Supporting Information

Assessment of macrocyclic triamine ligands as syntons for organometallic ^{99m}Tc radiopharmaceuticals

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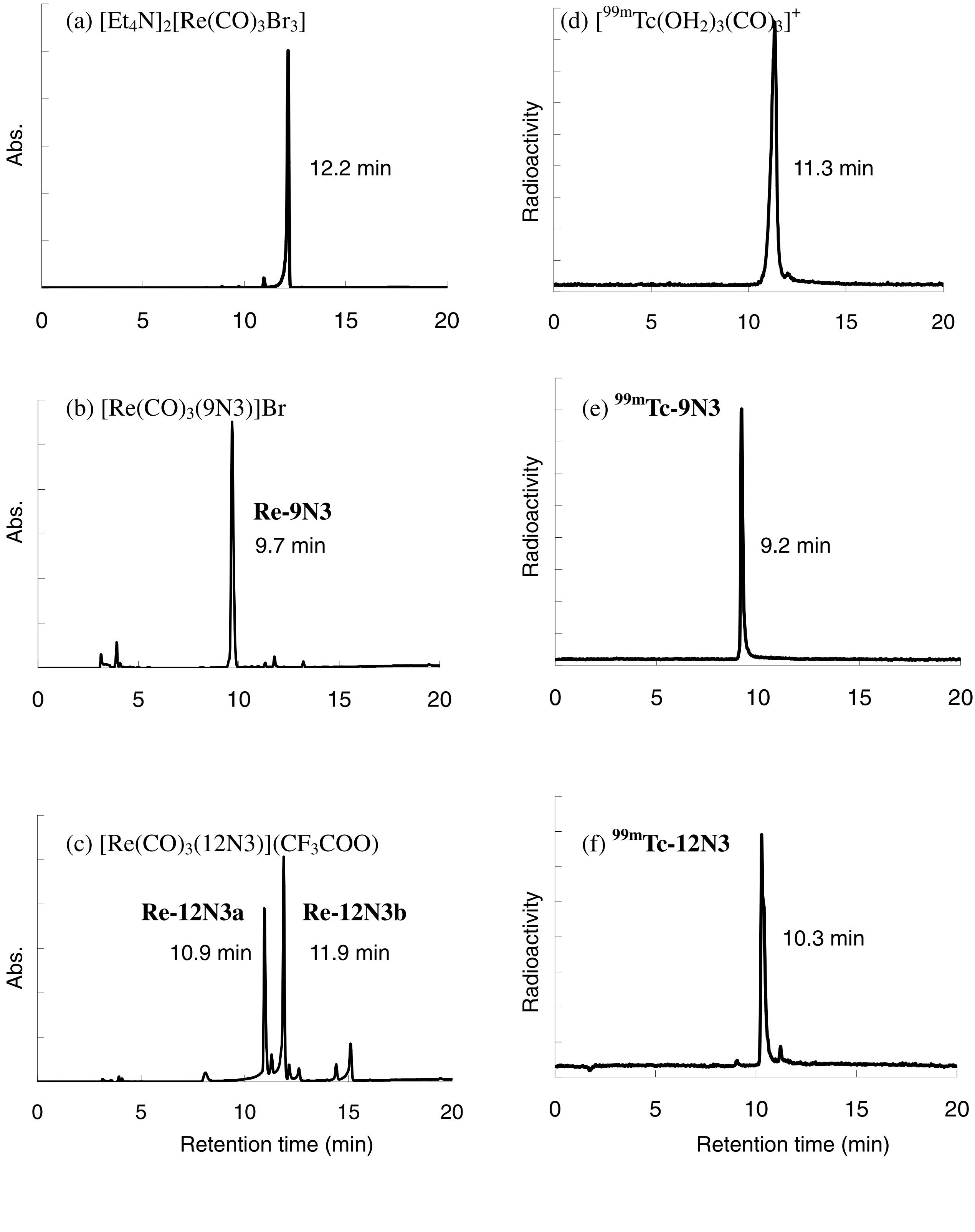

Figure S1. HPLC chromatograms of $[Et_4N]_2[Re(CO)_3Br_3]$ (a), Re complex of 9N3 (b), Re complex of 12N3 (c), $\{^{99m}Tc(CO)_3(H_2O)_3\}^+$ (d), ^{99m}Tc labeled compound of 9N3 (e) and ^{99m}Tc labeled compound of 12N3 (f).

