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Dibenzofurans from nature: Biosynthesis, structural diversity, sources, and bioactivities

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ABSTRACT

Dibenzofurans are a small class of natural products with versatile biological activities that used to be thought to come mainly from lichens and ascomycetes. In fact, they are also distributed widely in higher plants, especially in the families Rosaceae and Myrtaceae. Dibenzofurans and derivatives from lichens and ascomycetes have been well reviewed, but dibenzofurans from all biological sources in nature have not been reviewed. In this review, dibenzofurans from all natural sources have been comprehensively reviewed, and a total of 211 dibenzofurans isolated and identified from organisms between 1843 and March 2023 are categorized and discussed, including their biosynthesis, structural diversity, sources, and bioactivities.

1. Introduction

Dibenzofurans belong to a small class of natural products with various biological activities, are usually thought to be derived from lichens and ascomycetes. In 1843, the first dibenzofuran, usnic acid, was isolated from lichens [1,2], and is the most common dibenzofuran compound and an abundant characteristic secondary metabolite of lichens, with various pharmacological activities used widely in dietary supplements and medical drugs [3]. In recent years, growing attention has focused on the dibenzofurans from lichens and ascomycetes [3–6]. Approximatively 32 dibenzofurans and derivatives from lichens have been well reviewed by Millot et al. [4] in 2016, and their biological activities subsequently summarized by Ureña-Vacas and coauthors [6] in 2021. However, the research progress of dibenzofurans from all organisms in nature has not been reviewed. Therefore, this review aims to describe the biosynthesis, structural diversity, sources, and bioactivities of all dibenzofurans isolated from nature. In this review, dibenzofurans are classified into two groups, lichen dibenzofurans and non-lichen dibenzofurans, and further subclassified by their structural characteristics, sources, and biosynthesis. Lichen dibenzofurans are divided into four types (I: usnic acid type, II: isousnic acid type, III: pannaric acid type, IV: hypostrepsilic acid type), and non-lichen dibenzofurans are divided into two types (A: simple dibenzofuran type, B: alkyl substituted dibenzofuran type). It is important to note that some dibenzofurans included in previous reviews have been excluded from this review, because they are not derived from the proposed dibenzofuran biosynthetic pathway (Scheme 1), for example, kehokorin A [4] (derived from terphenyl) and balsaminone A [5] (derived from naphthoquinone).

Generally, dibenzofurans are produced *via* the polyketide biosynthetic pathway. The lichen dibenzofurans originate from malonyl-CoA and acetyl-CoA, and yield a linear tetraketide intermediate. Several studies have been shown that usnic acid is derived from methylphloroacetophenone, which is produced by this polyketide pathway through Claisen condensation [7–10]. However, the biosynthesis of lichen dibenzofurans from pannaric acid and hypostrepsilic acid types has not been studied, and is likely produced from orsellinic acid by the tetraketide *via* aldol condensation, and a hypothetical biosynthetic pathway for them was proposed as shown in Scheme 1A. For the non-lichen dibenzofurans, the key intermediates are the biphenyls obtained from the condensation reaction of three malonyl-CoA with benzoyl-CoA by a biphenyl synthase (BIS) [11–17]. Subsequently, these biphenyls lead to non-lichen dibenzofuran derivatives *via* a cyclase [14,16,17], and then the alkyl substituted dibenzofurans are formed by hypothetical alkyltransferase or prenyltransferase (Scheme 1B).

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2. Lichen dibenzofurans

2.1. Structural diversity

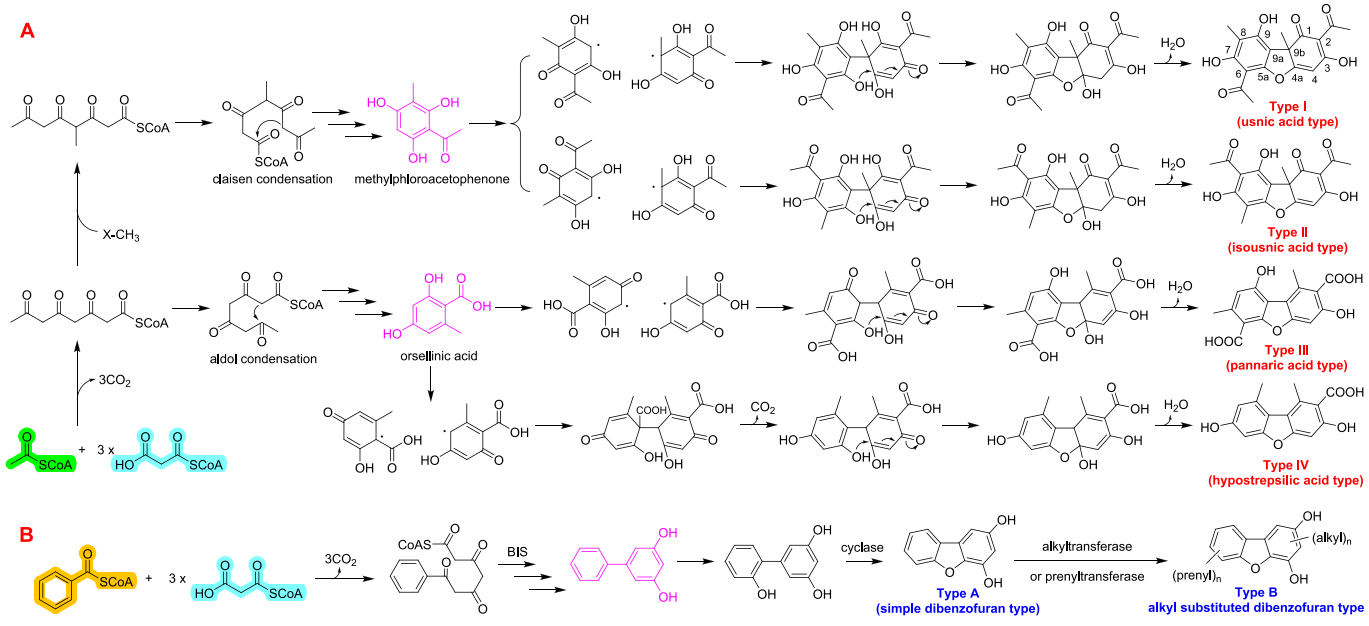
To date, 92 lichen dibenzofurans have been isolated from nature, which were derived mainly from lichens of the families Cladoniaceae and Parmeliaceae, followed by mycobionts and fungi (Tables 1–4). Based on structural characteristics, these lichen dibenzofurans were divided into four types (types I–IV). Dibenzofurans of type I (**1**–**33**) are usnic acid derivatives with 2,6-diacetyl and 8,9b-dimethyl skeletons, type II (**34**–**43**) are isousnic acid derivatives with 2,8-diacetyl and 6,9b-dimethyl substituents, type III (**44**–**56**) are pannaric acid derivatives with 2,6-dicarboxyl and 1,7-dimethyl moieties, and type IV (**57**–**92**) are hypostrepsilic acid derivatives with 2-carboxyl and 1,9-dimethyl substitutions.

Type I lichen dibenzofurans were isolated mainly from lichens of the genus *Usnea* in Parmeliaceae, followed by fungi of Mycosphaerellaceae (Table 1). The classic compound of this type is usnic acid (enantiomers **1** and **2**), which is widely distributed in lichens. As shown in Fig. 1, compounds **3** and **4** are hydration products of usnic acid isolated from lichens *Usnea* spp. [18,19]. Compounds **5**–**8** are methylated or ethylated derivatives of **3** and **4** found from lichens and fungi [20–27], and their reduction products **9** and **10** are found in *Ochroconis* sp. FS449 [28]. Longiusnine (**11**) was isolated from lichen *Usnea longissima* and identified as the product of acetyl group migration from *C*2 to C3 of usnic acid [29]. Compounds **12**–**18** are missing some carbons compared with the type I lichen dibenzofurans defined earlier, and are called nordibenzofurans. The nordibenzofurans are found mainly from fungi of the Mycosphaerellaceae [25,27,28,30,31]. Cercosporamide (**19**) [23,32] and usnic acid amide (**20**) [33], two acylamide compounds, have only been isolated from fungi. Compounds **21**–**30** with enamine side chains were found in lichen *Usnea* [24,34] and fungi *Ochroconis* [28], respectively. However, usimines A–C (**31**–**33**) with imine side chains were isolated from the Antarctic lichens *Stereocaulon alpinum* [35] and *Ramalina terebrata* [36].

Type II lichen dibenzofurans (Fig. 2) are the least common of the lichen dibenzofurans, and only ten compounds have been reported so far. The type II lichen dibenzofurans are mainly distributed in lichens of genus *Usnea* (Parmeliaceae) and fungi of *Mycosphaerella* (Mycosphaerellaceae). The model compound of this type is isousnic acid (enantiomers **34** and **35**), which is distributed in lichens of the Cladoniaceae, Leprocaulaceae, and Parmeliaceae (Table 2). After hydration, isousnic acid produced compounds **36**–**39** in lichens and fungi by methylation or ethylation [20–22,24,25,27,38,45,46]. Among them, 9-*O*-methylplacodiolic acid (**39**), a mixture of the major 1-hydroxy-3-one and the minor 3-hydroxy-1-one tautomers (63: 37), was isolated from *Leprocaulon microscopicum* in 2013 [38]. Mycousfuran B (**40**), isolated from a marine fungus *Mycosphaerella* sp., lacks a 2-acetyl group compared with typical type II lichen dibenzofurans [27]. Usenamine C (**41**) with an enamine group was found in a Chinese medicinal herb *Usnea longissima* [24]. Of note, compound **42**, with 4,6-dicarboxyl and 2,8-dimethyl, was isolated from the Antarctic lichen *Ramalina terebrata* [47]. In addition, usneaceratin A (**43**) with 4,6-dicarboxyl and 1,9-dimethyl substitutions was discovered in the lichen *Usnea ceratina* [48]. In theory, compounds **42** and **43** belong to two new structural types. However, since there is only one compound in both types, they are taken as special cases in this review and are not treated as new structural types, so they are arbitrarily and provisionally assigned to type II.

Hitherto, only 13 type III lichen dibenzofurans (Fig. 3) have been reported, and mainly distributed in lichens of Roccellaceae (Table 3). The typical compound of this type is pannaric acid (**44**), which was first isolated from lichen *Crocynia membranacea* (*Pannaria lanuginosa*) in 1904 [50]. Compounds **45**–**51** are methylated derivatives of pannaric acid produced by lichens [51–58]. Compound **52** is a 4-hydroxylated product of pannaric acid 2-methyl ester (**48**) generated by *Leproloma diffusum* [59]. Porphyrilic acid (**53**), a five-membered lactone derivative of pannaric acid, was discovered from lichens *Cladonia corniculate* [60] and *Haematomma coccineum* [61,62]. It is important to note that the decarboxylated derivatives (**54**–**56**) of pannaric acid were only found in a marine sponge-derived fungus Super1F1-09 (Botryosphaeriaceae) [63].

Type IV are the largest class of lichen dibenzofurans (Fig. 4), and are mainly distributed in lichens *Cladonia* spp. (Cladoniaceae) and mycobiont of *Lecanora* (Lecanoraceae) (Table 4). The representative compound of type IV is hypostrepsilic acid (norascomatic acid, **57**), which is distributed in lichens of *Usnea antarctica* [18] and *Bunodophoron patagonicum* [64], and mycobionts of *Evernia esorediosa* [65] and *Usnea orientalis* [44]. Compounds **58**–**61** are methylated products of hypostrepsilic acid from *Bunodophoron patagonicum* [64]. The 9-methyl of hypostrepsilic acid was oxidized to give compounds **62** [44,66], **65**



Scheme 1. Plausible biosynthetic pathway of lichen dibenzofurans (A) and non-lichen dibenzofurans (B).

