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Glycoconjugated Rhenium(I) and 99m-Technetium(I) Carbonyl Complexes from Pyridyltriazole Ligands Obtained by "Click Chemistry"

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A series of pyridyltriazole ligands containing sugar moieties have been prepared by copper(I)-mediated 1,3-dipolar cycloaddition ("click" reaction) of azides functionalized with D-glucose, D-galactose, D-mannose, D-xylose as well as D-maltose residues, and 2-ethynylpyridine as alkyne. The peracetylated saccharide residues as well as their water-soluble deprotected derivatives were treated with $Re(CO)_5Cl$ to obtain the corresponding mononuclear rhenium(I) carbonyl complexes $[LRe(CO)_3Cl]$. For comparison, one Re^I complex bearing a *tert*-butylbenzyl residue instead of a sugar moiety as well as two dinuclear rhenium complexes derived from a branched ligand containing two pyridyltriazole units were prepared. The structure and integrity of the ligands and complexes was established by NMR, IR, UV/Vis and fluorescence spectroscopy, mass spectrometry, and by elemental analysis. Coordination of the metal ion occurred by both the pyridyl nitrogen atoms and one of the triazole nitrogen atoms. Upon treatment with an excess of histidine, the Re^I complexes were stable for only 2.5 h. After a longer period (24 h) ligand exchange was detected by HPLC measurements. In contrast, a complex labeled with ^{99m}Tc was found to be stable for up to 24 h against an excess of histidine. Cytotoxicity was screened for all Re^I complexes against HepG2 cells using a concentration of 100 μM. All sugar-functionalized complexes were found to be nontoxic, except for the complex derived from the pyridyl (*tert*-butylbenzyl)-triazole, which exhibited remarkable toxicity.

Introduction

Technetium (^{99m}Tc) and rhenium ($^{186/188}Re$) isotopes are important radionuclides that possess diagnostic and therapeutic potential.[1–4] ^{99m}Tc complexes are popular radiotracers in medicine due to their nuclear properties and easy accessibility. ^{99m}Tc emits γ rays (140 keV) that are detectable by techniques using γ-radiation sensitive cameras for example scintigraphy or single-photon emission computed tomography (SPECT), and the radioisotope has a half-life of 6.01 h. The success of ^{186}Re-hydroxyethylidenediphosphonate (HEDP) as a radiopharmaceutical (treatment of bone metastasis)[5,6] has focused particular attention on the coordination chemistry of rhenium ions.[7–10] The half-life of ^{186}Re is 3.7 d, and it decays through emission of β (1.07 MeV) and γ (137 keV) rays. In contrast, the half-life for ^{188}Re is 17 h and this rhenium isotope also emits β (2.12 MeV) and γ (155 keV) rays.[3] Given that β-decay causes cell damage[11,12] and γ-rays can be easily detected and used for monitoring the distribution,[6,13] dual decay of $^{186/188}Re$ isotopes can be used for imaging as well as for radiotherapy.

Carbohydrates play an important role in many biological processes,[14–17] and there have been many attempts to take advantage of the high specificity and selectivity of processes involving saccharides. The most prominent example in terms of radio imaging is ^{18}F-2-fluoro-2-deoxyglucose (^{18}F-FDG), which is used as a tracer in positron emission tomography (PET), taking advantage of the increased

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glucose uptake and metabolization by cancerous cells. Combining the useful features of saccharides such as biocompatibility, hydrophilicity and targeting properties, with those of metal complexes (e.g., fluorescence, cytotoxicity, but also radioactive decay) has led to the synthetic analysis of a variety of sugar metal complexes for various applications.[18–20]

Many research groups have undertaken investigations on new ^{99m}Tc radiotracers and rhenium complexes bearing sugar residues, mainly with the aim of identify more economically viable substitutes for ^{18}F-FDG. Initially, Yang et al. synthesized the ^{99m}Tc complex of ethylenedicystein-deoxyglucose (^{99m}Tc-ECDG) and studied its biodistribution in lung-tumor-bearing mice.[21] The authors observed higher tumor-to-brain and tumor-to-muscle tissue ratios for the distribution of ^{99m}Tc-ECDG compared with ^{18}F-FDG, but a lower tumor-to-blood ratio. Connection of either monoamino-monoamide dithiol (MAMA) or mercaptoacetylglycylglycylglycine (MAG_3) to 2-deoxy-2-aminoglucose (DG), galactose (Gal) or glucose (Glc) with different linking units and radiolabeling with ^{99m}Tc yielded radiotracers with a sugar-dependent biodistribution in vivo, displaying promising tumor-to-muscle ratios (^{99m}Tc-MAG_3-DG in MA891 breast-tumor-bearing mice;[22] ^{99m}Tc-MAG_3-Glc in Ehrlich-tumor-bearing mice[23,24]) or enrichment in the liver as potential imaging agent for hepatic function (^{99m}Tc-MAG_3-Gal in healthy Swiss mice[25]). Moreover, additional binding functionalities such as 1,3-diamines,[26] 3-hydroxypyridone,[27] 2-hydroxybenzyl,[28] pyridyltriazole,[29,30] 2,2′-dipycolylamine,[31] bis(2-pyridylmethyl)amine (DPA),[32,33] bis(2-quinolylmethyl)amine (DQA),[32] *N*-(2-pyridylmethyl)glycine (NPG),[32] 2,2′-bipyridine,[34] *N*-(2-picolyl-4-hydroxy-3amino)benzoic acid (PHAB),[35] and tripodal amines,[36] functionalized with sugar moieties (limited to specific monosaccharides), have been used as ligands and reported as promising chelators for Tc^I and Re^I cores.

To be able to study the influence of a variety of saccharide residues and to reduce the time-consuming preparation and purification of ligands, we chose to apply the "Huisgen" cycloaddition reaction using readily available carbohydrate-linked azides.[37,38] The cytotoxicity and stability of the resulting complexes were studied as prerequisites for their ability to be applied as radiotracers.

