# Dibenzofurans and derivatives from lichens and ascomycetes


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| Complete List of Authors: | Millot, Marion; Université de Limoges, Faculté de Pharmacie<br>Dieu, Amandine; Université de Limoges, Faculté de Pharmacie<br>Tomasi, Sophie; Université de Rennes 1, Institut des Sciences Chimiques de Rennes |
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# Dibenzofurans and derivatives from lichens and ascomycetes

**Marion Millot,*[a] Amandine Dieu[a] and Sophie Tomasi[b]**

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When looking for dibenzofuran in the biochemical databases, most papers and reviews deal with pollutants and polychlorinated dibenzofurans like dioxins. But dibenzofurans are also biosynthetized by a wide diversity of organisms in nature. Even if dibenzofurans from natural sources represent a small class of secondary metabolites, compared to flavonoids, xanthones or terpenoids, they are often endowed with interesting biological properties which have been recently described. This review provides an update on papers describing dibenzofurans from lichens, ascomycetes and cultured mycobionts. Other sources, such as basidiomycetes, myxomycetes or plants produce sporadically interesting dibenzofurans in terms of structures and activities.

## Introduction

Dibenzofurans have been reported in the plant kingdom, marine organisms, edible mushrooms or myxomycetes (slime molds)[1-7] but these compounds are mainly biosynthesized by lichens (symbiotic association between fungi and algae or cyanobacteria) and ascomycetes. They are typically polyfunctionalized and occur as either totally aromatized or as partially saturated derivatives. Dibenzofurans were first identified in lichens but emerging research has increased their isolation from filamentous fungi and their biological evaluation. Usnic acid is the most common and the oldest known dibenzofuran derivative. Knop isolated usnic acid in 1844 in the early stages of organic chemistry. Its extraction from lichens was described by Hesse in 1898 from the Genus *Usnea*. Didymic acid, was the first aromatic dibenzofuran found in lichens by Shibata in 1944 and its structure was confirmed forty years later by Shibata and Iitaka thanks to X-Ray analysis of its oxidation product. Strepsilin was identified the same year and porphyrilic acid in 1954. Antibacterial effects of these derivatives have been studied since their discovery between 1948 and 1957. During the nineteen century, Huneck and Elix largely contributed to the development of research on lichens and described isolation and synthesis of many dibenzofurans.[8-10] Concerning ascomycetes, the first dibenzofuran was isolated in 1992 from *Cercosporidium henningsii*,[11] the causative agent of brown spot disease, and starting in the 21st century, isolation of these compounds has greatly increased. Many reviews focus on usnic acid, the most common dibenzofuran found in lichens.[12-13] However the literature on dibenzofurans is poor. For this reason, this review attempts to address the existing omissions and will provide structural description, biogenesis, sources, physical properties and bioactivities of the whole group.

## Classification

The dibenzofurans family could be split into the following categories based upon their structural characteristics: first into dibenzofurans monomers and dimers and then into three subclasses based upon the level oxidation of the C ring: fully aromatic, dihydrodibenzofurans and tetrahydrodibenzofurans. The numbering of the dibenzofuran nucleus is in accordance with IUPAC recommendations (Fig. 1).

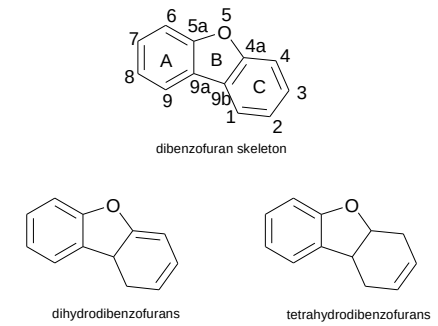



**Fig.1** Numerotation and classification of dibenzofurans.

### Monomeric dibenzofurans

The majority of dibenzofurans reported from lichens and fungi have a monomeric structure. With more than 90 different structures, this group exhibits a wide chemical diversity.

Aromatic dibenzofurans represent the largest group with 50 different structures. Structural diversity results from various substitutions on rings A and C.

Dihydrodibenzofurans are mainly represented by usnic acid and its derivatives. The introduction of a methyl group on the ring junction between B/C leads to the existence of enantiomers. Some of them contain nitrogen atoms.

Tetrahydrodibenzofurans are poorly represented and documented. Two groups can be distinguished following the stereochemistry of the B/C ring junction. Few derivatives have been described and their biological properties remain unexplored.

### Dimeric dibenzofurans

This group is poorly represented with only two derivatives isolated from cultured mycobionts. The linkage between the two dibenzofurans moieties is in position 4-4' or 2-4'.

