Computational and NMR studies on LOX inhibition

Eleni Chontzopoulou*, Rachil-Artemis Ioannidi**, Kalliopi Moschovou*, Primoz Sket***, Ioannis Kostakis**, Thomas Mavromoustakos*

***** Department of Chemistry, National and Kapodistrian University of Athens, Panepistimioupolis Zografou 15771, Greece

** Department of Pharmacy, National and Kapodistrian University of Athens, Panepistimioupolis-Zografou 15771, Greece

*** National Institute of Chemistry, Slovenian NMR Centre, Ljubljana, Slovenia.

Inflammation is the biological response of human's tissues against any type of harmful stimulus. Lipoxygenase (LOX) is an enzyme, which participates in the inflammation pathway and its metabolites are associated with a variety of different diseases, such as asthma, atherosclerosis, rheumatoid arthritis, psoriasis, brain disorders and cancer. In this study, we aim to discover novel LOX inhibitors, by targeting one of its main isoforms in the human cell, 5-LOX. Saturation Transfer Difference (STD) NMR studies have been performed in order to experimentally investigate the possible binding of a novel dipeptide LOX inhibitor, which has been recently synthesized. After evaluating the experimental results and having unveiled the strong binding of the inhibitor to 5-LOX, we performed *in silico* studies, in order to discover the inhibitor's mechanism of action towards the enzyme. The inhibitor exists in many conformations in the aquatic environment, thus we conducted Molecular Dynamics simulations in order to discover the statistically predominant conformations that the inhibitor adopts in the aquatic environment. Furthermore, molecular docking studies have been performed so as to obtain an initial pose of the inhibitor inside the enzyme's active site, while the stability of "LOX-inhibitor" complex has been evaluated with Molecular Dynamics simulations. Further Quantum Mechanics/Molecular Mechanics MD simulations have been conducted in order to observe the mechanism of action of the inhibitor towards the enzyme's catalytic site. All these experiments verified the inhibitor's strong binding to the enzyme's cavity and pinpointed that it could serve as a novel iron chelator.

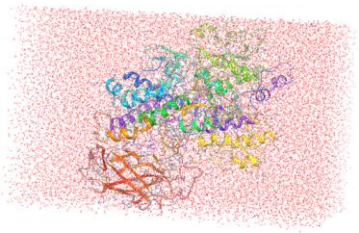

Figure 1. LOX enzyme in the aquatic environment.

References:

[1] Mashima, R.; Okuyama, T. The role of lipoxygenases in pathophysiology; new insights and future perspectives., Redox Biol. 6, (2015) 297–310.

[2] Oprea, T.I.; Bauman, J.E.; Bologa, C.G.; Buranda, T.; Chigaev, A.; Edwards, B.S.; Jarvik, J.W.; Gresham, H.D.; Haynes, M.K.; Hjelle, B. et al. Drug repurposing from an academic perspective., Drug Discov. Today Ther. Strateg. 8, (2011) 61-69.