Developing molecular tools for the study of the ion channel TRPM4

Christian E. Gerber, Philipp Grossenbacher, Simon Singer, Martin Lochner*

Institute of Biochemistry and Molecular Medicine, University of Bern, Switzerland
christian.gerber@ibmm.unibe.ch

TRPM4 is a non-selective monovalent cation channel, activated by an intracellular increase in Ca^{2+} concentration. The channel depolarizes cells by conducting $Na^+ > K^+ >> Cs^+ > Li^+$ 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 1) of the three most potent inhibitors reported in literature (CBA, NBA and LBA) [2] with the intention to further enhance the inhibitory potency, selectivity and *in vivo* stability. Such compounds would be valuable tools in biomedical research, e.g. as blockers in electrophysiology studies with TRPM4. Another goal is the development of fluorescent and halogenated analogues, whose inhibitory activity is maintained at the ion channel. Such fluorescent or electron-rich compounds can be valuable tools in TRPM4 research for staining experiments or as ligands in cryo-EM measurements.

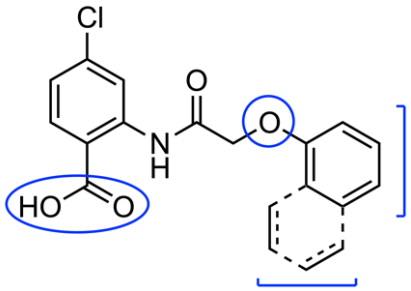

Figure 1: CBA/NBA/LBA core scaffold.
Sites of derivatizations are depicted in blue.

Useful SAR-trends were gained by the synthesis of a compound library and subsequent screening for their TRPM4 inhibitory activity. A HEK293 cell-based *in vitro* Na^+-influx assay developed in our own institute was used 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 the former most potent inhibitor NBA.

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[2] L. C. Ozhathil, 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. Szentandrássy, *Pharmaceuticals*, **2022**, *15(1)*, 81.