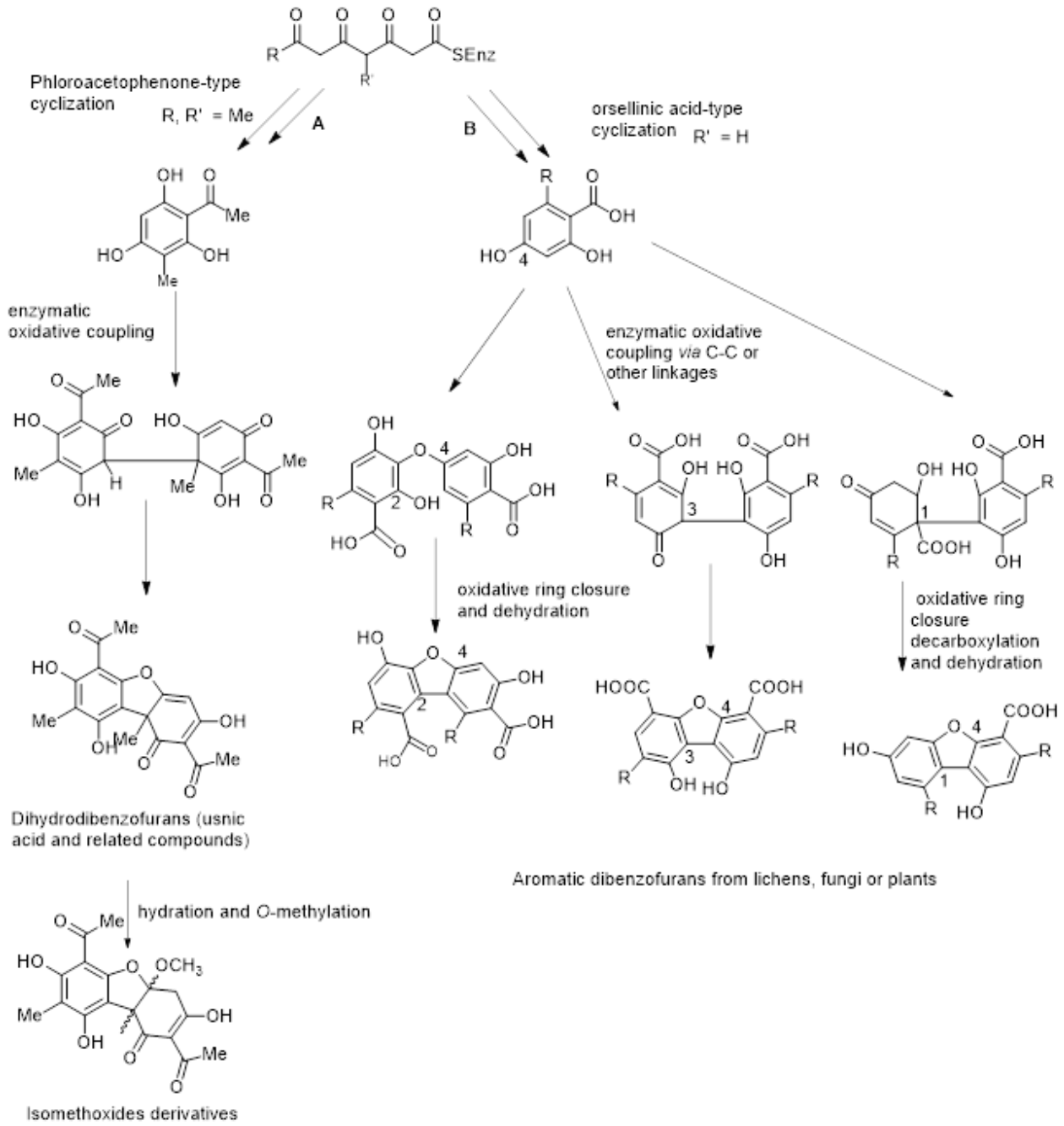



**Fig. 2** Overview of the biosynthesis of dibenzofuran metabolites

## Biogenesis and sources

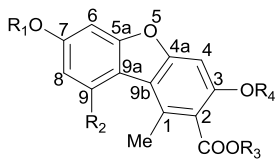
Dibenzofurans are produced *via* the polyketide pathway. The initial step consists of the sequential addition of 3-malonyl-CoA to either acetyl-CoA or another suitable acyl-CoA starting unit, yielding a linear tetraketide backbone. This polyketide leads to either orsellinic acid derivatives *via* aldol condensation or to phloroacetophenone-type compounds through Claisen condensation (Fig. 2). Different pathways lead to the three groups of dibenzofurans. True aromatic dibenzofurans are formed by an oxidative ring closure either between the carboxylic acid group and the hydroxyl group or by C-C linkage of two orsellinic moieties followed by sequential steps of dehydration and even decarboxylation.[8, 14] Recently a biosynthetic gene cluster coding for usnic acid was putatively identified in the fungal partner of *Cladonia uncialis* and its biosynthetic pathway confirmed *via* methyl-phloroacetophenone.[15] Structural diversity is due to final modifications including either additional lactone, more or less oxidable groups, aliphatic chains or acetyl functions. Chlorination is often observed for dibenzofurans from lichens while isoprenyl units are often encountered for dibenzofurans from plants, fungi and myxomycetes due to the possible interconnection with the mevalonate pathway. Dihydrodibenzofurans (found in lichens or fungi) are biosynthetized using two methyl-phloroacetophenone phenol rings followed by an oxidative ring closure. Biosynthesis of tetrahydrodibenzofurans, implies a supplementary step of hydration and *O*-methylation (Fig. 2).[16]

The majority of lichens producing dibenzofurans belonged to the group of chlorolichens containing a green algae as photosymbiont (Table S1, see supporting information).[17-39] Cultured mycobionts of various lichens led to ascomatate derivatives **1c-1e**[19, 40-42] and dibenzofurans **8a**, **8b**, **9a-9e**[43-44]. Other dibenzofurans and derivatives are produced by two marine fungi **10**[45] and **11a-11c**[46], one endophytic fungus (**15a-15b**)[47] or *Aspergillus* sp. (**12a-12b**[48] and **9a**, **13**[49]). Finally *Phoma* or *Cercosporidium* species yield cercosporamide **17c**, usnic acid amide **17d,** a placodiolic acid derivative **21b** and phomodione **22c** while *Mycosphaerella nawae* give mycousnine derivatives **22a-b**.[11, 50-52]

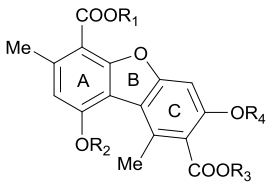
## 1 Dibenzofurans

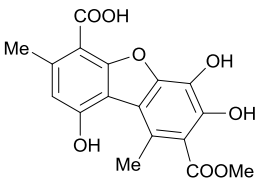
Approximatively 32 dibenzofurans have been isolated from lichens. The presence of a methyl group (or an alkyl chain) in position 1 and a carboxyl group in position 2 on the ring C can occur and characterizes these dibenzofurans which can be divided into four groups based on similarities in the chemical substitutions:

- ascomatic acid and derivatives (**1a-1g**), which can be found in *Bunodophoron patagonicum* (ascomata) and cultured mycobionts of *Evernia esoredosia*, *Usnea orientalis* and *Stereocaulon japonicum*;[19, 40-42]
- pannaric and shizopeltic acids derivatives (**2-3**), isolated from various genera: *Crocynea*, *Lepraria*, *Schizopelte*, *Psoroma*, *Roccella*, *Leproloma*, *Leprocaulon* and *Combea*;[53,17-18, 20-24]
- dibenzofurans bearing aliphatic chain(s) (**4**), mainly described in the genera *Cladonia* and also from *Roccella hypomecha*;[33-37, 54]
- dibenzofurans with a lactone ring (**5-7**) resulted from the cyclization of the carboxylic function in C2[8, 10] and found in numerous genera such as *Letrouitia*, *Phyllospora*, or *Alectoria*.[9, 21, 25-27, 38]



