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SYNTHESIS OF SOME NOVEL DIPEPTIDES AND THEIR COPPER(II) COMPLEXES OF (DIBENZO [b, d] FURAN-2-YLSULFONYL) PHENYLALANINE

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ABSTRACT. A new series of dipeptide candidates (**6-11**) and corresponding octahedral copper complexes (**12-15**) were prepared by the synthesis of dibenzofuran-2-sulfonyl chloride (**3**). Then, the acid chloride **(3)** was coupled, at low temperature, with DL-phenylalanine using triethylamine and gave the corresponding acid (**4**) as starting material, which was converted to dibenzofuran-2-sulphonyl-DL-phenylalanyl chloride (**5**) using thionyl chloride. The latter acid chloride (**5**) was coupled with some aliphatic amino acids and gave the corresponding dibenzofuran-2-sulphonyldipeptide candidates (**6**, **7**). Moreover, dibenzofuran-2-sulphonyldipeptide methyl ester derivatives (**8**, **9**) were prepared via the esterification of the corresponding candidates (**6**, **7**) and hydrazinolysis with hydrazine hydrate 99% of methyl esters (**8**, **9**) to give the corresponding peptide hydrazides (**10**, **11**). Then, all the newly prepared peptide derivatives (**6-11**) were reacted with copper acetate to afford the corresponding copper complexes (**12-15**). The newly synthesized compounds **(6-15**) were characterized.

KEY WORDS: Dibenzofuran-2-sulfonyl-DL-phenylalanyl chloride, Amino acids, Linear dipeptides, Copper complexes.

INTRODUCTION

Dibenzofuran and its hydroxylated derivatives have previously been synthesized from catechol [1]. Dibenzofuran and carbazole derivatives were synthesized [2] by selective bromination with N-bromosuccinimide on benzylic groups or aromatic rings [3]. Seven dipeptide complex derivatives of the form K[Pt(IV)(dipep)Cl(OH)] and K[Pt(IV)-(Hdipep)Cl$(OH)_2$] were prepared [4]. These complexes suggested that, with the platinum complexes, the growth of most fungal cells is selectively inhibited [4]. The synthesized complexes consist of copper(II) and cobalt(II) from which valine is derived *via* Schiff bases. The necessary biological studies of the complexes have been conducted in vitro for antimicrobial activity against both positive and negative bacteria. Moreover, studies have been performed for human pathogenic fungi. The biological results indicated that the growth of Gram-positive bacteria is highly inhibited, as well as the pathogenic fungi that were tested. On the other hand, the antibacterial activity of the Gram-negative type is moderately effective. It is worth noting that the cytotoxicity of the newly prepared complexes was evaluated, as it was found that the modern peptide complexes are non-toxic to human erythrocytes, even at a concentration of 500 µg/mL [5]. In addition, the synthesis of several peptide derivatives has recently been reported, which have been investigated and studied in terms of different biological activities [6-15]. Recently, a lot of systematic research has resulted in discoveries of different pharmacokinetic drugs, and some new peptide derivatives and

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heterocyclics have been synthesized and tested for anti-HIV, anti-inflammatory, anticoagulant, analgesic, anticonvulsant, anticancer, and antimicrobial activities [16]. We also noted the importance of protein-based bonding tuning of the copper active sites, including the high sensitivity of the Cu-O_2 structure as well as the interaction with the coordination number, shape, and bond atoms through which it was shown that the redox activity of the copper ion is permanently activated by the addition of Cu complexes (I) a third N-donor of HisHis dipeptides [17]. Furthermore, a strong positive correlation was observed between copper and all levels of free amino nitrogen in some herbs [18]. This intriguing new combination of potential different pharmaceutical properties and applications has stimulated significant and ongoing efforts to obtain effective novel derivatives incorporating a dibenzofuran unit for systemic antimicrobial and antifungal measurements.

EXPERIMENTAL

Chemistry

Melting points were determined in open glass capillary tubes using a digital thermoelectric melting point instrument. R_f was performed by using thin layer chromatography (TLC), 60 F254 (E. Merck), (n-hexane: ethyl acetate, 3:1). UV spectra in the 190–400 nm range were recorded for the ligands, and visible spectra in the 400–800 nm range were recorded on the PerkinElmer UV-160. Infrared spectra of KBr were measured on an IR 5300 PerkinElmer spectrometer. Mass spectra were measured on a GC MS-QP 1000 at 70 eV (EI, 70 eV), using the electron impact (EI) technique. Conductivity measurements in solution were performed using the TDS 72 conductivity model. The spectra (^{1}H NMR and ^{13}C NMR) were run on Jeol instruments (JöEL 500 MHz, δ, ppm, DMSO-d_6), and compounds (**1-5**) were previously prepared by reported procedures [19].

