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Rhenium(I) and Technetium(I) Tricarbonyl Complexes with [NSO]-Type Chelators: Synthesis, Structural Characterization, and Radiochemistry

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The reactions of the NSO ligands 2-[2-(pyridin-2-yl)ethylthio]acetic acid (HL1), 3-[2-(pyridin-2-yl)ethylthio]propanoic acid (HL2), 2-(carboxymethylthio)-3-(1*H*-imidazol-4-yl)-propanoic acid (H_2L3), and 2-(carboxyethylthio)-3-(1*H*-imidazol-4-yl)propanoic acid (H_2L4) with $[NEt_4]_2[ReBr_3(CO)_3]$ are presented. Ligands HL1, H_2L3, and H_2L4 act as tridentate NSO chelators and readily generate the *fac*-[Re(NSO)(CO)$_3$]complexes Re-L1, Re-HL3, and Re-HL4. Ligand HL2 acts as NSO tridentate chelator only in the presence of base to give complex Re-L2, while without base it coordinates as a NS bidentate chelator to generate complex *fac*-[ReBr(NS)(CO)$_3$], Re-HL2. All complexes were isolated and characterized by elemental analysis, IR and ^{1}H, ^{13}C NMR spectroscopy. Complex Re-L1, Re-HL2, and Re-HL3 were characterized also by X-ray crystallography. Furthermore, the analogous technetium complexes *fac*-[^{99m}Tc(NSO)(CO)$_3$]$^+$, ^{99m}Tc-L1, ^{99m}Tc-L2, ^{99m}Tc-HL3, and ^{99m}Tc-HL4 were synthesized by reacting ligands HL1–H_2L4 with the *fac*-[^{99m}Tc(OH$_2$)$_3$(CO)$_3$]$^+$ precursor for 30 min at 75 °C. The tracer complexes ^{99m}Tc-L1–^{99m}Tc-HL4 were found to be stable in L-cysteine and L-histidine challenge experiments. The bifunctional chelating agents that bear a second carboxylate group are promising for the development of targeted ^{99m}Tc radiopharmaceuticals.

Introduction

Technetium (^{99m}Tc) radiopharmaceuticals are routinely used in nuclear medicine as non-invasive diagnostic agents for scintigraphic/tomographic (γ-camera/SPECT) imaging. New generation ^{99m}Tc radiopharmaceuticals consist of a radionuclide unit (^{99m}Tc complex) and a pharmacophore group as the vector that carries the radionuclide to the target site. The design of these compounds is mostly accomplished by using a suitable bifunctional chelating agent (BFCA) for the chelation of the radionuclide and the conjugation of the target specific moiety. An ideal BFCA should be able to form stable and inert ^{99m}Tc complexes in high yield and at low concentration.[1–4]

Currently, many efforts to design novel ^{99m}Tc-radiopharmaceuticals focus on the *fac*-[^{99m}Tc^{I}(CO)$_3$]$^+$-type complexes, because of their high stability and their easy and efficient preparation in aqueous media.[5,6] The Tc-tricarbonyl complexes with tridentate chelating agents are fully coordinated, which results in in vivo stability and favorable pharmacokinetic properties.[7] A variety of NSO chelators has been developed that include an amine or aromatic N atom, a thioether S atom, and a carboxylate group O atom, which have been established as suitable systems for the ^{99m}Tc/[Re(CO)$_3$]$^+$ core.[8–12] These tridentate ligands form [M(CO)$_3$]$^+$ complexes with either a linear or tripodal configuration.[5–15] Interesting [M(CO)$_3$]$^+$ coordination chemistry has been reported with NSO ligands that offer more than one possible mode of complexation, such as [(2-pyridinyl)methyl]-S-cysteine, S-carboxymethyl-L-cysteine, and [2-(2-pyridinyl)ethyl]-S-homocysteine derivatives.[9–11,16,17] However, for radiopharmaceutical purposes, the formation of a single stable product is an essential requirement, and this becomes a challenge when more than one ligating possibility is available. In the case of bifunctional ligands designed to be joined with pharmacophores of interest, and therefore carry many active complexing groups, the generation of the desired product may be influenced by the experimental conditions (e.g. pH) and also by other structural or stereochemical factors such as the chelate ring size etc.

In our previous work, we described the syntheses of the rhenium and technetium tricarbonyl complexes with the NSO chelating agent, 2-(*p*-methoxybenzylthio)-3-(4-imidazolyl)propionic acid, as shown in Figure 1. This ligand was shown to have high potency at low ligand concentration ($<10^{-5}$ M), and the complexes formed were stable at tracer

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level (^{99m}Tc, ^{188}Re) in the presence of potent chelators.[18] Currently, our interest lies in the design of bifunctional chelators based on the NSO donor atom system with a second pendant carboxylate group for tethering to a pharmacophore. Within this framework, and in order to investigate the NSO coordination behavior, the tridentate ligands 2-[2-(pyridin-2-yl)ethylthio]acetic acid (HL1) and 3-[2-(pyridin-2-yl)ethylthio]propanoic acid (HL2) were synthesized and complexed with the $[M(CO)_3]^+$ core. Following that, in order to investigate the preference of this type of NSO ligand bearing a second carboxylate group for linear vs. tripodal coordination, the 2-(S-carboxymethylthio)-3-(1*H*-imidazol-4-yl)propanoic acid (H_2L3) and 2-(S-carboxyethylthio)-3-(1*H*-imidazol-4-yl)propanoic acid (H_2L4) were synthesized and complexed with the $[M^I(CO)_3]^+$ core. The results of this study are presented herein.

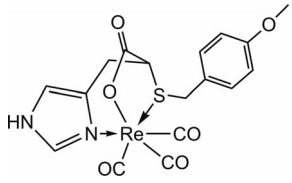


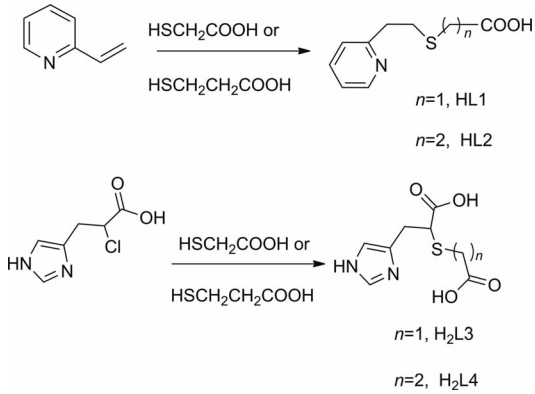
Figure 1. Structure of complex $[Re(NSO)(CO)_3]$.