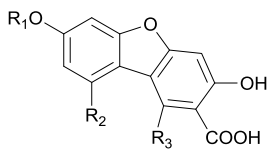
**1a**: $R_1$ = Me, $R_2$ = Me, $R_3$ = H, $R_4$ = Me, Ascomatic acid
**1b**: $R_1$ = Me, $R_2$ = Me, $R_3$ = Me, $R_4$ = Me, Methylascomatate
**1c**: $R_1$ = $R_3$ = H, $R_2$ = Me, $R_4$ = H, Hypostrepsilic acid = Norascomatic acid
**1d**: $R_1$ = $R_3$ = H, $R_2$ = CHO, $R_4$ = H, Hypostrepsilalic acid
**1e**: $R_1$ = $R_3$ = H, $R_2$ = $CH_2OH$, $R_4$ = H, Isostrepsilic acid
**1f**: $R_1$ = $R_2$ = Me $R_3$ = $R_4$ = H, 7-*O*-Methylnorascomatic acid
**1g**: $R_1$ = $R_2$ = Me, $R_3$ = Me, $R_4$ = H, Methyl 7-*O*-methylnorascomatic acid



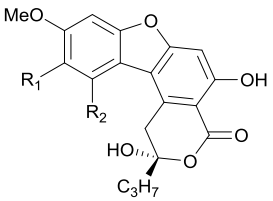


**2a**: $R_1$ = $R_2$ = $R_3$ = $R_4$ = H, Pannaric acid
**2b**: $R_1$ = $R_2$ = $R_3$ = H, $R_4$ = Me, 3-*O*-Methyl pannaric acid
**2c**: $R_1$ = $R_2$ = $R_4$ = H, $R_3$ = Me, 9-Methyl pannarate
**2d**: $R_1$ = Me, $R_2$ = $R_3$ = $R_4$ = H, 15-methyl pannarate
**2e**: $R_1$ = $R_2$ = $R_3$ = $R_4$ = Me, Dimethyl di-*O*-methyl pannarate
**2f**: $R_1$ = H, $R_2$ = $R_3$ = $R_4$= Me, Schizopeltic acid
**2g**: $R_1$ = $R_2$ = $R_4$ = Me, $R_3$ = H, Isoshizopeltic acid
**2h**: $R_1$ = $R_4$ = H, $R_2$ =$R_3$ = Me, H, 3-*O*-Demethylschizopeltic acid

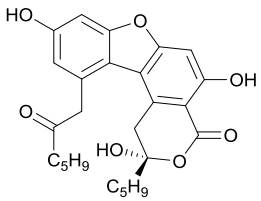
**3**: 9-Methyl 4-hydroxypannarate



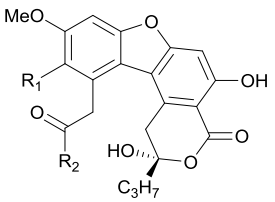
**4a**: $R_1$ = Me, $R_2$ = $C_3H_7$, $R_3$ = $C_5H_{11}$, Didymic acid
**4b**: $R_1$ = Me, $R_2$ = $C_5H_{11}$, $R_3$ = $C_5H_{11}$, Condidymic acid
**4c**: $R_1$ = Me, $R_2$ = $C_5H_{11}$, $R_3$ = $C_3H_7$, Isodidymic acid
**4d**: $R_1$ = Me, $R_2$ = $C_3H_5$, $R_3$ = $C_3H_5$, Subdidymic acid



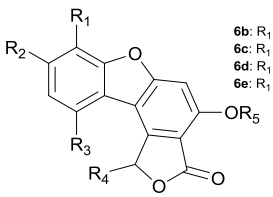
**5a**: $R_1$ = Cl, $R_2$ = Me, Letrouitic acid
**5b**: $R_1$ = H, $R_2$ = $C_3H_7$, Oxodidymic acid
**5c**: $R_1$ = Cl, $R_2$ = $C_3H_7$, 8-Chloroxodidymic acid



**6a**: Haemophaein = furfuraceic acid

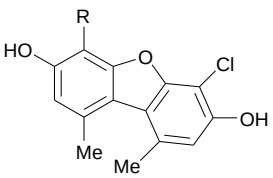


**6b**: $R_1$ = H, $R_2$ = $C_3H_7$, Dioxocondidymic acid
**6c**: $R_1$ = Cl, $R_2$ = $C_3H_7$, 8-Chlorodioxocondidymic acid
**6d**: $R_1$ = H, $R_2$ = Me, Dioxodidymic acid
**6e**: $R_1$ = Cl, $R_2$ = Me, 8-Chlorodioxodidymic acid

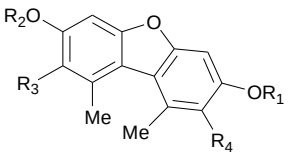


**7a**: $R_1$ = $R_4$ = $R_5$ = H, $R_2$ = OH, $R_3$ = Me, Strepsilin
**7b**: $R_1$ = $R_5$ = H, $R_3$ = Me, $R_2$ = $R_4$ = OH, Alectosarmentin
**7c**: $R_1$ = COOH, $R_2$ = Me, $R_3$ = OH, $R_4$ = $R_5$ = H, Porphyrilic acid
**7d**: $R_1$ = COOMe, $R_2$ = Me, $R_3$ = OH, $R_4$ = $R_5$ = H, Methyl porphyrilate

Dibenzofurans from ascomycetes are much more diversified and display some specific features. Beside simple polysubstituted dibenzofurans, those from cultured mycobionts of *Lecanora* sp. or from *Aspergillus* sp. incorporate chlorine atoms in their structures (**8-9**).[43-44, 49] Kon *et al* studied the effect of cultural conditions on the production of dibenzofurans by cultured mycobionts of lichens.[55] Experiments showed the interest in adding adonitol to the medium as well as the repressive effect of actively photosynthesizing photobionts on dibenzofurans production.



