Natural Chlorine-Containing Xanthones

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Abstract

Chlorine-containing xanthones were found in fungi, higher plants, and lichens. The structures of more than 70 compounds are considered, and data about their biological activity are given.

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INTRODUCTION

Xanthones are secondary metabolites found in the families of higher plants such as Asteraceae, Betulaceae, Caryophyllaceae, Clusiaceae, Gentianaceae, Gesneriaceae, Guttiferae, Iridaceae, Loganiaceae, Lytraceae, Moraceae, Podostemaceae, Polygalaceae, Polygalaceae [1, 2], in some species of fungi: *Aspergillus versicolor, Bipolaris sorokinian, Helminthosporium ravenelii, H. turcicum, Penicillium patulum* [2–4], and in lichens [1, 2, 5, 6].

While xanthones have a symmetric structure, the carbon atoms vary depending on the nature of biosynthesis. Thus carbon atoms 1–4 (ring A) are associated with biosynthesis from the acetate, and carbon atoms 5–8 (ring B) result from biosynthesis according to the known route followed by shikimic acid [7]. The numbering of the carbon atoms in xanthones is based on the structural skeleton of xanthen-9-one (**1**) [8]. If ring B is oxidized, the numbering of oxidized xanthones is preserved for ring A [7].

All of the currently known natural xanthones form five major groups: 1) simple oxidized xanthones, 2) xanthone glycosides, 3) prenyl(isopentyl)-containing and related xanthones, 4) xanthonolignoids, and 5) mixed xanthones [9]. Each of these major groups may be further subdivided into minor xanthone groups [1, 2, 5–9].

Xanthones are specific organic substances occasionally used in plant chemotaxonomy [1, 2].

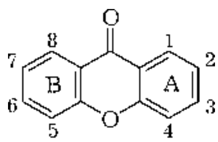

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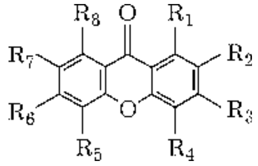
TABLE 1

Monochloroxanthones



Xanthone No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
2	OH	Cl	OH	H	H	OH	H	Me
3	OH	Cl	OH	H	H	OMe	H	Me
4	OH	Cl	OMe	H	H	OMe	H	Me
5	OH	H	OH	Cl	H	OH	H	Me
6	OH	H	OH	Cl	H	OMe	H	Me
7	OH	H	OH	H	Cl	OH	H	Me
8	OH	H	OH	H	Cl	OMe	H	Me
9	OH	H	OMe	H	Cl	OH	H	Me
10	OH	H	OMe	H	Cl	OMe	H	Me
11	OH	H	OH	H	H	OH	Cl	Me
12	OH	H	OH	H	H	OMe	Cl	Me
49	OH	H	Me	OMe	H	H	Cl	OH
50	OMe	H	Me	OMe	H	H	Cl	OH
51	OMe	H	Me	OMe	Cl	H	H	OH
52	OH	H	Me	OMe	Cl	H	H	OH

Of greatest interest, however, are the pharmacological properties of xanthones [10]. A number of publications have reported that they exhibit antibacterial, antifungal, and anticancer activities [1, 2]. They also inhibit the development of the human immunodeficiency virus [11, 12].

Of almost 800 xanthones found in nature, only 68 are chlorine-containing ones. These are primarily synthesized by lichens [1, 2, 5, 6, 13, 14] and are found in several species of fungi and plants [13, 14].

XANTHONES WITH AN UNCHANGED SKELETON

The first chlorine-containing xanthone, 2-chloronorlichexanthone (**2**), was found in 1966 in the lichen *Lecanora rupicola* [15]. Later it was isolated from the lichens *Lecanora* sp.: *L. populicola*, *L. salina* и *Lecidella vorax* [16]. 6-O-Methyl-2-chloronorlichexanthone (**3**) is present in extracts from the lichens *Lecanora salina*, *Pertusaria cicatricosa* [16] and *P. sulphurata* [17]. 2-Chlorolichexanthone (**4**) was found in *Lecanora* sp., *Pertusaria cicatricosa* [16] and *P. sulphurata* [17]. The lichen *Lecanora straminea* contains 4-chloronorlichexanthone (**5**), 6-O-methyl-5-chloronorlichexanthone (**7**) [18–21], and 2,4-dichloronorlichexanthone (**13**) [16, 21]. 6-O-Methyl-4-chloronorlichexanthone (**6**) is present in the lichen *Pertusaria sulphurata* [16].

