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Note

Histidine derivatives as tridentate chelators for the *fac*-[$M^{I}(CO)_3$] (Re, ^{99m}Tc, ^{188}Re) core: Synthesis, structural characterization, radiochemistry and stability

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ABSTRACT

The development of new rhenium(I)- and technetium(I)–tricarbonyl complexes can lead to potentially useful radiopharmaceuticals. In this work, the synthesis of the neutral rhenium complex *fac*-[Re(NSO)$(CO)_3$], **Re-1**, where NSO is the tridentate chelating agent 3-(1H-imidazol-4-yl)-2-(*p*-methoxybenzylthio)propionic acid **1** was effected via reaction with $(NEt_4)_2[ReBr_3(CO)_3]$ in the presence of $NaHCO_3$. Complex **Re-1** crystallized from methanol/water and its structure was established by IR, ^{1}H and ^{13}C NMR spectroscopies, ESI-MS analysis and X-ray crystallography. When the reaction took place in the absence of base, HPLC analysis revealed the presence of a second product (yield 7%) that was assigned by NMR and ESI analysis to be complex *fac*-[Re(NS)$(CO)_3$Br] Re-2. At the tracer level, the analogous complexes *fac*-[^{99m}Tc(NSO)$(CO)_3$], ^{99m}Tc-1 and *fac*-[^{188}Re(NSO)$(CO)_3$], **^{188}Re-1**, were synthesized and their radiochemical stability in physiological conditions was determined. Both tracer complexes **^{99m}Tc-1** and **^{188}Re-1** are stable in solution as well as in the presence of strongly coordinating agents like histidine or cysteine.

1. Introduction

The chemistry of technetium and rhenium has been studied extensively as a result of the significance of these radiometals in the development of radiopharmaceuticals for imaging (^{99m}Tc) and/or radiotherapy (^{188}Re) in Nuclear Medicine. The design of targeted radiopharmaceuticals by the conjugation of bioactive molecules to technetium and rhenium, is currently a challenging field of radiopharmaceutical research [1–4].

The radiopharmaceutical chemistry of ^{99m}Tc(I)–tricarbonyl complexes primarily involves the substitution of the labile water molecules of the *fac*-[^{99m}Tc$(H_2O)_3(CO)_3]^+$ precursor [5] with suitable bidentate or tridentate ligands in aqueous solution. Both bidentate and tridentate ligands give complexes of high kinetic and thermodynamic stability, with tridentate ligands exhibiting faster reaction rates and better stabilizing the complex against trans-chelation reactions. A series of suitable tridentate chelating agents, including histidine, has been applied to produce complexes with the *fac*-[^{99m}Tc$(CO)_3]^+$ core [6–8]. These agents may combine an amine or an aromatic nitrogen N, an S thioether group and a carboxylate group O for charge-neutralizing purposes. In parallel, therapeutic radiopharmaceuticals of ^{188}Re can be developed by using the same ligands designed for the *fac*-[^{99m}TcL$(CO)_3]^+$ complexes because of the similar chemical properties of technetium and rhenium. The currently applied efficient method for the preparation of the corresponding *fac*-[^{188}Re$(H_2O)_3(CO)_3]^+$ precursor, involves the use of $BH_3.NH_3$ as reducing agent and boranocarbonate as a solid CO source [9].

In this work our interest focuses on the *fac*-[^{99m}Tc(NSO)$(CO)_3$] complexes where NSO is a suitable tridentate chelating agent, combining a S thioether group, an aromatic N and a carboxylate O [10–15]. These agents can be either linear [12] or tripodal like methionine or S-substituted cysteine [10,14]. Within this framework, a new neutral *fac*-[Re(NSO)$(CO)_3$] complex (**Re-1**) with the tripodal histidine derivative 3-(1H-imidazol-4-yl)-2-(*p*-methoxybenzylthio)propionic acid (**1**) was synthesized and fully characterized by X-ray crystallography and other spectroscopic methods (Fig. 1). Chemistry was successfully transferred to the ^{99m}Tc and ^{188}Re tracer level to obtain the analogous to **Re-1** radioactive complexes **^{99m}Tc-1** and **^{188}Re-1**.

