Design and synthesis of novel inhibitors for the Tyrosine Hydroxylase enzyme

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Catecholamines are responsible for the fight or flight response and can be attributed to many functions within the sympathetic nervous system. Tyrosine Hydroxylase is the rate determining enzyme in the synthesis of the catecholamine, dopamine. Tyrosine Hydroxylase converts tyrosine to L-DOPA, which is administered in the treatment of Parkinson's patients. The inhibition of Tyrosine Hydroxylase allows for less feedback inhibition from catecholamines, aiding dopamine production. A crystal structure of the active site of Tyrosine Hydroxylase with a known inhibitor bound was obtained from the protein data bank (PDB ID: 2TOH) [1]. In this work, dopaminergic derivatives were inserted into the enzymatic active site *in silico* in order to test the strength of the interactions between the substrate and active site, to determine if any of these derivatives could be effective inhibitors. These derivatives were optimized with implicit solvent with M062X/6-31G and relaxed amino acid side-chains. Interaction energies between the ligands and protein were determined using M06L and MP2 with the 6- 311+G* basis set. Results shows that some of our dopaminergic derivatives show promise as inhibitors for Tyrosine Hydroxylase.

[1] Goodwill, K. E.; Sabatier, C.; Stevens, R. C. Biochemistry1998, 37 (39), 13437–13445.