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Synthesis and Structure of Novel Sugar-Substituted Bipyridine Complexes of Rhenium and 99m-Technetium

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Abstract: Novel ligands have been obtained from the reaction of 4,4′-dibromomethyl-2,2′-bipyridine with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthiol, 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosylthiol or 2,3,4,6-tetra-*O*-acetyl-α-D-thioacetylmannopyranoside in which the sugar residues are thioglycosidically linked to the bipyridine in the 4,4′-position. Cleavage of the acetyl groups affords hydrophilic symmetric ligands with free hydroxyl groups. Reaction of the new glycoconjugated ligands (L) with $[Re(CO)_5Cl]$ yields fluorescent complexes of general formula $[Re(L)(CO)_3Cl]$, which were characterised by mass spectrometry, elemental analysis and ^1H and ^{13}C NMR, IR, UV/Vis and fluorescence spectroscopy. These complexes exhibit excellent solubility and stability in organic solvents or water, depending on the residues of the sugar. One complex, namely tricarbonyl-4,4′-bis[(2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl)thiomethyl]-2,2′-bipyridinerheniumtricarbonylo chloride, has been characterised by X-ray crystallography. A non-symmetric structure of the complexes could be assigned. Radiolabelling of the unprotected ligands with $[^{99m}Tc(H_2O)_3(CO)_3]^+$ affords the corresponding water-soluble technetium complexes (in quantitative yields), which were characterised by their HPLC radiation traces. The formed complexes are stable for several hours in the presence of histidine but show partial ligand-exchange after one day.

Keywords: bioinorganic chemistry · bipyridine · carbohydrates · luminescence · N ligands · rhenium · technetium

Introduction

Radiolabelled metal complexes are very important substances for diagnosis and therapy in nuclear medicine. Because of their closely related chemical properties but differing radiation, the nuclides ^{99m}Tc and $^{186/188}Re$ form a so-called diagnostic and therapeutic pair, with the γ-emitter ^{99m}Tc used for imaging and the corresponding ^{186}Re or ^{188}Re complexes, which have a high β-component in their radioactive decay, used for therapy. In addition to their interesting radioactive properties, rhenium(I) polypyridine complexes have been employed as ion sensors,[1] intercalators or photocleavage agents for nucleic acid[2] and boronic acid esters and as sugar sensors.[3] It has been shown that the excited state of these complexes has MLCT character and that appropriate substitution of the bipyridine ligands influences the photophysical properties.[4] Rhenium(I) complexes have also been used in the photochemical and electrochemical reduction of carbon dioxide.[5] Various technetium complexes with different oxidation states containing bipyridyl ligands diazo-coupled to 4-amino-1-naphthalenesulfonic or salicylic acid (analogous to Congo Red or chrysamin G dyes) have been used to localise and quantify amyloidal fibrils in mammals for diagnosing the degree of progression of Alzheimer's disease;[6] many other complexes have been successfully synthesised and their structure determined.[7] In addition, polypyridyl ligands, including unmodified 2,2′:6′,2″-terpyridine and 1,10-phenanthroline systems, have been synthesised,

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characterised and the influence of additional ligands studied.[8]

Polypyridines functionalised with carbohydrates combine the useful properties of both basic functionalities. Thus, the polypyridyl residues provide not only versatile and stable complexation of metal ions but also analytically useful properties like fluorescence of the corresponding metal complexes. Addition of a carbohydrate to the polypyridine scaffold has the added advantage of reducing the toxicity and improving the solubility, and opens up the possibility of molecular targeting of carbohydrate binding domains in cells and tissues. Ir^{III}, Rh^{III}, Ru^{II} and Re^{I} complexes of 2,2′-bipyridine-functionalised cyclodextrins have been synthesised as potential photo- and electroactive receptors following this strategy.[9] Europium complexes of terpyridines substituted with saccharides have also been employed as target cell markers in time-resolved fluorometric assays.[10] Complexes of Ru or Fe with sugar-containing terpyridines have been shown to be stable against enzymatic cleavage by β-glucosidase, in contrast to their free ligands,[11] and Ru complexes containing cyclodextrins have been studied as cyclometallated luminescent probes and for the detection of photoinduced intercomponent processes; related iron complexes have been employed for modelling cyclodextrin recognition sites.[12] Metal complexes of *N*-acetylgalactosamine- and -glucosamine-substituted 2,2′-bipyridines have also been synthesised and structurally characterised and their binding properties for NAcGal-specific lectins determined.[13]

Enhanced luminescence and recognition of 2,2′-bipyridine complexes of Ru and Fe by lectins has been achieved by *O*-glycosidic coupling of mono- and disaccharides via long-chain spacers and diamide functions.[14] Ribose derivatives bound to 2,2′-bipyridines by different spacers in the 4,4′- or 5-position have also been prepared and tested for chiral induction during iron complexation or as building blocks for intra-duplex metal complexes of modified DNA.[15]

Metal complexes functionalised with carbohydrates but containing other cores for metal complexation are increasingly being studied in medicinal inorganic chemistry; examples include Re and Tc complexes for use as radiotracers.[16] 2,2′-Dipicolylamine,[17] 3-hydroxypyridone[18] and 2-hydroxybenzyl[19] derivatives of different monosaccharides, for example, have been used as chelators for Tc and Re carbonyl cores, and similar complexes have been reported from 1,3-diamines of sugars.[20] Saccharide-functionalised bis(quinolinolyl)amino acids have also been complexed to a rhenium tricarbonyl core,[21] and glucose and 2-deoxyglucose have been functionalised at C-1 with iminodiacetic acid and the resulting ligands complexed with Re and Tc.[22] In all of these examples the linkage between the saccharides and the metal complexing units was accomplished by employing amido or *O*-glycosidic linkers, although procedures for the fluorometric or colourimetric determination of sugar and protein processing enzymes reveal they may be not stable in vivo. For instance X-gal (5-bromo-4-chloro-3-indoyl-β-D-galactoside) is a well known histochemical substrate that is used to detect β-galactosidase, and several 4-methylumbelliferyl glycosides are used in the fluorometric detection of cleaving enzymes.[23] Only two compounds with a thioether linkage between a bipyridine and cyclodextrin exist in the chemical literature to date.[24] In comparison to *O*-glycosylated compounds, *S*-glycosyl bonds are resistant to endogenous hydrolysis catalysed by glycosidases,[25] therefore we have attempted to connect different monosaccharides to 2,2′-bipyridine *S*-glycosidically in order to obtain biologically stable ligands and complexes of Re and Tc and now report our first results in this area.