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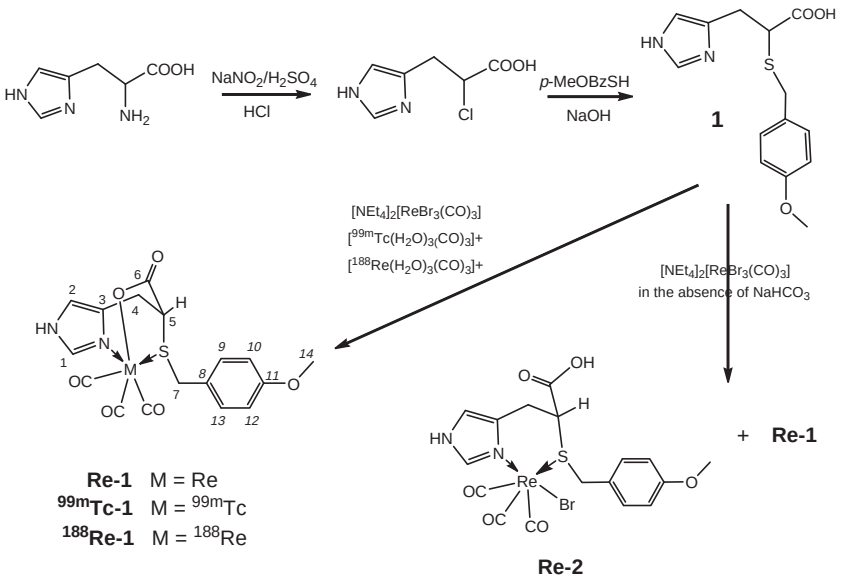

Fig. 1. Synthesis of ligand **1** and of the **Re-1**, ^{99m}**Tc-1**, ^{188}**Re-1** complexes.

2. Experimental

2.1. Materials

All chemicals were reagent grade and were used as such unless otherwise noted. Rhenium was purchased from Aldrich as $Re_2(CO)_{10}$ and was converted to $(NEt_4)_2[ReBr_3(CO)_3]$ as reported previously [16]. *L*-3-(1H-imidazol-4-yl)-2-chloropropionic acid was synthesized according to a literature method [17].

For labeling with ^{99m}Tc a kit containing 5.5 mg $NaBH_4$, 4 mg Na_2CO_3 and 10 mg Na-K tartrate was purged with CO gas prior to addition of $Na^{99m}TcO_4$, as described elsewhere [5]. For ^{188}Re labeling, the Isolink™ kit in combination with a pre-reduction kit ($BH_3{\cdot}NH_3$ reagent) was used [9].

Elemental analyses were performed on a Perkin-Elmer 2400 automated analyzer. IR spectra were recorded as KBr pellets on a Perkin-Elmer 1600 FT-IR spectrophotometer in the region 500–4000 cm^{-1}. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 500 MHz spectrometer. HPLC analysis was performed on an Agilent HP 1100 series pump, connected both to a Gabi gamma detector from Raytest and an HP 1100 multiple wavelength detector. Separations were achieved on an Agilent Eclipse XDB-C18 column (25 cm × 4.6 mm, 5 μm) eluted with a binary gradient system at 1 mL/min flow rate and composition 100% solvent A: 0.1% TFA in water at 0 min, linearly converting to 75% solvent B: methanol over 15 min. ESI mass spectral analysis was performed on an AQA Navigator, Finnigan mass spectrometer. Test solution in 50% aqueous methanol was infused into an electrospray interface at a flow rate of 0.1 mL/min, using a Harvant Syringe pump. Positive or negative ion ESI spectra were acquired by adjusting the needle and cone voltages accordingly. Hot nitrogen gas (Dominic-Hunter UHPLCMS-10) was used for desolvation at 170 °C. Isotopic pattern calculations were performed by List v.1.3.2. (Thermo Finnigan) software.

2.2. Synthesis of 3-(1H-imidazol-4-yl)-2-(p-methoxybenzylthio) propionic acid, ***1***

In a modified method [18], *L*-3-(1H-imidazol-4-yl)-2-chloropropionic acid (5.75 mmol, 1 g) and *p*-methoxybenzylmercaptan (6.89 mmol, 1.06 g) were mixed together in 30 mL of water:ethanol 1:1 and 7 mL NaOH 2 M were added dropwise under N_2. The mixture was stirred for 18 h. Then the solvents were evaporated, the residue was re-dissolved in 5 mL water and the pH was adjusted to ~7 by addition of HCl 5 M. The white solid formed was isolated and washed with water. Yield: 754 mg, 45%.

