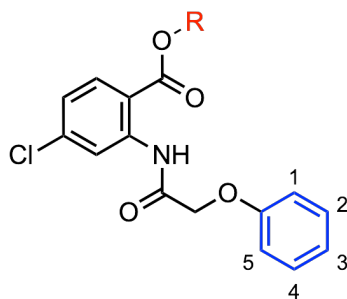


**Development of novel 4-chloro-2-(2-phenoxyacetamido)benzoic acid based TRPM4 inhibitors**C. E. Gerber<sup>1</sup>, P. Grossenbacher<sup>1</sup>, S. A. Singer<sup>1</sup>, M. Lochner<sup>1\*</sup><sup>1</sup>Institute of Biochemistry and Molecular Medicine, Faculty of Medicine, University of Bern, Switzerland

TRPM4 is a non-selective monovalent cation channel, activated by an intracellular increase in  $\text{Ca}^{2+}$  concentration. The channel depolarizes cells by conducting  $\text{Na}^+ > \text{K}^+ \gg \text{Cs}^+ > \text{Li}^+$  from the extracellular space into the cytosol. [1] Mutations of TRPM4 have been associated with cardiovascular and neuronal diseases [1] and only a few small molecules are known for their ability to inhibit TRPM4 [2, 3]. The goal of this project is to conduct an SAR-study on the core scaffold structure (Figure) of the three most potent inhibitors reported in literature (CBA, NBA and LBA) [2] with the intention to further improve the inhibitory potency and physicochemical properties for its use as a chemical probe. Such compounds would be valuable tools in biomedical research, e.g. as blockers in electrophysiology and *in vivo* animal model studies, or as ligands in cryo-EM studies with TRPM4.



Useful SAR-trends were gained by the synthesis of a compound library and subsequent evaluation of their TRPM4 inhibitory activity. A HEK293 cell-based *in vitro*  $\text{Na}^+$ -influx assay developed in-house was adapted for this purpose [2]. Several new analogues with sub-micromolar potencies have been discovered, with the best compound showing a 3-fold increase of inhibitory potency compared to NBA and a 7.5-fold increase of inhibitory potency compared to CBA.

[1] I. Mathar, G. Jacobs, M. Kecskes, A. Menigoz, K. Philippaert, R. Vennekens, *Handbook of Experimental Pharmacology*, **2014**, 222.

[2] L. C. Ozthail, C. Delalande, B. Bianchi, G. Nemeth, S. Kappel, U. Thomet, D. Ross-Kaschitza, C. Simonin, M. Rubin, J. Gertsch, M. Lochner, C. Peinelt, J.-L. Reymond & H. Abriel, *British Journal of Pharmacology*, **2018**, 175(12), 2504-2519.

[3] Z. M. Kovács, C. Dienes, T. Hézső, J. Almássy, J. Magyar, T. Bányász & N. Szentandrassy, *Pharmaceuticals*, **2022**, 15(1), 81.