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Microwave-Assisted Synthesis, Characterization, and Biological Activity of New Copper (II) Complex with Sulfonamide †

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Abstract: A fast and efficient synthesis was carried out to obtain a new derivative of an organometallic complex. This synthesis involved the complexation of a sulfonamide derived from phenylpiperazine with copper (II). The synthesis of this complex was achieved using an innovative and environmentally friendly method that used microwave irradiation as the energy source. The resulting complex was obtained as a green powder with a yield of 82%. The identification of the final compound was performed through infrared spectroscopy, UV-Visible spectroscopy, elemental analysis, and cyclic voltammetry. The obtained complex exhibited noteworthy activity against the tested bacterial and fungal strains. Regarding the anti-inflammatory activity, the highest percentage of inhibition of BSA denaturation (0.2%) was recorded in the fraction at a concentration of 5000 ppm, which was 67.32%.

Keywords: sulfonamide; microwave; complex; copper (II); UV-Visible

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1. Introduction

Sulfonamides and their derivatives constitute one of the families of biologically active molecules. They have broad applications in both human and veterinary medicine [1]. They have been employed as antimicrobial [2], antifungal, antimalarial, and anticancer agents [3], as well as carbonic anhydrase inhibitors, whether in the form of diuretics or hypoglycemic reagents [4–6].

In recent years, in addition to the significance of free molecules, there has been increased focus on the development of their metal and organometallic complexes [7]. In particular, copper complexes of sulfonamides have been proven to be effective topical antimicrobial agents, and they are also used in the treatment of burns [8].

Furthermore, several series of homoleptic and heteroleptic compounds of copper (II) have been investigated to illustrate the importance of coordination sites [9]. Research conducted into sulfonamide complexes containing Zn (II), Cu (II), Ni (II), Ce (III), Bi (III), Cd (II), Hg (II), Sm(III), and UO_2(II) has highlighted the versatility of sulfamides as ligands, underscoring the significance of their complexes for use in coordination chemistry and medicinal chemistry [10–13].

2. Materials and Methods

2.1. General Procedure for the Synthesis of the Complex

In a glass tube (diameter: 25 mm; thickness: 1 mm; volume: 20 cm^3), we introduced 2 equivalents of the ligand (**1**) and 1 equivalent of the metal ($CuCl_2$, $2H_2O$) in 3 mL of ethanol. The mixture was subjected to microwave irradiation at a frequency of 250 Hz

for 3 min. This resulted in a noticeable change in color, with the formation of a green precipitate. Subsequently, the reaction mixture was filtered, and the obtained solid was washed with diethyl ether.

IR (KBr): ν = 3377.91 (NH_2); 1339.98 and 1183.98 (SO_2) cm^{-1}.
Anal. Calc. for [Cu($C_{10}H_{15}N_3$**O_2S)$_2$**;2Cl]: C, 38.93; H, 4.90; N, 13.62; Cu, 10.30; Cl, 11.49; Found: C, 40.98; H, 5.54; N, 14.40; Cu, 11.63; Cl, 12.03.

2.2. Anti-Inflammatory Activity

The in vitro anti-inflammatory activity of molecule was accomplished using the Bovine Serum Albumin Protein Denaturation Assay (BSA) [14], albeit with some modifications (voltarene 75 mg). BSA solution (0.2%) prepared in Tris Buffered (pH 6.8) was added. The samples were incubated in the oven at 37 °C for 15 min and then immersed in a water bath at 72 °C for 5 min. After cooling the tubes, the turbidity (level of protein precipitation) was measured at 660 nm using a spectrophotometer, and the percentage inhibition of the denaturation of the proteins was calculated using the following equation:

$$\% \, I = ((Control - sample - White)/Control) \times 100$$

- Sample: 0.5 mL extract + 0.5 mL BSA.
- White: 0.5 mL extract + 0.5 mL Tris-phosphate (pH: 6.8).
- Control: 0.5 H_2O + 0.5 mL BSA. The control represents 100% of the denatured proteins, and the results are compared to 75 mg of voltarene.

2.3. Antimicrobial Activity Test

The in vitro evaluation of antimicrobial activity was carried out via the disk diffusion technique against seven different Gram-positive and Gram-negative bacterial strains and different yeasts of the genus Candida: *Staphylococcus aureus*, *Streptococcus* sp., *Acinetobacterbaumannii*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Candida* sp. Antimicrobial activity was determined using the method of Benzaid et al. [15], albeit with some modifications.

