Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 14, Issue 4, 2024, 92
https://doi.org/10.33263/BRIAC144.092

A Review of the Synthesis of Dibenzofuran Derivatives that Possess Various Medicinal Activities as Potent Anticancer and Antibacterial Agents

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Received: 8.07.2023; Accepted: 28.01.2024; Published: 20.07.2024

Abstract: Dibenzofuran (DBF) is a typical heterocyclic aromatic compound (O-HETs) capable of coexisting with Polycyclic Aromatic Hydrocarbons (PAHs) in settings of pyrolysis and combustion. This review focuses on reports entailing the synthesis of DBF derivatives possessing anticancer and antibacterial prowess, though it is not a comprehensive discussion of the compounds in question but rather an illustration of the range of anticancer and antibacterial activity possessed them besides variables synthesis sources thereof. Compounds with diminished benzene rings, e.g., morphine and its derivatives, are omitted, besides compounds with alkylation-disrupted aromaticity, such as usnic acid. It is worth noting that one of the most important issues that we learned in this review is that dibenzofuran derivatives have many medical advantages.

Keywords: dibenzofuran derivatives; anticancer activities; antibacterial activities; polychlorinated dibenzo-p-dioxins; polychlorinated biphenyl.

1. Introduction

Polycyclic Aromatic Compounds (PACs), such as Heterocyclic Aromatic Compounds (O-HETs) and Polycyclic Aromatic Hydrocarbons (PAHs), are becoming substantial threats to the Environment and human health due to their severe mutagenicity, general and photo-induced toxicity, and carcinogenicity [1-3]. PAHs emissions are correlated with the releases of NSO-HETs, it was observed that it comprises 10 and 40% of the total emissions of various PAHs in tar oil and also in coal tar, in addition to its water-soluble part [4-7]. DBF is a typical O-HET composed of furan and benzene rings. The furan ring is a five-membered ring where the heteroatom (oxygen atom) maintains a single pair of nonbinding valence shell electrons. DBF is composed of two benzene rings fused on both sides of the furan ring, found to be mutagenic and toxic [8]. Usually, DBF is employed as an insecticide, carrier for printing textiles and dyeing, and component in heat-transfer oils [9, 10]. DBFs are common in coal and coal tar, creosote, crude oils, some high-temperature incineration waste processes, tobacco smoke, forest fires, aluminum manufacturing petroleum, rubber, wood combustion, and fossil fuel [8, 11–19]; they always coexist with other aromatic compounds, like DBF derivatives [16, 20–26]. It has been observed during recent references that synthetic organic chemistry has a distinct biological activity in all different applied directions [27-51]. Therefore, this review will focus on reports related to the synthesis of DBF derivatives with demonstrated antibacterial activity.

2. Physicochemical properties of the DBF moiety

DBF is a white volatile aromatic organic solid compound and is a heterocyclic compound that contains a furan ring in the middle of two combined benzene rings and is soluble in nonpolar organic solvents; it is thermally robust with a convenient liquid range. A hydrogen atom binds all the numbered carbon atoms. DBF is obtainable from coal tar, making up 1% of it, and has relatively low toxicity [52]. These properties are utilized by using DBF as a good heat transfer agent [52]. Moreover, it undergoes many different electrical reactions, such as halogen reactions and Friedel-Crafts reactions. It was proved that the reaction of DBF with butyl lithium leads to dilithiation [53]. It is worth noting that the DBF compound is a precursor to furobufen, which was proven by the interaction of Friedel-Crafts with succinic anhydride. The toxicity of this new drug is also evident from the fact that the rats were not harmed, and this is evident after a complete diet for 200 days, provided that it consists of 0.025 - 0.4% of DBF [52]. However, DBFs containing many chlorine atoms are still of great interest due to their potential to be hazardous.

2.1. Health hazard Information.

2.1.1 Health effects.

PCDDs and PCDFs (Figure 1) are dibenzofuran derivatives and are among the important organic chemicals studied extensively. Therefore, there is a large number of publications on the toxic effects of these derivatives. Moreover, it has recently been found that a lot of reviews and ratings are available. On the other hand, the World Health Organization conducted a number of consultations on this interesting topic and published many reports on this subject. The most important ones are [54-64].

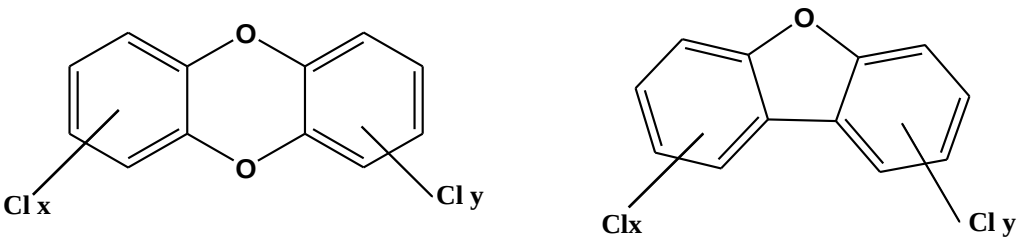


Figure 1. General structures of PCDDs (left) and PCDFs (right).

2.1.2. Acute effects.

No evidence is present on DBF's acute effects on humans or animals [65].

2.1.3. Chronic effects (noncancer).

There is no information on the chronic effects of DBF in humans or animals. The US EPA has no reference concentration (RfC) or reference dose (RfD) for DBF yet [66].

2.1.4. Cancer risk of DBF moiety.

No information is present on DBF's carcinogenic effects on humans or animals. EPA classified DBF as a Group D, meaning it is not classifiable regarding human carcinogenicity [66, 67].

2.1.5. Reproductive/developmental effects of DBF moiety.

No information is present on DBF's reproductive or developmental effects on humans or animals.

2.1.6. Hazard summary.

Subjects can be exposed to DBF through inhalation or ingesting contaminated drinking water or food. There is no information on DBF's acute (short-term), chronic (long-term), developmental, carcinogenic, and reproductive aspects in humans or animals. However, information on the health effects of polychlorinated DBFs is present. Yet, the U.S. Environmental Protection Agency (EPA) has noted that the immensely varying biological activity of different chlorinated DBFs, dismissing the feasibility of risk assessment by analogy to any of these frequently analyzed compounds and classifying DBF as a Group D, unclassifiable in terms of human carcinogenicity [68].

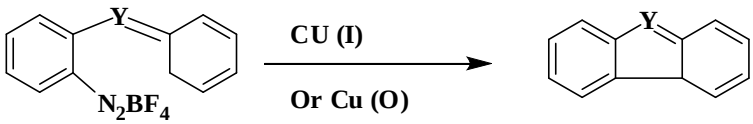
2.1.7. Sources and potential exposure.

Exposure could take place via inhaling or dermal contact, especially in areas with combustion/carbonization activities, e.g., coal gasification and tar operation sites [69]. DBF is released into the air through combustion and is usually found in grate, fly ash, coke dust, and flame soot. The population could consume DBF through contaminated air or contaminated drinking water or food [69, 70]. Also, DBF presides in tobacco smoke [69] and has been deemed a concerning pollutant to EPA's Great Waters Program due to its environmental presence and toxicity, bioaccumulation potential, and human toxicity [71].

3. Syntheses of DBF derivatives

3.1. Pschorr reaction.

The preparation of biaryl tricyclic rings is facilitated intramolecularly by the Pschorr Reaction through substituting one arene by the aryl radical. Copper catalysis creates The said radical in situ from the aryl diazonium salt. Despite the use of excess copper salts, the yield is optimally moderate. Two more soluble alternative electron donors were found (refer to modern literature on the subject). The method used in the current report improves output at a shorter reaction time (Scheme 1).

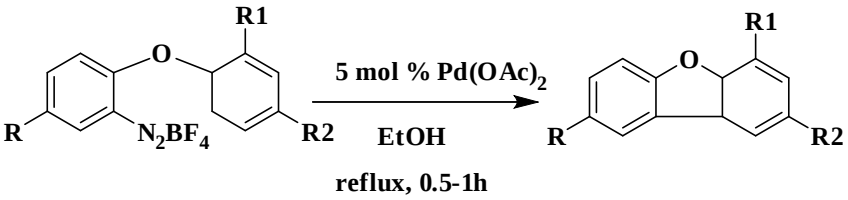


Y= -CH=CH-, -O-, -S-, -SO-, ...

Scheme 1. Synthesis of biaryl tricyclics.

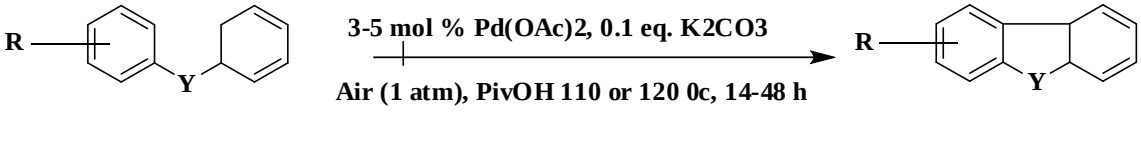
3.2. Recent methods.

Palladium catalysis provides an intracellular cycle for ethyl diazonium salts of diaryl ether to produce DBFs. This process uses 3% mol palladium acetate to reflux ethanol without a base (Scheme 2) [72].



Scheme 2. Synthesis of DBFs.