Table 1
Distribution of type I lichen dibenzofurans in organisms.

Category	Family	Species	Compounds
Lichen	Cladoniaceae	*Cladonia incrassata*	(-)-Usnic acid (**2**) [37]
Lichen	Haematommataceae	*Haematomma flexuosum*	Isopseudoplacodiolic acid (mycousnine, **5**) [20]
Lichen	Haematommataceae	*Haematomma matogrossense*	Isopseudoplacodiolic acid (**5**) [20]
Lichen	Lecanoraceae	*Rhizoplaca chrysoleuca*	(-)-Usnic acid (**2**) [21,22], (-)-pseudoplacodiolic acid (**7**) [21,22]
Lichen	Leprocaulaceae	*Leprocaulon microscopicum*	(-)-Usnic acid (**2**) [38]
Lichen	Parmeliaceae	*Alectoria sarmentosa*	(-)-Usnic acid (**2**) [39]
Lichen	Parmeliaceae	*Lethariella cladonioides*	Usnic acid (**1** or **2**) [40]
Lichen	Parmeliaceae	*Parmelia perlata*	(+)-Usnic acid (**1**) [30], 6-deacetyl-9b-carbmethoxy-9b-demethylusnic acid (**15**) [30]
Lichen	Parmeliaceae	*Parmelia saxatilis*	Usnic acid (**1** or **2**) [41]
Lichen	Parmeliaceae	*Usnea antarctica*	(+)-Usnic acid (**1**) [18], 2,6-diacetyl-3,4a,7,9-tetrahydroxy-8,9b-dimethyl-1-oxo-1,4,4a,9b-tetrahydrodibenzofuran (**4**) [18]
Lichen	Parmeliaceae	*Usnea diffracta*	(+)-Usnic acid (**1**) [34], usenamines E–H (**27**–**30**) [34]
Lichen	Parmeliaceae	*Usnea longissima*	(+)-Usnic acid (**1**) [24,42], (4a*R*,9b*S*)-2,6-diactyl-3,4a,7,9-tetrahydroxy-8,9b-dimethyl-1-oxo-1,4,4a,9b-tetrahydrodibenzofuran (**3**) [19], usone (**6**) [24], longiusnine (**11**) [29], usenamines A–B (**24**–**25**) [24], usenamines D–F (**26**–**28**) [24]
Lichen	Ramalinaceae	*Ramalina conduplicans*	(+)-Usnic acid (**1**) [43]
Lichen	Ramalinaceae	*Ramalina terebrata*	Usnic acid (**1** or **2**) [36], usimines A–C (**31**–**33**) [36]
Lichen	Stereocaulaceae	*Stereocaulon alpinum*	Usnic acid (**1** or **2**) [35], usimines A–C (**31**–**33**) [35]
Mycobiont	–	mycobiont of *Usnea orientalis*	Usnic acid (**1** or **2**) [44]
Fungus	Didymellaceae	*Phoma* sp.	Usnic acid (**1** or **2**) [23], phomodione (**8**) [23], (-)-cercosporamide (**19**) [23]
Fungus	Mycosphaerellaceae	*Cercosporidium henningsii*	(-)-Cercosporamide (**19**) [32], usnic acid amide (**20**) [33]
Fungus	Mycosphaerellaceae	*Mycosphaerella nawae*	(-)-Mycousnine (**5**) [25,26], (+)-oxymycousnine (**13**) [25]
Fungus	Mycosphaerellaceae	*Mycosphaerella* sp. (UFMGCB2032)	Mycousnicdiol (**14**) [31], mycousfuranine (**18**) [31]
Fungus	Mycosphaerellaceae	*Mycosphaerella* sp.	(+)-Usnic acid (**1**) [27], mycousfuran A (**12**) [27], (-)-mycousnine (**5**) [27]
Fungus	Sympoventuriaceae	*Ochroconis* sp. FS449	Ochuscins A–G (**16**, **17**, **21**–**23**, **9**, **10**) [28]

Table 2
Distribution of type II lichen dibenzofurans in organisms.

Category	Family	Species	Compounds
Lichen	Cladoniaceae	*Cladonia mitis*	(+)-Isousnic acid (**34**) [49]
Lichen	Haematommataceae	*Haematomma flexuosum*	Isoplacodiolic acid (isomycousnine, **36**) [20]
Lichen	Haematommataceae	*Haematomma matogrossense*	Isoplacodiolic acid (**36**) [20]
Lichen	Lecanoraceae	*Lecanora rubina*	(-)-Placodiolic acid (**38**) [45]
Lichen	Lecanoraceae	*Rhizoplaca chrysoleuca*	(-)-Placodiolic acid (**38**) [21,22]
Lichen	Leprocaulaceae	*Leprocaulon microscopicum*	(-)-Isousnic acid (**35**) [38], (-)-placodiolic acid (**38**) [38], (±)-9-*O*-methylplacodiolic acid (**39**) [38]
Lichen	Parmeliaceae	*Usnea antarctica*	(+)-Isousnic acid (**34**) [18]
Lichen	Parmeliaceae	*Usnea ceratina*	Isousnic acid (**34** or **35**) [48], usneaceratin A (**43**) [48]
Lichen	Parmeliaceae	*Usnea longissima*	Isousone (**37**) [24], usenamine C (**41**) [24]
Lichen	Ramalinaceae	*Ramalina terebrata*	1,3,7,9-Tetrahydroxy-2,8-dimethyl-4,6-di(ethanoyl) dibenzofuran (**42**) [47]
Fungus	Mycosphaerellaceae	*Mycosphaerella nawae*	(+)-Isomycousnine (**36**) [25,46]
Fungus	Mycosphaerellaceae	*Mycosphaerella* sp.	(-)-Placodiolic acid (**38**) [27], mycousfuran B (**40**) [27]

Table 3
Distribution of type III lichen dibenzofurans in organisms.

Category	Family	Species	Compounds
Lichen	Cladoniaceae	*Cladonia corniculata*	Porphyrilic acid (**53**) [60]
Lichen	Crocyniaceae	*Crocynia membranacea*	Pannaric acid (**44**) [50]
Lichen	Haematommataceae	*Haematomma coccineum*	Porphyrilic acid (**53**) [61,62]
Lichen	Opegraphaceae	*Schizopelte californica*	Pannaric acid 9-methyl ester (**46**) [52], schizopeltic acid (**49**) [55,56], isoschizopeltic acid (**51**) [52]
Lichen	Roccellaceae	*Reinkella parishii*	Schizopeltic acid (**49**) [55,56]
Lichen	Roccellaceae	*Roccella capensis*	3-*O*-Methylpannaric acid (**45**) [51], schizopeltic acid (**49**) [51]
Lichen	Roccellaceae	*Roccella hypomecha*	Schizopeltic acid (**49**) [57], 3-*O*-demethylschizopeltic acid (**50**) [57]
Lichen	Roccellaceae	*Roccellina luteola*	Schizopeltic acid (**49**) [56,58]
Lichen	Stereocaulaceae	*Leproloma diffusum*	Pannaric acid 2-methyl ester (**48**) [54], 4-oxypannaric acid 2-methyl ester (**52**) [59]
Lichen	Stereocaulaceae	*Leproloma vouauxii*	Pannaric acid 6-methyl ester (**47**) [53]
Fungus	Botryosphaeriaceae	Super1F1-09	3,9-Dimethyldibenzo[*b*,*d*] furan-1,7-diol (**54**) [63], 3-(hydroxymethyl)-9-methyldibenzo[*b*,*d*]furan-1,7-diol (**55**) [63], 1,7-dihydroxy-9-methyldibenzo [*b*,*d*]furan-3-carboxylic acid (**56**) [63]

[18,67], and **66** [66] in lichens and their mycobionts. In lichens *Cladonia* (Cladoniaceae) and *Alectoria sarmentosa* (Parmeliaceae), strepsilin (**63**) and alectosarmentin (**64**) each with a five-membered lactone were obtained from hypostrepsilic acid by oxidation of the 1-methyl to

Table 4
Distribution of type IV lichen dibenzofurans in organisms.

Category	Family	Species	Compounds
Lichen	Cladoniaceae	*Cladonia bacillaris*	Strepsilin (**63**) [68,69], didymic acid (**80**) [68,69]
Lichen	Cladoniaceae	*Cladonia corniculata*	Strepsilin (**63**) [60], alectosarmentin (**64**) [60]
Lichen	Cladoniaceae	*Cladonia didyma*	Strepsilin (**63**) [68,69], condidymic acid (**79**) [76], didymic acid (**80**) [68,69], isodidymic acid (**81**) [76], subdidymic acid (**82**) [76]
Lichen	Cladoniaceae	*Cladonia floerkeana*	Strepsilin (**63**) [68,69], didymic acid (**80**) [68,69]
Lichen	Cladoniaceae	*Cladonia incrassata*	Condidymic acid (**79**) [37], didymic acid (**80**) [37]
Lichen	Cladoniaceae	*Cladonia rangiferina*	Condidymic acid (**79**) [77], didymic acid (**80**) [77]
Lichen	Cladoniaceae	*Cladonia squamosula*	Condidymic acid (**79**) [78], didymic acid (**80**) [78]
Lichen	Cladoniaceae	*Cladonia strepsilis*	Strepsilin (**63**) [68,69]
Lichen	Cladoniaceae	*Gymnoderma melacarpum*	Didymic acid (**80**) [79], melacarpic acid (**83**) [79]
Lichen	Letrouitiaceae	*Letrouitia vulpina*	Letrouitic acid (**84**) [80], oxodidymic acid (**85**) [80], 8-chloroxodidymic acid (**86**) [80], dioxodidymic acid (**87**) [80], 8-chloro-dioxodidymic acid (**88**) [80], dioxocondidymic acid (**89**) [80], 8-chlorodioxo-condidymic acid (**90**) [80]
Lichen	Parmeliaceae	*Alectoria sarmentosa*	Alectosarmentin (**64**) [39]
Lichen	Parmeliaceae	*Usnea antarctica*	Hypostrepsilic acid (norascomatic acid, **57**) [18], hypostrepsilalic acid (**65**) [18]
Lichen	Parmeliaceae	*Usnea longissima*	3,7-Dihydroxy-1,9-dimethyldibenzofuran (**67**) [70]
Lichen	Ramalinaceae	*Phyllopsora furfuracea*	Furfuraceic acid (**91**) [81]
Lichen	Ramalinaceae	*Phyllopsora haemophaea*	Haemophaein (**92**) [82]
Lichen	Sphaerophoraceae	*Bunodophoron patagonicum*	Norascomatic acid (**57**) [64], 7-*O*-methylnorascomatic acid (**58**) [64], ascomatic acid (**59**) [64], methyl ascomatate (**60**) [64], methyl 7-*O*-methylnorascomatate (**61**) [64]
Lichen	Stereocaulaceae	*Stereocaulon paschale*	Isostrepsilic acid (**62**) [66], 3,7-dihydroxy-1-methyldibenzofuran-2,9-dicarboxylic acid (**66**) [66], 9-(hydroxymethyl)-1-methyldibenzofuran-3,7-diol (**70**) [66]
Mycobiont	–	mycobiont of *Evernia esorediosa*	Hypostrepsilic acid (**57**) [65]
Mycobiont	–	mycobiont of *Lecanora cinereocarnea*	3,7-Dihydroxy-1,9-dimethyldibenzofuran (**67**) [71], 3-hydroxy-7-methoxy-1,9-dimethyldibenzofuran (**68**) [71], 2-chloro-3,7-dihydroxy-1,9-dimethyldibenzofuran (**72**) [71], 2-chloro-7-hydroxy-3-methoxy-1,9-dimethyldibenzofuran (**73**) [71], 2,8-dichloro-3,7-dihydroxy-1,9-dimethyldibenzofuran (**75**) [71]
Mycobiont	–	mycobiont of *Lecanora iseana*	3,7-Dihydroxy-1,9-dimethyldibenzofuran (**67**) [72], 4-chloro-3,7-dihydroxy-1,9-dimethyldibenzofuran (**74**) [72], 4,6-dichloro-3,7-dihydroxy-1,9-dimethyldibenzofuran (**76**) [72], lecanorafurans A–B (**77**–**78**) [72]
Mycobiont	–	mycobiont of *Stereocaulon japonicum*	Hypostrepsilalic acid (**65**) [67]
Mycobiont	–	mycobiont of *Usnea orientalis*	Hypostrepsilic acid (**57**) [44], isostrepsilic acid (**62**) [44]
Fungus	Aspergillaceae	*Aspergillus versicolor*	3,7-Dihydroxy-1,9-dimethyldibenzofuran (**67**) [73], diorcinol H (**69**) [73]
Fungus	Aspergillaceae	*Penicillium* sp. L129	Penizofuran A (**71**) [75]
Fungus	Pseudeurotiaceae	*Pseudeurotium ovale*	3,7-Dihydroxy-1,9-dimethyldibenzofuran (**67**) [74]