*General procedure for the synthesis of dibenzofuran-2-sulfonyldipeptides (**6**, **7**)*

Method A. The β-Ala and DL-Ala in acid form (0.01 mol) were dissolved in a solution mixture of THF, triethylamine, and water, with 4, 2, and 8 mL, respectively. Then, dibenzofuran-2-sulfonyl-DL-phenylalanyl chloride (0.01 mol; **5**) was added slowly while stirring vigorously for 30 min, stirring continues for another 45 min, followed by the evaporation of the solvent in a vacuum. Then, 30 mL of water is added to acidify the mixture with HCl to reach pH = 5. The products (**6**, **7**) were purified by re-purification. Crystallization using ethanol and water solution obtained high yields of 80 and 74%, respectively.

Method B. The β-Ala and DL-Ala amino acid (0.01 mol) was dissolved in (20 mL) 1 N sodium hydroxide. (0.01 mol; **5**) was dissolved in benzene and added in portions during 30 min, for an alkaline solution of the amino acid with stirring. The reaction temperature during the addition phase was kept at 10 °C to 5 °C for a minimum of 30 min. Then, the stirring was continued for another 3 hours at room temperature. This was followed by removing the benzene layer and then acidifying the aqueous layer using a 2 N HCl solution until pH = 5. The products (**6**, **7**) were recrystallized from ethanol-water and obtained with 65 and 62% yields, respectively.

*Dibenzofuran-2-sulfonyl-DL-Phe-β-Ala (**6**)*. Yield: 80%: [A]; 65%: [B]; m.p. 221-223 ºC; R_f. 0.78, IR (cm^{-1}): ν = 3430 (NH_2 and NH, respectively), 2997 (CH, aromatic), 2912 cm^{-1} (CH_3 and CH-aliphatic), 1654 (C=O, amide), 1313 (SO_2). ^{1}H-NMR: δ = 12.56 (s, 1 H, OH, carboxylic acid, D_2O exchangeable), 8.30 (s, 1 H, 1 NH, D_2O exchangeable, amine β-Ala), 8.03 (s, 1 H, 1 NH, D_2O exchangeable, amine DL-Phe), 7.90-7.20 (12 H, aromatic), 4.40 (q, 1H, α CH, β-Ala), 3.85 (t, 1H, α CH, DL-Phe), 3.40 (d, 2H, β CH_2, DL-Phe), 1.40 (d, 3H, β CH_3, β-Ala). MS: *m/z* (%) = 467 (M^+, 0.08), 424 (34.87), 346 (8.35), 278 (85.34), 200 (17.32), **104** (**100.00**), 91 (71.33).

Molecular formula (M.wt.): $C_{24}H_{22}N_2O_6S$ (466.5); calculated analysis: C, 61.79; H, 4.75; N, 6.00; S, 6.87; found analysis: C, 61.85; H, 4.70; N, 6.00; S, 6.77.

Dibenzofuran-2-sulfonyl-DL-Phe-DL-Ala (**7**). Yield: 74%: [B]; 62%: [A]; m.p. 242-244 °C; R_f. 0.76, IR (cm^{-1}): ν = 3431 (NH_2 and NH, respectively), 2997 (CH, aromatic), 2912 cm^{-1} (CH_3 and CH-aliphatic), 1657 (C=O, amide), 1313 (SO_2). ^{1}H-NMR: δ = 12.50 (s, 1 H, OH, carboxylic acid, D_2O exchangeable), 8.25 (s, 1 H, 1 NH, D_2O exchangeable, amine DL-Ala), 7.99 (s, 1 H, 1 NH, D_2O exchangeable, amine DL-Phe), 7.80-7.15 (12 H, aromatic), 4.50 (q, 1H, α CH, DL-Ala), 3.92 (t, 2H, β CH_2, DL-Phe), 3.30 (d, 2H, α CH, DL-Ala), 1.44 (d, 3H, β CH_3, DL-Ala). MS: *m/z* (%) = 466 (M^+, 0.04), 422 (0.81), 352 (0.11), 178 (0.98), 104 (30.97), **91** (**100.00**), 51 (10.60) Molecular formula (M.wt.): $C_{24}H_{22}N_2O_6S$ (466.5); calculated analysis: C, 61.79; H, 4.75; N, 6.00; S, 6.87; found analysis: C, 61.72; H, 4.76; N, 6.63; S, 6.81.

