Electronic Supplementary Information (ESI) for:

Getting a Lead on Pb^{2+} - Amide Chelators for $^{203/212}$Pb Radiopharmaceuticals

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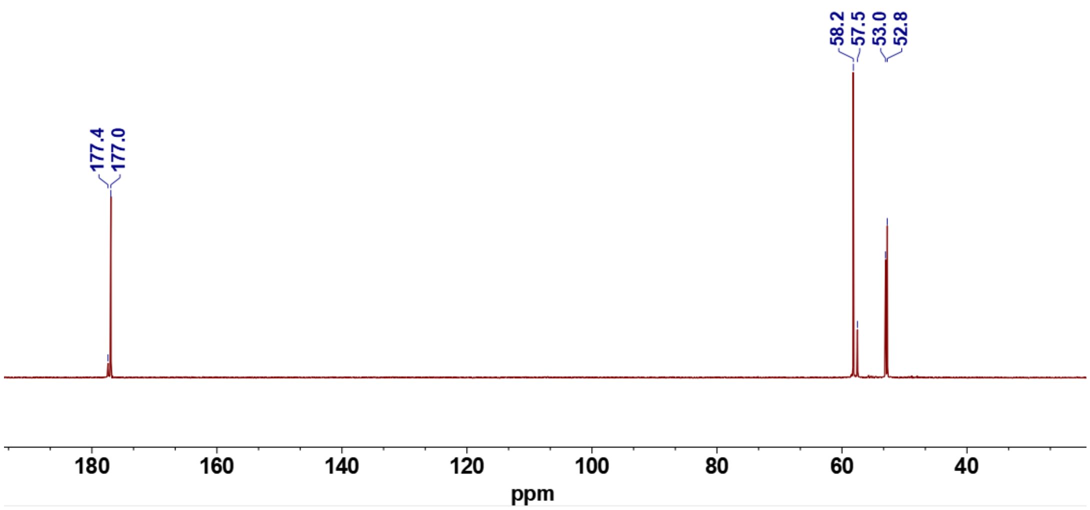

Figure S1. $^{13}C\{^1H\}$ NMR spectrum of DTPAm (**2**) (100 MHz, 25 °C, D_2O).

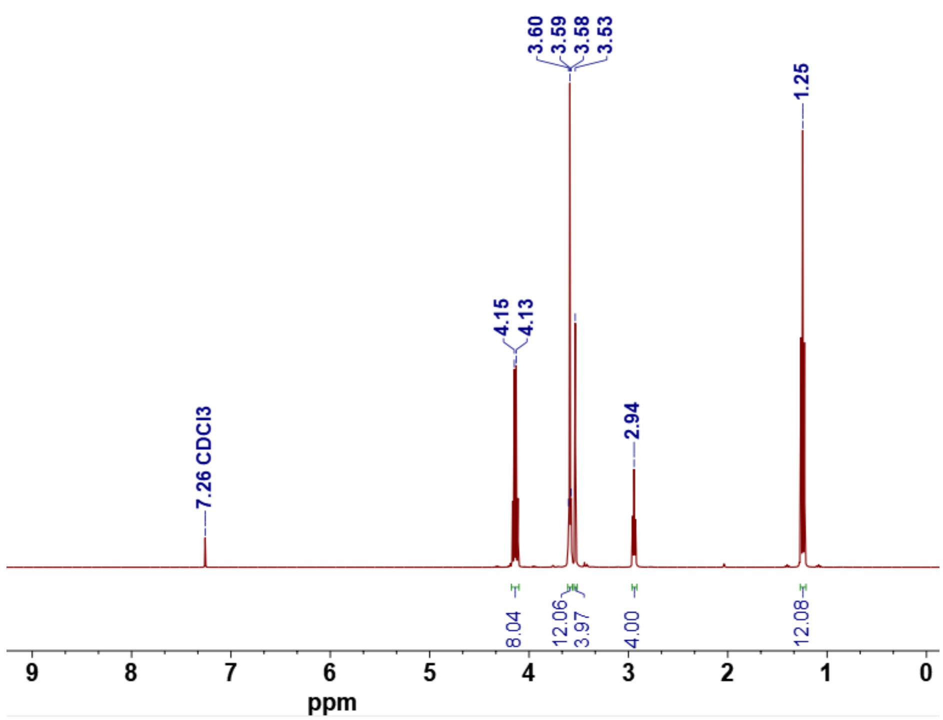

Figure S2. ^1H NMR spectrum of compound **3** (400 MHz, 25 °C, $CDCl_3$).

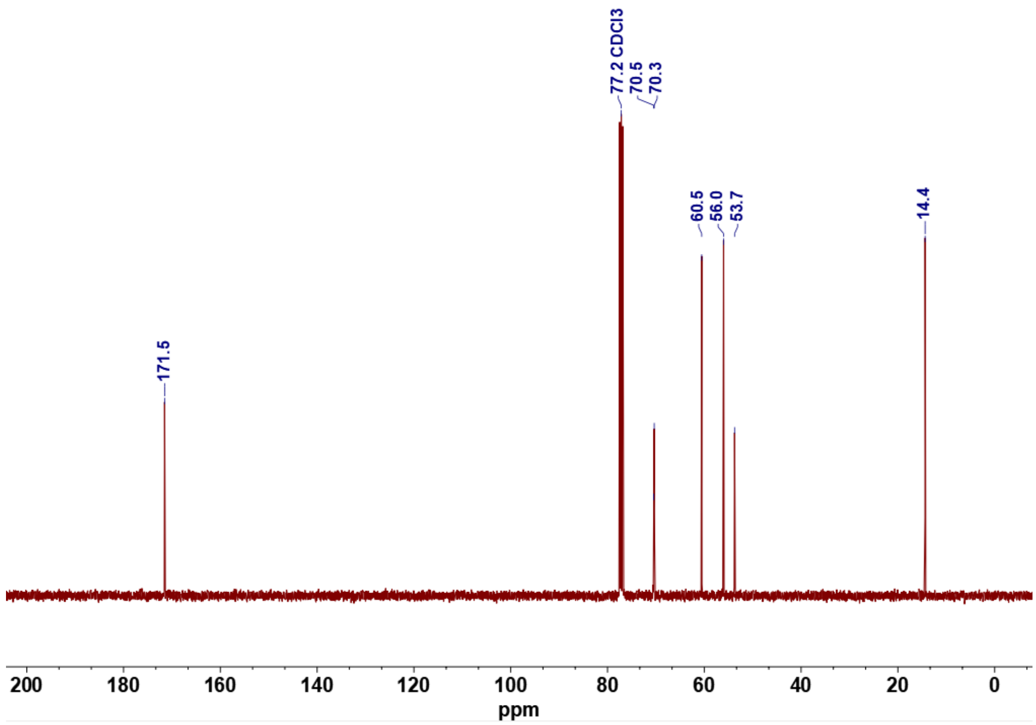

Figure S3. $^{13}C\{^1H\}$ NMR spectrum of compound **3** (100 MHz, 25 °C, $CDCl_3$).

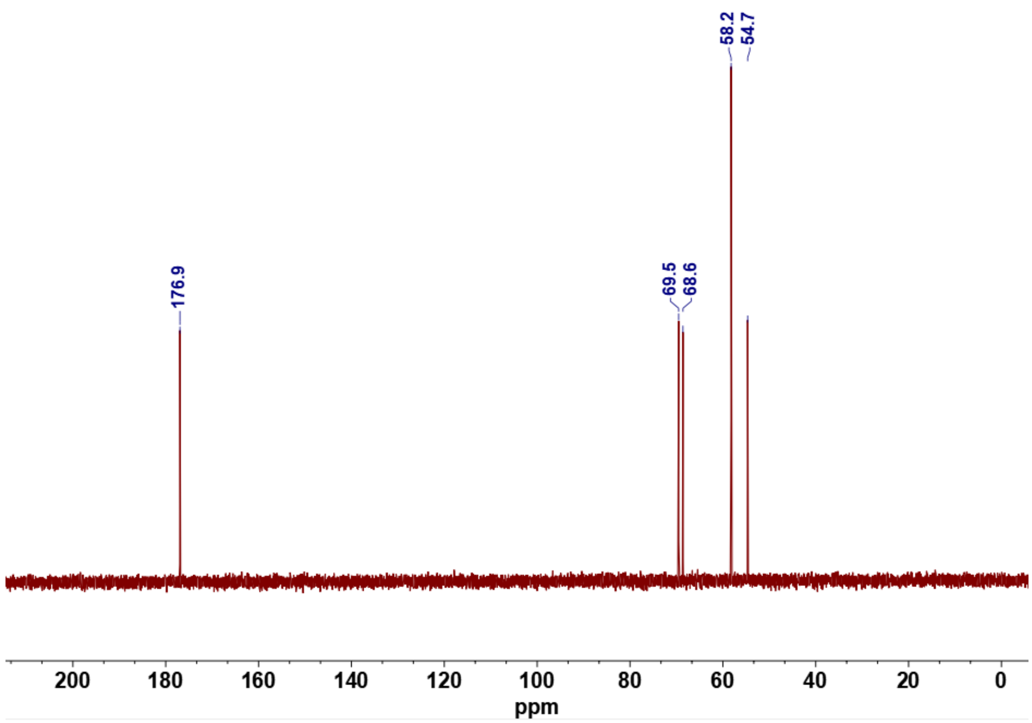

Figure S4. $^{13}C\{^1H\}$ NMR spectrum of compound **4** (EGTAm) (100 MHz, 25 °C, D_2O).

