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FULL PAPER

Synthesis and characterization of mixed-ligand oxorhenium(V) complexes with new [(PNO/S)(S)] donor atom sets

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Received 8th February 2001, Accepted 22nd May 2001
First published as an Advance Article on the web 12th July 2001

New oxorhenium complexes with 2-(diphenylphosphanyl)-*N*-(2-thioethyl)benzamide (H_2**PNS**) and 2-(diphenylphosphanyl)-*N*-(2-hydroxyethyl)benzamide (H_2**PNO**) and various monodentate thiols as co-ligands are reported. These new complexes, **1**–**6**, have been prepared by reacting $[^nBu_4][Re(O)Cl_4]$ or $[Re(O)Cl_3(PPh_3)_2]$ with the tridentate H_2**PNX** (X = O, S) ligands and different monothiols. The characterization of the complexes involved IR, ^{1}H and ^{31}P NMR spectroscopy and X-ray crystallographic analysis in the case of **1** and **2**. Complexes [Re(O)(κ^3-PNO)(SPh)] (**1**), and [Re(O)(κ^3-PNS)(SPh)] (**2**), adopt a distorted square pyramidal geometry (δ = 3.0°, **1** and δ = 1.3° for **2**), with the oxo group in the axial position and the equatorial plane being defined by the phosphorus, nitrogen and oxygen (**1**) or sulfur (**2**) atoms of the tridentate chelate and by the sulfur atom of the monothiol.

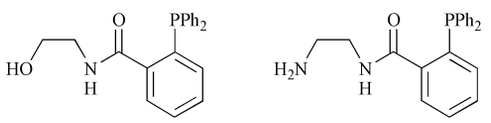
Introduction

Nowadays, one of the driving forces for the advances in nuclear medicine, namely for imaging the brain *in vivo* with the γ-emitter ^{99m}Tc, is the development of new coordination complexes which must be able to cross the blood/brain barrier (BBB), and bind with high affinity and selectivity to specific receptors.[1] Thus, the radiolabelling of central nervous system (CNS) receptor ligands with the most important nuclide for diagnostic purposes, ^{99m}Tc, is quite challenging and extensive efforts have been made in the past few years to achieve this goal.

Tropane derivatives, acting as dopamine transporter ligands, can be labeled with ^{99m}Tc, and the new synthon $[^{99m}Tc(CO)_3]^+$ was also used to label a derivative of an arylpiperazine (specific for a sub-class of serotonergic receptors) and a derivatised tropane, without considerable loss of specificity.[2–5] A common feature to both approaches is the fact that the ^{99m}Tc complexes attached to CNS receptor ligands are neutral in charge and lipophilic.

The mixed-ligand complexes of rhenium and technetium of the so called [3 + 1] type, which have been thoroughly investigated in the past few years, are also neutral and lipophilic, and some were proposed as agents for labelling CNS receptor ligands.[6,7] Different series of mixed-ligand complexes of this type, which are based on a tridentate ligand and a monothiol co-ligand have been described: [S,S,S]/[S][8,9] [S,O,S]/[S],[8,10] [O,N,S]/[S],[11,12] [S,N(R),S]/[S][13,14] and [S,N,N]/[S].[15,16] One of the drawbacks of using these complexes in radiopharmacy is the fact that they present low stability against nucleophiles. In fact, brain retention exhibited by many members of the ^{99m}TcO-(SNS/S) series is mediated by the nucleophilic substitution of the monothiolate co-ligand by gluthathione (GSH) with formation of the hydrophilic complex ^{99m}TcO(SNS/SG).[17] This type of ligand-exchange reaction is reversible and its kinetics depends not only on the nature of the tridentate and monodentate ligands but also on their concentration. We have been studying the new (bi)tridentate phosphines H_2**PNO** and H**PN**$_2$ (Scheme 1), which are quite versatile in terms of denticity and charge.[18,19]

We report herein the synthesis and characterization of a ligand of the same type, H_2**PNS**. We also describe a new series of 3 + 1 type compounds, stabilized by the chelates H_2**PNO** and H_2**PNS** and by several monothiols, including one bearing a $5HT_{1A}$ receptor ligand: [Re(O)(κ^3-PNX)(SPh)] [X = O, (**1**); X = S, (**2**)], [Re(O)(κ^3-PNS)(SR)] [R = *p*-$NH_2C_6H_4$ (**3**); R = CH_2CH_2COOH (**4**); R = κ^1-HPNS, (**5**); R = $(CH_2)_2C(O)NH(CH_2)_3\overline{N(CH_2)_2N(m\text{-}OMeC_6H_4)CH_2CH_2}$ (**6**)].

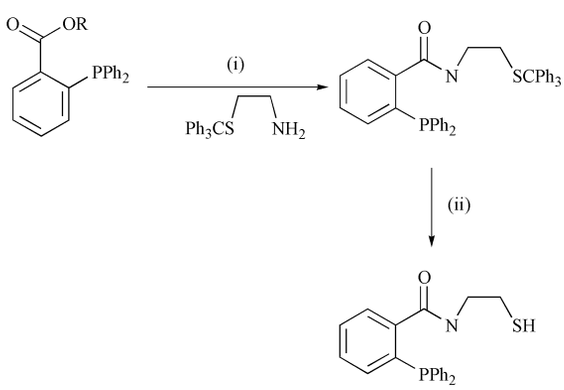


H_2**PNO** H**PN**$_2$

Scheme 1 Structures of the ligands H_2**PNO** and H**PN**$_2$.

