Egypt. J. Chem. **Vol. 64** No. 4 pp. 2075 - 2093 (2021)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis of Dibenzofuran Derivatives Possessing Anti-bacterial Activities

Gaber O. Moustafa

Peptide Chemistry Department, Chemical Industries Research Division, National Research Centre, 12622-Dokki, Cairo, Egypt

Abstract

dibenzofuran (DBF) are typical heterocyclic aromatic compounds (O-HETs), which can coexist with polycyclic aromatic hydrocarbons (PAHs) in combustion and pyrolysis conditions. In this review, Emphasis has already been placed on the reports on synthesis of dibenzofuran derivatives with possessing anti-bacterial activities. It is not a comprehensive discussion of all such compounds, but is instead intended to illustrate the range of anti-bacterial activity possessed by such compounds, the variety of sources from which they can be synthesized, and the various synthetic methods by which they can be prepared. Compounds with reduced benzene rings (such as morphine and its derivatives) are not included in this review, nor are compounds in which an aromaticity is disrupted by alkylation, as with usnic acid.

Keywords: dibenzofuran derivatives, anti-bacterial activities**,** Polychlorinated dibenzo-p-dioxins**,** Polychlorinated biphenyl**.**

Introduction

Polycyclic aromatic compounds (PACs), including polycyclic aromatic hydrocarbons (PAHs) and heterocyclic aromatic compounds (O-HETs), have become a considerable threat to the environment and human health because of their acute toxicity, mutagenicity, photoinduced toxicity, and carcinogenic potential [1, 2]. The emissions of PAHs are often associated with releases of NSO-HETs, which have been reported to comprise up to 10% and 40% of the total PAH emissions in tar-oil or coal tar and its water-soluble fraction, respectively [3–6]. dibenzofuran (DBF) are typical O-HETs, which are composed of a benzene ring and a furan ring. Furan ring are five-membered ring in which the heteroatom (Oxegen atom) have at one pair of non-binding valence shell electrons. DBF consist of two benzene rings fused together on either side of a furan ring, it has been found to be toxic and mutagenic [7]. DBF has been used as an insecticide, a component in heat-transfer oils, and a carrier for dyeing and printing textiles [8, 9]. Dibenzofurans are widely found in creosote, coal tar, and crude oils, as well as in some high temperature processes of waste incineration, tobacco smoke, aluminum manufacturing, forest fire, rubber, petroleum, fossil fuel, and coal and wood combustion [7, 10–18], and always coexist with other aromatic compounds, such as dibenzofuran drevatives [15,19–25]. Also, in general, it has been observed during recent references that synthetic organic chemistry has a distinct biological activity in all different applied directions [26-50]. Therefore, in this review, the focus will be on reports relating to the synthesis of dibenzofuran derivatives with demonstrated antibacterial activity.

2. Physicochemical Properties of Dibenzofuran moity

Dibenzofuran is a heterocyclic organic compound. It is an aromatic compound that has two benzene rings fused to a central furan ring. All

*Corresponding author e-mail: *gosman79@gmail.com*; (00201003123355).
Receive Date: 26 February 2021, Revise Date: 11 March 2021, Accept Date: 13 March 2021
DOI: 10.21608/EJCHEM.2021.65297.3398

the numbered carbon atoms have a hydrogen atom bonded to each of them. It is a volatile white solid that is soluble in nonpolar organic solvents. It is obtained from coal tar, where it exists as a 1% component [51]. Dibenzofuran is thermally robust with a convenient liquid range. These properties, together with its low toxicity, are exploited by the use of DBF as a heat transfer agent [51]. It undergoes electrophilic reactions, such as halogenation and Friedel-Crafts reactions. Reaction of DBF with butyl lithium results in dilithiation [52]. Dibenzofuran is the precursor to the drug furobufen by Friedel-Crafts reaction with succinic anhydride. Dibenzofuran is a relatively non-toxic compound as evidenced by rats being unaffected after a 200-day diet consisting of 0.025 – 0.4% of DBF [51]. The polychlorinated dibenzofurans are however controversial and potentially dangerous.

2.1. Health Hazard Information

2.1.1. Acute Effects:
No information is available on the acute effects of dibenzofuran in humans or animals [53].

2.1.2. Chronic Effects (Noncancer):
No information is available on the chronic effects of dibenzofuran in humans or animals. The U.S. Environmental Protection Agency (EPA) EPA has not established a Reference Concentration (RfC) or a Reference Dose (RfD) for dibenzofuran [54].

2.1.3. Cancer Risk of dibenzofuran moiety:
No information is available on the carcinogenic effects of dibenzofuran in humans or animals. EPA has classified dibenzofuran as a Group D, not classifiable as to human carcinogenicity [54, 55].

2.1.4. Reproductive/Developmental Effects: of dibenzofuran moiety:
No information is available on the reproductive or developmental effects of dibenzofuran in humans or animals.

2.1.5. Hazard Summary:
Exposure to dibenzofuran may occur from inhalation of contaminated air, or ingesting contaminated drinking water or food. No information is available on the acute (short-term), chronic (long-term), reproductive, developmental, and carcinogenic effects of dibenzofuran in humans or animals. Health effects information is available on the polychlorinated dibenzofurans; however, the U.S. Environmental Protection Agency (EPA) has noted that the biological activity of various chlorinated dibenzofurans varies greatly, thus, risk assessment by analogy to any of these more widely studied compounds would not be recommended. EPA has classified dibenzofuran as a Group D, not classifiable as to human carcinogenicity [56].

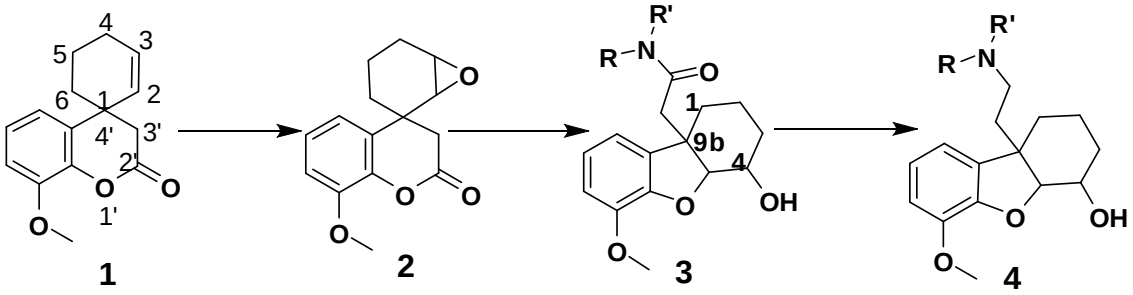
2.1.6. Sources and Potential Exposure:
Occupational exposure may occur through inhalation and dermal contact, particularly at sites engaged in combustion/carbonization processes, such as coal tar and coal gasification operations [57]. Dibenzofuran is released to the ambient air from combustion sources. It may be found in coke dust, grate ash, fly ash, and flame soot. The general public may be exposed to dibenzofuran through the inhalation of contaminated air or through the consumption of contaminated drinking water or food [57, 58]. Dibenzofuran has been identified in tobacco smoke [57]. Dibenzofuran has been listed as a pollutant of concern to EPA's Great Waters Program due to its persistence in the environment, potential to bioaccumulate, and toxicity to humans and the environment [59].

3. Syntheses of dibenzofuran derivatives.
Dibenzofuran is a polynuclear aromatic compound; dibenzofuran is a mancude organic heterotricyclic parent that consists of a furan ring flanked by two benzene rings ortho-fused across the 2, 3- and 4, 5-positions. It has a role as a xenobiotic. It is a member of dibenzofurans, a polycyclic heteroarene and a mancude organic heterotricyclic parent [60].

3.1. Effective and straightforward route
Effective and straightforward route has been accomplished for the synthesis of hexahydrodibenzo, furans based on rearrangement of a spirodihydrocoumarin [61]. In the course of these studies on the pharmacochemistry of dibenzofuran morphine-like analogs 24, it became necessary to improve and diversify the methods of stereospecific introduction of substituents (chiefly aminoalkyl groups) on the carbon 9b. The present time is mentioned that, note a synthetic way based upon the easy interconversion of spirodihydrocoumarin epoxide 2 to dibenzofuran structure 3. By this way, many have been synthesized several 4-hydroxy-6-methoxy-9b~-N-alkylaminoethyl hexahydrodibenzofuran compounds 4. Spirocoumarin 15 is stereospecifically converted to epoxide 2 (yield: 93%). The configuration of the epoxide ring was established by NMR, on the basis of data published by Tori and al.6-7. Comparing spectra of spirodihydrocoumarin 1 and of epoxide 2 shows that the allylic C4 and C4* signals are slightly shielded (1.4 and 1.9 ppm) and the homoallylic carbons C5 and Cg, bearing a cis-epoxide axial hydrogen are more shielded (2.4 and 2.8 ppm). Moreover, C3* is also strongly shielded (2.75 ppm), probably by 1, 3 diaxial interaction related to epoxide ring. Furthermore, the signal of the two protons H3* which is a singlet becomes a doublet-doublet in 2; such an effect is to be related to a cis configmation of epoxide and CH2-3'.

3.2. The nucleophilic attack:
The nucleophilic attack of primary or secondary amines proceeds regioselectively and results in opening lacton ring, generating a phenoxide ion which in turn attacks the oxiran with formation of

dihydrodibenzofuran structure. It can be controlled compound 4a was identical with a sample obtained by a different synthetic approach 3 **[62-67].**



a; R=R' = CH_3, b; R= CH_3, R' =CH_2CHCH_2, c; R=R' = $(CH_2)_2CH_2$

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

4. Anti-bacterial dibenzofurans:

Dibenzofuran and it's derivatives have multi function in different fields because they have pharmacological [68-70], physiological [71], and antimicrobial properties [72-74]. Dibenzofuran has many physiological properties because of its structural relationship to morphine alkaloids [75]. Dibenzofuran and its derivatives cause the depression of respiration and sharp fall in blood pressure [74, 76]. Also, dibenzofurans have many pharmacological properties because they act as analgesic [77] and powerfull local anesthetics [78, 79]. Dibenzofuran and its derivatives have a broad antimicrobial activity [74] therefore they have bactericidal action [80, 81].

The antifungal activity was evaluated for the isolated dibenzofuran bis(bibenzyl)s against *Candida albicans*, clinical pathogenic fungus, they showed moderate antifungal efficiency [82].

Two pyrazoline derivatives based on dibenzofuran, present excellent thermal stability and high fluorescence quantum yields, so it has a great interest as fluorescent probes and optoelectronic materials in organic light-emitting devices [83].

Dibenzofuran dicationic derivatives were examined for *anti-P. carinii* activity in an immunosuppressed rat, all strong DNA binding agents were active compounds. Because of DNA binding played a key role in antimicrobial activity in dicationic compounds [84].

Unusual dibenzofurans, preussiafurans, have been isolated through the fungus preussia sp. occurring, enantia chlorantha oliv, showed good antiplasmodial activity and moderate cytotoxicity [85].