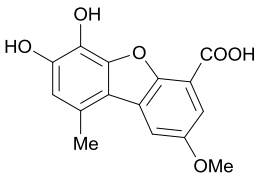
**8a**: R = H,
**8b**: R = Cl,



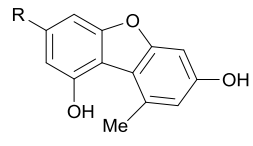
**9a**: $R_1$ = $R_2$ = $R_3$ = $R_4$ = H
**9b**: $R_1$ = $R_2$ = $R_3$ = H, $R_4$ = Cl
**9c**: $R_1$ = $R_2$ = H, $R_3$ = $R_4$ = Cl
**9d**: $R_1$ = $R_3$ = $R_4$ = H, $R_2$ = Me
**9e**: $R_1$ = Me, $R_2$ = $R_3$ = H, $R_4$ = Cl

Thus, marine-derived and endophytic fungi, such as *Alternaria* sp., *Aspergillus* sp. and *Preussia* sp., led to the extraction of dibenzofurans with additional structural features like furan rings, isoprenyl groups or aliphatic chains (**10**-**15**).[45-49, 56]

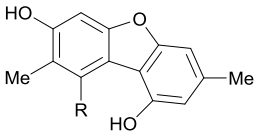
It is noteworthy that dibenzofurans isolated from cultured mycobionts have no carboxyl group in the structure in contrast to lichens. According to Culberson and Ahamdjan, this difference can be justified by the presence of decarboxylases in non-lichen fungi. In lichens, the algal partner may inhibit such enzymes.[57]



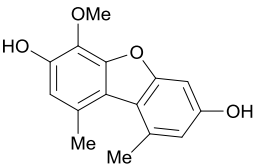
**10**: Porric acid D



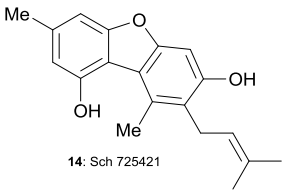
**11a**: R = Me
**11b**: R = $CH_2OH$
**11c**: R = COOH



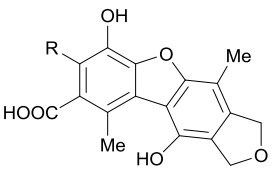
**12a**: R = $(CH_2)_2(CH_3)_2OH$, Karnatakafuran A
**12b**: R = $CH_2CH{=}C(CH_3)_2$, Karnatakafuran B



**13**: Diorcinol H



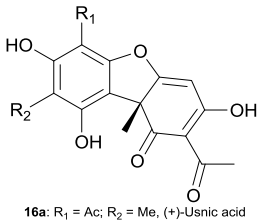
**14**: Sch 725421



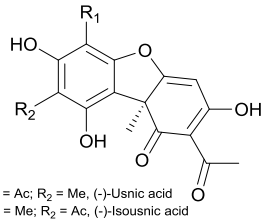
**15a**: R = $CH_2OH$, Preussiafuran A
**15b**: R = OH, Preussiafuran B

## 2 Dihydrodibenzofurans

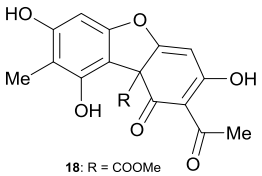
If usnic acid is, until recently, unique to lichen metabolism, its derivatives can be found in both lichens and ascomycetes. Usnic acid is a yellowish pigment commonly found in the genus *Usnea* but also present in various lichens and existing as two enantiomers (**16a**, **17a**) differing by the orientation of the methyl group at position 9b.[8] (+)-Usnic acid can be found in manifold genera (*Cladina, Evernia, Lecanora, Lobaria, Nephroma, Ophioparma, Ramalina, Rinodina, Usnea*) whereas (-)-usnic acid is reported in species of the following genera: *Alectoria, Cetraria, Cladonia, Haematomma, Rhizoplaca* and *Squamarina*.[8] Behera *et al* detected the production of usnic acid from *Usnea ghattensis* after cell culture.[58] Isousnic acids (**16b**, **17b**), isolated from *Cladonia mitis, C. pleurota* and *Leprocaulon microscopicum*,[8, 39, 59] differ from usnic acid by the inversion of the groupment at C6 and C9 in the ring A. Usimines A-C[30, 60] (**20a-c**), reported in *Stereocaulon alpinum* and *Ramalina terebrata*, are unique derivatives possessing nitrogen-bearing side chain presumably derived from glutamic acid. In fact, these latter exist in the more stable enamine form resulting from the rapid tautomerization of the initial formed imine[61-62]. We can note that cercosporamide and usnic acid amide (**17c**, **17d**) are dihydrodibenzofurans from *Cercosporidium henningsii* and *Phoma* sp., with an amide function in position 6.[11]



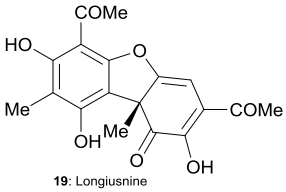
**16a**: $R_1$ = Ac; $R_2$ = Me, (+)-Usnic acid
**16b**: $R_1$ = Me; $R_2$ = Ac, (+)-isousnic acid



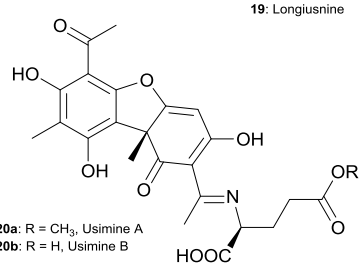
**17a**: $R_1$ = Ac; $R_2$ = Me, (-)-Usnic acid
**17b**: $R_1$ = Me; $R_2$ = Ac, (-)-Isousnic acid
**17c**: $R_1$ = $CONH_2$ ; $R_2$ = H, Cercosporamide
**17d**: $R_1$ = $CONH_2$ ; $R_2$ = Me, Usnic acid amide