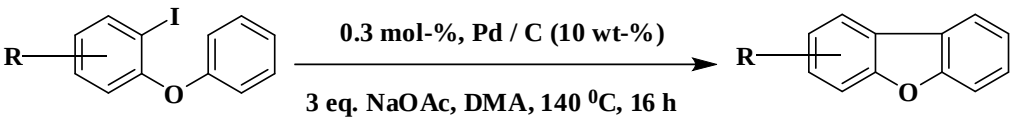
Intramolecular palladium (II) catalyzes the formation of carbon– and oxidized carbon bonds under air in the presence of pivalic acid in the reaction‘s solvent rather than the acetic acid. This leads to more reproduction and productivity and a wider substrate range. The reaction converts electron-rich amines and electron deficiency (Scheme 3) [73].



Y, NH (110 0C, 14 h) or O (120 0C, 42-48 h)

Scheme 3. Synthesis of DBFs and/or benzopyrols.

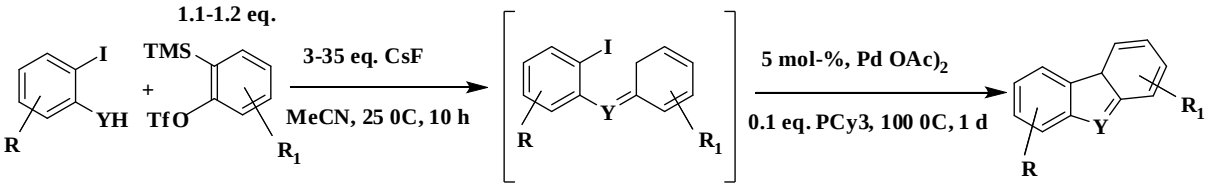
An effective method to synthesize DBFs from O-iododiaryl ethers is to let reusable Pd/C stimulate it within bonding- and ligand-free circumstances. O-ododiaryl ether synthesis in one vessel was accomplished through serial iodine and O-arylation of phenol under moderate reaction conditions (Scheme 4) [74].



R, EWG, H

Scheme 4. Synthesis of DBFs from o-iododiaryl ethers.

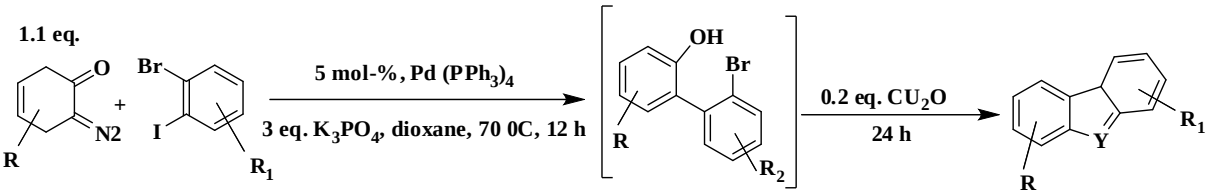
An effective route was developed to formulate carbazoles and DBFs. O-iodoanilines or o-iodophenols’ reaction with silyl aryl triflates was followed by exposure to CsF to provide N- or O-arylated products by cyclization using the Pd catalyst to obtain carbazoles and DBFs in acceptable-to-flawless yields; different functional groups were tolerated (Scheme 5) [75].



Y: O, NH, NMe, NCO_2Et, NMs, CH_2NMs

Scheme 5. Synthesis of DBFs and carbazoles.

Ullmann coupling is a new effective protocol for the rapid construction of 6-diazo-2-cyclohexanone and ortho haylo bio benzenes formations, including coupling/stirring, one Pd catalyst, Pd catalyst, and copper catalyst (Scheme 6) [76].



Scheme 6. Synthesis from DBFs 6-diazo-2-cyclohexenones and ortho-haloiodobenzenes.

4. Syntheses of DBF Derivatives

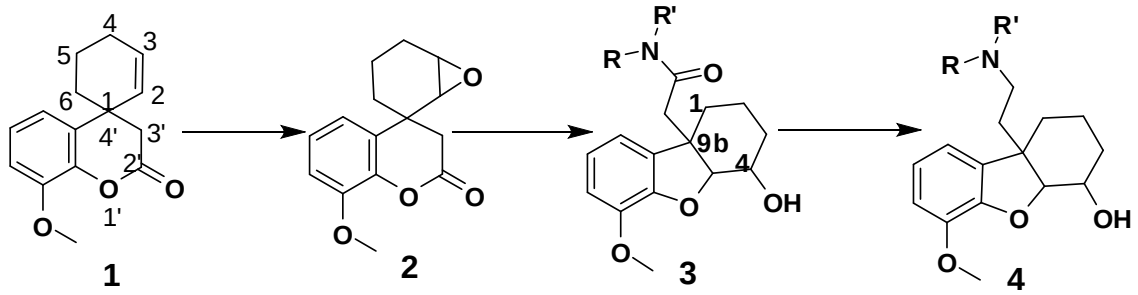
DBF is a polynuclear aromatic compound. It is also a xenobiotic heterocyclic parental, consisting of a furan ring surrounded by two benzene rings in the form of ortho fused across the second, third, fourth, and fifth positions [77].

4.1. An effective and straightforward route.

Hexahydrodibenzo was synthesized effectively and straightforwardly with its furans based on the rearrangement of a spirodihydrocoumarin [78]. During the assessment of DBF morphine-like analogs 24's pharmacochemistry, it was required to enhance and extend the introduction of the stereospecificity of the substitution methods (aminoalkyl groups only) on carbon 9b. Currently, interconversion of spirodihydrocoumarin epoxide **2** to DBF structure **3** is used for easy synthesis. Using this method, various DBF compounds **4** can be composed. It was observed that spirocoumarin 15 was successfully converted stereoisomerally to epoxide 2 (yield: 93%). NMR set the configuration of the epoxide ring according to publications in 1989 and 1992 [72, 73].

4.2. The nucleophilic attack.

Primary or secondary amines' nucleophilic attack proceeds regioselectively, causing the lactone ring to open and produce a phenoxide ion that subsequently attacks the oxiranes by forming a dihydro-DBF structure. It is controllable by 4a, obtainable through samples yielded from a different synthetic approach 3 (Scheme 7) [79-84].



Scheme 7. Synthetic routes for 1, 2, 3, 4, 4a, 9b-hexahydrodibenzo [b, d] and furan derivatives, 4a–4c.

5. Anticancer DBFs

Marine floras, such as bacteria, actinobacteria, cyanobacteria, fungi, microalgae, seaweeds, mangroves, and other halophytes, are extremely important oceanic resources, constituting over 90% of the oceanic biomass. They are taxonomically diverse, largely

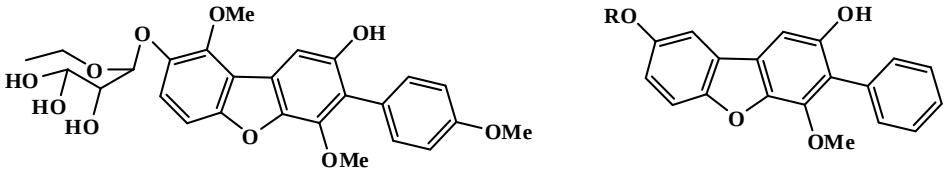
productive, biologically active, and chemically unique, offering a great scope for discovering new anticancer drugs. The marine floras are rich in medicinally potent chemicals predominantly belonging to polyphenols and sulfated polysaccharides. The chemicals have displayed various pharmacological properties, especially antioxidant, immunostimulatory, and antitumor activities. The phytochemicals possibly activate macrophages, induce apoptosis, and prevent oxidative damage of DNA, thereby controlling carcinogenesis. Despite vast resources enriched with chemicals, the marine floras are largely unexplored for anticancer lead compounds. Hence, this paper reviews the works conducted on this aspect to provide baseline information for promoting marine flora-based anticancer research in the present context of increasing cancer incidence, deprived of cheaper, safer, and more potent medicines to challenge the dreadful human disease.

Amongst diseases, cancer stands as one of the most terrible, increasing with impacted lifestyle and nutrition and global warming. Cancer treatments do not contain an effective drug because the currently available medications cause side effects in some cases. In this context, the synthetic compounds that depend on the DBF moiety and natural products extracted from medicinal plants are increasingly prominent in treating cancer. The World Health Organization recently discovered that almost 80% of the world's population mostly utilizes plant-derived medicines from developing countries for health care [85-88]. Potential antioxidant and anticancer properties of plant extracts or products isolated from plants' sources can be experimented upon to develop anticancer drugs [89]. Polychlorinated Dibenzo-p-Dioxins (PCDD/Fs) and Polychlorinated Biphenyl (PCBs) create similar types of toxic results and seem to work by employing a common mechanism of action. However, they vary widely in efficacy [90, 91]. Toxicity responses include skin toxicity, teratogenicity, bodyweight loss, immuno- and neurotoxicity, and carcinogenicity [92]. Biochemical and genetic studies imply that Aryl Hydrocarbon Receptor (AbR) halts most anticancer responses via 2, 3, 7 TCDD and affiliated compounds [93]. Common PCDD/Fs mechanism and common-level PCBs are used in the development of AhR to develop the concept of Toxic Equivalence Factor (TEF) wherein the effectiveness of a given constructor is present within the most effective congeners: 2, 3, 7, 8 TCDD [94]. The current TEF values are focused on the biological study of both cases *in vitro* and in vivo experimentation [95]. It is currently being used in the risk assessment of complex combination compounds. Structural Activity Relationships (SAR) for the various chemical responses and toxicity mediated by AbR indicated that the TEF approach applies to all alternative PCDD/Fs 2, 3, 7, and 8 PCBD/Fs, planar PCBs, and some relatively planar PCBs homogeneous. However, whether the AhR pathway mediates all toxic responses to organic halogen elements is unclear. For example, SARs for anticancer responses [96] and neurotoxicity [97] appear to swerve from the AbR pathway. The promotion of liver tumors was increased in vivo after exposure to Polyhalogenated Aromatic Hydrocarbons (PAHs) in experimental animal studies [98, 99].

