

Short thesis for the degree of doctor of philosophy (PhD)

**Synthesis and biological investigation of ^{68}Ga -
labeled lactosamine-based radiopharmaceuticals**

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1. Introduction

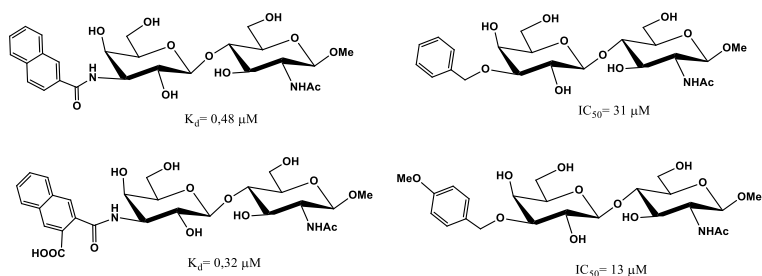
Positron emission tomography is one of the most effective functional imaging techniques in oncology, capable of detecting tumour lesions at an early stage. This method based on positron-electron annihilation, therefore bioactive molecules must be labelled with positron-emitting isotopes for PET imaging. The widely used 2-[^{18}F]fluoro-2-deoxy- β -D-glucose ([^{18}F]FDG) is not sufficiently tumour-specific, since in addition to tumours, increased [^{18}F]FDG uptake is also characteristic of infections and inflammations, which can be misdiagnosed as malignancies. Therefore, it is important to develop more tumour-specific PET probes, such as radiopharmaceuticals based on receptor-ligand interaction.

Peptide-based radioligands bind with high affinity and selectivity to receptors overexpressed on tumour cells. Angiogenesis induces tumour growth and increases the invasive capacity of neoplastic cells. It is characteristic of some receptors, so-called biomarkers, that they are overexpressed on newly formed angiogenic blood vessels, but are found in very small amounts or not at all in normal blood vessels. These biomarkers enable the design of personalized anticancer therapies as well as the development of tumour diagnostic agents that facilitate the detection of lesions and the monitoring of response to anticancer therapy. Integrins, aminopeptidase N and galectin-3 receptors are suitable biomarkers for this purpose. Among the integrins, $\alpha_v\beta_3$ integrins are the most involved in the regulation of angiogenesis. These cell adhesion proteins activate angiogenic growth factors and promote neoplastic cell survival by inhibiting apoptosis. The RGD peptide analogues containing arginine-glycine-aspartic acid tripeptide sequence can bind with high specificity and selectivity to $\alpha_v\beta_3$

integrin receptor. Therefore, the RGD-based radiopharmaceuticals are suitable for the detection of this receptor.

Aminopeptidase N (APN/CD13) is a multifunctional glycoprotein, which is involved in the process of angiogenesis as an enzyme, a receptor and signal transduction molecule. High levels of APN/CD13 on angiogenic blood vessels correlate with tumour progression and neoplastic cell invasion. The high-affinity ligands of the APN/CD13 receptor are peptide derivatives with an asparagine-glycine-arginine (NGR) tripeptide sequence.

The galectin-3 (Gal-3) protein is a member of the galectin family, which recognizes β -galactoside in various glycoconjugates. The extracellular Gal-3 is involved in the process of angiogenesis and metastasis and promotes the migration, adhesion, and invasion of tumour cells. The intracellular Gal-3 plays an important role in the regulation of apoptosis. The lactosamine and *N*-acetyl-lactosamine are the natural ligands of Gal-3 protein. There are many examples in the literature of the synthesis of high-affinity lactosamine-based galectin-3 inhibitors containing an aromatic group in the C-3' position (see Figure 1), since this chemical modification increases the affinity of lactosamine towards the Gal-3 receptor.



Scheme 1: C-3' modified lactosamine-based Gal-3 inhibitors.

The goal of our research was the synthesis and biological evaluation of peptide and carbohydrate-based radiopharmaceuticals that can bind to the above-mentioned biomarkers with high affinity and selectivity. Furthermore, we planned to improve the pharmacokinetic properties of peptide-based radiopharmaceuticals by glycosylation and pegylation. The designed ^{68}Ga -labeled lactosamine-containing glycopeptides can bind to two different types of receptors, which can increase tumour uptake of these ‘dual-targeting’ radiopharmaceuticals.

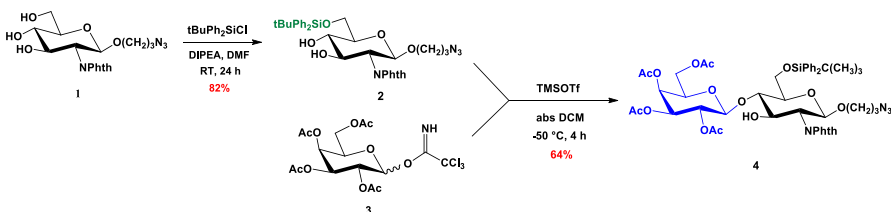
2. Applied methods

The prepared compounds were purified by column chromatography and semipreparative HPLC. The structure of the synthesized molecules was identified by mass spectroscopy and ^1H and ^{13}C NMR spectroscopy. The ^{68}Ga radionuclide was obtained from $^{68}\text{Ge}/^{68}\text{Ga}$ isotope generator and produced by $^{68}\text{Zn}(\text{p},\text{n})^{68}\text{Ga}$ nuclear reaction in cyclotron. The synthesized radiopharmaceuticals were purified by solid phase extraction using Oasis HLB 1cc column. Radiochemical purity was determined by analytical radio-HPLC using gradient elution, and radio-TLC. For determination of octanol/water partition coefficients, the radioactivity of the samples were measured by gamma counter. Stability studies were monitored by analytical radio-HPLC and radio-TLC after 0, 60, and 120 min. Subcutan induced B16F10 tumours were imaged with miniPET II and miniPET III cameras. For the *ex vivo* biodistribution studies, the radioactivity of the samples from different organs and tissues was determined by gamma counter.

