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New Bioconjugated Rhenium Carbonyls by Transmetalation Reaction with Zinc Derivatives

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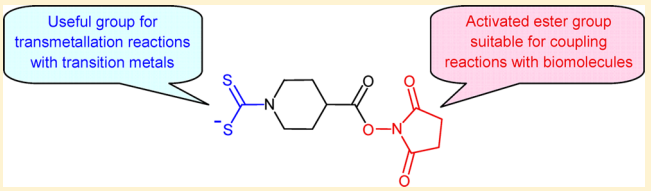
Supporting Information

ABSTRACT: The transmetalation reaction between zinc dithiocarbamates and rhenium carbonyls has been used as a new strategy to link biomolecules to transition metals. The zinc(II) dithiocarbamate of isonipecotic acid (**1**) and the succinimidyl ester derivative (**2**) were prepared by straightforward procedures and were fully characterized by spectroscopic and X-ray diffraction methods, showing in both cases the presence of dinuclear complexes. Complex **2** reacted with all the primary and secondary amines studied (glycine methyl ester, *β*-alanine methyl ester, 1-(2-methoxyphenyl)piperazine, and D-(+)-glucosamine) through the activated succinimidyl ester group, linking the metallic fragment with the biomolecule by the formation of a peptidic bond and leading to the respective bioconjugated zinc complexes **3**−**6**. In all cases, these zinc complexes could be isolated from the reaction medium by simple precipitation. These results evidence the potential of complex **2** to be used as a synthon to link the zinc dithiocarbamate fragment to biomolecules that contain an amine group. Complexes **3**−**6** were characterized by the usual spectroscopic methods, and all data agree with the proposed structures, which do not contain significant interactions between the zinc fragment and the functional groups of these biomolecules. The transmetalation reaction between the zinc complexes **3**−**6** and the rhenium carbonyl $[ReBr_3(CO)_3]^{2-}$ led to the expected rhenium dithiocarbamates **7**−**10** with no change in the organic dithiocarbamate fragments, confirming the viability of this reaction as a tool for linking biomolecules to transition elements. All complexes were characterized by spectroscopic methods, and the crystal structure of **8** was studied by X-ray diffraction analysis. All data demonstrated that the biomolecule is positioned far away from the *fac*-$\{Re(CO)_3\}$ fragment, and the octahedral coordination around the metal is completed by the functionalized dithiocarbamate and a phosphine ligand. Finally, analysis by ESI-MS spectrometry of the reaction between the zinc complex **4** and a water solution of $[Re(H_2O)_3(CO)_3]^+$ at a very low concentration (10 ppm) showed that the transmetalation reaction took place, even though the solubility of the zinc complex in water medium was as low as 0.66 ppm. This preliminary result supports the viability of this approach for the preparation of rhenium and technetium target-specific radiopharmaceuticals, since the preparations of these compounds are always performed in water medium.



INTRODUCTION

Transmetalation is one of the basic reactions in inorganic chemistry that is defined as the exchange of ligands between two metal atoms. It has been used since the beginnings of organometallic chemistry as a practical tool to prepare new compounds, being based on the substitution of a weak carbon−metal bond such as Hg−C by a stronger bond such as Zn−C.[1] Currently, this reaction continues to be extremely useful in the synthesis of new compounds, and one pertinent example is the use of silver N-heterocyclic carbenes (NHCs) for the preparation of transition-metal carbenes.[2]

The use of organometallics in biology and medicine, and particularly the search for organometallic pharmaceuticals, has become a relevant research topic in the last few decades.[3] In this context, the goal of this study is to apply the transmetalation reaction to improve the preparation of organometallic radiopharmaceuticals for nuclear medicine applications. The transmetalation reaction is currently employed in radiopharmacy to produce the organometallic compound (^{99m}Tc)sestamibi.[4] However, in our proposal we use this reaction innovatively for a very different goal.

Molecular imaging methods are useful in medicine because they allow the visualization of biochemical processes in living organisms and can help the diagnosis of some diseases by noninvasive techniques. The labeling of biologically active molecules with a radionuclide is currently a topic of great interest in radiopharmacy, because it can lead to specific tracers with potential new applications in oncology,[5,6] infection

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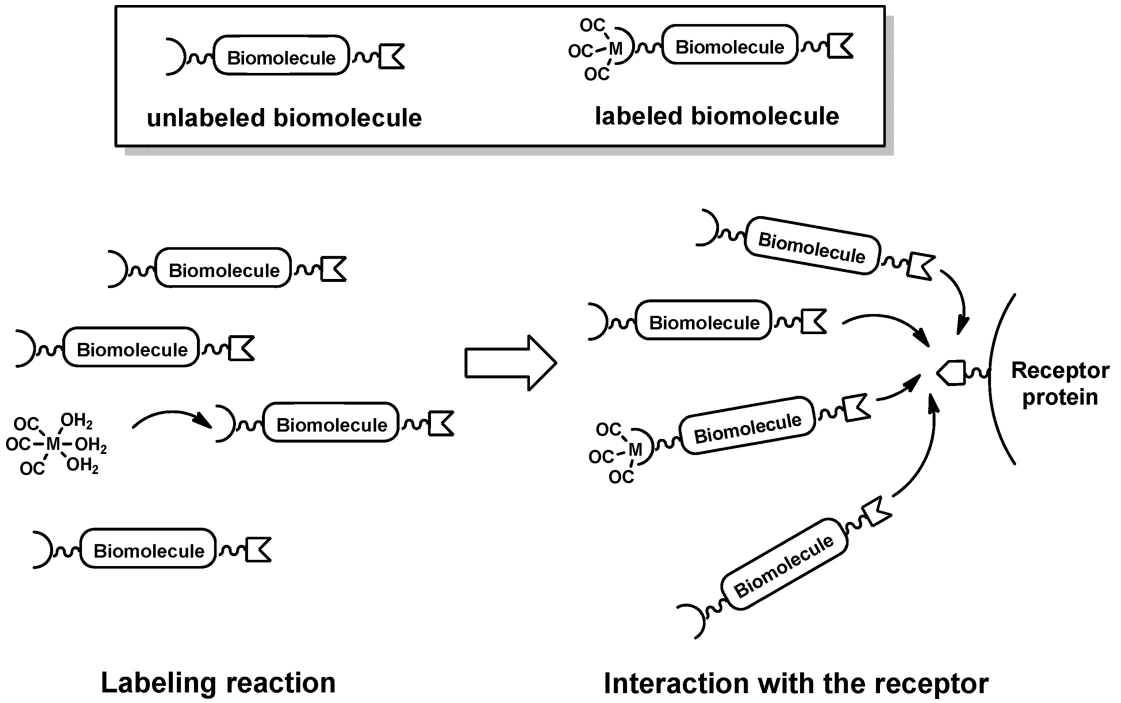
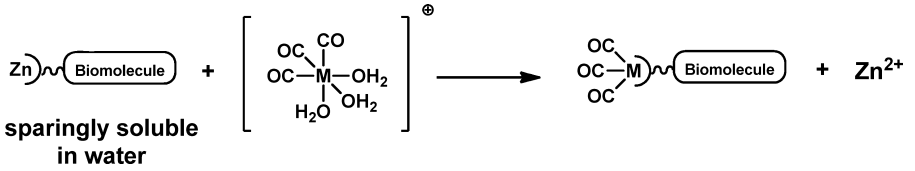
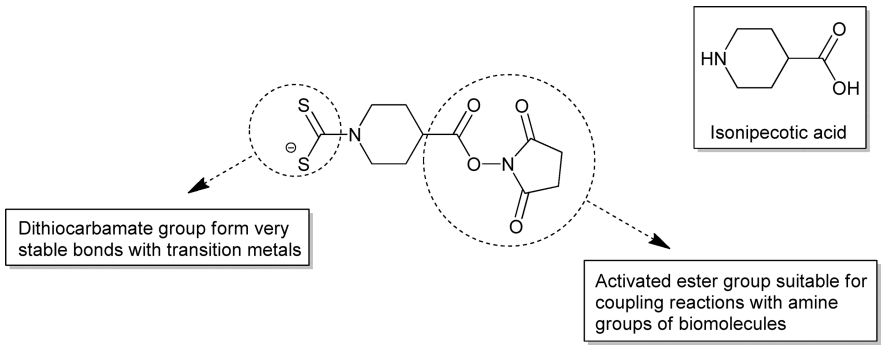


Figure 1. Schematic representation of the competition between labeled and unlabeled molecules for receptor sites after a labeling reaction.

