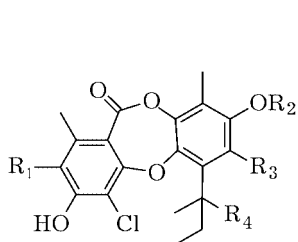**14.** R = n-C$_3$H$_7$
15. R = n-C$_5$H$_{11}$

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japonica [9, 25, 52] and *Eriodeerma chilense* [53]. The structure of pannarin (**19**) was additionally investigated by other authors [54, 55]. Three depsidones compounds: nidulin (**20**), nornidulin (**21**) and dechloronornidulin (**22**) were initially discovered in fungi belonging to the *Aspergillus* genus: *A. nidulans* [56–58], *A. ustus* [59, 60], *A. unguis* [61], while nidulin (**20**) was also discovered in *Emericella unguis* lichen [62, 63].

Vicanicin (**23**), which was initially discovered in *Telischistes flavicans* lichen [64, 65], was later isolated from other species: *Caloplaca* sp. [66, 67], *Psoroma sphinctrinum* [68], *P. allorhizum* [69] and *Erioderma chilense* [70]. Norvicanicin (**24**) [68, 71] and isovicanicin (**25**) [71] are emtabolytes in *Psoroma athrophyllum* [68,

69, 71], while O-methylvicanicin (**26**) is a metabolite of *Erioderma* sp. [71, 72]. The *Caloplaca* sp. [66, 67] lichen generates caploicin (**27**); its structure was confirmed by synthesis [73].

The *Aspergillus unguis* fungus (hyphomycete group *Hyphomycetales)* relates to the most widespread imperfect fungi. Aspergil colonies forming mold coatings of bluish-green colour, or other colours more rarely, are observed on the products of plant origin. A number of toxins, such as haiderin (**28**), roubinin (**29**), shirin (**30**) and nasrin (**31**), are generated by *Aspergillus unguis* fungus [74]. Structurally similar 2-chlorounguinol (**32**), as well as emeguicins A–C (**33**)–(**35**) were detected in *Emericella unguis* lichen [62, 63]. The metabolite 1-chlo-
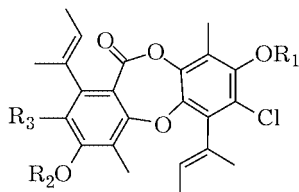

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20. R$_1$ = Cl, R$_2$ = CH$_3$
21. R$_1$ = Cl, R$_2$ = H
22. R$_1$ = R$_2$ = H

23. R$_1$ = H, R$_2$ = CH$_3$
24. R$_1$ = R$_2$ = H
25. R$_1$ = CH$_3$, R$_2$ = H
26. R$_1$ = R$_2$ = CH$_3$

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28. $R_1 = R_2 = R_3 = H$, $R_4 = OH$
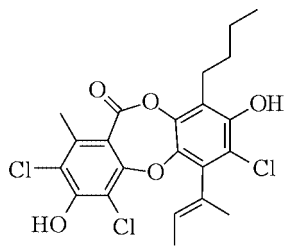29. $R_1 = R_3 = H$, $R_2 = CH_3$, $R_4 = OH$
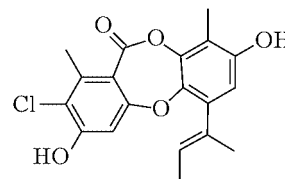30. $R_1 = R_3 = Cl$, $R_2 = R_4 = H$

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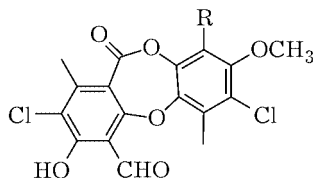
33. $R_1 = R_2 = R_3 = H$
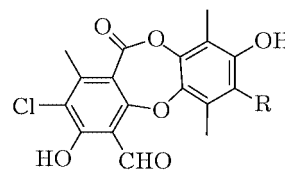34. $R_1 = R_3 = H$, $R_2 = CH_3$
35. $R_1 = CH_3$, $R_3 = Cl$, $R_2 = H$

