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 (H1). Based on a modification of a literature procedure, 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, H1 (5.09 g, 41%). $^1$H NMR (400 MHz, D$_2$O) 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$_2$O) 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 (CH$_2$-OH), 56.0 (N-CH$_2$), 11.8 (ring CH$_3$). MS (-ESI) m/z =168.3 [M - H$^-$]. Anal. Calc. (found): C$_8$H$_{11}$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 (H7). Based on a modification from a procedure reported previously in the Orvig group, 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, H7 (2.90 g, 40%). \(^1\)H NMR (400 MHz, 0.1 M NaOD) \(\delta = 7.18\) (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\(_3\)). \(^1^3\)C{\(^1\)H} NMR (101 MHz, 0.1 M NaOD) \(\delta = 175.2\) (CH\(_2\)-COOH), 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-CH\(_2\)), 12.3 (ring CH\(_3\)). MS (-ESI) \(m/z = 182.3\) [M - H]. Anal. Calc. (found): C\(_8\)H\(_9\)NO\(_4\): C, 52.46 (52.64); H, 4.85 (4.92); N, 7.65 (7.66).

3-Benzylxoy-2-methyl-4-pyrone (Bnma). The synthesis of Bnma 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\(_2\)SO\(_4\). 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, Bnma (9.484 g, 79%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.60\) (d, \(J = 5.5\) Hz, 1 H, \(H_a\)), 7.30 - 7.43 (m, 5 H, Bn C\(_6\)H\(_5\)), 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-Benzzyloxy-2-methyl-1-(2-hydroxyethyl)-4-pyridinone (Bn1). Based on a modification of a literature procedure, Bnma (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 (50 mL). 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 Na₂SO₄ 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, Bn1 (5.57 g, 37%). ¹H NMR (400 MHz, D₂O) δ = 7.71 (d, J = 7.4 Hz, 1 H, Hₐ), 7.40 (s, 5 H, Bn C₆H₅), 6.57 (d, J = 7.4 Hz, 1 H, Hₖ), 5.02 (s, 2 H, Bn-CH₂), 4.10 (t, J = 5.3 Hz, 2 H, CH₂-OH), 3.76 (t, J = 5.1 Hz, 2 H, CH₂-OH), 2.06 (s, 3 H, ring CH₃). MS (+ESI) m/z = 260.4 [M + H]⁺.

3-Benzzyloxy-2-methyl-1-(3-hydroxypropyl)-4-pyridinone hydrochloride (Bn2•HCl). Based on a modification of a literature procedure, Bnma (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 6 M NaOH and the product was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ 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$_2$O) $\delta$ = 8.04 (d, $J$ = 7.1 Hz, 1 H, $H_a$), 7.41 (s, 5 H, Bn C$_6$H$_5$), 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-Benzylxoy-2-methyl-1-(4-hydroxybutyl)-4-pyridinone hydrochloride (Bn$_3$•HCl). Based on a modification of a literature procedure, Bnma (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 HCl and washed with diethyl ether.

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M NaOH and the product was extracted with dichloromethane (3 × 40 mL). The combined organic layers were dried over anhydrous Na₂SO₄ 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, Bn3•HCl (3.23 g, 54%).

\[ \text{Bn3•HCl (3.23 g, 54%)} \]

\[ ^1H \text{ NMR (300 MHz, CDCl}_3) \delta = 8.69 (d, J = 7.1 Hz, 1 H, H_a), 8.03 (d, J = 7.1 Hz, 1 H, H_b), 7.36 (s, 5 H, Bn C}_6H_5), 5.23 (s, 2 H, Bn-CH}_2), 4.41 (t, J = 7.8 Hz, 2 H, N-CH}_2), 3.75 (t, J = 5.6 Hz, 2 H, CH_2-OH), 2.41 (s, 3 H, ring CH}_3), 1.96 (q, J = 7.5 Hz, 2 H, CH_2-CH_2-OH), 1.66 (q, J = 5.5 Hz, 2 H N-CH}_2-CH}_2). \]

\[ \text{MS (+ESI) } m/z = 288.2 [M + H]^+ \]