Scheme 1



Scheme 2



imaging,[6] neuroreceptor imaging,[7,8] and other medical specialties. Depending on the emission properties of the radionuclide, either of two imaging methods can be used: positron emission tomography (PET) or single photon emission computed tomography (SPECT). The radionuclide mainly used for SPECT is ^{99m}Tc,[4,8] which gives rise to a wide range of radiopharmaceuticals by simple preparation procedures and is easily accessible by ^{99}Mo/^{99m}Tc generators.

Furthermore, organometallic radiopharmaceutical chemistry has been greatly stimulated in recent years after the development of simple and convenient preparations of the aqua ions *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$ and *fac*-$[^{188}Re(H_2O)_3(CO)_3]^+$. The labile properties of water ligands in these cations permit the straightforward preparation of new rhenium and technetium radiopharmaceuticals with carbonyl ligands, which exhibit small size, high thermodynamic stability, kinetic inertia, and high in vivo stability.[9] All these properties make the *fac*-$\{M(CO)_3\}$ fragment (M = Tc, Re) an excellent synthon for developing new specific tracers with biologically active molecules. Therefore, most of the current research work with this metal carbonyl is oriented toward the development of new bioconjugated compounds.[10] However, there are some difficulties that are inherent to the preparation of specific tracers with ^{99m}Tc carbonyls. A problematic point regarding the preparation of such compounds for radiopharmaceutical application is shown schematically in Figure 1.

Since the concentration of radioactive metal in the labeling reactions is very low (10^{-7}–10^{-8} M), only a very small portion

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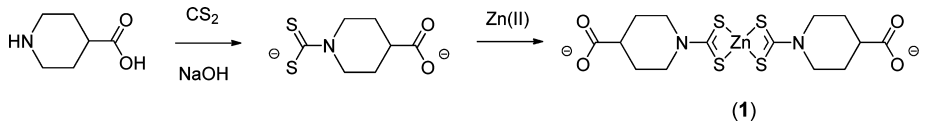
Scheme 3



(1)

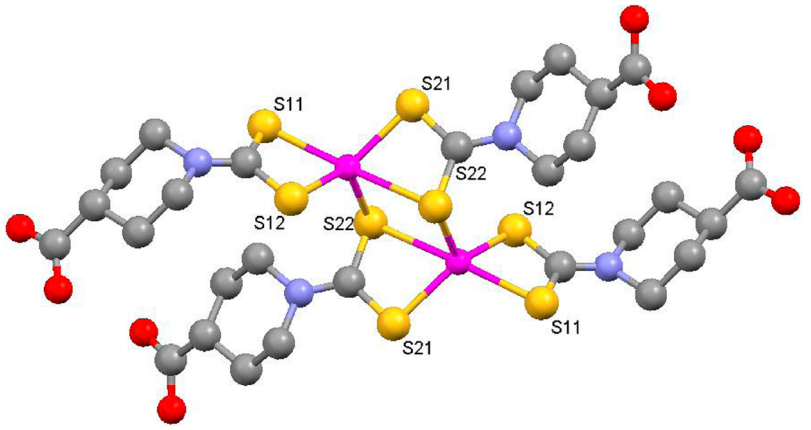


Figure 2. Perspective view of the centrosymmetric dimeric anion $[Zn_2(S_2CNC_5H_9COO)_4]^{4-}$ of complex **1**. Hydrogen atoms have been omitted for clarity.

of functionalized biomolecules are in fact labeled with the metal carbonyl fragment (functionalized biomolecules have the ability to bond to the metal fragment, as is shown in the figure). Consequently, in the radiopharmaceutical preparation the ratio of labeled to unlabeled biomolecules is very low, meaning that the labeled biomolecules must compete with unlabeled biomolecules for the receptor sites.[11] In order to improve the ratio of labeled to unlabeled biomolecules in radiopharmaceutical preparations, we have designed a new approach that allows two apparently contradictory objectives: (1) a high labeling yield (nearly all radioactive metals should be linked to the biomolecule) and (2) a low unlabeled biomolecule concentration in the reaction mixture. This new strategy is based on using a transmetalation reaction between a zinc complex of the functionalized biomolecule which is sparingly soluble in water and the radioactive metal in water solution (Scheme 1).

This reaction is shifted to the right by the higher thermodynamic stability of bonds with the $\{M(CO)_3\}$ fragment (M = Tc, Re) with respect to the zinc atom. Concurrently, the concentration of unlabeled biomolecule in the reaction mixture can be very low because it is limited by the low solubility of the bioconjugate zinc compound in water.

To this purpose, we designed a new compound based on a derivative of isonipecotic acid (Scheme 2) as a key compound in attaining our goal, given its following advantages.

(1) The dithiocarbamate of isonipecotic acid has been reported.[12] It displays an appropriate structure for our purposes because it can lead to very stable, symmetric compounds, since the amine group in isonipecotic acid is a symmetric secondary amine.

(2) Zinc dithiocarbamates are stable compounds[13] that exhibit transmetalation[14] reactions with transition metals. Therefore, a zinc dithiocarbamate with the structure shown in Scheme 2 can be useful for the transmetalation reaction displayed in Scheme 1.

(3) The above structure contains an *N*-hydroxysuccinimidyl ester group suitable for coupling reactions with amines in order to link the metal to a biomolecule.[15] Hence, this dithiocarbamate of isonipecotic acid can act as a bifunctional chelating agent[16] (BFCA) because it can work as a linker between the metal (bonded to the dithiocarbamate function) and the biomolecule (bonded by a peptidic bond).

