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PROCEEDINGS ABSTRACT

Study of a novel series of 1,2,4-triazole derivatives: synthesis, spectroscopic characterization, and *in silico* assessment as antifungal substances

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Invasive fungal infections pose a major global health issue, especially those arising from drug-resistant *Candida* species, highlighting the need for an ongoing creation of new antifungal medications. This study focuses on the development, formulation, and computational analysis of a novel series of eight 1,2,4-triazole derivatives (D1, D2, E–J) as potential antifungal agents targeting cytochrome P450 14α-demethylase (CYP51). The synthetic method utilized a multi-stage process that started with the Fischer esterification of a derivative of a carboxylic acid and ethanol, resulting in the formation of the corresponding ester. Next, hydrazide was produced by reacting with hydrazine hydrate. Following nucleophilic addition with aryl isothiocyanate produced intermediates (C1 and C2), while the base-promoted cyclization of these intermediates yielded the core 1,2,4-triazole-5(4H)-thione frameworks (D1 and D2). The last step consisted of alkylating the thione's sulfur atom with a range of alkylating agents such as iodoethane, phenacyl bromide derivatives, butyl iodide, and ethyl bromo acetate, yielding a varied collection of target compounds (E–J). All synthesized compounds were analysed and structurally verified through Fourier transform infrared (FTIR), proton nuclear magnetic resonance (^{1}H-NMR), and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy. FTIR spectroscopy demonstrated the disappearance of the carbonyl band after cyclization and the forming of compounds D1 and D2, the appearance of C=N stretching around 1608 cm^{-1}, a distinct carbonyl absorption at 1703 cm^{-1} for compound F, and ester-related peaks at 1663 cm^{-1} and 1259 cm^{-1} in the case of compound I. The spectroscopic data validated the successful creation of all intermediates and final products by displaying characteristic absorption bands and chemical shifts that align with the suggested structures. Molecular docking analyses on the CYP51 enzyme (a recognized target for azole antifungal drugs) were also performed through the use of the Molecular Operating Environment software. The docking analysis revealed several of the synthesized compounds to be demonstrating encouraging binding affinities that were similar to those of the reference drug (fluconazole). Throughout the series, the binding energies were advantageous, with two compounds exhibiting the most favourable ones: (i) compound F and (ii) compound I. An in-depth examination of the protein–ligand interactions revealed that the lead compound can establish several hydrogen bonds with active site residues such as threonine and serine, along with many hydrophobic interactions with alanine, leucine, proline, tyrosine, isoleucine, valine, lysine, and cysteine residues. A different promising compound can form an essential hydrogen bond with a cysteine residue, along with hydrophobic interactions and a pi–

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sulphur interaction involving phenylalanine. These interaction patterns suggest a consistent binding within the enzyme's active site. Subsequently, the compounds' ADME (absorption, distribution, metabolism, and excretion) characteristics were forecasted in order to evaluate their drug-likeness. The majority of the derivatives exhibited advantageous physicochemical characteristics, such as suitable molecular weights, counts of hydrogen bond donors and acceptors, and topological polar surface areas within acceptable limits. Most of the compounds exhibited significant gastrointestinal absorption and positive bioavailability ratings, but none of them demonstrated an ability to cross the blood-brain barrier. The majority of compounds adhered to standard drug-likeness criteria, while one of the compounds deviated because of its elevated molecular weight. Consensus log P values reflected significant lipophilicity for all compounds, thereby indicating favourable membrane permeability and potential for tissue distribution.

Keywords

antifungal agents; CYP51 inhibition; molecular docking; synthesis; 1,2,4-triazole

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Conflicts of interest statement

None to declare.

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