Results and Discussion

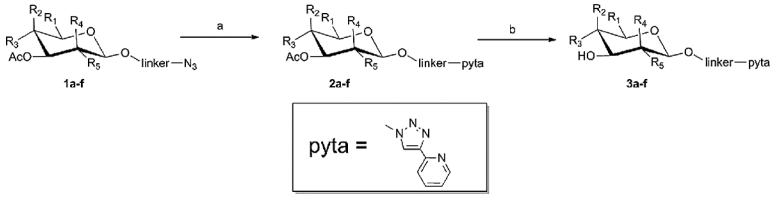
Synthesis and Characterization

Azide derivatives **1a–e** of sugars including glucose, xylose, galactose, and mannose, were synthesized from the corresponding bromides by reaction with sodium azide in *N*,*N*-dimethylformamide (DMF), according to a previously published method.[39] The products were converted into the corresponding pyridyltriazole derivatives **2a–e** by copper(I)-catalyzed "Huisgen" cycloaddition reaction with 2-ethynylpyridine (Scheme 1) using $CuSO_4$ and sodium ascorbate as catalytic system in a mixture of tetrahydrofuran (THF) and water. The yields of the reactions were between 80 and 88% (with exception of maltose with only 48% yield).

Deacetylation of **2a–e** using DOWEX OH^- exchange resin was performed in EtOH/H_2O (1:1). The reaction mixture was stirred overnight at 60 °C. After removing the resin by filtration through silica gel and evaporation of the solvent mixture, white powders were obtained. These reactions led to compounds **3a–e** containing deprotected sugar moieties. In an analogous procedure, ligands **2f** and **3f** containing two 2-pyridyltriazole groups and glucose as the sugar moiety were prepared.

One triazole ligand without a sugar moiety, namely 2-{1-[4-(*tert*-butyl)benzyl]-1*H*-1,2,3-triazol-4-yl}pyridine (**4**), was synthesized as a reference for further analysis and tests.[40] The synthesis of **4** was performed in a mixture of EtOH and water (7:3 ratio) in the presence of $CuSO_4$ and sodium ascorbate. This mixture was heated in a microwave at 125 °C for 45 min, crystallized from a mixture of CH_2Cl_2/*n*-pentane, and the product was collected as a white powder.

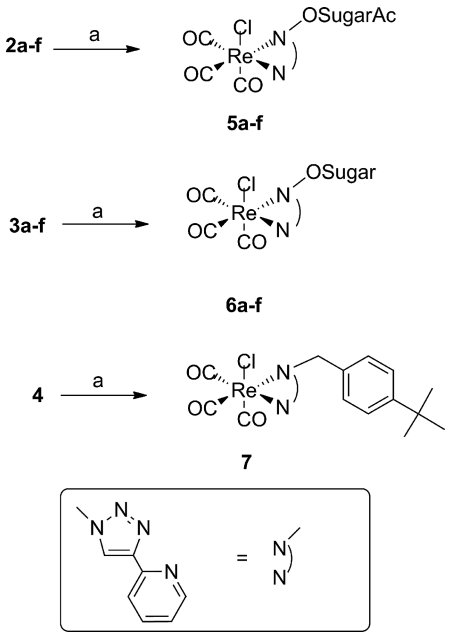
Ligands **2a–f**, **3a–f**, and **4** were used to prepare the rhenium complexes (Scheme 2) by reaction with $Re(CO)_5Cl$ in methanol.[29] The reaction mixture was stirred overnight at 60 °C, concentrated, and cooled to low temperature



	R_1	R_2	R_3	R_4	R_5	linker	pyta no.
Type **1-2a** (Glc)	CH_2OAc	H	OAc	H	OAc	Et	1
Type **1-2b** (Xyl)	H	H	OAc	H	OAc	Et	1
Type **1-2c** (Gal)	CH_2OAc	OAc	H	H	OAc	Et	1
Type **1-2d** (Man)	CH_2OAc	H	OAc	OAc	H	Et	1
Type **1-2e** (Mal)	CH_2OAc	H	(1→4)-α-AcGlc	H	OAc	Et	1
Type **1-2f** (Glc)	CH_2OAc	H	OAc	H	OAc	*i*-Pr	2
Type **3a** (Glc)	CH_2OH	H	OH	H	OH	Et	1
Type **3b** (Xyl)	H	H	OH	H	OH	Et	1
Type **3c** (Gal)	CH_2OH	OAc	H	H	OH	Et	1
Type **3d** (Man)	CH_2OH	H	OH	OH	H	Et	1
Type **3e** (Mal)	CH_2OH	H	(1→4)-α-Glc	H	OH	Et	1
Type **3f** (Glc)	CH_2OH	H	OH	H	OH	*i*-Pr	2

Scheme 1. Schematic representation of the synthesis of 2-pyridyltriazole ligands. Reagents and conditions: (a) 2-ethynylpyridine, $CuSO_4$, sodium ascorbate, THF/H_2O (1:1), 60 °C, overnight, in the dark; (b) DOWEX OH^-, EtOH/H_2O (1:1), 60 °C, overnight.

(4 °C). All complexes precipitated and were filtered off from the solutions and obtained as yellow powders.



Scheme 2. Synthesis of rhenium complexes **5a**–**f**, **6a**–**f**, and **7**. Reagents and conditions: (a) $Re(CO)_5Cl$, MeOH, 60 °C, overnight.

The purity of the compounds was established by NMR, UV/Vis, and IR spectroscopy, ESI-MS spectrometry as well as elemental analysis. The mass spectra of **5a**–**f**, **6a**–**f**, and **7** showed signals of the complexes corresponding to $[M - Cl^-]^+$ and $[M + Na]^+$ ions. The IR spectra of **5a**–**f**, **6a**–**f**, and **7** showed the appearance of new absorption bands corresponding to CO groups. Three absorption bands, which appeared at 1900–2000 cm^{-1} (Table 1) are characteristic for ν_{CO} stretching frequencies in rhenium carbonyl complexes.[41,42]

The NMR spectra indicated that the products consist of a mixture of diastereoisomers of complexes due to the chirality of the sugar moiety. ^1H NMR spectra displayed signals corresponding to the pyridyltriazole groups, which were shifted to low field compared with those of the uncomplexed ligands. Furthermore, the ^1H NMR spectra showed double singlets between δ = 8 and 9 ppm, which were assigned to the protons of the triazole rings in the 5-position of **5a**–**f**. Analogous peaks were observed for complexes **6a**–**f**. A typical ratio of 1:1 was observed by the 5-proton of the triazole ring in the ^1H NMR spectrum. The ^{13}C NMR spectra contained a doubled set of signals, which were caused by the obtained mixtures of diastereoisomers.