hydroxymethyl followed by lactonization with the adjacent carboxylic acid [39,60,68,69]. It is noted that the decarboxylated derivatives of hypostrepsilic acid (**67**–**78**) were isolated mainly from mycobionts [66,70–75]. Compounds **72**–**76** with chlorine, and dimeric dibenzofurans lecanorafurans A and B (**77** and **78**) were derived only from lichen mycobionts of *Lecanora* [71,72]. Interestingly, in contrast to typical type IV lichen dibenzofurans, the 1-methyl or 1, 9-dimethyl substitution pattern of compounds **79**–**92** were replaced by short-chain alkanes [37,68,69,76–82]. Compounds **79**–**92** were reported from the families Cladoniaceae, Letrouitiaceae, and Ramalinaceae of class Lecanoromycetes, especially in *Cladonia* of the Cladoniaceae (Table 4), and three chlorine-containing compounds 8-chloroxodidymic acid (**86**), 8-chlorodioxodidymic acid (**88**), and 8-chlorodioxocondidymic acid (**90**) were isolated from *Letrouitia vulpina* [80].

2.2. Biological activities

Herein, the bioactivities of lichen dibenzofurans except usnic acid are reviewed, because the bioactivities of usnic acid have already been reviewed extensively [3,83]. Usnic acid is a functional compound and is widely used in dietary supplements, daily chemical products, and medicine, and has various biological activities like antibacterial, antifungal, antiviral, antiprotozoal, insecticidal, anti-inflammatory, antiangiogenic, cytotoxic, antitumor, antioxidant, phytotoxic, immunostimulatory, and photoprotective effects, and promotes wound healing [3,83]. Of note, the allergic dermatitis and hepatotoxicity of usnic acid has also been observed [3,83,84].

2.2.1. Antibacterial activity

Antibacterial activity is one of the most studied bioactivities of lichen dibenzofurans, especially against *Staphylococcus aureus*. Lichen dibenzofurans are generally only active against Gram-positive bacteria and inactive toward Gram-negative bacteria. (-)-Mycousnine (**5**) [25], phomodione (**8**) [23], mycousfuran A (**12**) [27], cercosporamide (**19**) [23], (+)-isomycousnine (**36**) [25], (-)-placodiolic acid (**38**) [27], mycousfuran B (**40**) [27], 3,9-dimethyldibenzo[*b,d*]furan-1,7-diol (**54**) [63], alectosarmentin (**64**) [39], condidymic acid (**79**) [37], and didymic acid (**80**) [37] showed marked or moderate antibacterial properties against *Staphylococcus aureus*, with minimum inhibitory concentration (MIC) values of 6.2, 1.6, 4.0, 2.0, 6.2, 32, 32, 50, 25, 7.5, and 7.5 μg/mL, respectively. (-)-Mycousnine (**5**) [25], usimines A–C (**31**–**33**) [36],

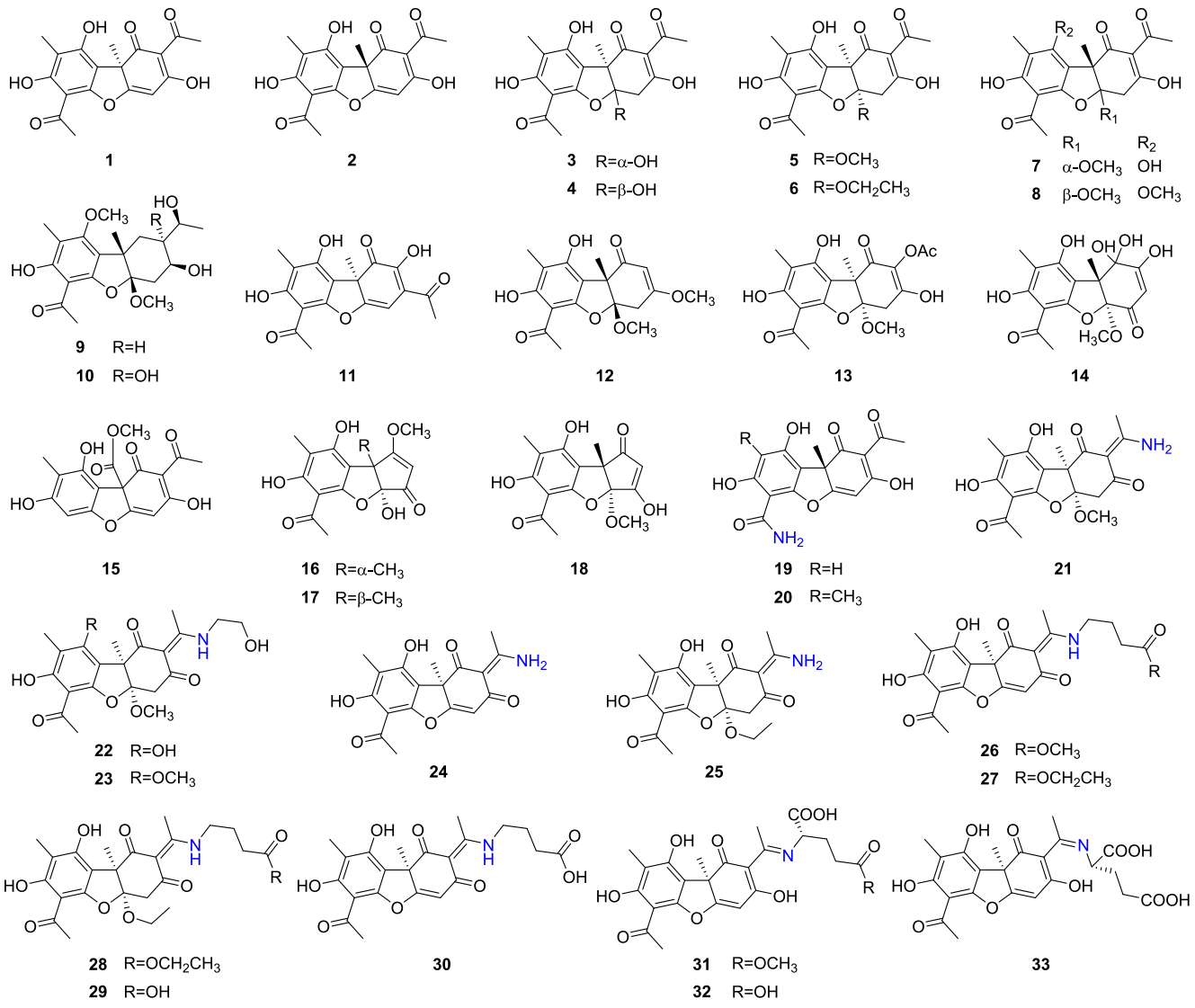


Fig. 1. Type I lichen dibenzofurans from organisms.

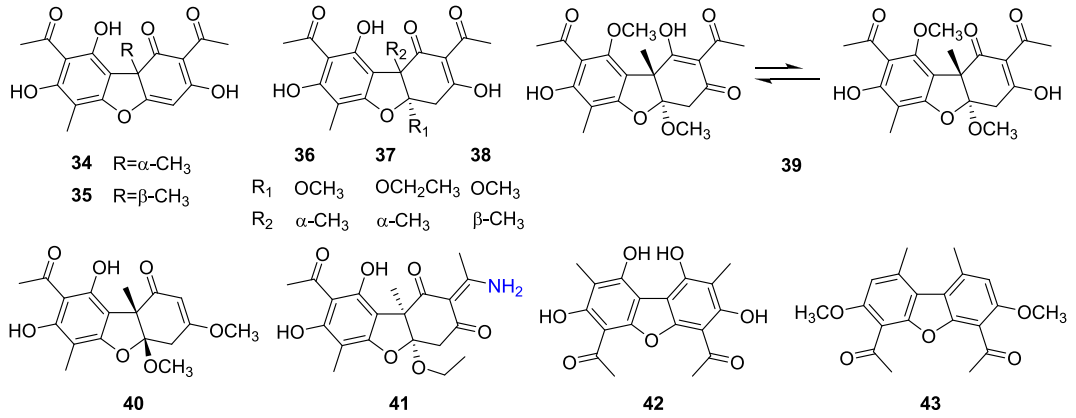


Fig. 2. Type II lichen dibenzofurans from organisms.

(+)-isomycousnine (**36**) [25], and (-)-placodiolic acid (**38**) [27] were found to have antibacterial activities against *Bacillus subtilis*, with MIC values of 6.2, 11.1, 12.7, 26.4, 6.2, and 4.0 μg/mL, respectively. Compounds **12**, **38**, and **40** were also found to have moderate activity against *Kocuria rhizophila* (MICs = 8, 8, and 16 μg/mL) [27]. Both compounds **54** [63] and **64** [39] had antibacterial activity toward *Mycobacterium* spp., with MIC values of 25 μg/mL. In addition, compounds **79** and **80** showed activities against methicillin-resistant *Staphylococcus aureus* (MRSA) (inhibition zones = 17 and 28 mm, respectively) and vancomycin-resistant *Enterococcus fuecium* (VRE) (inhibition zones = 22

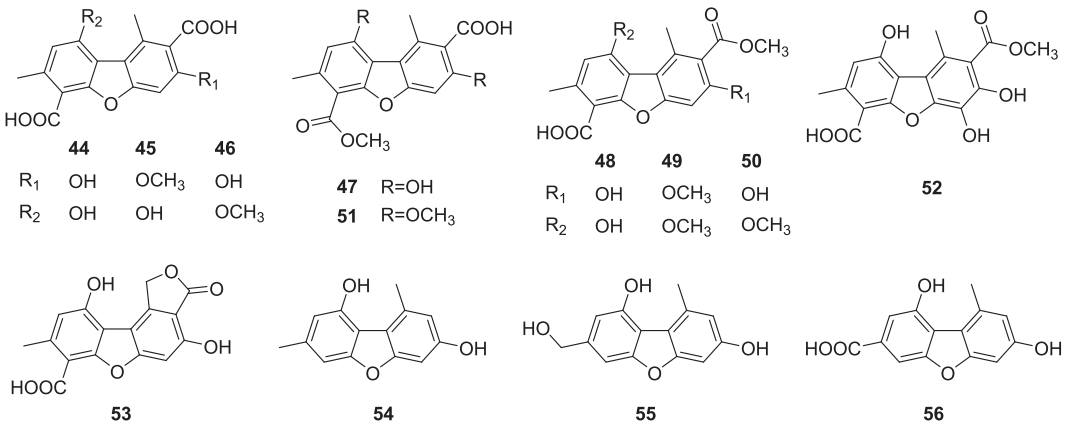


Fig. 3. Type III lichen dibenzofurans from organisms.