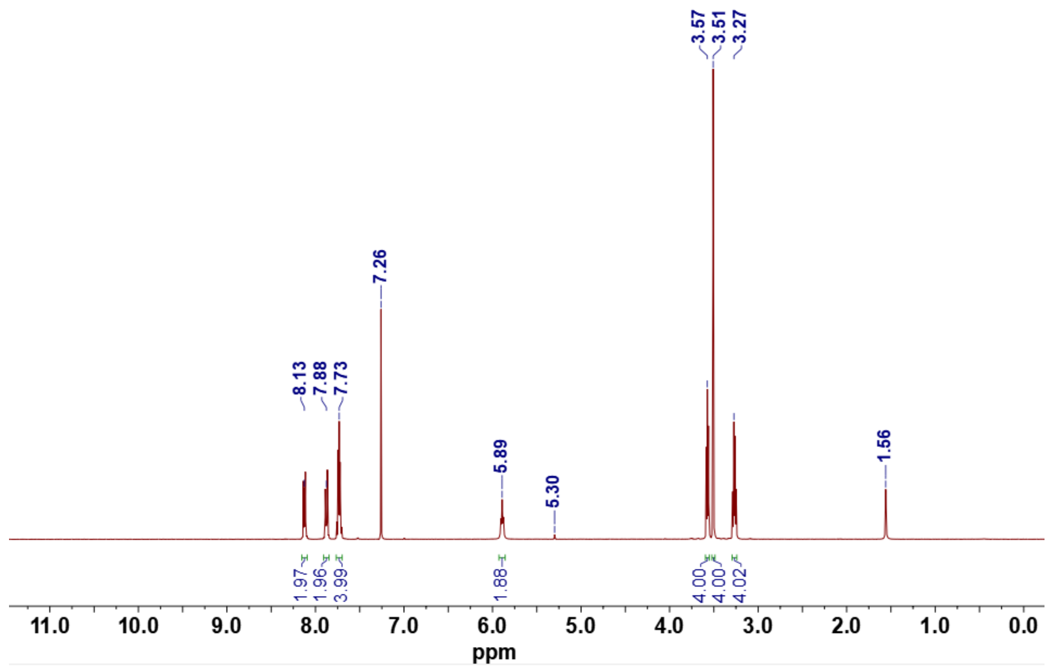

Figure S5. ^{1}H NMR spectrum of compound **7** (400 MHz, 25 °C, $CDCl_3$).

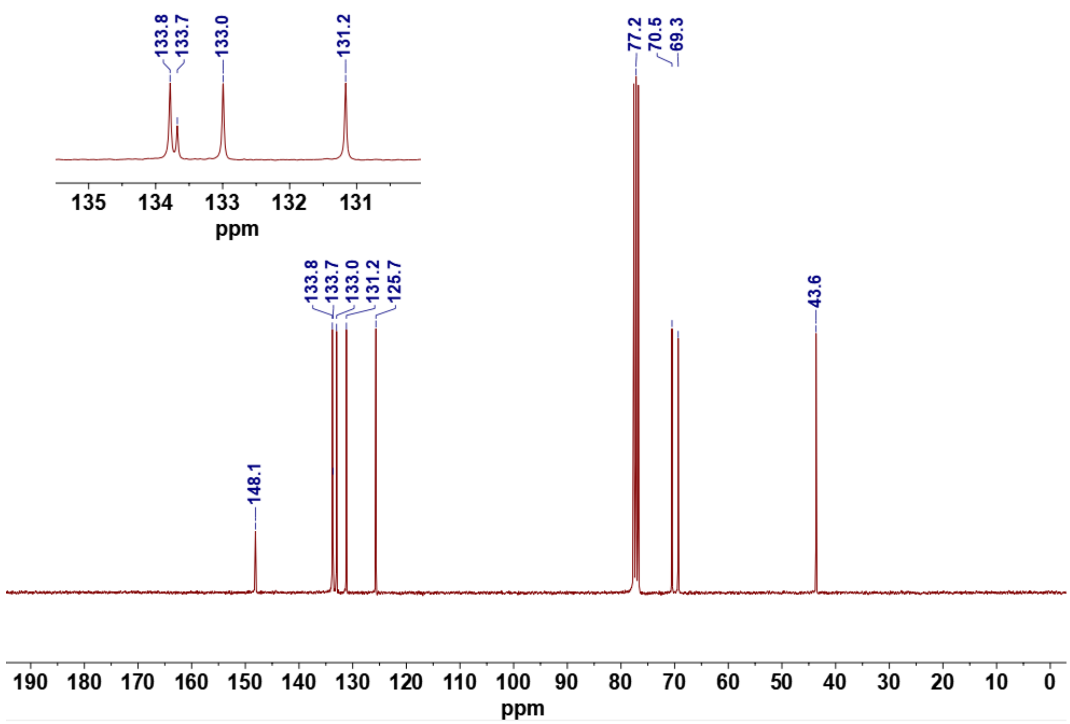

Figure S6. $^{13}C\{^{1}H\}$ NMR spectrum of compound **7** (75 MHz, 25 °C, $CDCl_3$).

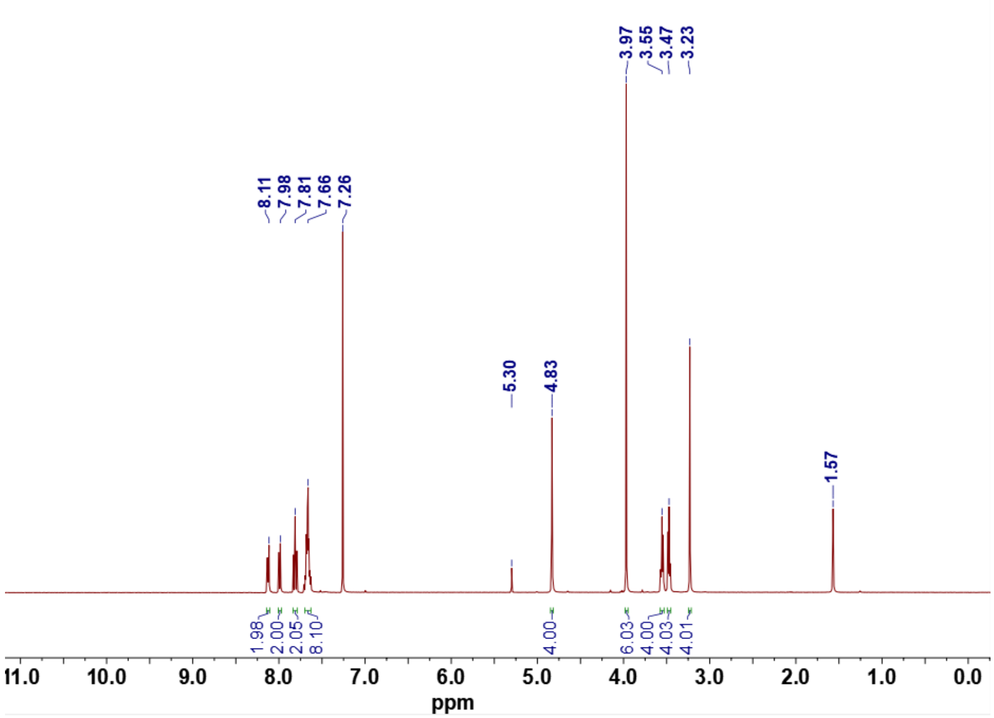

Figure S7. ^{1}H NMR spectrum of compound **8** (400 MHz, 25 °C, $CDCl_3$).

