DE NOVO DESIGN DRUG-LIKE MOLECULES WITH POTENCIAL ANTI- ALZHEIMER'S DISEASE PROPERTIES USING METHODS CHEMINFORMATICS

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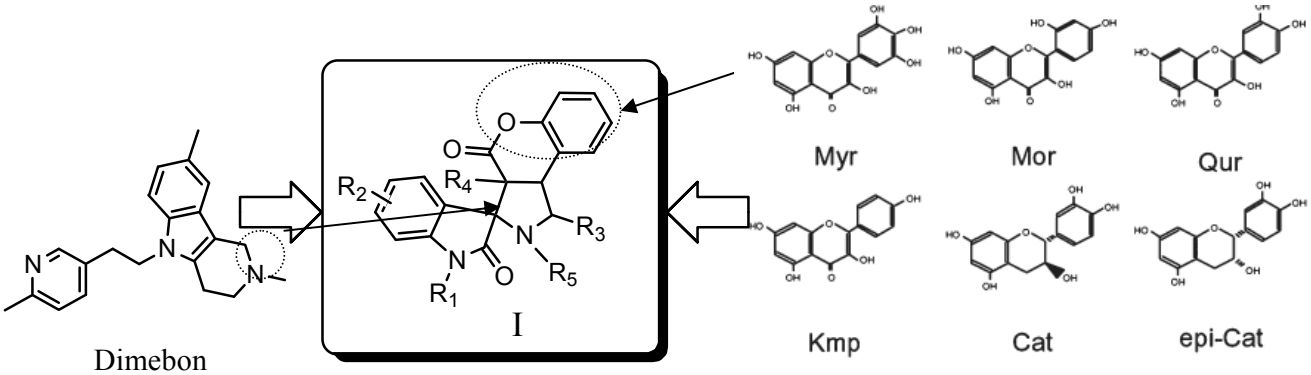
Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the deterioration of cognitive function and behavioral changes. Two main disease mechanism-based approaches are based on the involvement of two proteins, amyloid-β protein (Aβ) and tau. Aβ is the main constituent of senile plaques, and tau- is the main component of neurofibrillary tangles. Impairment of neuronal functions and loss of neurons Aβ is generated from APP by two proteases, β-secretase and γ-secretase. A third protease, α-secretase, which competes with β-secretase for the APP substrate, interferes with the production of Aβ. Therefore, three strategies to reduce Aβ have been proposed: inhibition of β-secretase, inhibition of γ-secretase and stimulation of α-secretase.



Recently, several studies have suggested that many kinds of natural polyphenols (myricetin (Myr), morin (Mor), quercetin (Qur), kaempferol (Kmp), (+)-catechin (Cat) and (-)-epicatechin (epi-Cat)) may have anti-amyloidogenic effects. Another promising molecule approved by the FDA for the treatment of Alzheimer's disease is known earlier H_1-histamine blockers Dimebon. We have tried to construct de novo drug-like molecules with potencial anti-Alzheimer's disease properties, containing both the indole moiety and the benzopyran nucleus, like natural compounds. In the first stage, we studied the QSAR for a known set of natural polyphenols using computational platform Molinspiration Cheminformatics, which allowed us to construct the correlation model to a number of molecular descriptors. In the second step, for focus screening libraries (I) in silico, predicted high anti protease activity to compounds (I) with over then 5 points of randomisation. More sensitive point is R_5, when R_5 is $CONH_2$. Thus, the proposed structures deserve attention for further research for potential anti-Alzheimer's drugs.