Supplementary Material (ESI) for Dalton Transactions

In Vitro Studies of Lanthanide Complexes for the Treatment of Osteoporosis

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3-Hydroxy-2-methyl-1-(2-hydroxyethyl)-4-pyridinone (H**1).** Based on a modification of a literature procedure,[1] maltol (9.30 g, 73.4 mmol, 1.0 equiv) was dissolved in hot water (50 mL); 2-aminoethanol (14.0 g, 0.229 mol, 3.1 equiv) was added and the mixture was stirred and refluxed for 70 h. The reaction mixture was cooled to room temperature and the water was removed under reduced pressure affording a dark brown oil. The crude oil was triturated with 2-propanol (30 mL) and maintained at 4 °C for 5 h, after which time a dark brown solid formed. The solid was collected by filtration, recrystallized from hot water (15 mL) and stored at 4 °C overnight. The resulting solid was subsequently filtered and dried *in vacuo*, affording light brown crystals, H**1** (5.09 g, 41%). ^{1}H NMR (400 MHz, D_2O) δ = 7.62 (d, *J* = 7.2 Hz, 1 H, H_a), 6.49 (d, *J* = 7.2 Hz, 1 H, H_b), 4.20 (t, *J* = 5.1 Hz, 2 H, CH_2-OH), 3.85 (t, *J* = 5.3 Hz, 2 H, N-CH_2), 2.40 (s, 3 H, ring CH_3). ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ = 169.1 (ring *C*=O), 144.8 (C_a), 139.2 (ring *C*-OH), 135.1 (ring *C*-CH_3), 112.3 (C_b), 60.3 (*C*H_2-OH), 56.0 (N-*C*H_2), 11.8 (ring *C*H_3). MS (-ESI) *m/z* =168.3 $[M - H]^-$. Anal. Calc. (found): $C_8H_{11}NO_3$: C, 56.80 (56.42); H, 6.55 (6.56); N, 8.28 (8.30).

1-Carboxymethyl-3-hydroxy-2-methyl-4-pyridinone (H**7).** Based on a modification from a procedure reported previously in the Orvig group,[2] maltol (4.98 g, 39.5 mmol, 1.0 equiv) was added to hot water (100 mL) in the presence of glycine (5.97 g, 79.5 mmol, 2.0 equiv). The mixture was stirred and heated to 80 °C; the pH was increased to 9 by the dropwise addition of 6 M NaOH and monitored by pH paper. The reaction was brought to reflux and maintained for 24 h. The reaction mixture was cooled to room temperature and half of the water was removed by rotary evaporation. The pH of the crude product was brought to ~3 with the addition of 6 M HCl, at which time a light brown solid precipitated. The precipitate was isolated by filtration and was

subsequently recrystallized from hot water and stored at 4 °C overnight. The resulting solid was filtered and dried *in vacuo* to yield light brown crystals, H**7** (2.90 g, 40%). ^{1}H NMR (400 MHz, 0.1 M NaOD) δ = 7.18 (d, *J* = 6.8 Hz, 1 H, H_a), 6.31 (d, *J* = 7.2 Hz, 1 H, H_b), 4.52 (s, 2 H, N-CH_2), 2.18 (s, 3 H, ring CH_3). ^{13}C{^{1}H} NMR (101 MHz, 0.1 M NaOD) δ = 175.2 (CH_2-*C*OOH), 173.0 (ring *C*=O), 155.3 (C_a), 135.7 (ring *C*-OH), 133.8 (ring *C*-CH_3), 111.6 (C_b), 58.6 (N-*C*H_2), 12.3 (ring *C*H_3). MS (-ESI) *m/z* =182.3 $[M - H]^-$. Anal. Calc. (found): $C_8H_9NO_4$: C, 52.46 (52.64); H, 4.85 (4.92); N, 7.65 (7.66).

3-Benzyloxy-2-methyl-4-pyrone (Bn**ma)**. The synthesis of Bn**ma** was achieved by a modified literature procedure.[3] To a mixture of 3-hydroxy-2-methyl-4-pyrone (maltol; 7.00 g, 55.5 mmol, 1 equiv) dissolved in methanol (50 mL) a solution of NaOH (2.47 g in 10 mL water, 61.7 mmol, 1.2 equiv) was added dropwise. Benzyl chloride (9.30 mL, 66.8 mmol, 1.2 equiv) was added to the stirred mixture, which was then refluxed for 40 h. The mixture was cooled to room temperature and the solvent was removed by rotary evaporation to afford an orange oil and a white precipitate (NaCl). The oil was partitioned in water (40 mL) and dichloromethane (30 mL), separated and the organic layer was dried over anhydrous Na_2SO_4. The organic layer was then filtered and concentrated, affording a yellow oil. The crude oil was recrystallized from ethanol and stored at 4 °C overnight. A white precipitate formed which was filtered through a coarse frit, rinsed with cold diethyl ether (4 °C), and dried *in vacuo*, to yield a white solid, Bn**ma** (9.484 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, *J* = 5.5 Hz, 1 H, H_a), 7.30 - 7.43 (m, 5 H, Bn C_6H_5), 6.37 (d, *J* = 5.8 Hz, 1 H, H_b), 5.17 (s, 2 H, Bn-CH_2), 2.09 (s, 3 H, ring CH_3). MS (+ESI) *m/z* =217.2 $[M + H]^+$.

3-Benzyloxy-2-methyl-1-(2-hydroxyethyl)-4-pyridinone (Bn**1)**. Based on a modification of a literature procedure,[4] Bn**ma** (12.55 g, 57.9 mmol, 1.0 equiv) and 2-aminoethanol (5.40 mL, 89.5 mmol, 1.5 equiv) were dissolved in a mixture of ethanol (50 mL) and deionized water (50mL). 6 M NaOH (1.70 mL, 10.2 mmol, 0.18 equiv) was added to adjust the pH > 11; the mixture was heated to reflux and maintained for 48 h. Upon cooling the mixture to room temperature, the solvent was concentrated by rotary evaporation affording a brown oil, which was then dissolved in water. The pH of the crude mixture was decreased to 1–2 using 6 M HCl and washed with diethyl ether. The pH of the aqueous layer was then adjusted to 7–8 with 6 M NaOH and the product was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the drying agent was removed by filtration. The filtrate was collected and the solvent was removed by rotary evaporation, yielding a dark brown solid. The solid was recrystallized from ethanol and diethyl ether; upon precipitation, the product was isolated by filtration and dried *in vacuo* affording a light brown solid, Bn**1** (5.57 g, 37%). ^{1}H NMR (400 MHz, D_2O) δ = 7.71 (d, J = 7.4 Hz, 1 H, H_a), 7.40 (s, 5 H, Bn C_6H_5), 6.57 (d, J = 7.4 Hz, 1 H, H_b), 5.02 (s, 2 H, Bn-CH_2), 4.10 (t, J = 5.3 Hz, 2 H, CH_2-OH), 3.76 (t, J = 5.1 Hz, 2 H, CH_2-OH), 2.06 (s, 3 H, ring CH_3). MS (+ESI) m/z =260.4 $[M + H]^+$.

3-Benzyloxy-2-methyl-1-(3-hydroxypropyl)-4-pyridinone hydrochloride (Bn**2**•HCl**).**[4] Based on a modification of a literature procedure,[4] Bn**ma** (5.09 g, 23.6 mmol, 1.0 equiv) and 3-aminopropanol (2.70 mL, 35.5 mmol, 1.5 equiv) were dissolved in a mixture of ethanol (40 mL) and deionized water (40 mL). 1 M NaOH (4.00 mL, 4.00 mmol, 0.17 equiv) was added to adjust the pH > 11; the mixture was heated to reflux and maintained for 18 h. Upon cooling the mixture

to room temperature, the solvent was concentrated by rotary evaporation affording a brown oil, which was then dissolved in water. The pH of the crude mixture was decreased to 1–2 using 6 M HCl and washed with diethyl ether. The pH of the aqueous layer was then adjusted to 7–8 with 6M NaOH and the product was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the drying agent was removed by filtration. The filtrate was collected and the solvent was removed by rotary evaporation, yielding a yellow oil. The oil was dissolved in ethanol and 6.0 M HCl was then used to lower the pH to ~0.5. The solvent was removed by rotary evaporation affording a pale yellow solid, which was recrystallized from ethanol and diethyl ether. Upon precipitation the product was collected by filtration and dried *in vacuo*, affording an off-white solid, Bn**2**•HCl (4.31 g, 59%). ^{1}H NMR (300 MHz, D_2O) δ = 8.04 (d, *J* = 7.1 Hz, 1 H, H_a), 7.41 (s, 5 H, Bn C_6H_5), 6.98 (d, *J* = 7.1 Hz, 1 H, H_b), 5.12 (s, 2 H, Bn-CH_2), 4.25 (t, *J* = 7.3 Hz, 2 H, N-CH_2), 3.53 (t, *J* = 5.9 Hz, 2 H, CH_2-OH), 2.28 (s, 3 H, ring CH_3), 1.81 - 1.99 (m, 2 H, N-CH_2-CH_2-CH_2-OH). MS (-ESI) *m/z* = 308.3, 310.3 $[M + Cl]^-$.

3-Benzyloxy-2-methyl-1-(4-hydroxybutyl)-4-pyridinone hydrochloride (Bn**3**•HCl**).**[4] Based on a modification of a literature procedure,[4] Bn**ma** (4.01 g, 18.5 mmol, 1.0 equiv) and 4-amino-1-butanol (2.56 mL, 2.78 mmol, 1.5 equiv) were dissolved in a mixture of ethanol (32 mL) and deionized water (32 mL). NaOH (0.126 g, 3.15 mmol, 0.17 equiv) was added to adjust the pH > 11; the mixture was heated to reflux and maintained for 15 h. Upon cooling the mixture to room temperature, the solvent was concentrated by rotary evaporation, affording a brown oil, which was then dissolved in water. The pH of the crude mixture was decreased to 1–2 using 6 M HCl and washed with diethyl ether. The pH of the aqueous layer was then adjusted to 7–8 with 6

M NaOH and the product was extracted with dichloromethane (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the drying agent was removed by filtration. The filtrate was collected and the solvent was removed by rotary evaporation, yielding a brown oil. The oil was dissolved in ethanol and 6.0 M HCl was then used to lower the pH to ~0.5. The solvent was removed by rotary evaporation affording a pale yellow solid, which was recrystallized from ethanol and diethyl ether. Upon precipitation, the product was collected by filtration and dried *in vacuo*, affording a light brown solid, Bn**3**•HCl (3.23 g, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.69 (d, *J* = 7.1 Hz, 1 H, H_a), 8.03 (d, *J* = 7.1 Hz, 1 H, H_b), 7.36 (s, 5 H, Bn C_6H_5), 5.23 (s, 2 H, Bn-CH_2), 4.41 (t, *J* = 7.8 Hz, 2 H, N-CH_2), 3.75 (t, *J* = 5.6 Hz, 2 H, CH_2-OH), 2.41 (s, 3 H, ring CH_3), 1.96 (q, *J* = 7.5 Hz, 2 H, CH_2-CH_2-OH), 1.66 (q, *J* = 5.5 Hz, 2 H N-CH_2-CH_2). MS (+ESI) *m/z* = 288.2 $[M + H]^+$.

