**Author Manuskript**

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**To be cited as:** 10.1002/ejic.202000547

**Link to VoR:** https://doi.org/10.1002/ejic.202000547

FULL PAPER

# Gallium Fluoride Complexes with Acyclic Bispicolinic Ligands as Potential New Fluorine-18 Labelled Imaging Agents

HuiJing Koay,[a] Mohammad B. Haskali,[b] Peter D. Roselt,[b] Jonathan M. White,[a] and Paul S. Donnelly*[a]

**Abstract:** The positron-emitting radionuclide, fluorine-18, is used to radiolabel molecules to develop tracers for diagnostic imaging with positron-emission tomography. There is growing interest in the potential of using strong coordinate bonds between electropositive Ga(III) and electronegative fluoride (~ 557 kJ/mol) to provide new methods of incorporating fluorine-18 into molecules. The potential of gallium(III) complexes with acyclic pentadentate bis-dipicolinic acid containing ligands ($H_2$**L**$^{1\text{-}3}$) to form ternary complexes with fluoride, [Ga**L**$^{1\text{-}3}$F] was investigated with a view to developing new methods for fluorine-18 radiolabelling. A solid-phase peptide synthesis approach was used to produce a bis-dipicolinic acid chelator with a lysine residue. Characterisation of [Ga**L**$^1$X] (X= OH, Cl, F) by X-ray crystallography revealed that **L**$^1$ acted as dianionic $N_2O_2$ donor to the Ga(III) with the fifth site occupied by a monodentate anion ($OH^-$, $Cl^-$ or $F^-$). Despite its high stability in aqueous mixture and $d_6$-DMSO and the straightforward synthesis of [Ga**L**$^1$F], it was only possible to form the radioactive analogue [$^{18}$F][Ga**L**$^1$F] in low radiochemical yields.

## Introduction

Molecular imaging with positron emission tomography (PET) can be used to assist clinicians in diagnosis and monitoring of progression of disease.[1] The technique relies on molecules radiolabelled with a positron-emitting radionuclide called 'tracers' injected into patient at 'trace' concentrations. The interaction of such tracers and the biological system provides quantitative information regarding the physiological and biochemical processes based on the three-dimensional images of the biodistribution of the tracers. Among the favourable properties of the positron-emitting isotope fluorine-18 ([$^{18}$F]$F^-$) are the high positron decay ratio (97%), low positron energy (635 keV) and the relatively small size of the radionuclide mean that it can often be incorporated into organic molecules without significant changes to biochemical interactions.[2] Conventional approaches to radiolabelling with fluorine-18 involve the formation of a covalent C-$^{18}$F bond. There is growing interest in developing alternative strategies utilising the coordinate bond formation between the electropositive group 13 elements Al(III) and Ga(III) and electronegative $F^-$ to develop fluorine-18 labelled PET diagnostic imaging agents. The principle behind this approach is based on the strength of the bonds between $F^-$ and Al(III) and Ga(III) cations (bond dissociation energies of Al-F and Ga-F are 665 and 557 kJ/mol respectively) that are known to be higher than the C-F bond (536 kJ/mol).[3] In comparison, the bond dissociation energies of Al-O and Ga-O are 512 and 285 kJ/mol respectively.[3] The first fluorine-18 labelled peptide using an Al(III) complex was reported in 2009.[4] Since the initial report, fluorine-18 labelling using Al(III) complexes has been explored extensively, mainly focusing on the use of 1,4,7-triazacyclononane-1,4-diacetic acid (NODA) and 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) analogues.[5] A limitation of the Al(III)-$F^-$ approach is that the formation of [$^{18}$F]Al(III)-$F^-$ complexes requires heating to a relatively high temperature typically above 100 °C. This methodology is only suitable for labelling peptides or molecules that are stable at high temperature. The use of the group 13 congener, gallium, has been suggested as a viable alternative to complexes containing an Al(III)-$F^-$ bond as the incorporation of fluorine-18 into Ga(III) complexes proved to be achievable at room temperature or 80 °C.[6]

Macrocyclic ligands are often employed to coordinate metal ions for radiopharmaceutical applications, but a family of acyclic ligands based on picolinic acid have been identified as being suitable ligands to coordinate a variety of different radionuclides. The 1,2-[[6-carboxy-pyridin-2-yl]-methylamino]ethane ($H_2$dedpa) ligand and its derivatives feature two picolinic acids joined by a diamine backbone. The $H_2$dedpa chelator coordinates to [$^{67/68}$Ga]Ga(III) at room temperature within minutes to form a six-coordinate complex and is stable for at least 2 h (Figure 1).[7] In this work, we aimed to prepare coordinatively unsaturated Ga(III) complexes with picolinic acid containing ligands of lower denticity to enable the formation of ternary Ga(III)-$F^-$ complexes. We focused on a variation where two picolinic acids are linked at the 6' position *via* two methylene bridges joined through a single secondary amine dipicolinic acid (dpa). The synthesis of the $H_2$dpa ligand and its coordination chemistry with Ga(III) and La(III) was published by Orvig *et. al.*[8]

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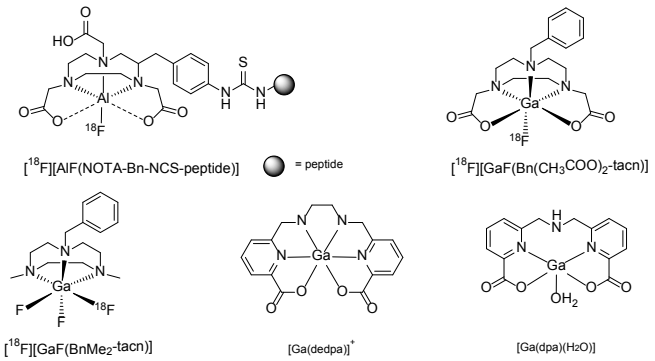
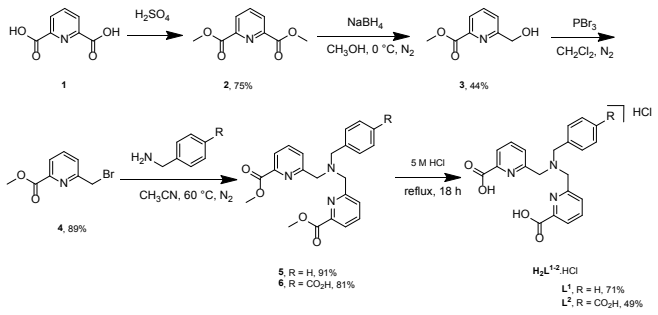



**Figure 1.** Chemical structures of [$^{18}$F][AlF(NOTA-Bn-NCS-peptide)], [$^{18}$F][GaF(Bn($CH_2COO$)$_2$-tacn)], [$^{18}$F][GaF(Bn$Me_2$-tacn)], [Ga(dedpa)]$^+$ and [Ga(dpa)($H_2O$)].