**3-Benzzyloxy-2-methyl-1-(2-hydroxypropyl)-4-pyridinone (Bn4). Bnma** (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 Na₂SO₄ 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, Bn4 (3.71 g, 59%). $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.22 - 7.45 (m, 6 H, $H_a$, Bn C$_6$H$_5$), 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, CH-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-Benzyl oxy-2-methyl-1-(1-hydroxy-3-methylbutan-2-yl)-4-pyridinone (Bn5). Bnma (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$_2$SO$_4$ 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$_3$OH), and the product was eluted in 95:5 CHCl$_3$: CH$_3$OH. 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,
Bn5 (0.429 g, 6%). $^1$H NMR (300 MHz, CD$_3$OD) $\delta$ = 7.85 (d, $J$ = 7.8 Hz, 1 H, $H_a$), 7.25 - 7.42 (m, 5 H, Bn C$_6$H$_5$), 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$_2$H$_2$-C$_2$H$_2$-OH), 2.15 (s, 3H, ring C$_3$H$_3$), 1.08 (d, $J$ = 6.6 Hz, 3 H, CH$_2$-CH$_3$), 0.65 (d, $J$ = 6.9 Hz, 3 H, CH-CH$_3$). MS (+ESI) $m/z$ = 625.8 [M$_2$ + Na]$^+$.  

3-Benzylolloxy-2-methyl-1-(1-hydroxybutan-2-yl)-4-pyridinone (Bn6). Bnma (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 x 50 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ 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, Bn6 (6.66 g, 30%). $^1$H NMR (300 MHz, D$_2$O) $\delta$ = 7.78 (d, $J$ = 7.8 Hz, 1 H, $H_a$), 7.21 - 7.49 (m, 5 H, Bn C$_6$H$_5$), 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-CH), 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$_2$CH$_3$), 0.64 (t, $J$ = 7.3 Hz, 3 H, CH$_2$CH$_3$). MS (+ESI) $m/z$ = 597.7 [M$_2$ + Na]$^+$.  

S8
1-Carboxyethyl-3-benzyl oxy-2-methyl-4-pyridinone (Bn8). Based on a modification of a literature procedure, Bnma (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 Na2SO4 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, Bn8 (3.05 g, 45%). 1H NMR (300 MHz, D2O) δ = 7.86 (d, J = 7.3 Hz, 1 H, Hα), 7.28 - 7.48 (m, 5 H, Bn C6H5), 6.68 (d, J = 7.3 Hz, 1 H, Hβ), 5.03 (s, 2 H, Bn-CH2), 4.28 (t, J = 6.9 Hz, 2 H, N-CH2), 2.68 (t, J = 7.0 Hz, 2 H, CH2-COOH), 2.13 (s, 3 H, ring CH3). MS (-ESI) m/z = 286.3 [M - H]-.

3-Hydroxy-2-methyl-1-(3-hydroxypropyl)-4-pyridinone hydrochloride (H2•HCl). Based on a modification of a literature procedure, 3-benzyloxy-2-methyl-1-(3-hydroxypropyl)-4-pyridinone hydrochloride (Bn2•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.
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$_2$O) $\delta = 8.02$ (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$_2$O) $\delta =$ 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 (CH$_2$-OH), 53.9 (N-CH$_2$), 31.8 (N-CH$_2$-CH$_2$-CH$_2$-OH), 12.3 (ring CH$_3$). MS (+ ESI) $m/z =$ 184.3 [M +H$^+$]. Anal. Calc. (found): C$_9$H$_{13}$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 hydrochloride (H$_3$•HCl).$^4$

