DOI: 10.1002/ejic.200900561

In^{III} and Ga^{III} Complexes of Sugar-Substituted Tripodal Trisalicylidene Imines: The First ^{68}Ga-Labelled Sugar Derivative

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Keywords: Carbohydrates / Gallium / Indium / Nuclear imaging / Isotopic labelling / Medicinal chemistry

Gallium and indium complexes derived from salicylaldimines of 1,1,1-tris(aminomethyl)ethane (TAME) with pendant xylose, glucose and galactose units have been synthesised as model compounds for potential application as radiotracers. The formed neutral complexes have been characterised by NMR spectroscopy, elemental analysis, mass spectrometry and, in the case of the galactose-bearing In^{III} complex, by single-crystal X-ray structure analysis. Octahedral coordination was observed with the appearance of an equilibrium of Λ- and Δ-isomers at the metal centre. The glucose-appended ligand was radiolabelled with ^{68}Ga^{III} ions in up to 98 % yield depending on the prevailing pH value. The in vitro stability of the radioactive complex was examined by challenge experiments against apo-transferrin and blood plasma. Very high stability was observed; even after a period of 2 h, 90 % of the complex could still be detected.

Introduction

Isotopes of gallium and indium are used in diagnostic nuclear medicine, e.g. the γ-emitting radionuclides ^{67}Ga (coupled to citrate for lymphoma and infection imaging) and ^{111}In (mainly for labelling of peptides or coupled to oxine for radiolabelling of blood cells). ^{68}Ga is a generator-produced metallic positron emitter with a half-life of 68 min.[1] It is nowadays used increasingly for molecular imaging of neuroendocrine tumours by receptor PET/CT.[2–5] Both the easy availability from a generator with high specific activity and the relatively short half-life make this radionuclide an optimal candidate for radiolabelling of molecules with fast pharmacokinetics such as small carbohydrates, peptides or oligonuclides.[6–8] A further important advantage in terms of radiolabelling is the variable complexation behaviour of the Ga^{3+} ion. Stable complexes were formed with substituted azamacrocyclic ligands such as 1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododecane (DOTA) as well as with many different tripodal and/or polydentate ligands such as tris(2-mercaptobenzyl)-amine.[9] ^{68}Ga–DOTA-labelled compounds are of particular interest for PET/CT imaging.[10,11] DOTA is also widely used as a ligand to bind useful β-emitters (e.g. ^{90}Y or ^{177}Lu) for therapy. Metal complexes structurally derived from 1,1,1-tris(aminomethyl)ethane (TAME) are known to complex a variety of metal ions, e.g. Cr, Co and Cu ions.[12–14] *N*-Functionalised TAME ligands [e.g. bis(carboxymethyl)-amino derivatives,[15,16] catecholamide[17] and aminophenolates[18,19]] were used for the complexation of gallium, indium and other metal ions. Tripodal tris(salicylaldimine) from 1,1,1-tris(aminomethyl)ethane is known to complex gallium(III) in a stable fashion.[20–24] Experiments concerning their biodistribution revealed the decomposition of these neutral lipophilic gallium complexes in vivo, suggesting the binding of the metal ions to macromolecules in the liver.

To introduce hydrophilicity and solubility, to lower cytotoxicity and to target carbohydrate-specific binding domains and transporters, the introduction of sugar moieties has become an ascending field of interest.[25] The most common, best studied example of imaging molecular processes at a cellular level is the use of the glucose analogue ^{18}F-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejic.200900561.

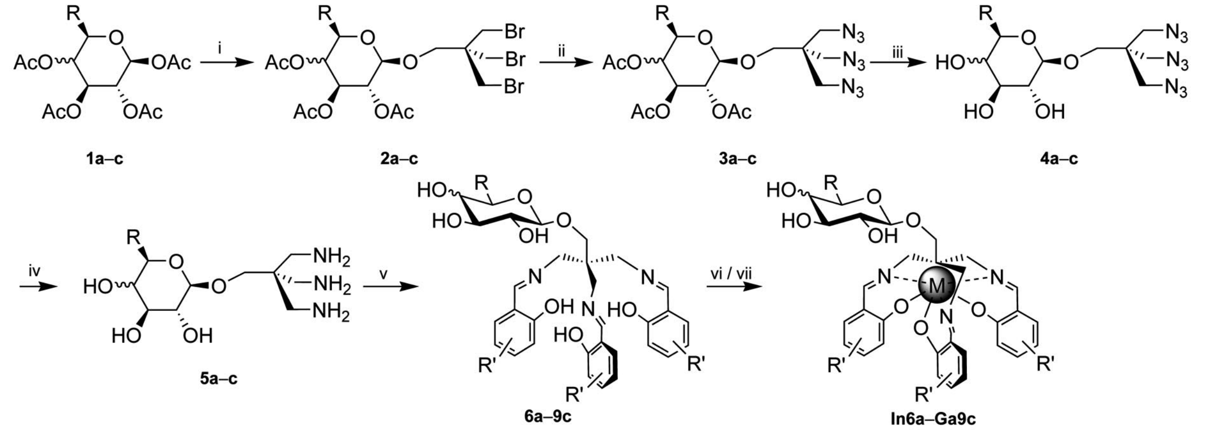
labelled 2-fluoro-2-deoxyglucose (FDG) with PET.[26] Most cancer cells over-express GLUT1, a high-affinity glucose transporter, and therefore have an increased glucose uptake when compared with normal cells.[27,28] Thus, most of the radiometal-labelled compounds containing sugar residues are therefore glucose-appended to take advantage of this phenomenon although it could be shown by in vitro experiments that glucose derivatives bearing metal-coordinating cores are not taken up by the GLUT1 transporter.[29] However, a number of carbohydrate-appending radiolabelled compounds have been synthesised, comprised of bi- and tridentate ligands. 2,2′-Bipyridyl,[30] 2,2′-dipicolylamine,[31,32] 3-hydroxypyridone,[33] 2-hydroxybenzyl-[34] and 2-(iminodiacetato)ethyl-functionalised[35] derivatives of different monosaccharides could be used as chelators for radionuclides. Similar complexes have been reported from 1,3-diamines of sugars.[36] Up to now most of the work was focused on ^{99m}Tc complexes.[37] Sugar-appending Ga and In complexes are rarely described in the literature. Solely glucose- and 2-amino-2-deoxyglucose-based 3-hydroxy-4-pyridonato complexes of In^{III} and Ga^{III} have been synthesised and structurally characterised.[38] Because ^{68}Ga is a generator product and therefore much more cost-effective than ^{18}F-labelled FDG, which depends on the availability of a cyclotron, the use of related complexes as tracers in imaging is very promising. Due to the specificity of the GLUT1 transporter such complexes will not be able to act as an FDG substitute but possess the alternative – in particular by the use of other sugar units – to trace more specific metabolic events. Alternative mechanisms for uptake and enrichment were shown, e.g. for galactose derivatives and their uptake by the hepatic asyaloglycoprotein receptor (ASGP-R) as shown for Gd^{III} and ^{153}Sm^{III} complexes of tetraazacyclododecanetetraacetic acid (DOTA) ligands functionalised with galactose residues used for molecular imaging.[39] Additionally, they are processed by galactosidase, a marker enzyme for gene expression in transgenic animals and were used for the localisation and visualisation of gene expression by MRI.[40,41] Recently it could be demonstrated that other carbohydrates are also able to target different transporter systems, e.g. fluorescent fructose derivatives are taken up by GLUT5 and were used for imaging breast cancer cells.[42] Xylosides are able to act as primers for the production of glucosaminoglycans (GAGs), like heparan sulfate or controitin sulfate in mammalian cell lines by being incorporated on the first position of the growing chain. The activity was found to be aglycon-dependent. In humans, GAGs are involved in the regulation of various biological functions including wound healing, cell signalling, cell differentiation, angiogenesis, blood clotting and tumour-cell migration.[43,44]

As models towards imaging such molecular events we herein report the synthesis of tripodal tris(salicylaldimine) ligands tentatively functionalised with xylose, glucose or galactose and the formation of some of their In^{III} and Ga^{III} complexes. Gallium-68 labelling was carried out for the glucose derivative, and the stability of the resultant complex against apo-transferin and blood plasma was examined.