36. $R = H$
37. $R = CH_3$

38. $R = H$
39. $R = Cl$

ropannarin (36) known also as argopsin, with its structure established by chlorination of pannarin (19) [75], was isolated from *Agropsis megalospora* lichen. This metabolite was also discovered in such lichens as *Agropsis friesiana* (otherwise called *Agropsis megalospora*) [55], *Erioderma chilense* [53, 70], *E. phaeorhizym* and *E. tomentosum* [71]. Eriodermin (37) was discovered in *Erioderma phyyscioides* [76] and *E. phaeorhizum* [71]. The *E. chilense* lichen generates norpannarin (38) and norargopsin (39) [53].

Physcosporin (40), a new chlorine-containing depsidones, was isolated from water-methanol extracts of *Pseudocyphellaris physciospora* lichen growing in Canada [77] and in Europe [78]. It was also discovered among metab-

olites of *P. granulata* [78, 79] and *P. flaveolata* [79]. Physcosporin (40), hypophyscosporin (41) and 3-O-methyl-physcosporin (42) are present among the extractives from *Erioderma phaeorhizum* lichen [71]. The Australian lichen *Lecidea* sp. generates lecideoidin (43) and its dechlorinated analogue 3'-dechlorolecideoidin (44) [22]. Depsidones, namely, dechlorolecideoidins (45) and (46), along with scencidin (47) and compound (48), were discovered in *Buellia canescens* [80, 81]. 3-O-demethylscencidin (48) and O-methyldiploicin (49) were isolated from Australian lichen *Diploicia canescens* [72].

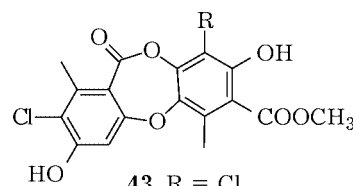Metabolite allorhizin (50) was found in *Psoroma allorhizum* lichen from New Zealand [69];
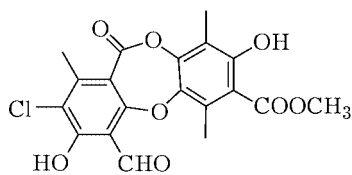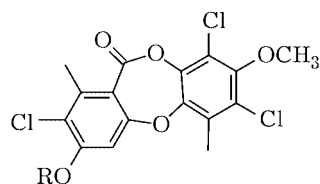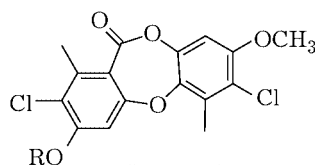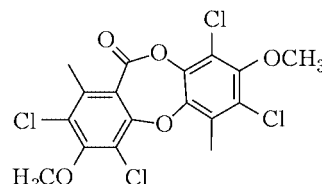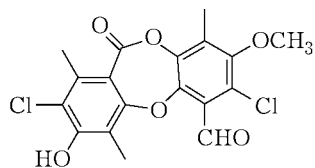
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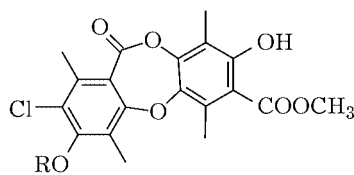
41. $R = H$
42. $R = CH_3$

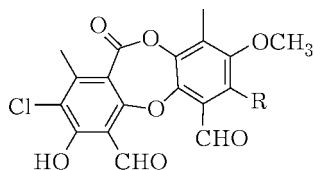43. $R = Cl$
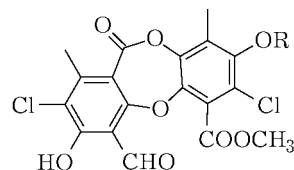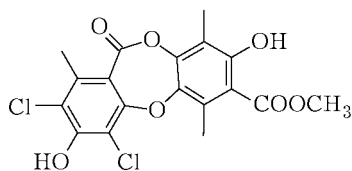44. $R = H$