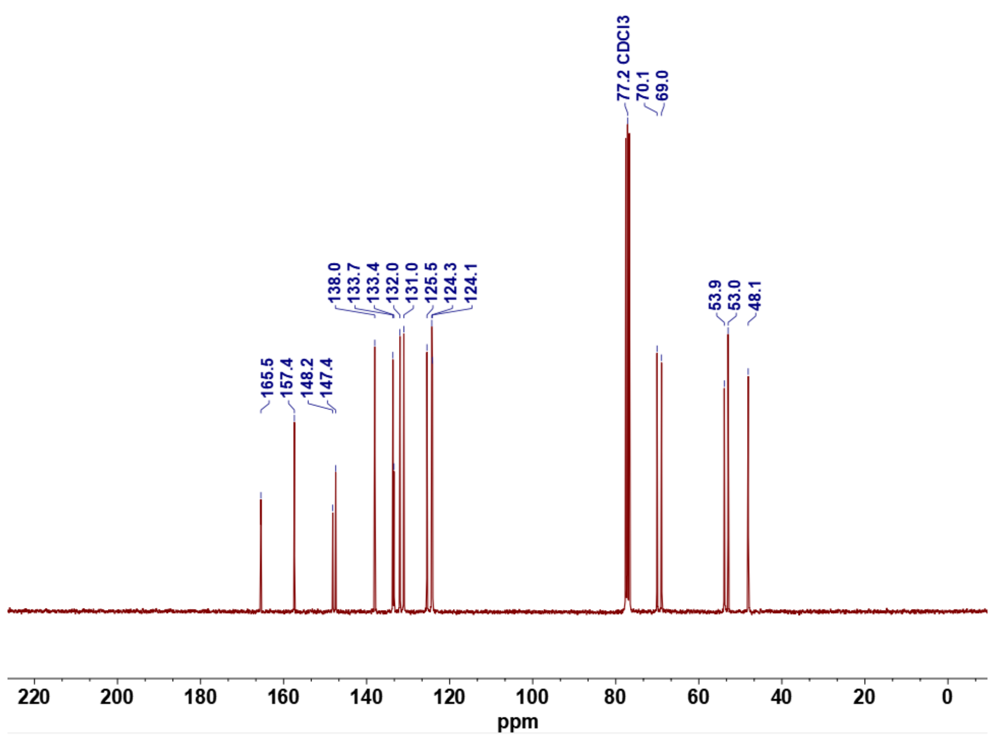

Figure S8. $^{13}C\{^{1}H\}$ NMR spectrum of compound **8** (75 MHz, 25 °C, $CDCl_3$).

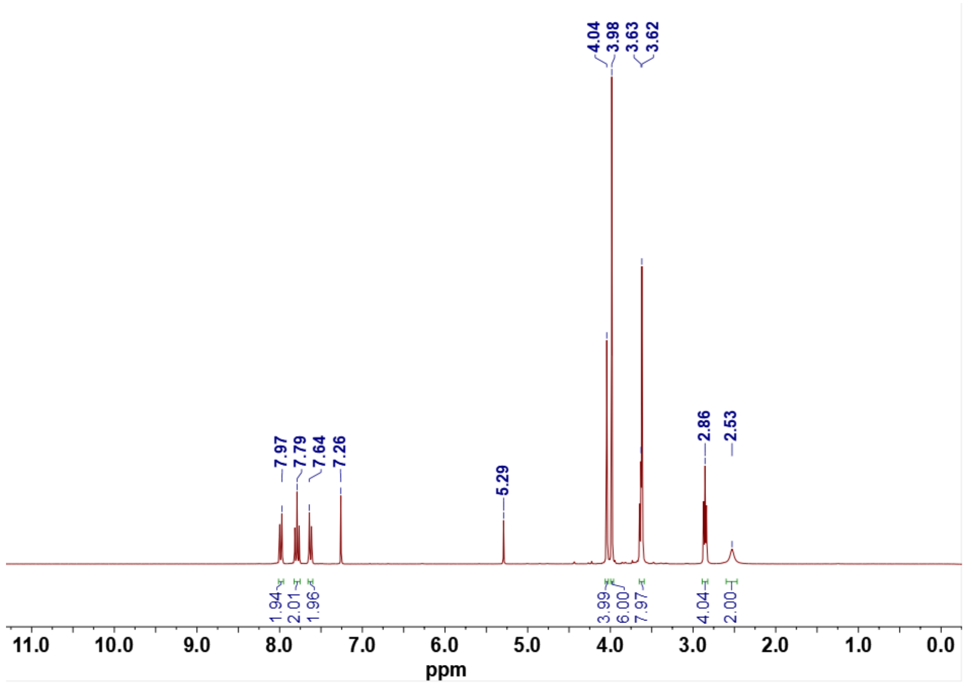

Figure S9. ^{1}H NMR spectrum of compound **9** (300 MHz, 25 °C, $CDCl_3$).

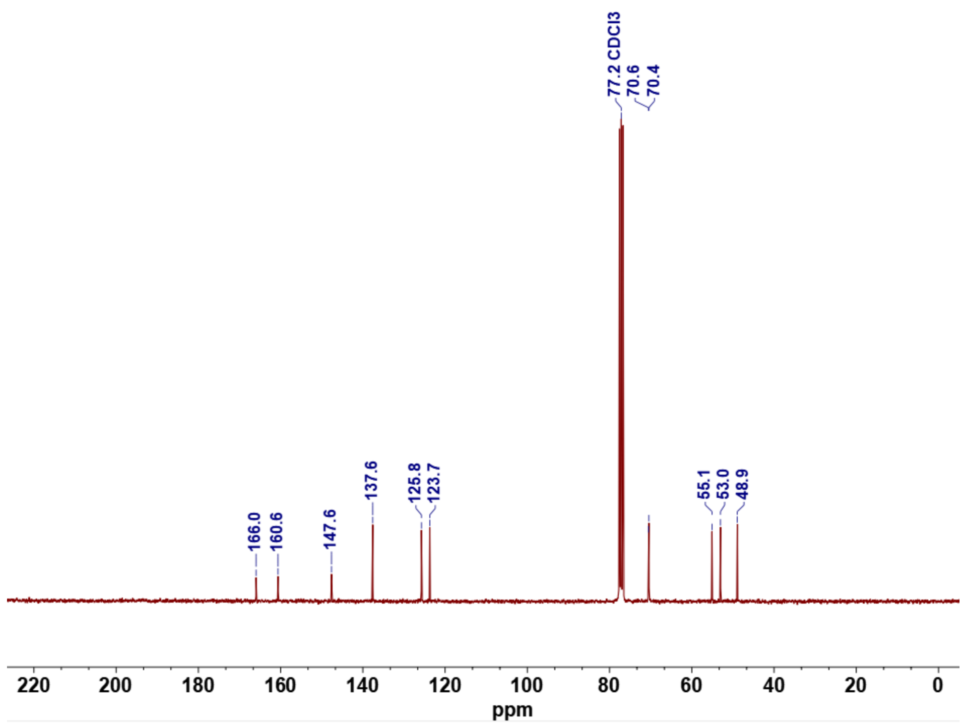

Figure S10. $^{13}C\{^{1}H\}$ NMR spectrum of compound **9** (75 MHz, 25 °C, $CDCl_3$).

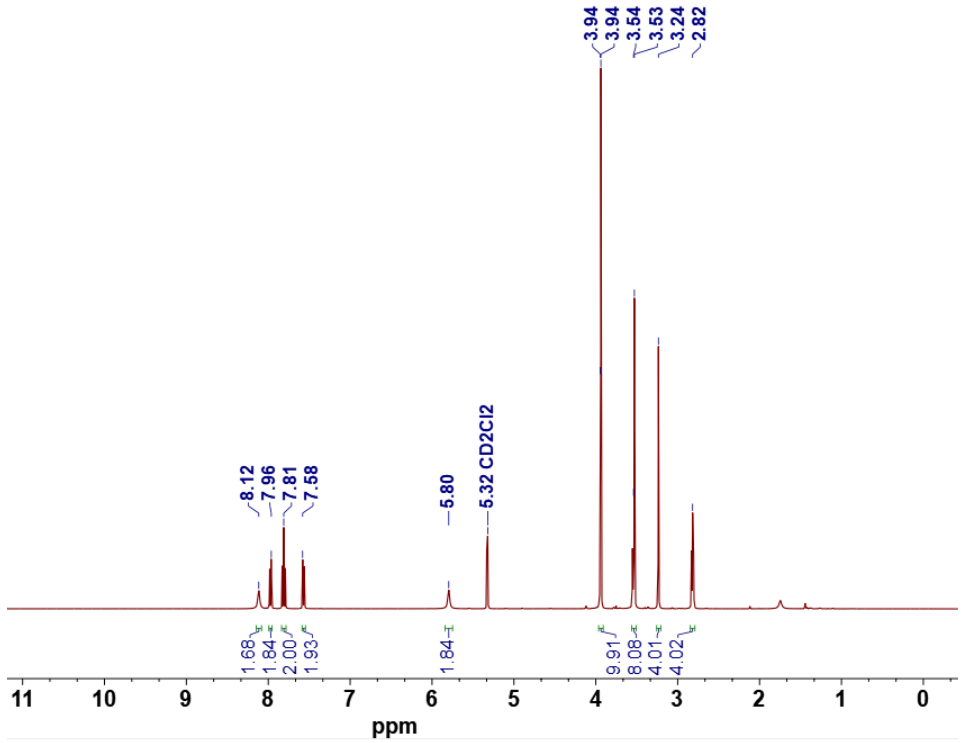

Figure S11. ^{1}H NMR spectrum of compound **10** (400 MHz, 25 °C, CD_2Cl_2).