Results and Discussion

Ligand Synthesis

We reported the synthesis of the tripodal triamines **5a**–**c** for the formation of Re^{I} and ^{99m}Tc^{I} complexes previously.[45] In brief, starting from pentaerythritol tribromide, a glycosidation reaction was performed with 1,2,3,4,6-*O*-pentaacetyl-β-D-glucopyranoside, 1,2,3,4-*O*-tetraacetyl-β-D-xylopyranoside and 1,2,3,4,6-*O*-pentaacetyl-β-D-galactopyranoside (**1a**–**c**) by using $BF_3{\cdot}Et_2O$ in dichloromethane. In the case of galactose, the anomeric pure tribromide **2c** was obtained in 70% yield after chromatographic purification (Scheme 1). The corresponding glucose (**2b**) and xylose (**2a**) derivatives crystallised from the combined fractions in moderate yields after column chromatography. Each ^{1}H NMR spectrum of compounds **2a**–**c** shows one sugar-specific signal for the protons at the anomeric carbon atoms. The methylene groups directly bound to the glycosidic oxygen atom are diastereotopic and therefore show two doublets with a coupling constant of around 9.4 Hz and separated by 0.4–0.5 ppm. In the mass spectra, the typical isotope pattern of molecules containing three bromine atoms was observed. Subsequently, the tribromides were converted in $> 80\%$ yield to the corresponding triazides **3a**–**c** by nucleophilic substitution with an excess of sodium azide in DMF as solvent at 70 °C. The successful conversion could easily be monitored by the appearance of absorption bands in the IR spectra at 2100 cm^{-1} and the shifts of the ^{13}C NMR signals of the three equivalent CH_2 groups from $\delta = 34$ ppm (for the tribromides) to $\delta = 51$ ppm (for the triazides). Deacetylation of **3a**–**c** was performed in methanol/water at 60 °C by stirring the mixtures with OH^{-}-loaded Dowex resin.[46] After filtration through silica gel, the pure products **4a**–**c** could be obtained. Although we did not observe any problems with these substances so far, with an azide nitrogen content of up to 34% (for **4a**) the compounds should be handled with circumspection to avoid accidents. Therefore, only small amounts were dried to completeness to obtain analytical data. Characteristically, the C=O absorption bands in the IR spectra of **3a**–**c** disappear after complete deprotection. Reduction of the azide functions was carried out with PtO_2 in methanol and H_2 by stirring the solutions under hydrogen at room temperature overnight. The formed platinum was removed by filtration through a membrane filter, and the products were obtained as white hygroscopic powders after the removal of the solvent. The successful conversion could be monitored by the disappearance of the sensitive N_3 absorption at 2100 cm^{-1} in the IR spectra of the products **5a**–**c**. In the ^{1}H NMR spectra in deuterated methanol the signals of the NH_2 groups appear as a singlet at $\delta = 2.6$ ppm. The triamines are soluble in methanol and water but could not be cleaned additionally by column chromatography due to their high affinity towards all common chromatographic materials. Their purity and integrity were demonstrated by NMR spectroscopy and high-resolution mass spectrometry. Subsequent condensation with salicylaldehydes in dry ethanol



Scheme 1. Schematic representation of the synthesis of the tripodal ligands and the subsequent complexation of metal ions. (i) Pentaerythrol tribromide, $BF_3\cdot Et_2O$, CH_2Cl_2, room temp., 12 h; (ii) NaN_3, DMF, 70 °C, 12 h; (iii) Dowex-OH^-, H_2O/MeOH, 60 °C, 12 h; (iv) PtO_2/H_2, MeOH, room temp., 12 h; (v) appropriate salicylaldehyde, EtOH, 3 h, reflux; (vi) $InCl_3\cdot 4H_2O$, TEA, MeOH, reflux; (vii) $Ga(NO_3)_3\cdot H_2O$, TEA, MeOH, reflux.

Table 1. Overview of the tripodal trisalicylideneimines and metal complexes synthesised in this study referring to Scheme 1.

Sugar	Salicylaldehyde	5-Methylsalicylaldehyde	5-Hydroxysalicylaldehyde	3,5-Di-*tert*-butylsalicylaldehyde
β-D-Xylose	**6a** (In, Ga)	**7a** (In, Ga)	–	–
β-D-Glucose	**6b** (In, Ga)	–	–	**9b** (In)
β-D-Galactose	**6c** (In, Ga)	**7c** (In)	**8c** (–, –)[a]	**9c** (In, Ga)

[a] Decomposition of the ligand under the applied reaction conditions.

resulted in the formation of the final ligands. The application of differently substituted salicylaldehydes allows the tuning of the solubility and polarity of the resultant complexes. In the present study 3,5-di-*tert*-butyl-, 5-methyl-, 5-hydroxy- as well as unsubstituted salicylaldehydes were used for the condensation to obtain selected ligands (Table 1).

IR spectroscopic measurements did not show the appearance of phenolic OH groups besides the sugar OH groups (usually free phenols give a strong OH band at around 3600 cm^{-1}). The absence of this IR band in the case of the imines might be due to the formation of N···H–O hydrogen bonds. Furthermore, the salicylaldimines are characterised by the C=N stretching vibrations appearing at 1630 cm^{-1}. Further strong bands around 2900 cm^{-1} and in the region of 1280–750 cm^{-1} belong to the C–H, C–OH and O–H vibrations of the carbohydrate fragment. The ^1H NMR spectra show a typical singlet for the formed imino groups at low field at $\delta \approx 8.2$–8.4 ppm. The carbon signal for this imino group appears at $\delta \approx 170$ ppm in the ^{13}C NMR spectra. The aromatic protons of ligand **6c** (H-3′/H-5′ and H-4′/H-6′) give two multiplets at $\delta = 6.85$ and 7.29 ppm. For compound **8c**, where an OH substituent has been introduced at position 5′, the positive mesomeric effect of the hydroxy group causes the signals of the protons H-4′ and H-6′ (*ortho* to the OH group) to shift to higher field. All aryl protons now appear as one multiplet at $\delta = 6.78$ ppm. Such strong shifts are not observed for the alkyl substitution pattern seen for compounds **7a** and **9c**. Introduction of two *tert*-butyl groups at C-3′ and C-5′ as for compound **9c** simplifies the aromatic signal pattern. Only two doublets may be observed with a coupling constant of $^4J = 2.3$ Hz which is typical for *meta* coupling in aromatic systems.