^{1}H and ^{13}C NMR data are given in Table 1.

2.3. Synthesis of ***Re-1***

0.1 mmol (77 mg) of $[NEt_4]_2[ReBr_3(CO)_3]$ reacted with 0.1 mmol (29 mg) of **1** and 0.1 mmol $NaHCO_3$ in refluxing methanol for 3 h to generate one product as shown by HPLC. The solvent was evaporated to dryness and the residue was crystallized by slow evaporation from methanol–water. Yield: 35 mg (62%), t_R: 19.9 min, IR (cm^{-1}, KBr): 2029, 1907, 1875(sh), 1623. *Anal.* Calc. for $C_{17}H_{15}N_2O_6ReS$: C, 36.36; H, 2.69; N, 4.99. Found: C, 36.06; H, 3.01; N, 4.89%.

When reaction took place in the absence of $NaHCO_3$ HPLC analysis of the reaction mixture showed the presence (7%) of a second product peak with a retention time of 19.4 min. Attempts to isolate the second product did not succeed in generating a pure sample; ESI and NMR data of the mixture – enriched in the second product by successive recrystallizations – were in agreement with the structure $Re(NS)Br(CO)_3$, **Re-2** (Fig. 1).

2.4. Synthesis of ^{99m}***Tc-1***

About 1 mL of an aqueous mixture of $[^{99m}Tc(OH_2)_3(CO)_3]^+$ (~0.5 GBq/ml) and ligand **1** (10 nmoL, 10^{-5} M) at pH 7, reacted at 85 °C for 30 min. The reaction mixture was analyzed by RP HPLC revealing the formation of only one product as in the case of **Re-1** t_R: 20.1 min.

2.5. Synthesis of ^{188}***Re-1***

About 1 mL of an aqueous mixture of $[^{188}Re(OH_2)_3(CO)_3]^+$ (~20 MBq) and ligand **1** (1.3×10^{-3} M) at pH 6.5 reacted at 65 °C for 30 min. The reaction mixture was analyzed by RP HPLC revealing the formation of only one product as in the case of **Re-1** t_R: 19.9 min.

Table 1
^{1}H and ^{13}C chemical shifts (ppm) for ligand **1** and the complexes **Re-1** and **Re-2** in DMSO-d_6 at 25 °C. The numbering of the atoms is shown in Fig. 1.

	Ligand **1**	Complex **Re-1**	Complex **Re-2**		Ligand **1**	Complex **Re-1**	Complex **Re-2**
H-1	7.52	8.34	8.63	C-1	134.56	141.28	140.66
H-2	6.74	7.15	7.35	C-2	116.70	116.12	114.79
H-4	3.00	3.44	2.79	C-3	134.56	133.74	133.78
	^{2}J = 14.5 Hz	^{2}J = 17.8 Hz	^{2}J = 14.7 Hz	C-4	29.41	26.97	28.03
	^{3}J = 9.3 Hz	^{3}J = 4.8 Hz	^{3}J = not measurable	C-5	46.12	44.54	42.88
	2.74	3.02	2.40	C-6	173.05	177.37	171.13
	^{2}J = 14.5 Hz	^{2}J = 17.8 Hz	^{2}J = 14.7 Hz	C-7	34.26	44.54	43.15
	^{3}J = 5.2 Hz	^{3}J = 3.1 Hz	^{3}J = 3.5 Hz	C-8	129.60	126.23	126.09
H-5	3.43	3.70	3.99	C-9,13	130.06	130.81	131.25
H-7	3.76	4.61, 3.92 ^{2}J = 13.0 Hz	3.97, 3.72 ^{2}J = 13.3 Hz	C-10,12	113.80	114.24	114.29
H-9,13	7.21	7.33	7.16	C≡O		193.20	192.48
H-10,12	6.86	6.98	6.92			195.67	195.51
						196.89	196.02
H-14	3.73	3.77	3.74				
NH	13.02	13.12	13.25				

