

# An Improved Synthesis and Preliminary Biodistribution Study of a Technetium-99m-labeled 2-amino-2-deoxy(thioacetyl)-D-glucose Complex ( $[^{99m}\text{Tc}]\text{-TA-DG}$ ) As a Tumor Imaging Agent

Fariba Johari Daha<sup>1</sup>, Masoud Sadeghzadeh (M.Sc.)<sup>1,2</sup>, Ghorbanali Charkhlooie (M.Sc.)<sup>1,3</sup>, Kazem Haghiri Ebrahimabadi (Ph.D.)<sup>1</sup>, Mohammad Reza Saidi (Ph.D.)<sup>2</sup>

<sup>1</sup>Nuclear Science Research School, NSTRI, P.O.Box:11365-3486, Tehran, Iran.

<sup>2</sup>Department of Chemistry, Sharif University of Technology, Tehran, Iran.

<sup>3</sup>Department of Chemistry, Mazandaran University, Babolsar, Iran.

(Received 18 August 2007, Revised 15 September 2007, Accepted 25 September 2007)

## ABSTRACT

**Introduction:** This report describes the synthesis of 2-Amino-2-deoxy(*S*-benzoylthioacetyl)-D-glucose (*S*-Bz-TA-DG), radiolabeled with  $[^{99m}\text{Tc}(\text{CO})_3(\text{OH}_2)_3]^+$  complex with a procedure including deprotection of the benzoyl group, characterization by HPLC using a C18 reverse phase column and preliminary biodistribution study in normal mice.

**Methods:**  $[^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$  complex was used to label TA-DG with  $^{99m}\text{Tc}$ . This complex was prepared using up to 46 mCi of  $\text{Na}^{99m}\text{TcO}_4$  in 1mL saline. The radiochemical purity (>95%) was determined by TLC in normal saline solution as the mobile phase. Radio-HPLC analysis of  $[^{99m}\text{Tc}]\text{-TA-DG}$  at pH=9.5-10, revealed that labeling with  $^{99m}\text{Tc}$  resulted in the formation of three radiochemical species ( $\text{Na}^{99m}\text{TcO}_4$  with  $t_R=5.7$  min,  $[^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$  complex with  $t_R=27.5$  min and  $[^{99m}\text{Tc}]\text{-TA-DG}$  [yield >85%] with  $t_R=8.2$  min) with different HPLC-profiles.

**Results:** The biodistribution of the  $[^{99m}\text{Tc}]\text{-TA-DG}$  complex was studied in normal mice (body mass 25–35 g) at 30 min and 1 h post-injection, according to a published procedure. This complex showed negligible brain uptake (0.13%±0.03 ID) at 30 min post-injection, an efficient clearance from the blood, a rapid excretion to the urine and a low retention in the liver and kidneys.

**Conclusion:** Nonfunctionalized carbohydrate compounds such as glucose are generally weak ligands for chelating with  $^{99m}\text{Tc}$ . Therefore, functionalization with an external chelating group or the insertion of some functional groups is essential to obtain strong metal-binding compounds. On the basis of our results, it seems that  $[^{99m}\text{Tc}]\text{-TA-DG}$  has not most of the favorable properties as an imaging agent for brain tumors.

**Key words:**  $^{99m}\text{Tc}$ , Glucosamine derivatives,  $^{99m}\text{Tc}$ -tricarbonyl complex, 2-amino-2-deoxy (thioacetyl)-D-glucose

Iran J Nucl Med 2007; 15(2): 43-48

**Corresponding Author:** Masoud Sadeghzadeh, Nuclear Science Research School, NSTRI, Tehran, Iran, P.O.Box:11365-3486, E-mail: msadeghzadeh@aeoi.org.ir