Synthesis and Characterisation of the Metal Complexes

According to Scheme 1, indium(III) and gallium(III) complexes **In6a**–**Ga9c** were synthesised by starting from the respective ligands in the presence of either $Ga(NO_3)_3\cdot H_2O$ or $InCl_3\cdot 4H_2O$. The salicylaldimine ligands were stirred with triethylamine before a methanolic solution of the respective metal salt was added, leading to the neutral metal complexes **In6a**–**Ga9c**. When treated with $InCl_3\cdot 4H_2O$, the yellow ligand solutions decolourised until they became almost colourless. The corresponding gallium(III) complexes exhibited a yellow colour. The resultant solutions were heated under reflux for several hours, and the formation of the complexes was monitored by TLC. The metal complexes showed blue fluorescence under UV light irradiation. However, reaction of **8c** with Ga^{III} and In^{III} resulted in black precipitates with hardly any solubility. ESI-MS examinations on the product obtained from the reaction with gallium(III) indicated decomposition of the complex. After evaporation of the solvent, the crude products **In6a**–**Ga9c** were purified by column chromatography. Since Schiff bases are very sensitive towards hydrolysis, the silica gel used for chromatographic cleaning was deactivated with TEA. Depending on the substitution pattern of the salicylidene residues, the metal complexes were eluted with either methanol/ethyl acetate mixtures (**In6a**–**Ga7a**) or with pure ethyl acetate (**In9c** and **Ga9c**). The products were obtained as yellow or slightly yellow powders after concentration. The products still contained triethylammonium nitrate even after column chromatography with methanol/ethyl acetate due to the good solubility of the triethylammonium salt. In contrast, indium(III) complexes **In6a**–**In6c** were obtained as small pink crystals from methanol/water. After filtration and washing with water, the complexes **In6a**–**In6c** were obtained in high purity. For the metal complexes **In9c** and **Ga9c**, the triethylammonium salts were already removed by chromatography with ethyl acetate. The free salicylaldimines can be characterised by the C=N stretching vibrations appearing at 1630 cm^{-1}. For the salicyl complexes the C=N stretching band should appear at lower energy, thus it can be used as an indicator for the strength of the metal–imine bonding. When a metal ion is coordinated to an imino donor atom, a shift of the IR absorption band to lower wave numbers (and lower energy) is expected due to the loss of electron density from the nitrogen atom to the metal ion. Shifts of the Ar–O absorption bands upon complexation are excluded from this discussion, since these bands are impossible to assign next to the C–H and O–H deformation vibrations and the C–O stretching vibrations of the carbohydrate residues. The IR absorption spectra of the indium(III) and the gallium(III) complexes revealed variable bathochromic shifts. Compound **In9c** showed a significant shift to 1610 cm^{-1} compared to the free ligand **9c** with an absorption of 1628 cm^{-1}. Complexation of **7a** with In^{III} resulted in a bathochromic shift of at least 12 cm^{-1} compared to the free ligand (1632 cm^{-1}). The other metal complexes showed only shifts from 1 to 7 cm^{-1}. NMR spectroscopic analysis of the gallium(III) complexes (**Ga6a**–**c**, **Ga7a**, **Ga9c**) revealed the occurrence of two diastereomeric forms (Λ and Δ) in a 1:1 ratio. Their existence is indicated by a double set of signals for protons and carbon atoms at room temperature. Characteristically, the ^{1}H NMR spectra show two singlets for the imine CH=N protons. The sugar H-1 protons give two doublets separated by an average of 0.04 ppm. The other sugar protons of the two diastereomeric forms appear together in multiplets, since they are not that strongly influenced by metal complexation like H-1. Another special feature in the ^{1}H NMR spectra is the split of the CH$_2$N methylene groups adjacent to the imino group. Whereas they appear as one multiplet in the ligand spectra, they split into two multiplets for the gallium(III) complexes with a seaparation of about 0.4 ppm. In the ^{13}C NMR spectra the imino carbon atom CH=N, the anomeric carbon atoms (C-1) and the methylene group (CH$_2$N) split by about 0.1–0.3 ppm. Also, the methylene group adjacent to the glycosidic oxygen atom O–CH$_2$ gives two signals with a separation of about 0.2 ppm. The signals of the remaining sugar and aromatic carbon atoms are either not split at all or are barely split into two signals. Measurement of the ^{1}H NMR spectrum of complex **Ga6b** at 343 K showed, that at this temperature, an equilibrium between the Λ and Δ isomers on the NMR time scale is reached indicated by the occurrence of only one set of signals. The corresponding indium(III) complexes (**In6a**–**c**, **In7a** and **In9c**) did not show the presence of two diastereomers in the NMR spectra at room temperature. Separate signals could also not be observed upon cooling the NMR samples to 213 K. Presumably, switching between the two diastereomers occurs so fast for the indium(III) complexes that they are not apparent in the NMR spectra. Therefore, the imino groups appear as one singlet. The anomeric protons and carbon atoms give one signal. Additionally, all ^{1}H NMR spectra of the metal complexes have in common that the OH resonance signals from the sugar residue are now visible in a region of δ = 4.5–5.4 ppm due to the use of [D$_7$]DMF as a solvent (Figure 1). It should be noted here that some NMR spectra showed signals of free ligands and also free salicylaldehydes in small amounts next to those of the metal complexes. This indicates the sensitivity of the imine ligands and the metal complexes towards hydrolysis during column chromatography, even on deactivated column material. Decomposition of the ligand system may also be caused by the Lewis acidic metal(III) ions. The degree of decomposition and also the contents of leftover TEA salts are reflected in the elemental analyses. Moreover, it was found that the stability of the complexes was decreased in coordinating solvents. For the gallium(III) complex **Ga9c** this could be seen in the NMR spectra, measured in [D$_7$]DMF. Two NMR measurements of the same sample in [D$_7$]DMF within 4 d showed a high degree of complex and also ligand decomposition (loss of 3,5-di-*tert*-butylsalicylaldehyde). However, the Ga^{III} complex **Ga9c** was sufficiently stable to obtain good results for NMR spectroscopy, mass spectrometry and elemental analysis. The corresponding indium(III) complex was found to be sensitive towards column chromatography. The loss of 3,5-di-*tert*-butylsalicylaldehyde is clearly indicated by elemental analysis. Good NMR spectra were only obtained from the crude product, still containing the TEA salt. Complexes **In7a** and **Ga7a** that were formed with the methyl-substituted xylose ligand revealed good stability upon column chromatography. The resultant NMR spectra did not show a loss of 5-methylsalicylaldehyde, despite the obtained product still containing TEA salts, which could not be removed by crystallisation from methanol/water mixtures. Comparable tripodal (salicylidene)gallium(III) and -indium(III) complexes that were synthesised for radiochemical application have not been investigated regarding their optical properties so far. Since the obtained metal complexes showed blue fluorescence under UV light (366 nm), absorption and emission spectra of the complexes and also of the free ligands were recorded. Selected absorption and emission spectra for the xylose derivatives **6a**, **In6a** and **Ga6a** are shown in Figure 2. The absorption maxima of the free ligands result from the imino chromophore and the adjacent substituted aromatic ring. All ligands showed three bands in the absorption spectra, resulting from $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions of the chromophore systems. As expected no differences were observed for ligands with the same aromatic substitution pattern and different appended sugar units. The spectrum was redshifted upon substitution of the

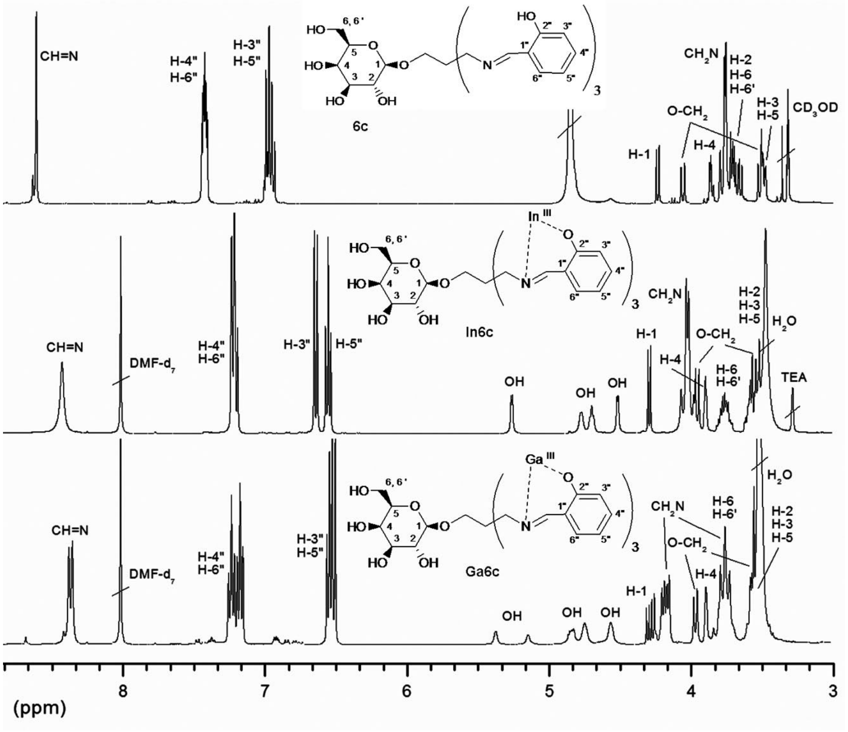


Figure 1. Details from the ^{1}H NMR spectra of compounds **6c** (in CD$_3$OD), **In6c** and **Ga6c** (in [D$_7$]DMF).