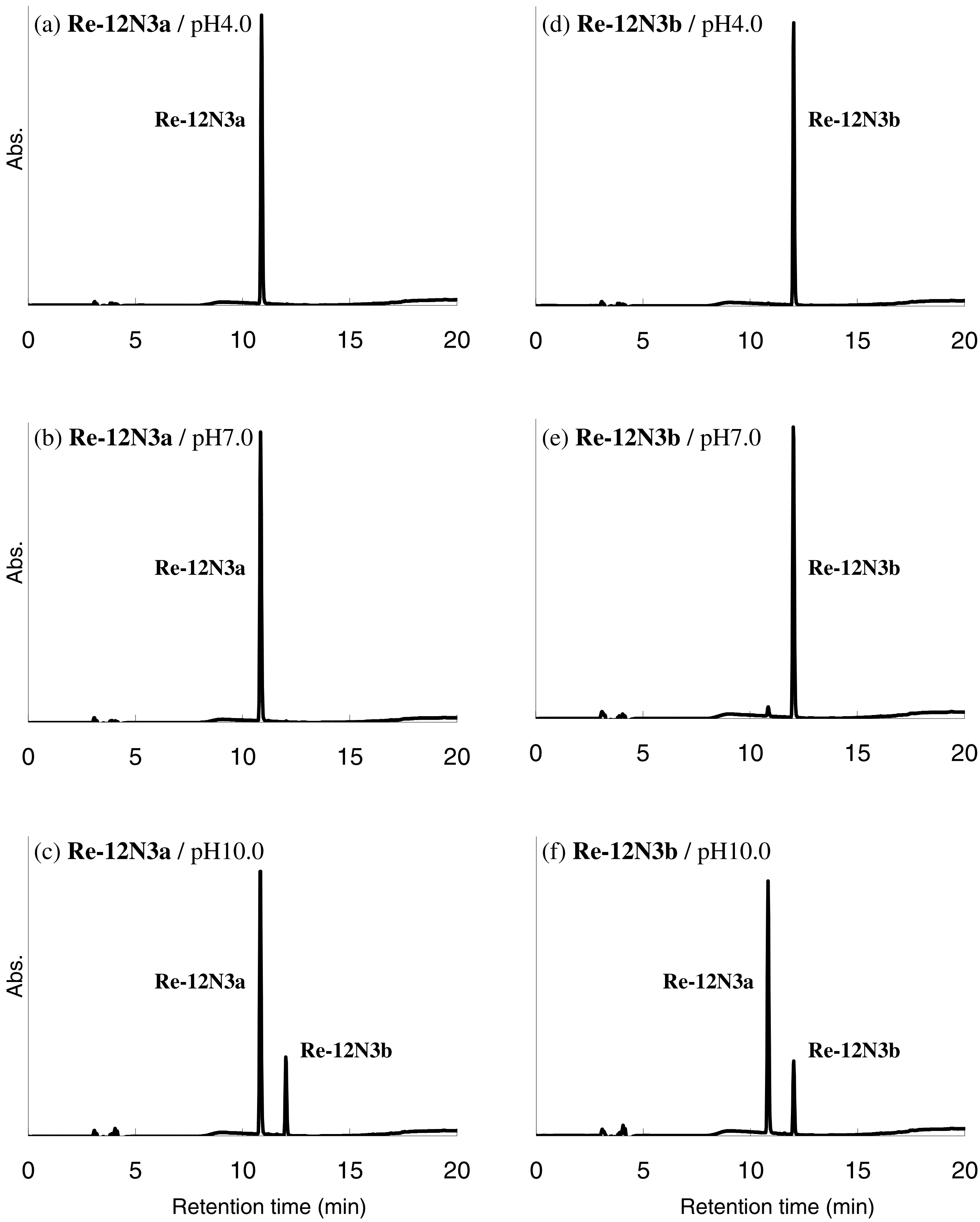

Figure S2. HPLC chromatograms of **Re-12N3a** and **Re-12N3b** in pH 4.0, pH 7.0 and pH 10.0. The pH of each solution was adjusted using diluted HCl or NaOH solution. Both Re12N3a and Re12N3b were rapidly interconverted and reached equilibrium (Re-12N3a:Re-12N3b=80:20) only in basic aqueous solution.

