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Synthesis and biodistribution of novel ^{99m}Tc labeled 4-nitroimidazole dithiocarbamate complexes as potential agents to target tumor hypoxia

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Sodium 3-(4-nitro-1*H*-imidazolyl)propyl dithiocarbamate (N4IPDTC) was synthesized and radiolabelled with a $[^{99m}TcO]^{3+}$, $[^{99m}Tc{\equiv}N]^{2+}$ or $[^{99m}Tc(CO)_3]^{+}$ core to produce ^{99m}TcO-N4IPDTC, ^{99m}TcN-N4IPDTC and $^{99m}Tc(CO)_3$-N4IPDTC, respectively. All of the three complexes were prepared with high radiochemical purity and had good *in vitro* stability over a period of 6 h. The partition coefficient results showed that ^{99m}TcO-N4IPDTC and ^{99m}TcN-N4IPDTC were lipophilic, while $^{99m}Tc(CO)_3$-N4IPDTC was hydrophilic. The tumor cell experiments and the biodistribution in mice bearing S180 tumors showed that all of the complexes exhibited good hypoxic selectivity and accumulation in the tumor. Among them, ^{99m}TcO-N4IPDTC had the advantages of higher tumor uptake, and higher tumor/blood and tumor/muscle ratios. Planar scintigraphic imaging studies showed there was a visible accumulation in tumor sites, suggesting its potential usefulness as a tumor hypoxia imaging agent.

Introduction

Tumor hypoxia is an important factor in resistance to radiotherapy and chemotherapy.[1] So, the early diagnosis of tumor hypoxia plays a critical role in tumor treatment planning. Due to the noninvasiveness of single photon emission computed tomography (SPECT) and positron emission tomography (PET) in imaging tumor hypoxia, many researchers are focused on developing targeted radiopharmaceuticals for tumor hypoxia imaging. In the development of hypoxia imaging agents, nitroimidazole derivatives are enzymatically reduced and accumulated in hypoxic regions, therefore labeled nitroimidazole analogues have received great attention. Currently, the PET tracer [^{18}F]Fluoromisonidazole ([^{18}F]FMISO) is one of the most clinically studied hypoxia markers.[2,3] However, the short half life, high cost and limited availability of the [^{18}F] isotope are realistic limitations. By comparison, technetium-99m has ideal physical and chemical characteristics, inexpensive cost and in-house availability. Therefore, there has been considerable clinical interest in developing ^{99m}Tc-labeled nitroimidazole derivatives for targeting tumor hypoxia. Recently, several ^{99m}Tc labeled nitroimidazole analogues (including 2-nitroimidazole, 4-nitroimidazole and 5-nitroimidazole) have been reported.[4–13] However, there exist some limitations for these complexes, such as their relatively low tumor uptake or their slow clearance from the blood. Thus, ongoing research is in progress to discover an ideal hypoxia imaging agent.

It is well-known that 2-nitroimidazole derivatives have been the most widely studied for their potential in hypoxia imaging because 2-nitroimidazole has a more positive single electron reduction potential (SERP) value, which means it can be efficiently reduced and retained in hypoxic cells. However, SERP is not the only factor which affects the uptake and retention of the imaging agent inside a hypoxic cell. The lipophilicity and the structure of the complex may also play important roles in determining the overall behavior of the hypoxia imaging agent. Although the SERP of 4-nitroimidazole is less positive compared to 2-nitroimidazole, 4-nitroimidazole is much cheaper than 2-nitroimidazole. Moreover, several 4-nitroimidazole derivatives as potential clinical hypoxia imaging agents have been successfully synthesized.[14–17] This fact shows the feasibility of 4-nitroimidazole derivatives as potential hypoxia imaging agents. It is known that the $[^{99m}TcO]^{3+}$, $[^{99m}Tc{\equiv}N]^{2+}$ and $[^{99m}Tc(CO)_3]^{+}$ cores may exhibit high stability and the presence of them in the molecular structures of radiopharmaceuticals may change their biological behavior. Moreover, $[^{99m}TcO]^{3+}$, $[^{99m}Tc{\equiv}N]^{2+}$ and $[^{99m}Tc(CO)_3]^{+}$ cores have been shown to complex well