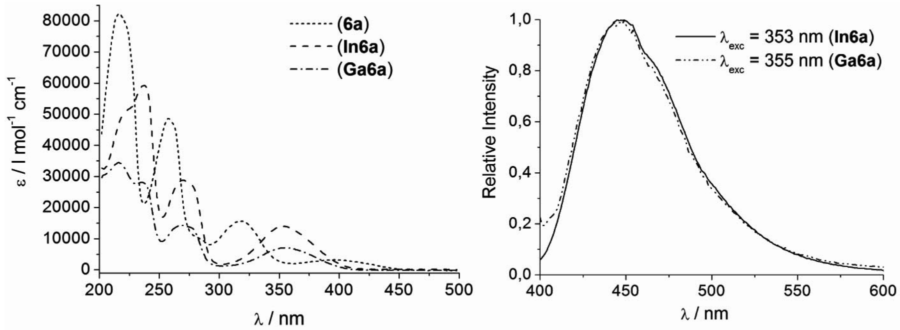


Figure 2. UV/Vis (left) and normalised emission spectra (right) of selected compounds in methanol.

aromatic ring. Alkyl substitution resulted in a shift of about 10 nm, whereas introduction of the OH group at C-5′ gave a redshift of about 15 nm. For the free ligand, the low-intense absorption bands at the lowest energies were assigned as n→π* transitions. Upon complexation, the lone pair of the imino nitrogen atom becomes a σ orbital, and therefore the n→π* transition is observed in the complex spectra. Generally, spectra of all complexes were redshifted by about 40–50 nm compared with the respective free ligands. Indium(III) as well as gallium(III) complexes shift by about the same values, thus the type of metal ion does not influence the shift. After complexation, the intense absorption bands for the free ligand at the highest energy split into two bands. As expected from the blue fluorescence under UV light, the emission spectra of all complexes showed bands from 445 to 475 nm in the blue region.

Crystals of the galactose complex **In6c** were suitable for single-crystal X-ray structure analysis. The complex crystallises in the chiral space group $P2_1$. The asymmetric unit contains four symmetry-independent molecules and included solvent. Two of the four molecules have a Λ-configuration (In1a and In1b), and two show a Δ-configuration (**In1c** and **In1d**). Figure 3a shows the metal complex (**In1c**). The two different configurations are depicted in Figure 3b and c for the complexes **Λ-In1c** and **Δ-In1a**, respectively. Furthermore, each molecule shows a different orientation of the sugar residues. They appear in the periphery of the complex and do not take part in the coordination to the metal centre. The galactose molecule is indicated by the axial orientation of the hydroxy group at C-4 of the sugar moiety. The In^{III} ion is coordinated by the chelating hexadentate N$_3$O$_3$ unit provided by the salicylaldimine residues.

They surround the metal centre in a distorted octahedral arrangement. This is confirmed by the O–In–N angles of around 84.21(18)° and 162.77(18)–165.05(18)° that are smaller than for an ideal octahedral coordination with angles of 90° and 180°. Furthermore, the In–O bond lengths vary between 2.077(4) and 2.257(5) Å, values which are a deviation from the formal C_3 symmetry at the In^{III} centre (Table 2). The deviations from an ideal complex geometry arise from the size of the In^{III} ion, which cannot be entirely enclosed by the ligand.

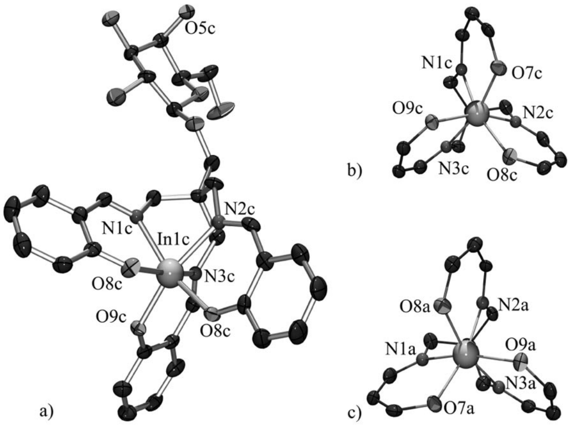


Figure 3. (a) Crystal structure of one of the molecules in the crystal of **In6c** (50% probability ellipsoids). (b) Bottom view of the Λ-configured indium(III) centre In1c. (c) Bottom view of the Δ-configured indium(III) centre In1a.

Table 2. Selected bond lengths [Å] and angles [°] for **In6c** (standard deviations in parentheses).

Bond lengths		Bond angles	
In(1c) O(7c)	2.077(4)	O(7c)–In(1c)–N(3c)	165.05(18)
In(1c) O(8c)	2.128(4)	O(8c)–In(1c)–N(1c)	162.97(18)
In(1c) O(9c)	2.122(4)	O(9c)–In(1c)–N(2c)	162.77(18)
In(1c) N(1c)	2.234(5)	O(7c)–In(1c)–N(1c)	85.20(18)
In(1c) N(2c)	2.257(5)	O(8c)–In(1c)–N(2c)	83.28(18)
In(1c) N(3c)	2.225(5)	O(9c)–In(1c)–N(3c)	84.21(17)

^{68}Ga Labelling of One Glucose-Appending Ligand

The preparation of the labelled complex **^{68}Ga6b** at "no-carrier-added (n.c.a.)" level has been carried out by using a procedure corresponding to the synthesis of [^{68}Ga(NS$_3$)R] complexes as described by Tolmachev et al.[6] The complex formation was investigated by taking into account different pH values of the reaction mixture, different reaction temperatures and varying ligand concentrations. "Carrier-added (c.a.)" preparations under addition of nonradioactive $^{69/71}$GaCl$_3$ were accomplished under identical conditions as proof of the complex identity. The investigations showed that in a pH range of 9–10 with a ligand concentration of 100 µg (0.165 µmol) per preparation at 90 °C after 15 min, a **^{68}Ga6b** complex was producible in high yields of 96–98%. In a pH range < 9, the yields decreased significantly. At pH = 4 the yield was 47% and at pH = 3 the yield dropped to 3%. To classify the stability of the **^{68}Ga6b** complex, in vitro challenge experiments were carried out with the plasma protein apo-transferrin and blood plasma, in which the **^{68}Ga6b** complex shows a high in vitro stability. After a period of 2 h, a purity decrease of only 3–6% to a minimum of 90% has been observed.

