Abstract
Design and Synthesis of 4-N-Alkanoyl and 4-N-Alkyl Gemcitabine Analogues Suitable for Positron Emission Tomography

By

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The coupling of gemcitabine to carboxylic acids with varying terminal moieties or reaction of 4-N-tosylgemcitabine with corresponding alkyl amines afforded the 4-N-alkanoyl and 4-N-alkyl gemcitabine analogues. Analogues bearing a terminal hydroxyl group on the alkyl chain were fluorinated with DAST or under conditions compatible with synthetic protocols for $^{18}$F labeling. The 4-N-alkylgemcitabine-NOTA conjugate underwent efficient chelation with gallium chloride under conditions compatible with $^{68}$Ga labeling protocols. The 4-N-alkanoylgemcitabine analogues exhibited potent cytostatic activities against murine and human tumor cell lines with IC$_{50}$ values in the low nM range. In comparison to the 4-N-alkanoyl analogues, the 4-N-alkylgemcitabines had modest cytostatic activities with IC$_{50}$ values in the low µM range. The cytostatic activity for the 4-N-alkanoylgemcitabines was drastically diminished in the deoxycytidine kinase deficient CEM/dCK- cell line whereas the 4-N-alkylgemcitabines were only moderately reduced. Although none of the selected compounds were found to be effective substrates for cytosolic dCK, both the 4-N-alkanoyl and 4-N-alkyl gemcitabine derivatives inhibited new DNA synthesis. Therefore, the 4-N-alkanoyl gemcitabine derivatives need to be converted to gemcitabine before realizing their cytostatic potential. In contrast, the 4-N-alkylgemcitabines achieve their modest activity without any "measurable" conversion to gemcitabine and possibly via alternative dCK-independent pathway.

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