*General procedure for the synthesis of dibenzofuran-2-sulfonyl-dipeptide methyl esters (**8**, **9**)*

The compounds (**8**, **9**) were prepared by the reported procedure [20]. Dibenzofuran-2-sulfonyldipeptide (**6**, **7**; 1 mol) was added to absolute methanol (30 mL), and the mixture reaction was cooled to -10 °C, and pure (1.1 mol) thionyl chloride was added in drops. After that, the reaction temperature was fixed at -5 °C. In addition, the vigorous stirring continued for another 3 additional hours, and then the mixture was left for another 24 hours at room temperature. The solvent is extracted by rotavapour, and another part of absolute methanol is added and re-evaporated. Finally, it is recrystallized using methanol-ether solution to obtain the new compounds (**8**, **9**) in high purity.

Dibenzofuran-2-sulfonyl-DL-Phe-β-Ala-OMe (**8**). Yield (%) 82; m.p. 166-168 °C; R_f. 0.61; IR (cm^{-1}): ν = 3426 (NH_2 and NH, respectively), 2999 (CH, aromatic), 2914 cm^{-1} (CH_3 and CH-aliphatic), 1655 (C=O, amide and C=O, ester), 1313 (SO_2). ^{1}H-NMR: δ = 8.40 (s, 1 H, 1 NH, D_2O exchangeable, amine β-Ala), 8.10 (s, 1 H, 1 NH, D_2O exchangeable, amine DL-Phe), 7.95-7.27 (12 H, aromatic), 4.45 (q, 1H, α CH, β-Ala), 4.00 (t, 1H, α CH, DL-Phe), 3.70 (s, 3H, COO$\underline{CH_3}$), 3.45 (d, 2H, β–CH_2, DL-Phe), 1.55 (d, 3H, β CH_3, β-Ala). MS: *m/z* (%) = 481 (M^+, 11.84), 271 (28.77), 167 (35.58), 77 (77.00), **73** (**100.00**), 52 (14.39). Molecular formula (M.wt.): $C_{25}H_{24}N_2O_6S$ (480.5); calculated analysis: C, 62.49; H, 5.03; N, 5.83; S, 6.67; found analysis: C, 62.55; H, 5.03; N, 5.88; S, 6.75.

Dibenzofuran-2-sulfonyl-DL-Phe-DL-Ala-OMe (**9**). Yield (%) 75; m.p. 191-193 °C; R_f. 0.81, IR (cm^{-1}): ν = 3435 (NH_2 and NH, respectively), 2996 (CH, aromatic), 2911 cm^{-1} (CH_3 and CH-aliphatic), 1657 (C=O, amide and C=O, ester), 1313 (SO_2). ^{1}H-NMR: δ = 8.45 (s, 1 H, 1 NH, D_2O exchangeable, amine DL-Ala), 8.05 (s, 1 H, 1 NH, D_2O exchangeable, amine DL-Phe), 7.90-7.27 (12 H, aromatic), 4.40 (q, 1H, α CH, DL-Ala), 4.95 (t, 1H, α CH, DL-Phe), 3.65 (s, 3H, COO$\underline{CH_3}$), 3.44 (d, 2H, β –CH_2, DL-Phe), 1.50 (d, 3H, β CH_3, DL–Ala). MS: *m/z* (%) = 481 (M^+ + 1, 0.26), **475** (**100.00**), 78 (0.52), 55 (0.53). Molecular formula (M.wt.): $C_{25}H_{24}N_2O_6S$ (480.5); calculated analysis: C, 62.49; H, 5.03; N, 5.83; S, 6.67; found analysis: C, 62.53; H, 4.98; N, 5.68; S, 6.70.

*General procedure for the synthesis of dibenzofuran-2-sulfonyl-dipeptide hydrazides (**10**, **11**)*

The hydrazide compounds (**10**, **11**) were prepared using the same procedure described in [6].

Dibenzofuran-2-sulfonyl-DL-Phe-β-Ala-$NHNH_2$ (**10**). Yield: 75%; m.p. 270-273 °C; R_f. 0.88, IR (cm^{-1}): ν = 3434 (NH_2 and NH, respectively), 2995 (CH, aromatic), 2911 cm^{-1} (CH_3 and CH-aliphatic), 1657 (C=O, amide), 1313 (SO_2). ^{1}H-NMR: δ = 9.07 (s, 1H, CO$\underline{NH}NH_2$), 8.33(s, 1 H, 1 NH, D_2O exchangeable, amine β -Ala), 8.05(s, 1 H, 1 NH, D_2O exchangeable, amine DL-Phe),