3. New scientific results of the dissertation

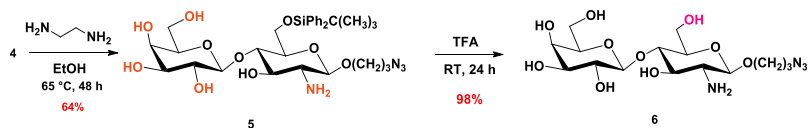
3.1. Synthesis of NODAGA-LacN-E[c(RGDfK)]₂ precursor

First, we developed a method for the synthesis of the lactosamine derivative **6**. We chose the known 3-azidopropyl 2-deoxy-2-phtalimido-2-*N*-ftálimido-β-D-glucopyranozide (**1**) as a starting material. The primary hydroxyl group of the compound **1** was protected with *tert*-butyldiphenylsilyl group. The 4-OH group of the glycosyl acceptor **2** was regioselectively glycosylated with the known 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl trichloroacetimidate (**3**) (Scheme 2).



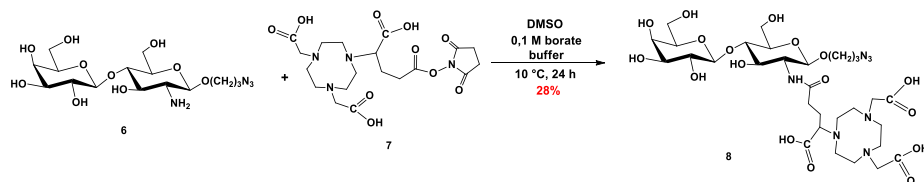
Scheme 2

In the next two steps, the deprotection of the disaccharide **4** was achieved. First, the acetyl groups and the phtalimido group were removed with ethylene diamine. Afterwards, the *tert*-butyldiphenylsilyl group was hydrolysed with trifluoroacetic acid to yield compound **6** (Scheme 3).



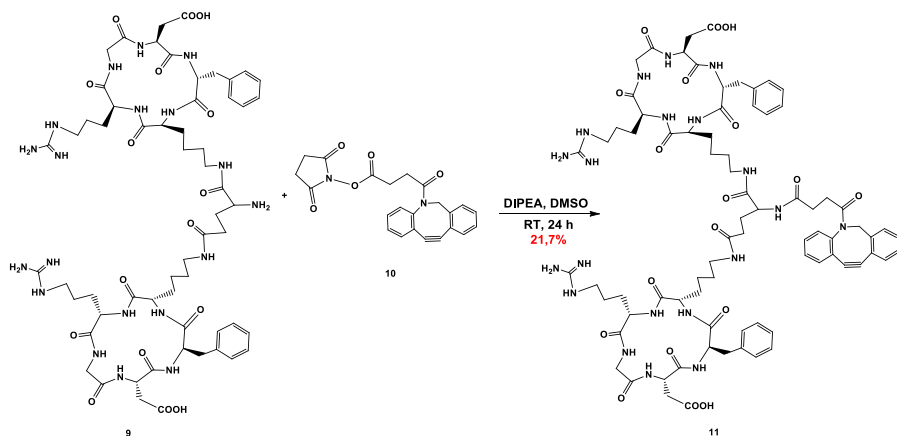
Scheme 3.

Then, the lactosamine derivative **6** was conjugated with NODAGA-NHS ester (**7**) in borate buffer and dimethyl sulfoxide (Scheme 4).



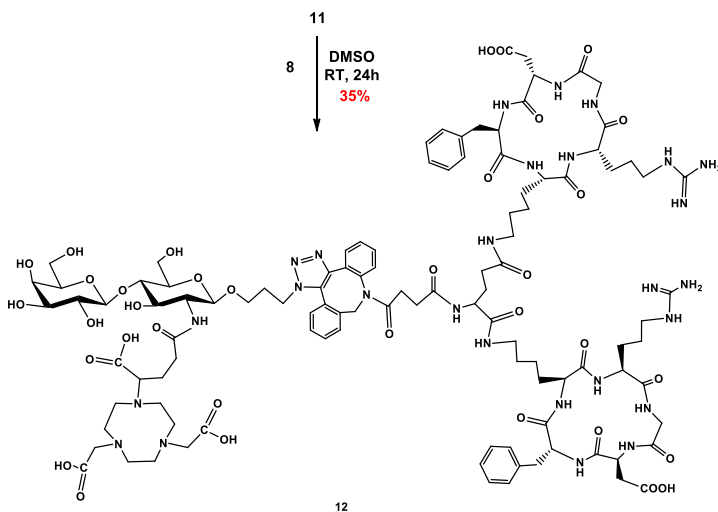
Scheme 4.

