Proceedings International
Platinum Open Access Journal (ISSN 2668-6384)

Proceedings, Abstract
Volume 4, Issue 2, 2022, 20
https://doi.org/10.33263/Proceedings42.020

Study of Substrate Selectivity of Carboxylesterases with Biopharmaceutical Relevance †

Sergio R. Ribone [1], Darío Estrín [2], Mario A. Quevedo [1,*]

[1] Unidad de Investigación y Desarrollo en Tecnología Farmacéutica (UNITEFA-CONICET). Departamento de Ciencias Farmacéuticas, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba; sribone@unc.edu.ar (S.R.R.), aquevedo@unc.edu.ar (M.A.Q.)
[2] Instituto de Química Física de los Materiales, Medio Ambiente y Energía (INQUIMAE-CONICET). Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires; dario.estrin@gmail.com (D.E.)
* Correspondence: aquevedo@unc.edu.ar (M.A.Q.);
† Presented at The Sixth International Meeting of Pharmaceutical Sciences (RICiFa), November 10-12, 2021, Córdoba, Argentina

Received: 26.04.2022; Revised: 4.05.2022; Accepted: 6.05.2022; Published: 8.05.2022

Abstract: Carboxylesterase subtypes, CES1 and CES2, are involved in the metabolism and bioactivation of drugs and prodrugs. Although previous reports described the structural specificity of the different CES subtypes towards their substrate, the molecular basis behind this selectivity remains unclear. The objective of this work is focused on the exploration of the atomistic details related to this molecular specificity, using a combination of molecular modeling strategies on two esters of p-nitrophenol containing different substituents. First, molecular docking studies were performed on the catalytic site of both CES (*DOCK6*). Second, molecular dynamic simulations were performed on the obtained ligand-enzyme complexes. Finally, hybrid quantum mechanics/molecular mechanics (QM/MM) simulations were performed on all the complexes using the Amber18 software package. Results obtained from the QM/MM simulation showed that the dealkylation was the limiting step on the enzymatic hydrolysis. In addition, the ΔG obtained displayed the same order of magnitude as the previously reported k_{cat} for the hydrolysis for these esters on both CES. In conclusion, the molecular modeling procedure developed in this work reproduces the trend in the hydrolysis of three different esters of p-nitrophenol by CES1 and 2, constituting a crucial key for the study of CES selectivity on newly selected substrates.

Keywords: carboxylesterases; selectivity; esters p-nitrophenol; molecular modeling; QM/MM.

Funding

This research was funded by Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT-FONCyT Grant PICT-2019-03461).

Acknowledgments

The authors want to acknowledge the CCAD, Universidad Nacional de Córdoba, (https://ccad.unc.edu.ar/) and the CSC, Conicet (https://csc.conicet.gov.ar/tupac/) for the computational resources.

Conflicts of Interest

The authors declare no conflict of interest.