

Chemical diversities, biological activities and chemical synthesis of marine diphenyl ether and their derivatives

Keisham S. Singh^{a,*}, Archana Singh^{a,b}

^aBioorganic Chemistry Laboratory, CSIR-National Institute of Oceanography,
Dona Paula-403004, Goa, India;

^bNational Centre of Polar and Ocean Research, Ministry of Earth Sciences,
Vasco da Gama, 403804, Goa, India

* For correspondence: keisham@nio.org; keisham.sarjit@gmail.com;
Ph: +91-0832-2450392; Fax: +91-0832-2450607

Abstract:

Marine organisms produce several secondary metabolites that find applications in pharmacology and biological systems. Vast biodiversity and unique environmental conditions endowed with marine ecosystem provide marine organisms as a rich sources of various fascinating molecules. It is estimated that more than 33,000 secondary metabolites have been discovered from marine organisms and studied for their chemical and biological properties. Diaryl/diphenyl ethers are a class of compounds possessing interesting biological properties including antimicrobial, antifouling, cytotoxicity and anti-proliferative activities. They have been mainly isolated from marine sponges although they are also known from numerous other marine organisms such as algae, ascidians, mussels, fungi, bacteria and marine mammals. Although, their isolations of diphenyl ethers and their biological activities have been documented in several published articles, a review dedicated to this class of compounds is lacking so far. Therefore, we believe that a comprehensive review of marine diphenyl ethers is timely and necessary. This review describes diphenyl ethers isolated from various marine organisms detailing their chemical structures and reported biological activities. Further, the review also presents postulated biosynthetic pathway and synthetic aspects of selected marine diphenyl ethers reported in literature.

Keywords: Marine organisms; Endophytic fungi, Polybromodiphenyl ethers; Flame retardants; Antiproliferative; Antibacterial; Cytotoxicity; Synthesis, Baeyer-Villiger Oxidation; Ullmann coupling.

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1. Introduction

Marine environment covers 70% of the earth surface and endowed with a vast biodiversity. It not only supports livelihood of millions of people in the way of providing food, minerals and valuable resources, but also is a rich source of biologically active compounds needed for pharmaceutical industries. It is estimated that more than 33,000 secondary metabolites have been discovered from various marine organisms. Chemical and biological activities of marine derived compounds have been well documented in several review articles [1]. In the early 1950s Bergmann and Feeny isolated unusual nucleosides spongouridin and spongothymidin from the sponge *Cryptotheca crypta* [2, 3]. These compounds served as the leading structures for antiviral drugs and subsequently, considerable progress has been made on the discovery of bioactive compounds from marine organisms. A pioneering work of marine natural product research was carried out by Faulkner [4], Blunt [5], Fenical [6] and Capon's [7] research groups. Among the secondary metabolites of marine organisms, halogenated compounds are considered as one of the most abundant compound with a vast structural diversity. Numerous organohalogen compounds, including bromopyrrole, bromoacetylenic acids, halogenated phenols and brominated diphenyl ethers have been isolated from marine organisms [8, 9].

Diphenyl ethers represent a group of marine natural products which are known for their remarkable biological activities [10]. Chemically they are phenyl/aryl ring with substituted groups such as -OH, OMe, X or R linked through ether bond (Figure 1). These natural products are formed by the coupling of two or more phenolic ring promoted by means of free radical reaction (Figure 2) [11]. Diaryl ether derivatives constitute a large number of organic compounds comprised of halogens or other substituent groups such as carboxylic acid, ester, hydroxy, methoxy, aldehyde etc. or even simple hydrocarbon chain and fused ring system. The family of diphenyl ethers particularly, polybromodiphenyl ethers (PBDEs) are widely distributed with numerous congeners. PBDEs have been widely used as flame retardants and the occurrence of bromodiphenyl ethers (BDEs) is an environmental concern due to their persistence in environment, toxic nature and biomagnification in food web. They are bio-accumulative anthropogenic and natural chemicals, widely found in marine environment. Over the years, the origin of hydroxylated polybromodiphenyl ethers (OH-PBDEs) and methoxylated polybromodiphenyl ethers (MeO-PBDEs) have been a hot debate among the scientific communities due to their structural similarities with the industrial flame retardants [12]. Recent studies showed that several BDEs particularly, MeO-PBDEs and OH-PBDEs are metabolites of marine organisms and in many cases, BDEs accumulated in the marine food chain, appeared to be natural in origin rather than anthropogenic [13].

In marine environment, PBDEs are found in several organisms such as sponges, algae, microbes etc. Teuten *et al.* has shown that abundant halogenated compounds bioaccumulated in many organisms are actually natural in origin [14]. Naturally produced PBDEs are distinguished from the man-made ones by the presence of hydroxyl and methoxy groups, which are ubiquitous to the natural compounds found in marine biota. The position of hydroxyl group (OH-) is a potential indicative source of OH-BDE congeners. OH-PBDEs and MeO-PBDEs with the hydroxyl group at *ortho*-position attached to the ether bridge are primarily of natural origin. In contrast, the OH-group in metabolically produced PBDEs occur at any of the position, *ortho*-, *meta*- or *para*- relative to the ether bridge. Biosynthetic studies using ^{14}C -measurement have shown that OMe-PBDEs and OH-PBDEs are mostly natural in origin [15]. Indeed, natural PBDEs are biosynthesized by marine bacteria [16] and red algae [17] by the coupling of simple bromophenols. Further, Agarwal *et al.* discovered gene clusters within sponge microbiome-associated cyanobacterial endosymbionts responsible for the biosynthesis of PBDEs by employing metagenome mining approach, which involves screening the DNA of one or many organisms and their associated microbiomes [18].

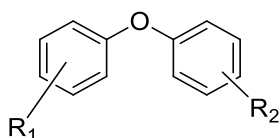


Figure 1. Chemical structure of Diphenyl Ether

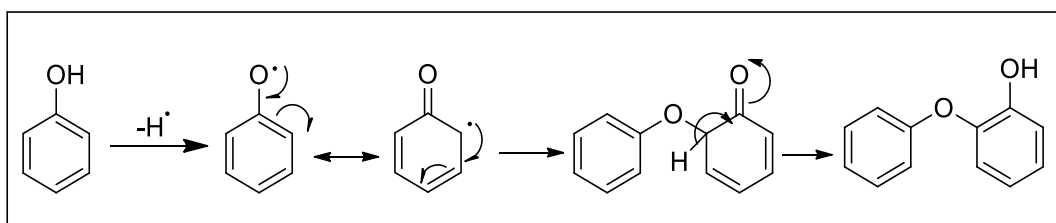


Figure 2. Phenolic oxidative coupling mechanisms (Dewick 2003) [11].

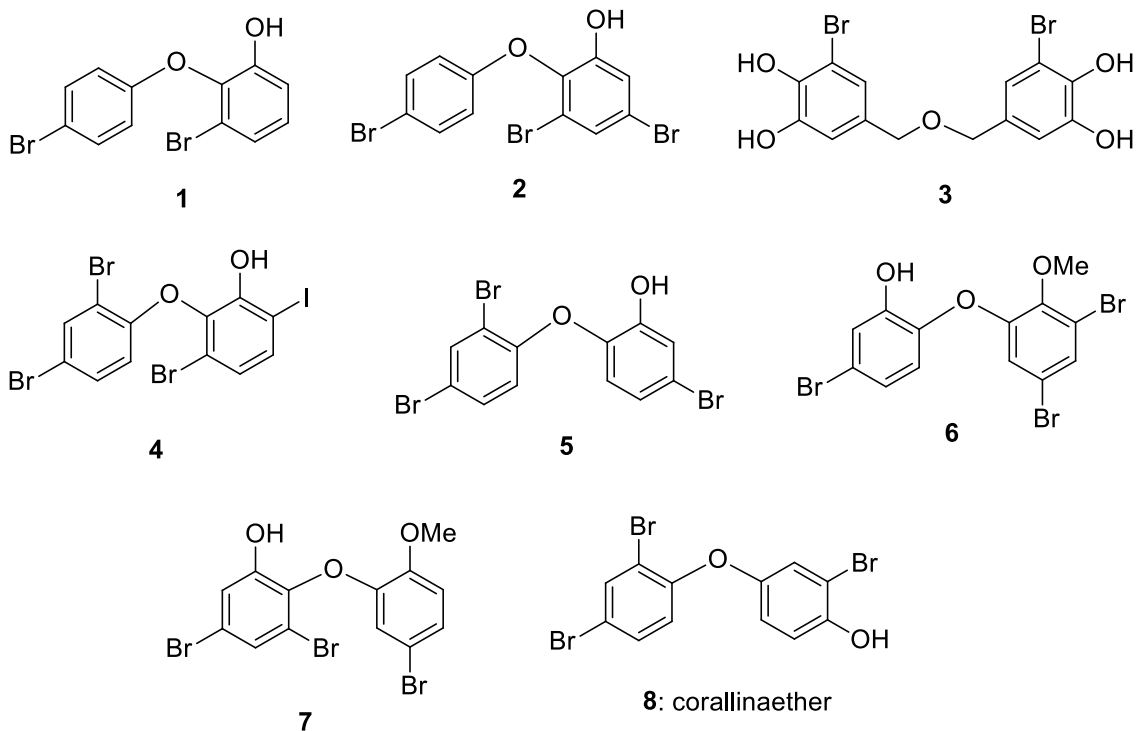
Diphenyl ether and its derivatives has a vast structural diversity and they are one of most abundant natural products in marine environment. They have been isolated from marine sponges [19], macro and micro algae [20], fungi [21] and nudibranchs [22]. Occurrence of organohalogen compounds is also reported from higher marine animals such as turtles and other mammals [23, 24]. PBDEs detected in marine fishes and mammals are seems to be mostly due to their bioaccumulation in food chain [25-27]. Diphenyl ethers, in particular the halogenated derivatives exhibit numerous biological activities, which include cytotoxicity [28, 29], antiviral [30], antimicrobial [10], regulating actin function [31], and phytocidal activities [32]. Moreover, certain *ortho*-OH-PBDE metabolites are

promising kinase inhibitors and can mediate neurotoxicity by impairing the MEK–ERK axis of mitogen activated protein kinase (MAPK) [33].

In the past years, chemicals and biological activities of secondary metabolites of marine organisms such as alkaloids [34], sterols [35], and pyrones [36] etc. have been described by several research groups. However, to the best of our knowledge, a comprehensive review dedicated to diphenyl ethers which represent a vast family of halogenated and non-halogenated compounds with numerous bioactivities is scarce [37]. This review presents chemical diversity and bioactivities of diphenyl ethers and their derivatives reported from marine organisms. Additionally, biosynthetic and synthetic aspects of a few marine-derived diphenyl ether derivatives are being discussed.

2. Diphenyl ether from marine organisms:

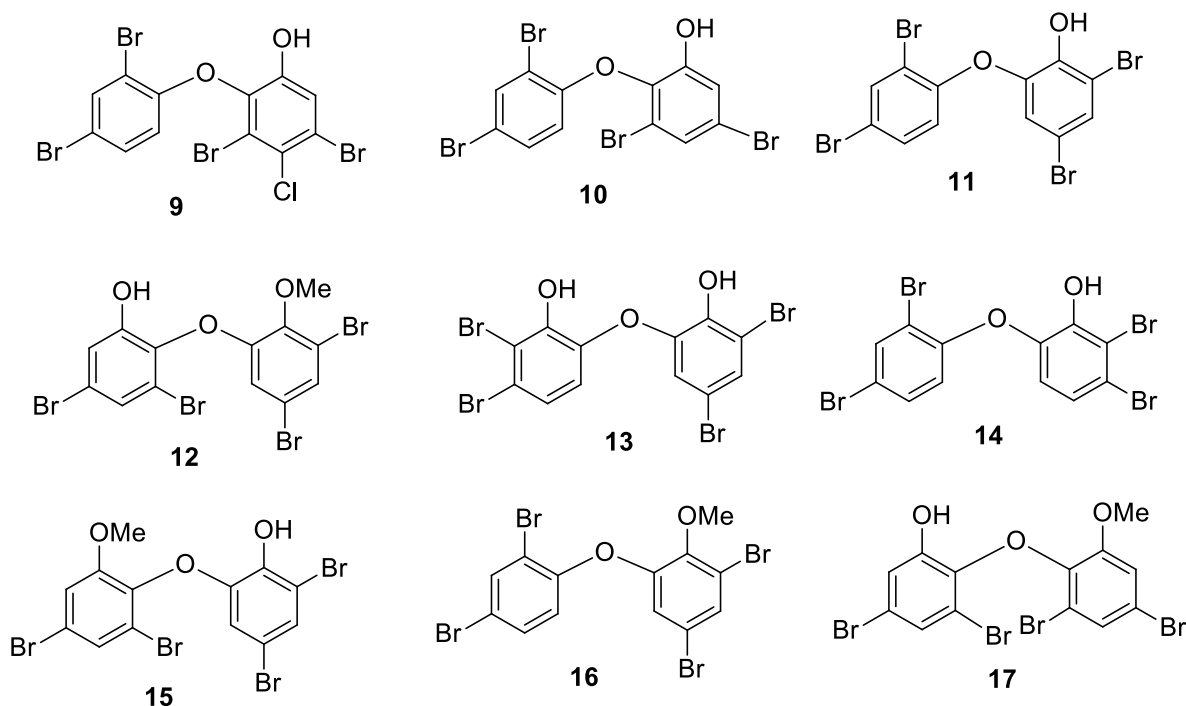
2.1. *Di- and tribrominated diphenyl ethers*: Diphenyl ethers containing 2 or 3 bromine substituents have been isolated from sponges and algae. In 1969, Sharma *et al.* isolated 3-bromo-2-(4-bromophenoxy)phenol (**1**) and 3,5-dibromo-2-(4-bromophenoxy)phenol (**2**) from the sponge *Dysidea herbacea* collected from the coast of western Caroline Islands [38]. A dibrominated dibenzyl ether, bis (3-bromo-4, 5-dihydroxybenzyl) ether (**3**) was reported from the red alga *Polysiphonia morrowii*. Compound (**3**) showed anti-inflammatory properties, as it significantly decreased lipopolysaccharide (LPS)-induced NO as well as PGE₂, and pro-inflammatory cytokines release by inhibiting the ROS-mediated ERK signalling pathway in RAW 264.7 macrophage [39]. Compound (**3**) also showed antimicrobial activity against Gram positive and Gram negative bacteria. Very recently, tribrominated diphenyl ethers (**2**), (**4**) and (**5**) were isolated from a Vietnamese sponge *Arenosclera* sp. [40]. The isolated compounds exhibited antibacterial activity against *B. subtilis*, *S. aureus* and *K. pneumonia* with MIC ranging from 0.5 to 6.3 μ M. Compound (**5**) was also isolated from the nudibranch, *Miamira magnifica* along with a tribrominated diphenyl ether (**6**) [41]. Two tribrominated compounds (**6-7**) were isolated by Hattori and co-workers from the Palauan sponge *Phyllospongia dendyi* [42]. Apart from marine sponges and nudibranch, tribrominated diphenyl ethers were reported also from marine algae. The tribrominated diphenyl ether, 2-bromo-4-(2'4'-dibromophenoxy) phenol or corallinaether (**8**) was isolated from the marine red algae, *Crutose coralline* [43]. Corallinaether (**8**) showed cytotoxicity against larvae *Pseudosiderastrea tayamai* with an LD₉₉ value of 0.14 μ g/mL.



2.2. Tetrabrominated diphenyl ethers:

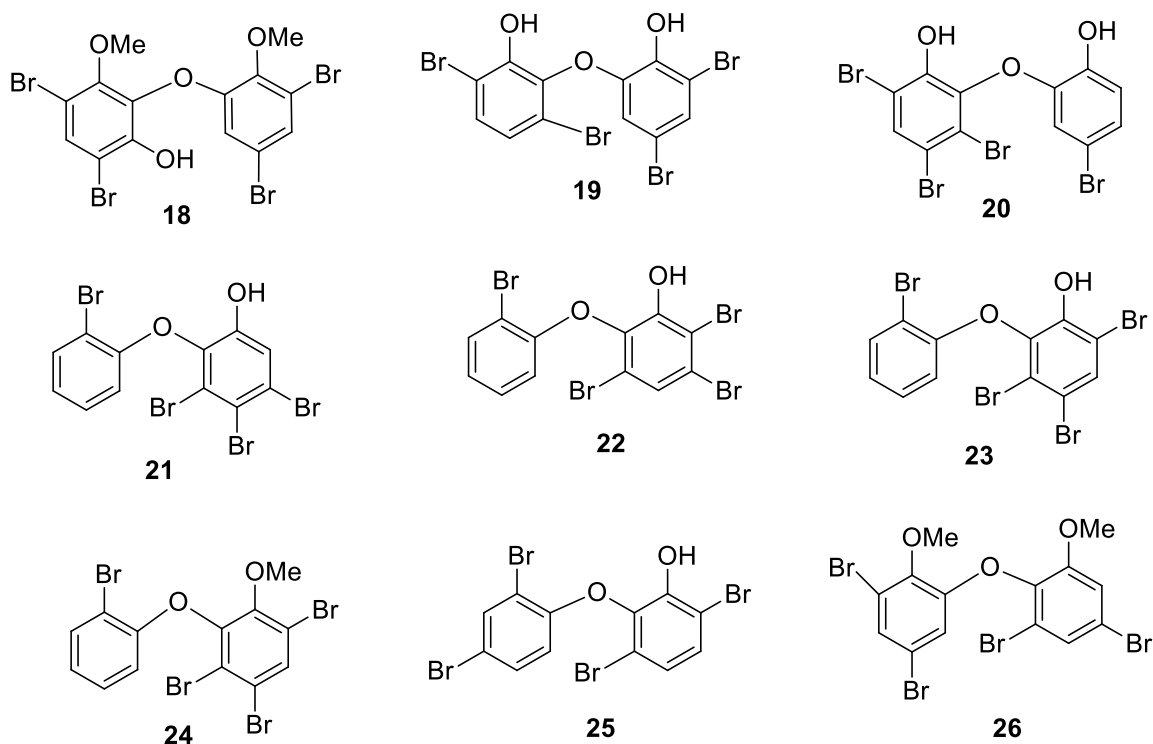
Tetrabromodiphenyl ethers contain four bromine atoms and they are one of the most widely occurred marine diphenyl ethers. They were mainly isolated from marine sponges, algae and nudibranch. In 1981, Cappon *et al.* isolated two diphenyl ether of this class, namely, 3, 5-dibromo-4-chloro-2-(2, 4-dibromophenoxy)phenol (**9**) and 3,5-dibromo-2-(2,4-dibromophenoxy)phenol (**10**) from an unidentified sponge [44]. The identity of the compounds were determined by NMR spectroscopic data and their structure was confirmed by X-ray crystallography. It is noteworthy that the marine sponge *Disidea sp.* is a rich source of several bromodiphenyl ethers including tetrabrominated derivative. Tetrabromodiphenyl ether, 4, 6-dibromo-2-(2',4'-dibromophenoxy)phenol (**11**) was isolated from the sponge *Dysidea herbacea* by Sharma *et al.* in the early 1969s along with the dibrominated diphenyl ethers (**1**) and (**2**) [38]. Later, compound (**11**) has been isolated from various other marine sponges including *D. granulosa* [45] and from the marine cyanobacterial symbiont of a marine sponge *Dysidea herbacea* [46]. Compound (**11**) displayed antibacterial activity against a broad spectrum of bacterial cultures, including 20 clinically derived strains, 10 standard strains of MRSA, 2 strains of MSSA, 11 clinical strains of VRE, 4 standard VRE strains and 5 standard strains of VSE. Further, compound (**11**) exhibited no cross-resistance to other key antibiotics and was susceptible to *Escherichia coli* and *Pseudomonas sp.* with MIC value >15 µg/mL [45]. Xu *et al.* isolated compounds (**10-11**) from a *Dysidea* species [47]. They exhibited significant potent inhibition of Tie2 kinase with IC₅₀ value of 2.1 and 6.2 µM, respectively. The BDE, (**10**) was also isolated from the soft coral

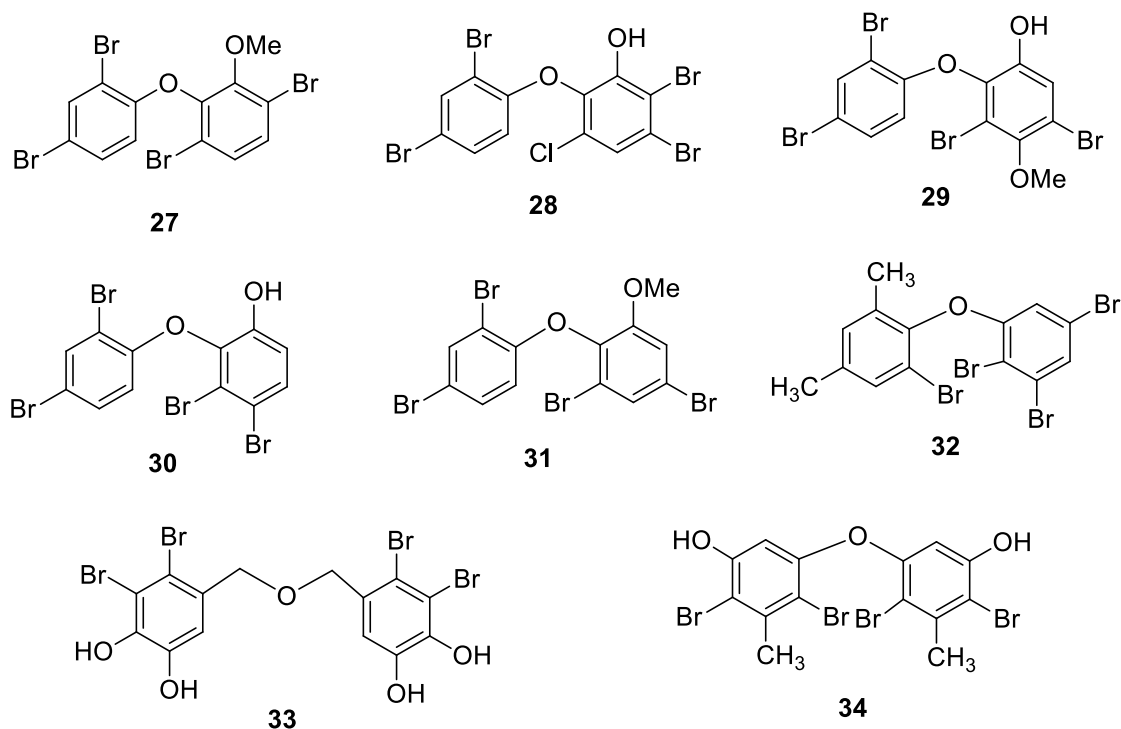
Sinularia dura of Papua New Guinea. [48]. To the best of our knowledge this is the only example of BDE reported from soft coral. Compound **10** showed significant antibacterial activity against MRSA with IC₅₀ value of <0.04 μM better than the positive control, ciprofloxacin (IC₅₀ = 0.23 μM). Tetrabromodiphenyl ethers (**12-13**) were obtained from the marine sponges *Dysidea herbacea*, *Phyllospongia dendyi* and *Lamellodysidea herbacea* [49-51], whereas, the compounds (**14-15**) were isolated from an unidentified *Dysidea species* [52] and from an Indo-Pacific *Dysidea* sponges, respectively [53]. Compound (**12**) exhibited cytotoxicity to HCT-15 and Jurkat cells whereas, compound (**15**) was found to be an inhibitor of IMPDH or 15-L0, but not active against PTK. Subsequently, tetrabromodiphenyl ethers (**16-18**) were obtained from the Palauan sponge *Phyllospongia dendyi* [42]. They exhibited antimicrobial activities with the IC₅₀ values 0.02-0.05 ppm. Previously, compound (**16**) was isolated from a green algae *Cladophora fascicularis* and it was found to be exhibited antimicrobial property against *E. coli*, *B. subtilis* and *S. aureus* [54].