Based on a modification of a literature procedure,$^4$ 3-benzzyloxy-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, H3\(\cdot\)HCl (0.261 g, 72\%). \(^1\)H NMR (400 MHz, D\(_2\)O) \(\delta = 8.00 (d, J = 7.2 \text{ Hz}, 1 \text{ H}, H_a), 7.05 (d, J = 7.2 \text{ Hz}, 1 \text{ H}, H_b), 4.31 (t, J = 7.7 \text{ Hz}, 2 \text{ H}, N-\text{CH}_2), 3.57 (t, J = 6.3 \text{ Hz}, 2 \text{ H}, \text{CH}_2-\text{OH}), 2.55 (s, 3 \text{ H}, \text{ring CH}_3), 1.76 - 1.91 (m, 2 \text{ H}, \text{CH}_2-\text{CH}_2-\text{OH}), 1.48 - 1.62 (m, 2 \text{ H}, N-\text{CH}_2-\text{CH}_2). \(^{13}\)C \(^1\)H NMR (101 MHz, D\(_2\)O) \(\delta = 158.6 (\text{ring C}=\text{O}), 142.7 (C_a), 142.3 (\text{ring C-OH}), 138.5 (\text{ring C-CH}_3), 111.3 (C_b), 60.9 (\text{CH}_2-\text{OH}), 56.5 (\text{N-CH}_2), 28.2 (\text{N-CH}_2-\text{CH}_2), 26.0 (\text{CH}_2-\text{CH}_2-\text{OH}), 12.2 (\text{ring CH}_3). \) MS (+ESI) \(m/z = 198.2 [\text{M} + \text{H}]^+. \) Anal. Calc. (found): C\(_{10}\)H\(_{15}\)NO\(_3\)\(\cdot\)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 (H4). To afford the free pyridinone, 3-benzylxoy-2-methyl-1-(2-hydroxypropyl)-4-pyridinone (Bn4; 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, H4 (0.170 g, 50\%). \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta = 7.59 (d, J = 7.2 \text{ Hz}, 1 \text{ H}, H_a), 6.39 (d, J = 7.2 \text{ Hz}, 1 \text{ H}, H_b), 4.10 (dd, J = 14.1, 3.2 \text{ Hz}, 1 \text{ H}, \text{CH-OH}), 3.96 - 4.05 (m, 1 \text{ H}, \text{N-CH}_2), 3.83 - 3.91 (m, 1 \text{ H}, \text{N-CH}_2), 2.45 (s, 3 \text{ H}, \text{ring CH}_3), 1.24 (d, J = 6.5 \text{ Hz}, 3 \text{ H}, \text{CH(OH)CH}_3). \)
13C{1H} NMR (101 MHz, CD3OD) δ = 170.8 (ring C=O), 147.1 (C\textsubscript{a}), 140.2 (ring C-OH), 133.4 (ring C-CH\textsubscript{3}), 112.3 (C\textsubscript{b}), 67.8 (CH-OH), 61.5 (N-CH\textsubscript{2}), 21.0 (CH(OH)CH\textsubscript{3}), 12.56 (ring CH\textsubscript{3}).

MS (+ESI) m/z = 184.3 [M + H]\textsuperscript{+}. Anal. Calc. (found): C\textsubscript{9}H\textsubscript{13}NO\textsubscript{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 (H5). To afford the free pyridinone, 3-benzyloxy-2-methyl-1-(1-hydroxy-3-methylbutan-2-yl)-4-pyridinone (Bn5; 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\textsubscript{2}(g). The reaction was stirred under the H\textsubscript{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 \textit{in vacuo}, affording an off-white solid, H5 (0.253 g, 28%). 1H NMR (300 MHz, CD3OD) δ = 7.78 (d, J = 7.3 Hz, 1 H, H\textsubscript{a}), 6.49 (d, J = 7.3 Hz, 1 H, H\textsubscript{b}), 4.03 - 4.19 (m, 1 H, CH-CH\textsubscript{2}-OH), 3.78 - 4.03 (m, 2 H, CH-CH\textsubscript{2}-OH), 2.46 (s, 3 H, ring CH\textsubscript{3}), 2.11 - 2.30 (m, 1 H, CH(CH\textsubscript{3})\textsubscript{2}), 1.06 - 1.19 (m, 3 H, CH-CH\textsubscript{3}), 0.76 (d, J = 6.6 Hz, 3 H, CH-CH\textsubscript{3}). 13C{1H} NMR (101 MHz, CD3OD) δ = 170.2 (C=O), 135.5 (ring C-CH\textsubscript{3}), 112.9 (C\textsubscript{b}), 69.9 (CH-OH), 63.2 (CH-CH\textsubscript{2}-OH), 31.4 (CH\textsubscript{2}-OH), 20.0 (CH(CH\textsubscript{3})\textsubscript{2}), 19.6 (CH(CH\textsubscript{3})\textsubscript{2}), 12.6 (ring CH\textsubscript{3}).

