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Synthesis and biological evaluation of novel ^{99m}Tc-oxo and ^{99m}Tc-nitrido complexes with phenylalanine dithiocarbamate for tumor imaging

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Abstract In this study, phenylalanine dithiocarbamate (PHEDTC) ligand was successfully synthesized and then radiolabeled with $[^{99m}TcO]^{3+}$ core and $[^{99m}Tc\equiv N]^{2+}$ core to produce ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC, respectively. Both complexes were prepared with high radiochemical purity and had good stability. The partition coefficient results showed they were hydrophilic, while ^{99m}TcN–PHEDTC was more hydrophilic than ^{99m}TcO–PHEDTC. The biodistribution study in mice bearing S 180 tumor showed that ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC had high tumor uptake at 2 h post-injection, 1.91 and 1.21, respectively. The good uptake and retention in tumor together with favorable tumor-to-muscle ratios make them promising candidates for further evaluation as potential tumor imaging agents.

Keywords Tumor imaging · L-phenylalanine · Dithiocarbamate · $[^{99m}TcO]^{3+}$ core · $[^{99m}TcN]^{2+}$ core

Introduction

The sugar-based PET radiotracer [^{18}F]fluorodeoxyglucose (^{18}F-FDG), the golden standard tracer for tumor detection and staging clinically, still has some limitations, like producing false-positive or -negative results, low image contrast in brain tumor diagnosis and poor differentiation of tumor from inflammatory [1–4]. Currently, great researches are being performed, with the aim to develop the alternative tracer of ^{18}F-FDG. So far, there has been an increasing interest on a wide range of radiolabeled amino acids, because they are the substrates of various amino acids transport systems, which can be upregulated in certain tumors. Recently, since the success of 6-[F-18]fluoro-3,4-dihydroxy-L-phenylalanine (^{18}F-DOPA) for tumor imaging, many studies have been focused on ^{18}F labeled L-phenylalanine derivates [5–13]. However, the limited availability (requiring cyclotron) and high costs of ^{18}F restrict its wide application in clinical practice, especially in many developing countries. Compared to radionuclide ^{18}F, ^{99m}Tc is more widely accessible because it can be produced from a commercial ^{99}Mo–^{99m}Tc generator and ^{99m}Tc labeled imaging agents can be easily prepared by using available kits, thus making ^{99m}Tc labeled tracers the mainstay of nuclear medicine imaging worldwide. Recently, we have reported the synthesis and evaluation of ^{99m}TcN–PRODTC (PRODTC: proline dithiocarbamate) as a potential tumor imaging agent [14]. As reported, ^{99m}TcN–PRODTC can be synthesized through easy procedures and exhibited relatively high tumor-to-muscle and tumor-to-blood ratio at 2 h post-injection. However, the uptake and retention in tumor of ^{99m}TcN–PRODTC was not satisfactory. Thus, it may be of great interest to probe other better ^{99m}Tc labeled amino acids derivatives for tumor imaging. Among all the radiolabeled amino acids, radiolabeled aromatic amino acids have the tendency to be more suitable for tumor imaging [15]. Bearing in mind L-phenylalanine is a natural aromatic amino acid and its molecular structure has an active amine group, thus making it possible to react with carbon disulfide in NaOH solutions to produce the phenylalanine dithiocarbamate (PHEDTC). Based on our previous reported work [16, 17], it can be assumed that PHEDTC can also be used to form stable

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^{99m}TcO and ^{99m}TcN complexes on the basis of efficient binding of the group to four sulfur atoms. This background encouraged us to synthesize ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC by ligand-exchange reaction to find good tumor imaging agents. In this study, the synthesis and biological evaluation of novel ^{99m}Tc-oxo and ^{99m}Tc-nitrido complexes with PHEDTC for tumor imaging are reported for the first time.

Experimental

Materials and methods

L–phenylalanine was purchased from J&K CHEMICA, China. Succinic dihydrazide (SDH) kit and glucoheptonate (GH) kit were obtained from Beijing Shihong Pharmaceutical Center, Beijing Normal University, China. All other chemicals were of reagent grade and were used without further purification. ^{99}Mo/^{99m}Tc generator was obtained from the China Institute of Atomic Energy (CIAE). IR spectrum was obtained with an AVATAR 360 FT-IR spectrometer using KBr pellets. NMR spectrum was recorded on a 500 MHz Bruker Avance spectrophotometer. Elemental analyses were performed on a Vario EL elemental analyzer model.