Chemical investigation of the marine sponge *Lamellodysidea herbacea* collected from Sangiang Island, Indonesia led to the isolation of the PBDEs (**19-20**) [55]. They exhibited antibacterial activity against the gram-positive bacterium *Bacillus subtilis* in the range of 1-10 μg/disk and even in a low concentration, 0.1 μg/disk. Further, compound (**19**) was found to be more active which was attributed to the presence of two phenolic hydroxyl groups as well as bromine atoms at C-2 and/or C-5 in compound (**19**).

Handayani *et al.* isolated four new PBDEs (**21-24**) during the chemical investigation of the sponge *Dysidea herbacea* collected from West Sumatra, Indonesia [56]. The isolated compounds (**21-24**) exhibited activity against the Gram-positive bacteria *B. subtilis* as well as the phytopathogenic fungus *Cladosporium cucumerinum*, but no activity against Gram-negative bacteria. In 2008, Zhang *et al.* [57] succeeded in the isolation of PBDEs (**25-26**) along with (**10**) and (**24**) from *Dysidea sp.* These compounds were exhibited hyphae formation inhibition (HFI) in *Streptomyces* 85E at a concentration of 20 µg/disk. Further, evaluation of antiproliferative activity using MCF-7 human breast cancer cell line revealed that compound (**10**) was most effective with IC₅₀ value of 2.84 µM. Presence of tetrabrominated compound (**27**) which is the methoxy analogue of (**25**), was detected from the red algae, *Ceramium tenuicorne* and blue mussels [58] whereas, tetrabromodiphenyl ethers (**28-29**) were reported from *D. herbacea* and *D. granulosa* [59]. Recently, O-PBDEs (**30**), (**14**) and (**27**) were isolated from the nudibranch *Miamira magnifica* [41] and PBDEs (**31-32**) were obtained from the Baltic Sea red algae, *Ceramium tenuicorne* [60] and *Laurencia similis* [61], respectively. Compound (**32**) showed inhibitory activity against PTP1B with IC₅₀ value of 2.97 µM.

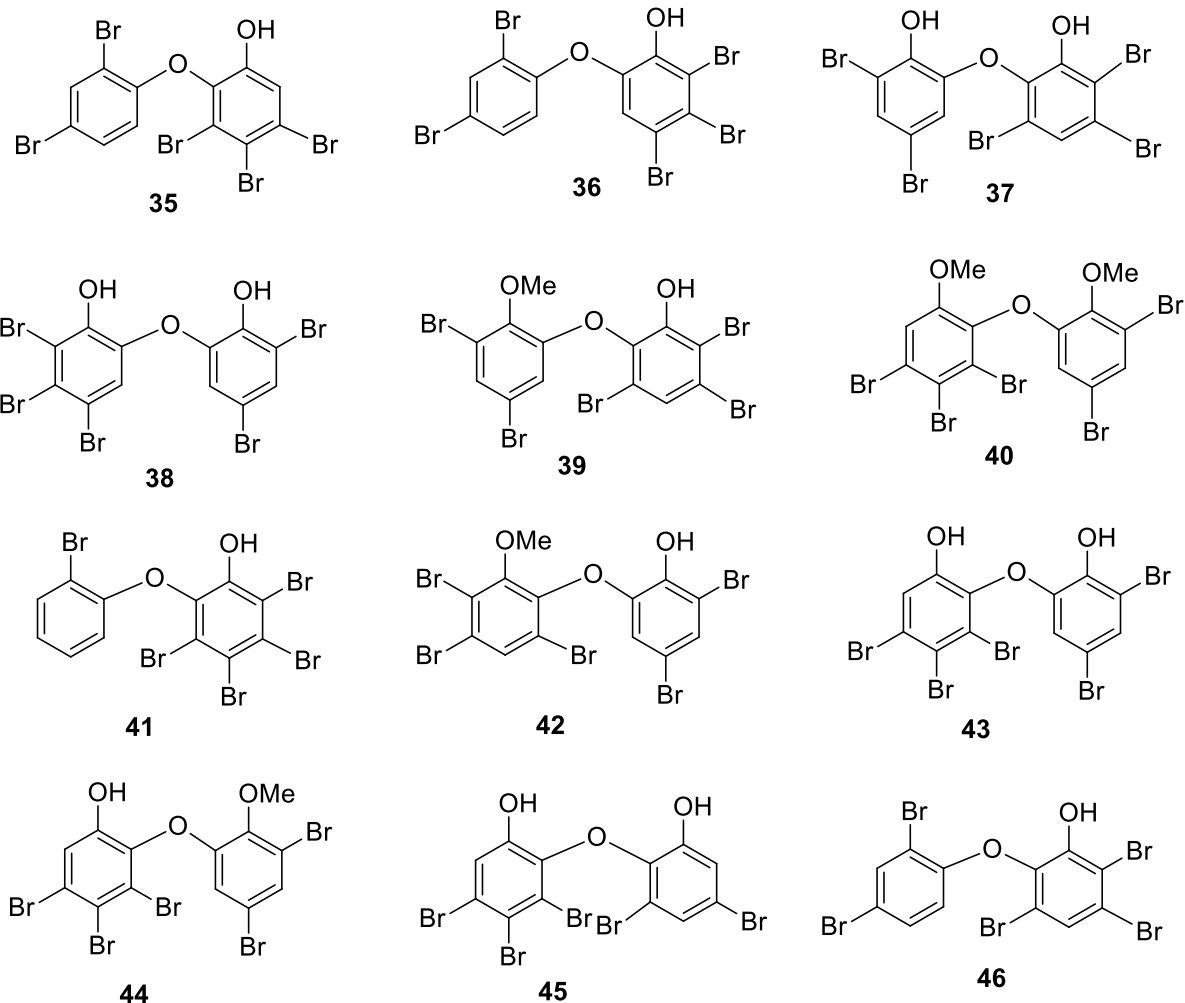




Tetrabrominated OH-PBDEs (**10-11**) and MeO-PBDEs (**17**) and (**31**) were also obtained from marine macroalgae and mussels [58]. These compounds displayed potential activity for endocrine disorders, genotoxicity and neurological toxicities [62]. Several brominated dibenzyl ethers closely related to the bromodiphenyl ethers have been isolated from marine organisms, particularly from marine algae. The marine algae *Leathesia nana* and *Rhodomela confervoides* gave dibenzyl ether (**33**) that exhibited inhibition of cell growth against various human cancer cell lines and tumor angiogenesis. The cytotoxicity displayed by (**33**) against human cervical carcinoma cell line HeLa, human colorectal carcinoma cell line (HCT-8), human colorectal carcinoma cell line (HCT-116), lung adenocarcinoma epithelial cell line (A549), hepatocellular carcinoma cell line (SMMC-7721) and myelogenous leukaemia cell line (K562) [63]. In addition, compound (**33**) exhibited a significant antifungal activity against various phytopathogenic fungi, including *Valsa mali*, *Botrytis cinerea*, and *Fusarium graminearum* [64]. The dibenzyl ether (**33**) was also reported from the red alga *Vertebrata lanosa*. The compound showed moderate antiradical property when investigated using an oxygen radical absorbance capacity assay, cellular lipid peroxidation assay and cellular antioxidant activity assay [65]. A related dihydroxy tetraaromated ether (**34**) was isolated from the marine derived fungus *Penicillium chrysogenum* [21] and from the red alga *Odonthalia corymbifera* [66]. The compound showed anti-diabetic property by inhibiting both the PTP1B and α -glucosidase with the IC₅₀ value of 0.098 μ M.

2.3. Pentabrominated diphenyl ethers:

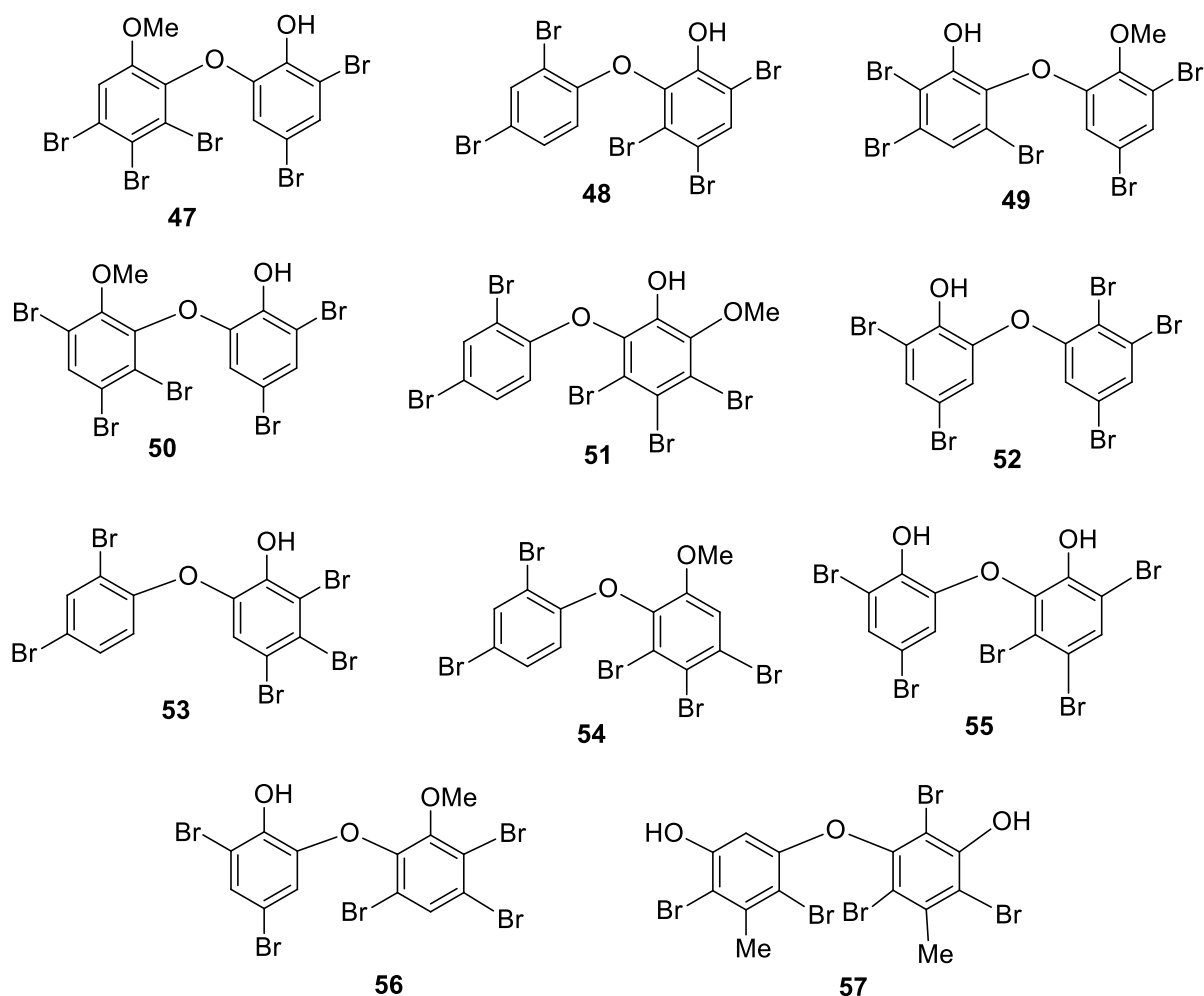
Pentabrominated diphenyl ethers are commonly found in marine sponges, particularly in *Dysidea species* along with other less brominated derivatives. The sponge *Dysidea herbacea* collected from the coast of western Caroline Islands gave two pentabrominated diphenyl ethers (**35-36**) [38]. Later compound (**36**) was re-isolated from the same sponge species and found to be possessing excellent antimicrobial activity [67]. Compounds (**35-36**) were also reported from the neutral fraction isolated from cyanobacteria [60]. Chemical investigation of extract of *Dysidea* and *Phyllospongia* species gave two related BDEs (**37-38**) [68] while two pentabrominated diphenyl ether (**39**) and (**40**) were isolated from *Dysidea herbacea* [49]. Faulkner and co-workers obtained a pentabrominated diphenyl ether (**41**) from a Philippine sponge of *Dysidea* species [69]. A few years later, Fu *et al.* isolated four pentabrominated ethers **42-45** from four Indo-Pacific *Dysidea* sponges along with several known metabolites [70]. These compounds were found to be the inhibitors of IMPDH or 15-L0, but not active against PTK. In 2000, Bowden reported the PBDE (**46**) during the chemical investigation of the marine sponge *Dysidea herbacea* collected from Cattle Bay [71] this is followed by isolation of another pentabrominated ether (**47**) by Liu *et al.* from the marine sponge *Phyllospongia dendyi* of Palau [50].



Extract of *Dysidea herbacea* collected from Pelorus Island upon chromatography gave a diphenyl ether (**48**) [72] whereas, (**49-50**) along with several known derivatives including (**40-44**) were isolated from a marine sponge *Lamellodysidea herbacea* collected from Sangiang Island, Indonesia [55]. Compound (**44**) exhibited cytotoxicity against NBT-T2 rat bladder epithelial cells with the IC₅₀ value of 2.8 µg/mL. PBDE (**51**) [73] possessing potential for hyphae formation inhibition (HFI) in *Streptomyces* 85E was isolated from a *Dysidea* sp. of Micronesia after repeated column chromatography [57].

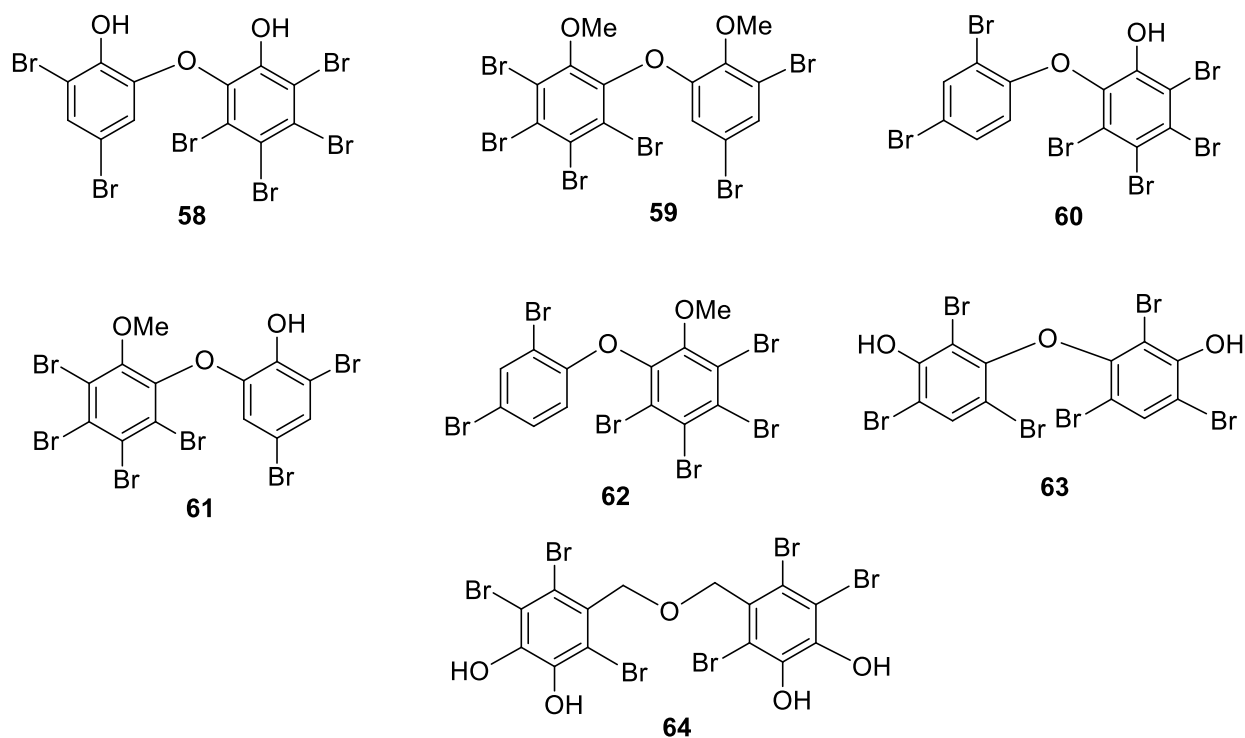
Crews and co-workers isolated two pentabrominated diphenyl ethers (**52**) and (**38**) from the sponges *D. herbacea* and *D. granulosa* [59]. Whereas, Malmvarn *et al.* reported hydroxylated pentabromodiphenyl ethers (**53**) & (**35**) from macroalgae and blue mussels [58]. Compound (**53**) showed cytotoxicity and genotoxicity towards chicken DT40 cell lines including wild-type cells and a panel of mutant cell lines [74]. Chemical investigation of the Baltic Sea red algae *Ceramium tenuicorne* gave a pentabrominated compound (**54**) along with compound (**48**) [60], while the sponge *Dysidea herbacea* yielded two related pentabrominated diphenyl ethers, OH-PBDE (**55**) and OMe-PBDE (**56**)

[59]. Both the compounds (**55-56**) showed no significant activity in the Mcl-1 FRET assay [59]. It is noteworthy that brominated diphenyl ether from marine fungi source is scarce, only a few examples are known in literature. To the best of our knowledge the pentabrominated ether (**57**) is the only example of brominated diphenyl ether isolated from a marine fungus [21]. Compound (**57**) exhibited radical-scavenging activities against DPPH.



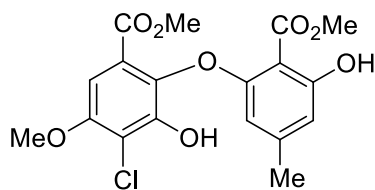
2.4. Hexabrominated diaryl ethers: These are BDEs containing six bromine atoms in the molecule, mostly isolated from marine sponges and algae. The hexabrominated diphenyl ethers (**58-59**) were isolated from a *Dysidea species* and *Phyllospongia foliascens* [68]. Compound (**58**) exhibited inhibitory activity towards microtubule proteins with an IC_{50} value of 33.5 μM and to the meiotic maturation of starfish oocytes with the IC_{50} values of 4.2 μM [50]. Another, hexabrominated diphenyl ethers (**60**) was reported from the marine sponge *Dysidea fragilis* and an unidentified *Dysidea species* [75]. PBDE (**61**) was isolated from the marine sponge *Phyllospongiadendyi* of Palau [50] whereas, MeO-BDE, (**62**) was obtained along with OH-BDE (**60**) from the Baltic Sea red algae *Ceramium tenuicorne* [58]. Compound (**61**) did not show inhibitory activity to the porcine brain microtubule

proteins. Mikami *et al.* reported a hexabrominated diphenyl ether (**63**) and benzyl diphenyl ether (**64**) from a marine algae [76]. Compound (**64**) showed a strong inhibitory effect on G6PD of prokaryotic *Leuconostoc mesenteroides*, with IC_{50} values of $0.97 \pm 0.1 \mu\text{M}$. Compound (**64**) was also reported from *Symphycladia latiuscula* and was found to exhibit anti-diabetic property by inhibiting PTP1B and α -glucosidase enzymes [77].

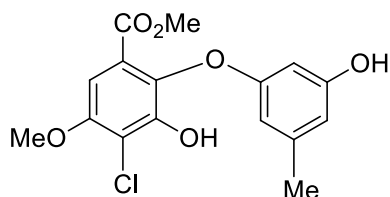


2.5. Chlorinated Diphenyl Ethers: Chlorinated diphenyl ethers are mainly isolated from marine fungi. They are chemical biomarkers of fungi, particularly, *Aspergillus sp.* and their biosynthesis is believed to proceed from the anthraquinone emodin, *via* sulochrin and the grisandienes such as geodin [78]. Klaiklay *et al.* isolated chlorinated diphenyl ethers, pestalotethers A-C (**65-67**) and pestheic acid (**68**) from the mangrove-derived fungus *Pestalotiopsis sp.* PSU-MA69 [79]. Pestalotethers A-C (**65-67**) were new diphenyl ethers, while pestheic acid (**68**) was previously known from *Pestalotiopsis sp.* [80]. In 2015, Nong *et al.* isolated a diphenyl ether derivative (**69**) from the marine-derived fungus *Aspergillus terreus* SCSGAF0162 [81]. This compound exhibited antifouling activity towards the larvae of barnacle *B. Amphitrite*, with the EC_{50} values $17.1 \pm 0.8 \mu\text{g mL}^{-1}$. Very recently in 2020, Jiang and co-workers isolated several chlorinated diphenyl ether derivatives (**70-77**) from the fungus *A. flavipes* obtained from a coastal sediment of China [82]. All the isolated compounds exhibited moderate to strong antibacterial activity against wide range of Gram positive bacteria including *Staphylococcus aureus* ATCC43300, ATCC 25923, ATCC 33591, ATCC29213, *Enterococcus faecalis*

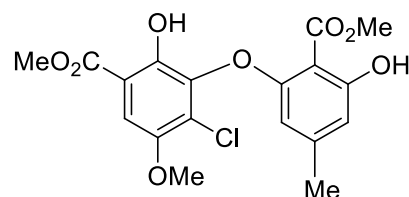
ATCC51299 and ATCC35667 with MIC values ranging from 3.13 to 50 $\mu\text{g/mL}$, however, none of the compounds showed activity against Gram negative bacteria *Vibrio parahaemolyticus* ATCC17802.