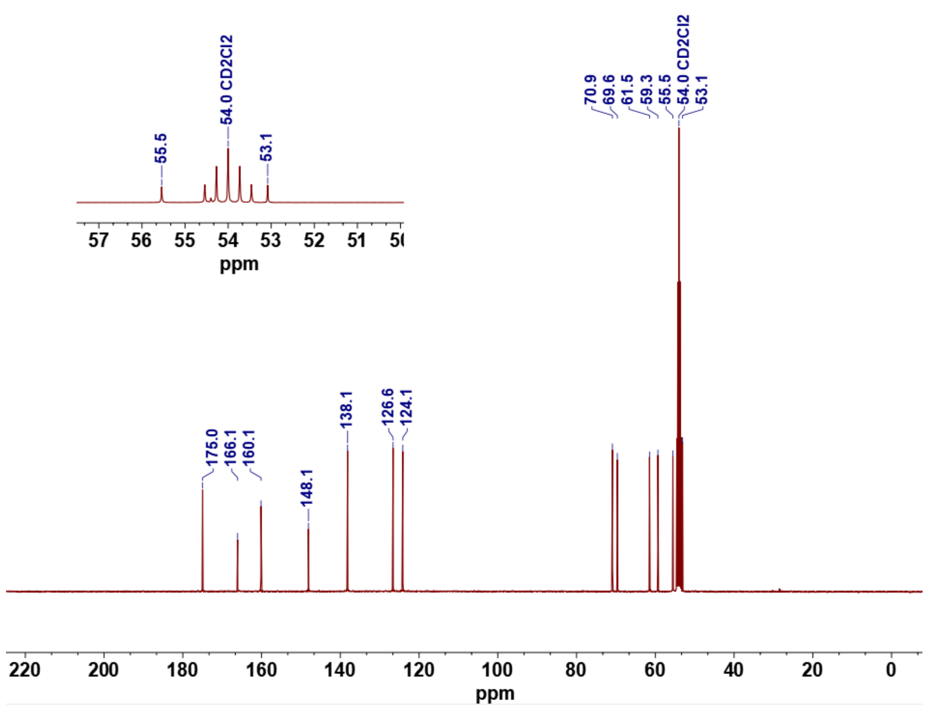

Figure S12. ^{13}C{^{1}H} NMR spectrum of compound **10** (100 MHz, 25 °C, CD_2Cl_2).

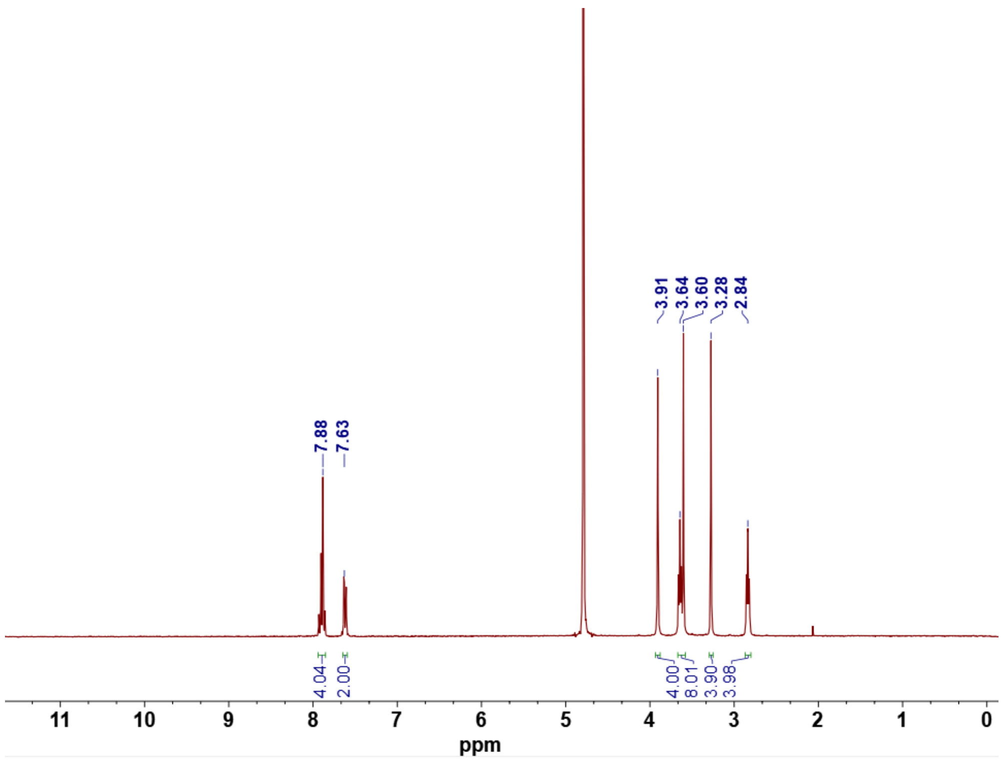

Figure S13. ^{1}H NMR spectrum of compound **11** (ampam) (300 MHz, 25 °C, D_2O).

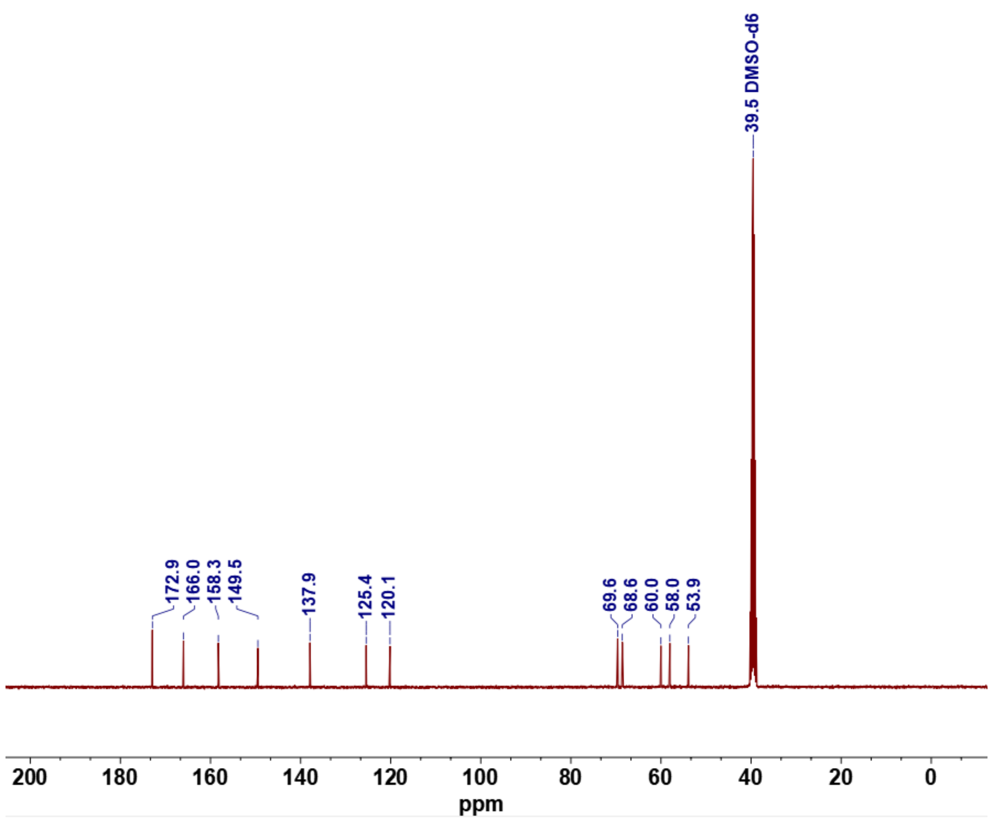

Figure S14. $^{13}C\{^{1}H\}$ NMR spectrum of compound **11** (ampam) (100 MHz, 25 °C, DMSO).

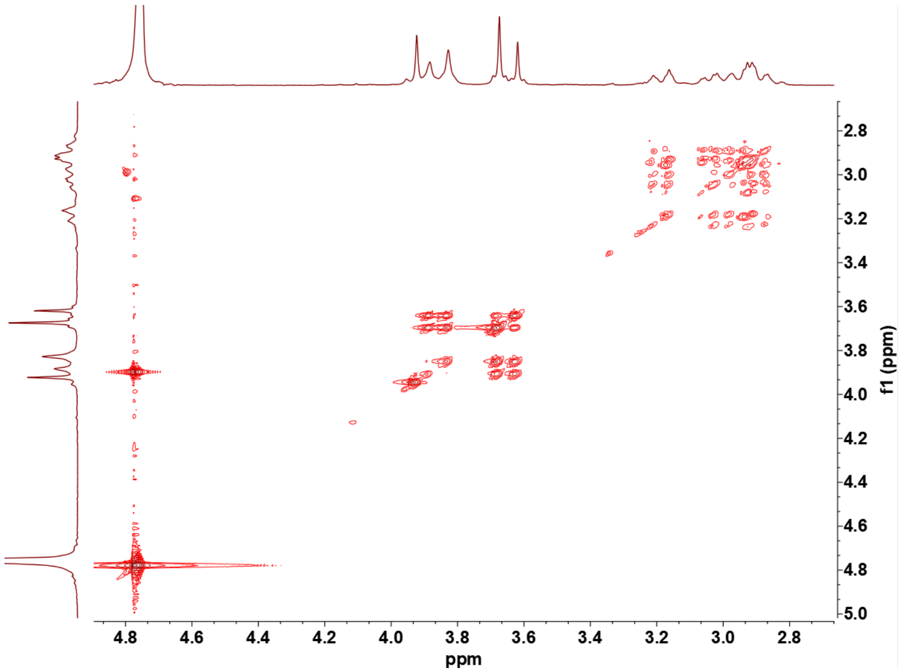

Figure S15. ^1H-^1H COSY spectrum of $[Pb(DTPAm)]^{2+}$ (400 MHz, 25 °C, D_2O, pD = 7).