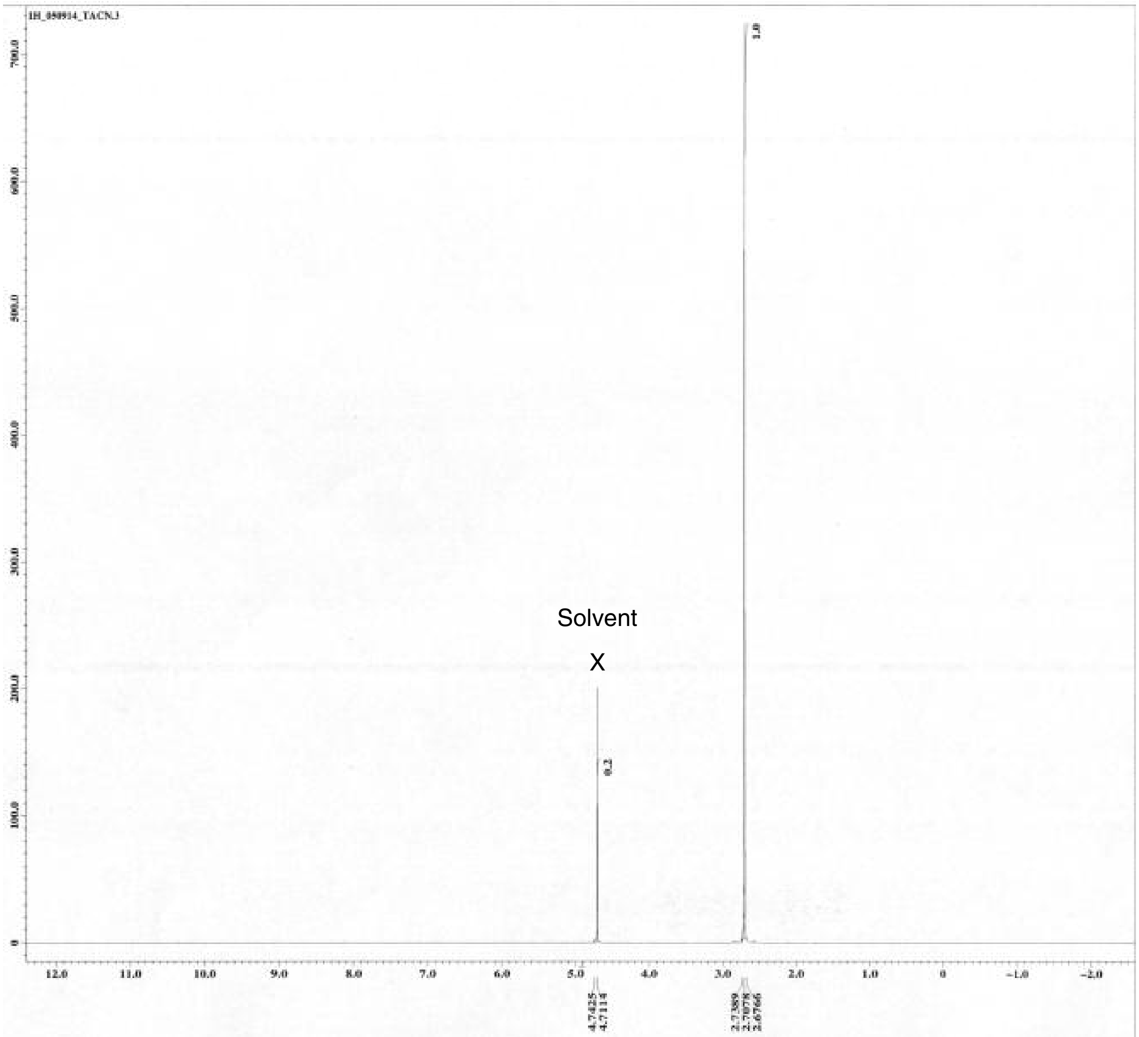

Figure S3. ^{1}H NMR spectrum of 9N3 in D_2O.

