Bifunctional chelators for trastuzumab conjugation and successful labeling with radioisotopes

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Introduction

- Bifunctional chelators (BFC) - molecules important for formulation of stable metal complex with targeting biomolecules such as antibodies, peptides or proteins.
- Covalently attached to the biomolecules on the one side and on the other coordinates to the radioisotopes.
- The goal is to produce a radiopharmaceuticals with pharmacokinetic and pharmacodynamic stability, without degradation of the complex in the physiological conditions and releasing of metal ion.
- The choice of the chelators depends of the type of radioactive isotope that will be used.

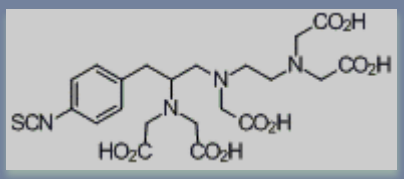

Fig. 1 p-SCN-Bn-DTPA

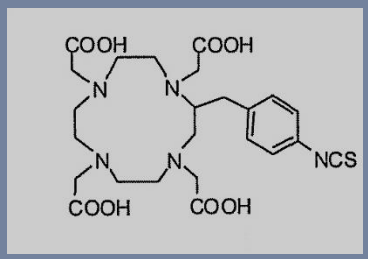

Fig. 2 p-SCN-Bn-DOTA

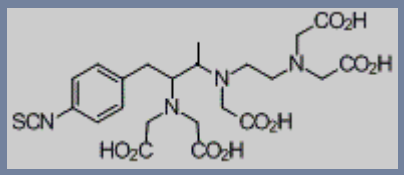

Fig. 3 1B4M-DTPA

Results and discussion

- Succinimidyl-hydrazinonicotinamide (HYNIC) is important for trastuzumab conjugation and labeling with ^{99m}Tc and ^{188}Re.
- For formulation of radioimmunoconjugates with ^{212}Pb 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraaza-cyclododecane (TCMC) have been used as a chelator.
- The most commonly used BFC are 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylene triamine pentaacetic acid (DTPA).
- Preclinical characterization was made of ^{111}In radiolabeled trastuzumab, previously conjugated with DTPA as a chelator. DTPA was used for trastuzuamab conjugation in a case of labeling with β emitters ^{86}Y and ^{90}Y.
- Chelating agent DOTA is significant for formulation of trastuzumab-radioimunoconjugates with gamma emitter ^{67}Ga, and potent therapeutic agents with β^- emitter ^{177}Lu and α emitter ^{225}Ac.

Conclusion

The aim of our study is to formulate a stable immunoconjugates of trastuzumab with DTPA, DOTA and DTPA derivate 1B4M-DTPA (2-(4-isothiocyanatobenzyl)-6-methyl-diethylene-triaminepentaacetic acid) for further labeling with ^{90}Y and ^{177}Lu.