DESIGN AND DEVELOPMENT OF NOVEL ASPARTAME ANALOGUES AS POTENTIAL ANTI-INFLAMMATORY AGENTS

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Human 5-lipoxygenase (5-LOX) is an enzyme playing a key-role in the inflammatory pathway and thus, its overexpression is implicated in many pathological states, such as cancer. [1] Aspartame, is among the many food supplements that have been studied for their pharmaceutical capacity and has been highlighted as a versatile anti-inflammatory LOX inhibitor in previous studies. [2] Our approach was based on modifying the chemical structure of aspartame in order to augment the compound's interactions with the active site of LOX. The molecular docking studies performed, explored the binding potency of our newly developed analogues to serve as LOX inhibitors, while the stability of the enzyme-inhibitor complexes was further evaluated by molecular dynamics simulations (Fig. 1). The most favored derivatives that were pinpointed by *in silico* experiments, were selected for synthesis. Starting from the commercially available phenylalanine, via a 6-step synthetic route, after protection with the Boc group and conjugation with the suitable amine, the desirable analogues were afforded. As for now, the molecular profile of two of these compounds inside the enzyme's cavity was evaluated by Saturation Transfer Difference (STD) NMR experiments and the results acquired are very promising. To assess the anti-inflammatory potential of these aspartame analogues, the human monocytic leukemia cell line THP-1 was selected as an *in vitro* model, and the analogues are currently evaluated using the MTT assay.

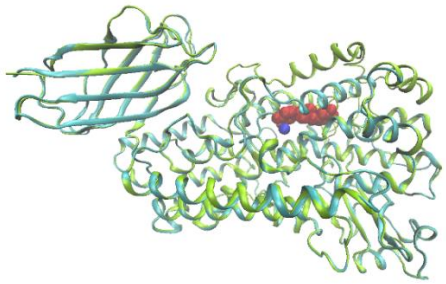

Figure 1. Indicative LOX-compound complex derived by molecular docking studies.

References: [1] Mashima R., Okuyama T. The role of lipoxygenases in pathophysiology; new insights and future perspectives. *Redox Biol.* 6, 297–310 (2015); [2] Chontzopoulou E., Papaemmanouil C., Chatziathanasiadou M., Kolokouris D., Kiriakidi S., Konstantinidi A., Gerogianni I., Tselios T., Kostakis I., Chrysina E., Hadjipavlou-Litina D., Tzeli D., Tzakos A., Mavromoustakos T. Molecular investigation of artificial and natural sweeteners as potential anti-inflammatory agents. *J Biomol Struct Dyn.* 40, 1-13 (2021).