(4) It is expected that the zinc dithiocarbamate derivative of isonipecotic acid will show low toxicity. Indeed, isonipecotic acid[17] and zinc dithiocarbamates[18] are involved in pharmacological studies and the dithiocarbamate of isonipecotic acid exhibits anti-inflammatory activity.[19]

RESULTS AND DISCUSSION

Zinc(II) Dithiocarbamate of Isonipecotic Acid (1). This compound was prepared by the reaction between a solution of the sodium dithiocarbamate of isonipecotate prepared "in situ" from the amine[12] and a water solution of zinc(II) acetate (Scheme 3). Complex **1** was obtained in high yield (84%) and high purity by simple crystallization from the reaction medium. One interesting aspect is that this compound is scarcely soluble in water and, as was stated in the Introduction, the low solubility of zinc compounds may be useful to improve the labeled/unlabeled ratio in radiopharmaceutical preparation. Thus, the compound was characterized by NMR spectroscopy in D_2O but all spectra were recorded at a temperature of 40 °C in order to improve the solubility of **1**. All spectroscopic data agree with the proposed structure. For instance, the characteristic signals of the dithiocarbamate group observed in the ^{13}C NMR (201.8 ppm) and the IR spectra (1493 cm^{-1}, $\nu(C{=}N)$) are consistent with reported data for bidentate metal dithiocarbamates.[20] The presence of the isonipecotic fragment is evidenced by the ^1H NMR spectrum, in which all observed signals could be assigned to the hydrogen atoms of the heterocycle by means of 2D experiments (COSY, HSQC, and NOESY), and these assignments agree with reported data for isonipecotic acid.[21]

The crystal structure of **1** (Figure 2) shows the formation of the postulated zinc dithiocarbamate but also reveals that it is a

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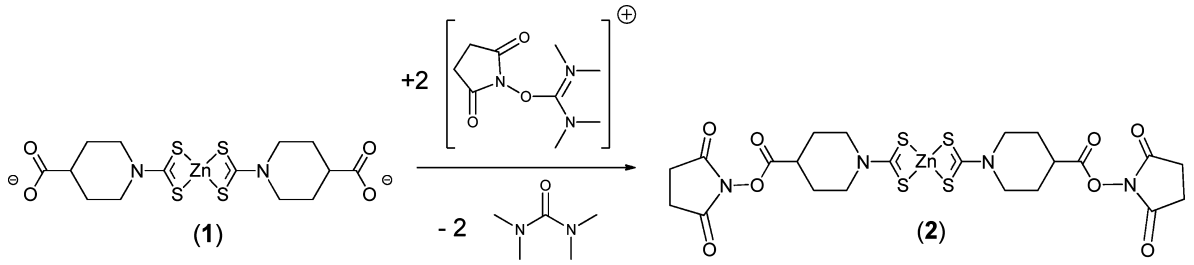
Scheme 4



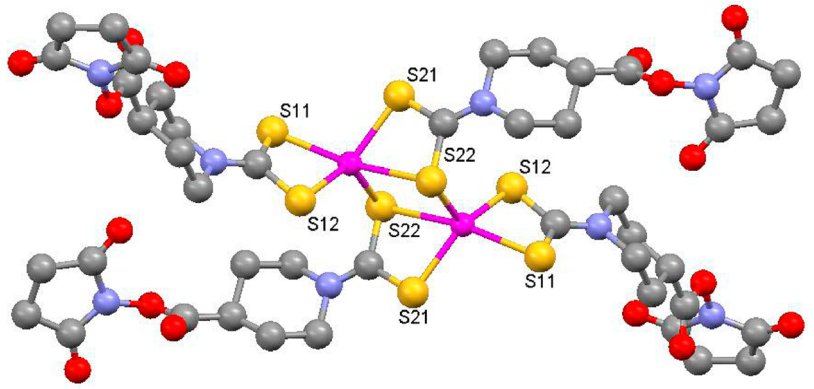
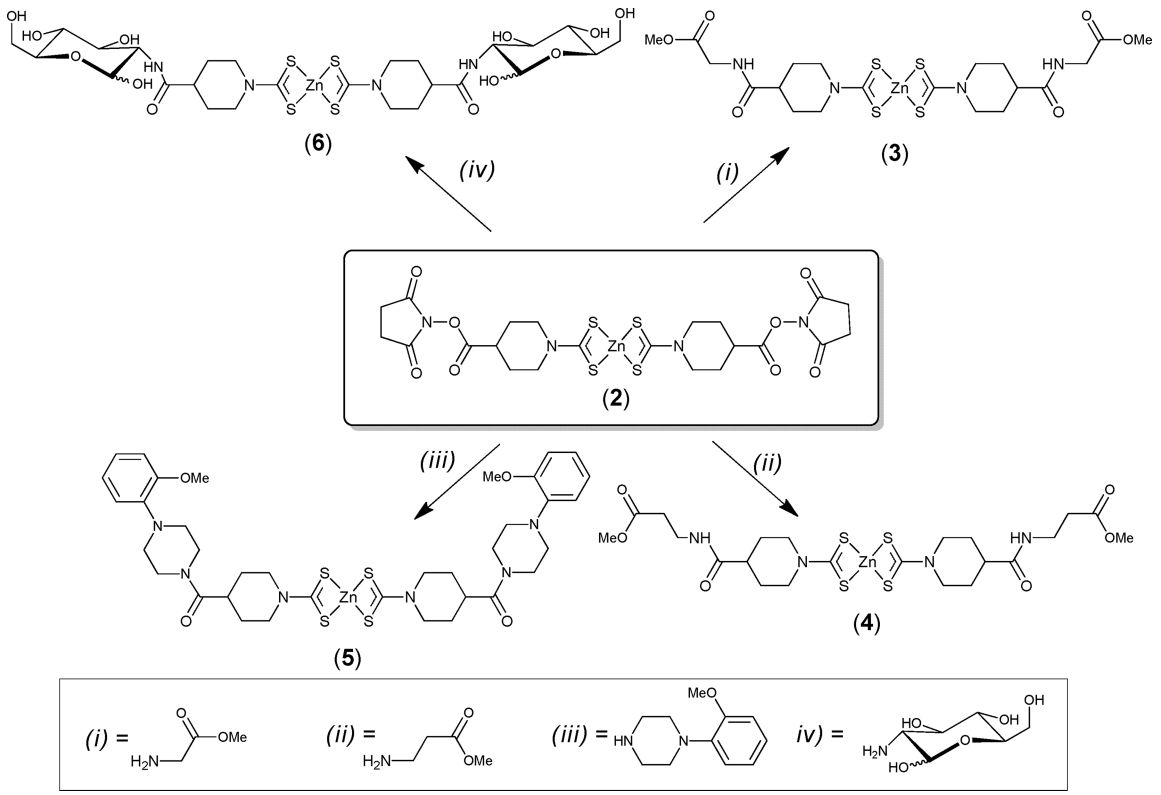


Figure 3. Perspective view of the centrosymmetric dimeric complex **2**. Hydrogen atoms have been omitted for clarity.

Scheme 5



dinuclear centrosymmetric compound in the solid state. This is a common arrangement for zinc dithiocarbamates,[22] although monomeric compounds have also been reported.[23] The analysis of this structure shows that bond distances and angles of the core $\{Zn_2S_8\}$ are very similar to previously reported data for dinuclear zinc dithiocarbamates with simple alkyl groups such as ethyl[24] and isopropyl.[25] The geometry around the zinc atom is intermediate between trigonal bipyramidal and tetragonal pyramidal, with four similar Zn−S distances (Zn−S21 = 2.3433(5) Å, Zn−S12 = 2.3457(6) Å, Zn−S22^{i} = 2.3972(5) Å, Zn−S11 = 2.4780(5) Å; i denotes an equivalent atom by an inversion center), whereas one Zn−S bond is significantly

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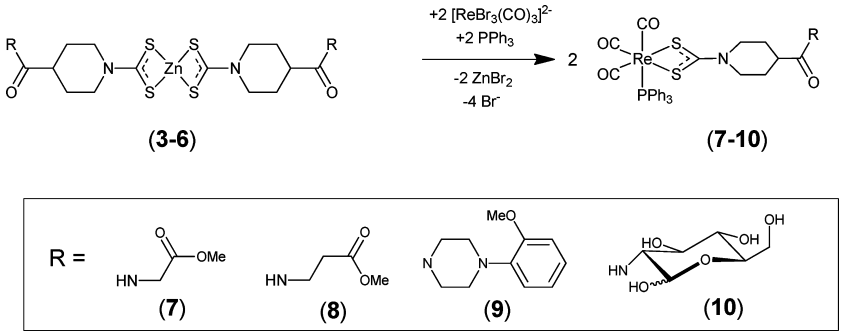
Scheme 6



longer (Zn−S22 = 2.8162(5) Å). Similar values have been reported for zinc diethyldithiocarbamate (2.331, 2.355, 2.383, 2.443, 2.815 Å)[24] and zinc diisopropyldithiocarbamate (2.335, 2.342, 2.377, 2.454, 2.815 Å).[25]