## Introduction

Carbohydrates are interesting building blocks in organic chemistry and drug development due to their involvement in various biological systems, water solubility, and optical activity (1). Accurate and early non-invasive detection of malignant disease is an important factor in the treatment and prognosis of a patient with cancer. Improvements in tumor radionuclide imaging depend on the development of more tumor-specific radiopharmaceuticals (2). Fluorine-18 ( $^{18}\text{F}$ ) fluorodeoxyglucose (FDG) has been used to measure normal tissue and tumor glucose utilization rates. Although metabolic tumor imaging with [ $^{18}\text{F}$ ]-FDG has been studied for more than two decades, the use of this examination in clinical practice is still limited by factors such as difficult access, limited availability, and high cost. In addition, positron emission tomography (PET) radio-synthesis must be performed rapidly because the half-life of  $^{18}\text{F}$  is only 109 min. Thus, it would be very desirable to develop less costly imaging agents based on  $\gamma$ -emitter isotopes, especially for developing countries, where single photon emission computed tomography (SPECT) is still dominant. Technetium-99m ( $^{99m}\text{Tc}$ ) has been mostly used for radiopharmaceuticals labeling due to its suitable physical and chemical characteristics and inexpensive isotope cost (3). Organometallic metal cores often exhibit advantages in terms of kinetic inertness, stability, and size and thus could lead to the development of more efficient and stable compounds compared to classical inorganic complexes (4). We elected to use the versatile low valent *fac*-[ $^{99m}\text{Tc}(\text{I})-(\text{CO})_3$ ] core, which its chemistry has recently been pioneered by Alberto and co-workers. The facially coordinated carbonyl ligands stabilize the Tc +1 oxidation state, obviating the elaborate, often macrocyclic, polydentate structures required to stabilize other intermediate oxidation states of Tc. In neutral complexes with simple N,O donors the *fac*-[ $^{99m}\text{Tc}(\text{I})-(\text{CO})_3$ ] core possesses intermediate lipophilicity, an advantage in living systems (5). Lots of  $^{99m}\text{Tc}$ -labeled glucose derivatives have been synthesized in order to develop one subrogate in SPECT for [ $^{18}\text{F}$ ]-FDG in PET recently. Developed by Yang,  $^{99m}\text{Tc}$ -labeled ethylenedicysteine-deoxyglucose (ECDG) showed similarities with [ $^{18}\text{F}$ ]-FDG in tumor uptake. This suggests that there is feasibility for  $^{99m}\text{Tc}$ -labeled deoxyglucose as a metabolic tumor imaging agent. However, [ $^{99m}\text{Tc}$ ]-ECDG still has some drawbacks such as slow cleanup from the blood, which would cause high background activity; and large molecular weight, which would limit its

penetration through blood-brain barrier (BBB). Thus, it would be desirable to develop a smaller  $^{99m}\text{Tc}$ -based deoxyglucose derivative with rapid blood clearance and still maintaining its high tumor uptake (3).

2-Amino-2-deoxy(*S*-benzoylthioacetyl)-D-glucose (*S*-Bz-TA-DG) was synthesized and labeled with  $^{99m}\text{Tc}$ . The overall yield of *S*-Bz-TA-DG is higher than that published in the literature (3). Radio-HPLC analysis of [ $^{99m}\text{Tc}$ ]-(*S*-Bz-TA-DG) at pH=10, revealed that labeling with  $^{99m}\text{Tc}$  resulted in the formation of radiochemical species [ $^{99m}\text{Tc}$ ]-(*S*-Bz-TA-DG) (>85%) with different HPLC-profiles and comparable retention times to those of the pertechnetate and [ $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3$ ] $^+$  complex. The concentration procedure was succeeded with reverse phase C18 column to obtain highly concentrated [ $^{99m}\text{Tc}$ ]-(*S*-Bz-TA-DG). This report describes the synthesis, radiolabelling with  $^{99m}\text{Tc}$  and preliminary biodistribution study in normal mice.

## Methods

All chemicals were purchased from Fluka and Merck companies and used without further purification. Carbon monoxide was obtained in the form of refillable canisters (0.5 L) from M/s Alchemie Gases & Chemicals, Atomic Energy Organization of Iran.  $^{99m}\text{TcO}_4^-$  was eluted from an in-house  $^{99}\text{Mo}/^{99m}\text{Tc}$  column generator using normal saline. High Performance Liquid Chromatography analyses were performed on a JASCO 880-PU HPLC (Tokyo, Japan) equipped with a Raytest-Gabi gamma ray detector. A Polygosil  $5\mu\text{m}$  RP-C18 analytical column (reverse phase) with dimensions of  $250\times 4.6$  mm was used. The NMR spectra were measured on a 500 MHz, and IR spectra were recorded on a FT-IR BOMEM MB-Series. All radioactivity measurements were carried out using NaI(Tl) scintillation counter.