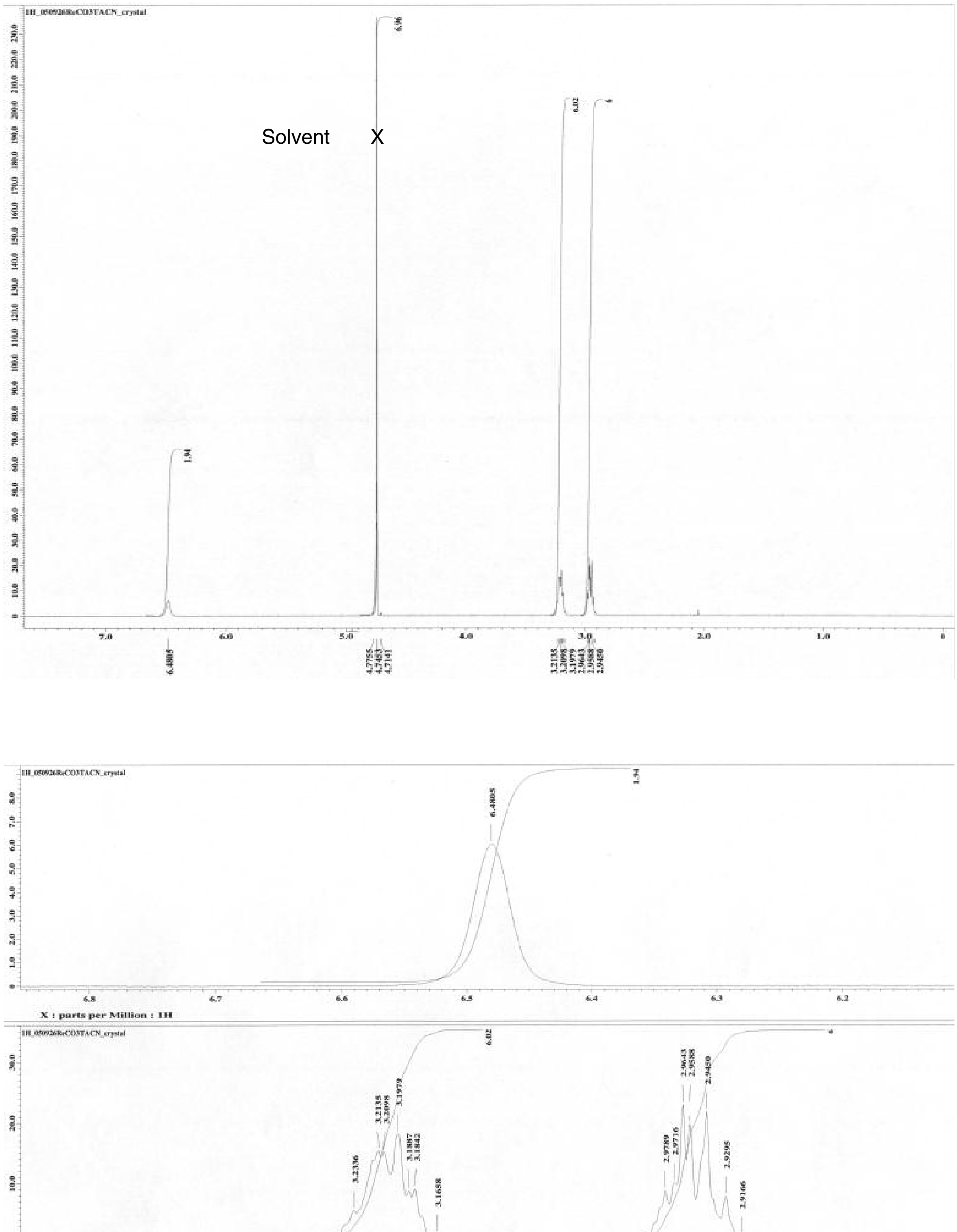

Figure S4. ^{1}H NMR spectra of **Re-9N3** in D_2O.

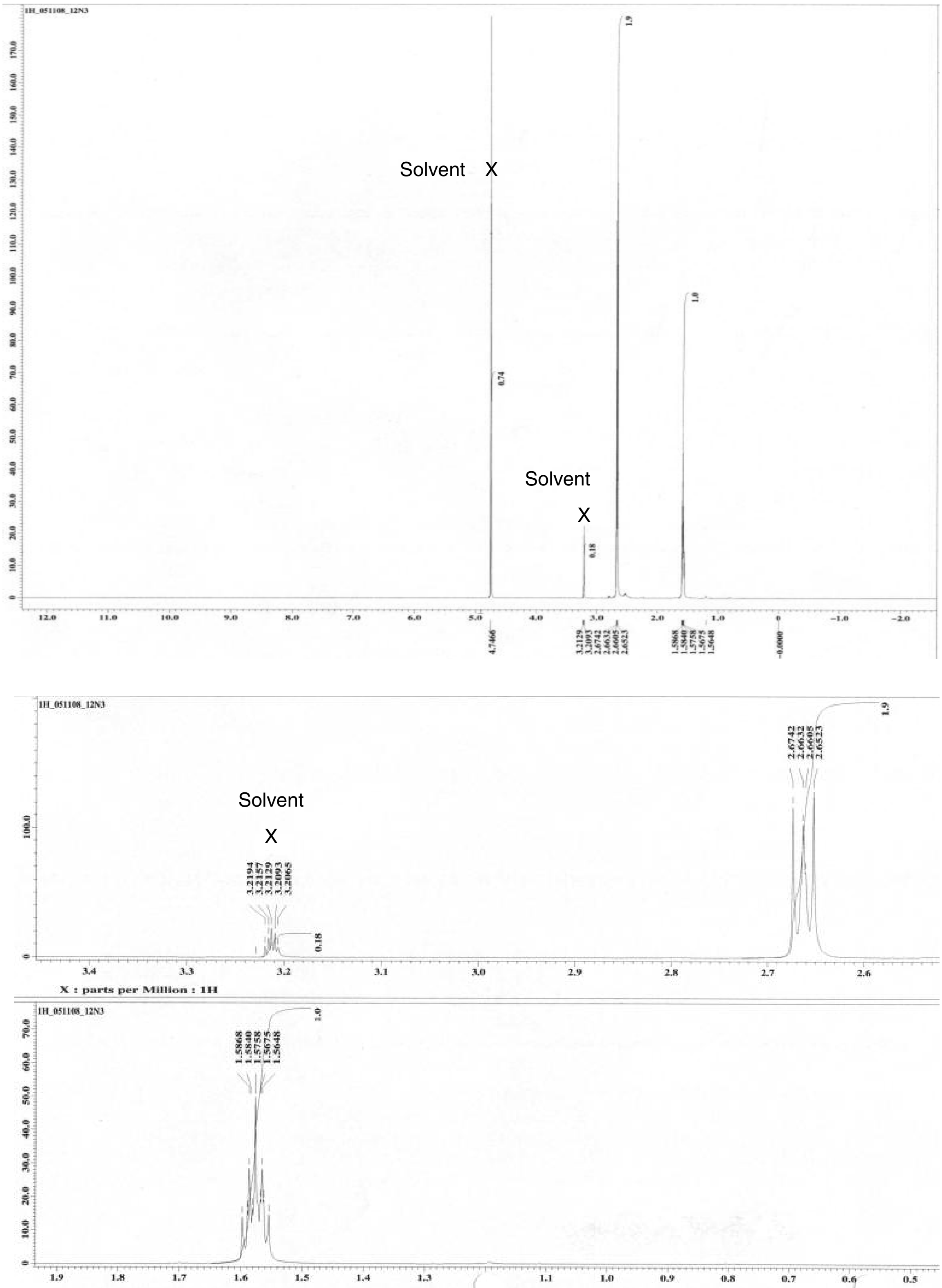

Figure S5. ^{1}H NMR spectra of 12N3 in CD_3OD.

