Identification and Optimization of Novel GPR126 Positive Allosteric Modulators - targeting a highly lipophilic cavity at the TM/lipid bilayer interface

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The adhesion receptor GPR126 has been reported to have a critical role in Schwann cell function during peripheral nerve regeneration [1]. To date, only agonistic tool compounds which allow to study function of the receptor have been reported.

In an HTS campaign with the Novartis compound collection, several positive allosteric modulators (PAMs) for GPR126 were identified, which are so far unprecedented in literature. These PAMs are characterized by high logD values (>5) which led to very low solubility and restricted their usefulness as in vivo tool compounds. Cryo-EM analysis of the HTS hit elucidated its binding site at the interface of TM5-7 to the lipid bilayer. Despite the high lipophilicity of the PAM binding site, efforts were made to reduce lipophilicity and plasma protein binding of the PAMs to identify compounds suitable for in vivo studies. A knowledge based computational analysis identified several hotspots for weakly polar groups in the PAM binding site. This information was used to further optimize the PAM series. In addition, we used the chromatographic %HSA as a surrogate [2], which proved to be a valuable parameter for efficiently monitoring changes in the highly lipophilic compound series.

By employing these approaches, we identified the first known orally in vivo active PAMs with nanomolar activity, high alpha shifts and logD values less than 4.

[1] J. Neurosci 2017; 37 (12) 3106-3108.
[2] J. Pharm. Sci. 2003; 92 (11), 2236-2248.