Results and Discussion

The dibromide **1** was synthesised from 4,4′-dimethyl-2,2′-bipyridine according to a literature procedure.[26] However, only a 1:1 mixture with isomeric 4′-(dibromomethylene)-4-methyl-2,2′-bipyridine was obtained after chromatographic separation from the tri- and monobromo products. Reaction of the crude product containing **1** with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthiol (**2**) or 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosylthiol (**3**)[27] in a mixture of DMF and sodium carbonate led to the acetyl-protected ligands **5** and **6**, respectively, after chromatographic purification. The corresponding mannose derivative **7** was synthesised in a one-pot reaction in DMF starting from 2,3,4,6-tetra-*O*-acetyl-α-D-thioacetylmannopyranose (**4**).[28] This was achieved by hydrolysis of the thioacetyl group in situ by stirring with diethylamine at 0 °C and subsequent addition of sodium carbonate and the dibromide **1** (Scheme 1).

In addition to the single set of signals for the sugar residue and the pyridine ring expected for a C_2-symmetric compound, the ^{1}H NMR spectra of these ligands show two signals for the non-equivalent CH_2 protons of the thio-substituted methylene group at $\delta = 4.0$ and 3.8 ppm with a large coupling constant of 13 Hz. Cleavage of the acetyl esters was carried out under basic conditions with sodium methoxide in methanol to give the unprotected ligands **8**–**10** as white solids. These compounds, which are the first bipyridines with thioglycosidically linked saccharides, precipitate as partial sodium alkoxides and were characterised by high-resolution mass spectrometry (HRMS) and NMR spectroscopy. They do not dissolve in common organic solvents but are readily soluble in water.

Complexation to the rhenium carbonyl core was achieved by refluxing a methanolic suspension of the corresponding ligand (**5**–**10**) with $[Re(CO)_5Cl]$ (Scheme 2). The resulting yellow-orange raw products were purified by column chromatography over silica gel. Complexes **11**–**13** were found to be very soluble in organic solvents such as ethyl acetate or chloroform. Complexes **14**–**16** exhibit very good water solubility and stability, since even arduous treatment in aqueous solutions caused no change in their spectra. Complexes **11**–**13** show absorption maxima at 299 and 393 nm in dichloromethane in their UV/Vis spectra, with the absorption maxima of complexes **14**–**16** appearing at 323 and 389 nm, respectively, in water. The low-energy absorption band at

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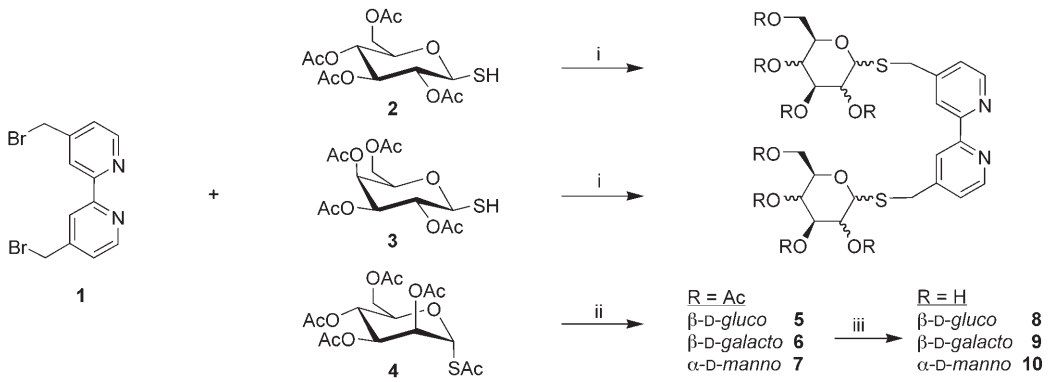
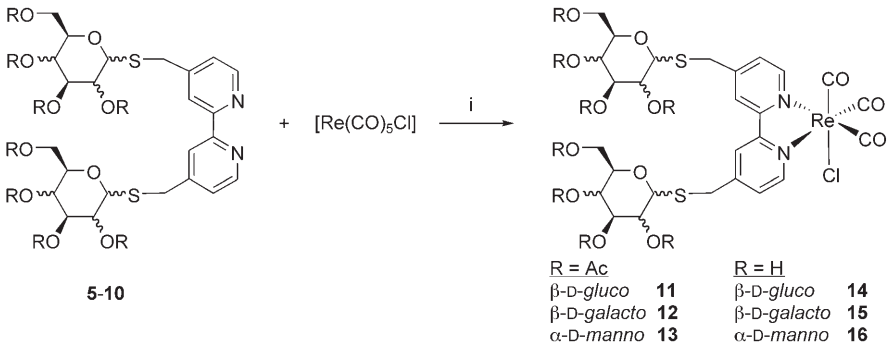


Scheme 1. Synthesis of the ligands: i) Na_2CO_3, DMF, room temp.; ii) $HNEt_2$, DMF, 0 °C, 15 min and then Na_2CO_3, 12 h, room temp.; iii) NaOMe, MeOH, 12 h, room temp.



Scheme 2. Synthesis of the rhenium complexes: i) methanol, 10 h, reflux.

around 390 nm for all these complexes is typical for the MLCT transition of rhenium(I) diimines (Table 1). The emission of the Re compounds **11–13** upon excitation at 400 nm occurs at around 610 nm (dichloromethane) and for complexes **14–16** upon excitation at 350 nm emission occurs between 600 and 640 nm (water). These values are typical for the phosphorescence derived from the triplet rhenium-to-ligand charge transfer (^{3}MLCT) excited state.[3d]

Table 1. Absorption and emission of the rhenium complexes.

Compd[a]	UV/Vis [nm]	Emission [nm][b]	Compd[c]	UV/Vis [nm]	Emission[d] [nm]
11	298, 389	609	**14**	323, 345	643
12	298, 390	612	**15**	323, 349	597
13	299, 394	615	**16**	321, 358	642

[a] In dichloromethane. [b] Excitation at 400 nm. [c] In water. [d] Excitation at 350 nm.

The IR spectra of the complexes are consistent with the proposed structures since bands attributable to the $[Re(CO)_3Cl]$ core and the residues of the sugar moieties are present. The single absorption at 2020 cm^{-1} can be assigned to the axial CO group, whereas the absorption at 1880 cm^{-1} for the equatorial carbonyl ligands splits into two peaks in most cases. The acetyl-protected complexes **11–13** exhibit strong signals at 1740 cm^{-1} for the carboxyl groups that are absent for the non-protected complexes **14–16**.