3-Benzyloxy-2-methyl-1-(2-hydroxypropyl)-4-pyridinone (Bn**4).** Bn**ma** (5.01 g, 23.2 mmol, 1.0 equiv) and (±)-1-aminopropan-2-ol (3.58 mL, 46.4 mmol, 2.0 equiv) were dissolved in a mixture of ethanol (40 mL) and deionized water (40 mL). NaOH (0.157 g, 3.94 mmol, 0.17 equiv) was added to adjust the pH > 11; the mixture was heated to reflux and maintained at reflux for 92 h. Upon cooling the mixture to room temperature, the solvent was concentrated by rotary evaporation, affording a brown oil, which was then dissolved in water. The pH of the crude mixture was decreased to 1–2 using 6 M HCl and washed with diethyl ether. The pH of the aqueous layer was then adjusted to 7–8 with 6M NaOH and the product was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the drying agent was removed by filtration. The filtrate was collected and the solvent was

removed by rotary evaporation, yielding a brownish-orange solid. The solid was recrystallized from ethanol and diethyl ether; upon precipitation, the product was isolated by filtration and dried *in vacuo* affording a light orange-brown solid, Bn**4** (3.71 g, 59%). ^{1}H NMR (400 MHz , $CDCl_3$) δ = 7.22 - 7.45 (m, 6 H, H_a, Bn C_6H_5), 6.16 (d, 7.3 Hz, 1 H, H_b), 5.07 (dd, *J* = 1.7, 11.2 Hz, 1 H, Bn-CH_2), 4.93 (dd, *J* = 3.4, 11.3 Hz, 1 H, Bn-CH_2), 4.02 - 4.16 (m, 1 H, C*H*-OH), 3.76 (dd, *J* = 2.1, 14.3 Hz, 1 H, N-CH_2), 3.51 (dd, *J* = 9.6, 14.3 Hz, 1 H, N-CH_2), 2.11 (s, 3 H ring CH_3), 1.20 (d, *J* = 6.5 Hz, 3 H, CH(OH)CH_3). MS (+ESI) *m/z* = 569.3 $[M_2 + Na]^+$.

3-Benzyloxy-2-methyl-1-(1-hydroxy-3-methylbutan-2-yl)-4-pyridinone (Bn**5).** Bn**ma** (5.06 g, 23.4 mmol, 1.0 equiv) and (±)-2-amino-3-methyl-1-butanol (4.00 mL, 36.3 mmol, 1.6 equiv) were dissolved in a mixture of ethanol (25 mL) and deionized water (25 mL). NaOH (0.172 g, 4.31 mmol, 0.18 equiv) was added to adjust the pH > 11; the mixture was heated to reflux and maintained at reflux for 90 h. Upon cooling the mixture to room temperature, the solvent was concentrated by rotary evaporation, affording a brown oil, which was then dissolved in water. The pH of the crude mixture was decreased to 1–2 using 6 M HCl and washed with diethyl ether. The pH of the aqueous layer was then adjusted to 7–8 with 6M NaOH and the product was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the drying agent was removed by filtration. The filtrate was collected and the solvent was removed by rotary evaporation, yielding an orange oil. The orange oil was loaded onto a silica column (95:5 $CHCl_3$: CH_3OH), and the product was eluted in 95:5 $CHCl_3$: CH_3OH. The appropriate fractions were collected and concentrated by rotary evaporation, which yielded an orange solid, which was subsequently recrystallized from ethanol and diethyl ether. The resulting solid was recovered by filtration to afford a light brown solid,

Bn**5** (0.429 g, 6%). ^{1}H NMR (300 MHz, CD_3OD) δ = 7.85 (d, *J* = 7.8 Hz, 1 H, H_a), 7.25 - 7.42 (m, 5 H, Bn C_6H_5), 6.57 (d, *J* = 7.5 Hz, 1 H, H_b), 5.15 (d, J = 11.2 Hz, 1 H, Bn-CH_2), 5.05 (d, J = 11.2, 1 H, Bn-CH_2), 3.73 - 4.05 (m, 3 H, C*H*-CH_2-OH), 2.07-2.20 (m, 1 H, C*H*$(CH_3)_2$), 2.15 (s, 3H, ring CH_3), 1.08 (d, *J* = 6.6 Hz, 3 H, CH-CH_3), 0.65 (d, *J* = 6.9 Hz, 3 H, CH-CH_3). MS (+ESI) *m/z* = 625.8 $[M_2 + Na]^+$.

3-Benzyloxy-2-methyl-1-(1-hydroxybutan-2-yl)-4-pyridinone (Bn**6).** Bn**ma** (5.02 g, 23.2 mmol, 1.0 equiv) and (±)-2-amino-1-butanol (4.37 mL, 4.13 mmol, 2.0 equiv) were dissolved in a 1:1 mixture of ethanol (40 mL) and deionized water (40 mL). NaOH (0.160 g, 4.00 mmol, 0.17 equiv) was added to adjust the pH > 11; the mixture was heated to reflux and maintained there for 88 h. Upon cooling the mixture to room temperature, the solvent was concentrated by rotary evaporation, affording a brown oil, which was then dissolved in water. The pH of the crude mixture was decreased to 1–2 using 6 M HCl and washed with diethyl ether. The pH of the aqueous layer was then adjusted to 7–8 with 6M NaOH and the product was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the drying agent was removed by filtration. The filtrate was collected and the solvent was removed by rotary evaporation, yielding an orange oil. The solid was recrystallized from ethanol and diethyl ether; upon precipitation, the product was isolated by filtration and dried *in vacuo* affording a light brown solid, Bn**6** (6.66 g, 30%). ^{1}H NMR (300 MHz, D_2O) δ = 7.78 (d, *J* = 7.8 Hz, 1 H, H_a), 7.21 - 7.49 (m, 5 H, Bn C_6H_5), 6.64 (d, *J* = 7.5 Hz, 1 H, H_b), 5.01 (s, 2 H, Bn-CH_2), 4.22 - 4.40 (m, 1 H, N-C*H*), 3.59 - 3.84 (m, 2 H, CH_2-OH), 1.98 (s, 3 H, ring CH_3), 1.53 - 1.88 (m, 2 H, CH_2CH$_3$), 0.64 (t, *J* = 7.3 Hz, 3 H, CH$_2$CH_3). MS (+ESI) *m/z* = 597.7 $[M_2 + Na]^+$.

1-Carboxyethyl-3-benzyloxy-2-methyl-4-pyridinone (Bn**8).**[4] Based on a modification of a literature procedure,[4] Bn**ma** (5.09 g, 23.5 mmol, 1.0 equiv) and β-alanine (3.22 g, 3.61 mmol, 1.5 equiv) were dissolved in a mixture of ethanol (40 mL) and deionized water (40 mL). The pH was increased from 7 to 13 using 6M NaOH; the mixture was heated to reflux and maintained for 18 h. Upon cooling the mixture to room temperature, the solvent was concentrated by rotary evaporation to afford a brown oil, which was then dissolved in water. The pH of the crude mixture was decreased to 1–2 using 6 M HCl and washed with diethyl ether. The pH of the aqueous layer was then adjusted to 7–8 with 6M NaOH and the product was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the drying agent was removed by filtration. The filtrate was collected and the solvent was removed by rotary evaporation, yielding a yellow oil. The oil was dissolved in ethanol and 6.0 M HCl was then used to lower the pH to ~0.5. The solvent was removed by rotary evaporation to afford a pale yellow solid, which was recrystallized from ethanol and diethyl ether. Upon precipitation the product was collected by filtration and dried *in vacuo*, affording a pale yellow solid, Bn**8** (3.05 g, 45%). ^{1}H NMR (300 MHz, D_2O) δ = 7.86 (d, J = 7.3 Hz, 1 H, H_a), 7.28 - 7.48 (m, 5 H, Bn C_6H_5), 6.68 (d, J = 7.3 Hz, 1 H, H_b), 5.03 (s, 2 H, Bn-CH_2), 4.28 (t, J = 6.9 Hz, 2 H, N-CH_2), 2.68 (t, J = 7.0 Hz, 2 H, CH_2-COOH), 2.13 (s, 3 H, ring CH_3). MS (-ESI) m/z = 286.3 $[M - H]^-$.

3-Hydroxy-2-methyl-1-(3-hydroxypropyl)-4-pyridinone hydrochloride (H**2**•HCl**).**[4] Based on a modification of a literature procedure,[4] 3-benzyloxy-2-methyl-1-(3-hydroxypropyl)-4-pyridinone hydrochloride (Bn**2**•HCl; 1.00 g, 3.23 mmol, 1.0 equiv) was suspended in a mixture of ethanol (9 mL) and deionized water (1 mL) and the pH was lowered to 1 with 6 M

HCl. The hydrogenation catalyst (10% w/w of Pd on C; 0.406 g) was added and the flask was flushed once with a balloon filled with $H_{2(g)}$. The reaction was stirred under the $H_{2(g)}$-filled balloon for 6 h at room temperature. The dark suspension was filtered to remove the catalyst, which was rinsed with ethanol, methanol and water. The solvent was removed by rotary evaporation to afford the crude product as an oil. The oil was dissolved in ethanol and 6.0 M HCl was then used to lower the pH to ~0.5. The solvent was removed by rotary evaporation affording a pale yellow solid, which was recrystallized from ethanol and diethyl ether. Upon precipitation the product was collected by filtration and dried *in vacuo*, affording a white solid, H**2**•HCl (0.519 g, 73%). ^{1}H NMR (300 MHz, D_2O) δ = 8.02 (d, *J* = 7.1 Hz, 1 H, H_a), 7.07 (d, *J* = 6.9 Hz, 1 H, H_b), 4.40 (t, *J* = 7.4 Hz, 2 H, N-CH_2), 3.63 (t, *J* = 5.8 Hz, 2 H, CH_2-OH), 2.58 (s, 3 H, ring CH_3), 2.05 (quin, *J* = 6.7 Hz, 2 H, N-CH_2-CH_2-CH_2-OH). ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ = 158.5 (ring *C*=O), 142.7 (C_a), 142.6 (ring *C*-OH), 138.7 (ring *C*-CH_3), 111.1 (C_b), 57.9 (*C*H_2-OH), 53.9 (N-*C*H_2), 31.8 (N-CH_2-*C*H_2-CH_2-OH), 12.3 (ring *C*H_3). MS (+ ESI) *m/z* = 184.3 [M +H]$^+$. Anal. Calc. (found): $C_9H_{13}NO_3$•HCl: C, 49.21 (48.91); H, 6.42 (6.35); N, 6.38 (6.32).

3-Hydroxy-2-methyl-1-(4-hydroxybutyl)-4-pyridinone hydrohloride (H**3**•HCl**).**[4]

Based on a modification of a literature procedure,[4] 3-benzyloxy-2-methyl-1-(4-hydroxybutyl)-4-pyridinone hydrochloride (Bn**3**•HCl; 0.501 g, 1.55 mmol, 1.0 equiv) was dissolved in a mixture of ethanol (8 mL) and deionized water (1 mL). The hydrogenation catalyst (10% w/w of Pd on C; 93.0 mg) was added and the flask was flushed once with a balloon filled with $H_{2(g)}$. The reaction was stirred under the $H_{2(g)}$-filled balloon for 6 h at room temperature. The dark suspension was filtered to remove the catalyst, which was rinsed with ethanol, methanol and water. The solvent was removed by rotary evaporation to afford the crude product as an oil. The

oil was dissolved in ethanol and 6.0 M HCl was then used to lower the pH to ~0.5. The solvent was removed by rotary evaporation affording a pale yellow solid, which was recrystallized from ethanol and diethyl ether. Upon precipitation the product was collected by filtration and dried *in vacuo*, affording an off-white solid, H**3**•HCl (0.261 g, 72%). ^{1}H NMR (400 MHz, D_2O) δ = 8.00 (d, *J* = 7.2 Hz, 1 H, H_a), 7.05 (d, *J* = 7.2 Hz, 1 H, H_b), 4.31 (t, *J* = 7.7 Hz, 2 H, N-CH_2), 3.57 (t, *J* = 6.3 Hz, 2 H, CH_2-OH), 2.55 (s, 3 H, ring CH_3), 1.76 - 1.91 (m, 2 H, CH_2-CH_2-OH), 1.48 - 1.62 (m, 2 H, N-CH_2-CH_2). ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ = 158.6 (ring *C*=O), 142.7(C_a), 142.3 (ring *C*-OH), 138.5 (ring *C*-CH_3), 111.3 (C_b), 60.9 (*C*H_2-OH), 56.5 (N-*C*H_2), 28.2 (N-CH_2-*C*H_2), 26.0 (*C*H_2-CH_2-OH), 12.2 (ring *C*H_3). MS (+ESI) *m/z* = 198.2 $[M + H]^+$. Anal. Calc. (found): $C_{10}H_{15}NO_3$•HCl: C, 51.40 (51.49); H, 6.90 (6.95); N, 5.99 (5.95).