45. $R = H$
46. $R = CH_3$

47. $R = CH_3$
48. $R = H$

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51. R = H
52. R = Cl

53. R = H
54. R = CH₃

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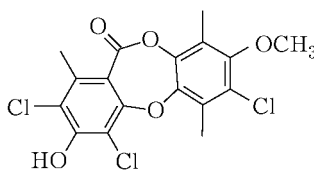
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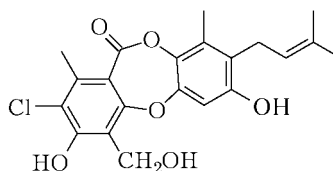
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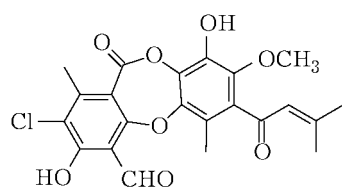
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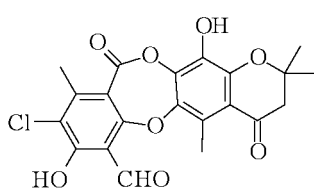**59**

four depsidones, i. e., phyllopsorin (**51**) and chlorophyllopsorins (**52**)–(**54**), are vital products of the Australian lichen *Phyllopsora coralline* [82]. The *Lecanora gangaleoides* lichen synthesizes leonidin (**55**) [33], while *Fulgensia* sp. generates metabolite fulgidin (**56**) [83, 84].

The *Chaetomium mollicellum* fungus, which belongs to the Chaetomiaceae family, is a typical saprophyte inhabiting plant residues and taking active part in their decomposition. Chlorine-containing depsidones called mollicellins D (**57**), E (**58**) and F (**59**) are synthesized by *Chaetomium mollicellum* fungus [85].

Two metabolites, buellolide (**60**) and canescolide (**61**), which are lactones, are considered as depsidones derivatives which can be formed during their catabolism. These anomalous components are discovered in the Australian lichen *Buellia canescens* [80].
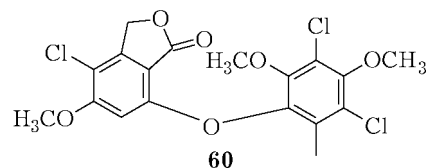
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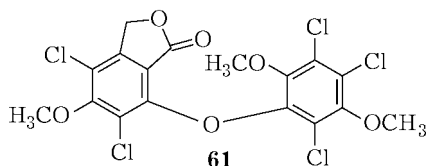
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FUNGI PHENOL METABOLITES

About 800 different metabolites were discovered in fungi; however, only a small part of them contained halogen atom. As a rule, it was chlorine. The majority of chlorine-containing metabolites of parasitic fungi are toxic not only for plants but also for animals and for people.

A series of metabolites ilicolins A (**62**), C (**63**), D (**64**), F (**65**) and E (**66**) are generated by parasitic fungi *Ascochyta viciae* [86–88], *Fusarium* sp. [89] and *Cylindrocladium ilicicola* [90–92]. For instance, fungi of the genus *Ascochyta* cause extremely dangerous disease in above ground organs of plants: leaves, stems and seeds. The developing yellowish-brown spores strike mainly legumes, in particular pea. On the contrary, fungi of the genus *Fusarium* strike rhizome of many plants, in particular cotton plant. Fungi of the genus *Cylindrocladium* strike crucifers [93].

Another parasitic fungus species, *Nectria coccinea*, which causes root rot and stem affection in different plants, generates chloronectrine (**67**) [94], while *Ascochyta viciae* fungus generates compound (**68**) [95].

