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Design and synthesis of 4-substituted azoles and prediction of their binding to 14α-demethylase using molecular docking

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Background and Aims: Fungal infections are a major burden to the health and welfare of modern humans. They range from simply cosmetic, non-life-threatening skin infections to severe systemic infections that may lead to significant debilitation or death. This situation has been led to an ongoing search for new selective and potent azoles. Imidazoles and triazoles are clinically useful in the treatment of systemic fungal infections as well as in agriculture. In this study, two new series of imidazole derivatives in which both of nitrogen of imidazole are un-substituted have been docked and synthesized in order to achieve the better antifungal activity.
Methods: The method used for the preparation of imines derived from 4-imidazole carbaldehyde and six primary amines consists by stirring both reagents in absolute methanol in the presence of molecular sieves. The imines were reduced using $NaBH_4$ at the room temperature .Thin layer chromatography was used to monitoring the progress of the reactions and determining the purity of the products. Various purification methods such as extraction, chromatography and recrystallization were used. The chemical structures of azoles were constructed using Hyperchem software. Semi-empirical molecular orbital calculations (PM3) of the structure were performed and among all energy-minimal conformers, the global minimum compounds were considered in docking calculations by using Auto-dock software (version 4.2).
Results: 12 derivatives were synthesized in good yields (50-60%). All compounds characterized by TLC followed by IR and proton NMR. Docking studies revealed all of compounds interact with the 14-alpha-demethylase and azole-heme coordination, pi-pi and pi-cation interactions are involved in drug-receptor interaction.
Conclusions: Our docking studies revealed azole in which both of nitrogen of imidazole ring is un-substituted, has a good drug-receptor interaction profile.We suggest these newly synthesized ligands are very potent, so their ability to protect against fungal infections in-vitro is under investigation.

Keywords: Imidazole; 14α-demethylase; Docking