Results and discussion

The novel heterofunctionalized phosphine ligand H_2**PNS** was synthesized by reacting *N*-[2-(diphenylphosphanyl)benzoyloxy]-succinimide with *S*-(triphenylmethyl)-2-aminoethanethiol in CH_2Cl_2, as previously described for H_2**PNO** (Scheme 2).[18] An

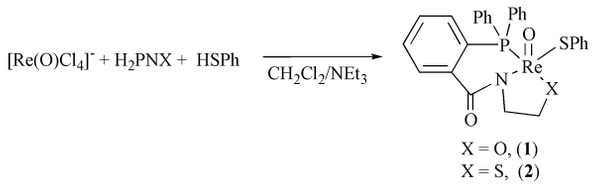


H_2**PNS**

Scheme 2 Synthesis of the H_2**PNS** ligand; R = *N*-succinimido; (i) dichloromethane, r.t., 24 h; (ii) CF_3COOH, Et_3SiH.

important point in the synthesis of H_2**PNS** is the deprotection of the thiol group, which has to be carried out with triethylsilane in trifluoroacetic acid, to avoid the oxidation of the phosphorus atom.

Using the new ligands H_2**PNO** and H_2**PNS**, the neutral mixed-ligand complexes **1** and **2** have been prepared, in relatively high yield (60–70%), using the synthetic process indicated in Scheme 3.



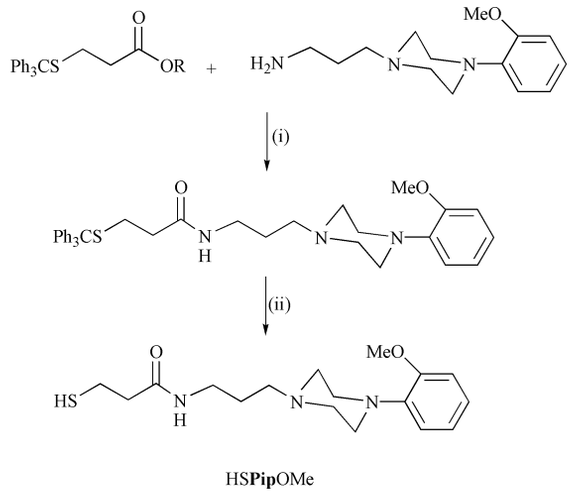
Scheme 3 Synthesis of the complexes **1** and **2**.

Taking into account our interest in potential medical applications, we prepared these model complexes with Tc at the n.c.a. (non carrier added) level and studied their stability *in vitro*, in phosphate buffer and in exchange reactions with glutathione. In both cases, no exchange is observed with glutathione and [^{99m}Tc(O)(κ^3-PNS)(SPh)](**2a**) remains stable in solution for a long period.[20] These results prompted us to explore the chemistry of H_2**PNS** with other bifunctional monodentate co-ligands, such as *p*-$NH_2C_6H_4SH$ and $HSCH_2$-CH_2COOH, bearing functional groups suitable for binding to biomolecules. Using these monothiolates and H_2**PNS** we isolated and characterized the new complexes [Re(O)(κ^3-PNS)-(SC_6H_4-*p*-NH_2)] (**3**) and [Re(O)(κ^3-PNS)(SCH_2CH_2COOH)] (**4**), following the synthetic procedure indicated in Scheme 3. These compounds were obtained analytically pure in 60% yield, after appropriate work-up. An important point in the synthesis of **3** and **4** is the $[Re(O)Cl_4]^-$: H_2**PNS** : SR molar ratio. This ratio has to be maintained at 1 : 1 : 1 to avoid the formation of another complex that was identified as [Re(O)(κ^3-PNS)-(κ^1-HPNS)] (**5**). This compound can be obtained in 58% yield by reacting $[Re(O)Cl_4]^-$ with an excess of H_2**PNS** in the presence of NEt_3. The formation of **5** is due to the coordinative versatility of H_2**PNS**. In fact, this chelate can coordinate to the metal either in a κ^3 or a κ^1 -fashion. This result contrasts with what has been observed for the ligands of the same family, H_2**PNO** and HPN_2, which, so far, have only shown an κ^3 or κ^2-coordination mode.[18,19] The different coordinative capability of this family of **PNX** ligands is related to the nature of the X atom, and to their tendency for stabilizing a $[ReO]^{3+}$ core. The identification of **5** is important for studies at the n.c.a. level, and suggests a careful optimisation of the ligand concentration in the preparations with ^{99m}Tc. Another monothiolate co-ligand that we tried was a piperazine derivative, bearing the receptor-binding 1-(2-methoxyphenyl)piperazine moiety: *N*-[4-(3-aminopropyl)-1-(2-methoxyphenyl)piperazine]-*N*-[(3-thio)propiamide] (HS**Pip**OMe). This ligand was prepared as described in Scheme 4.

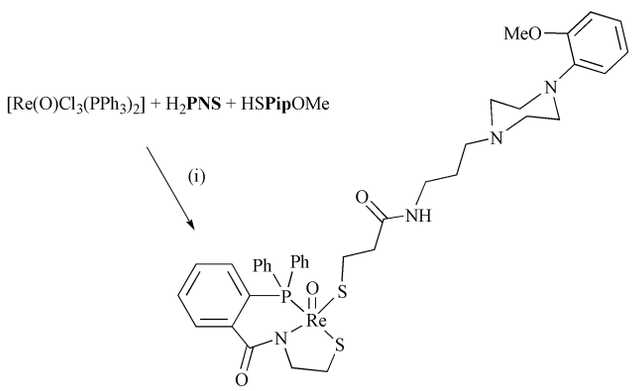
The neutral oxorhenium(v) complex [Re(O)(κ^3-PNS)-(κ^1-HS**Pip**OMe)] (**6**), with the receptor-binding 1-(2-methoxyphenyl)piperazine moiety, specific for the 5-HT_{1A} serotonergic receptors, was prepared as indicated in Scheme 5. Complexes **1**–**6** are air and moisture stable, soluble in chlorinated solvents and alcohols but insoluble in water and hydrocarbons.

The ligands H_2**PNS** and HS**Pip**OMe and the complexes **1**–**6** were fully characterized by elemental analysis, IR, ^{1}H and ^{31}P NMR spectroscopy, and by X-ray diffraction analysis in the case of **1** and **2**.

