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Unraveling fiscalin derivatives' interactions with P-glycoprotein: a computational study

Jéssica Veiga-Matos [1,2,3,*], Daniel J. V. A. dos Santos [4], Emília Sousa [5,6], Ana Morales [3], Marta Prieto [3], Fernando Remião [1,2] and Renata Silva [1,2]

[1] UCIBIO/REQUIMTE, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313, Porto, Portugal
[2] Associate Laboratory i4HB – Institute for Health and Bioeconomy, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313, Porto, Portugal
[3] Toxicology Unit; Group of Translational Research on Renal and Cardiovascular Diseases; Instituto de Investigación Biomédica de Salamanca (IBSAL); University of Salamanca, Campus Miguel de Unamuno, Edificio Departamental, 37007, Salamanca, Spain
[4] CBIOS – Research Center for Biosciences and Health Technologies, Lusófona University, Campo Grande, 376, 1749-024, Lisbon, Portugal
[5] Laboratory of Organic and Pharmaceutical Chemistry, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313, Porto, Portugal
[6] CIIMAR – Interdisciplinary Centre of Marine and Environmental Research, Terminal de Cruzeiros do Porto de Leixões, Matosinhos, Portugal

* Correspondence: jessicamatos1996@outlook.com

Abstract

Background: P-glycoprotein (P-gp), a crucial efflux transporter located on the apical membrane of vital barrier tissues, plays a critical role in the detoxification of several endobiotics and xenobiotics [1,2]. Notably, fiscalin derivatives exhibit diverse interactions with P-gp, demonstrating inhibitory or activating effects. This interaction leads to a reduction or increase in the transported substrate levels, respectively [3]. **Objective:** The aim of this study was to elucidate, in silico, the P-gp binding sites and interactions of different fiscalin derivatives. Methods: Molecular Operating Environment (MOE) software was used to build all the energy minimized small-molecules 3D-structures, and Autodock Vina was used to perform the molecular docking to estimate the binding affinity between fiscalins and two human P-gp models [4,5] [at the drug-binding pocket (DBP) and nucleotide binding domains (NBDs) 1 and 2]. The best ranked poses were visualized and the interactions of the ligands with specific P-gp residues were analyzed using the BINANA software. **Results:** Molecular docking analysis unveiled a notable preference of fiscalins for binding to DBP, where all the ligands bind to residues located in the modulators (M)-site. Additionally, the assessment of interactions between fiscalins and P-gp residues within NBD1 and NBD2 revealed potential novel binding sites. Across these three locations, fiscalins exhibited binding to specific P-gp residues, establishing shared hydrophobic contacts and other significant interactions, including hydrogen-bonds; pi-pi, t-stacking and cation-pi interactions; and salt bridges. **Conclusions:** The present study confirmed the ability of fiscalin derivatives to bind to P-gp, especially at the M-site of the DBP, as well as at both NBDs. The identified binding interactions may potentially be involved in the fiscalins-mediated P-gp activation.

Keywords: *in silico* studies; fiscalin derivatives; molecular docking; MOE software; BINANA software

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References

1. Veiga-Matos, J.; Morales, A.I.; Prieto, M.; Remião, F.; Silva, R.. Study Models of Drug–Drug Interactions Involving P-Glycoprotein: The Potential Benefit of P-Glycoprotein Modulation at the Kidney and Intestinal Levels. Molecules (2023), 28, 7532-54.
2. Veiga-Matos, J.; Remião, F.; Morales, A.I. Pharmacokinetics and Toxicokinetics Roles of Membrane Transporters at Kidney Level. J Pharm Pharm Sci. (2020), 23, 333–56.
3. Barreiro, S.; Silva, B.; Long, S.; Pinto, M.; Remião, F.; Sousa, E.; Silva, R. Fiscalin Derivatives as Potential Neuroprotective Agents. Pharmaceutics. (2022). 14, 1–27.
4. Bonito, C.A.; Ferreira, R.J.; Ferreira, M.J.U.; Gillet, J.P.; Cordeiro, M.N.D.S; dos Santos, D.J.V.A. Theoretical Insights on Helix Repacking as the Origin of P-Glycoprotein Promiscuity. Sci Rep. (2020), 10, 1–13.
5. Nosol, K.; Romane, K.; Irobalieva, R.N.; Alam, A.; Kowal, J.; Fujita, N.; Locher, K.P. Cryo-EM Structures Reveal Distinct Mechanisms of Inhibition of the Human Multidrug Transporter ABCB1. Proc Natl Acad Sci. (2020), 117, 26245–53.

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