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with ligands containing sulfur atoms, as in dithiocarbamates.[18–20] The above background encouraged us to prepare several ^{99m}Tc labeled 4-nitroimidazole dithiocarbamate complexes by using different ^{99m}Tc cores to find good tumor hypoxia imaging agents. In this study, the synthesis and biological evaluation of novel ^{99m}Tc labeled 4-nitroimidazole dithiocarbamate complexes for tumor hypoxia imaging are reported.

Results and discussion

Chemistry

The 3-(4-nitro-1*H*-imidazolyl)propyl dithiocarbamate (N4IPDTC) was prepared by reacting 3-(4-nitro-1*H*-imidazolyl) propylamine hydrochloride with carbon disulfide in NaOH solution. The reaction is schematically shown in Scheme 1.

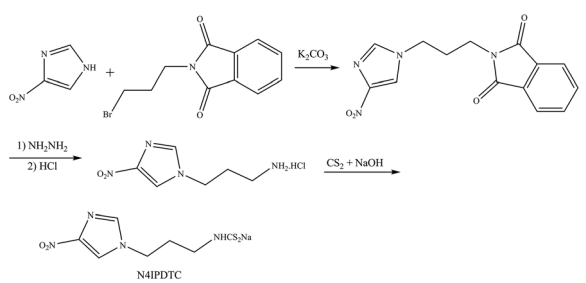
Radiolabeling and quality control

The preparations of ^{99m}TcN-N4IPDTC, ^{99m}TcO-N4IPDTC and ^{99m}Tc(CO)$_3$-N4IPDTC can be carried out using the following procedures in Scheme 2.

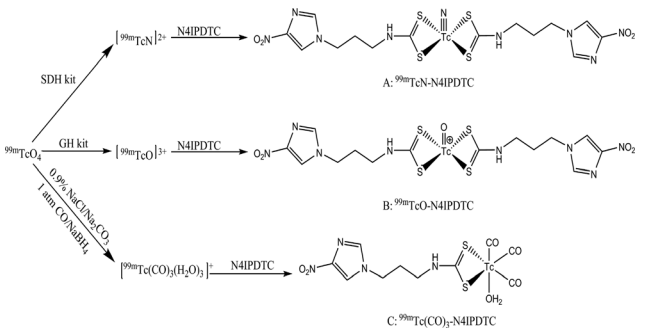
For labeling, ^{99m}TcN-N4IPDTC was prepared by adding N4IPDTC to the $[^{99m}TcN]^{2+}$ intermediate, which was produced by the reaction of $[^{99m}TcO_4]^-$ with succinic dihydrazide (SDH) in the presence of stannous chloride as a reducing agent. The $[^{99m}TcN]^{2+}$ core is a suitable substrate for the substitution reaction with N4IPDTC to prepare ^{99m}TcN-N4IPDTC in high yield.

^{99m}TcO-N4IPDTC was prepared by a ligand-exchange reaction with ^{99m}Tc-glucoheptonate (GH). ^{99m}Tc-GH is a suitable substrate for the substitution reaction with N4IPDTC to give the final complex, ^{99m}TcO-N4IPDTC. As for preparing ^{99m}Tc(CO)$_3$-N4IPDTC, the H_2O molecules in the fac-$[^{99m}Tc(CO)_3(H_2O)_3]^+$ precursor are readily substituted by sulfur atoms in the N4IPDTC ligand. The N4IPDTC ligand displaces two of the H_2O molecules in the fac-$[^{99m}Tc(CO)_3(H_2O)_3]^+$ precursor.