3-Hydroxy-2-methyl-1-(2-hydroxypropyl)-4-pyridinone (H**4).** To afford the free pyridinone, 3-benzyloxy-2-methyl-1-(2-hydroxypropyl)-4-pyridinone (Bn**4**; 0.508 g, 1.86 mmol, 1.0 equiv) was dissolved in a mixture of ethanol (8 mL) and deionized water (2 mL). The hydrogenation catalyst (10% w/w of Pd on C; 89.2 mg) was added and the flask was flushed once with a balloon filled with $H_{2(g)}$. The reaction was stirred under the $H_{2(g)}$-filled balloon for 6 h at room temperature. The dark suspension was filtered to remove the catalyst, which was rinsed with ethanol, methanol and water. The solvent was removed by rotary evaporation to afford the crude product as brown solid, which was recrystallized from ethanol and diethyl ether. The precipitate that formed was collected by filtration and dried *in vacuo*, affording a pale brown solid, H**4** (0.170 g, 50%). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.59 (d, *J* = 7.2 Hz, 1 H, H_a), 6.39 (d, *J* = 7.2 Hz, 1 H, H_b), 4.10 (dd, *J* = 14.1, 3.2 Hz, 1 H, C*H*-OH), 3.96 - 4.05 (m, 1 H, N-CH_2), 3.83 - 3.91 (m, 1 H, N-CH_2), 2.45 (s, 3 H, ring CH_3), 1.24 (d, *J* = 6.5 Hz, 3 H, CH(OH)CH_3).

$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3OD) δ = 170.8 (ring *C*=O), 147.1 (C_a), 140.2 (ring *C*-OH), 133.4 (ring *C*-CH_3), 112.3 (C_b), 67.8 (*C*H-OH), 61.5 (N-*C*H_2), 21.0 (CH(OH)*C*H_3), 12.56 (ring *C*H_3). MS (+ESI) *m/z* = 184.3 $[M + H]^+$. Anal. Calc. (found): $C_9H_{13}NO_3$: C, 59.00 (59.03); H, 7.15 (7.15); N, 7.65 (7.38).

3-Hydroxy-2-methyl-1-(1-hydroxy-3-methylbutan-2-yl)-4-pyridinone (H**5).** To afford the free pyridinone, 3-benzyloxy-2-methyl-1-(1-hydroxy-3-methylbutan-2-yl)-4-pyridinone (Bn**5;** 1.30 g, 4.32 mmol, 1.0 equiv) was dissolved in a mixture of ethanol (18 mL) and deionized water (3 mL). The hydrogenation catalyst (10% w/w of Pd on C; 0.104 g) was added and the flask was flushed once with a balloon filled with $H_{2(g)}$. The reaction was stirred under the $H_{2(g)}$-filled balloon for 6 h at room temperature. The dark suspension was filtered to remove the catalyst, which was rinsed with ethanol, methanol, dichloromethane, 2-propanol and water. The solvent was removed by rotary evaporation to afford the crude product as an orange solid, which was recrystallized from ethanol and diethyl ether. The precipitate that formed was collected by filtration and dried *in vacuo*, affording an off-white solid, H**5** (0.253 g, 28%). ^{1}H NMR (300 MHz, CD_3OD) δ = 7.78 (d, *J* = 7.3 Hz, 1 H, H_a), 6.49 (d, *J* = 7.3 Hz, 1 H, H_b), 4.03 - 4.19 (m, 1 H, C*H*-CH_2-OH), 3.78 - 4.03 (m, 2 H, CH-*C*H_2-OH), 2.46 (s, 3 H, ring C*H*$_3$), 2.11 - 2.30 (m, 1 H, C*H*$(CH_3)_2$), 1.06 - 1.19 (m, 3 H, CH-C*H*$_3$), 0.76 (d, *J* = 6.6 Hz, 3 H, CH-C*H*$_3$). $^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3OD) δ = 170.2 (*C*=O), 135.5 (ring *C*-CH_3), 112.9 (C_b), 69.9 (*C*H-OH), 63.2 (*C*H-CH_2-OH), 31.4 (*C*H_2-OH), 20.0 (*C*H$(CH_3)_2$), 19.6 (CH(*C*$H_3)_2$), 12.6 (ring *C*H_3). Anal. Calc. (found): $C_{11}H_{17}NO_3$: C, 62.54 (62.29); H, 8.11 (8.15); N, 6.63 (6.71). MS (+ESI) *m/z* = 212.3 $[M + H]^+$.

3-Hydroxy-2-methyl-1-(1-hydroxybutan-2-yl)-4-pyridinone (H6). To afford the free pyridinone, 3-benzyloxy-2-methyl-1-(1-hydroxybutan-2-yl)-4-pyridinone (Bn**6**; 0.465 g, 1.62 mmol, 1.0 equiv) was dissolved in a mixture of ethanol (8 mL) and deionized water (2 mL). The hydrogenation catalyst (10% w/w of Pd on C; 88.2 mg) was added and the flask was flushed once with a balloon filled with $H_{2(g)}$. The reaction was stirred under the $H_{2(g)}$-filled balloon for 6 h at room temperature. The dark suspension was filtered to remove the catalyst, which was rinsed with ethanol, methanol and water. The solvent was removed by rotary evaporation to afford the crude product as pink solid, which was recrystallized from ethanol and diethyl ether. The precipitate that formed was collected by filtration and dried *in vacuo*, affording a pale pink solid, H**6** (0.262 g, 82%). ^{1}H NMR (400 MHz, CD_3OD) δ = 7.73 (d, *J* = 7.5 Hz, 1 H, H_a), 6.49 (d, *J* = 7.2 Hz, 1 H, H_b), 4.36 - 4.48 (m, 1 H, N-C*H*), 3.70 - 3.87 (m, 2 H, CH_2-OH), 2.48 (s, 3 H, ring CH_3), 1.71 - 1.99 (m, 2 H, CH_2CH_3), 0.86 (t, *J* = 7.3 Hz, 3 H, CH_2-CH_3). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ = 170.5 (ring *C*=O), 146.8 (C_a), 135.0 (ring *C*-OH), 134.5 (ring *C*-CH_3), 113.2 (C_b), 65.5 (N-*C*H), 65.3 (CH_2-OH), 25.4 (CH_2-CH_3), 12.6 (CH_2CH_3), 10.5 (ring CH_3). MS (+ESI) *m/z* = 198.2 $[M + H]^+$. Anal. Calc. (found): $C_{10}H_{15}NO_3$: C, 60.90 (60.80); H, 7.67 (7.68); N, 7.10 (7.19).

1-Carboxyethyl-3-hydroxy-2-methyl-4-pyridinone (H8).[4] To afford the free pyridinone, 1-carboxyethyl-3-benzyloxy-2-methyl-4-pyridinone (Bn**8**; 0.447 g, 1.56 mmol, 1.0 equiv) was refluxed in a solution of 33% w/v hydrobromic acid in glacial acetic acid (4.00 mL) for 1 h. The solvent was removed under reduced pressure affording a light peach coloured solid. The precipitate was dissolved in water (10 mL), and the acid was neutralized by the additon of 6M NaOH. After the removal of water by rotary evaporation, the ensuing solid was redissolved

in water and acidified in the presence of 6 M HCl to a pH of 2.5. The water was removed under reduced pressure resulting in a solid, which was recrystallized in ethanol and diethyl ether. The product precipitated, was recovered by filtration, and dried *in vacuo*, affording a light pink solid, H**8** (0.150 g, 58%). ^{1}H NMR (400 MHz, 0.1 M NaOD) δ = 7.27 (d, *J* = 6.8 Hz, 1 H, H_a), 6.30 (d, *J* = 6.8 Hz, 1 H, H_b), 4.20 (t, *J* = 7.3 Hz, 2 H, N-CH_2), 2.56 (t, *J* = 7.2 Hz, 2 H, CH_2-COOH), 2.32 (s, 3 H, ring CH_3). ^{13}C{^{1}H} NMR (101 MHz, 0.1 M NaOD) δ = 179.0 (CH_2-*C*OOH), 172.6 (ring *C*=O), 155.6 (C_a), 135.0 (ring *C*-OH), 132.7 (ring *C*-CH_3), 111.7 (C_b), 52.2 (N-CH_2), 38.6 (*C*H_2-COOH), 12.1 (ring *C*H_3). MS (+ESI) *m/z* = 198.2 $[M + H]^+$. Anal. Calc. (found): $C_9H_{11}NO_4$: C, 54.82 (54.93); H, 5.62 (5.72); N, 7.10 (6.98).

General procedure for *tris*(1-(2-hydroxyethyl)-2-methyl-3-oxy-4-pyridinonato)lanthanide(III), Ln(**1**)$_3$. H**1** (0.100 g, 0.60 mmol, 3.0 equiv) was suspended in water (10 mL); the pH of the ligand solution was increased to 3.17–3.44 with the addition of 1 M NaOH in order to solubilize the ligand. $Ln(NO_3)_3$•$6H_2O$ (86.0–99.2 mg, 0.20 mmol, 1.0 equiv) was added to the ligand solution and the pH of the mixture was raised slowly over 10–15 min with the dropwise addition of 1 M NaOH (Ln^{3+} = La, pH 10.9; Eu, pH 10.9; Lu, pH 10.2) and the resulting mixture was continuously stirred for 1 h. The solution was concentrated under reduced pressure, redissolved in 1 – 2 mL of water and precipitated out with the addition of acetone (50 mL). The metal complex was collected by centrifugation (4000 RPM); the supernatant was discarded. All the complexes were dried *in vacuo* to yield 41–89% of Ln(**1**)$_3$.

***Tris*(1-(2-hydroxyethyl)-2-methyl-3-oxy-4-pyridinonato)lanthanum(III),** La(**1**)$_3$. ^{1}H NMR (400 MHz, D_2O) d = 7.29 (br. s., 3 H, H_a), 6.32 (br. s., 3 H, H_b), 4.11 (br. s., 6 H, CH_2-OH), 3.79 (br. s., 6 H, N-CH_2), 2.21 (br. s., 9 H, ring CH_3). ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ =

172.4 (ring *C*=O), 136.0 (ring *C*-OH, C_a), 134.8 (ring *C*-CH_3), 110.5 (C_b), 60.4 (*C*H_2-OH), 56.5 (N-*C*H_2), 12.0 (ring *C*H_3)**.** MS (+ESI) *m/z* = 644.1, 645.1, 646.2 $[M + H]^+$. HRMS (+ESI); Calc. (found): $C_{24}H_{31}{}^{139}LaN_3O_9$: 644.1124 (644.1119) $[M + H]^+$.