To avoid potential metal contamination that could interfere with radiolabelling, the chelator conjugated lactosamine derivative **8** was designed to be coupled to the cyclic RGD peptide analogue by copper free strain promoted click reaction (SPAAC). Therefore, the E[c(RGDfK)]₂ (**9**) dimer peptide was functionalized with dibenzocyclooctine NHS ester (**10**) (Scheme 5).



Scheme 5.

Subsequently, the functionalized peptide **11** was conjugated to compound **8** containing azidopropyl aglycon by SPAAC reaction to give compound **12** (Scheme 6).



Scheme 6.

3.2. Radiochemical study of NODAGA-LacN-E[c(RGDfK)]₂ precursor (**12**)

The radiolabelling of the precursor molecule **12** was achieved with [⁶⁸Ga]GaCl₃ solution obtained from the elution of ⁶⁸Ge/⁶⁸Ga isotope generator. The pH of the [⁶⁸Ga]GaCl₃ solution was adjusted with NH₄OAc buffer (3 M; pH 4). 1 mg/mL concentration of precursor stock solution was used for the radiolabelling. First, we determined the optimal labelling conditions regarding amount of peptide ligand and reaction temperature. The radiolabelling efficiency was given by radiochemical purity of the reaction mixtures determined by analytical radio-HPLC. The reaction mixtures were incubated at 95 °C for 15 minutes and the highest radiolabelling yield (95%) was observed at a ligand concentration of 32 μM (Table 1).

Table 1. Radiolabelling efficiency using different ligand concentration for 15 min at 95 °C.

<i>Ligand concentration (μM)</i>	<i>Radiochemical yield (%)</i>
10	85,96 ± 5,02
17	90,80 ± 1,51
23	92,82 ± 1,13
32	95,02 ± 0,62

Subsequently, the radiolabelling was performed at different temperatures using the previously established 32 μM ligand concentration. The highest radiochemical efficiency was determined at 95 °C (Table 2).

Table 2. Radiolabelling efficiency applying 32 μ M ligand concentration and 15 min reaction time at different reaction temperature.

<i>Temperature (°C)</i>	<i>Radiochemical yield (%)</i>
<i>room temperature</i>	<i>0</i>
<i>37</i>	<i>8,53 $\pm$ 1,06</i>
<i>60</i>	<i>92,84 $\pm$ 0,96</i>
<i>80</i>	<i>94,26 $\pm$ 0,72</i>
<i>95</i>	<i>95,02 $\pm$ 0,62</i>

After that, the radiochemical synthesis of the glycopeptide was achieved on a larger scale under the optimal reaction conditions. The ^{68}Ga -labelled complex was purified by solid phase extraction using Oasis HLB 1cc column. The radiochemical purity of the purified glycopeptide was determined by radio-TLC using iTLC paper and 0.5 M citrate buffer (pH 5.5) as an eluent, and reverse-phase radio-HPLC. The radiochemical purity exceeded 99% for both methods. The octanol/water partition coefficient of the radiolabelled glycopeptide was also determined. According to the low $\log P$ value (-2.58), the radiopharmaceutical was hydrophilic. We carried out the stability test of the radioligand in human serum, 0.01 M Na_2EDTA and 0.01 M oxalic acid solutions. From the mixtures, samples were taken at different time points (0, 60, 120 min). The radiochemical purity of the samples was analysed by radio-HPLC. Based on the radiochromatograms, the [^{68}Ga]Ga-NODAGA-LacN-E[c(RGDfK)]₂ glycopeptide was inert for two hours.

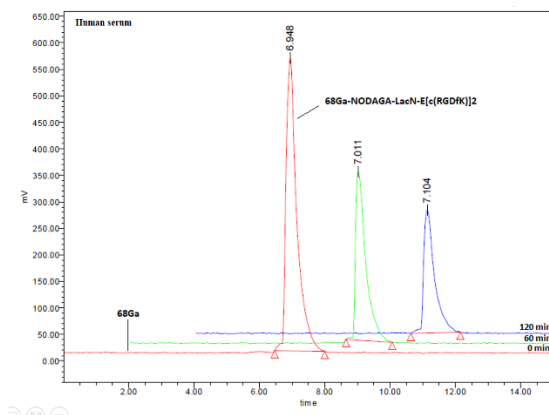


Figure 1: The stability test of the purified radiopharmaceutical in human serum

In the preliminary biological study, the [^{68}Ga]Ga-NODAGA-LacN-E[c(RGDfK)]₂ glycopeptide accumulated only at a low level in the B16F10 tumor. This was probably caused by the rigid structure of the DBCO unit was too close to the vector molecule, that decreased the affinity of the RGD peptide to the $\alpha_v\beta_3$ integrin receptor. Therefore, later on, we used a pegylated DBCO unit for the functionalization of peptide analogues.