### Synthesis of *S*-benzoylthioglycolic acid (1)

Synthesis of (1) was done according to the previously reported method (6). Sodium hydroxide (8.8 g, 220 mmol) and thioglycolic acid (9.2 g, 100 mmol) were dissolved in a mixture of toluene (75 mL) and water (75 mL). The mixture cooled in an ice-acetone bath to about  $-5-0$  °C. Benzoyl chloride (14.05 g, 100 mmol) was added over 30 minutes, and stirring was continued for 30 minutes at  $-5-0$  °C and another 30 minutes at room temperature. The organic layer was separated, washed with water ( $4\times 50$  mL) and the combined aqueous phases were acidified to pH 1.5 by hydrochloric acid. The precipitated product was

filtered and dried. Recrystallization from ethyl acetate gave 16.1 g (83.0%) of product as colorless crystals with a melting point of 99–101 °C (literature value = 102–103 °C). IR (KBr),  $\nu$  ( $\text{cm}^{-1}$ ); 1712 (-COOH), 1660 (-COS-), 2916 (-CH, stretching).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$  (ppm); 3.97 (s, 2H), 7.49-8.02 (m, 5H, aromatic), 11.35 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ),  $\delta$  (ppm); 31.6, 127.9, 129.2, 134.4, 136.3, 175.4, 190.5.

#### Synthesis of *S*-benzoylthioacetyl Chloride (2)

Synthesis of (2) was done according to the previously reported method (7). A solution of *S*-benzoylthioglycolic acid (1 g, 5.1 mmol, 0.26 equiv) in dichloromethane (5 mL) was charged sequentially with oxalyl chloride (1.05 mL, 12.1 mmol) and *N,N*-dimethylformamide (10  $\mu\text{L}$ , 0.13 mmol, 0.005 equiv), and the mixture was stirred under argon for 1 h at room temperature. The color of the reaction mixture changed from colorless to yellow. The solvent was evaporated under reduced pressure. The excess of oxalyl chloride was removed by evaporating with a vacuum pump. The obtained yellow solid (m.p = 72–75 °C) was used for the next step. IR (KBr),  $\nu$  ( $\text{cm}^{-1}$ ); 2987 (-CH, stretching), 1815 (-COCl), 1660 (-COS-), 1203 (-C-O);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$  (ppm); 4.4 (s, 2H), 7.5-8.03 (m, 5H, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ),  $\delta$  (ppm); 42.3, 128.1, 129.3, 134.7, 135.9, 169.7, 189.2.

#### Synthesis of 2-Amino-2-Deoxy(*S*-Benzoylthioacetyl)-*D*-Glucose (3)

Synthesis of (3) was done according to the previously reported method (8). *S*-benzoylthioacetyl chloride (1.0 g, 4.66 mmol) was dissolved in dichloromethane (2 mL). This solution was added drop wise to a solution of glucosamine hydrochloride (0.67 g, 3.11 mmol) and sodium hydrogen carbonate (0.52 g, 6.22 mmol) in 5 mL of water. The mixture was stirred for 1 hour at 60 °C, and then the precipitated product was filtered and dried. The resulting precipitate was washed with cold water (20 mL) and diethyl ether (15 mL). The solid was dried in a desiccators containing silica gel under vacuum. The yield of **3** was 78.0%; m.p = 193–195 °C (dec.). IR (KBr),  $\nu$  ( $\text{cm}^{-1}$ ); 3300-3500 (-OH and -NH, stretching), 2916 (-CH, stretching), 1660.5 (-COS- and -CON-), 1557 (-NH);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ),  $\delta$  (ppm); 1.8-1.9 (m, 2H), 2.19-2.45 (m, 9H), 3.6 (d, 1H), 6.01-6.5 (m, 5H, aromatic);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ ),  $\delta$  (ppm); 31.1, 53.8, 60.3, 69.9, 70.3, 70.6, 89.9, 125.8, 127.5, 132.5, 135.3, 168.4, 189.7.

