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Synthesis and biological evaluation of technetium-labeled D-glucose-MAG_3 derivative as agent for tumor diagnosis

André Luís Branco de Barros, Valbert Nascimento Cardoso, Luciene das Graças Mota, Elaine Amaral Leite, Mônica Cristina de Oliveira, Ricardo José Alves *

Faculdade de Farmácia, Universidade Federal de Minas Gerais, Av. Antônio Carlos, 6627, 31279-901 Belo Horizonte, Minas Gerais, Brazil

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ABSTRACT

A D-glucose-MAG_3 derivative was successfully synthesized and radiolabeled in high labeling yield. Biodistribution studies in Ehrlich tumor-bearing mice were performed. This compound showed high accumulation in tumor tissue with high tumor-to-muscle ratio and moderate tumor-to-blood ratio. Thus, D-glucose-MAG_3 is a potential agent for tumor diagnosis.

Tumor is among the most common causes of death in the world. Diagnosticians have traditionally been trained to interpret information provided by anatomically based imaging techniques. With the advent of molecular biology-based medicine, a transition is being made to incorporate into diagnostic interpretation information based on biochemical perturbations that exist in the disease. In vivo functional imaging technique can help to diagnose and stage tumors, optimize drug scheduling, and predict response to a therapeutic modality, which would be advantageous to both patient and oncologist.[1,2] In this manner, this method allows for the viewing of physiopathological process in the initial stages, which runs contrary to the images conventional methods based on anatomical alterations.[3]

The radioactive labeled glucose analogue [^{18}F]-2-fluorodeoxy glucose ([^{18}F]-FDG) has gained relevance in clinical tumor diagnosis in recent years. [^{18}F]-FDG has been used to measure normal tissue and tumor glucose utilization rates.[4–7] Although tumor metabolic imaging with [^{18}F]-FDG has been studied for more than two decades, the use of this examination in clinical practice is still limited by such factors as difficult access, limited availability, and high cost.[8]

Technetium-99m (^{99m}Tc) has been mostly used for labeling radiopharmaceuticals owing to its suitable physical and chemical characteristics and inexpensive isotope cost.[9–11] Some ^{99m}Tc-labeled D-glucosamine derivatives have been synthesized recently and evaluated as tumor diagnosis agents.[1,11,12] As carbohydrates are generally weak ligands for chelating with ^{99m}Tc, functionalization with an external chelating group or the insertion of some functional groups is essential to obtain strong metal-binding compounds. The mercaptoacetyl triglycine (MAG_3) is an efficient complexing agent for ^{99m}Tc which has been used as tubular renal radiotracer.[13,14] Its structure has an carboxylic acid that allows the coupling with some derivatives bearing an amino group.

The purpose of this study was to conjugate D-glucose with MAG_3 and to evaluate the feasibility of the ^{99m}Tc-labeled glucose derivative as candidate for tumor diagnosis agent.

The D-glucose-MAG_3-SBz derivative **6** was synthesized according to the procedure outlined in Scheme 1.

The glucopyranosyl azide **1** was reduced to glucopyranosyl amine **2** using catalytic hydrogenation. The glucopyranosyl amine **2** was then reacted with benzoylated MAG_3 **5**, previously synthesized from **3**, using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDAC) as coupling agent to obtain **6**. All compounds were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. The technetium-99m labeled D-glucose-MAG_3 (^{99m}Tc-MAG_3-G) was prepared by ligand-exchange reaction with ^{99m}Tc-tartarate at pH 6–8. In these conditions the benzoyl protecting group of **6** is removed.[13]

After radiolabeling the product was purified by column chromatography on Florisil mesh 60–100, using, first, acetone to remove TcO_4^- and next, 0.9% saline to elute the ^{99m}Tc-MAG_3-G. The radiolabeling yield of ^{99m}Tc-MAG_3-G was determined by Instant Thin Layer Chromatograph (ITLC) on two systems: 0.9% saline to

* Corresponding author. Tel.: +55 31 3409 6955; fax: +55 31 3409 6935.
E-mail address: ricardodylan@farmacia.ufmg.br (R.J. Alves).