Table 1. ^{13}C NMR and IR data for selected rhenium complexes **5a**,**e** and **6a**,**e**.

Compound	^{13}C NMR δ CO (ppm)	IR ν_{ReCO} [cm^{-1}]
5a	197.09, 195.70, 189.13[a]	2027 (ν_{sym}) 1926 (ν_{asym}) 1900 (ν_{asym})[c]
5e	197.07, 195.57, 189.10[a]	2022 (ν_{sym}) 1914 (ν_{asym}) 1887 (ν_{asym})[d]
6a	197.90, 197.11, 189.80[b]	2022 (ν_{sym}) 1933 (ν_{asym}) 1898 (ν_{asym})[d]
6e	198.14, 197.13, 194.01[b]	2022 (ν_{sym}) 1925 (ν_{asym}) 1891 (ν_{asym})[d]

[a] Measured in $CDCl_3$. [b] Measured in $[D_7]DMF + D_2O$. [c] Measured in KBr. [d] ATR-IR.

The UV/Vis spectra of the ligands (Figure 1) and complexes **5a**–**f**, **6a**–**f**, and **7** (Figure 2) were measured in aceto-

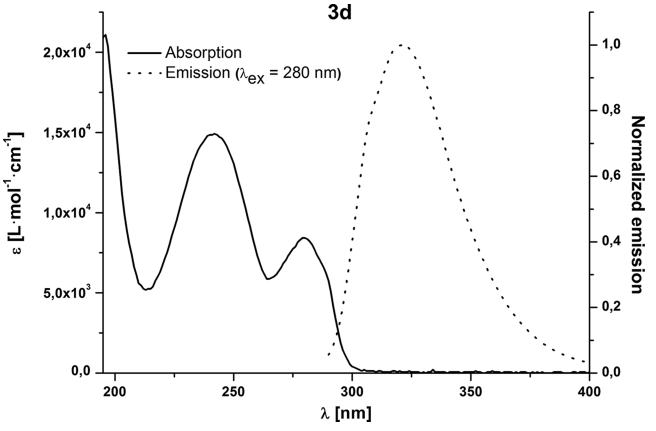


Figure 1. Absorption and emission spectra for selected 2-pyridyltriazole ligand **3d** bearing a mannose moiety in acetonitrile.

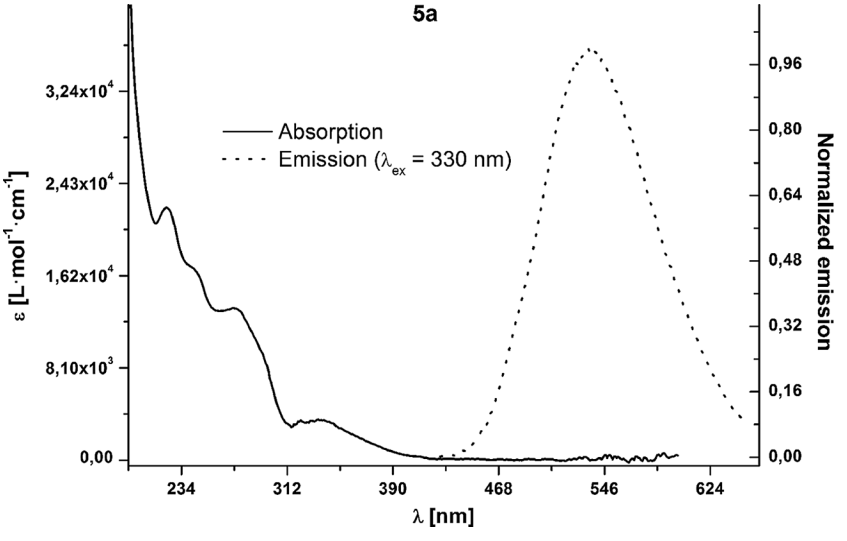


Figure 2. Absorption and emission spectra for a selected rhenium(I) complex **5a** bearing a glucose moiety in acetonitrile.

nitrile. The absorption bands at 330 nm can be assigned to the metal-to-ligand charge transfer (MLCT) transitions. The strong absorptions at 200 nm were associated with $\pi\rightarrow\pi^*$ transitions of the ligands. Emission spectra have been measured for all ligands and rhenium complexes in acetonitrile (Figure 2). The complexes exhibited luminescence in the visible region, with λ_{max} at 530 nm. In comparison to bipyridine-based rhenium complexes (λ_{max} = 633 nm), which were measured previously,[29] the absorption and emission spectra of the pyridyltriazole-based rhenium complexes is blueshifted by 100 nm.

In Vitro Stability Test for Rhenium Complexes

A histidine challenge experiment was performed to check the stability of the chosen complexes based on a slightly modified method described previously.[34,43,44] The experiment was performed in the presence of histidine (20 fold excess) in PBS buffer at 37 °C. The HPLC traces (MeOH/triethylamine phosphate) of samples taken from the reaction mixture were measured after 0, 2.5, 4.5, and 24 h. The results of the stability tests for rhenium complexes are shown in Figure 3.

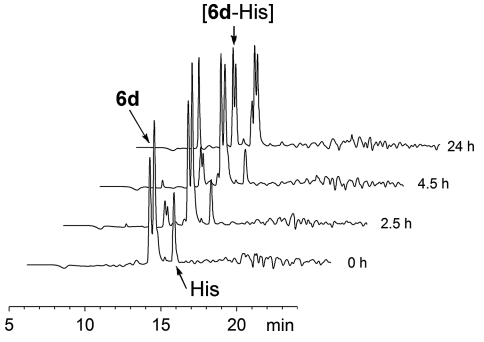


Figure 3. Histidine challenge experiment results (HPLC, UV/Vis detector) for the mannose-bearing rhenium complex **6d**.