Succinimidyl Ester of Zinc(II) Dithiocarbamate of Isonipecotic Acid (2). Although the preparation of succinimidyl ester derivatives from carboxylic acid is a well-known process, in most synthetic pathways reported the starting reagent is carboxylic acid; this route is not feasible in our case, since dithiocarbamates are not stable in acidic medium. This problem was solved by using the peptide coupling reagent TSTU (*N*,*N*,*N*′,*N*′-tetramethyl-*O*-(*N*-succinimidyl)uronium tetrafluoroborate; CAS 105832-38-0), since it can react directly with the carboxylate group and it avoids working in acid media (Scheme 4). Furthermore, the preparation procedure by this way is very straightforward and convenient because compound **2** can be isolated from the dimethylformamide reaction medium by simple precipitation after addition of an ethanol/water mixture, allowing us to obtain **2** in high yield (above 95%) and purity.

Spectroscopic data of **2** are fully consistent with the proposed structure. Thus, ESI-MS shows a molecular weight increase due to the formation of the succinimidyl ester group and NMR spectroscopy displays all signals of the succinimidyl fragment, as well as the shift of resonances of the isonipecotic fragment atoms closer to the ester group such as the carbonyl carbon and the hydrogen in position 4 of the piperidine ring. Single crystals of **2** could be obtained by recrystallization from acetonitrile. The X-ray diffraction analysis corroborated the proposed structure, represented in Figure 3.

When this structure is compared with that of compound **1**, the strong similarity between the $\{Zn_2S_8\}$ cores in both complexes is obvious. This result evidences that the conversion of the carboxylate group in **1** to the corresponding succinimidyl ester has a minimum influence on the dithiocarbamate group. The coordination around the zinc atoms is analogous in both complexes, with one Zn−S distance being significantly longer than the others (Zn−S distances for **2**: Zn−S21 = 2.369(2) Å, Zn−S12 = 2. 2.364(3) Å, Zn−S22^{i} = 2.371(2) Å, Zn−S11 = 2.413(2) Å, Zn−S22 = 2.753(2) Å; i denotes an equivalent atom by an inversion center).

Bioconjugated Zn(II) Dithiocarbamates (3−6). As stated in the Introduction, complex **2** was designed with activated ester groups with the aim of preparing bioconjugated compounds by means of a coupling reaction with an amine group of a biomolecule. In the first stage, we studied the reaction between **2** and the methyl esters of the amino acids glycine and *β*-alanine as a test for the application of this reaction to the preparation of bioconjugated Zn(II) dithiocarbamates (Scheme 5).

The NMR analysis of the reaction mixture showed that the reaction of **2** with the methyl esters of glycine and *β*-alanine is nearly quantitative after a few hours at room temperature. Thus, complexes **3** and **4** could be isolated from the reaction mixture by the simple addition of an ethanol/water mixture. This very direct procedure gives pure compounds that can be used without recrystallization in subsequent reactions.

Once the viability of this approach was established with the model compounds **3** and **4**, 1-(2-methoxyphenyl)piperazine was chosen as the next reagent to be studied. This amine can be viewed as a small biomolecule, because compounds with an arylpiperazine moiety are useful for binding to 5-HT_{1A}[26] serotonergic receptors in the central nervous system and radiopharmaceuticals with this fragment[27] are highly relevant for the study of neuropsychiatric diseases. Furthermore, since this compound is a piperazine derivative, it is useful for testing if the ability of **2** to react with amines can be extended to secondary amines. Experimental results confirmed this hypothesis, and the functionalized zinc dithiocarbamate **5** was prepared by following a method as simple as that used for the synthesis of the model compounds **3** and **4**; as was noted for those compounds, **5** was also obtained pure in good yield (71%).

The last compound of this family was prepared by reaction between **2** and D-(+)-glucosamine to yield the bioconjugate dithiocarbamate **6**. This reagent was chosen because obtaining ^{99m}Tc-glucose derivatives is a subject of prime interest, due to the notion that these compounds could be a more readily available and less expensive alternative to ^{18}*F*-2-deoxy-2-fluoro-D-glucopyranose (FDG), which is currently employed for tumor imaging.[28] As in previous complexes, **6** was also obtained as a pure compound by a similarly simple procedure with minor differences due to the different solubilities of glucose derivatives.

All synthesized compounds were characterized by the usual spectroscopic and spectrometric techniques. NMR signals corresponding to the isonipecotic fragment were observed in all compounds in positions similar to those found for **2**, the most shifted signal being the resonance in ^{1}H NMR assigned to the hydrogen at position 4 of the piperidine ring, which is consistent with the substitution of the succinimidyl ester located in the same position by the amide group in **3**−**6**. In addition, the expected signals of all amide fragments were observed in ^{1}H and ^{13}C NMR spectroscopy, as well as the molecular ion peak (M + Na^{+}) for the functionalized zinc dithiocarbamates **3**−**6**.

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Rhenium Carbonyl Compounds Prepared by Transmetalation Reactions (7−10). The transmetalation reaction between the functionalized zinc complexes **3**−**6** and rhenium was studied with the carbonyl $[ReBr_3(CO)_3]^{2-}$, as shown in Scheme 6.

This reaction was carried out in methanol, although the solubility of zinc complexes **3**−**6** is very low in this medium. Thus, the fast conversion of suspensions of zinc complexes **3**−**6** in methanol into clear solutions after the addition of rhenium carbonyl is indicative of the driving force of the transmetalation reaction. ^{13}C NMR spectroscopy confirms the nearly quantitative character of this reaction, since NMR analysis of the reaction mixture shows the complete absence of the signal assigned to the carbon atom of a dithiocarbamate group linked to zinc (∼204 ppm) and it displays a downfield-shifted peak (∼210 ppm) assigned to the dithiocarbamate bonded to rhenium.

Carbonyl complexes **7**−**10** were characterized by the usual spectroscopic and spectrometric techniques. The NMR chemical shifts of groups coordinated to rhenium metal are consistent with reported data for other $[Re(CO)_3(SS)(P)]$ complexes,[29] showing the resonances of coordinated phosphine (^{31}P) and the carbon atom of the dithiocarbamate group linked to rhenium. The signals of the characteristic set of *fac*-$\{Re(CO)_3\}$ fragments are displayed in the IR spectra, and the molecular peaks ($M + Na^+$) are observed for complexes **7**−**10** in ESI-MS spectrometry. Spectroscopic data of functional groups linked to dithiocarbamate are similar to those of complexes **3**−**6**, showing that the substitution of zinc metal by rhenium has very little influence on the biomolecular fragment.

