Interactions of 2-phenyl-benzotriazole xenobiotic compounds with human Cytochrome P450-CYP1A1 by means of docking, molecular dynamics simulations and MM-GBSA calculations

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2-phenyl-benzotriazole xenobiotic compounds (PBTA-4, PBTA-6, PBTA-7 and PBTA-8) that were previously isolated and identified in waters of the Yodo river, in Japan (Nukaya et al., 2001; Ohe et al., 2004; Watanabe et al., 2001) were characterized as powerful pro-mutagens. In order to predict the activation mechanism of these pro-mutagens, we designed a computational biochemistry protocol, which includes, docking experiments, molecular dynamics simulations and free energy decomposition calculations to obtain information about the interaction of 2-phenyl-benzotriazole molecules into the active center of cytochrome P450-CYP1A1 (CYP1A1). Molecular docking calculations using AutoDock Vina software shows that PBTAs are proportionally oriented in the pocket of CYP1A1, establishing ?-? stacking attractive interactions between the triazole group and the Phe224, as well as, the hydrogen bonds of the terminal NH2 over the benzotriazole units with the Asn255 and Ser116 amino acids. Molecular dynamics simulations using NAMD package showed that these interactions are stable along 100.0 ns of trajectories. Into this context, free binding energy calculations employing the MM-GBSA approach, shows that some differences exists among the interaction of PBTAs with CYP1A1, regarding the solvation, electrostatic and van der Waals interaction energy components. These results suggest that PBTA molecules might be activated by CYP1A1. Thus, enhancing their mutagenicity when compared with the pro-mutagen parent species.

2-Phenyl-benzotriazole

MM-GBSA

Molecular docking

Molecular dynamics simulations

Binding energy

Complexation

Computational chemistry

Free energy

Hydrogen bonds

Molecular modeling

Molecules

Mutagenesis

Mutagens

Van der Waals forces

2-Phenyl-benzotriazole

Activation mechanisms

Attractive interactions

Computational biochemistries

MM-GBSA

Molecular docking

Molecular dynamics simulations

Van der Waals interaction energy

Molecular dynamics

2-(2-(acetylamino)-4-(bis(2-hydroxyethyl)amino)-5-methoxyphenyl)-5-amino-7-bromo-4-chloro-2H-benzotriazole

2-(2-(acetylamino)-4-(diallylamino)-5-methoxyphenyl)-5-amino-7-bromo-4-chloro-2H-benzotriazole

2-(2-(acetylamino)-4-(diethylamino)-5-methoxyphenyl)-5-amino-7-bromo-4-chloro-2H-benzotriazole

2-(2-(acetylamino)-4-amino-5-methoxyphenyl)-5-amino-7-bromo-4-chloro-2H-benzotriazole

aniline derivative

cytochrome P450 1A1

triazole derivative

xenobiotic agent

chemical structure

chemistry

human

metabolism

molecular docking

molecular dynamics

thermodynamics

Aniline Compounds

Cytochrome P-450 CYP1A1

Humans

Molecular Docking Simulation

Molecular Dynamics Simulation

Molecular Structure

Thermodynamics

Triazoles

Xenobiotics