The radiochemical purities of the complexes were assessed by HPLC. The retention times of $[^{99m}TcN]^{2+}$, $[^{99m}TcO]^{3+}$ and $[^{99m}Tc(CO)_3(H_2O)_3]^+$ were 4.73 min, 4.13 min, and 15.60 min, respectively, while those of ^{99m}TcN-N4IPDTC, ^{99m}TcO-N4IPDTC and ^{99m}Tc(CO)$_3$-N4IPDTC were 18.45 min, 11.74 min and 7.38 min (Fig. 1). The mean radiochemical purities of the products were all over 95% immediately after preparation.



Scheme 1 Synthesis of N4IPDTC.



Scheme 2 Preparation procedures for ^{99m}TcN-N4IPDTC, ^{99m}TcO-N4IPDTC and ^{99m}Tc(CO)$_3$-N4IPDTC.

In vitro stability studies

The complexes were stable over 6 h in the reaction mixture at room temperature. On the other hand, no decomposition of the above complexes occurred over 6 h at 37 °C in mouse serum, suggesting they had good *in vitro* stability.

Determination of the partition coefficients

The partition coefficient (log*P*) values of ^{99m}TcN-N4IPDTC, ^{99m}TcO-N4IPDTC and ^{99m}Tc(CO)$_3$-N4IPDTC were 0.60 ± 0.01,

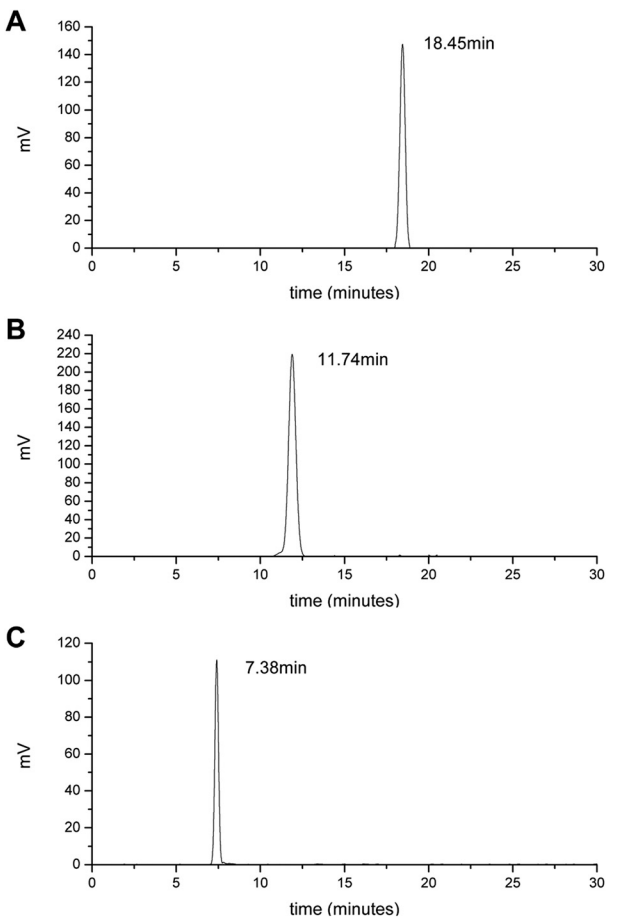


Fig. 1 HPLC patterns of ^{99m}TcN-N4IPDTC (A), ^{99m}TcO-N4IPDTC (B) and ^{99m}Tc(CO)$_3$-N4IPDTC (C).

0.27 ± 0.01 and −0.71 ± 0.01, suggesting that ^{99m}Tc(CO)$_3$-N4IPDTC was hydrophilic, while ^{99m}TcN-N4IPDTC and ^{99m}TcO-N4IPDTC were lipophilic. Furthermore, ^{99m}TcN-N4IPDTC was more lipophilic than ^{99m}TcO-N4IPDTC.