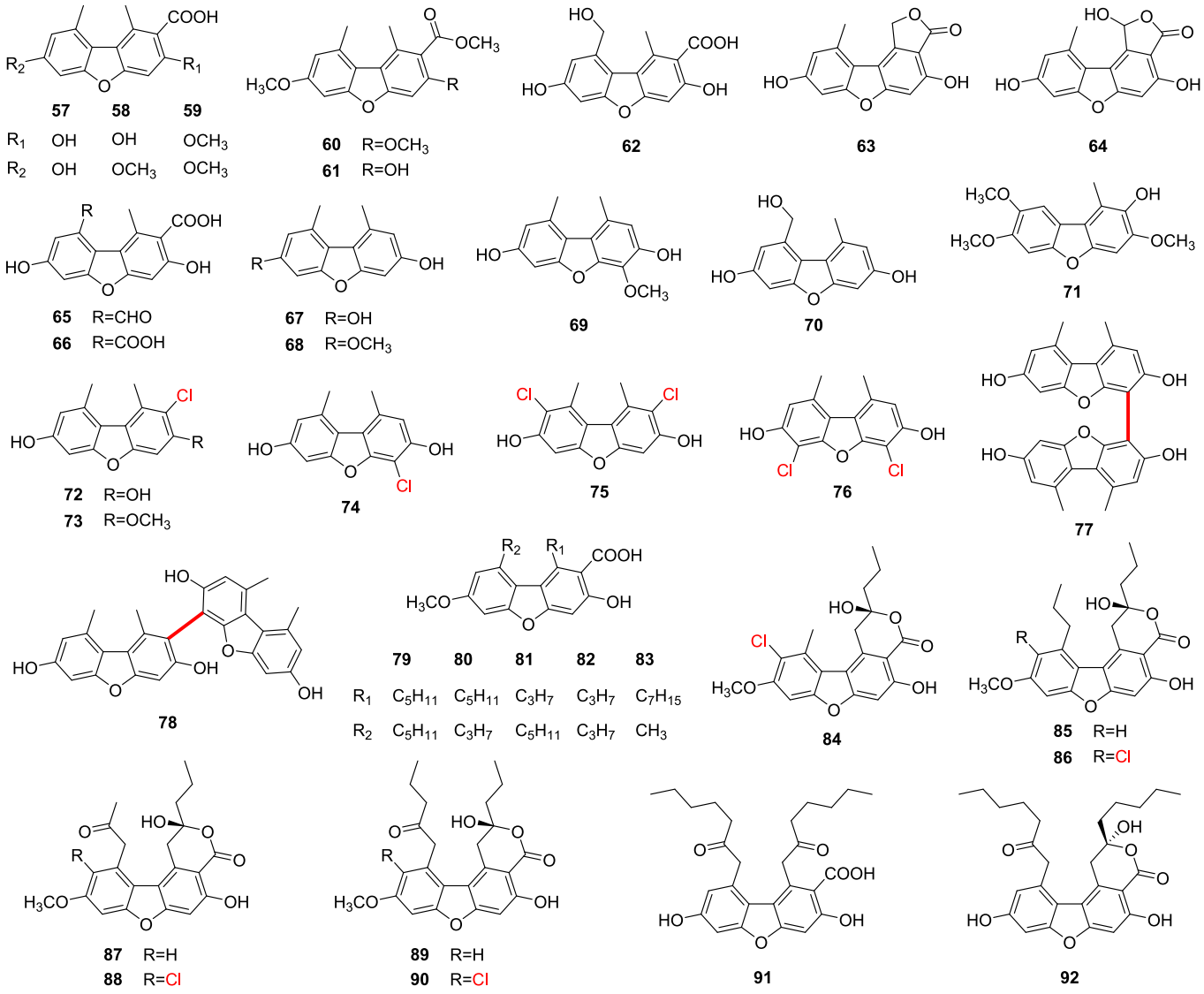


Fig. 4. Type IV lichen dibenzofurans from organisms.

mm) at 100 μg/disk [77]. Of note, compound **42** inhibited Gram-negative bacteria *Escherichia coli* with the IC_{50} value of 18 μg/mL (apramycin, IC_{50} = 2 μg/mL) [47].

2.2.2. Antifungal activity

At present, the antifungal activities of only types I and II lichen dibenzofurans have been reported. (-)-Mycousnine (**5**) [25], usone (**6**) [24], (+)-isomycousnine (**36**) [25], and isousone (**37**) [24] showed

antifungal effects against *Trichophyton rubrum*, with MIC values of 25, 41, 25, and 41 μg/mL, respectively. Furthermore, **5** and **36** also showed antifungal properties against *Trichophyton asteroides*, with MIC values of 25 and 6.2 μg/mL [25]. Nordibenzofuran mycousfuranine (**18**) exhibited antifungal activities against *Cryptococcus neoformans* and *C. gattii*, with MIC values of 50.0 μg/mL [31]. Phomodione (**8**) and cercosporamide (**19**) were active against *Pythium ultimum*, *Sclerotinia sclerotiorum*, and *Rhizoctonium solani* at 3–10 μg/mL [23]. In addition, compound **19** [32] was also against various human pathogenic yeasts, dermatophytes, and opportunistic fungi with MICs as low as 1 μg/mL by an *in vitro* minimum concentration test, and the usnic acid amide (**20**) [33], a methylated derivative of **19**, showed weaker activities than **19**.

2.2.3. Antiviral activity

(+)-Oxymycousnine (**13**) showed selective antiviral activity against an influenza B virus with 70 % plaque inhibition at 30 μg/mL, whereas the IC_{50} against the carrier cells was 190 μg/mL [25].

2.2.4. Anti-inflammatory activity

The *in vitro* anti-inflammatory and anti-gout effects of porphyrilic acid (**53**), strepsilin (**63**), and alectosarmentin (**64**) were assessed using cyclooxygenase (COX1/2), 5-lipoxygenase (5-LOX), and xanthine oxidase (XO) enzymes, and all compounds showed some inhibition of cyclooxygenase enzymes (IC_{50} values between 42 and 89 μg/mL), compounds **53** and **64** exhibited inhibition of 5-lipoxygenase enzyme (IC_{50} values of 49 and 71 μg/mL), but only compound **63** inhibited xanthine oxidase enzyme with an IC_{50} value of 80 μg/mL [60]. In addition, compound **67** showed conspicuous anti-inflammatory activity against NO production in RAW264.7 cells with IC_{50} value of 3.9 μM, compared with the positive controls curcumin (IC_{50} = 15.3 μM) and indomethacin (IC_{50} = 42.9 μM) [70].

2.2.5. Cytotoxic activity

Usenamines A–B (**24**–**25**), and isousone (**37**) exhibited cytotoxicities against human hepatocellular carcinoma HepG2 cells with IC_{50} values of 6.0, 50.2, and 53.3 μM, respectively [24]. In addition, 3,7-dihydroxy-1,9-dimethyldibenzofuran (**67**) showed cytotoxicities against human prostate adenocarcinoma PC3, human metastatic breast adenocarcinoma MDA-MB-231, and HepG2 cell lines (IC_{50} values of 39.4, 44.9, and 45.2 μM), and diorcinol H (**69**) also showed cytotoxicity against MDA-MB-231 cells (IC_{50} = 43.2 μM) [73].

2.2.6. Serine/threonine kinases inhibitory activity

Cercosporamide (**19**) showed significant inhibitory activity toward serine/threonine kinases, including protein kinase C (IC_{50} 1.6 μM) and myosin light chain kinase (IC_{50} 13 μM) [32]. Moreover, a methylated derivative of **19**, usnic acid amide (**20**), was also observed to inhibit protein kinase C (IC_{50} = 0.8 μM) [33].

2.2.7. Protein tyrosine phosphatase inhibitory activity

Usimines A–C (**31**–**33**) showed inhibitory activity against therapeutically targeted protein tyrosine phosphatase 1B (PTP1B), and their IC_{50} values were determined as 15.0 ± 0.1, 27.7 ± 2.1, and 23.2 ± 3.2 μM, respectively [35].

2.2.8. Acetylcholinesterase inhibitory activity

Ochuscins B–D (**17**, **21**, and **22**) and ochuscin G (**10**) exhibited weak inhibitory activities against acetylcholinesterase (AChE) with the IC_{50} values in the range from 50 to 75 μM (neosigmine, 0.99 μM) [28].

2.2.9. Phytotoxic activity

In leaf puncture wound tests (2 μL of a 0.1 mg/mL solution), fungal metabolite cercosporamide (**19**) [32] showed host-selective toxicity causing lesions on cassava, corn (*Zea mays*), and purslane (*Portulaca oleracea*), and its methylated product usnic acid amide (**20**) [33] also exhibited a more potent phytotoxic effect toward host plants *Citrus reticulata*, *Medicago hispida*, *Lactuca sativa*, *Musa paradisiaca*, *Acroptilon repens*, *Centaurea maculosa*, *Centaurea diffusa*, *Hibiscus sabdariffa*, *Avena sativa*, and *Zea mays*.

3. Non-lichen dibenzofurans

3.1. Structural diversity

Compared with lichen dibenzofurans, the number of non-lichen dibenzofurans is relatively higher. A total of 119 non-lichen dibenzofurans have been isolated and identified from nature, which are mainly distributed in higher plants, especially in the family Rosaceae, followed by the Myrtaceae. A small number of non-lichen dibenzofuran were also discovered from fungi, higher fungi, slime molds, and algae (Tables 5–8). Based on structural characteristics, these non-lichen dibenzofurans were divided into two types (types A and B). Dibenzofurans of type A (**93**–**139**, **196**–**203**, **210**, and **211**) are the dibenzofurans without alkyl substitution, and type B (**140**–**195**, and **204**–**209**) are the dibenzofurans with alkyl substitution, including methyl, ethyl, isobutyryl, isopentenyl, and larger alkyl chains.

Type A non-lichen dibenzofurans were isolated mainly from higher plants of the Rosaceae (Table 5). Compounds **93**–**133** with several hydroxyl and/or methoxy groups were isolated from higher plants (Table 5 and Fig. 5), of which sorbusin A (**101**) possesses a rare benzothiazole moiety and represents the first example of thiazole fused dibenzofuran, and sorbusin B (**102**) with a thiomethyl moiety was discovered from a *Sorbus pohuashanensis* cell suspension [85]. Three compounds (**111**, **129**, and **130**) isolated and identified from *Ribes takare* [86] and *Rhaphiolepis indica* [87], respectively, were found to contain the rare dioxymethylene functional group. 2,3,4,7-Tetramethoxydibenzofuran-6,9-quinone (**134**) having an unusual benzoquinone fragment was isolated from *Cydonia oblonga* [88]. Corallinafuran (**135**) with *meta*-dibromine substitution was discovered from crustose coralline red algae [89]. It is worth noting that four new benzofuran derivatives ribisins A–D (**136**–**139**) were isolated from the fruiting bodies of medicinal fungus *Phellinus ribis*, and one of their aromatic rings were reduced to the corresponding conjugated cyclohexenones [90].