Synthesis of phenylalanine dithiocarbamate (PHEDTC)

The synthesis of PHEDTC was carried out according to the literature [18]. Carbon disulfide (0.35 mL, 5.70 mmol) was dissolved in 5 mL anhydrous diethyl ether and cooled to 0 °C in an ice bath. L-phenylalanine (936 mg, 5.70 mmol) and NaOH (456 mg, 11.4 mmol) were dissolved in 10 mL anhydrous methanol and added dropwise to the carbon disulfide solution. The mixture was stirred for 3 h in an ice bath. The solvent was removed and the resulting residue was triturated with diethyl ether. The white solid was filtered and washed with Et_2O and dried in vacuo to yield PHEDTC as a pale yellow solid (0.631 g, 39 %).

Radiolabeling of ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC and quality control techniques

^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC were prepared by using GH kit and SDH kit, separately.

For preparing ^{99m}TcO–PHEDTC, 1 mL of saline containing $^{99m}TcO_4^-$ (370 MBq) was added to a GH kit containing 0.1 mg of stannous chloride dihydrate, 20.0 mg of GH. The reaction vial was incubated at room temperature for 15 min. Successively, 1.0 mg of PHEDTC dissolved in 1.0 mL water was added and the resulting solution was heated at 100 °C for 30 min.

As for preparing ^{99m}TcN–PHEDTC, 1 mL of saline containing $[^{99m}TcO_4]^-$ (370 MBq) was added to a SDH kit, which contained 0.05 mg of stannous chloride dihydrate, 5.0 mg of SDH and 5.0 mg of propylenediamine tetraacetic acid (PDTA). The mixture was kept at room temperature for 15 min. Then, 1.0 mg of PHEDTC dissolved in 1.0 mL water was added to the mixture and the reaction vial was incubated for 20 min on a boiling water bath.

The radiochemical purities of the complexes were routinely checked by thin layer chromatography (TLC). TLC was performed on a polyamide strip and eluted with saline and acetonitrile, respectively.

In vitro stability study

^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC were kept in the labeling milieu at room temperature (25 °C) and the radiochemical purities were assayed by TLC analysis for up to 6 h after labeling. To test the stabilities of the complexes in serum, 0.5 mL of each labeled complex was separately incubated in 1.0 mL human serum (1 mg/mL) at 37 °C for 4 h and then the radiochemical purity of each complex was analyzed by TLC.

Human serum albumin binding assay

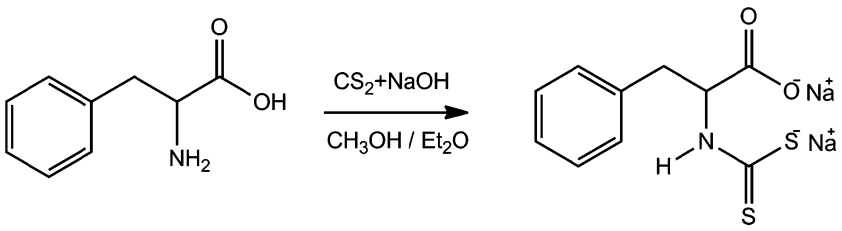
10 μL of labeled complex (370 KBq) was added in 100 μL human serum albumin (100 mg/mL) in the centrifuge tube. After the mixture was incubated at 37 °C for 2 h, the serum protein was precipitated by adding 1 mL trichloroacetic acid (250 mg/mL) to the mixture. The supernatant and precipitate were separated by centrifugation at 2,000 g for 5 min. Then the radioactivity of each phase was measured separately. This experimental procedure was repeated three times and the percentage of human serum protein binding was determined as the following equation:

$$\begin{aligned}&\text{Serum protein binding } \%\\&= (\text{counts per minute in precipitate})\\&\quad /(\text{counts per minute in precipitate}\\&\quad + countsperminuteinsupernatant) \times 100\%.\end{aligned}$$

