Selective Interactions of *O*-Methylated Flavonoid Natural Products with Human Monoamine Oxidase-A and –B

Abstract

A set of structurally related *O*-methylated flavonoid natural products isolated from *Senecio roseiflorus* (**1**), *Polygonum senegalense* (**2** and **3**), *Bhaphia macrocalyx* (**4**), *Gardenia ternifolia* (**5**), and *Psiadia punctulata* (**6**) plant species were characterized for their interaction with human monoamine oxidases (MAO-A and -B) in vitro. Compounds **1**, **2**, and **5** showed selective inhibition of MAO-A, while **4** and **6** showed selective inhibition of MAO-B. Compound **3** showed ~2-fold selectivity towards inhibition of MAO-A. Binding of compounds **1**-**3** and **5** with MAO-A, and compounds **3** and **6** with MAO-B was reversible and not time-independent. The analysis of enzyme-inhibition kinetics suggested a reversible-competitive mechanism for inhibition of MAO-A by **1** and **3**, while a partially-reversible mixed-type inhibition by **5**. Similarly, enzyme inhibition-kinetics analysis with compounds **3**, **4**, and **6**, suggested a competitive reversible inhibition of MAO-B. The molecular docking study suggested that **1** selectively interacts with the active-site of human MAO-A near N5 of FAD. The calculated binding free energies of the *O*-methylated flavonoids (**1** and **4**-**6**) and chalcones (**2** and **3**) to MAO-A matched closely with the trend in the experimental IC_{50}s. Analysis of the binding free-energies suggested better interaction of **4** and **6** with MAO-B than with MAO-A. The natural *O*-methylated flavonoid (**1**) with highly potent inhibition (IC_{50} 33 nM; Ki 37.9 nM) and >292 fold selectivity against human MAO-A (vs. MAO-B) provides a new drug lead for the treatment of neurological disorders.

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