A decrease of the main peak and an increase in the size of new peaks was observed over time. Two peaks of rhenium complexes were observed in the HPLC profile (retention time: 13 min) corresponding to the mixture of the diastereoisomers. The in vitro stability test showed that the rhenium complex was stable for approximately 2.5 h. After that time a new peak appeared (retention time: 11.5 min) corresponding to binding of histidine to the rhenium complex, with concomitant reduction in the size of the histidine peak over time (retention time: 15.5 min). Some peaks related to decomposition and other side products were also observed (retention time: 9 and 13 min).

Labeling with ^{99m}Tc

Technetium and rhenium isotopes (^{99m}Tc, $^{186/188}$Re) of tricarbonyl cores have been studied intensively. The ^{99m}Tc isotope is one of the most important radionuclides due to its short half-life (6 h) and emissions of readily detectable 140 keV γ-rays.

The preparation of ^{99m}Tc-labeled compound was performed by addition of $^{99m}TcO_4^-$ in 0.9% NaCl solution to the TYCO isolink kit and was followed by heating for 30 min at 100 °C. After cooling to room temperature, a mixture of PBS and HCl was added for neutralization. The resulting solution of $[^{99m}Tc(H_2O)_3(CO)_3]^+$ was added to 2-[4-(2-pyridyl)-1,2,3-triazol-1-yl]ethyl β-D-glucopyranoside (**3a**) and the mixture was heated to 100 °C for another 30 min. After cooling to room temperature, the radiochemical purity of the product **8** (Figure 4) was analyzed by HPLC and found to be 94%.

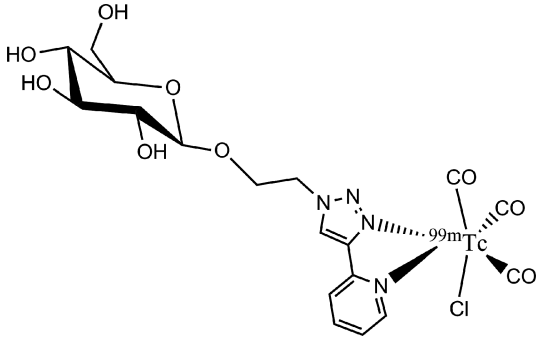


Figure 4. $^{99m}Tc^{I}$ complex **8** of glucosylated ligand **3a**.

Histidine Stability Test of ^{99m}Tc Complex 8

A histidine stability test was performed for the technetium complex of the pyridyltriazole ligand containing a glucose moiety. The experiment was done in an analogous way to the stability test of the rhenium complex described above. A solution of histidine in PBS was added to a solution of technetium complex of 2-[4-(2-pyridyl)-1,2,3-triazol-1-yl]ethyl β-D-glucopyranoside (**8**). The resulting mixture was incubated at 37 °C and samples for HPLC analysis were taken after 1, 2, 3, 4, 6, and 24 h. The HPLC traces for the stability test are shown in Figure 5. Surprisingly, the signal corresponding to the ^{99m}Tc labeled complex did not change over time (retention time: 16.5 min) and the complex was stable up to 24 h, with no other radioactive species

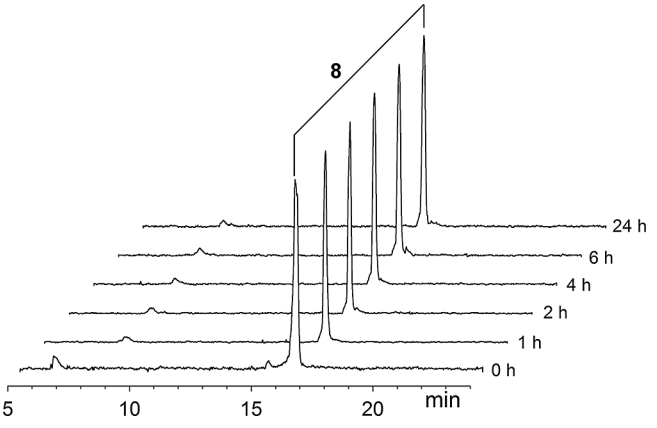


Figure 5. Histidine challenge experiment results (HPLC radiodetector traces) for the ^{99m}Tc complex **8**.

being detected. This is in contrast to the observations for the Re complexes described above as well as to previously published trials with sugar-containing ^{99m}Tc complexes based on bipyridine (stable only 4.5 h).[34] To our knowledge, this is the first histidine-stable ^{99m}Tc complex with a bidentate pyridyltriazole ligand. There is only one pyridyltriazole ligand described (without a sugar moiety) that was used for complexation of ^{99m}Tc, but no stability tests were performed in that study.[45] The described stable ^{99m}Tc^{I} complexes are derived from ligands that are at least tridentate and always require a third coordination side.

Cytotoxicity Test

For all rhenium(I) complexes, cytotoxicity tests were performed against HepG2 cells. Cells were cultivated in 37 °C in DMEM-F12 and incubated for 24 to 96 h. Every 24 h, 96-well-plates were taken to perform a CellTiter-Blue Cell Viability Assay. For detection, resazurin dye was used. The resazurin itself is a non-fluorescent, dark-blue dye (absorption maximum at 650 nm) and it is reduced to resorufin in viable cells (the color changes to pink, emission maximum at 590 nm, absorption maximum at 573 nm). The absorbance was measured at 0, 1, 2, and 4 h. The cytotoxicity tests for the complexes against HepG2 cells showed that none of the sugar-bearing ligands or complexes was cytotoxic up to a concentration of 100 μM. In contrast, the rhenium complex of the ligand which did not contain a sugar moiety (**7**) showed significant toxicity.

