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PROCEEDINGS ABSTRACT

Study of a novel series of compounds deriving from the 4-(4-chlorophenyl) cyclohexane-1-carboxylic acid: synthesis, spectroscopic characterization, and computational targeting of the CYP51 enzyme

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Heterocyclic compounds constitute a fundamental aspect of medicinal chemistry, with nitrogen-containing heterocycles being particularly important for drug discovery and development processes. Amongst these, the 1,2,4-triazole ring structure is a favoured framework due to the variety of its biological effects and its capacity to establish numerous non-covalent interactions with biological targets. The increasing occurrence of fungal infections and the development of resistance to current antifungal treatments highlight the critical demand for new therapeutic options. The aim of this study was to synthesise and to analyse a novel series of four 1,2,4-triazole derivatives (namely, compounds 5, 5a, 5b, and 5c), as well as to assess their antifungal activity potential. To this end, we have used molecular docking and *in silico* ADMET (absorption, distribution, metabolism, excretion, and toxicity) analysis in order to target the fungal cytochrome P450 14α-demethylase (CYP51). The synthesis began with the Fischer esterification of 4-(4-chlorophenyl) cyclohexane-1-carboxylic acid, followed by the formation of hydrazides, the preparation of the thiosemicarbazide intermediate compound 4, and its subsequent cyclisation leading to the production of the triazole core structure (compound 5). The last step included an *S*-alkylation with different alkylating agents so as to produce three unique derivatives (compounds 5a–5c). All compounds were analysed through the use of Fourier-transform infrared (FTIR) and proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy, thereby verifying the successful creation of the intended structures with the identification of the distinctive spectral characteristics of the triazole ring system and of the added functional groups. The computational assessment of these new 1,2,4-triazole derivatives as prospective antifungal agents focused on the fungal CYP51; a critical target (enzyme) in the ergosterol biosynthesis process. Molecular docking analyses were undertaken on the fungal CYP51 in order to assess the binding affinities and modes of the four synthesized compounds. The docking findings have indicated that all four compounds can effectively fit into the enzyme's active site, forming multiple interactions with essential amino acid residues. The primary binding interactions comprised pi–alkyl, pi–sulphur, and alkyl interactions with important residues such as LYS_{151}, TYR_{140}, HIS_{468}, PHE_{463}, and CYS_{470}. Moreover, the binding affinities of the newly synthesized compounds were found to be similar to that of fluconazole (i.e., the reference antifungal medi-

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cation), thereby suggesting a potential antifungal effect through the inhibition of CYP51. Compound 5c exhibited particularly notable binding properties, displaying extensive interactions within the CYP51 active site with a binding affinity of -10.1 kcal/mol. *In silico* ADMET assessments were performed through the use of the SwissADME tool in order to assess the drug-likeness and the pharmacokinetic properties of the synthesized compounds. All of the herein assessed compounds adhered to Lipinski's rule of five, thereby indicating that they possess favourable physicochemical traits for oral bioavailability. In fact, the compounds exhibited suitable topological polar surface area values and high bioavailability scores, revealing a promising potential for oral absorption. Interestingly, while most compounds were expected to be found to be suitable substrates for P-glycoprotein efflux transporters with generally low gastrointestinal absorption, compound 5 exhibited high gastrointestinal absorption. Finally, none of the herein assessed compounds is expected to be able to penetrate the blood–brain barrier, suggesting a lower risk of central nervous system-associated side effects. The promise of these novel 1,2,4-triazole derivatives as viable candidates for antifungal drug development is supported by the aforementioned computational findings; however, the undertaking of *in vitro* and *in vivo* studies is required in order to confirm their therapeutic efficacy and safety profiles.

Keywords

antifungal agents; CYP51 inhibition; heterocyclic compounds; Lipinski's rule of five; SwissADME

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Conflicts of interest statement

None to declare.

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