Anal. Calc. (found): C\textsubscript{11}H\textsubscript{17}NO\textsubscript{3}: C, 62.54 (62.29); H, 8.11 (8.15); N, 6.63 (6.71). MS (+ESI) m/z = 212.3 [M + H]\textsuperscript{+}. 

S12
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 (Bn6; 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 H₂(g). The reaction was stirred under the H₂(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, H6 (0.262 g, 82%). ¹H NMR (400 MHz, CD₃OD) δ = 7.73 (d, J = 7.5 Hz, 1 H, Hₐ), 6.49 (d, J = 7.2 Hz, 1 H, Hₖ), 4.36 - 4.48 (m, 1 H, N-CH), 3.70 - 3.87 (m, 2 H, CH₂-OH), 2.48 (s, 3 H, ring CH₃), 1.71 - 1.99 (m, 2 H, CH₂CH₃), 0.86 (t, J = 7.3 Hz, 3 H, CH₂-CH₃). ¹³C¹H NMR (100 MHz, CD₃OD) δ = 170.5 (ring C=O), 146.8 (Cₐ), 135.0 (ring C-OH), 134.5 (ring C-CH₃), 113.2 (Cₖ), 65.5 (N-CH), 65.3 (CH₂-OH), 25.4 (CH₂-CH₃), 12.6 (CH₂CH₃), 10.5 (ring CH₃). MS (+ESI) m/z = 198.2 [M + H]⁺. Anal. Calc. (found): C₁₀H₁₅NO₃: C, 60.90 (60.80); H, 7.67 (7.68); N, 7.10 (7.19).

1-Carboxyethyl-3-hydroxy-2-methyl-4-pyridinone (H8). To afford the free pyridinone, 1-carboxyethyl-3-benzyloxy-2-methyl-4-pyridinone (Bn8; 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 addition of 6M NaOH. After the removal of water by rotary evaporation, the ensuing solid was redissolved.

S13
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, H8 (0.150 g, 58%). 

\[ ^1H \text{NMR} (400 \text{ MHz}, 0.1 \text{ M NaOD}) \delta = 7.27 (d, J = 6.8 \text{ Hz}, 1 \text{ H}, H_a), 6.30 (d, J = 6.8 \text{ Hz}, 1 \text{ H}, H_b), 4.20 (t, J = 7.3 \text{ Hz}, 2 \text{ H}, N\text{-C}H_2), 2.56 (t, J = 7.2 \text{ Hz}, 2 \text{ H}, CH_2\text{-COOH}), 2.32 (s, 3 \text{ H}, \text{ring } C_3H_3). \]

\[ ^{13}C\{^1H\} \text{NMR} (101 \text{ MHz}, 0.1 \text{ M NaOD}) \delta = 179.0 (\text{CH}_2\text{-COOH}), 172.6 (\text{ring } C=O), 155.6 (C_a), 135.0 (\text{ring } C\text{-OH}), 132.7 (\text{ring } C\text{-CH}_3), 111.7 (C_b), 52.2 (\text{N-CH}_2), 38.6 (\text{CH}_2\text{-COOH}), 12.1 (\text{ring } CH_3). \]

MS (+ESI) m/z = 198.2 [M + H]^+.

Anal. Calc. (found): C_{9}H_{11}\text{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.** H1 (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(NO₃)₃•6H₂O (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 (Ln³⁺ = 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.** 

\[ ^1H \text{NMR} (400 \text{ MHz}, D_2O) d = 7.29 (\text{br. s.}, 3 \text{ H}, H_a), 6.32 (\text{br. s.}, 3 \text{ H}, H_b), 4.11 (\text{br. s.}, 6 \text{ H}, CH_2\text{-OH}), 3.79 (\text{br. s.}, 6 \text{ H}, N\text{-CH}_2), 2.21 (\text{br. s.}, 9 \text{ H}, \text{ring } CH_3). \]

\[ ^{13}C\{^1H\} \text{NMR} (101 \text{ MHz}, D_2O) \delta = \]
172.4 (ring C=O), 136.0 (ring C-OH, C\text{a}), 134.8 (ring C-CH$_3$), 110.5 (C\text{b}), 60.4 (CH$_2$-OH), 56.5 (N-CH$_2$), 12.0 (ring CH$_3$). MS (+ESI) \text{m/z} = 644.1, 645.1, 646.2 [M + H]$^+$. HRMS (+ESI); Calc. (found): C$_{24}$H$_{31}$LaN$_3$O$_9$: 644.1124 (644.1119) [M + H]$^+$.

