SYNTHESIS OF N-SUBSTITUTED 2-((4-(BENZIMIDAZO (2,1-b)(1,3)THIAZIN-4-YL)PHENYL)(BOC)AMINO)ACETAMIDES FOR THE RESEARCH OF AMYLOID AGGREGATION MODULATORS

Tadas Vasiliauskas[1], Ieva Žutautė[1]

[1] Vilnius University, Faculty of Chemistry and Geosciences, Vilnius, Lithuania
tadas.vasiliauskas@chgf.stud.vu.lt

α-Synuclein is a small protein that can be found in the neurons of the central and peripheral nervous system. In Parkinson's disease, α-syn adopts a β-sheet conformation that, with additional monomers, forms oligomers and amyloid fibrils [1]. The accumulation of amyloid aggregates is associated with neuronal dysfunction. The search for compounds that inhibit α-synuclein aggregation is one approach to treating the disease. Such compounds range from small molecular-weight substances to complex drug mixtures. Work has been done to analyze the potential of a small-molecular-weight compound group, called imidazo[2,1-*b*][1,3]thiazines [2].

The purpose of this research is to synthesize modified imidazo[2,1-*b*][1,3]thiazines for further investigation of amyloid modulators. In this work, 4-iodoaniline is treated with di-*tert*-butyldicarbonate to introduce the *tert*-butoxycarbonyl (Boc) group. The nitrogen atom of the obtained product is alkylated with ethylbromoacetate. Then iodine is replaced with propargyl alcohol using the *Sonogashira* method, and the resulting product is brominated to replace the hydroxy group. During nucleophilic substitution, bromine is replaced with thiobenzimidazole. In the next step of cyclization, imidazo[2,1-*b*][1,3]thiazine is formed. In this work, the obtained product is modified in several steps with different amines, yielding amides.

During this research several *N*-substituted 2-((4-(benzimidazo[2,1-*b*][1,3]thiazin-4-yl)phenyl)(Boc)amino)acetamides were synthesized. The compounds will be further analyzed to determine their effectiveness in modulating amyloid aggregation.

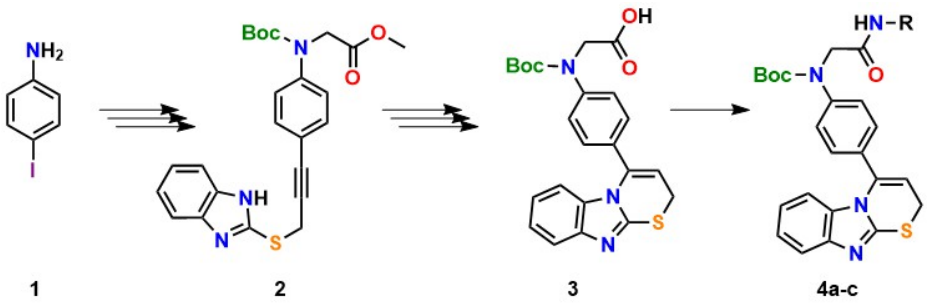

Fig. 1. Synthesis pathway for compounds 4a-c.

[1] P. Calabresi, A. Mechelli, G. Natale, L. Volpicelli-Daley, G. Di Lazzaro, and V. Ghiglieri, "Alpha-synuclein in Parkinson's disease and other synucleinopathies: from overt neurodegeneration back to early synaptic dysfunction," Cell Death and Disease, vol. 14, no. 3, p. 176, Mar. 2023, doi: 10.1038/s41419-023-05672-9.

[2] I. Misiūnaitė et al., "Imidazo[2,1-b][1,3]thiazine Derivatives as Potential Modulators of Alpha-Synuclein Amyloid Aggregation," ACS Chemical Neuroscience, vol. 15, no. 24, pp. 4418–4430, Nov. 2024, doi: 10.1021/acschemneuro.4c00451.