SYNTHESIS OF SUBSTITUTED BENZIMIDAZOTHIAZINES AND THIAZOLES FOR THE SEARCH OF AMYLOID AGGREGATION MODULATORS

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Amyloid fibril formation is a common pathological feature of protein-misfolding disorders, where nucleation-dependent aggregation can generate heterogeneous intermediates such as oligomeric species, before mature cross-beta fibrils accumulate [1]. In synucleinopathies such as Parkinson's disease, the presynaptic alpha-synuclein undergoes misfolding, oligomerization and fibrillization, contributing to cellular stress pathways and progressive neurodegeneration [2], [3]. Because toxic effects are frequently linked to early assemblies rather than mature fibrils, targeting the aggregation pathway with small-molecule compounds is a promising therapeutic direction [1], [2]. Among emerging scaffolds, imidazo[2,1-b][1,3]thiazine derivatives were shown to inhibit primary nucleation and stabilize alpha-synuclein oligomeric states [4]. The pharmacophore could be a promising source of derivatives for modulating amyloid aggregation. This study aims to synthesize and characterize different benzimidazothiazines and appropriate thiazoles with potential amyloid aggregation reducing activity.

Firstly, the starting compound, a benzoimidazole-2-thione intermediate, was synthesized via the thiocarbonylation and intramolecular cyclocondensation of N-propargylated diaminobenzene with thiocarbonyldiimidazole. Multiple reaction pathways were chosen to produce the following compounds. Base-mediated intramolecular nucleophilic cyclization favors the formation of the benzoimidazothiazole core. Alternatively, electrophilic halocyclization with NCS produces a similar chlorinated derivative. Finally, the benzoimidazothiazine core was achieved through metal-activated intramolecular cyclization with gold(III) bromide.

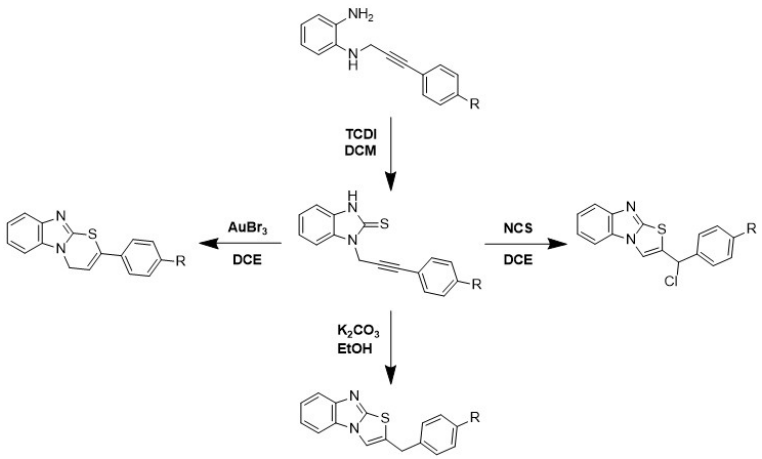

Fig. 1. General scheme of reactions

[1] P. C. Ke et al., "Half a century of amyloids: past, present and future," Chem. Soc. Rev., vol. 49, no. 15, pp. 5473–5509, 2020, doi: 10.1039/C9CS00199A
[2] O. Arias-Carrión, M. Guerra-Crespo, F. J. Padilla-Godínez, L. O. Soto-Rojas, and E. Manjarrez, "α-Synuclein Pathology in Synucleinopathies: Mechanisms, Biomarkers, and Therapeutic Challenges," IJMS, vol. 26, no. 11, p. 5405, Jun. 2025, doi: 10.3390/ijms26115405.
[3] J. Pitton Rissardo, A. McGarry, Y. Shi, A. L. Fornari Caprara, and G. T. Kannarkat, "Alpha-Synuclein Neurobiology in Parkinson's Disease: A Comprehensive Review of Its Role, Mechanisms, and Therapeutic Perspectives," Brain Sciences, vol. 15, no. 12, p. 1260, Nov. 2025, doi: 10.3390/brainsci15121260.
[4] I. Misiūnaitė et al., "Imidazo[2,1- b][1,3]thiazine Derivatives as Potential Modulators of Alpha-Synuclein Amyloid Aggregation," ACS Chem. Neurosci., vol. 15, no. 24, pp. 4418–4430, Dec. 2024, doi: 10.1021/acschemneuro.4c00451.