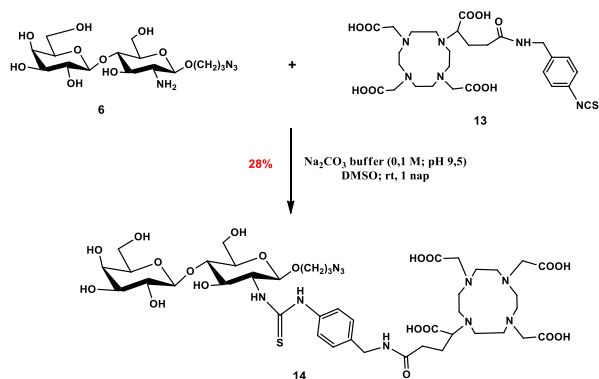
3.3. Synthesis of DOTAGA-LacN and cKNGRE-based precursors

In the next stage of our research, we prepared radiopharmaceuticals for the detection of aminopeptidase N (APN/CD13) positive tumor cells, whose pharmacological properties we planned to improve by glycosylation and pegylation. In addition, we also synthesized a lactosamine based radioligand that may be capable to detection of galectin-3 protein.

To the synthesis of precursor molecules we applied a similar synthetic strategy that was used for NODAGA-LacN-E[c(RGDfK)]₂ (**12**). The previously

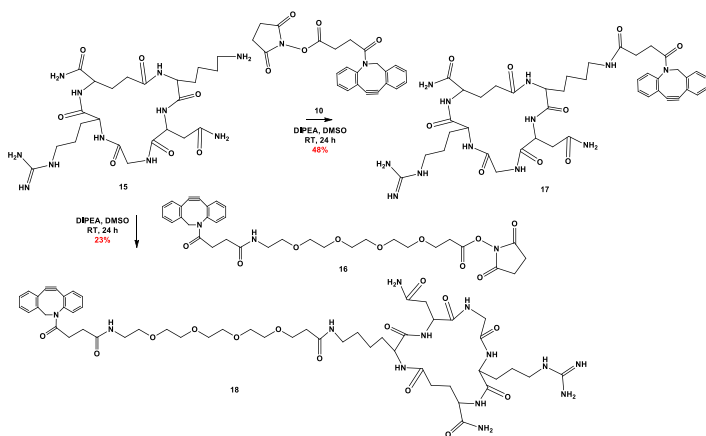
prepared lactosamine derivative (**6**) was used as a carbohydrate unit and cKNGRE peptide as vector molecule. Furthermore, NODAGA-NHS (**7**) was replaced by the p-SCN-Bn-DOTAGA (**13**) chelator, because the larger ring size of the DOTA derivative allows the coordination of therapeutic radionuclides (e.g. ^{213}Bi , ^{177}Lu).

In the first step of the synthetic route, thiocarbamide bond was formed between the amino group of lactosamine derivative (**6**) and the isothiocyanate group of p-SCN-Bn-DOTAGA (**13**) (Scheme 7).



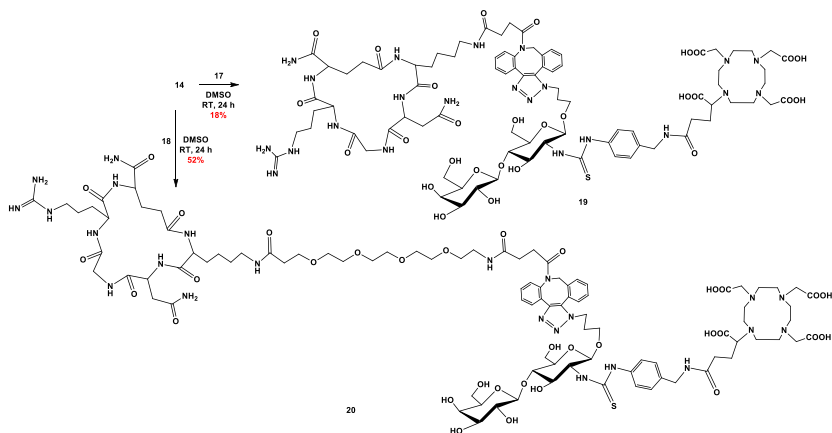
Scheme 7

Subsequently, the functionalization of cKNGRE peptide (**15**) was achieved with DBCO-NHS (**10**) and PEG₄-DBCO-NHS (**16**) esters (Scheme 8).



Scheme 8

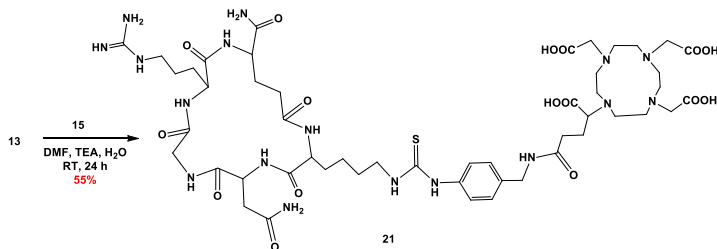
For the synthesis of the glycopeptides **19** and **20**, the chelator-conjugated lactosamine (**14**) was coupled to the functionalized peptides (**17**, **18**) by copper free click reaction (Scheme 9).



Scheme 9

The synthesis of compounds **14**, **17** and **19** was achieved and described by Katalin Berta in her SRS (Student's Research Society) essay written under my supervision.

For the biological investigation of the cKNGRE-based glycopeptides, the DOTAGA-cKNGRE (**21**) was synthesized by Dr. Noémi Dénes, as a reference compound (Scheme 10).