Results and Discussion

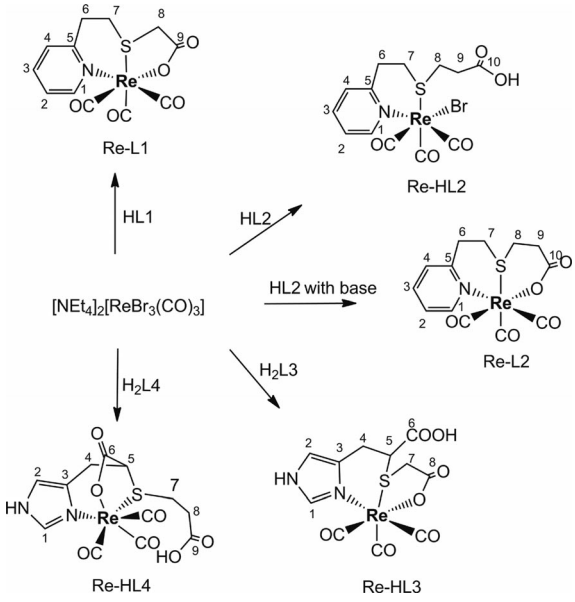
Synthesis and Characterization

Ligands HL1 and HL2 were prepared in high yields by 2-(pyridin-2-yl)ethylation,[19,20] and the pure products were isolated by crystallization from THF (Scheme 1). The reaction of the precursor $[NEt_4]_2[ReBr_3(CO)_3]$ with an equimolar amount of ligand HL1 in methanol led to the expected NSO mode of complexation and the formation of complex Re-L1 (Scheme 2). Reaction of HL2 with $[NEt_4]_2$-$[ReBr_3(CO)_3]$ in methanol led to the isolation of complex Re-HL2 with the structure *fac*-[ReBr(HL2-NS)$(CO)_3$] in which the propionic acid chain remains free. When the reaction was carried out in the presence of 1 equiv. NaOH, the NSO mode of complexation prevailed, and complex Re-L2 was formed as a single product (Scheme 2). Both in the absence and presence of base, the yields of complexes obtained were quantitative, and the complexes were characterized by elemental analysis and IR and NMR spectroscopy. These results indicate that the formation of a 5-membered ring (Re–S–C–C–O) is favored over that of a 6-membered ring (Re–S–C–C–C–O) upon coordination of the carboxylate group in complex Re-L1 and Re-L2, respectively. This fact has also been noted in the literature in a similar NSO system by He et al.[16]

Ligands H_2L3 and H_2L4 were designed as NSO bifunctional ligands carrying two carboxylic acid chains. They were prepared from α-chloro-L-histidine (Scheme 1).[18] Several efforts to isolate the pure ligands H_2L3 and H_2L4 by multiple crystallizations from ethanol/water mixtures afforded only a very low yield for H_2L3 (<10%) or were unsuccessful for H_2L4. However, the pure ligands were isolated in moderate yields after esterification of the diacids H_2L3 and H_2L4 to the ethyl esters Et_2L3 and Et_2L4. The purified diesters were then hydrolyzed by base, and the sodium salts of H_2L3 and H_2L4 were used directly for complexation. Ligands H_2L3 and H_2L4 are soluble in water and DMSO and slightly soluble in methanol and ethanol.



Scheme 1. Synthesis of ligands HL1–H_2L4.



Scheme 2. Syntheses of complexes Re-L1, Re-L2, Re-HL2, Re-HL3 and Re-HL4.

Ligands H_2L3 and H_2L4 reacted with $[NEt_4]_2[ReBr_3$-$(CO)_3]$ in water at pH 7. Analysis of the reaction mixture by HPLC after 3 h of reflux indicated in both cases the formation of a single product Re-HL3 and Re-HL4, respectively. The complexes were characterized by elemental analysis and spectroscopic methods. In Re-HL3 coordination takes place in a linear mode to form two chelate rings, one six-membered and one five-membered, as in the case of Re-L1 (Scheme 2). Although coordination of the second carboxylate group is in principle possible, leading to a five-membered ring as well (Figure 2), it was not observed. In the case of Re-HL4, coordination takes place in the tripodal

mode with formation of three chelate rings, one six-membered, one five-membered, and one seven-membered, while the alternative coordination of the S-carboxylate side chain (Figure 2) was not observed. As in the cases of Re-L1/Re-HL2, formation of a five-membered carboxylate ring is preferred.

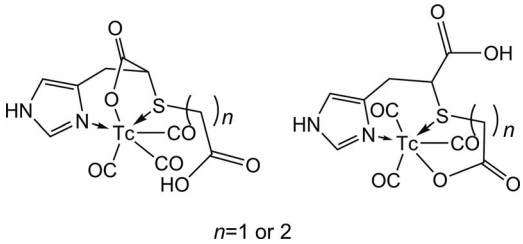


Figure 2. Possible complexation of H_2L3 and H_2L4 with $[M(CO)_3]^+$.

Strong bands in the region 2029–1894 cm^{-1} in the IR spectra of the complexes indicate the presence of three carbonyl ligands in a facial arrangement.[9–12,16–18,21,22] Furthermore, the bands for the coordinated carboxylate groups in complexes Re-L1, Re-L2, Re-HL3, and Re-HL4 appear between 1639 and 1602 cm^{-1} and those for the uncoordinated carboxylate of Re-HL2, Re-HL3, and Re-HL4 in the region 1739–1709 cm^{-1}. All rhenium complexes are soluble in DMSO, slightly soluble in methanol and ethanol, and insoluble in water and are stable in the solid state and in solution for a period of months, as proven by HPLC and NMR spectroscopy.

