30G-pm01

1,4,7-Triazacyclononane-1,4,7-triglutaric acid (NOTGA), a bifunctional ligand for the preparation of trivalent 68Ga-radiopharmaceuticals

◯Francisco Lazaro GUERRA GOMEZ[1], 六川　武美[1], 上原　知也[1], 荒野　泰[1]([1]千葉大院薬)

Purpose: Gallium-68 (^{68}Ga) is a positron emission radionuclides produced from a generator system. It forms stable complexes with 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA). To conjugate NOTA to biomolecules of interest, a NOTA derivative such as 1-(2-glutaric acid)-4,7-(diacetic acid)-1,4,7-triazacyclononane (NODAGA) has been developed. Since multivalent compounds exhibit higher avidity to their targets than their monovalent counterparts, the purpose of this work was the development of the NOTA based bifunctional ligand 1,4,7-triazacyclononane-1, 4, 7- triglutaric acid (NOTGA) for the preparation of trivalent ^{68}Ga-radiopharmaceuticals. As a proof of concept, a model compound with three phenethylamine was synthesized, and its labelling and stability were compared with a recently reported *N, N', N''*-trisubstituted triazacyclononane with methyl(2-carboxyethyl)phosphinic acid pendant (PrP9). **Methods:** α-Bromo glutaric acid 1-tert-butyl ester 5- benzyl ester was synthesized, coupled to 1,4,7-triazacyclononane, and finally conjugated with phenethylamine (PEA). PrP9 was synthesized as reported and also conjugated with PEA. ^{67}Ga radiolabeling and stability of the resulting complexes in apo-transferrin (apo-Tf) were compared. **Results:** Both ligands provided ^{67}Ga-labeled complexes quantitatively 15 min at 100 °C, pH 3 with ligand concentration of 10 μM. However, PrP9 generated two complexes attributable to two enantiomeric [Ga(H_3PrP9)], which may limit its further application. Both ^{67}Ga-NOTGA-PEA and the two isomers of ^{67}Ga-PrP9-PEA remained stable for 24 h in the presence of apo-Tf. **Conclusion:** These findings indicated that NOTGA would constitute a new precursor for the preparation of trivalent ^{68}Ga-radiopharmaceuticals.