Type B non-lichen dibenzofurans have mainly been isolated from higher plants of the Myrtaceae (Table 6). Compounds **140**–**156** with several methyl and/or ethyl groups were isolated from higher plants and fungi (Table 6 and Fig. 6), including xylariaquinone A (**150**) [111] with a benzoquinone structural fragment, alternethanoxin B (**151**) [112] and alternethanoxin E (**152**) [113] with a six-membered cyclic hemiacetal, and preussiafurans A–B (**154**–**155**) [114] fused with a tetrahydrofuran. Compounds **157**–**179** with several methyl, isobutyryl, and/or isopentenyl groups were isolated from higher plants, fungi, and higher fungi (Table 6 and Fig. 6), of which paucinervin C (**161**) [115] fused with a furan and a α-pyran, and **166** [116], albatrelin D (**178**) [117], and albatrelin F (**179**) [117] all have an α-pyran group. However, three novel compounds **180**–**182** each with 3 chlorine atoms and a short chain alkane substituent were discovered in cellular slime molds of Dictyosteliaceae [118,119]. In addition, except for scyphocephalione A (**190**) [120] which was isolated from *Scyphocephalium ochocoa* (Myristicaceae), all the other compounds (**183**–**189** and **191**–**195**) with two long chain alkane or alkene substituents were isolated from higher plants of families Primulaceae and Iridaceae (Table 6 and Fig. 6). Interestingly, except for compounds **189** and **190**, all the compounds contain a *p*-benzoquinone (**183**–**186**, **188**, and **191**–**195**) or *o*-benzoquinone (**187**) group.

Unlike lichen dibenzofurans, excluding aglycones, glycosylated derivatives of non-lichen dibenzofurans were also discovered from nature. Up to now, only ten non-lichen dibenzofuran glycosides (**196**–**205**) were discovered from higher plants and slime molds, of which seven are biosynthesized by higher plants of Rosaceae [107,128,149–152]. Of these, the glycosides of A-type non-lichen dibenzofuran are dominant, and one (aervfuranoside, **203** [149]) containing a chlorine atom, was

Table 5
Distribution of type A non-lichen dibenzofurans in organisms.

Category	Family	Species	Compounds
Higher plant	Berberidaceae	*Berberis koreana*	Eriobofuran (**96**) [91], δ-cotonefuran (**114**) [91], 9-hydroxyeriobofuran (**117**) [91], ε-cotonefuran (**120**) [91]
Higher plant	Fabaceae	*Bauhinia championii*	Bauhichamines A–B (**123**–**124**) [92]
Higher plant	Grossulariaceae	*Ribes takare*	7-Hydroxy-4,8-dimethoxy-2,3-methylenedioxydibenzofuran (**129**) [86], 4,7,8-trimethoxy-2,3-methylenedioxydibenzofuran (**130**) [86]
Higher plant	Hypericaceae	*Hypericum choisianum*	3-Hydroxy-1,4,7-trimethoxydibenzofuran (**116**) [93]
Higher plant	Hypericaceae	*Hypericum revolutum*	3-Hydroxy-1,4,7-trimethoxydibenzofuran (**116**) [93]
Higher plant	Lycopodiaceae	*Huperzia serrata*	1-Dibenzofuranol (**93**) [94]
Higher plant	Piperaceae	*Piper wallichii*	9-Hydroxyeriobofuran (**117**) [95]
Higher plant	Rosaceae	*Cotoneaster acutifolius*	γ-Cotonefuran (**112**) [96], δ-cotonefuran (**114**) [96], ε-cotonefuran (**120**) [96], α-cotonefuran (**126**) [96], β-cotonefuran (**127**) [96]
Higher plant	Rosaceae	*Cotoneaster divaricatus*	γ-Cotonefuran (**112**) [96], α-cotonefuran (**126**) [96], β-cotonefuran (**127**) [96]
Higher plant	Rosaceae	*Cotoneaster henryanus*	γ-Cotonefuran (**112**) [96], α-cotonefuran (**126**) [96], β-cotonefuran (**127**) [96]
Higher plant	Rosaceae	*Cotoneaster horizontalis*	γ-Cotonefuran (**112**) [96], α-cotonefuran (**126**) [96], β-cotonefuran (**127**) [96]
Higher plant	Rosaceae	*Cotoneaster lactea*	Cotonefuran (α-cotonefuran, **126**) [96,97]
Higher plant	Rosaceae	*Cotoneaster splendens*	γ-Cotonefuran (**112**) [96]
Higher plant	Rosaceae	*Crataegus monogyna*	2,8-Dihydroxy-3,4,7-trimethoxydibenzofuran (**128**) [98]
Higher plant	Rosaceae	*Crataegus pinnatifida*	1-Hydroxy-2,3,4-trimethoxydibenzofuran (**98**) [99], 1,6-dihydroxy-2,3,4-trimethoxydibenzofuran (**107**) [99], 2,3,4,6-tetramethoxy-7-hydroxydibenzofuran (β-cotonefuran, **127**) [100]
Higher plant	Rosaceae	*Crataegus pontica*	2,8-Dihydroxy-3,4,7-trimethoxydibenzofuran (**128**) [98]
Higher plant	Rosaceae	*Crataegus pycnoloba*	6-Hydroxy-2,3,4-trimethoxydibenzofuran (**104**) [101], 4-demethyl-6-hydroxy-β-pyrufuran (**105**) [101], 6-hydroxy-α-pyrufuran (**106**) [101], 7-methoxyeriobofuran (**115**) [101]
Higher plant	Rosaceae	*Crataegus oresbia*	2-Hydroxy-3,4-dimethoxydibenzofuran (**97**) [102], 1-hydroxy-2,3,4-trimethoxydibenzofuran (**98**) [102], 1,6-dihydroxy-2,3,4-trimethoxydibenzofuran (**107**) [102], 2-hydroxy-3,4,6-trimethoxydibenzofuran (**109**) [102], 2,8-dihydroxy-3,4,9-trimethoxydibenzofuran (**131**) [102], 2-hydroxy-3,4,6,8-tetramethoxydibenzofuran (**132**) [102]
Higher plant	Rosaceae	*Cydonia oblonga*	ε-Cotonefuran (**120**) [88], 6-hydroxy-2,3,4,7-tetramethoxydibenzofuran (**121**) [88], 1,6-dihydroxy-2,3,4,7-tetramethoxydibenzofuran (**122**) [88], 2,3,4,7-tetramethoxydibenzofuran-6,9-quinone (**134**) [88]
Higher plant	Rosaceae	*Eriobotrya japonica*	Eriobofuran (**96**) [103]
Higher plant	Rosaceae	*Malus rockii*	2-Hydroxy-4-methoxydibenzofuran (**94**) [104], 2-hydroxy-4,6-dimethoxydibenzofuran (**108**) [104]
Higher plant	Rosaceae	*Mespilus germanica*	6-Hydroxy-α-pyrufuran (**106**) [105], 6-methoxy-α-pyrufuran (**110**) [105], 7-hydroxy-6-methoxy-α-pyrufuran (**125**) [105], α-cotonefuran (**126**) [96,105]
Higher plant	Rosaceae	*Photinia davidiana*	Eriobofuran (**96**) [98], 7-methoxyeriobofuran (**115**) [98], 9-hydroxyeriobofuran (**117**) [98]
Higher plant	Rosaceae	*Pourthiaea lucida*	Lucidafuran (**95**) [106], eriobofuran (**96**) [106]
Higher plant	Rosaceae	*Pyracantha coccinea*	Eriobofuran (**96**) [98], 7-methoxyeriobofuran (**115**) [98], 9-hydroxyeriobofuran (**117**) [98]
Higher plant	Rosaceae	*Pyracantha koidzumii*	3,6-Dihydroxy-2,4-dimethoxydibenzofuran (**103**) [107], 9-hydroxyeriobofuran (**117**) [107]
Higher plant	Rosaceae	*Pyrus communis*	α-Pyrufuran (**99**) [108], β-pyrufuran (**100**) [108], γ-pyrufuran (**113**) [109]
Higher plant	Rosaceae	*Rhaphiolepis indica*	2-Hydroxy-3,4,6-trimethoxydibenzofuran (**109**) [87], 1,2-methylenedioxy-3,4,6-trimethoxydibenzofuran (**111**) [87], 2-hydroxy-3,4,9-trimethoxydibenzofuran (**119**) [87], 2-hydroxy-3,4,6,9-tetramethoxydibenzofuran (**133**) [87]
Higher plant	Rosaceae	*Sorbus aucuparia*	Eriobofuran (**96**) [13]
Higher plant	Rosaceae	*Sorbus commixta*	β-Pyrufuran (**100**) [110], 1,2,4-trimethoxydibenzofuran-3,9-diol (**118**) [110]
Higher plant cell suspension	Rosaceae	*Sorbus pohuashanensis* cell suspension	Eriobofuran (**96**) [85], sorbusins A–B (**101**–**102**) [85]
Higher fungus	Hymenochaetaceae	*Phellinus ribis*	Ribisins A–D (**136**–**139**) [90]
Red alga	–	crustose coralline red algae	Corallinafuran (**135**) [89]

isolated from *Aerva javanica* (Table 7 and Fig. 7).

Furthermore, six non-lichen dibenzofuran heterodimers were isolated from higher plants and green algae. As shown in Fig. 8, eleucanainone A (**206**) as a heterodimer of a B-type non-lichen dibenzofuran and a naphthoquinone derivative was isolated from the bulbs of *Eleutherine americana* [153]. An adduct of a B-type non-lichen dibenzofuran and a biphenyl derivative (**207**) and its sulfate (**208**) were found from the green alga *Cladophora socialis* [154]. In addition, lavandufurandiol (**209**) [155], piperwalliol A (**210**) [156], and sorbalanin (**211**) [157], three heterodimers of non-lichen dibenzofurans and phenylpropanoids, were produced by *Lavandula angustifolia*, *Piper wallichii*, and *Sorbus lanata*, respectively.

3.2. Biological activities

Generally, simple non-lichen dibenzofurans (type A) are considered as phytoalexins in the plants of the Rosaceae. Besides their activities against plant pathogens, non-lichen dibenzofurans have a variety of biological activities similar to lichen dibenzofurans, such as antibacterial and cytotoxic activities. The biological activities of the diverse non-lichen dibenzofurans are summarized below.

3.2.1. Anti-plant pathogenic fungi activity

Eriobofuran (**96**), β-pyrufuran (**100**), 6-hydroxy-α-pyrufuran (**106**), 6-methoxy-α-pyrufuran (**110**), γ-cotonefuran (**112**), δ-cotonefuran (**114**), 7-methoxyeriobofuran (**115**), and 9-hydroxyeriobofuran (**117**), ε-cotonefuran (**120**), 7-hydroxy-6-methoxy-α-pyrufuran (**125**), α-cotonefuran (**126**), and β-cotonefuran (**127**) showed antifungal activity against *Alternaria alternata*, *Botrytis cinerea*, and *Fusarium culmorum* with ED_{50} values ranging from 12 to 100 μg/mL [96,98,105]. Furthermore, **96** showed complete inhibition on the spore germination and spore germ tube growth of *Pestalotia funereal* at a concentration of 43.2 μg/mL [103]. It is noted that three alkyl substituted dibenzofurans (type B) porric acids A–C (**140**–**142**) were found to exhibit antifungal activity against *Fusarium culmorum* with ED_{50} values of 20–30 μg/mL [121]. Furthermore, the dibenzofuran glycoside fulicineroside (**205**) showed inhibition of the growth (about 83 % at 50 μg/disk) of crown gall tumors on potato disks inoculated with *Agrobacterium tumefaciens* [152].

3.2.2. Antibacterial activity

Like the lichen dibenzofurans, antibacterial activity is also one of the most studied bioactivities for non-lichen dibenzofurans. However, the

Table 6
Distribution of type B non-lichen dibenzofurans in organisms.