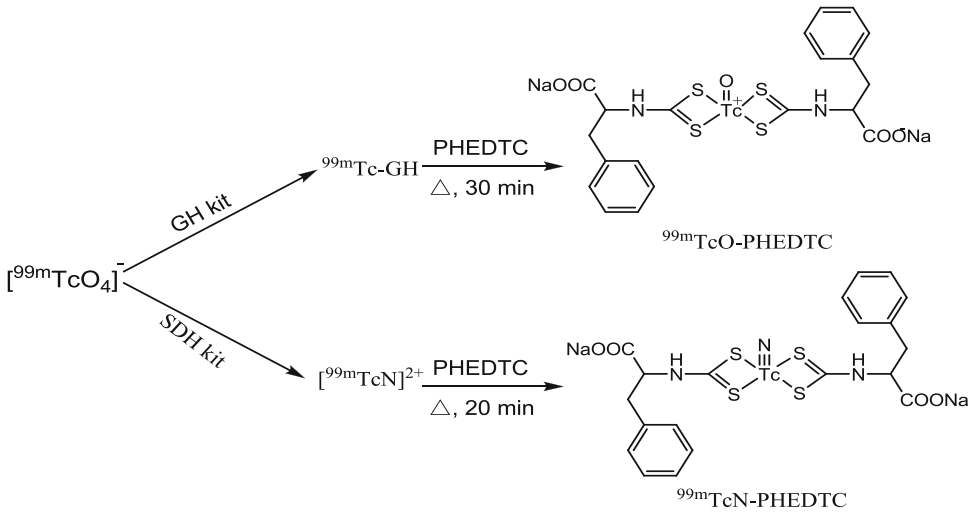
Determination of the partition coefficient

The partition coefficient was determined by mixing the complex with an equal volume of 1-octanol and phosphate buffer (0.025 mol/L, pH 7.4). In a centrifuge tube, containing 2 mL of each phase, 0.1 mL of the labeled complex solution was added, and the mixture was shacked on a Vortex mixer for 1 min and then centrifuged at 5,000 g for 5 min. Three samples (0.1 mL each) from each layer were counted in a well gamma γ-counter. The partition coefficient, P, was calculated as the mean value of counts per

Scheme 1 Synthesis of PHEDTC The preparations of ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC were carried out using the following procedure in Scheme 2



Scheme 2 Preparation procedures and speculative structures of ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC



minute in octanol divided by that of the buffer. Usually the final partition coefficient value was expressed as log *P*. The log *P* value was reported as an average of three measurements plus the standard deviation.

Biodistribution study

All biodistribution studies were carried out in compliance with the national laws related to the conduct of animal experimentation. 0.1 mL of ^{99m}TcO–PHEDTC (7.4×10^5 Bq) was injected into the Kunming male mice (18–20 g) bearing S180 tumor via a tail vein. The mice were sacrificed in groups of five at 2 and 4 h post-injection. The tumor, other organs of interest and blood were collected, weighed and measured for radioactivity. The counting tubes, including a standard equivalent to 1 % of the injected dose, were assayed in a well-type NaI (Tl) detector and the results were expressed as the percent uptake of injected dose per gram of tissue (% ID/g). The final results are expressed as mean ± standard deviation. The biodistribution study of ^{99m}TcN–PHEDTC was conducted in the same way.

Results and discussion

Synthesis and radiolabeling

PHEDTC was prepared by reacting L-phenylalanine with an equivalent amount of carbon disulfide in NaOH solutions. The reaction equation is shown in Scheme 1. It was characterized by IR, ^{1}H NMR, ^{13}C NMR and Elemental analysis. Specific rotation $[\alpha]_D^{25}(H_2O) = +53.9°$. IR(KBr)/cm^{-1}: 3418 (N–H), 1651 (C=O), 1614 (C=C), 1111 (C=S). ^{1}H-NMR (D_2O) δ: 7.11–7.26 (m, 5H), 4.77–4.80 (dd, 1H), 2.88–3.17 (m, 2H). ^{13}C-NMR (D_2O) δ: 210.54, 177.79, 137.55, 129.342, 129.37, 129.02, 128.57, 126.74, 63.61, 37.24. Elemental analysis calculated (%) for $C_{10}H_9NNa_2O_2S_2{\cdot}0.5H_2O$: C, 40.82; N, 4.76; H, 3.40. Found: C, 41.21; N, 4.82; H, 3.98.

For preparing ^{99m}TcO–PHEDTC, the method is based on the reaction of $[^{99m}TcO_4]^-$ with GH in the presence of stannous chloride as reducing agent to form ^{99m}Tc(V)–GH which contains the $[^{99m}TcO]^{3+}$ core and ^{99m}Tc(V)–GH is a suitable substrate for the substitution reaction with PHEDTC to produce the final complex ^{99m}TcO–PHEDTC.