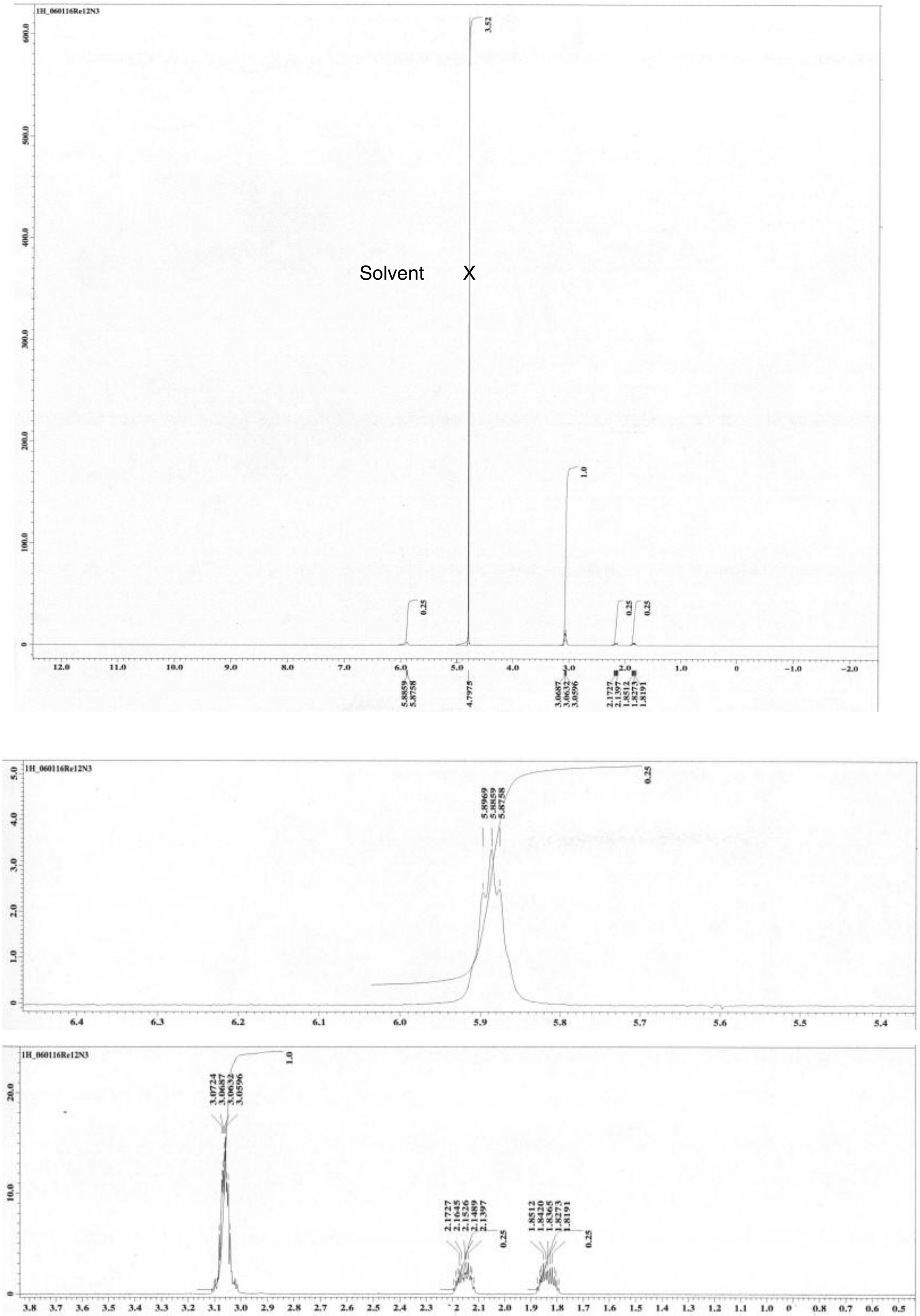

Figure S6. ^{1}H NMR spectra of **Re-12N3a** in D_2O.