7.90-7.20 (12 H, aromatic), 4.75 (q, 1H, α CH, β-Ala), 4.20(s, 2H, CONHNH$_2$), 3.94(t, 1H, α CH, DL-Phe), 3.46 (d, 2H, β–CH$_2$, DL-Phe), 1.50(d, 3H, β CH$_3$, β -Ala). -MS (EI, 70 eV): *m/z* (%) = 481 (M^+ + 1, 1.91), 480 (M^+, 1.69), **370** (**100.00**), 302 (11.74), 57 (15.14), 51 (5.33). Molecular formula (M.wt.): $C_{24}H_{24}N_4O_5S$ (480.5); calculated analysis: C, 59.99; H, 5.03; N, 11.66; S, 6.67; found analysis: C, 60.00; H, 5.15; N, 11.63; S, 6.74.

Dibenzofuran-2-sulfonyl-DL-Phe-DL-Ala-NHNH$_2$ (**11**). Yield: 68%; m.p. 197-199 °C; R_f. 0.67, IR (cm^{-1}): ν = 3425 (NH$_2$, NH), 3000 (CH-aromatic), 1654, 1431 and 1412 (C=O, amide I, II and III, respectively), 1025 (SO$_2$). ^{1}H-NMR: δ = 9.11 (s, 1H, CONHNH$_2$), 8.40(s, 1 H, 1 NH, D$_2$O exchangeable, amine DL-Ala), 8.15(s, 1 H, 1 NH, D$_2$O exchangeable, amine DL-Phe), 7.95-7.30(12 H, aromatic), 4.81(q, 1H, α CH, DL -Ala), 4.24(s, 2H, CONHNH$_2$), 3.90(t, 1H, α CH, DL-Phe), 3.48(d, 2H, β –CH$_2$, DL-Phe), 1.41(d, 3H, β CH$_3$, DL-Ala). MS: *m/z* (%) = 481 (M^+ + 1, 18.21), 157 (30.15), 91 (82.99), **57** (**100.00**), 55 (98.21), 50 (15.37). Molecular formula (M. wt.): $C_{24}H_{24}N_4O_5S$ (480.5); calculated analysis: C, 59.99; H, 5.03; N, 11.66; S, 6.67; found analysis; C, 59.90; H, 5.03; N, 11.65; S, 6.55.

*General procedure for the synthesis of octahedral complexes of dibenzofuran-2-sulfonyldipeptide derivatives-Cu(II) (**12-15**)*

The following experiments have been utilized in the preparation of copper complexes [21].

Quantitative analysis of the Cu(II) ion complexometric titration

An accurate weight (0.005 g) of the solid complex was placed into 250 mL conical flask; 30 mL of dilute HNO$_3$ was added and evaporated. Then, the solution formed was diluted with pure distilled water and then filtered to remove any precipitated bonds. Ammonium hydroxide was added to neutralize the acidic solution, then diluted, and immediately titrated with (0.01 mol) EDTA solution (muroxide is used as an indicator to determine the endpoint, characterized by the brilliant color change from yellow to purple).

Conductometric titration

In this method (0.0001 mol, 15 mL copper acetate II), the solution was titrated in ethanol using 0.001 mol of ligands (**6-11**) at 25 °C. The previous experiment was repeated, but by taking different volumes of the ligand at different concentrations.

Chromatographic studies and spot reactions

Chromatographic studies of all copper complexes (**12-15**) showed that they were completely homogeneous chromatographically, and it was observed that when they were developed with iodine solution, in the presence of benzidine, they gave a negative ninhydrin test. Moreover, a positive hydroxamate reaction was observed for compounds (**12**, **13**), as well as a positive silver nitrate reaction for compounds (**14**, **15**).

IR spectra

IR spectra of the novel ligands (**6-11**) and their Cu(II) complexes [M:L; 1:1] were recorded. The main characteristic bands of novel ligands (**6-11**) and their Cu(II) complexes showed that there is [OH] hydrogen bonded at 3480–3430 (cm^{-1}) which attributed to the NH stretch and shifted due to the complex formation with Cu(II). Furthermore, from the spectra we found that there are bands at 496 (cm^{-1}) due to the (Cu–O) or the formation of Cu(II) complex.

UV and visible spectra

UV spectra are recorded for the ligands and corresponding complexes (Table 1).

Ninhydrin positive spot

Finally, complete acid hydrolysis for novel compounds using the 6 N HCl solution at 100 °C for 24 hours gave ninhydrin positive spot of the corresponding amino acids and confirmed its structure.

Table 1. UV spectrum for the ligand and corresponding complexes.