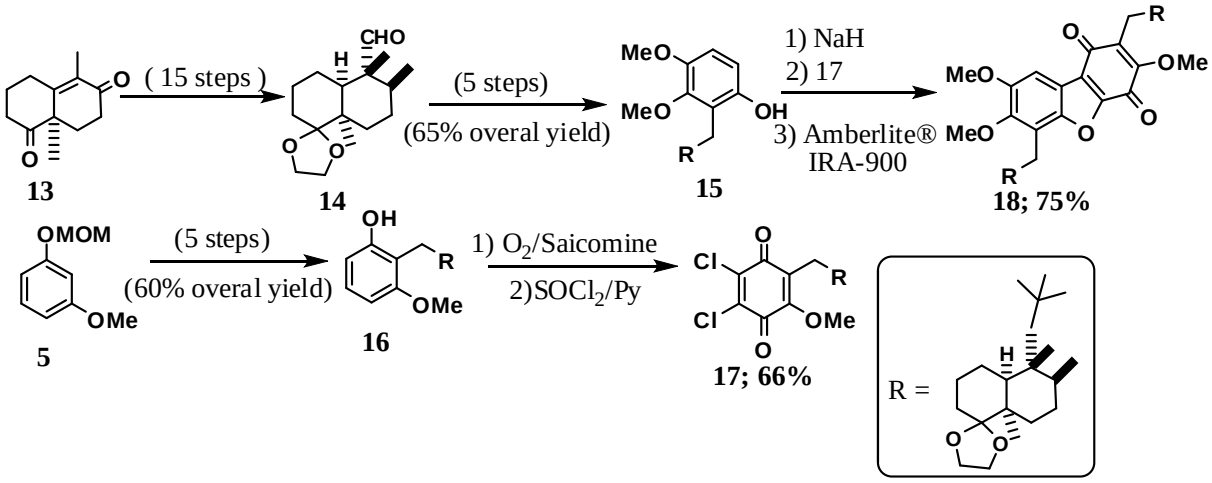
A natural product for dibenzofuran [86] embodied homoisoflavonoids designed by molecular hybridization and synthesized by a reaction of 2-dibenzofuran carboxaldehyde with methyl acrylate; dibenzofurans screened for in vitro antimycobacterial activity against Mycobacterium tuberculosis were found to be active with MIC 12.5 lg/mL [87].

Copper (II) or zinc (II) complex of dibenzofuran derivatives of cyclen have been prepared and characterized, a fluorescence emission study revealed that the emission intensity of ligands is quenched by the addition of either Cu_2^+ or Zn_2^+. Seven dipeptide complexe derivatives of the form K[Pt(IV) (dipep)Cl(OH),] and K[Pt(IV)-(Hdipep)Cl,(OH) 2] were prepared, [88] these complexes suggested that the platinumcomplexes selectively inhibited the growth of fungal cells [88]. The synthesized copper (II) and cobalt (II) complexes of valine-derived via Schiff bases, biological studies of complexes had been carried out in *vitro* for antimicrobial activity against Gram-positive, Gram-negative bacteria and human pathogenic fungi, showed a significant inhibition of the growth of Gram-positive bacteria (*Staphylococcus aureus, methicillin-resistant S. aureus, Bacillus subtilis, Micrococcus luteus), and pathogenic fungi (Candida spp., Cryptococcus neoformans, Rhodothece glutinis,Saccharomyces cerevisia, Aspergillus spp., Rhizopus nigricans)* tested and a moderate activity against Gram-negative bacteria *(Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris and Enterobacter aerogenes*) tested. The in *vitro* cytotoxicity of complexes was evaluated, in which the complexes were found to be non-toxic to human erythrocytes even at a concentration 500 µg/mL [89].

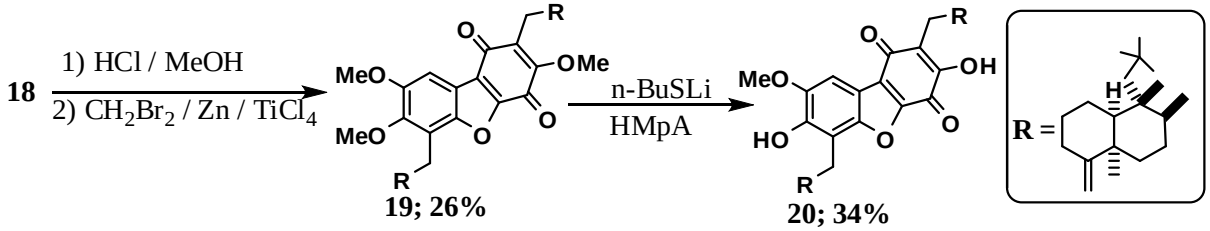
Kehokorins A–C, three novel dibenzofurans, have been isolated from field-collected fruit bodies of the myxomycete, *Trichia favoginea* var. *persimilis*, and their structures were elucidated by spectral data. Kehokorin A was a α-L-rhamnopyranoside of kehokorin B, while kehokorin C was a 1-demethoxy analog of Kehokorin A was cytotoxic against HeLa cells with an IC_{50} value of 1.5 µg/mL [90]. Dibenzofurans, Kehokorins A–C, have been isolated from *trichia favoginea var. persimilis*, were cytotoxic against *HeLa cells* [91, 92].

Peptides based on rhodamine B, dibenzofurans, had been carried out in *vitro* for Antibacterial activities compared to those of the antimicrobial peptides cathelicidin LL37

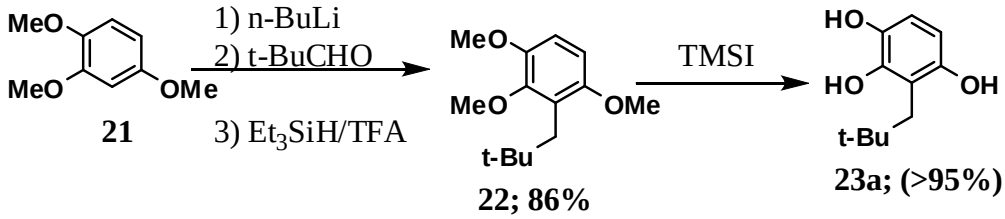
(Cathelicidin antimicrobial peptides are polypeptide that is primarily stored in the lysosomes of macrophages and polymorphonuclear leukocytes), magainin II (the magainins are a class of antimicrobial peptides found in the African clawed frog), and melittin **(**Melittin is a relatively short peptide consisting of 26 amino acids**)** [93]. Rhodomyrtoxin B (Fig. 1) has also demonstrated antibacterial activity. MIC values of 0.14 mM and 0.28 mM against *Bacillus cereus and Staphylococcus aureus*, respectively, have been reported for this compound [94]. Structurally similar rhodomyrtoxin C has shown slightly less activity against two different strains of *S. aureus*, with MIC values of 0.9 mM and 7.2 mM [96]. Like rhodomyrtoxin B, rhodomyrtoxin C has been isolated from *R. macrocarpa* [95], and has also been isolated from *Pilidiostigma glabrum* [96]. A synthesis of rhodomyrtoxin C was reported in 1983 by Sargent and coworkers [97]. Iodination of 1, 3, 5-trimethoxybenzene followed by Ullmann coupling produced biphenyl 28 (Scheme 6). Heating 28 with hydriodic acid followed by methylation with iodomethane then provided 1, 3, 7, 9 tetramethoxybenzofuran 29 in 24% yield starting from 1, 3, 5-trimethoxybenzene. Vilsmeier-Haack formylation of 29 followed by reduction with Lithium aluminium hydride (LAH) gave alcohol 30.



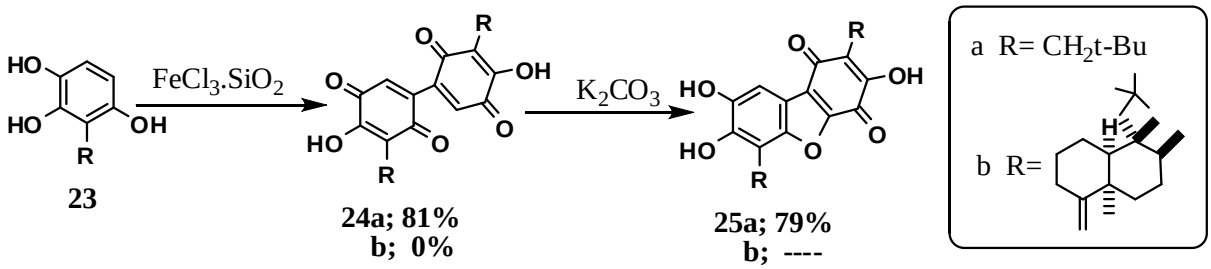
Scheme 2. Synthesis of popolohuanone E precursor.



Scheme 3. Synthesis of 8-O-methylpopolohuanone E.



Scheme 4. Synthesis of triol 23a.



Scheme 5. Oxidative dimerizations of triols

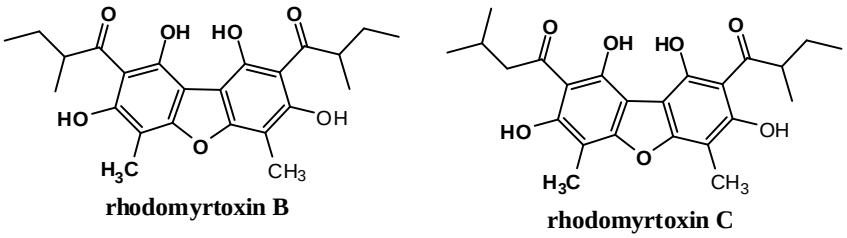


Fig. 1. Structures of rhodomyrtoxins B and C.

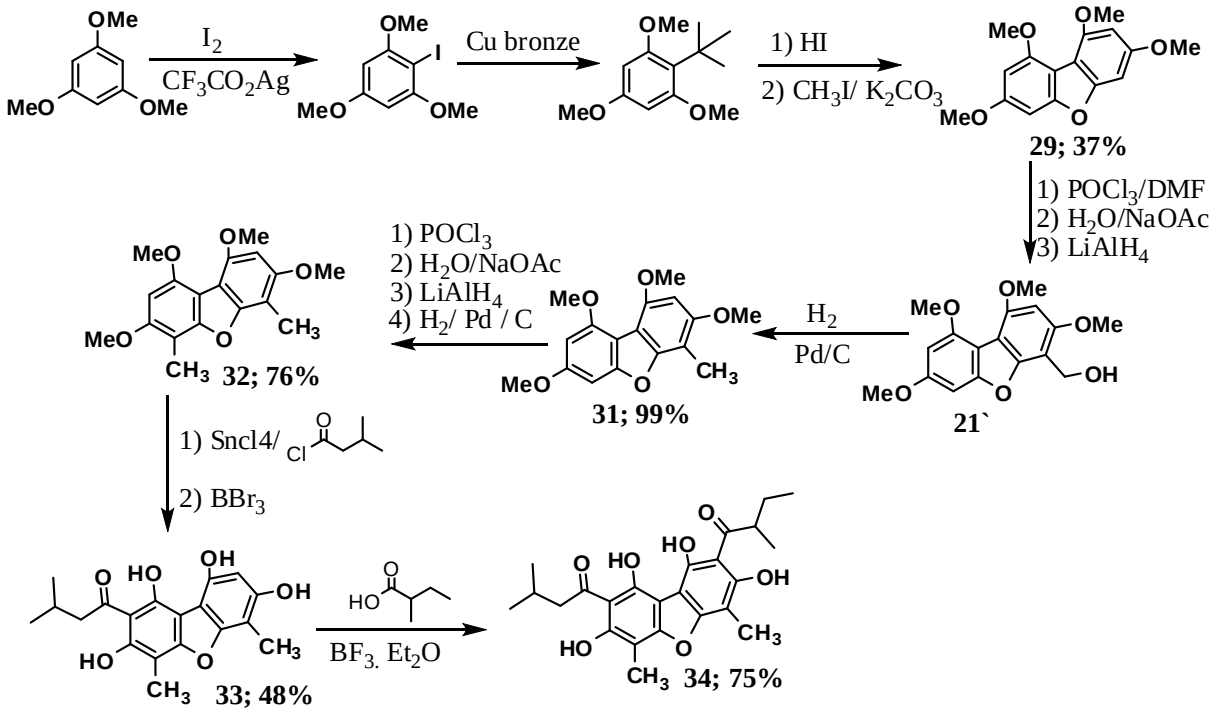
In 81% yield for the two steps. Further reduction to 31 was accomplished by catalytic hydrogenation in near quantitative yield. These steps were then repeated to give the dimethylated derivative 32 in 76% yield from 31. Two Friedel-Crafts acylations and demethylation using boron tribromide completed the synthesis of *rhodomyrtoxin C.*

Structurally similar to the rhodomyrtoxins is the natural product achyrofuran (Fig. 2). This compound has been isolated from Achyrocline satureioides, which has previously been used as a medicinal plant in South America [98]. Achyrofuran has been found to be effective against a methicillin-resistant strain of *S. aureus* (NRS402), with a MIC of 0.12 mM. It is also effective against a methicillin-sensitive strain of *S. aureus* (ATCC25923) as well as *Enterococcus faecalis* (ATCC29212) with MIC values of 0.25 mM and 3.96 mM, respectively [98].