Scheme 10

3.4. Radiochemical study of DOTAGA-LacN and cKNGRE-based precursors

Precursors **14**, **19** and **20** were radiolabelled in a similar manner to compound **12**. For the radiolabelling, the ⁶⁸Ga radionuclide was obtained by elution of ⁶⁸Ge/⁶⁸Ga isotope generator. The pH of the [⁶⁸Ga]GaCl₃ solution was adjusted to pH 4 with NH₄OAc (3 M, pH 4) buffer, and then the stock solution (1 mg/mL) of the different precursors was added to the mixture, respectively. The reaction mixtures were heated at 95 °C for 15 min, then the radioligands were purified on SPE Oasis HLB 1cc cartridge. The radiochemical purity of the labelled complexes was analysed by RP radio-HPLC and it exceeded 95% in all three cases. The molar activity value of the radiopharmaceuticals was also determined, which was 3.02 ± 0.23 GBq/μmol for [⁶⁸Ga]Ga-DOTAGA-LacN, 4.69 ± 0.15 GBq/μmol for [⁶⁸Ga]Ga-DOTAGA-LacN-cKNGRE and finally 4.33 ± GBq/μmol for [⁶⁸Ga]Ga-DOTAGA-LacN-PEG4-cKNGRE. The

radiochemical labelling of the reference DOTAGA-cKNGRE precursor was performed by Dr. Noémi Dénes.

We determined the $\log P$ value of the radiolabelled compounds, which were: -3.34 for [^{68}Ga]Ga-DOTAGA-LacN, -3.68 for [^{68}Ga]Ga-DOTAGA-LacN-cKNGRE, -3.69 for [^{68}Ga]Ga-DOTAGA-LacN-PEG4-cKNGRE, and -4.13 for [^{68}Ga]Ga-DOTAGA-cKNGRE. According to the low $\log P$ values the synthesized radioligands were hydrophilic. Subsequently, *in vitro* stability studies of the radiolabelled complexes were carried out using the same method as for [^{68}Ga]Ga-NODAGA-LacN-E[c(RGDfK)]₂. Based on the radiochromatograms of the samples, all 4 radioligands showed high stability after 2 hours under the three investigated condition.

3.5. Biological evaluation of DOTAGA-LacN and cKNGRE based radioligands.

Preclinical studies of the synthesized [^{68}Ga]Ga-DOTAGA-LacN, [^{68}Ga]Ga-DOTAGA-LacN-cKNGRE, and [^{68}Ga]Ga-DOTAGA-LacN-PEG4-cKNGRE radiopharmaceuticals were performed in subcutaneously injected B16F10 melanoma tumour-bearing mice. This tumour type overexpressed the aminopeptidase N and the galectin-3 receptors. The biological efficacy of the radiolabelled compounds was confirmed by *in vivo* miniPET and *ex vivo* biodistribution studies. Figure 2/A shows the decay-corrected PET images. The subcutaneously growth B16F10 tumour were clearly detected by the cKNGRE peptide-based radioligands. However, the study with the [^{68}Ga]Ga-DOTAGA-LacN radioligand resulted in moderate tumour uptake.

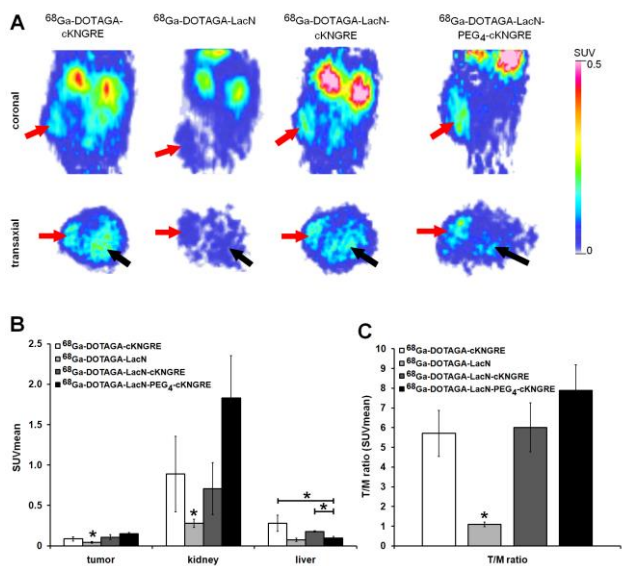
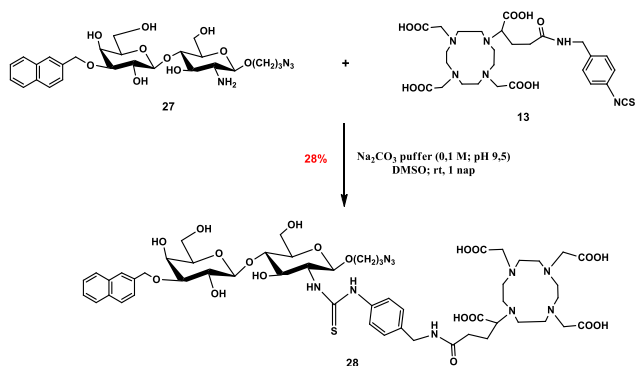


Figure 2: A: In vivo PET imaging of B16-F10 tumour-bearing mice 70 min after intravenous injection of the radiotracers. Red arrow: B16F10 tumour, black arrow: liver. B: Quantitative analyses of miniPET images.