#### Preparation of $^{99m}\text{Tc}$ tricarbonyl precursor, [ $^{99m}\text{Tc}(\text{OH}_2)_3(\text{CO})_3$ ] $^+$ , (4)

Synthesis of (4) was done according to the previously reported method (9). The  $^{99m}\text{Tc}$  tricarbonyl precursor

4 was prepared using a modification of the procedure described by Alberto et al. A 10 ml vial containing  $\text{Na}_2\text{CO}_3$  (5 mg),  $\text{NaBH}_4$  (4 mg) and sodium potassium tartarate (10 mg) was capped with a rubber stopper and then flushed with a stream of CO gas (99.5%) at room temperature for 10 min. One mL of sodium pertechnetate ( $\text{Na}^{99m}\text{TcO}_4$ ) with up to 20-100 mCi was added by a syringe and then heated to 75 °C for 30 min. After rapid cooling down to room temperature, 0.3 ml of 0.1M HCl was added to decrease the pH (pH=9.5-10). The yield was >98% which was determined by HPLC.

#### Preparation of $^{99m}\text{Tc}(\text{I})$ tricarbonyl (TA-DG) complex (5)

Synthesis of (5) was done according to the previously reported method (4).  $^{99m}\text{Tc}(\text{I})$  tricarbonyl precursor **4** (300  $\mu\text{L}$ ) was added into 1 mL of *S*-Bz-TA-DG solution (0.0010M in phosphate buffer 0.05M with pH=9.5-10) and then the reaction mixture was heated 75 °C for 30 min. After cooling it to room temperature,  $^{99m}\text{Tc}(\text{I})$  tricarbonyl (TA-DG) was characterized. Analytical data for yield: >85% determined by means of HPLC with solvents consisted of 0.1% trifluoroacetic acid in water (solvent A) and acetonitrile (solvent B).