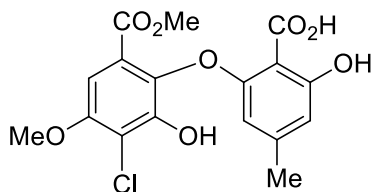
65: pestalotether A



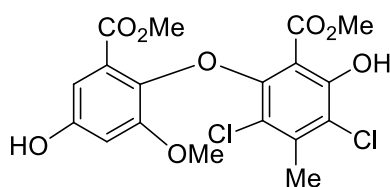
66: pestalotether B



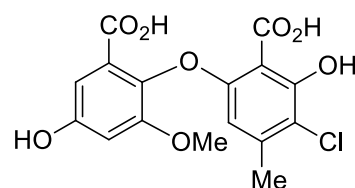
67: pestalotether C



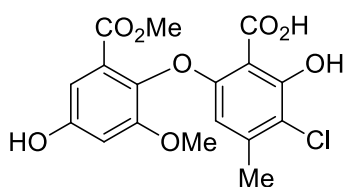
68: pestheic acid



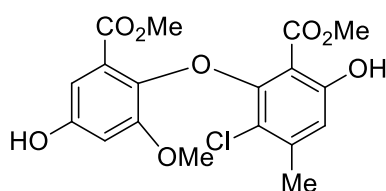
69: methyl dichloroasterrate



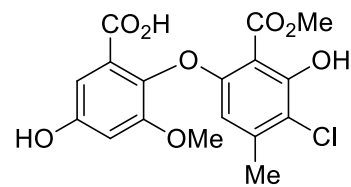
70: 4'-chloroasterric acid



71: chloroasterrate

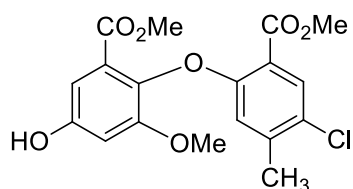


72: penicillither

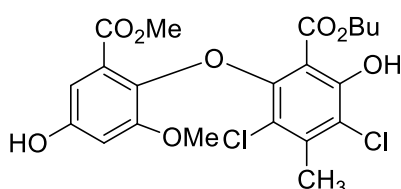


73: iizukine A

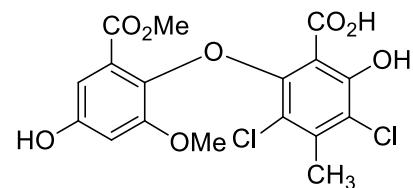
Previously, chloroasterrate (**71**), iizukine A (**73**), methylchloroasterrate (**74**), 2,4-dichloroasterric acid (**76**) and geodin hydrate (**77**) were reported from the fungus *Aspergillus iizukae* and *Aspergillus flavipes* PJ03-11 [83, 84]. All the isolated compounds showed weak cytotoxic activity against human cancer cell lines HL-60, BEL-7402 and A-549. Further, 2, 4-dichloroasterric acid (**76**) showed inhibition towards α -glucosidase with IC_{50} value of 0.091 mM. Recently, Wang and co-workers isolated four chlorinated diphenyl ethers, namely chrysines A–D (**78–81**) and 5-chloroasterric acid (**82**) from a deep-sea-derived fungus *Penicillium chrysogenum* SCSIO 41001 [85]. None of these compounds showed α -glucosidase inhibitory activity using PNPG method. Zhu and co-workers obtained the gentisyl alcohol derivatives, terrestrols B (**83**) and D (**84**) from *Penicillium terrestre* isolated from a deep-sea sediment [86]. Both the compounds showed cytotoxicity to MOLT-4, HL-60, A-549, and BEL-7402 with the IC_{50} values ranging from 5.3 to 64.7 μM .



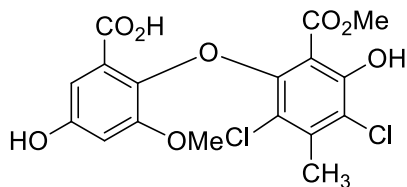
74: methylchloroasterrate



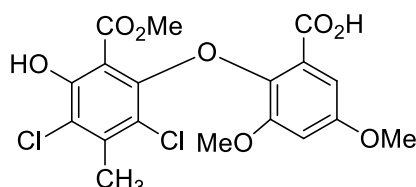
75: butyl-2,4-dichloroasterrate



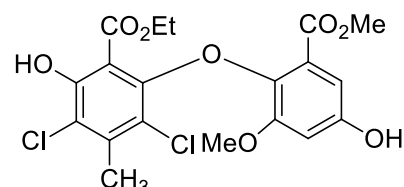
76 : 2,4-dichloroasterric acid



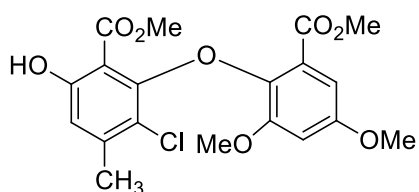
77: geodin hydrate



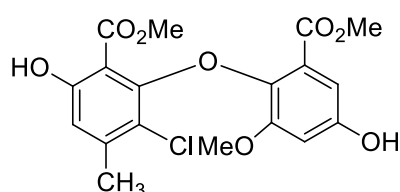
78: chryisine A



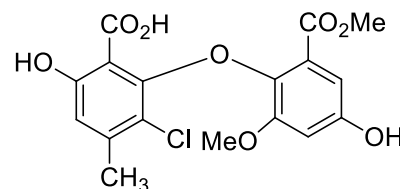
79: chryisine B



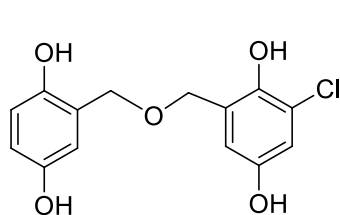
80: chryisine C



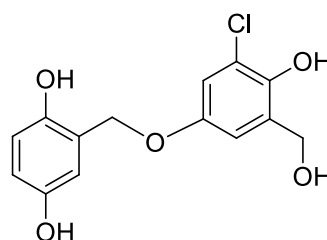
81: chryisine D



82: 5-chloroasterric acid



83: terrestrol B



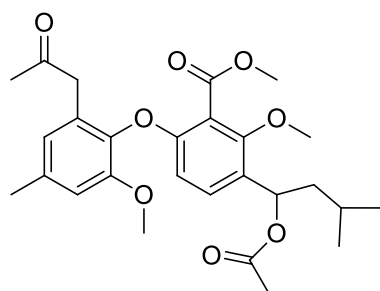
84: terrestrol D

2.6. Non-halogenated diaryl ethers

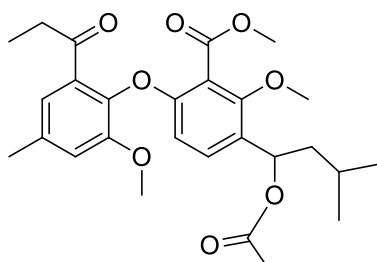
Non-halogenated diaryl ethers are mostly isolated from marine fungi and not found in other marine organisms except a few examples reported from marine bacteria. In 2009, Liu *et al.* isolated three diphenyl ether derivatives viz., tenelate A (**85**), tenelate B (**86**) and tenellic acid (**87**) from a mangrove endophytic fungus SBE-14 obtained from the South China Sea [87]. The fungus was identified as *Talaromyces* sp. by 18S ribosomal DNA (rDNA) fingerprint characteristics. However, bioactive potential of the compounds was not studied in their report. Ether derivative (**88**) and inseparable mixture of compounds, violacerol-I (**89**), violacerol-II (**90**) along with the brominated compounds (**33**) and (**57**) were obtained from a marine derived fungus *Penicillium chrysogenum* [21]. The brominated compounds and inseparable mixtures exhibited radical scavenger properties against

1, 1-diphenyl-2-picrylhydrazyl (DPPH) with IC₅₀ values of 18, 15, 42, and 6 μm, respectively. Interestingly, with the exception of compound (88) the inseparable mixtures of (89) and (90) as well as (34) and (57) showed higher scavenger activity than the positive control, ascorbic acid for which the IC₅₀ value was 20 μm indicating that halogenated and higher hydroxylation enhanced the activity.

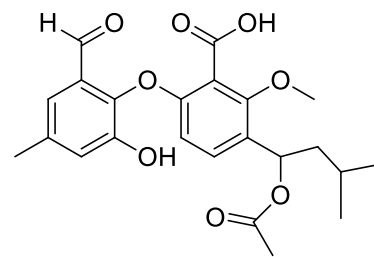
A diphenyl ether containing ester group, 2, 3'-dimethylosoate (91) was isolated by Liu *et al.* from the marine-derived fungus *Aspergillus sp.* B-F-2 [88]. Compound (91) was tested for cytotoxicity against K562 cell line by MTT method and flow cytometer. A reduction of MTT was observed in the presence of the compound (91) (IC₅₀ = 76.5 μm), whereas for apoptosis assay, compound (91) induced an increased in the percentage of cells in the S phase of the cell cycle from 38.3% (control) to 56.4%, indicating that compound (91) inhibited cell viability through S-phase blockage of the cell cycle and cell apoptosis. A few years later, a diphenyl ether containing ester group, pestoloether D (92) was isolated along with chlorinated analogues (65-67), from the mangrove-derived fungus *Pestalotiopsis sp.* PSU-MA69 [79]. The diphenyl ether, 5-hydroxymethylasterric acid (93), monomethylosoic acid (94) and asteric acid (95) were recently isolated along with chlorinated derivatives (69), (71), (73) and (77) from the fungus *Aspergillus flavipes PJ03-11* [84]. Compound (95) was isolated as a pale yellow solid and represent a rare diphenyl ether containing a hydroxyl group. It was also isolated from the mangrove endophytic fungus, *Pleosporales sp.* SK7 [89]. The glycosidase inhibitory study revealed that the chlorinated diphenyl ether derivatives (69), (71), (73) and (77) displayed higher activity than the non-chlorinated compounds (93-95) suggesting that such activity is influenced by the substituted chlorine atoms.



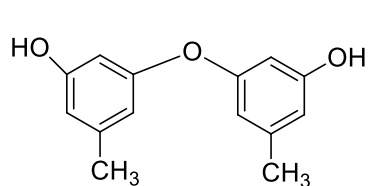
85 : tenelate A



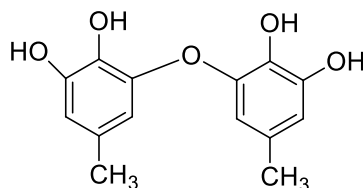
86: tenelate B



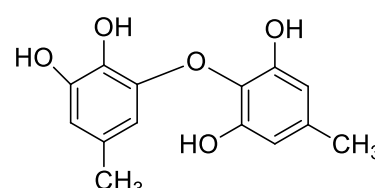
87: tenellic acid



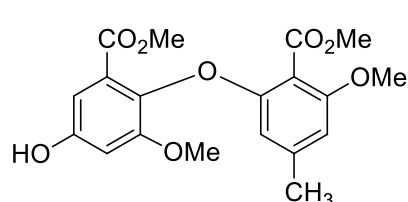
88



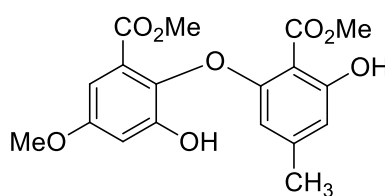
89: violacerol-I



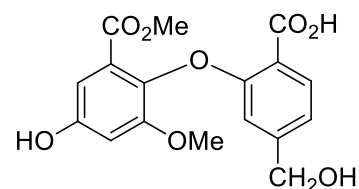
90: violacerol-II



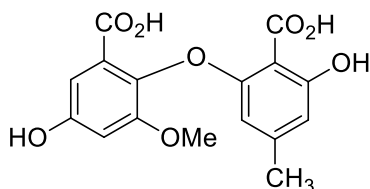
91



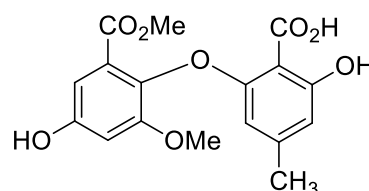
92: pestalotether D



93: 5-Hydroxymethylasterric acid

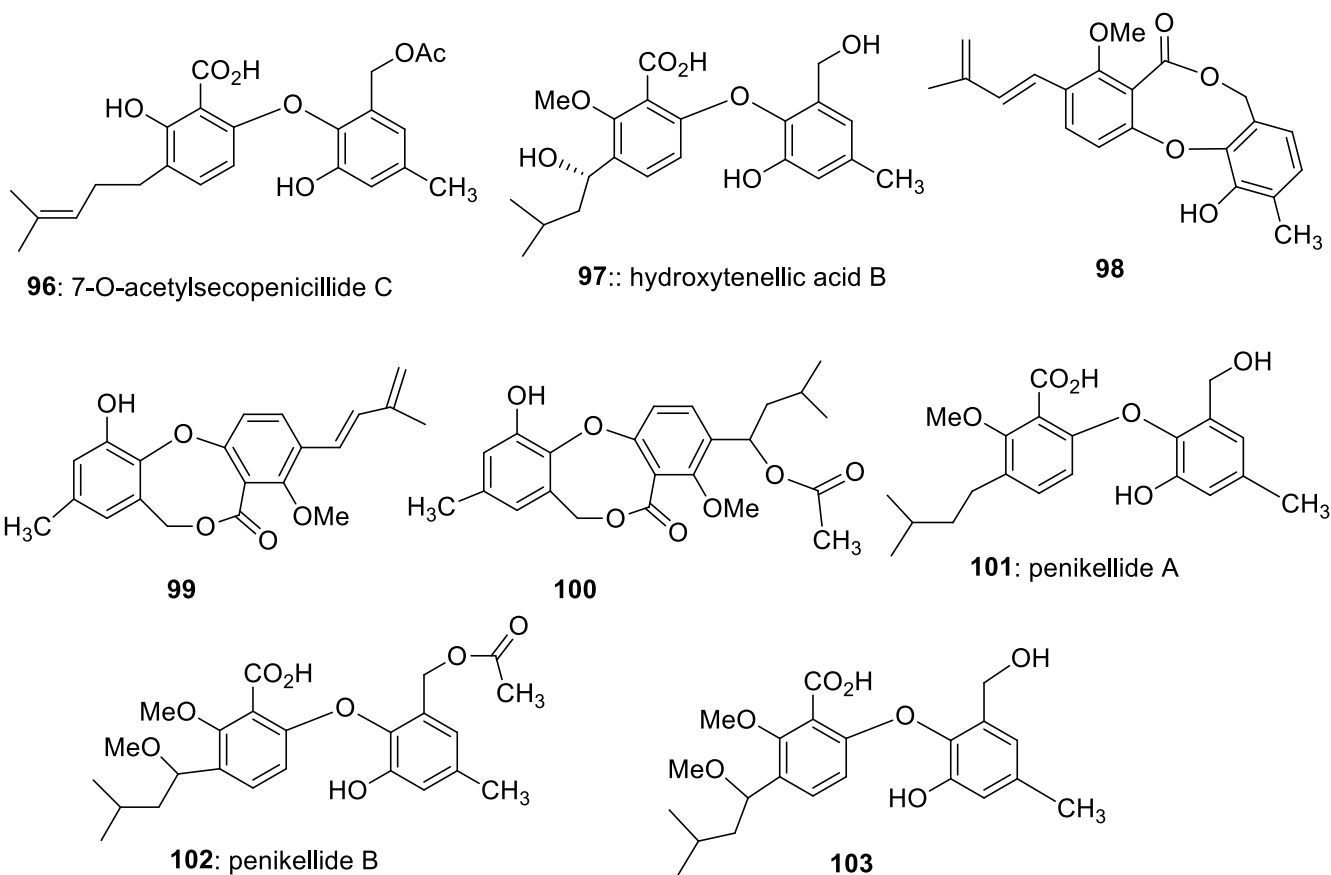


94: monomethylsoic acid

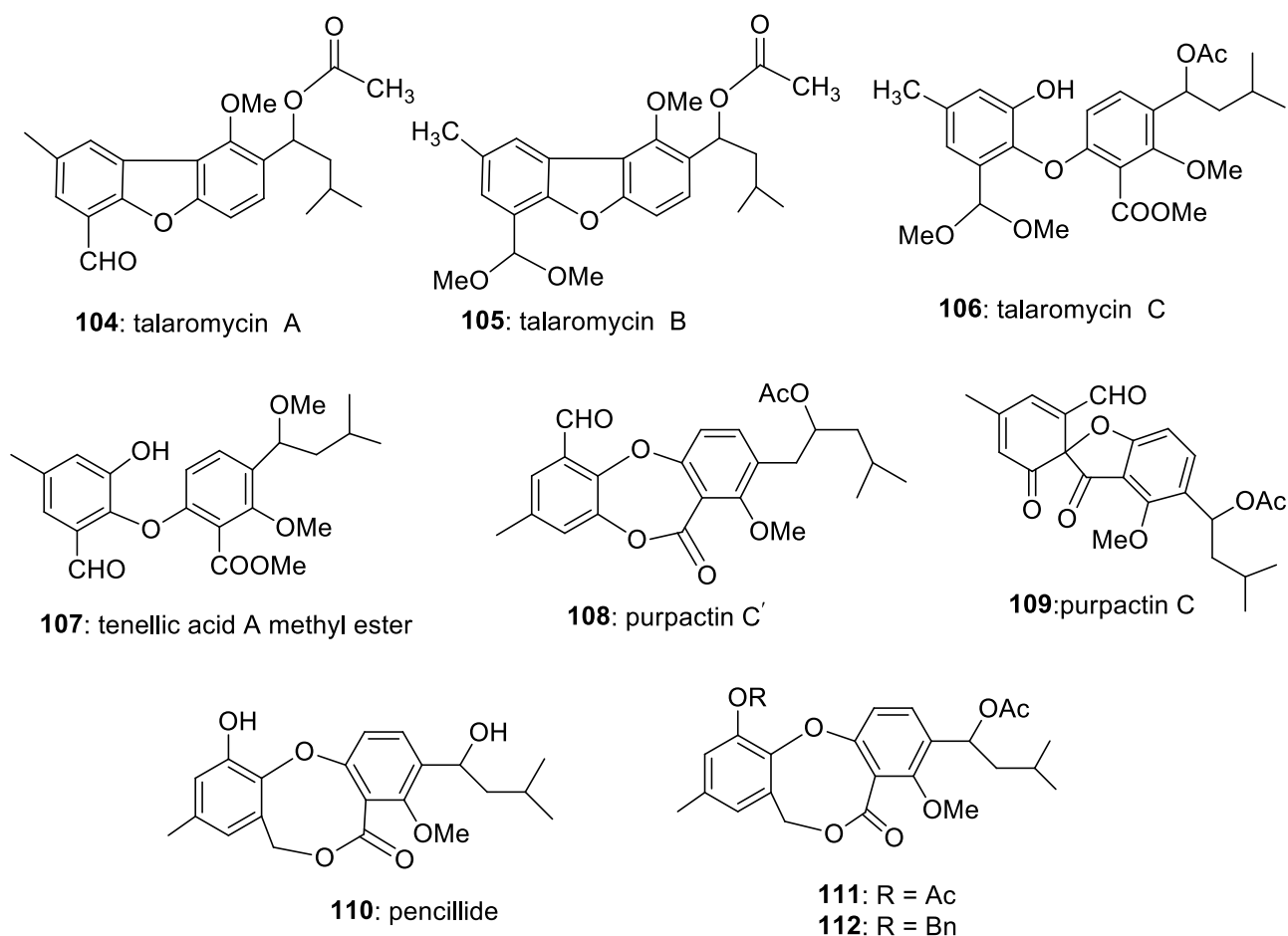


95: asteric acid

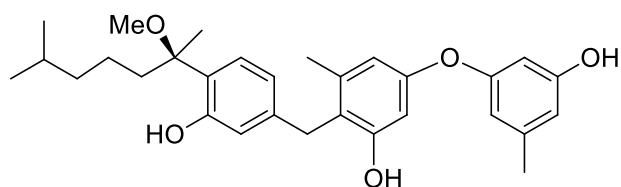
During the chemical investigation of the fungus *Penicillium* sp. MA-37, isolated from marine mangrove rhizospheric soil yielded diphenyl ether derivatives having carboxylic acid group (**96-98**) [90]. The compounds were screened for brine shrimp lethality assay and were found to be active against *Micrococcus luteus* and *E. coli*. 7-O-acetylsecopenicillide C (**96**) exhibited antibacterial activity against *M. luteus* and *E. coli* with MICs of 64 and 16 $\mu\text{g/mL}$, respectively. Further, two diphenyl ether derivatives (**99-100**) were isolated from a mangrove-derived fungus of south China sea [91] whereas, other three related diphenyl ethers, penikellides A (**101**), B (**102**) and analogue (**103**) were obtained from another mangrove-derived fungus *Penicillium* sp. MA-37 [92]. Brine shrimp lethality assay against *Artemiasalina* showed activity for penikellides A (**101**) and B (**102**) with LD_{50} values of 14.2 and 39.2 μM , respectively.



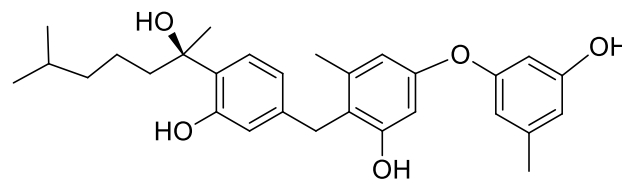
Chen *et al.* isolated diphenyl ether derivatives (**104-112**) along with (**98**) and (**100**) from the fungus *Talaromyces* sp. obtained from Gorgonian [93]. The isolated compounds were screened for their cytotoxicity and antifouling activities. Cytotoxicity screening of compounds 100, renellic acid methyl A ester (**107**) and purpactin C (**108**) against the human cancer cell lines hepatoma HepG2 and Hep3B, human breast cancer MCF-7/ADR, human prostatic cancer PC-3, and human colon carcinoma HCT-116 showed a moderate-to-strong cytotoxicity. In particular, compound (**107**) showed a strong cytotoxicity against all the tested cell lines with the IC_{50} values ranging from 4.3 to 9.8 mM. Compound (**100**) showed a moderate cytotoxicity against MCF-7/ADR and HCT-116 cell lines, while penicillide (**110**) was inactive indicating acetylation of OH group enhanced cytotoxic activity. The isolated compounds were also tested for antifouling property against the larval settlement of the barnacle *Balanus amphitrite*. The authors found that compounds (**100**), (**106**), (**108**) and (**110**) inhibited the barnacle larval settlement with the EC_{50} values ranging from 2.8 ± 0.2 to $3.3 \pm 0.3 \mu\text{g/mL}$. Interestingly, both compounds (**111-112**), which lack a free phenolic group did not show antifouling activity, suggesting that OH group played a crucial role in the antifouling activity.