Category	Family	Species	Compounds
Higher plant	Amaryllidaceae	*Allium Porrum*	Porric acids A–C (**140**–**142**) [121]
Higher plant	Asparagaceae	*Ruscus aculeatus*	Ruscodibenzofuran (**153**) [122]
Higher plant	Asteraceae	*Achyrocline satureioides*	Achyrofuran (**165**) [123], 1′,1′′-[6,7,9-trihydroxy-8-(2-hydroxy-3-methylbut-3-en-1-yl)-3,3-dimethyl-3H-benzofuro[2,3-*f*]chromene-5,10-diyl]bis(2-(*S*)-methylbutan-1-one) (**166**) [116]
Higher plant	Asteraceae	*Ligularia caloxantha*	1,2,4-Trimethyl-7,8-dimethoxy-dibenzofuran (**148**) [124]
Higher plant	Asteraceae	*Ligularia intermedia*	Ligumedial (**146**) [125], ligumediaoic acid (**147**) [125]
Higher plant	Calophyllaceae	*Calophyllum panciflorum*	Calophyfuran (**159**) [126]
Higher plant	Clusiaceae	*Garcinia paucinervis*	Paucinervin C (**161**) [115]
Higher plant	Hamamelidaceae	*Distylium racemosum*	2,7-Dihydroxy-1,6-dimethoxy-9-methyldibenzofuran (**144**) [127], 2-hydroxy-1,6,7-trimethoxy-9-methyldibenzofuran (**145**) [128], 3,7-dihydroxy-6-methoxy-2,7-dimethyldibenzofuran (**149**) [127]
Higher plant	Iridaceae	*Belamcanda chinensis*	Belamcandones A–D (**191**–**194**) [129]
Higher plant	Iridaceae	*Iris pallasii*	Belamcandone P (**195**) [130]
Higher plant	Myristicaceae	*Scyphocephalium ochocoa*	Scyphocephalione A (**190**) [120]
Higher plant	Myrtaceae	*Callistemon viminalis*	Callistemenonone A (**167**) [131], callistemonol A (**168**) [132]
Higher plant	Myrtaceae	*Myrtus communis*	1,1′-(1,3,7,9-Tetrahydroxydibenzo[*b*,*d*]furan-2,8-diyl)bis(ethan-1-one) (**156**) [133]
Higher plant	Myrtaceae	*Pilidiostigma glabrum*	Rhodomyrtoxin C (**172**) [134], 1,3,7,9-tetrahydroxy-2,8-dimethyl-4,6-di(2-methylbutanoyl)dibenzofuran (**173**) [134], 1,3,7,9-tetrahydroxy-2,8-dimethyl-4-(2-methylbutanoyl)-6-(2-methylpropionyl)dibenzofuran (**174**) [134], 1,3,7,9-tetrahydroxy-4,6-dimethyl-2-(2-methylbutanoyl)-8-(2-methylpropionyl)dibenzofuran (**175**) [134], 1,3,7,9-tetrahydroxy-2,8-dimethyl-4,6-di(2-methylpropionyl)dibenzofuran (**176**) [134], 1,3,7,9-tetrahydroxy-4,6-dimethyl-2,8-di(2-methylpropionyl)dibenzofuran (**177**) [134]
Higher plant	Myrtaceae	*Pilidiostigma tropicum*	Rhodomyrtoxin B (**171**) [135]
Higher plant	Myrtaceae	*Rhodomyrtus macrocarpa*	Rhodomyrtoxin (**169**) [136,137], ψ-rhodomyrtoxin (**170**) [138], rhodomyrtoxins B–C (**171**–**172**) [139]
Higher plant	Primulaceae	*Aegiceras corniculatum*	2,7-Dihydroxy-8-methoxy-3,6-diundecyldibenzofuran-1,4-dione (**183**) [140], 2,8-dihydroxy-7-methoxy-3,9-diundecyldibenzofuran-1,4-dione (**184**) [140]
Higher plant	Primulaceae	*Labisia pumila*	Fatimahol (**189**) [141]
Higher plant	Primulaceae	*Lysimachia fordiana*	Fordianaquinones A–B (**187**–**188**) [142]
Higher plant	Primulaceae	*Parathesis amplifolia*	Parathesiquinones A–B (**185**–**186**) [143]
Fungus	–	an unidentified fungus	3,9-Dihydroxy-1,7-dimethyl-2-isopentenyldibenzofuran (**164**) [144]
Fungus	Aspergillaceae	*Aspergillus karnatakaensis*	Karnatakafurans A–B (**162**–**163**) [145]
Fungus	Pleosporaceae	*Alternaria sonchi*	Alternethanoxin B (**151**) [112], alternethanoxin E (**152**) [113]
Fungus	Pleosporaceae	*Alternaria* sp.	Porric acid D (**143**) [146]
Fungus	Sporormiaceae	*Preussia* sp.	Preussiafurans A–B (**154**–**155**) [114]
Fungus	Trichocomaceae	*Talaromyces* sp.	Talaromycins A–B (**157**–**158**) [147]
Fungus	Xylariaceae	*Xylaria* sp.	Xylariaquinone A (**150**) [111]
Higher fungus	Albatrellaceae	*Albatrellus ovinus*	Albatrelin D (**178**) [117], albatrelin F (**179**) [117]
Higher fungus	Polyporaceae	*Ganoderma lucidum*	Lingzhifuran A (**160**) [148]
Slime mold	Dictyosteliaceae	*Dictyostelium purpureum*	1,9-Dihydroxy-3,7-dimethoxy-2-hexanoyl-4,6,8-trichlorodibenzofuran (**182**) [118]
Slime mold	Dictyosteliaceae	*Polysphondylium filamentosum*	1-(4,6,8-Trichloro-1,9-dihydroxy-3,7-dimethoxy-2-dibenzofuranyl)butanone (**180**) [119], 1-(4,6,8-trichloro-9-hydroxy-1,3,7-trimethoxy-2-dibenzofuranyl)butanone (**181**) [119]

Table 7
Distribution of non-lichen dibenzofuran glycosides in organisms.

Category	Family	Species	Compounds
Higher plant	Amaranthaceae	*Aerva javanica*	Aervfuranoside (**203**) [149]
Higher plant	Hamamelidaceae	*Distylium racemosum*	7-[(β-D-Glucopyranosyl)oxy]-3-hydroxy-6-methoxy-2,9-dimethyldibenzofuran (**204**) [128]
Higher plant	Rosaceae	*Malus* × *domestica*	Malusfuran (**196**) [150]
Higher plant	Rosaceae	*Pyracantha fortuneana*	Fortuneanosides G–L (**197**–**202**) [151]
Higher plant	Rosaceae	*Pyracantha koidzumii*	Fortuneanoside J (**200**) [107], fortuneanoside L (**202**) [107]
Slime mold	Physaraceae	*Fuligo cinerea*	Fulicineroside (**205**) [152]

number of non-lichen dibenzofurans active against multidrug-resistant strains of *Staphylococcus aureus* is higher than that of lichen dibenzofurans. For example, compounds **116**, **165**–**168**, and **206** were active against a panel of multidrug-resistant strains of *Staphylococcus aureus* [93,116,131,132,153], of which achyrofuran (**165**) showed strong *in vitro* antibacterial activities against methicillin-resistant and vancomycin-intermediate *S. aureus* NRS402 (MIC = 0.1 μM) [116], callistemonol A (**168**) exhibited significant activities against two methicillin-resistant *S. aureus* (MRSA) strains, with MIC and MBC (minimum bactericidal concentration) values ranging from 3.12 to 6.25 μg/mL [132], and the dimeric non-lichen dibenzofuran eleucanainone A

Table 8
Distribution of dimeric non-lichen dibenzofurans in organisms.

Category	Family	Species	Compounds
Higher plant	Iridaceae	*Eleutherine americana*	Eleucanainone A (**206**) [153]
Higher plant	Labiatae	*Lavandula angustifolia*	Lavandufurandiol (**209**) [155]
Higher plant	Piperaceae	*Piper wallichii*	Piperwalliol A (**210**) [156]
Higher plant	Rosaceae	*Sorbus lanata*	Sorbalanin (**211**) [157]
Green alga	Caldophoraceae	*Cladophora socialis*	Vanillic acid derivative (**207**) [154] and its sulfate adduct (**208**) [154]

(**206**) exhibited remarkable anti-MRSA activity *in vitro* with MIC value of 0.78 μg/mL by downregulation of basal expression of resistance genes *agr*A, *cid*A, *ica*A, and *sar*A [153]. Moreover, sorbusin B (**102**) was active against multidrug-resistant *Enterococcus faecium* with MIC value of 12.5 μg/mL (ciprofloxacin, 3.13 μg/mL) [85]. Besides the abovementioned resistant strains, non-lichen dibenzofurans also showed good activity against other non-resistant strains, such as 3,9-dihydroxy-1,7-dimethyl-2-isopentenyldibenzofuran (**164**) that showed inhibitory activity against *Staphylococcus aureus*, *Enterococcus faecalis*, *Saccharomyces cerevisiae*, and *Candida albican* strains with MIC values of 4, 2, 1 and 8 μg/mL, respectively [144]. Rhodomyrtoxin B (**171**) exhibited noteworthy activities against *Bacillus cereus* (MIC = 0.14 μM, gentamicin sulfate 2.14 μM) and *Staphylococcus aureus* (MIC = 0.28 μM, gentamicin sulfate 1.07 μM) [135]. Compounds **172**–**177** displayed distinct bactericidal activity against *Staphylococcus aureus* ATCC 29213, *S. aureus* ATCC 25923 and *S. epidermidis* ATCC 35984 with MIC values from 0.5 to 26.5 μM and MBC values from 0.9 to 26.5 μM [134]. l,9-Dihydroxy-3,7-dimethoxy-2-hexanoyl-4,6,8-trichlorodibenzofuran (**182**) inhibited the growth of a panel of Gram-positive bacteria, and its MICs ranged from 0.39 to 50 μg/mL [118]. In addition, the dibenzofuran glycoside

