Contribution ID: **361** Type: **Poster**

Chemical and biological studies on 105Rh-labelled tetrathioethers conjugated to TATE

Thursday, 15 May 2014 17:30 (1h 15m)

Objectives: In clinical practice, there is a demand for no-carrier-added radionuclides emitting particles of short range that demonstrate a therapeutic effect on small neoplastic lesions diffuse over a large area of tissue or tumour metastases. Rhodium-105 meets all requirements for application in radionuclide therapy [1] and might be an alternative to 177Lu. Tetrathioether crown complexes with 105Rh have been generally considered as candidates for radiopharmaceutical precursors to be combined with carrier biomolecules. The aims of our work were: (i) synthesis of 105Rh labelled bioconjugates with bifunctional acyclic (333S4diAcOH) and cyclic (16S4COOH) tetrathioether ligands conjugated to [Tyr3]octreotate, (ii) studies of their properties and (iii) conduction of in vitro experiments on cell line AR42J.
Methods: Rhodium-105 was obtained by neutron activation of ruthenium salt, (NH4)2[Ru(H2O)Cl5], for 8 h with flux of 7·1013 n·cm-2·s-1 in the Maria reactor in Świerk, Poland. 105Rh was separated from the ruthenium target material by method described previously [2].
Acyclic ligand was synthesised through 1,5,9,13-tetrathiatridecane intermediate and 16S4COOH by method previously described [3]. The ligands were combined with N-hydroxysuccinimide to obtain active esters, which were subsequently conjugated with N-terminus of TATE. The respective products were isolated and analyzed by MS, NMR and elemental analysis.
Results: The bifunctional ligands were synthesized with total reaction yield of 21% and 1% for 333S4diAcOH and 16S4COOH, respectively. The active esters and bioconjugates were obtained in high yield. The last step of synthesis was cleavage of Dde protecting group from Lys.
The complex [RhCl2(16S4COTATE)]+ was obtained as reference material for HPLC. The bioconjugates were labelled with 105Rh, their distribution coefficients were measured. For bioconjugate [105Rh(16S4COTATE)]+, the stability in PBS, Cys, GSH and human serum was examined, and the kinetics of internalization into AR42J cells was set.
Conclusions: The use of 105Rh-labelled tetrathioether precursors conjugated to peptides in radionuclide therapy seems possible, but requires further biological studies. Good stability of 105Rh-labelled bioconjugate 16S4COTATE in human serum with a high degree of its internalization meet the requirements for potential receptor radiopharmaceuticals.
Research Support: The work has been carried out within the system project "The scientific potential as support to the economy of Mazovia - scholarships for doctoral students"under Sub-measure 8.2.2 Human Capital Operational Programme 2007-2013.
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Primary author: Dr KRAJEWSKI, Seweryn (Institute of Nuclear Chemistry and Technology, Warsaw, Poland)

Co-authors: Prof. BILEWICZ, Aleksander (Institute of Nuclear Chemistry and Technology, Warsaw, Poland); Mrs LASZUK, Ewa (National Centre for Nuclear Research, Świerk, Poland); Dr PRUSZYŃSKI, Marek (Institute of Nu-

clear Chemistry and Technology, Warsaw, Poland); Dr GARNUSZEK, Piotr (National Centre for Nuclear Research, Świerk, Poland); Prof. MIKOŁAJCZAK, Renata (National Centre for Nuclear Research, Świerk, Poland); Dr KARCZ-MARCZYK, Urszula (National Centre for Nuclear Research, Świerk, Poland); Dr WOJDOWSKA, Wioletta (National Centre for Nuclear Research, Świerk, Poland)

Presenter: Dr KRAJEWSKI, Seweryn (Institute of Nuclear Chemistry and Technology, Warsaw, Poland)

Session Classification: Poster Session - Radiopharmaceutical Chemistry, Labelled Compounds

Track Classification: Radiopharmaceutical Chemistry, Labelled Compounds