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RESEARCH ARTICLE

Exploration of a new class of monoamine oxidase B inhibitors by assembling benzyloxy pharmacophore on halogenated chalcones

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Abstract

Eight derivatives of benzyloxy-derived halogenated chalcones (**BB1-BB8**) were synthesized and tested for their ability to inhibit monoamine oxidases (MAOs). MAO-A was less efficiently inhibited by all compounds than MAO-B. Additionally, the majority of the compounds displayed significant MAO-B inhibitory activities at 1 μM with residual activities of less than 50%. With an IC_{50} value of 0.062 μM, compound **BB4** was the most effective in inhibiting MAO-B, followed by compound **BB2** ($IC_{50} = 0.093$ μM). The lead molecules showed good activity than the reference MAO-B inhibitors (Lazabemide $IC_{50} = 0.11$ μM and Pargyline Pargyline $IC_{50} = 0.14$). The high selectivity index (SI) values for MAO-B were observed in compounds **BB2** and **BB4** (430.108 and 645.161, respectively). Kinetics and reversibility experiments revealed that **BB2** and **BB4** were reversible competitive MAO-B inhibitors with K_i values of 0.030 ± 0.014 and 0.011 ± 0.005 μM, respectively. Swiss target prediction confirmed the high probability in the targets of MAO-B for both compounds. Hypothetical binding mode revealed that the **BB2** or **BB4** is similarly oriented to the binding cavity of MAO-B. Based on the modelling results, **BB4** showed a stable confirmation during the dynamic simulation. From these results, it was concluded that **BB2** and **BB4** were potent selective reversible MAO-B inhibitors and they can be considered drug candidates for treating related neurodegenerative diseases such as Parkinson's disease.

Ashutosh Kumar Singh and Seong-Min Kim authors contributed equally to this work.