The ^1H and ^{13}C NMR assignments for the complexes Re-L1, Re-L2, Re-HL2, Re-HL3, and Re-HL4 are based on the combined analysis of a series of ^1H–^1H and ^1H–^{13}C correlation spectra and are presented in Tables 1 and 2. For complexes Re-L2 and Re-HL4 for which no X-ray structure exists, structural characterization was based on their characteristic NMR spectral patterns and on chemical shift comparisons with structurally related complexes herein and in the literature.[9–12,16–18] Upon complexation of the ligands HL1–H_2L4, the signal C-1 pyridinyl and imidazoyl carbon atom adjacent to the coordinating nitrogen is shifted downfield by approximately 7 ppm, while the signal for the corresponding 1-H proton is shifted downfield by 0.4–0.7 ppm. These downfield shifts are typical for the coordination of heterocyclic aromatic nitrogen atoms. In addition, upon coordination, differentiation of the previously equivalent protons of the methylene groups of the chelated NSO (Re-L1, Re-L2, Re-HL3, Re-HL4) or NS backbone (Re-HL2) is noted. In complexes Re-HL2 and Re-HL4 bearing the free mercaptopropionic acid chain, the methylene protons close to coordinated sulfur (8-H and 7-H) are also differentiated, while those close to the carboxyl group (9-H and 10-H0) appear together at approximately 2.75 ppm. In complexes Re-L1, Re-L2, and Re-HL2, the 6-H protons are distinguished from the 7-H protons on the basis of the presence of a NOESY correlation peak with the pyridinyl 4-H proton. The assignment is further confirmed through the observation of the long-range heteronuclear coupling of 4-H

Table 1. ^1H and ^{13}C chemical shifts for complexes Re-L1, Re-HL2, Re-L2 in [D_6]DMSO at 25 °C. The numbering of the atoms is shown in Figure 3.

	Re-L1	Re-HL2	Re-L2
1-H	8.74	9.05	8.79
2-H	7.57	7.49	7.61
3-H	8.10	8.04	8.13
4-H	7.69	7.64	7.76
6-H	3.47, 3.00	3.56, 3.16	3.48, 2.54
7-H	3.43, 2.64	3.12, 2.43	3.56, 3.02
8-H	2.96, 3.59	3.34, 3.18	3.05, 2.31
9-H		2.75	2.18, 1.90
OH		12.57 broad	
C-1	156.04	157.85	155.10
C-2	124.95	124.43	124.70
C-3	140.66	140.19	140.66
C-4	127.10	127.89	126.93
C-5	159.72	161.38	159.40
C-6	38.07	36.76	37.99
C-7	30.80	26.29	28.46
C-8	35.86	34.41	32.16
C-9	178.06	32.73	33.70
C-10		171.95	172.93
C≡O	195.12, 193.21, 192.61	193.19, 191.69	196.54, 194.23, 193.18

Table 2. ^1H and ^{13}C NMR chemical shifts (ppm) for complexes Re-HL3 and Re-HL4 in [D_6]DMSO at 25 °C. The numbering of the atoms is shown in Figure 3.

	Re-HL3	Re-HL4
1-H	8.34	8.33
2-H	7.20	7.17
4-H	2.93, 3.19; ^2J = 16.4 Hz	3.47, 3.18; ^2J = 17.7 Hz, ^3J = 3.8 Hz
5-H	4.23	4.27; ^3J = 3.8 Hz
7-H	3.67, 3.60	3.23, 3.08
8-H		2.78
NH	13.02	13.11
OH	not visible	12.63 broad
C-1	141.99	141.35
C-2	116.47	116.31
C-3	132.78	133.61
C-4	26.36	27.38
C-5	47.77	45.60
C-6	169.53	178.01
C-7	35.49	35.68
C-8	178.03	32.29
C-9		171.97
C≡O	195.41, 193.22	193.17, 195.96, 196.67

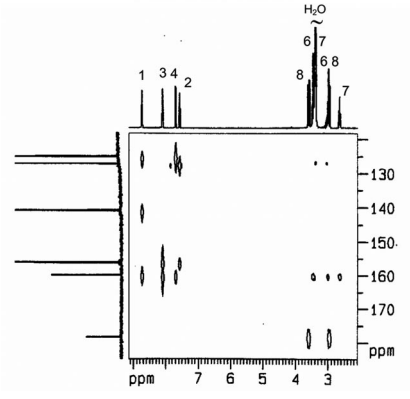


Figure 3. ^1H–^{13}C long range correlation (HMBC) spectrum for complex Re-L1 in [D_6]DMSO at 25 °C.

and C-6 (Figure 3). It is of interest that the chemical shift of the carboxylate C=O group appears at δ = 178 ppm when the carboxylate group participates in a five-membered ring (complexes Re-L1, Re-HL3, Re-HL4) and at δ = 173 ppm when it participates in a six-membered ring (complex Re-L2), which indicates a weaker bonding to the metal, in agreement with the synthesis results that indicate a preference for formation of a five-membered chelate ring.

Description of the Structure

The structures of complexes Re-L1, Re-HL2, and Re-HL3 were determined by X-ray crystallography. Important crystallographic and refinement data are listed in Table 3. Complex Re-L1 crystallizes in the triclinic space group $P\bar{1}$ with two crystallographically independent molecules in the asymmetric unit, denoted as molA and molB respectively. A labeled plot of molA is shown in Figure 4, and selected bond lengths and angles are listed in Table 4. The structure consists of neutral mononuclear entities in which the rhenium ions are in a distorted octahedral geometry comprising of three facially bound CO groups and the NSO donor atom set of the tridentate L1 ligand. The Re–carbonyl bond lengths, 1.912(6)–1.928(6) Å in molA and 1.902(5)–1.928(5) Å in molB, are consistent with those found in other Re-tricarbonyl complexes. The Re–(NSO) bonding distances are also in the ranges observed for other well-characterized complexes, with Re–N bond lengths of 2.233(4) and 2.213(4) Å, Re–S bond lengths of 2.476(1) and 2.469(1) Å, and Re–$O_{carboxyl}$ bond lengths of 2.126(3) and 2.128(3) Å, for molA and molB, respectively. There is one five-membered ring, Re–S–C–C–O, and one six-membered ring, Re–S–C–C–C–N, in the coordination sphere; the former is planar and the latter adopts the less–stable, twist-boat conformation. In molA, atoms C6 and Re1 are displaced by 0.65 and 0.78 Å above the best mean plane defined by the remaining four atoms, and in molB, C26 and Re2 are displaced by 0.75 and 0.72 Å above the S–C–C–N plane. In the crystal lattice of Re-L1, the molecules are linked through intermolecular S···S contacts and form dimers. In particular, molA is associated into molA–molA dimers through the S1···S1′ (1 – x, –y, 1 – z) [3.482 Å] contacts, and similarly molB is linked into molB–molB dimers through the S2···S2′′ (-x, 1 – y, 2 – z) [3.497 Å] contacts.