All the Polychlorinated Biphenyl (PCB) and Polychlorinated Dibenzo-p-Dioxins (PCDD/F) congeners tested in this study showed the inhibition capabilities of Intercellular Communication (IC), except for 2.2', 4.4', and 5.5'-HxCB. At least two mechanisms, such as independent paths based on AhR, may contribute to IC inhibition. PCDD/Fs and coplanar PCBs are likely to raise their impact through a pathway based on the AhR receptor, a bidirectional PCB, yet applying an autonomous mechanism (AhR) and monochrome PCBs, most likely by a mixture of both tracks. The provided information suggests that current values of TEF based on intermediate effects of the AhR used to assess the risks of carcinogenic implications may

instigate serious risks for individuals prone to complicated combinations of PCBs and PCDD/Fs. Moreover, *in vitro* inhibition seems to be a beneficial model for anticipating the potential for tumor acceleration, such as organic halogens and machine studies in the cause of IC inhibition by these compounds [100].

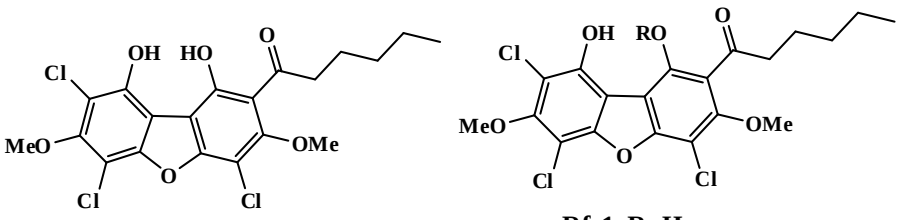
Multiple naturally occurring DBFs exhibited activity against different cancer types. For example, a DBFs series known as kehokorins A-E was secluded from two differing types of trichia favoginea, a slime mold [101, 102]. Three kehokorins, A, D, and E, showed counter-HeLa cell activity and maintained IC_{50} values of a range of 1.5 mg/mL to 6.1 mg/mL for kehokorin A and kehokorin D., respectively (Figure 2). Two DBFs, Pf-1 and Pf-2, were recently secluded from Dictyostelium discoideum, another slime mold [103].



Kehokorin A | **Kehokorin D R=H** **Kehokorin E R=CH3**

Figure 2. Structures of kehokorins.

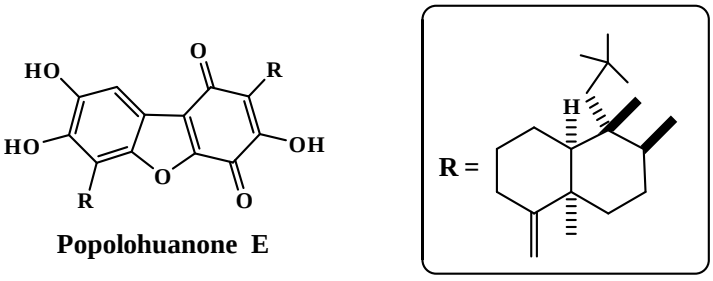
The compounds designated AB0022A are structurally similar to a compound isolated from another slime mold species, Dictyostelium purpureum K1001; conversely, it was confirmed to possess antibacterial properties [104]. On the other hand, Pf-2 lacked any substantial cytotoxicity. Furthermore, Pf-1 and AB0022A showed the limitation of several tested cell lines (K562, HeLa, and 3T3-L1), indicating that the free carbonyl-linked phenolic group is essential for activity. Despite the lack of IC_{50} values reports, AB0022A proved effectual against the three cell lines compared with Pf-1 [103] (Figure 3).



AB0022A | **Rf-1 R=H** **Rf-2 R=CH_3**

Figure 3. Cytotoxically active chlorinated DBFs.

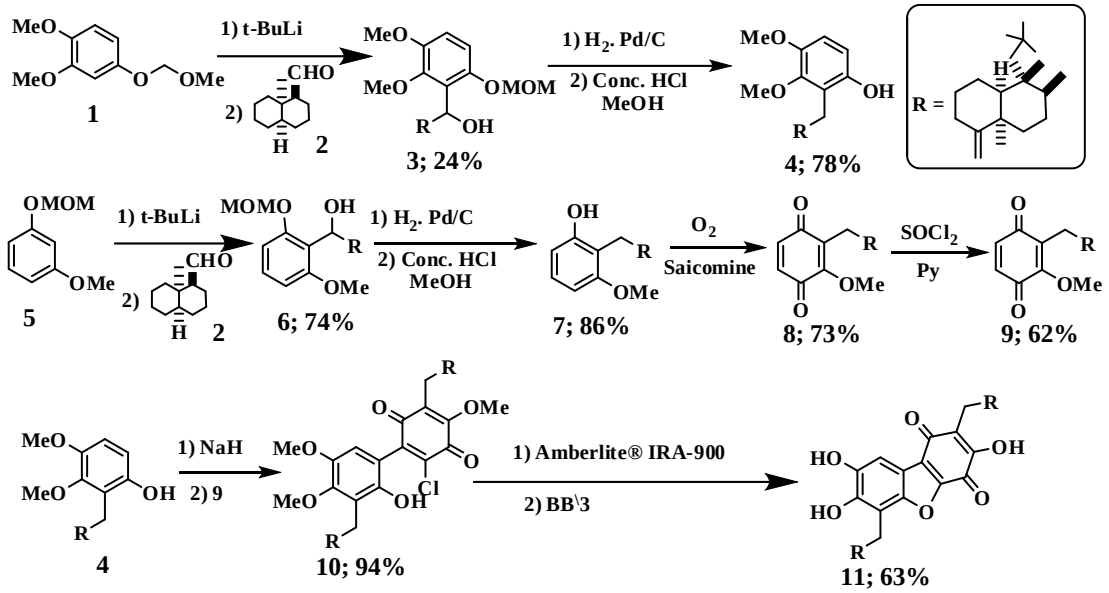
Due to its anticancer potency, considerable interest in DBF quinine popolohuanone E was raised following its 1993 isolation report [105]. Secluded from the Dysidea sponge, it exhibited suppressive behavior toward topoisomerase II (IC_{50} ¼ 400 nM) and human lung cancer cells in type A549 (IC_{50} ¼ 2.5 mg/mL) [105]. An enormous amount of work has been devoted to its synthesis, however (Figure 4).



Popolohuanone E

Figure 4. Structure of popolohuanone E.

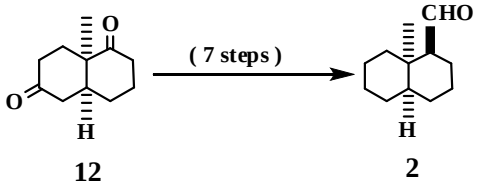
Terashima, Katoh, and coworkers spearheaded the earliest attempts at the complete synthesis of popolohuanone E, where a series of typical compounds of the five assorted isotopes were readied, with the most common in popolohuanone E structure was 11 as shown [106] (Scheme 8):



Scheme 8. Synthesis of popolohuanone E analog.

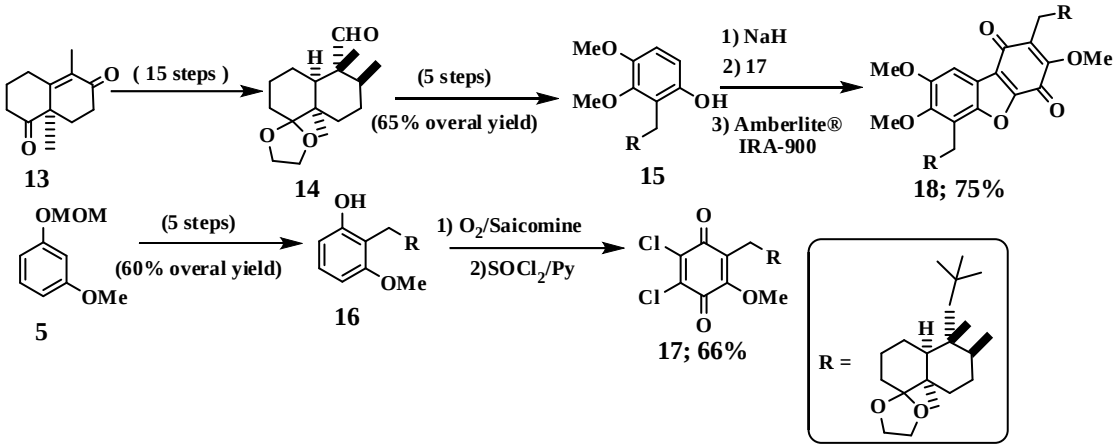
Terashim's synthesis method began with converting 3, 4-dimethoxyphenol to methoxymethyl ether 1. *Tert*-butyllithium was used to lithiate 1, followed by a reaction with 2 that yielded alcohol 3 (24% yield). The catalytic hydrogenation of reduced benzyl alcohol and MOM group, which undergoes acid removal, led to the production of alternative phenol (4) at a yield of 78%. MOM-protected 3-methoxyphenyl 5 was used to prepare phenol 7 by a similar sequence of transformations; the resulting yields were higher in comparison. Phenol 7 was converted to quinone 8 through molecular oxygen oxidation. Salcomine was used to catalyze the oxidation. Then, thionyl chloride was used to chlorinate quinone 8 to yield intermediate 9. Sodium salt from 4 C-alkylated product 10 was used to condense this medium. Previous model studies on much plainer compounds concluded that a phenolic methoxy group was necessary for this reaction in C-6 of 4 rather than phenolic oxygen.