2.6. X-ray crystal structure determination of complex *Re-1*

A crystal with approximate dimensions 0.18 × 0.20 × 0.22 mm was mounted in air and covered with epoxy glue. Diffraction measurements were made on a $P2_1$ Nicolet diffractometer upgraded by Crystal Logic using graphite monochromated Cu radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range $22 < 2\theta < 54°$ and they appear in Table 2. Intensity data were recorded using a $\theta - 2\theta$ scan. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization corrections were applied using Crystal Logic software. The structure was solved by direct methods using SHELXS-97 [19] and refined by full-matrix least-squares techniques on F^2 with SHELXL-97 [20]. Further experimental crystallographic details for **Re-1**: $2\theta_{max} = 118°$; reflections collected/unique/used, 3270/2706 [$R_{int} = 0.0380$]/2706; parameters refined; $(\Delta/\sigma)_{max} = 0.001$; $(\Delta\rho)_{max}/(\Delta\rho)_{min} = 0.815/-1.308$ e/Å^3; R_1/wR_2 (for all data), 0.0335/0.0892. Hydrogen atoms were either located by difference maps and were refined isotropically or were introduced at calculated positions as riding on bonded atoms. All non-hydrogen atoms were refined anisotropically.

2.7. Stability studies of ^{99m}Tc-1 and ^{188}Re-1

About 0.1 mL of the isolated by HPLC pure ^{99m}**Tc-1** or ^{188}**Re-1** complex was mixed with 0.9 mL of saline or 1 mM L-histidine or L-cysteine. The mixtures were incubated at 37 °C and were analyzed by HPLC or TLC after 4 h and 24 h.

Table 2
Crystallographic data for complex **Re-1**.

Formula	$C_{17}H_{15}N_2O_6ReS$
Formula weight	561.57
Space group	$P2_12_12_1$
a (Å)	15.272(9)
b (Å)	10.632(5)
c (Å)	11.556(6)
α (°)	90
β (°)	90
γ (°)	90
V (Å^3)	1876.4(17)
Z	4
T (°C)	25
Radiation	Cu Kα
ρ_{calc} (g cm^{-3})	1.988
μ (mm^{-1})	14.044
Reflections with $I > 2\sigma(I)$	2604
R_1[a]	0.0324
wR_2[a]	0.0881

[a] $w = 1/[\sigma^2(F_o^2) + (\alpha P)^2 + bP]$ and $P = [\max(F_o^2, 0) + 2F_c^2]/3$, $R_1 = \Sigma(|F_o| - |F_c|)/\Sigma(|F_o|)$ and $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

2.8. Lipophilicity studies

About 50 μL of purified ^{99m}**Tc-1** complex were mixed with 1.95 mL PBS pH 7.4 and 2.0 mL of octanol-1 in triplicates. The mixtures were shaken for 3 min and centrifuged for 5 min and then 50 μL aliquots of each phase were withdrawn and measured in a NaI scintillation counter. The remaining organic phase was re-extracted with equal volume of aqueous phase and the procedure was repeated until the counts measured in both phases reached a stable value. The ratios of the extractions were averaged as $D_{7.4}$ values.

3. Results and discussion

3.1. Synthesis

Complex **Re-1** was synthesized in refluxing methanol by reacting the $(NEt_4)_2[ReBr_3(CO)_3]$ precursor with ligand **1** in the presence of 1 equiv. of $NaHCO_3$. HPLC analysis of the reaction mixture showed one product peak in the chromatogram with 19.9 min elution time. Even though two diastereomers are expected due to the fact that the coordinating S-atom is a prochiral center, only one species was observed in HPLC and NMR analysis. The complex was collected as crystals suitable for X-ray crystallography by slow crystallization from methanol–water. When the reaction took place in the absence of the $NaHCO_3$ two peaks appeared in the HPLC chromatogram a major one (>90%) at $t_R = 19.9$ min and a minor one (~7%) at 19.4 min. The identity of the minor product was assigned as being $Re(NS)Br(CO)_3$, **Re-2** by NMR and ESI-MS analysis of an enriched in the minor product sample, obtained through multiple crystallizations. It should be noted that when $NaHCO_3$ was added in the mixture of **Re-1** and **Re-2** complete conversion of **Re-2** to **Re-1** was effected as witnessed by HPLC analysis.