Table 3. Crystallographic data for Re-L1, Re-HL2 and Re-HL3.

	Re-L1	Re-HL2	Re-HL3
Formula	$C_{12}H_{10}NO_5ReS$	$C_{13}H_{13}BrNO_5ReS$	$C_{12}H_{13}N_2O_8ReS$
F_w	466.47	561.41	531.51
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
a [Å]	7.732(2)	8.531(4)	7.655(3)
b [Å]	13.255(4)	9.319(4)	19.703(7)
c [Å]	13.806(4)	10.842(5)	10.781(4)
α [°]	88.93(1)	81.81(1)	90
β [°]	82.84(1)	85.20(1)	93.88(2)
γ [°]	83.16(1)	75.866(9)	90
V [Å^3]	1393.9(7)	826.3(6)	1622.3(10)
Z	4	2	4
T [°C]	25	25	25
Radiation	Mo-K_α	Mo-K_α	Mo-K_α
$\rho_{calcd.}$ [gcm^{-3}]	2.223	2.257	2.176
μ [mm^{-1}]	8.884	9.917	7.662
Reflections with $I>2\sigma(I)$	4341	2693	2543
R_1[a]	0.0231	0.0343	0.0299
wR_2[a]	0.0576	0.0947	0.0782

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

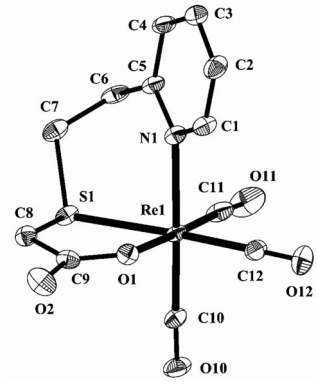


Figure 4. Labeled plot of one of the crystallographically independent molecules in the asymmetric unit of Re-L1 with ellipsoids drawn at the 30% probability level. Hydrogen atoms have been omitted for clarity.

Table 4. Selected bond lengths [Å] and angles [°] for Re-L1.

Distances			
Re1–C12	1.912(6)	Re2–C31	1.902(5)
Re1–C11	1.915(6)	Re2–C30	1.910(5)
Re1–C10	1.928(6)	Re2–C32	1.928(5)
Re1–O1	2.126(3)	Re2–O21	2.128(3)
Re1–N1	2.233(4)	Re2–N21	2.213(4)
Re1–S1	2.476(1)	Re2–S2	2.469(1)
Angles			
C12–Re1–C11	88.6(3)	C31–Re2–C30	87.4(2)
C12–Re1–C10	89.1(2)	C31–Re2–C32	88.3(2)
C11–Re1–C10	86.1(2)	C30–Re2–C32	88.6(2)
C12–Re1–O1	91.8(2)	C31–Re2–O21	176.1(2)
C11–Re1–O1	178.2(2)	C30–Re2–O21	93.6(2)
C10–Re1–O1	95.7(2)	C32–Re2–O21	95.5(2)
C12–Re1–N1	91.6(2)	C31–Re2–N21	97.0(2)
C11–Re1–N1	94.4(2)	C30–Re2–N21	175.6(2)
C10–Re1–N1	179.1(2)	C32–Re2–N21	91.9(2)
O1–Re1–N1	83.8(1)	O21–Re2–N21	82.0(1)
C12–Re1–S1	171.9(2)	C31–Re2–S2	96.0(2)
C11–Re1–S1	99.6(2)	C30–Re2–S2	91.5(2)
C10–Re1–S1	91.9(2)	C32–Re2–S2	175.6(2)
O1–Re1–S1	80.1(1)	O21–Re2–S2	80.1(1)
N1–Re1–S1	87.4(1)	N21–Re2–S2	87.7(1)

Complex Re-HL2 crystallizes in the triclinic space group $P\bar{1}$ with one molecule in the asymmetric unit. A labeled plot of Re-HL2 is shown in Figure 5, and selected bond lengths and angles are listed in Table 5. The structure consists of neutral mononuclear rhenium(I) entities in which the metal ion is in a distorted octahedral environment comprising of three facially bound CO groups, the NS donor atom set of L2, and a bromide ion. The carboxylate group of L2 remains protonated and is directed away from the

coordination sphere of the metal ion. The observed Re–CO, Re–N, and Re–S bond lengths fall in the ranges found in analogous rhenium(I) complexes. The Re–S–C–C–C–N six-membered ring in the coordination sphere adopts the less–stable, twist-boat conformation in which atoms C6 and Re1 lie 0.71 and 0.55 Å above the best mean plane defined by the remaining four atoms. In the crystal lattice, the molecules of Re-HL2 are associated into dimers through intermolecular O–H···Br hydrogen-bonding interactions between the protonated carboxylate of HL2 and the coordinated Br^- of a neighboring molecule [O1···Br (1 – *x*, –*y*, –*z*) 3.323 Å, H1O···Br 2.382 Å, O1–H1O···Br 165.9°].

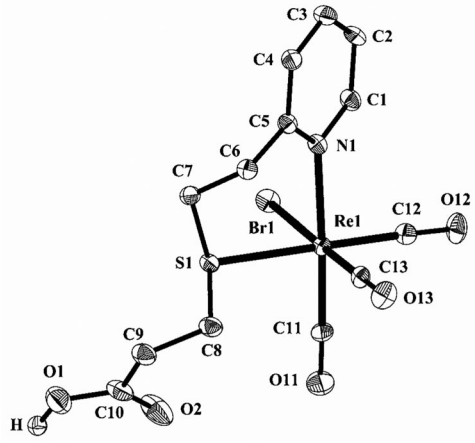


Figure 5. Labeled plot of Re-HL2 with ellipsoids drawn at the 30% probability level. Only the H atom of the carboxylate moiety is shown, the rest have been omitted for clarity.

Table 5. Selected bond lengths [Å] and angles [°] for Re-HL2 and Re-HL3.