Conclusions

New carbohydrate-based 2-pyridyltriazole ligands have been synthesized by using the copper(I)-catalyzed azide-alkyne 1,3-dipolar Huisgen cycloaddition, which allowed the straightforward synthesis of the desired compounds (yields >80%) under mild conditions. Synthesis of pyridyltriazole ligands can be applied to different saccharides. The obtained organic ligands were treated with $[Re(CO)_5Cl]$ and the formed complexes were characterized by means of NMR, IR, and UV/Vis absorption and by emission spectroscopy, elemental analysis as well as mass spectrometry to verify their molecular structure. Radiolabeling of one of the ligands with ^{99m}Tc resulted in the formation of the corresponding complex in high radiochemical purity. The in vitro stability tests for selected rhenium complexes showed that the complexes are stable for only about 2.5 h before they undergo side reactions. In contrast, the ^{99m}Tc complex containing solely the *gluco*-conjugated 2-pyridyltriazole ligand is stable for over 24 h in the histidine stability test. Additionally, the cytotoxicity of the rhenium(I) complexes against HepG2 cells was tested and the results showed that the obtained complexes bearing sugar residues are not toxic up to a concentration of 100 μM. Considering the stability of the ^{99m}Tc complex and the observed nontoxicity, the synthesized derivatives are potential candidates for in vivo determination of sugar-dependent biodistribution and further development of selective radiotracers.

Experimental Section

Materials and General Experimental Details: All reagents and solvents were commercial products purchased from Aldrich, Sigma, Fluka, Across Organics, or Alfa Aesar and were used without further purification. The Isolink kits were a gift from Mallinckrodt. Chromatographic separation was performed with standardized silica gel 60 (Merck). The progress of reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel 60 (Merck). Azides **1a**–**f** were prepared according reported procedures.[46–50] For cytotoxicity tests, HepG2 cells, 96-well-plates (Greiner Bio-One), Trypsin (Lonza), HBBS (Lonza), DMEM-F12 (Invitrogen) + 1% Penicillin/Streptomycin 100x (PAA) + 10% fetal calf serum (Sigma–Aldrich), plate reader POLARstar Omega (BMG Labtech), CellTiter-Blue Cell Viability Assay (Promega), DMSO (AppliChem) were used.

Instrumentation: ^{1}H and ^{13}C NMR spectra were recorded with Bruker spectrometers (400, 300 and 250 MHz). UV/Vis absorption spectra were recorded with a Specord 250 (Analytik Jena) and emission spectra with a FP 6500 (JASCO) spectrometer (298 K, 10^{-6} and 10^{-5} M solutions in acetonitrile or methanol). IR spectra were recorded with a Bruker Tensor 37 and a Nicolet AVATAR 370 DTGS spectrometer using the ATR technique or with a Shimadzu FTIR 8700 as KBr disks. MALDI-TOF MS spectra were obtained with a Voyager DE PRO Biospectrometry Workstation (Applied Biosystems) time-of-flight mass spectrometer with dithranol as matrix. Elemental analyses were measured with a Leco CHN-932. Electrospray ionization mass spectrometry (ESI-MS) performed with a JEOL JMS-T100LC and a Bruker MicroQTof. For HPLC analysis during the histidine stability test, a JASCO system equipped with detector MWL (MD-1510), pump (PU-980), and column (Daicel Chiracel OD-H; Phenomenex Synergi 4u Hydro-RP 80A; 250 × 4.6 mm) was used. To assess the radiochemical purity, a HPLC-system was used with a Binary pump (HP 1100), radio detector (Knauer Radioflow Detector LB 509), refractive index detector (Agilent technologies 1260 Infinity), and column (HP ODS Hypersil; 5 μm, 100 × 4.6 mm).

General Procedure for the Preparation of Azides: Azide derivatives **1a**–**e** were synthesized from suitable bromides by reaction with an excess of sodium azide in DMF.[46–50]

General Procedure for the Copper(I)-Catalyzed Azide-Alkyne 1,3-Cycloaddition: To a solution of suitable azide **1a**–**f** and 2-ethynylpyridine in THF/H_2O (1:1), copper(II) sulfate solution (5–10 mol-%) in water and a sodium ascorbate solution (50–100 mol-%) in water were added. The mixture was stirred at 60 °C for 2 d in the dark. The products were extracted with ethyl acetate, washed with 25% ammonia solution or filtered through silica gel to remove copper residue and collected as white powders.

2-[4-(2-Pyridyl)-1,2,3-triazol-1-yl]ethyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (2a):[51] 2-Ethynylpyridine (0.5 g, 4.86 mmol) was added to a solution of **1a** (1.87 g, 4.48 mmol), then sodium ascorbate (297 mg, 1.5 mmol) and $CuSO_4 \cdot 5H_2O$ (22 mg, 0.1 mmol) were added.[29] Yield: 1.8 g (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57–8.55 (m, 1 H, 6-pyH), 8.17 (s, 1 H, 5-triazoleH), 8.13 (d, ^{3}J = 7.8 Hz, 1 H, 3-pyH), 7.79–7.73 (dt, ^{3}J = 7.8, ^{4}J = 2.4 Hz, 1 H, 4-pyH), 7.24–7.19 (ddd, ^{3}J = 7.5, ^{3}J = 3.8, ^{4}J = 1.1 Hz, 1 H, 5-pyH), 5.19–4.98 (m, 3 H, 3-H, 4-H, 2-H), 4.68 (m, 1 H, CH_2N), 4.61–4.51 (m, 1 H, CH_2-N), 4.49 (d, ^{3}J = 7.5 Hz, 1 H, 1-H), 4.33–4.21

