Abstract

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Title of diploma thesis: Synthesis and evaluation of dual acting potential drugs for neurodegenerative diseases

Alzheimer's disease (AD) and Parkinson's disease (PD) are neurodegenerative diseases that mainly affect the elderly population. The incidence of these diseases is still increasing worldwide, and currently, there is no cure that can permanently treat patients.

Current medications mainly aim to slow the progression of these diseases. The goal is to improve the accessibility of treatment, prevent progression, or completely cure patients suffering from AD and PD.

New potential drugs are also developing in this direction, which could exhibit a satisfactory effect in inhibiting cholinesterases. Acetylcholinesterase (ACh) and butyrylcholinesterase (BuChE) play a significant role in the pathogenesis of these diseases. Particularly in Alzheimer's disease (AD), there is a decrease in acetylcholine as a neurotransmitter that ensures the homeostasis and proper functioning of the central nervous system (CNS).

In AD treatment, acetylcholinesterase inhibitors (AChEIs) such as rivastigmine, galantamine, and donepezil are used to increase acetylcholine levels in the brain. Another group of drugs that helps in the treatment of AD are N-methyl-D-aspartate (NMDA) receptor inhibitors, which affect the level of glutamate in the brain and help slow down the development of AD.

In PD treatment, drugs that increase dopamine levels are used. Dopamine plays an important role in regulating body movement and proper coordination of movements. Therefore, PD treatment aims to replenish dopamine in the brain. The first drug used in PD treatment is levodopa, a dopamine precursor. Peripheral DOPA decarboxylase inhibitors

(benserazide, carbidopa), and catechol-O-methyltransferase inhibitors (COMT) entacapone and tolcapone are used to improve the transition of levodopa into the central nervous system (CNS). Other drugs used include dopamine agonists (pramipexole, ropinirole) and MAO-B inhibitors (rasagiline, selegiline).

As mentioned, the development of new treatment aims to move towards multi-target-directed ligands (MTDLs) drugs, which function as hybrid molecules and eliminate as many disease symptoms as possible. It is believed that oxidative stress, lack of ACh, and excessive degradation of catecholamines (which produce harmful aldehydes and hydrogen peroxides) are the causes of AD.

Based on these findings, a series of compounds were prepared in this study, which were based on three compounds used in the therapy of neuropsychiatric diseases. The first was isoniazid (a compound mainly used to treat tuberculosis) or its derivative iproniazid, phenelzine (a drug used in the US for depression therapy), and 5-methylisoxazole-3-carbohydrazide as part of the isocarboxazid drug. All of these starting compounds have the ability to inhibit monoamine oxidase (MAO), which is why they were further modified.

In this work, a total of 15 compounds were successfully synthesized. In most cases, hydrazine reacted with carbonyl compounds to form hydrazides and hydrazones in methanol as a solvent. These compounds were sent for *in vitro* biological evaluation of cholinesterase inhibition.

The efficacy evaluation was based on the IC_{50} value. Some of the compounds showed very good inhibition of AChE. The compounds prepared from 3-nitro derivatives had the best affinity for AChE, followed by compounds prepared from 4-nitro derivatives. The range of IC_{50} values ranged from 16.49 µM (best activity) to 159.57 µM (worst activity). For comparison, the standard rivastigmine has an IC50 of 56.10 µM.

The compounds did not show good activity in BuChE inhibition compared to standards. The best compound had an IC50 of 53.03 µM. The standard rivastigmine has a BuChE inhibition IC50 of 38.40 µM. The range of IC50 values ranged from 53.03 µM to 407.49 µM.