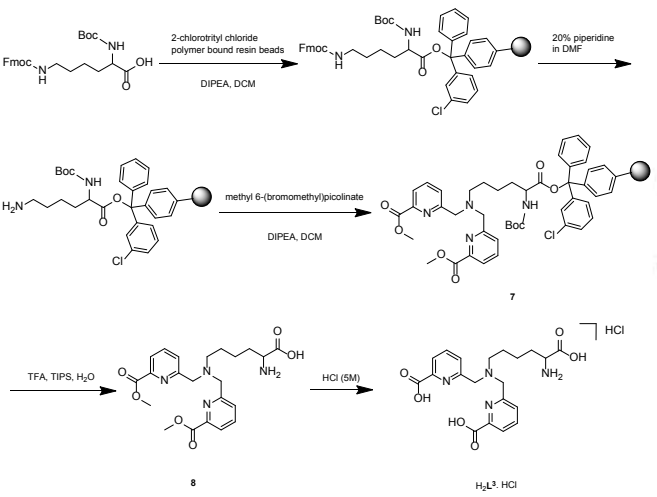
## Results and Discussion

**Synthesis and Characterisation.** A 'dpa' chelator with a benzyl functional group on the central nitrogen, $H_2$**L$^1$** was synthesised by minor modifications of a literature procedure.[9] Esterification of the carboxylic acid groups of 2,6-pyridinedicarboxylic acid (**1**) allowed isolation of dimethyl pyridine-2,6-dicarboxylate (**2**) (Scheme 1). A selective reduction of one methyl ester of (**2**) with sodium borohydride in methanol gave methyl 6-(hydroxymethyl)picolinate (**3**). Treatment of (**3**) with phosphorus tribromide in anhydrous dichloromethane yielded methyl 6-(bromomethyl)picolinate (**4**). Reductive amination reaction between two equivalents of methyl 6-(bromomethyl)picolinate (**4**) and benzylamine in anhydrous acetonitrile followed by hydrolysis of the methyl ester functional groups with 5 M HCl gave the product $H_2$**L$^1$**·HCl. A bifunctional ligand containing a free carboxylic acid group, $H_2$**L$^2$**, was prepared by replacing benzylamine with aminobenzoic acid, which allowed the isolation of (**6**). The compounds were characterised by $^1$H and $^{13}$C{$^1$H} nuclear magnetic resonance (NMR) spectroscopy and electrospray ionisation-mass spectrometry (ESI-MS).



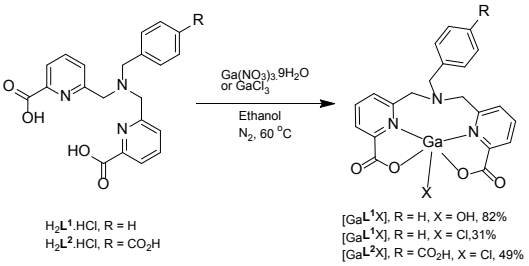

**Scheme 1.** Synthesis of $H_2$**L$^1$**·HCl and $H_2$**L$^2$**·*x*HCl.

To prepare a versatile ligand that could be inserted at any position along a peptide sequence, a single amino acid chelate (SAAC)[10] variant of 'dpa' was prepared using solid-phase peptide synthesis (SPPS). The ξ-amine of lysine that had been immobilised on resin was functionalised with two dipicolinic acid molecules by the addition of an excess of methyl 6-(bromomethyl)picolinate in dichloromethane (DCM) with *N*,*N*-Diisopropylethylamine (DIPEA) (Scheme 2). The product (**7**) was cleaved from the resin beads using an aqueous solution of trifluoroacetic acid (TFA) and triisopropylsilane (TIPS) to afford compound (**8**). The methyl ester protecting groups were removed under acidic conditions to give $H_2$**L$^3$**·*x*HCl.




**Scheme 2.** Synthesis of $H_2$**L$^3$**·HCl using the solid-phase peptide synthesis. Black circle indicates polymer-bound resin beads.

The preparation of **L$^2$** and **L$^3$** demonstrates the capacity of this family of ligands to be further elaborated to incorporate biological targeting molecules. Investigations of the coordination chemistry focused on **L$^1$** in this work. The Ga(III) complexes, [Ga**L$^1$**(OH)] and [Ga**L$^{1\text{-}2}$**Cl] were synthesised in anhydrous ethanol at 60 ºC under an atmosphere of nitrogen (Scheme 3). Analysis of both complexes by ESI-MS gave signals at *m/z* 444.05 and 488.037 for [Ga**L$^1$**]$^+$ and [Ga**L$^2$**]$^+$ respectively with the expected isotope patterns.




**Scheme 3.** Synthesis of [Ga**L$^1$**OH)] and [Ga**L$^{1\text{-}2}$**Cl].

Upon coordination to Ga(III), there is an upfield shift of the signals attributed to the methylene protons of $H_2$**L$^1$** and $H_2$**L$^2$** as well as a significant change in resonance attributed to the aromatic protons (Figure 2). The $^1$H and $^{13}$C{$^1$H} NMR spectra of [Ga**L$^1$**(OH)] and [Ga**L$^1$**Cl] in $d_6$-DMSO were identical.

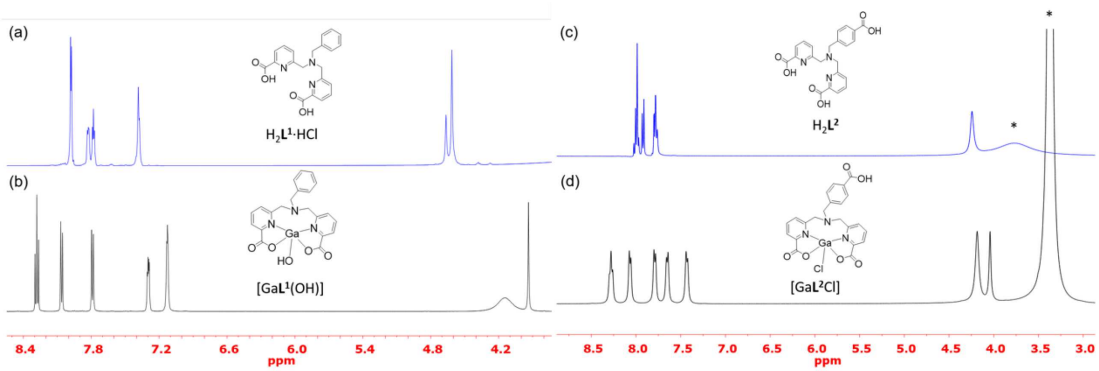
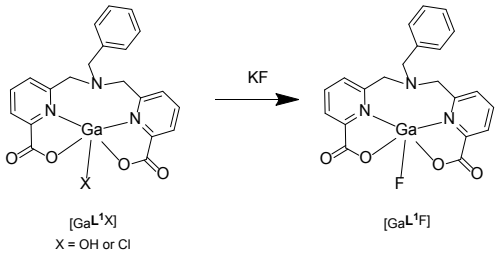



**Figure 2.** Regions of $^{1}$H NMR spectra of $H_2$**L**$^{1}$, [Ga**L**$^{1}$(OH)], $H_2$**L**$^{2}$ and [Ga**L**$^{2}$Cl]. Asterisk indicates residual solvent peak.

The fluoride-containing complex, [Ga**L**$^{1}$F], was readily obtained by treatment of either [Ga**L**$^{1}$(OH)] or [Ga**L**$^{1}$Cl] with potassium fluoride (Scheme 4). Analysis of [Ga**L**$^{1}$F] by $^{19}$F NMR spectroscopy revealed a single resonance at $\delta_F$ = -141 ppm, confirming the formation of a Ga(III)-F$^{-}$ bond. In addition, the resonances in the $^{1}$H NMR spectrum of [Ga**L**$^{1}$F] slightly shifted compared to [Ga**L**$^{1}$(OH)] and [Ga**L**$^{1}$Cl].




**Scheme 4.** Synthesis of [Ga**L**$^{1}$OH)] and [Ga**L**$^{1\text{-}2}$Cl].

Crystals suitable for single X-ray crystallography of $H_2$**L**$^{1}$·HCl, [Ga**L**$^{1}$(OH)], [Ga**L**$^{1}$Cl] and [Ga**L**$^{1}$F] were grown by evaporation of an aqueous solution of the compounds at room temperature (Figure 3). The 'free' ligand, $H_2$**L**$^{1}$·HCl, crystallised with one molecule of hydrochloric acid with the hydrogen bonding between Cl$^{-}$ and three hydrogen atoms attached to the central nitrogen atom (N(2)) and two oxygen atoms (O(1) and O(3)). For each complex, **L**$^{1}$ acts as a tetradentate dianionic $N_2O_2$ donor to the Ga(III). The tertiary nitrogen atom, N(2), is involved in a close contact with the Ga(III) (Ga(1)-N(2) ~ 2.440 (2) – 2.471 (2) Å) but this distance is greater than the sum of the effective ionic radii for Ga-N (Van der Waals radii of Ga-N ~2.08 Å) so the complexes are best described as five-coordinate. Calculation of the tau parameters confirmed the coordination geometries of each complex as best described as distorted square pyramidal.[11] The Ga(1)-N(1) and Ga(1)-N(3) bond lengths range from 2.001 Å to 2.075 Å, and the Ga(1)-O(1) and Ga(1)-O(3) bond lengths range from 1.981 Å to 2.056 Å (Table 1). In each of the Ga(III) complexes, the fifth site is occupied by a monodentate anion (OH$^{-}$, Cl$^{-}$ or F$^{-}$).