Starting compounds		Ligand		Complexes	
Comp.	λ_{max} (nm)	Comp.	λ_{max} (nm)	Comp.	λ_{max} (nm)
1	280 [17]	**6**	282	**12**	693
2	280 [17]	**7**	284	**13**	697
3	282 [17]	**8**	288	**14**	691
4	297 [15]	**9**	286	**15**	711
5	294 [15]	**10**	287		
		11	288		

*General procedure for the synthesis of copper complexes of dibenzofuran-2-sulfonyldipeptide derivatives (**12**, **13**)*

The compounds (**12**, **13**) were prepared from (50 mL ethanol, 0.001 mol copper acetate), added slowly to a solution (0.001 mol of lignins **6-9**) at room temperature with vigorous stirring for 10 min. Then, the reaction mixture was refluxed for 1.5 hours. On cooling, the crude copper complexes were separated out and washed with ethanol. The crude copper complexes (**12**, **13**) were recrystallized from ethanol-water [21].

Dibenzofuran-2-sulfonyl-DL-Phe-β-Ala-Cu(II) (**12**). Yield: 55%; R_f. 0.68, IR (cm^{-1}): ν = 3394 (NH stretching), 3030 (CH, aromatic), 2926 and 2859 cm^{-1} (CH_2, alkane), 1720 (C=O, ester), 1446 and 1337 (C=O, amide I and II, respectively), 1098 (SO_2), 501 [Cu–O, Cu (II)]. -MS: *m/z* (%) = 675 (M^+, 14.55), 576 (49.37), 409 (73.24), **370** (**100.00**), 86 (53.29), 57 (69.33), 55 (51.02). Molecular formula (M.wt.): $C_{27}H_{35}CuN_2O_{12}S$ (675.2). Calculated analysis: C, 48.03; H, 5.22; Cu, 9.41; N, 4.15; S, 4.75; found analysis: C, 47.95; H, 5.15; Cu, 9.38; N, 4.14; S, 4.65.

Dibenzofuran-2-sulfonyl-DL-Phe-DL-Ala-Cu(II) (**13**). Yield: 75%; R_f. 0.71, IR (cm^{-1}): ν = 3926 (NH stretching), 3428 (CH, aromatic), 2995 (CH_3), 2100 (CH, aliphatic), 1656 (C=O, ester), 1433 and 1313 (C=O, amide I and II, respectively), 1031(SO_2), 604 [Cu–O, formation of Cu (II)]. MS: *m/z* (%) = 676 (M^+ + 1, 15.72), 597 (34.42), 60 (57.72), **57** (**100.00**), 55 (84.01). Molecular formula (M.wt.): $C_{27}H_{35}CuN_2O_{12}S$ (675.2). Calculated analysis: C, 48.03; H, 5.22; Cu, 9.41; N, 4.15; S, 4.75; found analysis: C, 48.09; H, 5.28; Cu, 9.46; N, 4.19; S, 4.59.

*General procedure for the synthesis of copper complexes of dibenzofuran-2-sulfonyldipeptide hydrazides (**14**, **15**)*

The compounds (**14**, **15**) were prepared from (0.001 mol copper acetate, 50 mL ethanol) and (0.002 mol of ligands **10, 11**), using the same procedure, previously described in preparing the compounds (**12**, **13**). The crude copper complexes (**14**, **15**) were purified by recrystallization from ethanol-water [20-23].

Dibenzofuran-2-sulfonyl-DL-Phe-β-Ala-NHNH$_2$-Cu(II) (**14**). Yield: 77%; R_f. 0.56, IR (cm^1): ν = 3309 (NH_2, NH, and CH-aromatic), 3069 cm^{-1} (CH_3), 2927 (CH, aliphatic), 2667 (C=O, amide I, II and III), 557 [Cu–O, Cu (II)]. MS: m/z (%) = 689 (M^+, 05.05), 636 (37.92), **621** (**100.00**), 588 (8.55), 67 (4.61), 55 (11.41). Molecular formula (M.wt.), $C_{27}H_{37}CuN_4O_{11}S$ (689.2): calculated analysis: C, 47.05; H, 5.41; Cu, 9.22; N, 8.13; S, 4.65; found analysis: C, 47.08; H, 5.45; Cu, 9.27; N, 8.12; S, 4.62.