The NMR spectra of complexes **11–16** show that, in contrast to the C_2-symmetric free ligands, each sugar residue and pyridine unit in the complex now exhibits a separate set of signals in the ^{13}C NMR spectra. The ^{1}H NMR chemical shifts are also affected. The most pronounced effect is observed for the signals of the protons attached to the anomeric carbons: in compound **11**, for instance, they appear as two doublets with the same coupling constant ($J_{1,2}$ = 9.8 Hz) but at different positions (δ = 4.51 and 4.49 ppm). These results indicate a non-symmetric metallocomplex structure.

Crystallisation of **11** from methanol resulted in yellow needles which were suitable for X-ray structure analysis (Figure 1).

The rhenium atom is coordinated to the bipyridyl nitrogen atoms, three carbonyl groups and one axial chloride. The sugar residues are located outside the coordination sphere. A closer look at the bond lengths and angles at the rhenium centre (Table 2) provides additional support for the conclusions derived from the IR and NMR spectra. Thus, the different angles at the rhenium centre, for instance N1-Re-Cl1 (83.3(2)°) and N2-Re-Cl1 (90.5(2)°), confirm that the structure is not symmetric and explain the separate signals observed for every part of the molecule, such as the pyridine rings of the bipyridine unit.

Technetium is the most widely used isotope in nuclear medicine. Its nuclear properties ($t_{1/2}$ = 6.01 h and γ = 142.7 keV) allow the decay process to be conveniently measured by single photon emission computed tomography (SPECT). Due to the similar chemical properties of Re and Tc, rhenium complexes are good structural models for technetium complexes. The $[^{99}Tc(CO)_3(H_2O)_3]^+$ cation was gen-

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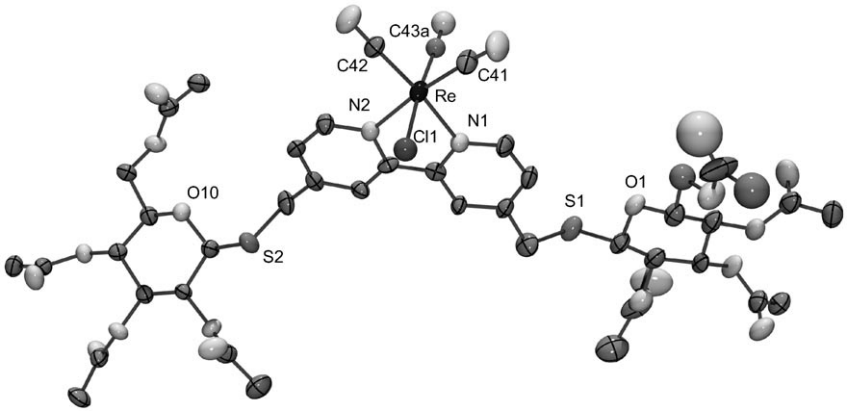
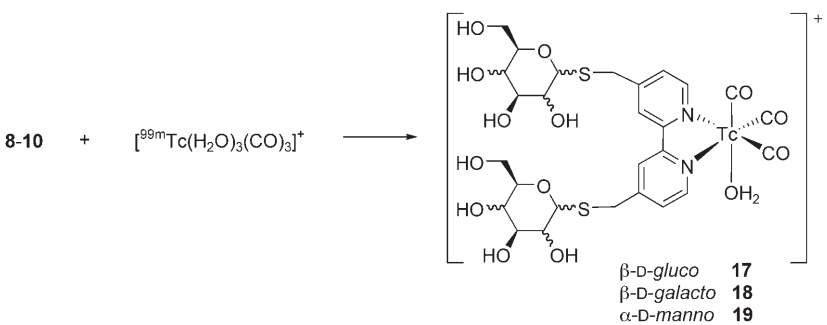


Figure 1. ORTEP view (50% probability) of one of the molecules in the structure of **11**. H atoms have been omitted for clarity.

Table 2. Selected bond lengths [Å] and angles [°] for **11**.

Re–N1	2.168(6)	C41-Re-N2	173.6(3)
Re–N2	2.182(6)	C42-Re-N1	169.8(3)
Re–C41	1.912(8)	C43-Re-Cl1	175.2(6)
Re–C42	1.924(7)	N1-Re-Cl1	83.3(2)
Re–C43a	2.005(18)	N2-Re-Cl1	90.5(2)
Re–Cl1	2.387(7)	C41-Re-C42	90.3(3)

erated in 0.9% saline solution from the $^{99m}TcO_4^-$ anion by using the Isolink kit from TYCO; the pH was adjusted with phosphate buffer. Complexation of ligands **8–10** was carried out under neutral conditions by addition of this technetium-containing solution to the appropriate ligand (Scheme 3). Increased formation of by-products upon heating the reaction mixtures to 100°C was not detected and the complexes formed (**17–19**) were found to be stable for several hours in this aqueous solution. HPLC analysis showed no retransformation into $^{99m}TcO_4^-$ anion ($R_f = 7.8$ min). The $[^{99m}Tc(CO)_3(H_2O)_3]^+$ ion ($R_f = 3.2$ min) reacted completely and the radiochemical impurities were lower than 5% without the need for an additional purification step. The retention times of the formed compounds **17–19** are between 11.9 and 12.4 min using a triethylamine phosphate solution/methanol gradient and an RP-18 column.



Scheme 3. Synthesis of the ^{99m}Tc complexes using the Isolink kit.

As an example of these ^{99m}Tc compounds we determined the in vitro stability of compound **17** following standard procedures (incubation with solutions of histidine in PBS buffer at 37°C).[29] The susceptibility of the complex to undergo ligand-exchange reactions with this amino acid was followed over a 24-h period (Figure 2).

