ESRF	**Experiment title:** **Inhibition of Human Monoamine Oxidases by Analogues of the Anti-Parkinson Drug Rasagiline**	**Experiment number**: MX267 MX394

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Report:

Binda, C., Hubalek, F., Li, M., Herzig, Y., Sterling, J., Edmondson, D.E., Mattevi, A. (2005). Inhibition of Human Monoamine Oxidases by Analogues of the Anti-Parkinson Drug Rasagiline*, J. Med. Chem.* in press

Abstract Monoamine oxidases A and B (MAO A and B) catalyze neurotransmitters degradation and represent drug targets for the treatment of neurodegenerative disorders. Rasagiline is an irreversible, MAO B-selective inhibitor that has been approved as a novel anti-Parkinson's drug. In this study we investigate the inhibition of recombinant human MAO

A and MAO B by several rasagiline analogues. Different substituents added onto the rasagiline scaffold alter the binding affinity depending on the position on the aminoindan ring and on the size of the substituent. Compounds with a hydroxyl group on either the C4 or the C6 atom inhibit both isozymes, whereas a bulkier substituent such as a carbamate is tolerated only at the C4 position. The 1.7 Å crystal structure of MAO B in complex with 4-(*N*-methyl-*N*-ethyl-carbamoyloxy)-*N*-methyl-*N*-propargyl-1(*R*)-aminoindan shows that the binding mode is similar to that of rasagiline with the carbamate moiety occupying the entrance cavity space. 1(*R*)-aminoindan, the major metabolic product of rasagiline, and its analogues reversibly inhibit both MAO A and MAO B. The crystal structure of *N*-methyl-1(*R*)-aminoindan bound to MAO B shows that its aminoindan ring adopts a different orientation compared to that of rasagiline.