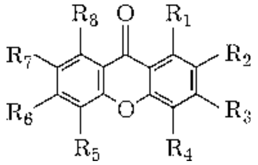
The lichen *Lecanora contractula* contains 5-chloro-6-O-methylnorlichexanthone (**8**) and 5-chlorolichexanthone (**10**) [16]. Other compounds isolated from the lichens of the same genus include vinetorin (**9**) (*L. vinetorum*) [16, 22], 7-chloronorlichexanthone (**11**) (*L. populicola*) [16], and 7-chloro-6-O-methylnorlichexanthone (**12**) (*L. populicola* and *L. salina*) [16]. 2,4-Dichloronorlichexanthone (**13**) [21] was isolated from the lichen *Lecidella vorax*.

Thiophaninic acid (**14**) is synthesized by several species of lichen: *Dimelaena* sp. [23], *D.* cf. *australiensis* [16], *Pertusaria* sp. [24], *P. flavicans* [25], *P. flavicunda* [26] and *P. sulphurata* [17].

2,4-Dichlorolichexanthone (15) was found in extracts from the lichens *Dimelaena* cf. *australiensis* [16], *Pertusaria* sp. [27] and *P. cicatricosa* [16]. 2,5-Dichloronorlichexanthone (**16**) was found in the lichens *Buellia* sp. [28], *Lecanora*

TABLE 2

Dichloroxanthones



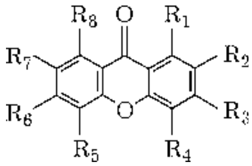
Xanthone No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
13	OH	Cl	OH	Cl	H	OH	H	Me
14	OH	Cl	OH	Cl	H	OMe	H	Me
15	OH	Cl	OMe	Cl	H	OMe	H	Me
16	OH	Cl	OH	H	Cl	OH	H	Me
17	OH	Cl	OH	H	Cl	OMe	H	Me
18	OH	Cl	OMe	H	Cl	OH	H	Me
19	OH	Cl	OMe	H	Cl	OMe	H	Me
20	OH	Cl	OH	H	H	OH	Cl	Me
21	OH	Cl	OH	H	H	OMe	Cl	Me
22	OH	Cl	OMe	H	H	OH	Cl	Me
23	OH	Cl	OMe	H	H	OMe	Cl	Me
24	OH	H	OH	Cl	Cl	OH	H	Me
25	OH	H	OH	Cl	Cl	OMe	H	Me
26	OH	H	OMe	Cl	Cl	OMe	H	Me
27	OH	H	OH	Cl	H	OH	Cl	Me
28	OH	H	OH	H	Cl	OH	Cl	Me
29	OH	H	OMe	H	Cl	OH	Cl	Me
46	OH	H	Me	OMe	Cl	H	Cl	OH
47	OMe	H	Me	OMe	Cl	H	Cl	OH
48	OH	H	Me	OH	Cl	H	Cl	OH
53	Me	OH	Me	H	Cl	H	Cl	OH
54	Me	OMe	Me	H	Cl	H	Cl	OH

broccha, *Lecidella meiococca* and *L. vorax* [16]. 2,5-Dichloro-6-O-methylnorlichexanthone (**17**) was isolated from *Dimelaena* sp. [23], *D.* cf. *australiensis*, *Pertusaria cicatricose* and *Lecanora contracta* [16]. The rarely occurring 3-O-methyl-2,5-dichloronorlichexanthone (**18**) was also found in *Dimelaena* cf. *australiensis* [16], *Lecanora* sp. [29]. 2,5-Dichlorolichexanthone (**19**) was isolated from the lichens *Pertusaria* sp., *Pertusaria aleianata* and *Pertusaria cicatricose* [16, 27].