The results clearly show that complex **17** possesses good stability over the first 4.5 h, after which time two additional signals indicative of more lipophilic complexes appear in the HPLC trace. Complete ligand exchange, which would result in the formation of the ^{99m}Tc histidine carbonyl complex $[^{99m}Tc(His)(CO)_3]$ ($R_f = 9.9$ min) synthesised under the same conditions for comparison, was not detected. Exchange of only the H_2O ligand at the technetium centre with histidine could, in principle, be possible with the complex core remaining intact. This has been observed, for example, for related Re complexes containing imidazole- or pyridine-based ligands.[30]

Conclusion

We have developed a general synthetic pathway for obtaining novel sugar-substituted bipyridines. The carbohydrate residues are coupled thioglycosidically to bipyridine to obtain biologically stable ligands. Complexation of the ligands with $[Re(CO)_5Cl]$ affords the expected luminescent rhenium complexes, whose properties and structures were determined by NMR, UV/Vis, IR and fluorescence spectroscopy and mass spectrometry. In addition, the solid-state structure of one complex has been elucidated by X-ray structure analysis. The solubility of these complexes is strongly influenced by the residues on the sugar units. For example, the protected complexes **11–13** are soluble in organic solvents whereas the unprotected compounds **14–16** exhibit very good solubility in water. The corresponding radiolabelled ^{99m}Tc complexes of the unprotected ligands have been synthesised in quantitative yields using $[^{99m}Tc(CO)_3(H_2O)_3]^+$ as the metal ion source and characterised by their HPLC radiation traces. These results show that luminescent probes based on the rhenium(I) centre with peripheral sugar substitution can be obtained and that the observed

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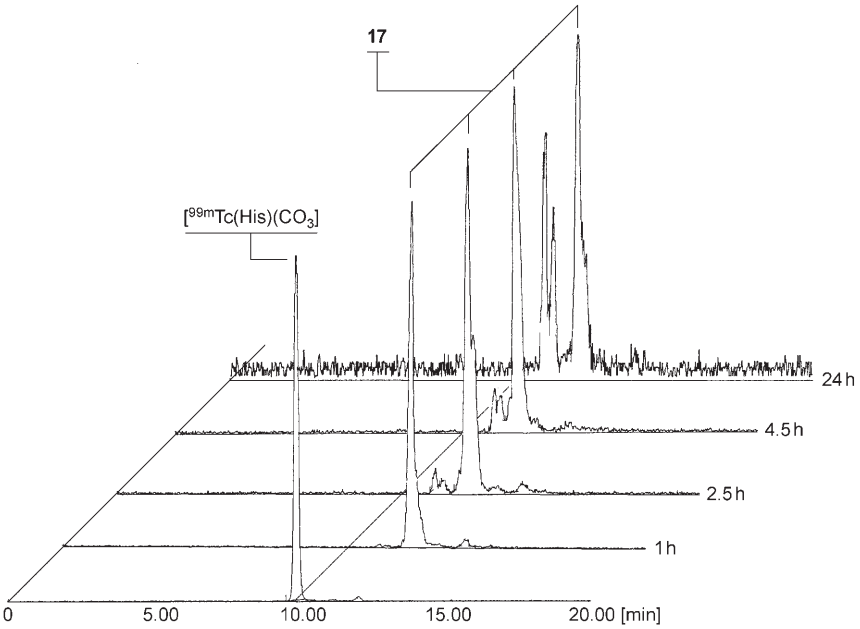

Figure 2. HPLC radiation traces for the histidine challenge experiment with **17** compared to the sample [^{99m}Tc(His)(CO)$_3$].

independency of the complex formation reaction on the nature of the sugar substituent can be exploited for the synthesis of the corresponding technetium(I) complexes.

In a histidine challenge experiment, the glucose-substituted ^{99m}Tc complex **17**, which is representative of all the complexes, is stable in vitro for 4.5 h. This stability is rather low compared to other sugar-containing complexes derived from 2,2′-dipicolylamine for instance.[17] In light of the intrinsic fluorescence and the possibility of binding different carbohydrates externally, future in vivo experiments are expected to show a sugar-dependent biodistribution.

Experimental Section

General: All reagents and solvents were purchased from commercial sources and were used as received. IR spectra were recorded with a Perkin–Elmer 2000 spectrometer, NMR spectra with a JEOL JMTC-400/54/SS or a Bruker AC-200 spectrometer and ESI mass spectra with a JEOL JMS-T100 LC, Finnigan MAT SSQ 710 or a Finnigan MAT 95XL TRAP spectrometer. Elemental analyses were performed with a Leco CHNS 932 or Perkin Elmer PE2400 Series II CHNS/O Analyzer (Nara Institute of Science and Technology). UV/Vis absorption spectra (accuracy: ±2 nm) were recorded with an Analytikjena Specord S 600 spectrometer with standard software-based tools. Emission spectra (accuracy: ±5 nm) were recorded at 298 K with a Perkin–Elmer LS50B luminescence spectrophotometer equipped with a red-sensitive Hamamatsu R298 PMT detector and interfaced with an Elonex PC466 employing the Perkin–Elmer FlWinLab custom-built software. Emission spectra are uncorrected for the photomultiplier response. Quartz cells (path length: 10 mm) were used.

4,4′-Bis[(2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl)thiomethyl]-2,2′-bipyridine (5): 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylthiol (2.114 g, 5.801 mmol) and Na_2CO_3 (2 g) were added to a solution of a mixture of the two dibromomethylenebipyridyls (902 mg, 2.637 mmol) in DMF and this suspension was stirred at room temperature for two days. After removal of the solvent the residue was extracted with ethyl acetate and water, dried over sodium sulfate and evaporated. TLC (ethyl acetate/hexane, 3:2) showed two spots (R_f=0.22 and 0.26) along with that of the disulfide (R_f=0.38). Chromatographic separation (ethyl acetate/hexane, 3:1) gave 800 mg (86% with respect to the 50% purity of the starting material) of the desired product as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.61 (d, $^3J_{6'',5''}$=4.9 Hz, 2H; H-6″), 7.30 (d, 2H; H-5″), 8.39 (s, 2H; H-3″), 4.37 (d, $^3J_{1,2}$=9.8 Hz, 2H; H-1), 5.16 (t, $^3J_{2,3}$=9.0 Hz, 2H; H-2), 5.10 (t, $^3J_{3,4}$=9.5 Hz, 2H; H-3), 5.09 (t, $^3J_{4,5}$=9.5 Hz, 2H; H-4), 3.69 (ddd, $^3J_{5,6}$=4.2 Hz, $^3J_{5,6'}$=2.9 Hz, 2H; H-5), 4.19–4.27 (m, 4H; H-6, H-6′), 4.04, 3.85 (2d, $^2J_{H,H}$=13.4 Hz, 4H; CH_2), 2.10, 2.04, 2.02, 1.99 ppm (4 s, 24H; CH_3-acetyl); ^{13}C NMR ($CDCl_3$): δ=170.4, 169.8, 169.1 (CO-acetyl), 155.8 (C2″), 149.3 (C6″), 147.0 (C4″), 124.0 (C5″), 121.3 (C3″), 81.8 (C1), 75.8 (C2), 73.6 (C3), 69.7 (C4), 68.1 (C5), 61.9 (C6), 32.8 (S-CH_2-), 20.7 ppm (CH_3-acetyl); ESI-MS: *m*/*z* (%): 931.26 (100) $[M+Na]^+$, 1839.53 (5) $[2M+Na]^+$; elemental analysis calcd (%) for $C_{40}H_{48}N_2O_{18}S_2$: C 52.86, H 5.32, N 3.08; found: C 52.76, H 5.33, N 3.01.

