B-8

TEVC Studies of Potent Antagonists of Human $P2X_3$ Receptor

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$P2X_3$ receptor, a member of P2 purine receptors, is a ligand-gated ion channel activated by extracellular ATP as an endogenous ligand, and highly localized in peripheral and central sensory neurons. The activation of P2X3 receptor by ATP as the pronociceptive effect has been known to initiate the pain signaling involved in chronic inflammatory nociception and neuropathic pain by nerve injury, implicating the possibility of new drug development to control pains. In this study, we have developed a two electrode voltage clamp (TEVC) assay system to evaluate the inhibitory activity of several newly synthesized PPADS and a novel non-ionic antagonist against ATP activation of human P2X3 receptor. PPADS derivatives include several pyridoxine and pyridoxic acid analogs to study the effects of phosphate and aldehyde functional groups in PPADS. All new PPADS analogs were less potent than PPADS at human $P2X_3$ receptors, however, LDD130, a non-ionic analog showed potent antagonistic property with IC_{50} of 8.34 pM. In order to uncover the structure activity relationships of LDD130, and design new structural analogs, we synthesized and investigated a few structural variants of LDD130, and the results will be discussed in this presentation.