(m, 2 H, O-CH_2, 6-H), 4.15–4.09 (m, 1 H, 6-H), 4.00–3.93 (m, 1 H, O-CH_2), 3.71–3.65 (m, 1 H, 5-H), 2.07, 2.00, 1.98, 1.89 (4s, 12 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.58, 170.12, 169.44, 169.35 (CO), 150.17 (2-pyC), 149.40 (6-pyC), 148.37 (4-triazoleC), 136.78 (4-pyC), 123.27 (5-triazoleC), 122.80 (5-pyC), 120.08 (3-pyC), 100.53 (C-1), 72.55 (C-3), 71.98 (C-5), 70.85 (C-2), 68.18 (C-4), 67.73 (O-CH_2), 61.68 (C-6), 50.14 (CH_2-N), 20.68, 20.53, 20.36 (CH_3) ppm. ESI-TOF MS: *m/z* calcd. for $C_{23}H_{28}N_4O_{10}Na$ [M + Na]$^+$ 543.17; found 543.1; *m/z* calcd for $C_{23}H_{29}N_4O_{10}$ [M + H]$^+$ 521.19; found 521.1. $C_{23}H_{28}N_4O_{10}$ (520.50): calcd. C 53.07, H 5.42, N 10.76; found C 53.11, H 5.36, N 10.42. IR (ATR): $\tilde{\nu}$ = 1736 (ν_{CO}) cm^{-1}. UV/Vis (CH_3CN): λ ($\varepsilon \times 10^{-3}$/M^{-1}cm^{-1}) = 281 (4.76), 244 (8.91), 207 (16.72) nm. FL (CH_3CN, λ_{ex} = 281 nm): λ = 314 nm.

Ligands **2b**–**f** were prepared as described for **2a**. For more details see the Supporting Information.

General Procedure for the Preparation of Deprotected Ligands: The protected triazole ligands **2a**–**f** were dissolved in an ethanol/water solution, then DOWEX 550 OH^- anion exchange resin was added. The reaction mixture was stirred at 60 °C overnight. When TLC (ethyl acetate) indicated that no starting material remained, the reaction mixture was filtered and evaporated to afford the deprotected triazole ligands **3a**–**f** as white powders. In the case of **3e**, compound **2e** was dissolved in methanol and sodium methoxide was added until pH 9. After 1 h, TLC (ethyl acetate) indicated that no starting material remained and DOWEX H^+ was added gradually to reach pH 7.

2-[4-(2-Pyridyl)-1,2,3-triazol-1-yl]ethyl β-D-Glucopyranoside (3a): DOWEX 550 OH^- anion exchange resin (10 g) was added to a solution of **2a** (1 g, 1.92 mmol).[26] Yield: 0.32 g (60%). ^{1}H NMR (400 MHz, D_2O): δ = 8.46–8.44 (m, 1 H, 6-pyH), 8.37 (s, 1 H, 5-triazoleH), 7.89–7.82 (m, 2 H, 3-pyH, 4-pyH), 7.38–7.36 (t, ^3J = 6.6 Hz, 1 H, 5-pyH), 4.69 (m, 2 H, CH_2-N), 4.45 (d, ^3J = 7.92 Hz, 1-H), 4.35–4.30 (m, 1 H, O-CH_2), 4.18–4.13 (m, 1 H, O-CH_2), 3.87–3.83 (m, 1 H, 4-H), 3.67–3.63 (dd, ^2J = 12.8, ^3J = 6.8 Hz, 1 H, 6-H), 3.48–3.32 (m, 3 H, 6-H, 5-H, 3-H), 3.28–3.24 (t, ^3J = 9.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR (D_2O): δ = 148.93 (6-pyC), 148.09, 146.77 (2-pyC, 4-triazoleC), 138.59 (4-pyC), 124.39 (5-triazoleC), 123.98 (5-pyC), 120.93 (3-pyC), 102.53 (C-1), 75.98 (C-5), 75.71 (C-3), 73.03 (C-2), 69.65 (C-4), 68.06 (O-CH_2), 60.79 (C-6), 50.59 (CH_2-N) ppm. ESI-TOF MS: *m/z* calcd. for $C_{15}H_{20}N_4O_6Na$ [M + Na]$^+$ 375.13; found 375.2; *m/z* calcd. for $C_{15}H_{21}N_4O_6$ [M + H]$^+$ 353.15; found 353.2. $C_{15}H_{20}N_4O_6$ (352.35): calcd. C 51.13, H 5.72, N 15.90; found C 51.31, H 5.75, N 15.82. IR (ATR): $\tilde{\nu}$ = 3279 (ν_{OH}) cm^{-1}. UV/Vis (CH_3CN): λ ($\varepsilon \times 10^{-3}$/M^{-1}cm^{-1}) = 281 (4.54), 243 (8.22), 204 (10.78) nm. FL (CH_3CN, λ_{ex} = 281 nm): λ = 322 nm.

Ligands **3b**–**f** were prepared as described for **3a**. For more details see the Supporting Information.

2-{1-[4-(*tert*-Butyl)benzyl]-1*H*-1,2,3-triazol-4-yl}pyridine (4): The ligand was prepared according to a previously described procedure.[40] For more details see the Supporting Information.

General Procedure for Preparation of Rhenium(I) Complexes: To a solution of the ligands **2a**–**f** or **3a**–**f** in methanol, rhenium pentacarbonyl chloride was added. The mixture was stirred overnight at 60 °C. After cooling to room temperature, the solution was concentrated and left for precipitation. Yellow powders were collected.