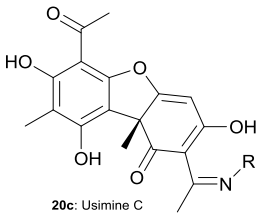
**18**: R = COOMe



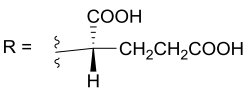
**19**: Longiusnine



**20a**: R = $CH_3$, Usimine A
**20b**: R = H, Usimine B

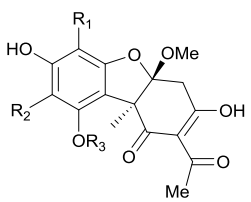


**20c**: Usimine C

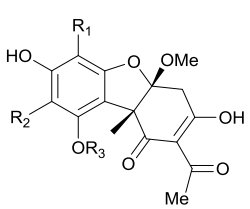


## 3 Tetrahydrodibenzofurans

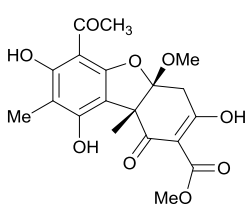
These partially saturated dibenzofurans derivatives have been described both in lichens and fungi and their distribution is restricted to a few species: *Lecanora* sp., *Rhizoplaca* sp., *Leprocaulon* sp., *Phoma* sp., *Haematomma* sp., *Mycosphaerella nawae*.[10, 16, 31-32, 39, 50, 52, 59, 63] The stereochemistry has been



**21a**: $R_1$ = Me, $R_2$ = Ac, $R_3$ = H, (-)-Placodiolic acid
**21b**: $R_1$ = Ac, $R_2$ = Me, $R_3$ = H, (-)-Pseudoplacodiolic acid
**21c**: $R_1$ = Me, $R_2$ = Ac, $R_3$ = Me, (-)-9-*O*-Methylplacodiolic acid



**22a**: $R_1$ = Me, $R_2$ = Ac, $R_3$ = H, (+)-Isomycousnine
**22b**: $R_1$ = Ac, $R_2$ = Me, $R_3$ = H, (-)-Mycousnine
**22c**: $R_1$ = Ac, $R_2$ = Me, $R_3$ = Me, Phomodione

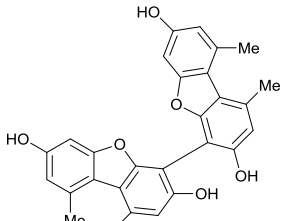


**22d**: (+)-Oxymycousnine

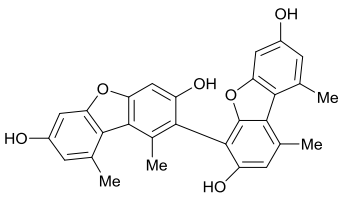
established as *trans* for placodiolic acid derivatives (**21a-c**) and as *cis* for mycousnine derivatives (**22a-22d**).[52, 63] The stereochemistry is organism dependent since the latter compounds are exclusively produced by lichens or ascomycetes, respectively.

**Dimeric dibenzofurans**

To date, lecanorafurans A and B are the only two dimeric dibenzofurans reported (**23a-b**). They have been uniquely identified in cultured mycobionts of *Lecanora iseana* along with monomeric dibenzofurans.[43]



**23a**: Lecanorafuran A



**23b**: Lecanorafuran B

## Isolation and physicochemical properties

The majority of compounds was extracted from lichens or cultured mycobionts using acetone or anhydrous ether. While usnic acid was easily isolated using *n*-hexane or $CHCl_3$ followed by recrystallization, usimines **20a-c** were obtained using MeOH.[60] The compounds **10, 11a-11b, 12a-b, 13, 15a-b**, **17c-d**, **21b**, **22a-c**, produced by fermentation of various fungi, were isolated from MeOH, EtOAc, $CHCl_3$ or $CH_2Cl_2$ extracts. The purification steps were usually performed using either preparative TLC, flash chromatography, column chromatography with silica gel, sephadex LH-20 or semi-preparative HPLC. The final step was recrystallization in appropriate solvents yielding compounds as crystals (Table S1, see supporting information).

The presence of the benzofuran moiety is highlighted by characteristic UV absorptions around 300, 310, 340 nm and more rarely around 370 nm (Table S1, see supporting information). For derivatives possessing partially saturated C-ring, a typical mass fragmentation appears with C-ring fission *via* a retro Diels-Alder fragmentation and homolysis process.[8, 59] The fragmentation pattern of other dibenzofurans corresponds to the loss of $H_2O$, $CO_2$ or fragment chain depending on the substitution of the aromatic groups (e.g. fragmentation observed for condidymic acid).[54] Complete structural identification of dibenzofurans was carried out using classical 1D and 2D NMR data and is based on characteristic chemical shift for typical groups (e.g. aryl methyl groups, more or less acidic exchangeable hydroxyl groups, aromatic patterns, aldehyde, carboxylic groups…). NOE measurement has also been useful for the correct assignment of signals.[41, 48] For compounds existing in various tautomeric forms, e.g. phomodione, the comparison of data with theoretical NMR data and with those of closely related compounds supported the assignment.[50] Total synthesis of some compounds was also helpful to confirm the structural identification (e.g. 4-oxypannaric acid 2-methyl ester[18]).

## Biological activities

Dibenzofurans, especially usnic acid, are biosynthetized by lichens in order to prevent the attack and degradation by insects and herbivores.[64-65] Phytotoxic activity has also been described for usnic acid as well as for didymic acid and its derivatives.[66] The majority of studies published on biological activities of dibenzofurans concerns usnic acid and more specifically its cytotoxic and antibacterial activities. Despite their promising biological properties, other derivatives remain less studied probably due to their low abundance in nature.