As for ^{99m}TcN–PHEDTC, it was prepared by adding PHEDTC to the $[^{99m}TcN]^{2+}$ intermediate, which was produced by the reaction of $[^{99m}TcO_4]^-$ with SDH in the presence of stannous chloride as reducing agent. The $[^{99m}TcN]^{2+}$ core is an appropriate substrate for the substitution reaction with PHEDTC to obtain ^{99m}TcN–PHEDTC with high yield.

Based on a previous characterization of the molecular structure of ^{99m}Tc(V)O-DMSA (DMSA: dimercaptosuccinic acid) and bis(*N*-ethoxy, *N*-ethyl dithiocarbamato) nitrido technetium-99m complex $[^{99m}TcN(NOEt)_2]$ [19–21], it can be presumed that ^{99m}TcO–PHEDTC or ^{99m}TcN–PHEDTC would have a square pyramidal geometry with an

apical Tc=O bond or Tc≡N bond and two PHEDTC ligands spanning the four positions in the basal plane through the four sulfur atoms. Clearly, its detailed structure needs to be determined by further research work.

The radiochemical purities of the complexes were routinely checked by TLC. For ^{99m}TcO–PHEDTC, in saline, $^{99m}TcO_4^-$ and ^{99m}TcO–PHEDTC migrated at $R_f = 0.1$ while ^{99m}Tc–GH migrated at $R_f = 0.8$–1.0. In acetonitrile, $^{99m}TcO_4^-$ migrated at $R_f = 0.3$–0.5, while ^{99m}TcO–PHEDTC and ^{99m}Tc–GH migrated at $R_f = 0.1$. For ^{99m}TcN–PHEDTC, in saline, $^{99m}TcO_4^-$ and ^{99m}TcN–PHEDTC remained at the origin while $[^{99m}TcN]^{2+}$ migrated with the front. In acetonitrile, $^{99m}TcO_4^-$ migrated at $R_f = 0.3$–0.5, while ^{99m}TcN–PHEDTC and $[^{99m}TcN]^{2+}$ remained at the origin.

Stability study

The radiochemical purities of ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC were both over 90 % at 6 h after preparation. On the other hand, in serum at 37 °C, the radiochemical purities of the complexes were higher than 90 % even up to 4 h after synthesis, suggesting they possessed a great stability in human serum.

Human serum albumin binding assay

As described in the experiment of human serum albumin binding assay [14], the percentage of human serum protein binding ability for both complexes was measured and calculated. The results showed that the percentage of human serum protein binding of ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC were high, 85.68 ± 0.61 and 86.32 ± 0.19 %, respectively. When compared with ^{99m}TcN–PRODTC (87.42 ± 0.01 %), there was no great difference in the serum protein binding ability among these three complexes.

Partition coefficient (log *P*)

The log P values of ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC were found to be −1.33 ± 0.07 and −1.52 ± 0.03, respectively, indicating both tracers were hydrophilic. Moreover, ^{99m}TcN–PHEDTC was more hydrophilic than ^{99m}TcO–PHEDTC. As compared to ^{99m}TcN–PRODTC (log *P*: −2.80 ± 0.11), ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC had a higher lipophilicity due to their structures containing aromatic groups.

Biodistribution study

The results of biodistribution of ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC in mice bearing S180 tumor are shown in Table 1. Results of biodistribution of recently reported ^{99m}Tc complexes as tumor imaging agents are shown in Table 2 for comparison.

Table 1 Biodistribution of ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC in mice bearing S 180 tumor (%ID/g) [a]

