Development of novel 4-chloro-2-(2-phenoxyacetamido)benzoic acid based TRPM4 inhibitors

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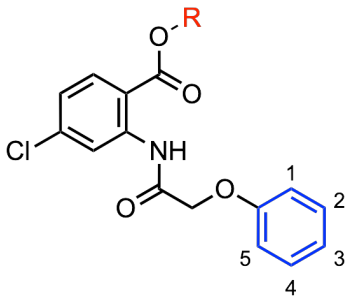
TRPM4 is a non-selective monovalent cation channel, activated by an intracellular increase in Ca^{2+} concentration. The channel depolarizes cells by conducting $Na^+ > K^+ >> Cs^+ > Li^+$ from the extracellular space into the cytosol. [1] Mutations of TRPM4 have been associated with cardiovascular and 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) 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* 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.

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