2-[4-(2-Pyridyl)-1,2,3-triazol-1-yl]ethyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside Rhenium Complex (5a):[29] Rhenium pentacarbonyl chloride (42 mg, 0.12) was added to a solution of **2a** (0.06 g, 0.12 mmol).[29] Yield: 60 mg (63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.00 (d, J = 5.7 Hz, 2 H, 6-pyH), 8.42, 8.38 (2s, 2 H, 5-triazoleH), 8.04–8.01 (m, 4 H, 3-pyH, 4-pyH), 7.47–7.44 (m, 2 H, 5-pyH), 5.26–5.19 (m, 2 H, 3-H), 5.11–5.00 (m, 4 H, 4-H, 2-H), 4.84–4.65 (m, 4 H, CH_2), 4.56 (d, ^3J = 7.8 Hz, 1 H, 1-H), 4.51 (d, ^3J = 7.8 Hz, 1 H, 1-H), 4.32–4.15 (m, 6 H, CH_2, 6-H), 4.87–3.92 (m, 5-, 2 H, H), 3.80–3.72 (m, 2 H, 6-H), 2.09–1.65 (8s, 24 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 197.09, 195.70, 189.13 (CO), 170.58–169.44 (CO,OAc), 153.20 (6-pyC), 149.37, 149.28, 148.77, 148.68 (2-pyC, 4-triazoleC), 139.28, 139.22 (4-pyC), 125.83 (5-triazoleC), 125.50, 125.37 (5-pyC), 122.22 (3-pyC), 100.48, 100.11 (C-1), 72.19, 72.09 (C-3), 71.23, 71.11 (C-5), 68.21, 68.13 (C-2), 66.77 (C-4), 66.23 (CH_2), 61.64, 61.57 (C-6), 52.05, 51.84 (CH_2), 20.97–20.51 (CH_3,OAc) ppm. ESI-TOF MS: *m/z* calcd. for $C_{26}H_{28}O_{13}N_4Re$ [M – Cl]$^+$ 790.73; found 790.9; *m/z* calcd. for $C_{26}H_{28}O_{13}N_4ClReNa$ [M + Na]$^+$ 849.08; found 848.9. $C_{26}H_{28}ClN_4O_{13}Re$ (826.18): calcd. C 37.80, H 3.42, N 6.78; found C 37.54, H 3.16, N 6.61. IR (ATR): $\tilde{\nu}$ = 1736 ($\nu_{C=O}$), 1879 (broad), 2022 (ν_{MCO}) cm^{-1}. UV/Vis (CH_3CN): λ ($\varepsilon \times 10^{-3}$/M^{-1}cm^{-1}) = 332 (3.72), 275 (10.26), 222 (22.52) nm. FL (CH_3CN, λ_{ex} = 332 nm): λ = 533 nm.

Complexes **5b**–**f** were prepared as described for **5a**. For more details see the Supporting Information.

2-[4-(2-Pyridyl)-1,2,3-triazol-1-yl]ethyl β-D-Glucopyranoside Rhenium Complex (6a):[29] Rhenium pentacarbonyl chloride (69 mg, 0.19 mmol) was added to a solution of **3a** (0.06 g, 0.17 mmol). Yield: 96 mg (86%). ^{1}H NMR (300 MHz, [D_7]DMF + D_2O): δ = 9.38 (2s, 2 H, 5triazoleH), 9.07 (d, ^3J = 5.49 Hz, 4 H, 6-pyH), 8.33–7.76 (m, 4 H, 3-pyH, 4-pyH), 7.75–7.71 (m, 2 H, 5-pyH), 4.98–4.92 (m, 4 H, CH_2), 4.49 (dd, ^3J = 7.6 Hz, 2 H, 1-H), 4.37–4.33 (m, 2 H, CH_2), 4.21–4.17 (m, 2 H, CH_2), 3.91–3.66 (m, 2 H, 6-Ha), 3.65–3.41 (m, 2 H, 6-Hb), 3.40–3.18 (m, 4 H, 5-H,4-H, 3-H,2-H) ppm. ^{13}C NMR ([D_7]DMF + D_2O): δ = 197.90, 197.11, 189.80 (CO), 153.19 (6-pyC), 149.37,148.56, 148.54 (2-pyC, 4-triazoleC), 126.89, 126.82 (5-triazoleC), 126.52 (5-pyC), 122.73 (3-pyC), 103.51, 103.35 (C-1), 77.29 (C-4), 77.00 (C-5), 73.81 (C-2), 70.56 (C-3), 67.31, 67.09 (CH_2), 61.65 (C-6), 52.31, 52.24 (CH_2) ppm. ESI-TOF MS: *m/z* calcd. for $C_{18}H_{20}O_9N_4Re$ [M – Cl]$^+$ 622.07; found 622.9; *m/z* calcd. for $C_{18}H_{20}O_9N_4ClReNa$ [M + Na]$^+$ 681.04; found 680.9. $C_{18}H_{20}ClN_4O_9Re{\cdot}0.5H_2O$ (667.0): calcd. C 32.41, H 3.17, N 8.40, Cl 5.31; found C 32.41, H 2.97, N, 8.22, Cl 5.58. IR (ATR): $\tilde{\nu}$ = 1898, 1933, 2022 (ν_{MCO}), 3434 (ν_{OH}) cm^{-1}. UV/Vis (CH_3CN): λ ($\varepsilon \times 10^{-3}$/M^{-1}cm^{-1}) = 330 (3.57), 271 (12.62), 222 (20.13) nm. FL (CH_3CN, λ_{ex} = 330 nm): λ = 533 nm.

Complexes **6b**–**f** were prepared as described for **6a**. For more details see the Supporting Information.

***tert*-Butylbenzyl-4-(2-pyridyl)-1,2,3-triazole Rhenium Complex (7):** Rhenium pentacarbonyl chloride (124 mg, 0.34 mmol) was added to a solution of **4** (0.10 g, 0.34 mmol). Yield: 129 mg (65%). ^{1}H NMR (300 MHz, [D_7]DMF): δ = 9.59 (s, 1 H, 5triazoleH), 9.27 (d, ^3J = 5.4 Hz, 1 H, 6-pyH), 8.58 (d, ^3J = 7.75 Hz, 1 H, 3-pyH), 8.49 (td, ^4J = 1.38, ^3J = 7.65 Hz, 1 H, 4-pyH), 7.92–7.86 (m, 1 H, 5-py), 7.71 (m, 4 H, benzylH), 6.14 (s, 2 H, CH_2), 1.47 (s, 9 H, CH_3) ppm. ^{13}C NMR ([D_7]DMF): δ = 198.06, 197.21, 189.82 (CO), 153.24 (6-pyC), 151.96 (benzylCq), 149.36, 149.10 (2-pyC, 4-triazoleC), 140.64 (4-pyC), 131.57 (benzylCq), 128.51 (benzylC), 126.51 (5-pyC), 126.08 (benzylC), 125.98 (5triazoleC), 122.88 (3-pyC), 54.99 (CH_2), 30.79 (CH_3) ppm. ESI-TOF MS: *m/z* calcd. for $C_{21}H_{20}O_3N_4Re$ [M – Cl]$^+$ 563.11; found 563.0; *m/z* calcd. for $C_{21}H_{20}O_3N_4ClReNa$ [M + Na]$^+$ 621.07; found 620.9. $C_{21}H_{20}ClN_4O_3Re$ (598.07): calcd. C 42.17, H 3.37, N 9.37; found C 42.35, H 3.62, N 9.72. IR (ATR): $\tilde{\nu}$ = 1895 (ν_{MCO} broad), 2022 (ν_{MCO}) cm^{-1}. UV/Vis (CH_3CN): λ ($\varepsilon \times 10^{-3}$/M^{-1}cm^{-1}) = 335 (3.89),

