ABSTRACT

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Title of Thesis: **Synthesis of novel derivates of 7-aryl tacrines as potential multipotent therapeutics against Alzheimer´s disease**

Alzheimer's disease (AD) is the most prevalent form of dementia, characterized by multifactorial and progressive neurodegeneration. The complexity of AD pathophysiology is the main limiting factor for the difficulty of developing new therapeutic compounds. Current treatment merely alleviate symptoms without addressing the underlying causes of the disease. Tacrine was the first used and promising molecule in the therapy of AD due to its multifaceted mechanism of action. Studies demonstrated its inhibitory effect on cholinesterases (ChE) as well as its antagonism at NMDA receptors (NMDAR). However, severe hepatotoxicity led to the withdrawal of tacrine from the market. Consequently, there is ongoing research into tacrine derivatives to find molecules with lower toxicity but retained dual action. This thesis presents a new series of tacrine derivatives substituted at position seven with various heteroaromatic groups. A series of 16 compounds was synthesized through a two-step process involving Friedländer condensation and Suzuki coupling. Inhibitory activity against cholinesterases, cytotoxicity, and predicted blood-brain barrier (BBB) permeability were evaluated for all resultant products. The most promising derivatives were compounds **5a**, **5e**, **5i**, and **5m**, which also showed relative inhibition at NMDAR.

Keywords: Alzheimer's disease, tacrine, 7-heteroaryltacrine, cholinesterases, *N*-methyl-D-aspartate receptor