The IR and NMR spectra of H_2**PNS** compare well with those of the analogous H_2**PNO** and HPN_2, previously reported.[18] The most important features in the IR spectrum of H_2**PNS** are a weak stretching band at 2540 cm^{-1} and a strong



Scheme 4 Synthesis of the monothiol *N*-[4-(3-aminopropyl)-1-(2-methoxyphenyl)piperazine]-*N*-[(3-thio)propiamide] (HS**Pip**OMe); R = *N*-succinimido; (i) dichloromethane, r.t., 20 h; (ii) CF_3COOH, Et_3SiH.



Scheme 5 Synthesis of the complex **6**; (i) NaOAc/MeOH, reflux.

band at 1620 cm^{-1} due to the ν(SH) and ν(C=O) stretching vibrations, respectively. In the ^{1}H NMR spectrum, all the resonances appear in the expected range, namely broad triplets at $\delta = 6.58$ and 1.36, which were assigned to the NH and SH protons, respectively. The ^{31}P NMR spectrum show only one resonance at $\delta = -9.3$, comparable to that found for the H_2**PNO** (−9.9 ppm).[18] For the piperazine derivative, the IR spectrum presents a strong band at 1640 cm^{-1} due to the carbonyl stretching vibration, and the ^{1}H NMR spectrum shows all the expected resonances, including broad triplets at δ 7.43 and 1.59, assigned to the protons of the amide and thiol groups, respectively.

The IR spectra of **1**–**6** exhibit strong bands in the 970–980 cm^{-1} range assigned to the ν(Re=O) stretching vibrations. The values found compare well with the frequencies found for the same stretching vibration in other compounds of the 3 + 1 type (930–980 cm^{-1}).[8–17] In all the spectra, there are also two strong absorption bands, typical of the phenylphosphine moiety, which appear at 750 and 690 cm^{-1}.[21] Another common feature of all IR spectra is the presence of very strong bands in the range 1590–1610 cm^{-1}, which are due to the carbonyl stretching vibrations. Relative to the corresponding free ligands, the values found for ν(C=O) in **1**–**6** are lower in energy (by *ca.* 10–30 cm^{-1}), confirming the coordination of the tridentate dianionic chelate. The lowering in energy compares well with the values found for the complexes [Re(O)(κ^3-**PNO**)(κ^2-**PNO**)]Cl (1580 cm^{-1}) and [Re(O)(κ^3-**PNO**)(κ^2-DPPBA)] [1580 cm^{-1}; DPPBA = 2-(diphenylphosphanyl)benzoic acid], which present heterofunctionalized phosphane ligands of the same type.[19] For complexes **4**, **5** and **6** the IR spectra also present very strong bands

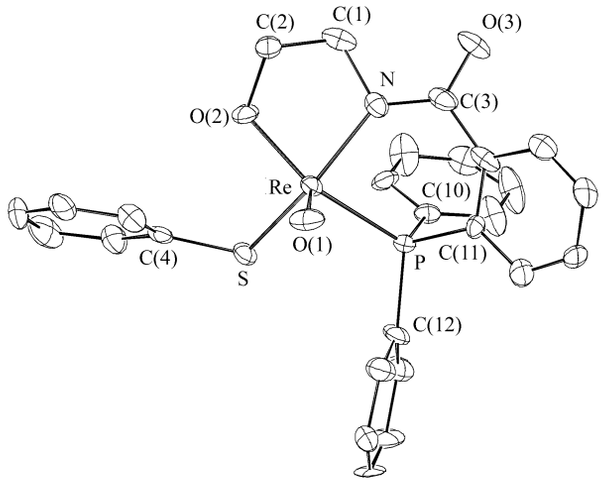


Fig. 1 ORTEP drawing of complex **1** with atom numbering scheme. The thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

at 1700, 1650 and 1640 cm^{-1} due to the carbonyl function of the monodentate thiolates.

The ^{31}P NMR spectra of compounds **1**–**6** all show one singlet, which appears in the range 15.9–20.3 ppm. These resonances are due to the tridentate H_2PNX ligands and are low-field shifted relative to the value found for the corresponding free ligands.

This indicates clearly that the phosphorus is deshielded, and confirms the strongly acidic character of the $[ReO]^{3+}$ moiety. For compound **5**, the resonance of the phosphorus atom of the chelate ligand appears specifically at 19.7 ppm, but a second resonance is observed in this ^{31}P NMR spectrum at −8.4 ppm, which is due to the phosphorus atom of the heterofunctionalized κ^1-coordinated phosphine. The small low field shift of this resonance, relative to the free ligand ($\Delta = 0.9$ ppm) confirms that the P atom of this monodentate ligand is not involved in the coordination of the metal.

In the ^1H NMR spectra of **1**–**6** several sets of multiplet appear, attributed to the protons of the aromatic rings, most of them low-field shifted relative to the resonances of the free ligand. The only important feature of note is that the methylenic protons of the chelate ligands become diastereotopic because of the asymmetry introduced in the molecule by the oxo group (*exo* and *endo* positions) and by some steric constraints, which place these protons in different magnetic environments.

Crystals suitable for X-ray structural analysis were obtained for complexes **1** and **2**. ORTEP drawings are shown in Fig. 1 and 2. Selected bond distances and angles for both complexes are presented in Table 1

In both compounds, the coordination geometry is best described as distorted square pyramidal (C_{4v}), with the axial Re–O(1) bond distance significantly shorter than the Re–L (basal) distances. The O(1)–Re–L(basal) angles average 109(1)° for both compounds, compared with the value of 102° for the regular C_{4v}. From the pattern of these angles, it can be seen that those involving the atoms in the chelate ligand are greater than the other two angles, which may be due to the presence of the chelate ligand which introduces significant distortion from the idealized polyhedron. The Re atom lies 0.69 and 0.74 Å out of the basal plane in **1** and **2**, respectively. The values of the main shape parameters for the normalized polyhedron,[22] namely the dihedral angles of the diagonals of the basal face [S(1)–N(1), $\delta_{e3} = 3.0°$ for **1** and 1.3° for **2**], and the dihedral angles referred to the edges O(1)–N(1) and O(1)–S(1) (δ_{e1}, $\delta_{e2} = 72.8$, 99.0° and 75.5, 80.0° for **1** and **2**, respectively) compared with the values (0 and 75.7, 75.7°) for the "idealized" dihedral angles for C_{4v}, show a clear distortion for both compounds, being greater for