The chemical shifts for the complexes **Re-1** and **Re-2** as well as the ligand **1** are presented in Table 1. In both complexes upon coordination downfield shifts are noted for the protons on C-1, C-5 and C-7 directly attached to the donor N and S atoms. The effect of coordination is especially dramatic for the benzyl group; e.g. in complex **Re-1** the previously equivalent benzyl H-7 protons appear as two well separated doublets shifted downfield by ~0.5 ppm on average, while the benzyl carbon C-7 is downfield shifted by ~10 ppm compared to its position in ligand **1**. In complex **Re-2**, the chemical shift of the carbonyl carbon C-6 at 171.13 ppm

(6.2 ppm upfield compared to **Re-1**) as well as the presence of a hydroxyl peak at 13.0 ppm in spectra obtained in $CDCl_3$ is suggestive of the presence of an uncoordinated carboxyl group. In this case, the presence of a bromine in the coordination sphere of **Re-2** is expected, a hypothesis that was confirmed with ESI-MS analysis.

ESI analysis of the mixture in the positive mode generated $(M+H)^+$ charged states at m/z 563.3, in perfect agreement to the molecular mass calculated for **Re-1** ($C_{17}H_{15}N_2O_6ReS$, $M = 562$) on the basis of the complex primary structure. In the ESI negative mass spectrum of the mixture, the major ion observed was again the $(M-H)^-$ charged state at m/z 561.3. In addition, a second minor ion was also observed at m/z 641.3, in agreement to the structure **Re-2** ($C_{17}H_{16}BrN_2O_6ReS$, $M = 642$) confirmed by isotopic pattern calculation by the List software.

Infrared spectroscopy of complex **Re-1** reveals the characteristic stretching bands of facially coordinated CO with ν(CO) at 2029, 1907 and 1875(sh) cm^{-1}. Furthermore, the band at 1623 cm^{-1} indicates the complexation of the carboxylate group of the ligand. The complex is soluble in CH_2Cl_2, $CHCl_3$ and methanol and insoluble in ether, hexane and water. It is stable in solution for a period of months as shown by HPLC and NMR.

3.2. Description of crystallographic structure

Compound **Re-1** crystallizes in the orthorhombic space group with one crystallographically independent molecule in the asymmetric unit. The molecular structure of **Re-1** is given in Fig. 2 and selected bond distances and angles are listed in Table 3. The coordination geometry about rhenium is distorted octahedral comprised by the NSO donor atom set of the tridentate ligand and the three carbonyl groups. The apical positions of the octahedron are occupied by the carboxylate oxygen atom of the tridentate ligand and one of the carbonyl groups. Rhenium lies 0.09 Å above the equatorial plane. The five-membered ring in the coordination sphere, defined by the S–C–C–O chelating atoms of the tridentate ligand and the metal ion, adopt the envelope configuration with S1 displaced by 0.82 Å out of the best mean plane of the remaining four atoms. The six-membered ring in the coordination sphere, defined by the S–C–C–C–N chelating atoms of the tridentate ligand and the metal ion, adopt the half-chair or envelope configuration with S1 displaced by 1.21 Å out of the best mean plane of the remaining five atoms. The angles around the metal within the tetragonal plane of the octahedron range from 83.5(2)° to 94.2(3)° whereas those involving the apical atoms range from 79.5(1)° to 97.8(3)°. The Re–carbonyl bond distances (1.87–1.91) are consistent with those found in other Re–tricarbonyl complexes [10–15]. The Re–S, Re–N and Re–O bond distances 2.47, 2.19 and 2.13 respectively, fall well in the ranges observed in analogous complexes [10–15]. The bond angles around rhenium are also consistent with those of analogous complexes found in the literature [10–15].

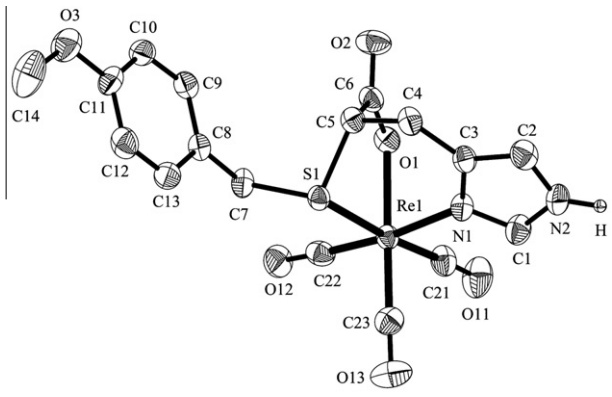

Fig. 2. Labeled plot of the molecular structure of **Re-1** with thermal ellipsoids drawn at 40% probability.

