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In silico study of (thio)xanthones-mediated P-glycoprotein activation

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Abstract

Background: P-glycoprotein (P-gp) is an efflux transporter located at the apical membrane of important barrier tissues, playing a crucial role in the detoxification of endobiotics and xenobiotics [1]. (Thio)xanthonic derivatives have been shown to be able of activating P-gp without increasing its expression, promoting an immediate increase in the amount of transported substrates. Thus, P-gp activation limits the intracellular accumulation of harmful P-gp substrates and, consequently, reduces their toxicity [2,3]. **Objective:** The aim of this study was to elucidate, *in silico*, by molecular docking analysis, the P-gp binding sites of different (thio)xanthonic derivatives previously reported as P-gp activators, and to correlate the *in silico* predictions with *in vitro* data reported in the literature. **Methods:** Molecular Operating Environment (MOE) software was used to build all the 3D-structures (with minimized energy) and Autodock Vina was used to perform the molecular docking analysis, to obtain the affinity energy between the human P-gp model [at the drug-binding pocket (DBP) and nucleotide binding domains (NBDs) 1 and 2] and P-gp activators. The best pose was visualized and the number and type of interactions of the evaluated compounds with specific P-gp residues was verified by using the BINANA software. **Results:** The molecular docking analysis revealed that most of P-gp activators preferentially bind to DBP or NBD1. Relatively to DBP, almost all P-gp activators bind to residues located in the modulators (M)-site. Furthermore, the evaluation of interactions between P-gp activators and P-gp residues indicated a pattern, since several P-gp activators shared the same hydrophobic contacts and other interactions (hydrogen-bonds and pi-pi, t-stacking and cation-pi interactions) with specific P-gp residues. **Conclusions:** The present study confirmed that (thio)xanthonic derivatives are capable of binding to P-gp, specifically at the M-site of the DBP and at the NBD1 and, therefore, these binding interactions may potentially be involved in (thio)xanthonic derivatives-mediated P-gp activation.

Keywords: computational studies; xanthones; molecular docking; Molecular Operating Environment (MOE) software; BINANA software

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References

1. Veiga-Matos, J. Remião, F. Morales, A. I. Pharmacokinetics and Toxicokinetics Roles of Membrane Transporters at Kidney Level. *J. Pharm. Pharm. Sci* **2020**, *23*, 333–356.
2. Silva, R. Palmeira, A. Carmo, H. Barbosa, D. J. Gameiro, M. Gomes, A. Paiva, A. M. Sousa, E. Pinto, M. Bastos, M. L. Remião, F. P-glycoprotein induction in Caco-2 cells by newly synthetized thioxanthones prevents paraquat cytotoxicity. *Arch. Toxicol* **2015**, *89*, 1783–1800.
3. Martins, E. Silva, V. Lemos, A. Palmeira, A. Puthongking, P. Sousa, E. Rocha-Pereira, C. Ghanem, C. I. Carmo, H. Remião, F. Silva, R. Newly synthesized oxygenated xanthones as potential P-glycoprotein activators: In vitro, ex vivo, and in silico studies, *Molecules* **2019**, *24, 0-27*.