Table 1 Selected bond lengths (Å) and angles (°) for [Re(O)(κ^3-PNO)(SPh)] (**1**), and [Re(O)(κ^3-PNS)(SPh)] (**2**) (X = O, **1**; S, **2**)

	1	**2**
Re–O(1)	1.638(12)	1.639(11)
Re–X(2)	1.940(12)	2.273(5)
Re–N	2.051(14)	2.070(12)
Re–S(1)	2.296(4)	2.305(4)
Re–P	2.387(4)	2.410(4)
O(1)–Re–X(2)	112.0(6)	110.7(4)
O(1)–Re–N	113.2(6)	110.8(5)
O(1)–Re–S(1)	105.4(5)	107.6(4)
O(1)–Re–P	104.0(5)	106.7(4)
N–Re–X(2)	81.1(6)	83.2(4)
S(1)–Re–X(2)	88.1(4)	89.5(2)
P–Re–X(2)	143.9(4)	142.5(2)
N–Re–S(1)	141.2(4)	141.0(4)
N–Re–P	82.3(4)	81.5(4)
S(1)–Re–P	85.1(4)	81.5(2)
Re–S(1)–C(4)	112.1(6)	113.4(6)

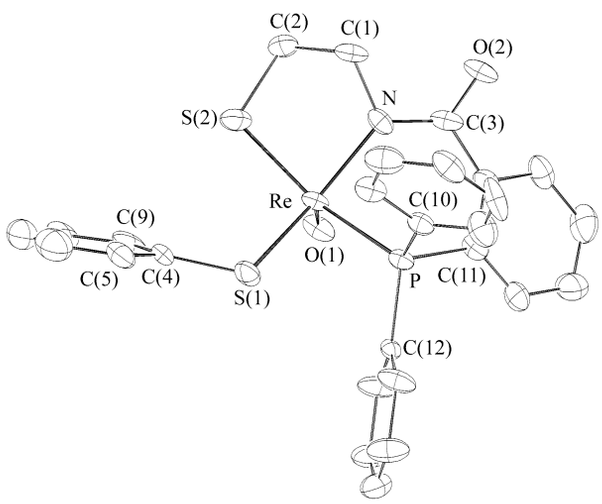


Fig. 2 ORTEP drawing of complex **2** with atom numbering scheme. The thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

compound **1**. In terms of trigonality index, τ,[23] the values are 0.045 and 0.025 for **1** and **2**, respectively ($\tau = 0$ for a regular square pyramid, $\tau = 1$ for a regular trigonal bipyramid).

The five-membered ring in **1**, formed by the atoms Re, O(2), C(2), C(1) and N are in the twisted form, with C(2) and C(1) 0.51 and −0.12 Å above and below the plane defined by the atoms Re, O(2) and N. The five-membered ring in **2**, formed by the atoms Re, N(1), C(2), C(1) and S(2) adopt the envelope conformation, where C(1) lies 0.63 Å out of the plane defined by the remaining four atoms. The six-membered rings are, as usual, non-planar in both compounds. The disparity between the traditional chair or boat conformation with the irregular conformations found here is very great and so no description for the conformations will be attempted.

The Re=O(1) bond lengths in **1** [1.638(12) Å] and **2** [1.639(11) Å] are comparable but are slightly shorter than the values normally found in this type of 3 + 1 compound, which normally are in the range 1.67–1.70 Å.[8–17] This difference is certainly related to the different donor atoms sets of our chelate, namely, the presence of the phosphorus atom. The Re–S(1) bond distances in **1** [2.296(4) Å] and **2** [2.305(4) Å] are comparable and typical of a monothiolate. The Re–S(2) bond distance in **2** compares with the values found for the same type of bond in complexes of the 3 + 1 type, stabilized by SSS or SNS chelates. The Re–P bond distances in **1** [2.387(4) Å] and **2** [2.410(4) Å] are comparable to the value of 2.397(2) Å found in a complex of the same family [ReO(κ^3-PN_2)(OMe)Cl].[19] The Re–N bond

distances in **1** [2.051(14) Å] and **2** [2.070(12) Å] are within the expected range when amide groups are involved.

Concluding remarks

The complexes of general formula [Re(O)(κ³-**PNX**)(SR)] (X = O, S) (**1**–**6**) are the first examples of 3 + 1 compounds stabilized by chelates with **PNO** and **PNS** donor atom sets. The X-ray structural analysis for two examples of this series confirms a coordination number of 5 for the metal and indicates a distorted square pyramidal coordination geometry. The synthesis and characterization of [Re(O)(κ³-**PNS**)(κ¹-H**PNS**)] (**5**) shows two different coordination modes for the H_2**PNS** chelate, which are different from what has been previously observed for the H_2**PNO** chelate (κ³/κ²-coordination mode). Studies involving these neutral and liphophilic compounds at the n.c.a. level are in progress.

Experimental

General

All chemicals were of reagent grade and used without further purification. 2-(Diphenylphosphanyl)-*N*-(2-hydroxyethyl)benzamide (H_2**PNO**), *N*-[2-(diphenylphosphanyl)benzoyloxy]-succinimide, 4-(3-aminopropyl)-1-(2-methoxyphenyl)piperazine, *S*-(triphenylmethyl)-2-aminoethanethiol and succinimido-3-[(triphenylmethyl)thio]propionate were prepared according to literature methods.[5,18,24,25] [^{n}Bu$_4$N][Re(O)Cl$_4$] and [Re(O)Cl$_3$(PPh$_3$)] were prepared as reported in the literature.[26,27] Reactions were carried out in air, unless otherwise indicated. ^{1}H and ^{31}P NMR spectra were recorded on a Varian Unity 300 MHz spectrometer; ^{1}H chemical shifts were referenced relative to tetramethylsilane and the ^{31}P chemical shifts to external 85% H_3PO_4 solution. Chemical shifts are given in ppm. The NMR samples were prepared in $CDCl_3$. Infrared spectra were recorded in the range 4000–200 cm^{-1} on a Perkin-Elmer 577 spectrometer from KBr pellets. Elemental analyses were performed on a Perkin-Elmer automatic analyser.