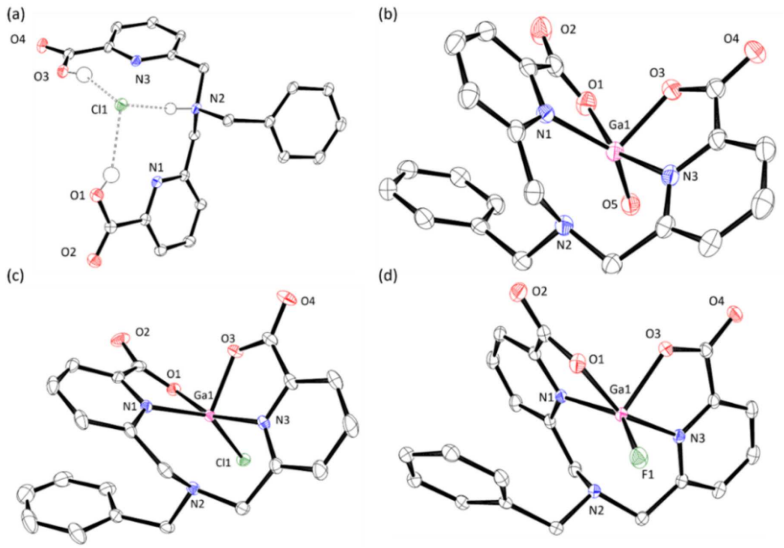



**Figure 3.** ORTEP representations of the X-ray crystal structures (30% ellipsoids) of (a) $H_2$**L**$^{1}$·HCl, (b) [Ga**L**$^{1}$(OH)]·5$H_2O$, (c) [Ga**L**$^{1}$Cl] and (d) [Ga**L**$^{1}$F]·5$H_2O$ with solvent and selected hydrogen atoms omitted for clarity.

**Table 1.** Selected bond lengths (Å) for the Ga(III) complexes.

| Bond length (Å) | [GaL1(OH)] | [GaL1Cl] | [GaL1F] |
|---|---|---|---|
| Ga(1)-N(1) | 2.029(2) | 2.001(2) | 2.063(2) |
| Ga(1)-N(2) | 2.471(2) | 2.442(1) | 2.440(2) |
| Ga(1)-N(3) | 2.075(2) | 2.072(2) | 2.012(2) |
| Ga(1)-O(1) | 2.056(2) | 2.002(2) | 1.996(2) |
| Ga(1)-O(3) | 2.006(2) | 1.981(1) | 2.024(2) |
| Ga(1)-O(5) | 1.831(2) | | |
| Ga(1)-Cl(1) | | 2.2194(6) | |
| Ga(1)-F(1) | | | 1.797(2) |

The Ga(1)-F(1) bond length of [Ga**L**$^1$F] was found to be 1.797(2) Å, which is relatively short. The ORTEP representation revealed an extensive hydrogen bonding (F…H-OH) interaction between $F^-$ and the lattice water molecules (Figure 4).

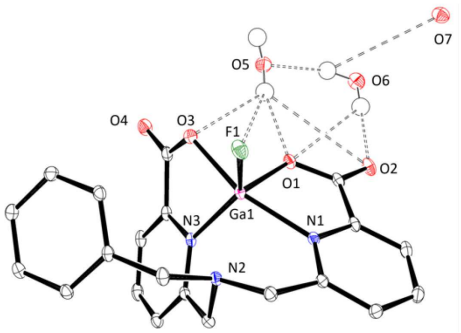



**Figure 4.** ORTEP representation of the X-ray crystal structure (30% ellipsoids) of the hydrogen bonding network of [Ga**L**$^1$F]·5$H_2O$. Selected hydrogen atoms and solvent atoms have been omitted for clarity.

**Stability of Ga(III) complexes.** Acquisition of $^1$H and $^{19}$F NMR spectra of a mixture of [Ga**L**$^1$F] in $d_6$-DMSO over several weeks revealed no shift changes to the spectra demonstrating [Ga**L**$^1$F] is stable in DMSO for several weeks. As suspected, the Ga(III) complexes are susceptible to strong acids likely due to protonation of the carboxylic acid groups. Analysis by $^1$H NMR spectroscopy of a mixture of [Ga**L**$^1$F] in $d_6$-DMSO in the presence of trifluoroacetic acid (TFA, 0.1%) demonstrated that within one hour approximately 50% of the complex had dissociated to give the protonated free ligand (Figure 5). This decomposition was most likely due to the cleavage of the Ga-O bonds by acid-catalysed dissociation.

**Analysis of Ga(III) complexes by RP-HPLC.** The Ga(III) complexes, [Ga**L**$^1$Cl] and [Ga**L**$^1$F] were characterised by analytical RP-HPLC with an elution gradient of 0-95% B (acetonitrile) in A (Milli-Q $H_2O$) over 15 min, 1 mL/min (Figure 6). The elution profile of [Ga**L**$^1$F] detected at UV absorbance λ 254 nm (retention time = 10.2 min, Figure 6a) is different to that of [Ga**L**$^1$Cl], which elutes at 9.5 min (Figure 6b) under the same conditions. Co-injection of [Ga**L**$^1$Cl] with [Ga**L**$^1$F] showed two distinct peaks corresponding to each Ga(III) complexes (Figure 6c).

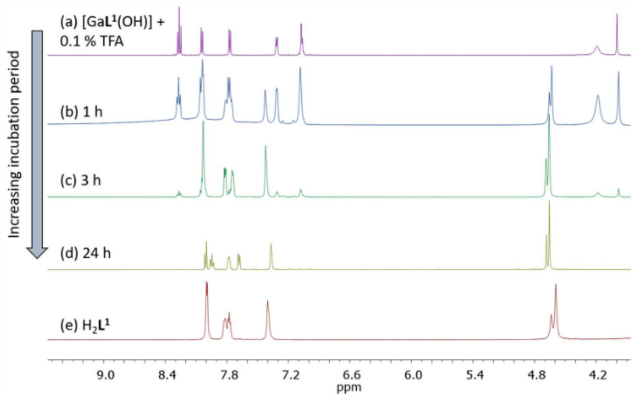



**Figure 5.** $^1$H NMR spectrum of [Ga**L**$^1$(OH)] and TFA (0.1%) in $d_6$-DMSO upon addition (a), at 1 h (b), 3 h (c) and 24 h (d). $^1$H NMR spectrum of $H_2$**L**$^1$·HCl (e).

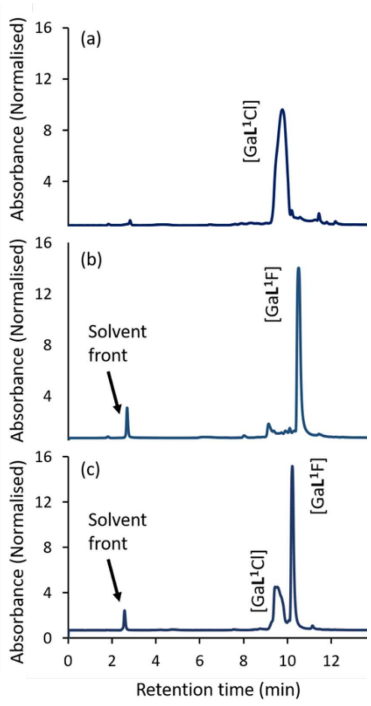



**Figure 6.** RP-HPLC chromatogram (UV absorbance at λ 254 nm) of (a) [Ga**L**$^1$Cl] (retention time = 9.5 min), (b) [Ga**L**$^1$F] (retention time = 10.2 min) and (c) co-injection of [Ga**L**$^1$Cl] (retention time = 9.5 min) with [Ga**L**$^1$F] (retention time = 10.2 min).

