Synthesis of phosphinic pseudopeptidic inhibitors of M1 aminopeptidases using a late-stage diversification strategy

Konstantinos Patiniotis[a], Dimitris Georgiadis[a], Giannis Papaefstathiou[b], Alexis Plessas[b]

[a]: *Laboratory of Organic Chemistry, Faculty of Chemistry, National and Kapodistrian University of Athens, Panepistimioupolis, Zografou, 15771, Athens, Greece*
[b]: *Laboratory of Inorganic Chemistry, Faculty of Chemistry, National and Kapodistrian University of Athens, Panepistimioupolis, Zografou, 15771, Athens, Greece*
e-mail: konstantinp@chem.uoa.gr

M1 aminopeptidases ERAP1, ERAP2 and IRAP is a group of Zn-metallopeptidases that participate in several biological functions and are involved in human immune responses. Numerous recent studies have shown that these enzymes are important therapeutic targets which prompted the development of inhibitors [1]. Among these inhibitors, phosphinic pseudopeptides are particularly promising due to the high specificity for target enzymes, which derives from their weaker binding affinity to the Zn atom, as compared to other types of inhibitors, allowing a more significant contribution of secondary non-covalent interactions.

After the development of phosphinic pseudopeptide DG013A by our research group [1], a very potent but non-selective inhibitor of ERAPs/IRAP, further attempts towards the improvement of selectivity have been carried out following synthetic strategies that focus on the late-stage diversification of their P_1, P_1' and P_2' positions. Among these, synthetic tools targeting the P_1 position, which, according to studies, is believed to be crucial for selective inhibition of ERAP1, has been less studied compared to methodologies aiming at P_1' and P_2' positions. For this reason, we decided to investigate the synthesis of stereochemically defined phosphinic pseudopeptidic inhibitors suitable for late-stage diversification of P_1 position. In this presentation, the application of a synthetic protocol based on a facile oxidative Heck reaction, which afforded such pseudotripeptides functionalised at the P_1 position, is described [2].

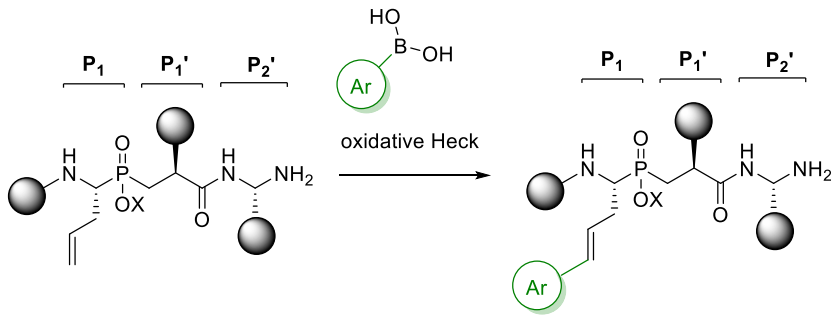

Figure 1: General structure of phosphinic pseudopeptidic substrates

[1] Zervoudi, E., Saridakis, E., Birtley, J.R., Seregin, S.S., Reeves, E., Kokkala, P., Aldhamen, Y.A., Amalfitano, A., Mavridis, I.M., James, E., Georgiadis, D., and Stratikos, E. *Proc Natl Acad Sci U S A.*, **110**, (2013), 19890-19895.

[2] Delcamp, J. H., Brucks, A. P., and White, M. C., *J. Am. Chem. Soc.*, **130**, (2018), 11270-11271.