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IN SILICO PHARMACOKINETIC PREDICTION OF NOVEL THIAZOLIDINE-2,4-DIONE THIAZOLE DERIVATIVES

Pedro C. Souza (PG)[1,3], Thaynara P. W. Bezerra (PG)[1,3], José A. S. Moura (PG)[1,3], Isabella L. R. Oliveira (Res)[1,2,3], Maria Isabela Ferreira de Araújo (Res)[1,2,3], Paulo A. T. M. Gomes (Res)[1,3], Michelle M. Rosa (Prof)[1,2,3], Marina G. R. Pitta (Res)[1,3], Maira G. R. Pitta (Prof)[1,2,3], Moacyr J. B. Melo (Prof).[1,2,3,*]

Categories: Professor (Prof), Researcher (Res), Post-Graduation student (PG), Undergraduate student (G), Technical student or professional (T).

pedro.cesars@ufpe.br

[1]Research Center for Therapeutic Innovation Suely Galdino, Federal University of Pernambuco, Recife, Brazil; [2]Laboratory of Immunomodulation and New Therapeutic Approaches, Federal University of Pernambuco, Recife, Brazil; [3]Laboratory of Drug Design and Synthesis;

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ABSTRACT

Introduction: Thiazolidines and thiazoles are heterocyclic compounds known for their diverse biological activities, such as anti-inflammatory, antioxidant, antitumor and antimicrobial action. Hybridization of these molecules can improve chemical stability, improve solubility and increase affinity for biological targets. In silico analysis may indicate that these modifications also improve pharmacokinetic properties, such as absorption, distribution, metabolism and excretion (ADME), which may contribute to the development of more effective compounds with less toxicity. **Objective**: To evaluate the potential of eighteen new thiazolidine-2,4-dione-thiazole derivatives as drug candidates through in silico pharmacokinetic analysis. **Methods**: For pharmacokinetic prediction, the SwissADME platform (swissadme.ch) was used to obtain the results of gastrointestinal absorption, blood-brain barrier permeability, P-glycoprotein (Pgp) substrate, inhibition of isoenzymes of the cytochrome P450 (CYP) monooxygenase family, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. **Results and Discussion**: The eighteen thiazolidine-2,4-dione-thiazole derivatives of the PA-B-C series (PA2-7, PB2-7, and PC2-7) were analyzed for their pharmacokinetic properties. In gastrointestinal absorption, five derivatives (PA2, PC2, PC3, PC4, and PC5) stood out with high absorption, while the others (PA3 to PA7 to PB7, PC6, and PC7) showed lower levels. This difference may be associated with the molecular weight and polarity of the molecules. PA1 (408.50 g/mol) and compounds PC2 to PC5 (422.52-456.97 g/mol) present characteristics favorable to gastrointestinal absorption, such as adequate solubility, moderate lipophilicity and less than 10 rotatable bonds, facilitating cellular permeability. Derivatives PB3 and PB5, with weights above 500 g/mol, demonstrated low absorption, indicating the need for structural modifications for oral optimization. In the screening rules (Lipinski, Ghose, Veber, Egan and Muegge), PA1 and PC2 to PC5 did not violate criteria, suggesting good bioavailability, while PB5 and PC6 violated up to two Ghose rules, indicating possible limitations. Most compounds obtained a bioavailability score of 0.55, except for PB5, which presented 0.17, indicating lower absorption compared to the ideal limit of 1. No compound was permeable to the blood-brain barrier, which is advantageous, since low permeability avoids potential adverse effects on the central nervous system. All compounds were classified as non-substrates of P-glycoprotein, suggesting good bioavailability and lower risk of active efflux. Regarding cytochrome P450 isoenzymes, all inhibited CYP2C9 and CYP2C19, which may moderately increase the risk of drug interactions, although these are not the main isoforms in drug metabolism. No compound inhibited CYP2D6, which may reduce possible adverse interactions. PB6, PB7 and PC7 also did not inhibit CYP3A4, possibly due to structural features such as associations between phenyl, nitro and methyl groups, which may reduce the affinity for this enzyme, the main isoform in drug metabolism. **Conclusion**: In silico analysis suggests that thiazolidine-2,4-dione-thiazole derivatives have broad pharmacokinetic properties. Compounds PA1, PC1, PC2, PC4 and PC5 show promise due to their high gastrointestinal absorption and favorable profile regarding interactions with CYPs. However, the possible inhibition of CYP3A4 by some compounds (PA3, PA6 and PB3) highlights the need for further studies to optimize their characteristics and minimize potential drug interactions.