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-(1H-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 antifungalazole pharmacophore. Their structures were characterized by spectral (IR, 1H NMR, 13C 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 MIC50 value of 0.78 μg/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 14α-sterol demethylase. In addition to good antifungal activity, all compounds in the series exhibited a good predicted pharmacokinetics profile.

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References
