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Novel Class of Chalcone Oxime Ethers as Potent Monoamine Oxidase-B and Acetylcholinesterase Inhibitors

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Abstract: Previously synthesized novel chalcone oxime ethers (COEs) were evaluated for inhibitory activities against monoamine oxidases (MAOs) and acetylcholinesterase (AChE). Twenty-two of the 24 COEs synthesized, except **COE-17** and **COE-24**, had potent and/or significant selective inhibitory effects on MAO-B. **COE-6** potently inhibited MAO-B with an IC_{50} value of 0.018 μM, which was 105, 2.3, and 1.1 times more potent than clorgyline, lazabemide, and pargyline (reference drugs), respectively. **COE-7**, and **COE-22** were also active against MAO-B, both had an IC_{50} value of 0.028 μM, which was 67 and 1.5 times lower than those of clorgyline and lazabemide, respectively. Most of the COEs exhibited weak inhibitory effects on MAO-A and AChE. **COE-13** most potently inhibited MAO-A (IC_{50} = 0.88 μM) and also significantly inhibited MAO-B (IC_{50} = 0.13 μM), and it could be considered as a potential nonselective MAO inhibitor. **COE-19** and **COE-22** inhibited AChE with IC_{50} values of 5.35 and 4.39 μM, respectively. The selectivity index (SI) of **COE-22** for MAO-B was higher than that of **COE-6** (SI = 778.6 vs. 222.2), but the IC_{50} value (0.028 μM) was slightly lower than that of **COE-6** (0.018 μM). In reversibility experiments, inhibitions of MAO-B by **COE-6** and **COE-22** were recovered to the levels of reference reversible inhibitors and both competitively inhibited MAO-B, with K_i values of 0.0075 and 0.010 μM, respectively. Our results show that **COE-6** and **COE-22** are potent, selective MAO-B inhibitors, and **COE-22** is a candidate of dual-targeting molecule for MAO-B and AChE.

Keywords: monoamine oxidase; acetylcholinesterase; chalcones; oximes; kinetics; reversibility