Tissue	^{99m}TcO–PHEDTC		^{99m}TcN–PHEDTC	
	2 h	4 h	2 h	4 h
Heart	0.54 ± 0.32	0.64 ± 0.17	1.07 ± 0.18	0.93 ± 0.33
Liver	3.82 ± 0.67	4.02 ± 0.65	3.32 ± 0.31	2.83 ± 0.33
Lung	1.71 ± 0.39	1.23 ± 0.59	3.79 ± 0.88	2.99 ± 0.50
Kidney	5.11 ± 0.58	6.49 ± 0.55	8.11 ± 1.75	6.15 ± 0.82
Spleen	1.56 ± 0.10	1.73 ± 0.28	1.26 ± 0.03	0.97 ± 0.04
Stomach	0.49 ± 0.12	0.69 ± 0.06	0.94 ± 0.10	0.95 ± 0.08
Bone	0.47 ± 0.20	0.51 ± 0.25	0.26 ± 0.14	0.37 ± 0.07
Intestine	1.38 ± 0.30	0.87 ± 0.43	2.46 ± 0.39	1.04 ± 0.23
Muscle	0.24 ± 0.01	0.24 ± 0.05	0.64 ± 0.07	0.48 ± 0.08
Tumor	1.91 ± 0.16	1.39 ± 0.26	1.21 ± 0.59	0.86 ± 0.15
Blood	3.48 ± 0.45	2.58 ± 0.30	0.94 ± 0.12	0.59 ± 0.12
T/N	7.96	5.79	1.89	1.79
T/B	0.55	0.54	1.29	1.46

T/N tumor to muscle, *T/B* tumor to blood

[a] All the data are the mean percentage ($n = 5$) of the injected dose of ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC per gram of tissue, ±the standard deviation of the mean

As shown in Table 1, both ^{99m}TcO–PHEDTC and ^{99m}TcN–PHEDTC have a high uptake and good retention in tumor. The muscle uptakes are low so the T/N ratios are better. Activity accumulation in the kidneys and liver shows that the major route of excretion is renal and hepatobiliary. Low uptake in the stomach is suggestive of in vivo stability of the above ^{99m}Tc labeled complexes. As compare to ^{99m}TcN–PHEDTC, ^{99m}TcO–PHEDTC has a higher tumor and liver uptake than ^{99m}TcN–PHEDTC and this possibly be related to its higher lipophilicity. ^{99m}TcO–PHEDTC has a lower muscle uptake and higher tumor uptake, so the T/N ratio of ^{99m}TcO–PHEDTC is much higher than that of ^{99m}TcN–PHEDTC. However, due to the higher blood uptake, the T/B ratio of ^{99m}TcO–PHEDTC is lower than that of ^{99m}TcN–PHEDTC.

From Table 2, it is observed that ^{99m}TcO–PHEDTC and ^{99m}TcN–PRODTC show a much higher tumor uptake when compared to the other three complexes. A decrease in the order is observed: ^{99m}TcO–PHEDTC > ^{99m}TcN–PHEDTC > $[^{99m}Tc(CO)_3(IDA–PEG3–CB)]^-$ > ^{99m}TcN–PRODTC > $[^{99m}Tc(CO)_3(PA–TZ–CHC)]^+$. In the limits of our study, among ^{99m}TcO–PHEDTC, ^{99m}TcO–PHEDTC and ^{99m}TcN–PRODTC, the results demonstrated that the ^{99m}Tc labeled complexes containing aromatic amino acid moieties possibly increased the tumor uptake, confirming our hypothesis that radiolabeled aromatic amino acids are

Table 2 Comparison of biodistribution of some reported ^{99m}Tc complexes

Complex	1	2	3	4	5
Time p.i. (h)	2	2	2	2	2
Tumor uptake (%ID/g)	1.91 ± 0.16	1.21 ± 0.59	0.59 ± 0.09	0.33 ± 0.08	0.85 ± 0.13
T/N	7.96	1.89	4.54	3.81	2.61
T/B	0.55	1.29	2.19	1.43	0.50
Reference	Present study	Present study	[14]	[22]	[23]

Complex 1: ^{99m}TcO–PHEDTC; 2: ^{99m}TcN–PHEDTC; 3: ^{99m}TcN–PRODTC; 4: $[^{99m}Tc(CO)_3(PA–TZ–CHC)]^+$; 5: $[^{99m}Tc(CO)_3(IDA–PEG3–CB)]^-$

possibly more promising for tumor imaging. Moreover, different ^{99m}Tc core for preparing the complexes may exhibit significant impact on the tumor uptake, T/B and T/N ratios.

Conclusion

In present study, a novel ligand PHEDTC was synthesized and its ^{99m}Tc-oxo core and ^{99m}Tc-nitrido core complexes were successfully prepared in high yields through a ligand-exchange reaction. The preliminary in vivo studies showed both of them had a relative high tumor uptake and good tumor-to-muscle ratios. Especially for ^{99m}TcO–PHEDTC, it would be a promising tumor imaging agent, justifying further investigations.

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