Cyclization of 10 took place via basic ion exchange resins, and demethylation was derived from methoxy three groups via boron propropide, resulting in representative E-populohuanon 11. It was suggested that ion-exchange resins be used to cyclize 10 through yields in previous model studies wherein "traditional" rules did not result in the desired cyclized outcome of more than 20%. The required aldehyde 2, vital for these studies, was prepared across the seven steps of Wieland-Meiser 12 optically pure ketone (Scheme 8). Indeed, compound 2 is shown in Scheme 7 as a single isomer, except that it is a mixture of epimers; stereoisomers' segregation took place following the interaction with the arylithium reagent (scheme 9).



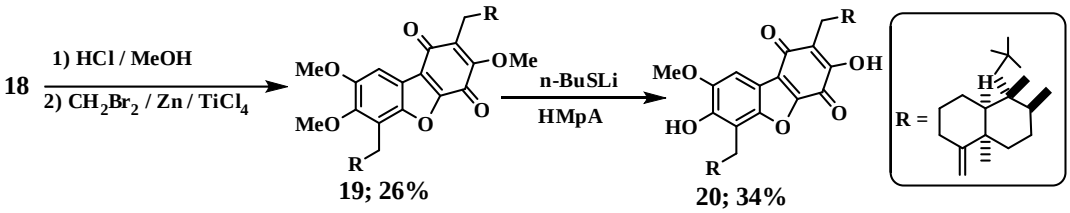
Scheme 9. Preparation of aldehyde 2.

Years later, Katoh, Terashima, and his research group started their work to apply a correspondent combination of conversions to consolidate popolohuanone E itself [107]. Ketone 13 was used to prepare aldehyde 14 across 15 steps [108, 109]. Aldehyde 14 was converted to the derivative of methoxyphenol 15as before some changes were applied to the experiment's conditions, of which the most important was benzylic alcohol reduction accomplished by using the Barton reaction (converting alcohol into a matching xanthate, succeeded by a radical depreciation with tributyltin hydride) rather than catalysis by hydrogenation. Also, within these sequences of experiments, arylithium reagents were created by exchanging halogen lithium with the matching bromoarene instead of immediate lithiation, as shown in scheme 7. Eventually, 15 in the 65% yields of 14 were obtained across five steps. Conjugation partner 16 was generated similarly immediately to 15 and then converted to quinone 17 as previously described for the synthesis of **9**. Coupling and cyclization were performed similarly to typical compounds, yielding DBF quinone 18 at 75% yield (Scheme 10).



Scheme 10. Synthesis of popolohuanone E precursor.

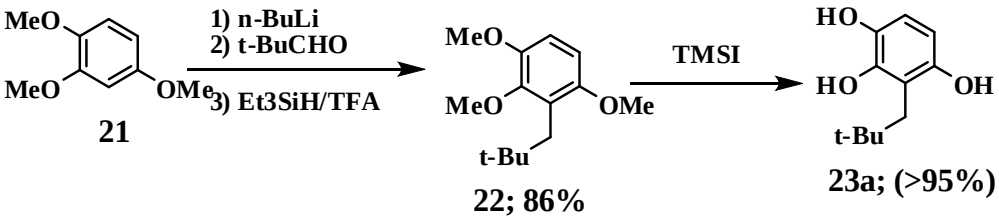
On the other hand, the hydrolysis of the acetal-protecting groups in 18 occurred in a quantitative yield. Still, the conversion of the produced ketones to the parallel methylene groups turned out to be problematic. The use of Wittig and Tebbe reagents causes the starting material to be consumed with no desired product formed as planned, while the Peterson olefination attempt only returned the initial material. Eventually, applying Oshima and his research group's reported protocol [110] produced 19 in a 26% yield (Scheme 11). At this point, what remained was the removal of methyl from the three methoxy groups to produce the E-polyphuanone. Unfortunately, this shift was not achieved, and the closest result was 8-O methyl popolohuanone E 20 production at 34% of the yield when 19 was heated at 110°C with lithium n butyl thiolate. Till now, no conditions were reported to remove the conclusive methyl group from 20 to obtain popolohuanone E or to use other protection groups.



Scheme 11. Synthesis of 8-O-methylpopolohuanone E.

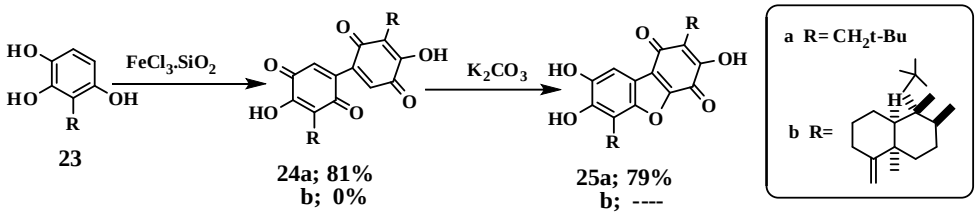
During Terashima and Katoh's investigation to create popolohuanone E, Anderson and coworkers were trying to synthesize it wholly. Again, they were preceded by a model study. 1, 2, 4-trimethoxybenzene, followed by adding pivaldehyde, created the expected benzyl alcohol

(Scheme 12), then reduced to 22 via triethylsilane and trifluoroacetic acid [111]. Demethylation occurred via trimethylsilyl iodide, followed by furnishing of triol-23a. This provided an excellent return as a result:



Scheme 12. Synthesis of triol 23a.

Furthermore, this triol can be oxidized using silica-supported ferric trichloride, yielding 81% diquinone-24a. Then, diquinone 24a is treated with potassium carbonate, producing analog E-25P in a single step within a 79% yield (scheme 13).



Scheme 13. Oxidative dimerization of triols.

According to the optimistic results attained with the typical compound 23a, 60 hydroxy-arenarol 23b was derived and exposed to the same oxidation circumstances. However, the required diquinone 24b was not created, creating the affiliated hydroxyl benzonine instead [112]. Likewise, the testing of other oxidants failed to produce diquinone 24b. Therefore, it was not possible to cyclize e-populohuanon. The last dibenzofuran to exhibit anticancer properties is rhodomartoxin B, extracted from pylidostigmatropicum's bark extract [113], and Australian cherry, rhodomyrtus macrocarpa [114]. The said compound showed behavior against Hep-G2 and MDA-MB-231 cell lines with an LC_{50} value of 19.0 (±9.0) mm former and 2.50 (±0.27) mm latter [92, 115-117]. Setzer and coworkers suggested that the anticancer activity results from the intercalation of rhodomartoxin B into cytosine base pairs. Djaballah and collaborators also found that rhodomartoxin B suppressed the growth of NCEB1 cells with an IC_{50} value of ca. 9 mm [118-120]. Despite the absence of combinations of rhodomartoxin B in modern literature, rhodomeratoxin C was reported and exhibited a similar structure (figure 5).

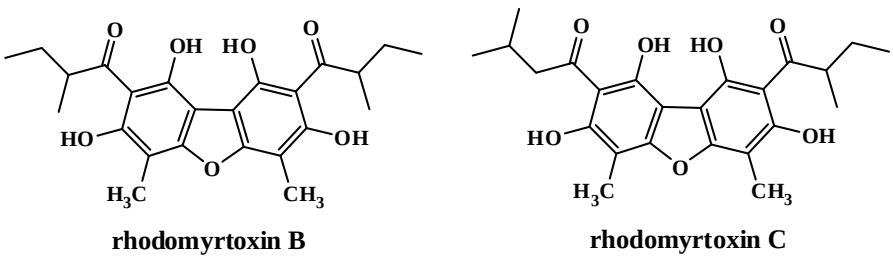


Figure 5. Structures of rhodomartoxins B and C.

6. Antibacterial DBFs

DBF and its derivatives are multifunctional due to their pharmacological [121–123], physiological [124], and antimicrobial properties [125–127]. DBF has many physiological

properties because of its structural relationship to morphine alkaloids [128]. DBF and its derivatives cause the depression of respiration and a sharp fall in blood pressure [127, 129]. Also, DBFs have many pharmacological properties because they act as analgesics [130] and powerful local anesthetics [131, 132]. DBF and its derivatives have a broad antimicrobial bactericidal activity [127, 133, 134]. The antifungal activity was evaluated for the isolated DBF bis (bibenzyl) against *Candida albicans*, a clinical pathogenic fungus; they showed moderate antifungal efficiency [135]. Two pyrazoline derivatives based on DBF presented excellent thermal stability and high fluorescence quantum yields, so they are of great interest as fluorescent probes and optoelectronic materials in organic light-emitting devices [136]. Dicationic DBF derivatives of anti-P. carinii activity was examined in the immunosuppressed rat. Moreover, different DNA binding agents were active compounds because DNA binding played a key role in antimicrobial activity in dicationic compounds [137-139]. Unusual DBFs, preussiafurans isolated through the fungus Preussia sp., Enantia chlorantha oliv, showed good antiplasmodial activity and moderate cytotoxicity [140]. A natural product for DBF [141] embodied homoisoflavonoids designed by molecular hybridization and synthesized by a reaction of 2-DBF carboxaldehyde with methyl acrylate; DBFs screened for *in vitro* antimycobacterial activity against mycobacterium tuberculosis was found to be active with MIC 12.5 mg/mL [142].