Conclusions

The synthesis of tripodal triamines containing D-xylosyl, D-glucosyl and D-galactosyl appendages could be achieved in reasonable overall yields. Their condensation with different salicylaldehydes leads to the formation of tripodal trisalicylideneimines with an [N$_3$O$_3$] donor set, which represent versatile ligands for the coordination of trivalent metal ions. Depending on the substituents at the salicylidene residues the solubility, lipophilicity and stability of the resultant complexes can be adjusted. Coordination of the ligands to In^{III} and Ga^{III} ions under basic conditions gives the respective neutral complexes (except for the 5-hydroxy-substituted salicylidene ligand). They possess an octahedral coordination sphere at the metal centre and are obtained as Λ/Δ diastereomeric mixtures, which show an equilibrium between both forms in solution and also in the crystal, as evidenced by single-crystal X-ray analysis of the indium complex **In6c**. All complexes exhibit blue fluorescence with an emission maximum of around 350 nm. The ligands as well as the complexes are less stable in an acidic environment due to the hydrolytic cleavage of the imine bonds. On the one hand, this is a drawback since new protocols for the labelling at high pH level with ^{68}Ga-generator-produced acidic solutions have to be developed. On the other hand, it may lead to a different way of enrichment within certain tissue since it is known that, e.g., in cancerous tissue the pH value is lower than in normal cells. Once the complexes are formed, a sufficient stability against blood plasma and apo-transferrin was observed over the crucial period of 120 min. To the best of our knowledge **^{68}Ga6b** represents the first ^{68}Ga-labelled saccharide. Preparation of the full set of ligands, introduction of varying spacers between the sugar moiety and the metal-coordinating core, ^{68}Ga-labelling experiments to obtain injectable solutions and coordination of other metal ions are therefore ongoing research topics in our laboratories.

Experimental Section

General: All reagents and solvents were purchased from commercial sources and used as received. IR spectra were measured with a Perkin–Elmer 2000 spectrometer, NMR spectra witrh a JEOL JMTC-400/54/SS or Bruker AC-200 instrument, ESI MS data were recorded with a JEOL JMS-T100LC, a Finnigan MAT SSQ 710, a Finnigan MAT 95XL TRAP, a Bruker micrOTOF-Q or by using a Micromass Tandem Quadropole Mass Spectrometer (Quattro LC). Elemental analyses were carried out with a Leco CHNS 932 or Perkin–Elmer PE2400 Series II CHNS/O Analyser (Nara Institute of Science and Technology). ^{68}Ga was eluted from a $^{68+}$Ge/

^{68}Ga generator (Obninsk, Russia) as $GaCl_3$ in hydrochloric acid solution (0.1 M) and added to the aqueous/methanolic solution of the ligand (**6b**). All solvents and dry $GaCl_3$ (Aldrich) applied were of analytical grade and used as purchased. Challenge experiments were carried out at 37 °C with apo-transferrin (Sigma) (5 $mg\,mL^{-1}$), the exchange was controlled by thin layer chromatography (TLC) on silica gel (Merck) and methanol as eluent. Analysis of the radio-TLC of the ^{68}Ga-labeled compounds was performed by using a FUJI BAS-1800II-scanner.

3′-Salicylaldimino-2′,2′-bis(salicylaldiminomethyl)propyl-β-D-xylopyranoside (6a): For the Schiff base reaction, the crude triamine **5a** (312 mg, 1.13 mmol) and salicylaldehyde (431 mg, 3.39 mmol) were heated to reflux in absolute ethanol (50 mL) for 3 h. The solvent was removed, and the yellow residue was extracted with ethyl acetate and water. The combined organic layers were dried with sodium sulfate, and the solvent was evaporated in vacuo. Subsequent column chromatography (ethyl acetate; R_f = 0.68) gave 320 mg (47 %) of the product as yellow powder. ^{1}H NMR (400 MHz, CD_3OD): δ = 8.44 (s, 3 H, CH=N), 7.32–7.28 (m, 6 H, 4′-H, 6′-H), 6.88–6.82 (m, 6 H, 3′-H, 5′-H), 4.16 (d, ^3J = 6.8 Hz, 1 H, 1-H), 3.90 (d, ^2J = 9.7 Hz, 1 H, OCH_2), 3.80–3.76 (m, 1 H, 5-H), 3.74 (br. s, 6 H, 3 CH_2N) 3.52–3.46 (m, 2 H, 4-H, OCH_2′), 3.33–3.29 (m, 2 H, 2-H, 3-H), 3.12 (t, ^2J = 10.8 Hz, 1 H, 5′-H) ppm. ^{13}C NMR (CD_3OD): δ = 169.2 (CH=N), 163.2 (C-2′), 134.0 (C-4′), 133.2 (C-6′), 120.0 (C-1′), 119.7 (C-5′), 118.1 (C-3′), 105.5 (C-1), 77.9 (C-3), 75.0 (C-2), 71.3 (C-4), 70.8 (O-CH_2), 67.0 (C-5), 61.27 (CH_2N), 45.2 (C_{quart}) ppm. IR (ATR): $\tilde{\nu}$ = 1627 (CH=N), 3300 (OH) cm^{-1}. UV/Vis (MeOH): λ_{max} (ε) = 396 (3457), 318 (15705), 258 (48740), 216 (82090 $M^{-1}\,cm^{-1}$) nm. ESI-MS: *m/z* (%) = 578.2 (62) [M + H]$^+$, 600.2 (100) [M + Na]$^+$. $C_{31}H_{35}N_3O_8$ (577.24) · 0.5(ethyl acetate): calcd. C 64.00, H 6.41, N 6.68; found C 64.09, H 6.44, N 6.71.

3′-Salicylaldimino-2′,2′-bis(salicylaldiminomethyl)propyl-β-D-glucopyranoside (6b): Analogous to the synthesis of **6a** by using 3′-amino-2′,2′-bis(aminomethyl)propyl-β-D-glucopyranoside (**5b**; 260 mg, 0.88 mmol) and salicylaldehyde (322 mg, 2.64 mmol) to yield, after column chromatography (ethyl acetate/methanol, 3:1; R_f = 0.8), 406 mg (76 %) of yellow product. ^{1}H NMR (400 MHz, CD_3OD): δ = 8.41 (s, 3 H, CH=N), 7.30–7.28 (m, 6 H, 4′-H, 6′-H), 6.92–6.81 (m, 6 H, 3′-H, 5′-H), 4.27 (d, ^3J = 7.5 Hz, 1 H, 1-H), 4.06 (d, ^2J = 9.7 Hz, 1 H, OCH_2), 3.85 (dd, ^3J = 2.0, ^2J = 12.0 Hz, 1 H, 6-H), 3.77–3.65 (m, 6 H, 3 CH_2N) 3.66 (dd, ^3J = 4.6, ^2J = 12.0 Hz, 1 H, 6′-H), 3.51 (d, ^2J = 9.7 Hz, 1 H, OCH_2′), 3.42–3.32 (m, 4 H, 2-H, 3-H, 4-H, 5-H) ppm. ^{13}C NMR (CD_3OD): δ = 167.6 (CH=N), 161.9 (C-2′), 132.6 (C-4′), 131.8 (C-6′), 118.6 (C-1′), 118.3 (C-5′), 116.8 (C-3′), 103.1 (C-1), 76.7 (C-3), 76.6 (C-5), 73.7 (C-2), 70.3 (C-4), 69.5 (O-CH_2), 61.4 (C-6), 59.6 (CH_2N), 43.6 (C_{quart}) ppm. IR (ATR): $\tilde{\nu}$ = 3372 (OH), 1632 (CH=N) cm^{-1}. UV/Vis (MeOH): λ_{max} (ε) = 405 (2382), 318 (10937), 257 (34257), 220 (56968 $M^{-1}\,cm^{-1}$) nm. FAB-MS: *m/z* (%) = 608 (20) [M + H]$^+$. $C_{32}H_{37}N_3O_8$ (591.26) ·0.5H_2O: calcd. C 62.33, H 6.21, N 6.81; found C 62.01, H 6.10, N 6.80.

