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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 involved 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, 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, with 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 find broad applications in both human and veterinary medicine [1]. They have been employed as antimicrobial agents [2], antifungals, antimalarials, 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 an increased focus on the development of their metal and organometallic complexes [7]. In particular, copper complexes of sulfonamides have proven to be effective topical antimicrobial agents and 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 on sulfonamide complexes containing Zn (II), Cu (II), Ni (II), Ce (III), Bi (III), Cd (II), Hg (II), Sm(III) et UO_2(II) has highlighted the versatility of sulfamides as ligands, underscoring the significance of their complexes in coordination chemistry and medicinal chemistry [10–14].

2. Materials and Methods

2.1. General Procedure for the Synthesis of Complex

In a glass tube (diameter: 25 mm; thickness: 1 mm; volume: 20 cm^3), we introduced 2 equivalents of the ligand (**1**) and one 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**); 1339.98–1183.98 (**SO_2**) cm^{-1}.
Anal. Calc. for [$Cu(C_{10}H_{15}N_3O_2S)_2$;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) [15] 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 in a spectrophotometer and the percentage inhibition of 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 with 75 mg voltarene.

2.3. Antimicrobial Activity Test

The in vitro evaluation of antimicrobial activity was carried out by the disk diffusion technique against seven different gram-positive and gram-negative bacterial strains and three 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. [16] with some modifications.

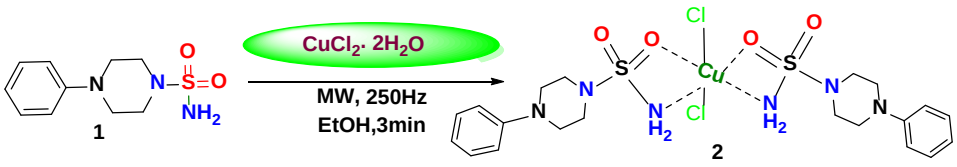
Ampicillin was used as a negative control for bacteria and amphotericin B for yeast, and dimethyl sulfoxide (DMSO) was used as a negative control. The plates were incubated at 37 °C for 24 h.

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 small quantity of ethanol in a reaction tube. The reaction mixture was then subjected to microwave (MW) irradiation for a duration of 3 min. The progression of the reaction was monitored by 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, yielding an 82% over all yield (Scheme 1).



Scheme 1. Synthesis of complex 2.

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

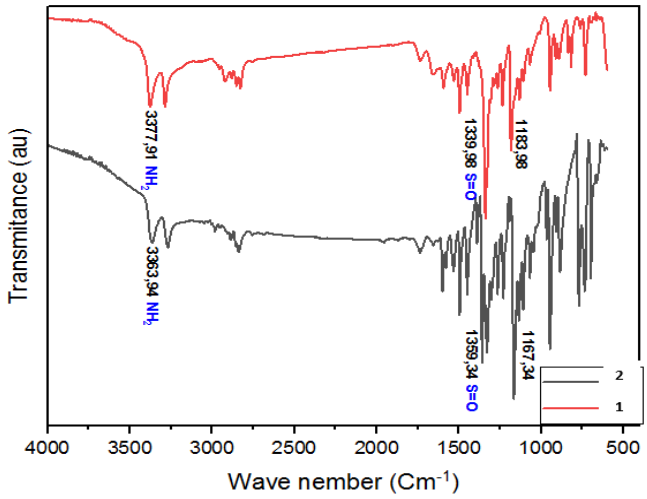


Figure 1. IR Spectrum of ligand **1** and complex **2**.

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). This band is shifted to a higher frequency (1339.98–1183.98 cm^{-1}). Furthermore, we can notice the movement of a band towards (3377.91cm^{-1}) according to (NH_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 can be associated with the intraligand $\pi \rightarrow \pi^*$ transition. In the spectrum of the complex, these bands are shifted between 220 and 260 nm, which is due to intraligand 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).

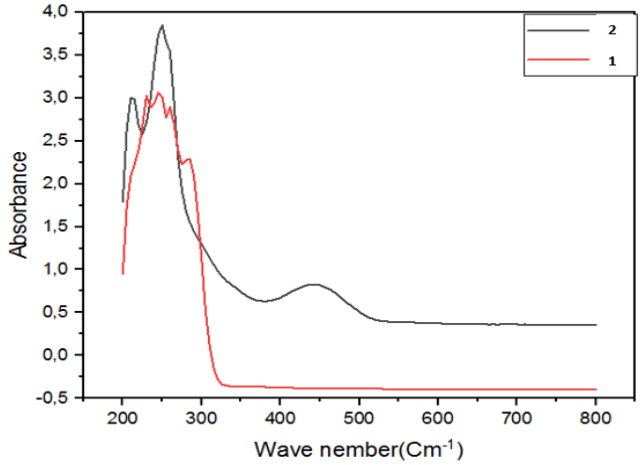


Figure 2. UV-Vis Spectrum of final compound.

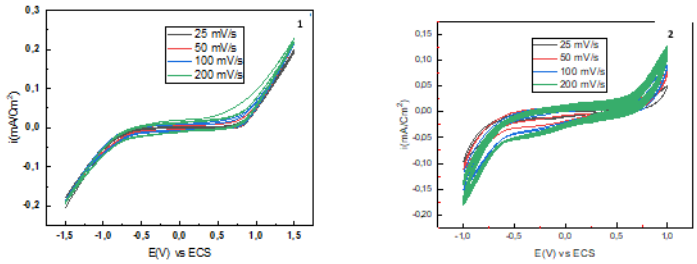


Figure 3. Cyclic voltammetry spectrum of final compound to different scan speeds from 25 mV/s to 400 mV/s.

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

Compound	λ (nm)	Electronic Transitions
Ligand	230	π→π *
	300	π→π *
Complex	220–260	π→π *
	400–470	charge transfer

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

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 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, with 67.32%. However, these values are interesting compared to those obtained for Voltaren (75 mg), used as a standard; an anti-inflammatory medication, and it's 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/positive bacteria and 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 tested bacterial and fungal strains. These results suggest that the compound may be a better option for therapeutic investigation among others.

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 when compared to conventional heating methods. The compound displayed significant activity against the tested bacterial and fungal strains. The percentage of inhibition of BSA denaturation (0.2%) is particularly noteworthy when compared to the values obtained for Voltaren (75 mg).

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

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