Re-HL2		Re-HL3	
Distances			
Re1–C12	1.912(8)	Re–C10	1.902(6)
Re1–C13	1.914(8)	Re–C11	1.930(6)
Re1–C11	1.920(7)	Re–C12	1.935(6)
Re1–N1	2.225(6)	Re–O1	2.154(4)
Re1–S1	2.490(2)	Re–N1	2.174(4)
Re1–Br1	2.626(1)	Re–S	2.487(2)
Angles			
C12–Re1–C13	89.4(3)	C10–Re–C11	88.7(2)
C12–Re1–C11	88.8(3)	C10–Re–C12	88.2(2)
C13–Re1–C11	89.5(3)	C11–Re–C12	89.4(2)
C12–Re1–N1	92.2(3)	C10–Re–O1	173.6(2)
C13–Re1–N1	93.9(3)	C11–Re–O1	94.4(2)
C11–Re1–N1	176.5(3)	C12–Re–O1	97.4(2)
C12–Re1–S1	175.2(2)	C10–Re–N1	91.7(2)
C13–Re1–S1	94.9(2)	C11–Re–N1	91.1(2)
C11–Re1–S1	89.0(2)	C12–Re–N1	179.5(2)
N1–Re1–S1	89.7(2)	O1–Re–N1	82.7(2)
C12–Re1–Br1	91.2(2)	C10–Re–S	97.8(2)
C13–Re1–Br1	178.7(2)	C11–Re–S	173.4(2)
C11–Re1–Br1	91.7(3)	C12–Re–S	90.0(2)
N1–Re1–Br1	84.9(1)	O1–Re–S	79.2(1)
S1–Re1–Br1	84.7(1)	N1–Re–S	89.6(1)

Complex Re-HL3 crystallizes in the monoclinic space group $P2_1/n$ in which one complex molecule and a solvate methanol molecule are in the asymmetric unit. A labeled plot of Re-HL3 is shown in Figure 6, and selected bond lengths and angles are listed in Table 5. The structure consists of neutral mononuclear rhenium(I) entities comprising the *fac*-[$Re(CO)_3$] group and the NSO donor atom set of the tridentate L3 ligand. The second carboxylate group of L3 remains protonated and is directed away from the metal ion. The imidazole ring of L3 is also protonated and coordinates to rhenium(I) through the second nitrogen atom. The Re–carbonyl bond lengths, 1.902(6)–1.935(6) Å, are consistent with those found in other Re-tricarbonyl complexes, with the longest being the one opposite to N_{im} and the shortest opposite to $O_{carboxyl}$.[5,8–12,13,18] The Re–(NSO) bonding distances are also in the ranges observed for other well-characterized complexes, with a Re–N_{im} bond length of 2.174(4) Å, Re–S bond length of 2.486(2) Å, and Re–$O_{carboxyl}$ bond length of 2.154(4) Å.[8–12,18,23] The Re–S–C2–C1–O1 five-membered ring in the coordination sphere adopts the envelope conformation in which the atom S is 0.65 Å above the mean plane of the remaining four atoms. There is also a six-membered ring in the coordination sphere defined by the atoms Re–S–C3–C5–C6–N, whose conformation cannot be easily described in terms of the known conformations of cyclohexane. The best way to describe this particular six-membered ring is to define the mean plane passing through Re–S–C3–N (largest deviation 0.03 Å for C3) from which atoms C6 and C5 are displaced by 0.61 and 1.15 Å, respectively. This thus suggests a conformation "frozen" between half-chair and twist-boat with regard to the displacement of C6 and the orientation of the imidazole ring. The observed intermolecular hydrogen-bonding interactions of the O–H···O and N–H···O type involving the protonated carboxylate group and the imidazole nitrogen atom of L3, as well as the solvate methanol, are very likely to contribute to the stability of the above intermediate conformation of the six-membered ring. In the crystal lattice, the molecules of Re-HL3 form two-dimensional sheets parallel to the *ac* plane as a result of their linkage through hydrogen bonds [O4···O2 (–0.5 + *x*, 0.5 – *y*, 0.5 + *z*) 2.570 Å, H4O···O2 1.927 Å, O4 – H4O···O2 167.3°; N2···O1m (–1 + *x*, *y*, –1 + *z*) 2.866 Å, H2N···O1m 2.183 Å,

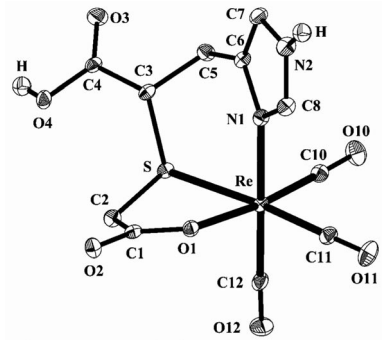


Figure 6. Labeled plot of Re-HL3 with ellipsoids drawn at the 30% probability level. Only significant H atoms are shown; the rest have been omitted for clarity.

N2 – H2N···O1m 161.8°; O1m···O3 (1 + *x*, *y*, *z*) 2.907 Å, H1m···O3 2.257 Å, O1m–H1m···O3 167.8°].

Radiochemistry

The *fac*-[^{99m}Tc(NSO)(CO)$_3$] complexes ^{99m}Tc-L1, ^{99m}Tc-HL3 and ^{99m}Tc-HL4 were synthesized in high yield (>95%) by the reaction of the *fac*-[^{99m}Tc(H$_2$O)$_3$(CO)$_3$]$^+$ precursor with ligand HL1, H$_2$L3 or H$_2$L4 (10^{-4} M) at 75 °C for 30 min at pH 6–7. HPLC analysis of the reaction mixture showed the formation of a single product, the same as that for the rhenium analogues. The identity of the tracer complexes was established by HPLC γ-detection after co-injection with the rhenium complexes Re-L1 (t_R: 16.3 min), Re-HL3 (t_R: 15.6 min), and Re-HL4 (t_R: 14.9 min). It was found that ^{99m}Tc-L1 elutes with t_R = 16.7 min, ^{99m}Tc-HL3, t_R = 15.7 min and ^{99m}Tc-HL4, t_R = 15.1 min. A representative HPLC co-injection chromatogram is shown in Figure 7. The formation of the *fac*-[^{99m}Tc(NSO)(CO)$_3$] ^{99m}Tc-L2 complex was quantitative only at a higher HL2 ligand concentration of 10^{-3} M. The radiochemical yield of ^{99m}Tc-L2 at lower HL2 concentrations was low, and many products were observed in the chromatogram. All ^{99m}Tc complexes were challenged against 1 mM histidine and cysteine, and the analysis showed that they were ≈85–95% stable after 24 h. In particular, analysis of the complexes with bifunctional ligands showed that the percentage of intact ^{99m}Tc-HL3 was 83% after 24 h in histidine and 98% after 24 h in cysteine, while ^{99m}Tc-HL4 was about 93% and 99% intact after 24 h in histidine and cysteine, respectively. These results indicate that the tracer complexes will be stable in biological fluids where histidine and cysteine are present.