X-ray Crystallography Data

Table S1. Crystallographic information for [Pb(DTPAm)]$(NO_3)_2$.$4H_2O$, [Pb(EGTAm)(NO_3)](NO_3).H_2O and [Pb(ampam)]$(NO_3)_2$.xH_2O

Compound	[Pb(DTPAm)]$(NO_3)_2$.$4H_2O$	[Pb(EGTAm)(NO_3)](NO_3) .H_2O	[Pb(ampam)]$(NO_3)_2$ .xH_2O
Formula	$C_{14}H_{36}N_{10}O_{15}Pb$	$C_{14}H_{30}N_8O_{13}Pb$	$C_{24}H_{38.17}N_{10}O_{14.67}Pb$
D_{calc}/g cm^{-3}	1.455	2.008	1.833
μ/mm^{-1}	6.239	7.108	5.208
Formula Weight	791.73	725.65	908.68
Colour	colourless	colourless	colourless
Shape	needle	needle	irregular
Size/mm^3	0.32x0.27x0.07	0.29x0.15x0.08	0.19x0.15x0.07
T/K	296(2)	110(2)	115(2)
Crystal System	monoclinic	monoclinic	monoclinic
Space Group	$P2_1/c$	$P2_1/c$	$C2/c$
a/Å	8.9884(7)	11.2179(2)	14.0872(7)
b/Å	20.3731(16)	27.5158(5)	22.5964(10)
c/Å	14.8713(11)	7.7860(2)	12.3531(9)
α/°	90	90	90
β/°	93.436(2)	92.6860(10)	123.133(2)
γ/°	90	90	90
V/Å^3	2718.4(4)	2400.66(9)	3292.9(3)
Z	4	4	4
Z'	1	1	0.5
Wavelength/Å	0.71073	0.71073	0.71073
Radiation type	MoK_α	MoK_α	MoK_α
Θ_{min}/°	1.697	1.962	1.802
Θ_{max}/°	30.548	30.553	30.705
Measured Refl.	50045	34585	19580
Independent Refl.	8315	7328	5069
Reflections with I > 2(I)	7492	5751	4486
R_{int}	0.0389	0.0689	0.0615
Parameters	369	344	333
Restraints	0	0	139
Largest Peak	0.970	2.514	1.568
Deepest Hole	-1.015	-2.005	-2.072
GooF	1.057	1.075	1.022
wR_2 (all data)	0.0519	0.0785	0.0742
wR_2	0.0492	0.0735	0.0710
R_1 (all data)	0.0293	0.0600	0.0388
R_1	0.0236	0.0400	0.0319

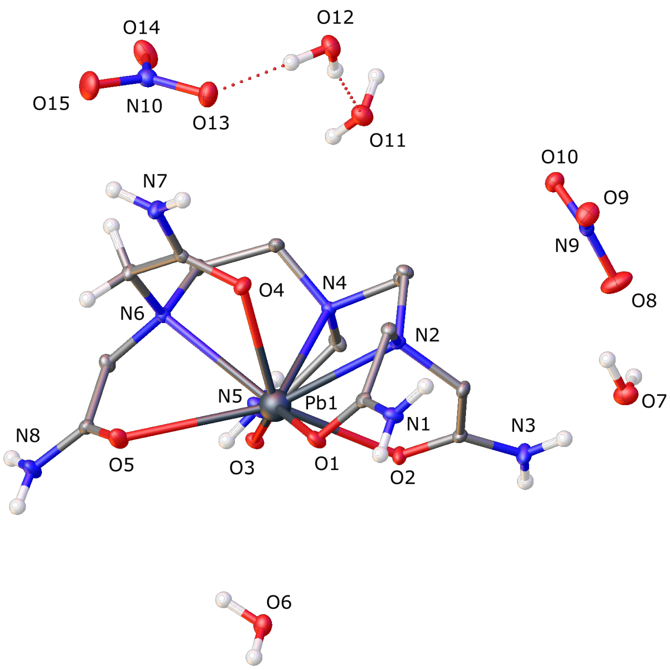

Figure S16. Molecular diagram of [Pb(DTPAm)]$(NO_3)_2$.4H_2O crystal structure showing the intermolecular bonding between solvent and anion molecules; ellipsoids are drawn at 50% probability level, except the Pb atom that is at 80%. Hydrogen atoms are omitted for clarity, except in the amide groups.

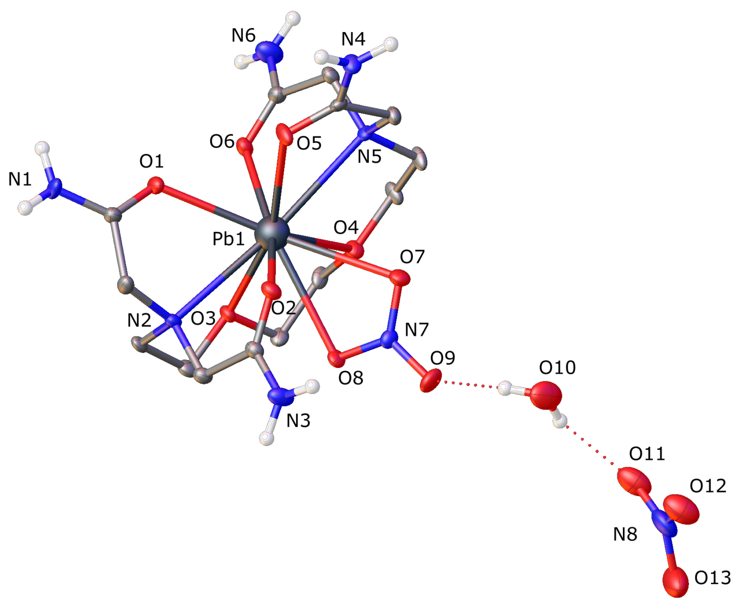

Figure S17. Molecular diagram of [Pb(EGTAm)(NO_3)](NO_3).H_2O crystal structure showing the intermolecular bonding between solvent and anion molecules; ellipsoids are drawn at 50% probability level, except the Pb atom that is at 80%. Hydrogen atoms are omitted for clarity, except in the amide groups.

Table S2. Selected crystallographic bond angle information for $[Pb(DTPAm)](NO_3)_2.4H_2O$

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	Pb1	O5	98.02(6)	O4	Pb1	O2	131.80(6)
O1	Pb1	N6	133.88(6)	O4	Pb1	O3	129.78(6)
O2	Pb1	O1	90.78(6)	O4	Pb1	O5	84.67(6)
O2	Pb1	O5	143.52(6)	O4	Pb1	N2	70.06(6)
O2	Pb1	N2	63.70(6)	O4	Pb1	N4	80.76(6)
O2	Pb1	N4	71.30(6)	O4	Pb1	N6	62.17(6)
O2	Pb1	N6	133.21(6)	N2	Pb1	O1	61.93(6)
O3	Pb1	O1	151.26(6)	N2	Pb1	O5	149.85(6)
O3	Pb1	O2	72.19(6)	N2	Pb1	N6	119.39(6)
O3	Pb1	O5	84.02(6)	N4	Pb1	O1	131.14(6)
O3	Pb1	N2	124.70(6)	N4	Pb1	O5	123.62(6)
O3	Pb1	N4	65.93(6)	N4	Pb1	N2	69.45(6)
O3	Pb1	N6	70.74(6)	N4	Pb1	N6	68.11(6)
O4	Pb1	O1	78.83(6)	N6	Pb1	O5	57.01(6)

Table S3. Selected crystallographic bond angle information for $[Pb(EGTAm)(NO_3)](NO_3).H_2O$