Although no total synthesis of achyrofuran has been reported, a preparation of 39, dubbed "pre-achyrofuran" has been reported by Kingsbury and coworkers [99] (Scheme 7). Prenylation of 1, 3, 5-trimethoxybenzene followed by Vilsmeier-Haack formylation using oxalyl chloride afforded 36 in 75% yield. Scandium triflate catalyzed diazoalkyl insertion gave acylated product 37 in 91% yield, but demethylation of 37 with boron tribromide proceeded in only 15% yield. A three step conversion of 37 into 38 was also reported which produced 38 in 65% overall yield from 37. This route consisted of reduction of the ketone to an alcohol, demethylation using trimethylsilyl iodide, followed by oxidation of the alcohol back up to the ketone using the Dess-Martin periodinane. Oxidative dimerization/cyclization of 38 using iron (III) chloride supported on silica gel afforded the final product 39 in 51% yield.

The following year, Kantrowitz and coworkers reported the synthesis of achyrofuran analog 41 (Scheme 8) [100]. Hexamethoxybiphenyl 28 was prepared in 67% yield from 1, 3, 5-trimethoxybenzene in a fashion very similar to that shown in Scheme 6. Cyclization and demethylation was accomplished by treatment with HBr, and the resulting tetrahydroxydibenzofuran was acylated (albeit in low yield) to give 41. Though antibacterial activity was not reported for 41, it was found to inhibit fructose 1, 6-bisphosphatase [100] and, like achyrofuran itself which has shown significant antihyperglycemic activity [99], is thus of interest in the development of compounds for the treatment of diabetes.

Though not as potent as the rhodomyrtoxins, porric acid D has also shown activity against *S. aureus*, with an MIC of 100 mg/mL (which corresponds to 347 mM) [101]. This compound was isolated from an *Alternaria* marine fungus, but no synthesis of it has yet been reported (Fig. 6).



Scheme 6. Synthesis of rhodomyrtoxin C.

Over the years, a number of compounds collectively known as boletopsins have been isolated from mushrooms of the genus Boletopsis [102-105]. At present, twelve different boletopsins have been reported, but all have the general structure shown below in Fig. 4, differing only in whether the oxygen substituents are protonated, acetylated, or methylated, and whether or not there is a second oxygen substituent on the non-fused aromatic ring. Different naming conventions have been used as each set of boletopsins was discovered, but recently a unified system of notation has been proposed in which all are named "boletopsin" followed by an Arabic number [105].

Though several of the boletopsins display weak antibacterial activity, one of the more active compounds is boletopsin 11 **56** (Scheme 10). This compound (along with others) was tested against *Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, and Mycobacterium smegmatis*, with IC_{50} values (in mg/mL) of 242, 424, 272 and 96, respectively, being reported [105]. Synthetic boletopsin 11 was subjected to the same panel of bacteria and produced similar results. For example, the IC_{50} value against *P. aeruginosa* was 261 mg/mL, and the MIC value was 631 mg/mL [106]. Closely related to the boletopsins is cycloleucomelone (Fig. 5), which has been isolated from the same (and other) [102, 105, 107, 108] species of mushrooms, and has also shown weak antibacterial activity [105].

Recently a synthesis of three of the boletopsins (7, 11 and 12) has been reported [106]. The syntheses began with chlorination of catechol with sulfuryl chloride to give 42 in excellent yield (Scheme 9). Methylation and bromination also proceeded in high yield, as did conversion to the corresponding boronic acid 44 via lithiationhalogen exchange and treatment with trimethylborate followed by acidic work-up. 4-Methoxyphenylboronic acid 45 was prepared similarly in unspecified yield.

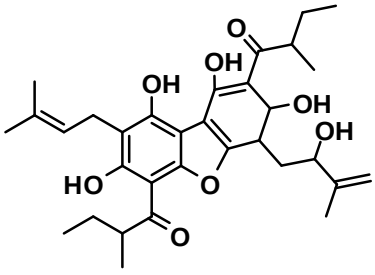
The third aromatic ring in the final product was derived from sesamol 46. Formulation via dichloromethyl methyl ether was followed by bromination in the presence of aluminum trichloride. The Lewis acid catalyst was found to be necessary for the introduction of both bromine atoms onto the ring (without it, only monobromination took place). Finally, the phenol was protected as its methoxymethyl ether to give 49 in 53% overall yield from sesamol.

With the three aromatic rings suitably substituted, their combination to give the boletopsins could begin. The synthetic approach they followed closely mirrored that reported by Takahashi and coworkers in their synthesis of Vialinin B [109] (see following section). Suzuki-Miyaura coupling of boronic acid 44 with aryl bromide 49 took place regioselectivity to give biphenyl derivative 50 (Scheme 10), though this reaction turned out to be exceptionally sensitive to the presence of trace quantities of oxygen. A similar coupling of 45 with 50 gave terphenyl derivative 51 in moderate yield. Baeyer-Villiger oxidation of the aldehyde proved somewhat problematic, though eventually reaction conditions were found that provided formate ester 52 in reasonable yield. This ester could then be

cyclized to dibenzofuran 53 under Ullmanntype conditions by refluxing a pyridine solution of 52 in the presence of excess copper (I) oxide (isolation of the free phenol proved impractical owing to the instability of the compound). This then completed the formation of the basic ring system common to the boletopsins. Replacement of the methoxymethyl protecting group with a benzyloxycarbonyl group was accomplished in 72% overall yield, and was found to be necessary in order to accomplish the subsequent transformation of the methylendioxy group. Product instability also plagued the subsequent three transformations, and thus 54 was converted into 55 as shown below without purification of any of the intermediates. 55 was obtained in 55% overall yield, and subsequently could be methylated in excellent yield to give boletopsin 11 in 56%.

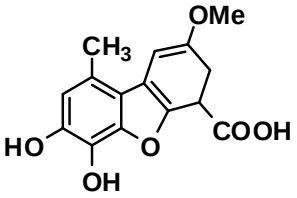
Demethylation of intermediate 55 using boron tribromide afforded boletopsin 7 in 57, and subsequent partial methylation of 57 then completed the synthesis of boletopsin 12 58. The boletopsin.

12 prepared in this manner was contaminated with boletopsin 11, from which it could be separated by HPLC. The authors suggest that the desired selectivity of this final methylationwas due to the lower acidity of the last remaining phenolic group in 58, owing to the absence of any adjacent hydrogen-bonding groups.



achyrofuran

Fig. 2. Structure of achyrofuran.



Porric acid D

Fig. 3. Structure of porric acid D.

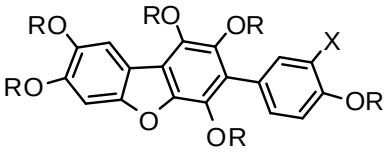
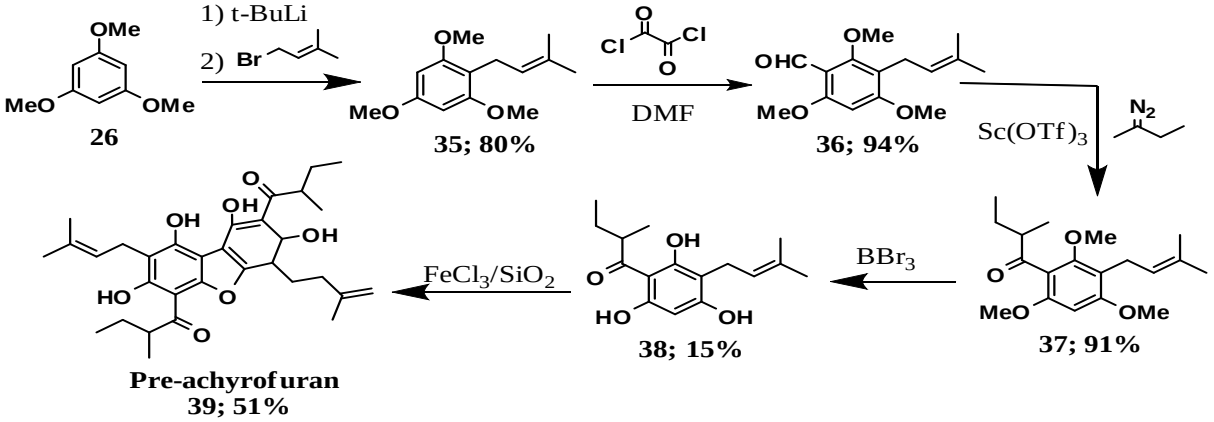
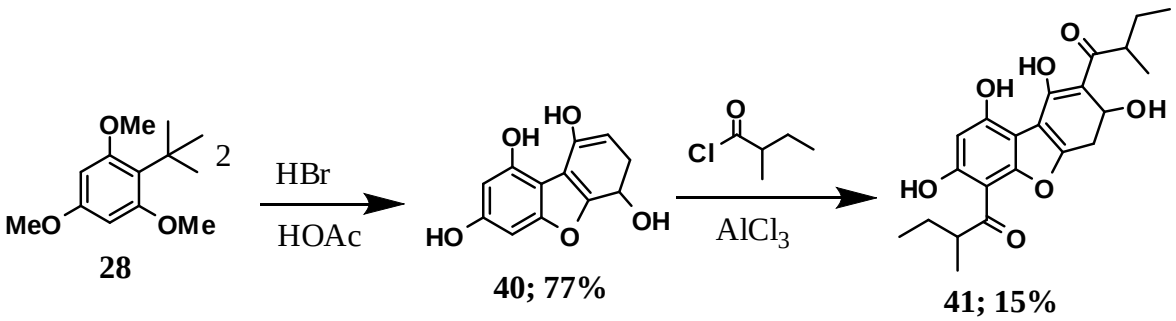


Fig. 4. General structure of boletopsins.

