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Replacement of Chalcone-Ethers with Chalcone-Thioethers as Potent and Highly Selective Monoamine Oxidase-B Inhibitors and Their Protein-Ligand Interactions

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Abstract: To develop new potent and highly selective MAO-B inhibitors from chalcone-thioethers, eleven chalcones-thioethers were synthesized and their monoamine oxidase (MAO) inhibition, kinetics, reversibility, and cytotoxicity of lead compounds were analyzed. Molecular dynamics were carried out to investigate the interactions. Compound **TM8** showed potent inhibitory activity against MAO-B, with an IC_{50} value of 0.010 μM, followed by **TM1**, **TM2**, **TM7**, and **TM10** (IC_{50} = 0.017, 0.021, 0.023, and 0.026 μM, respectively). Interestingly, **TM8** had an extremely high selectivity index (SI; 4860) for MAO-B. Reversibility and kinetic experiments showed that **TM8** and **TM1** were reversible and competitive inhibitors of MAO-B with K_i values of 0.0031 ± 0.0013 and 0.011± 0.001 μM, respectively. Both **TM1** and **TM8** were non-toxic to Vero cells with IC_{50} values of 241.8 and 116.3 μg/mL (i.e., 947.7 and 402.4 μM), respectively, and at these IC_{50} values, both significantly reduced reactive oxygen species (ROS) levels. **TM1** and **TM8** showed high blood-brain barrier permeabilities in the parallel artificial membrane permeability assay. Molecular dynamics studies were conducted to investigate interactions between **TM1** and **TM8** and the active site of MAO-B. Conclusively, **TM8** and **TM1** are potent and highly selective MAO-B inhibitors with little toxicity and good ROS scavenging abilities and it is suggested that both are attractive prospective candidates for the treatment of neurological disorders.

Keywords: chalcone; MAO-B; selectivity; reversibility; cytotoxicity; ROS; molecular dynamics

1. Introduction

Parkinson's disease (PD) is considered the second most common progressive neurodegenerative disorder in the elderly and is characterized by motor system disruption [1].