4,4′-Bis[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thiomethyl]-2,2′-bipyridine (6): This compound was synthesised in an analogous manner to **5** from crude **1** (2.479 g, 7.25 mmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosylthiol (5.81 g, 15.95 mmol) to yield 2.19 g (85%) of **6**. ^{1}H NMR (250 MHz, $CDCl_3$): δ=8.59 (d, $^3J_{6'',5''}$=4.9 Hz, 2H; H-6″), 7.29 (d, 2H; H-5″), 8.39 (s, 2H; H-3″), 4.36 (d, $^3J_{1,2}$=9.9 Hz, 2H; H-1), 5.29 (t, $^3J_{2,3}$=10.0 Hz, 2H; H-2), 4.98 (dd, $^3J_{3,4}$=3.4 Hz, 2H; H-3), 5.41 (dd, $^3J_{4,5}$=0.9 Hz, 2H; H-4), 3.92 (dd, $^3J_{5,6}$=6.6 Hz, 2H; H-5), 4.13 (d, 4H; H-6), 4.04, 3.85 (2d, $^2J_{H,H}$=13.5 Hz, 4H; CH_2), 2.15, 2.04, 2.03, 1.95 ppm (4 s, 24H; CH_3-acetyl); ^{13}C NMR ($CDCl_3$): δ=170.3, 170.2, 169.9, 169.6 (CO-acetyl), 156.1 (C2″), 149.4 (C6″), 147.5 (C4″), 124.1 (C5″), 121.5 (C3″), 82.5 (C1), 74.6 (C2), 71.7 (C3), 67.3 (C4), 67.0 (C5), 61.4 (C6), 32.8 (S-CH_2-), 21.0, 20.7, 20.6, 20.5 ppm (CH_3-acetyl); DEI-MS: *m*/*z* (%): 908 (15) $[M]^+$; elemental analysis calcd (%) for $C_{40}H_{48}N_2O_{18}S_2$: C 52.86, H 5.32, N 3.08, S 7.06; found: C 52.80, H 5.27, N 3.05, S 6.88.

4,4′-Bis[(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)thiomethyl]-2,2′-bipyridine (7): Diethylamine (1.84 g, 25 mmol) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl thioacetate (10.2 g, 25 mmol) in 50 mL of DMF at 0°C. After stirring for 15 min an excess of sodium carbonate and the two dibromobipyridyls (12.6 g, 12.6 mmol) in DMF (30 mL) were added. The mixture was stirred for two days and worked up analogous to **5** to give 3.2 g (56%) of **7** as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.63 (d $^3J_{6'',5''}$=4.9 Hz, 2H; H-6″), 7.30 (d, 2H; H-5″), 8.37 (s, 2H; H-3″), 5.11 (d, $^3J_{1,2}$=1.2 Hz, 2H; H-1), 5.24–5.33 (m, 6H; H-2, H-3, H-4), 4.37 (m, $J_{5,6}$=5.4 Hz, $J_{5,6'}$=2.2 Hz, 2H; H-5), 4.31 (dd, $^2J_{6,6'}$=12.2 Hz, $^3J_{5,6}$=5.4 Hz, 2H; H-6), 4.03 (dd, $^3J_{5,6'}$=2.2 Hz, 2H; H-6′), 3.87 and 3.79 (2d, $^2J_{H,H}$=13.9 Hz, 4H; CH_2), 2.14, 2.12, 2.05, 1.98 ppm (4 s, 24H; CH_3-acetyl); ^{13}C NMR ($CDCl_3$): δ=170.3, 169.5, (CO-acetyl), 155.9 (C2″), 149.3 (C6″), 146.9 (C4″), 123.9 (C5″), 121.3 (C3″), 81.4 (C1), 70.3 (C2); 69.5 (C3), 69.1 (C4), 66.0 (C5), 62.3 (C6), 33.8 (S-CH_2-), 20.9 ppm (CH_3-acetyl); ESI-MS: *m*/*z* (%): 931.23 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{40}H_{48}N_2O_{18}S_2$: C 52.86, H 5.32, N 3.08; found: C 52.61, H 5.40, N 2.94.

General procedure for the synthesis of unprotected ligands 8–10: The corresponding peracetylated ligand **5–7** (1.09 g, 1.2 mmol) was dissolved in methanol (50 mL), sodium methoxide (200 mg) was added and the so-

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lution was stirred for 12 h. The white precipitate formed was filtered off, washed with methanol and dried to give the unprotected ligand as a white powder in about 70% yield.

4,4′-Bis[(β-D-glycopyranosyl)thiomethyl]-2,2′-bipyridine (8): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=8.58 (d, $^3J_{6'',5''}$=5.1 Hz, 2H; H-6″), 7.41 (d, 2H; H-5″), 8.38 (s, 2H; H-3″), 4.71–4.74 (m, 2H; OH), 4.96 (s, 2H; OH), 5.06 (s, 2H; OH), 5.17 (s, 2H; OH), 4.04 (d, $^3J_{1,2}$=9.8 Hz, 2H; H-1), 3.74 (dd, $^3J_{5,6}$=5.4 Hz, $^2J_{6,6'}$=11.7 Hz, 2H; H-6), 3.46 (dd, $^3J_{5,6'}$=6.8 Hz, 2H; H-6′), 3.05–3.15 (m, 8H; H-2, H-3, H4, H-5), 4.03, 3.90 ppm (2d, $^2J_{H,H}$= 13.1 Hz, 4H; CH$_2$); ^{13}C NMR ([D$_6$]DMSO): δ=155.0 (C2″), 149.0 (C6″), 148.7 (C4″), 124.5 (C5″), 120.9 (C3″), 83.0 (C1), 81.1 (C2), 78.1 (C3), 73.1 (C4), 70.1 (C5), 61.3 (C6), 31.5 ppm (S-CH$_2$-); ESI-HRMS: *m*/*z* calcd for $C_{24}H_{32}N_2NaO_{10}S_2$: 595.13961; found: 595.13994; elemental analysis calcd (%) for $C_{24}H_{32}N_2O_{10}S_2{\cdot}0.5\,H_2O$: C 49.56, H 5.72, N 4.82, S 11.03; found: C 49.51, H 5.51, N 4.76, S 10.67.