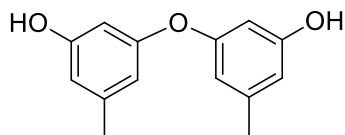
Lu *et al.* isolated polyphenols containing both bisabolene sesquiterpenoid and diphenyl ethers namely, expansols A-B (**113-114**) along with diorcinol (**115**) from the marine-derived fungus *Penicillium expansum* isolated from mangrove plant *Excoecaria agallocha* [28]. Expansols A-B (**113-114**) are chemically same except that a hydroxyl group is present in expansol B (**114**) in place of methoxy group present in expansol A (**113**). Cytotoxicity assay of expansols A-B (**113-114**) against A549 and HL-60 cell lines by SRB24 and MTT25 methods, showed a moderate cytotoxicity for expansol A (**113**) against the HL-60 cell line with the IC_{50} value of 15.7 μM , whereas, expansol B (**114**) inhibited the proliferation of A549 and HL-60 cells with the IC_{50} values of 1.9 and 5.4 μM , respectively. Subsequently, Zhao *et al.* isolated novel diphenyl ether derivatives (**116-119**) from a Gorgonian derived fungus *Penicillium pinophilum* collected from the coral reef of South China Sea [94]. Compounds (**116-119**) exhibited inhibitory activity against the larval settlement of the barnacle *Balanus amphitrite* with EC_{50} values of 6.0, 2.6, 20, and 10 $\mu\text{g/mL}$ ($LC_{50}/EC_{50} > 50$). Further, compound (**116**) exhibited cytotoxic activity against the human cervical carcinoma (HeLa) cell line with the IC_{50} value of 6.1 μM , while compound (**117**) showed cytotoxicity against the human laryngeal carcinoma (Hep-2) cells and human rhabdomyosarcoma (RD) cells with IC_{50} values of 6.7 and 7.8 μM , respectively.



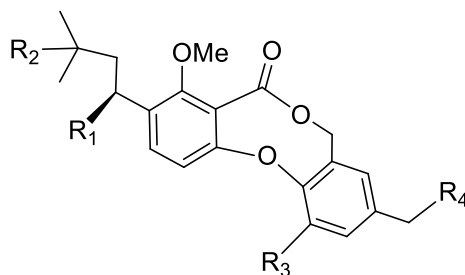
113 : expansol A



114: expansol B



115: diorcinol



116: R₁ = H, R₂ = OH, R₃ = OH, R₄ = OH

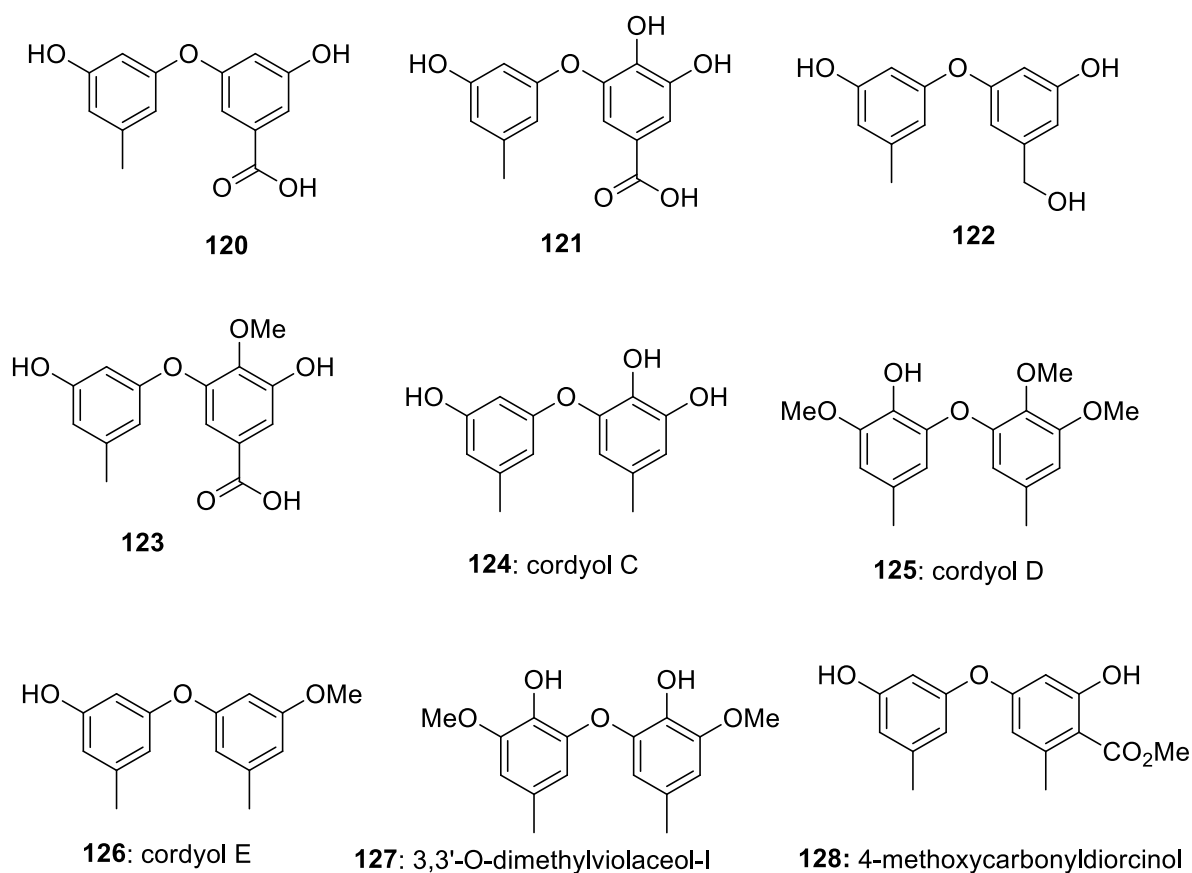
117: R₁ = OH, R₂ = H, R₃ = OH, R₄ = H

118: R₁ = OH, R₂ = OH, R₃ = OH, R₄ = H

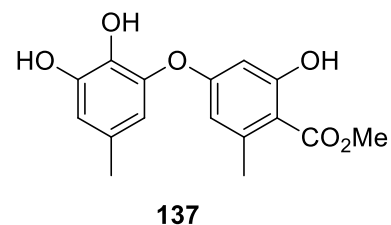
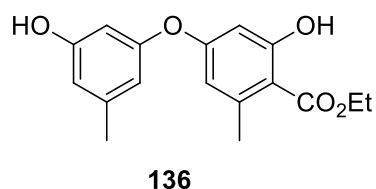
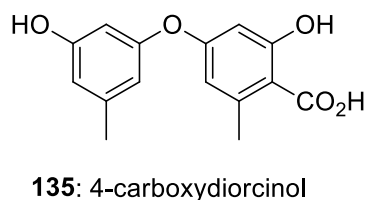
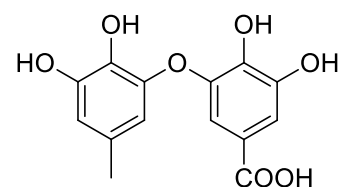
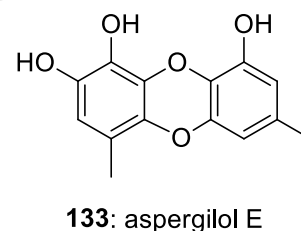
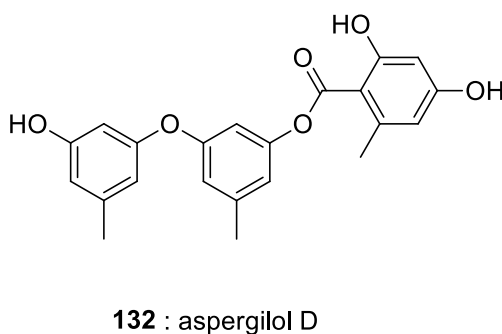
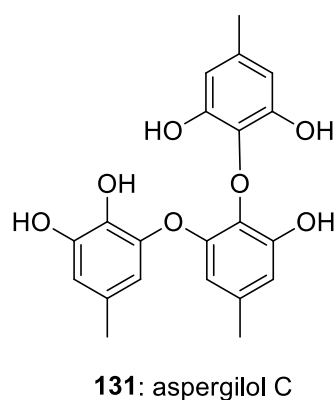
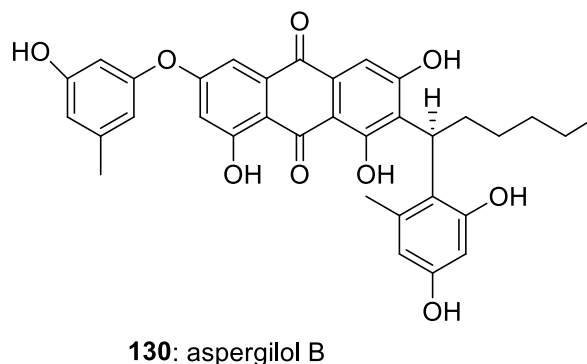
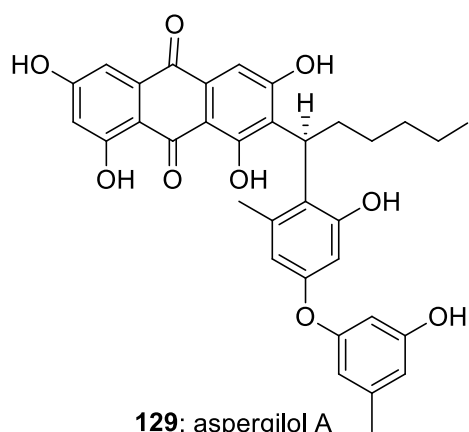
119: R₁ = OAc, R₂ = OH, R₃ = OH, R₄ = H

In 2015, He *et al.* isolated three diphenyl ether derivatives, 3-hydroxy-5-(3-hydroxy-5-methylphenoxy)benzoic acid (**120**), 3,4-dihydroxy-5-(3-hydroxy-5-methylphenoxy) benzoic acid (**121**) and 3-[3-hydroxy-5-(hydroxymethyl)phenoxy]-5-methylphenol (**122**) from the fungus *Aspergillus carneus* obtained from the South China sea water [95]. A few years later, another related diphenyl ether (**123**) was isolated along with the known compounds (**121-122**) from the marine-derived fungus *Aspergillus carneus* [96]. Compound (**121**) exhibited a strong antioxidant activity with the IC₅₀ value of 19.3 μM comparable to that of the positive control, ascorbic acid (IC₅₀ = 15.3 μM).

A study on chemical constituents of a marine derived fungus *Aspergillus* sp. yielded five diphenyl ether derivatives (**124-128**) along with the previously reported compound (**119**) [97]. Cordyols D-E (**125-126**) were reported as the new compounds, while 3, 3'-O-dimethylviolaceol-I (**127**), cordyol C (**124**), 4-methoxycarbonyl diorcinol (**128**) and diorcinol (**115**) were previously known from non-marine sources [98, 99]. Diorcinol (**115**) as well as the compounds (**124**), (**126**) and (**127**) exhibited moderate to strong antibacterial activity against the pathogenic bacteria, *S. epidermidis*, *S. aureus*, *V. anguillarum*, *P. putida* and *V. parahemolyticus*. Notably, compound (**128**) displayed most significant activity against *S. epidermidis* with the MIC value of 2.71 μM which is comparable to the positive control ciprofloxacin (MIC = 3.13 μM). Interestingly, diorcinol (**115**) showed weaker antibacterial activity than the analogous, cordyol E (**126**) indicating the methylation of OH group increased the activity. Further, diphenyl ether with methoxycarbonyl group at C-4 position (**128**) exhibited higher activity than the dihydroxy derivative (**115**).



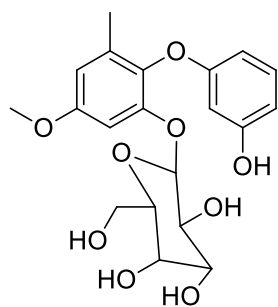
Several halogen free diphenyl/diaryl ethers were isolated from the deep sea fungus *Aspergillus versicolor* [100], which included the new compounds, aspergilols A-F (**129-134**) along with the known compounds cordyol D (**125**), cordyol E (**126**), diorcinol (**115**), methoxycarbonyldiorcinol (**128**) [86], violaceol II (**90**) and compounds (**135-137**) [67, 101, 102]. Aspergilols A (**129**) and B (**130**) contained a new scaffold with a C-C fusion of anthraquinone and orcinol unit. Antioxidant activity of the isolated compounds was studied by TEAC assay method. Cordyol-C (**124**) exhibited potent free radical scavenging activity five folds more than trolox. Further, cordyol C (**124**) showed more antioxidant effect (TEAC, 5.40) than diorcinol (TEAC, 0.61). It was found that diphenyl ether with an acidic group, 4-carboxydiorcinol (**135**) showed more potency than those substituted by methyl ester (**128**) (TEAC 1.04) or by ethyl ester (**136**) (TEAC 0.76). They also investigated the compounds for their ability to regulate the nuclear factor E2-related factor 2 (Nrf2), a transcription factor that responds to oxidative stress by binding to antioxidant response element (ARE). Aspergilol E (**133**), compounds (**124**), (**137**) and violaceol II (**90**) showed Nrf2-activation significantly, suggesting that these compounds activate the expression of Nrf2-regulated gene.



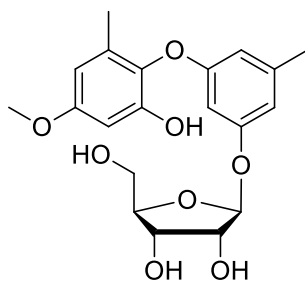
Three new diphenyl ether derivatives, phomaethers A–C (**138-140**) along with the known diphenyl ether (**141**) [103] were isolated from a gorgonian derived fungus [104]. Compounds (**138**) and (**139**) contained a sugar residue namely, hexose and ribose, respectively, while compound (**140**) contained two each of methoxy and hydroxyl groups. The isolated compounds (**138-141**) were tested against Gram-positive bacteria, *S. albus* and *S. aureus* and gram-negative bacteria, *E. coli*, *V. parahaemolyticus*, and *V. anguillarum*. Phomaether A (**138**) exhibited activity against *S. albus*, *S. aureus*, *E. coli*, and *V. parahaemolyticus* with MIC and MBC values ranging from 0.312-0.625 μM and 0.625-2.50 μM , respectively. Whereas, phomaether C (**140**) showed strong activity against *S. albus*, *S. aureus*, and *E. coli* with the MIC and MBC values ranging from 0.312-0.125 μM and 0.625-5.00 μM , respectively.

Interestingly, phomaether B (**139**) having a ribose residue did not show activity while compound (**141**) exhibited strong antibacterial activity against all the tested pathogens. Phomaethers A (**138**), C (**140**) and compound (**141**) also exhibited lethality to brine shrimp *Artemia salina* with the LC₅₀ values ranging from 14.01±0.36 to 37±0.16 µg/mL. Subsequently, another diphenyl ether derivative (**142**) containing a ribose residue was obtained from the marine fungus SCSIOW3 isolated from a deep-sea marine sediment sample collected from the South China [105]. Compound (**142**) was isolated along with the known compounds diorcinol (**115**), 3,3'-dihydroxy-5,50-dimethyldibenzofuran (**143**), cordyol C (**124**) and gibellulin (**144**) [106]. The glycosylated compound (**142**) showed reduction in biomembrane protective activity test with EC₅₀ at 20.8 µM while, diorcinol (**115**) exhibited algicidal activity against *Chattonella marina*. Diphenyl ether (**145**) was obtained along with two other known derivatives (**120**) and (**121**) from the fungus *Aspergillus carneus* isolated from sea water [107]. Antioxidant activity screening of the compounds showed significant activity only for compound (**120**) with IC₅₀ value of 19.3 µM comparable to that of positive control, ascorbic acid (15.3 µM).

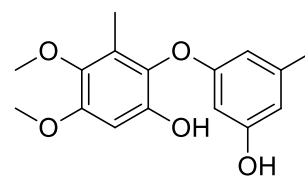
In 2017, Liu *et al.* isolated diorcinolic acid (**146**) along with the known diphenyl ethers, cordyol E (**126**), 4-carbonyldiorcinol (**135**), cordyol C (**124**), diorcinol (**115**), violacerol-I (**89**) and violacerol II (**90**) from the sponge-derived fungus *Aspergillus sydowii* J05B-7F-4 [108]. Compound (**146**) exhibited a mild cytotoxicity against three human cancer cell lines namely, KB (human nasopharyngeal carcinoma cells), HepG2 (human liver cancer cells) and HCT 116 (human colon cancer cells). However, in the nitric oxide inhibition screening, the compound (**146**) was found to be inactive, while violacerol II (**90**) and cordyol E (**126**) showed NO inhibition on LPS-induced NO production with 73 µM and 18 µM, respectively.



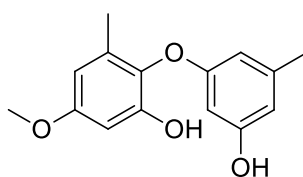
138: phomaether-A



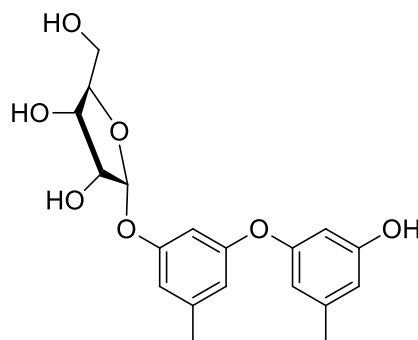
139: phomaether-B



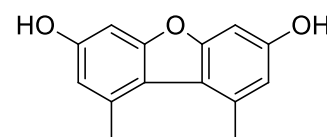
140: phomaether-C



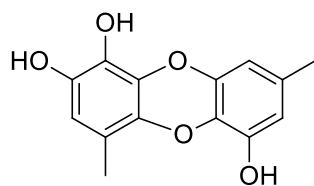
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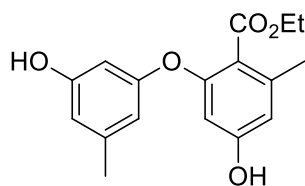
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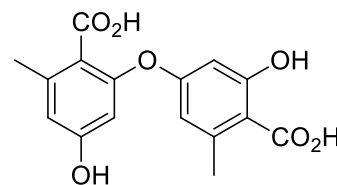
143: 3,3'-dihydroxy-5,50-dimethyldibenzofuran



144: gibellulin

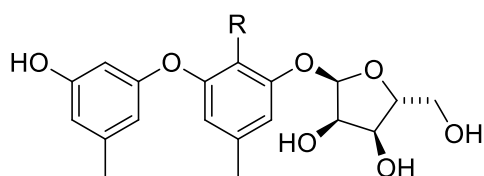


145



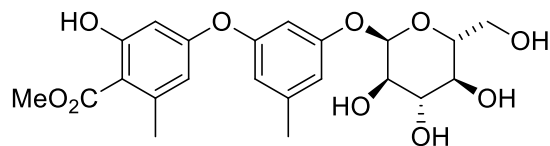
146: diorcinolic acid

Recently, Wang *et al.* isolated six diphenyl ether derivatives (**147-152**) and the known derivatives diorcinol (**115**), cordyol C (**124**), aspergilol E (**133**), 4-methoxycarbonyl diorcinol (**135**) [74], glyceryldiorcenolic acid (**153**) [109], and compounds (**154-156**) [110-112], from a marine derived fungus *Aspergillus sydowii* [113]. Compounds (**147**) and (**148**) are diphenyl ether glycosides having pentose sugar, while (**149**) contained a hexose sugar residue. Cytotoxicity of the isolated compounds were evaluated against the cell lines, 4T1, U937, PC3, HT-29, HL-60, A549 and NCI-H460. However, none of the isolated compounds exhibited activity against the 4T1, U937, PC3, HT-29, HL-60 and NCI-H460. Compounds (**147**), (**151**), (**153**) and diorcinol (**115**), showed moderate activity only against the cell line A549 and were not active against the rest of the tested cell lines. The authors suggested that the glycosylation of 3-hydroxy group decreased the activity against the cell line A549, while substitution of the OH at 3-carbon positively contributed for cytotoxicity. Further, the compounds (**135**), (**151**), (**152**), cordyol C (**124**) and aspergilol E (**133**) displayed cytotoxicity selectively against the cancer cell lines U937, HL-60, and K562.