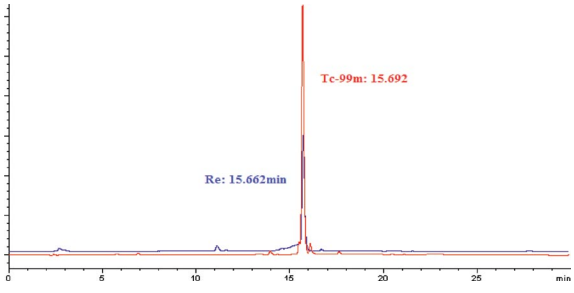


Figure 7. Comparative HPLC analysis of Re-HL3 (UV) and the labeling mixture of ^{99m}Tc-HL3 (γ detection) co-injected.

Conclusions

The HL1–H$_2$L4 ligands employed, which contain an aromatic N, a thioether S and a carboxylate O atom, led to the formation of a single, stable complex with a Re-tricarbonyl core. Our results allow for some conclusions to be reached with regard to the coordination behavior of this type of SNO ligand. Specifically, the study with ligands HL1 and HL2 show that formation of a five-membered ring by the S-carboxylate chain is preferred over formation of a six-membered ring. In addition, the study with ligand H$_2$L3 that carries two carboxylate groups with coordinating potential demonstrates that coordination in the linear mode is preferred over the tripodal mode, since only the linear complex is formed even though coordination of either carboxylate group would lead to formation of a five-membered ring (Figure 2). The study with H$_2$L4 confirms the preference for the formation of a five-membered ring over the six-membered ring, a preference that apparently overcomes that for linear coordination.

With technetium, the ligands HL1–H$_2$L4 behave in an analogous way with the generation of single, stable complexes. In particular ligands H$_2$L3 and H$_2$L4, which react at very low concentrations with ^{99m}Tc, could be used for the conjugation of a pharmacophore group of interest toward the development of novel diagnostic and therapeutic radiopharmaceuticals.

Experimental Section

General: All chemicals were reagent grade and were used as such unless otherwise noted. Re$_2$(CO)$_{10}$ was purchased from Aldrich and was converted to (NEt$_4$)$_2$[ReBr$_3$(CO)$_3$] as previously reported.[24] Solvents for high-performance liquid chromatography (HPLC) were HPLC grade. They were filtered through membrane filters (0.22 μm, Millipore, Milford, MA) and degassed.

For the ^{99m}Tc labeling, a kit containing 5.5 mg of NaBH$_4$, 4 mg of Na$_2$CO$_3$, and 10 mg of Na-K tartrate was purged with CO gas prior to addition of Na^{99m}TcO$_4$, as described in the literature.[13]

Elemental analyses were performed on a Perkin–Elmer 2400 automated analyzer. IR spectra were recorded as KBr pellets on a Perkin–Elmer 1600 FTIR spectrophotometer in the region 4000–500 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz or 500 MHz Avance DRX spectrometer and by using (CH$_3$)$_4$Si as the internal reference. 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 of the rhenium and technetium-99m complexes were achieved on an Agilent Eclipse XDB-C18 column (25 cm × 4.6 mm, 5 μm) eluted with a binary gradient system at a 1 mL/min flow rate and with a composition of 100% solvent A: 0.1% trifluoroacetic acid in water at 0 min, linearly converting to 75% solvent B: methanol, over 15 min.

Ligand Syntheses

2-[2-(Pyridin-2-yl)ethylthio]acetic Acid (HL1): 2-vinylpyridine (3.26 g, 31 mmol) freshly distilled under vacuum was added dropwise in a solution of mercaptoacetic acid (2.86 g, 31 mmol) in methanol (50 mL). The reaction mixture was heated under reflux for 4 h. Methanol was then removed on a rotary evaporator, and the residue was dissolved in ethanol (5 mL) and kept at –20 °C for 24 h. The white precipitate formed was recrystallized from tetrahydrofuran. Yield 5.86 g (96%). IR (KBr): $\tilde{\nu}$ = 1703 (COOH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.56 (1 H, py) 8.36 (1 H, py), 7.82 (1 H, py) 7.70 (1 H, py), 3.24 (t, 2 H, C*H*$_2$), 3.18 (t, 2 H, C*H*$_2$), 2.95 (t, 2 H, C*H*$_2$) ppm. C$_9$H$_{11}$NO$_2$S (197.25): calcd. C 54.82, H 5.62, N 7.10; found C 55.00, H 5.70, N 7.14.

3-[2-(Pyridin-2-yl)ethylthio]propanoic Acid (HL2): Ligand HL2 was prepared following the same method as that for HL1 by using 3-mercaptopropionic acid (3.29 g, 31 mmol) in place of mercaptoacetic acid. Yield: 6.22 g (95%). IR (KBr): $\tilde{\nu}$ = 1704 (COOH) cm^{-1}.

^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.60 (1 H, py), 8.35 (1 H, py), 7.85 (1 H, py), 7.75 (1 H, py), 3.25 (t, 2 H, CH_2), 3.00 (t, 2 H, CH_2), 2.70 (t, 2 H, CH_2), 2.45 (t, 2 H, CH_2) ppm. $C_{10}H_{13}NO_2S$ (211.28): calcd. C 56.85, H 6.20, N 6.63; found C 56.59, H 6.55, N 6.60.