Dibenzofuran-2-sulfonyl-DL-Phe-DL-Ala-NHNH$_2$-Cu(II) (**15**). Yield: 71%; R_f. 0.76, IR (cm^{-1}): ν = 3313 (NH_2, NH, and CH-aromatic), 2944 (CH_2-alkane, CH_3 and CH-aliphatic), 2611 and 2494 (C=O, amide I, II and III), 1742 (SO_2), 455 [Cu–O, formation of Cu(II)]. MS: *m/z* (%) = 689 (M^+, 8.02), 571 (30.36), 458 (25.09), **370** (**100.00**), 57 (11.89), 50 (3.80). Molecular formula (M.wt.), $C_{27}H_{37}CuN_4O_{11}S$ (689.2): calculated analysis: C, 47.05; H, 5.41; Cu, 9.22; N, 8.13; S, 4.65; found analysis: C, 47.11; H, 5.42; Cu, 9.23; N, 8.10; S, 4.64.

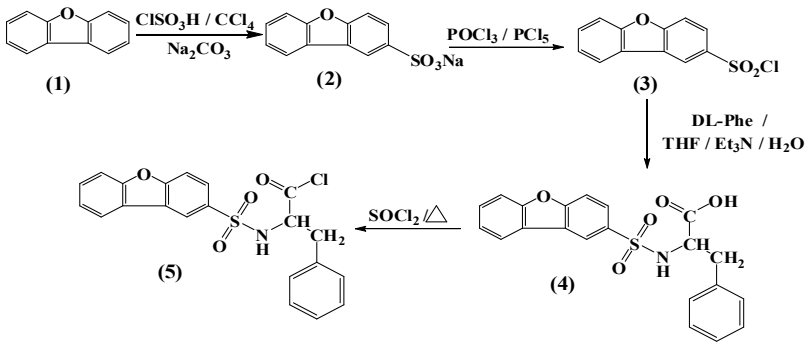
RESULTS AND DISCUSSION

Chemistry

It has been observed throughout recent references that synthetic peptides have distinct biological activity in all different applied directions [24-27]. Previous important studies have been conducted for both dibenzofuran and sulfonamide derivatives, which have reported antimicrobial, pharmacological, and physiological properties [26]. Additionally, in previous research, we found that the combination of dibenzofuran-2-sulfonylchloride and DL-phenylalanine produced an intriguing biologically active compound (**4**). In communication of previous studies, we synthesized some novel amino acid derivatives based on dibenzofuran-2-sulfonyl-DL-phenylalanine, which may be expected to have various antibacterial and antifungal properties [28]. Furthermore, dibenzofuran-2-sulfonyl-DL-phenylalanine is combined with different amino acids; the synthesized compounds contain three active centers: the heterocyclic moiety, sulfonyl group, and amino acid residues. These compounds are expected to have verified or intensified biological and pharmacological properties. Previous investigation of sulfonamides and their derivatives demonstrated that many of these compounds possess antimicrobial activities [28], such as sulfanilamide and its derivatives (e.g., sulfathiazole, sulfapyridine, sulfadiazine, sulfapyrazine, and sulfamethazine). In addition, many sulfonamide derivatives have physiological and pharmacological properties such as sulfaguanidine, sulfisoxazole, and sulfamethizole [29].

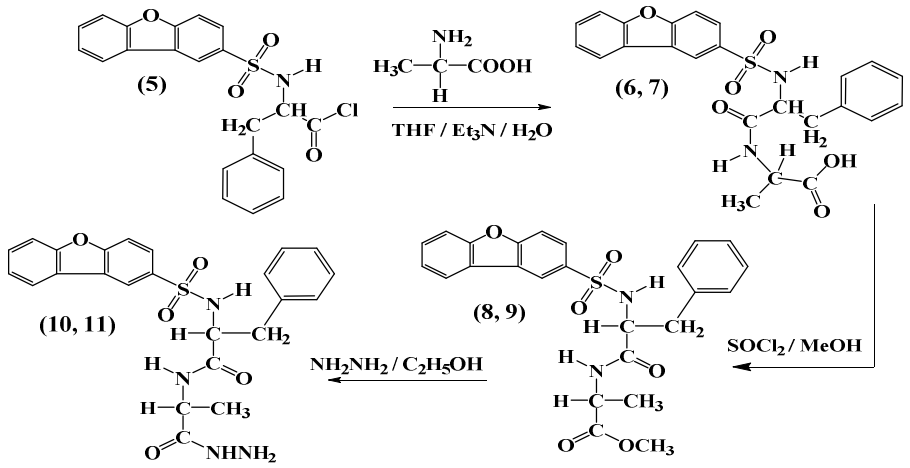
According to the previous distinguished results, the successful rational design and synthesis were conceptualized as well as the purification and then the structural characterization of six new linear peptide derivatives, having the general structure: dibenzofuran-2-sulfonyl-[DL-Phe-Amino Acid]-Y and the corresponding four novel complex compounds, whereas “Amino Acid” stands for β-Ala and DL-Ala amino acid and Y presents carboxylic, methyl ester, or hydrazide group, optimally synthesized, by conventional synthetic different peptide conjugation methods, in solution.