Moreover, we observed a difference between renal and hepatic uptake of radiopharmaceuticals. The ^{68}Ga [Ga]-DOTAGA-LacN-cKNGRE and ^{68}Ga [Ga]-DOTAGA-LacN-PEG₄-cKNGRE glycopeptides were characterized by lower liver uptake than the ^{68}Ga [Ga]-DOTAGA-cKNGRE reference (Figure 2/B), which can be explained by the effect of glycosylation and pegylation. Furthermore, the ^{68}Ga [Ga]-DOTAGA-LacN-cKNGRE and ^{68}Ga [Ga]-DOTAGA-LacN-PEG₄-cKNGRE radioligands were characterized by a higher tumor/muscle ratio, which resulted in more contrasted PET images. So, we successfully improved the pharmacokinetic properties of ^{68}Ga [Ga]-DOTAGA-cKNGRE radioligand with pegylation and glycosylation.

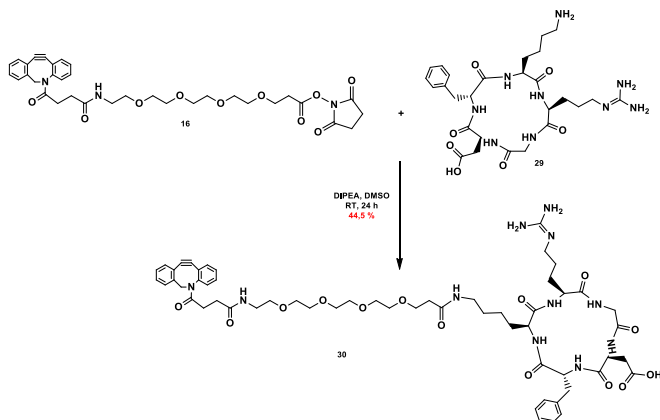
3.6. Synthesis of DOTAGA-LacN(NAP) and cRGDfK peptide-based precursors

In the third stage of our research, we designed to increase the affinity of the lactosamine unit to the galectin-3 receptor by introducing an aromatic group at the C-3' position of galactose unit. For this purpose, we chose the (2-naphthyl)-methyl group, which can be easily introduced via stannylene acetal. The synthesis of compound **27** was achieved and described by Ágnes Szűcs in her MSc Thesis. Compound **27** was conjugated via thiourea bond to the *p*-SCN-Bn-DOTAGA (**13**) chelator (Scheme 11). On the one hand, the obtained **28** was radiolabelled, and on the other hand, this molecule was one of the building blocks of the designed heterodimer compound.



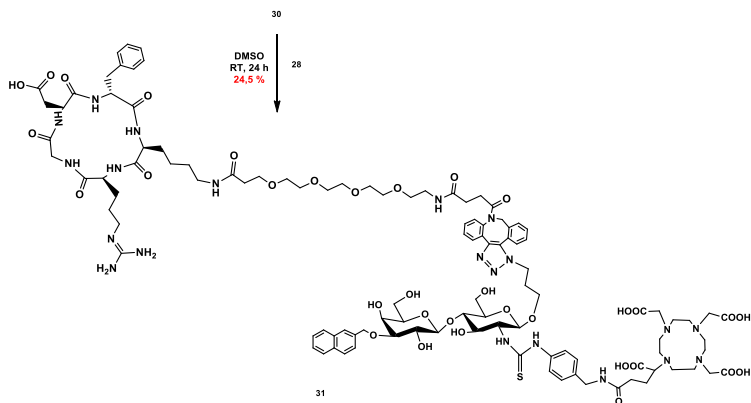
Scheme 11.

For the synthesis of the heterodimer molecule, the cRGDfK peptide (**29**) was functionalized with PEG₄-DBCO-NHS ester (**16**) (Scheme 12).



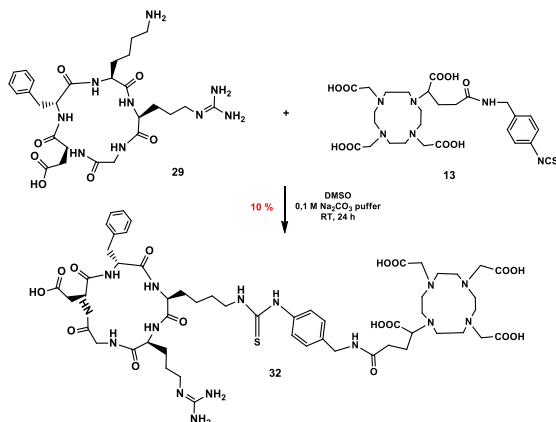
Scheme 12.

Then, glycopeptide **31** was prepared by conjugating compound **28** to compound **30** using a copper-free click reaction (Scheme 13).



Scheme 13.

For the biological studies, DOTAGA-cRGDfK (**32**) was synthesized as a reference molecule (Scheme 14).



Scheme 14.

3.7. Radiochemical study of DOTAGA-LacN(NAP) and cRGDfK peptide based precursors.

The radiolabelling of the synthesized precursors **28**, **30** and **31** was carried out using a method similar to that applied for compound **12**, except that the ^{68}Ga radionuclide was produced by $^{68}\text{Zn}(\text{p,n})^{68}\text{Ga}$ nuclear reaction in a cyclotron. The radiolabelled compounds were purified by SPE on Oasis HLB 1 cc cartridge. The radiochemical purity of the radioligands was determined by RP radio-HPLC, and it was exceeded 97% for all three labelled compounds. The octanol/water partition coefficient of the radiopharmaceuticals was determined, which was -2.63 for ^{68}Ga -DOTAGA-LacN(NAP), -2.27 for ^{68}Ga -DOTAGA-LacN(NAP)-cRGDfK, and -3.03 for ^{68}Ga -DOTAGA-cRGDfK. The *in vitro* stability test of the metal complexes was performed using the same method used to the ^{68}Ga -NODAGA-LacN-E[c(RGDfK)]₂ radiotracer. The radioligands were stable after 2 hours in the three conditions. The stability of the samples was examined by radio-TLC (Figure 3-4).