275 (13.97), 221 (36.71) nm. FL (CH_3CN, λ_{ex} = 335 nm): λ = 533 nm.

In Vitro Stability Test for Rhenium Complex: A solution of histidine (20 molar excess) in a mixture of PBS (phosphate buffered saline) and water (1:9) was added to a solution of the complex in PBS. The experiment was performed at 37 °C for 24 h and the progress of the experiment was monitored by HPLC (MeOH/TEAP). The samples were taken from the reaction mixture after 0, 1, 2.5, 4.5, and 24 h. R_t = 9 (unidentified product), 11.5 {[$Re(CO)_3$-His]}, 13 (Re complex), 15.5 (histidine) min.

Labeling: Addition of $^{99m}TcO_4$ (2.0 GBq) in a solution of NaCl (0.9%, 2 mL) to the TYCO isolink kit was followed by heating for 30 min at 100 °C. After cooling to room temperature, a mixture of phosphate buffer (0.6 M, 0.8 mL) and HCl (1.0 M, 1.2 mL) was added to neutralize the solution. an aliquot of the resulting $[^{99m}Tc(H_2O)_3(CO)_3]^+$ solution (300 MBq, ca. 0.4 mL) was added to 2-[4-(2-pyridyl)-1,2,3-triazol-1-yl]ethyl β-D-glucopyranoside (**3a**; 2.0 mg, 5.68 μmol) and the mixture was heated in a glass vial at 100 °C for another 30 min. After cooling to room temperature, the radiochemical purity of the product was analyzed by HPLC [solvent A: triethylamine phosphate (0.05 M) aqueous solution, adjusted with H_3PO_4 to pH 2.25, solvent B: methanol; flow rate: 0.7 mL min^{-1}; gradient: 0–10 min 100% A, 10–15 min to 100% B, 15–25 min 100% B, 25–27 min to 100% A, 27–35 min 100% A]: R_t = 6.4 and 8.3 (unidentified products), 16.5 (^{99m}Tc-labeled compound) min. Radiochemical purity: 94%.

Histidine Stability Test of ^{99m}Tc Complex: A solution of histidine (0.1 mmol, 1.0 mL, PBS, pH 7.4) was added to a solution of the technetium complex of 2-[4-(2-pyridyl)-1,2,3-triazol-1-yl]ethyl β-D-glucopyranoside (1.0 mL). The resulting mixture was incubated at 37 °C and samples for HPLC analysis were taken after 1, 2, 3, 4, 6, and 24 h. R_t = 6–9 (unidentified byproducts), 16.5 (99mTc-labeled compound) min; R_t (standard) [$^{99m}Tc(His)(CO)_3$] = 15.0 min.

Cytotoxicity Test: HepG2 cells were cultivated under standard conditions (37 °C, 5% CO_2) in DMEM-F12 (Invitrogen) containing 10% fetal calf serum (Sigma–Aldrich) and 1% Penicillin/Streptomycin 100× (PAA). For cell viability assay, cells were incubated for 10 min with Trypsin (Lonza) and seeded into 96-well-plates (Greiner Bio-One) at a concentration of 10,000 cells per well. After 24 h incubation, rhenium complexes were dissolved in water-free DMSO (AppliChem) at a concentration of 10 mM. Cells were washed twice with HBSS (Lonza). Rhenium complexes were diluted to a final concentration of 100 μM by using DMEM-F12 medium. Aliquots (200 μL) of each solution was added to the cells, which were incubated for 24–96 h. Every 24 h 96-well-plates were taken to perform a CellTiter-Blue Cell Viability Assay (Promega). Before performing CellTiter-Blue experiment, the absorbance (605 nm, 573 nm) of untreated cells was measured with a plate reader (Polarstar Omega, BMG Labtech). CellTiter-Blue reagent was then added at a volume of 20 μL/100 μL cell culture medium. The absorbance was measured at 0, 1, 2, and 4 h. As positive control, cisplatin, dissolved in water, and added at a final concentration of 100 μM, was used. The negative control was incubated with DMEM-F12 medium, containing 1% DMSO only.

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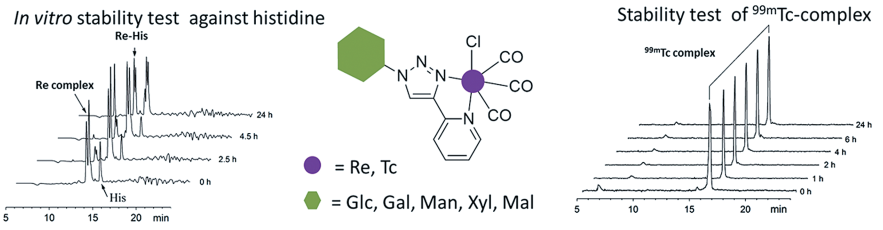

A series of pyridyltriazole ligands containing sugar moieties and their corresponding Re(I) complexes were synthesized and characterized. Stability tests against histidine showed that the complexes are stable up to 2.5 h; the ^{99m}Tc-labeled complex was stable up to 24 h. All sugar-based Re^{I} complexes were nontoxic against HepG2 cells; in contrast, the Re^{I} complex without a carbohydrate moiety was toxic.

