CYP3A4-ORGANOSELENIUM BINDING DYNAMICS: A SIMULATION STUDY ON STRUCTURAL STABILITY THROUGH COMPUTATIONAL CHEMISTRY

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INTRODUCTION: Selenium is for human health, and its pharmacological significance lies in its ability to perform antioxidant/neuroprotective properties. Low-concentration of organoselenium molecules are non-toxic, with structurally versatile functional groups modulating pharmacological effects. OBJECTIVE: This study aims to assess the pharmacological profile of organoselenium compounds via interaction analysis with CYP3A4 using molecular dynamics simulations. METHOD: To understand the toxicological risks associated with the metabolism of organoselenium molecules (ebselen (EbSe), diphenyl diselenide $(PhSe)_2$, p-chloro-diphenyl diselenide $(p\text{-}ClPhSe)_2$, and m-trifluoromethyl-diphenyl diselenide $(m\text{-}CF_3PhSe)_2$), we performed molecular dynamics to investigate the interaction of organoselenium molecules with CYP3A4, responsible for major drug metabolism. Midazolam (MDZ) was used as a physiological control for CYP3A4. Crystallographic model of CYP3A4 was obtained from the PDB (8S02). To evaluate the conformational stability of the ligand-protein complexes between organoselenium molecules and CYP3A4, we conducted molecular dynamics simulations assessing root mean square deviation (RMSD) fluctuations, solvent accessible surface area (SASA), and radius of gyration (Rg), and root mean square fluctuation (RMSF) over 50 ns. RESULTS: RMSD revealed a similar average fluctuation, with MDZ: 3.01Å, EbSe: 2.74Å, $(PhSe)_2$: 2.50Å, $(p\text{-}ClPhSe)_2$: 2.26Å, $(m\text{-}CF_3PhSe)_2$: 2.68Å. SASA simulation results indicated an encompassing area of approximately MDZ: 2289Å², EbSe: 2261Å², $(PhSe)_2$: 2194Å², $(p\text{-}ClPhSe)_2$: 1974Å², $(m\text{-}CF_3PhSe)_2$: 2189Å². The compactness of the complex was assessed by Rg compactness, which showed mean values of MDZ: 22.44Å, EbSe: 19.74Å, $(PhSe)_2$: 23.09Å, $(p\text{-}ClPhSe)_2$: 19.23Å, and $(m\text{-}CF_3PhSe)_2$: 20.43Å. The spatial arrangement of critical CYP3A4 activation residues (Arg105, Arg106, Phe108, Phe215, Arg372, Glu374, Cys442) was assessed by RMSF, along with the distances between the backbone structures and CYP3A4, which indicates shorter distance to $(p\text{-}ClPhSe)_2$. CONCLUSION: Thus, $(p\text{-}ClPhSe)_2$ demonstrated enhanced stability, compactness, reduced solvent exposure, and lower residue fluctuations in CYP3A4, indicating high binding capacity in comparison to other organoselenium molecules. Of note, this indicates possible toxicity in hepatic metabolic processes and underscoring the importance of exercising caution in their pharmacological application, along with the necessity for further research into their metabolic profiles.

Keywords: Selenium, CYP3A4, Molecular Dynamics