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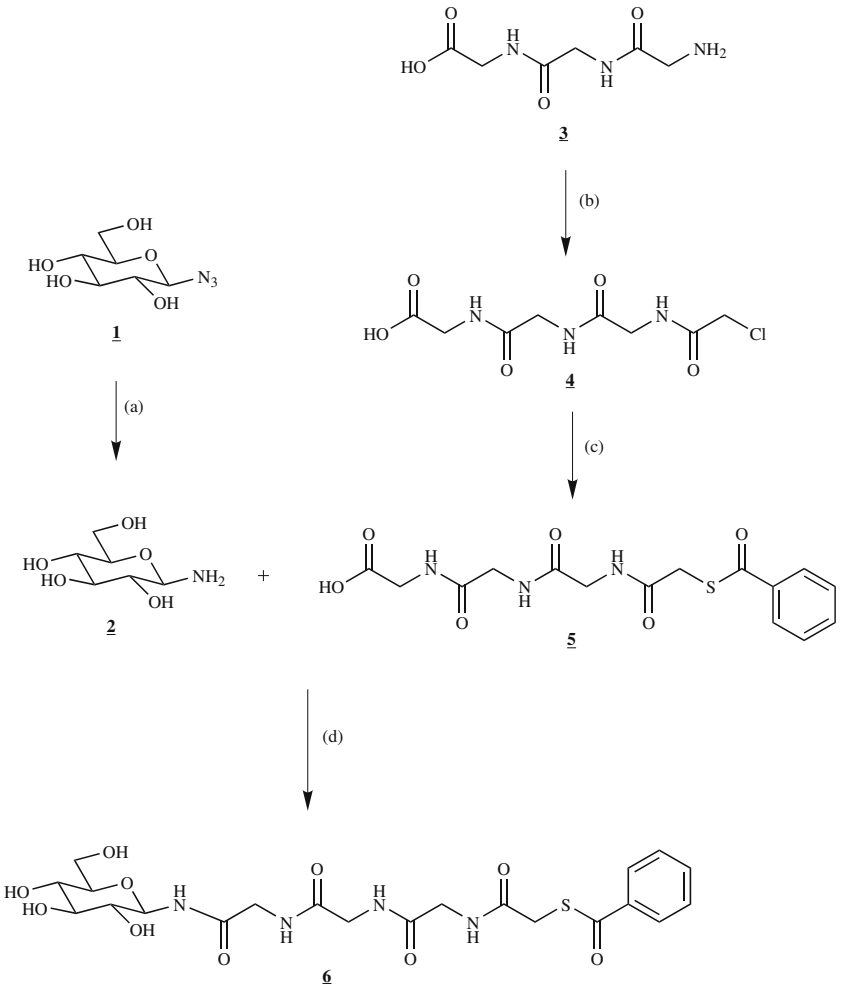

Scheme 1. Synthesis of D-glucose-MAG_3-SBz **6**. Reagents and conditions: (a) H_2, Pd/C, solvent: methanol, yield: 100%; (b) chloroacetylchloride, solvent: diethylether and water; (c) thiobenzoic acid, solvent: methanol, yield: 78%; two steps (d) EDAC, solvent: dry DMF, yield: 15%.

determine TcO_2 and acetone to determine TcO_4^-, as published elsewhere.[15] The radiochemical purity was higher than 90%.

Biodistribution of this complex was performed in Ehrlich tumor-bearing Swiss mice (25–30 g) at 5, 30, 120, 240 and 480 min post injection.[16] The results are summarized in Table 1. ^{99m}Tc-MAG_3-G was excreted rapidly through kidneys and presented low heart uptake. It had high tumor-to-muscle (T/M) ratio that increased up to 480 min post injection. The results showed also fast blood clearance with moderate tumor-to-blood (T/B) ratio. When the biodistribution study was performed with ^{99m}Tc-MAG_3 in the same time intervals, a tumor-to-muscle ratio of approximately 1.0 was obtained at all times (data not shown). Therefore, the data of the present study suggest a tropism of ^{99m}Tc-MAG_3-G to tumor.

In summary, the D-glucose-MAG_3 derivative **6** was synthesized and labeled with technetium-99m successfully. It presented high tumor-to-muscle ratio in Ehrlich tumor-bearing mice. Biodistribution results showed the feasibility of ^{99m}Tc-MAG_3-G as a functional agent for tumor diagnosis. Further studies will be carried out to evaluate the real potential of **6** for tumor diagnosis and will be reported in due course.

Table 1
Biodistribution of ^{99m}Tc-MAG_3-G in Ehrlich tumor-bearing mice (%ID/g)[a]

Tissue	5 min	30 min	120 min	240 min	480 min
Liver	9.63 ± 1.36	6.59 ± 1.46	4.20 ± 0.37	1.42 ± 0.35	1.05 ± 0.30
Spleen	1.70 ± 0.17	1.35 ± 0.33	0.56 ± 0.11	0.10 ± 0.02	0.10 ± 0.03
Kidney	21.54 ± 6.56	5.62 ± 1.05	5.19 ± 0.89	3.36 ± 0.89	3.82 ± 0.83
Stomach	1.66 ± 0.25	2.65 ± 0.47	2.15 ± 0.21	0.61 ± 0.15	0.50 ± 0.10
Heart	2.44 ± 0.22	1.62 ± 0.22	0.60 ± 0.12	0.15 ± 0.03	0.12 ± 0.03
Lung	3.21 ± 0.47	2.16 ± 0.25	0.74 ± 0.20	0.25 ± 0.04	0.24 ± 0.05
Blood	3.78 ± 1.10	2.33 ± 0.48	1.05 ± 0.15	0.28 ± 0.07	0.16 ± 0.04
Tumor	1.97 ± 0.43	1.64 ± 0.19	0.79 ± 0.14	0.32 ± 0.07	0.39 ± 0.12
Muscle	1.01 ± 0.16	0.68 ± 0.11	0.23 ± 0.03	0.08 ± 0.02	0.08 ± 0.02
T/M ratio	1.96 ± 0.34	2.47 ± 0.41	3.38 ± 0.52	3.91 ± 0.68	5.03 ± 0.98
T/B ratio	0.55 ± 0.21	0.72 ± 0.14	0.76 ± 0.15	1.18 ± 0.12	2.42 ± 0.50

[a] All data are the mean percentage ($n = 5$) of the injected dose of ^{99m}Tc-MAG_3-G per gram of wet tissue, ± standard deviation of the mean.

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