Design and synthesis of novel inhibitors for the catechol-O-methyltransferase enzyme

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L-DOPA is commonly used as a xenobiotic for patients with conditions such as Parkinson's disease. L-DOPA is transformed into dopamine by DOPA-decarboxylase. Dopamine derived from L-DOPA is deactivated via metabolism by the COMT enzyme. The targeted inhibition of the COMT enzyme prolongs the effectiveness of L-DOPA, resulting in a net increase in pharmacological efficiency. By selectively designing an inhibitor for the catechol-O-methyltransferase enzyme, the effectiveness of the L-DOPA can be extended by regulating the metabolism of dopamine derived from L-DOPA. The effectiveness of these dopaminergic derivatives has been measured via *in silico* models in which the strength of interaction between each substrate and the enzymatic active site was analyzed. A crystal-structure of the COMT enzyme active site, docked with a known COMT inhibitor, BIA 8-176, was isolated from the Protein Data Bank (PDB ID: 2CL5). Novel dopaminergic derivatives were optimized using M062X/6-31G in vacuum and in implicit solvation with rigid amino acid side-chains. Interaction energies between the ligands and the protein were calculated using M06L and MP2 with the 6-311+G* basis set. Interesting differences were noted between *in vaccuo* and solvated calculations. For example, ligands with a nitrile substituent were favored over other substituent variations in vacuum, but this preference was not retained when the same ligands were optimized with implicit solvation. Preliminary results on synthesis of nitrile substituent derivate will be presented as well.

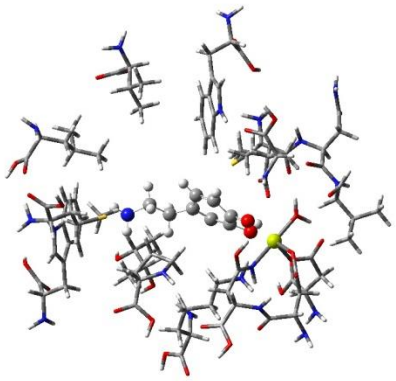

Figure 1 Dopamine docked in the active site of the COMT enzyme