**Radiolabelling of [GaL$^1$]$^+$ with fluorine-18.** The ease of synthesis [Ga**L**$^1$F] in aqueous solutions at room temperature and the stability of the complex in aqueous mixtures encouraged the investigation of the preparation of the complex with radioactive fluorine-18 in relatively challenging aqueous conditions. A mixture of [$^{18}$F]$F^-$/$H_2O$ was obtained from a $^{18}$O(p,n)$^{18}$F nuclear reaction (98% $^{18}$O isotopic enrichment) on a 16.5 MeV cyclotron (~1,000-1,500 MBq/mL). Formation of [$^{18}$F][Ga**L**$^1$F] was attempted by adding either [Ga**L**$^1$(OH)] or [Ga**L**$^1$Cl] to a mixture of [$^{18}$F]$F^-$/$H_2O$ (500 MBq, ~ 25 nM) in sodium acetate buffer (pH 4.0) at room

temperature and 80 °C (method A). Despite the relatively straightforward preparation of the non-radioactive [Ga**L**$^1$F], the radioactive analogue, [$^{18}$F][Ga**L**$^1$F], could only be synthesised in very low radiochemical yield. This was presumably due to the incompatibility of the nanomolar concentration of [$^{18}$F]F$^-$ in the diluted buffer solution at pH 4. The instability of [Ga**L**$^1$*X*] (X = OH$^-$, Cl$^-$, F$^-$) in low pH (<3) precluded the possibility of attempting the radiolabelling at lower pH. Preparation of [$^{18}$F][Ga**L**$^1$F] was then attempted using a source of [$^{18}$F]F$^-$ that was azeotropically dried, adsorbed on a QMA cartridge and then eluted with potassium carbonate and [2,2,2]Kryptofix mixture (~1% $H_2O$ in acetonitrile). This [$^{18}$F]F$^-$ mixture was reacted with [Ga**L**$^1$Cl] (method B). The incorporation of [$^{18}$F]F$^-$ was determined from the chromatogram of an RP-HPLC equipped with a radiation detector of the crude reaction mixture, where [$^{18}$F][Ga**L**$^1$F] (retention time = 12.6 min) elutes with a similar retention time to the non-radioactive analogue, [Ga**L**$^1$F] detected at λ 254 nm (retention time = 12.7 min) (Figure 7). [$^{18}$F][Ga**L**$^1$F] was prepared in a radiochemical yield of ~ 2%, estimated from the integration of the peak corresponding to the radioactive species in the HPLC chromatogram. Unreacted [$^{18}$F]F$^-$ elutes with the solvent front at 2 min (recovered percentage ~ 96%). The non-radioactive elution profile (blue trace) detected by UV absorbance at λ 254 nm shows a second peak at retention time = 12.3 min that corresponds to [Ga**L**$^1$Cl], which is consistent with the order of elution of the Ga(III) complexes in Figure 6c. The addition of an excess of 'carrier-added' [$^{18}$F]F$^-$, [$^{19}$F]KF may improve the synthetic yield of [$^{18}$F][Ga**L**$^1$F] in acetonitrile as was demonstrated in the synthesis of [$GaF_3$($BzMe_2$-tacn)].[6a] Considering that a goal of this research was to prepare an alternative facile approach to incorporate fluorine-18 into molecules in aqueous mixtures, this was not pursued further.

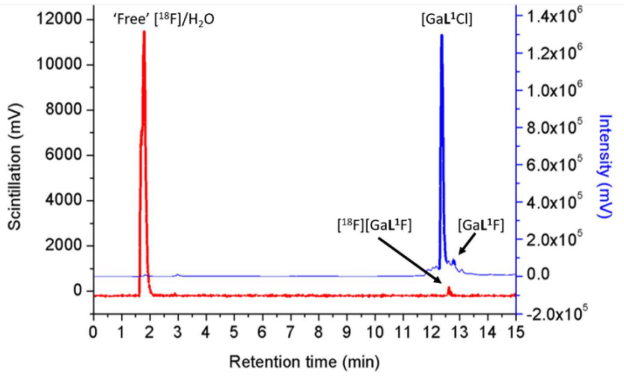



**Figure 7.** Radio- HPLC trace (red = radiation detection, blue = non-radioactive analogue at λ 254 nm) of the reaction mixture of [Ga**L**$^1$Cl] and [$^{18}$F]/$H_2O$ in acetonitrile.

## Conclusion

A series of picolinic acid derived acyclic chelators $H_2$**L**$^1$, $H_2$**L**$^2$ and $H_2$**L**$^3$ were prepared. The SPPS approach employed to functionalise the chelator with a single lysine residue has an advantage of simplifying the purification process and could be useful to incorporate other amino acids for other picolinic acid derived ligands. The SAAC system can also be incorporated within any peptide sequence of interest. The new ligands formed complexes with Ga(III) and encouragingly it was straightforward to prepare Ga(III)-F$^-$ complexes in an aqueous mixture. The structures of [Ga**L**$^1$(OH)], [Ga**L**$^1$Cl] and [Ga**L**$^1$F] were determined by X-ray crystallography revealed that in each case **L**$^1$ acted as tetradentate dianion ligand with an additional weaker interaction to the tertiary nitrogen atom N(2). Although the close contact between Ga(III) and N(2) could not considered a bond it was hoped that it might confer some enhanced resistance to the substitution of the coordinated fluoride by disfavouring associative (*A*) ligand exchange processes with competing nucleophiles. [Ga**L**$^1$F] is stable for at least several weeks in aqueous mixture and $d_6$-DMSO. Despite the facile synthesis of [Ga**L**$^1$F] in aqueous solutions by the simple addition of potassium fluoride to either [Ga**L**$^1$(OH)] or [Ga**L**$^1$Cl], we were unable to prepare [$^{18}$F][Ga**L**$^1$F] in significant quantities using aqueous sources of [$^{18}$F]F$^-$. The inability to form [$^{18}$F]Ga-F complexes using nanomolar concentrations of [$^{18}$F]F$^-$, in aqueous buffer at pH 4, may reflect the strength of hydrogen bonds in HF and bifluoride ($HF_2^-$) under these conditions. The bond dissociation energy of $HF_2^-$ is 184 kJ mol$^{-1}$.[12] Considering these limitations, the Ga(III) complexes with the acyclic 'dpa' chelator presented in this work do not offer any advantages when compared to the cyclic [$^{18}$F][AlF(NOTA-Bn-NCS)] and [$^{18}$F][GaF(Bn($CH_2COO$)$_2$-tacn)] systems presented previously.[4, 6b]

