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Synthesis and docking studies of novel antifungals based on 4-substituted imidazole

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Background and Aims: Fungal infection is one of the most important causes of life-threatening in immunocompromised patients. In clinic, azoles are the most widely used antifungal agents because of they have high therapeutic index and can be administered orally. However, their clinical value has limited by their relatively high risk of toxicity and the emerging of drug resistance. This situation has led to an ongoing search for new azoles. In this research, a two series (amine and imine) of new azole based on 4-substituted imidazole were designed and synthetized. Moreover, all of the compounds were docked into the active site of CYP51.
Methods: The chemical structures of azoles were constructed using Hyperchem software. The global minimum conformers were considered in docking calculations, performed using Autodock software. The designed imine derivatives were synthesized by condensation of the respective aromatic amine with imidazolecarboxaldehyde in methanol at reflux temperature. Then, Purification was performed by column chromatography. The amine series were prepared by reduction of imine using NaBH4 at the room temperature. The solvent was removed, and the residue was dissolved in water and filtered. The filtrate was extracted with dichlomethane. The organic layer was washed with water, dried (Na2SO4), and evaporated to give desired compounds.
Results: 18 derivatives of 4-substituted imidazole analogs were synthesized in good yields (45-79 %). All of compounds were characterized by TLC followed by IR and proton NMR. Docking studies revealed all of compounds were interacted with the 14-α-demethylase.
Conclusions: Our docking studies revealed in this type of azole in which both of nitrogen of imidazole ring is unsubstituted, there is a good drug-receptor interaction profile. We suggest these newly synthetized ligands are very potent, so their ability to protect against fungal infections in vitro is under investigation.

Keywords: Azoles; Lanosterol 14-α demethylase (CYP51); Rational design and molecular docking; Antifungal agents