COMPARATIVE ANALYSIS OF SELENIUM DERIVATIVES AFFINITY FOR CYP3A4: IMPLICATIONS FOR DRUG METABOLISM AND SAFETY TROUGH COMPUTATIONAL CHEMISTRY

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INTRODUCTION: Selenium is an essential element in pharmacology, known for its antioxidant properties and neuromodulatory importance. Although it has low hepatic toxicity when used in lower concentrations, selenium-derived molecules share a basic structure that allows variations in the substitution of functional groups, which can affect their pharmacological and toxicological properties. Therefore, analyzing selenium-derived molecules, such as ebselen (EbSe), diphenyl diselenide $(PhSe)_2$, p-chlorodiphenyl diselenide $(p\text{-}ClPhSe)_2$, and m-trifluoromethyl-diphenyl diselenide $(m\text{-}CF_3PhSe)_2$, in interaction with CYP3A4, the main enzyme responsible for drug metabolism in the liver, is crucial to understanding their potential toxicological risks associated with metabolism. OBJECTIVE: Using molecular docking methods, we analyzed the interactions of selenium derivatives with CYP3A4, employing midazolam (MDZ) as a native physiological control for CYP3A4 binding. MATERIALS AND METHODS: The crystallographic model of CYP3A4 was obtained from the Protein Data Bank (8S02). We evaluated the interactions and affinity between critical activation residues, including Arg105, Arg106, Phe108, Phe215, Arg372, Glu374, and Cys442 in CYP3A4 proteins, expressing affinity through the energy released from the reaction (ΔG_{bind}). RESULTS: MDZ showed an affinity of ΔG_{bind} = -9.0 kcal/mol with CYP3A4, with closer interactions to critical residues, except Cys442. The selenium-derived molecules that exhibited the lowest affinity were EbSe and $(PhSe)_2$, with affinities of -8.2 and -7.3 kcal/mol, respectively, showing higher distances from the critical activation residues. In contrast, the selenium-based molecules demonstrating the highest affinity were $(p\text{-}ClPhSe)_2$ and $(m\text{-}CF_3PhSe)_2$, with affinities of -10.0 and -10.5 kcal/mol, respectively. $(p\text{-}ClPhSe)_2$ interacted with residues Arg106 (4.34 Å), Phe215 (3.83 Å), and Glu374 (4.53 Å), while $(m\text{-}CF_3PhSe)_2$ interacted only with Cys442 (4.98 Å). The Cys442 binding is relevant, as this residue plays a fundamental role in catalyzing reactions mediated by CYP3A4, directly influencing the efficiency of drug metabolism. Furthermore, we hypothesize that $(m\text{-}CF_3PhSe)_2$ may interact with the heme group of CYP3A4, often implicated in irreversible binding, potentially forming a strong covalent bond with the heme moiety. CONCLUSION: These results suggest that $(p\text{-}ClPhSe)_2$ and $(m\text{-}CF_3PhSe)_2$ have a greater potential for interaction with CYP3A4, indicating possible hepatic metabolism mechanism and highlighting the need for caution in their pharmacological use, as well as further investigation into their metabolic profile.

Keywords: Selenium, CYP3A4, Molecular Docking.