2-(Diphenylphosphanyl)-*N*-(2-thioethyl)benzamide (H_2PNS)

N-[2-(diphenylphosphanyl)benzoyloxy]succinimide (1.00 g, 2.48 mmol) dissolved in dichloromethane (10 mL) was added dropwise to a solution of *S*-(triphenylmethyl)-2-aminoethanethiol (1.66 g, 5.19 mmol) in the same solvent (10 mL). After 24 h at room temperature, under stirring, the solution was evaporated to dryness. The resulting viscous oil was chromatographed on a silica gel column with 15–30% ethyl acetate–dichloromethane (gradient) to afford a white solid (1.21 g, 80%), *N*-2-[*S*-(triphenylmethyl)thioethyl]-2-(diphenylphosphanyl)benzamide. This product was used in the next step without further purification. IR (cm^{-1}, KBr): 1630 (C=O), 740, 700. ^{1}H NMR (δ, $CDCl_3$): 7.85 (m, 1H, arom.), 7.60–7.17 (m, 28H, arom.), 7.08 (b t, 1H, NH), 3.06 (q, 2H, CH_2), 2.39 (t, 2H, CH_2); ^{31}P NMR (δ, $CDCl_3$) −8.4.

Deprotection of the thiol group was carried out as described in the literature.[25] A colorless viscous oil was obtained, yielding a white solid after washing with hexane (0.63 g, 86%). The product was used without further purification. IR (cm^{-1}, KBr): 2540, 1620 (C=O), 1540, 740, 690. ^{1}H NMR (δ, $CDCl_3$) 7.66 (m, 1H, arom.), 7.42–7.25 (m, 12H, arom.), 6.97 (m, 1H, arom.) 6.58 (b t, 1H, NH), 3.44 (m, 2H, CH_2), 2.52 (m, 2H, CH_2), 1.36 (m, 1H, SH); ^{31}P NMR (δ, $CDCl_3$) −9.4. Anal. calc for $C_{21}H_{20}NOPS$: C, 69.02; H, 5.52; N, 3.83; S, 8.77; found: C, 68.56; H, 4.84; N, 3.76; S, 8.73%.

N-[4-(3-Aminopropyl)-1-(2-methoxyphenyl)]piperazine]-*N*-[(3-thio)propiamide] (HSPipOMe)

To a stirred solution of 4-(3-aminopropyl)-1-(methoxy-phenyl)-piperazine (0.34 g, 1.36 mmol) in dichloromethane (8 mL), succinimido 3-[(triphenylmethyl)thio]propionate (0.61 g, 1.36 mmol) dissolved in the same solvent (5 mL) was added at room temperature under an inert atmosphere. After 20 h, a dilute solution of HCl was added to the reaction and the aqueous phase was extracted three times with dichloromethane. The organic phases were collected, washed with water, dried over $MgSO_4$, filtered, and the solvent evaporated. A highly viscous oil, which gave a white solid on standing under vacuum was obtained (0.72 g, 91%). This product, *N*-[4-(3-aminopropyl)-1-(2-methoxyphenyl)piperazine]-*N*-{[3-(triphenylmethyl)thio]-propiamide}, was used in the next step without further purification. IR (cm^{-1}, KBr): 1640 (C=O), 1490, 1240, 740, 700. ^{1}H NMR (δ, $CDCl_3$): 7.39–7.14 (15H, arom.), 7.01–6.83 (m, 4 + 1H, arom. + NH), 3.84 (s, 3H, OCH_3), 3.30 (q, 2H, CH_2), 3.07 (br s, 4H, CH_2), 2.67 (br s, 4H, CH_2), 2.55 (m, 2H, CH_2), 2.48 (t, 2H, CH_2), 2.06 (t, 2H, CH_2), 1.70 (m, 2H, CH_2).

Deprotection of the thiol group was carried out as described in the literature.[25] A colorless viscous oil, which gave a white solid on standing was obtained (0.33 g, 79%). The product was used in the preparation of **6** without further purification. IR (cm^{-1}, KBr) 1640 (C=O), 1490, 1240, 750, 700. ^{1}H NMR (δ, $CDCl_3$): 7.43 (br t, 1H, NH), 7.04–6.84 (m, 4H, arom.), 3.85 (s, 3H, OCH_3), 3.39 (q, 2H, CH_2), 3.16 (br s, 4H, CH_2), 2.79 (m, 6H, CH_2), 2.64 (t, 2H, CH_2), 2.45 (t, 2H, CH_2), 1.78 (t, 2H, CH_2), 1.59 (t 1H, SH).

General procedure for the preparation of complexes 1–4

A solution of H_2**PNX** (X = O, S), triethylamine and the corresponding monothiol in dichloromethane was added dropwise, at room temperature, to a stirred solution of [^{n}Bu$_4$N][Re(O)Cl$_4$] in dichloromethane. The mixture was allowed to react at room temperature under a nitrogen atmosphere (**1**, 3 h; **2**, 6 h; **3**, 18 h, **4**, 18 h), and the solvent evaporated.

