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Exploring novel metallopharmaceuticals candidates: synthesis and biological studies of a copper(II) complex with ethylmafenide Schiff Base

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Bacterial infections are a global public health case of concern due to their high prevalence and the challenges posed by inadequate treatment or by the emergence of multidrug-resistant strains[1]. Simultaneously, research into alternatives for treating skin tumours is increasing, as the primary treatment—surgical resection—often results in significant mutilation of patients[2]. One promising strategy in the search for new antibacterial and/or antitumor species is the synthesis of metallopharmaceutical agents[3]. Such compounds combine metal ions with well-established biological activities, such as copper and silver, with organic ligands that may have known biological properties.

In this study, ethylmafenide, structurally analogous to mafenide (the active ingredient of the antibacterial drug Sulfamylon®), was selected for the synthesis of a novel Schiff Base (SB) with salicylaldehyde, which was further applied in the synthesis of a new Cu(II) complex. The SB was synthesized by the reaction of (1:1,1) ethylmafenide and salicylaldehyde in acidic medium via reflux in methanol, for 3 hours, leading to bright yellow crystals with a yield of 97.3%. The Cu(II) complex was then synthesized using the (1:1:1) ethylmafenide/salicylaldehyde SB crystals, copper nitrate and potassium hydroxide in methanol, under stirring and at room temperature for 2 hours. Dark-green crystals of the complex with a yield of 36.5% were obtained. The Schiff base and the complex were characterized by elemental analysis, FT-IR and single crystal X-ray diffraction. Elemental analysis indicated the composition $C_{15}H_{16}N_2O_3$ for the SB, while for the complex the composition $CuC_{30}H_{30}N_4O_6$ was obtained. The complex consists of one Cu(II) atom coordinated by two SB molecule. FT-IR analysis indicated two coordination sites of SB to Cu(II): one on the hydroxyl group and the other on the imine group of the SB. Single crystal X-ray diffraction studies confirmed coordination sites of the SB to copper(II) and revealed the formation of a square-planar geometry around Cu(II) as Figure 1. Both SB and the complex were able to inhibit the growth of Gram-positive (*S. aureus* and *B. cereus*) and Gram-negative (*E. coli* and *P. aeruginosa*) bacterial strains, with a minimal inhibitory concentration (MIC) of 2.25 mg·mL^{-1}.

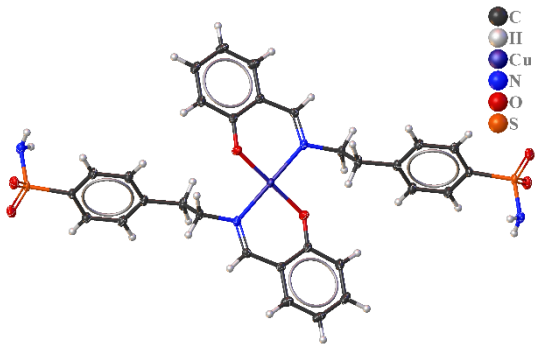

Figure 1 *Crystal structure for the Cu(II) complex with ethyl-mafenide/salicylaldehyde Schiff base*

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