Abstract of PhD dissertation

"3,4-Dihydropyridin-2(1*H*)-ones and their sulfur analogs as precursors of polycyclic compounds with potential biological activity"

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3,4-Dihydropyridin-2(1*H*)-ones (3,4-DHP) and their sulfur analogues are compounds of great pharmacological importance. Promising biological activity makes 3,4-DHP derivatives a high among candidates for developing new drugs. In addition to the broad spectrum of biological activity exhibited by 3,4-DHP derivatives, it is primarily their exciting and not fully explored reactivity, potentially valuable for the synthesis of bioactive polycyclic derivatives, that motivates scientists to expand knowledge about the properties of these compounds and justifies the need to conduct broader research on their synthesis. This dissertation focuses on developing methods for obtaining new derivatives of 3,4 -dihydropyridin-2(1*H*)-ones and their use as precursors in synthesising new bicyclic systems obtained in intra- and intermolecular reactions. The literature part systematises the described methods of synthesising 3,4 dihydropyridin-2(1*H*)-ones and presents their reactivity in processes aimed at obtaining bioactive polycyclic compounds. Despite an extensive range of published methods for obtaining the 3,4-DHP system, the doctoral thesis included research on the synthesis of these compounds using the process of adding organomagnesium complexes to 2-pyridones, which has been explored for several years at the Department of Organic Chemistry and Physical Chemistry of ZUT, and which enables the functionalisation of DHP products through the initial synthesis of appropriately substituted 2-pyridones as substrates. The novelty and, at the same time, a challenge of the research undertaken as part of this doctoral thesis in this area was to direct the addition process in such a way that the main products were 3,4-DHP derivatives because the results obtained so far indicated 3,6-DHP isomers as the main products of these reactions.

As a result of research carried out as part of the doctoral thesis, methods for the synthesis of previously undescribed dihydropyridine(o)-2-(thi)one derivatives containing a benzhydryl group that can significantly modify the pharmacological properties of the compound, were developed. For the first time, a broad optimization of the nucleophilic addition reaction to 2-(thio)pyridones focused on directing the reaction on forming 3,4-DHP isomer as a major product, was carried out. It has been shown that selecting an appropriate organomagnesium reagent, using specific substituents in the 2-pyridone ring, and the appropriate temperature and concentration significantly increase the efficiency of forming the 3,4 DHP isomer. A positive effect of these studies is also the successful extension of the applicability of the nucleophilic addition method to 2 (thio)pyridones to the use of organometallic heterocyclic reagents derived from methylbenzothiazole, methylbenzoxazole and 1,2-dimethylindole.In the second part of this work, various azabicyclo[4.1.0]heptane derivatives

were obtained, first by adding dichlorocarbene to 3,4-DHP, and then by further derivatization. In reactions which proceed via intramolecular cyclization - optimized in terms of the solvent used, acid and reaction temperature - new 7,8-benzomorphanone derivatives and completely new bridged δ-lactams were obtained, forming a previously unknown carbon skeleton. Using methods developed as a part of the work, simple, two-step synthesis of the 1.5-methanoazocine[4,3-*b*]indole was designed and successfully carried out. The structures of obtained compounds were determined mainly by NMR spectroscopy techniques, GC-MS and HR-MS methods, and IR. The last part describes the preliminary, promising results of tests on the antiproliferative activity against A375 melanoma cells for selected compounds.

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