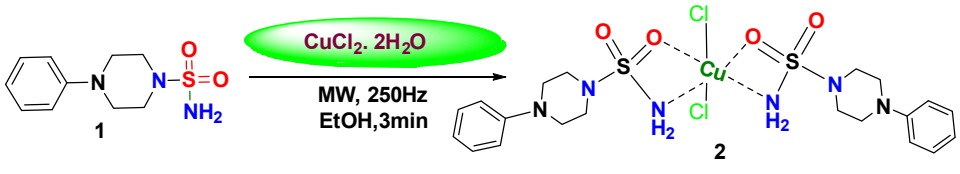
Ampicillin was used as a negative control for bacteria, and amphotericin B was used as a negative control for yeast, while dimethyl sulfoxide (DMSO) was also used as a negative control. The plates were incubated at 37 °C for 24 h.

The antimicrobial activity of the synthesized compounds was determined by measuring the diameter inhibition zone of the sample.

3. Results and Discussion

3.1. Synthesis

The complex was synthesized by combining two equivalents of sulfonamide and one equivalent of $CuCl_2 \cdot 2H_2O$ in a small quantity of ethanol in a reaction tube. The reaction mixture was then subjected to microwave (MW) irradiation for a period of 3 min. The progression of the reaction was monitored via thin-layer chromatography (TLC), which indicated the emergence of a new, less polar product in comparison to the initial sulfonamide. The desired complex subsequently precipitated as a green powder. The reaction mixture was filtered, and the product was collected, producing an 82% overall yield (Scheme 1).



Scheme 1. Synthesis of complex **2**.

The structure of the synthesized compound is confirmed via elemental analysis, as well as via IR, UV-VIS and cyclic voltammetry.

The IR spectra provide information regarding the nature of the functional group attached to the metal atom. The IR spectra show a band of average intensity attributed to (SO_2) (Figure 1). This band is shifted toward a higher frequency (1339.98–1183.98 cm^{-1}). Furthermore, we notice the movement of a band toward (3377.91 cm^{-1}) based on (NH_2).

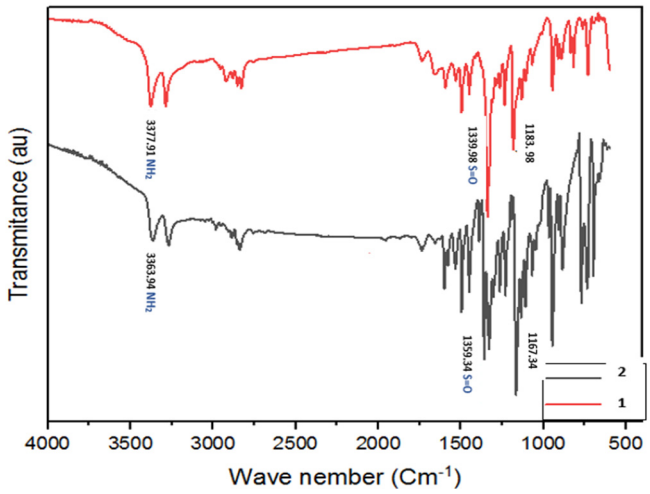


Figure 1. IR spectra of ligand **1** and complex **2**.

The electronic spectra of the ligand and the Cu (II) complex were recorded in EtOH, and the results are respectively presented in (Figure 2). In the UV spectrum, bands in the 230–300 nm range are associated with the intra-ligand $\pi \rightarrow \pi^*$ transition. In the spectrum of the complex, these bands shifted between 220 and 260 nm, which is due to intra-ligand transitions $\pi \rightarrow \pi^*$. Additionally, the spectrum of complex **2** indicates a band in the 400–470 nm regions, which is assigned to the ligand–metal charge transfer transition (Table 1).

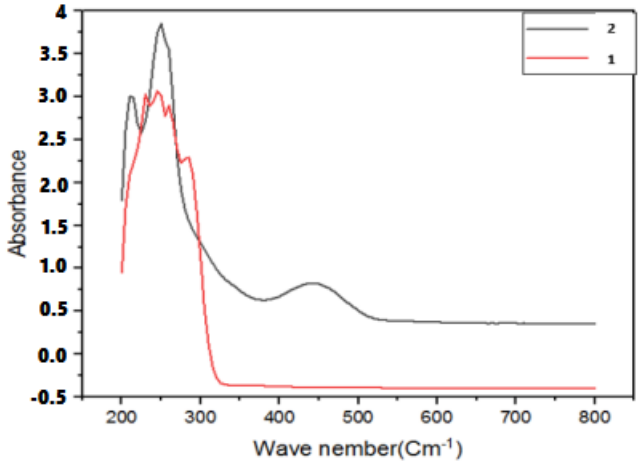


Figure 2. UV-Vis spectrum of final compound.

