MS45.O04

X-ray structures of Aldose Reductase and AKR1B10 with the lead inhibitor JF0064

F. Ruiz[1], A. Cousido-Siah[1], A. Mitschler[1], S. Porté[2], J. de la Fuente[3], F. Terwesten[4], G. Klebe[4], J. Farrés[2], X. Parés[2], A. Podjarny[1]

[1]Institut de Génétique et de Biologie Moléculaire et Cellulaire, Department of Integrative Biology, Illkirch, France, [2]Universitat Autònoma de Barcelona, Department of Biochemistry and Molecular Biology, Bellaterra, Spain, [3]Biomar Microbial Technologies S.A., León, Spain, [4]University of Marburg, Department of Pharmaceutical Chemistry, Marburg, Germany

Human enzymes Aldose Reductase (AR or AKR1B1) and AKR1B10 are of biomedical interest because of their involvement in secondary diabetic complications and inflammatory disorders (AR) and in several type of cancers, e.g. hepatocellular carcinoma and smoking related lung cancer (AKR1B10). They belong to the Aldo-keto reductase family (AKRs) which present a highly conserved (α/β)8 barrel folding. Their substrate specificity and inhibitor selectivity are determined by interaction with residues located in three highly variable external loops. JF0064 (2,2',3,3',5,5',6,6'-octafluoro-4,4'-biphenyldiol) has been identified in a series of polyhalogenated compounds as a lead inhibitor of both enzymes. The determination of the X-ray structure of the AR:NADP+:JF0064 complex at ultrahigh-resolution (0.85 Å) allows to observe JF0064 interacting with the catalytic residue Tyr48 through a negatively charged hydroxyl group of the inhibitor (i.e., the acidic phenol). The non-competitive inhibition pattern observed for JF0064 with both enzymes suggests that this acidic hydroxyl group will also be present in the case of AKR1B10. The X-ray structure of the AKR1B10:NADP+:JF0064 complex (achieved with the combination of surface lysine methylation and the introduction of K125R/V301L mutations) and the comparison between both structures unveils some important hints for a structure-based drug design optimization.

[1] *A. Cousido-Siah, F.X. Ruiz, A. Mitschler, S. Porté, A. Rodríguez de Lera, M.J. Martín,S. Manzanaro, J.A. de la Fuente, F. Terwesten, M. Betz, G. Klebe, J. Farrés, X. Parés, Alberto Podjarny, Acta Crystallogr D Biol Crystallogr, Accepted 10 December 2013 (*

Keywords: Aldose Reductase Inhibitor, Diabetes, Drug design