***Tris*(1-(2-hydroxyethyl)-2-methyl-3-oxy-4-pyridinonato)europium(III),** Eu(**1**)$_3$ MS (+ESI) *m/z* = 656.3, 657.2, 658.2, 659.2, 660.2 $[M + H]^+$. HRMS (+ESI); Calc. (found): $C_{24}H_{31}{}^{151}EuN_3O_9$: 656.1259 (656.1275) $[M + H]^+$.

***Tris*(1-(2-hydroxyethyl)-2-methyl-3-oxy-4-pyridinonato)lutetium(III)**Lu(**1**)$_3$ ^{1}H NMR (400 MHz, D_2O) δ = 7.31 (br. s., 3 H, H_a), 6.32 (br. s., 3 H, H_b), 4.08 (br. s., 6 H, CH_2-OH), 3.74 (br. s., 6 H, N-CH_2), 2.17 (br. s., 9 H, ring CH_3). MS (+ESI) *m/z* = 680.1, 681.2, 682.1 $[M + H]^+$. HRMS (+ESI); Calc. (found): $C_{24}H_{31}{}^{175}LuN_3O_9$: 680.1468 (680.1473) $[M + H]^+$.

General procedure for *tris*(1-(3-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)lanthanide(III), Ln(**2**)$_3$. H**2**•HCl (0.100 g, 0.46 mmol, 3.0 equiv) was suspended in water (10 mL); $Ln(NO_3)_3$•$6H_2O$ (79.2–85.9 mg, 0.18 mmol, 1.0 equiv) was added to the ligand solution. The pH of the mixture was raised slowly over 10–15 min with the dropwise addition of 1 M NaOH (Ln^{3+} = La, pH 9.7; Eu, pH 10.1; Gd, pH 10.0; Lu, pH 9.6) and the resulting mixture was continuously stirred for 1 h. The solution was concentrated under reduced pressure, redissolved in 1–2 mL of water and precipitated out with the addition of acetone (50 mL). The metal complex was collected by centrifugation (4000 RPM); the supernatant was discarded. All the complexes were dried *in vacuo* to yield 34–91% of Ln(**2**)$_3$.

General procedure for *tris*(1-(3-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)lanthanum(III), La(**2**)$_3$. ^{1}H NMR (400 MHz, D_2O) δ = 7.31 (br. s., 3 H, H_a), 6.31 (br. s., 3 H, H_b), 4.06 (br. s., 6 H, N-CH_2), 3.55 (br. s., 6 H, CH_2-OH), 2.24 (br. s., 9 H, ring

C*H*$_3$), 1.74 - 2.04 (m, 6 H, N-CH$_2$-C*H*$_2$-CH$_2$-OH). ^{13}C{^{1}H} NMR (101 MHz, D$_2$O) δ = 162.2 (ring *C*=O), 135.4 (*C*$_a$), 134.3 (ring *C*-OH) 133.8 (ring *C*-CH$_3$) 109.6 (*C*$_b$), 58.2 (CH$_2$-OH), 52.0 (N-*C*H$_2$), 32.4, (N-CH$_2$-*C*H$_2$-CH$_2$-OH) 7.5 (ring *C*H$_3$). MS (+ESI) *m/z* = 686.2, 687.2, 688.3 [M + H]$^+$.HRMS (+ESI); Calc. (found): $C_{27}H_{37}{}^{139}LaN_3O_9$: 686.1593 (686.1591) [M + H]$^+$.

***Tris*(1-(3-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)europium(III),** Eu(**2**)$_3$. MS (+ESI) *m/z* = 698.3, 699.3, 700.3, 701.2, 702.3 [M + H]$^+$. HRMS (+ESI); Calc. (found): $C_{27}H_{37}{}^{151}EuN_3O_9$: 698.1728 (698.1723) [M + H]$^+$.

***Tris*(1-(3-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)gadolinium(III),** Gd(**2**)$_3$. MS (+ESI) *m/z* = 723.0, 724.2, 725.2, 726.2, 727.2, 728.2, 729.2, 730.1 [M + Na]$^+$.HRMS (+ESI); Calc. (found): $C_{27}H_{36}{}^{155}GdN_3NaO_9$: 724.1576 (724.1563) [M + Na]$^+$.

***Tris*(1-(3-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)lutetium(III),** Lu(**2**)$_3$

^{1}H NMR (300 MHz, CD$_3$OD) δ = 7.40 (br. s., 3 H, *H*$_a$), 6.28 (br. s., 3 H, *H*$_b$), 4.13 (br. s., 6 H, N-C*H*$_2$), 3.54 (br. s., 6 H, C*H*$_2$-OH), 2.52 (br. s., 3 H, ring C*H*$_3$), 2.38 (br. s., 6 H, N-CH$_2$-CH$_2$-CH$_2$-OH). MS (+ESI) *m/z* = 722.3, 723.2, 724.3 [M + H]$^+$. HRMS (+ESI); Calc. (Found): $C_{27}H_{37}{}^{175}LuN_3O_9$: 722.1938 (722.1937) [M + H]$^+$.

General procedure for *tris*(1-(4-hydroxybutyl)-2-methyl-3-oxy-4-pyridinonato)lanthanide(III), Ln(**3**)$_3$. H**3**•HCl (0.100 g, 0.43 mmol, 3.0 equiv) was dissolved in water (10 mL); Ln(NO$_3$)$_3$•6H$_2$O (62.7–66.8 mg, 0.14 mmol, 1.0 equiv) was added to the ligand solution. The pH of the mixture was raised slowly over 10–15 min with the dropwise addition of 1 M NaOH (Ln^{3+} = La, pH 10.2; Eu, pH 9.4; Lu, pH 9.4) and the resulting mixture was continuously stirred for 1 h. The solution was concentrated under reduced pressure, redissolved in 1–2 mL of water and precipitated out with the addition of acetone (50 mL). The

metal complex was collected by centrifugation (4000 RPM); the supernatant was discarded. All of the complexes were dried *in vacuo* to yield 63–95% of Ln(**3**)$_3$.

***Tris*(1-(4-hydroxybutyl)-2-methyl-3-oxy-4-pyridinonato)lanthanum(III),** La(**3**)$_3$. ^{1}H NMR (400 MHz, D_2O) δ = 7.25 (br. s., 3 H, H_a), 6.28 (br. s., 3 H, H_b), 3.96 (br. s., 6 H, N-CH_2), 3.53 (br. s., 6 H, CH_2-OH), 2.18 (br. s., 9 H, ring CH_3), 1.69 (br. s., 6 H, CH_2-CH$_2$-OH), 1.49 (br. s., 6 H, N-CH$_2$-CH_2). ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ = 172.6 (ring *C*=O), 157.4 (C_a, ring *C*-OH), 134.4 (ring *C*-CH$_3$), 112.3 (C_b), 61.1 (*C*H$_2$-OH), 54.8 (N-*C*H$_2$), 28.3 (N-CH$_2$-*C*H$_2$), 26.8 (*C*H$_2$-CH$_2$-OH), 11.8 (ring *C*H$_3$). MS (+ESI) *m/z* = 728.2, 729.2, 730.2 $[M + H]^+$. HRMS (+ESI); Calc. (found): $C_{30}H_{43}{}^{139}LaN_3O_9$: 728.2063 (728.2065) $[M + H]^+$.

***Tris*(1-(4-hydroxybutyl)-2-methyl-3-oxy-4-pyridinonato)europium(III),** Eu(**3**)$_3$. MS (+ESI) *m/z* = 740.4, 741.3, 742.3, 743.3, 744.3 $[M + H]^+$. HRMS (+ESI); Calc. (Found): $C_{30}H_{43}{}^{151}EuN_3O_9$: 740.2198 (740.2202) $[M + H]^+$.

***Tris*(1-(4-hydroxybutyl)-2-methyl-3-oxy-4-pyridinonato)lutetium(III),** Lu(**3**)$_3$. ^{1}H NMR (300 MHz, CD_3OD) δ = 7.36 (br. s., 3 H, H_a), 6.26 (br. s., 3 H, H_b), 4.03 (br. s., 6 H, N-CH_2), 3.55 (br. s., 6 H, CH_2-OH), 2.51 (br. s., 9 H, ring CH_3), 2.37 (br. s., 6 H, CH_2-CH$_2$-OH), 1.54 (br. s., 6 H, N-CH$_2$-CH_2). MS (+ESI) *m/z* = 764.4, 765.3, 766.4 $[M + H]^+$. HRMS (+ESI); Calc. (found): $C_{30}H_{43}{}^{175}LuN_3O_9$: 764.2407 (764.2402) $[M + H]^+$.

General procedure for *tris*(1-(2-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)lanthanide(III), Ln(**4**)$_3$. H**4** (0.106 g, 0.58 mmol, 3.0 equiv) was dissolved in water (10 mL); Ln(NO$_3$)$_3$•6H$_2$O (82.0–87.3 mg, 0.19 mmol, 1.0 equiv) was added to the ligand solution. The pH of the mixture was raised slowly over 10–15 min with the dropwise addition of

1 M NaOH (Ln^{3+} = La, pH 10.3; Eu, pH 11.7; Gd, pH 10.7 Lu, pH 9.4) and the resulting mixture was continuously stirred for 1 h. The solution was concentrated under reduced pressure, redissolved in 1–2 mL of water and precipitated out with the addition of acetone (50 mL). The metal complex was collected by centrifugation (4000 RPM), the supernatant was discarded. All of the complexes were dried *in vacuo* to yield 54–96% of Ln(**4**)$_3$.

***Tris*(1-(2-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)lanthanum(III),** La(**4**)$_3$. ^{1}H NMR (300 MHz, CD_3OD) δ = 7.18 (br. s., 3 H, H_a), 6.35 (br. s., 3 H, H_b), 3.96 (br. s., 6 H, N-CH_2), 3.80 (d, *J* = 6.8 Hz, 3 H, C*H*-OH), 2.30 (s, 9 H, ring CH_3), 1.16 (d, *J* = 5.0 Hz, 9 H, CH(OH)CH_3). MS (+ESI) *m/z* = 686.2, 687.2, 688.3 $[M + H]^+$. HRMS (+ESI); Calc. (found): $C_{27}H_{37}{}^{139}LaN_3O_9$: 686.1593 (686.1594) $[M + H]^+$.

***Tris*(1-(2-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)europium(III),** Eu(**4**)$_3$. MS (+ESI) *m/z* = 698.3, 699.3, 700.3, 701.2, 702.3, 703.4 $[M + H]^+$. HRMS (+ESI); Calc. (Found): $C_{27}H_{37}{}^{151}EuN_3O_9$: 698.1728 (698.1727) $[M + H]^+$.

***Tris*(1-(2-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)gadolinium(III),** Gd(**4**)$_3$. MS (+ESI) *m/z* = 701.4, 702.4, 703.4, 704.4, 705.4, 706.3, 707.3, 708.3, 709.3 $[M + H]^+$. HRMS (+ESI); Calc. (Found): $C_{27}H_{37}{}^{155}GdN_3O_9$: 702.1756 (702.1758) $[M + H]^+$.

***Tris*(1-(2-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)lutetium(III),** Lu(**4**)$_3$. ^{1}H NMR (400 MHz, D_2O) δ = 7.37 (br. s., 3 H, H_a), 6.38 (d, *J* = 6.7 Hz, 3 H, H_b), 4.16 (br. s., 3 H, N-CH_2), 4.06 (br. s., 3 H, N-CH_2), 3.87 (m, 3 H, C*H*-OH), 2.28 (br. s., 3 H, ring CH_3), 1.20 (d, *J* = 6.1 Hz, 9 H, $CH(OH)CH_3$) MS (+ESI) *m/z* = 722.4, 723.2, 724.3, 725.4 $[M + H]^+$. HRMS (+ESI); Calc. (Found): $C_{27}H_{37}{}^{175}LuN_3O_9$: 722.1938 (722.1932) $[M + H]^+$.