In vitro cellular uptake

The effect of hypoxic and aerobic conditions on the accumulation of the three ^{99m}Tc complexes in S180 cells as a function of time is illustrated in Fig. 2. From Fig. 2, it is shown that the uptake of the three ^{99m}Tc complexes in hypoxic cells is constantly more than that in aerobic cells, suggesting all of them exhibit preferential uptake in hypoxic conditions.

Biodistribution studies

The results of biodistribution of the complexes are shown in Table 1.

As described in Table 1, all of the three complexes have a certain uptake and good retention in tumors. The muscle uptakes are low so the T/N ratios are high. Activity accumulation in the kidneys, liver, feces and urine shows that the major routes of excretion are renal and hepatobiliary. In the limits of our study, the results demonstrate that different ^{99m}Tc cores for preparing the complexes may have a significant impact on the tumor uptake, and the T/B and T/N ratios. By comparison, interestingly, ^{99m}TcN-N4IPDTC (log *P*: 0.60) and ^{99m}TcO-N4IPDTC (log *P*: 0.27) show much higher tumor uptakes, along with higher lipophilicity than ^{99m}Tc(CO)$_3$-N4IPDTC (log *P*: −0.71). Among the three complexes, ^{99m}TcN-N4IPDTC is more lipophilic than the others, thus possibly explaining the much higher liver uptake of the former than the latter. Among them, the tumor uptake, T/N ratio and T/B ratio of ^{99m}TcO-N4IPDTC are the highest, showing the most promising properties for further studies in other animal models.

Although many ^{99m}Tc labelled 4-nitroimidazole derivatives have been evaluated as hypoxia imaging agents, their direct comparison is not easy due to both the different kinds of tumors used and the heterogeneity in the animal models. Because the biodistribution studies of ^{99m}TcO-N4IPDTC and ^{99m}Tc-N4IPA (N4IPA: 1-(4-nitroimidazole-1-yl)-propanhydroxyiminoamide) were performed in the same animals bearing S180 tumors,[14] the direct comparison between them are as follows. The tumor uptake of ^{99m}TcO-N4IPDTC is much higher than that of ^{99m}Tc-N4IPA. The tumor uptake of ^{99m}TcO-N4IPDTC (2.63 ± 0.35% ID/g) is nearly eight times better than that of ^{99m}Tc-N4IPA (0.34 ± 0.06% ID/g) at 4 h post-injection. With regard to the T/B ratio, there is no great difference between the two complexes. As for the T/N ratio, ^{99m}Tc-N4IPA is superior to ^{99m}TcO-N4IPDTC. The T/N ratio of ^{99m}Tc-N4IPA (8.60) is more than two times better than that of ^{99m}TcO-N4IPDTC (3.87) at 4 h post-injection. A good tumor hypoxia imaging agent should exhibit high detectability of tumors, which depends on both the absolute tumor uptake and tumor to background ratio. From the above data, ^{99m}TcO-N4IPDTC shows more potential usefulness as a tumor hypoxia imaging agent and needs further investigation.

SPECT imaging study

The SPECT imaging result showed that tumor uptake was clearly observable (Fig. 3), however, the high uptake of ^{99m}TcO-N4IPDTC in the liver and kidneys is the drawback of the complex. The imaging findings were similar to the biodistribution results in mice.

Experimental section

General

4-Nitroimidazole was purchased from Alfa Aesar, China. A succinic dihydrazide (SDH) kit, which contains 0.05 mg of stannous chloride dihydrate, 5.0 mg of succinic dihydrazide (SDH) and 5.0 mg of propylenediamine tetraacetic acid (PDTA), and a glucoheptonate (GH) kit containing 0.1 mg of stannous chloride dihydrate and 20.0 mg of GH 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 spectra were obtained with an AVATAR 360 FT-IR spectrometer using KBr pellets. NMR spectra were recorded on a 400 MHz Bruker Avance spectrometer.