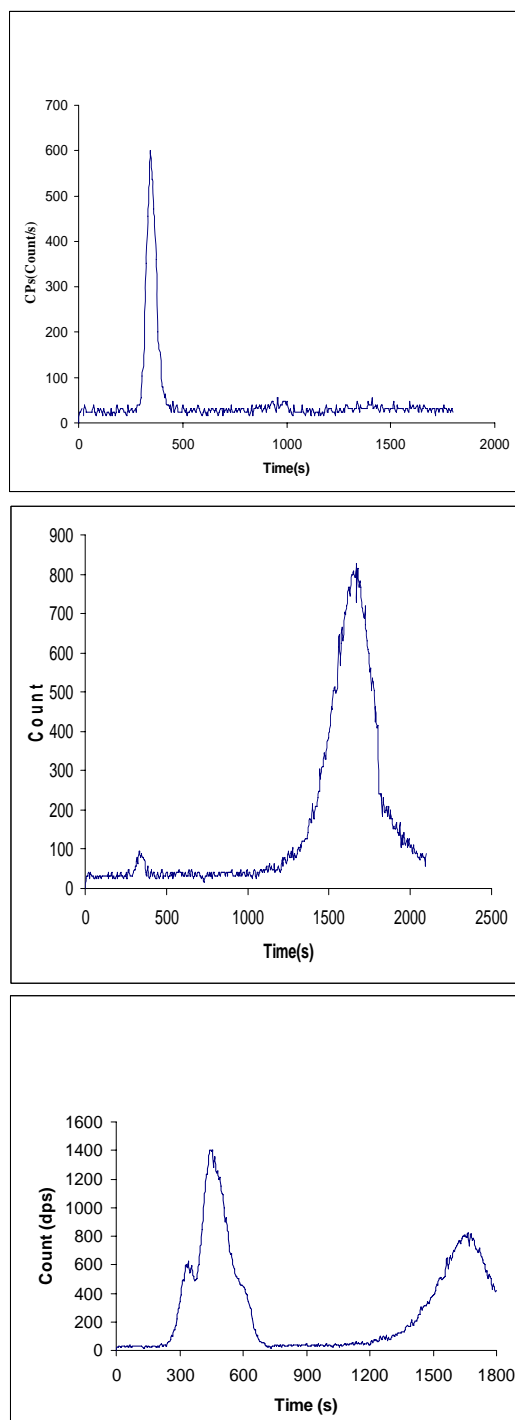
## Results and Discussion

### Chemistry/synthesis

The chemistry necessary for the synthesis of the *S*-Bz-TA-DG was mainly based on organic chemistry techniques. Due to the poor chemical stability of the thiol-group, *S*-Bz-TA-DG were synthesized as the thiol-protected precursors, the *S*-benzoyl protecting group being split off during chelation with  $^{99m}\text{Tc}$  at elevated temperature and high pH (10). [ $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3$ ] $^+$  has proved to be an excellent agent for labeling different kind of ligands. It can be formed in high yield directly from generator eluted pertechnetate in aqueous solution. As three coordinated water are labile, they could be exchanged readily with a variety of mono-, bi- and tridentate ligands forming complexes. The major advantage of using the carbonyl precursor is that high specific activity labeling of biomolecules can be obtained (11).

### HPLC characterization

Characterization of the [ $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3$ ] $^+$  and  $^{99m}\text{Tc}$ -(TA-DG) complex was carried out by HPLC using a C18 reverse phase column. HPLC solvents consisted of 0.1% trifluoroacetic acid in water (solvent A) and acetonitrile (solvent B).



**Figure 1.** Radio-HPLC chromatograms using an C18-column eluting with 0.1% TFA in water (solvent A) and acetonitrile (solvent B) for 30 min. (A)  $\text{Na}^{99m}\text{TcO}_4$ ,  $t_R = 5.7$  min; (B)  $[\text{}^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ ,  $t_R = 27.5$  min; (C)  $[\text{}^{99m}\text{Tc}]\text{-TA-DG}$ ,  $t_R = 8.2$  min.

Samples were analyzed with a linear gradient method (100% solvent A to 100% solvent B over 30 min). The test solution (20 mL) was injected into the column and the elution was monitored by observing the radioactivity profile. The flow rate was maintained at 1 mL/min.

#### Stability studies

The  $^{99m}\text{Tc}$ - (TA-DG) complex (0.5 mL) was incubated with human serum (0.4 mL) at 37 °C for 7h. The stability of this complex was studied by HPLC analysis and monitoring the elution profile.

#### Animal biodistribution studies

Biodistribution experiments of injected radiolabeled sugar was performed in normal mice (25–35 g) as previously described (12). Each animal was cited in specific container. After the injection of 0.1-0.3 mL (5mCi) of the complex 5 into a lateral tail vein, the blood, lung, liver, spleen, kidney, stomach, intestine, brain and heart were harvested, weighted, counted and the %ID/g were determined.

#### Labeling with $^{99m}\text{Tc}$

$^{99m}\text{Tc}(\text{I})$  tricarbonyl precursor 4,  $[\text{}^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ , was successfully prepared with 98% radiolabeling using a modification of the procedure described by Alberto et al. The complex is stable (>62%) for approximately 3 h. After this time, decomposition of the complex was observed. The  $^{99m}\text{Tc}$  complex of the TA-DG was obtained by addition of  $[\text{}^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$  at alkaline pH values (pH 9.5-10). Since the deprotonation of the amide nitrogens and removal of the *S*-protecting group in  $\text{MAG}_3$ -like agents is facilitated under alkaline conditions, a relatively high pH for the labeling reaction mixtures was preferred in order to maximize the labeling yield as well as to minimize the formation of side products. Radio-HPLC analysis of  $[\text{}^{99m}\text{Tc}]\text{-TA-DG}$  at pH=9.5-10, revealed that labelling with  $^{99m}\text{Tc}$  resulted in the formation of three radiochemical species ( $\text{Na}^{99m}\text{TcO}_4$  with  $t_R=5.7$  min,  $[\text{}^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$  complex with  $t_R=27.5$  min and  $[\text{}^{99m}\text{Tc}]\text{-TA-DG}$  >85% with  $t_R=8.2$  min) with different HPLC-profiles. The HPLC chromatograms of compound 5 in the reaction mixture with pH=9.5-10, sodium pertechnetate and complex 4 are shown in Figure 1.