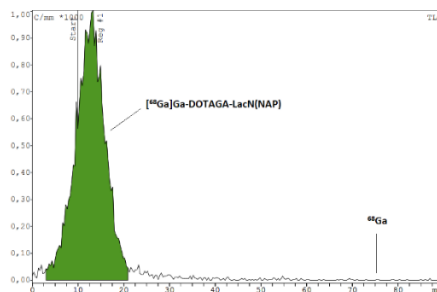


Figure 3: Stability test of the purified [^{68}Ga]Ga-DOTAGA-LacN(NAP) in human serum after 2 hours.

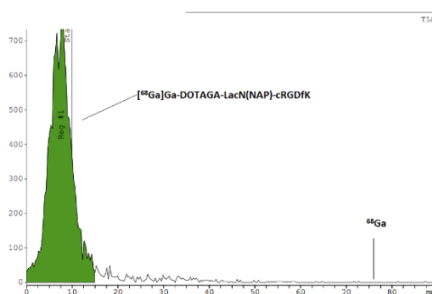


Figure 4: Stability test of the purified [^{68}Ga]Ga-DOTAGA-LacN(NAP)-cRGDfK in human serum after 2 hours.

3.8. Biological evaluation of DOTAGA-LacN(NAP) and cRGDfK based radiopharmaceuticals.

The imaging feature of the [^{68}Ga]Ga-DOTAGA-LacN(NAP), [^{68}Ga]Ga-DOTAGA-LacN(NAP)-cRGDfK and [^{68}Ga]Ga-DOTAGA-cRGDfK radiopharmaceuticals was investigated on B16F10 melanoma tumour-bearing mice, because this tumour is overexpressed the $\alpha_v\beta_3$ integrin and galectin-3 receptors.

The pharmacokinetic properties of the radioligands were first determined *in vivo* miniPET and *ex vivo* biodistribution studies on healthy C57BL/6 mice. Figure

5 shows the decay-corrected PET images. According to the qualitative analysis of the PET images clearly identifies the urinary system that is correlated with the $\log P$ values.

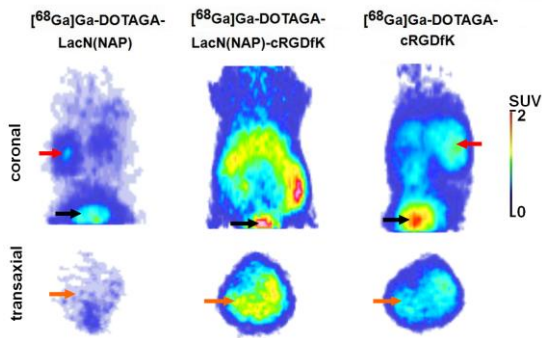


Figure 5: Decay-corrected miniPET images of healthy C57BL/6 mice 70 min after intravenous injection of the radiotracers. Red arrow: B16F10 tumour, black arrow: liver.

Higher liver uptake was observed when the radioligands containing RGD peptide was used, which was the highest for the heterodimer compound. The miniPET results correlates well the data of *ex vivo* biodistribution studies (Figure 6).

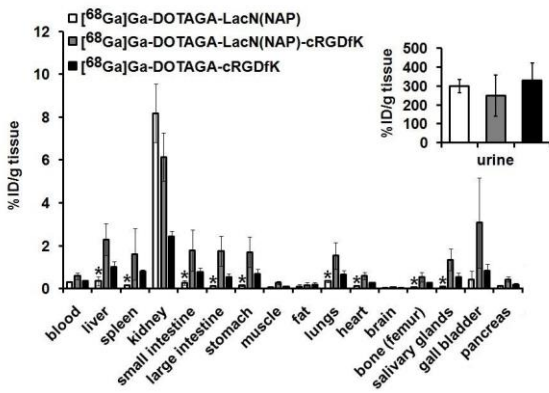


Figure 6: *Ex vivo* biodistribution studies of healthy C57BL/6 mice.

The biological efficacy of the radiopharmaceuticals was demonstrated on C57BL/6 mice subcutaneously injected with B16F10 melanoma cells. Figure 7 shows the qualitative and quantitative analysis of decay-corrected miniPET images.

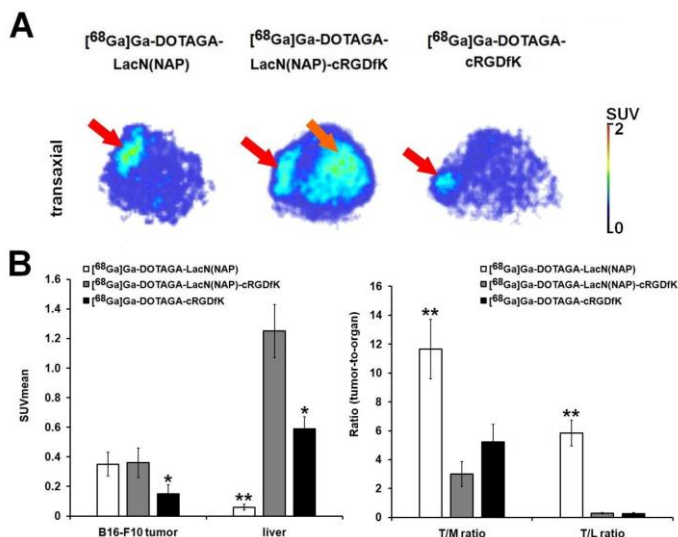


Figure 7: A: In vivo PET imaging of B16-F10 tumour-bearing mice 70 min after intravenous injection of the radiotracers. Red arrows: B16-F10 tumour. B: Quantitative analysis of PET images.