## Experimental Section

**General procedures:** All standard reagents and solvents were obtained from commercial suppliers and were used as received. Nuclear magnetic resonance (NMR) spectra were acquired on a Varian FT-NMR 500 spectrometer or a Varian FT-NMR 400 spectrometer. $^1$H NMR spectra were acquired at 400 or 500 MHz, $^{13}$C{$^1$H} NMR spectra were acquired at 125.7 MHz and referenced to an internal solvent residue. $^{19}$F{$^1$H} NMR spectra were acquired at 470.4 MHz. All spectra were recorded at 297 K. Spectra were analysed on MestReNova software (MestreLab Research). High-resolution ESI-QTOF mass spectra were recorded on an Exactive Plus Orbitrap Infusion mass spectrometer (Exactive Series, 2.8 Build 268801, Thermo Fisher Scientific). The analysis was performed using Xcalibur 4.0.27.10 (Thermo Fisher Scientific). Elemental analysis for C, H and N was carried out by The Campbell Microanalytical Laboratory, The University of Otago, Dunedin, New Zealand. UV-Visible spectra were acquired on a Shimadzu UV-1650 PC UV-Visible spectrophotometer (Shimadzu, Kyoto, Japan) from 800 nm to 250 nm. Analytical RP-HPLC traces were acquired using an Agilent (Santa Clara, CA) 1100 Series HPLC system with an SGE Analytical Science (Ringwood, VIC) ProteCol C18 HPH 125 column (4.6 x 150 mm, 5 μm, 120 A) and were monitored at λ = 220, 254 and 280 nm. Agilent 1200 HPLC system equipped with an Alltech Hypersil BDS C18 analytical HPLC column (4.6 x 150 mm, 5 μm, 120 A) with a flow rate of 1 mL/min and were monitored at λ = 220, 254 and 280 nm. Retention times were recorded using a gradient elution of 5-100% B (0.1% TFA in acetonitrile) in A (0.1% TFA in Milli-Q water) over 30 min. [$^{18}$F]/$H_2O$ was obtained from Cyclotek Melbourne Pty Ltd, prepared using a PETtrace 16.5 MeV cyclotron incorporating a high-pressure niobium target by proton bombardment [$^{18}$O(p,n)$^{18}$F] of 98% $^{18}$O enriched [$^{18}$O]$H_2O$ (GE healthcare). For method B, drying of [$^{18}$F]F$^-$ was performed on an iPHASE Flexlab radiochemistry module purchased from iPHASE Technologies Pty. Ltd. Fluorine-18 was trapped on a QMA strong anion exchange cartridge (Waters) preconditioned with potassium bicarbonate, [2,2,2]Kryptofix (0.5 mL, 0.05 M solution) and water (5 mL). The azeotropically dried $^{18}$F[F$^-$] was eluted and removed from the module and then dissolved in acetonitrile and a minimal amount of water to be used for the synthesis. Radio-RP-HPLC traces were acquired using a Shimadzu SPD-10ATvP HPLC system equipped with a Waters C column (4.6 x 150 mm, 5 μm) with a 1 mL/min flow rate. Chromatograms were recorded with a scintillation detector and a UV-vis detector (254 nm and 280 nm).

Retention times were recorded using a gradient elution of 0-95% B (acetonitrile) in A (Milli-Q water) over 15 min.

General method 1: Cleavage from the 2-chlorotrityl polymer-bound resin beads. Cleavage was performed using TFA in the presence of triisopropylsilane (TIPS) as scavengers. A 1 mL solution containing $H_2O$ (50 μL), TIPS (25 μL) and TFA (925 μL) was mixed with the resin beads (25 mg). The resin was filtered, and the filtrate was concentrated under nitrogen. The product was precipitated using diethyl ether, centrifuged, collected, redissolved in water: acetonitrile (50:50) and freeze-dried.

**Synthetic Procedures**

**Dimethyl pyridine-2,6-dicarboxylate (2):** Dimethyl 2,6-pyridine-2,6-dicarboxylate was synthesised using an adapted literature protocol.[9] Pyridine-2,6-dicarboxylic acid (10.4 g, 62.0 mmol) and sulfuric acid (2 mL) were heated at reflux in methanol (50 mL) for 18 h. The solid that formed was collected by filtration then dissolved in dichloromethane and washed with saturated $NaHCO_3$ and water. The combined organic layers were dried over $Na_2SO_4$, and the solvent was removed under reduced pressure to give dimethyl pyridine-2,6-dicarboxylate as a colourless solid (9.12 g, 75%). $^1$H NMR (400 MHz $CDCl_3$): $\delta_H$ (ppm) 8.30 (d, 2H, Pyr*H*), 8.02 (t, 1H, Pyr*H*), 4.02 (s, 6H, C$H_3$). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$): $\delta_C$ (ppm) = 165.1 (*C*=O), 148.2 (Pyr*C*), 138.4 (Pyr*C*), 128.1 (Pyr*C*), 53.2 (*C*$H_3$). HR-MS(ESI/O-TOF): $[C_9H_9NO_4+H]^+$ *m/z* 196.061 (experimental), 196.061 (calculated).

M**ethyl 6-(hydroxymethyl)picolinate (3):** Methyl 6-(hydroxymethyl) picolinate was synthesised using an adapted literature protocol.[9] To dimethyl 2,6-pyridine-2,6-dicarboxylate (5.1 g, 26 mmol) in dry methanol (100 mL) at 0 ºC under nitrogen, was added sodium borohydride (1.8 g, 48 mmol). The reaction mixture was stirred for 4 h under nitrogen. The solution was diluted using dichloromethane (200 mL) and quenched using saturated $NaHCO_3$ (200 mL). The aqueous and organic layers were separated. The aqueous layer was extracted with chloroform (2 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The methyl 6-(hydroxymethyl)picolinate was purified by column chromatography (100% ethyl acetate) to give a colourless solid (1.89 g, 44%). $^1$H NMR (400 MHz, $CDCl_3$, 25 ºC) : δ = 8.03 (d, 1H; Pyr*H*), 7.85 (t, 1H; Pyr*H*), 7.52 (d, 1H; Pyr*H*), 4.86 (s, 2H; C$H_2$), 4.00 ppm (s, 3H; C$H_3$). HR-MS(ESI/O-TOF): $[C_8H_9NO_3+H]^+$ *m/z* 168.066 (experimental), 168.066 (calculated).

**Methyl 6-(bromomethyl)picolinate (4):** Methyl 6-(bromomethyl) picolinate was synthesised using an adapted literature protocol.[9] To methyl 6-(hydroxymethyl)picolinate (1.9 g, 11 mmol) in dry dichloromethane (80 mL) at 0 ºC under nitrogen, was added phosphorus tribromide (1.2 mL, 14 mmol) dropwise. The reaction was stirred at 0 ºC under nitrogen for 4 h. The reaction mixture was quenched using $Na_2CO_3$ in water (50 mL) and extracted using dichloromethane (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give methyl 6-(bromomethyl)picolinate as a colourless solid (2.32 g, 89%). $^1$H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 8.05 (d, 1H; Pyr*H*), 7.87 (t, 1H; Pyr*H*), 7.68 (d, 1H; Pyr*H*), 4.64 (s, 2H; C$H_2$), 4.01 ppm (s, 3H; $CH_3$). HR-MS(ESI/O-TOF): $[C_8H_8BrNO_2+H]^+$ *m/z* 229.982 (experimental), 229.982 (calculated).

**Dimethyl 6,6'-(benzylazanediyl)bis(methylene))dipicolinate (5):** To a solution of methyl 6-(bromomethyl)picolinate (1.98 g, 8.61 mmol) in dry acetonitrile (50 mL) at 60 ºC under nitrogen, was added benzylamine (0.44 mL, 4.0 mmol) and $K_2CO_3$ (1.9 g, 13 mmol). The solution was stirred for 18 h. $K_2CO_3$ was removed by filtration and washed with acetonitrile. The filtrate was collected and solvent was removed under reduced pressure to and was purified by column chromatography (100% dichloromethane to 3% methanol in dichloromethane) to afford dimethyl 6,6'-(benzylazanediyl)bis(methylene))dipicolinate as a yellow oil (1.5 g, 91%). $^1$H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.88 (m, 2H; Pyr*H*), 7.82 (m, 4H; Pyr*H*), 7.38 (m, 2H; Ar*H*), 7.30 (m, 2H; Ar*H*), 7.22 (m, 1H; Ar*H*), 3.98 (s, 6H; $CH_3$), 3.93 (s, 4H; $CH_2$), 3.70 ppm (s, 2H; $CH_2$). HR-MS(ESI/O-TOF): $[C_{23}H_{23}N_3O_4+H]^+$ *m/z* 406.177 (experimental), 406.177 (calculated).