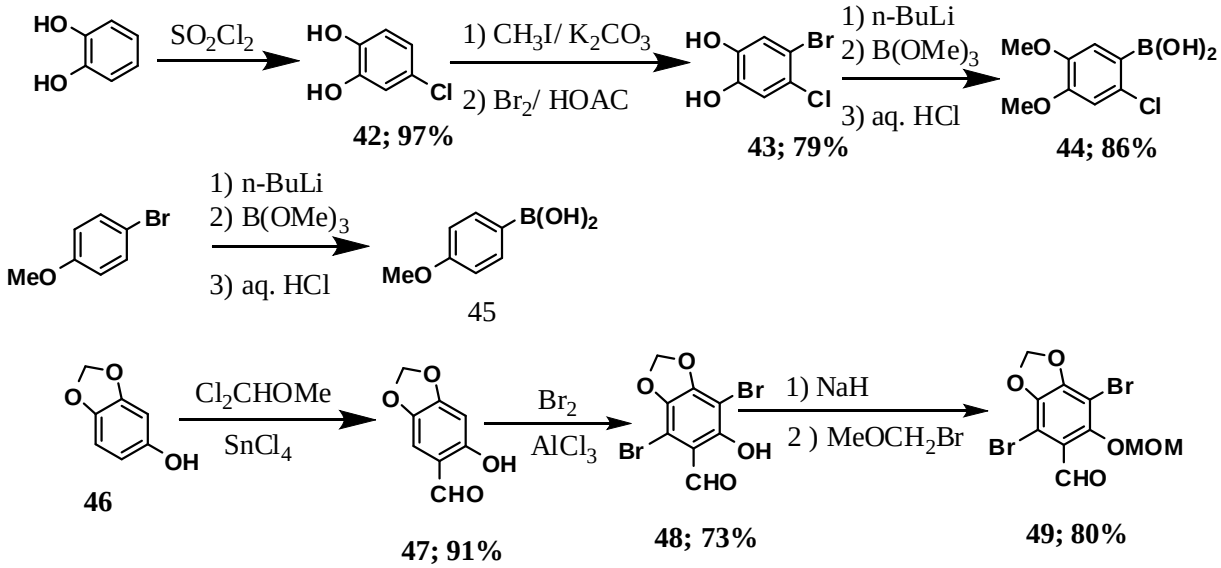


Pre-achyrofuran
39; 51%

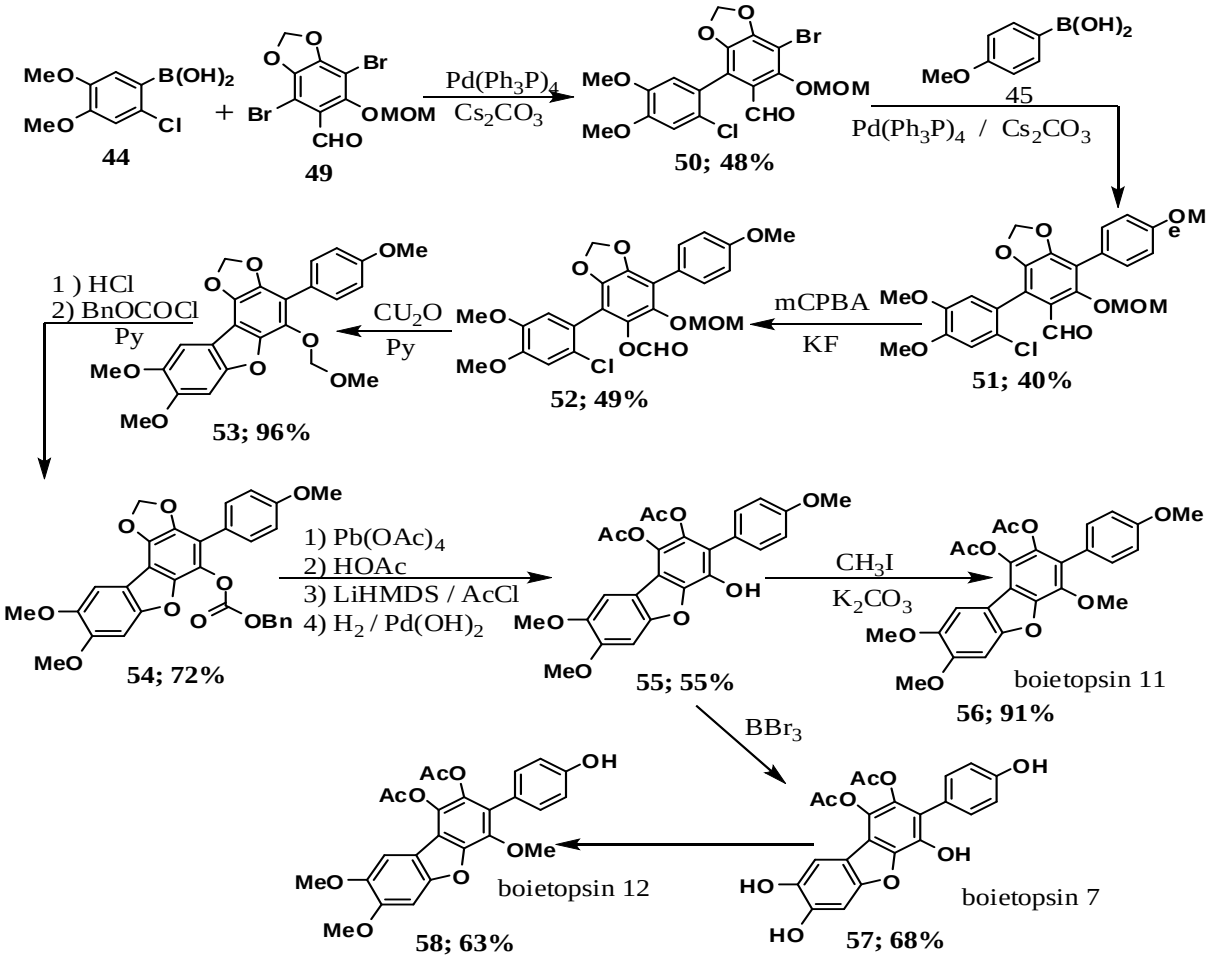
Scheme 7. Synthesis of "pre-achyrofuran".



Scheme 8. Synthesis of an achyrofuran analog.



Scheme 9. Synthesis of boletopsin precursors.



Scheme 10. Synthesis of boletopsins 7, 11 and 12.

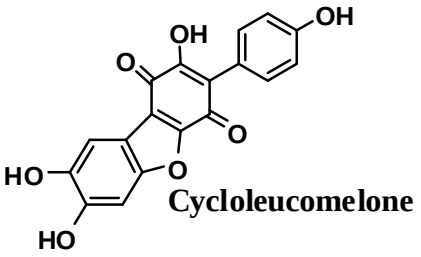
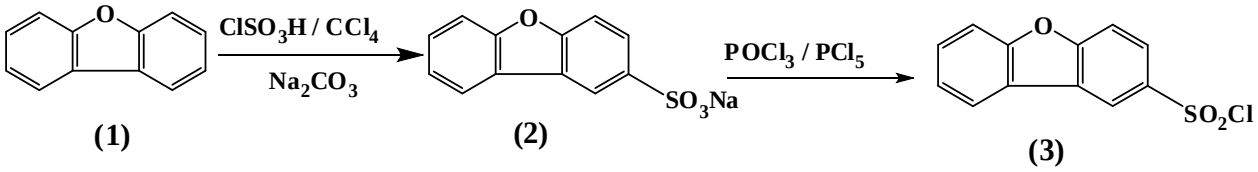
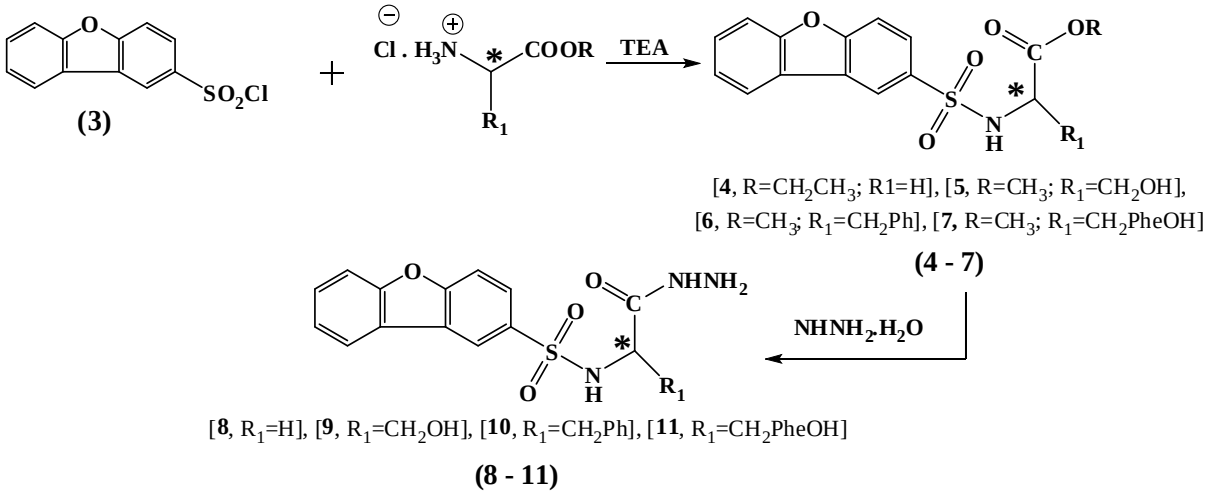


Fig. 5. Structure of cycloleucomelone.