Copper (II) or zinc (II) complexes of DBF derivatives of cyclen were prepared and characterized. It was revealed through a fluorescence emission study that the introduction of either Cu^{2+} or Zn^{2+} stints ligands' emission intensity. Seven dipeptide complex derivatives were assorted [143]. These complexes indicate platinum complexes specifically hindered fungal cell growth [143]. Valine-derived synthesized copper (II) and cobalt (II) complexes via Schiff bases were studied biologically *in vitro* for antimicrobial activity against human pathogenic fungi and Gram-positive and negative bacteria; they exhibited a remarkable hindrance of Gram-positive bacteria's growth and pathogenic fungi. The cytotoxicity of the complexes was evaluated *in vitro* and shown to be non-toxic to human erythrocytes, even at a concentration of 500 μg/mL [144].

Furthermore, Kehokorins A–C and three different new DBFs were isolated from field-collected fruit bodies of a myxomycete, Trichia favoginea var. persimmons, and their structures via spectral data. Kehokorin A was an α-L-rhamnopyranoside of kehokorin B, while kehokorin C was a 1-demethoxy analog of Kehokorin A showing distinct cytotoxicity against HeLa cells with an IC50 value of 1.5 μg/mL [145, 146]. DBFs and Kehokorins A–C isolated from *Trichia favoginea var. persimilis* were cytotoxic against *HeLa cells* [147, 148].

Peptides based on rhodamine B and DBFs were evaluated *in vitro* for antibacterial activities and compared with those of the antimicrobial peptides cathelicidin LL37: cathelicidin (polypeptide that is primarily stored in the lysosomes of macrophages and polymorphonuclear leukocytes), magainin II (a class of antimicrobial peptides found in the African clawed frog), and melittin **(**melittin consists of 26 amino acids and is a relatively short peptide**)** [149]. Also, rhodomartoxin B (Figure 6) showed significant antibacterial activity. Different values of MIC of 0.14 mM and 0.28 mM were recorded against several Staphylococcus aureus as well as Bacillus bacillus of this compound [150].

Moreover, rhodomartoxin C, which has a similar structure, showed lower biological activity when fighting two strains of S. aureus with MIC values of 0.9 mM and 7.2 mM. This turns out just as rhodomartoxin B and rhodomartoxin C can be chemically extracted from Peledisostigma glabram and R. Macrocarpa [151, 152]. Then, Sargent and coworkers studied

the synthesis of rhodomartoxin C in 1983 [153]. Iodination of 1, 3, and 5 trimethoxybenzene followed by Ullmann coupling yielded biphenyl 28. Heating 28 with hydriodic acid, then methylated with iodomethane, yielded 24% 1, 3, 7, 9 tetra methoxy benzofuran 29 beginning from 1, 3, 5 trimethoxybenzene. 29 was formylated via Vilsmeier-Haack formylation, followed by diminishing via lithium aluminum hydride (LAH), giving alcohol 30.

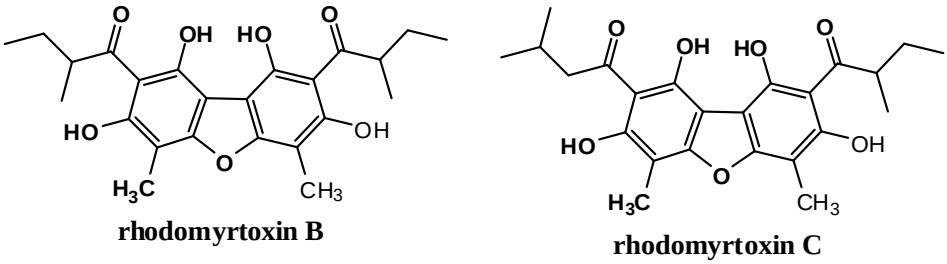


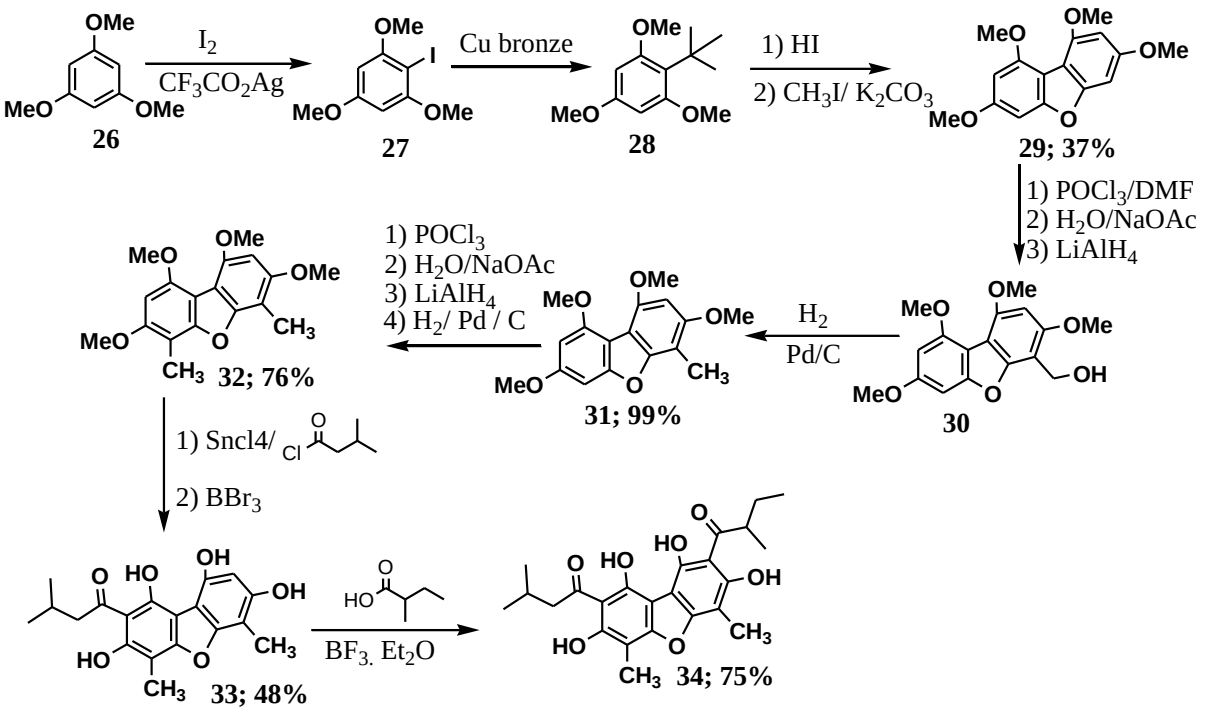
Figure 6. Structures of rhodomartoxins B and C.

The following occurred on an 81% yield for the two steps: a further reduction to 31 by catalytic hydrogenation occurred in a semi-quantitative yield. The steps were repeated to give the dimethylated derivative **32** a yield of 76% of 31 (Scheme 14). Two Friedel-Kraft-induced boron tribromide acyls and demethylation resulted in the synthesis of rhodomartoxin C. Achyrofuran, a natural product that structurally resembles rhodomartoxins (Figure 7) was isolated from a medicinal plant from South America. Achyrocline saturejoides [154, 155] was found to be a good antibiotic against different methicillin-resistant strains of S. aureus, NRS402, and ATCC25923, with MIC values of 0.12 mM and 0.25 mM, the same for Enterococcus faecalis (ATCC29212) with MIC values of 3.96 millimolar [154, 155].

Even though achyrofuran total synthesis was reported in previous pieces of research, a preparation of 39, or pre-achyrofuran, was reported by Kingsbury and coworkers [156] (scheme 15). Prenylation of 1, 3, and 5 trimethoxybenzene followed by Vilsmeier-Haack formylation using oxalyl chloride availed 36 in a 75% yield. Scandium triflate catalyzed diazo alkyl insertion availed acylated product 37 in a 91% yield. However, 37's demethylation with boron tribromide provided only a 15% yield. A three-step conversion of 37 into 38 yielded 38 a 65% overall yield from 37. This method entailed the reduction of the ketone to an alcohol, demethylation via trimethylsilyl iodide, followed by oxidation of the alcohol back up to the ketone via the Dess-Martin periodinane. Oxidative dimerization/cyclization of 38 using iron (III) chloride supported on silica gel gave the final product 39 a 51% yield.

The following year, Kantrowitz and coworkers analyzed achyrofuran analog 41 syntheses (Scheme 16) [157]. Hexamethoxybiphenyl 28 was prepared with a 67% yield from 1, 3, and 5 trimethoxybenzene, similar to the methodology in Scheme 6. Cyclization and demethylation occurred via HBr treatment, and the yielded tetrahydroxy DBF was acylated (though in low yield) to give 41. Despite the lack of 41's reported antibacterial activity, it inhibited fructose 1, 6-bisphosphatase [157] and, like achyrofuran that showed significant antihyperglycemic activity [156], is intriguing for the development of antidiabetic compounds.

Also, porric acid D showed activity against *S. aureus*, though not as potent as rhodomartoxins, with a MIC of 100 mg/mL (equivalent to 347 mM) [158]. This compound was isolated from an *Alternaria marine fungus*, but its synthesis has not yet been studied (Figure 8).



Scheme 14. Synthesis of rhodomartoxin C.