#### Biodistribution in mice

The animals were housed at The Animal Center of Atomic Energy Organization of Iran. The biodistribution of the  $[\text{}^{99m}\text{Tc}]\text{-TA-DG}$  complex was studied in normal mice (body mass 25–35 g) at 30

min and 1 h post-injection, according to a published procedure (12). The results of the biodistribution study of [ $^{99m}\text{Tc}$ ]-TA-DG is summarized in Table 1.

**Table 1.** Biodistribution of  $^{99m}\text{Tc}$ -TA-DG in normal mice <sup>a</sup>

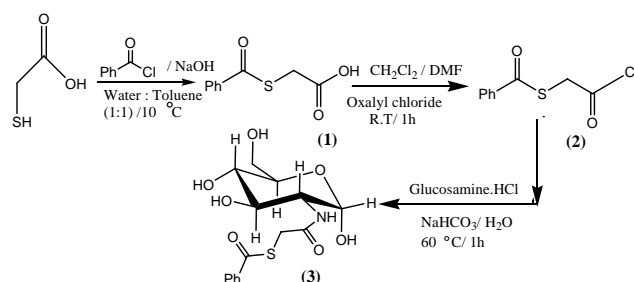
Tissue	30min	1 h
Brain	0.13±0.03	0.07±0.05
Kidney	8.80±0.61	10.81±5.03
Lung	2.61±0.32	1.68±0.15
Heart	0.91±0.16	0.52±0.10
Spleen	1.97±0.18	1.36 ± 1.29
Stomach	3.62 ± 0.08	3.08 ± 0.21
intestine	1.98 ± 0.71	3.07 ± 1.32
Liver	5.80 ± 1.01	7.19 ± 1.61
Blood	3.24 ± 0.43	1.52 ± 0.61

<sup>a</sup> All data are the mean percentage (n = 3) of the injected dose of  $^{99m}\text{Tc}$ -TA-DG per gram of wet tissue ± the standard deviation of the mean.

This complex showed negligible brain uptake (0.13%±0.03 ID) at 30 min post-injection, an efficient clearance from the blood, a rapid excretion to the urine and a low retention in the liver and kidneys. On the basis of these results, it seems that [ $^{99m}\text{Tc}$ ]-TA-DG has not most of the favorable properties as an imaging agent for brain tumors.

The benzoyl protected precursor of thioacetylglucosamine was synthesized following the synthetic route outlined in Scheme 1. In the course of synthesis of S-benzoylthioglycolic acid **1**, the time of adding benzoyl chloride must be over 30 minutes. The rate of adjusting pH should not be fast otherwise the product yield is lower. S-benzoylthioacetyl chloride **2** is a suitable product, which can be coupled with a variety of sugars. This can offer the possibility of synthesizing modified NS ligands in a simple one-step reaction. Compounds **1** and **2** were easily prepared in good yield. The product was confirmed by melting point, IR and NMR. The overall yield of

S-Bz-TA-DG is 78.0%. In our studies, the optimal pH value for deprotection of S-benzoyl group was between 9.5-10, and the reaction time was 30 minutes. We did not obtain [ $^{99m}\text{Tc}$ ]-TA-DG at neutral pH value or at pH values above 10, because the thioester bond of S-Bz-TA-DG is hardly disassociated in aqueous solution of pH neutral, and the glucosamine was destroyed in aqueous solution with pH values above 10.