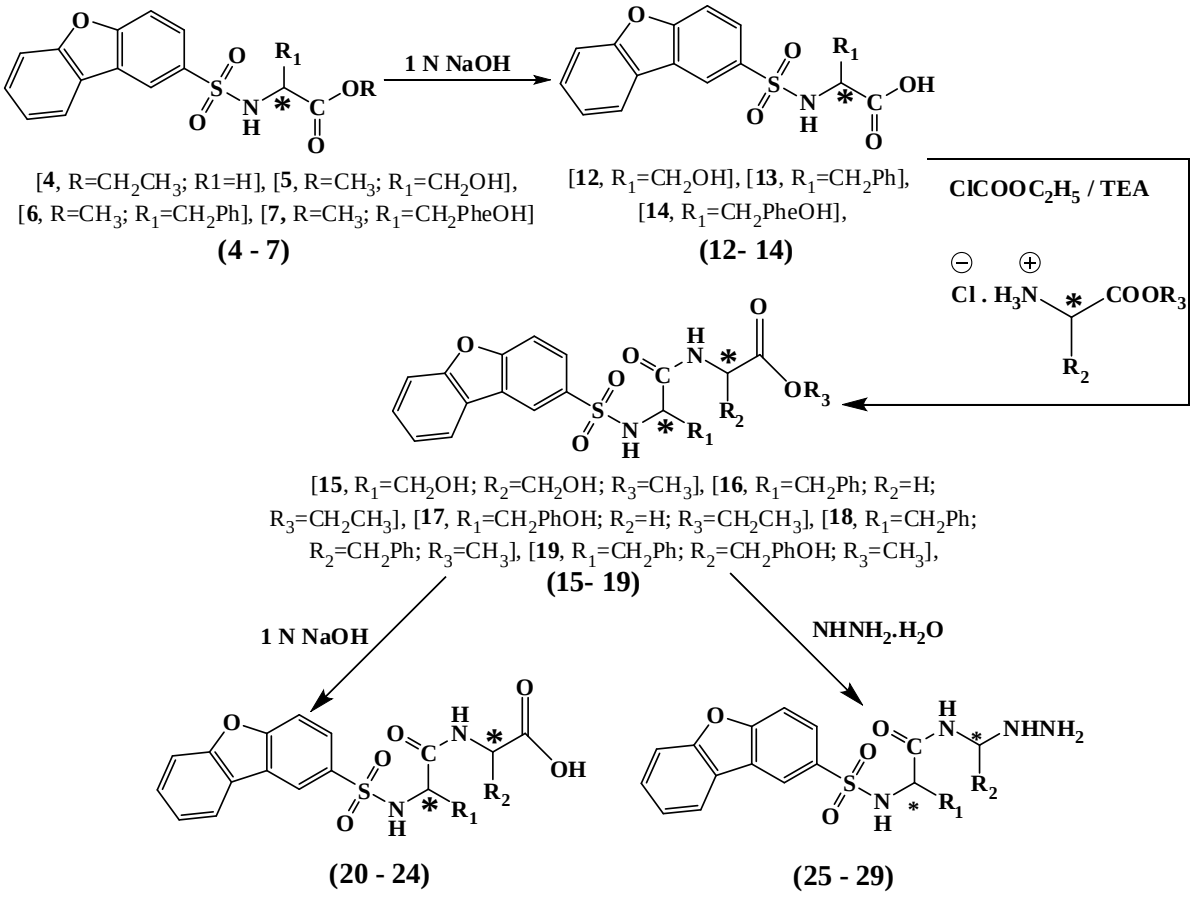
A series of linear dipeptide derivatives (4–29) have been prepared and evaluated as antimicrobial agents via the synthesis of dibenzofuran-2-sulfonyl chloride (3). The compound (3) was then coupled with amino acid ester, at low temperature, in the presence of organic base, gave dibenzofuran-2-sulphonyl-amino acid ester (4–7), which were converted to dibenzofuran-2-sulphonyl- hydrazides (8–11). The ester compounds were converted to dibenzofuran-2-sulphonyl-amino acid (12–14). The latter compounds (12–14) were coupled with different amino acid esters, gave the corresponding dibenzofuran-2-sulphonyl-dipeptide ester derivatives (15–19). The ester compounds (15–19) were converted to dibenzofuran-2-sulphonyl-dipeptide (20–24), the hydrazinolysis of esters (15–19) with alcoholic hydrazine hydrate afforded the corresponding hydrazides (25–29), respectively. All the newly synthesized amino acid and dipeptide compounds were fully characterized by means of their spectral data. The in vitro antimicrobial evaluation of the obtained compounds was tested against different types of pathogenic microorganisms: Gram-positive and Gram-negative bacteria, some of compounds were found to possess significant antimicrobial properties [38].



Scheme 11. Synthetic routes for dibenzofuran-2-sulfonyl chloride, 3



Scheme 12. Synthetic routes for compounds (4-11)



[**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)

[**12**, R_1=CH_2OH], [**13**, R_1=CH_2Ph], [**14**, R_1=CH_2PheOH],

(12- 14)

[**15**, R_1=CH_2OH; R_2=CH_2OH; R_3=CH_3], [**16**, R_1=CH_2Ph; R_2=H; R_3=CH_2CH_3], [**17**, R_1=CH_2PhOH; R_2=H; R_3=CH_2CH_3], [**18**, R_1=CH_2Ph; R_2=CH_2Ph; R_3=CH_3], [**19**, R_1=CH_2Ph; R_2=CH_2PhOH; R_3=CH_3],

(15- 19)

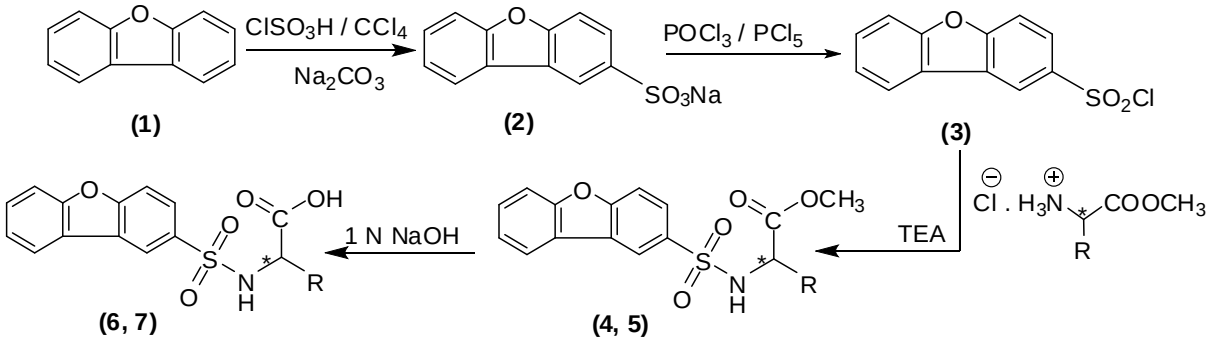
(20 - 24)

(25 - 29)

[**20, 25**, R_1=CH_2OH; R_2=CH_2OH], [**21, 26**, R_1=CH_2Ph; R_2=H], [**22, 27**, R_1=CH_2PhOH; R_2=H], [**23, 28**, R_1=CH_2Ph; R_2=CH_2Ph], [**24, 29,** R_1=CH_2Ph; R_2=CH_2PhOH],

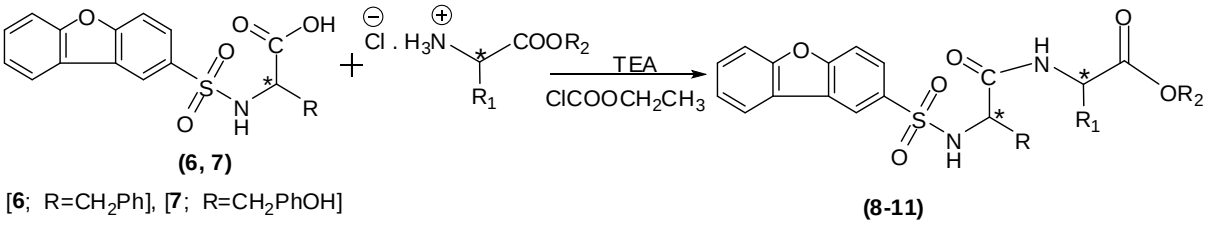
Scheme 13. Synthetic routes for compounds (12-29)

A series of linear tripeptide derivatives (4–29) have been prepared and evaluated as antimicrobial agents via the synthesis of dibenzofuran-2-sulfonyl chloride (3). The compound (3) was then coupled with amino acid ester at low temperature in the presence of organic base gave dibenzofuran-2-sulphonyl-amino acid ester (4, 5), which were converted to dibenzofuran-2-sulphonyl-amino acid (6, 7). The later compounds (6, 7) were coupled with different amino acid esters at low temperature in the presence of organic base gave the corresponding dibenzofuran-2-sulphonyldipeptide ester derivatives (8–11). The ester compounds (8–11) were converted to dibenzofuran-2-sulphonyl-dipeptide (12–15), respectively. The latter compounds (12–15) were coupled with different amino acid esters at low temperature in the presence of organic base gave the corresponding dibenzofuran-2-sulphonyl-tripeptide ester derivatives (16–19). The ester compounds were converted to dibenzofuran-2-sulphonyl-amino acid (20–23), respectively. The hydrazinolysis of esters (16–19) with alcoholic hydrazine hydrate afforded the corresponding hydrazides (24–27), respectively. The whole compounds were fully characterized by means of their spectral data. The in vitro antimicrobial evaluation of the obtained compounds was tested against seven strains; the different types of pathogenic microorganisms were Gram-positive, Gram-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 against the test organisms *Staph. aureus*, *Bacillus subtilis* as Gram-positive as well as *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Pseudomonas aeruginosa*, as Gram-negative was studied. It may be concluded that the suggested molecular structural features for these novel tripeptides based on Dibenzofuran-2-Sulfonyl-[aromatic and hydroxy aromatic residues] seemed significant for prospectively investigable novel antimicrobial candidates [39].



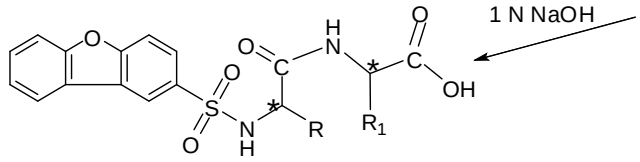
[**4, 6**; R=CH_2Ph], [**5, 7**; R=CH_2PhOH]

Scheme 14. Synthetic routes for compounds (6, 7)



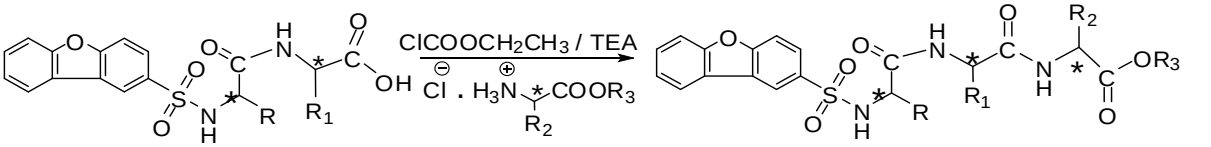
[**6**; R=CH_2Ph], [**7**; R=CH_2PhOH]

[**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]



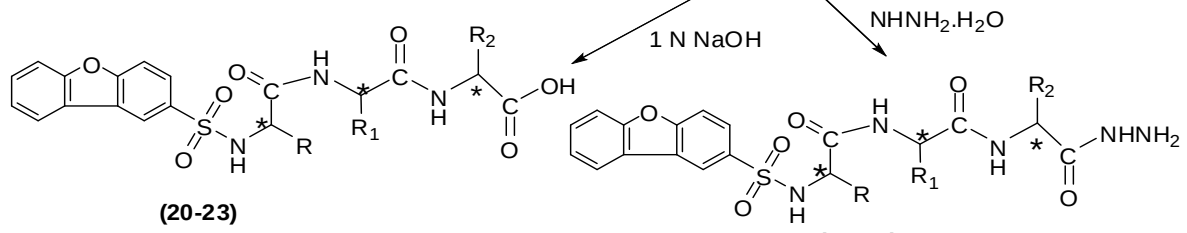
[**12**; R=CH_2Ph, R_1=H], [**13**; R=CH_2Ph, R_1=CH_2Ph],
[**14**; R=CH_2Ph, R_1=CH_2PhOH], [**15**; R=CH_2PhOH, R_1=H]

Scheme 15. 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 16. Synthetic routes for compounds (16-27)

5. Conclusions

The previous literature reports conclude that highly oxygenated dibenzofurans may be extracted from many natural sources; many members of this group of compounds have exhibited significant antimicrobial activity, which has led to various efforts focusing on their wholesome synthesis.

References

1. Johansen, S.S.; Hansen, A.B.; Mosbæk, H.; Arvin, E. Identification of heteroaromatic and other organic compounds in ground water at creosote-contaminated sites in Denmark. *Groundwater Monit. Remediat.* **1997**, *17*, 106–115.

2. Gichner, T. IARC monographs on the evaluation of carcinogenic risks to humans. Wood Dust and Formaldehyde. *Biol. Plant.* **1995**, *37*, 500.

3. Bleeker, E.A.J.;Wiegman, S.; Voogt, P.D.; Kraak, M.; Admiraal,W. Toxicity of azaarenes. Rev. Environ. Contam. *Toxicol.* **2002**, *173*, 39–83.

