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Synthesis and biological evaluation of technetium-99m-labeled deoxyglucose derivatives as imaging agents for tumor

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Abstract—Three deoxyglucose (DG) derivatives, S-DG, MAG_3-DG and MAMA-BA-DG, were synthesized and labeled successfully with high labeling yields and high radio-chemical purities. Biodistribution in tumor-bearing mice demonstrated that these three new ^{99m}Tc-deoxyglucose derivatives showed accumulation in tumor and high tumor-to-muscle ratios. Among them, the ^{99m}Tc-MAG_3-DG showed the best characteristics as a potential tumor marker for single photon emission computed tomography (SPECT).

Tumor is among the most common causes of death in the world. 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.

Flourine-18 (^{18}F) fluorodeoxyglucose (FDG) has been used to measure normal tissue and tumor glucose utilization rates.[1–5] 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.[6] In addition, positron emission tomography (PET) radio-synthesis must be performed rapidly because the half-life of F-18 is only 109 min. Thus, it would be very desirable to develop less costly imaging agents based on γ-emitter isotope, especially for developing country, where single photon emission computed tomography (SPECT) is still dominant.

Technetium-99m (^{99m}Tc) has been mostly used for labeling radiopharmaceuticals owing to its suitable physical and chemical characteristics and inexpensive isotope cost. Lots of ^{99m}Tc-labeled glucose derivatives have been synthesized in order to develop one subrogate in SPECT for [^{18}F]FDG in PET recently.[7–11] Developed by Yang, ^{99m}Tc-labeled ethylenedicysteine-deoxyglucose (ECDG) showed similarities with [^{18}F]FDG in tumor uptake.[12] This suggests that there is feasibility for ^{99m}Tc-labeled deoxyglucose as tumor metabolic imaging agents. However, [^{99m}Tc]ECDG still has some drawbacks such as slow cleanup from blood, which would cause high blood background; and large molecular weight, which would limit its penetration through blood–brain barrier (BBB).

Thus, it would be desirable to develop a smaller ^{99m}Tc-based deoxyglucose derivative with rapid blood clearance and still maintaining its high tumor uptake.

The purpose of this study is to conjugate deoxyglucose with different chelating agents and to evaluate the feasibility of the ^{99m}Tc-labeled deoxyglucose derivatives as candidates for tumor-imaging agents.

The ^{99m}Tc-S-DG was synthesized according to the procedure outlined in Scheme 1. After protecting the thiol group of mercaptoacetic acid with trityl chloride, the resulting compound **3** was reacted with glucosamine using *N*,*N*′-dicyclohexyl-carbodiimide (DCC) as condensation reagent to obtain compound **4**. Next, the thiol groups were deprotected in trifluoroacetic acid (TFA) to give **5**. For labeling, ^{99m}Tc-S-DG was prepared by ligand-exchange reaction with ^{99m}Tc-glucoheptonate (GH).

Synthesis of ^{99m}Tc-MAG_3-DG (Scheme 2) was performed from mercaptoacetic acid. After protecting the thiol group with trityl chloride, the resulting compound **3** was reacted with *N*-hydroxysuccinimide (NHS) using

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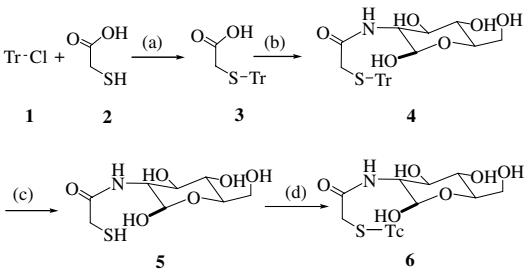
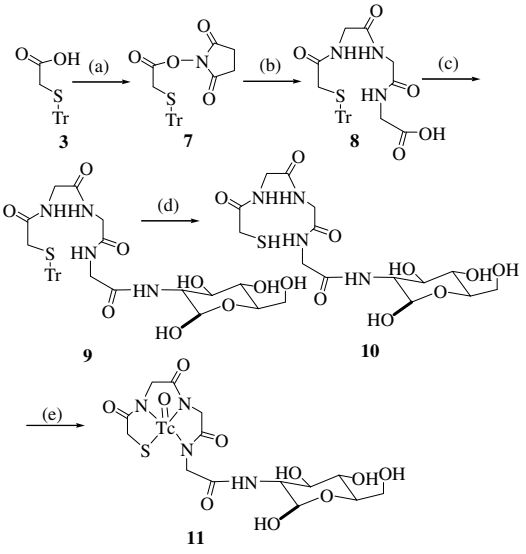


Scheme 1. Synthesis of ^{99m}Tc-S-DG. Reagents and solvents: (a) solvent: dichloromethane/acetic acid, yield: 95%; (b) glucosamine, DCC, solvent: ethanol/water, yield: 12%; (c) triethylsilane, solvent: TFA; (d) ^{99m}Tc-GH.