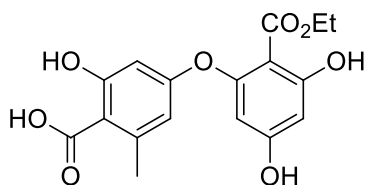


147: R = OH

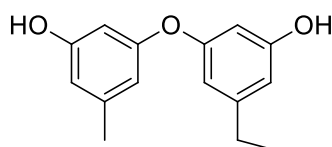
148: R = H



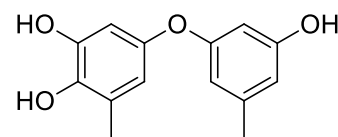
149



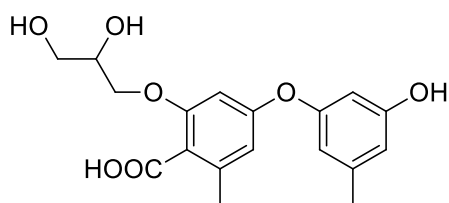
150



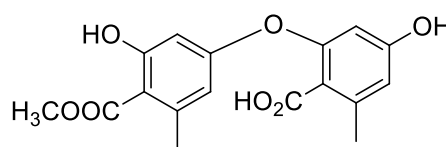
151: 7-ethyldiorcinol



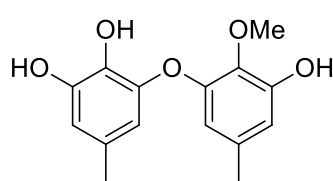
152: 3-hydroxydiorcinol



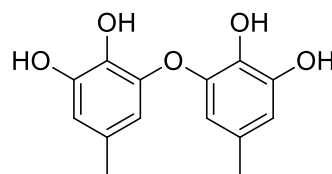
153: glyceryl diorcinolic acid



154

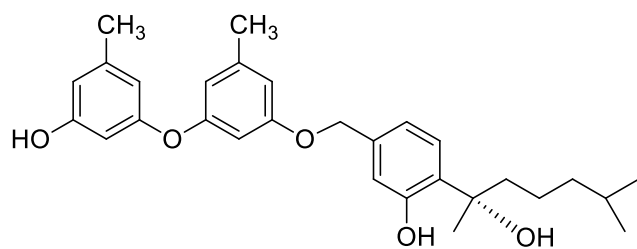


155: diorcinol F

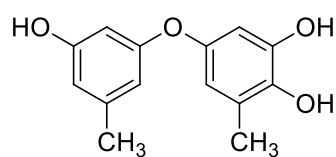


156: aspermutarubrol

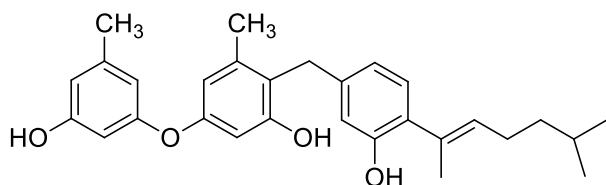
In 2015, Wang and co-workers isolated peniciaculin A (**157**) and the known compound expansol D (**158**) [114] from the fungus *Penicillium aculeatum* derived from a deep sea sediment [115]. Peniciaculin A (**157**) exhibited antibacterial activity against *M. luteus* and *V. alginolyticus* with the MIC values of 1.0 and 2.0 $\mu\text{g/mL}$. Compound (**157**) also displayed inhibitory activity against the fungus *A. brassicae* with the MIC value of 0.5 $\mu\text{g/mL}$. A few years later, two new diphenyl ethers (**159**) and (**160**) were obtained together with diorcinol (**115**), peniciaculin A (**157**) and expansol D (**158**) were obtained from the endophytic fungus *Aspergillus flavus* QQSG-3 isolated from the mangrove plant *Kandelia obovata* [116]. Peniciaculin A (**157**) and expansol D (**158**) exhibited strong inhibitory activity against α -glucosidase with the IC_{50} values of 1.5 and 2.3 μM , respectively. However, compounds (**159**) and diorcinol (**115**) displayed a weak inhibitory activity, but better than the positive control, acarbose.



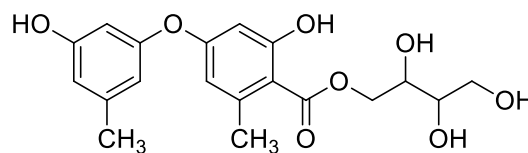
157: peniciaculin A



159

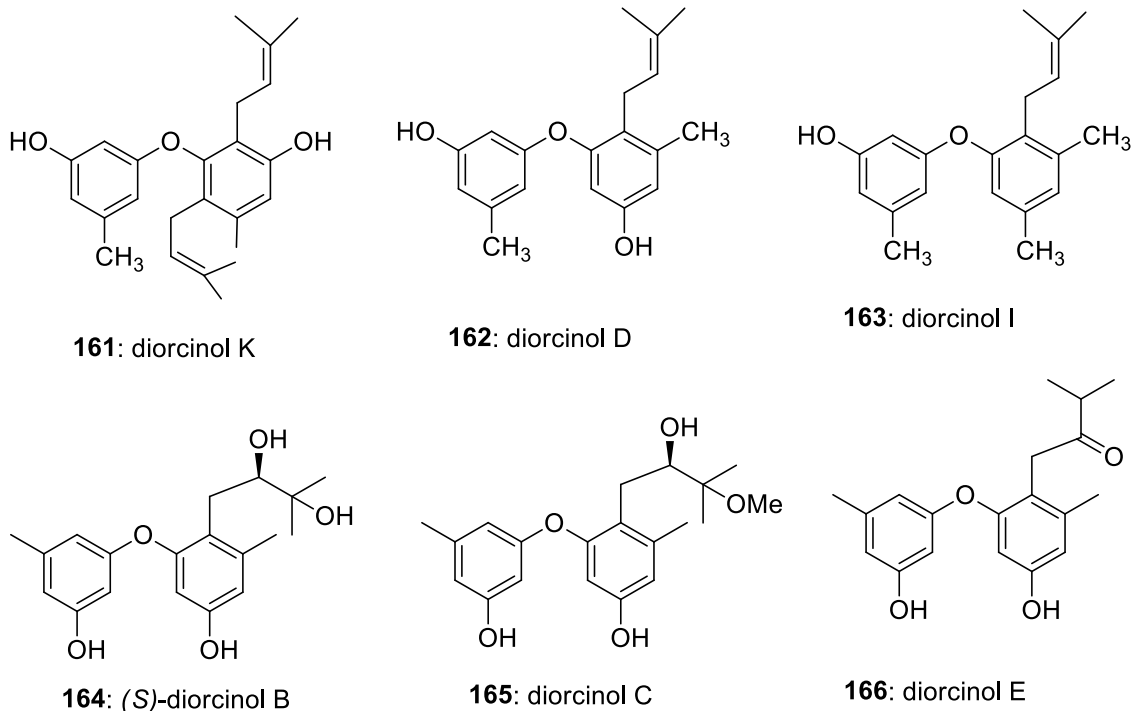


158: expansol D



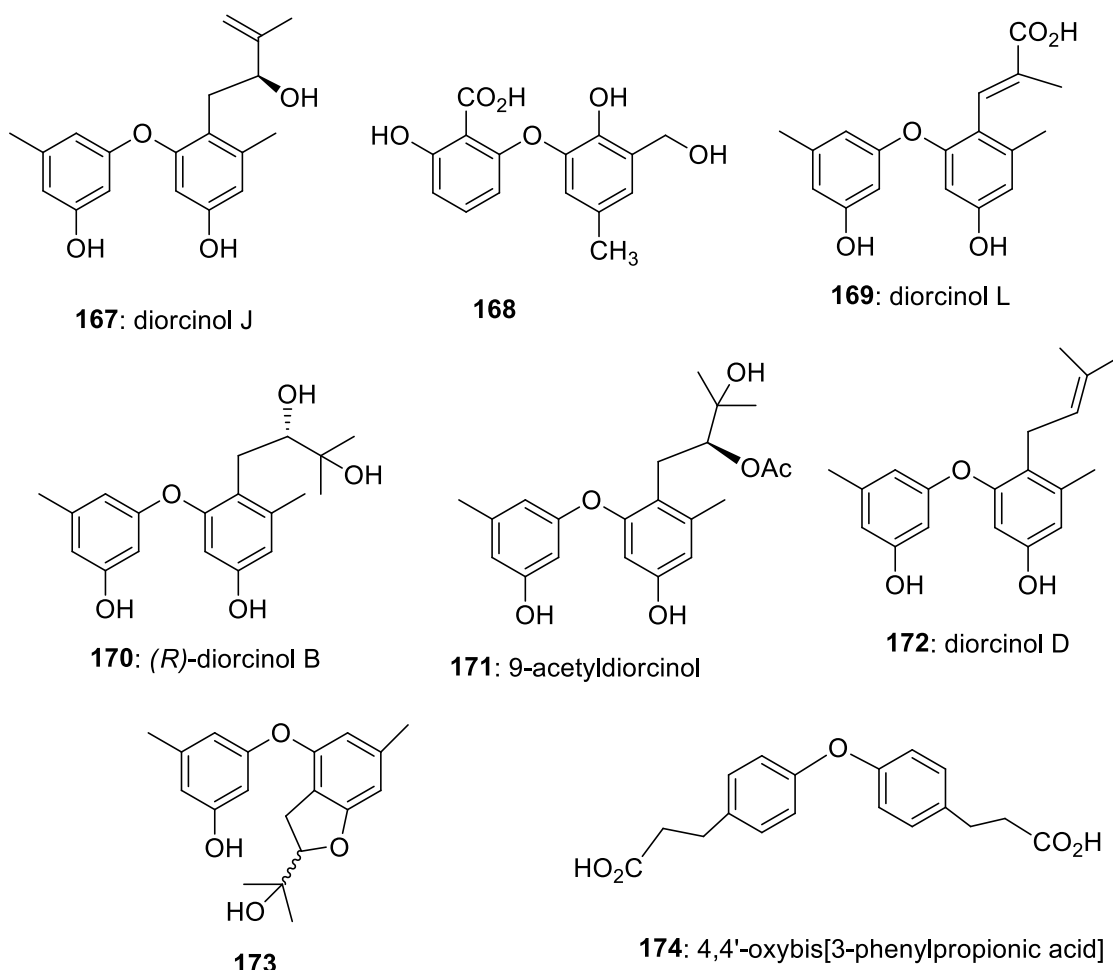
160

Numerous diphenyl ether derivatives, namely, diorcinol K (**161**), diorcinol D (**162**), diorcinol F (**155**) and diorcinol I (**163**) were isolated from the marine-derived fungus *Aspergillus* sp.CUGB-F046 obtained from sediment [117]. Diorcinols K (**161**), D (**162**) and I (**163**) exhibited remarkable antibacterial activities against *S. aureus* and methicillin resistant *S. aureus* with the MIC values of 3.12, 6.25 and 3.12 $\mu\text{g/mL}$, respectively. Whereas, the fungus *versicolor* OUCMDZ-2738 derived from a marine algae [118] and the co-cultivation of marine fungi *Aspergillus sulphurous* and *Isaria feline* found to contain the diphenyl ethers, namely, (S)- diorcinols B (**164**), C (**165**), E (**166**), J (**167**), diorcinol (**115**) and 4-methoxycarbonyl diorcinol (**128**) [119]. Diorcinol (**115**) exhibited selective antibacterial activity against *Pseudomonas aeruginosa* with the MIC value of 17.4 μM while 4-methoxycarbonyl diorcinol (**128**) exhibit inhibition against *Pseudomonas aeruginosa* and *C. glabrata* with the MIC values of 13.9 and 27.8 μM , whereas, diorcinol E (**166**) showed moderate α -glucosidase inhibitory.



Chemical investigation of an ascidian-derived fungus, *Penicillium albobiverticillium* TPU1432 gave a new diphenyl ether (**168**) upon extraction and successive chromatography [120]. Compound (**168**) showed no inhibitory activity against protein tyrosine phosphatase (PTP), but exhibited moderate inhibitory against CD45 with an IC_{50} value of 43 μ M. In the following year, Zhang and co-workers isolated diorcinol L (**169**), (*R*)-diorcinol B (**170**) along with the known compounds, (*S*)-diorcinol B (**166**), diorcinol J (**167**), 9-acetyldiorcinol (**171**), diorcinol D (**172**) and dihydrobenzofuran derivative (**173**) from a marine alga-derived endophytic fungus *Aspergillus tennesseensis* [121]. Antimicrobial study of the isolated compounds showed activity against several plants and human pathogenic microbes. For instances, (*R*)-diorcinol B (**170**) and diorcinol J (**167**) showed antibacterial activity against *E. coli* and *B. subtilis* with the MIC values of 4 μ g/mL while a promising activity was observed against *Bacillus subtilis* for compound (**173**) with the MIC value of 2 μ g/mL. Further, compound (**173**) selectively displayed cytotoxicity against the THP-1 cell line (IC_{50} , 7.0 μ g/mL).

It is noteworthy that only a few nonhalogenated diphenyl ethers were isolated from marine bacteria as compared to fungi although bacteria are the responsible for the production of several brominated diphenyl ethers in marine sponges. A diphenyl ether, having dimeric structure, 4,4'-oxybis[3-phenylpropionic acid (**174**) was isolated from a sponge-associated bacterium *Bacillus licheniformis* SAB1 [122]. However, the authors did not report bioactivity of this compound.



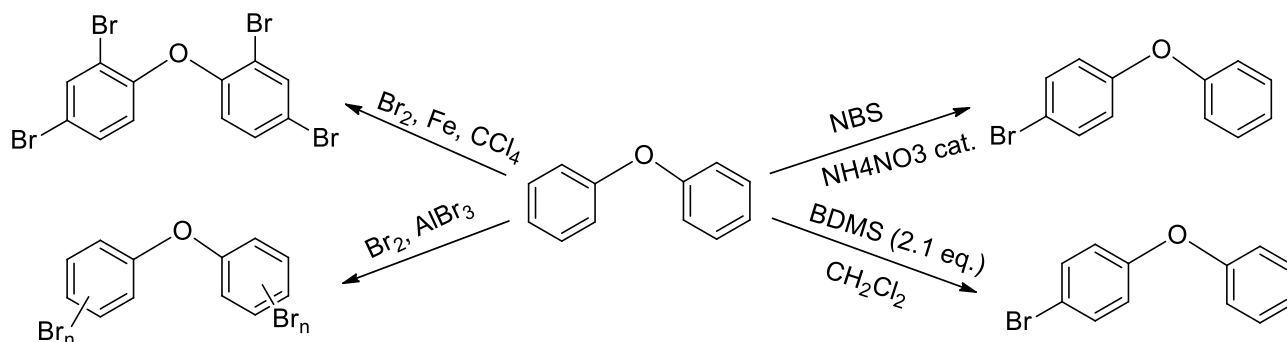
3. Synthetic aspects of marine diphenyl ether derivatives

In recent years, synthesis of marine diphenyl ethers has been paid considerable attention owing to their bioactivities, such as cytotoxicity, anticancer, antimicrobial and antioxidant properties. However, a straight forward synthesis of marine diphenyl ethers remains challenging due to the difficulty in the installation of bromine atom at the desired position. The synthesis of PBDEs was first reported in 1871 [123]. In general, diphenyl ethers can be accessed through various processes such as copper catalysed Ullman reaction, synthesis via diaryliodonium salts or aminodiphenyl ethers and using aryl boronic acid to name a few. The subsequent sections will briefly highlight the synthetic route to brominated diphenyl ethers and selected synthesis of marine derived BDEs and their derivatives.

3.1. General methods for the synthesis of diphenyl ethers

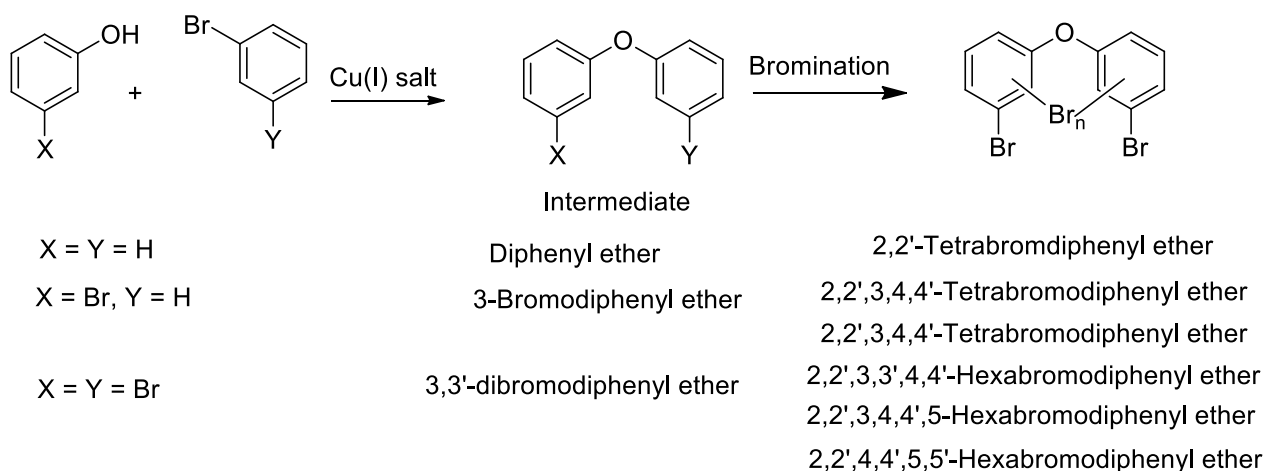
(a) *Direct bromination of diphenyl ethers*: The aromatic ring of diphenyl ethers can be brominated via electrophilic substitution using elemental bromine in the presence of Lewis acid catalysts namely, $AlBr_3$ or $FeBr_3$ etc. (Scheme 1). However, monobromination are usually achieved either by using NBS

in the presence of ammonium nitrate as catalyst or bromodimethylsulfonium bromide (BDMS) (Scheme 1) [124].



Scheme 1. Reaction pathways for direct bromination of diphenyl ether.

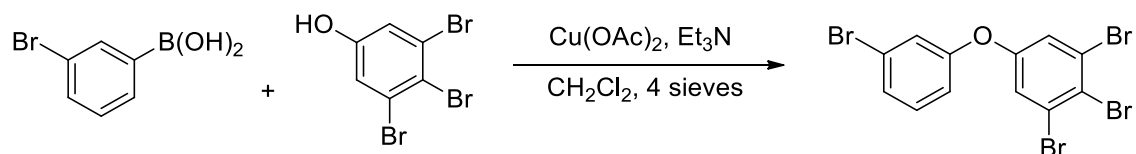
(b) *Ullmann ether synthesis*: This copper catalysed reaction is a useful process for the synthesis of biaryl compounds [125]. A modified Ullmann ether synthesis has been successfully employed in the synthesis of BDE congeners (Scheme 2) [126]. First step is the preparation of diphenyl ether in the presence of copper(I) salt then each of the compound was subsequently brominated to yield *tetra*-, *penta*- and *hexa*-BDE derivatives.



Scheme 2. Ullmann synthesis of bromodiphenyl ethers.

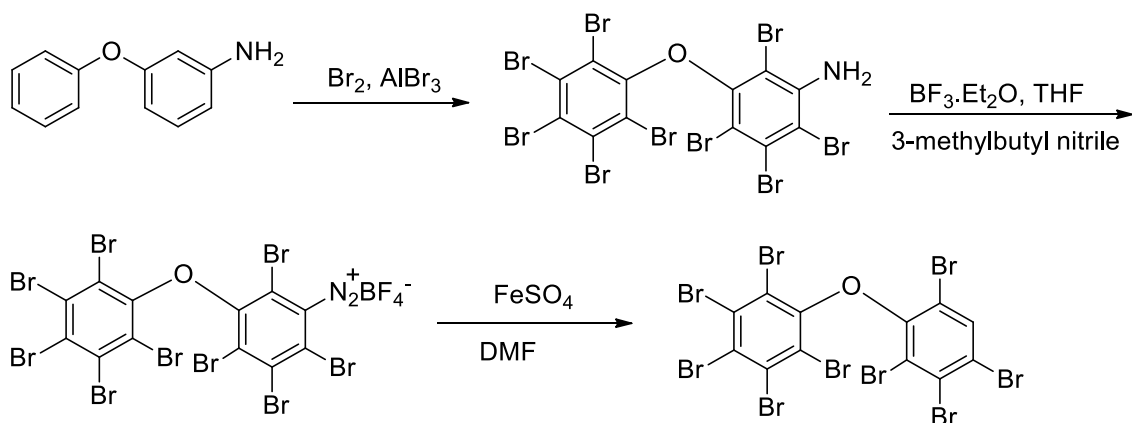
(c)

Synthesis of PBDEs from arylboronic acids: Synthesis of diaryl ethers can be achieved by the reaction of arylboronic acids with phenols in the presence of copper(II) acetate (Scheme 3) [127]. This method used a preinstalled brominated arylboronic acid and brominated phenol and it is convenient for the preparation of simple brominated diphenyl ethers.



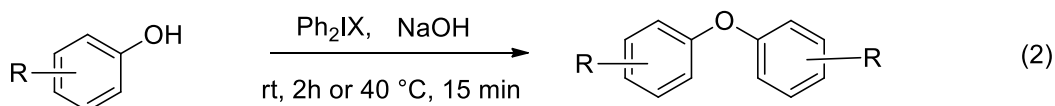
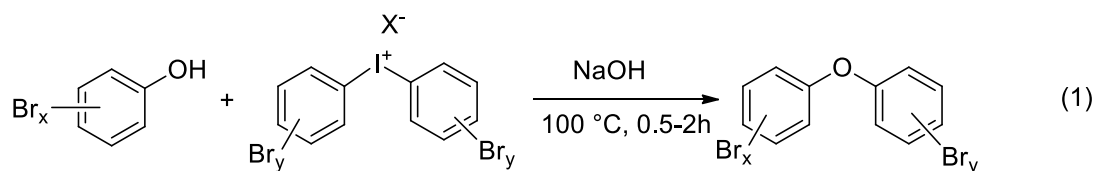
Scheme 3. Reaction pathways for the synthesis of bromodiphenyl ether from arylboronic acids.

(d) *Synthesis PBDEs via aminodiphenyl ethers*: One of the most widely used protocols for the synthesis of BDEs is the preparation via perbromination of NH_2 -BDEs [128]. This process allows a ready access to PBDEs by perbromination of *ortho*-, *meta*- or *para*-aminodiphenyl ether followed by diazotisation with 3-methylbutyl nitrite and boron trifluoride diethyl etherate in THF. The diazonium salt formed was subsequently reduced to the corresponding ether derivatives using iron sulphate in DMF [129] (Scheme 4).



Scheme 4. Reaction pathway for the synthesis of PBDEs via aminodiphenyl ethers.

(e) *Synthesis PBDEs via diaryliodonium salts*: Crowder *et al.* [130] developed a general method for the synthesis of PBDEs via the *O*-arylation of bromophenolates with symmetrically brominated diphenyl iodonium salts. Synthesis of PBDEs was readily achieved by refluxing bromophenols with symmetrical brominated diphenyliodonium halides in an alkaline solution under reflux for 24 h (Scheme 5, eq. 1). Later, an improved method was developed using this diaryl diazonium salts by Jalalian *et al.* employing aprotic solvent at room temperature requiring only 2h reaction or 40 °C for 15 min [131] (Scheme 5, eq. 2).



