Promising Antifungal Activity of Novel Copper (II) Complexes Containing Ligands Derived from Azoles and Coumarins Against Fluconazole-Tolerant *Cryptococcus* strains

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Cryptococcosis, a neglected fungal disease caused by *Cryptococcus neoformans* and *C. gattii*, imposes a considerable global health burden, particularly among immunosuppressed individuals such as those living with HIV. Current therapeutic options—mainly amphotericin B, fluconazole, and 5-flucytosine—often induce adverse effects including electrolyte imbalances and nephrotoxicity, which restrict their clinical use. Furthermore, the emergence of azole-resistant strains aggravates this challenge, highlighting the urgent need for new antifungal compounds. This study evaluated the antifungal potential of five novel coumarin-derived azole copper (II) complexes (C1–C5) against *C. neoformans* strains with different fluconazole susceptibility profiles. The minimal inhibitory concentration (MIC) and minimal fungicidal concentration (MFC) were determined for *C. neoformans* H99 (reference strain), T1 and 89-610 (fluconazole-tolerant), and *C. gattii* NIH198, following the Clinical and Laboratory Standards Institute (CLSI) M27-A3 guidelines. Growth kinetics were analyzed at 30 °C in YPD medium using the most active compounds. Cytotoxicity on human keratinocytes (HaCaT) and red blood cells was assessed through MTT and hemolysis assays, respectively. All *C. neoformans* strains were susceptible to the complexes (MICs: 3.7–68 μM). C2 and C3 showed the strongest antifungal activity, with MIC values lower than those of fluconazole and minimal cytotoxicity toward HaCaT cells (selectivity index: 6.4–25.7). Neither compound exhibited hemolytic activity. *C. gattii* was less susceptible (MICs: 51–136 μM) than *C. neoformans*. Notably, all compounds displayed fungicidal properties, underscoring the enhanced antifungal potential of these coumarin-based azole–copper (II) complexes. Overall, copper (II) complexes may represent promising candidates for the development of new therapeutic alternatives against cryptococcal infections.

Keywords: Drug resistance, fungal; Metallodrugs; Cryptococcosis; Drug discovery; Pyrazoles.