Dibenzofuran-2-sulfonyl-DL-phenylalanyl chloride **(5)** was prepared *via* the reaction with thionyl chloride (Scheme I), by procedures [19].



Scheme I. Synthetic routes for compounds **4** and **5**.

The synthesis of compounds (**6**, **7**) using the same procedure described [19], dibenzofuran-2-sulphonyldipeptide derivatives in acid form, containing β-Ala and DL-Ala amino acid residues (**6**, **7**), was based on dibenzofuran-2-sulfonyl-DL-phenylalanyl chloride (**5**). The treatment of the latter acid chloride (**5**) with β-Ala and DL-Ala in the presence of triethylamine in tetrahydrofuran and water afforded the corresponding dibenzofuran-2-sulphonyl [dipeptide] derivatives (**6**, **7**), respectively. The latter acids (**6**, **7**) were recrystallized from the ethanol-water mixture and obtained in high yields (80, 74%) (Scheme II).



6: dibenzofuran-2-sulfonyl-[DL-Phe-β-Ala]-OH; **7**: dibenzofuran-2-sulfonyl-[DL-Phe-DL-Ala]-OH; **8**: dibenzofuran-2-sulfonyl-[DL-Phe-β-Ala]-Ome; **9**: dibenzofuran-2-sulfonyl-[DL-Phe-DL-Ala]-Ome; **10**: dibenzofuran-2-sulfonyl-[DL-Phe-β-Ala]-$NHNH_2$; **11**: dibenzofuran-2-sulfonyl-[DL-Phe-DL-Ala]-$NHNH_2$

Scheme II. Synthetic routes for compounds (**6-11**).

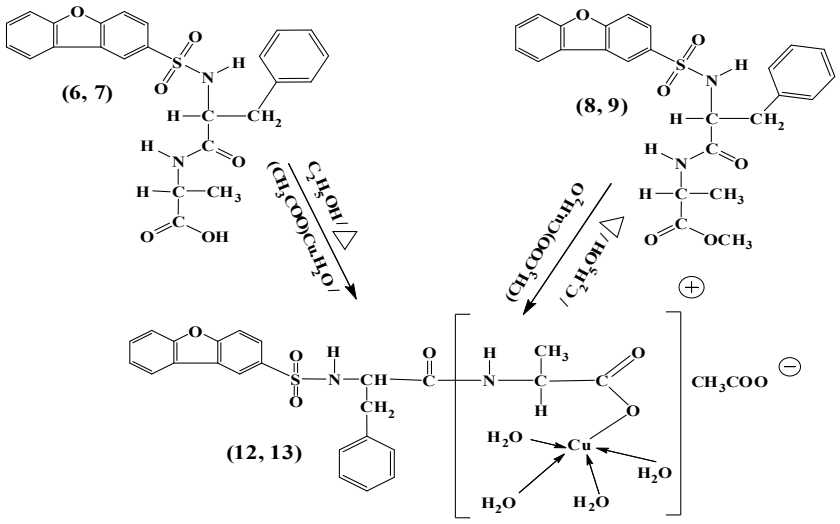
Moreover, compounds (**6**, **7**) were obtained by conjugating compound **(5)** with the desired amino acids in a low concentration of NaOH (1 N) medium containing benzene. The amino acids are dissolved in a solution of 1 N-NaOH and then cooled down to 10 °C, and the solution of

compound (**5**) in benzene is added to it dropwise within 30 min. After the slow addition is completed, the rapid stirring should continue for an additional 3 hours at room temperature. Then, the aqueous layer is separated from the reaction and then acidified with 2 N HCl to pH = 5. Then, the resulting compounds were recrystallized from an ethanol-water solution.

The yields in this method were poor (less than 25%) so we preferred the first method in preparation compounds (**6**, **7**).

We noticed that the esterification of amino acid derivatives affected their antifungal activities [30]. Thus, we synthesized methyl esters of compounds (**8**, **9**) to study the effect of esterification on the biological properties. The compounds (**8**, **9**) were easily prepared by the reaction of dibenzofuran-2-sulphonyl [dipeptide] derivatives (**6**, **7**) with thionyl chloride in methanol to afford the corresponding dibenzofuran-2-sulphonyl [dipeptide] ester derivatives (**8**, **9**), respectively (Scheme II).