***Tris*(1-(1-hydroxy-3-methylbutan-2-yl)-2-methyl-3-oxy-4-pyridinonato) lanthanum(III),** La(**5**)$_3$. H**5** (95.8 mg, 0.45 mmol, 3.0 equiv) was dissolved in methanol (10 mL); La(NO$_3$)$_3$•6H$_2$O (73.0 mg, 0.15 mmol, 1.0 equiv) was added to the ligand solution. The pH of the mixture was raised slowly over 10–15 min with the dropwise addition of 1 M NaOH to pH 9.5, and the resulting mixture was continuously stirred for 1 h. The solution was concentrated under reduced pressure, redissolved in 1–2 mL of water and precipitated out with the addition of acetone (50 mL). The metal complex was collected by centrifugation (4000 RPM) and the supernatant was discarded. The lanthanum complex was dried *in vacuo* to yield 53% of product. ^{1}H NMR (400 MHz, CD$_3$OD) δ = 7.49 (br. s., 3 H, *H*$_a$), 6.64 (br. s., 3 H, *H*$_b$), 4.08 (br. s., 3 H, C*H*-CH$_2$-OH), 3.86 (br. s., 6 H, CH-*CH*$_2$-OH), 2.41 (br. s., 9 H, ring C*H*$_3$), 2.16 (s, 3 H, C*H*(CH$_3$)$_2$), 1.08 (br. s., 9 H, CH-C*H*$_3$), 0.66 (br. s., 9 H, CH-C*H*$_3$). ^{13}C{^{1}H} NMR (101 MHz, CD$_3$OD) δ = 158.4 (*C*=O), 140.7 (*C*$_a$), 134.6 (ring *C*-CH$_3$), 129.8 (ring *C*-OH), 121.3 (*C*$_b$), 62.2 (N-*C*H), 45.1 (*C*H$_2$-OH), 30.4 (*C*(CH$_3$)$_2$), 18.8 (C(*C*H$_3$)$_2$), 18.6 (C(*C*H$_3$)$_2$) 11.3 (ring *C*H$_3$). MS (+ESI) *m/z* = 792.2, 793.2, 794.2 [M + Na]$^+$. HRMS (+ESI); Calc. (found): C$_{33}$H$_{48}$^{139}LaN$_3$O$_9$Na: 792.2352 (792.2355) [M + Na]$^+$.

***Tris*(1-(1-hydroxybutan-2-yl)-2-methyl-3-oxy-4-pyridinonato)lanthanide(III),** Ln(**6**)$_3$. H**6** (0.100 g, 0.51 mmol, 3.0 equiv) was suspended in water (10 mL); the pH was decreased to 3.5–3.7 with the addition of 1 M NaOH in order to solubilize the ligand. Ln(NO$_3$)$_3$•6H$_2$O (73.0–81.4 mg, 0.17 mmol, 1.0 equiv) was added to the ligand solution. The pH of the mixture was raised slowly over 10–15 min with the dropwise addition of 1 M NaOH (Ln^{3+} = La, pH 9.5; Eu, pH 10.9; Gd, pH 9.45 Lu, pH 10.2) and the resulting mixture was continuously stirred for 1 h. The solution was concentrated under reduced pressure, redissolved in 1–2 mL of water and

precipitated out with the addition of acetone (50 mL). The metal complex was collected by centrifugation (4000 RPM), the supernatant was discarded. All of the complexes were dried *in vacuo* to yield 65–73% of Ln(**6**)$_3$.

***Tris*(1-(1-hydroxybutan-2-yl)-2-methyl-3-oxy-4-pyridinonato)lanthanum(III),** La(**6**)$_3$ ^{1}H NMR (400 MHz, CD_3OD) δ = 7.34 (br. s., 3 H, H_a), 6.46 (d, J = 2.0 Hz, 3 H, H_b), 4.37 (br. s., 3 H, N-C*H*), 3.73 (br. s., 6 H, CH_2-OH), 2.37 (br. s., 9 H, ring CH_3), 1.58 - 1.97 (m, 6 H, CH_2CH$_3$), 0.79 (br. s., 9 H, CH$_2$CH_3). ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ = 159.5 (ring *C*=O, C_a), 129.4 (ring *C*-OH, ring *C*-CH$_3$), 111.9 (C_b), 69.0 (N-*C*H), 65.5 (*C*H$_2$-OH), 25.8 (*C*H$_2$CH$_3$), 13.2 (CH$_2$*C*H$_3$), 10.7 (ring *C*H$_3$). MS (+ESI) *m/z* = 728.3, 729.2, 730.2 $[M + H]^+$. HRMS (+ESI); Calc. (found): $C_{30}H_{43}{}^{139}LaN_3O_9$: 728.2063 (728.2072) $[M + H]^+$.

***Tris*(1-(1-hydroxybutan-2-yl)-2-methyl-3-oxy-4-pyridinonato)europium(III),** Eu(**6**)$_3$ MS (+ESI) *m/z* = 740.5, 741.4, 742.4, 743.3, 744.4, 745.4, 746.3 $[M + H]^+$. HRMS (+ESI); Calc. (found): $C_{30}H_{43}{}^{151}EuN_3O_9$: 740.2198 (740.2202) $[M + H]^+$.

***Tris*(1-(1-hydroxybutan-2-yl)-2-methyl-3-oxy-4-pyridinonato)gadolinium(III),** Gd(**6**)$_3$

MS (+ESI) *m/z* = 743.2, 744.4, 745.4, 746.4, 747.3, 748.3, 749.3, 750.3, 751.3 $[M + H]^+$. HRMS (+ESI); Calc. (found): $C_{30}H_{43}{}^{153}GdN_3O_9$: 744.2226 (744.2232) $[M + H]^+$.

***Tris*(1-(1-hydroxybutan-2-yl)-2-methyl-3-oxy-4-pyridinonato)lutetium(III),** Lu(**6**)$_3$ ^{1}H NMR (400 MHz, D_2O) δ = 7.47 (br. s., 3 H, H_a), 6.49 (br. s., 3 H, H_b), 4.46 (br. s., 3 H, N-C*H*), 3.79 (br. s., 6 H, CH_2-OH), 2.29 (br. s., 9 H ring CH_3), 1.80 (br. s., 3 H, CH_2CH$_3$), 1.66 (br. s., 3 H, CH_2CH$_3$), 0.72 (br. s., 9 H, CH$_2$CH_3). MS (+ESI) *m/z* = 764.4, 765.4, 766.3, 767.3 $[M + H]^+$. HRMS (+ESI); Calc. (found): $C_{30}H_{43}{}^{175}LuN_3O_9$: 764.2407 (764.2407) $[M + H]^+$.

General procedure for sodium *tris*(1-carboxymethyl-2-methyl-3-oxy-4-pyridinonato)lanthanide(III), $Na_3[Ln(\mathbf{7})_3]$. H**8** (0.101 g, 0.55 mmol, 3.0 equiv) was suspended in water (10 mL); the pH was increased to 3.9 with the addition of 1 M NaOH in order to solubilize the ligand. $Ln(NO_3)_3 \bullet 6H_2O$ (78.6–85.6 mg, 0.18 mmol, 1.0 equiv) was added to the ligand solution. The pH of the mixture was raised slowly over 10–15 min with the dropwise addition of 1 M NaOH (Ln^{3+} = La, pH 9.5; Eu, pH 10.9; Gd, pH 9.45 Lu, pH 10.2) and the resulting mixture was continuously stirred for 1 h. The solution was concentrated under reduced pressure, redissolved in 1–2 mL of water and precipitated out with the addition of acetone (50 mL). The metal complex was collected by centrifugation (4000 RPM), the supernatant was discarded. All complexes were dried *in vacuo* to yield 81–95% of $Na_3[Ln(\mathbf{7})_3]$.

Sodium *tris*(1-carboxymethyl-2-methyl-3-oxy-4-pyridinonato)lanthanum(III), $Na_3[La(\mathbf{7})_3]$. ^{1}H NMR (400 MHz, D_2O) δ = 7.24 (d, *J* = 6.1 Hz, 3 H, H_a), 6.36 (br. s., 3 H, H_b), 4.53 (br. s., 6 H, CH_2-COOH), 2.12 (br. s., 9 H, ring CH_3). ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ = 174.6 (CH_2-*C*OO^-), 172.6 (ring *C*=O), 156.1 (C_a), 134.8 (ring *C*-CH_3, ring *C*-OH), 110.5 (C_b), 58.4 (N-*C*H_2), 12.0 (ring *C*H_3). MS (-ESI) *m/z* = 706.0, 707.0, 708.0 $[M - 2Na + H]^-$. HRMS (-ESI); Calc. (found): $C_{24}H_{22}{}^{139}LaN_3NaO_{12}$: 706.0165 (706.0167) $[M - 2Na + H]^-$. Anal. Calc. (found): $C_{24}H_{21}LaN_3Na_3O_{12} \bullet H_2O$: C, 37.47 (37.81); H, 3.01 (3.14); N, 5.46 (5.46).

Sodium *tris*(1-carboxymethyl-2-methyl-3-oxy-4-pyridinonato)europium(III), $Na_3[Eu(\mathbf{7})_3]$. MS (-ESI) *m/z* = 718.0, 719.0, 720.0, 721.0, 722.7 $[M - 2Na + H]^-$. HRMS (-ESI); Calc. (found): $C_{24}H_{22}{}^{151}EuN_3NaO_{12}$: 718.0300 (718.0292) $[M - 2Na + H]^-$. Anal. Calc. (found): $C_{24}H_{21}EuN_3Na_3O_{12} \bullet H_2O$: C, 36.84 (37.84); H, 2.96 (3.33); N, 5.37 (5.12).

Sodium *tris*(1-carboxymethyl-2-methyl-3-oxy-4-pyridinonato)gadolinium(III), $Na_3[Gd(\mathbf{7})_3]$. MS (-ESI) *m/z* = 721.0, 722.0, 723.0, 724.0, 725.0, 726.0, 727.1, 728.0, 729.0 [M - 2Na + H]$^-$. HRMS (-ESI); Calc. (found): $C_{24}H_{22}{}^{154}GdN_3NaO_{12}$: 721.0310 (721.0330) [M - 2Na + H]$^-$. Anal. Calc. (found): $C_{24}H_{21}GdN_3Na_3O_{12}\bullet 2H_2O$: C, 35.78 (35.98); H, 3.13 (3.22); N, 5.22 (5.36).

Sodium *tris*(1-carboxymethyl-2-methyl-3-oxy-4-pyridinonato)lutetium(III), $Na_3[Lu(\mathbf{7})_3]$. ^{1}H NMR (300 MHz, D_2O) δ = 7.34 (br. s., 3 H, H_a), 6.43 (br. s., 3 H, H_b), 4.60 (br. s., 6 H, CH_2-COOH), 2.17 (br. s., 9 H, ring CH_3). MS (-ESI) *m/z* = 720.1, 721.1, 722.1, 723.1 [M - 3Na + 2H]$^-$. HRMS (-ESI); Calc. (found): $C_{24}H_{23}{}^{175}LuN_3O_{12}$: 720.0690 (720.0675) [M - 3Na + 2H]$^-$.