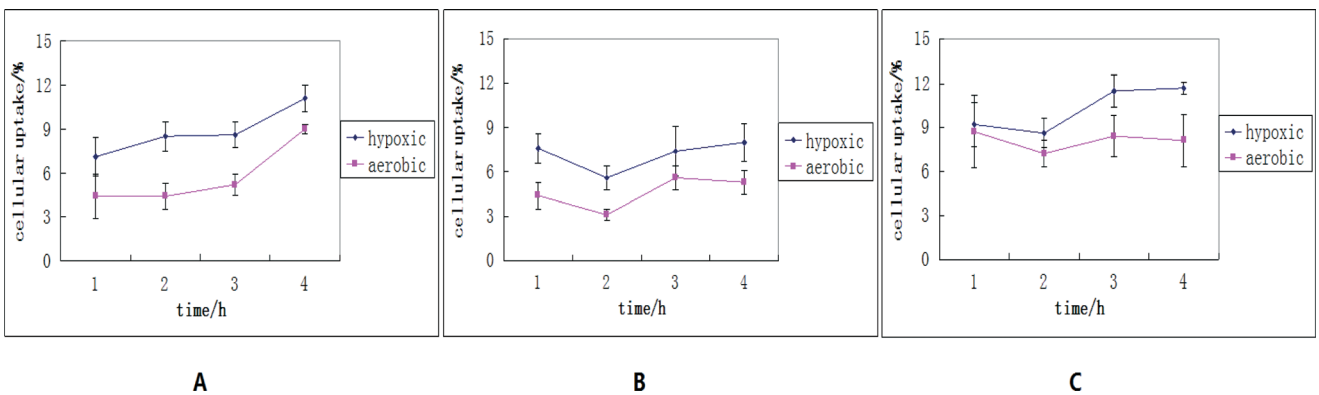


Fig. 2 Cellular uptakes of ^{99m}TcN-N4IPDTC (A), ^{99m}TcO-N4IPDTC (B) and ^{99m}Tc(CO)$_3$-N4IPDTC (C).

Table 1 Biodistributions of ^{99m}TcN-N4IPDTC (A), ^{99m}TcO-N4IPDTC (B) and ^{99m}Tc(CO)$_3$-N4IPDTC (C) in mice bearing S180 tumors (% ID/g)[a]

Complex	A		B		C	
Time	2 h	4 h	2 h	4 h	2 h	4 h
Heart	1.60 ± 0.24	1.27 ± 0.48	0.93 ± 0.03	0.88 ± 0.22	0.30 ± 0.03	0.21 ± 0.03
Liver	35.7 ± 2.70	34.2 ± 5.00	6.81 ± 1.28	6.21 ± 0.84	2.20 ± 0.21	1.06 ± 0.20
Lung	5.03 ± 1.38	5.71 ± 0.94	1.77 ± 0.17	1.41 ±0.18	0.64 ± 0.06	0.45 ± 0.08
Kidney	13.1 ± 1.50	12.3 ± 2.40	16.7 ± 3.11	13.2 ± 1.18	3.28 ± 0.42	2.31 ± 0.37
Spleen	5.99 ±0.82	6.48± 0.82	1.17 ± 0.23	1.07 ± 0.13	0.29 ± 0.05	0.25 ± 0.05
Muscle	0.74 ± 0.26	0.59 ± 0.09	0.64 ± 0.17	0.68 ± 0.13	0.24 ± 0.06	0.20 ± 0.04
Tumor	1.11 ± 0.24	1.15 ± 0.24	2.84 ± 0.19	2.63 ± 0.35	0.49 ± 0.10	0.36 ± 0.08
Blood	1.20 ± 0.23	0.71 ± 0.21	1.91 ± 0.18	1.59 ± 0.33	0.62 ± 0.03	0.43 ± 0.07
Feces	25.4 ± 6.38	33.2 ± 8.77	17.9 ± 4.23	11.6 ± 3.17	11.4 ± 3.30	14.3 ± 2.61
Urine	32.8 ±12.4	35.1 ± 10.4	62.1 ±17.1	64.6±9.30	22.3 ± 4.67	20.3 ± 5.17
T/N	1.50	1.95	4.44	3.87	2.04	1.80
T/B	0.93	1.62	1.49	1.65	0.79	0.84

[a] All data are the mean percentage (n = 5) of the injected dose of the three complexes per gram of tissue, ± the standard deviation of the mean. T/N = tumor-to-muscle ratio and T/B = tumor-to-blood ratio.