Scheme 2. Synthesis of ^{99m}Tc-MAG$_3$-DG. Reagents and solvent: (a) NHS, solvent: dry THF, yield: 47%; (b) glycylglycylglycine, solvent: acetonitrile, yield: 30%; (c) glucosamine, DCC, solvent: acetonitrile/water, yield: 19%; (d) triethylsilane, solvent: TFA; (e) ^{99m}Tc-GH.

DCC as condensation reagent to obtain the active ester **7**. The active ester **7** was reacted with the amine group of glycylglycylglycine to provide the Tr-MAG$_3$ **8**. Tr-MAG$_3$ was conjugated with glucosamine with DCC as condensation agent to provide the compound **9**. Deprotecting and labeling were performed with the same procedure as ^{99m}Tc-S-DG.

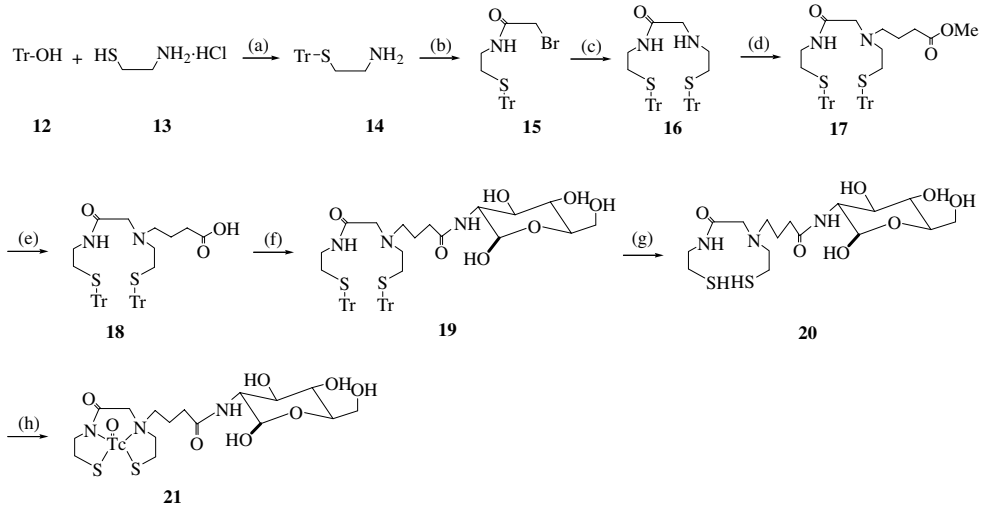
^{99m}Tc-MAMA-BA-DG was synthesized according to the procedure in Scheme 3. After protecting the thiol group of cysteamine chloride with trityl chloride, the resulting compound **14** was reacted with bromoacetal bromide to prepare **16**. The amine group of **16** was then alkylated with methyl 4-bromobutyrate to produce **17**. After hydrolysis of the ester group, the resulting compound **18** was conjugated with glucosamine with DCC to obtain compound **19**. Deprotecting and labeling were performed with the same procedure as ^{99m}Tc-S-DG.

The radiochemical yields of ^{99m}Tc-labeled deoxyglucose analogues were determined by TLC on three systems and the R_f values of ^{99m}Tc-species are listed in Table 1. HPLC analysis showed that the radiochemical purity is high (Fig. 1).

Table 1. R_f values of ^{99m}Tc-species on TLC

^{99m}Tc-species	System 1[a]	System 2[b]	System 3[c]
^{99m}Tc-S-DG	0.0	0.7–0.8	0.9–1.0
^{99m}Tc-MAG$_3$-DG	0.0	0.6–0.7	0.9–1.0
^{99m}Tc-MAMA-BA-DG	0.0	0.6–0.7	0.9–1.0
^{99m}Tc-GH	0.0	0.9–1.0	0.9–1.0
$^{99m}TcO_4^-$	0.8–0.9	0.5–0.7	0.0
$^{99m}TcO_2{\cdot}nH_2O$	0.0	0.0	0.0

[a] Xinhua No.1 paper strip developed by eluent A (1 mol/l of ammonium acetate/methanol (4:1)).
[b] Xinhua No. 1 paper strip developed by ketone.
[c] Polyamide strip developed by saline.



Scheme 3. Synthesis of ^{99m}Tc-MAMA-BA-DG. Reagents and solvent: (a) solvent: TFA, yield: 75%; (b) bromoacetyl bromide, triethylamine, solvent: dichloromethane, yield: 90%; (c) compound **14**, triethylamine, solvent: dichloromethane, yield: 64%; (d) methyl 4-bromobutyrate, potassium iodide, potassium carbonate, solvent: acetonitrile, yield: 40%; (e) 5% NaOH/THF, yield: 95%; (f) glucosamine, DCC, solvent: THF/water, yield: 7.3%; (g) triethylsilane solvent: TFA; (h) ^{99m}Tc-GH.