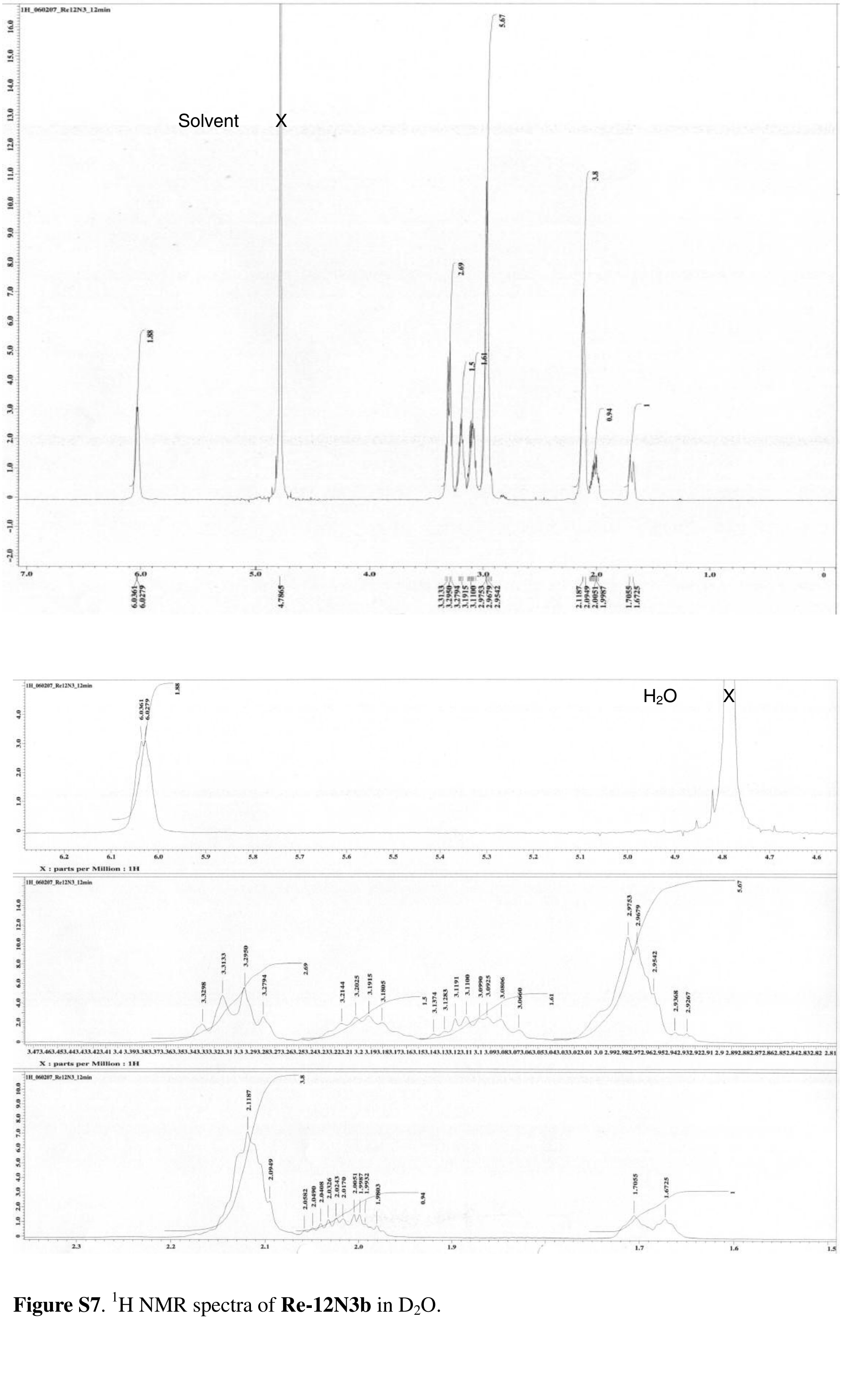

Figure S7. ^{1}H NMR spectra of **Re-12N3b** in D_2O.

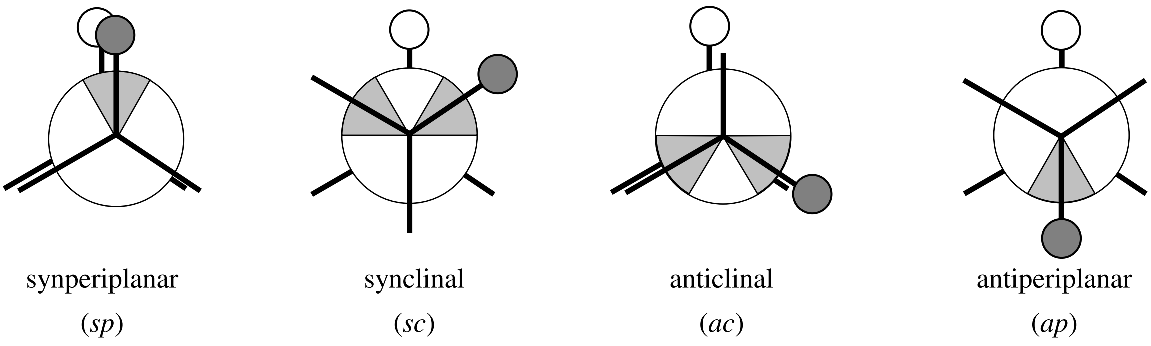

Figure S4. The torsion angles stated in this article. The designation *sp* represents synperiplanar conformation with torsion angle between 0° to ±30°, *sc* synclinal conformation (30° to 90° and -30° to -90°), *ac* anticlinal conformation (90° to 150° and -90° to -150°),and *ap* antiperiplanar (±150° to 180°).

