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Nucleoside drug safety improvement via pronucleotide approaches

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Antiviral and anticancer nucleoside analogs have been used in clinical practice for decades. For example, a number of dideoxynucleoside drugs such as Zidovudine, Stavudine and Lamivudine are widely used in the treatment of HIV and HBV infections. However, major concerns such as drug toxicity, ineffectiveness and resistance resulting from the inefficient phosphorylation (by cellular kinases) and other processes are often associated. To overcome these disadvantages, various nucleosides and other prodrug analogs such as pronucleotides have been chemically synthesized and investigated. The pronucleotide approach involves modifying the drug to enable it to better enter the cell, and be converted to an active drug via either chemical and/or enzymatic activations. This approach allows the bypass of the rate-limiting phosphorylation step(s) with the prospect of improving the stability, bioavailability and efficacy of the parent nucleoside drug, and decreasing the toxicity as well. In this report, pronucleotide approaches and toxicity profiles for some typical nucleoside analogs are reviewed, and our pronucleotide chemical approach which might be useful for the synthesis of a number of nucleoside triphosphate prodrugs will be discussed. The chemical activation/degradation pathways of selected pronucleotides are proposed based on LC-MS analysis.

Biography

Zhihong Xu obtained her first PhD in Natural Product Chemistry from Shanghai Institute of Materia Medica, Chinese Academy of Sciences, and her second PhD with a Double Major in Organic Synthesis and Biochemistry from Duke University, USA. She is currently an Associate Professor of Pharmaceutical Sciences in South College School of Pharmacy at Knoxville, Tennessee, USA. Her teaching and research are centered on medicinal chemistry at the interface of natural product chemistry, organic chemistry and biochemistry, including lead discovery and investigation of small molecule chemicals and pharmacological properties.

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