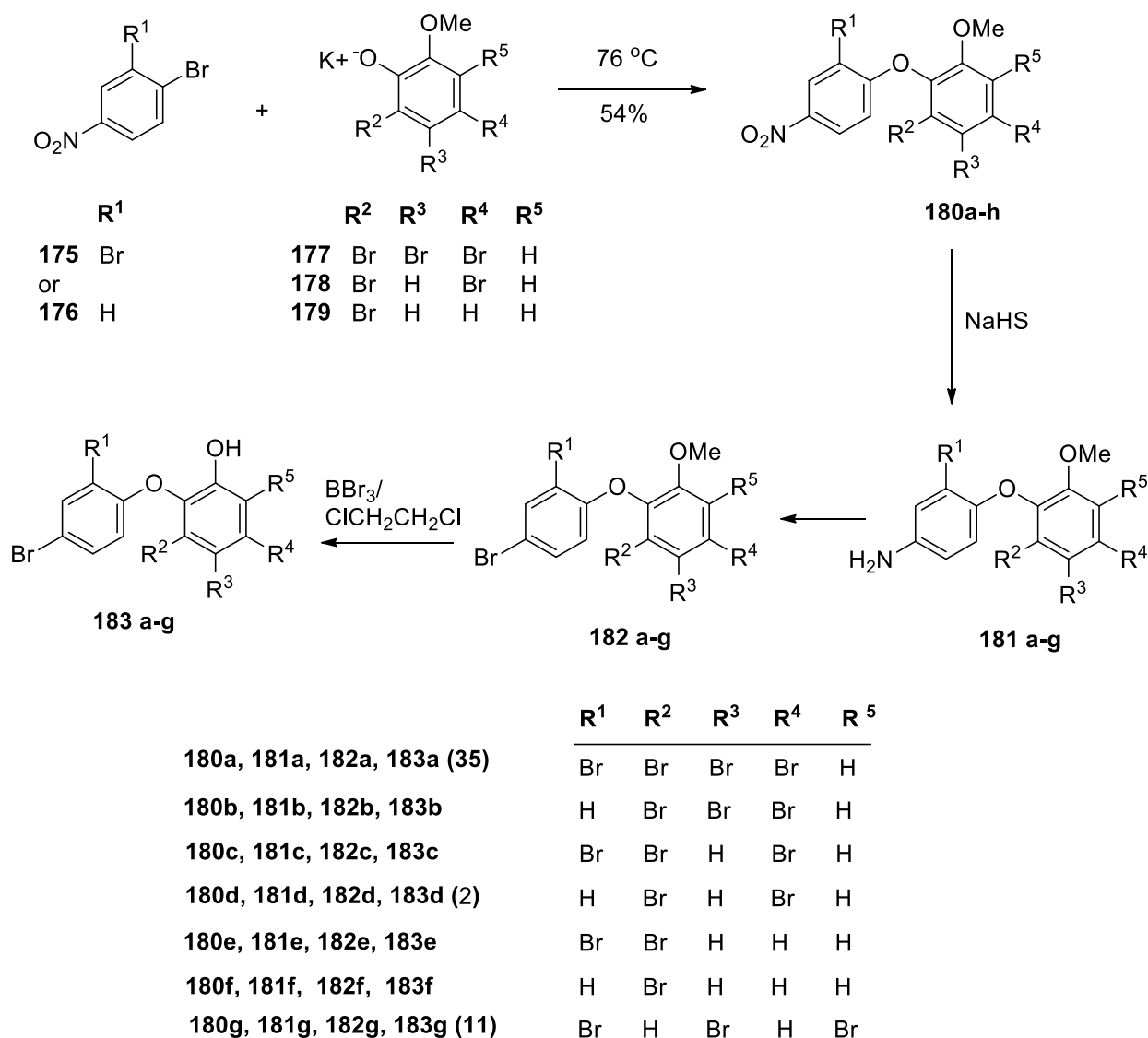
Scheme 5. Synthetic cascades of BDEs via diaryliodonium salts

3.2. Total chemical synthesis of marine-derived brominated and their derivatives

In the past years, several methods for the synthesis of brominated diphenyl ethers of marine origin and their analogues, have been described by various research groups. Herein, we present the synthetic methods for some selected BDEs of marine origin such as **(2)**, **(11)**, **(35)** and their analogues described by Francesconi and Ghisalberti [132], Utkina [133], Marsh *et al.* [73, 134], Fuente *et al.* [135], and Lin and co-workers [136].

(a) Synthesis of BDE derivatives by the method of Francesconi and Ghisalberti

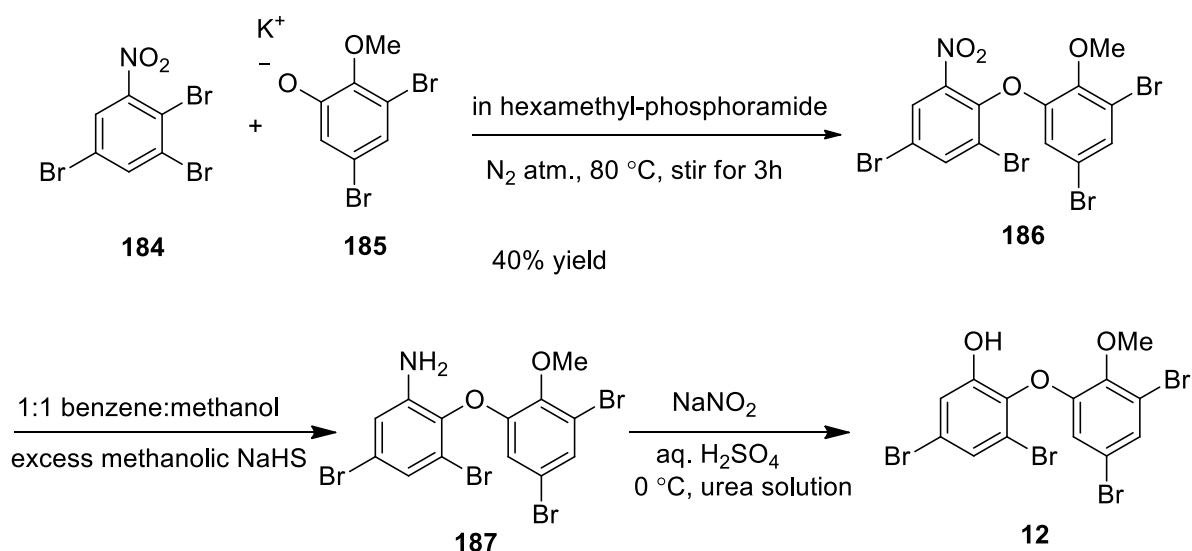
Francesconi and Ghisalberti [132] designed a general procedure for the preparation of BDEs, and the methyl ether derivative of the pentabromo-2-phenoxyphenol. The key synthetic reaction involved condensation of 1,2-dibromo-4-nitrobenzene (**175**) or 4-bromonitrobenzene (**176**) and the potassium salt of the brominated 2-methoxyphenols (**177-179**) to furnish mononitrodiphenyl ethers (**180 a-g**) (Scheme 6). Mild reduction of the nitro group in the compounds (**180 a-g**) afforded the amines (**181a-g**), which underwent replacement of the amine group by bromine atom yielded 2-phenoxyanisoles (**182a-g**). Finally, demethylation with boron tribromide in ethylene chloride produced PBDEs (**183a-g**) including the marine diphenyl ethers **35** (**183a**), **2** (**183d**) and **11** (**183 g**) in good yields (Scheme 6).



Scheme 6. Synthetic cascade of marine diphenyl ethers (**35**), (**2**) and (**11**) and their analogues.

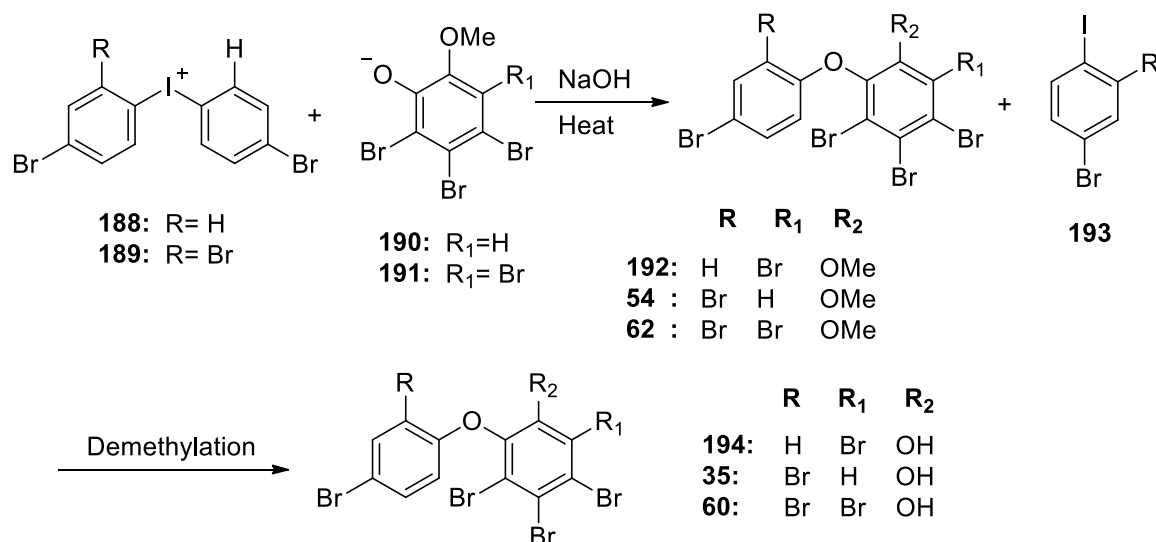
(b) *Synthesis of BDEs by Utkina et al. (1993)*

In 1993, Utkina *et al.* [133] succeeded in the synthesis of BDE (**12**) which was isolated from the marine sponge, *Dysidea herbacea* [49]. The synthesis of **12** was initiated by condensation of a solution of tribromonitrobenzene (**184**) in hexamethylphosphoramide with a solution of potassium salt of dibromomethoxyphenol (**185**) in dry hexamethylphosphoramide in an atmosphere of nitrogen at 80°C (Scheme 7). The resulting product was stirred for 3h followed by pouring in water, lead to the formation of nitrodiphenyl ether (**186**) in 40% yield. The reduction of the nitro group in (**186**) was carried out in a 1:1 mixture of benzene and methanol with an excess of methanolic sodium hydrogen sulfide to afford the amine (**187**) with a yield of 59%. The desired ether (**12**) was obtained in 10% yield after the diazotization of the amine (**187**) using NaNO_2 and the hydrolysis of the diazonium salt in aqueous sulfuric acid.



Scheme 7. Reaction pathways for the synthesis of marine diphenyl ether (**12**).

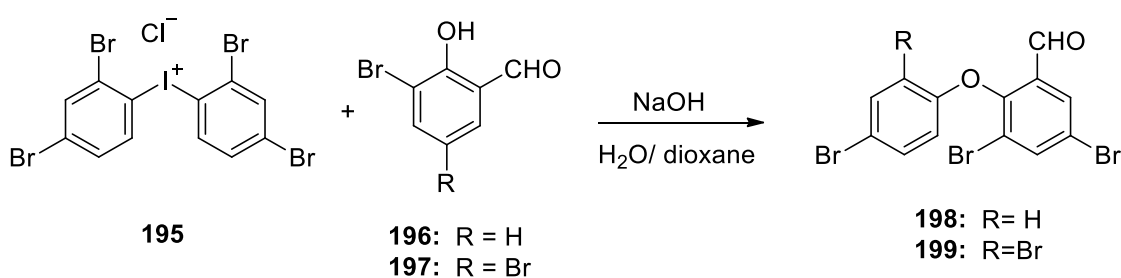
For the synthesis of the marine diphenyl ethers (**35**), (**54**), (**60**), (**62**) and derivatives (**192**) and (**194**), they coupled the symmetrical brominated diphenyliodonium salts (**188**) or (**189**) with brominated guaiacol (**190**) or (**191**) to give in one step the marine diphenyl ethers (**54**), (**62**) and analogue (**192**). The subsequent demethylation of the methoxydiphenyl ethers **192**, **54**, **62** afforded the OH-BDE (**194**), including marine derived OH-BDEs (**35**) and (**60**) (Scheme 8).



Scheme 8. Reaction pathways for the synthesis of marine sponge derived bromodiphenyl ethers (**54**), (**62**), (**35**), (**60**) and analogues (**192**) & (**194**).

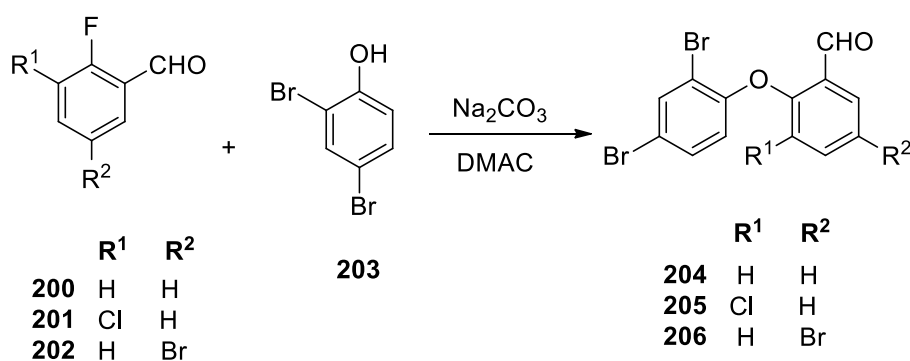
(c) Synthesis of BDE by Marsh et al., 2003 [73]

In 2003, Marsh *et al.* [73] reported synthesis of OH-PBDEs (**207-209**) and several marine sponge derived BDEs (**5**) and (**10**) by Baeyer-Villiger oxidation and acid-catalyzed hydrolysis using precursor compounds, brominated phenoxybenzaldehydes (**198**), (**199**) and (**204-206**). The brominated phenoxybenzaldehydes, precursors of the OH- and MeO-PBDEs with the hydroxyl and methoxy group in the *ortho* position to the ether bond, were prepared by two different diphenyl ether coupling reactions. In the first coupling reaction, they prepared the brominated phenoxybenzaldehydes (**198**) and (**199**) by the treatment of 2, 2', 4, 4'-tetrabromodiphenyliodonium chloride (**195**) with the brominated 2-hydroxybenzaldehydes (**196**) and (**197**), respectively, in aqueous NaOH/dioxane (Scheme 9). They found that use of dioxane as co-solvent improved the reaction yield.



Scheme 9. Reaction pathway for the preparation of phenoxybenzaldehydes (**198**) and (**199**).

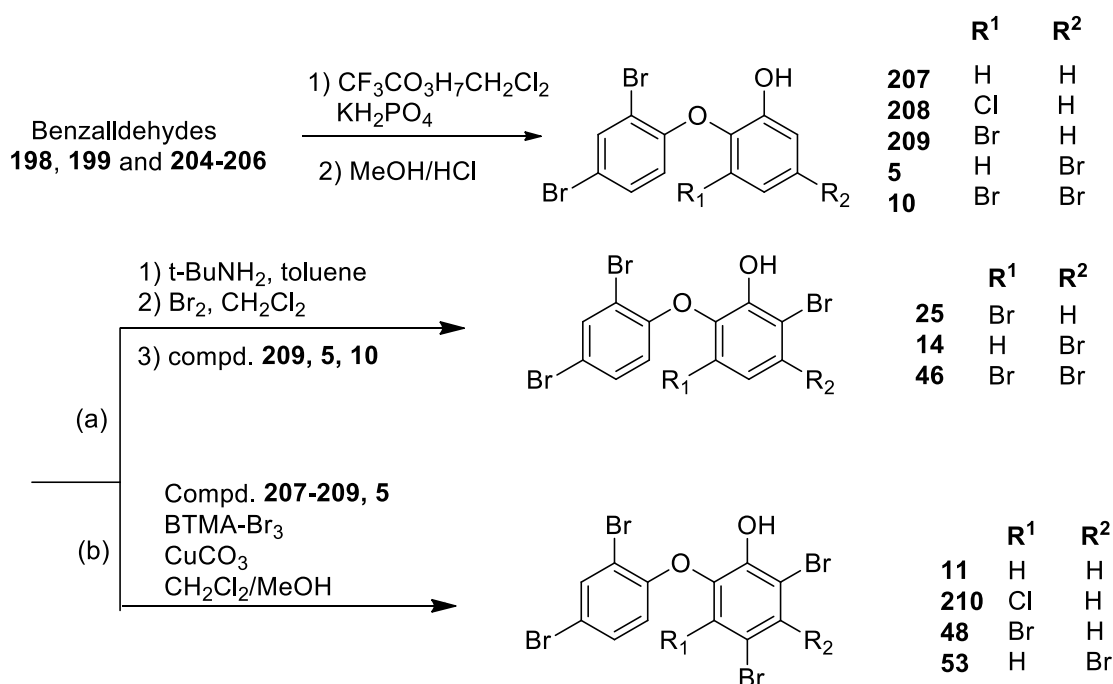
In the other diphenyl ether coupling, substitution of commercially available fluorobenzaldehydes (**200-202**) and 2, 4-dibromophenol (**203**) was carried out to give the brominated phenoxybenzaldehydes (**204-206**) (Scheme 10).



Scheme 10. Reaction scheme for the preparation of phenoxyaldehydes (**204-206**).

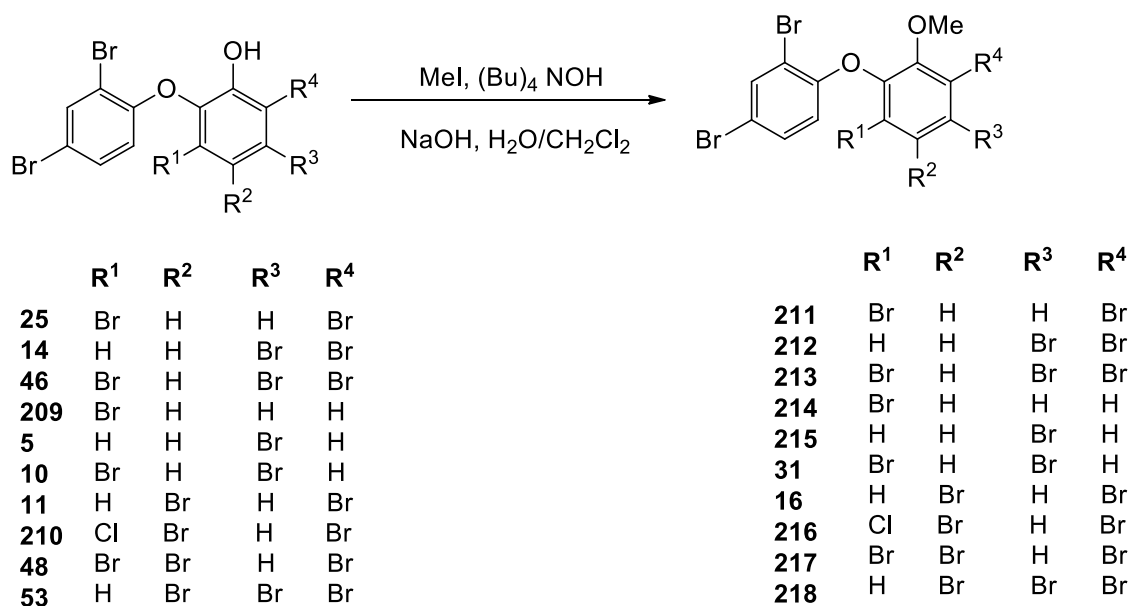
The precursor compounds, phenoxyaldehydes (**198**), (**199**) and (**204-206**) were then subjected to Baeyer-Villiger oxidation followed by acid-catalyzed hydrolysis to give the desired OH-BDEs (**207-209**) and the marine metabolites (**5**) and (**10**) (Scheme 11). Participation of buffer in the reaction is important as the absence of it resulted in side reactions such as the cleavage of ether bond and rearrangement reactions. The bromination of *ortho* to the hydroxyl group of OH-PBDEs (**209**), (**5**) and (**10**) was achieved by Pearson *et al.* [137] method which involved treatment of bromine and *tert*-

butylamine in toluene at -30 °C followed by addition of OH-PBDEs (**209**), (**5**) and (**10**) in CH₂Cl₂ to the bromine/*tert*-butylamine complex at -70 °C which afforded the marine sponge metabolites, OH-BDEs (**25**), (**14**) and (**46**) (Scheme 11a). Further, dibromination at the *ortho*- and *para*-position to the hydroxyl groups of OH-PBDEs (**207-209**) and (**5**) was carried out in CH₂Cl₂/MeOH solution using benzyltrimethylammonium tribromide (BTMA-Br₃) by adding in small portions in the presence of calcium carbonate to avoid ether cleavage affording (**11**), (**210**), (**48**) and (**53**) (Scheme 11b).



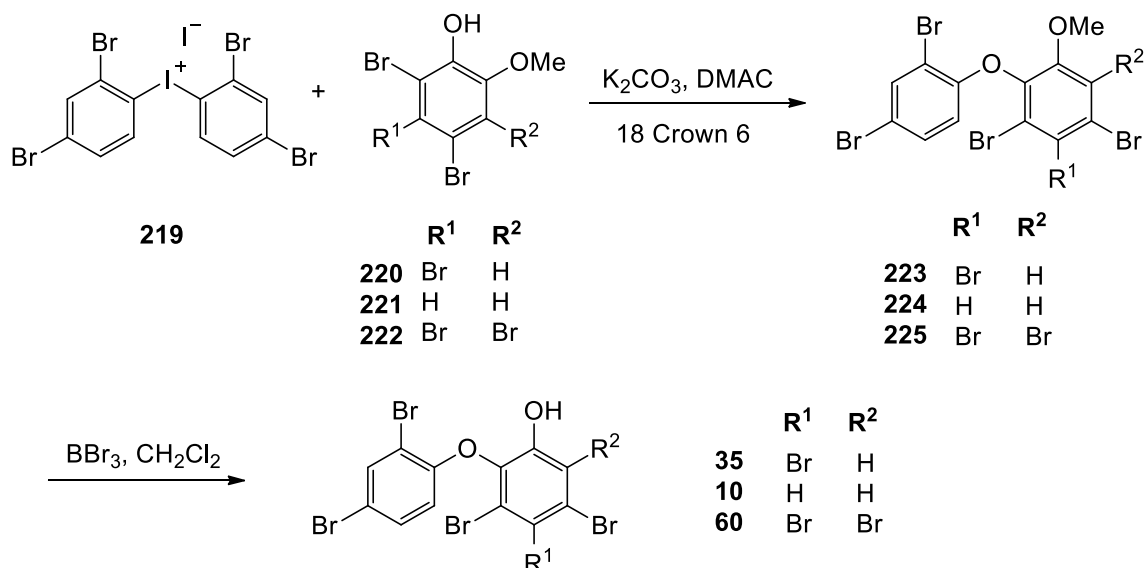
Scheme 11. Synthesis of OH-PBDEs by Baeyer Villiger oxidation subsequent hydrolysis of brominated 2-phenoxybenzaldehydes, followed by bromination; (a) *t*-BuNH₂, Br₂, CH₂Cl₂ (b) BTMA-Br₃, CuCO₃, CH₂Cl₂/MeOH, BTMA-Br₃ = benzyltrimethylammonium tribromide.

Then treatment of OH-BDEs (**25**), (**14**), (**46**), (**209**), (**5**), (**10**), (**11**), (**210**), (**48**) and (**53**) with iodomethane gave the corresponding MeO-BDEs (**211-215**), (**216**), (**217**) and (**218**) including marine metabolites (**31**) and (**16**) [138] (Scheme 12).



