2-Arylthiomorpholine derivatives as potent and selective monoamine oxidase B inhibitors

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2-Arylthiomorpholine and 2-arylthiomorpholin-5-one derivatives, designed as rigid and/or non-basic phenylethylamine analogues, were evaluated as rat and human monoamine oxidase inhibitors. Molecular docking provided insight into the binding mode of these inhibitors and rationalized their different potencies. Making the phenylethylamine scaffold rigid by fixing the amine chain in an extended six-membered ring conformation increased MAO-B (but not MAO-A) inhibitory activity relative to the more flexible ?-methylated derivative. The presence of a basic nitrogen atom is not a prerequisite in either MAO-A or MAO-B. The best Ki values were in the 10-8 M range, with selectivities towards human MAO-B exceeding 2000-fold.