

INVESTIGATING MONOAMINE OXIDASE ISOFORM SELECTIVITY FOR NEUROTRANSMITTER SUBSTRATES THROUGH THE PRODUCTION OF THERMODYNAMIC CYCLES

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To investigate the molecular recognition of neurotransmitters by the monoamine oxidase isoforms A and B drug targets for central nervous system diseases thermodynamic cycles have been built that quantify the change in selectivity for MAOB over MAOA as a function of structural change. Substrate binding constants for the endogenous dopamine, tyramine and phenethylamine plus four non-endogenous substrates were measured using Michaelis–Menten kinetics. The binding constants measured were used to construct thermodynamic cycles that measure the change in selectivity for MAOB over MAOA upon addition of hydroxyl groups to the *meta* and *para* positions of the phenyl ethylamine scaffold to give the two mono hydroxyl substituted substrates and the di-hydroxyl substituted dopamine. Addition of a *meta* hydroxyl to phenethylamine makes the substrate 9.5 kJ mol^{-1} less selective for MAOB, a *para* hydroxyl 7.7 kJ mol^{-1} less selective for MAOB and the addition of a second hydroxyl group 1.2 kJ mol^{-1} or 3.0 kJ mol^{-1} less selective for MAOB respectively. To probe the effect of removing hydrogen bond donors the *meta* position was substituted with a methyl group, the *para* with a methoxy group and both *meta* and *para* positions with two methyl groups. Removing hydrogen bond donors in this way made the substrates -1.1 kJ mol^{-1} , -5.7 kJ mol^{-1} and -6.9 kJ mol^{-1} more selective for MAOB. These thermodynamic cycles have been successfully used to investigate dopamine and related neurotransmitter binding and isoform selectivity for the active site of the MAO enzymes.