**Usnic acid**

Antiproliferative and pro-apoptotic effects of usnic acid have already been well described on several cell lines.[67-68]

Antimicrobial effects of usnic acid are widely reported in literature while mechanisms of action remain poorly studied.[69-71] Previous studies deal with the mode of action of this compound in particular on Gram-positive bacteria[72] and suggest that the antibacterial activity of usnic acid against methicillin-resistant *Staphylococcus aureus* is caused by disruption of the cell membrane. More recently, this hypothesis has been reconsidered. It has been proposed that inhibition of RNA synthesis may be a general mechanism of antibacterial action of usnic acid, with additional direct mechanisms such as impairment of DNA replication in *Bacillus subtilis* and *Staphylococcus aureus*.[73] The activities toward bacterial biofilms are recently reported in several papers.[74-75]

Beside these remarkable activities, several biological properties have been reported for usnic acid including, anti-inflammatory[76], gastroprotective[77], cardiovascular[78], immunostimulatory[79], anti- and pro-oxidant,[80-81] analgesic and antipyretic[82] activities. It can also promote wound healing.[83] These different properties are described more fully in a number of reviews.[12-13, 84-85] Nevertheless, the medicinal use of usnic acid remains limited due to its hepatotoxicity[86-87]. It has also been reported to be a contact allergen which limits its use in cosmetics.[88-89]

**Other dibenzofurans and derivatives**

1 Antimicrobial and antiviral activities

Antimicrobial properties are the most commonly described activities. Some compounds exhibit effects against different microbial strains including bacteria, mycobacteria, yeasts and fungi. These activities, which were generally evaluated by disc diffusion methods or by broth microdilution assays, are presented in Table S2 (see supporting information). [11, 26, 30, 33, 34, 42, 45, 46, 48-50, 52, 91-93, 97, 102] MICs values obtained by broth microdilution assays range between 3 and 64 µg/mL depending on the tested microbial strains. More specifically, phomodione (**22c**) exhibited significant activity against several strains of fungi (MICs between 3 and 8 µg/mL).[50] Compound **14** also showed good activity against some bacteria and yeasts (MICs between 2 and 8 µg/mL).[102]

Oxymycousnine (**22d**) demonstrated significant selective antiviral activity using a plaque reduction test on influenza B virus with 70% plaque inhibition at 30 µg/mL.[52]

2 Cytotoxic activity

The cytotoxic activity is generally evaluated using the MTT

method on various cell lines (P388, A549, HL60, BEL7402, K562, HT-29…) and usually expressed as $IC_{50}$. However, the incubation time is not always stated. The obtained values for some dibenzofurans are shown in Table S3 (see supporting information)[47, 49, 52, 59, 94-95] and range between 0.96 (compound **22a**) and 485 µM (compound **22d**) depending on the tested cell lines.

### 3 Antiplasmodial activity

Compounds **12a** and **12b** were found to exhibit moderate *in vitro* activity against a chloroquine-sensitive *Plasmodium falciparum* 3D7 parasite, with a respective $IC_{50}$ of 3.9 and 3.6 µg/mL, in comparison with the reference drug chloroquine (0.012 µg/mL)[48]. Antiplasmodial activity was also reported for compounds **15a** and **15b** against a chloroquine-resistante *P. falciparum* (NF54). They showed modest activity against erythrocyte stages of this strain with $IC_{50}$ values of 8.76 and 15.0 µg/mL respectively, in comparison with chloroquine (0.002 µg/mL)[47].

### 4 Miscellaneous activities

The inhibitory properties of compounds **11a**, **11b**, and **11c** towards the EGF-R tyrosine kinase were investigated using an ELISA-based *in vitro* assay. At 100 µM, compound **11c** showed the most potent activity with 58.8% inhibition, followed by **11b** and **11a** with 42.5% and 32.5% inhibition, respectively. These compounds were less potent than the positive control genistein, which displayed 80% inhibition.[46]

Compound **17d** was a weak protein kinase C inhibitor with an $IC_{50}$ of 0.8 µM while compound **17c** possessed an $IC_{50}$ of 1.6 µM.[11] ompound **17d** was also tested against various host plants employing a leaf wound test. Phytotoxic activity was found for this compound against *Citrus reticulata* Blanco, *Medicago hispida* Gaerth., *Glycine max* (L.) Merr., *Lactuca sativa* L., *Manihot esculenta* Crantz, *Musa paradisiaca* L., *Acroptilon repens* L., *Centaurea maculosa* L., *Centaurea diffusa* L., *Hibiscus sabdariffa* L., *Avena sativa* L. and *Zea mays* L.[11]

## Structure-activity relationships

Cercosporamide and usnic acid amide (**17c**, **17d**), two dihydrodibenzofurans, exhibited stronger protein kinase C inhibition than usnic acid, probably due to the presence of an amide function in position 6. Concerning the antifungal activity of these derivatives, compound **17c** showed a better activity than usnic acid against *Candida* sp., *Trichophyton* sp., *Aspergillus* sp. and *Saccharomyces* sp.[11] Against *Pythium ultimum* (oomycete), *Sclerotinia sclerotiorum* (ascomycete) and *Rhizoctonium solani* (basidiomycete), usnic acid was less effective than cercosporamide (**17c**) or phomodione (**22c**), whereas activities of the three compounds were similar against *Staphylococcus aureus*.[50] Depending on the strains tested, the structural differences therefore have a significant influence on the antimicrobial activity of the compounds.

For usimines A-C (**20a-c**), the presence of nitrogen-bearing side chains seems to decrease their antibacterial activities against *Bacillus subtilis* and *Staphylococcus aureus* compared to usnic acid.

In a previous study we showed that compounds **4a** and **4b** have a similar but faster antibacterial activity against *S. aureus* than usnic acid.[96] Contrary to usnic acid, which is considered to inhibit RNA synthesis, the antibacterial activity of these two compounds could be caused by disruption of the cell membrane due to the presence of non polar aliphatic chains. However the mechanism of action by molecular modelling needs to be studied to validate this hypothesis.

Gollapudi *et al* (1994) and Shibata and Miura (1949) demonstrated that dibenzofurans bearing a lactone ring (strepsilin and alectosarmentin, **7a-b**) are less effective against *Mycobacterium smegmatis* and *Candida albicans* than usnic acid.[26, 97] Compound **7a** had a lower activity than usnic acid against *Staphylococcus aureus* whereas compound **7b** had an activity similar to that of (-)-usnic acid.