Ethyl 2-(2-Ethoxy-2-oxoethylthio)-3-(1*H*-imidazol-4-yl)propanoate (Et_2L3): Ligand L3 was synthesized according to the following procedure.[18] 2-Chloro-3-(1*H*-imidazol-4-yl)propanoic acid[25] (500 mg, 2.88 mmol) and mercaptoacetic acid (396 mg, 4.3 mmol) were mixed in water/ethanol (1:1 v/v, 10 mL), and 2 M NaOH (6 mL) was added dropwise under N_2. The mixture was stirred for 3 d. The pH was then adjusted to 5 by addition of 5 M HCl, and the solvents were evaporated to dryness. The residue was slurried in dry ethanol (25 mL), and thionyl chloride (3 mL, 40 mmol) was added dropwise at 0 °C under N_2. The mixture was heated under reflux for 12 h and concentrated in vacuo. The oily residue was purified by silica gel column chromatography by eluting with 5% methanol in dichloromethane. Yield: 303 mg (37%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.0 (br. s, 1 H, N*H*), 7.64 (s, 1 H, 1-H), 6.88 (s, 1 H, 2-H), 4.13–4.21 (m, 4 H, CH_2CH$_3$), 3.78 (t, J = 7.4 Hz, 1 H, 5-H), 3.47 (d, J = 15.7 Hz, 1 H, 7-H), 3.36 (d, J = 15.7 Hz, 1 H, 7-H), 3.22 (dd, J = 15.1, 8.1 Hz, 1 H, 4-H), 3.02 (dd, J = 15.0, 6.7 Hz, 1 H, 4-H), 1.26 (t, 3 H, CH$_2$CH_3), 1.24 (t, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.72 (*C*OOEt), 170.01 (*C*OOEt), 134.75 (C-1), 132.80 (C-3), 118.35 (C-2), 61.63 (*C*H$_2$CH$_3$), 61.42 (*C*H$_2$CH$_3$), 46.57 (C-5), 33.26 (*C*H$_2$), 28.68 (*C*H$_2$), 14.01 (CH$_2$*C*H$_3$) ppm (the NMR numbering is shown in Scheme 2, with the exception of the ethyl esters). $C_{12}H_{18}N_2O_4S\cdot(0.5H_2O)$ (286.35): calcd. C 48.80, H 6.48, N 9.48; found C 49.00, H 6.12, N 9.52.

Ethyl 2-(3-Ethoxy-3-oxopropylthio)-3-(1*H*-imidazol-4-yl)propanoate (Et_2L4): Ligand L4 was prepared according to the procedure given above for L3; 3-mercaptopropanoic acid (456 mg, 4.3 mmol) was used in the place of mercaptoacetic acid. Yield: 350 mg (41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.15 (br. s, 1 H, N*H*), 7.57 (s, 1 H, 1-H), 6.86 (s, 1 H, 2-H), 4.09–4.24 (m, 4 H, CH_2CH$_3$), 3.64 (dd, J = 8.5, 6.4 Hz, 1 H, 5-H), 3.22 (dd, J = 14.9, 8.6 Hz, 1 H, 4-H), 2.99 (dd, J = 14.8, 6.4 Hz, 1 H, 4-H), 2.86–2.94 (m, 2 H, 8-H), 2.56–2.65 (m, 2 H, 7-H), 1.26 (t, 3 H, CH$_2$CH_3), 1.25 (t, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.36 (*C*OOEt), 171.67 (*C*OOEt), 134.77 (C-1), 133.63 (C-3), 118.18 (C-2), 61.27 (*C*H$_2$CH$_3$), 60.71 (*C*H$_2$CH$_3$), 46.64 (C-5), 34.51 (CH$_2$), 29.18 (CH$_2$), 26.56 (CH$_2$), 14.12 (CH$_2$*C*H$_3$), 14.04 (CH$_2$*C*H$_3$) ppm (the NMR numbering is shown in Scheme 2, with the exception of the ethyl esters). $C_{13}H_{20}N_2O_4S$ (300.37): calcd. C 51.98, H 6.71, N 9.33; found C 51.69, H 6.87, N 9.21.

Syntheses of the Rhenium Complexes

Synthesis of *fac*-[Re(L1-NSO)(CO)$_3$] (Re-L1): [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (154 mg, 0.2 mmol) was dissolved in methanol (10 mL), and a solution of ligand HL1 (40 mg, 0.2 mmol) in methanol (5 mL) was added. The mixture was heated under reflux for 2 h. The solvent was evaporated to dryness, and the residue was crystallized by slow evaporation from methanol/water. Crystals suitable for X-ray crystallography were obtained by slow evaporation from CH_2Cl_2/MeOH. Yield: 75 mg (81%). t_R = 16.30 min. IR (KBr): $\tilde{\nu}$ = 2025, 1926, 1894, 1639 cm^{-1}. ^{1}H and ^{13}C NMR data in Table 1. $C_{12}H_{10}NO_5ReS$ (466.47): calcd. C 30.90, H 2.16, N 3.00; found C 30.69, H 2.22, N 2.98.

Synthesis of *fac*-[Re(HL2-NS)(Br)(CO)$_3$] (Re-HL2): [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (154 mg, 0.2 mmol) was dissolved in methanol (10 mL), and a solution of ligand HL2 (42 mg, 0.2 mmol) in methanol (5 mL) was added. The mixture was heated under reflux for 2 h. Crystals suitable for X-ray analysis were isolated by dissolving the precipitate in CH_2Cl_2/MeOH and by allowing the solvent mixture to slowly evaporate. Yield: 95 mg (85%). t_R = 16.46 min. IR (KBr): $\tilde{\nu}$ = 2023, 1901, 1739 cm^{-1}. ^{1}H and ^{13}C NMR data in Table 1. $C_{13}H_{13}BrNO_5ReS$ (561.41): calcd. C 27.81, H 2.33, N 2.49; found C 27.58, H 2.55, N 2.34.

Synthesis of *fac*-[ReBr(L2-NSO)(CO)$_3$] (Re-L2): [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (154 mg, 0.2 mmol) was dissolved in methanol (10 mL), and a solution of ligand HL2 (42 mg, 0.2 mmoL) in methanol (5 mL) and 1 M NaOH (0.2 mL) were added. The mixture was heated under reflux for 2 h. Yield: 74 mg (77%). t_R = 17.78 min. IR (KBr): $\tilde{\nu}$ = 2020, 1900, 1626 cm^{-1}. ^{1}H and ^{13}C NMR data in Table 1. $C_{13}H_{12}NO_5ReS$ (480.50): calcd. C 32.49, H 2.52, N 2.91; found C 32.20, H 2.68, N 2.95.

