Discovery of novel human aquaporin-1 blockers

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Human aquaporin-1 (hAQP1) is a water channel found in many tissues and potentially involved in several human pathologies. Selective inhibitors of hAQP1 are discussed as novel treatment opportunities for glaucoma, brain edema, inflammatory pain, and certain types of cancer.

However, only very few potent and chemically attractive blockers have been reported to date. In this study we present three novel hAQP1 blockers that have been identified by virtual screening and inhibit water flux through hAQP1 in Xenopus laevis oocyte swelling assays at low micromolar concentrations. The newly discovered compounds display no chemical similarity to hitherto known hAQP1 blockers and bind at the extracellular entrance of the channel, close to the ar/R selectivity filter.

Futhermore, mutagenesis studies showed that Lys36, which is not conserved among the hAQP family, is crucially involved in binding and renders the discovered compounds suitable as leads for the development of selective hAQP1 inhibitors.

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