[Re(O)(κ³-PNO)(κ¹-SPh)] 1

Using 0.117 g (0.20 mmol) of [^{n}Bu$_4$N][Re(O)Cl$_4$], 0.070 g (0.20 mmol) of H_2**PNO**, 0.110 mL (0.80 mmol) of triethylamine and 0.021 mL (0.20 mmol) of thiophenol in 10 mL of dichloromethane, a dark brown residue was obtained. This residue was chromatographed on a silica gel column with 20% ethyl acetate–dichloromethane to afford a brown solid that was formulated as **1** (0.090 g, 70% yield). Brown–yellow crystals of **1**, suitable for X-ray diffraction analysis, were obtained by slow diffusion of hexane into a solution of the complex in dichloromethane. IR (cm^{-1}, KBr): 1590 (C=O), 980 (Re=O), 750, 690. ^{1}H NMR (δ, $CDCl_3$): 8.25 (m, 1H, arom.), 7.73–6.99 (m, 17H, arom), 6.78 (m, 1H, arom.), 4.51 (m, 1H, CH, tridentate ligand), 4.20 (m, 1H, CH of tridentate ligand) 4.02 (m, 1H, CH of tridentate ligand), 2.65 (m, 1H, CH of tridentate ligand); ^{31}P NMR (δ, $CDCl_3$): 15.9. Anal. calc for $C_{27}H_{23}NO_3PSRe\cdot H_2O$: C, 47.85; H, 3.72; N, 2.07; S 4.72; found: C, 47.77; H, 3.81; N, 1.97; S, 4.27%.

[Re(O)(κ³-PNS)(κ¹-SPh)] 2

Using H_2**PNS** (0.062 g, 0.17 mmol), triethylamine (0.094 mL, 0.68 mmol) and thiophenol (0.018 mL, 0.17 mmol) in dry dichloromethane (4 mL) and a solution of [^{n}Bu$_4$N][Re(O)Cl$_4$] (0.100 g, 0.17 mmol) in dichloromethane (5 mL), a dark brown oily residue was obtained, after evaporation of the solvent. After column chromatography (silica gel, 5% ethyl acetate–dichloromethane) a deep brown solid was obtained and formulated as **2** (0.070 g, 59%). Brown–orange crystals of **2** were obtained by layering a solution of the complex in dichloromethane with hexane. IR (cm^{-1}, KBr): 1600 (C=O), 980 (Re=O), 740, 700. ^{1}H NMR (δ, $CDCl_3$): 8.14 (m, 1H, arom.), 7.73–7.08 (m, 17H, arom), 6.83 (m, 1H, arom.), 5.07 (m, 1H, CH tridentate ligand), 2.79 (m, 1H, CH of tridentate ligand) 2.65 (m,

Table 2 Crystallographic data for complexes **1** and **2**

	1	**2**
Formula	$C_{27}H_{23}NO_3PSRe$	$C_{27}H_{23}NO_2PS_2Re{\cdot}0.5C_6H_{14}$
MW	658.69	717.84
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$
a/Å	9.2050(8)	9.4660(9)
b/Å	11.9708(10)	11.9835(10)
c/Å	24.627(3)	24.510(3)
β/°	94.989(10)	97.612(9)
V/Å^3	2703.4(5)	2755.8(5)
Z	4	4
d_{calc}/g cm^{-3}	1.618	1.730
μ/mm^{-1}	4.658	4.648
Measured reflections	6225	6392
Independent reflections [R(int)]	5857(0.1185)	6026(0.0686)
Observed reflections [$I > 2\sigma(I)$]	2987	3258
R_1[a]	0.0798	0.0844
wR_2[a]	0.1547	0.1402

[a] The values were calculated for data with [$I > 2\sigma(I)$].

1H, CH of tridentate ligand), 2.22 (m, 1H, CH of tridentate ligand); ^{31}P NMR (δ, $CDCl_3$): 19.6. Anal. calc for $C_{27}H_{23}NO_2PS_2Re{\cdot}H_2O$: C, 46.75; H, 3.64; N, 2.02; S 9.23; found: C, 46.11; H, 3.57; N, 1.96; S, 9.53%.

[Re(O)(κ^3-PNS)(κ^1-SPhNH$_2$)] 3

A solution of H_2**PNS** (0.062 g, 0.17 mmol), triethylamine (0.094 mL, 0.68 mmol) and *p*-aminothiophenol (0.021 g, 0.17 mmol) in dry dichloromethane (4 mL) was added dropwise to a stirred solution of [^{n}Bu$_4$N][Re(O)Cl$_4$] (0.100 g, 0.17 mmol). After reaction, the solvent was evaporated yielding a brown–orange oily residue. After chromatography (silica gel column, 20% ethyl acetate–dichloromethane) an orange–brown solid (**3**) was obtained (0.065 g, 55%). IR (cm^{-1}, KBr): 1590 (C=O), 980 (Re=O), 750, 690. ^{1}H NMR (δ, $CDCl_3$): 8.13 (m, 1H, arom.), 7.72–7.21 (12H, arom), 6.81 (m, 1H, arom.), 6.71 (m, 2H) 6.57 (m, 2H, arom), 5.06 (m, 1H, CH tridentate ligand), 2.80 (m, 1H, CH of tridentate ligand) 2.64 (m, 1H, CH of tridentate ligand), 2.22 (m, 1H, CH of tridentate ligand); ^{31}P NMR (δ, $CDCl_3$): 20.3. Anal. calc for $C_{27}H_{24}N_2O_2PS_2Re$: C, 47.01; H, 3.51; N, 4.06; S, 9.30; found: C, 46.78; H, 3.77; N, 4.02; S, 9.94%.

[Re(O)(κ^3-PNS)(κ^1-SCH$_2$CH$_2$COOH)] 4

A solution of H_2**PNS** (0.031 g, 0.085 mmol), triethylamine (0.012 mL, 0.085 mmol) and 3-mercaptopropionic acid (0.08 ml, 0.085 mmol) in dry dichloromethane (2 mL) reacted with [^{n}Bu$_4$N][Re(O)Cl$_4$] (0.050 g, 0.085 mmol) in dichloromethane (3 mL). After evaporation of the solvent, a brown oily residue was obtained. Addition of methanol to this residue allowed the precipitation of a solid which was further washed with methanol. After drying under vacuum a pale brown solid (**4**) was obtained (0.034 g, 60%). IR (cm^{-1}, KBr): 1700 (C=O), 1610 (C=O), 970 (Re=O), 750, 690. ^{1}H NMR (δ, $CDCl_3$): 8.13 (m, 1H, arom.), 7.68–7.20 (m, 12H, arom), 6.77 (m, 1H, arom.), 5.08 (m, 1H, CH tridentate ligand), 4.04 (m, 1H, CH of tridentate ligand) 3.98 (m, 1H, CH of tridentate ligand), 2.95 (m, 2H, CH_2), 2.76 (m, 2H, CH_2), 2.21 (m, 1H, CH of tridentate ligand); ^{31}P NMR (δ, $CDCl_3$): 19.8. Anal. calc for $C_{24}H_{23}NO_4PS_2Re$: C, 42.92; H, 3.45; N, 2.09; S, 9.53; found: C, 43.59; H, 3.34; N, 2.16; S, 10.10%.

