DFT and MP2 analysis of ligand selectivity in the catechol-O-methyltransferase enzyme

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The catechol-O-methyltransferase enzyme interacts with catecholamines, a type of molecule characterized by an amine group that functions as a neurotransmitter or as a hormonal signal. It is most pharmacologically prevalent in interactions with L-DOPA, a dopamine precursor, and with dopamine itself. L-DOPA is commonly used as a xenobiotic for patients with conditions such as Parkinson's disease in which endogenous dopaminergic signaling is dysfunctional and reduced. L-DOPA is transformed into dopamine by DOPA decarboxylase, increasing the bioavailability of dopamine and correcting either low endogenous dopamine concentrations or increasing the stimulation in areas that have reduced dopaminergic-signaling due to degeneration. After it is activated by DOPA decarboxylase, the dopamine derived from L-DOPA can be deactivated via metabolism by the COMT enzyme, which occurs in a shallow active site located peripherally on the enzyme. The targeted inhibition of the COMT enzyme results in the prolonged effectiveness of L-DOPA, resulting in a net increase in pharmacological efficiency by preventing the medication from being metabolized prematurely. By selectively designing an inhibitor for the catechol-O-methyltransferase enzyme, the efficiency of the L-DOPA can be extended by regulating the metabolism of dopamine derived from L-DOPA, thus prolonging its effect in the brain. The effectiveness of these dopaminergic derivatives has been measured via *in silico* models which analyzed the strength of binding between each substrate and the enzymatic active site. A crystal structure of the COMT enzyme active site was isolated from the Protein Data Bank.The derivatives were docked using ArgusLab and optimized using M062X/6-31G. Interaction energies between the ligands and the proteins were calculated using M06L and MP2 with the 6-311+G* basis set.

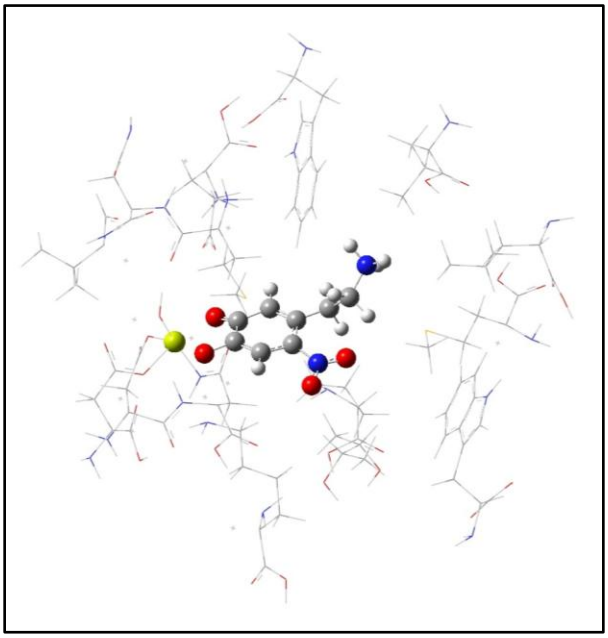

Figure 1: Dopamine docked in the COMT active site