Pathogenous fungus *Colletotrichum nicotianae* which affects tobacco plant generates such chlorine-containing metabolites as colletochlorines
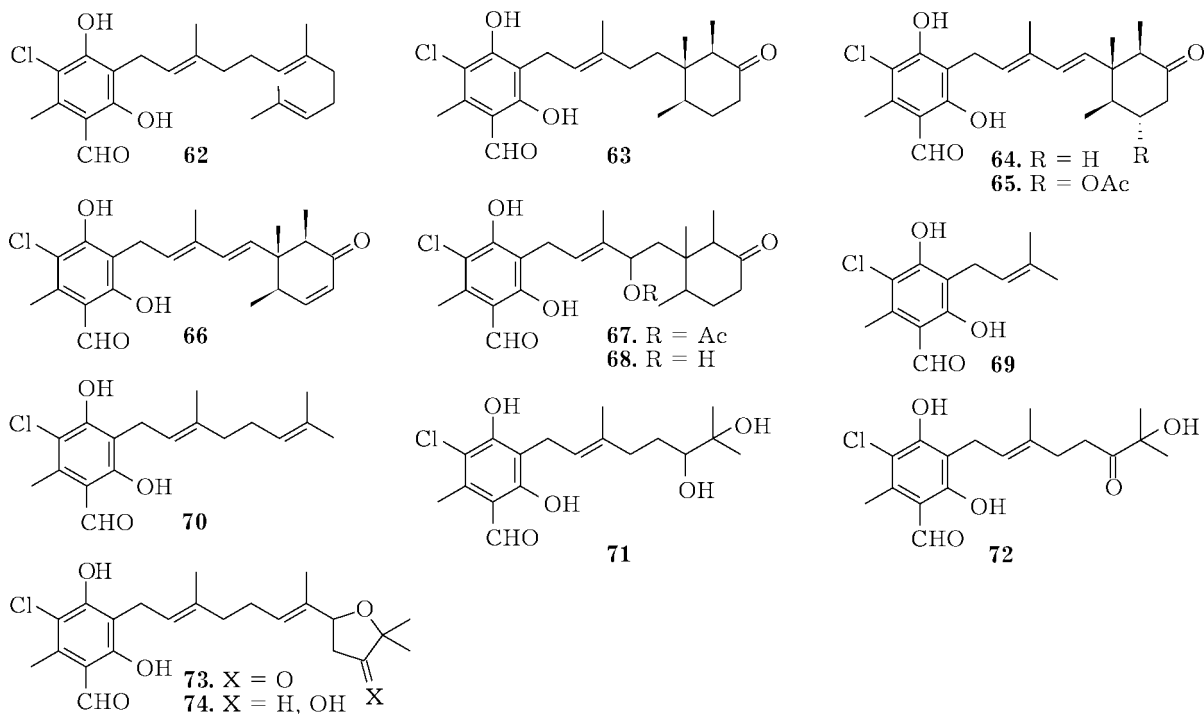
D (**69**), B (**70**), A (**71**) and C (**72**) [96–98]. Ascofuranone (**73**) and ascofuranol (**74**) were discovered in *Ascochyta viciae* [99].

Ascochlorin (**64**) was discovered in *Acremonium luzulae* fungus [100]. Fungi *Strobiluris tenacellus* and *Mycena* sp. growing on rotten stubs of conifers and deciduous trees generate one and the same metabolite strobilurin (**75**) [101]. The history of strobilurin discovery is very instructive. More than 20 years ago, strobilurins A and B, powerful fungicide compounds, were isolated from mycelium of *Strobiluris mucida* Basidiomycete. This stimulated investigations of secondary metabolites and various fungi, including those parasitizing on trees. Among them, chlorine-containing metabolites were also discovered. At present, synthetic an-

alogues of strobilurins are developed and manufactured on industrial scale as the protective means for agricultural plants.

Two chlorine-containing derivatives of naphthalic acid (**76**) and (**77**) were found in parasitic fungus *Verticillium lamellicola* which