4,4′-Bis[(β-D-galactopyranosyl)thiomethyl]-2,2′-bipyridine (9): ^{1}H NMR (400 MHz, [D$_7$]DMF): δ=8.65 (d, $^3J_{6'',5''}$=4.9 Hz, 2H; H-6″), 7.51 (d, 2H; H-5″), 8.53 (s, 2H; H-3″), 4.27 (d, $^3J_{1,2}$=10.4 Hz, 2H; H-1), 3.64 (t, $^3J_{2,3}$= 9.3 Hz, 2H; H-2), 3.45 (dd, $^3J_{3,4}$=3.2 Hz, 2H; H-3), 3.91 (d, 2H; H-4), 3.56 (t, $^3J_{5,6}$=$^3J_{5,6'}$=6.2 Hz, 2H; H-5), 3.83 (dd, $^2J_{6,6'}$=11.1 Hz, 2H; H-6′), 3.75 (dd, 2H; H-6), 4.15, 3.99 ppm (2d, 4H; S-CH$_2$, $^2J_{H,H}$=13.4 Hz); ^{13}C NMR ([D$_7$]DMF): δ=155.9 (C2″), 149.6 (C6″), 149.4 (C4″), 124.6 (C5″), 121.3 (C3″), 84.5 (C1), 80.0 (C2), 75.6 (C3), 69.4 (C4), 68.6 (C5), 61.6 (C6), 32.1 ppm (S-CH$_2$-); ESI-HRMS: *m*/*z* calcd for $C_{24}H_{32}N_2NaO_{10}S_2$: 595.13961; found: 595.13955; elemental analysis calcd (%) for $C_{24}H_{30.5}N_2Na_{1.5}O_{10}S_2$: C 47.64, H 5.00, N 4.63, S 10.60; found: C 47.98, H 5.32, N 4.64, S 10.55.

4,4′-Bis[(α-D-mannopyranosyl)thiomethyl]-2,2′-bipyridine (10): ^{1}H NMR (400 MHz, D$_2$O): δ=8.32 (d, $^3J_{6'',5''}$=5.2 Hz, 2H; H-6″), 7.24 (d, 2H; H-5″), 7.71 (s, 2H; H-3″), 5.11 (d, $^3J_{1,2}$=1.2 Hz, 2H; H-1), 3.92 (dd, $^3J_{2,3}$= 3.2 Hz, 2H; H-2), 3.81 (m, 2H; H-5), 3.74–3.58 ppm (m, 12H; H-3, H-4, H-6, H-6′, S-CH$_2$); ^{13}C NMR (D$_2$O): δ=154.7 (C2″), 149.5 (C6″), 149.1 (C4″), 124.7(C5″), 122.0 (C3″), 84.5 (C1), 73.3 (C2), 71.6 (C-3), 71.5 (C4), 67.1 (C5), 60.6 (C6), 33.4 ppm (S-CH$_2$-); ESI-HRMS: *m*/*z* calcd for $C_{24}H_{32}N_2NaO_{10}S_2$: 595.13961; found: 595.14023; elemental analysis calcd (%) for $C_{24}H_{30}N_2Na_2O_{10}S_2$: C 46.75, H 4.90, N 4.54, S 10.40; found: C 46.67, H 5.26, N 4.40, S 10.15.

General procedure for the synthesis of Re complexes 11–16: The corresponding ligand **5–10** (0.2 mmol) and [Re(CO)$_5$Cl] (0.2 mmol) in methanol (30 mL) were heated under reflux for 10 h. The solvent was then evaporated from the resulting yellow solution and the raw product purified by column chromatography (silica gel 60; ethyl acetate/hexane 2:1; R_f=0.4 for **11–13**; ethyl acetate/methanol 1:1; R_f=0.5 for **14–16**) to yield 80% of the complex.

Tricarbonyl-4,4′-bis[(2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl)thiomethyl]-2,2′-bipyridinerhenium chloride (11): Crystallisation from methanol gave yellow needles suitable for a single-crystal X-ray structure analysis. ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.94 (d, $^3J_{6'',5''}$=5.6 Hz, 2H; H-6″), 7.51 (d, 2H; H-5″), 8.27 (s, 2H; H-3″), 4.51, 4.49 (2d, $^3J_{1,2}$=9.8 Hz, 2H; H-1), 5.25 (t, $^3J_{2,3}$=9.3 Hz, 2H; H-2), 5.16 (t, $^3J_{3,4}$=9.8 Hz, 2H; H-3), 5.11 (t, $^3J_{4,5}$=9.8 Hz, 2H; H-4), 3.77 (ddd, $^3J_{5,6}$=4.4 Hz, $^3J_{5,6'}$=2.2 Hz, 2H; H-5), 4.16 (dd, $^2J_{6,6'}$=12.5 Hz, 2H; H-6′), 4.23–4.29 (m, 2H; H-6), 4.09, 3.97 (2d, $^2J_{H,H}$=13.2 Hz, 4H; S-C*H*$_2$), 2.10, 2.07, 2.04, 2.03 ppm (4 s, 24H; CH$_3$-acetyl); ^{13}C NMR (CDCl$_3$): δ=196.7, 189.1 (CO-carbonyl), 170.2, 169.7, 169.4, 169.2 (CO-acetyl), 155.5 (C2″), 152.7 (C6″), 150.6, 150.5 (C4″), 127.4 (C5″), 123.7 (C3″), 82.0, 81.9 (C1), 76.2 (C2), 73.3 (C3), 69.2 (C4), 68.0 (C5), 61.8 (C6), 31.9 (S-CH$_2$-), 20.7, 20.9 ppm (CH$_3$-acetyl); IR (ATR): $\tilde{\nu}$=2019, 1886, 1865 (C=O), 1742 cm^{-1} (C=O); UV/Vis (CH$_2$Cl$_2$): λ_{max} (ε)=389 (4300), 298 nm (19900 M^{-1}cm^{-1}); ESI-MS: *m*/*z* (%): 1179.12 (100) [*M*−Cl$^-$]$^+$; elemental analysis calcd (%) for $C_{43}H_{48}ClN_2O_{21}ReS_2{\cdot}H_2O$: C 41.90, H 4.09, N 2.27; found: C 41.66, H 4.00, N 2.26.