Over the years, boletopsis compounds have been extracted from Boletopsis mushrooms [159–162]. Furthermore, there are **12** different known boletopsis with the general structure shown in Figure 7; they were found to differ in terms of whether the oxygen substituents were acetylated, protonated, or methylated, and also whether there was a second oxygen substituent on the unfused aromatic ring. Then, different approaches were used for nomenclature with the success of discovering each group of boletopsis, and then the study was completed by developing a proposal for a unified notation system recently where all of them were named "boletopsis" followed by an Arabic number [162]. Despite the weak antibacterial activity of many boletopsis, boletopsis 11 **56** stands among them as an active component (Scheme 18). It was evaluated (along with others) against *Escherichia coli, Staphylococcus epidermidis, Pseudomonas aeruginosa, and Mycobacterium smegmatis* with IC_{50} values (in mg/mL) of 424, 242, 272, and 96, respectively. Synthetic boletopsis **11** was exposed to similar bacteria with similar outcomes [162, 163]. Cycloleucomelone is closely similar to boletopsis (Figure 9), isolated from the same (and other) [159, 162, 164-168] mushroom species, and it has also exhibited weak antibacterial activity [160].

The assembly of three polyposes (7, 11, and 12) has recently been detailed [163]. The combination of catechol chlorination with sulfuryl chloride started to yield 42, which is an excellent yield (Scheme 17). Bromination and methylation yielded a high yield, as did conversion to the corresponding boronic acid 44 by exchange of lithium-halogen and treatment with trimethylborate, followed by an acid treatment process. 4-methoxyphenylboronic acid 45- although with an indefinite yield--was similarly formed. The third aromatic ring in the final result was extracted from sesamol 46. The formulation was followed by bromination of dichloromethyl methyl ether in the presence of aluminum trichloride. A Lewis acid biocatalyst was found to introduce both bromine atoms into the ring - the only monomeric bromine occurring when it was not present. Finally, phenol was protected since methoxymethyl ether gave 49 in total yield of 53% sesamol. With the three aromatic rings suitably replaced, they began to give polytopes through their combinations. The synthetic approach is similar to that described by Takahashi *et al*. in their Vialinin B synthesis [169, 170] (see next section). The

Suzuki-Miyaura coupling of boronic acid 44 with aryl bromide 49 was selective, and the biphenyl derivative 50 was taken advantage of (Scheme 18). This reaction has been shown to be very sensitive to the presence of trace amounts of oxygen. A similar coupling of 45 with 50 gave the terfinyl derivative 51 a moderate yield. The Baeyer-Villiger oxidation of the aldehyde proved somewhat problematic, although reaction conditions eventually provided the 52-formate ester with a reasonable yield. It is noteworthy that this ester can then be cycled to DBF 53 under Ullmann-type conditions by re-flushing a pyridine solution of 52 in the presence of excess copper(I) oxide; it was impractical to isolate free phenol due to the instability of the compound). This then completed the formation of the primary ring system, which is common in polytopes. A benzyloxycarbonyl group replaced the protecting methoxymethyl group in an overall yield of 72%, which is considered necessary for the subsequent transformation of the methoxy group. The three subsequent transitions instabilized the product; thus, 54 were converted to 55, as indicated, without purification of any of the mediators. 55 was obtained in an overall yield of 55%, which could have been methylated in an excellent available polytopes in 11 yield of 56%. Using boron tribromide, demethylation of intermediate 55 availed boletopsis 7 in 57. Then, this study concluded with the process of partial methylation of **57** in the synthesis of polytopes 12 58.

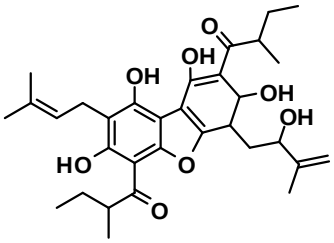


Figure 6. Structure of achyrofuran.

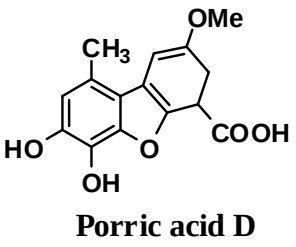
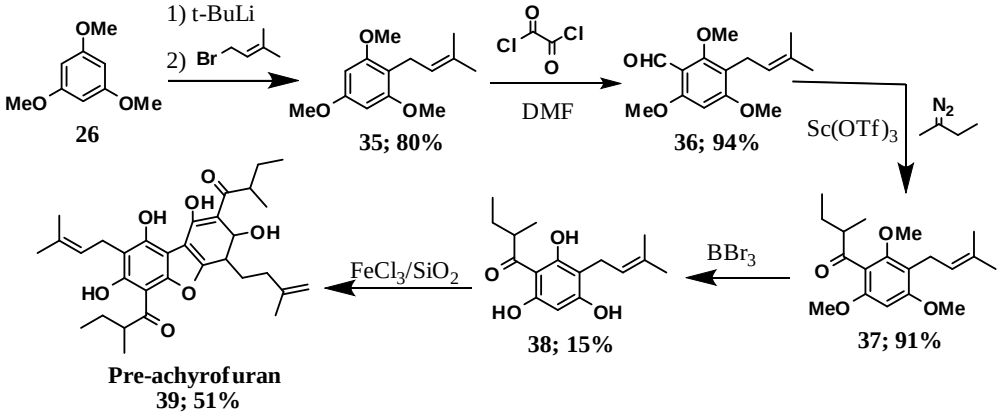
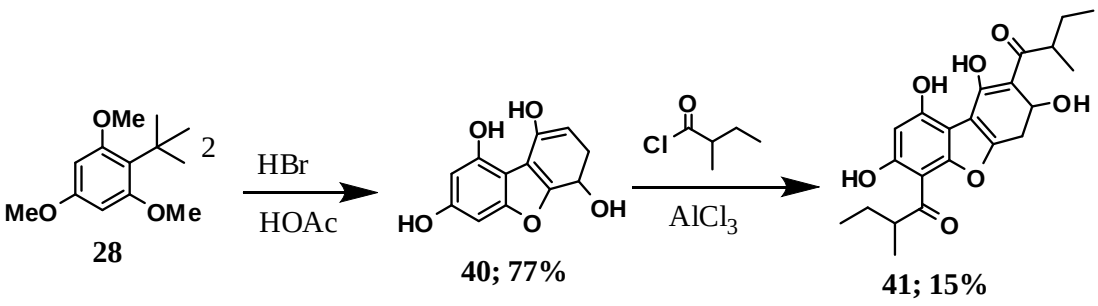


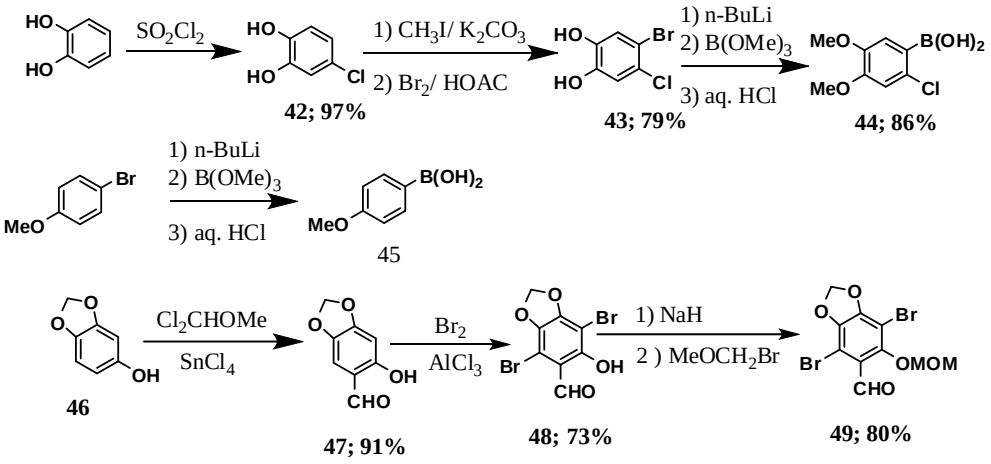
Figure 7. Structure of porric acid D.



Scheme 15. Synthesis of "pre-achyrofuran".



Scheme 16. Synthesis of an achyrofuran analog.



Scheme 17. Synthesis of boletopsis precursors.

Bolytopsin-12 prepared in this previously mentioned manner was contaminated with boletopsis **11**, which HPLC could have separated. We believe that the required selectivity for this final methylation was due to the lower acidity of the remaining phenolic group in 58 due to the absence of any neighboring hydrogen bonding groups.

