Novel Design and Total Synthesis of Aza-C-Nucleosides From Furfuryl Alcohol, the Key to Fighting RNA Viral Diseases

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In our research we focused on antivirotics, broad-spectrum drugs against RNA viral diseases. Galidesivir, a molecule that today appears to be the most optimal inhibitor of viral RdRp, became a point of interest for us. However, this drug was unusable in practice due to its high cost of production (around 5000 €/g). Therefore, we decided to look for a new innovative way to produce this molecule and other aza-C-nucleosides cheaper and faster. After a literature search and retrosynthetic analysis, we created a new total synthesis of Galidesivir. This starts with furfuryl alcohol, as an inexpensive and green starting material. It is then converted into a key aza-saccharide precursor in 6 steps. The reaction cascade begins with Achmatowicz oxidation of protected furfuryl alcohol, and the product's double bond can be dihydroxylated in two ways. The key and most complex step, the closure of the aza-saccharide ring, was performed by stereoselective reductive amination with (+)-benzylethylamine. This brings us to the key precursor in <95:5 e.e. selectivity for the (D)-ribo, or even the new (D)-aribo configuration. After 3 more steps, we got to Galidesivir citrate in a total yield of 35%. Our work was also used in another study that was the first describe the IC50 values on the RdRp mutation of the SARS-CoV-2 virus. If our methodology was to be applied to industry, the production price would be reduced by at least 625%. Our synthesis is also a possible building block for the development of new drugs. In this way, we brough a commertialy viable antivirotic with seemingly minor side effects, that could possibily save hundreds of thousand lives that sucome to RNA-viral dissieses every year.

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