Tricarbonyl-4,4′-bis[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thiomethyl]-2,2′-bipyridinerhenium chloride (12): ^{1}H NMR (250 MHz, CDCl$_3$): δ=8.88 (d, $^3J_{6'',5''}$=5.7 Hz, 2H; H-6″), 7.46 (d, 2H; H-5″), 8.19 (s, 2H; H-3″), 4.44 (d, $^3J_{1,2}$=9.8 Hz, 2H; H-1), 5.25 (dd, $^3J_{2,3}$=9.9 Hz, 2H; H-2), 5.02 (dd, $^3J_{3,4}$=3.4 Hz, 2H; H-3), 5.39 (d, 2H; H-4), 4.08–3.89 (m, 10H; H-5, H-6, H-6′, 2CH$_2$), 2.11, 2.04, 1.97, 1.93 ppm (4 s, 24H; CH$_3$-acetyl); ^{13}C NMR (CDCl$_3$): δ=197.1, 189.4 (CO-carbonyl), 170.3, 170.2, 169.9, 169.8 (CO-acetyl), 155.7 (C2″), 152.9 (C6″), 151.0 (C4″), 127.6, 127.5 (C5″), 123.8 (C3″), 82.6 (C1), 74.9 (C2), 71.4 (C3), 67.1 (C4), 66.7 (C5), 61.3 (C6), 29.6 (S-CH$_2$-), 21.0, 20.7, 20.6, 20.5 ppm (CH$_3$-acetyl); IR (ATR): $\tilde{\nu}$=2018, 1886 (C=O), 1740 cm^{-1} (C=O); UV/Vis (CH$_2$Cl$_2$): λ_{max} (ε)=390 (3900), 298 nm (16800 M^{-1}cm^{-1}); DEI-MS: *m*/*z* (%): 1213 (30) [*M*−H]$^+$, 1185 (80) [*M*−CO]$^+$, 1178 (100) [*M*−Cl$^-$]$^+$, 1157 (60) [*M*−2CO]$^+$; elemental analysis calcd (%) for $C_{43}H_{48}ClN_2O_{21}ReS_2{\cdot}C_6H_{14}$: C 45.24, H 4.80, N 2.15, S 4.93; found: C 44.93, H 4.66, N 1.98, S 4.31.

Tricarbonyl-4,4′-bis[(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)thiomethyl]-2,2′-bipyridinerhenium chloride (13): ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.96, 8.97 (2d, $^3J_{6'',5''}$=5.6 Hz, 2H; H-6″), 7.51, 7.49 (2d, 2H; H-5″), 8.31 (s, 2H; H-3″), 5.01, 5.06 (2d, $^3J_{1,2}$=1.2 Hz, 2H; H-1), 5.26–5.37 (m, 6H; H-2, H-3, H-4), 4.31 (m, 2H; H-5), 4.26, 4.25 (2 s, 4H; H-6, H-6′), 3.84–3.95 (m, 4H; CH$_2$), 2.12, 2.05, 2.04, 1.70 ppm (4 s, 24H; CH$_3$-acetyl); ^{13}C NMR (CDCl$_3$): δ=197.0, 196.9, 189.3 (CO-carbonyl), 170.5, 169.9, 169.8, 169.5 (CO-acetyl), 155.9, 155.8 (C2″), 153.1, 153.0 (C6″), 150.4, 150.3 (C4″), 127.5, 127.4 (C5″), 123.9, 123.8 (C3″), 81.0, 80.8 (C1), 69.9 (C2), 69.8, 69.7 (C3), 69.4 (C4), 66.0, 65.8 (C5), 62.1, 62.0 (C6), 32.9, 32.8 (S-CH$_2$-), 20.9, 20.8, 20.7, 20.6 ppm (CH$_3$-acetyl); IR (ATR): $\tilde{\nu}$= 2019, 1887 (C=O), 1740 cm^{-1} (C=O); UV/Vis (CH$_2$Cl$_2$): λ_{max} (ε)=394 (4500), 299 nm (20900 M^{-1}cm^{-1}); ESI-MS: *m*/*z* (%): 1237.12 (15) [*M*+Na]$^+$, 1179.20 (100) [*M*−Cl$^-$]$^+$; elemental analysis calcd (%) for $C_{43}H_{48}ClN_2O_{21}ReS_2{\cdot}0.5\,C_6H_{14}$: C 43.93, H 4.41, Cl 2.82, N 2.23, S 5.10; found: C 43.76, H 4.54, Cl 2.93, N 2.14, S 4.75.

Tricarbonyl-4,4′-bis(β-D-glycopyranosylthiomethyl)-2,2′-bipyridinerhenium chloride (14): ^{1}H NMR (400 MHz, CD$_3$OD): δ=8.87 (d, $^3J_{6'',5''}$= 5.6 Hz, 2H; H-6″), 7.64 (d, 2H; H-5″), 8.69, 8.63 (2 s, 2H; H-3″), 4.10 (m, 2H; H-1), 3.29–3.20 (m, 8H; H-2, H-3, H4, H-5), 3.61 (m, 2H; H-6′), 3.88–3.96 (m, 4H; H-6, CH$_2$), 4.25, 4.23 ppm (2d, $^2J_{H,H}$=13.9 Hz, 2H; CH$_2$); ^{13}C NMR (CD$_3$OD): δ=198.1, 190.4 (CO), 157.0 (C2″), 154.3 (C6″), 153.7 (C4″), 128.8 (C5″), 125.5, 125.4 (C3″), 84.4, 84.2 (C1), 82.0 (C2), 79.3 (C3), 74.5 (C4), 71.8 (C5), 63.2 (C6), 32.9 ppm (S-CH$_2$-); IR (ATR): $\tilde{\nu}$=2020, 1878 cm^{-1} (C=O); UV/Vis (H$_2$O): λ_{max} (ε)=345 (5300), 323 (14400), 311 nm (13400 M^{-1}cm^{-1}); ESI-MS: *m*/*z* (%): 901.01 (10) [*M*+Na]$^+$, 843.05 (100) [*M*−Cl$^-$]$^+$; elemental analysis calcd (%) for $C_{27}H_{32}ClN_2O_{13}ReS_2{\cdot}H_2O$: C 36.18, H 3.82, N 3.13; found: C 36.11, H 3.89, N 2.93.