85. R = H
86. R = Ac

87. R = H
88. R = Ac

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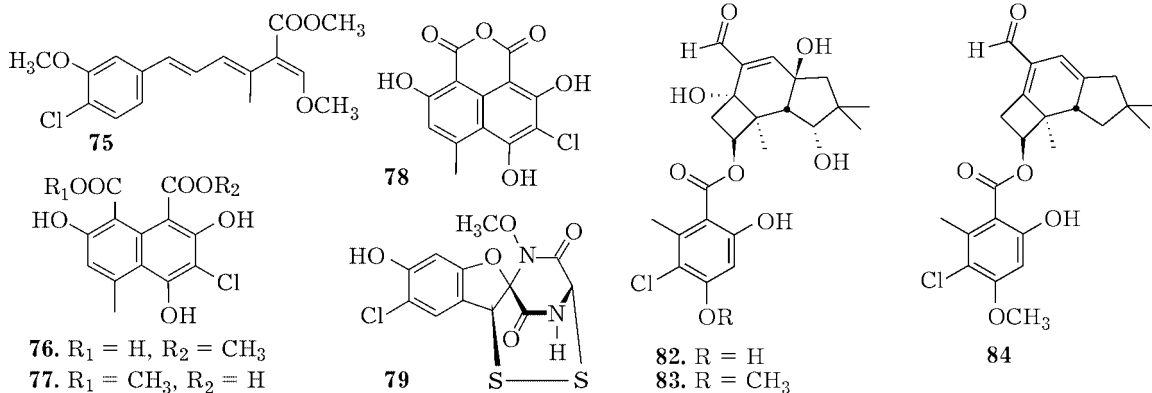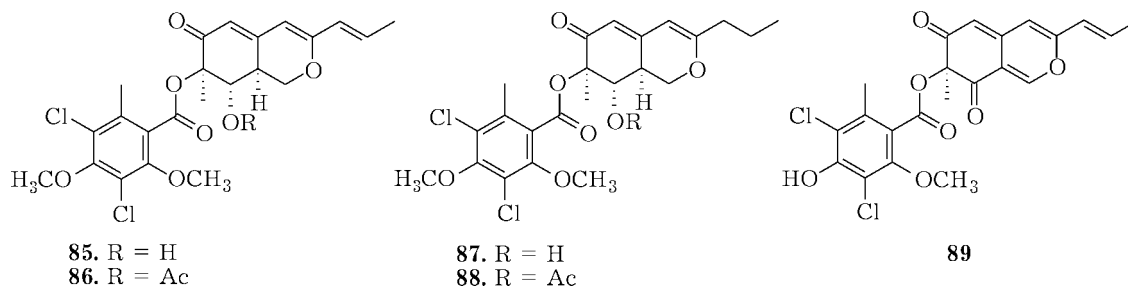
uses many plants and even fungi as substrates [102]. Metabolite (72) was found in extracts of *Scolecobaasidiella avellanea* fungus [103].

A series of new antibiotics (**79**)–(**84**) was isolated from some cultivated fungi species. Chlorine-containing antibiotic A30641 with unusual structure, which is also called aspirochlorin (**79**), is generated by several fungi species belonging to the genus *Aspergillus*: *A. tamarii* [104], *A. flavus* [105] and *A. oryzae* [106]. The structure of aspirochlorin (**79**) was established by means of X-ray structural analysis [107]; synthesis of the antibiotic was carried out in full [108]. Aspirochlorin (**79**) exhibited high antibacterial activity against pathogenous fungus

Candida albicans. It inhibits selectively the synthesis of some proteins, in particular the synthesis of RNA; however, the mechanism of its action is not quite clear yet.

Antibiotics (**80**)–(**84**), possessing the structure of the esters of 2-oxa-4-methoxy-5-chloro-6-methyl benzoic acid with sesquiterpenic alcohols of the new structural type, are generated by *Armillaria mellea* fungus which is called honey mushroom. The first compound identified among the indicated antibiotics was armillaridin (**80**) [110]. It was followed by isolation of melleolide D (**81**) [11, 112], melledonales B (**82**), C (**83**) [113], then armillaricin (**84**) [114]. All these compounds exhibit antibacterial activity.