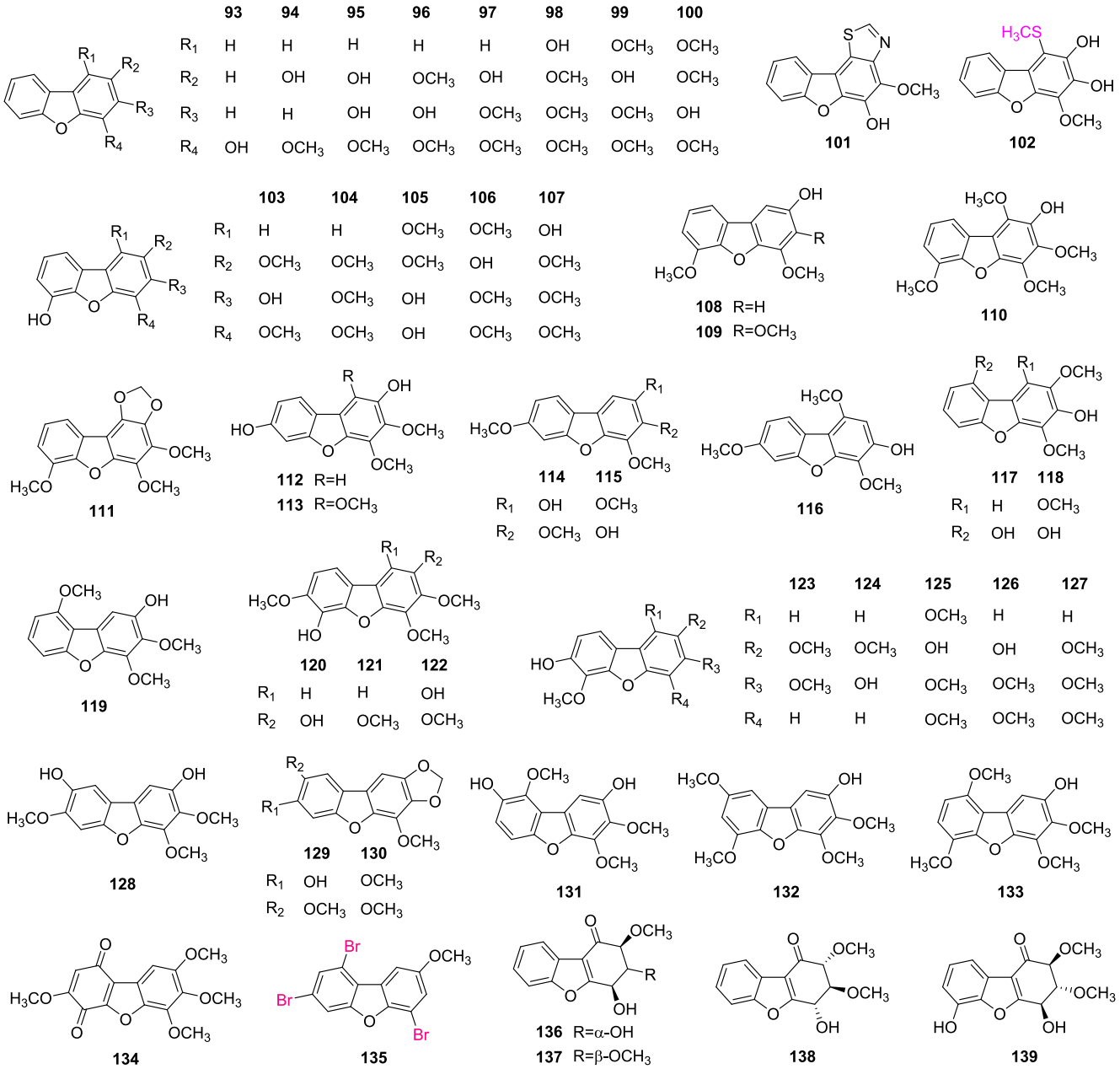


Fig. 5. Type A non-lichen dibenzofurans from organisms.

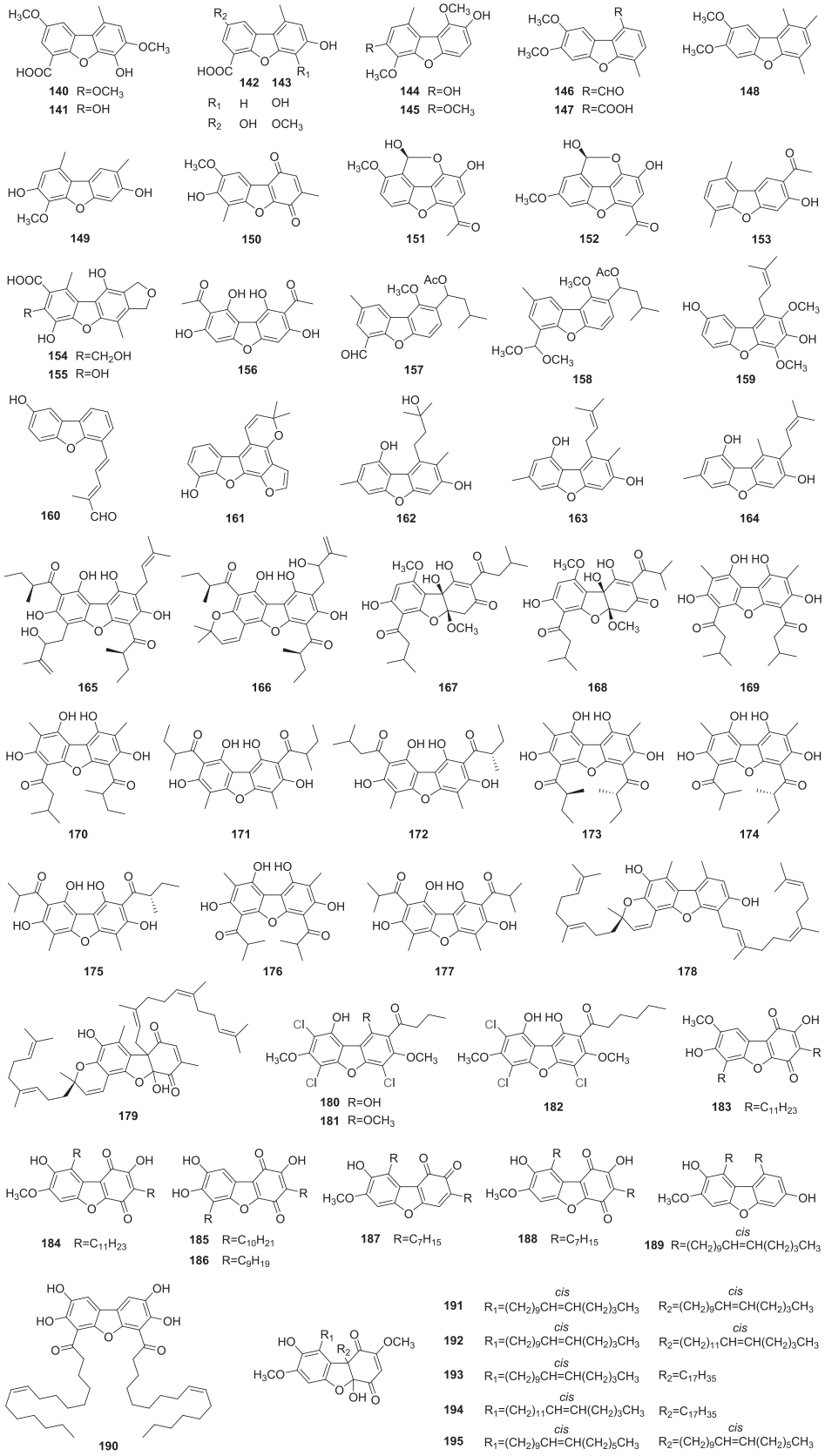


Fig. 6. Type B non-lichen dibenzofurans from organisms.

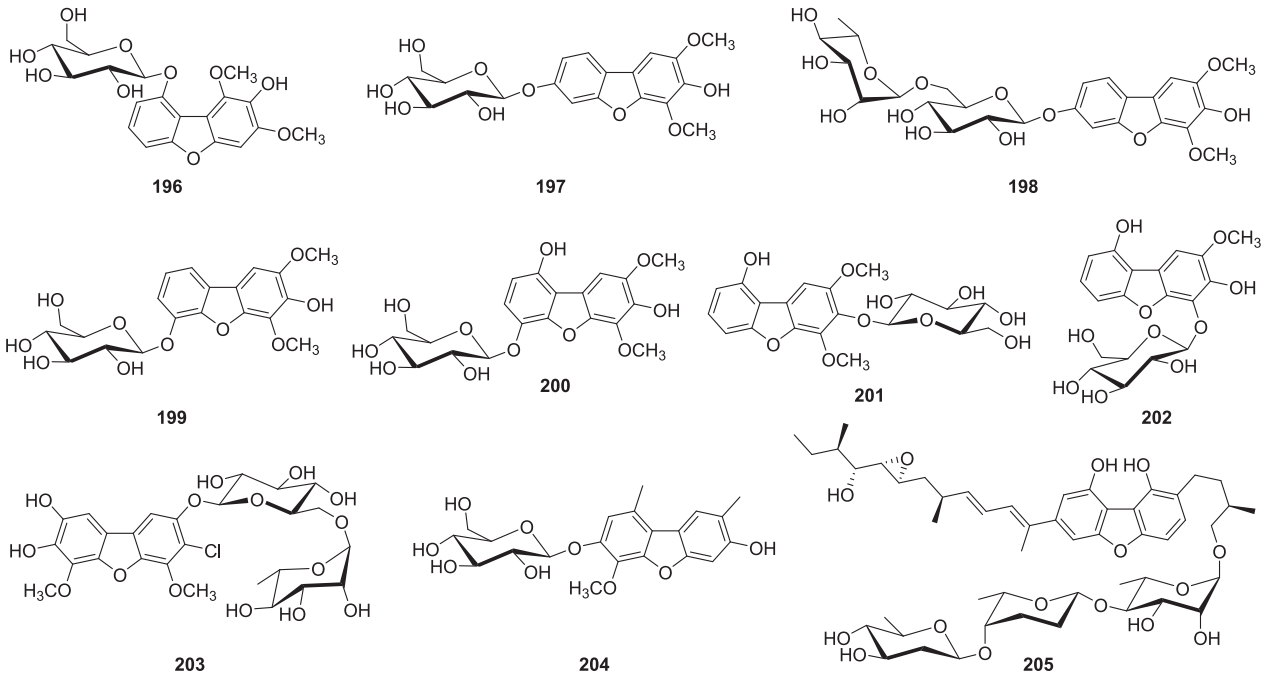


Fig. 7. Non-lichen dibenzofuran glycosides from organisms.

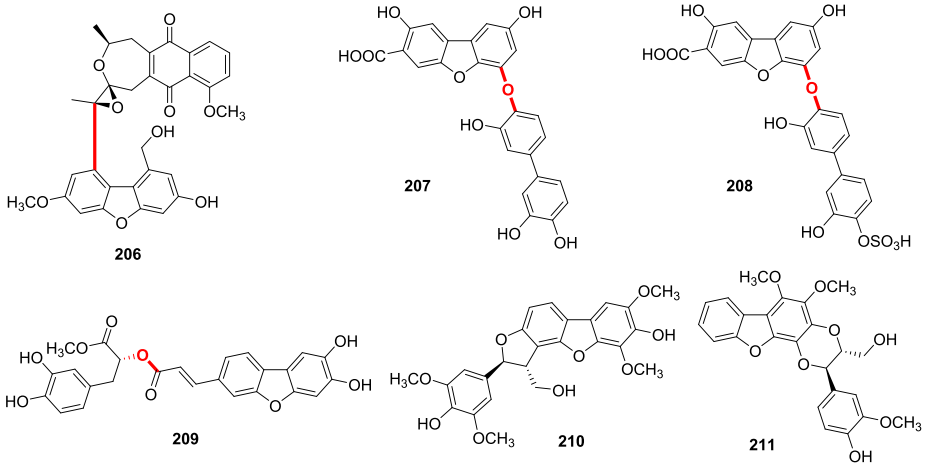


Fig. 8. Dimeric non-lichen dibenzofurans from organisms.

fulicineroside (**205**) was highly active against *Staphylococcus aureus* and *Bacillus subtilis* with diameters of inhibitory zones of 48 and 56 mm at 10 μg/disk, respectively [152].

3.2.3. Cytotoxic activity

1-Hydroxy-2,3,4-trimethoxydibenzofuran (**98**) and 1,6-dihydroxy-2,3,4-trimethoxydibenzofuran (**107**) exhibited cytotoxicity against human hepatoma cell lines HepG2 (IC_{50} values of 41.5 and 53.1 μM) and Hep3B (IC_{50} values of 41.9 and 51.0 μM) [99]. Preussiafurans A–B (**154**–**155**) showed cytotoxicity on rat skeletal myoblast L6 cells with IC_{50} values of 36.7 and 60.8 μM, respectively [114]. Paucinervin C (**161**) showed cytotoxicity against HeLa-C3 cells with IC_{50} value of 52.5 μM [115]. Rhodomyrtoxin B (**171**) showed *in vitro* cytotoxic activity against HepG2 (LC_{50} = 19.0 μM) and human mammary adenocarcinoma MDA-MB-231 (LC_{50} = 2.50 μM) cell lines [135]. Chlorinated dibenzofurans **180** and **182** showed cytotoxicity toward leukemia K562 (IC_{50} < 2 μM), cervical carcinoma HeLa (IC_{50} < 5 μM), and mouse embryo fibroblast 3 T3-L1 (IC_{50} < 10 μM) cell lines [119]. The IC_{50} of fordianaquinones A (**187**) and B (**188**) against human lung cancer A549 cells were 50 and 120 μg/mL, respectively [142]. Furthermore, scyphocephalione A (**190**) reduced the cell viability of MCF-7 with an IC_{50} of 5.25 μM by an MTT test [120].