Scheme 12. Preparation of MeO-PBDEs from OH-PBDEs using iodoform.

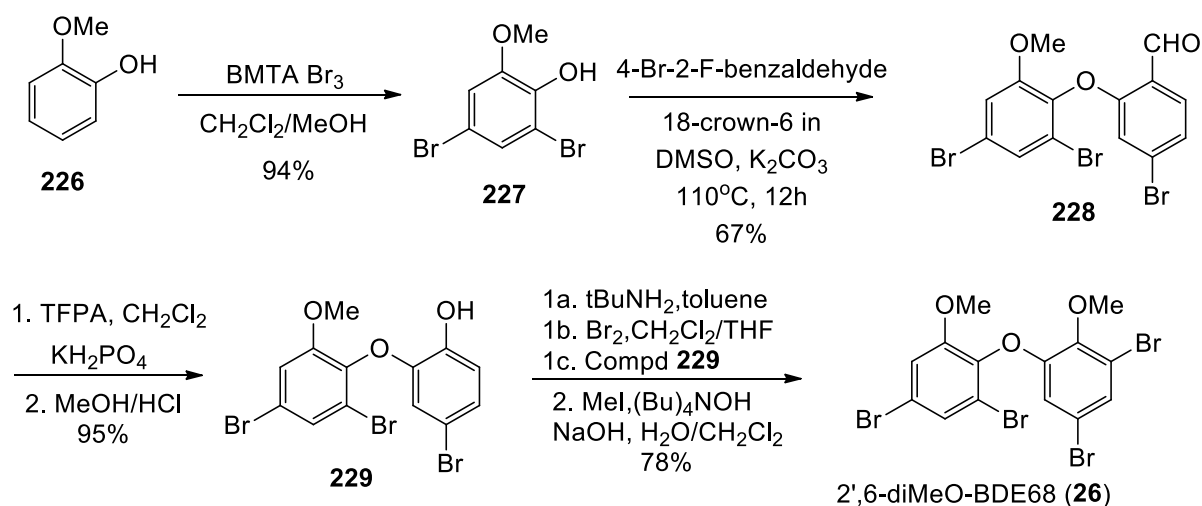
Marsh *et al.* [73] also described a convenient method for the synthesis of marine BDEs (**35**), (**10**) and (**60**). These metabolites were reported from the marine sponge by Sharma and followed by Capon [38, 44]. Synthesis of the metabolites was achieved by the coupling of brominated 2-methoxyphenols (**220-222**) with iodonium iodide (**219**) in the presence of K_2CO_3 and 18-crown-6 in *N,N'*-dimethylacetamide (DMAc) affording MeO-PBDEs (**223-225**) in 40-60 % yield (Scheme 13). Demethylation of MeO-PBDEs (**223-225**) with BBr_3 in CH_2Cl_2 [132] afforded the desired marine sponge OH-PBDEs (**35**), (**10**) and (**60**) (Scheme 13).



Scheme 13. Reaction pathways for the synthesis of marine sponge OH-BDEs (**35**), (**10**) and (**60**).

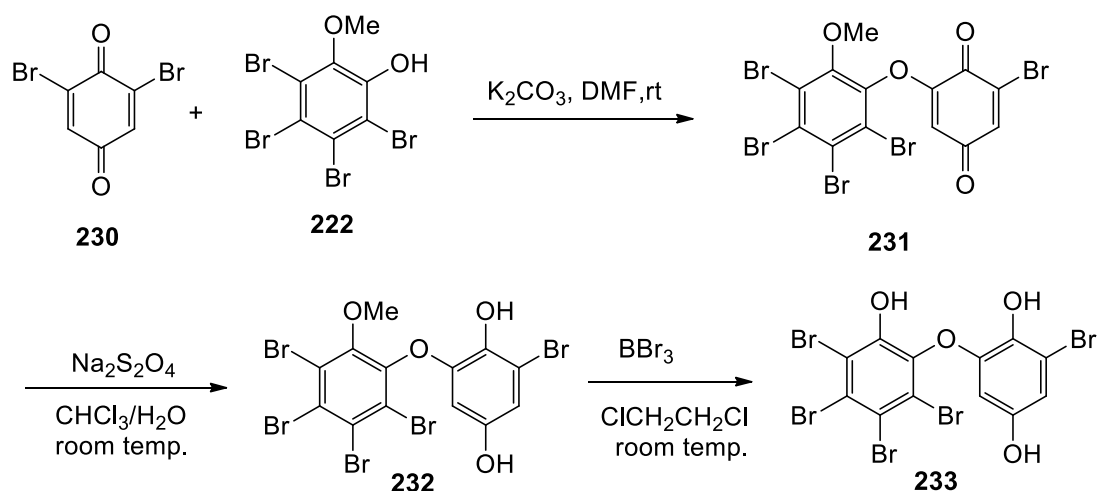
(d) *Synthesis of BDEs by Marsh et al., 2005 [134]*

In 2005, Marsh *et al.* [133] developed a protocol for synthesis of 2, 6-diMeO-BDE68 (**26**) commonly found in marine sponge and mammals [23]. The preparation was initiated by dibromination of 2-methoxyphenol (**226**) to give 4, 6-dibromo-2-methoxyphenol (**227**). Subsequently, coupling of the compound (**227**) with 4-bromo-2-fluorobenzaldehyde in DMSO in the presence of potassium carbonate gave 2-(4, 6-dibromo-2-methoxyphenoxy)-4-bromobenzaldehyde (**228**). Thereafter, the aldehyde moiety in (**228**) was converted into a hydroxy group by trifluoroacetic acid (TFPA) using a Baeyer-Villiger oxidation followed by acid-catalyzed hydrolysis to give 2-(4, 6-dibromo-2-methoxyphenoxy)-4-bromophenol (**229**). Then the compound was brominated at *ortho* position to the hydroxy group by employing a bromine/*t*-butylamine and subsequently the hydroxy group was methylated to yield the desired product 2',6-diMeO-BDE68 (**26**) (Scheme 14).



Scheme 14. Marsh *et al.* Synthesis of 2',6-diMeO-BDE68 (**26**), a PBDE of marine mammal.

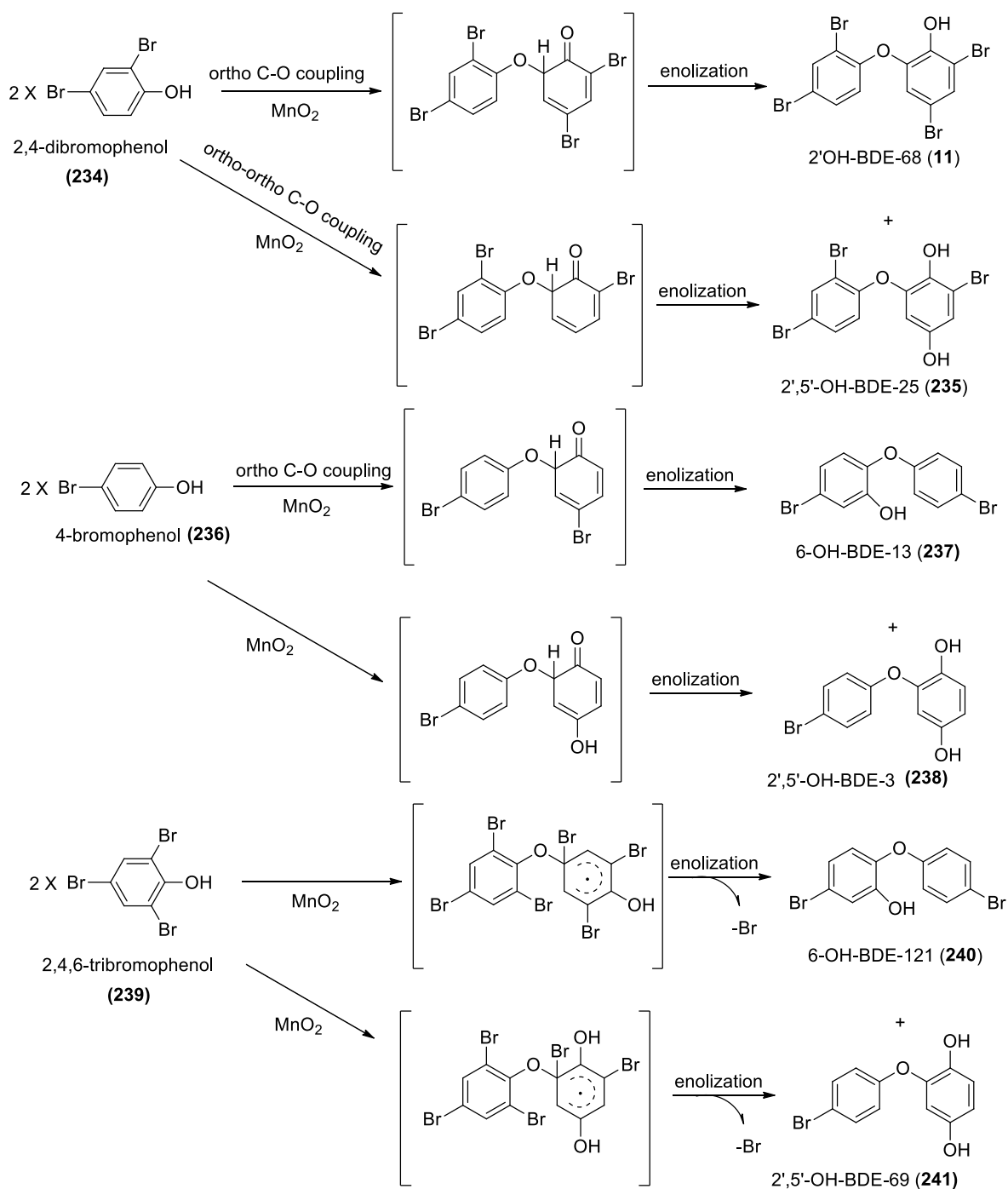
(e) *Synthesis of BDEs by Fuente et al., 2003 [135]*: In 2003, Fuente *et al.* described the total synthesis of novel polybrominated ether derivative (**233**) in three steps. The first step is the treatment of a solution of tetrabromomethoxyphenol (**222**) with 2, 6-dibromobenzoquinone (**230**) followed by addition of K_2CO_3 in DMF to give the compound (**231**). Then, the compound (**231**) was reacted with $\text{Na}_2\text{S}_2\text{O}_4$ in CHCl_3 affording the polybrominated methoxy ether derivative (**232**). Finally, demethylation of (**232**) with BBr_3 in dichloroethane afforded the OH-PBDE (**233**) (Scheme 15).



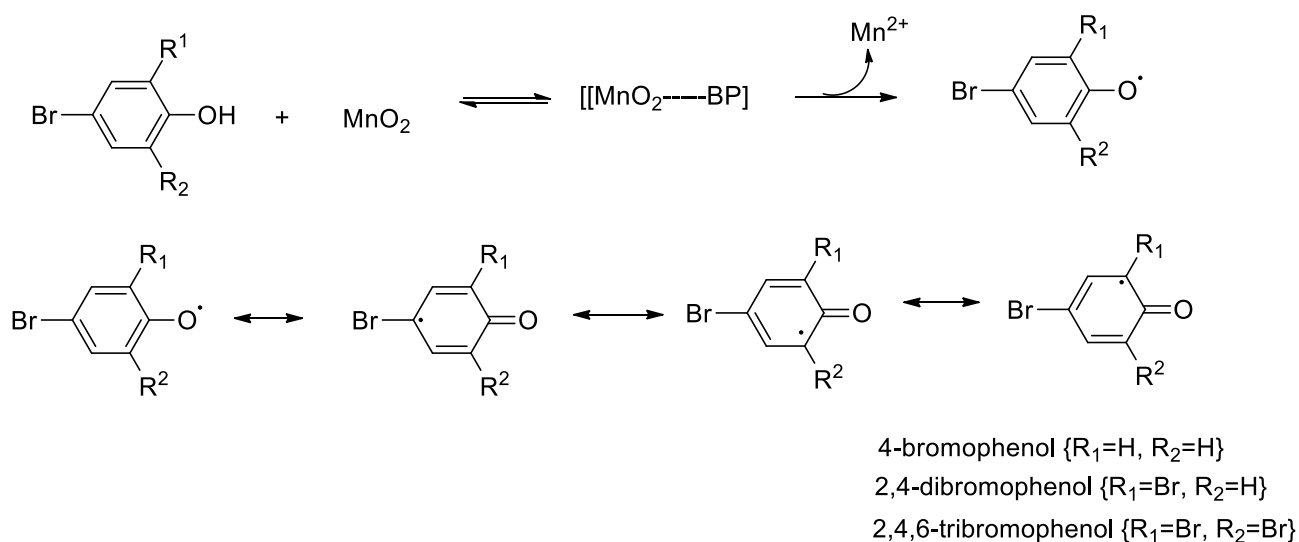
Scheme 15. Synthesis of novel polybrominated diphenyl ether derivative (**233**).

(f) Synthesis of BDE by Lin *et al.* [136]

In 2014, Lin *et al.* [136] explored formation of OH-PBDEs via the oxidative transformation of simple bromophenols (BPs, e.g., 4-BP, 2, 4-DBP, and 2, 4, 6-TBP) by birnessite (δ - MnO_2). They observed that OH-PBDEs were readily produced by δ - MnO_2 with BPs as precursors. For example, the oxidation of 2,4-DBP (**234**) by δ - MnO_2 yielded the marine sponge metabolite 2'-OH-BDE-68 (**11**) [139] and 2',5'-OH-BDE-25 (**235**). Similarly, OH-PBDEs, such as 6-OH-BDE-13 (**237**), 2',5'-OH-BDE-3 (**238**) were detected from the reaction of 4-bromophenol (**236**) whereas, 6-OH-BDE-121 (**240**) and 2',5'-OH-BDE-69 (**241**) from the reaction of 2,4,6-TBP (**239**). (Scheme 16). They proposed that the formation of OH-PBDEs likely resulted from the oxidative coupling of bromophenoxy radicals (Scheme 17).



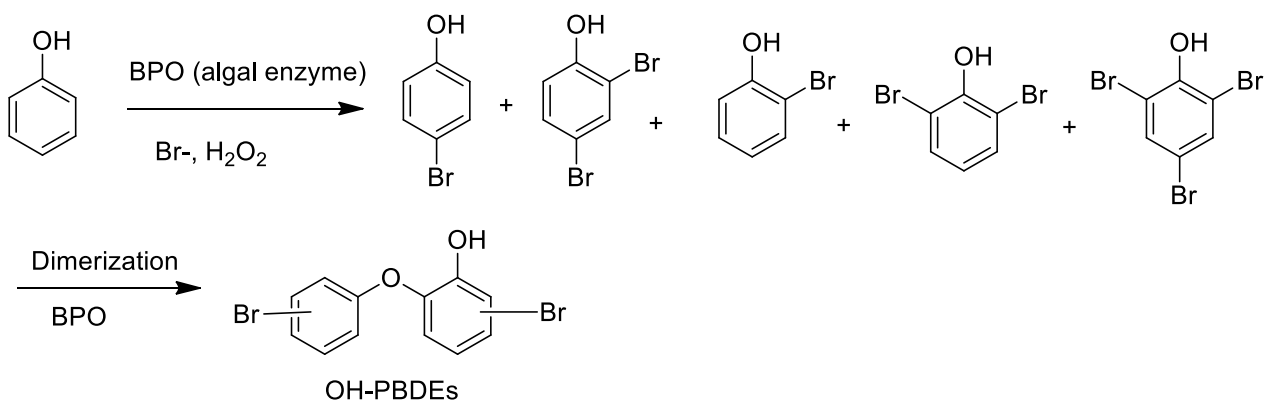
Scheme 16. Transformation of bromophenols to brominated diphenyl ether by catalyzed by MnO₂.



Scheme 17. Plausible pathway for the formation of OH-PBDEs from the oxidative coupling of bromophenoxy radicals.

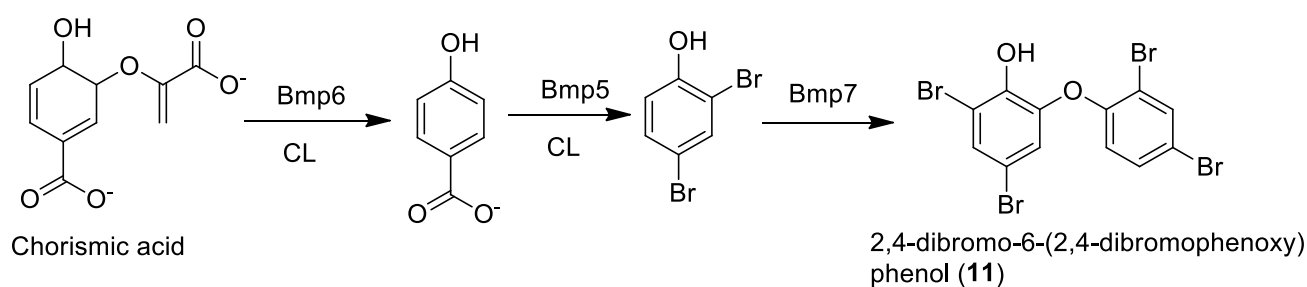
4. Biosynthesis of bromodiphenyl ethers (BDEs):

Polybromodiphenyl ethers (PBDEs) are flame retardants persistent to environment and are toxic in nature. However, unlike PBDEs, many of the OH-PBDEs or OMe-PBDEs are not man-made chemicals rather they are natural in origin. Several studies attributed the origin of OH-PBDEs to the metabolism of PBDEs and natural production in the environment [139]. Two possible theories for the sources of OH-PBDEs are: (i) Transformation of PBDEs via biological hydroxylation or aerobic oxidation [138] and (ii) Natural production of OH-PBDEs by marine algae [17] and cyanobacteria associated with sponges [140]. On the other hand, MeO-PBDEs are formed via methylation of OH-PBDEs [141]. However, *in vitro* and *in vivo* studies showed that exposure concentration of PBDEs is much greater than the resultant OH-PBDEs which were detected in traces and thus ruled out the possibility of metabolic biotransformation as the source of OH-PBDEs which are present in great concentration in marine organisms. Indeed, high concentration of OH-PBDEs was reported from several marine organisms as compared to pg/g to ng/g level of environmental concentration suggesting natural production of OH-PBDEs. Lindqvist *et al.* studied biosynthesis of brominated organic compounds (BOCs) in marine algae catalysed by an antioxidant enzyme, bromoperoxidase (BPO) [17]. It is noteworthy that hydrogen peroxide (H₂O₂) formed as a result of photoelectron and respiratory electron transport oxidized bromide to hypobromous acid (HOBr) which is subsequently used to brominate organic substrate. Further, Shang *et al.* showed bromination of phenol to 2, 4, 6-tribromophenol (TBP) catalysed by BPO isolated from algae. Dimerization of bromophenol in the presence of BPO via bromination to bromophenoxy radicals which subsequently underwent bi-radical coupling resulted in OH-PBDEs [142] (Scheme 18).



Scheme 18. Plausible biogenesis of OH-PBDEs in marine algae catalysed by BPO.

PBDEs are rich in marine sponges of *Dysidea* sp. and it was reported that the cyanobacteria associated with sponges [140, 143] are responsible for the production of PBDEs. However, biosynthesis and mechanism remain unclear. In 2014, Agarwal *et al.* has shown that the *bmp* gene cluster of *Pseudoalteromonas* is responsible for the biosynthesis and production of PBDEs in marine sponges [16]. In the subsequent years, they reported the biosynthesis of PBDEs within sponge microbiome-associated cyanobacterial by metagenome mining approach [17]. They identified the gene responsible for the production of PBDEs in the marine sponges of *Dysidea* sp. The biosynthesis of PBDEs in *Pseudoalteromonas* started from chorismic acid which was converted to *p*-hydroxybenzoic acid by the chorismate lyase Bmp6. The next step was decarboxylative bromination of *p*-hydroxybenzoic acid to 2, 4-dibromophenol by flavin dependent brominase, Bmp5 to give the intermediate 2, 4-dibromophenol which underwent oxidative coupling in the presence of cytochrome P450 enzyme (CYP450), Bmp7 to yield PBDEs (**11**) and its regioisomeric products (Scheme 19).



Scheme 19. Biosynthetic pathway of marine polybrominated diphenyl ethers by *bmp* pathway.

5. Biological activity of diphenyl ether derivatives

6.1. *Antibacterial activities*: Several marine diphenyl ethers exhibit promising antibacterial activities against both Gram-positive and Gram-negative bacteria. In 1997 Handayani *et al.* reported for the first-time antibacterial activity against the gram positive bacteria *Bacillus subtilis* and fungus

Cladosporium cucumerinum for marine sponge diphenyl ethers [56]. The diphenyl ether derivatives (**41**) and (**60**) exhibited activity against *Bacillus subtilis* with MIC values of 0.20 and 0.31 µg/mL (Table 1). The BDE, 2-(2',4'-dibromophenoxy)-4,6-dibromophenol (**11**) have been isolated from several marine sponges. The compound displayed potent antibacterial activity against numerous strains especially against methicillin resistant *Staphylococcus aureus* (MRSA), methicillin sensitive *Staphylococcus aureus* (MSSA) vancomycin resistant Enterococci (VRE), vancomycin sensitive Enterococci (VSE) and *Bacillus sp.* [45]. A related tetrabromodiphenyl ether (**10**) exhibited broad spectrum of antibacterial activities including MRSA, MSSA, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae* and *Pseudomonas* [144]. Numerous diphenyl ethers derived from marine fungi including compound (**63**), talaromycin C (**106**), diorcinol (**115**), peniciaculin A (**157**), diorcinol B (**164**), diorcinol C (**165**), diorcinol J (**167**), dihydrobenzofuran derivative (**173**) exhibited remarkable antibacterial activities [122]. Most of the diphenyl ether reported from marine fungi are non-halogenated derivative and few are chlorinated derivatives. Fungal diphenyl ethers, Iizukine A (**73**) butyldichloroasterrate (**75**) dichloroasterrate (**76**), asterric acid (**95**) exhibited antibacterial activity against both the Gram positive, *S. aureus* as well as Gram negative bacteria, *G. vibrio*. Table 1 summarises antibacterial properties of diphenyl ethers isolated from marine organisms.