General procedure for sodium *tris*(1-carboxyethyl-2-methyl-3-oxy-4-pyridinonato)lanthanide(III), $Na_3[Ln(\mathbf{8})_3]$. H**8** (0.102 g, 0.52 mmol, 3.0 equiv) was suspended in water (10 mL); $Ln(NO_3)_3\bullet 6H_2O$ (74.6–81.9 mg, 0.18 mmol, 1.0 equiv) was added to the ligand solution. The pH of the mixture was raised slowly over 10–15 min with the dropwise addition of 1 M NaOH (Ln^{3+} = La, pH 10.6; Eu, pH 10.3; Gd, pH 10.8 Lu, pH 11.1) and the resulting mixture was continuously stirred for 1 h. The solution was concentrated under reduced pressure, redissolved in 1–2 mL of water and precipitated out with the addition of acetone (50 mL). The metal complex was collected by centrifugation (4000 RPM), the supernatant was discarded. All compounds were dried *in vacuo* to yield 45–99% of $Na_3[Ln(\mathbf{8})_3]$.

Sodium *tris*(1-carboxyethyl-2-methyl-3-oxy-4-pyridinonato)lanthanum(III), $Na_3[La(\mathbf{8})_3]$. ^{1}H NMR (400 MHz, D_2O) δ = 7.31 (br. s., 3 H, H_a), 6.29 (br. s., 3 H, H_b), 4.18 (br. s., 6 H, N-CH_2), 2.53 (br. s., 6 H, CH_2-COOH), 2.22 (br. s., 9 H, ring CH_3). ^{13}C{^{1}H} NMR (101

MHz, D_2O) δ = 178.7 (CH_2-*C*OO^-), 172.4 (ring *C*=O), 156.4 (C_a), 134.1 (ring *C*-OH), 133.5 (ring *C*-CH_3), 110.6 (C_b), 52.1 (N-CH_2), 38.4 (*C*H_2-COOH), 11.8 (ring *C*H_3). MS (-ESI) *m/z* = 748.1, 749.1, 749.2, 750.1 $[M - 2Na + H]^-$. HRMS (-ESI); Calc. (found): $C_{27}H_{28}{}^{139}LaN_3NaO_{12}$: 748.0634 (748.0632) $[M - 2Na + H]^-$. Anal. Calc. (found): $C_{27}H_{27}LaN_3Na_3O_{12}$•$2H_2O$: C, 39.87 (39.28); H, 3.84 (3.60); N, 5.17 (5.08).

Sodium *tris*(1-carboxyethyl-2-methyl-3-oxy-4-pyridinonato)europium(III), $Na_3[Eu(\mathbf{8})_3]$. MS (-ESI) *m/z* = 738.1, 739.1, 740.1, 741.1, 742.1 $[M - 3Na + 2H]^-$. HRMS (-ESI); Calc. (found): $C_{27}H_{29}{}^{151}EuN_3O_{12}$: 738.0950 (738.0938) $[M - 3Na + 2H]^-$.

Sodium *tris*(1-carboxyethyl-2-methyl-3-oxy-4-pyridinonato)gadolinium(III) $Na_3[Gd(\mathbf{8})_3]$. MS (-ESI) *m/z* = 741.1, 742.1, 743.1, 744.1, 745.1, 746.1, 747.1, 748.1, 749.1 $[M - 3Na + 2H]^+$. HRMS (-ESI); Calc. (found): $C_{27}H_{29}{}^{155}GdN_3O_{12}$: 742.0978 (742.0972) $[M - 3Na + 2H]^-$.

Sodium *tris*(1-carboxyethyl-2-methyl-3-oxy-4-pyridinonato)lutetium(III), $Na_3[Lu(\mathbf{8})_3]$. ^{1}H NMR (300 MHz, D_2O) δ = 7.41 (d, *J* = 5.7 Hz, 3 H, H_a), 6.36 (d, *J* = 6.2 Hz, 3 H, H_b), 4.23 (br. s., 6 H, N-CH_2), 2.57 (br. s., 6 H, CH_2-COOH), 2.26 (br. s., 9 H, ring CH_3). MS (-ESI) *m/z* = 784.1, 785.1, 786.1, 787.1 $[M - 2Na + H]^-$. HRMS (-ESI); Calc. (found): $C_{27}H_{28}{}^{175}LuNaN_3O_{12}$: 784.0979 (784.0980) $[M - 2Na + H]^-$.

Bis[[bis(carboxymethyl)amino]methyl]phosphinate (H_5**XT**•HCl**)** This was prepared as previously published by our laboratory.[5] Iminodiacetic acid (2.7 g, 20 mmol) was dissolved in a 50% aq. solution of H_3PO_2 (1.3 g, 10 mmol). To this mixture, hydrochloric acid (6 M, 4.0 mL, 24.0 mmol) was added and the solution was heated to reflux. An aqueous solution of formaldehyde (37%; 3.2 g, 40 mmol) was added dropwise to the reaction mixture and the reflux

was continued for an additional 12 h. Upon cooling to room temperature a white precipitate formed and was collected by filtration, rinsed with methanol and dried *in vacuo*, affording a white solid, H_5**XT**•HCl, (0.502 g, 13%) $^1H\{^{31}P\}$ NMR (300 MHz, D_2O) δ = 4.20 (s, 8 H, N-C*H*$_2$-COOH), 3.58 (d, *J* = 9.6 Hz, 4 H, N-C*H*$_2$-PO). $^{31}P\{^1H\}$ NMR (121 MHz, D_2O) δ = 18.75. MS (+ESI) *m/z* = 357.1 $[M + H]^+$. Anal. Calc. (found): $C_{10}H_{17}N_2O_{10}P$•HCl: C, 30.59 (30.93); H, 4.62 (4.68); N, 7.13 (7.05).

General Synthesis of K_2[Ln(**XT**)]. The synthesis of K_2[Ln(**XT**)] was achieved by a method published from our group.[5] H_5**XT**•HCl (40 mg, 0.10 mmol) and $Ln(NO_3)_3$•$6H_2O$ (Ln = La, Eu, Lu) were dissolved in a minimum amount of water (2 mL). The pH was increased slowly by the dropwise addition of 0.1 M KOH until the solution reached a pH of 7 – 8. The solution was then concentrated by rotary evaporation. The residue was redissolved in methanol (3 mL) and water (0.5 mL), precipitated with acetone and centrifuged (4000 ppm) to collect the white or yellow precipitate. The supernatant was decanted and remaining white pellet was dissolved in methanol, precipitated with acetone and the product was isolated by centrifugation and dried, affording a white or yellow solid. All complexes were dried *in vacuo* to yield 72 – 89% of K_2[Ln(**XT**)].

K_2[La(**XT**)]. HRMS (-ESI); Calc. (found): $C_{10}H_{12}K^{139}La\ N_2O_{10}P$: 528.8930 (528.8933) $[M - K]^-$.

K_2[Eu(**XT**)]. HRMS (-ESI); Calc. (found): $C_{10}H_{12}{}^{151}EuKN_2O_{10}P$: 540.9065 (540.9062) $[M - K]^-$.

K_2[Lu(**XT**)]. HRMS (-ESI); Calc. (found): $C_{10}H_{12}K^{175}LuN_2O_{10}P$: 564.9275 (564.9279) $[M - K]^-$.

Determination of the Octanol-water Partition Coefficient ($P_{o/w}$)

The shake-flask method[6] was used to determine the octanol-water partition coefficients of the free ligands, and were calculated according to Equation 3. Solutions of ligands (1 mM; H**1**, H**2**, H**3**, H**4**, H**6**, H**8** and H**9**) were dissolved in HEPES buffer (25 mM HEPES, pH 7.4, 0.16 M NaCl). Exactly 0.6 mL of the ligand solutions were placed in a 2 mL Eppendorf tube containing exactly 0.6 mL of 1-octanol. The samples were mixed using a vortex (VWR vortex mixer, speed 10) for 1 min, and inverted for 6 min. Phase separation was achieved by centrifugation of the samples at 6000 rotations per minute (RPM) for 1–2 minutes. The water layer was removed by partially filling a syringe with a detachable needle with air, gentle expulsion of the air while passing through the 1-octanol layer, and withdrawal of the aqueous layer; the syringe was then quickly removed from the mixture, the needle was removed from the syringe and the water layer was collected in a separate Eppendorf tube. The aqueous layer was diluted appropriately using HEPES buffer, and the organic layer was diluted using ethanol. The UV-vis spectrum of each of the solutions was measured, with λ_{max} between 278–281 nm indicating the absorbances of the free ligands. Utilizing Beer's law, the molar absorptivities ($cm^{-1}M^{-1}$) of the ligands in HEPES were determined. From this the concentration of ligand in each layer was calculated. Log $P_{o/w}$ was then calculated using Equation 3.

Caco-2 Cell Protein Concentration Assay

After performing the cell uptake and bifunctional transport assays, cells were lysed (*vide infra*), and protein concentrations of the cell lysates cells were measured by a bicinchoninic acid protein assay (BCA Protein Assay Kit).[7] A bovine serum albumin (BSA) calibration curve was constructed in the range of 25 µg/mL to 2000 µg/mL; aliquots of exactly 20 or 25 µL of cell

lysates were pipetted into a 96-well microtiter plate and 200 µL of reagent (mixture of BCA reagents A and B in a ratio of 50:1) was added to each well. Absorbance was measured after 1 h at room temperature at 540 nm with a Multiskan Ascent Multi-plate reader from Labsystems. Protein concentration of each sample was determined against the standard BCA curve. Each concentration was measured in triplicate, and the averaged value was used in further calculations.

Hydroxyapatite *in vitro* Binding Study

As samples in this study were analyzed by ICP-MS, all materials used in this study were washed in a 5% Extran bath overnight, then washed with 18.2 MΩ-cm water, and placed in an 1% Optima nitric acid bath overnight. The materials were then washed with 18.2 MΩ-cm water and left to dry in a dust free environment.

A procedure modified from that reported previously by our group was used to study the *in vitro* hydroxyapatite binding of the metal complexes.[8] Samples containing exactly 20.0 mg (39.8 nmol) of dried hydroxyapatite (HAP) were suspended in 0.900 mL of HEPES buffer (25 mM HEPES, pH 7.4, 0.16 M NaCl) in 2 mL microcentrifuge tubes and incubated overnight at 37 °C in a shaker at 225 RPM, allowing for equilibration of samples.

The metal complexes were dissolved at a concentration of 1 mM, and serially diluted to afford a concentration of 20 µM in the same HEPES buffer. Exactly 0.100 mL of the ligand solutions were added to the HAP suspended in HEPES buffer to afford a 2 µM concentration of the metal complex with the HAP. After 5 min, 15 min, 3 h or 24 h incubation of the metal complex at 37 °C in a shaker at 225 RPM, the samples were centrifuged at 6000 RPM for 1–2 minutes with each time point measured in triplicate. Supernatants were carefully removed and

placed in 20 mL scintillation vials. Each pellet was washed twice with exactly 1.00 mL of HEPES buffer to remove any unbound metal ion from the HAP. The supernatant was filtered through a 0.22 μm Millipore filter and exactly 1.00 mL was pipetted into 1.5 mL Eppendorf tubes. The HAP pellets and the supernatant were vacuum centrifuged at 60 °C overnight; the dried HAP pellets and supernatant samples were acid digested for ICP-MS analysis. Percent HAP-binding ± SD was determined by dividing the lanthanide ion concentration from the HAP sample by the total concentration found in both the HAP and supernatant samples and multiplying by 100.