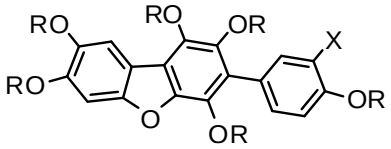
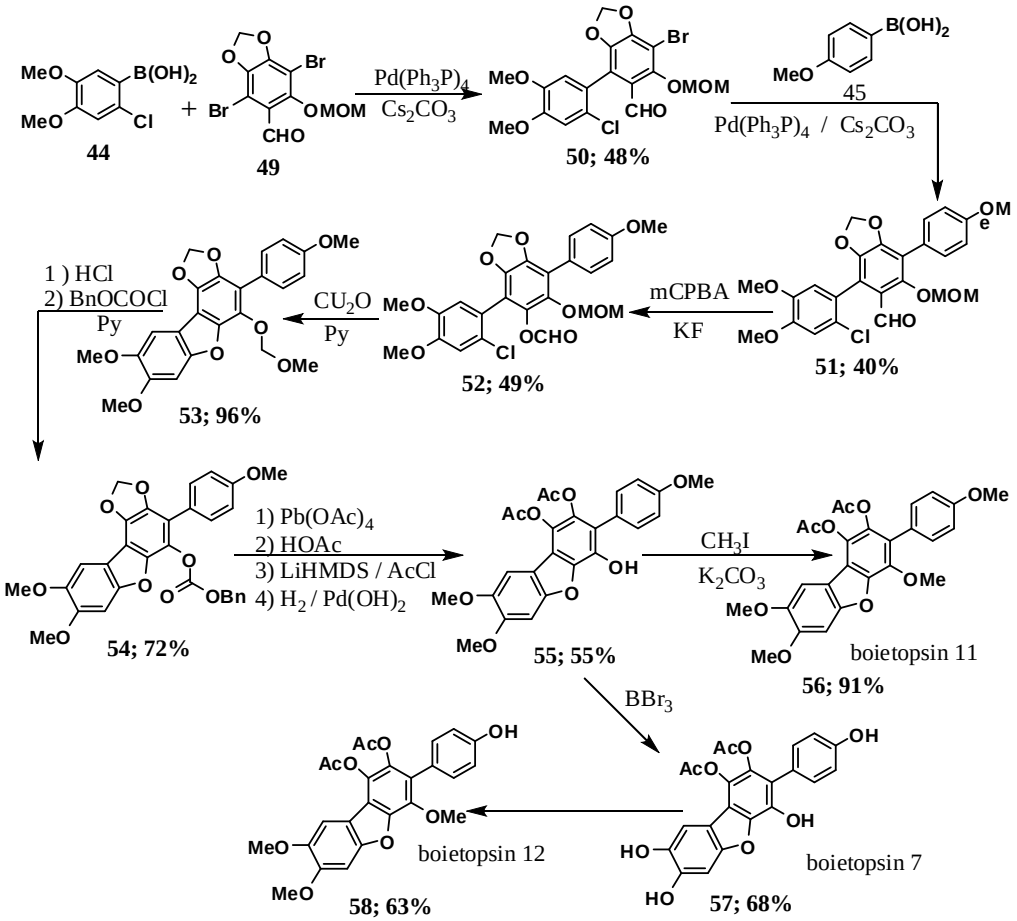


Figure 8. The general structure of boletopsis.



Scheme 18. Synthesis of boletopsis 7, 11, and 12.

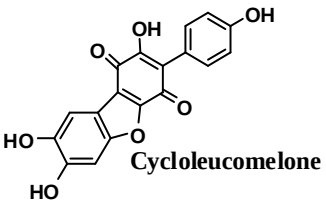
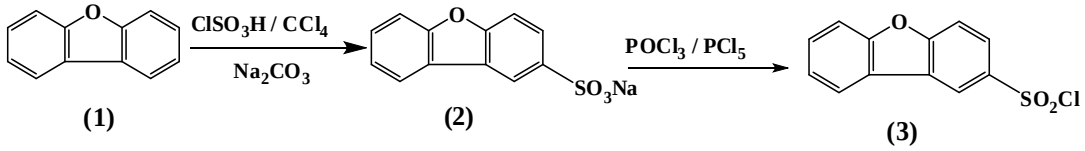
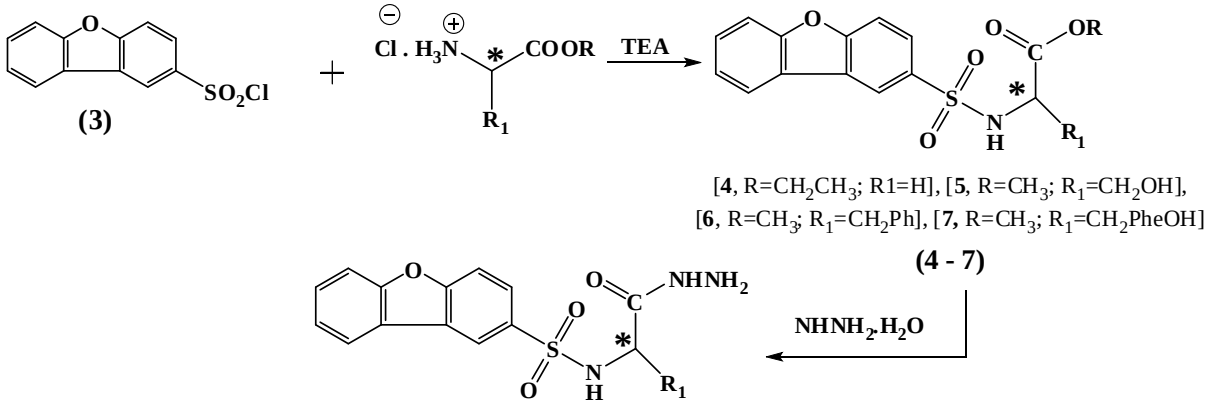


Figure 9. Structure of cycloleucomelone.

Recently, derivatives of different dipeptides **4-29** were synthesized, followed by their evaluation as antimicrobial agents by the synthesis of DBF-2-sulfonyl chloride (**3**) (Scheme 19). Then, compound **3** was conjugated with different amino acid esters at a low temperature, under the condition of a strong organic base, to give compounds DBF-2-sulphonyl-amino acid ester **4-7**, and they were converted in the same study to DBF -2-sulphonyl-hydrazides **8-11** (Scheme 20). Moreover, the previous esters were converted to DBF-2-sulphonyl-amino acid **12–14** (Scheme 21). Furthermore, the latter peptides **12-14** were conjugated with several different amino acid esters to give the corresponding DBF-2-sulphonyl-dipeptide ester derivatives **15-19** (Scheme 21). On the other hand, the ester of peptides **15-19** was converted to DBF-2-sulphonyl-dipeptide **20-24** (Scheme 21), which enabled the hydrazine hydrolysis of esters **15–19** with the corresponding alcoholic hydrazine hydrate hydrazides **25–29** (Scheme 21), respectively. On the other hand, at the end of this study, a distinct biological study was carried out, and *in vitro*, antimicrobial evaluation was crosschecked against various pathogenic microorganisms and Gram-positive and negative bacteria. A portion of the compounds exhibited remarkable antimicrobial aspects [39].



Scheme 19. Synthetic routes for DBF-2-sulfonyl chloride, 3.



[**4**, R=CH_2CH_3; R1=H], [**5**, R=CH_3; R_1=CH_2OH], [**6**, R=CH_3; R_1=CH_2Ph], [**7**, R=CH_3; R_1=CH_2PheOH]

(4 - 7)

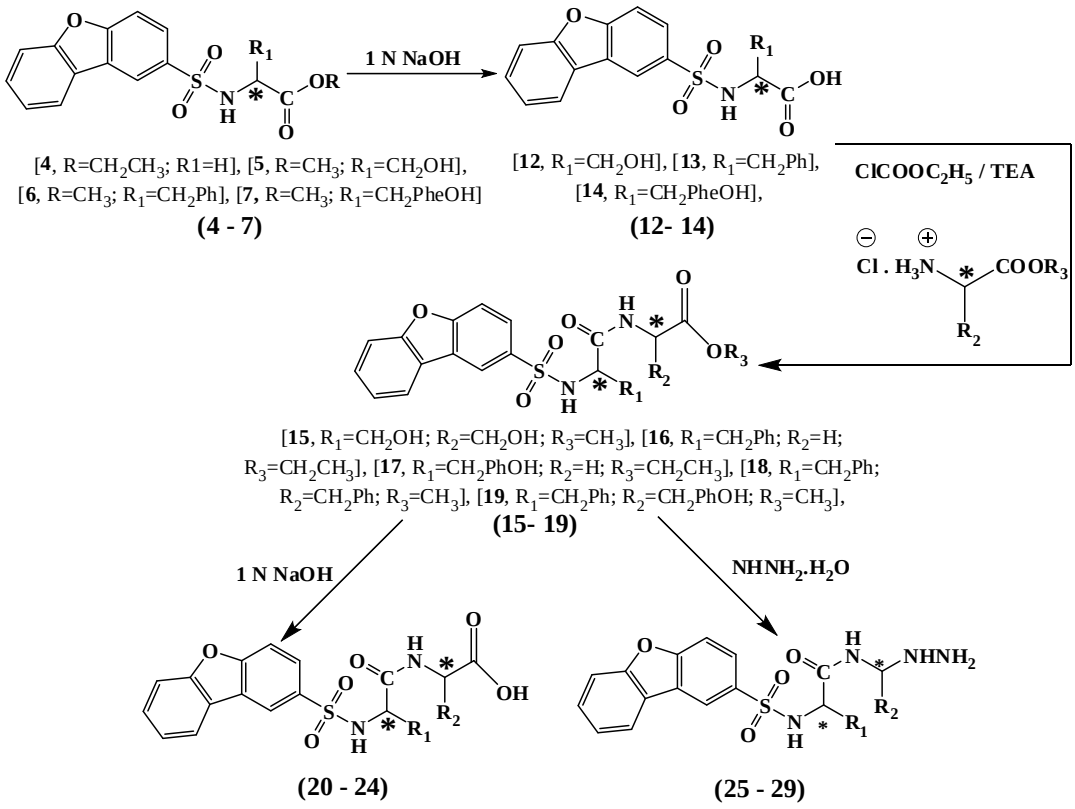
[**8**, R_1=H], [**9**, R_1=CH_2OH], [**10**, R_1=CH_2Ph], [**11**, R_1=CH_2PheOH]

(8 - 11)

Scheme 20. Synthetic routes for compounds 4–11.