**Scheme 1.** Synthesis of 2-Amino-2-Deoxy(S-Benzoylthioacetyl)-D-Glucose (**3**)

## Conclusion

Nonfunctionalized carbohydrate compounds such as glucose are generally weak ligands for chelating with  $^{99m}\text{Tc}$ . Therefore, functionalization with an external chelating group or the insertion of some functional groups is essential to obtain strong metal-binding compounds. In our studies, [ $^{99m}\text{Tc}$ ]-TA-DG was synthesized by procedure including deprotection of the benzoyl group. The labeling procedure took place at higher pH. Low molecular weight accelerated clearance from blood, and different linkers and chelate cores changed excretion path. On the basis of our results, it seems that [ $^{99m}\text{Tc}$ ]-TA-DG has not most of the favourable properties as an imaging agent for brain tumors.

## Acknowledgment

Financial support by Nuclear Science Research School of Nuclear Science & Technology Research Institute is gratefully acknowledged. We are also thankful to Dr. Mostafa Gandomkar for his support and encouragement.

## References

- Dumas C, Schibli R, Schubiger PA. Versatile routes to C-2-and C-6-functionalized glucose derivatives of iminodiacetic acid. *J Org Chem.* 2003; 68: 512-518.
- Chen Y, Huang ZW, He L, Zheng SL, Lian Li J, Lian Qin D. Synthesis and evaluation of a technetium-99m-labeled diethylenetriaminepentaacetate-deoxyglucose complex ([ $^{99m}\text{Tc}$ ]-DTPA-DG) as a potential imaging modality for tumors. *Appl Radiat Isot.* 2006; 64: 342-347.
- Bar-Shalom, R.; Valdivia, A. Y.; Blaufox, M. D. *Semin. Nucl. Med.* 2000, 30, 150.
- Chen X, Li L, Liu F, Liu B. Synthesis and biological evaluation of technetium-99m-labeled deoxyglucose derivatives as imaging agents for tumor. *Bioorg Med Chem Let.* 2006; 16 (21): 5503-5506.
- Petrig J, Schibli R, Dumas C, Alberto R, Schubiger PA. Derivatization of glucose and 2-deoxyglucose for transition metal complexation: substitution reactions with organometallic  $^{99m}\text{Tc}$  and Re precursors and fundamental NMR investigations. *Chem Eur J.* 2001; 7(9): 1868-73.
- Bayly SR, Fisher CL, Storr T, Adam MJ, Orvig C. Carbohydrate conjugates for molecular imaging and radiotherapy:  $^{99m}\text{Tc}(\text{I})$  and  $^{186}\text{Re}(\text{I})$  tricarbonyl complexes of N-(2'-Hydroxybenzyl)-2-amino-2-deoxy-D-glucose. *Bioconjug Chem.* 2004; 15(4): 923-6.
- Xiuli Z, Yongxian W, Junling L, Duanzhi Y. An improved synthesis of S-benzoylmercaptoacetyltriglycine as BFCA and the labeling of IgG with carrier-free  $^{188}\text{Re}$ . *J Radioanalytical & Nucl Chem.* 2003; 256 (2): 339-343.
- Mackman LR, Micklefield J, Block HM, Leeper GF, Battersby RA. Development of a new coupling procedure leading to the synthesis of isobacteriochlorins. *J Chem Soc.* 1997; *Perkin Trans. 1*: 2111-2122.
- Zhao B. A water-soluble SWCN-poly(M-aminobenzene sulfonic acid) copolymer. *Lab Chip.* 2005; 5: 163-170.
- Park SH, Jang BS, Park KB. Synthesis and biological characterization of  $^{99m}\text{Tc}(\text{I})$  tricarbonyl cysteine complex, a potential diagnostic for assessment of renal function. *J Label Compd Radiopharm.* 2005; 48: 63-73.
- Okarvi SM, Adriaens P, Verbruggen AM. Synthesis and biological characteristics of the technetium-99m triamide derivatives of mercaptoacetyltriglycine ( $\text{MAG}_3$ ). *J Label Compd Radiopharm.* 2003; 46: 73-84.
- Stamenkovic LL, Dokic DD, Pirmettis I, Jankovic DL, Nikolic NS. Tricarbonyl technetium (I) complexes with different diphosphate ligands. *J Label Compd Radiopharm.* 2003; 46: S256.
- Okarvi SM, Verbeke K, Adriaens P, Verbruggen A. *J Label Compd Radiopharm.* 2002; 45: 115-137.