\textit{Tris}(1-(2-hydroxyethyl)-2-methyl-3-oxy-4-pyridinonato)europium(III), Eu(1)$_3$

MS (+ESI) \text{m/z} = 656.3, 657.2, 658.2, 659.2, 660.2 [M + H]$^+$. HRMS (+ESI); Calc. (found): C$_{24}$H$_{31}$EuN$_3$O$_9$: 656.1259 (656.1275) [M + H]$^+$.

\textit{Tris}(1-(2-hydroxyethyl)-2-methyl-3-oxy-4-pyridinonato)lutetium(III)Lu(1)$_3$

$^1$H NMR (400 MHz, D$_2$O) \(\delta = 7.31\) (br. s., 3 H, H\text{a}), 6.32 (br. s., 3 H, H\text{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) \text{m/z} = 680.1, 681.2, 682.1 [M + H]$^+$. HRMS (+ESI); Calc. (found): C$_{24}$H$_{31}$LuN$_3$O$_9$: 680.1468 (680.1473) [M + H]$^+$.

\textbf{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$_2$O (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 \textit{in vacuo} to yield 34–91% of Ln(2)$_3$.

\textbf{General procedure for tris(1-(3-hydroxypropyl)-2-methyl-3-oxy-4-pyridinonato)lanthanum(III)}, La(2)$_3$.

$^1$H NMR (400 MHz, D$_2$O) \(\delta = 7.31\) (br. s., 3 H, H\text{a}), 6.31 (br. s., 3 H, H\text{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 CH$_3$).
CH$_3$), 1.74 - 2.04 (m, 6 H, N-CH$_2$-CH$_2$-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-CH$_2$), 32.4, (N-CH$_2$-CH$_2$-CH$_2$-OH) 7.5 (ring CH$_3$). MS (+ESI) $m/z$ = 686.2, 687.2, 688.3 [M + H]$^+$. HRMS (+ESI); Calc. (found): C$_{27}$H$_{37}$LaN$_3$O$_9$: 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$_{37}$EuN$_3$O$_9$: 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$_{36}$GdN$_3$NaO$_9$: 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-CH$_2$), 3.54 (br. s., 6 H, CH$_2$-OH), 2.52 (br. s., 3 H, ring CH$_3$), 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$_{37}$LuN$_3$O$_9$: 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$$\cdot$6H$_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$_2$O) $\delta$ = 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$_2$O) $\delta$ = 172.6 (ring C=O), 157.4 (C$_a$, ring C-OH), 134.4 (ring C-CH$_3$), 112.3 (C$_b$), 61.1 (CH$_2$-OH), 54.8 (N-CH$_2$), 28.3 (N-CH$_2$-CH$_2$), 26.8 (CH$_2$-CH$_2$-OH), 11.8 (ring CH$_3$). MS (+ESI) $m/z$ = 728.2, 729.2, 730.2 [M + H]$^+$. HRMS (+ESI); Calc. (found): C$_{30}$H$_{43}$LaN$_3$O$_9$: 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$_{43}$EuN$_3$O$_9$: 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$_3$OD) $\delta$ = 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$_{43}$LuN$_3$O$_9$: 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$$\cdot$6H$_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$_3$OD) δ = 7.18 (br. s., 3 H, $H_a$), 6.35 (br. s., 3 H, $H_b$), 3.96 (br. s., 6 H, $N\cdot CH$_2$), 3.80 (d, $J = 6.8$ Hz, 3 H, CH-OH), 2.30 (s, 9 H, ring $CH_3$). MS (+ESI) $m/z$ = 686.2, 687.2, 688.3 [M + H]$^+$. HRMS (+ESI); Calc. (found): C$_{27}$H$_{37}$LaN$_3$O$_9$: 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$_{37}$EuN$_3$O$_9$: 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$_{37}$GdN$_3$O$_9$: 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$_2$O) 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, CH-OH), 2.28 (br. s., 3 H, ring $CH_3$). MS (+ESI) $m/z$ = 722.4, 723.2, 724.3, 725.4 [M + H]$^+$. HRMS (+ESI); Calc. (Found): C$_{27}$H$_{37}$LuN$_3$O$_9$: 722.1938 (722.1932) [M + H]$^+$.  