3′-Salicylaldimino-2′,2′-bis(salicylaldiminomethyl)propyl-β-D-galactopyranoside (6c): The Schiff base reaction was analogous to that for the synthesis of **6a** by using triamine **5c** (150 mg, 0.51 mmol) and salicylaldehyde (186 mg, 1.53 mmol) to yield, after column chromatography (ethyl acetate/methanol, 3:1; R_f = 0.76) 232 mg (75 %) of yellow product. ^{1}H NMR (400 MHz, CD_3OD): δ = 8.45 (s, 3 H, CH=N), 7.31–7.27 (m, 6 H, 4′-H, 6′-H), 6.89–6.82 (m, 6 H, 3′-H, 5′-H), 4.21 (d, ^3J = 7.7 Hz, 1 H, 1-H), 4.03 (d, ^2J = 9.7 Hz, 1 H, OCH_2), 3.85 (d, ^3J = 3.0 Hz, 1 H, 4-H), 3.78–3.71 (m, 6 H, 3 CH_2N), 3.70–3.67 (m, 2 H, 6-H, 6′-H), 3.65 (dd, ^3J = 9.8 Hz, 1 H, 2-H), 3.51 (d, ^2J = 9.7 Hz, 1 H, OCH_2′), 3.49–3.47 (m, 2 H, 3-H, 5-H) ppm. ^{13}C NMR (CD_3OD): δ = 169.1 (CH=N), 163.1 (C-2′), 134.1 (C-4′), 133.2 (C-6′), 119.9 (C-1′), 119.6 (C-5′), 118.2 (C-3′), 105.3 (C-1), 76.8 (C-5), 75.0 (C-3), 72.6 (C-2), 70.8 (O-CH_2), 70.4 (C-4), 62.5 (C-6), 60.8 (CH_2N), 45.2 (C_{quart}) ppm. IR (ATR): $\tilde{\nu}$ = 3390 (OH), 1630 (CH=N) cm^{-1}. UV/Vis (MeOH): λ_{max} (ε) = 403 (2580), 318 (11792), 257 (36882), 220 (59002 $M^{-1}\,cm^{-1}$) nm. ESI-MS: *m/z* (%) = 630.2 (100) [M + Na]$^+$. $C_{32}H_{37}N_3O_8$ (591.26) ·H_2O: calcd. C 61.43, H 6.28, N 6.72; found C 61.92, H 6.31, N 6.64.

[3′-Salicylaldimino-2′,2′-bis(salicylaldiminomethyl)propyl-β-D-xylopyranosido]indium(III) (In6a): **6a** (20 mg) was dissolved in methanol (8 mL) and deprotonated with triethylamine (TEA, 10 mg). $InCl_3·4H_2O$ (10 mg, 0.034 mmol) was slowly added to the solution in methanol (5 mL). The reaction mixture was heated to reflux for 4 h during which time the colour lightened. After concentration, the crude product was purified by chromatography on deactivated (TEA) silica gel (ethyl acetate/methanol, 2:1) giving 6.7 mg (28 %) of the product. Pink crystals forming small rosettes were obtained from methanol/water. ^{1}H NMR (400 MHz, [D_7]DMF): δ = 8.44 (s, 3 H, CH=N), 7.25–7.19 (m, 6 H, 4′-H, 6′-H), 6.64 (d, ^3J = 8.3 Hz, 3 H, 3′-H) 6.57–6.54 (m, 3 H, 5′-H), 5.39 (s, 1 H, OH), 5.16 (s, 1 H, OH), 4.30 (d, ^3J = 7.5 Hz, 1 H, 1-H), 4.08–3.99 (m, 6 H, 3 CH_2N) 3.91 (d, ^2J = 9.7 Hz, 1 H, OCH_2), 3.87 (dd, ^3J = 5.4, ^2J = 11.3 Hz, 1 H, 5-H), 3.55 (d, ^2J = 9.7 Hz, 1 H, OCH_2′), 3.52–3.48 (m, 1 H, 5′-H), 3.37 (t, ^3J = 9.7 Hz, 1 H, 3-H), 3.28–3.21 (m, 2 H, 2-H, 4-H) ppm. ^{13}C NMR ([D_7]DMF): δ = 174.0 (CH=N), 171.6 (C-2′), 136.1 (C-4′), 134.7 (C-6′), 123.4 (C-3′), 119.6 (C-1′), 114.8 (C-5′), 105.6 (C-1), 77.6 (C-3), 74.5 (C-2), 73.3 (O-CH_2), 70.9 (C-4), 66.8 (C-5), 64.2 (CH_2N), 41.4 (C_{quart}) ppm. IR (ATR): $\tilde{\nu}$ = 1620 (CH=N), 3290 (OH) cm^{-1}. UV/Vis (MeOH): λ_{max} (ε) = 352 (14074), 270 (28822), 237 (59370), 220 (50672 $M^{-1}\,cm^{-1}$) nm. ESI-MS: *m/z* (%) = 712.0 (100) [M + Na]$^+$. $C_{31}H_{32}InN_3O_8$ (689.12) ·0.5H_2O: calcd. C 53.31, H 4.76, N 6.02; found C 53.41, H 4.75, N 5.93.

[3′-Salicylaldimino-2′,2′-bis(salicylaldiminomethyl)propyl-β-D-glucopyranosido]indium(III) (In6b): Analogous to the synthesis of **In6a** by using **6b** (40 mg, 0.066 mmol) and $InCl_3·4H_2O$ (19 mg, 0.066 mmol) in methanol (10 mL). After concentration and column chromatography on deactivated (TEA) silica gel (ethyl acetate/methanol, 2:1), 40 mg (80 %) was obtained as slightly yellow powder. ^{1}H NMR (250 MHz, [D_7]DMF): δ = 8.46 (s, 3 H, CH=N), 7.26–7.16 (m, 6 H, 4′-H, 6′-H), 6.64 (d, ^3J = 8.0 Hz, 3 H, 3′-H) 6.59–6.53 (m, 3 H, 5′-H), 5.42–4.68 (m, 4 H, OH), 4.35 (d, ^3J = 7.7 Hz, 1 H, 1-H), 4.11–3.97 (m, 7 H, 3 CH_2N, OCH_2), 3.74–3.53 (m, 2 H, 6′-H, OCH_2′), 3.44–3.21 (m, 4 H, 2-H, 3-H, 4-H, 5-H) ppm. ^{13}C NMR ([D_7]DMF): δ = 173.9 (CH=N), 171.5 (C-2′), 136.1 (C-4′), 134.6 (C-6′), 123.3 (C-3′), 119.5 (C-1′), 114.8 (C-5′), 105.0 (C-1), 78.1 (C-3), 77.7 (C-5), 74.7 (C-2), 73.43 (OCH_2), 71.4 (C-4), 64.1 (CH_2N), 62.4 (C-6), 41.4 (C_{quart}) ppm. IR (ATR): $\tilde{\nu}$ = 1630 (CH=N), 3360, 2930, 2600 (OH) cm^{-1}. UV/Vis (MeOH): λ_{max} (ε) = 353 (7439), 270 (15952), 237 (3309 $M^{-1}\,cm^{-1}$) nm. ESI-MS: *m/z* (%) = 1461.0 (32) [2 M + Na]$^+$, 1439.1 (20) [2 M + H]$^+$, 742.0 (9) [M + Na]$^+$, 720.0 (100) [M + H]$^+$. $C_{32}H_{34}InN_3O_9$ (719.13) · $H_2O·CH_3OH$: calcd. C 51.51, H 5.24, N 5.46; found C 51.83, H 4.89, N 5.17.