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	Pb1	O2	90.19(11)	O5	Pb1	O4	123.17(10)
O1	Pb1	O3	92.53(10)	O5	Pb1	O6	90.30(11)
O1	Pb1	O4	135.14(10)	O5	Pb1	O7	88.98(10)
O1	Pb1	O5	72.28(10)	O5	Pb1	O8	128.52(10)
O1	Pb1	O6	71.91(11)	O5	Pb1	N2	112.19(11)
O1	Pb1	O7	154.91(11)	O5	Pb1	N5	60.37(10)
O1	Pb1	O8	138.45(10)	O6	Pb1	O2	159.46(10)
O1	Pb1	N2	62.55(11)	O6	Pb1	O3	76.60(10)
O1	Pb1	N5	111.51(10)	O6	Pb1	O4	66.66(10)
O2	Pb1	O4	133.24(10)	O6	Pb1	O7	126.05(10)
O2	Pb1	O7	68.29(10)	O6	Pb1	O8	132.68(10)
O2	Pb1	O8	67.65(10)	O6	Pb1	N2	117.56(10)
O2	Pb1	N5	117.91(10)	O6	Pb1	N5	62.55(10)
O3	Pb1	O2	115.19(9)	O7	Pb1	O8	45.51(9)
O3	Pb1	O4	62.15(9)	N2	Pb1	O2	58.96(10)
O3	Pb1	O7	107.95(9)	N2	Pb1	O4	124.61(10)
O3	Pb1	O8	68.61(9)	N2	Pb1	O7	112.38(11)
O3	Pb1	N2	65.72(11)	N2	Pb1	O8	75.91(10)
O3	Pb1	N5	120.67(10)	N2	Pb1	N5	172.31(11)
O4	Pb1	O7	69.14(10)	N5	Pb1	O4	62.93(10)
O4	Pb1	O8	69.07(10)	N5	Pb1	O7	70.71(10)
O5	Pb1	O2	74.30(11)	N5	Pb1	O8	109.92(10)
O5	Pb1	O3	162.59(11)				

Table S4. Selected crystallographic bond angle information for [Pb(ampam)]$(NO_3)_2.xH_2O$

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	Pb1	O1^{1}	84.37(10)	O3^{1}	Pb1	O1	143.73(7)
O1^{1}	Pb1	N2^{1}	59.12(7)	O3^{1}	Pb1	O1^{1}	116.90(7)
O1	Pb1	N2^{1}	111.33(7)	O3	Pb1	O1^{1}	143.73(7)
O1^{1}	Pb1	N2	111.33(7)	O3^{1}	Pb1	O2	67.83(7)
O1	Pb1	N2	59.12(7)	O3	Pb1	O2^{1}	67.83(7)
O1^{1}	Pb1	N3	70.95(7)	O3	Pb1	O2	77.57(7)
O1^{1}	Pb1	N3^{1}	94.98(8)	O3^{1}	Pb1	O2^{1}	77.57(7)
O1	Pb1	N3	94.98(8)	O3^{1}	Pb1	O3	63.73(10)
O1	Pb1	N3^{1}	70.95(7)	O3^{1}	Pb1	N2^{1}	64.55(7)
O2^{1}	Pb1	O1^{1}	147.99(7)	O3	Pb1	N2^{1}	126.95(7)
O2^{1}	Pb1	O1	70.68(7)	O3^{1}	Pb1	N2	126.95(7)
O2	Pb1	O1^{1}	70.68(7)	O3	Pb1	N2	64.55(7)
O2	Pb1	O1	147.99(7)	O3	Pb1	N3^{1}	119.02(8)
O2	Pb1	O2^{1}	139.16(10)	O3^{1}	Pb1	N3^{1}	77.84(8)
O2^{1}	Pb1	N2	73.05(8)	O3	Pb1	N3	77.84(8)
O2^{1}	Pb1	N2^{1}	111.22(8)	O3^{1}	Pb1	N3	119.02(8)
O2	Pb1	N2	111.22(8)	N2	Pb1	N2^{1}	168.42(11)
O2	Pb1	N2^{1}	73.05(8)	N3	Pb1	N2	58.72(8)
O2^{1}	Pb1	N3	129.36(8)	N3^{1}	Pb1	N2	119.12(8)
O2^{1}	Pb1	N3^{1}	58.57(8)	N3	Pb1	N2^{1}	119.12(8)
O2	Pb1	N3^{1}	129.36(8)	N3^{1}	Pb1	N2^{1}	58.72(8)
O2	Pb1	N3	58.57(8)	N3	Pb1	N3^{1}	161.40(12)
O3	Pb1	O1	116.90(7)				

Solution Thermodynamics Results

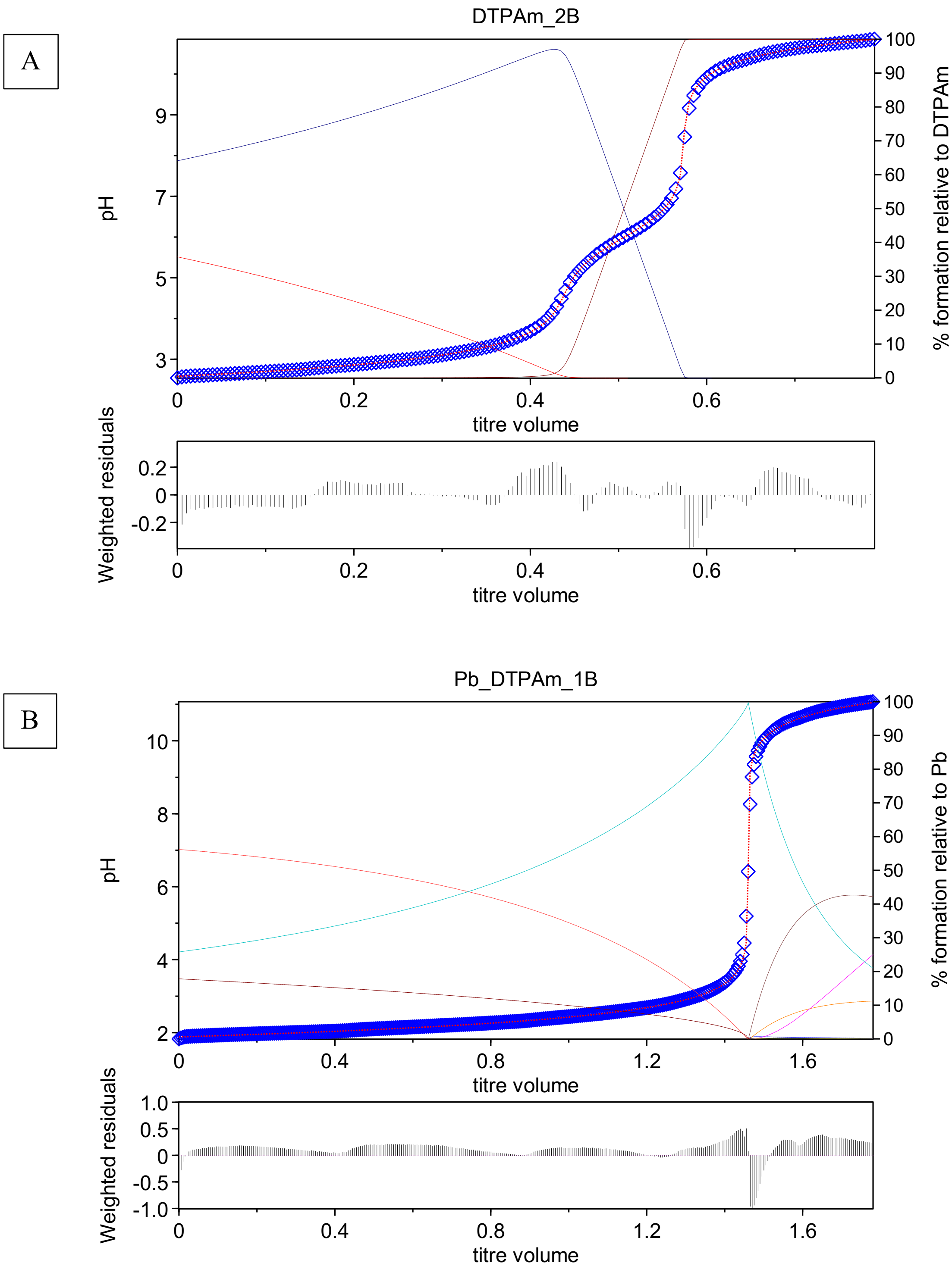

Figure S18. A) Titration plot of ~20 mL of [DTPAm] = 9.13 × 10^{-4} M with [NaOH] = 0.16 M at 25 °C and I = 0.16 M (NaCl); B) Titration plot of ~15 mL of [Pb^{2+}] = [DTPAm] = 6.35 × 10^{-4} M with [NaOH] = 0.16 M at 25 °C and I = 0.16 M (NaCl).

