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Abstract

Synthesis, Anticandidal Activity and Molecular Docking Study of Some New Imidazole Derivatives †

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The azole pharmacophore is still regarded as a viable lead structure for the synthesis of more effective antifungal agents [1–3]. In this study, new 2-substituted-*N*-[4-(1*H*-imidazole-1-yl) phenyl] acetamide (**5a–5g, 6a–6n**) derivatives were synthesized and the antifungal activities of these compounds were evaluated. The synthesized compounds consisted of two novel series of imidazole derivatives containing dithiocarbamate (**5a–5g**) and (benz) azolethiol (**6a–6n**) side chains that are structurally related to the famous antifungal azole pharmacophore. Their structures were characterized by spectral (IR, ^{1}H NMR, ^{13}C NMR, and MS spectra) analyses. The synthesized compounds were screened for in vitro antifungal activity against pathogenic strains of fungi. Theoretical ADME predictions were calculated for final compounds. A molecular docking study of the most active compound with target 'lanosterol 14α-demethylase' (CYP51) [4] was performed to unravel the mode of antifungal action.

Compound **5e**, which features imidazole and 4-methoxybenzyl piperazine scaffolds, showed the most promising antifungal activity with a MIC_{50} value of 0.78 ug/mL against *Candida krusei*. The effect of the compound **5e** against ergosterol biosynthesis was observed by the LC-MS-MS method, which is based on quantification of the ergosterol level in *C. krusei*. Significant interactions were also observed between compound **5e** and 14-α-sterol demethylase. In addition to good antifungal activity, all compounds in the series exhibited a good predicted pharmacokinetics profile.

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