[3′-Salicylaldimino-2′,2′-bis(salicylaldiminomethyl)propyl-β-D-galactopyranosido]indium(III) (In6c): Analogous to the synthesis of **In6a** by using **6c** (40 mg, 0.066 mmol) and $InCl_3·4H_2O$ (19 mg, 0.066 mmol) in methanol (10 mL). After evaporation and column chromatography on deactivated (TEA) silica gel (ethyl acetate/methanol, 2:1), 35 mg (74 %) was obtained as slightly yellow powder. Recrystallisation from methanol/water gave crystals suitable for X-ray structure analysis. ^{1}H NMR (400 MHz, [D_7]DMF): δ =

8.45 (s, 3 H, CH=N), 7.26–7.21 (m, 6 H, 4′-H, 6′-H), 6.66 (d, ^3J = 8.4 Hz, 3 H, 3′-H) 6.58 (t, ^3J = 7.2 Hz, 3 H, 5′-H), 5.26 (d, ^3J = 4.0 Hz, 1 H, OH), 4.76 (s, 1 H, OH), 4.69 (m, 1 H, OH), 4.51 (d, ^3J = 3.2 Hz, 1 H, OH), 4.29 (d, ^3J = 7.2 Hz, 1 H, 1-H), 4.06–3.97 (m, 6 H, 3 CH_2N), 3.95 (d, ^2J = 9.6 Hz, 1 H, OCH_2), 3.89 (m, 1 H, 4-H), 3.81–3.71 (m, 2 H, 6-H, 6′-H), 3.62–3.47 (m, 4 H, 2-H, 3-H, 5-H, OCH_2′) ppm. ^{13}C NMR ([D$_7$]DMF): δ = 173.9 (CH=N), 171.5 (C-2′), 136.1 (C-4′), 134.6 (C-6′), 123.3 (C-3′), 119.5 (C-1′), 115.8 (C-5′), 105.7 (C-1), 76.5 (C-5), 74.5 (C-5), 73.4 (C-2), 72.0 (C-4), 67.4 (OCH_2), 64.2 (CH_2N), 61.8 (C-6), 41.4 (C_{quart}) ppm. IR (ATR): $\tilde{\nu}$ = 1631 (CH=N), 3365, 2920 (OH) cm^{-1}. UV/Vis (MeOH): λ_{max} (ε) = 353 (7568), 272 (16223), 239 (34810 M^{-1}cm^{-1}) nm. FAB-MS: m/z (%) = 720.0 (16) [M + H]$^+$. $C_{32}H_{34}InN_3O_9$ (719.13) ·1.5H_2O: calcd. C 51.49, H 5.00, N 5.63; found C 51.30, H 5.03, N 5.65.

[3′-Salicylaldimino-2′,2′-bis(salicylaldiminomethyl)propyl-β-D-xylopyranosido]gallium(III) (Ga6a): Analogous to the synthesis of **In6a** by using ligand **6a** (20 mg, 0.034 mmol), $Ga(NO_3)_3{\cdot}H_2O$ (8.7 mg, 0.034 mmol) and TEA (10 mg) to yield, after column chromatography on deactivated (TEA) silica gel (ethyl acetate/methanol, 2:1), 18 mg (83%) of pale yellow product. Pink crystals forming small rosettes were obtained from methanol/water. ^{1}H NMR (400 MHz, [D$_7$]DMF): δ = 8.37/8.35 (s, 3 H, CH=N), 7.25–7.21 (m, 3 H, 4′-H), 7.19–7.15 (m, 3 H, 6′-H) 6.54 (t, ^3J = 7.3 Hz, 3 H, 5′-H) 6.49 (d, ^3J = 8.5 Hz, 3 H, 3′-H), 5.45 (s, 1 H, OH), 5.24 (s, 1 H, OH), 5.11 (s, 1 H, OH), 5.04 (s, 1 H, OH), 4.32/4.28 (d, ^3J = 7.5 Hz, 1 H, 1-H), 4.21–4.16 (m, 6 H, 3 CH_2N) 3.92 (d, ^2J = 9.8 Hz, 2 H, OCH_2), 3.87 (dd, ^3J = 5.2, ^2J = 11.3 Hz, 2 H, 5-H), 3.79–3.73 (m, 6 H, 3 CH_2N), 3.57/3.56 (d, ^2J = 9.7 Hz, 1 H, OCH_2) 3.48–3.46 (m, 4-H), 3.38–3.20 (m, 2-H, 3-H, 5′-H) ppm. ^{13}C NMR ([D$_7$]DMF): δ = 170.7/170.6 (CH=N), 169.5 (C-2′), 134.7 (C-4′), 134.5 (C-6′), 122.5 (C-3′), 119.7 (C-1′), 114.7 (C-5′), 105.7/105.4 (C-1), 77.6/77.5 (C-3), 74.6/74.5 (C-2), 72.7/72.4 (OCH_2), 70.9 (C-4), 66.7 (C-5), 62.7/62.5 (CH_2N), 39.9/39.7 (C_{quart}) ppm. IR (ATR): $\tilde{\nu}$ = 1628 (CH=N), 3370 (OH) cm^{-1}. UV/Vis (MeOH): λ_{max} (ε) = 354 (7285), 277 (13785), 268 (14219), 235 (28085), 216 (34426 M^{-1}cm^{-1}) nm. ESI-MS: m/z (%) = 1311.2 (2) [2 M + Na]$^+$, 666.0 (100) [M + Na]$^+$. $C_{31}H_{32}GaN_3O_8$ (643.14): calcd. C 57.79, H 5.01, N 6.52; found C 57.90, H 4.90, N 6.51.

[3′-Salicylaldimino-2′,2′-bis(salicylaldiminomethyl)propyl-β-D-glucopyranosido]gallium(III) (Ga6b): Analogous to the synthesis of **In6a** by using **6b** (40 mg, 0.066 mmol) and $Ga(NO_3)_3{\cdot}H_2O$ (17 mg, 0.066 mmol) to yield, after column chromatography on deactivated (TEA) silica gel (ethyl acetate/methanol, 2:1), 30 mg (69%) of pale yellow product. ^{1}H NMR (400 MHz, [D$_7$]DMF): δ = 8.39/8.36 (s, 3 H, CH=N), 7.26–7.16 (m, 6 H, 4′-H, 6′-H) 6.57–6.51 (m, 6 H, 3′-H, 5′-H), 5.47 (s, 2 H, OH), 5.12 (s, 4 H, OH), 4.62 (s, 2 H, OH), 4.36/4.33 (d, ^3J = 7.7 Hz, 1 H, 1-H), 4.21–4.16 (m, 6 H, 3 CH_2N), 4.00/3.98 (d, ^2J = 9.8/10.0 Hz, 1 H, OCH_2), 3.91–3.88 (m, 2 H, 6-H), 3.80–3.74 (m, 6 H, 3 CH_2N), 3.68 (dd, ^3J = 4.8, ^2J = 11.6 Hz, 1 H, 6′-H), 3.60/3.57 (d, ^2J = 10.2/9.9 Hz, 2 H, OCH_2′), 3.44–3.30 (m, 6 H, 3-H, 4-H, 5-H), 3.25–3.20 (m, 2 H, 2-H) ppm. ^{13}C NMR ([D$_7$]DMF): δ = 170.8/170.7 (CH=N), 169.4 (C-2′), 134.7 (C-4′), 134.5 (C-6′), 122.5 (C-3′), 119.6 (C-1′), 114.7 (C-5′), 105.0/104.8 (C-1), 78.0 (C-3), 77.7/77.6 (C-5) 74.7 (C-2), 72.6/72.5 (OCH_2), 71.5/71.4 (C-4), 62.7 (C-6), 61.5 (CH_2N), 39.9/39.7 (C_{quart}) ppm. IR (ATR): $\tilde{\nu}$ = 1630 (CH=N), 3370 (OH) cm^{-1}. UV/Vis (MeOH): λ_{max} (ε) = 354 (6813), 267 (14896), 237 (28269), 219 (36063 M^{-1}cm^{-1}) nm. ESI-MS: m/z (%) = 1371.3 (27) [2 M + Na]$^+$, 696.0 (100) [M + Na]$^+$. $C_{32}H_{34}GaN_3O_9$ (673.16): calcd. C 56.99, H 5.08, N 6.23; found C 57.04, H 4.85, N 5.94.