3.2.4. Anti-inflammatory activity

The anti-inflammatory effects of dibenzofurans were evaluated by suppressing fMet-Leu-Phe (fMLP)-induced superoxide anion generation by human neutrophils. Lucidafuran (**95**), eriobofuran (**96**), 2-hydroxy-3,4,6-trimethoxydibenzofuran (**109**), 2-hydroxy-3,4,9-trimethoxydibenzofuran (**119**), and 2-hydroxy-3,4,6,9-tetramethoxydibenzofuran (**133**) exhibited some inhibitory activity against fMLP-induced superoxide anion production by human neutrophils with IC_{50} values of 7.6–32.7 μM (ibuprofen, IC_{50} = 27.5 μM) [87,106]. *ε*-Cotonefuran (**120**) inhibited lipopolysaccharide (LPS)-activated NO production of murine microglial cells BV-2, with IC_{50} value of 33.0 μM [91]. Compounds **172**–**175**, and **177** inhibited the synthesis of NO in RAW264 macrophages with IC_{50} values in the low micromolar range (0.6–5.0

μM), of which compounds **172**, **175**, and **177** with 2,8-diacyl substitutions also inhibited the synthesis of PGE_2 in 3 T3 cells (IC_{50} values of 3.4, 6.0, and 4.5 μM, respectively) [134]. In addition, scyphocephalione A (**190**) significantly inhibited NO production (88.7 %) of murine macrophage cells J774.2 at 25 μg/mL. This activity is greater than that of the reference substance monomethyl-L-arginine acetate NG (65.6 % inhibition at 25 μg/mL) [120].

3.2.5. Melanin synthesis inhibitory activity

Tyrosinase is a key enzyme for the synthesis of melanin in human melanocytes, so inhibitory activity against tyrosinase is often used to evaluate whether a substance has inhibitory activity towards melanin production. Four dibenzofuran glycosides fortuneanosides G–J (**197**–**200**) showed greater *in vitro* tyrosinase-inhibitory activities (IC_{50} values of 80–190 μM) than the positive control arbutin (IC_{50} 230 μM) [151]. Furthermore, 6-hydroxy-2,3,4-trimethoxydibenzofuran (**104**), 6-hydroxy-*α*-pyrufuran (**106**), and 7-methoxyeriobofuran (**115**) show reversible inhibition of melanin synthesis and do not act *via* inhibition of tyrosinase or interfere with melanocyte differentiation or migration. Molecular modeling suggests that they can bind to aryl hydrocarbon receptor (AHR) and qPCR experiments demonstrated that they can activate downstream effector genes of AHR [101].

3.2.6. Lipid-lowering activity

The lipid-lowering activities of dibenzofurans have been reported recently by the authors, and all of them are from Rosaceae. The *in vitro* lipid-lowering activities of dibenzofurans were evaluated by lipid accumulation assay of HepG2 cells, and 2-hydroxy-4-methoxydibenzofuran (**94**), 2-hydroxy-3,4-dimethoxydibenzofuran (**97**), 1-hydroxy-2,3,4-trimethoxydibenzofuran (**98**), 2-hydroxy-4,6-dimethoxydibenzofuran (**108**), and 2-hydroxy-3,4,6-trimethoxydibenzofuran (**109**) showed some activities with lipid-lowering rates of 10.9 ± 5.6 %, 8.1 ± 5.0 %, 8.0 ± 6.9 %, 9.0 ± 3.6 %, and 16.0 ± 3.4 % at 100 μM, and of 4.7 ± 2.0 %, 6.1 ± 3.5 %, 7.6 ± 6.2 %, 3.6 ± 2.3 %, and 13.5 ± 4.2 % at a concentration of 50 μM, respectively [102,104]. Among them, the activity of compound **109** was stronger than simvastatin (lipid-lowering rate of 11.4 ± 3.0 % at 50 μM) [102], suggesting that dibenzofurans may be a good prospect for hypolipidemic treatment leads.

3.2.7. Antimalarial activity

Xylariaquinone A (**150**) showed *in vitro* activity against *Plasmodium falciparum* K1 strain, with IC_{50} value of 6.68 μM [111]. Preussiafurans A–B (**154**–**155**) showed antiplasmodial activity against erythrocytic stages of chloroquine-resistant *Plasmodium falciparum* (NF54) (IC_{50} values of 8.76 and 15.0 μM, respectively) [114]. Moreover, karnatakafurans A (**162**) and B (**163**) showed moderate *in vitro* activity against a chloroquine-sensitive *Plasmodium falciparum* 3D7 parasite with IC_{50} values of 3.9 and 3.6 μg/mL (chloroquine IC_{50} = 0.012 μg/mL), respectively [145].

3.2.8. Anti-rheumatoid arthritis activity

Bauhichamines A (**123**) and B (**124**) were evaluated for their anti-rheumatoid arthritis activities *via* examining their anti-proliferative effects on synoviocytes *in vitro*, and they exhibited inhibitory effects on the proliferation of synoviocytes with the IC_{50} values of 103.1 ± 1.8 and 146.4 ± 1.2 μM (methotrexate, IC_{50} = 112.8 ± 1.9 μM), respectively [92].

3.2.9. Antioxidant activity

Scyphocephalione A (**190**) has inhibitory activities on reactive oxygen species (ROS) production by human whole blood phagocytes with IC_{50} value of 37.8 μM. Regarding neutrophils and mouse peritoneal macrophages, compound **190** also showed an inhibitory effect on intracellular ROS (IC_{50} = 24.56 and 17.23 μM) and on extracellular ROS production (IC_{50} = 36.20 and 7.44 μM) [120]. In addition, lavandufurandiol (**209**) (IC_{50} = 0.81 ± 0.04 μg/mL) had stronger free radical scavenging activity compared to vitamin C (IC_{50} = 5.34 ± 0.42 μg/mL) [155].

3.2.10. Neurite outgrowth-promoting activity

Ribisins A–D (**136**–**139**), with a hydrogenated dibenzofuranone skeleton, were found to promote neurite outgrowth of NGF-mediated PC12 cells in a dose-dependent manner at concentrations ranging from 1 to 30 μM [90].

3.2.11. Others

Corallinafuran (**135**) exhibited toxic activity against larvae of the scleractinian coral *Pseudosiderastrea tayamai*, with LD_{99} value of 1.9 μg/mL [89]. Tested by leaf disk-puncture assay on the fungal host plant and a number of nonhost plants, alternethanoxin B (**151**) was shown to be a nonselective phytotoxic [112].

Achyrofuran (**165**) significantly lowered blood glucose levels in a type 2 diabetes *db/db* mouse model when administered orally at 20 mg/kg q.d, along with a slight decrease in body weight and food intake, but the animals appeared healthy during treatment [123]. In addition, vanillic acid derivative (**207**) and its sulfate adduct (**208**) showed potent inhibitory activity against the target protein tyrosine phosphatase 1B (PTP1B) in the treatment of type 2 diabetes and obesity, with IC_{50} values of 3.71 and 1.70 μM, respectively [154].

When examined for elastase inhibition activity, 3,7-dihydroxy-6-methoxy-2,7-dimethyldibenzofuran (**149**) (IC_{50} = 7.7 μg/mL) was more active than oleanolic acid (IC_{50} = 9.7 μg/mL), a compound commercially applied as the whitening ingredient in functional cosmetics. However, 2,7-dihydroxy-1,6-dimethoxy-9-methyldibenzofuran (**144**) (IC_{50} = 97.4 μg/mL) showed weak activity [127].

Unilateral ureteral obstruction (UUO) is commonly used to induce progressive renal fibrosis in rodent models. The *in vivo* experiments show that oral administration of lingzhifuran A (**160**) (50 mg/kg and 100 mg/kg) in rats immediately after unilateral UUO suppresses renal expression of *α*-SMA, collagen I, and fibronectin at both mRNA and protein levels. Late oral administration of **160** (100 mg/kg) 7 days after UUO also markedly attenuates fibrotic lesions in obstructive nephropathy. In addition, **160** could selectively inhibit TGF-*β*1-induced Smad3 phosphorylation in rat renal tubular epithelial cells [148].

Chlorinated dibenzofurans **180** and **182** showed a selective inhibitory effect on broad gene expressions in *Drosophila melanogaster*, which decreased the activity of *β*-galactosidase and inhibited the innate immune response at 1 μM, and decreased heat shock-mediated gene expression at 0.5 μM [119].

4. Conclusions

This review provides the first comprehensive overview on all dibenzofurans from nature. Dibenzofurans are still a small class of natural products, altogether 211 dibenzofurans isolated and identified from organisms were reviewed in this paper, which were divided into two groups and six subgroups (or types). The dibenzofurans are distributed not only in lichens but also in higher plants, breaking the conventional understanding that dibenzofurans are mainly from lichens and ascomycetes, and show a broad spectrum of biological activities. From the perspective of source, lichen dibenzofurans are mainly derived from lichens, and a small number from mycobionts and fungi. However, non-lichen dibenzofurans are almost exclusively distributed in higher plants. Types I and II lichen dibenzofurans are mainly from lichens of the Parmeliaceae, especially in genus *Usnea*. Among them, nitrogen-containing lichen dibenzofurans are distributed in genus *Usnea*, Antarctic lichens, and fungi *Ochroconis* sp. and *Cercosporidium henningsii*, but nordibenzofurans are found mainly from fungi of the Mycosphaerellaceae. Type III lichen dibenzofurans are mainly distributed in lichens of Roccellaceae. Type IV are the largest group of lichen dibenzofurans, and are mainly distributed in lichens of genus *Cladonia* (Cladoniaceae) and mycobiont of *Lecanora* (Lecanoraceae), of which chlorinated

derivatives are only from lichen *Letrouitia vulpina* and mycobionts of *Lecanora*. Type A non-lichen dibenzofurans are almost wholly from the Rosaceae. Type B non-lichen dibenzofurans isolated from the Myrtaceae have several isobutyryl and/or isopentenyl groups, while from the families Primulaceae and Iridaceae have two larger alkyl chains and a benzoquinone structural fragment. As for biological activity, antibacterial and cytotoxic activities are common to both lichen dibenzofurans and non-lichen dibenzofurans. Both lichen and non-lichen dibenzofurans have antifungal activity, but the former is mainly against human pathogenic fungi, while the latter, usually regarded as plant antitoxin, is mainly toward plant pathogenic fungi. However, some activities like lipid-lowering were only reported for non-lichen dibenzofurans. In addition, the biosynthetic pathways for dibenzofurans were also summarized in this review. Finally, although the dibenzofurans found in nature are very limited, they have a wide range of significant biological activities, especially the representative compound usnic acid which has been widely used in dietary supplements, daily chemical products, and medicine. Therefore, it is believed that through in-depth study of the structural diversity and biological activity of benzofurans, new medicinal lead compounds and functional components will be discovered.

CRediT authorship contribution statement

Xin Liang: Data curation, Investigation, Methodology, Writing – review & editing. **Wei Chen:** Data curation, Investigation, Methodology, Writing – review & editing. **Bei Jiang:** Formal analysis, Project administration, Supervision. **Chao-Jiang Xiao:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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