S18
**Tris(1-(1-hydroxy-3-methylbutan-2-yl)-2-methyl-3-oxy-4-pyridinonato) lanthanum(III), La(5)**

H5 (95.8 mg, 0.45 mmol, 3.0 equiv) was dissolved in methanol (10 mL); La(NO3)3•6H2O (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.

1H NMR (400 MHz, CD3OD) δ = 7.49 (br. s., 3 H, Ha), 6.64 (br. s., 3 H, Hb), 4.08 (br. s., 3 H, CH-CH2-OH), 3.86 (br. s., 6 H, CH-CH2-OH), 2.41 (br. s., 9 H, ring CH3), 2.16 (s, 3 H, CH(CH3)2), 1.08 (br. s., 9 H, CH-CH3), 0.66 (br. s., 9 H, CH-CH3). 13C{1H} NMR (101 MHz, CD3OD) δ = 158.4 (C=O), 140.7 (Ca), 134.6 (ring C-CH3), 129.8 (ring C-OH), 121.3 (Cb), 62.2 (N-CH), 45.1 (CH2-OH), 30.4 (C(CH3)2), 18.8 (C(CH3)2), 18.6 (C(CH3)2) 11.3 (ring CH3). MS (+ESI) m/z = 792.2, 793.2, 794.2 [M + Na]+. HRMS (+ESI); Calc. (found): C33H48139LaN3O13Na: 792.2352 (792.2355) [M + Na]+.

**Tris(1-(1-hydroxybutan-2-yl)-2-methyl-3-oxy-4-pyridinonato)lanthanide(III), Ln(6)**

H6 (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(NO3)3•6H2O (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 (Ln3+ = 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, CD₃OD) $\delta$ = 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-CH), 3.73 (br. s., 6 H, CH₂-OH), 2.37 (br. s., 9 H, ring CH₃), 1.58 - 1.97 (m, 6 H, CH₂CH₃), 0.79 (br. s., 9 H, CH₂CH₃). $^{13}$C {$^1$H} NMR (101 MHz, CD₃OD) $\delta$ = 159.5 (ring C=O, $C_a$), 129.4 (ring C-OH, ring C-CH₃), 111.9 ($C_b$), 69.0 (N-CH), 65.5 (CH₂-OH), 25.8 (CH₂CH₃), 13.2 (CH₂CH₃), 10.7 (ring CH₃). MS (+ESI) m/z = 728.3, 729.2, 730.2 [M + H]$^+$. HRMS (+ESI); Calc. (found): C₃₀H₄₃LaN₃O₉: 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): C₃₀H₄₃EuN₃O₉: 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): C₃₀H₄₃GdN₃O₉: 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, D₂O) $\delta$ = 7.47 (br. s., 3 H, $H_a$), 6.49 (br. s., 3 H, $H_b$), 4.46 (br. s., 3 H, N-CH), 3.79 (br. s., 6 H, CH₂-OH), 2.29 (br. s., 9 H ring CH₃), 1.80 (br. s., 3 H, CH₂CH₃), 1.66 (br. s., 3 H, CH₂CH₃), 0.72 (br. s., 9 H, CH₂CH₃). MS (+ESI) m/z = 764.4, 765.4, 766.3, 767.3 [M + H]$^+$. HRMS (+ESI); Calc. (found): C₃₀H₄₃LuN₃O₉: 764.2407 (764.2407) [M + H]$^+$.
General procedure for sodium tris(1-carboxymethyl-2-methyl-3-oxy-4-pyridinonato)lanthanide(III), Na₃[Ln(7)]₃. H₈ (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(NO₃)₃•6H₂O (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 (Ln³⁺ = 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 Na₃[Ln(7)]₃.