Analysis by Xylenol Orange Assay

A procedure modified from that reported previously by our group was used to qualitatively analyze the *in vitro* hydroxyapatite binding of the metal complexes.[8] Approximately 10 mg of ligand, HAP, metal complex and $Ln(NO_3)_3$ samples from the Ln(III)-HAP were qualitatively assayed for the presence of free lanthanide. All the samples were dissolved in hexamethylenetetramine buffer (20% v/v in water, pH 5.0). Additionally HAP and Ln(III)-HAP samples were dissolved in a few drops of 6 M HCl, dissolved in hexamethylenetetramine buffer and adjusted to pH 5.0. Xylenol orange was dissolved in the same buffer. A few drops were added to each of the solutions – presence of free lanthanide was determined by the appearance of a deep red/purple colour upon the addition of the indicator.

Structural Studies of Lanthanum Binding with Hydroxyapatite

For the purposes of the TGA, PXRD, and FTIR studies, samples containing exactly 0.5000 g (0.995 mmol) of hydroxyapatite were incubated overnight in a shaker at 37 °C at 225

revolutions per minute (RPM) with exactly 50.00 mL of HEPES buffer (25 mM HEPES, pH 7.4, 0.16 M NaCl). $Na_3[La(\mathbf{8})_3]$ was dissolved in HEPES buffer (0.202 mmol), and H**8** was dissolved in HEPES buffer (0.606 mmol). Exactly 0.500 mL of the metal complex and ligand solution was added to HAP-HEPES suspensions. Samples were incubated for 24 h in a shaker at 37 °C at 225 RPM. Samples were centrifuged, rinsed twice with HEPES buffer (2 × 50.00 mL), vortexed and dried *in vacuo* overnight. Samples were analyzed by TGA, PXRD and FTIR for their structural and physical properties.

Powder X-ray diffraction samples were run on a Bruker AXS D8 Advance powder X-ray diffractometer, wavelength of CuK_α (1.54 Å). Hydroxyapatite samples were made into a fine powder using a mortar and pestle. Samples were run from 2θ = 5.000–80.000°, at a step point of 0.040° and a step time of 1.6 s at 25 °C. For thermogravimetric analysis (TGA), samples were analyzed on a Perkin Elmer Pyris 6 thermogravimetric analyser. Hydroxyapatite samples were heated from 23.5–900 °C under an inert atmosphere.

Table S.1. Equivalents of amine used to synthesize each ligand, and the respective yields.

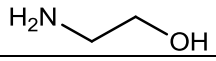
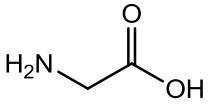
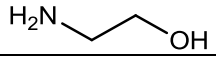
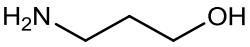
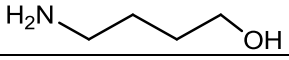
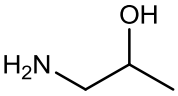
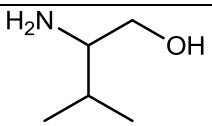
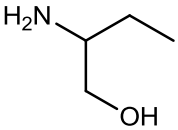
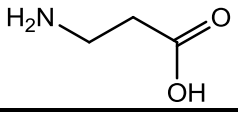
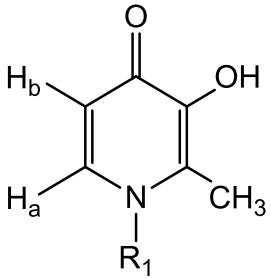
Compound	Nucleophile (amine)	Equivalent of amine	Yield (%)
H**1**	2-aminoethanol 	3.1	41
H**7**	glycine 	2.0	40
Bn**1**	2-aminoethanol 	1.5	37
Bn**2**•HCl	3-aminopropanol 	1.5	59
Bn**3**•HCl	4-amino-1-butanol 	1.5	54
Bn**4**	(±)-1-aminopropan-2-ol 	2.0	59
Bn**5**	(±)-2-amino-3-methyl-1-butanol 	1.6	6
Bn**6**	(±)-2-amino-1-butanol 	2.0	30
Bn**8**	β-alanine 	1.5	45

Table S.2. A comparison of ^{1}H NMR spectral shifts for H**L** and La(**L**)$_3$.



Compound	Solvent	H_a	H_b	Ring CH_3	N-CH_2 or N-CH	N-CH$_2$-CH_2	CH_2-CH$_2$-OH	CH_2-OH or CH-OH	alkyl-CH_3	CH-CH$_2$ or CH-CH
H**1**	D_2O	7.62	6.49	2.40	3.85	-	-	4.20		
La(**1**)$_3$	D_2O	7.29	6.32	2.21	3.79			4.11		
H**2**•HCl	D_2O	8.02	7.07	2.58	4.40	2.05	-	3.63		
La(**2**)$_3$	D_2O	7.31	6.31	2.24	4.06	1.74 - 2.04		3.55		
H**3**•HCl	D_2O	8.00	7.05	2.55	4.31	1.48 - 1.62	1.76 - 1.91	3.57		
La(**3**)$_3$	D_2O	7.25	6.28	2.18	3.96	1.49	1.69	3.53		
H**4**	CD_3OD	7.59	6.39	2.45	3.96 - 4.05; 3.83 - 3.91			4.10	1.24	
La(**4**)$_3$	CD_3OD	7.18	6.35	2.30	3.96			3.80	1.16	
H**5**	CD_3OD	7.78	6.49	2.46	4.03 - 4.19			3.78 - 4.03	1.06 - 1.19; 0.76	2.11 - 2.30
La(**5**)$_3$	CD_3OD	7.49	6.64	2.41	4.08			3.86	1.08; 0.66	2.16
H**6**	CD_3OD	7.73	6.49	2.48	4.36 - 4.48			3.70 - 3.87	0.86	1.71 - 1.99
La(**6**)$_3$	CD_3OD	7.34	6.46	2.37	*4.37*			3.73	0.79	1.58 – 1.97
H**7**	D_2O	7.89	7.00	2.43	4.87	-	-	-		
Na_3[La(**7**)$_3$]	D_2O	7.24	6.36	2.12	4.53					
H**8**	0.1M NaOD	7.27	6.30	2.32	4.20	2.56				
Na_3[La(**8**)$_3$]	D_2O	7.31	6.29	2.22	4.18	2.53				

Table S.3. Selected IR stretching frequencies of the free ligands and their lanthanide complexes.

Compound	ν_{OH}	ν_{C-H} (CH_3 or CH_2)			$\nu_{C=O}$ or ν_{ring}				ν_{C-O}	ν_{C-N}	ν_{M-O}		
H**1**	3292	2938	2923		1620	1562	1558	1495	1336	1223			
La(**1**)$_3$	~3200	2916	2874		1593	1538	1498	1478	1341	1282	526	460	424
Eu(**1**)$_3$	~3200	2916	2873		1590	1537	1497	1477	1341	1279	523	457	430
Lu(**1**)$_3$	~3200	2929	2879		1594	1543	1504	1486	1341	1283	533	458	-
H**2**	3247	2956	2931		1640	1583w	1529	1506	1329	1235			
La(**2**)$_3$	~3200	2915	2877		1588	1537	1496	1463	1339	1279	522	460	424
Eu(**2**)$_3$	~3200	2929	2874		1592	1539	1497	1464	1337	1279	531	458	434
Lu(**2**)$_3$	~3200	2929	2879		1594	1543	1530	1470	1339	1283	534	459	-
H**3**	3301	2964	2933		1637	1586w	1531	1509	1333	1235			
La(**3**)$_3$	~3200	2929	2854		1590	1537	1497	1464	1338	1277	528	471	422
Eu(**3**)$_3$	~3200	2930	2868		1592	1538	1497	1467	1338	1278	525	478	428
Lu(**3**)$_3$	~3200	2930	2866		1593	1538	1502	1470	1339	1285	532	471	452
H**4**	3232	2960	2925		1625	1558	1504	1456	1351	1233			
La(**4**)$_3$	~3200	2968	2916		1590	1537	1497	1476	1352	1279	536	453	413
Eu(**4**)$_3$	~3200	2968	2914		1590	1538	1499	1480	1372	1281	536	452	428
Gd(**4**)$_3$	~3200	2969	2916		1592	1540	1501	-	1339	1281	538	452	433
Lu(**4**)$_3$	~3200	2970	2917		1593	1544	1504	1486	1374	1287	540	450	-
H**5**	3117	2966	2948		1624	1570	1527w	1504	1339	1234			
La(**5**)$_3$	3306	2963	2874		1591	1538	1495	1463	1337	1274	528	464	423
H**6**	3085	2964	2930	2875	1625	1570	1527w	1504	1358	1274			
La(**6**)$_3$	~3200	2965	2931	2876	1590	1537	1495	1463	1358	1274	524	495	417
Eu(**6**)$_3$	~3200	2964	2930	2876	1592	1540	1496	1464	1340	1258	528	496	438
Gd(**6**)$_3$	~3200	2964	2930	2876	1592	1541	1496	1464	1340	1258	529	497	438

Compound	ν_{OH}	ν_{C-H} (CH_3 or CH_2)			$\nu_{C=O}$ or ν_{ring}				ν_{C-O}	ν_{C-N}	ν_{M-O}		
Lu(**6**)$_3$	~3200	2966	2932	2877	1595	1546	1501	1475	1342	1279	537	497	446
H**8**	~3200	3067	2950		1657	1634	1553	1464	1385	1256			
La(**8**)$_3$	~3200		-		1597	1538	1498	1476	1359	1281	540	437	419
Eu(**8**)$_3$	~3200		-		1598	1539	1499	1480	1361	1283	539	435	421
Gd(**8**)$_3$	~3200		-		1597	1540	1499	1480	1361	1283	538	439	427
Lu(**8**)$_3$	~3200		-		1600	1546	1504	1482	1363	1286	540	456	428
H**9**	~3200	3091	3041		1681	1634	1567	1519	1354	1238			
La(**9**)$_3$	~3200		-		1583	1537	1497		1341	1278	512	479	422
Eu(**9**)$_3$	~3200		-		1587	1539	1497		1344	1280	524	480	429
Gd(**9**)$_3$	~3200		-		1584	1538	1498		1346	1280	524	480	430
Lu(**9**)$_3$	~3200		-		1591	1544	1504		1348	1285	529	485	450

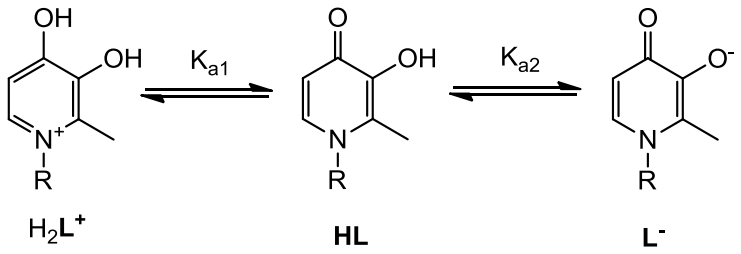
w = weak

Table S.4. Cytotoxicity data (MTT assay) for the free ligands in MG-63 cells, n = 3.

Compound	Functional group	EC_{50} MG-63 Cell (μM)
H**1**	ethyl-OH	> 296
H**2**•HCl	propyl-OH	> 273
H**3**•HCl	butyl-OH	> 1268
H**4**	isopropyl-OH	> 2729
H**6**	secbutyl-OH	> 5070
H**8**	ethyl-carboxylate	> 5071
H_5**XT**•HCl	phosphinate-EDTA derivative	> 562
H**L1**	methyl	> 360

Table S.5. Cytotoxicity data (MTT assay) for the Ln^{3+} complexes in MG-63 cells, n = 3.

