

RESEARCH ARTICLE

Synthesis and Cholinesterase Inhibitory Activity of *N*-Phosphorylated / *N*-Thiophosphorylated Tacrine

Maja Przybyłowska¹, Iwona Inkielewicz-Stepniak², Szymon Kowalski², Krystyna Dzierzbicka^{1,*}, Sebastian Demkowicz¹ and Mateusz Daśko³

¹Department of Organic Chemistry, Gdansk University of Technology, G. Narutowicza 11/12, 80-233 Gdansk, Poland;

²Department of Medical Chemistry, Medical University of Gdansk, Debinki 1, 80-211 Gdansk, Poland; ³Department of Inorganic Chemistry, Gdansk University of Technology, G. Narutowicza 11/12, 80-233 Gdansk, Poland

Abstract: Background: Alzheimer's disease (AD) is progressive and irreversible neurodegenerative disorder. Current pharmacotherapy is not able to stop progression of the disease and can only improve cognitive functions. Therefore, new drugs are being sought that will slow down the development of the disease.

Objective: Novel phosphorus and thiophosphorus tacrine derivatives **7-14** were designed, synthesized and their biological activity and molecular modeling was investigated as a new potential anti-Alzheimer's disease (AD) agents.

Method: 9-Chlorotacrine was treated with propane-1,3-diamine in the presence of sodium iodide to yield *N*¹-(1,2,3,4-tetrahydroacridin-9-yl)propane-1,3-diamine **6**. Finally, it was treated with corresponding acid ester or thioester to give phosphorus or thiophosphorus tacrine derivative **7-14**. All of the obtained final structures were characterized by ¹H NMR, ¹³C NMR, ³¹P NMR and MS.

Results: The results of the docking studies showed that the newly designed phosphorus and thiophosphorus tacrine analogs, theoretically possess AChE and BChE-binding ability. Kinetic study showed that **8** and **12** in the series proved to be more potent *electric eel* AChE (eeAChE) and human (hAChE) inhibitors than tacrine, where **8** inhibited eeAChE three times more than the referenced drug. The highest BChE inhibition revealed **11** and **13**. The most active compounds against eeAChE, hAChE and BChE showed mixed type of inhibition.

Conclusion: All new synthesized compound exhibited lower toxicity against *neuroblastoma* cell line (*SH-SY5Y*) in comparison with tacrine. Two analogues in the series, **7** and **9**, demonstrated lack of cytotoxicity against hepatocellular cells (hepG2).

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1. INTRODUCTION

Alzheimer disease (AD) is progressive and irreversible neurodegenerative disorder that is the most common form of dementia [1]. The elderly people are mainly affected. Current pharmacotherapy is not able to stop the progression of the disease and can only improve progressive functions. In 2015, there were about 29.8 million people with AD and it is estimated that the number will triple in the middle of this century [2, 3]. Despite extensive knowledge of the etiology, genetics and pathophysiological mechanism of AD, an effective method of treating this disease has still not been found [4]. As a result, new substances are sought that will slow

down the progression of the disease. One of the cognitive symptoms of AD, related to deficit of cholinergic transmission, is memory loss. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibition play a significant role in counteracting these symptoms. AChE is present in pre- and postsynaptic membranes and plays a major role in cholinergic transmission. BChE is located in neurofibrillary tangles and senile plaques. It hydrolyzes many esters including xenobiotics (e.g. cocaine or heroin), through which it performs the detoxifying function. In the central nervous system, it is mainly present in glial cells and neurons. Its role is regulating extracellular acetylcholine concentration. The role of BChE in the regulation of cholinergic transmission increases, when the activity of AChE declines with the death of cholinergic neurons [5].

One of the first drugs used to treat AD was tacrine, a strong, reversible AChE and BChE inhibitor. It was with-

*Address correspondence to this author at Department of Organic Chemistry, Chemical Faculty, Gdansk University of Technology, G. Narutowicza 11/12, 80-233 Gdansk, Poland. Tel.: +48-58-347-20-54; E-mail: krydzier@pg.edu.pl