2,7-Dichloronorlichexanthone (**20**) was extracted from the lichens *Buellia* sp. [28], *Lecanora* sp., *L. behringii* [16], *L. broccha* [16, 28], *L. populicola*, *L. salina*, and *Lecidella meiococca* [16]. 2,5-Dichloro-6-O-methylnorlichexanthone (**21**) was found in the lichens *Lecanora* sp., *L. behringii*, *L. populicola*, *L. salina* [16]; 2,7-dichloro-3-O-methylnorlichexanthone (**22**), in the lichens *Lecanora* sp., *L. behringii*, *L. salina* [16]. The species *Buellia glaziouana* [30], *Lecanora* sp., *L. behringii*, *L. populicola*, *L. salina* [16], and *Lopadium* sp., *Pertusaria* sp. [31] contained 2,7-dichlorolichexanthone (**23**), while 4,5-dichloronorlichexanthone (**24**) was revealed in *Lecanora flavo-pallescens* [32], *L. straminea* [18–20, 33], *Lecidella asema* [28], *L. vorax* [16], *Micarea austroternaria* [32], and *M. isabellina*, *Pertusaria pycnothelia* [16]. 4,5-Dichloro-6-O-methylnorlichexanthone (**25**) was found in only two Australian lichens: *Dimelaena* sp. [23] and *D.* cf. *australiensis* [16]. 4,5-Dichlorolichexanthone (**26**) was isolated from four species: *Buellia glaziouana* [18–20, 33], *Dimelaena* cf. *australiensis* [16], *Lecanora straminea* [18–20, 33], and *Pertusaria cicatricosa* [16]. 4,7-Dichloronorlichexanthone (**27**) was found in only two species belonging to the genus Lecidella: *Lec. asema* [28] and *Lec. meiococca* [16]. The

TABLE 3

Tri- and Tetrachloroxanthones



Xanthone No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
30	OH	Cl	OH	Cl	Cl	OH	H	Me
31	OH	Cl	OH	Cl	Cl	OMe	H	Me
32	OH	Cl	OMe	Cl	Cl	OH	H	Me
33	OH	Cl	OMe	Cl	Cl	OMe	H	Me
34	OMe	Cl	OMe	Cl	Cl	OMe	H	Me
35	OH	Cl	OAc	Cl	Cl	OAc	H	Me
36	OH	Cl	OH	Cl	H	OH	Cl	Me
37	OH	Cl	OH	H	Cl	OH	Cl	Me
38	OH	Cl	OMe	H	Cl	OH	Cl	Me
39	OH	Cl	OMe	H	Cl	OMe	Cl	Me
40	OH	H	OH	Cl	Cl	OH	Cl	Me
41	OH	H	OH	Cl	Cl	OMe	Cl	Me
42	OH	H	OMe	Cl	Cl	OH	Cl	Me
43	OH	Cl	OH	Cl	Cl	OH	Cl	Me
44	OH	Cl	OH	Cl	Cl	OMe	Cl	Me
45	OH	Cl	OMe	Cl	Cl	OH	Cl	Me

lichens *Buellia* sp. [28], *Lecanora broccha* [16, 28], *Lecidella asema, Lec. subalpicida* [28] and *Lec. vorax* [16] contain 5,7-dichloronorlichexanthone (**28**); the lichens *Lecanora broccha, Lec. vinetorum*, [16, 28], *Lecidella meiococca* and *Lec. vorax* [16] produce 5,7-dichloro-3-O-methylnorlichexanthone (**29**).