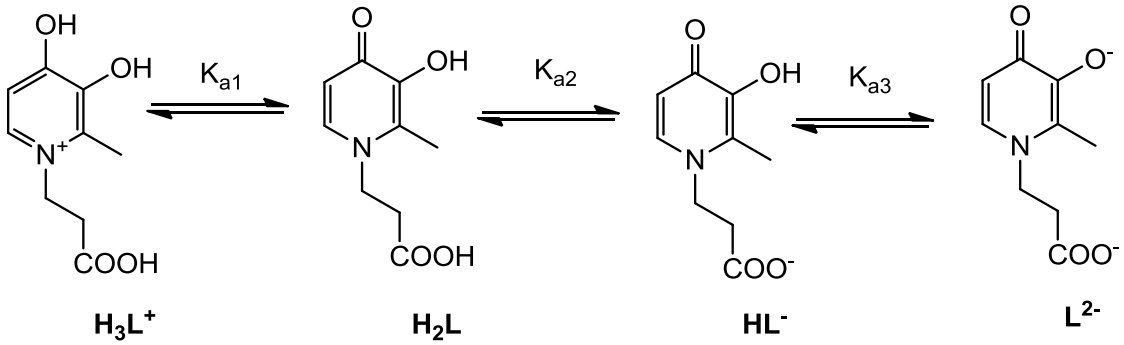
Compound	Functional group	EC_{50} MG-63 Cell (μM)
La(**1**)$_3$	ethyl-OH	> 147
Eu(**1**)$_3$	ethyl-OH	> 289
Lu(**1**)$_3$	ethyl-OH	> 1400
La(**2**)$_3$	propyl-OH	133 ± 3
Eu(**2**)$_3$	propyl-OH	> 681
La(**3**)$_3$	butyl-OH	> 131
La(**4**)$_3$	isopropyl-OH	> 139
Eu(**4**)$_3$	isopropyl-OH	> 136
Gd(**4**)$_3$	isopropyl-OH	> 676
Na_3[La(**7**)$_3$]	methyl-carboxylate	> 1263
Na_3[Eu(**7**)$_3$]	methyl-carboxylate	> 625
Na_3[Gd(**7**)$_3$]	methyl-carboxylate	> 1241
Na_3[Lu(**7**)$_3$]	methyl-carboxylate	> 1209
Na_3[La(**8**)$_3$]	ethyl-carboxylate	> 1206
Na_3[Eu(**8**)$_3$]	ethyl-carboxylate	> 1187
Na_3[Gd(**8**)$_3$]	ethyl-carboxylate	> 590
Na_3[Lu(**8**)$_3$]	ethyl-carboxylate	> 1155
K_2[La(**XT**)]	phosphinate-EDTA derivative	> 1655
K_2[Eu(**XT**)]	phosphinate-EDTA derivative	> 1620
K_2[Lu(**XT**)]	phosphinate-EDTA derivative	>1562
La(**L1**)$_3$	methyl	> 102



R = CH_3, H**L1**; R = $CH_2CH(OH)CH_3$, H**4**

$$H_2L^+ \rightleftharpoons H^+ + HL \qquad K_{a1} = \frac{[H^+][HL]}{[H_2L^+]} \tag{1}$$

$$HL \rightleftharpoons H^+ + L^- \qquad K_{a2} = \frac{[H^+][L^-]}{[HL]} \tag{2}$$



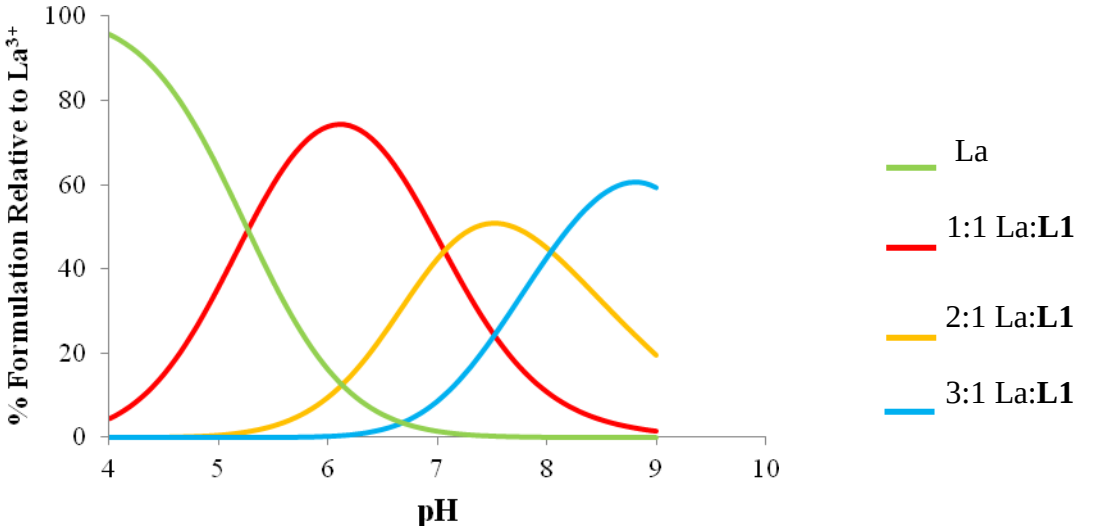
$$H_3L^+ \rightleftharpoons H^+ + H_2L \qquad K_{a1} = \frac{[H^+][H_2L]}{[H_3L^+]} \tag{3}$$

$$H_2L \rightleftharpoons H^+ + HL^- \qquad K_{a2} = \frac{[H^+][HL^-]}{[H_2L]} \tag{4}$$

$$HL^- \rightleftharpoons H^+ + L^{2-} \qquad K_{a3} = \frac{[H^+][L^{2-}]}{[HL^-]} \tag{5}$$

Figure S.1. The stepwise acid dissociation (pK_{an}) equilibria of the 3-hydroxy-4-pyridinones, where $pK_{an} = -\log K_{an}$.

a)



b)

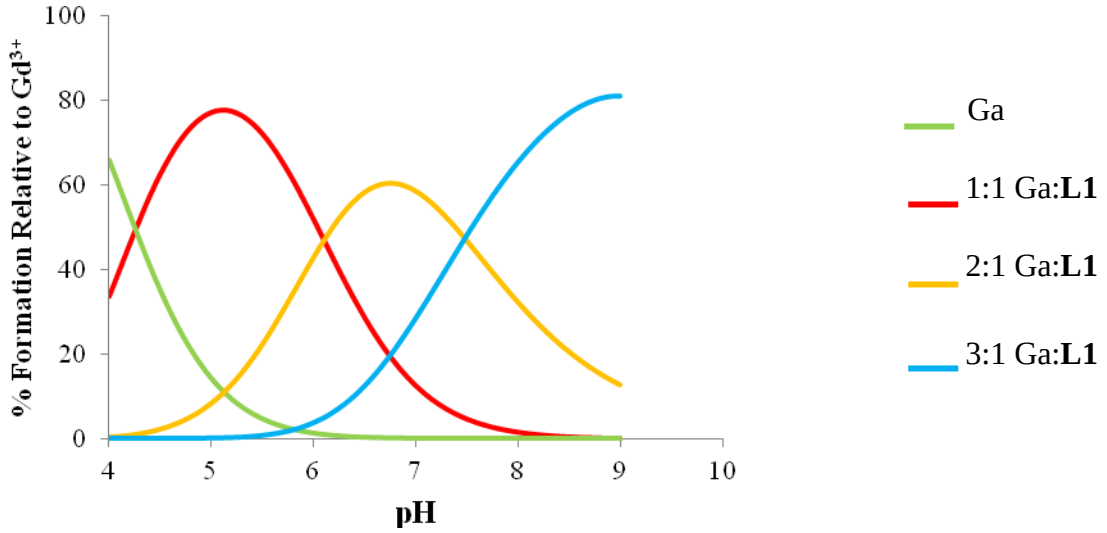


Figure S.2. Speciation diagrams for solutions containing 1 mM M^{3+} and 3 mM H**L1**: a) La^{3+}; b) Gd^{3+}.

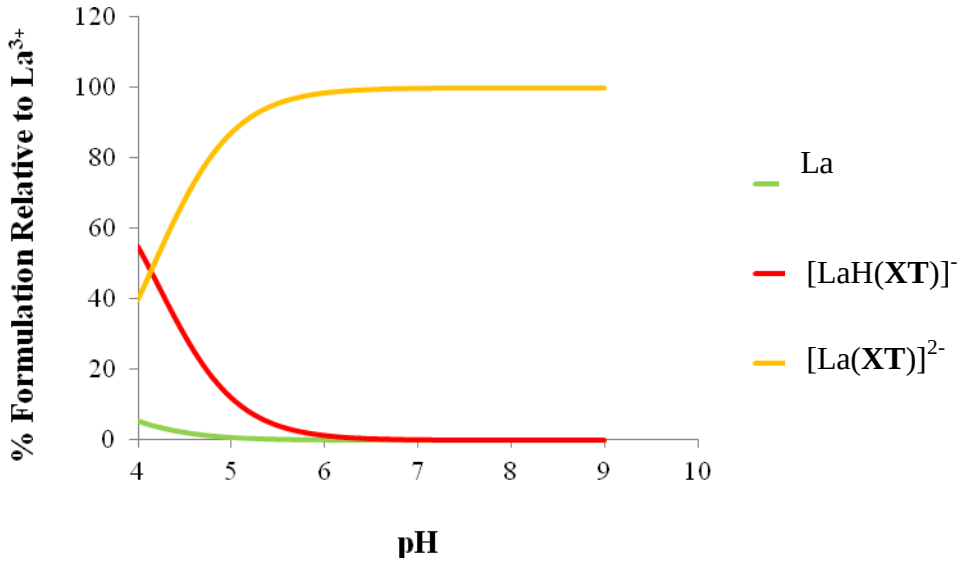


Figure S.3. Speciation diagrams for solutions containing 1 mM La^{3+} and 1 mM H_5**XT**.

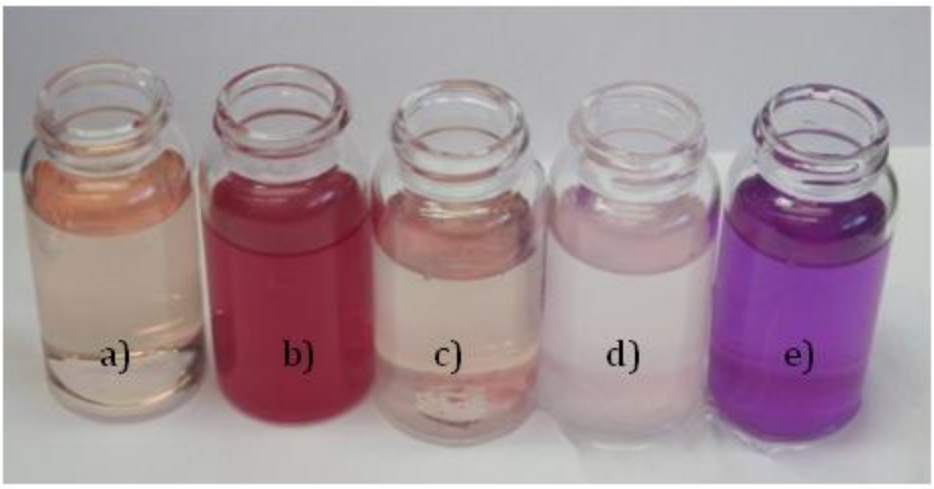


Figure S.4. Colourimetric xylenol orange assay where: a) Ln-HAP supernatant, b) digested Ln-HAP, c) undigested Ln-HAP d) HAP (control) e) $La(NO_3)_3$ (control). The appearance of purple/red indicates the presence of unbound Ln^{3+}.

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