Synthesis of *fac*-[Re(HL3-NSO)(CO)$_3$] (Re-HL3) and *fac*-[Re(HL4-NSO)(CO)$_3$] (Re-HL4): The esterified ligands Et_2L3 (28.6 mg, 0.1 mmol) or Et_2L4 (29.8 mg, 0.1 mmol) was stirred in water (2 mL) with 6 equiv. 2 M NaOH (0.3 mL) for 2 h, until complete hydrolysis was confirmed by HPLC. The pH was then adjusted to 7 with 1 M HCl, and [NEt$_4$]$_2$[ReBr$_3$(CO)$_3$] (77 mg, 0.1 mmol) was subsequently added. The mixture was heated under reflux for 3 h. The solvent was evaporated to dryness, and the residue was crystallized by slow evaporation from methanol/water. Crystals suitable for X-ray crystallography were obtained for complex Re-HL3.

Re-HL3: Yield: 22 mg (41%). t_R = 15.6 min. IR (KBr): 2028, 1918, 1709, 1611 cm^{-1}. ^{1}H and ^{13}C NMR data in Table 2. $C_{11}H_9N_2O_7ReS\cdot CH_3OH$ (531.5): calcd. C 27.12, H 2.47, N 5.27; found C 26.75, H 2.77, N 5.20.

Re-HL4: Yield: 17 mg (33%). t_R = 14.9 min IR (KBr): $\tilde{\nu}$ = 2029, 1896, 1718, 1602 cm^{-1}. ^{1}H and ^{13}C NMR data in Table 2. $C_{12}H_{11}N_2O_7ReS$ (513.49): calcd. C 28.07, H 2.16, N 5.46; found C 28.37, H 2.33, N 5.58.

X-ray Crystal Structure Determination: Diffraction measurements were made on a Crystal Logic Dual Goniometer diffractometer by using graphite monochromated Mo-K_α radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range $11 < 2\theta < 23°$. Intensity data were recorded by using a θ–2θ scan. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization and ψ-scan absorption corrections were applied by using the Crystal Logic software. The structure was solved by direct methods with SHELXS-97[26] and refined by full-matrix least-squares techniques on F with SHELXL-97.[27]

Re-L1: $2\theta_{max}$ = 50°; reflections collected/unique/used, 5307/4907 [R_{int} = 0.0087]/4907; parameters refined, 441; Δ/σ = 0.002; $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 1.511/–0.665 e/Å^3; R_1/wR_2 (all data) = 0.0284/0.0603. All hydrogen atoms were located by difference maps and were refined isotropically; all non-hydrogen atoms were refined anisotropically.

Re-HL2: $2\theta_{max}$ = 50°; reflections collected/unique/used, 3109/2896 [R_{int} = 0.0128]/2896; parameters refined, 251; Δ/σ = 0.001; $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 1.820/–1.309 e/Å^3; R_1/wR_2 (all data) = 0.0374/0.0980. All hydrogen atoms were located by difference maps and were refined isotropically; all non-hydrogen atoms were refined anisotropically.

Re-HL3: $2\theta_{max}$ = 50°; reflections collected/unique/used, 3006/2849 [R_{int} = 0.0428]/2849; parameters refined, 258; Δ/σ = 0.004; $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 1.213/–1.362 e/Å^3; R_1/wR_2 (all data) = 0.0352/0.0820. All hydrogen atoms were located by difference maps and were refined isotropically, except those of the methyl group of the methanol solvate, which were introduced at calculated positions as riding on

bonded atoms; all non-hydrogen atoms were refined anisotropically.

CCDC-862474 (for Re-L1), -862475 (for Re-HL2), and -862476 (for Re-HL3) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of Technetium Complexes ^{99m}Tc-L1–^{99m}Tc-HL4: A freshly prepared solution of the *fac*-[^{99m}Tc(CO)$_3$(H$_2$O)$_3$]$^+$ precursor (450 μL, 5–10 mCi/mL) at pH 7 was added to a vial containing a solution of ligands HL1, H$_2$L3, H$_2$L4 (50 μL, 10^{-3} M or 10^{-4} M), or a solution of HL2 (50 μL, 10^{-2} M). The vial was sealed, flushed with N$_2$ for 5 min and heated for 30 min at 75 °C. The reaction mixture was analyzed by HPLC, which revealed the formation of a single product: ^{99m}Tc-L1, t_R = 16.7 min; ^{99m}Tc-L2, t_R = 18.48 min; ^{99m}Tc-HL3, t_R = 15.7; ^{99m}Tc-HL4, t_R = 15.1 min. The ligand concentrations in the labeling mixture that led to quantitative formation (≥95%) of ^{99m}Tc-L1, ^{99m}Tc-HL3 and ^{99m}Tc-HL4 were as low as 10^{-4} M, and at concentration of 10^{-5} M, a radiochemical yield (RCY) of approximately 80–90% was achieved. The RCY for ^{99m}Tc-L2 was 95% at 10^{-3} M ligand concentration in the reaction mixture.

In Vitro Histidine and Cysteine Challenge of ^{99m}Tc Complexes: The procedure was the same for all ^{99m}Tc complexes; the HPLC-purified ^{99m}Tc complex (0.2 mL) was mixed with a solution of 1 mM histidine or cysteine in 0.1 M PBS, pH 7.4 (0.8 mL), and the mixture was incubated at 37 °C for 24 h. The mixture was analyzed by HPLC at 1, 4 and 24 h intervals.

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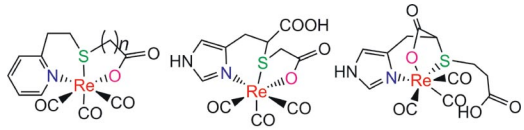

fac-[Re(NSO)(CO)$_3$] complexes were synthesized with varying chelate ring size and geometry. The order of complex formation preference is: linear (6,5-membered rings) > tripodal (6,5,7-membered rings) > linear (two six-membered rings). The analogous *fac*-[^{99m}Tc(NSO)(CO)$_3$] complexes were prepared in high yield and were stable in solution.

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Rhenium(I) and Technetium(I) Tricarbonyl Complexes with [NSO]-Type Chelators: Synthesis, Structural Characterization, and Radiochemistry

Keywords: Rhenium / Technetium / Carbonyl ligands / Radiopharmaceuticals / NSO ligands