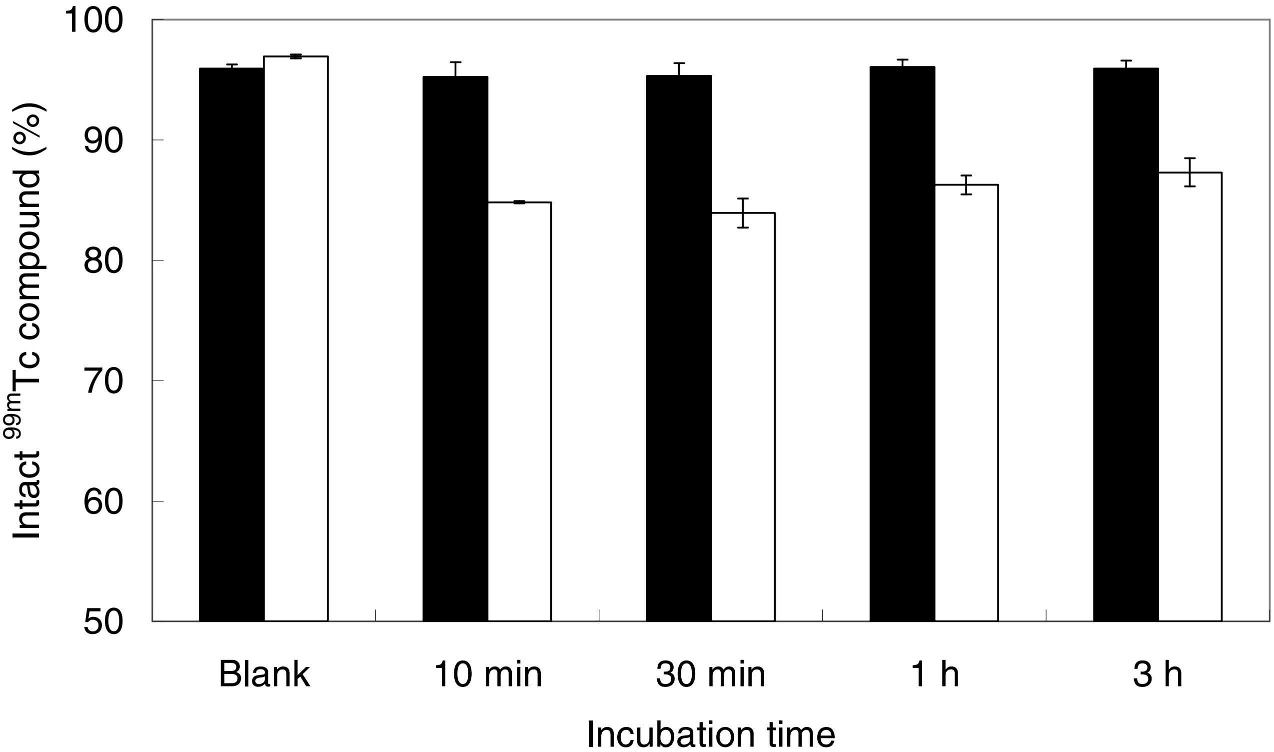

Figure S5. Stability of ^{99m}**Tc-9N3** and ^{99m}**Tc-12N3** in the rat plasma. ■ : ^{99m}**Tc-9N3**; □ : ^{99m}**Tc-12N3**.

Equation S1. Bateman equations.

$$\left.\begin{aligned}
N_n &= C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + \cdots + C_n e^{-\lambda_n t} \\
C_1 &= \frac{\lambda_1 \lambda_2 \cdots \lambda_{n-1}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)\cdots(\lambda_n - \lambda_1)} N_{1,0} \\
C_2 &= \frac{\lambda_1 \lambda_2 \cdots \lambda_{n-1}}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)\cdots(\lambda_n - \lambda_2)} N_{1,0} \\
C_n &= \frac{\lambda_1 \lambda_2 \cdots \lambda_{n-1}}{(\lambda_1 - \lambda_n)(\lambda_2 - \lambda_n)\cdots(\lambda_{n-1} - \lambda_n)} N_{1,0}
\end{aligned}\right\}$$

Equation S2. Bateman equations in case of ${}^{99}\mathrm{Mo} \xrightarrow{\lambda_1} {}^{99\mathrm{m}}\mathrm{Tc} \xrightarrow{\lambda_2} {}^{99}\mathrm{Tc} \xrightarrow{\lambda_3} {}^{99}\mathrm{Ru}$.

$$\left.\begin{aligned}
N_3 &= C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_3 e^{-\lambda_3 t} \\
C_1 &= \frac{\lambda_1 \lambda_2}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} N_{1,0} \\
C_2 &= \frac{\lambda_1 \lambda_2}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} N_{1,0} \\
C_3 &= \frac{\lambda_1 \lambda_2}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} N_{1,0}
\end{aligned}\right\}$$

Equation S3. Equation to calculate the number of ${}^{99\mathrm{m}}$Tc atoms generated from ^{99}Mo.

$$N_2 = \frac{\lambda_1 \left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right)}{\lambda_2 - \lambda_1} N_{1,0} + e^{-\lambda_2 t} N_{2,0}$$

Equation S4. Equations to calculate the mol quantity of ^{99m}Tc and ^{99}Tc in the elution in use. The amount of $^{99m/99}$Tc molar quantity could be calculated from the time interval of elution between preliminary elution and elution in use (t) and radioactivity in elution in use (A_2). The equations were considered a rate of ^{99}Mo decayed to ^{99m}Tc (r_1 = 87.7%) and a rate of ^{99}Mo decayed to ^{99}Tc (r_2 = 12.3%). Constant numbers and variable numbers used in Equation S1 - S4 were arranged in Table S1. N_A indicates the Avogadro constant (= 6.02×10^{23}).