**$H_2$L$^1$·HCl:** Dimethyl 6,6'-(benzylazanediyl)bis(methylene))dipicolinate (1.4 g, 3.4 mmol) was dissolved in HCl (5 M) and heated at reflux for 18 h. A white solid that formed was collected by filtration and washed with cold water to give $H_2$**L$^1$** as the HCl salt (0.98 g, 70%). $^1$H NMR (500 MHz, DMSO-$d_6$, 25 ºC): δ = 7.97 (d, 4H, *J* = 4.3 Hz; Pyr*H*), 7.82 (d, 2H, *J* = 4.0 Hz; Ar*H*), 7.77 (t, 2H, *J* = 4.3 Hz; Pyr*H*), 7.38 (d, 3H, *J* = 4.2 Hz; Ar*H*), 4.67 (s, 2H; C$H_2$), 4.61 ppm (s, 4H; C$H_2$). $^{13}$C{$^1$H} NMR (126 MHz, DMSO-$d_6$, 25 ºC): δ = 165.4 (*C*=O), 151.1 (*C*=O), 147.3, 138.8 (Pyr*C*), 132.0 (Ar*C*), 129.6 (Ar*C*), 128.6 (Ar*C*), 128.2 (Pyr*C*), 124.3 (Pyr*C*), 57.6 (*C*$H_2$), 56.0 ppm (*C*$H_2$). HR-MS(ESI/O-TOF): $[C_{21}H_{19}N_3O_4+H]^+$ *m/z* 378.145 (experimental), 378.145 (calculated). Crystals of $H_2$**L$^1$**·HCl suitable for analysis by X-ray crystallography were grown from a solution of the compound dissolved in water [CCDC: 2004698].

**[GaL$^1$(OH)]:** To a solution of $H_2$**L$^1$**·HCl (0.51 g, 1.2 mmol) in anhydrous ethanol (50 mL) was added $Ga(NO_3)_3·9H_2O$ (0.60 g, 1.4 mmol, 1.2 eq) in dry ethanol (6 mL). The reaction mixture was stirred for 2 h at 60 ºC under nitrogen. The precipitate was collected by filtration, washed with cold ethanol and dried *in vacuo* to give [Ga**L$^1$**(OH)] as a colourless solid (0.45 g, 82%). $^1$H NMR (500 MHz, DMSO-$d_6$, 25 ºC): δ = 8.27 (t, 2H, *J* = 7.7 Hz; Pyr*H*), 8.06 (d, 2H, *J* = 7.2 Hz; Pyr*H*), 7.76 (d, 2H, *J* = 7.7 Hz; Pyr*H*), 7.31 (dd, 2H, *J* = 6.4, 2.9 Hz; Ar*H*), 7.08 (m, 3H; Ar*H*), 4.18 (s, 4H; C$H_2$), 3.99 ppm (s, 2H; C$H_2$). $^{13}$C{$^1$H} NMR (126 MHz, DMSO-$d_6$, 25 ºC): δ = 163.0 (*C*=O), 154.2 (*C*=O), 146.6, 143.7 (Pyr*C*), 134.2, 130.5 (Ar*C*), 128.1 (Ar*C*), 127.8 (Pyr*C*), 127.5 (Pyr*C*), 122.2 (Pyr*C*), 58.6 (*C*$H_2$), 54.7 ppm (*C*$H_2$). HR-MS(ESI/O-TOF): $[C_{21}H_{17}GaN_3O_4]^+$ *m/z* 444.047 (experimental), 444.047 (calculated). Anal. Calcd for $C_{21}H_{18}GaN_3O_5·1.5H_2O$: C, 51.6; H, 4.3; N, 8.6. Found: C, 51.6; H, 3.3; N, 8.6. RP-HPLC: $R_t$ = 9.5 min. Crystals of [Ga**L$^1$**(OH).5$H_2O$] suitable for analysis by X-ray crystallography were grown from a solution of the complex dissolved in water [CCDC: 2004697].

**[GaL$^1$Cl]:** To a solution of $H_2$**L$^1$**·HCl (0.20 g, 0.48 mmol) in dry ethanol (100 mL) was added $GaCl_3$ in pentane (1.9 mL, 0.96 mmol, 0.5 M). The reaction mixture was stirred for 2 h at 60 ºC under nitrogen. A precipitate formed and was collected by filtration, washed with cold ethanol and dried *in vacuo* to give [Ga**L$^1$**Cl] as a colourless solid (0.072 g, 31%). $^1$H NMR (500 MHz, DMSO-$d_6$, 25 ºC): δ = 8.26 (t, 2H; Pyr*H*), 8.05 (d, 2H; Pyr*H*), 7.77 (d, 2H; Pyr*H*), 7.32 (dd, 2H; Ar*H*), 7.07 (m, 3H; Ar*H*), 4.19 (s, 4H; $CH_2$), 4.00 ppm (s, 2H; $CH_2$). $^{13}$C{$^1$H} NMR (126 MHz, DMSO-$d_6$, 25 ºC): δ = 162.6 (*C*=O), 153.9, 145.8, 143.9, 133.7, 130.7, 128.0, 127.4, 122.2, 58.6 (*C*$H_2$), 54.5 ppm (*C*$H_2$). HR-MS(ESI/O-TOF): $[C_{21}H_{17}GaN_3O_4]^+$ *m/z* 444.047 (experimental), 444.047 (calculated), 480.02 (experimental), 480.02416 (calculated). Anal. Calcd for $C_{21}H_{17}ClGaN_3O_4·C_2H_5OH$: C, 52.46; H, 4.40; N, 7.98. Found: C, 52.46; H, 3.68; N, 7.86. RP-HPLC: $R_t$ = 9.5 min. Crystals of [Ga**L$^1$**Cl] suitable for analysis by X-ray crystallography were grown from a solution of the complex dissolved in water [CCDC: 2004695].

**[GaL$^1$F]:** Method 1: To a solution of [Ga**L$^1$**(OH)] (0.10 g, 0.19 mmol) in water/acetonitrile mixture (10 mL, 1:1) was added dropwise aqueous potassium fluoride (0.012 g, 0.21 mmol, 60 μL). The reaction was stirred at room temperature for 2 h. A colourless precipitate formed that was collected by filtration and washed with cold water (5 mL) to give [Ga**L$^1$**F] as a colourless crystal (0.053 g, 52%). Method 2: A mixture of [Ga**L$^1$**Cl] (0.047 g, 98 μmol), potassium fluoride (0.018 g, 0.31 mmol) and 18-crown-6 (0.026 g, 98 μmol) in acetonitrile was heated to reflux for 3 h. The solution was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was washed with cold acetonitrile and diethyl ether to afford [Ga**L$^1$**F] as a colourless solid (0.019 g, 42%). $^1$H NMR (500 MHz, DMSO-$d_6$, 25 ºC): δ = 8.18 (t, 2H, *J* = 7.5 Hz; Pyr*H*), 8.12 (d, 2H, *J* = 7.3 Hz; Pyr*H*), 7.65 (d, 2H, *J* = 7.4 Hz; Pyr*H*), 7.41 (m, 2H, *J* = 7.3 Hz; Ar*H*),7.34 (m, 3H, *J* = 7.2 Hz; Ar*H*), 3.98 (s, 4H; C$H_2$), 3.61 ppm (s, 2H; C$H_2$). $^{13}$C{$^1$H} NMR (126 MHz, DMSO-$d_6$, 25 ºC): δ = 163.0 (*C*=O), 154.3 (*C*=O), 146.6, 143.7 (Pyr*C*), 134.2, 130.5 (Ar*C*), 128.1 (Ar*C*), 127.8 (Pyr*C*), 127.4 (Pyr*C*), 122.2 (Pyr*C*), 59.6 (*C*$H_2$), 54.7 ppm (*C*$H_2$). $^{19}$F NMR (470 MHz, DMSO-$d_6$, 25 ºC): δ = -141.2 ppm. HR-MS(ESI/O-TOF):

$[C_{21}H_{17}GaN_3O_4]^+$ *m/z* 444.047 (experimental), 444.047 (calculated). Anal. Calcd for $C_{21}H_{17}FGaN_3O_4 \cdot 5H_2O$: C, 45.51; H, 4.91; N, 7.58. Found: C, 45.66; H, 4.89; N, 7.59. RP-HPLC: $R_t$ = 10.2 min. Crystals of [Ga**L**$^1$F.$5H_2O$] suitable for analysis by X-ray crystallography were grown from a solution of the complex dissolved in water [CCDC: 2004696].