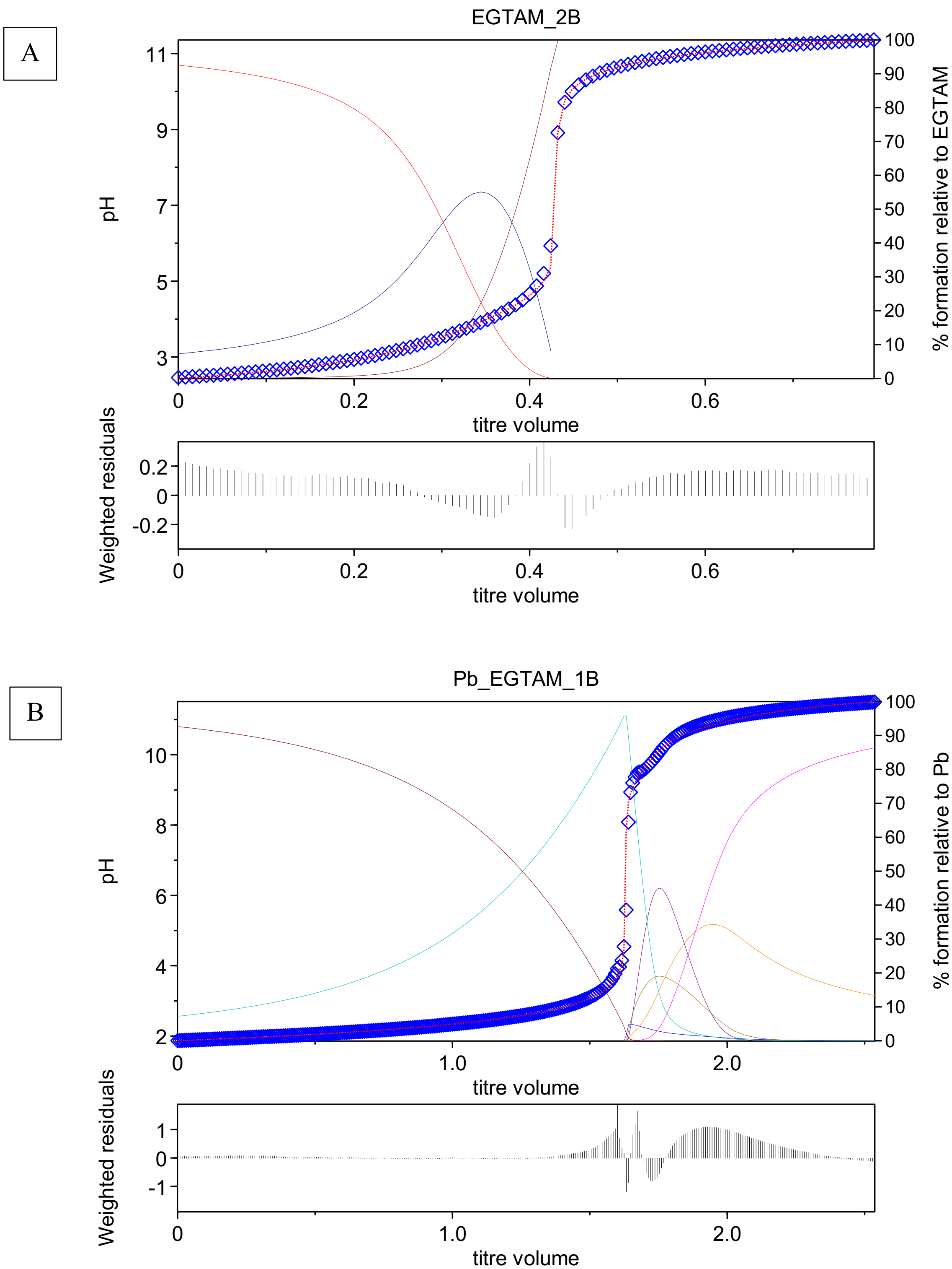

Figure S19. A) Titration plot of ~11 mL of [EGTAm] = 9.99 × 10^{-4} M with [NaOH] = 0.16 M at 25 °C and I = 0.16 M (NaCl); B) Titration plot of ~15 mL of [Pb^{2+}] = [EGTAm] = 6.63 × 10^{-4} M with [NaOH] = 0.16 M at 25 °C and I = 0.16 M (NaCl).

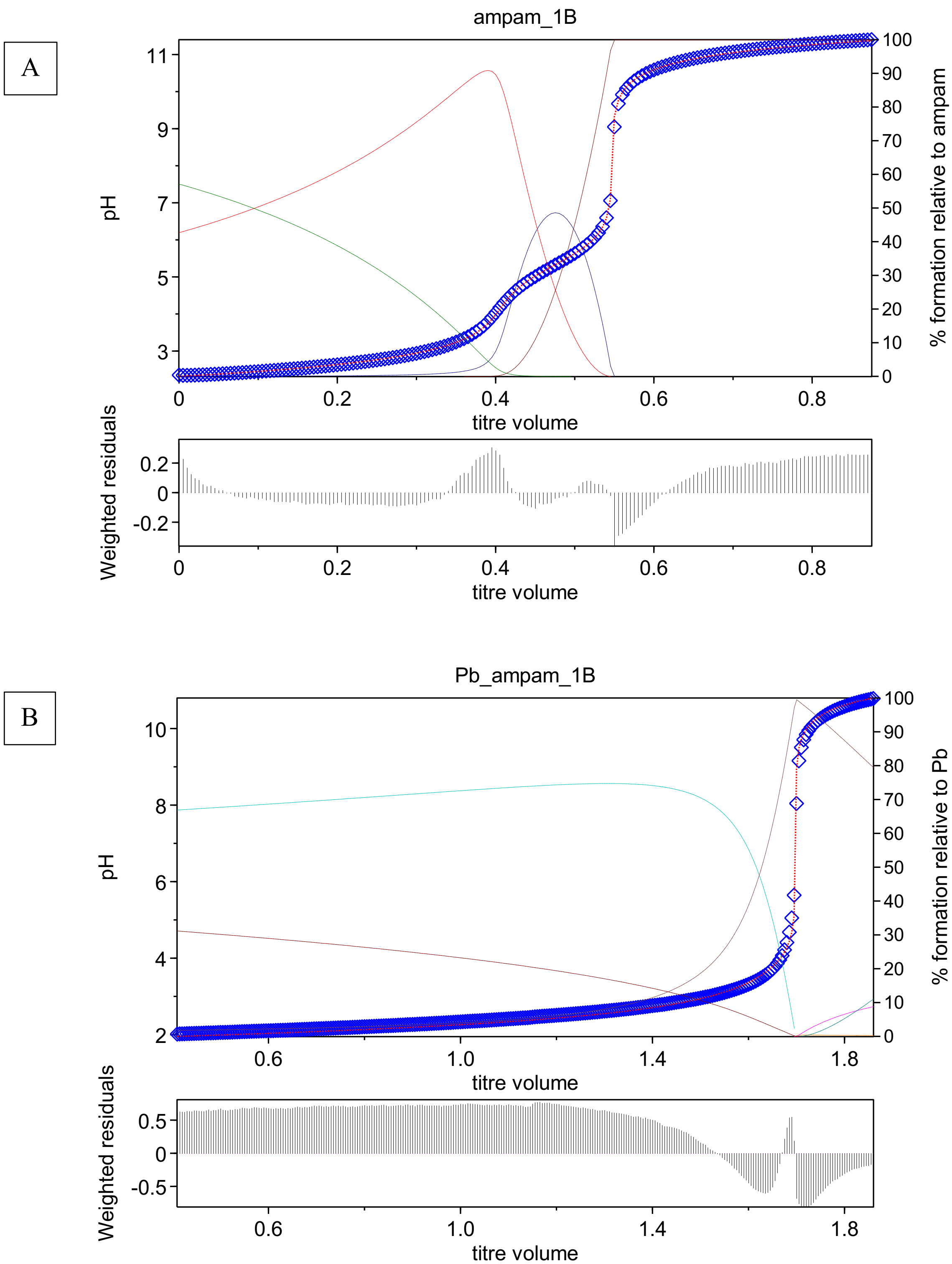

Figure S20. A) Titration plot of ~11 mL of [ampam] = 9.50 × 10^{-4} M with [NaOH] = 0.16 M at 25 °C and I = 0.16 M (NaCl); B) Titration plot of ~15 mL of [Pb^{2+}] = [ampam] = 6.78 × 10^{-4} M with [NaOH] = 0.16 M at 25 °C and I = 0.16 M (NaCl).

