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RESEARCH ARTICLE

Ethyl Acetohydroxamate Incorporated Chalcones: Unveiling a Novel Class of Chalcones for Multitarget Monoamine Oxidase-B Inhibitors Against Alzheimer's Disease

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Abstract: ***Background*:** Chalcones are considered as the selective scaffold for the inhibition of MAO-B.

***Objectives*:** A previously synthesized ethyl acetohydroxamate-chalcones (**L1**-**L22**) were studied for their inhibitory activities against human recombinant monoamine oxidase A and B (hMAO-A and hMAO-B, respectively) and acetylcholinesterase (AChE) as multi-target directed ligands for the treatment of Alzheimer's disease (AD).

***Methods*:** Enzyme inhibition studies of MAO-A, MAO-B and AChE is carried out. Computational studies such as Molecular docking, Molecular Mechanics/Generalized Born Surface Area calculations, ADMET prediction, and protein target prediction are also performed.

***Results*:** Among the screened compounds, compound **L3** has most potent hMAO-B inhibition with an IC_{50} value of 0.028 ± 0.0016 μM, and other compounds, **L1**, **L2**, **L4**, **L8**, **L12**, and **L21** showed significant potent hMAO-B inhibition with IC_{50} values of 0.051 ± 0.0014, 0.086 ± 0.0035, 0.036 ± 0.0011, 0.096 ± 0.0061, 0.083 ± 0.0016, and 0.038 ± 0.0021 μM, respectively. On the other hand, among the tested compounds, compound **L13** showed highest hMAO-A inhibition with an IC_{50} value of 0.51± 0.051 μM and **L9** has a significant value of 1.85 ± 0.045 μM. However, the compounds **L3** and **L4** only showed high selectivities for hMAO-B with selectivity index (SI) values of 621.4 and 416.7, respectively. Among the substituents in ring A of ethyl acetohydroxamate-chalcones (**L1**-**L9**), F atom at *p*-position (**L3**) showed highest inhibitory effect against hMAO-B. This result supports the uniqness and bizarre behavior of fluorine. Moreover, chalcones **L3**, **L4**, **L9**, **L11**, and **L12** showed potential AChE inhibitory effect with IC_{50} values of 0.67, 0.85, 0.39, 0.30, and 0.45 μM, respectively. Inhibitions of hMAO-B by **L3** or **L4** were recovered to the level of the reversible reference (lazabemide), and were competitive with K_i values of 0.0030 ± 0.0002 and 0.0046 ± 0.0005 μM, respectively. Inhibitions of AChE by **L3** and **L11** were of the competitive and mixed types with K_i values of 0.30 ± 0.044 and 0.14 ± 0.0054 μM, respectively.

***Conclusion*:** The studies indicated that **L3** and **L4** are considered to be promising multitarget drug molecules with potent, selective, and reversible competitive inhibitors of hMAO-B and with highly potent AChE inhibitory effect.

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