The crystal structure of complex **8** confirms the proposed structure for rhenium complexes, showing an arrangement very similar to those previously reported for other $[Re(CO)_3(SS)(P)]$ complexes[29,30] (Figure 4). The coordination around

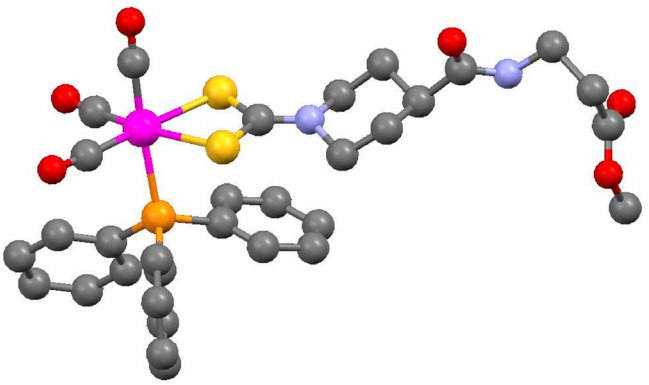

Figure 4. Perspective view of complex **8**. Hydrogen atoms have been omitted for clarity.

rhenium metal can be described as a slightly distorted octahedron, in which the main distortion comes from the chelated dithiocarbamate, which forces the S−Re−S angle to be near 70°.

A remarkable detail of complexes **7**−**10** is that two signals of different intensity and with similar chemical shifts (separated by 0.4−0.6 ppm) are observed in the ^{31}P NMR spectra and an analogous situation is detected for some ^{1}H NMR signals. This phenomenon was not observed in previous studies with other $[Re(CO)_3(SS)(P)]$ complexes, and it suggests the presence of two isomers in solution. The shape of this signal evolves with temperature and shows the coalescence of the two signals at temperatures of nearly 50 °C. This result is consistent with the existence of two isomers differing in the position of the biomolecular fragment linked to the C4 atom of the piperidine ring (axial or equatorial). The position of this group can be interconverted at low temperatures via different mechanisms, such as a rotation around the C−N bond of dithiocarbamate.[31] No separation between the two isomers was possible by HPLC analysis of **7**−**10**, and a single peak was always observed. These results support the hypothesis of a fast conversion between the two isomers that makes their separation unviable.

Although the reaction between the zinc dithiocarbamates **3**−**6** and the rhenium carbonyl $[ReBr_3(CO)_3]^{2-}$ confirms the viability of the transmetalation reaction, to take advantage of this approach in radiopharmacy, the reaction must be feasible in aqueous medium. With the aim of exploring this possibility, the reaction of an aqueous solution of $[Re(H_2O)_3(CO)_3]^+$ at a very low concentration (10 ppm) with the zinc complex **4** was studied as shown in Scheme 7. Complex **4** and triphenylphosphine were successively added as solid compounds to an aqueous solution of $[Re(H_2O)_3(CO)_3]^+$, yielding a suspension that was heated and finally centrifuged. The formation of the rhenium complex **8** was evidenced by the ESI-MS of the clear water solution, which gave a unique signal with the isotopic pattern of rhenium. This peak corresponds to the molecular signal ($M + Na^+$) previously observed for complex **8**. It should be emphasized that this reaction runs in aqueous medium, even though the solubility of the reactants in water is very low (the solubility of the zinc complex **4** was measured by inductively coupled plasma optical emission spectrometry (ICP-OES); it was as low as 0.66 ppm). Consequently, this approach provides a simple method for performing high-yield reactions with a low concentration of the reactants in the reaction medium. The application of this method to radiopharmacy could provide radiopharmaceuticals with a very high ratio of labeled to unlabeled biomolecules (see Figure 1).[32]

CONCLUSIONS

The zinc dithiocarbamate of isonipecotic acid (**1**) and its succinimidyl ester (**2**) are new complexes that have been synthesized using simple preparation procedures which allow obtaining the desired complex in high yield and purity for use in subsequent reactions. The X-ray diffraction analyses of these complexes have shown very similar dinuclear structures for both, confirming that there are no relevant interactions between the succinimidyl fragment and the metal atom in **2**. All these results indicate that compound **2** can be an excellent starting material for the conjugation of biomolecules to zinc. Hence, we established the versatility of complex **2** to act as a synthon for linking the zinc dithiocarbamate fragment to molecules that contain a primary or secondary amine by a coupling reaction with the succinimidyl ester group. This reaction has been performed with glycine, *β*-alanine, 1-(2-methoxyphenyl)piperazine, and D-(+)-glucosamine, yielding the zinc complexes **3**−**6**. The low solubility of these complexes, in conjunction with the high yield of the coupling reaction, permits obtaining pure **3**−**6** by simple addition of an alcohol or alcohol/water mixture to the reaction medium.

The study of the transmetalation reaction between the rhenium carbonyl $[ReBr_3(CO)_3]^{2-}$ and the zinc dithiocarbamates **3**−**6** has led to the rhenium dithiocarbamates **7**−**10**, in accord with the higher stability of complexes with an element of the third transition series with a d^6 configuration with respect to

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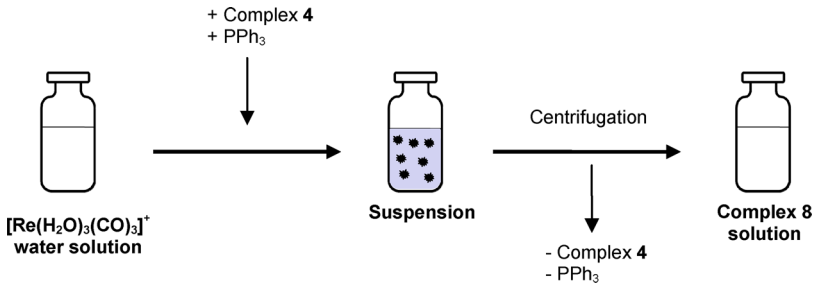
Scheme 7



the zinc (d^{10}). The crystal structure analysis of **8** was solved, showing a coordination set around the rhenium metal similar to that of other $[Re(CO)_3(SS)(P)]$ complexes. The study of the transmetalation between a very dilute solution of $[Re(H_2O)_3(CO)_3]^+$ (10 ppm) and complex **4** has evidenced that this reaction is so favorable that it takes place at very low metal concentration, although the water solubility of the zinc complex **4** is as low as 0.66 ppm. This result highlights the potential application of this approach to the preparation of radiopharmaceuticals, since it can improve the ratio of labeled to unlabeled biomolecules because the concentration of the zinc labeling reagent in the reaction media is limited by its low solubility. If it is true that the radionuclide concentration under labeling conditions is still below the solubility of **4**, it should be noted that complex **4** is just a model compound (β-alanine methyl ester derivative) and it is reasonable to think that zinc complexes bioconjugated to larger biomolecules may show lower solubility.

EXPERIMENTAL SECTION

All reactions were performed under nitrogen using standard Schlenk tube techniques. Infrared spectra were recorded with a Perkin-Elmer 2000 FT spectrometer. The NMR spectra were recorded in the *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona* on Bruker DPX-250, DPX-360, and AV400 instruments. Microanalyses were performed by the *Servei d'Anàlisi Química del Departament de Química de la Universitat Autònoma de Barcelona*. Mass spectra and exact mass measurements were respectively obtained on an Esquire 3000 with electrospray ionization and a Bruker Daltonics ion trap and on a Bruker Apollo microTOFQ with electrospray ionization by the *Servei d'Anàlisi Química del Departament de Química de la Universitat Autònoma de Barcelona*. The zinc concentration in water solutions was measured by inductively coupled plasma optical emission spectrometry (ICP-OES) on a Polyscan 61E (Thermo Jarrell Ash) spectrometer by *Servei d'Anàlisi Química del Departament de Química de la Universitat Autònoma de Barcelona*.

