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Introduction of benzyloxy pharmacophore into aryl/heteroaryl chalcone motifs as a new class of monoamine oxidase B inhibitors

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The inhibitory action of fifteen benzyloxy *ortho/para*-substituted chalcones (B1-B15) was evaluated against human monoamine oxidases (hMAOs). All the molecules inhibited hMAO-B isoform more potently than hMAO-A. Furthermore, the majority of the molecules showed strong inhibitory actions against hMAO-B at 10 μ M level with residual activities of less than 50%. Compound B10 has an IC_{50} value of 0.067 μ M, making it the most potent inhibitor of hMAO-B, trailed by compound B15 (IC_{50} = 0.12 μ M). The thiophene substituent (B10) in the A-ring exhibited the strongest hMAO-B inhibition structurally, however, increased residue synthesis did not result in a rise in hMAO-B inhibition. In contrast, the benzyl group at the *para* position of the B-ring displayed more hMAO-B inhibition than the other positions. Compounds B10 and B15 had relatively high selectivity index (SI) values for hMAO-B (504.791 and 287.600, respectively). K_i values of B10 and B15 were 0.030 ± 0.001 and 0.033 ± 0.001 μ M, respectively. The reversibility study showed that B10 and B15 were reversible inhibitors of hMAO-B. PAMPA assay manifested that the benzyloxy chalcones (B10 and B15) had a significant permeability and CNS bioavailability with Pe value higher than 4.0×10^{-6} cm/s. Both compounds were stabilized in protein–ligand complexes by the π - π stacking, which enabled them to bind to the hMAO-B enzyme's active site incredibly effectively. The hMAO-B was stabilized by B10- and B15-hMAO-B complexes, with binding energies of – 74.57 and – 87.72 kcal/mol, respectively. Using a genetic algorithm and multiple linear regression, the QSAR model was created. Based on the best 2D and 3D descriptor-based QSAR model, the following statistics were displayed: R^2 = 0.9125, Q^2_{loo} = 0.8347. These findings imply that B10 and B15 are effective, selective, and reversible hMAO-B inhibitors.

Following Alzheimer's disease (AD), Parkinson's disease (PD) is by far the second most prevalent neurological condition. Persistent atrophy of dopaminergic neurons in the substantia nigra (SN) pars compacta is indeed a pathological attribute of PD. Non-dopaminergic systems, including noradrenergic, serotonergic, as well as

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