In the literature, some hydrazide derivatives were found to be utilized as anti-tubercular drugs [31] and have broad antimicrobial activities [18]. Therefore, various amino acid derivatives were prepared for studying their medicinal properties. Hence, we reported the synthesis of dibenzofuran-2-sulfonyldipeptide hydrazides and studied their biological activities. In addition, compounds (**10**, **11**) were prepared by the hydrazinolysis of (**8**, **9**), respectively, with hydrazine hydrate 99% in methanol, which afforded the corresponding dibenzofuran-2-sulfonyl [dipeptide] hydrazide derivatives (**10**, **11**), respectively (Scheme II).



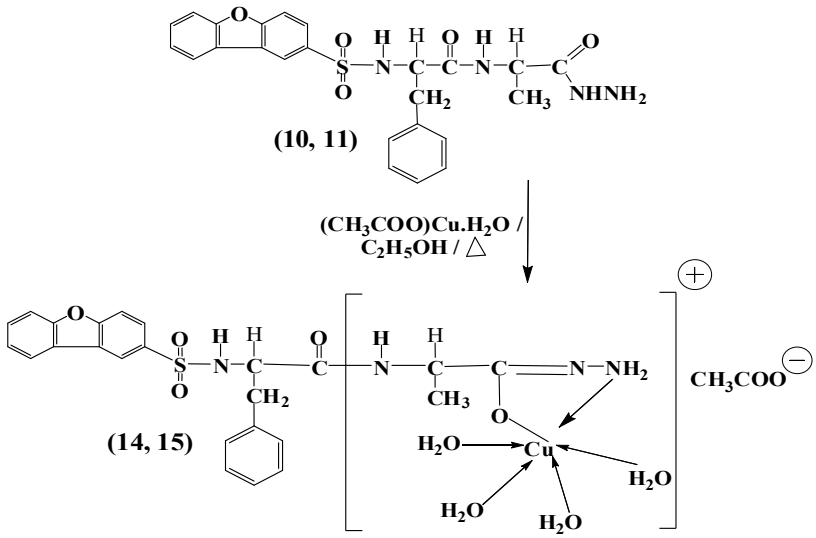
12: Dibenzofuran-2-sulfonyl-[DL-Phe-β-Ala]-Cu (II)
13: Dibenzofuran-2-sulfonyl-[DL-Phe-DL-Ala]-Cu (II)

Scheme III. Synthetic routes for dibenzofuran-2-sulfonyl dipeptide-Cu(II) derivatives (**12**, **13**).

*Synthesis of copper complexes dibenzofuran-2-sulfonyldipeptides, corresponding methyl esters, and hydrazides (**12**, **15**)*

The complexes (**12**, **15**) were prepared by adding a solution of copper acetate in equal molar ratios (1:1 molar ratio) to the alcohol solution of the ligands (**6**-**11**), and the mixture was heated for 30

min. On cooling, the desired crude compounds were obtained and then purified by recrystallization from solution of ethanol and water. The complexes (**12-15**) were obtained in (55–71%) yields (Schemes III and IV). Copper was determined in all complexes (**12-15**) by complex metrical titration, indicating that the ratio of copper to the ligand in the complexes is 1:1 molar ratio. The titration of all complexes (**12-15**) showed one break at curves which happened at certain species in solution, indicating 1:1 [copper (M): ligand (L)] complexes. From the above results, we can conclude that the proposed structure of novel complexes is octahedral.



14: Dibenzofuran-2-sulfonyl-[DL-Phe-β-Ala]-Cu(II)
15: Dibenzofuran-2-sulfonyl-[DL-Phe-DL-Ala]-Cu(II)

Scheme IV. Synthetic routes for dibenzofuran-2-sulfonyl dipeptide hydrazides-Cu(II) (**14**, **15**).

CONCLUSIONS

In the light of the interesting biological activity a new series of dipeptide candidates (**6-11**) and their corresponding octahedral copper complexes (**12-15**) were prepared. In this study, we improved the yield of some intermediates. On the other hand, the peptide derivatives that were prepared in high percentage, dibenzofuran-2-sulfonyl-DL-Phe-β-Ala-$NHNH_2$-Cu(II) (**14,** 77%); dibenzofuran-2-sulfonyl-DL-Phe-β-Ala-OMe (**8**, 82%), dibenzofuran-2-sulfonyl-DL-Phe-β-Ala (**6**, 80%). The structure features of the synthesized compounds simulate our interest to the evaluation of their antimicrobial activity which showed very promising results. The latter results need further investigations in the future for the lead potent compounds to as possible antimicrobial drugs.

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Conflicts of interest

The authors declare no conflicts of interest.

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