Synthesis of Complex 1. A solution of NaOH (2.8 g, 70 mmol) in water (70 mL) was added to a solution of isonipecotic acid (4.5 g, 35 mmol) in methanol (MeOH, 140 mL), and the resulting solution was cooled to 0 °C. Carbon disulfide (2.45 mL, 40.9 mmol) was slowly added to this cold solution, and the mixture was stirred at this temperature for 1 h. Next, the cooling bath was removed and the mixture was stirred overnight at room temperature. After this time, a solution of zinc acetate (3.8 g, 17.5 mmol) in water (35 mL) was added dropwise with vigorous stirring to the previous mixture for a period of 4 h. The resulting solution was cooled to 4 °C, and colorless crystals precipitated after 12−24 h. This solid was filtered off, washed with MeOH and Et_2O, and dried under vacuum, giving a white powder (8.1 g, 84% yield). IR (KBr, cm^{-1}): 1553 (COO^-), 1493 (CN, S_2CN). ^1H NMR (D_2O, δ in ppm): 4.97 (d, J = 12.9 Hz, 2H, $S_2CNCH_{2,eq}$), 3.32 (dt, J = 12.7 Hz, J = 2.7 Hz, 2H, $S_2CNCH_{2,ax}$), 2.30 (m, 1H, $S_2CNCH_2CH_2CH$), 1.95 (dd, J = 13.7 Hz, J = 3.3 Hz, 2H, $S_2CNCH_2CH_{2,eq}$), 1.65 (dq, J = 13.2 Hz, J = 3.7 Hz, 2H, $S_2CNCH_2CH_{2,ax}$). ^{13}C NMR (D_2O, δ in ppm): 201.8 (S_2CN), 184.1 (COO^-), 52.5 (S_2CNCH_2), 43.8 ($S_2CNCH_2CH_2CH$), 29,4 ($S_2CNCH_2CH_2$). ESI MS (negative mode, m/z): 493 ($M - Na^+$). Anal. Calcd for $C_{14}H_{18}N_2Na_2O_4S_4Zn{\cdot}2H_2O$: C, 30.35; H, 4.00; N, 5.06. Found: C, 30.39; H, 3.91; N, 4.97.

Synthesis of Complex 2. *N,N,N′,N′*-Tetramethyl-*O*-(*N*-succinimidyl)uronium tetrafluoroborate (TSTU; 256 mg, 0.85 mmol) was added to a solution of complex **1** (200 mg, 0.36 mmol) and *N,N*-diisopropylethylamine (DIPEA; 13 μL, 0.07 mmol) in dry dimethylformamide (DMF; 1 mL). The heterogeneous mixture was stirred for 16 h, and then 140 mL of a H_2O/EtOH mixture (1/1, v/v) was added. The crude precipitate was centrifuged and washed with EtOH and Et_2O to give a white solid (239 mg, 99% yield) that can be recrystallized from hot acetonitrile. IR (KBr, cm^{-1}): 1736 (C═O, succinimidyl), 1634 (C═O, ester), 1493 (C−N, S_2CN). ^1H NMR (DMSO-d_6, δ in ppm): 4.73 (d, J = 13.4 Hz, 2H, $S_2CNCH_{2,eq}$), 3.53 (t, J = 12.4 Hz, 2H, $S_2CNCH_{2,ax}$), 3.22 (m, 1; H, $S_2CNCH_2CH_2CH$), 2.83 (s, 4H, succinimidyl), 2.10 (m, 2H, $S_2CNCH_2CH_{2,eq}$), 1.70 (m, 2H, $S_2CNCH_2CH_{2,ax}$). ^{13}C NMR (DMSO-d_6, δ in ppm): 203.4 (S_2CN), 170.1 (*C*O, succinimidyl), 169.8 (*C*O, ester), 49.9 (S_2CNCH_2), 36.3 ($S_2CNCH_2CH_2CH$), 27.4 (CH_2, succinimidyl), 25.5 ($S_2CNCH_2CH_2$). ESI MS (positive mode, m/z): 688.9 ($M + Na^+$). Anal. Calcd for $C_{22}H_{26}N_4O_8S_4Zn$: C, 39.55; H, 3.92; N, 8.39. Found: C, 39.82; H, 3.83; N, 8.61.

Synthesis of Complexes 3−5. Complex **2** (1.0 g, 1.5 mmol) was dissolved in dry DMF (10 mL). The appropriate amine (3.8 mmol) and DIPEA (7.5 mmol) was added to the solution, and the reaction mixture was stirred overnight. A mixture of water and EtOH (1/1, v/v) (100 mL) was added, and the crude product was centrifuged and washed with the same mixture to eliminate the excess of the amine and DIPEA. The product was dried under vacuum.

Complex 3. Yield: 678 mg, 74%. IR (KBr, cm^{-1}): 3294 (N−H, amide), 1753 (C═O, amide), 1646 (C═O, ester), 1492 (C−N, S_2CN). ^1H NMR (DMSO-d_6, δ in ppm): 8.4 (t, J = 5.96 Hz, 1H, N*H*), 4.8 (d, J = 12.86 Hz, 2H, $S_2CNCH_{2,eq}$), 3.8 (d, J = 5.96 Hz, 2H, NCH_2CO), 3.62 (s, 3H, OCH_3), 3.31 (m, 2H, $S_2CNCH_{2,ax}$), 2.53 (m, 1H, $S_2CNCH_2CH_2CH$), 1.82 (m, 2H, $S_2CNCH_2CH_{2,eq}$), 1.58 (m, 2H, $S_2CNCH_2CH_{2,ax}$). ^{13}C NMR (DMSO-d_6, δ in ppm): 202.7 (S_2CN), 174.6 (*C*O, amide), 170.6 (NCH_2CO), 51.7 (OCH_3), 50.6 (S_2CNCH_2), 39.9 ($S_2CNCH_2CH_2CH$), 28.2 ($S_2CNCH_2CH_2$). ESI MS (positive mode, m/z): 637.0 ($M + Na^+$). Anal. Calcd for $C_{20}H_{30}N_4O_6S_4Zn$: C, 38.99; H, 4.91; N, 9.09. Found: C, 38.71; H, 4.91; N, 8.92.

Complex 4. Yield: 580 mg, 58%. IR (KBr, cm^{-1}): 3271 (N−H, amide), 1746 (C═O, amide), 1640 (C═O, ester), 1492 (C−N, S_2CN). ^1H NMR (DMSO-d_6, δ in ppm): 8.0 (t, J = 5.41 Hz, 1H, N*H*), 4.8 (d, J = 12.6 Hz, 2H, $S_2CNCH_{2,eq}$), 3.60 (s, 3H, OCH_3), 3.27 (m, 4H, S_2CNCH_{ax}, NCH_2CH_2CO), 2.45 (m, 3H, $S_2CNCH_2CH_2CH$, NCH_2CH_2CO), 1.76 (m, 2H, $S_2CNCH_2CH_{2,eq}$), 1.57 (m, 2H, $S_2CNCH_2CH_{2,ax}$). ^{13}C NMR (DMSO-d_6, δ in ppm): 202.7 (S_2CN), 174.0 (CO, amide), 172.2 ($NHCH_2CH_2CO$), 51.8 (OCH_3), 51.1 (S_2CNCH_2), 40.6 ($S_2CNCH_2CH_2CH$), 35.1 ($NHCH_2CH_2CO$), 34.0 ($NHCH_2CH_2CO$), 28.7 ($S_2CNCH_2CH_2$). ESI MS (positive mode, m/z): 665.1 ($M + Na^+$). Anal. Calcd for $C_{22}H_{34}N_4O_6S_4Zn{\cdot}H_2O$: C, 39.90;; H, 5.48; N, 8.46. Found: C, 39.96; H, 5.37; N, 8.41.