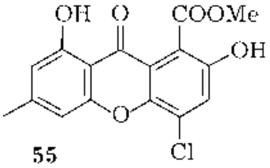
A new xanthone, arthothelin (**30**), was first isolated from the lichen *Arthothelium pacificum* [26]. Later it was found in 16 other species: *Buellia* sp. [28, 34], *Dimelaena* cf. *australiensis* [16], *Lecanora broccha* [34], *L. flavo-pallescens* [32], *L. pinguis* [26], *L. reuteri* [35], *Lecanora straminea* [36], *L. sulphurata* [16, 32], *Lecidella meiococca* [16] и *Lec. vorax* [24], *Micarea austroternaria* [32], *M. isabellina* [16], *Pertusaria cicatricosa* [16] and *Tapellaria epiphylla* [31]. 6-O-Methylfluorothelin (**31**) and thuringione (**32**) were isolated from the lichens *Dimelaena* sp. [23, 37], *D.* cf. *australiensis*, *Micarea isabellina, Pertusaria pycnothelia* [16], and *Lecidea pinguis* [24], *L. carpathica* [37], respectively.

2,4,6-Trichlorolichexanthone (**33**) and 1,3,6-tri-O-methylarthothelin (**34**) were extracted from two species of lichen: *Dimelaena* sp. and *D.* cf. *australiensis* [23, 38]. Compound (**33**) was also found in two species of Australian lichen: *Pertusaria* sp. [27] and *P. cicatricosa* [16].

Erythrommone (**35**) was isolated from only one species: *Haematomma erythromma* [27, 39], while 2,4,7-trichloro-norlichexanthone (**36**) was found in two species of the genus *Lecanora*: *L. flavo-pallescens* [30, 32] and *L. sulphurata* [16, 30, 32].

Isoarthothelin (**37**) was isolated from *Buellia* sp. [28, 34], *Lecanora broccha* [16, 28, 34], *L. sulphurata* [16, 32], *Lecidella meiococca* [16], *L. subalpicida* [28] and *L. vorax* [16]. 3-O-Methyl-2,5,7-trichloronorlichexanthone (38) was found in *Lecanora broccha* [16, 28], *L. capistrata* [30], *Lecidella meiococca* [16], *L. subalpicida* [28] and *Lecidella vorax* [16].

2,5,7-trichloronorlichexanthone (**39**) was found in two species: *Dimelaena* cf. *australiensis* and *Lecanora broccha* [16]. 6-O-Methylasemone (**41**) was isolated from one species: *Pertusaria pycnothelia* [16]. Asemone (**40**) and 3-O-methylasemone (**42**) were extracted from



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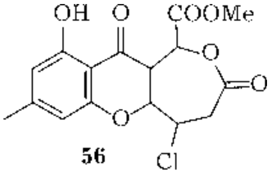

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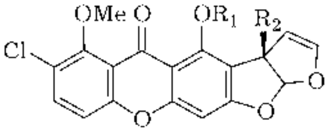
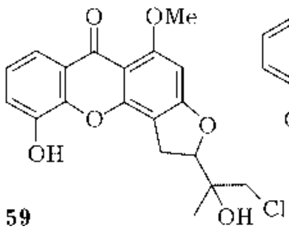


57. R_1 = Me, R_2 = H
58. R_1 = H, R_2 = OH



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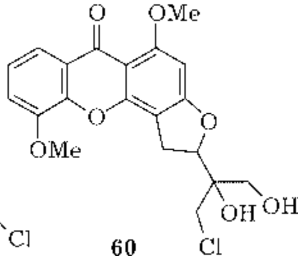

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Lecanora broccha [16]; (**40**) was additionally found in *Lecidella asema* [28], *Micarea isabellina* [16, 32], *Pertusaria pycnothelia* [16], while (**42**) was also identified in *Lecidella meiococca* [16].