**Sodium tris(1-carboxymethyl-2-methyl-3-oxy-4-pyridinonato)lanthanum(III),** Na₃[La(7)]₃. ¹H NMR (400 MHz, D₂O) δ = 7.24 (d, J = 6.1 Hz, 3 H, H₆), 6.36 (br. s., 3 H, H₅), 4.53 (br. s., 6 H, CH₂-COOH), 2.12 (br. s., 9 H, ring CH₃). ¹³C{¹H} NMR (101 MHz, D₂O) δ = 174.6 (CH₂-COO⁻), 172.6 (ring C=O), 156.1 (Cₙ), 134.8 (ring C-CH₃, ring C-OH), 110.5 (Cₚ), 58.4 (N-CH₂), 12.0 (ring CH₃). MS (-ESI) m/z = 706.0, 707.0, 708.0 [M - 2Na + H]⁻. HRMS (-ESI); Calc. (found): C₂₄H₂₁LaN₃NaO₁₂•H₂O: 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),** Na₃[Eu(7)]₃. MS (-ESI) m/z = 718.0, 719.0, 720.0, 721.0, 722.7 [M - 2Na + H]⁻. HRMS (-ESI); Calc. (found): C₂₄H₂₁EuN₃NaO₁₂•H₂O: 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),
Na₃[Gd(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): C₂₄H₂₂₁₅₄GdN₃NaO₁₂: 721.0310 (721.0330) [M - 2Na + H⁺].

Sodium tris(1-carboxymethyl-2-methyl-3-oxy-4-pyridinonato)lutetium(III),
Na₃[Lu(7)₃]. ¹H NMR (300 MHz, D₂O) δ = 7.34 (br. s., 3 H, Hₐ), 6.43 (br. s., 3 H, Hₐ), 4.60 (br. s., 6 H, C₉H₂-COOH), 2.17 (br. s., 9 H, ring C₃H₃). MS (-ESI) m/z = 720.1, 721.1, 722.1, 723.1 [M - 3Na + 2H⁺]. HRMS (-ESI); Calc. (found): C₂₄H₂₃₁₇₅LuN₃O₁₂: 720.0690 (720.0675) [M - 3Na + 2H⁺].

General procedure for sodium tris(1-carboxyethyl-2-methyl-3-oxy-4-pyridinonato)lanthanide(III), Na₃[Ln(8)₃]. H₈ (0.102 g, 0.52 mmol, 3.0 equiv) was suspended in water (10 mL); Ln(NO₃)₃·6H₂O (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 (Ln³⁺ = 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 Na₃[Ln(8)₃].

Sodium tris(1-carboxyethyl-2-methyl-3-oxy-4-pyridinonato)lanthanum(III),
Na₃[La(8)₃]. ¹H NMR (400 MHz, D₂O) δ = 7.31 (br. s., 3 H, Hₐ), 6.29 (br. s., 3 H, Hₐ), 4.18 (br. s., 6 H, N-CH₂), 2.53 (br. s., 6 H, CH₂-COOH), 2.22 (br. s., 9 H, ring CH₃). ¹³C{¹H} NMR (101
MHz, D$_2$O) $\delta$ = 178.7 (CH$_2$-COO$^-$), 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 (CH$_2$-COOH), 11.8 (ring CH$_3$). MS (-ESI) m/z = 748.1, 749.1, 749.2, 750.1 [M - 2Na + H]$^+$. HRMS (-ESI); Calc. (found): C$_{27}$H$_{28}$LaN$_3$NaO$_{12}$: 748.0634 (748.0632) [M - 2Na + H]$^+$. Anal. Calc. (found): C$_{27}$H$_{27}$LaN$_3$Na$_3$O$_{12}$$\cdot$2H$_2$O: 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(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$_{29}$EuN$_3$O$_{12}$: 738.0950 (738.0938) [M - 3Na + 2H]$^+$.  

**Sodium tris(1-carboxyethyl-2-methyl-3-oxy-4-pyridinonato)gadolinium(III)**  

Na$_3$[Gd(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$_{29}$GdN$_3$O$_{12}$: 742.0978 (742.0972) [M - 3Na + 2H]$^+$.  

