INVESTIGATING $^{99m}$TECHNETIUM/RHENIUM(V)-CYCLIZED OCTREOTIDE ANALOGUES USING EXPERIMENTAL AND COMPUTATIONAL METHODS

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ABSTRACT

Radiolabeled proteolytic degradation-resistant somatostatin analogues have been of long-standing interest as cancer imaging and radiotherapy agents for targeting somatostatin receptor-positive tumors. Our interest in developing $^{186}$Re- and $^{188}$Re-based therapeutic radiopharmaceuticals led to investigation of a new Re(V)-cyclized octreotide analogue, Re(V)-cyclized SDPhe$^1$-Tyr$^3$-octreotate [thiolated-DPhe$^1$-Cys$^2$-Tyr$^3$-DTlp$^4$-Lys$^5$-Thr$^6$-Cys$^7$-Thr(OH)$^8$] (Re-SDPhe-TATE). The four isolated/semi-isolated Re-SDPhe-TATE isomers exhibited different receptor binding affinities in vitro. Two-dimensional NMR experiments and electronic structure calculations were employed to elucidate the structural differences among the isomers. The Re-cyclization reaction was translated to the $^{99m}$Tc radiotracer level. About 85% total $^{99m}$Tc labeling yield was achieved; the chemical stability of $^{99m}$Tc-SDPhe-TATE was examined in PBS solution and 1 mM cysteine solution under physiological conditions.

A reliable computational method for modeling Re-peptide complexes may facilitate the design of $^{99m}$Tc/Re(V)-cyclized octreotide analogues for targeting somatostatin receptor-positive tumors. Therefore, a relaxed PES scan approach was assessed for various Re(V) model complexes to calculate bond dissociation energies for different Re–N/S bonds. The conformational equilibrium of Tyr$^3$-octreotate in the presence of explicit water was studied using molecular dynamics simulations, and different partitioning schemes were explored for modeling Re-SDPhe-TATE using the ONIOM method.