Elemental analyses were performed on a Vario EL elemental analyzer model. HPLC analysis was carried out with a reversed-phase column (Kromasil 100-5C, 250 4.6 mm), Shimadzu LC-20AT series.

Chemistry

3-(4-Nitro-1*H*-imidazolyl) propylamine hydrochloride (compound 1) was prepared as reported previously.[21] The synthetic procedures and the spectral data for N4IPDTC are as follows; 3-(4-nitro-1*H*-imidazolyl) propylamine hydrochloride (0.206 g), carbon disulfide (0.304 g) and NaOH (0.048 g) were dissolved in 25.0 mL water. The mixture was stirred at 3 °C for 2.0 h and continued to react overnight at room temperature. Most of the solvent was removed, and the precipitate was collected by filtration. The crude product was recrystallized from $CH_3OH/CH_3CH_2OCH_2CH_3$ to give yellow crystals of N4IPDTC in 62% yield. N4IPDTC was characterized by ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. ^{1}H NMR $\delta(D_2O)$: 8.06 (d, 1H, imi-H), 7.62–7.61 (d, 1H, imi-H), 4.10–4.07 (t, 2H, CH_2), 2.88–2.84 (t, 2H, CH_2), 2.11–2.04 (m, 2H, CH_2); ^{13}C NMR $\delta(D_2O)$: 211.85 (CS_2), 161.88 (C), 149.02 (CH), 132.84 (CH), 65.96 (CH_2), 44.49 (CH_2), 28.84 (CH_2); IR (KBr)/cm^{-1}: NH: 3431.0, NO_2: 1535.4, 1379.5, C═S: 1046.7; elemental analysis calculated (%) for $C_7H_9N_4NaO_2S_2$: C, 31.34; N, 20.88; H, 3.38. Found: C, 31.52; N, 20.71; H, 3.35.

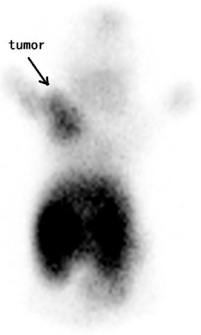


Fig. 3 The SPECT image of ^{99m}TcO-N4IPDTC in a mouse bearing a S180 tumor.

Radiolabeling and quality control

The preparations of ^{99m}TcN-N4IPDTC, ^{99m}TcO-N4IPDTC and ^{99m}Tc(CO)$_3$-N4IPDTC were carried out according to our previously reported methods.[18–20] The radiochemical purities of the complexes were assessed by HPLC. The HPLC analysis conditions were as follows; HPLC analysis was carried out with a reversed-phase column (Kromasil 100-5C, 250 × 4.6 mm), Shimadzu SCL-10A VP series, working at a flow rate of 1.0 mL min^{-1}. For ^{99m}TcN-N4IPDTC and ^{99m}TcO-N4IPDTC, water (A) and acetonitrile (B) were used as the mobile phase. For ^{99m}Tc(CO)$_3$-N4IPDTC, water (containing 0.1% TFA) (A) and acetonitrile (containing 0.1% TFA) (B) mixtures were used as the mobile phase. The following gradient elution technique was adopted for the analysis: for ^{99m}TcN-N4IPDTC, 0 min 70% B, 10 min 70% B, 15 min 90% B, 40 min 100% B; for ^{99m}TcO-N4IPDTC, 0 min 50% B, 20 min 90% B, 30 min 90% B, 40 min 100% B; for ^{99m}Tc(CO)$_3$-N4IPDTC, 0 min 10% B, 28 min 90% B, 30 min 100% B, 40 min 100% B.

