	Experiment title: Crystal Structures of human monoamine oxidase B in Complex with Four Inhibitors of the N-Propargylaminoindan Class	**Experiment number**: MX129
Beamline: ID29 ID14 2 ID14 1 ID14 2	**Date of experiment**: 21 June 2003 / 23 June 2003 10 July 2003 / 11 July 2003 04 October 2003 / 06 October 2003 05 December 2003 / 06 December 2003	**Date of report**: 11 May 2004
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Report:

Abstract of the article: Binda, C., Li, M., Hubálek, F., Herzig, Y., Sterling, J., Edmondson, D.E., Mattevi, A. (2004) Crystal structures of MAO B in complex with four inhibitors of the N-propargylaminoindan class. *J. Medicinal Chemistry* **47**, 1767-1774.

Monoamine oxidase B (MAO B) is an outer-mitochondrial membrane enzyme that catalyses the oxidation of arylalkylmine neurotrasmitters. The crystal structures of MAO B in complex with four of the N-propargylaminoindan class of MAO covalent inhibitors (rasagiline, N-propargyl-1(S)-aminoindan, 6-hydroxy-N-propargyl-1(R)-aminoindan and N-methyl-N-propargyl-1(R)-aminoindan) have been determined at a resolution better than 2.1 Å. Rasagiline, 6-hydroxy-N-propargyl-1(R)-aminoindan and N-methyl-N-

propargyl-1(R)-aminoindan adopt essentially the same conformation with the extended propargyl chain covalently bound to the flavin and the indan ring located in the rear of the substrate cavity. N-propargyl-1(S)-aminoindan binds with the indan ring in a flipped conformation with respect to the other inhibitors, which causes a slight movement of the Tyr326 side chain. Four ordered water molecules are an integral part of the active site and establish H-bond interactions to the inhibitor atoms. These structural studies may guide future drug-design to improve selectivity and efficacy by introducing appropriate substituents on the rasagiline molecular scaffold.

Abstract of the article: Hubálek, F., Binda, C., Li, M., Herzig, Y., Sterling, J., Youdim, M.B.H., Mattevi, A., Edmondson, D.E., (2004) Inactivation of Purified Human Recombinant Monoamine Oxidases A and B by Rasagiline and Its Analogues. *J. Medicinal Chemistry*, **47**, 1760-1766.

The inactivation of purified human recombinant monoamine oxidase (MAO) A and B by rasagiline [*N*-propargyl-1(*R*)-aminoindan] and four of its analogues [*N*-propargyl-1(*S*)-aminoindan (*S*-PAI), 6-hydroxy-N-propargyl-1(*R*)-aminoindan (*R*-HPAI), N-methyl-N-propargyl-1(*R*)-aminoindan (*R*-MPAI) and 6-(N-methyl,N-ethyl carbamoyloxy)-N-propargyl-1(*R*)-aminoindan (*R*-CPAI)] has been investigated. All compounds tested, with the exception of *R*-CPAI, form stoichiometric N(5) flavocyanine adducts with the FAD moiety of either enzyme. No H_2O_2 is produced during either MAO A or MAO B inactivation which demonstrates that covalent addition occurs in a single turnover. Rasagiline has the highest specificity for MAO B as demonstrated by a 100-fold higher inhibition potency (k_{inact}/K_i) as compared to MAO A, with the remaining compounds exhibiting lower isozyme specificities. MAO B and MAO A are more selective for the *R*-enantiomer (rasagiline) as compared to the *S*-enantiomer (*S*-PAI) by 2,500-fold and 17-fold, respectively. Differences in UV/VIS and CD spectral data of the complexes of the studied compounds with both MAO A and MAO B are interpreted in light of crystallographic data of complexes of MAO B with rasagiline and its analogues

Abstract of the article: Binda, C., Li, M., Hubálek, F., Edmondson, D.E., Mattevi, A. (2004) Crystal structure of human monoamine oxidase B, a drug target enzyme monotopically inserted into the mitochondrial outer membrane. *FEBS Lett.* **564**, 225 - 228.

Monoamine oxidase B (MAO B) is an outer mitochondrial membrane protein that oxidizes arylalkylamine neurotransmitters and has been a valuable drug target for many neurological disorders. The 1.7 Å resolution structure of human MAO B shows the enzyme is dimeric with a C-terminal trans-membrane helix protruding from each monomer and anchoring the protein to the membrane. This helix departs perpendicularly from the base of the structure in a different way with respect to other monotopic membrane proteins. Several apolar loops exposed on the protein surface are located in proximity of the C-terminal helix, providing additional membrane binding interactions. One of these loops (residues 99-112) also functions in opening and closing the MAO B active site cavity, which suggests that the membrane may have a role in controlling substrate binding.

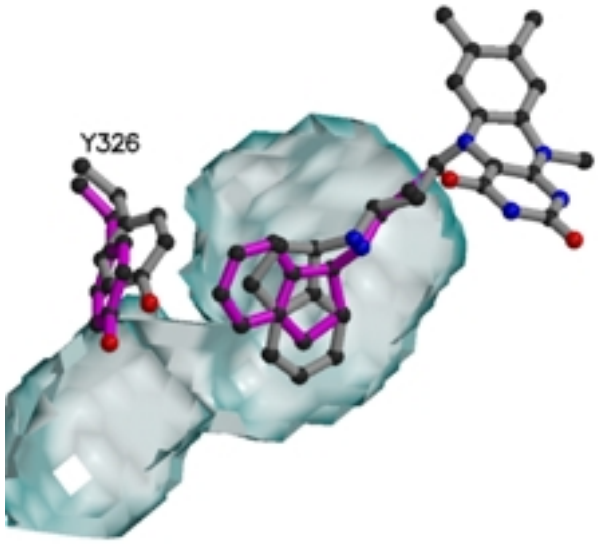

Figure. Comparison of the binding modes of rasagiline and S-PAI. The picture was produced by superimposing the Cα atoms of the two inhibitor complexes. The flavin ring, the inhibitor, and the Tyr326 side chain of the rasagiline structure are in gray. The inhibitor and the Tyr326 side chain of the S-PAI complex are in magenta. The substrate and inhibitor cavities are shown as semitransparent cyan surface and were calculated from the coordinates of the rasagiline complex.