4. Meyer, S.; Steinhart, H. E_ects of heterocyclic PAHs (N, S, O) on the biodegradation of typical tar oil pahs in a soil/compost mixture. *Chemosphere*, **2000**, *40*, 359–367.

5. Lopes, T.J.; Furlong, E.T. Occurrence and potential adverse e_ects of semivolatile organic compounds in streambed sediment, united states, 1992–1995. *Environ. Toxicol. Chem.* **2001**, *20*, 727–737.

6. Dyreborg, S.; Arvin, E.; Broholm, K. Biodegradation of NSO-compounds under di_erent redox-conditions. *J. Contam. Hydrol.* **1997**, *25*, 177–197.

7. Zhu, X.; Ni, J.; Lai, P. Advanced treatment of biologically pretreated coking wastewater by electrochemical oxidation using boron-doped diamond electrodes. *Water Res.* **2009**, *43*, 4347–4355.

8. Morita, M., Nakagawa, J., & Rappe, C. Polychlorinated dibenzofuran (PCDF) formation from PCB mixture by heat and oxygen. *Bulletin of environmental contamination and toxicology*, **1978**, *19*(1), 665-670.

9. Horstmann, M., & McLachlan, M. S. Results of an initial survey of polychlorinated dibenzo-p-dioxins (PCDD) and dibenzofurans (PCDF) in textiles. *Chemosphere*, **1995**, *31*(2), 2579-2589.

10. Hartnik, T., Norli, H. R., Eggen, T., & Breedveld, G. D. Bioassay-directed identification of toxic organic compounds in creosote-contaminated groundwater. *Chemosphere*, **2007**, *66*(3), 435-443.

11. Mateus, E. P., da Silva, M. D. G., Ribeiro, A. B., & Marriott, P. J. Qualitative mass spectrometric analysis of the volatile fraction of creosote-treated railway wood sleepers by using comprehensive two-dimensional gas chromatography. *Journal of Chromatography A*, **2008**, *1178* (1-2), 215-222.

12. Ma, S., Ma, C., Qian, K., Zhou, Y., & Shi, Q. Characterization of phenolic compounds in coal tar by gas chromatography/negative-ion atmospheric pressure chemical ionization mass spectrometry. *Rapid Communications in Mass Spectrometry*, **2016**, *30* (15), 1806-1810.

13. Li, J., Li, M., & Wang, Z. Dibenzofuran series in terrestrial source rocks and curde oils and applications to oil-source rock correlations in the Kuche depression of Tarim Basin, NW China. *Chinese Journal of Geochemistry*, **2004**, *23*(2), 113-123.

14. Lim, B.R.; Hu, H.Y.; Fujie, K. Biological degradation and chemical oxidation characteristics of coke-oven wastewater. *Water Air Soil Pollut.* **2003**, *146*, 23–33.

15. Zhang, M.; Tay, J.H.; Qian, Y.; Gu, X.S. Coke plant wastewater treatment by fixed biofilm system for COD and NH_3–N removal. *Water Res.* **1998**, *32*, 519–527.

16. Smith, J. H. **1977**, *Environmental Pathways of Selected Chemicals in Freshwater Systems: Laboratory studies*. Environmental Protection Agency, Office of Research and Development, Environmental Research Laboratory.

17. Jacobs, B.W.; Billings, C.E. Characterization and temperature dependence of PAH emissions from a simulated rubber combustion operation. *Am. Ind. Hyg. Assoc. J.* **1985**, *46*, 547–554.

18. Perreira, W.E.; Rostard, C.E.; Updegraft, D.L.; Bennett, J.M. Fate and movement of azaarenes and their anaerobic biotransformation products in an aquifer contaminated by wood-treatment chemicals. Environ. *Toxicol. Chem.* **1987**, *6*, 163–176.

19. Ishikawa, S.; Sakazaki, Y.; Eguchi, Y.; Suetomi, R.; Nakamura, E. Identification of chemical substances in industrial wastes and their pyrolytic decomposition products. *Chemosphere* **2005**, *59*, 1343–1353.

20. Dartiguelongue, C.; Behar, F.; Budzinski, H.; Scacchi, G.; Marquaire, P.M. Thermal stability of dibenzothiophene in closed system pyrolysis: Experimental study and kinetic modelling. *Org. Geochem.* **2006**, *37*, 98–116.

21. Sobkowiak, M.; Gri_th, J.M.; Wang, B.; Beaver, B. Insight into the mechanisms of middle distillate fuel oxidative degradation. Part 1: On the role of phenol, indole, and carbazole derivatives in the thermal oxidative stability of Fischer-Tropsch/petroleum jet fuel blends. *Energy Fuel***, 2009**, *23*, 2041–2046.

22. Freitas, V.L.; Gomes, J.R.; DaSilva, M.D.R. Dibenzofuran and methyldibenzofuran derivatives: Assessment of thermochemical data. *Struct. Chem.* **2013**, *24*, 1923–1933.

23. Gu, Y.; Yperman, J.; Reggers, G.; Carleer, R.; Vandewijngaarden, J. Characterisation of volatile organic sulphur compounds release during coal pyrolysis in inert, hydrogen and CO_2 atmosphere. *Fuel* **2016**, *184*, 304–313.

24. Wikström, E.; Marklund, S. Secondary formation of chlorinated dibenzo-p-dioxins, dibenzofurans, biphenyls, benzenes, and phenols during MSW combustion. Environ. *Sci. Technol.* **2000**, *34*, 604–609.

25. Melius, C.F.; Colvin, M.E.; Marinov, N.M.; Pitz, W.J.; Senkan, S.M. Reaction mechanisms in aromatic hydrocarbon formation involving the C5H5 cyclopentadienyl. *Symp. Combust.* **1996**, *26*, 685–692.

26. Abo-Ghalia, M.H.; Moustafa, G.O.; Alwasidi, A.S.; Naglah, A.M. Cytotoxic Investigation of Isophthaloyl Cyclopenta peptides. *Lat. Am. J. Pharm.***2017**, *36*, 1957-1962.

27. Moustafa, G.O.; El-Sawy, A.A.; Abo-Ghalia, M.H. Synthesis of novel cyclopeptide candidates: I-cyclo-[N^{α}-isophthaloyl-*bis*-(Glycine-amino acid)-L-lysine] derivatives with expected anticancer activity.Egypt. J. Chem. **2013**, *5*, 473–494.

28. Hassan, A.S.; Moustafa, G.O.; Awad, H.M. Synthesis and *in vitro* anticancer activity of pyrazolo [1, 5-a] pyrimidines and pyrazolo [3, 4-d][1, 2, 3] triazines. *Synth. Commun.***2017**, *47*, 21, 1963-1972.

29. Amr, A.E.; Abo-Ghalia, M.H.; Moustafa, G.O.; Al-Omar, M.A.; Nossier, E.S.; Elsayed, E.A. Design, synthesis and docking studies of novel macrocyclic pentapeptides as anticancer multi-targeted kinase inhibitors.*Molecules.***2018**, *23*, 10.

30. Moustafa, G.O; Younis, A.; Al-Yousef, S.A.; Mahmoud, S.Y. Design, synthesis of novel cyclic pentapeptide derivatives based on 1, 2-benzenedicarbonyl chloride with expected anticancer activity. *J. Comput. Theor. Nanosci.***2019**, *16*, 5–6, 1733–1739.

31. Kassem, A.F.; Moustafa, G.O.; Nossier, E.S.; Khalaf, H.S.; Mounier, M.M.; Al-Yousef, S.A.; Mahmoud, S.Y. *In vitro* anticancer potentiality and molecular modelling study of novel amino acid derivatives based on N^{1}, N^{3}-*bis*-(1-hydrazinyl-1-oxopropan-2-yl)

isophthalamide. *J. Enzyme Inhib. Med. Chem.***2019**, *34*, 1, 1247–1258.

32. Mohamed, F.H.; Shalaby, A.M.; Soliman, H.A.; Abdelazem, A.Z.; Mounier, M.M.; Nossier, E.S.; Moustafa, G.O.Design, Synthesis and Molecular Docking Studies of Novel Cyclic Pentapeptides Based on Phthaloyl Chloride with Expected Anticancer Activity. *Egypt. J. Chem.***2020**, *63*, 5, 1723-1736, DOI: 10.21608/EJCHEM.2019.18452.2137

33. Abo-Ghalia, M.H.; Moustafa, G.O.; Amr, A.E.; Naglah, A.M.; Elsayed, E.A.; Bakheit, A.H.Anticancer activities and 3D-QSAR studies of some new synthesized macrocyclic heptapeptide derivatives. *Molecules.* **2020**, *25*(5), 1253. *https://doi.org/10.3390/molecules25051253*

34. Kalmouch, A.; Radwan, M.A.A.; Omran, M.M.; Sharaky, M.; Moustafa, G.O.Synthesis of novel 2, 3'-bipyrrole derivatives from chalcone and amino acids as antitumor agents. *Egypt. J. Chem.* **2020**, *63*, 11, 4409 – 4421

35 Moustafa, G.O., Al-Wasidi, A.S., Naglah, A.M., Refat, M.S. Isolation and Synthesis of Dibenzofuran Derivatives Possessing Anticancer Activities: A Review. *Egyptian Journal of Chemistry*, **2020**, *63 (6),* 2355-2367.

36. Elhenawy, A.A; Al-Harbi, L.M.; Moustafa, G.O.; El-Gazzar, M.A.; Abdel-Rahman, R.F.; Salim, A.E.Synthesis, comparative docking, and pharmacological activity of naproxen amino acid derivatives as possible anti-inflammatory and analgesic agents. *Drug Des. Devel. Ther*.**2019**, *13*, 1773.

37. Moustafa, G.O.; khalaf, H.; Naglah, A.; Al-Wasidi, A.; Al-Jafshar, N.; Awad, H. Synthesis, Molecular Docking Studies, *In Vitro* Antimicrobialand Antifungal Activities of Novel Dipeptide Derivatives Based on N-(2-(2-hydrazinyl-2-oxoethylamino)-2-oxoethyl)-Nicotinamide.*Molecules*.**2018**, *23*, 761, doi: 10.3390/molecules23040761

38. Naglah, A.M.; Moustafa, G.O.; Al-Omar, M.A.; Al-Salem, H.A.S.; Hozzein, W.N. Synthesis, Characterization andInVitroAntimicrobial Investigation of Novel Amino Acids and Dipeptides Based on Dibenzofuran-2-Sulfonyl-Chloride. *J. Comput. Theor. Nanosci.***2017**, *14*, 3183-3190.

39. Al-Salem, H.A.S.; Naglah, A.M.; Moustafa, G.O.; Mahmoud, A.Z.; Al-Omar, M.A. Synthesis of Novel Tripeptides Based on Dibenzofuran-2-Sulfonyl-[Aromatic and Hydroxy Aromatic Residues]: Towards Antimicrobial and Antifungal Agents. *J. Comput. Theor. Nanosci.***2017**, *14*, 3958–3966.

40. Hassan, A.S.; Moustafa, G.O.; Askar, A.A.; Naglah, A.M.; Al-Omar, M.A.Synthesis and antibacterial evaluation of fused pyrazoles and Schiff bases. *Synth. Commun* .**2018**, *48*, 21, 2761-2772.

41. Hassan, A.S.; Askar, A.A.; Nossier, E.S.; Naglah, A.M.; Moustafa, G.O.; Al-Omar, M.A. Antibacterial Evaluation, In Silico Characters and Molecular Docking of Schiff Bases Derived from 5-aminopyrazoles. *Molecules.***2019**, *24*, 17, 3130.

