A Drug Discovery Project: Allosteric Inhibition of Indolethylamine N-Methyl Transferase

Vorperian, Sevahn

Indolethylamine N-Methyl Transferase (INMT), an enzyme known for its production of N,N-dimethyltryptamine (DMT) via endogenous substrates tryptamine and S-Adenosyl L-Methionine (SAM), colocalizes with the Sigma 1-Receptor (S1R) in spinal cord motoneurons; DMT is a known positive regulator of the S1R. A possible protein-protein interaction between INMT and the S1R may increase DMT production and reduce the cytotoxicity associated with Amyotrophic Lateral Sclerosis (ALS). Because the biochemical mechanisms for INMT's regulation remains greatly unknown, experiments were performed to assess the precise kinetic details for DMT's inhibition of INMT. After applying Michaelis-Menten and Lineweaver Burk analyses for inhibition, DMT was found to be a mixed non-competitive inhibitor when measured against tryptamine. Additionally, a novel tryptamine derivative, N-(2-(1H-indol-3-yl)ethyl)-N',N'-dimethylpropane-1,3-diamine (Propyl Dimethyl Amino Tryptamine, PDAT), was shown to effectively inhibit rabbit INMT (rINMT) by a noncompetitive mechanism when measured against tryptamine (Ki = 83.4 uM). This demonstration of noncompetitive mechanisms for INMT inhibition implies the discovery of an inhibitory allosteric site (also supported by in silico analysis), which provides important new knowledge on INMT regulation. Future experiments to modify the activity of the allosteric site could illuminate new biochemical pathway(s) for control of the motoneuron INMT/S1R axis and possibly promote longevity in ALS patients.

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