Tight-Binding Inhibition of Human Monoamine Oxidase B by Chromone Analogs: A Kinetic, Crystallographic, and Biological Analysis

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Monoamine oxidase B (MAO-B) is a validated drug target for Parkinson's disease. Chromone derivatives were identified as novel potent and reversible MAO-B inhibitors, and herewith we report on a crystallographic and biochemical analysis to investigate their inhibition mechanism. The crystal structures of human MAO-B in complex with three chromone analogs bearing different substituents on the exocyclic aromatic ring (determined at 1.6-1.8 Å resolution) showed that they all bind in the active site cavity of the protein with the chromone moiety located in front of the FAD cofactor. These inhibitors form two hydrogen bonds with Tyr435 and Cys172 and perfectly fit the hydrophobic flat active site of human MAO-B. This is reflected in their tight-binding mechanism of inhibition with K i values of 55, 17, and 31 nM for N-(3?,4?-dimethylphenyl)-4-oxo-4H-chromene-3-carboxamide (1), N-(3?-chlorophenyl)-4-oxo-4H-chromene-3-carboxamide (2), and N-(3?-fluorophenyl)-4-oxo-4H-chromene-3-carboxamide (3), respectively. These compounds were also 1000-fold more effective than l-deprenyl in reducing the cellular levels of reactive oxygen species (ROS).