During their research, Millot *et al* (2013) evaluated (-)-usnic acid, (-)-isousnic acid (**17b**), (-)-placodiolic acid (**21a**) and (-)-9-*O*-methylplacodiolic acid (**21c**) for their anti-proliferative activity on HT-29 cells. Only (-)-usnic acid exhibited a moderate activity at 48h ($IC_{50}$ 55µM), whereas all other dibenzofuran derivatives were less effective ($IC_{50}$ > 100 µM). These results indicate clearly the key role of an A-ring substitution pattern for cytotoxicity.[59]

## Other sources

If dibenzofurans and derivatives are mainly isolated from lichens or filamentous fungi, they have been occasionally reported in eudicotyledon angiosperm families as well as in basidiomycetes and myxomycetes (slime molds). Notably, usnic acid has recently been isolated by PNSCM team from *Streptomyces cyaneofuscatu*s, a bacterium associated with *Lichina confinis*, a marine lichen which does not produce this dibenzofuran.[98]

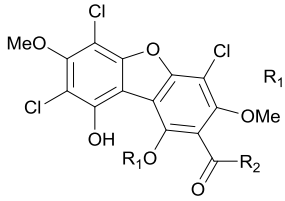
In these other sources, dibenzofuran dimers have not been reported and dihydrodibenzofurans and tetrahydrodibenzofurans have been sporadically described.

A recent review[4] focuses on these dibenzofurans with remarkable biological activities. We will herein emphasis their structural diversity and compare their antimicrobial and cytotoxic activities to those of dibenzofurans from lichens and ascomycetes.

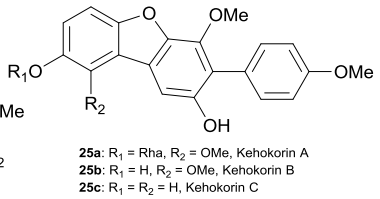
### Myxomycetes

The emerging research on myxomycetes led to the isolation of original dibenzofurans often endowed with interesting biological activities. Only a few structures have been described but this should be increased in the future. Structural diversity is notable and substitution by chlorine atoms (**24a-c**), sugars (**25a**, **26**), or phenyl group (**25b-e**, **27a-b**) can be observed. [3, 6-7, 100] Chlorinated dibenzofurans (**24a-c**), isolated from *Polysphondylium filamentosum* and *Dictyostelium purpureum* K1001 respectively, were tested for their anti-proliferative activities on K562, HeLa and 3T3-L1. While Pf-2 showed no effect, Pf-1 and compound **24c** suppressed the proliferation of the three cell lines investigated suggesting the importance of the hydroxyl substituents and the size of the alkyl chain.[3] Compound **24c** was found to have antibacterial properties against Gram-

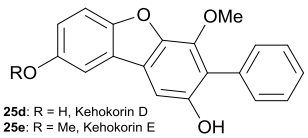
positive bacteria in particular *Bacillus* sp., *Staphylococcus* sp. and *Streptococcus* sp.[99] The substitution by sugar(s) seems to confer cytotoxic activity to the dibenzofurans.[6, 100]



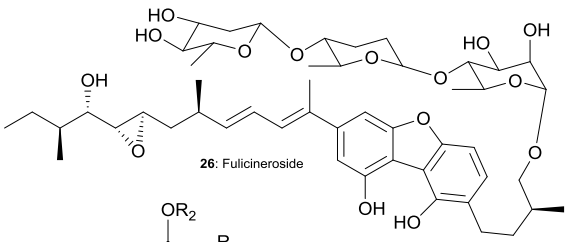
**24a**: $R_1$ = H ; $R_2$ = $C_3H_7$, Pf-1
**24b**: $R_1$ = Me ; $R_2$ = $C_3H_7$, Pf-2
**24c**: $R_1$ = H ; $R_2$ = $C_5H_{11}$, AB0022A



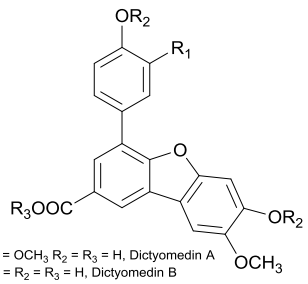
**25a**: $R_1$ = Rha, $R_2$ = OMe, Kehokorin A
**25b**: $R_1$ = H, $R_2$ = OMe, Kehokorin B
**25c**: $R_1$ = $R_2$ = H, Kehokorin C



**25d**: R = H, Kehokorin D
**25e**: R = Me, Kehokorin E



**26**: Fulicineroside

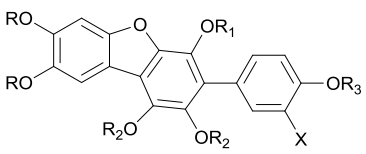


**27a**: $R_1$ = $OCH_3$ $R_2$ = $R_3$ = H, Dictyomedin A
**27b**: $R_1$ = $R_2$ = $R_3$ = H, Dictyomedin B

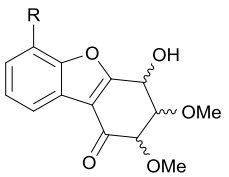
Biological evaluation of dictyomedins A and B (**27a-b**), isolated from *Dictyostelium medium*, showed that these compounds did not inhibit but delayed the differentiation of *D. discoideum* cells.[7]

## Basidiomycetes

A literature review shows that basidiomycetes do not represent an important source of natural dibenzofurans and chemical diversity is limited. These organisms biosynthetized aromatic dibenzofurans with additional phenol ring(s) (boletospins **28a**, ganbajunin B **28b** and vialinins **28c-d**) as well as dioxotetrahydrodibenzofurans (ribisins **29a-b**).