42. Hasanin, M.S.; Moustafa, G.O.New potential green, bioactive and antimicrobial nanocomposites based on cellulose and amino acid. *International Journal of Biological Macromolecules.***2019**, *144*, 441-448. DOI: 10.1016/j.ijbiomac.2019.12.133.

43. Elsherif, M.A.; Hassan, A.S.; Moustafa, G.O.; Awad, H.M.; Morsy, N.M., Antimicrobial Evaluation and Molecular Properties Prediction of Pyrazolines Incorporating Benzofuran and Pyrazole Moieties. *J Appl Pharm Sci*, **2020**, *10* (02), 037-043, DOI: 10.7324/JAPS.2020.102006

44. Hassan, A.S.; Moustafa, G.O.; Morsy, N.M.; Abdou, A.M.; Hafez, T.S. Design, synthesis and antibacterial activity of N-aryl-3-(arylamino)-5-(((5-substituted furan-2-yl)methylene)amino)-1H-pyrazole-4-

carboxamide as Nitrofurantoin® analogues. *Egypt. J. Chem.* **2020**, *63*, 11, 4485 - 4497.

45. Khalaf, H.S., Naglah, A.M., Al-Omar, M.A., Awad, H.M., Bakheit, A.H. Synthesis, docking, computational studies, and antimicrobial evaluations of new dipeptide derivatives based on nicotinoylglycylglycine hydrazide. *Molecules*, **2020**, *25 (16)*, 3589.

46. Al-Wasidi, A.S., Naglah, A.M., Kalmouch, A., Adam, A.M.A., Refat, M.S., Moustafa, G.O. Preparation of Cr_2O_3, MnO_2, Fe_2O_3, NiO, CuO, and ZnO oxides using their glycine complexes as precursors for in situ thermal decomposition. *Egyptian Journal of Chemistry*, **2020**, *63 (3)*, 1109-1118.

47. Al-Wasidi, A.S., Naglah, A.M., Refat, M.S., El-Megharbel, S.M., Kalmouch, A., Moustafa, G.O. Synthesis, spectroscopic characterization and antimicrobial studies of Mn(II), Co(II), Ni(II), Cr(III) and Fe(III) melatonin drug complexes. *Egyptian Journal of Chemistry*, **2020**, *63 (4)*, 1469-1481.

48. Al-Wasidi, A.S., Wafeek, M. Abd El-Ghaffar, H.A., Naglah, A.M., Kalmouch, A., Hamed, M., Moustafa, G.O. Effect of Density on Growth Hormone and Some Physiological Parameters and its Relation to Growth Performance. *Egyptian Journal of Chemistry*, **2020**, *63 (4)*, 1575-1584

49. Naglah, A.M., Moustafa, G.O., Elhenawy, A.A., Mounier, M.M., El-Sayed, H.,. Al-Omar, M.A Almehizia, A.A., Bhat, M.A. N^{α}-1, 3-Benzenedicarbonyl-bis-(Amino Acid) and Dipeptide Candidates: Synthesis, Cytotoxic, Antimicrobial, Antifungal and Molecular Docking Investigation. *Drug Des. Devel. Ther.***2021**, *15*, 1315-1332.

50. Moustafa, G.O., Therapeutic Potentials of Cyclic Peptides as Promising Anticancer Drugs. *Egyptian Journal of Chemistry*, **2021**, *64 (4)*, 1777-1787.

51. Collin, G., Höke, H., Benzofurans, Ullmann's Encyclopedia of Industrial Chemistry, *Wiley-VCH, Weinheim*, **2007**, DOI:10.1002/14356007.l03_l01

52. Iserloh, U., Oderaotoshi, Y., Kanemasa, S., Curran, D.P., Synthesis of (R, R)-4, 6-Dibenzofurandiyl-2, 2'-Bis (4-Phenyloxazoline) (DBFOX/PH) – A Novel Trridentate Ligand, *Org. Synth*., **2003**, *80*, 46-56. DOI:10.15227/orgsyn.080.0046

53. Kashima, S., Yorifuji, T., & Tsuda, T. Acute non-cancer mortality excess after polychlorinated biphenyls and polychlorinated dibenzofurans mixed exposure from contaminated rice oil: Yusho. *Science of the total environment*, **2011**, *409*(18), 3288-3294.

54. Scott, L. L., Staskal, D. F., Williams, E. S., Luksemburg, W. J., Urban, J. D., Nguyen, L. M., Harris, M. A. Levels of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in southern Mississippi catfish and estimation of potential health risks. *Chemosphere*, **2009**, *74*(7), 1002-1010.

55. Kelly, K. J., Connelly, E., Reinhold, G. A., Byrne, M., & Prezant, D. J. Assessment of health effects in New York City firefighters after exposure to polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs): the Staten Island Transformer Fire Health Surveillance Project. *Archives of Environmental Health: An International Journal*, **2002**, *57*(4), 282-293.

56. Pereira, M.D., Polychlorinated dibenzo-p-dioxins (PCDD), dibenzofurans (PCDF) and polychlorinated biphenyls (PCB): main sources, environmental behaviour and risk to man and biota. *Química Nova.* **2004**, *27(6)*, 934-943.

57. Dhhs, U., US Department of Health and Human Services. Hazardous substances data bank (HSDB, online database). *National Toxicology Information Program, National Library of Medicine, Bethesda, MD*, **1993**.

58. Kelly, K. J., Connelly, E., Reinhold, G. A., Byrne, M., & Prezant, D. J. Assessment of health effects in New York City firefighters after exposure to polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans

(PCDFs): the Staten Island Transformer Fire Health Surveillance Project. *Archives of Environmental Health: An International Journal*, **2002**, *57*(4), 282-293.

59. Ackermann, J. M. *Deposition of air pollutants to the Great Waters. Second report to Congress* (No. PB-97-189815/XAB; EPA-453/R-97/011). Environmental Protection Agency, Research Triangle Park, NC (United States). Office of Air Quality Planning and Standards, **1997**.

60. Zhang D, Gong L, Ding S, Tian Y, Jia C, Liu D, Han M, Cheng X, Sun D, Cai P, Tian Y. FRCD: A comprehensive food risk component database with molecular scaffold, chemical diversity, toxicity, and biodegradability analysis. *Food chemistry*, **2020**, *15*, 318, 126470.

61. Zhang, Y. M., Boukaache, A., Mayrargue, J., Moskowitz, H., Miocque, M., Thal, C. Synthesis of Dibenzofuran Derivatives from Spirodihydrocoumarins. *Synthetic communications*, **1992**, *22*(10), 1403-1408. DOI: 10.1080/00397919208021605

62. Labidalle S, Min ZY, Reynet A, Moskowitz H, Vierfond JM, Miocque M, Bucourt R, Thal C. Analogues morphiniques derives des tetra-et hexahydrodibenzofurannes: I-Synthese et epoxydation stereospecifiques des arylalkylcyclohexenes intermediaires. *Tetrahedron.* **1988**, *1*, 44(4), 1159-1169.

63. Labidalle, S., Min, Z. Y., Reynet, A., Moskowitz, H., Vierfond, J. M., Miocque, M., Thal, C. Analogues morphiniques derives des tetra-et hexahydrodibenzofurannes: II-Synthese et fonctionnalisation stereoselective des derives dibenzofuranniques. *Tetrahedron*, **1988**, *44*(4), 1171-1186.

64. Labidalle, S., Zhang, Y. M., Moskowitz, H., Thal, C., Miocque, M., Degryse, M., Delevallée, F., Analogues morphiniques dérivés des tétra-et hexahydrodibenzofurannes. *European journal of medicinal chemistry*, **1989**, *24*(4), 385-390.

65. Zhang, Y. M., Boukaache, A., Mayrargue, J., Moskowitz, H., Miocque, M., Thal, C., Synthesis of Dibenzofuran Derivatives from Spirodihydrocoumarins. *Synthetic communications*, **1992**, *22*(10), 1403-1408.

66. Tori, K., Kitahonoki, K., Takano, Y., Tanida, H., Tsuji, T. NMR studies of bridged ring systems. IV. Epoxides. *Tetrahedron Letters*, **1964**, *5*(11), 559-564.

67. Tori, K., Komeno, T., Sangaré, M., Septe, B., Delpech, B., Ahond, A., Lukacs, G. Carbon-13 NMR spectra of steroidal epoxides. Configurational assignment of an epoxy group on six-membered ring by carbon-13 NMR spectroscopy. *Tetrahedron Letters*, **1974**, *15*(13), 1157-1160.

68. Barfknecht, C. F., Keckler, D., Long, J. P., Greenberg, S. The pharmacology of dibenzofuran and terphenyl derivatives of DMAE and hemicholinium-3. *Archives internationales de pharmacodynamie et de therapie*, **1973**, *205*(2), 238-237.

69. Wommack, A. J., Moebius, D.C., Travis, A.L., Kingsbury, J. S. Diverse Alkanones by Catalytic Carbon Insertion into the Formyl C−H Bond. Concise Access to the Natural Precursor of Achyrofuran. *Organic letters*, **2009**, *11*(15), 3202-3205. DOI: 10.1021/ol9010932.

70. Safe, S., Mason, G., Keys, B., Farrell, K., Zmudzka, B., Sawyer, T., Safe, L., Romkes, M., Bandiera, S. Polychlorinated dibenzo-p-dioxins and dibenzofurans: correlation between in vitro and in vivo structure-activity relationships (SARs). *Chemosphere*, **1986**, *15*(9-12), 1725-1731. DOI:10.1016/0045-6535(86)90460-1

71. Setzer, W. N., Rozmus, G. F., Setzer, M. C., Schmidt, J. M., Vogler, B., Reeb, S., Jackes, B.R., Irvine, A. K., Bioactive principles in the bark of Pilidiostigma tropicum. *Journal of molecular modeling*, **2006**, *12*(5), 703-711.

DOI: 10.1007/s00894-005-0047-1
PMID:16601968

72. Kikuchi, H., Kubohara, Y., Nguyen, V. H., Katou, Y., Oshima, Y. Novel chlorinated dibenzofurans isolated from the cellular slime mold, Polysphondylium filamentosum, and their biological activities. *Bioorganic & medicinal chemistry*, **2013**, *21*(15), 4628-4633. DOI:10.1016/j.bmc.2013.05.022

73. Sawada, T., Aono, M., Asakawa, S., Ito, A., & Awano, K. Structure determination and total synthesis of a novel antibacterial substance, AB0022A, produced by a cellular slime mold. *The Journal of antibiotics*, **2000**, *53*(9), 959-966. DOI: 10.7164/antibiotics.53.959, PMID:11099230

74. West, D. H., Hopkins, B. S. Observations on the Rare Earths. XLV. Preparation of Rare Earth Amalgams by Displacement1. *Journal of the American Chemical Society*, **1935**, *57*(11), 2185-2186. DOI: 10.1021/ja01314a044

75. Yekkirala, A. S., Kalyuzhny, A. E., & Portoghese, P. S. Standard opioid agonists activate heteromeric opioid receptors: Evidence for morphine and [D-Ala2-MePhe4-Glyol5] enkephalin as selective μ− δ agonists. *ACS chemical neuroscience*, **2010**, *1*(2), 146-154. DOI: 10.1021/cn9000236. PMC 3398540. PMID 22816017.