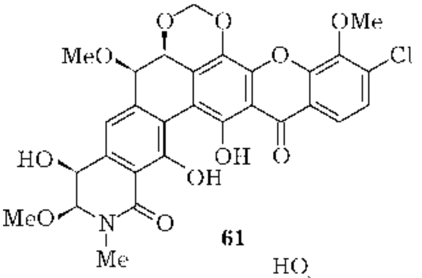
Thiophanic acid (**43**) was extracted from 12 species of lichen: *Buellia* sp. [28], *Lecanora flavo-pallescens* [32], *L. rupicola* [15], *L. straminea* [36], *L. sulphurata* [16,32], *Lecidella asema* [28], *L. meiococca* [16], *L. quernea* [24], *L. vorax* [16], *Micarea austroternaria* [32], *M. isabellina, Pertusaria pycnothelia* [16]. 6-O-Methylthiophanic ether (**44**) was found in only one species: *Micarea isabellina* [16], while 3-O-methylthiophanic ether (**45**) was contained in *Lecidella meiococca* [16].

Thiophanic acid (**43**), isolated from the lichen *Lecanora rupicola* [15], is the first member of the large group of xanthones (**2**)–(**45**). This acid (**40**) and other xanthones from this series were synthesized independently by different research groups [16, 18–20, 27]. These are related compounds, which are formed in nature from polyketides via the polyhydroxybenzophenone intermediate [5, 6].

A comparatively small group of biogenically related xanthones know as ravenelines was discovered in the Australian lichen *Rinodina thiomela* and *R. lepida*. These are thiomelin (**46**) and its analogs (**47**)–(**54**) [41, 42].

OTHER COMPOUNDS WITH A XANTHONE FRAGMENT IN THE MOLECULE

About a dozen chlorine-containing compounds with a classical or modified xanthone fragment in a molecule have been isolated and identified. For example, the parasitic fungus *Monilinia fructicola*, affecting the cherry-tree, produces not only 4-chloropinselin (**5**), but also the product of its oxidative transformation – chloromonilicin (**56**) [43–46]. Another parasitic fungus, *Aspergillus ustus*, whose home is South Africa, synthesizes two new metabolites: austocystin A (**57**) and austocystin C (**58**) [47, 48].



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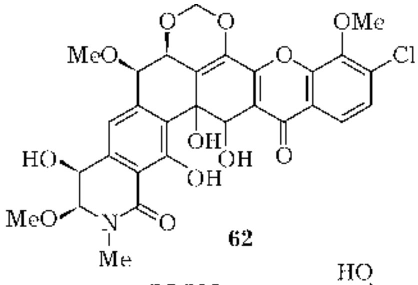

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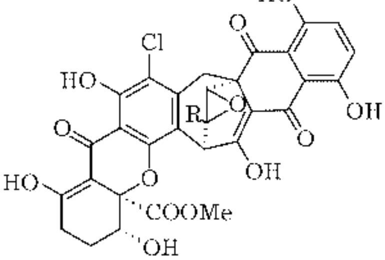
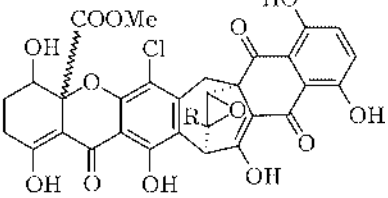


63. R = Me
64. R = CH_2OH



65. R = Me, α-COOMe
66. R = CH_2OH, α-COOMe
67. R = Me, β-COOMe
68. R = CH_2OH, β-COOMe

The African plant *Psorospermum febrifugum* (family Guttiferae) contains two highly toxic xanthones: psorospermin chlorohydrin (**59**) and its analog (**60**) [49, 50]. The latter shows high activity against the 9PS cancer cells (ED_{50} < 0.01 ng/ml) [50].

Lysolipin I (**61**), produced by the microorganism *Streptomyces violaceoniger*, is a derivative of an unstable antibiotic lysolipin X (**62**) [51, 52]. Biosynthesis of these interesting antibiotics was reported in [53].

The parasitic beetroot fungus *Cercospora beticola*, occurring worldwide, produces a series of interesting complex metabolites: beticolin-1 (**63**), 2 (**64**), 3 (**65**), 4 (**66**), 6 (**67**), and beticolin-8 (**68**) [54–59]. Beticolin-2 (**64**) was also isolated by another research group and was named "cebetin A" [58].

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