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Quantitative determination of O, O' -di-[4-(methylthio)phenyl]-phosphonates of AZT in rat plasma by HPLC-ESI-MS/MS

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Abstract

The O,O'-di-[4-(methylthio)phenyl]-phosphonates of AZT, a pro-drug of AZT, was found to have a pronounced and selective anti-HIV-2 effect in CEM/0, MT4[1,2]. However, the drug mechanisms of its *in vivo* behavior still remain unclear and the pharmacokinetics research will significantly enhance our understanding it. In this context, we developed and validated a HPLC/ESI-MS/MS method for the efficient, specific, sensitive analysis for the pharmacokinetic study on the model pronucleotide of AZT using d4T as internal standard (IS).

The compound was separated on a Shim-pack VP-ODS C_{18} analytical column using a mobile phase of methanol / 10 mM ammonium acetate with gradient elution. The analyte was detected in positive ion mode using multiple reaction monitoring (MRM). The method was validated and the specificity, linearity, lower limit of quantitation (LLOQ), precision, accuracy, recoveries and stability were determined. LLOQs was 40 ng/mL for the pro-drug. Rat plasma samples spiked with the pro-drug showed no matrix-specific interfering peaks at the retention times of the analyte and the IS. Correlation coefficient (r) value for the linear range of 40–10,000 ng/mL was greater than 0.999. The intra-day and inter-day precision and accuracy were better than 7.13%. The relative and absolute recovery was above 72%. This validated method has been successfully used to quantify the plasma concentration of the analyte after intravenous administration to rats (n = 6). The mean ± S.D. (n = 6) plasma concentration versus time profile for the pro-drug is depicted in Figure 1, after administration to six rats at a dose of 5 mg/kg.

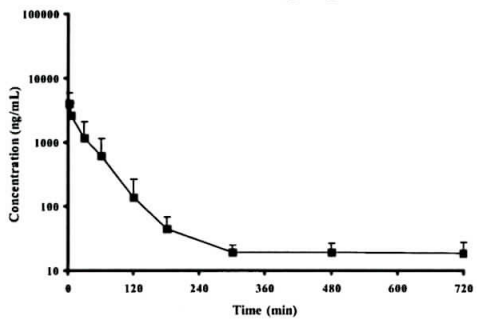

Figure 1. Mean drug plasma concentration time curve (mean ± S.D., n = 6) of pro-drugs in rats after i.v. administration of O,O'-di-[4-(methylthio)phenyl]-phosphonates of AZT.

References:

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2. Christopher M, Ranjith NP, Naheed M and Alan JH. *Bioorg. Med. Chem. Lett.* 1992; **2**: 201.