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How to get highly polar nucleoside analogue triphosphates into cells – An impossible task? – No!

Over the last decades a variety of nucleoside analogues were applied clinically in antiviral chemotherapy. However, quite often the antiviral potency of the nucleoside analogues is limited due to the lack of intracellular phosphorylation into the triphosphorylated forms by cellular kinases. This problem cannot be solved by using the phosphorylated nucleosides due to their high polarity which prevent an efficient cell membrane passage. An option to overcome this hurdle is the use of lipophilic precursors of nucleotides, which are able to pass the cell membrane and deliver the corresponding nucleotides intracellularly (pronucleotides). In the past we developed nucleoside mono- (cycloSal-system) and nucleoside diphosphate prodrug approaches (DiPPro-approach). Of course, the final aim should be to develop nucleoside triphosphate prodrugs because the delivered triphosphate is the direct acting inhibitor of the viral polymerases. In contrast, mono- or diphosphate delivery systems are still dependent on the forward phosphorylation into the triphosphate. So far, no example of such a prodrug system has been reported. In our work, d4TTP prodrugs with different aliphatic masking units have been synthesized via two different routes based on phosphoramidite or H-phosphonate chemistry. Our triphosphate delivery system is comprised of enzymatically cleavable system is comprised of enzymatically cleavable masking groups (acyloxybenzyl-moieties) which are covalently attached to the □-phosphate group of the nucleoside triphosphate. In addition, a variety of nucleotide analogues have been investigated. The target prodrug compounds were obtained in yields up to 85%. Chemical hydrolysis studies, pig liver esterase studies, enzymatic cleavage in CEM/0 cell extract, primer extension assays, PCR assays, whole-cell incubations and antiviral HIV tests will be discussed and proved the successful delivery of nucleoside triphosphates. This new TriPPPro-concept will open up unknown possibilities not only in Medicinal Chemistry but also in Chemical Biology.

Biography

Chris Meier obtained a diploma and Ph.D. degrees in Chemistry from the University of Marburg, Germany in 1989. He joined the Organic Chemistry Department at the Pasteur-Institute in Paris, France from 1990 to 1991 as a Post-Doc. In 1996 he obtained the Habilitation in Organic Chemistry from the University of Frankfurt/Main, Germany. 1997 he was appointed as associate professor at the University of Würzburg, Germany and then in 1999 he joined Universität Hamburg, Germany as a full professor for Organic Chemistry. He received several awards, one being the Williams Prusoff-Award from the International Society of Antiviral Research (ISAR). He is currently the president elect of the International Society on Nucleoside, Nucleotides and Nucleic Acids (IS3NA) and a board of directors member of the ISAR. Recently he was awarded with the Zhiqiang-guestprofessorship from Shanghai University. He has published more than 220 scientific publications and is the inventor of 12 issued patents

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