Protein photoaptenation by β-Lactams. Photobinding of Ezetimibe to Human Serum Albumin

M. Consuelo Jiménez[1], Raúl Pérez-Ruiz[1], Daniel Limones-Herrero[1], Inmaculada Andreu[2], Emilio Lence[3], Concepción González-Bello[3], Miguel A. Miranda[1]

[1] Departamento de Química/Instituto de Tecnología Química UPV-CSIC, Universitat Politècnica de Valencia, Camino de Vera s/n, 46071 Valencia, Spain.
[2] Instituto de Investigación Sanitaria La Fe, Hospital Universitari i Politècnic La Fe, Avenida de Fernando Abril Martorell 106, 46026 Valencia, Spain
[3]Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain.

E-mail: mcjimene@qim.upv.es

Currently marketed β-lactams are responsible for inducing a variety of adverse reactions; in this context, allergy to penicillins is probably the most frequently reported problem. The interaction of β-lactam drugs with the immune system is often explained by the hapten hypothesis, which is based on the observation that small organic molecules do not induce an immune response unless they are covalently bound to a protein. [1] Thus, the covalent binding of β-lactams to carrier proteins, such as human serum albumin (HSA) has been investigated, paying attention to detection and identification of the products [2]. With this background, it is relevant to explore whether photochemical activation of β-lactams may enhance covalent binding to proteins, a process that constitutes the key step in the sequence of events leading to photoallergy.

In this work, the photoinduced binding of β-lactams to proteins has been investigated selecting HSA as target protein and ezetimibe (Chart 1) as probe. This recently marketed drug, whose main function is to decrease the plasma cholesterol levels [3], contains a monocyclic β-lactam core and therefore it can undergo photochemical ring splitting to give reactive intermediates, whereas it should react only sluggishly with nucleophiles in the dark. The results, obtained by photochemical, proteomic and molecular dynamics simulation studies indicate that, after photoactivation, modification of HSA by ezetimibe occurs at two specific lysine residues.

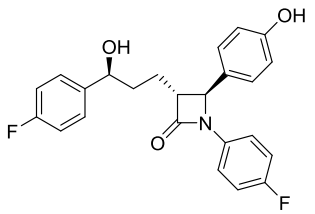

Figure 1. Chemical structure of ezetimibe

Funding: Spanish Ministry of Economy and Competiveness (CTQ2013-47872-C2-1-P and CTQ2016-78875-P).

Acknowledgement: We are grateful to the Centro de Supercomputación de Galicia (CESGA) and to the proteomics facility of SCSIE University of Valencia.

References:

[1] A. Ariza, C. Mayorga, T. D. Fernández, N. Barbero, A. Martín-Serrano, D. Pérez-Sala, F. J. Sánchez-Gómez, M. Blanca, M. J. Torres, M. I. Montañez, *J. Investig. Allergol. Clin. Immunol.* **2015**, *25*, 12.

[2] C. P. Cannon, *New Engl. J. Med.*, **2015**, *372*, 2387.

[3] D. Garzon, A. Ariza, L. Regazzoni, R. Clerici, A. Altomare, F. R. Sirtori, M. Carini, M. J. Torres, D. Perez-Sala, G. Aldini, *Chem. Res. Toxicol*. **2014**, *27*, 1566.