Complex 5. Yield: 870 mg, 71%. IR (KBr, cm^{-1}): 1639 (C═O, amide), 1436 (C−N, S_2CN). ^1H NMR (DMSO-d_6, δ in ppm): 6.96−

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6.89 (m, 4H, ArH), 4.87 (d, J = 12.26 Hz, 2H, $S_2CNCH_{2,eq}$), 3.79 (s, 3H, OCH_3), 3.68 (s, 2 H, piperazine ring), 3.60 (s, 2H, piperazine ring), 3.40 (m, 2H, $S_2CNCH_{2,ax}$), 3.05 (m, 1H, $S_2CNCH_2CH_2CH$), 2.97 (s, 2H, piperazine ring), 2.90 (s, 2H, piperazine ring), 1.80 (m, 2H, $S_2CNCH_2CH_{2,eq}$), 1.59 (m, 2H, $S_2CNCH_2CH_{2,ax}$). ^{13}C NMR (DMSO-d_6, δ in ppm): 202.6 (S_2CN), 172.0 (CO, amide), 152.0–111.9 (ArH), 55.4 (OCH_3), 50.8 (piperazine ring), 50.6 (S_2CNCH_2), 50.2 (piperazine ring), 45.2 (piperazine ring), 41.4 (piperazine ring), 35.6 ($S_2CNCH_2CH_2CH$), 28.3 ($S_2CNCH_2CH_2$). ESI MS (positive mode, m/z): 843.4 (M + Na^+). Anal. Calcd for $C_{36}H_{48}N_6O_4S_4Zn$: C, 52.57; H, 5.88; N, 10.22. Found: C, 52.24; H, 5.82; N, 9.86.

Synthesis of Complex 6. The complex **2** (1.0 g, 1.5 mmol) was dissolved in dry DMF (10 mL). Glucosamine chlorhydrate (3.8 mmol) and DIPEA (3.8 mmol) was added to the solution, which was then stirred for 3 h. Methanol (100 mL) was added, and the crude mixture was centrifuged and washed with the same solvent to eliminate the excess glucosamine and DIPEA. The product was dried under vacuum (550 mg, 44% yield). IR (KBr, cm^{-1}): 3411 (O–H, alcohols), 1644 (C═O, amide), 1492 (C–N, S_2CN). ^{1}H NMR (DMSO-d_6, δ in ppm): 7.69 (d, J = 8.31 Hz, 1H, NH), 7.64 (d, J = 7.65 Hz, 1H, NH), 6.47 (d, J = 6.34 Hz, 1H, NHCHCHO), 6.41 (d, J = 4.28 Hz, 1H, NHCHCHO), 4.90–4.30 (m, 6 H, $S_2CNCH_{2,eq}$, glucosamine ring), 3.60–3.40 (m, 5H, $S_2CNCH_{2,ax}$, glucosamine ring), 3.31–3.00 (m, 2H, glucosamine ring), 2.56 (m, 1H, $S_2CNCH_2CH_2CH$), 1.71 (m, 2H, $S_2CNCH_2CH_{2,eq}$), 1.60 (m, 2H, $S_2CNCH_2CH_{2,ax}$). ^{13}C NMR (DMSO-d_6, δ in ppm, except glucosamine ring resonances): 192.5 (S_2CN), 163.8 (CO, amide), 51.2 (S_2CNCH_2), 40.8 ($S_2CNCH_2CH_2CH$), 28.5 ($S_2CNCH_2CH_2$). ESI MS (positive mode, m/z): 817.2 (M + Na^+); Anal. Calcd for $C_{26}H_{42}N_4O_{12}S_4Zn{\cdot}2H_2O$: C, 37.52; H, 5.57; N, 6.73. Found: C, 37.88; H, 5.42; N, 6.69.

Synthesis of Complexes 7–10. The precursor $[NEt_4]_2[Re(CO)_3Br_3]$ (100 mg, 0.14 mmol) was dissolved in MeOH (10 mL) and added to a suspension of **3**–**6** (0.08 mmol) in the same solvent (30 mL). The mixture was heated to reflux for 1 h. Next, triphenylphosphine (34 mg, 0.14 mmol) was added and the resulting suspension was heated to reflux for an additional 1 h. The clear solution that was obtained was concentrated under vacuum to 5 mL, and the resulting solution was cooled to 4 °C to crystallize the complex. The complex was washed with cold MeOH and Et_2O to give a white solid.

Complex ***7***. Yield: 58 mg, 51%. IR (KBr, cm^{-1}): 2009, 1912, 1905, 1892 (C≡O), 1723 (C═O, amide), 1678 (C═O, ester), 1497 (C–N, S_2CN). ^{1}H NMR ($CDCl_3$, δ in ppm): 7.53–7.28 (m, 15 H, ArH), 5.92 (t, J = 5.07 Hz, 1H, NH), 4.31 (d, J = 13.81 Hz, 2H, $S_2CNCH_{2,eq}$), also observed 4.21 (d, J = 13.81 Hz, 2H, $S_2CNCH_{2,eq}$), 4.05 (d, J = 5.07 Hz, 2H, NCH_2CO), 3.81 (s, 3H, OCH_3), 2.74 (t, J = 11.96 Hz, 2H, $S_2CNCH_{2,ax}$), also observed 2.50 (t, J = 11.96 Hz, 2 H, $S_2CNCH_{2,ax}$), 2.28 (m, 1H, $S_2CNCH_2CH_2CH$), 1.67 (m, 2H, $S_2CNCH_2CH_{2,eq}$), 1.30 (m, 2H, $S_2CNCH_2CH_{2,ax}$). ^{13}C NMR ($CDCl_3$, δ in ppm, except phenyl resonances): 210.1 (S_2CN), 193.2–190.4 (carbonyls), 173.7 (amide), 170.5 (ester), 51.6 (OCH_3), 43.4 ($S_2CNCH_2CH_2CH$), 41.3 ($S_2CNCH_2CH_2CH$), 40.4 (NCH_2CO), 26.6 ($S_2CNCH_2CH_2CH$). ^{31}P NMR ($CDCl_3$, δ in ppm): 14.8, also observed 14.4. ESI MS (positive mode, m/z): 831.0 (M + Na^+); Anal. Calcd for $C_{31}H_{30}N_2O_6PReS_2{\cdot}H_2O$: C, 45.08; H, 3.91; N, 3.39. Found: C, 45.24; H, 4.08; N, 3.53.

