INVESTIGATION OF PENICILLAMINE REPLACEMENT OF CYSTEINE RESIDUES IN DOTA-[TYR^3]-OCTREOTATE: SYNTHESIS, CHARACTERIZATION AND EVALUATION OF BIOLOGICAL ACTIVITIES

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ABSTRACT

Modification of the peptide sequence of DOTA-Tyr^3-octreotate is carried out by substituting the cysteine moieties with *D*-Cysteine, *L*-Penicillamine and *D*-Penicillamine in one or both positions to study the effect of this replacement on chemical and receptor binding properties. Fmoc-solid phase peptide synthesis was used to construct the linear sequence of the peptides, including the attachment of DOTA. The cyclization of the peptides were carried out by use of $[Pt(en)_2Cl_2]Cl_2$ or DMSO. Steric constraints imposed by the gem-dimethyl groups on the penicillamine moieties resulted in longer reaction times and lower yields compared to the cysteine moieties. After preparative HPLC or Sep-Pak® purification, these peptides were characterized by using LCMS. ^{nat}In-DOTA^0-peptides were synthesized and characterized by LCMS. Using ^{111}In, radiolabelling of these peptides was carried out. These were purified by using HPLC and the isolated radiolabelled peptide was used to carry out in vitro studies. In serum stability studies, all radiolabelled peptides were found to be stable. Preliminary results from cell uptake studies (using AR42J cell line)

showed all modified peptides had lower uptakes in comparison to the control peptide, ^{111}In-DOTA-Tyr^3-octreotate. IC_{50} values of two peptides, ^{nat}In-DOTA^0-[*D*Cys^2, Tyr^3, *D*Cys^7]-octreotate and ^{nat}In-DOTA^0-[Pen^2, Tyr^3, Pen^7]-octreotate were in the range of 10^{-6}-10^{-5} M range.