# Synthesis and profiling of novel GPR39 agonists and positive allosteric modulators

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G protein-coupled receptor 39 (GPR39) is a member of the ghrelin receptor family of GPCRs, activated by the endogenous ligand zinc with signaling mediated through $G\alpha_q$ and $G\alpha_{12/13}$ pathways[1]. GPR39 expression is widespread peripherally, including in the pancreas, liver, intestine and pituitary gland however, it is also expressed in brain, including in the medium spiny neurons (MSNs) of the striatum. Using our proprietary NETSseq platform[2], we identified through transcriptomic analysis that GPR39 expression is reduced in MSNs from post-mortem brain samples from individuals with Parkinson's disease. As GPR39 signaling results in the production of the neuroprotective pigment epithelium-derived factor (PEDF), known for increasing pro-survival gene expression and reducing pro-inflammatory cytokines[3], we hypothesized that stimulation of GPR39 may compensate for the reduced expression observed in the striatum of Parkinson's disease patients and exert a beneficial therapeutic effect.

Our hypothesis was investigated using a screening cascade where we explored the structure-activity relationship (SAR) of known GPR39 agonists developed for peripheral indications. Through design and synthesis of analogs followed by *in vitro* assessment using calcium flux assays, we identified that minor structural changes could result in either GPR39 agonism or positive allosteric modulation. To assess the question of GPR39 mediated neuroprotection, a GPR39 transfected SH-SY5Y system challenged with the neurotoxin 6-hydroxy dopamine was used as a model for Parkinson's related neurodegeneration. Two GPR39 agonists were tested in this system, with trends towards neuroprotection observed.

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