Tricarbonyl-4,4′-bis(β-D-galactopyranosylthiomethyl)-2,2′-bipyridinerhenium chloride (15): ^{1}H NMR (250 MHz, CD$_3$OD): δ=8.90 (d, $^3J_{6'',5''}$= 5.7 Hz, 2H; H-6″), 7.70 (d, 2H; H-5″), 8.73, 8.69 (2 s, 2H; H-3″), 4.14, 4.13 (2d, $^3J_{1,2}$=9.5 Hz, 2H; H-1), 3.63 (t, $^3J_{2,3}$=9.5 Hz, 2H; H-2), 3.39 (dd, $^3J_{3,4}$=3.2 Hz, 2H; H-3), 3.84 (d, 2H; H-4), 3.50 (dd, $^3J_{5,6}$=3.7 Hz, $^3J_{5,6'}$=7.3 Hz, 2H; H-5), 3.79–3.64 (m, 4H; H-6′, H-6), 4.28, 3.97 ppm (2d, $^2J_{H,H}$=13.9 Hz, 4H; S-CH$_2$); ^{13}C NMR (CD$_3$OD): δ=198.5 and 190.7 (CO), 157.21/157.16 (C2″), 154.76 (C6″), 153.83 (C4″), 129.06/129.01 (C5″), 125.85/125.76 (C3″), 84.95 (C1), 81.05 (C2), 76.11 (C3), 71.51 (C4), 70.71 (C5), 63.16 (C6), 32.82 ppm (S-CH$_2$-); IR (ATR): $\tilde{\nu}$=2018, 1876 cm^{-1} (C=O); UV/Vis (H$_2$O): λ_{max} (ε)=349 (4600), 323 (11600), 310 nm (11300 M^{-1}cm^{-1}); FAB-MS: *m*/*z* (%): 878 (30) [*M*]$^+$, 843 (50) [*M*−Cl$^-$]$^+$; elemental analysis calcd (%) for $C_{27}H_{32}ClN_2O_{13}ReS_2{\cdot}2\,H_2O$: C 35.47, H 3.06, N 3.19; found: C 35.18, H 3.41, N 3.07.

Tricarbonyl-4,4′-bis(α-D-mannopyranosylthiomethyl)-2,2′-bipyridinerhenium chloride (16): ^{1}H NMR (400 MHz, CD$_3$OD): δ=8.88 (d, $^3J_{6'',5''}$= 5.6 Hz, 2H; H-6″), 7.67 (dd, 2H; H-5″), 8.57 (s, 2H; H-3″), 5.08 (d, $^3J_{1,2}$= 2.0 Hz, 2H; H-1), 3.84–3.57 (m, 6H; H-2, H-3, H-4, H-5, H-6, H-6′), 4.02, 3.94 ppm (2d, $^2J_{H,H}$=13.9 Hz, 4H; S-C*H*$_2$); ^{13}C NMR (CD$_3$OD): δ=198.1, 190.3 (CO), 156.8 (C2″), 154.1 (C6″), 153.7 (C4″), 128.8 (C5″), 125.4 (C3″), 85.0 (C1), 75.3 (C2), 73.1 (C-3), 73.0 (C4), 68.6 (C5), 62.5 (C6), 33.9 ppm (S-CH$_2$-); IR (ATR): $\tilde{\nu}$=2009, 1865 cm^{-1} (C=O); UV/Vis (H$_2$O): λ_{max} (ε)=358 (4200), 321 (12100), 283 nm (15400 M^{-1}cm^{-1}); ESI-MS: *m*/*z* (%): 901.07 (30) [*M*+Na]$^+$, 843.12 (100) [*M*−Cl$^-$]$^+$; elemental analysis calcd (%) for $C_{27}H_{32}ClN_2O_{13}ReS_2{\cdot}5\,H_2O$: C 33.49, H 4.37, N 2.89; found: C 33.49, H 3.86, N 2.61.

General procedure for the synthesis of ^{99m}Tc complexes 17–19: the Isolink kit from TYCO, which contains sodium boranocarbonate (4.5 mg), sodium tetraboronate decahydrate (2.85 mg), sodium tartrate dihydrate (8.5 mg) and sodium carbonate (7.15 mg), was used for the labelling reac-

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tions. After the addition of $^{99m}TcO_4^-$ in 0.9% saline solution the mixture was heated at 100°C for 30 min, then cooled to room temperature and neutralised to pH 7 with a mixture of phosphate buffer (0.6 M, 0.4 mL) and HCl (1.0 M, 0.6 mL). A 250-μL aliquot of this $[^{99m}Tc(H_2O)_3(CO)_3]^+$ solution was added to compounds **8–10** (1.0 mg, 1.75 μmol) and the mixture heated in a glass vial at 100°C for 30 min. After cooling to room temperature the products were analysed for their radiochemical purity (>95%) by HPLC under the following conditions: HPLC pump: Jasco PU-1580; quaternary gradient unit: Jasco LG-1580-04; radio detector: biostep IsoScan LC γ; RI detector: Jasco RI 1530; column: RP-18, LiChroCART 250-4, LiChrospher 100, RP-18e (5 μm); solvent A: triethylamine phosphate (0.05 M) aqueous solution, adjusted with H_3PO_4 to pH 2.25; solvent B: methanol; flow rate: 1.2 mL min^{-1}; gradient: from 0–3 min 100% A, 3–17 min to 100% B, from 17–22 min 100% B.

Histidine stability test of ^{99m}Tc complex 17: A solution of histidine (0.1 mM, 500 μL PBS, pH 7.4) was added to a solution of complex **17** (500 μL; final ligand concentration: 0.05 mM) and the mixture was incubated at 37°C. Samples were taken at 1, 2.5, 4.5 and 24 h for HPLC analysis.

X-ray crystallography: The intensity data for compound **11** were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated $Mo_{K\alpha}$ radiation. Data were corrected for Lorentz and polarisation effects, but not for absorption.[31] The structures were solved by direct methods (SHELXS[32]) and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97[33]). The hydrogen atoms of the structures were included at calculated positions with fixed thermal parameters. All non-disordered, non-hydrogen atoms were refined anisotropically.[33] XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

Crystal data for **11**:[34] $C_{43}H_{48}ClN_2O_{21}ReS_2$, $M_r = 1214.60$ g mol^{-1}, yellow prism, $0.04 \times 0.04 \times 0.04$ mm^3, monoclinic, space group $P2_1$, $a = 13.566(3)$, $b = 7.1534(14)$, $c = 25.791(5)$ Å, $\beta = 96.34(3)°$, $V = 2487.5(9)$ Å^3, $T = -90$°C, $Z = 2$, $\rho_{calcd} = 1.622$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 26.6$ cm^{-1}, $F(000) = 1224$, 17408 reflections $h(-17/17)$, $k(-9/9)$, $l(-30/33)$, measured in the range $2.31° \le \Theta \le 27.53°$, completeness to $\Theta_{max} = 99.3\%$, 10877 independent reflections, $R_{int} = 0.0421$, 8658 reflections with $F_o > 4\sigma(F_o)$, 620 parameters, one restraint, $R_{obs} = 0.0494$, $wR^2_{obs} = 0.0974$, $R_{all} = 0.0744$, $wR^2_{all} = 0.1061$, GOOF = 1.033, Flack parameter = 0.014(7), largest difference peak and hole: 1.103/−0.783 e Å^{-3}.

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