**$H_2$L$^2$·*x*HCl:** To a solution of methyl 6-(bromomethyl)picolinate (0.70 g, 3.0 mmol) in anhydrous acetonitrile (50 mL) at 60 ºC under nitrogen, was added 4-(aminomethyl)benzoic acid (0.19 g, 1.3 mmol) and $K_2CO_3$ (1.4 g, 10 mmol). The solution was stirred for 18 h. $K_2CO_3$ was removed by filtration and washed with acetonitrile. The solvent was removed under reduced pressure to give a yellow oil. The yellow oil was dissolved in HCl (5 M) and heated at reflux for 18 h. The colourless solid was collected by filtration and washed with cold water. Purification by semi-prep RP-HPLC yielded $H_2$L$^2$·*x*HCl as a colourless solid (0.43 g, 81%). $^1$H NMR (500 MHz, DMSO-$d_6$, 25 ºC): δ = 8.04-7.96 (m, 4H; Ar*H*), 7.92 (d, *J* = 8.1 Hz, 2H; Ar*H*), 7.78 (dt, *J* = 8.6, 4.5 Hz, 4H; Ar*H*), 4.24 ppm (s, 6H; C$H_2$). $^{13}$C{$^1$H} NMR (126 MHz, DMSO-$d_6$, 25 ºC): δ = 166.9 (*C*=O), 165.6 (*C*=O), 147.5 (Pyr*C*), 138.7 (Pyr*C*), 131.5 (Pyr*C*), 129.3 (Ar*C*), 127.7 (Ar*C*), 124.1 (Pyr*C*), 56.9 (*C*H$_2$), 56.7 ppm (*C*H$_2$). HR-MS(ESI/O-TOF): $[C_{22}H_{19}N_3O_6+H]^+$ *m/z* 422.135 (experimental), 422.135 (calculated).

**[GaL$^2$Cl]:** To a solution of $H_2$L$^2$·*x*HCl (53 mg, 0.13 mmol) in anhydrous ethanol (50 mL) was added $GaCl_3$ in pentane (0.50 mL, 0.25 mmol, 0.5 M). The reaction mixture was stirred for 2 h at 60 ºC under nitrogen. The precipitate was collected by filtration, washed with cold ethanol and dried *in vacuo* to give [Ga**L**$^2$Cl] as a colourless solid (32 mg, 49%). $^1$H NMR (500 MHz, DMSO-$d_6$, 25 ºC): δ = 8.28 (t, 2H, *J* = 7.0 Hz; Pyr*H*), 8.07 (d, 2H, *J* = 6.9 Hz; Pyr*H*), 7.79 (d, 2H, *J* = 7.1 Hz; Pyr*H*), 7.65 (d, 2H, *J* = 6.9 Hz; Ar*H*), 7.43 (d, 2H, *J* = 6.9 Hz; Ar*H*), 4.19 (s, 4H; C$H_2$), 4.04 ppm (s, 2H; C$H_2$). $^{13}$C{$^1$H} NMR (126 MHz, DMSO-$d_6$, 25 ºC): δ = 162.7 (*C*=O), 153.9 (Pyr*C*), 145.9 (Pyr*C*), 144.1 (Pyr*C*), 130.9 (Ar*C*), 129.0 (Ar*C*), 127.7 (Ar*C*), 122.4 (Pyr*C*), 57.8 (*C*H$_2$), 54.4 ppm (*C*H$_2$). HR-MS(ESI/O-TOF): $[C_{22}H_{17}GaN_3O_6]^+$ *m/z* 488.037 (experimental), 488.037 (calculated). Anal. Calcd for $C_{22}H_{16}ClGaN_3O_6 \cdot 2H_2O$: C, 47.22; H, 3.60; N, 7.51. Found: C, 47.72; H, 3.66; N, 6.56.

**$H_2$L$^3$·*x*HCl:** 2-chlorotrityl polymer-bound resin beads (0.516 g) were suspended in DCM. Boc-Lys(Fmoc)-OH protected amino acid (0.241 g, 0.514 mmol) was dissolved in DCM (10 mL), and DIPEA (3 x) was added. The mixture was added to the resin beads and gently shaken overnight. The beads were washed with DCM (3 x 5 mL) to remove excess reagents and then incubated with methanol (5 mL) for 30 minutes to deactivate any unreacted resin. The resin was washed with DCM (3 x), DMF (3 x) and DCM (3 x) and allowed to dry. The Fmoc group was then cleaved with 20% piperidine in DMF (2 x 5 mL), stirring the resin for 2 x 10 min at RT, and then washed with DMF (3 x) and DCM (3 x) and allowed to dry. Methyl 6-(bromomethyl)picolinate (0.356 g, 3 eq, 1.54 mmol) was dissolved in DCM (5 mL) and DIPEA (3 eq.). The solution was added to the resin and left shaking overnight. Cleavage of compound (**8**) from the resin beads was performed using general method 1. $^1$H NMR (500 MHz, DMSO-$d_6$, 25 ºC): δ =7.86 (d, J = 7.7 Hz, 2H; Pyr*H*), 7.79 (t, J = 7.7 Hz, 2H; Pyr*H*), 7.45 (d, J = 7.5 Hz, 2H; Pyr*H*), 4.68 (s, 4H; C$H_2$), 3.92 (s, 6H; C$H_3$), 3.86 (m, 1H; -NH$_2$C*H*), 3.12 – 3.03 (m, 2H; -NH$_2$C$H_2$), 1.90 – 1.29 ppm (m, 6H; C$H_2$). $^{13}$C{$^1$H} NMR (126 MHz, DMSO-$d_6$, 25 ºC): δ = 174.1, 171.0, 164.7, 162.4, 151.3, 147.2, 138.9, 128.7, 124.9, 56.3, 54.2, 53.3, 52.7, 51.9, 35.8, 30.8, 30.3, 29.5, 28.2, 23.0, 21.7 ppm. HR-MS(ESI/O-TOF): $[C_{22}H_{28}N_4O_6+H]^+$ *m/z* 445.209 (experimental), 445.209 (calculated). The compound (**8**) dissolved in HCl (5 M, 15 mL) and heated at reflux for 18 h. A white solid that formed was collected by filtration and washed with cold water to give $H_2$L$^3$ as the HCl salt (0.14 g, 61%). $^1$H NMR (500 MHz, DMSO-$d_6$, 25 ºC): δ = 8.00 (d, J = 6.8 Hz, 4H; Pyr*H*), 7.81 (d, J = 8.6 Hz, 2H; Pyr*H*), 4.69 (s, 4H; C$H_2$), 3.85 (s, 1H; -NH$_2$C*H*), 3.32 (d, 2H; -NH$_2$C$H_2$), 1.92-1.21 ppm (s, 6H; C$H_2$). $^{13}$C{$^1$H} NMR (126 MHz, DMSO-$d_6$, 25 ºC): δ = 171.3, 165.7, 151.2, 147.8, 139.4, 128.7, 124.8, 56.8, 54.7, 52.0, 34.5, 31.2, 29.8, 23.1, 22.0 ppm. HR-MS(ESI/O-TOF): $[C_{20}H_{24}N_4O_6+H]^+$ *m/z* 417.177 (experimental), 417.177 (calculated).