$$A_2 = \lambda_2 N_2 = \frac{\lambda_1\lambda_2\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right)}{\lambda_2 - \lambda_1} N_{1,0} r_1 + \lambda_2 e^{-\lambda_2 t} N_{2,0} = \frac{\lambda_1\lambda_2\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right)}{\lambda_2 - \lambda_1} N_{1,0} r_1$$

$$N_{1,0} = \frac{\lambda_2 - \lambda_1}{\lambda_1\lambda_2\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right) r_1} A_2$$

$$N_1 = e^{-\lambda_1 t} N_{1,0} = \frac{(\lambda_2 - \lambda_1) e^{-\lambda_1 t}}{\lambda_1\lambda_2\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right) r_1} A_2$$

$$N_2 = \frac{A_2}{\lambda_2}$$

$$N_3 = \left\{ \frac{\lambda_1\lambda_2 e^{-\lambda_1 t}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} + \frac{\lambda_1\lambda_2 e^{-\lambda_2 t}}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} + \frac{\lambda_1\lambda_2 e^{-\lambda_3 t}}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} \right\} N_{1,0} r_1 + \frac{\lambda_1\left(e^{-\lambda_1 t} - e^{-\lambda_3 t}\right)}{\lambda_3 - \lambda_1} N_{1,0} r_2$$

$$= \left\{ \frac{e^{-\lambda_1 t}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} + \frac{e^{-\lambda_2 t}}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} + \frac{e^{-\lambda_3 t}}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} + \frac{\left(e^{-\lambda_1 t} - e^{-\lambda_3 t}\right) r_2}{\lambda_2(\lambda_3 - \lambda_1) r_1} \right\} \frac{\lambda_2 - \lambda_1}{e^{-\lambda_1 t} - e^{-\lambda_2 t}} A_2$$

$$n_2 + n_3 = \frac{N_2 + N_3}{N_A}$$

$$= \frac{A_2}{\lambda_2 N_A} + \left\{ \frac{e^{-\lambda_1 t}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} + \frac{e^{-\lambda_2 t}}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} + \frac{e^{-\lambda_3 t}}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} + \frac{\left(e^{-\lambda_1 t} - e^{-\lambda_3 t}\right) r_2}{\lambda_2(\lambda_3 - \lambda_1) r_1} \right\} \frac{\lambda_2 - \lambda_1}{\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right) N_A} A_2$$

Table S1. Constant numbers and variable numbers used in Equation S1 - S4.

Nuclear species		^{99}Mo	^{99m}Tc	^{99}Tc
After preliminary elution	Number of atoms	$N_{1,0}$	$N_{2,0} \approx 0$	$N_{3,0} \approx 0$
Elution in use	Number of atoms	N_1	N_2	N_3
	Radioactivity	A_1	A_2	A_3
	mol	n_1	n_2	n_3
Half life		t_1=2.75 day	t_2=6.01 h	$t_3=2.11\times10^5$ y
Decay constant		$\lambda_1=2.92\times10^{-6}$ s^{-1}	$\lambda_2=3.20\times10^{-5}$ s^{-1}	$\lambda_3=1.04\times10^{-13}$ s^{-1}
Rates of ^{99}Mo decayed to ^{99m}Tc or ^{99}Tc		—	r_1=87.7%	r_2=12.3%

Table S2. An Example of Tc content calculation result based on Equation S4.

Time and date of preliminary elution	October 23rd, 2006, 10:48
Time and date of elution in use	October 24th, 2006, 09:51
Time interval of elution (*t*)	82980 s
Radioactivity of elution in use (A_2)	17.62 GBq
^{99m}Tc content (n_2)	914 pmol
^{99}Tc content (n_3)	2214 pmol
Tc content ($n_2 + n_3$)	3127 pmol

Table S3. Torsion angles of 9N3 and 9S3 ligands in coordinated and uncoordinated conformations.

	Re-9N3	9N3 *[1]	*fac*-$[Tc(CO)_3(9S3)]Br$ *[2]	9S3 *[3]
N/S - C - C - N/S	42.9	49.0	63.9	58.5
C - C - N/S - C	74.6	66.3	48.6	55.1
C - N/S - C - C	-134.3	-130.8	-131.7	-131.1
N/S - C - C - N/S	40.9		64.7	
C - C - N/S - C	74.3		48.3	
C - N/S - C - C	-133.0		-144.2	
N/S - C -C - N/S	42.8		63.1	
C - C - N/S - C	74.0		52.1	
C - N/S - C - C	-134.7		-134.3	

*[1] Andrew, R. B.; Daniel, L. J.; Lisandra, L. M. *Acta Crystallographica Section E* **2005**, *61*, o330-o332.

*[2] Schibli, R.; Alberto, R.; Abram, U.; Abram, S.; Egli, A.; Schubiger, P. A.; Kaden, T. A. *Inorg. Chem.* **1998**; *37*, 3509-3516.

*[3] Glass, R. S.; Wilson, G. S.; Setzer, W. N. *J. Am. Chem. Soc.* **1980**, *102*, 5068-5069.