UNIVERSITY GRADUATE SCHOOL BULLETIN ANNOUNCEMENT

Florida International University
University Graduate School

Doctoral Dissertation Defense

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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