Complex ***8***. Yield: 45 mg, 40%. IR (KBr, cm^{-1}): 2009, 1912, 1905, 1892 (C≡O), 1723 (C═O, amide), 1678 (C═O, ester), 1497 (C–N, S_2CN). ^{1}H NMR ($CDCl_3$, δ in ppm): 7.53–7.28 (m, 15 H, ArH), 6.10 (m, 1H, NH), 4.31 (d, J = 13.54 Hz, 2H, $S_2CNCH_{2,eq}$), also observed 4.21 (d, J = 13.54 Hz, 2 H, $S_2CNCH_{2,eq}$), 3.71 (s, 3H, OCH_3), 3.55 (q, J = 5.81 Hz, 2H, NCH_2CH_2CO), 2.70 (t, J = 13.54 Hz, 2H, $S_2CNCH_{2,ax}$), also observed 2.40 (t, J = 13.54 Hz, 2 H, $S_2CNCH_{2,ax}$), 2.56 (q, J = 5.81 Hz, 2H, NCH_2CH_2CO), 2.17 (m, 1H, $S_2CNCH_2CH_2CH$), 1.68 (m, 2H, $S_2CNCH_2CH_{2,eq}$), 1.26 (m, 2H, $S_2CNCH_2CH_{2,ax}$). ^{13}C NMR ($CDCl_3$, δ in ppm, except phenyl resonances): 210.9 (S_2CN), 193.2–190.4 (carbonyls), 174.2 (amide), 44.5 (S_2CNCH_2), 34.9 (OCH_3), 33.8 (NCH_2CH_2CO), 33.7 (NCH_2CH_2CO), 29.8 ($S_2CNCH_2CH_2CH$), 27.6 ($S_2CNCH_2CH_2$). ^{31}P NMR ($CDCl_3$, δ in ppm): 15.3, also observed 14.7. ESI MS (positive mode, m/z): 845.0 (M + Na^+). Anal. Calcd for $C_{32}H_{32}N_2O_6PReS_2$: C, 46.76; H, 3.92; N, 3.41. Found: C, 46.68; H, 4.00; N, 3.34.

Complex ***9***. Yield: 74 mg, 58%. IR (KBr, cm^{-1}): 2009, 1912, 1905, 1892 (C≡O), 1723 (C═O, amide), 1678 (C═O, ester), 1497 (C–N, S_2CN). ^{1}H NMR ($CDCl_3$, δ in ppm): 7.55–6.87 (m, 19H, ArH), 4.31 (d, J = 13.05 Hz, 2H, $S_2CNCH_{2,eq}$), also observed 4.21 (d, J = 13.05 Hz, 2H, $S_2CNCH_{2,eq}$), 3.88 (s, 3H, OCH_3), 3.82 s, 2H, piperazine ring), 3.66 (s, 2H, piperazine ring), 3.10 (s, 4H, piperazine ring), 2.77 (t, J = 11.51 Hz, 2H, $S_2CNCH_{2,ax}$), also observed 2.53 (t, J = 11.51 Hz, 2H, $S_2CNCH_{2,ax}$), 2.66 (m, 1H, $S_2CNCH_2CH_2CH$), 1.65 (m, 2H, $S_2CNCH_2CH_{2,eq}$), 1.44 (m, 2H, $S_2CNCH_2CH_{2,ax}$). ^{13}C NMR ($CDCl_3$, δ in ppm, except phenyl resonances): 211.0 (S_2CN), 193.4–190.3 (carbonyls), 172.2 (amide), 55.6 (OCH_3), 51.4 (piperazine ring), 44.5 (S_2CNCH_2), 37.6 ($S_2CNCH_2CH_2CH$), 27.4 ($S_2CNCH_2CH_2$). ^{31}P NMR ($CDCl_3$, δ in ppm): 15.3, also observed 14.7. ESI MS (positive mode, m/z): 912.0 (M + H^+). Anal. Calcd for $C_{39}H_{39}N_3O_4PReS_2{\cdot}H_2O$: C, 50.42; H, 4.45; N, 4.52. Found: C, 50.55; H, 4.43; N, 4.52.

Complex ***10***. Yield: 88 mg, 70%. IR (KBr, cm^{-1}): 2006, 1915, 1906, 1892 (C≡O), 1722 (C═O, amide), 1498 (C–N, S_2CN) cm^{-1}. ^{1}H NMR (acetone-d_6, δ in ppm): 7.58–7.46 (m, 15H, ArH), 6.89 (d, J = 8.22 Hz, 1H, NH), 6.86 (d, J = 8.22 Hz, 1H, NH), 5.66 (m, 1H, NHCHCHO), 5.62 (m, 1H, NHCHCHO), 5.17 (m, 1H, NHCHCHO), 5.10 (m, 1H, NHCHCHO), 4.31–3.33 (m, 6H, $S_2CNCH_{2,eq}$, glucosamine ring), 2.83 (alcohols), 2.67 (t, J = 11.04 Hz, 2H, $S_2CNCH_{2,ax}$), 2.55 (m, 1H, $S_2CNCH_2CH_2CH$), 1.73 (m, 2H, $S_2CNCH_2CH_{2,eq}$), 1.56 (m, 2H, $S_2CNCH_2CH_{2,ax}$). ^{13}C NMR (acetone-d_6, δ in ppm, except phenyl resonance): 209.8 (S_2CN), 194.2 (CO, amide), 91.4 (NHCHCHO), 76.8 (OCH(OH)CH_2OH), 72.2 (NHCHCH(OH)), (NHCHCH(OH)CH(OH)), 61.8 (CH_2OH), 54.7 (NHCH), 45.4 (S_2CNCH_2), 42.1 ($S_2CNCH_2CH_2CH$), 28.3 ($S_2CNCH_2CH_2$). ^{31}P NMR (acetone-d_6, δ in ppm): 12.0, also observed 11.6. ESI MS (positive mode, m/z): 921.1 (M + Na^+). Anal. Calcd for $C_{34}H_{36}N_2O_9PReS_2{\cdot}2H_2O$: C, 43.72; H, 4.32; N, 3.00. Found: C, 44.02; H, 4.26; N, 3.02.

Synthesis of Complex 8 in Water Medium. A solution of $[Re(H_2O)_3(CO)_3]^+$ (10 ppm) was prepared according to a previously reported method[33] and added to a suspension of **4** (1 mg, 2 μmol) in water (1 mL). The mixture was heated in a boiling water bath for 1 h. Next, triphenylphosphine (1 mg, 4 μmol) was added and heated in a boiling water bath for an additional 1 h. The solution was centrifuged and analyzed by ESI MS. ESI MS (positive ion): 845.0 (M + Na^+).

Determination of Solubility of Compounds 3 and 4 in Water. A suspension in water (10 mL) of the appropriate Zn(II) compound (**3** and **4**; 1 mg) was heated to 40 °C for 1 h. Next, the solution was filtered through a 0.2 μm filter and centrifuged at 13 000 rpm for 20 min. The resulting clear solution was diluted in 1% HNO_3 and the Zn content was analyzed by means of inductively coupled plasma optical emission spectrometry (ICP-OES). Solubility in water: 3.1 ppm for **3** and 0.66 ppm for **4**.

X-ray Crystallography. Data were collected by the *Servei de Difracció de Raigs X de la UAB* using SMART[34] software on a Bruker APEX CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) at 100 K for **2** and at room temperature for **1** and **8**. Data reductions were performed using the SAINT[35] software. Data were corrected for absorption using SADABS.[36] Structures were solved by direct methods using SHELXS-97[37] and refined by full-matrix least squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[37] The C- and N-hydrogen atoms were included from calculated positions and refined riding on their respective carbon or nitrogen atoms with isotropic displacement parameters.

In the crystal structure of complex **1** MeOH/water disorder is present in one site. Fifteen of the eighteen water hydrogen atoms were located in a difference Fourier map. In the crystal structure of complex **2** MeCN is present, the dimer/MeCN ratio being 1/3. One MeCN molecule is disordered about an inversion center. In the crystal structure of complex **8** two molecules with similar conformations are present in the asymmetric unit.

Details of the structure solution and refinement are provided as Supporting Information for complexes **1**, **2**, and **8**.

■ ASSOCIATED CONTENT

Supporting Information

Tables of selected bond distances and angles, tables of crystal data and structure refinement parameters, ellipsoid plots showing atom numbering, and CIF files giving X-ray crystallographic data for structure determinations of compounds **1**, **2**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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