[Re(O)(κ^3-PNS)(κ^1-HPNS)] 5

To a stirred solution of [^{n}Bu$_4$N][Re(O)Cl$_4$] (0.10 g, 0.17 mmol) in dry dichloromethane (5 mL), was added a solution of the same solvent (3 mL) containing H_2**PNS** (0.12 g, 0.33 mmol) and triethylamine (0.19 mL, 1.36 mmol). The mixture was allowed to react for 6 h at room temperature under a nitrogen atmosphere, after which the solution was dark brown. The solvent was evaporated and the residue obtained was purified by chromatograpy, using a silica gel column and a mixture of 5–10% ethyl acetate–dichloromethane (gradient). The light brown oil, yielded solid **5**, after washing with hexane (0.92 g, 59%). IR (cm^{-1}, KBr): 1650 (C=O), 1590 (C=O), 980 (Re=O), 740, 690. ^{1}H NMR (δ, $CDCl_3$): 8.13 (m, 1H, arom.), 7.70–7.19 (m, 26H, arom), 7.05 (br t, 1H, NH), 6.79 (m, 1H, arom.), 5.09 (m, 1H, CH tridentate ligand), 4.06 (m, 1H, CH), 3.81 (m, 1H, CH), 3.70 (m, 2H, CH_2), 2.96 (m, 1H, CH), 2.69 (m, 1H, CH) 2.20 (m, 1H, CH); ^{31}P NMR (δ, $CDCl_3$): 19.5 and −8.5. Anal. calc for $C_{42}H_{37}N_2O_3P_2S_2Re{\cdot}2H_2O$: C, 52.22; H, 4.28; N, 2.90; S, 6.64; found: C, 52.40; H, 4.21; N, 2.84; S, 7.29%.

[Re(O)(κ^3-PNS)(κ^1-SPipOMe)] 6

To a stirred suspension of [$Re(O)Cl_3(PPh_3)_2$] (0.42 g, 0.50 mmol) in a 0.15 M methanolic solution of sodium acetate (9 mL), a mixture of H_2**PNS** (0.18 g, 0.50 mmol) and HS**Pip**OMe (0.17 g, 0.50 mmol) in the same solution (5 mL) was added. The suspension was stirred and refluxed for 60 min, after which, a dark brown solution was obtained. After cooling to room temperature, the reaction mixture was diluted with dichloromethane and a 0.01 M HCl solution. The aqueous phase was then extracted three times with dichloromethane and the organic phases collected. After drying over magnesium sulfate, the solution was filtered and the solvent evaporated. The dark brown residue obtained was washed three times with diethyl ether and chromatographed on a silica gel column with 5% methanol–chloroform to afford a brown solid **6** (0.116 g, 26%). IR (cm^{-1}, KBr): 1640 (C=O), 1590 (C=O), 970 (Re=O), 750, 690. 1H NMR (δ, $CDCl_3$): 8.13 (m, 1H, arom.), 7.69–7.18 (m, 12H, arom), 7.02–6.73 (m, 4H, arom. + NH), 6.77 (m, 1H, arom.), 5.05 (m, 1H, CH of tridentate ligand) 4.07 (m, 2H, SCH_2), 3.83 (s, 3H, OCH_3), 3.35 (m, 2H, CH_2 of propyl), 3.16 (br s, 4H, CH_2 of piperazine), 4.38 (m, 1H, CH of tridentate ligand), 2.81–2.58 (m, 9H, SCH_2CH_2CO of ethyl, CH_2 of piperazine, CH of tridentate ligand), 2.16 (m, 1H, CH of tridentate ligand); ^{3}1P NMR (δ, $CDCl_3$): 19.9. Anal. calc for $C_{38}H_{44}N_4O_4PS_2Re$: C, 50.60; H, 4.92; N, 6.21; S, 7.11; found: C, 50.16; H, 4.92; N, 5.25; S, 7.63%.

X-Ray crystallographic analysis

A brown–yellow crystal of **1** and a brown–orange crystal of **2** were fixed inside thin-walled glass capillaries. Data were collected at room temperature on an Enraf-Nonius CAD4 diffractometer with graphite-monochromatized Mo-Kα radiation, using a ω–2θ scan mode. Unit cell dimensions were

obtained by least-squares refinement of the setting angles of 25 reflections with $15.5 < 2\theta < 27.9°$ for **1** and $14.7 < 2\theta < 24.0°$ for **2**. For **1** and **2**, a summary of the crystallographic data is given in Table 2. Data were corrected for Lorentz and polarization effects and for absorption by empirical corrections based on Ψ-scans.[28] The heavy atom positions were located by Patterson methods using SHELXS-86.[29] The remaining atoms were located by sucessive difference Fourier maps and refined by least-squares refinements on F^2 using SHELXL-93.[30] In the residual electron density map of **1**, a set of three peaks were located which were assumed to be a disordered solvent molecule, but to which no chemical identity could be assigned. They were introduced into the refinement as full occupancy carbon atoms. The lattice solvent was then excluded from the formula, from the molecular weight and from the calculation of the density in Table 2. A disordered half-hexane molecule of crystallization was also located in the Fourier difference map of **2**. All the non-hydrogen atoms (except the solvent atoms in **2**) were refined with anisotropic thermal motion parameters and the contributions of the hydrogen atoms were included in calculated positions (except those of the solvent). Atomic scattering factors and anomalous disperson terms were taken from ref. 28. The drawings were made with ORTEPII[31] and all the calculations were performed on a DEC α 3000 computer.

CCDC reference numbers 158068 and 158069.