Table 3
Selected bond distances (Å) and angles (°) for **Re-1**.

Distances			
Re(1)–C(23)	1.866(10)	Re(1)–O(1)	2.132(5)
Re(1)–C(21)	1.896(9)	Re(1)–N(1)	2.186(7)
Re(1)–C(22)	1.910(10)	Re(1)–S(1)	2.473(2)
Angles			
C(23)–Re(1)–C(22)	90.9(4)	C(21)–Re(1)–N(1)	93.7(3)
C(23)–Re(1)–C(21)	86.3(4)	O(1)–Re(1)–N(1)	81.2(2)
C(22)–Re(1)–C(21)	88.2(4)	C(23)–Re(1)–S(1)	97.8(3)
C(23)–Re(1)–O(1)	175.9(3)	C(22)–Re(1)–S(1)	94.2(3)
C(22)–Re(1)–O(1)	92.3(3)	C(21)–Re(1)–S(1)	175.2(3)
C(21)–Re(1)–O(1)	96.3(3)	O(1)–Re(1)–S(1)	79.5(1)
C(23)–Re(1)–N(1)	95.5(3)	N(1)–Re(1)–S(1)	83.5(2)
C(22)–Re(1)–N(1)	173.4(3)		

3.3. Radiochemistry

Complex **^{99m}Tc-1** was synthesized by reaction of *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$ precursor with ligand **1** after heating at 85 °C for 30 min at pH 7. The reaction yield was greater than 95% at low ligand concentration (10^{-5} M). Complex formation could also be observed (yield approximately 40%) even at the lower concentration of 10^{-6} M of **1**. The identity of tracer complex **^{99m}Tc-1** was established by HPLC γ-detection and comparison of its retention time to that of the authentic well-characterized complex **Re-1**. Distribution coefficient of **^{99m}Tc-1** was calculated to be log $D_{7.4} = 1.6 \pm 0.2$. Complex **^{188}Re-1** was synthesized by reacting the *fac*-$[^{188}Re(H_2O)_3(CO)_3]^+$ precursor with ligand **1** (1.3 mM) at 65 °C for 30 min. The identity of the tracer complex **^{188}Re-1** was established in the same way as **^{99m}Tc-1** and its radiochemical yield was about 80%.

^{99m}Tc-1 was incubated in saline as well as in 1 mM histidine and 1 mM cysteine solutions at 37 °C and was found to be >95% stable in all these conditions for 24 h, with no decomposition or trans-chelation being observed. The stability of **^{188}Re-1** was also evaluated and was found to be greater than 95% under the above experimental conditions. The longer half-life of ^{188}Re allowed stability tests at longer incubation times in which **^{188}Re-1** proved intact even after 48 h. Therefore, both tracer complexes **^{99m}Tc-1** and **^{188}Re-1** are expected to be stable in the physiological L-histidine and L-cysteine concentrations [21].

4. Conclusions

The histidine derivative ligand **1** proved to be an efficient NSO chelator for the $M(CO)_3^+$ (M = Re, ^{99m}Tc, ^{188}Re) core generating stable neutral complexes of the *fac*-[M(NSO)(CO)$_3$] type. In these complexes the ligand forms three (five-, six-, and seven-membered) bridged chelate rings as is the case with plain histidine. For the $[Re(CO)_3]^+$ core in the absence of any base, ligand **1** also acted as a bidentate NS ligand generating a *fac*-[Re(NS)Br(CO)$_3$] complex in which one of the three bromines of the precursor is present in the coordination sphere while the carboxylate group remains free.

Both tracer complexes **^{99m}Tc-1** and **^{188}Re-1** are stable in solution as well as in the presence of strongly coordinating agents like histidine or cysteine. Since the NSO chelating system **1** is prepared in a facile two-step synthesis by nucleophilic attack of a thiol on a suitable intermediate halide derived from histidine, in principle any bioactive thiol can be used to generate target-specific complexes for diagnostic or therapeutic applications.

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Appendix A. Supplementary material

CCDC 820715 contains the supplementary crystallographic data for **Re-1**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2011.08.062.

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