VIRTUAL SCREENING AND RATIONAL DESIGN OF THIOUREA DERIVATIVES WITH ANTIPLATELET ACTIVITY.

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Introduction

Cardiovascular diseases are the leading causes of mortality in Brazil and worldwide (1), with atherosclerosis being an underlying factor in most of these disorders (2). The first-line treatment for atherosclerosis involves the use of antithrombotic agents. However, these therapies face significant limitations, such as severe adverse reactions and the development of tolerance, underscoring the urgent need for more effective and safer antithrombotic options (3). In this context, thiourea derivatives have attracted interest due to their antithrombotic potential, prompting our research group to previously synthesize a series of thiourea derivatives and evaluate their antiplatelet aggregation activity *in vitro*. In this scenario, the objective of this study is to analyze *in silico* the chemical profile of thiourea derivatives with antiplatelet activity, proposing a novel series, potentially effective and safe.

Material and Methods

The structures of cyclooxygenase-1 (COX-1) and thromboxane A2 receptor (TBXA2r) were obtained from the Protein Data Bank, while the structure of thromboxane synthase (TXAS) was modeled and validated. The ADMET Predictor™ XI software was used to predict the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profile of the series of thiourea derivatives previously synthesized by our research group. For this purpose, the ADMET global risk factor was employed, integrating computational models for toxicity (TOX risk), absorption (Absn risk), and metabolism (CYP risk), along with two models focused on distribution/excretion: volume of distribution and unbound fraction. The activity values previously determined by our group, as well as the predicted ADMET parameters, were used as input for the decision-making method, Analytic Hierarchy Process - Gaussian, to identify the most promising compounds in the series. A redocking procedure was then conducted to validate the docking protocol used in predicting the interaction of the most promising thioureas with their potential targets, namely COX-1, TBXA2r, and TXAS (4). Molecular docking simulations were performed using the software Gold 2023.2.0 (5).

Results and Discussion

This study generated a validated theoretical model of the human TXAS protein. The evaluated thiourea derivatives exhibited drug-like properties and an adequate safety profile, although further studies are required to confirm the predicted results. Molecular docking analysis indicated that particularly compounds LabTIF76, LabTIF105, LabTIF160, and LabTIF180 displayed binding modes involving key protein residues for the inhibition of the studied receptors.

Conclusion

Therefore, the compounds previously synthesized by our group and evaluated *in silico* in this study pave the way for the discovery of effective and less toxic antithrombotic agents, offering opportunities to improve the quality of life for individuals affected by or at risk of cardiovascular diseases.

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