See http://www.rsc.org/suppdata/dt/b1/b101278i/ for crystallographic data in CIF or other electronic format.

Acknowledgements

J. D. G. C. thanks the FCT for a PRAXIS XXI postdoctoral fellowship. This work is being supported by SAPIENS/QUI/35423/99 and by COST Action B12.

References

1 S. S. Jurisson and J. D. Lydon, *Chem. Rev.*, 1999, **99**, 2205.
2 S. K. Meegalla, K. Plossl, M. P. Kung, D. A. Stevenson, M. Mu, S. Kushner, L. M. Liable-Sands, A. L. Rheingold and H. F. Kung, *J. Med. Chem.*, 1998, **41**, 428.
3 M. P. Kung, D. A. Stevenson, K. Plossl, S. K. Meegalla, A. Beckwith, W. D. Essman, M. Mu, I. Lucki and H. F. Kung, *Eur. J. Nucl. Med.*, 1997, **24**, 372.
4 A. Hoepping, M. Reisgys, P. Brust, S. Seifert, H. Spies, R. Alberto and B. Johannsen, *J. Med. Chem.*, 1998, **41**, 4429.
5 R. Alberto, R. Schibli, A. P. Schubiger, U. Abram, H. J. Pietzsch and B. Johannsen, *J. Am. Chem. Soc.*, 1999, **121**, 6076.
6 A. Hoepping, P. Brust, R. Berger, P. Leibnitz, H. Spies, S. Machill, D. Scheller and B. Johannsen, *Bioorg. Med. Chem.*, 1998, **6**, 1663.
7 S. Meegalla, K. Plossl, M. P. Kung, D. A. Stevenson, L. M. Liable-Sands, A. L. Rheingold and H. F. Kung, *J. Am. Chem. Soc.*, 1995, **117**, 11037.
8 H. Spies, T. Fietz, H. J. Pietsch, B. Johannsen, P. Leibnitz, G. Reck, D. Scheller and K. Klostermann, *J. Chem. Soc., Dalton Trans.*, 1995, 2277.
9 K. P. Maresca, F. J. Femia, G. H. Bonavia, J. W. Babich and J. Zubieta, *Inorg. Chim. Acta*, 2000, **297**, 98.
10 K. P. Maresca, F. J. Femia, G. H. Bonavia, J. W. Babich and J. Zubieta, *Inorg. Chem. Commun.*, 1998, **1**, 209.
11 X. Chen, F. J. Fermia, J. W. Babich and J. Zubieta, *Inorg. Chim. Acta*, 2000, **306**, 113.
12 F. Tisato, F. Refosco, U. Mazzi, G. Bandoli and M. Nicolini, *J. Chem. Soc., Dalton Trans.*, 1987, 1693.
13 M. Friebe, H. Spies, W. Seichter, P. Leibnitz and B. Johannsen, *J. Chem Soc., Dalton Trans.*, 2000, 2471.
14 M. Pelecanou, I. C. Pirmettis, M. S. Papadopoulos, C. P. Raptopoulou, A. Terzis, E. Chiotellis and C. I. Stassinopoulou, *Inorg. Chim. Acta*, 1999, **287**, 142.
15 M. S. Papadopoulos, M. Pelecanou, I. C. Pirmettis, D. M. Spyriounis, C. P. Raptopoulou, A. Terzis, C. I. Stassinopoulou and E. Chiotellis, *Inorg. Chem.*, 1996, **35**, 4478.
16 A. Rey, I. Pirmettis, M. Pelecanou, M. Papadopoulos, C. P. Raptopoulou, L. Mallo, C. I. Stassinopoulou, A. Terzis, E. Chiotellis and A. Léon, *Inorg. Chem.*, 2000, **39**, 4211.
17 (*a*) R. Syhre, S. Seifert, H. Spies, A. Gupta and B. Johannsen, *Eur. J. Nucl. Med.*, 1998, **25**, 793; (*b*) B. Nock, T. Maina, A. Tsortos, M. Pelecanou, C. P. Raptopoulou, M. Papadopoulos, H. J. Pietzsch, C. I. Stassinopoulou, A. Terzis, H. Spies, G. Nounesis and E. Chiotellis, *Inorg. Chem.*, 2000, **39**, 4433.
18 J. D. G. Correia, Â. Domingos and I. Santos, *Eur. J. Inorg. Chem.*, 2000, 1523.
19 J. D. G. Correia, Â. Domingos, A. Paulo and I. Santos, *J. Chem. Soc., Dalton Trans.*, 2000, 2477.
20 C. Fernandes, S. Seifert, H. Spies J. D. G. Correia and I. Santos, manuscript in preparation.
21 K. Nakamoto, *Infrared Spectra of Inorganic and Coordination Compounds*, 2nd edn., Wiley-Interscience, New York, 1970, Ch. 3–9.
22 E. L Muetterties and L. J. Guggenberger, *J. Am. Chem. Soc.*, 1974, **96**, 1748.
23 A. W. Addison and T. N. Rao, *J. Chem. Soc., Dalton Trans.*, 1984, 1349.
24 J. P. O' Neil, S. R. Wilson and J. A. Katzenellenbogen, *Inorg. Chem.*, 1994, **33**, 319.
25 D. Brenner, A. Davison, J. Lister-James and A. G. Jones, *Inorg. Chem.*, 1984, **23**, 3793.
26 R. Alberto, R. Schibli, A. Egli, P. August Schubiger, W. A. Herrmann, G. Artus, U. Abram and T. A. Kaden, *J. Organomet. Chem.*, 1995, **493**, 119.
27 M. S. Ram and J. T. Hupp, *Inorg. Chem.*, 1991, **30**, 130.
28 C. K. Fair, MOLEN, Enraf-Nonius, Delft, The Netherlands, 1990.
29 G. M. Sheldrick, SHELXS-86, Program for the Solution of Crystal Structures, University of Göttingen, Germany, 1986.
30 G. M. Sheldrick, SHELXL-93, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1993.
31 C. K. Johnson, ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.