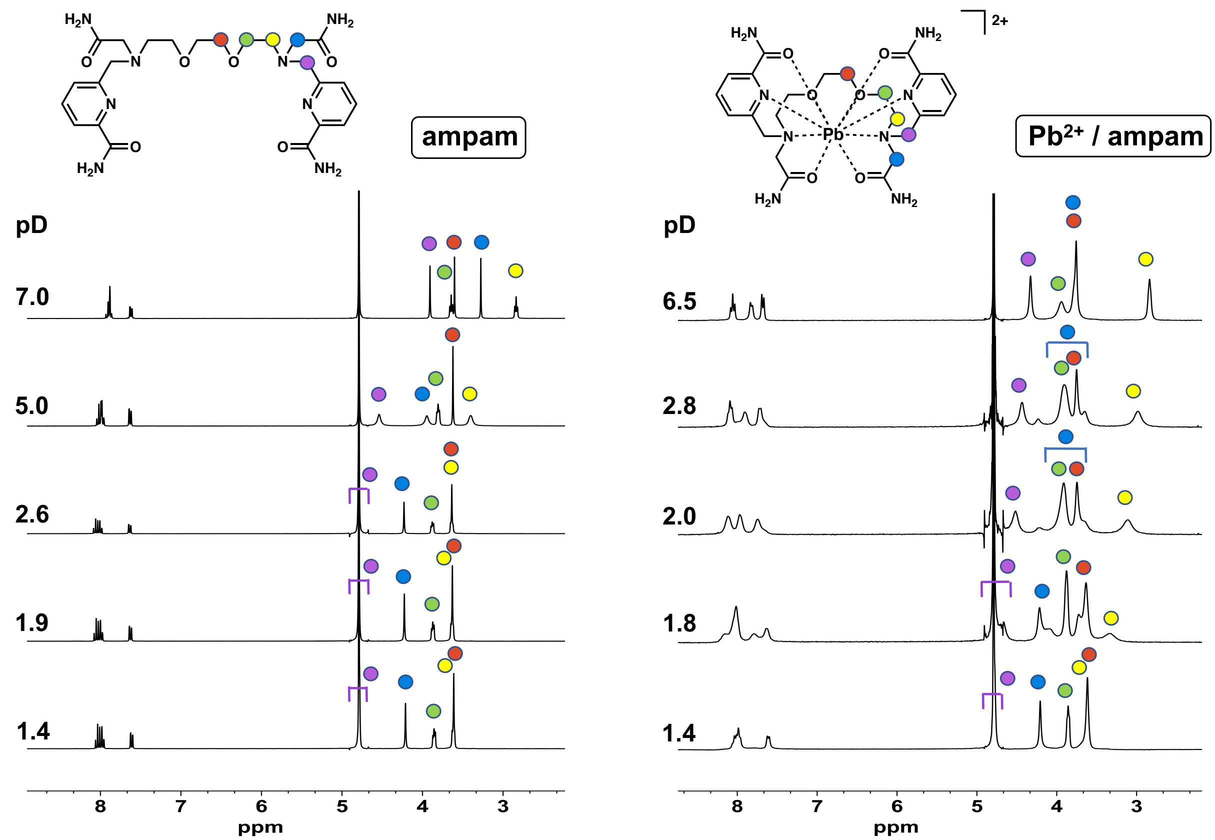

Figure S21. ^{1}H NMR spectra of ampam versus $[Pb(ampam)]^{2+}$ at various pD values (300 MHz, 25 °C, D_2O).

Table S5. Protonation constants (log K_{HqL}) and pM[a] ($M = Pb^{2+}$) values of discussed chelating ligands.

equilibrium reaction[b]	DOTA[c]	TCMC[e]	DTPA[g]	DTPAm[h]	EDTA[i]	EDTAm[j]	EGTA[g]	EGTAm[h]	ampam[h]
$L + H^+ \leftrightarrows HL$	12.6	7.70(1)	11.84	5.99(1)	9.55	4.36(2)	9.40	4.32(1)	5.61(1)
$HL + H^+ \leftrightarrows H_2L$	9.70	6.21(1)	9.40	2.33(1)	6.01		8.78	3.53(1)	5.05(1)
$H_2L + H^+ \leftrightarrows H_3L$	4.50		4.85		2.92				2.44(2)
$H_3L + H^+ \leftrightarrows H_4L$	4.14		3.10		2.17				
$H_4L + H^+ \leftrightarrows H_5L$	2.32		2.20		-				
∑log K_{HqL} {[H_qL] / [$H_{q-1}L$][H^+]}	**33.26**	**13.91**	**31.39**	**8.32**	**20.65**	**4.36(2)**	**18.18**	**7.85**	**13.1**
log K_{PbL}	24.3[d]	>19[e]	18.66[d]	8.79(2)	18[d]	5.85(5)	14.54	6.24(3)	9.21(4)
pPb^{2+}	18.4[d]	19.5[f]	15[d]	9.7	15.9[d]	6.9[f]	12.1[f]	7.2	**10.2**

[a] From ref 1; [b] charges omitted for simplicity; [c] from ref 2; [d] from ref 3; [e] from ref 4; [f] calculated with stability constants in this table; [g] from ref 5; [h] this work; [i] from ref 6; [j] from ref 7.

Radiolabeling Data

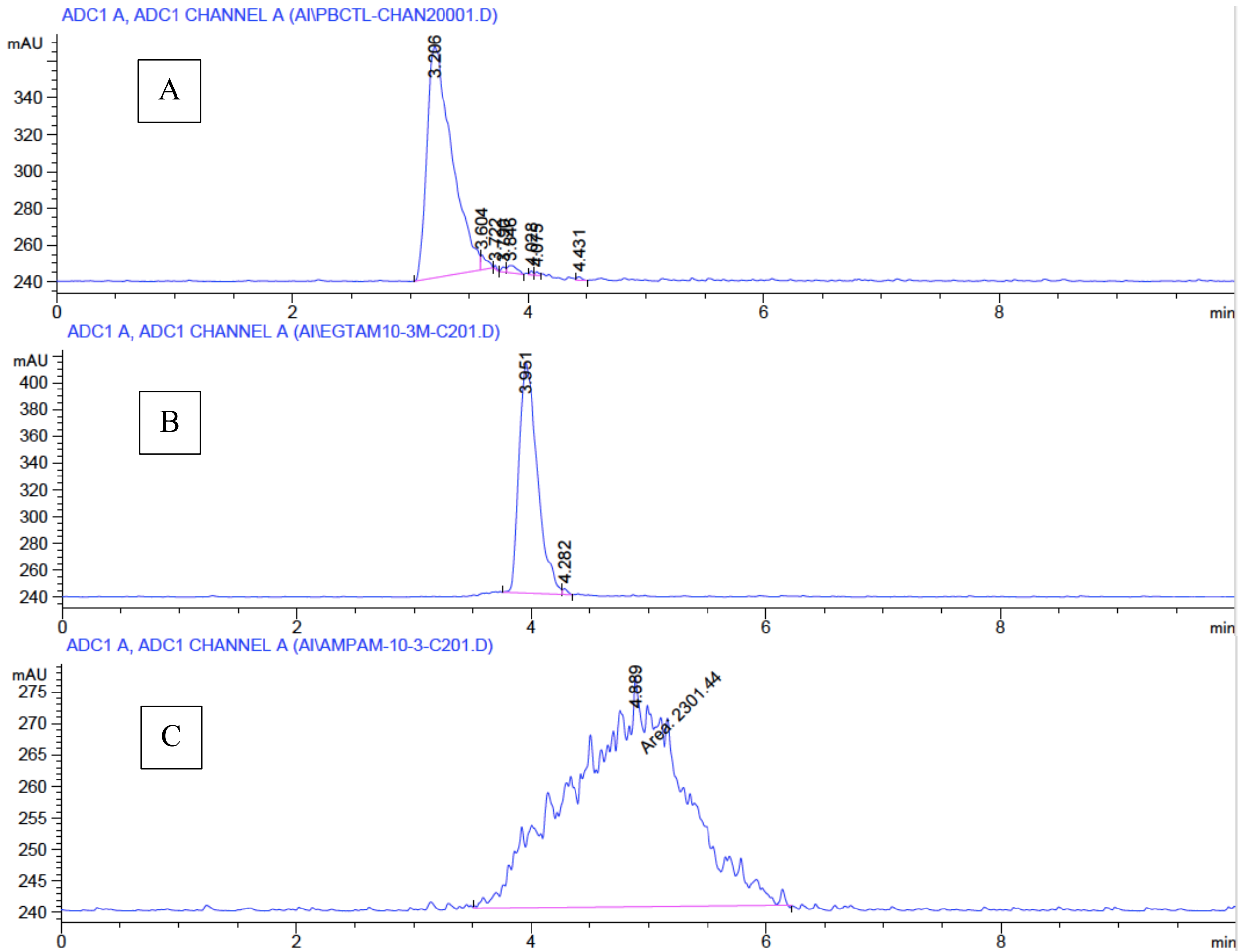

Figure S22. Radio-HPLC traces: A = free [^{203}Pb]Pb^{2+}, B = 10^{-3} mol dm^{-3} [^{203}Pb][Pb(EGTAm)]$^{2+}$ and C = 10^{-3} mol dm^{-3} [^{203}Pb][Pb(ampam)]$^{2+}$. A 250 mm synerigi hydro analytical column was used with the flow rate set to 1 mL/min. The gradient set up was: A = H_2O (0.1% TFA), B = MeCN (0.1% TFA), A = 95%, 0-2 min, A = 95-80%, 2-18 min, with the stop time set to 10 min.

High-Resolution Mass Spectrometry Data

Table S6. HR-ESI-MS data for EGTAm, DTPAm and ampam, as well as their respective Pb^{2+} complexes.

Species	Formula	Calcd (m/z)	Found (m/z)
EGTAm	$C_{14}H_{28}N_6O_6$	376.2074	376.2070
EGTAm-Pb	$C_{14}H_{27}N_6O_6Pb$	579.1722	579.1724
DTPAm	$C_{14}H_{28}N_8O_5$	388.2183	388.2184
DTPAm-Pb	$C_{14}H_{27}N_8O_5Pb$	591.1835	591.1835
Ampam	$C_{24}H_{34}N_8O_6$	530.2601	530.2606
Ampam-Pb	$C_{24}H_{33}N_8O_6Pb$	733.2253	733.2256

References

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