Qualitative analysis of PET images clearly showed that all three radiopharmaceuticals were suitable for detection of B16F10 melanoma tumour. In the quantitative analysis of PET images was observed significantly lower tumour uptake for the [⁶⁸Ga]Ga-DOTAGA-cRGDfK radiotracer, that was used as a reference. There was no significant difference between the two novel radioligands, [⁶⁸Ga]Ga-DOTAGA-LacN(NAP) and [⁶⁸Ga]Ga-DOTAGA-LacN(NAP)-cRGDfK, in terms of tumour uptake values. However, the evaluation of PET scans with the radioligands containing cRGDfK peptide was

difficult because of the high accumulation of liver and the highest liver uptake was determined in the case of the radiolabelled heterodimer.

In addition, the [^{68}Ga]Ga-DOTAGA-LacN(NAP) was showed 2-3 fold higher tumour/muscle ratio and approximately 21 fold higher tumour/liver ratio than the other two radioligands. The results of the *ex vivo* biodistribution studies of B16F10 tumour-bearing mice correlated well with the *in vivo* miniPET analysis. The obtained data confirmed the outstanding imaging properties of [^{68}Ga]Ga-DOTAGA-LacN(NAP) radiopharmaceutical.

4. Possible utilization of the results

We developed a synthetic method for the synthesis of chelator-conjugate precursor molecules containing peptide and lactosamine derivatives, which were successfully labelled with positron emitting ^{68}Ga isotope.

Based on the radiochemical and biological investigation of the radioligands, the newly synthesized radiopharmaceuticals were characterized by high serum stability. Therefore, the application of these radioligands do not cause radiotoxicity.

The pharmacokinetic properties of the [^{68}Ga]Ga-DOTAGA-cKNGRE radioligand were improved by glycosylation and pegylation, which allowed to the PET imaging of B16F10 melanoma with higher contrast.

In addition, we synthesized the [^{68}Ga]Ga-DOTAGA-LacN(NAP)-cRGDfK heterodimer, which is able to bind to $\alpha_v\beta_3$ integrin and galectin-3 receptors. According to the preclinical studies this radiolabelled glycopeptide was also suitable for the visualization of B16F10 melanoma tumours. However, the evaluation of the PET images was difficult due to the high accumulation of the radiolabelled compounds in the liver.

Finally, we successfully achieved the synthesis and preclinical investigation of [^{68}Ga]Ga-DOTAGA-LacN(NAP) radiopharmaceutical. According to the *in vivo* miniPET and *ex vivo* biodistribution studies of healthy C57BL/6 mice, the radioligand was excreted via kidneys that is advantageous property for potential clinical use.

The *in vivo* miniPET and *ex vivo* biodistribution study of B16F10 melanoma-bearing mice confirmed, that the [^{68}Ga]Ga-DOTAGA-LacN(NAP) radiopharmaceutical is suitable for the detection of galectin-3 positive tumour. Based on the high tumour uptake, tumour/muscle ratio and tumour/liver ratio, the [^{68}Ga]Ga-DOTAGA-LacN(NAP) has outstanding images properties. Furthermore, it is the first carbohydrate-based PET diagnostic agent capable of detecting galectin-3 positive B16F10 melanoma.



Registry number:
Subject:

DEENK/51/2023.PL
PhD Publication List

Candidate: Barbara Gyuricza

Doctoral School: Doctoral School of Chemistry

List of publications related to the dissertation

Foreign language scientific articles in international journals (3)

1. **Gyuricza, B.**, Szűcs, Á., Péli-Szabó, J., Arató, V. Z., Képes, Z., Szűcs, D., Szikra, D. P., Trencsényi, G., Fekete, A.: The Synthesis and Preclinical Investigation of Lactosamine-Based Radiopharmaceuticals for the Detection of Galectin-3-Expressing Melanoma Cells. *Pharmaceutics*. 14, 1-16, 2022. EISSN: 1999-4923.
DOI: <http://dx.doi.org/10.3390/pharmaceutics14112504>
IF: 6.525 (2021)
2. **Gyuricza, B.**, Péli-Szabó, J., Arató, V. Z., Dénes, N., Szűcs, Á., Berta, K., Kis, A., Szűcs, D., Forgács, V., Szikra, D. P., Kertész, I., Trencsényi, G., Fekete, A.: Synthesis of ⁶⁸Ga-Labeled cNGR-Based Glycopeptides and In Vivo Evaluation by PET Imaging. *Pharmaceutics*. 13 (12), 1-14, 2021. EISSN: 1999-4923.
DOI: <http://dx.doi.org/10.3390/pharmaceutics13122103>
IF: 6.525
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