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Synthesis and characterization of Bombesin derivatives with potential applications as nuclear medicine imaging/therapeutic agents

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The use of tissue specific radiopharmaceuticals presents great promise for diagnostic and therapeutic applications in a number of human cancers. Gastrin-releasing peptide (GRP) receptors are known to be over-expressed on a variety of malignancies including breast, gastric, colon, pancreatic, prostate, and small-cell lung cancers. Experimental work with bombesin (BBN), an amphibian analogue to mammalian GRP, has demonstrated the ability of BBN to bind, with high affinity and specificity, to the GRP receptor. The use of a bifunctional chelating agent (BFCA) allows biologically active molecules to maintain receptor affinity while at the same time complexing a radionuclide. Spacer groups separating the BFCA and biological vector allow for fine tuning of the pharmacokinetics. Bombesin conjugates effectively complexing radioactive copper (i.e. Cu-64; $t_{1/2}$=12.7h, E_{γ}=1345.8keV, $E_{\beta-}$=578keV, $E_{\beta+}$=651keV) posses potential as imaging agents for diagnostic positron emission tomography (PET) and therapeutic applications.Recently our research group has focused efforts on developing new BBN derivatives of Triaza (1,4,7-triazacyclononane) or functionalized derivatives of Triaza for complexing of specific radionuclides. Our laboratory has previously reported on a series of new Triaza-BBN conjugates. A derivative of this Triaza ligand system, 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), has been synthesized by alkylation of the secondary amines of triaza by α–chloroacetic acid prior to conjugation to the biologically active BBN targeting vector. Bombesin conjugates were derived of the form, NOTA-X-BBN (X = ßAla, GGG, SSS). Synthesis of the unligated BBN [7-14] peptide with spacer group was conducted by Fmoc-protected solid-phase peptide synthesis (SPPS). The bombesin constructs were purified prior to conjugation of the ligand framework by means of reverse phase-high performance liquid chromatography (RP-HPLC). The NOTA ligand was conjugated to the N-terminus of the peptide by means of an activated ester derived from N-hydroxysulfosuccinimide and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide HCl in aqueous solution. The final NOTA-X-BBN derivatives were purified by RP-HPLC and confirmed via electrospray ionization-mass spectrometry (ESI-MS). Further studies to evaluate the ability of the derivatives to complex Cu-64 are underway. Subsequent studies will be conducted to evaluate the in vitro and in vivo characteristics of the radiopharmaceuticals.