Table 1. Antimicrobial properties of diphenyl ethers from marine organisms

Compounds	Sources	Microbes	MIC/ IC ₅₀	Ref.
(20)	Sponge: <i>Lamellodysidea herbacea</i>	<i>B. subtilis</i>	0.1 µg/mL (a)	Hanif <i>et al.</i> 2007 [55]
(11)	<i>Dysidea granulosa</i>	<i>S. aureus</i> (MRSA) <i>S. aureus</i> (MSSA) <i>E. faecalis</i> VSE Enterococci VRE <i>Salmonella typhi</i>	0.313 0.177-0.313 1.25 0.625 0.5 µg/mL	Shridhar <i>et al.</i> 2009 [45]
(10)	Marine sponge: <i>Dysidea sp.</i>	<i>Listeria monocytogenis</i> , MSSA, <i>Bacillus cereus</i> , MRSA, <i>Pseudomonas</i> , <i>Klebsiella pneumoniae</i> , <i>Neisseria gonorrhoeae</i>	2.0, (MIC) 1.0, 0.1, 0.1, 4.0, 0.1, 2.0 µ/mL	Sun <i>et al.</i> 2015 [144]
(41) and (60)	Sponge: <i>Dysidea herbacea</i>	<i>B. subtilis</i>	0.20 and 3.14 µg/mL (MIC)	Handayani <i>et al.</i> 1997 [56]
(49), (58), (37-38)	Marine Sponge: <i>Lendenfeldia dendyi</i>	methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	0.98, 2.94 and 0.1, 0.05 µM (IC ₅₀)	Radwan <i>et al.</i> 2015 [48]
(2) (4) (11) (25)	Marine sponge: <i>Arenosclera sp.</i>	<i>B. subtilis</i> , <i>S. aureus</i> , <i>K. pneumoniae</i>	MIC (µM) 0.8, 0.5 & 6.3 3.1, 6.3 & 6.3 0.5, 0.5 & 3.1 3.1, 6.3 & 6.3	Ki <i>et al.</i> 2019 [40]
Peniciaculin A (157)	Fungus: <i>Penicillium aculeatum</i>	<i>M. luteus</i> , <i>A. brassicae</i>	1.0 µg/mL (a) 0.5 µg/mL (a)	Li <i>et al.</i> 2015 [115]
Diorcinol (115) (137)	Fungus: <i>Aspergillus versicolor</i> OUCMDZ-2738	<i>Pseudomonas aeruginosa</i>	17.4 µM (b) 13.9 µM (b)	Liu <i>et al.</i> 2019 [118]
Diorcinol (115) and 4-methoxycarbonyl diorcinol (128)	Fungi: <i>Aspergillus versicolor</i>	<i>Pseudomonas aeruginosa</i>	17.4 and 13.9 µM (MIC)	Liu <i>et al.</i> 2019 [118]
(63)	Fungus: <i>Aspergillus sp.</i>	<i>Staphylococcus epidermidis</i>	0.556 µM 1.11 µM	Chen <i>et al.</i> 2013 [97]

		<i>Staphylococcus aureus</i>		
Diorcinol B (164), diorcinol C (165), diorcinol J (167) dihydrobenzofuran derivative (173)	<i>Aspergillus tennesseensis</i>	<i>Bacillus subtilis</i>	MIC = 8, 8, 4 and 2 µg/ mL	Li <i>et al.</i> 2018 [121]
Cordylol C (124) Diorcinol (115)	<i>Aspergillus sydowii J05B-7F-4</i>	<i>S. aureus SG S11, S. iniae</i>	MIC = 20, 2 µg/ mL	Liu <i>et al.</i> 2017 [108]
Diorcinol K (161) Diorcinol D (172) Diorcinol I (163)	<i>Aspergillus sp. CUGB-F046</i>	<i>Staphylococcus aureus</i>	MIC = 3.125, 6.25 and 6.25 µg/ mL	Xu <i>et al.</i> 2018 [117]
Phomaether A (138) Phomaether C (140) (141)	<i>Fungus: Phoma sp. (TA07-1)</i>	<i>S. albus, S. aureus, E. coli,</i>	0.312-0.625 µM, 0.312-1.25 0.312-0.156 µM	Shi <i>et al.</i> 2017 [104]
Talaromycin C (106)	Fungus: <i>Talaromyces sp.</i>	<i>Balanus amphitrite</i>	EC ₅₀ = 2.28 µg/ mL	Chen <i>et al.</i> 2015 [93]
7- <i>O</i> -acetylsecopenicillide C (96)	fungus <i>Penicillium sp. MA-37</i>	<i>M. luteus and E. coli</i>	MICs = 64 and 16 µg/ mL	Zhang <i>et al.</i> 2012 [90]
Iizukine A (73) Butyl-2,4-dichloroasterrate (75) 2,4-dichloroasterric acid (76) Asterric acid (95)	<i>Aspergillus flavipes</i>	<i>S. aureus</i> <i>G. vibrio</i>	(MIC, µg/ mL) (75): 3.13 (76): 6.25 (73): 3.13 (95): 3.13	Ji <i>et al.</i> 2020 [82]

6.2. Anticancer, apoptosis and cytotoxicity:

Diphenyl ether derived from marine organisms displayed anticancer properties against numerous cancer cell lines. Brominated ether derivatives (**10**) and (**11**) exhibited antiproliferative activity against the MCF-7 cancer cell line as well as inhibit overexpression of Mcl-1 (Table 2). Compounds (**10**) and (**35**) displayed antiproliferative activity against PANC-1 cells [145] whereas, (**11**) and (**23**) showed apoptosis in Jurkat and Ramos cells [146]. Three other brominated sponge derived diphenyl ethers (**36**), (**43**) and (**61**) displayed activity against Chinese hamster V79 and microtubule proteins [147] (Table 2). Chlorinated diphenyl ethers, terrestrol B (**83**) and terrestrol D (**84**) were cytotoxic to several cancer cell lines such as MOLT-4, HL-60, A-549, and BEL-7402 [93] whereas, expanasol B (**114**)

showed inhibition to A549 and HL-60 cells. Dimethyl 2, 3'-dimethoxyosoaate (**91**) and dihydrobenzofuran derivative (**173**) obtained from the marine fungi *Aspergillus sp.* showed activity against K562 and THP-1 cell, respectively. 3,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)phenol (**13**) and 3,4,5-tribromo-2-(3, 5-dibromo-2-methoxyphenoxy)phenol (**44**) were isolated from marine sponge *Lamellodysidea herbacea* showed activity against NBT-T2 rat bladder epithelial, HCT-15 and Jurkat cells [51] (Table 2). Non-halogenated diphenyl ether isolated from marine fungi, *Aspergillus sp.* viz. diocinolic acid (**146**), cordyol C-3-O- α -D-ribofuranoside (**147**), 7-ethyl diorcinol (**151**), 3-hydroxydiorcinol (**152**), glyceryldiorcinolic acid (**159**) showed cytotoxicity to A549, U937, HL-60 & K562 cells [113]. (Table 2).

6.3. Other Bioactivity:

Apart from antibacterial, anticancer, apoptosis and cytotoxicity, marine diphenyl ether and derivatives showed anti-diabetic, free radical scavenging, antioxidant and anti-inflammatory activity. Several diphenyl ethers displayed anti-diabetic by inhibiting PTP1B, α -galactosidase, α -glucosidase, etc. The marine sponge derived diphenyl ethers, 3,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)phenol (**13**) and 1,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)-3-methoxybenzene (**27**) showed anti-diabetic property by inhibiting the activity of PTP1B which is the target enzyme for the treatment of type-II diabetes with the IC₅₀ values of 0.85 and 1.7 μ M, respectively (Table 3). *Dysidea* sponge derived diphenyl ethers (**58**) and (**60**) inhibited α -galactosidase with IC₅₀ value of 4.26, 16.0 μ M [148]. Very few of diphenyl ethers have been isolated from marine algae as compared to marine sponges and marine fungi. Algae derived ether compounds (**33**), (**64**), (**35**) and (**32**) inhibited LmG6PD, α -glucosidase and PTP1B while the bis (3-bromo-4,5-dibromobenzyl) ether (**3**) displayed anti-inflammatory property. It is noteworthy that marine fungi are rich source of several secondary metabolites including diphenyl ethers. They produce mostly non-halogenated diphenyl ethers and a few halogenated ether derivatives primarily chlorinated compounds. Geodin hydrate (**77**), monomethylsoic acid (**94**), methylchloroesterate (**69**), expanasol D (**158**) show anti-diabetic property by inhibiting α -glucosidase [76]. Whereas, diphenyl ethers derived from marine fungi such as terrestrol D (**84**), diorcinol E (**166**) and compounds (**34**), (**57**) and (**115**) which are non-halogenated compounds exhibited antioxidant activity (Table 3).

Table 2. Anticancer or anti-proliferative/cytotoxicity

Compounds	Sources	Apoptosis effect or Cell lines	IC ₅₀	Ref.
(10) and (11)	Sponge: <i>Dysidea sp.</i>	Antiproliferative against MCF-7 cells	2.84, 8.90 μ M	Zhang <i>et al.</i> , 2008 [57]
(10), (11) and (35)	Sponge: <i>Dysidea herbecia</i>	Mcl-1/Bak FRET screen	2.1, 2.4, 7.4 μ M	Calcul <i>et al.</i> , 2009 [59]
(10) and (35)	Sponge: <i>Dysidea</i>	Antiproliferative activity against PANC-1 cells	3.8 2.1 μ M	Arai <i>et al.</i> , 2017 [145]
(37) and (38)	<i>Dysidea and Phyllospongia</i>	Inhibitory activity against human reticulocyte 15-LO	2.2 \pm 0.4, 0.79 \pm 0.07 μ M	Carte <i>et al.</i> 1981 [68], Segraves <i>et al.</i> , 2004 [149]
(11) and (23)	<i>Dysidea herbacea</i>	Apoptosis in Jurkat and Ramos cells, THP-1, HL-60, PBMNCs cells	11 : 2.15, 1.81, 25.26, 31.4, 28.15 μ M 23 : 2.95, 1.61, 6.74, 19.67, 5.65 μ M	Handayani <i>et al.</i> 1997 [56] Mayer <i>et al.</i> , 2019 [146]
(36), (43) and (61)	Sponge: <i>Phyllospongia dendyi</i>	Inhibitory to Chinese hamster V79, Inhibitory to microtubule proteins	29.6, 33.5, and 20.9 μ M	Oda <i>et al.</i> , 2005 [147]
Terrestrol B (83) Terrestrol D (84)	Fungi: <i>Penicillium Terrestre</i>	Cytotoxic to MOLT-4, HL-60, A-549, and BEL-7402	5.3-64.7 μ M	Chen <i>et al.</i> 2010 [86]
Expanasol B (114)	<i>Penicillium expansum</i>	Inhibition to A549 and HL-60 cells	IC ₅₀ = 1.9 and 5.4 μ M	Lu <i>et al.</i> 2010 [28]
dihydrobenzofuran derivative (173)	<i>Aspergillus tennesseensis</i>	THP-1 cell	IC ₅₀ = 76.5 μ M	Li <i>et al.</i> 2018 [121]
3,4,5-tribromo-2-(3,5-dibromo-2-methoxyphenoxy) phenol (44)	<i>Lamellodysidea herbacea</i>	Cytotoxic to NBT-T2 rat bladder epithelial	2.8 μ g/mL	Hanif <i>et al.</i> 2007 [55]
3,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)phenol (13)	Sponge: <i>Lamellodysidea herbacea</i> <i>Dysidea herbacea</i>	HCT-15 and Jurkat cells	12 and 9.5 μ M	Yamazaki <i>et al.</i> 2013 [51]
2,3'-Dimethylsoate (91)	<i>Aspergillus sp. B-F-2</i>	K562 cells	IC ₅₀ = 76.5 mM)	Liu <i>et al.</i> 2006 [88]
Diorcinolic acid (146)	<i>Aspergillus sydowii J05B-7F-4</i>	KB, HepG2, HCT-116 cells	IC ₅₀ = 50 μ M	Liu <i>et al.</i> 2017 [108]

Cordyol C-3-O- α -D-ribofuranoside (147) 7-ethyldiorcinol (151) 3-hydroxydiorcinol (152) Glycerildiorcinolic acid (159)	<i>Aspergillus sydowii</i>	A549, U937, HL-60 & K562	IC ₅₀ = 8.97 & 4.64 ^(a) 16.13 ^(b) 11.98 & 18.89 ^(c) 3.36 & 21.22 ^(d) μ M	Wang <i>et al.</i> 2018 [113]
Diorcinol D (162) Diorcinol E (165)	<i>Aspergillus versicolor</i> <i>ZLN-60</i>	HeLa & K562 HeLa	31.5, 48.9 μ M 36.5 μ M	Gao <i>et al.</i> 2013 [150]

Cytotoxicity (IC₅₀ in μ M) of: Compounds (**147**) against A549 and U937 (a); (**151**) against A549 (b); (**152**) against HL-60 & K562 (c); (**159**) against A549 and HL-60 (d).

Compound	Sources	Bioactivity	Ref.
Compounds (11) and (12)	Sponge: <i>Dysidea sp.</i>	Inhibit Tie2 kinase	Xu <i>et al.</i> 2005 [47]
3,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)phenol (12) 1,5-dibromo-2-(3,5-dibromo-2-methoxyphenoxy)-3-methoxybenzene (26)	Sponge: <i>Lamellodysidea herbacea</i>	Anti-diabetic Inhibited PTP1B IC ₅₀ = 0.85 and 1.7 μM	Yamazaki <i>et al.</i> 2013 [51]
Compounds (58) and (60)	<i>Dysidea herbacea</i>	Anti-diabetic (inhibited α-galactosidase) IC ₅₀ = 4.26, 16.0 μM	Utkina <i>et al.</i> 2019 [148]
2,4-dichloroasteric acid (76)	<i>Aspergillus flavipes PJ03-11</i>	Inhibit α-glucosidase (IC ₅₀ = 0.091 ± 0.001 mM)	Zhang <i>et al.</i> 2016 [84]
Compounds (33) and (64)	Alga: <i>Odonthalia corymbifera</i>	Inhibited LmG6PD IC ₅₀ = 0.85, 0.96 μM	Mikami <i>et al.</i> 2016 [76]
Compound (35)	Red alga: <i>Odonthalia corymbifera</i>	Anti-diabetic (inhibit α-glucosidase; IC ₅₀ = 0.098 μM)	Liu <i>et al.</i> 2011 [151]
Bis (3-bromo-4,5-dibromobenzyl) ether (3)	Red alga <i>Polysiphonia morrowii</i>	Anti-inflammatory (reduced LPS induced NO, PGE ₂)	Choi <i>et al.</i> [152]
3',5',6',6-tetrabromo-2,4-dimethyldiphenyl ether (32)	Algae: <i>Laurencia similis</i>	Inhibit PTP1B (IC ₅₀ = 2.97 μM)	Qin <i>et al.</i> 2010 [61]
Diorcinol (115)	Fungi: <i>Penicillium expansum</i> , <i>Aspergillus versicolor</i> , <i>SCSIOW3</i> , <i>Aspergillus sydowii</i> J05B-7F-4	Antioxidant, Activated nrf-regulated gene	Wu <i>et al.</i> 2016 [100]
Geodin hydrate (77)	Fungi: <i>Aspergillus iizukae</i> , <i>Aspergillus flavipes HN4-13</i>	Anti-diabetic (α-glycosidase inhibitors) IC ₅₀ = 1.476 μM	Liu <i>et al.</i> 2014 [64] Wang <i>et al.</i> 2016 [153]
Monomethylsoic acid (94)	<i>Aspergillus flavipes HN4-13</i>	Anti-diabetic (α-glucosidase inhibitors)	Wang <i>et al.</i> 2016 [153]

Methyldichloroesterate (69) Compound (94)			
Expansol D (158)	<i>Aspergillus flavus</i> QQSG-3	α -glucosidase inhibitory	Wu <i>et al.</i> 2018 [116]
Terrestrol D (84)	Fungi: <i>Penicillium Terrestre</i>	Antioxidant (DPPH activity)	Chen <i>et al.</i> 2008 [86]
Diorcinol E (166)	Fungus: <i>Aspergillus versicolor</i> OUCMDZ-2738	Antioxidant (DPPH activity) IC ₅₀ = 117.3 μ M	Liu <i>et al.</i> 2019 [118]
2,4-dichloroasterric acid (76) Chrysine B (79) Chrysine C (80)	<i>Penicillium chrysogenum</i> SCSIO 41001	α -glucosidase IC ₅₀ : 0.09, 0.35, 0.20 mM.	Wang <i>et al.</i> 2018 [85]
Compounds (34), (57) and (115)	<i>Penicillium chrysogenum</i>	Exhibited radical-scavenging activity against (IC ₅₀ = 18, 15 and 42 μ M)	Yang <i>et al.</i> 2010 [21]
Compound (120)	<i>Aspergillus carneus</i>	Antioxidant activity IC ₅₀ = 19.3 μ M	Xu <i>et al.</i> 2017 [107]
Compound (168)	<i>Penicillium albobiverticillium</i>	Inhibit CD45 tyrosine phosphatase	Sumilat <i>et al.</i> 2017 [120]

Table 3. Other activities exhibited by marine-derived diphenyl ether compounds

6. Conclusion

This manuscript presents an account of chemical diversity, bioactivity and selected chemical synthesis of diphenyl ether derivatives isolated from marine organisms covering literature report from 1969 to 2021. Isolation of 174 diphenyl ether metabolites from marine organisms such as sponges, algae, fungi and bacteria have been deliberated under the headings: brominated, chlorinated and non-halogenated derivatives. Most of the brominated diphenyl ethers were obtained from marine sponges reporting around 50 compounds. While 14 BDEs have been isolated from algae while several are detected. On the other hand, fungi are the main source of all the non-halogenated diphenyl ether (89 metabolites) and most of the chlorinated compounds (20 BDE derivatives). Very few diphenyl ethers were reported from marine bacteria although they are believed to be the main contributors of brominated compounds in marine sponges. Some of the BDEs such as compounds (16), (46), (48) and (60) etc. were isolated from multiple sources, viz. algae as well as sponges. Majority of diaryl ethers with antibacterial activity were derived from fungi (approx. 40) followed by sponges (approx. 24) and a few of them from algae (approx.3). Further, a considerable number of cytotoxic diaryl ethers were

reported from marine organisms while only a few anticancer compounds were reported (Figure 3). In addition, diary ethers with other activities such as anti-diabetic, antioxidant, anti-inflammatory kinase and NO inhibition were also reported from marine organisms. Biological activities of the isolated compounds with IC₅₀ values have been presented in details (Tables 1-3). We presents plausible biosynthetic and chemical synthesis of selected diphenyl ethers. We believe that the survey on chemical and bioactivity of marine derived diaryl ethers will be helpful in the understanding of diversity and biological potential of these versatile compounds and thus offers a ready reference for identification of synthetic target compounds. Further, synthesis presented herein, may be helpful in developing synthetic strategy for the preparation of analogues and in the study of structure and activity relationship that can lead to potential compounds of pharmaceutical interest.

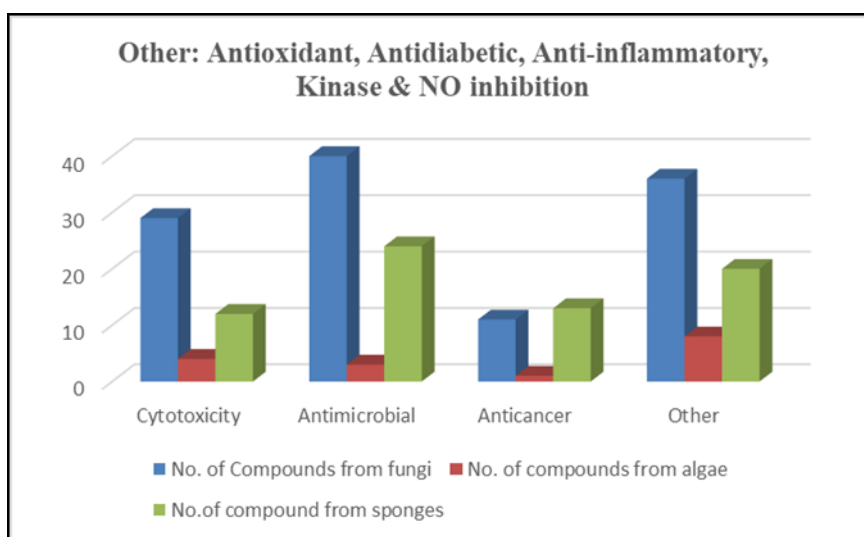


Figure 3 Biographic graph showing number of diaryl ether exhibiting cytotoxic, anticancer, antimicrobial and other activities reported from marine organisms.

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Table 4. List of Abbreviations

ARE	Antioxidant response element	LD	Lethal Dose
ATCC	American Type Culture Collection	LPS	Lipopolysaccharides
BDEs	Bromodiphenyl ethers	MCF	Michigan Cancer Foundation
(BDMS)	bromodimethylsulfonium bromide	MAPK	Mitogen activated protein kinase
BPs	bromophenols	MeO-PBDEs	Methoxylated polybromodiphenyl ethers
2,4-DBP	2,4-dibromophenol	MIC	Minimum Inhibition concentration
2,4,6-TBP	2,4,6-tribromophenol	MASA	Methicillin sensitive Staphylococcus aureus
2,4-diBA	2,4-dibromoanisole	MTT	Metallothionein
(DMAc)	N,N-dimethylacetamide	MIC	Minimum Inhibition concentration
DPPH	Diphenyl-2-picrylhydrazyl	MRSA	Methicillin-resistant Staphylococcus aureus
2,4,6-triBA	2,4,6-tribromoanisole	MTT	Metallothionein
EC ₅₀	Half maximal Effective concentration	NBS	N-Bromosuccinimide
EI	Electron ionization	NCI	National Cancer Institute
ECNI	Electron capture negative ionization	NO	Nitric Oxide
ERK	Extracellular Signal-Regulated Kinase	PTP1B	Protein tyrosine phosphatase 1B
GC-MS		OH-PBDEs	Hydroxylated polybromodiphenyl ethers

HeLa	human cervical carcinoma	O-PHDE	Oxy-polyhalogenated diphenyl ethers
HCT	human colon cancer cells		
HL	human promyelocytic leukemia cell line	PC	Human Prostatic Cancer
HepG2	human liver cancer cells	PTK	Potorous tridactylis) epithelial kidney
PBDEs	Polybromodiphenyl ethers	RD	rhabdomyosarcoma
PGE2	Prostaglandin E2	ROS	Reactive Oxygen Species
IC	Inhibition concentration	SRB	sulforhodamine B
IMPDH	Inosine-5'-monophosphate dehydrogenase	TEAC	Trolox Equivalent Antioxidant Capacity
LC	Lethal Concentration	TFPA VSE	trifluoroacetic acid Vancomycin sensitive Enterococci

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