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Synthesis of 5'-Azidonucleosides as Building Blocks for the Preparation of Biologically Active Bioconjugates

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Abstract : The cancer cells require higher amount of nucleoside building blocks for their proliferation, therefore they have significantly higher uptake of nucleosides by the different nucleoside transporters. Therefore, the conjugation with nucleosides may significantly increase the efficiency and selectivity of potential active pharmaceutical ingredients. On the other hand, the advantage of using a nucleoside could be either the higher activity on targeted enzymes overrepresented in cancer cells or an enhanced cellular uptake of the bioconjugates in these cells compared to the healthy ones. This fact can be used to make the nucleosides, as targeting moieties covalently bound to anti-cancer drug molecules which can selectively accumulate in cancer cells. However, in order to form the nucleoside-drug conjugates, such nucleoside building blocks are needed, which can selectively be coupled to the drug molecules containing even a high number of diverse functional groups. One of the most selective conjugation techniques is the copper-catalyzed azide-alkyne click reaction that requires the presence of an alkyl group on one of the conjugated molecules and an azide group on the other. In case of nucleosides, the development of azide group is simpler for which the replacement of the 5'-hydroxy group is the most suitable. This transformation generally involves many side reactions and result in very low yields. In addition, during our experiments, the transformation of the 2'-deoxyguanosine to the corresponding 5'-deoxy-5’-azido-2’-deoxyguanosine could not be performed with any of the methods described in the literature. Therefore, we have tried to overcome these difficulties with not only using the traditional process based on the 2 step exchange of tosyl to azide, but also using the Mitsunobu reaction which requires only one step. However, this path proved to be unsuccessful in spite of the optimizing the reaction conditions. Finally, a method has been developed whereby the azide groups were incorporated into the 5’-position resulting in significantly better yields compared to all other previous methods, and we were able to produce all the four nucleoside derivatives.

Keywords : 5'-azidonucleosides, bioconjugate, click reaction, proliferation
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