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94. R = H
95. R = OH

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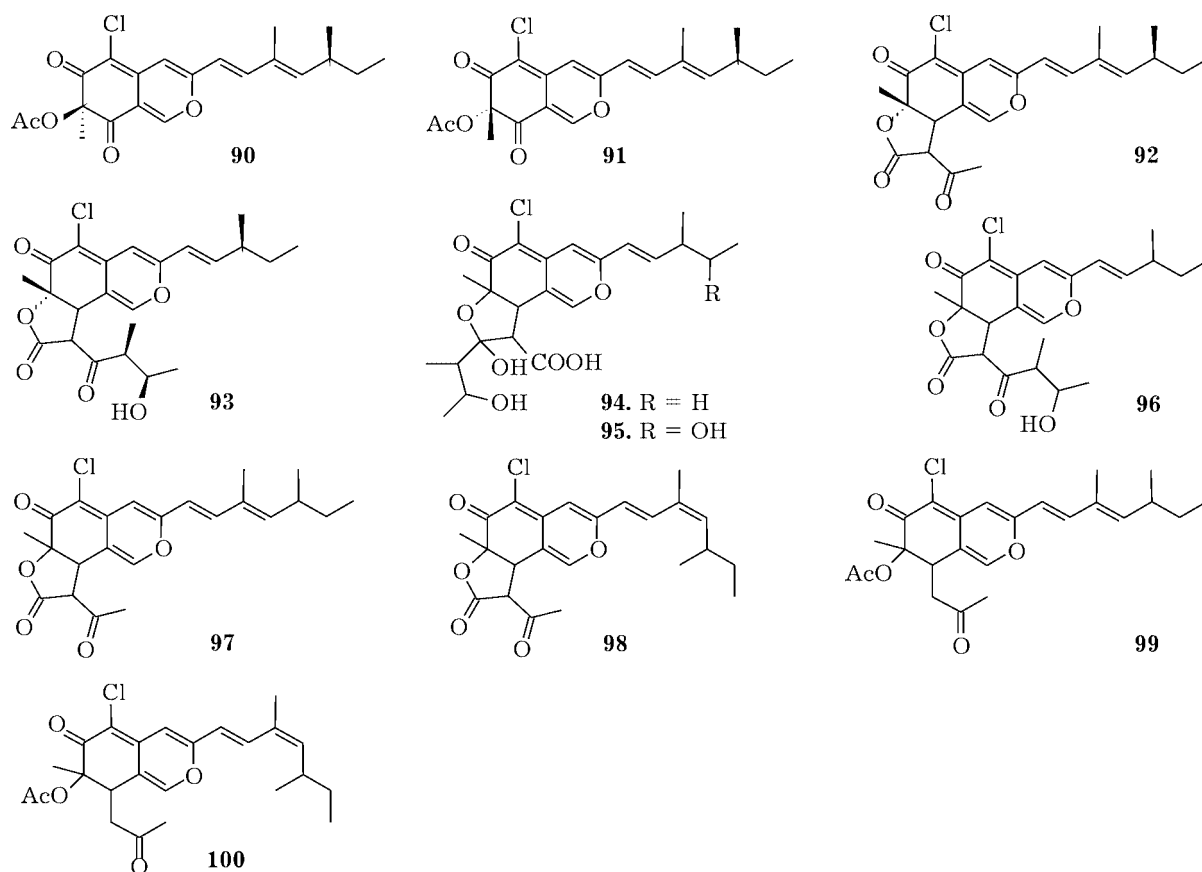
An interesting group of fungous metabolites is united by the presence of 3-oxabicyclo[4,4,0]deca-4,6-dien-8-one or 3-oxabicyclo-[4,4,0]deca-1,4,6-trien-8-one fragments. For instance, soil fungus *Emericella falconensis* collected in Venezuela generates metabolites: falconensins A (**85**), C (**86**), B (**87**), D (**88**) [115], and falconensin H (**89**) [116]. All of them are esters of 2-methoxy-3,5-dichloro-4-oxy-6-methyl benzoic acid.

Metabolites of *Penicillium* and *Chaetomium* fungi are characterized by the presence of trienic bicyclic fragment. Sclerotiorin (**90**) was isolated from *Penicillium sclerotiorum* fungus [117, 118]; its 7-epimer (**91**) and rubrotiorin (**92**) were isolated from *P. nirayamae* [119–123]. The *Chaetomium globossum* fungi generate azaphilones A−D (**93**)−(**96**) [124]. Isochromophilones (**97**)−(**100**) were isolated from cultural liquid of *Penicillium* sp. fungus; it inhibits the growth of HIV dr-120-CD4 cells [125].

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