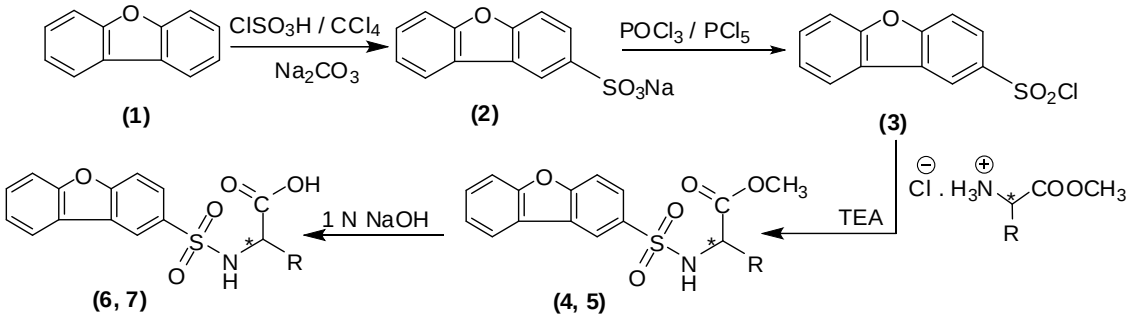
In this study, many tripeptides 4-29 derivatives were classified and studied as different antimicrobial agents through the synthesis of DBF-2-sulfonyl chloride (**3**). Compound **3** is then combined with different amino acid esters at a low temperature, and a strong organic base must be present in order to give a high percentage yield of DBF-2-sulphonyl-amino acid ester **4** and **5,** which is then converted to DBF-2-sulphonyl- amino acid **6** and **7** (Scheme 22). Subsequent

compounds **6** and **7** were then conjugated to different amino acid esters, giving the corresponding DBF-2-sulfonyl dipeptide ester derivatives **8–11** (Scheme 23).



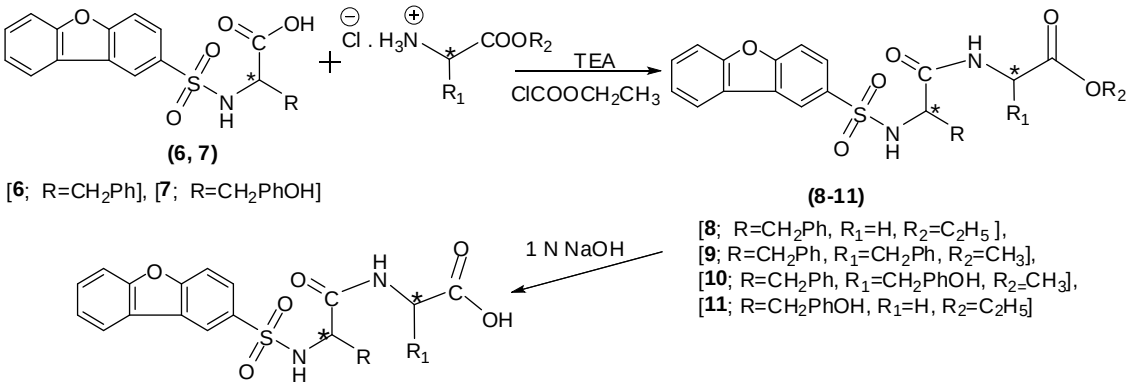
Scheme 21. Synthetic routes for compounds 12–29.

Moreover, in this study, ester compounds **8-11** were converted to DBF-2-sulphonyl-dipeptide **12-15** (Scheme 23), respectively. On the other hand, the latter compounds **12-15** were conjugated with different amino acid esters, giving the corresponding DBF-2-sulphonyl-tripeptide ester derivatives **16-19** (Scheme 24). Then, the previous ester compounds are converted to DBF-2-sulphonyl-amino acid **20-23** (Scheme 24), respectively. Finally, hydrazine hydrolyzed the esters **16-19** with alcoholic hydrazine hydrate to form the corresponding hydrazides **24-27** (Scheme 24), respectively. The whole compounds were analyzed using spectral data. Their *in vitro* antimicrobial evaluation was tested against seven strains of Gram-positive and negative bacteria and fungi. Some of these compounds (16, 18, 20–22, 24, 25, and 26) were found to possess significant antimicrobial properties. The MIC values of the most active compounds were studied against the test organism *Staph. aureus*, *Bacillus subtilis*, and *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Pseudomonas aeruginosa*, as Gram-positive and Gram-negative bacteria, respectively. It is believed that the presented molecular structural features of these novel tripeptides based on DBF-2-Sulfonyl- with both types [aromatic and hydroxy residues] appeared to be important for new antimicrobial candidates that could be investigated in the future [40].



[**4, 6**; R=CH_2Ph], [**5, 7**; R=CH_2PhOH]

Scheme 22. Synthetic routes for compounds 6 and 7.

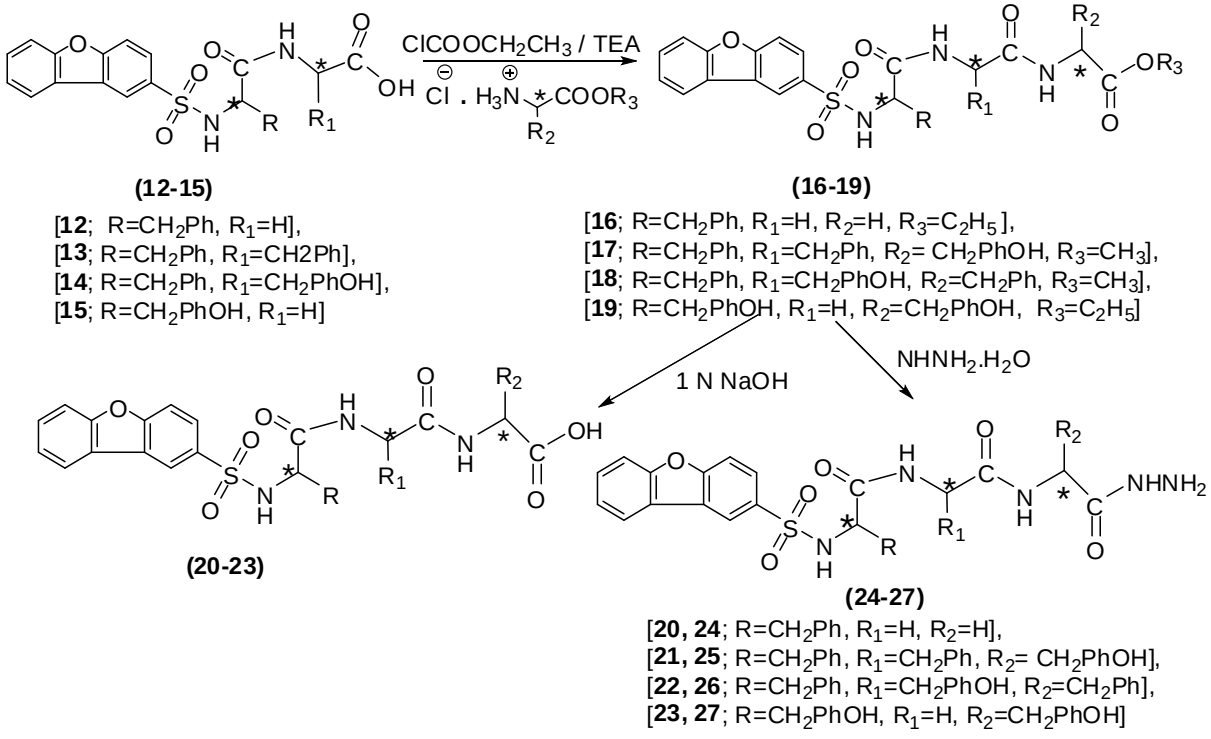


[**6**; R=CH_2Ph], [**7**; R=CH_2PhOH]

[**8**; R=CH_2Ph, R_1=H, $R_2=C_2H_5$],
[**9**; R=CH_2Ph, $R_1=CH_2Ph$, $R_2=CH_3$],
[**10**; R=CH_2Ph, $R_1=CH_2PhOH$, $R_2=CH_3$],
[**11**; R=CH_2PhOH, R_1=H, $R_2=C_2H_5$]

[**12**; R=CH_2Ph, R_1=H], [**13**; R=CH_2Ph, $R_1=CH_2Ph$],
[**14**; R=CH_2Ph, $R_1=CH_2PhOH$], [**15**; R=CH_2PhOH, R_1=H]

Scheme 23. Synthetic routes for compounds 12–15.



[**12**; R=CH_2Ph, R_1=H],
[**13**; R=CH_2Ph, R_1=CH2Ph],
[**14**; R=CH_2Ph, $R_1=CH_2PhOH$],
[**15**; R=CH_2PhOH, R_1=H]

[**16**; R=CH_2Ph, R_1=H, R_2=H, $R_3=C_2H_5$],
[**17**; R=CH_2Ph, $R_1=CH_2Ph$, R_2= CH_2PhOH, $R_3=CH_3$],
[**18**; R=CH_2Ph, $R_1=CH_2PhOH$, $R_2=CH_2Ph$, $R_3=CH_3$],
[**19**; R=CH_2PhOH, R_1=H, $R_2=CH_2PhOH$, $R_3=C_2H_5$]

[**20, 24**; R=CH_2Ph, R_1=H, R_2=H],
[**21, 25**; R=CH_2Ph, $R_1=CH_2Ph$, R_2= CH_2PhOH],
[**22, 26**; R=CH_2Ph, $R_1=CH_2PhOH$, $R_2=CH_2Ph$],
[**23, 27**; R=CH_2PhOH, R_1=H, $R_2=CH_2PhOH$]

Scheme 24. Synthetic routes for compounds 16–27.

7. Conclusions

Previous literature reports in this review concluded that highly oxygenated DBFs can be extracted from both marine and terrestrial natural sources, from slime molds to giant evergreen trees. On the other hand, many members of this group of compounds showed great activity in the medical field in general. It has particularly distinct anticancer and antimicrobial activity, which encouraged efforts to focus on its healthy composition. Many of these natural products are made exclusively by living organisms isolated from them; thus, they continue to present artificial challenges for the future.

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