**28a**: $R_1$ = $R_2$ = $R_3$ = H, Me or Ac ; X = H or OH, Boletopsins
**28b**: $R_1$ = $R_2$ = $COOCH_2Ph$, $R_3$ = X = H, Ganbajunin B
**28c**: $R_1$ = H, $R_2$ = $COOCH_2Ph$, $R_3$ = X = H, Vialinin B
**28d**: $R_1$ = H, $R_2$ = COO*p*-(OH)Ph, $R_3$ = X = H, Vialinin C



**29a:** R = H, Ribisins A, B, C
**29b:** R= OH, Ribisin D

Ganbajunin B (**28b**), identified in *Thelephora ganbajun*, displayed a significant antioxidant activity.[101-102] Boletopsins (**28a**), isolated for various *Boletopsis* species, showed weak antibacterial activity.[103] Boletopsins and its derivatives have also been evaluated against inflammatory markers (5-lipooxygenase, TNF-α) and KDR kinase implicated in angiogenesis.[104-105]

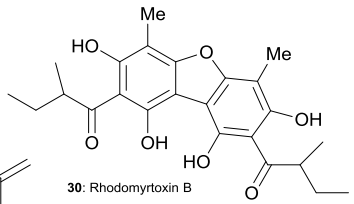
Vialinin B (**28c**) and vialinin C (**28d**), isolated from *Thelephora vialis*, were found to inhibit TNF production with an $IC_{50}$ value of 0.02 nM and were 2 x $10^5$ fold more effective than **28b** highlighting the importance of an additional free hydroxyl function.[106-107] Ribisins A-D (**29a-b**) possessed strong nerve growth factor-potentiating activity in PC12 cells. The presence of a hydroxyl group in position 4 significantly decreases the activity.[1]

## Plants

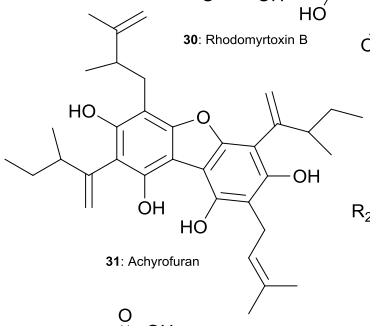
Dibenzofurans have been found in various angiosperms families like Iridaceae, Liliaceae, Clusiaceae, Hamamelidaceae, Rosaceae, Asteraceae, Hypericaceae or Myrtaceae. The number of isolated structures is greater than in myxomycetes, or basidiomycetes but remains proportionally weak.[108-111]

Like for lichens, the antimicrobial effect is well known for these classes of metabolites and the majority of these inducible defense compounds were found as a result of fungal attack. Thus, cotonefurans, eriobofurans and pyrufurans are phytoalexins. For these structures, aglycones were most effective than the glycosides.[112]

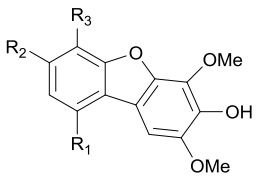
Structural diversity is close to that of dibenzofurans from myxomycetes. In addition to the simple polyoxygenated dibenzofurans substitution by isoprenyl or acyl chains (**30**, **31**), sugar(s) (**32**) as well as tetrahydrodibenzofurans (**33**) have been reported.[109, 113-115]



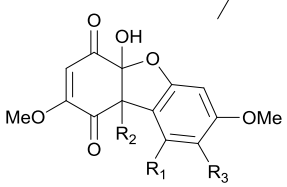
**30**: Rhodomyrtoxin B



**31**: Achyrofuran



**32**: $R_1$ = $R_3$ = H, $R_2$ = O-Glc, Fortuneanoside G



**33**: $R_1$ = $R_2$ = $(CH_2)_9CH{=}CH(CH_2)_3Me$ ; $R_3$ = H, Belamcandone A

Antibacterial, anti-inflammatory and cytotoxic activities have been described among the dibenzofurans isolated from plants. Nine compounds related to rhodomyrtoxin B, bearing acyl or isoprenyl chains have been isolated from *Pilidiostigma* sp., *Calophyllum panciflorum* and *Achyrocline satureioides*. Shou *et al* showed the importance of the acyl substitution in positions 2 and 8 compared with positions 4 and 6 for the cytotoxic and anti-inflammatory activities.[5] Concerning antibacterial activity these derivatives have been tested against *Staphylococcus aureus* with

MIC ranging from 0.25 to 26.5 µM. Rhodomyrtoxin B (**30**) and achyrofuran (**31**) were the most active included against methicillin resistant *S. aureus*.[113-114] Fortuneanosides G-L are glycosides dibenzofurans extracted from *Pyracantha fortuneana* and were examined for tyrosinase inhibition. Fortuneanoside G (**32**) was found to be the most active against this enzyme.[109] Among dioxotetrahydrodibenzofurans, eight derivatives have been isolated from seeds of Iradaceae and named belamcandones (**33**).[115] None of them have been evaluated for their potential biological activities.

## Conclusion

Dibenzofurans remain a small class of secondary metabolites mainly isolated from lichens or fungi. Monomeric dibenzofurans constitute the major group of dibenzofurans isolated from lichens. Due to the intensification of research on filamentous fungi, new derivatives have been recently isolated.

Ongoing research on the common usnic acid deals with its mechanism of action. Other dibenzofurans display interesting antimicrobial properties while cytotoxic activities are generally weak for tested compounds excepted for mycousnine and usnic acid derivatives. Also, due to their interesting physico-chemical properties (good solubility, colorless crystals,...) dibenzofurans are attractive for future medicinal or cosmetic applications. The principal source of dibenzofurans, lichens, is limited because of the slow growth of such organisms. This major point delays the future development and biological use of this class of compounds. However development of research on filamentous fungi or myxomycetes will probably increase the number of dibenzofurans and will lead to the production of sufficient amounts for biological evaluation particularly as antimicrobial agents.

## Notes and references

[a] *EA 1069 « Laboratoire de Chimie des Substances Naturelles », Laboratoire de Pharmacognosie, Faculté de Pharmacie, Université de Limoges, 2 rue du Dr Marcland, 87025 Limoges Cedex, France. Fax: (+33) 5 55 43 59 10; Tel: (+33) 5 55 43 58 35; E-mail: marion.millot@unilim.fr*

[b] *UMR CNRS ISCR 6226 "Institut des Sciences chimiques de Rennes" Equipe PNSCM "Produits Naturels-Synthèse-Chimie Médicinale", UFR des Sciences Pharmaceutiques et Biologiques, Université Bretagne Loire, Université de Rennes 1, 2 Avenue du Pr Léon Bernard, 35043 Rennes Cedex, France. Fax: (+33) 2 23 23 47 04; Tel: (+33) 2 23 23 48 17; E-mail: sophie.tomasi@univ-rennes1.fr*

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