Table 1. Electronic absorption spectra data of complex **2** and its ligand.

Compound	λ (nm)	Electronic Transitions
Ligand	230	$\pi \rightarrow \pi^*$
	300	$\pi \rightarrow \pi^*$
Complex	220–260	$\pi \rightarrow \pi^*$
	400–470	charge transfer

* anti-bonding molecular orbital.

We observed that all compounds examined were electroactive (Figure 3). In addition, we observed similar results for the ligand **1** and its complex **2**, for which increasing the scan speed increases the strength of the oxidation and reduction peaks, indicating that the ligand and the complex are stabilized.

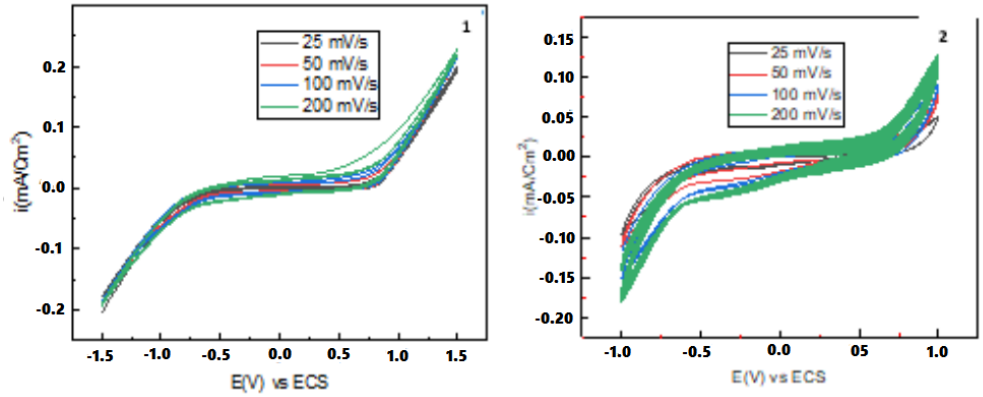


Figure 3. Cyclic voltammetry spectra of final compound for different scan speeds, ranging from 25 mV/s to 400 mV/s.

3.2. Anti-Inflammatory Activity

Table 1 shows the results of the in vitro anti-inflammatory activity of the complex **2**. We note that the percentage inhibition of the denaturation of BSA (0.2%) is proportional to the concentration to molecule tested, where the highest percentage was recorded in the fraction at the 5000 ppm concentration, which was 67.32%. However, these values are interesting compared to those obtained for voltarene (75 mg) when used as a standard; it is an anti-inflammatory medication, and it completely prevented the denaturation of BSA at the same concentration (Table 2).

Table 2. Effect of the molecule on albumin denaturation.

PPM	**%Inhibition**	
	Molecule	Voltarene (75 mg)
5000	67.32	100
1500	31.09	90
1250	18.98	58
625	5.76	30

3.3. Antimicrobial Activity

Our new complex has been evaluated for its antimicrobial activity and against Gram-negative and Gram-positive bacteria, and the *Candida* spices results are shown in Table 3.

Table 3. The diameter zone inhibition of the tested compound.

Compounds	***S. aureus***	***Streptococcus* sp.**	***A. baumannii***	***K. pneumonaie***	***E. coli***	***P. aeruginosa***	***C. albicans***	***Candida* sp.**
BRC	12	8	R	24	R	R	33	41
Ampicillin	R	R	128	**64**	R	32	32	32
Amphoterin b	R	R	R	**R**	R	R	-	-

The compound showed interesting activity against the tested bacterial and fungal strains. These results suggest that the compound may be a better option for therapeutic investigation compared to other options.

4. Conclusions

In summary, a straightforward and environmentally friendly synthetic method was employed to synthesize a new sulfonamide complex using microwave irradiation. The described reaction offers several advantages, including mild reaction conditions, short reaction times, high yields, simplicity, and a reduced environmental impact, compared to conventional heating methods. The compound displayed significant activity against the tested bacterial and fungal strains. The percentage inhibition of BSA denaturation (0.2%) is particularly noteworthy compared to the values obtained for voltarene (75 mg).

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Conflicts of Interest: The authors declare that there is no conflict of interest.

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