

Tytuł pracy: Design and synthesis of biologically active C-aryl derivatives of 2-pyridone and their sulfur analogues

Autor: mgr inż. Aleksandra Borzyszkowska-Ledwig

Promotor: dr hab. Jacek G. Sośnicki, prof. ZUT

Promotor pomocniczy: dr inż. Łukasz Struk

Streszczenie rozprawy doktorskiej w języku angielskim

The doctoral thesis describes synthetic and biological studies of selected aryl-benzyl dihydropyridin-2-one derivatives, and their sulfur analogues. In the synthetic part the influence of C-aryl rings on the reactivity and course of the addition reaction of benzyl organomagnesium reagents to 2-pyridones, and the cyclization of the obtained adducts under the influence of brominating and iodinating reagents were researched. The starting C-aryl 2-pyridones were obtained in good yields in cross-coupling reactions between 2-methoxypyridine and arylboronic acids or their derivatives followed by *N*-alkylation reactions, coupled with demethylation. Alternatively, *N*-alkylation and additional *N*-arylation have been performed for *NH* 2 -pyridones. Magnesates of the R_3MgLi type were used in the nucleophilic addition reactions to obtain C-aryl 6 (4) benzyl-substituted β , γ (γ , δ) -unsaturated δ -lactams. C6 Adducts were reacted with a brominating reagent (*N*-bromosuccinimide; NBS) and an iodinating reagent (*N*-iodosuccinimide; NIS), leading to various products depending on the C-aryl 2-pyridone used, as well as the applied conditions. When using C4-aryl derivatives of 3,6-dihydropyridin-2-ones in the halocarbocyclization reaction with NBS, 5-bromo- α , β -unsaturated 6-benzyl- δ -lactams were obtained as the main product and also a small amount of bromobenzomorphanone derivatives. The distribution of these products is different from the reaction using the C4-H (Me) 3,6-dihydropyridin-2-one derivatives as starting materials, which indicates the essential influence of C4-aryl groups on the direction of the reaction. This part of the research was supplemented by development of a selective method for the synthesis of 5-bromo-substituted α , β -unsaturated δ -lactams. C5-Aryl 3,6-dihydropyridin-2-one derivatives also behaved differently when reacted with NBS than derivatives without a C5 substituent. In the case of these substrates, a 5-aryl- or 5-benzyl-, 6-hydroxy δ -lactam was obtained, which spontaneously or under optimized conditions cyclized to the bromoindeno [2,1-b] pyridin--2-one derivative, a valuable system in terms of potential biological properties. An important result of this part of the research

was the development of a method of synthesis of bromoindeno [2,1-b] pyridin-2-one derivatives without isolating the intermediate 6-hydroxy-lactam. It is worth emphasizing, that in the above-mentioned reactions there is a new version of the aza-pinacoline rearrangement, as a result of which the benzyl group migrates from the C6 to C5 position of the 2-pyridone ring. A similar rearrangement was observed, investigated and reported for the reaction of 4-aryl-3,6-dihydro-2-pyridones with NIS to give 3-iodo-5-benzyl-2-pyridones. It has been shown that the obtained bromoindenopyridones and iodopyridones can then be functionalized in the elimination and Suzuki and Sonogashira reactions, respectively.

The second part of the research was devoted to designing C5-aryl C4-benzyl derivatives of 3,4-dihydropyridine-2-thiones for antitumor activity and the development of a method of their preparation, antiproliferative studies involved five cancer cell lines: MCF-7 - breast cancer cell line, A375 - melanoma cell line, HT-29 - colon cancer cell line, SK-OV3 - ovarian cancer cell line, PC-3 - prostate cell line. As part of the research, 21 new derivatives were designed, which were obtained as a result of the previously developed synthesis method, universal for most of the obtained derivatives. Compounds were designed based on previous results of antitumor studies obtained for bioisosteric 3,4-dihydropyrimidine-2-thiones, which indicated a decisive influence of aryl rings on antiproliferative activity, and on theoretically predicted logP partition coefficients for the proposed structures. The research was carried out in stages by modifying the structure of the compounds on the basis of the obtained results of research on antitumor activity. The developed method of obtaining the most active NH-substituted derivatives of 4-benzyl-5-aryl-3,4-dihydropyridine-2-thione included the synthesis of 5-aryl-2-methoxypyridines using the Suzuki coupling reaction, conversion of the obtained compounds into NH-substituted 2-pyridones, regioselective, nucleophilic 1,4-addition of benzylmagnesate to 2-pyridones and thionation reactions using Lawesson's reagent. As a result of the research, it was found that the most active compound is the NH 3,4-dihydro-pyridine-2-thion derivative, having a thiophene ring at the C5 position, as indicated by IC₅₀ values: 1.71 ±0.58 and 1.67 ±1,47 μM, obtained against A375 and SK-OV3 cell line, respectively. Importantly, this compound showed relatively low cytotoxicity in relation to healthy cells.

30.09.2022

Aleksandra Borzyszkowska-Ledwig