[3′-Salicylaldimino-2′,2′-bis(salicylaldiminomethyl)propyl-β-D-galactopyranosido]gallium(III) (Ga6c): Analogous to the synthesis of **In6a** by using ligand **6c** (40 mg, 0.066 mmol) and $Ga(NO_3)_3{\cdot}H_2O$ (17 mg, 0.066 mmol) to yield, after column chromatography on deactivated (TEA) silica gel (ethyl acetate/methanol, 2:1), 28 mg (64%) of pale yellow product. ^{1}H NMR (400 MHz, [D$_7$]DMF): δ = 8.38/8.36 (s, 3 H, CH=N), 7.26–7.16 (m, 6 H, 4′-H, 6′-H) 6.57–6.51 (m, 6 H, 5′-H, 3′-H), 5.38 (s, 1 H, OH), 5.15 (s, 1 H, OH), 4.84 (s, 2 H, OH), 4.75 (s, 2 H, OH), 4.57 (s, 2 H, OH), 4.31/4.27 (d, ^3J = 7.5/7.4 Hz, 1 H, 1-H), 4.21–4.16 (m, 6 H, 3 CH_2N), 3.98 (d, ^2J = 9.7 Hz, 2 H, OCH_2), 3.91 (m, 2 H, 4-H), 3.80–3.73 (m, 8 H, 3 CH_2N, 6-H, 6′-H), 3.59–3.53 (m, 4 H, 2-H, 3-H, 5-H, OCH_2′) ppm. ^{13}C NMR ([D$_7$]DMF): δ = 170.8/170.7 (CH=N), 169.4 (C-2′), 134.7 (C-4′), 134.5 (C-6′), 122.5 (C-3′), 119.6 (C-1′), 114.8 (C-5′), 105.7/105.4 (C-1), 76.4/77.5 (C-5), 74.4 (C-3), 72.7/72.5 (OCH_2), 72.0 (C-2), 69.4 (C-4), 62.8/62.6 (CH_2N), 61.8/61.7 (C-6), 39.9/39.8 (C_{quart}) ppm. IR (ATR): $\tilde{\nu}$ = 1631 (CH=N), 3365 (OH) cm^{-1}. UV/Vis (MeOH): λ_{max} (ε) = 355 (6520), 268 (13702), 237 (28009), 220 (35058 M^{-1}cm^{-1}) nm. ESI-MS: m/z (%) = 1371.2 (43) [2 M + Na]$^+$, 696.0 (100) [M + Na]$^+$. $C_{32}H_{34}GaN_3O_9$ (673.16): calcd. C 56.99, H 5.08, N 6.23; found C 56.94, H 5.22, N 6.01.

Synthesis of the Corresponding ^{68}Ga^{III} Complex by Using 3′-Salicylaldimino-2′,2′-bis(salicylaldiminomethyl)propyl-β-D-glucopyranoside (6b). No-Carrier-Added Preparation of ^{68}Ga6b: To ammonium acetate buffer (400 μL 1 M) in a 1 mL Eppendorf vial were added a solution of **6b** [100 μL, 0.165 μmol; 1 mg of ligand **6b** dissolved in 1 mL of methanol/water (1:1)] and ^{68}Ga eluate (70–100 μL). The resultant pH of 6–7 for the reaction mixture was adjusted to 9–9.5 by addition of 1 M NaOH. The reaction was complete after 15 min of shaking in a thermo mixer at 90 °C. After neutralisation of the reaction mixture with 1 N HCl, the radiochemical purity was controlled by radio thin layer chromatography on silica gel (methanol/1 M ammonium acetate, 1:1). The **^{68}Ga6b** complex was formed with a yield of 96–98%, the R_f value of 0.9 was dedicated to the complex, unreacted ^{68}Ga eluate remains at the start as gallium hydroxide. **Carrier-Added Preparation of ^{68}Ga6b:** To ligand **6b** (5 mg, 8.2 μmol), dissolved in methanol (1 mL), were added a $GaCl_3$ stock solution (8.1 μL, 8.2 μmol; 179 mg of $GaCl_3$ in 1 mL of H_2O) and ^{68}Ga eluate (100 μL). The pH was adjusted to 9–9.5 by addition of 1 N NaOH (90 μL). The reaction was complete after 15 min of shaking in the thermo mixer at 90 °C. After neutralisation of the reaction mixture with 1 N HCl, the yield and purity were controlled by thin layer chromatography. Both, the UV detection and the radioactivity detection, showed peaks with identical R_f values of 0.9. The radiochemical yield was determined as $>$ 90%. The complex was identified by mass spectrometry from the c.a. reaction mixture (without further purification). ESI-MS (MeOH): m/z = 696.3, 698.6 [M + Na = $C_{32}H_{34}GaN_3NaO_9$]$^+$; in agreement with the predicted isotopic distribution (see Figure S11 in Supporting Information).

Challenge Experiments with Apo-Transferrin and Blood Plasma: To a mixture of phosphate buffer (200 μL 0.1 M) and apo-transferrin solution (200 μL) in a 1 mL Eppendorf vial (1.25 mg of apo-transferrin in 200 μL of 0.1 M phosphate buffer pH = 7.4) was added the **^{68}Ga6b** complex solution (100 μL). Analogously, to a mixture of phosphate buffer (200 μL, 0.1 M) and human blood plasma (200 μL) in a 1 mL Eppendorf vial was added the **^{68}Ga6b** complex solution (100 μL). The mixtures were incubated for 120 min at 37 °C. After 60 and 120 min, the percentage of complex **^{68}Ga6b** was determined by radio TLC.

X-ray Crystallography for In6c: The intensity data for the compound were collected with a Nonius Kappa CCD diffractometer by using graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarisation effects but not for absorption.[47,48] The structures were solved by direct methods (SHELXS) and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97).[49,50] The hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms of the complex were refined anisotropically.[50] Crystal data:[51] $C_{32}H_{34}InN_3O_9 \cdot 0.625CH_3OH \cdot 1.125H_2O$, M_r = 759.74 g mol^{-1}, colourless prism, size $0.04 \times 0.04 \times 0.04$ mm, monoclinic, space group $P2_1$, a = 16.2212(3), b = 16.1880(2), c = 27.2163(6) Å, β = 106.922(1)°, V = 6837.3(2) Å^3, T = –90 °C, Z = 8, $\rho_{calcd.}$ = 1.476 g cm^{-3}, μ(Mo-K_α) = 7.53 cm^{-1}, F(000) = 3124, 44855 reflections in h (–21/18), k (–21/20), l (–32/35), measured in the range $2.35° \leq \theta \leq 27.50°$, completeness θ_{max} 99.6%, 29850 independent reflections, R_{int} = 0.0404, 23445 reflections with $F_o > 4\sigma(F_o)$, 1694 parameters, 1 restraint, R_{1obs} = 0.0556, wR_{2obs} = 0.1252, R_{1all} = 0.0829, wR_{2all} = 0.1406, GooF = 1.031, Flack parameter –0.014(17), largest difference peak/hole 1.293/–1.038 e Å^{-3}.

Supporting Information (see footnote on the first page of this article): Experimental details for the synthesis of the tripodal triamines for compounds **2a**–**5c**, the additional ligands and complexes noted in Table 1 as well as selected spectra (^{1}H NMR, ^{13}C NMR, MS, IR) from the synthesis pathway; data for the single-crystal X-ray structure of **2a**, mass spectrometric analysis of carrier-added formation, radio TLC determination and details for the stability studies for **^{68}Ga6b**.

Acknowledgments

Financial support of the Dutch Polymer Institute (DPI) and the European Commission (FP6, Marie Curie OIF) is gratefully acknowledged.

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[51] CCDC-680061 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: June 20, 2009