In vitro stability studies

^{99m}TcN-N4IPDTC, ^{99m}TcO-N4IPDTC and ^{99m}Tc(CO)$_3$-N4IPDTC complexes were incubated in the labeling medium at room temperature for 6 h, the radiochemical purity was assessed by HPLC. *In vitro* serum stability studies in mouse serum were also performed, using a method reported earlier.[22]

Determination of the partition coefficients (log *P*)

The partition coefficients (log *P*) between 1-octanol and phosphate buffer (0.025 mol L^{-1}, pH 7.4) of the three complexes were measured in order to evaluate their lipophilicity.[18] The measurements were repeated five times and reported as an

average of the five measurements plus the standard deviation.

In vitro cellular uptake

In vitro uptake of the complexes, both in hypoxic and aerobic conditions, was evaluated using the previously reported methods.[6] In brief, S180 cells at a concentration of 1.0×10^{-6} cells mL^{-1} were suspended in 20.0 mL DMEM containing 10% (v/v) of fetal bovine serum and incubated at 37.0 °C. The hypoxic and aerobic conditions were produced following the previous methods.[6] Then, 0.2 mL of the complex (3.7×10^{-6} Bq mL^{-1}) was added to the suspension. 1000 μL aliquots were pipetted at 1.0, 2.0, 3.0 and 4.0 h post-incubation, and were centrifuged at 3000 rpm for 5.0 min. 900 μL of the supernatant medium were taken for counting (C_{out}) and the remaining sample, containing cells within 100 μL of medium, was also counted (C_{in}). At each time point three samples were taken. The cell accumulation, A, was calculated from the following equation: $A = (C_{in} - C_{out}/9)/(C_{in} + C_{out})$.

The final results were expressed as the mean ± the standard deviation.

Biodistribution studies

Animal studies were carried out in compliance with the Regulations on Laboratory Animals of Beijing Municipality and the guidelines of the Ethics Committee of Beijing Normal University. The experiments were approved by the Ethics Committee of Beijing Normal University. 0.1 mL of ^{99m}TcN-N4IPDTC (5.0×10^{-6} Bq mL^{-1}) was injected into Kunming female mice (18–20 g) bearing S180 tumors *via* a tail vein. The mice were sacrificed in groups of five at 2 h and 4 h post-injection. The tumor, other organs of interest, blood, urine and feces were collected, weighed and measured for radioactivity. The prepared samples, 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 the mean ± the standard deviation. The biodistribution studies of ^{99m}TcO-N4IPDTC and ^{99m}Tc(CO)$_3$-N4IPDTC were conducted in the same way.

SPECT imaging studies

0.2 mL of ^{99m}TcO-N4IPDTC (1.85×10^{-8} Bq mL^{-1}) was injected intravenously through a tail vein in mice (18–22 g) bearing S180 tumors. A dual-head SPECT system (Skylight; Philips, Milpitas, CA, USA), using a low-energy parallel-hole collimator (diameter 3.5 mm), was used for the SPECT imaging studies. Static images were acquired 4 h after injection.

Conclusion

In summary, a novel ligand, N4IPDTC, was successfully synthesized and its ^{99m}Tc-nitrido core, ^{99m}Tc-oxo core and $[^{99m}Tc(CO)_3]^+$ core complexes were prepared in high yields through ligand-exchange reactions. The preliminary studies showed all of them had a certain hypoxic selectivity and tumor uptake. In particular, ^{99m}TcO-N4IPDTC, which was prepared from a kit without the need for purification, showed high tumor uptake, and high tumor/blood and tumor/muscle ratios, suggesting it would be a promising hypoxia imaging agent.

Acknowledgements

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