76. Trasande, L., Urbina, E. M., Khoder, M., Alghamdi, M., Shabaj, I., Alam, M. S., Harrison R.M., Shamy, M. Polycyclic aromatic hydrocarbons, brachial artery distensibility and blood pressure among children residing near an oil refinery. *Environmental research*, **2015**, *136*, 133-140. PMID: 25460629, DOI: 10.1016/j.envres.2014.08.038.

77. Parker, P.T., analgesics from dibenzofurans, **1937**, *Iowa State University*, Ames, Iowa, United State 115 Pages, a thesis submitted to the Graduate Faculty for the degree of Doctor of Philosophy, major Subject organic chemistry, UMI Microform DP12356, Copyright 2005 by ProQuest Information and Learning Company. All rights reserved. This microform edition is protected against unauthorized copying under Title 17, United States Code. ProQuest Information and Learning Company 300 North Zeeb Road P.O. Box 1346. Ann Arbor, Ml 48106-1346.

78. Burtner, R.R., Lehmann, G., Heterocyclic Local Anesthetics. Carbazole, Dibenzofuran and Dibenzothiophene Derivatives1. *Journal of the American Chemical Society*, **1940**, *62*(3), 527-532. DOI: 10.1021/ja01860a020

79. Thomas, J.O., Wilson, R.H., Eddy, C.W. Effects of continued feeding of diphenylene oxide 1. *Journal of Food Science*, **1940**, *5*(1), 23-31. DOI: 10.1111/j.1365-2621.1940.tb17162.x

80. Heng, S., Harris, K.M., Kantrowitz, E.R. Designing inhibitors against fructose 1, 6-bisphosphatase: Exploring natural products for novel inhibitor scaffolds. *European journal of medicinal chemistry*, **2010**, *45*(4), 1478-1484. DOI: 10.1016/j.ejmech.2009.12.055.

81. Chizzali, C., Khalil, M.N., Beuerle, T., Schuehly, W., Richter, K., Flachowsky, H., Peil, A., Hanke, M.V., Liu, B., Beerhues, L. Formation of biphenyl and dibenzofuran phytoalexins in the transition zones of fire blight-infected stems of Malus domestica cv.'Holsteiner Cox'and Pyrus communis cv.'Conference'. *Phytochemistry*, **2012**, *77*, 179-185. DOI: 10.1016/j.phytochem. 2012.01.023

82. Qu, J., Xie, C., Guo, H., Yu, W., Lou, H. Antifungal dibenzofuran bis (bibenzyl) s from the liverwort Asterella angusta. *Phytochemistry*, **2007**, *68*(13), 1767-1774. DOI:10.1016/j.phytochem.2007.04.036

83. Shi, H.P., Dai, J.X., Zhang, X.F., Xu, L., Wang, L., Shi, L.W., Fang, L. Experimental and theoretical study of two new pyrazoline derivatives based on dibenzofuran. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, **2011**, *83*(1), 242-249.

DOI:10.1016/j.saa.2011.08.026

84. Wang, S., Hall, J.E., Tanious, F.A., Wilson, W.D., Patrick, D.A., McCurdy, D.R., Benderb, B.C., Tidwell, R.R. Dicationic dibenzofuran derivatives as anti-Pneumocystis carinii pneumonia agents: synthesis, DNA binding affinity, and anti-P. carinii activity in an immunosuppressed rat model. *European journal of medicinal chemistry*, **1999**, *34*(3), 215-224. 10.1016/S0223-5234(99)80054-3

85. Talontsi, F.M., Lamshöft, M., Douanla-Meli, C., Kouam, S.F., Spiteller, M. Antiplasmodial and cytotoxic dibenzofurans from Preussia sp. harboured in Enantia chlorantha Oliv. *Fitoterapia*, **2014**, *93*, 233-238. DOI: 10.1016/j.fitote.2014.01.003

86. Kikuchi, H., Kubohara, Y., Nguyen, V. H., Katou, Y., & Oshima, Y. Novel chlorinated dibenzofurans isolated from the cellular slime mold, Polysphondylium filamentosum, and their biological activities. *Bioorganic & medicinal chemistry*, **2013**, *21*(15), 4628-4633. DOI: 10.1016/j.bmc.2013.05.022

87. Yempala, T., Sriram, D., Yogeeswari, P., Kantevari, S. Molecular hybridization of bioactives: synthesis and antitubercular evaluation of novel dibenzofuran embodied homoisoflavonoids via Baylis–Hillman reaction. *Bioorganic & medicinal chemistry letters*, **2012**, *22*(24), 7426-7430. DOI: 10.1016/j.bmcl.2012.10.056

88. Watabe, M., Kobayashi, T., Kawahashi, T., Hino, A., Watanabe, T., Mikami, T., Matsumoto, T., Suzuki, M. Preparation, 195Pt NMR spectra and biological activity of platinum (IV) complexes with dipeptides. *Journal of inorganic biochemistry*, **1999**, *73*(1-2), 1-5. DOI: 10.1016/S0162-0134(98)10084-3, PMID:10212991

89. Lv, J., Liu, T., Cai, S., Wang, X., Liu, L., Wang, Y. Synthesis, structure and biological activity of cobalt (II) and copper (II) complexes of valine-derived schiff bases. *Journal of Inorganic Biochemistry*, **2006**, *100*(11), 1888-1896. DOI:10.1016/j.jinorgbio.2006.07.014

90. Kaniwa, K., Ohtsuki, T., Yamamoto, Y., & Ishibashi, M. (2006). Kehokorins A–C, novel cytotoxic dibenzofurans isolated from the myxomycete Trichia favoginea var. persimilis. *Tetrahedron letters*, *47*(10), 1505-1508.

91. Watanabe, K., Ohtsuki, T., Yamamoto, Y. New kehokorins and trichiols from the myxomycete Trichia favoginea. *Heterocycles*, **2007**, *71*(8), 1807-1814.

92. Kaniwa, K., Ohtsuki, T., Yamamoto, Y., & Ishibashi, M. Kehokorins A–C, novel cytotoxic dibenzofurans isolated from the myxomycete Trichia favoginea var. persimilis. *Tetrahedron letters*, **2006**, *47*(10), 1505-1508. DOI:10.1016/j.tetlet.2006.01.012

93. Bucki, R., Pastore, J.J., Randhawa, P., Vegners, R., Weiner, D. J., Janmey, P.A. Antibacterial activities of rhodamine B-conjugated gelsolin-derived peptides compared to those of the antimicrobial peptides cathelicidin LL37, magainin II, and melittin. *Antimicrobial agents and chemotherapy*, **2004**, *48*(5), 1526-1533. PMID: 15105101, PMCID: PMC400557 DOI: 10.1128/AAC.48.5.1526-1533.2004

94. Setzer, W.N., Rozmus, G.F., Setzer, M.C., Schmidt, J.M., Vogler, B., Reeb, S., Jackes, B.R., Irvine, A. K. Bioactive principles in the bark of Pilidiostigma tropicum. *Journal of molecular modeling*, **2006**, *12*(5), 703-711.

95. Igboechi, C.A., Parfitt, R.T., Rowan, M.G. Two dibenzofuran derivatives from fruits of Rhodomyrtus macrocarpa. *Phytochemistry*, **1984**, *23*(5), 1139-1141.

96. Shou, Q., Banbury, L.K., Renshaw, D.E., Lambley, E.H., Mon, H., Macfarlane, G.A., Griesser, H.J., Heinrich, M.M., Wohlmuth, H. Biologically active dibenzofurans from Pilidiostigma glabrum, an endemic Australian

Myrtaceae. *Journal of natural products*, **2012**, *75*(9), 1612-1617.

97. Sargent, M.V., Stransky, P.O., Patrick, V.A., White, A.H. Naturally occurring dibenzofurans. Part 3. On the structures of the rhodomyrtoxins. *Journal of the Chemical Society, Perkin Transactions*, **1983**, *1*, 231-239.

98. Casero, C., Estevez-Braun, A., Ravelo, A.G., Demo, M., Méndez-Álvarez, S., Machin, F. Achyrofuran is an antibacterial agent capable of killing methicillin-resistant vancomycin-intermediate Staphylococcus aureus in the nanomolar range. *Phytomedicine*, **2013**, *20*(2), 133-138.

99. Wommack, A.J., Moebius, D.C., Travis, A.L., Kingsbury, J.S. Diverse Alkanones by Catalytic Carbon Insertion into the Formyl C− H Bond. Concise Access to the Natural Precursor of Achyrofuran. *Organic letters*, **2009**, *11*(15), 3202-3205.

100. Heng, S., Harris, K.M., Kantrowitz, E.R. Designing inhibitors against fructose 1, 6-bisphosphatase: Exploring natural products for novel inhibitor scaffolds. *European journal of medicinal chemistry*, **2010**, *45*(4), 1478-1484.

101. Xu, X., Zhao, S., Wei, J., Fang, N., Yin, L., Sun, J. Porric acid D from marine-derived fungus Alternaria sp. isolated from Bohai Sea. *Chemistry of Natural Compounds*, **2012**, *47*(6), 893-895.

102. Jagers, E., Hillenmaske, E., Steglich, W. Fungal pigments. 54. metabolites of boletopsis-leucomelaena (basidiomycetes)-clarification of the chemical nature of leucomelone and protoleucomelone. *Zeitschrift Fur Naturforschung Section Ba Journal Of Chemical Sciences*, **1987**, *42*(10), 1349-1353.

103. Takahashi, A., Kudo, R., Kusano, G., Nozoe, S. 5-Lipoxygenase inhibitors isolated from the mushroom Boletopsis leucomelas (Pers.) Fayod. *Chemical and pharmaceutical bulletin*, **1992**, *40*(12), 3194-3196.

104. Kaneko, A., Tsukada, M., Fukai, M., Suzuki, T., Nishio, K., Miki, K., Kinoshita, K., Takahashi, K., Koyama, K. KDR kinase inhibitor isolated from the mushroom Boletopsis leucomelas. *Journal of natural products*, **2010**, *73*(5), 1002-1004.

105. Wossa, S.W., Beekman, A.M., Ma, P., Kevo, O., Barrow, R.A. Identification of Boletopsin 11 and 12, Antibiotics from the Traditionally Used Fungus Boletopsis sp. *Asian Journal of Organic Chemistry*, **2013**, *2*(7), 565-567.

106. Beekman, A.M., Barrow, R.A. Syntheses of the fungal metabolites boletopsins 7, 11, and 12 from the Papua New Guinea medicinal mushroom Boletopsis sp. *The Journal of organic chemistry*, **2014**, *79*(3), 1017-1024.

107. Lin, H., Ji-Kai, L. Two novel phenylacetoxylated p-terphenyls from Thelephora ganbajun Zang. *Zeitschrift für Naturforschung C*, **2001**, *56*(11-12), 983-987.

108 Jagers, E., Hillenmaske, E., Schmidt, H., Steglich, W., Horak, E. Fungal pigments. 55. Acetylated terphenylquinone derivatives from Anthracophyllum species (Agaricales). *Zeitschrift Fur Naturforschung Section Ba Journal of Chemical Sciences*, **1987**, *42*(10), 1354-1360.

109 Ye, Y.Q., Koshino, H., Onose, J.I., Yoshikawa, K., Abe, N., Takahashi, S. Expeditious synthesis of vialinin B, an extremely potent inhibitor of TNF-α production. *Organic letters*, **2009**, *11*(21), 5074-5077.