**Attempted radiolabelling.** [$^{18}$F][Ga**L**$^1$F]. Method A: To a solution of [Ga**L**$^1$Cl] (1.0 mg, 2.1 μmol) in sodium acetate buffer (1 mM, pH 4.0, 600 μL) was added a solution of $^{18}$F[F$^-$] (500 MBq, ~ 25 nM) in water. The reaction was incubated for 30 min at 80 ºC. The radiolabelled complex was analysed by RP-HPLC (elution gradient 0-95% B (acetonitrile) in A (Milli-Q $H_2O$) over 15 min, 1 mL/min). Method B: $^{18}$F[F$^-$] (~ 500 MBq) trapped on the QMA cartridge was eluted with potassium bicarbonate (2.0 mg, 20 μmol) and [2,2,2]Kryptofix (6.3 mg, 16 μmol) in water:acetonitrile (1 mL, 1:4). The azeotropically dried $^{18}$F[F$^-$] was removed from the iPHASE Flexlab module and was then dissolved in acetonitrile (400 mL) and a minimal amount of water (50 mL). To this was added [Ga**L**$^1$Cl] (1.7 mg, 3.5 μmol, 200 mL in acetonitrile) and the reaction was incubated for 30 min at 80 ºC. An aliquot of the diluted reaction mixture (100 μL, 2.08 MBq) was analysed by RP-HPLC (elution gradient 0-95% B (acetonitrile) in A (Milli-Q $H_2O$) over 15 min, 1 mL/min). [$^{18}$F][Ga**L**$^1$F] $R_t$ = 12.6 min (2%); unreacted [$^{18}$F]F$^-$ $R_t$ = 2.0 min (recovered 2.00 MBq, ~ 96%).

**X-ray Crystallography**

Crystals were mounted in low-temperature oil and then flash-cooled. Intensity data were collected at 130 K or 100 K on an X-ray diffractometer with a CCD detector using Cu Kα (λ = 1.54184 Å) or Mo Kα (λ = 0.71073 Å) radiation. The structures were solved by methods using SHELXT[13] and refined using SHELXL[14] employing full-matrix least-squares on $F^2$ using the OLEX2 software package.[15] Thermal ellipsoid plots were generated using ORTEP integrated within OLEX2 program.

Crystal Data for $H_2$L$^1$·HCl: $C_{21}H_{20}ClN_3O_4$, 0.551 x 0.205 x 0.123 mm$^3$, triclinic, space group P1, a = 8.1655(6), b = 10.5274(4), c = 12.3713(6) Å, α = 75.104 (4)º, β = 79.386(5)º, γ = 89.774(4)º, V = 1009.08 Å$^3$, *ρcalcd* 1.362 Mg/m$^3$, λ 1.54184 Å, T = 100(10) K, Z = 2, *μ* 1.957 mm$^{-1}$, Semi-empirical from equivalents (1.00000 and 0.58327 transmission), Full-matrix least-squares on F$^2$, 274 parameters, 0 restraints, F(000) = 432, 11600 measured reflections, 4130 independent reflections ($R_{int}$ = 0.0685), final *R* indices [I>2σ(I)] $R_1$ = 0.0599, w$R^2$ = 0.1720, final *R* indices (all data) $R_1$ = 0.0639, w$R^2$ = 0.1861, Goodness-of-fit on F$^2$ = 1.081. [CCDC: 2004698].

Crystal Data for [Ga**L**$^1$(OH)]·$5H_2O$: $C_{21}H_{28}GaN_3O_{10}$, 0.544 x 0.323 x 0.313 mm$^3$, monoclinic, space group P 2$_1$/n, a = 11.6817(2), b = 16.2098(3), c = 12.2210(3) Å, α = 90º, β = 91.268(2)º, γ = 90º, V = 2313.58(8) Å$^3$, *ρcalcd* 1.585 Mg/m$^3$, λ 0.71073 Å, T = 130.0(1) K, Z = 4, *μ* 1.252 mm$^{-1}$, Semi-empirical from equivalents (1.00000 and 0.75153 transmission), Full-matrix least-squares on F$^2$, 352 parameters, 8 restraints, F(000) = 1144, 14031 measured reflections, 4060 independent reflections ($R_{int}$ = 0.0202), final *R* indices [I>2σ(I)] $R_1$ = 0.0328, w$R^2$ = 0.0853, final *R* indices (all data) $R_1$ = 0.0352, w$R^2$ = 0.0866, Goodness-of-fit on F$^2$ = 1.052. [CCDC: 2004697].

Crystal Data for [Ga**L**$^1$Cl]: $C_{21}H_{17}ClGaN_3O_4$, 0.361 x 0.267 x 0.135 mm$^3$, monoclinic, space group I 2/a, a = 14.4262(2), b = 9.08430(10), c = 31.6400(5) Å, α = 90º, β = 99.306(2)º, γ = 90º, V = 4091.91(10) Å$^3$, *ρcalcd* 1.560 Mg/m$^3$, λ 1.54184 Å, T = 130.00(10) K, Z = 8, *μ* 3.336 mm$^{-1}$, Semi-empirical from equivalents (0.692 and 0.451 transmission), Full-matrix least-squares on F$^2$, 271 parameters, 0 restraints, F(000) = 1952, 14985 measured reflections, 4289 independent reflections ($R_{int}$ = 0.0205), final *R* indices [I>2σ(I)] $R_1$ = 0.0323, w$R^2$ = 0.0852, final *R* indices (all data) $R_1$ = 0.0330, w$R^2$ = 0.0858, Goodness-of-fit on F$^2$ = 1.059. [CCDC: 2004695].

Crystal Data for [Ga**L**$^1$F]·$5H_2O$: $C_{21}H_{27}FGaN_3O_9$, 0.377 x 0.320 x 0.203 mm$^3$, monoclinic, space group P 2$_1$/n, a = 11.7761(5), b = 16.0638(6), c = 12.1853(4) Å, α = 90º, β = 91.841(3)º, γ = 90º, V = 2303.89(15) Å$^3$, *ρcalcd* 1.598 Mg/m$^3$, λ 0.71073 Å, T = 130.0(1) K, Z = 4, *μ* 1.261 mm$^{-1}$, Semi-empirical from equivalents (1.00000 and 0.74069 transmission), Full-matrix least-squares on F$^2$, 326 parameters, 9 restraints, F(000) = 1144, 16907 measured reflections, 6130 independent reflections ($R_{int}$ = 0.0223), final *R* indices [I>2σ(I)] $R_1$ = 0.0356, w$R^2$ = 0.0904, final *R* indices (all data)

$R_1$ = 0.0427, $wR^2$ = 0.0952, Goodness-of-fit on $F^2$ = 1.063. [CCDC: 2004696].

## Acknowledgements

We would like to thank the Melbourne Mass Spectrometry and Proteomics Facility (MSPF) of The Bio21 Molecular Science and Biotechnology Institute at The University of Melbourne for the support of mass spectrometry analysis. Financial support from an Australian Research Council Linkage Grant (LP150100656) where the Industry Partner was Clarity Pharmaceuticals is acknowledged. Professor Rodney J. Hicks is acknowledged for his support of this research.

**Keywords:** bioinorganic chemistry • fluorides • gallium • imaging agents • radiopharmaceuticals

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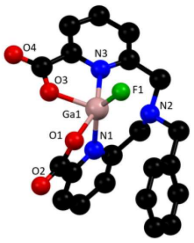
## Entry for the Table of Contents

## Gallium Fluoride-18 Complexes as Radiopharmaceuticals




The potential of gallium(III) complexes with acyclic pentadentate bis-dipicolinic acid containing ligands ($H_2$**L**$^{1\text{-}3}$) to form ternary complexes with fluoride, [Ga**L**$^{1\text{-}3}$F] was investigated with a view to developing new methods for radiolabelling molecules with fluorine-18.