**Sodium tris(1-carboxyethyl-2-methyl-3-oxy-4-pyridinonato)lutetium(III),**

Na$_3$[Lu(8)$_3$]. $^1$H NMR (300 MHz, D$_2$O) $\delta$ = 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$_{28}$LuNa$_3$O$_{12}$: 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$_3$PO$_2$ (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$_3$XT•HCl, (0.502 g, 13%) $^1$H($^{31}$P) NMR (300 MHz, D$_2$O) $\delta$ = 4.20 (s, 8 H, N-CH$_2$-COOH), 3.58 (d, $J$ = 9.6 Hz, 4 H, N-CH$_2$-PO). $^{31}$P($^1$H) NMR (121 MHz, D$_2$O) $\delta$ = 18.75. MS (+ESI) m/z = 357.1 [M + H]$^+$. Anal. Calc. (found): C$_{10}$H$_{17}$N$_2$O$_{10}$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. H$_3$XT•HCl (40 mg, 0.10 mmol) and Ln(NO$_3$)$_3$•6H$_2$O (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$_2$O$_{10}$P: 528.8930 (528.8933) [M - K]$^-$.

K$_2$[Eu(XT)]. HRMS (-ESI); Calc. (found): C$_{10}$H$_{12}$Eu$^{151}$KN$_2$O$_{10}$P: 540.9065 (540.9062) [M - K]$^-$.

K$_2$[Lu(XT)]. HRMS (-ESI); Calc. (found): C$_{10}$H$_{12}$K$^{175}$LuN$_2$O$_{10}$P: 564.9275 (564.9279) [M - K]$^-$.
Determination of the Octanol-water Partition Coefficient ($P_{o/w}$)

The shake-flask method\textsuperscript{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\textsubscript{1}, H\textsubscript{2}, H\textsubscript{3}, H\textsubscript{4}, H\textsubscript{6}, H\textsubscript{8} and H\textsubscript{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 $\lambda_{\text{max}}$ 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 (\textit{vide infra}), and protein concentrations of the cell lysates cells were measured by a bicinchoninic acid protein assay (BCA Protein Assay Kit).\textsuperscript{7} A bovine serum albumin (BSA) calibration curve was constructed in the range of 25 $\mu$g/mL to 2000 $\mu$g/mL; aliquots of exactly 20 or 25 $\mu$L 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. 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. Eighty approximately 10 mg of ligand, HAP, metal complex and Ln(NO₃)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). Na₃[La₈] was dissolved in HEPES buffer (0.202 mmol), and H₈ 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 CuKα (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.

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<th>Compound</th>
<th>Nucleophile (amine)</th>
<th>Equivalent of amine</th>
<th>Yield (%)</th>
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<td>glycine</td>
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<td></td>
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<td>37</td>
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<td>4-amino-1-butanol</td>
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<td>59</td>
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<td>(±)-2-amino-3-methyl-1-butanol</td>
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<td>Bn6</td>
<td>(±)-2-amino-1-butanol</td>
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Table S.2. A comparison of $^1$H NMR spectral shifts for HL and La(L)$_3$.

![Diagram of the molecule](image)

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<th>Compound</th>
<th>Solvent</th>
<th>$H_a$</th>
<th>$H_b$</th>
<th>Ring CH$_3$ or N-CH</th>
<th>N-CH$_2$-CH$_2$</th>
<th>CH$_2$-CH$_2$-OH</th>
<th>CH$_2$-OH or CH-OH</th>
<th>alkyl-CH$_3$ or CH-CH</th>
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<td>D$_2$O</td>
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<td>3.85</td>
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<td>6.32</td>
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<td>7.07</td>
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<td>La(2)$_3$</td>
<td>D$_2$O</td>
<td>7.31</td>
<td>6.31</td>
<td>2.24</td>
<td>4.06</td>
<td>1.74 - 2.04</td>
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<tr>
<td>La(6)$_3$</td>
<td>CD$_3$OD</td>
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<td>6.46</td>
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<td>4.37</td>
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<td>4.18</td>
<td>2.53</td>
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Table S.3. Selected IR stretching frequencies of the free ligands and their lanthanide complexes.

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<tr>
<th>Compound</th>
<th>ν(_{\text{OH}})</th>
<th>ν(_{\text{C-CH}_3\ or\ CH}_2)</th>
<th>ν(_{\text{C=O or ring}})</th>
<th>ν(_{\text{C-O}})</th>
<th>ν(_{\text{C-N}})</th>
<th>ν(_{\text{M-O}})</th>
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</thead>
<tbody>
<tr>
<td>H1</td>
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<td>ν\textsubscript{C-H (CH\textsubscript{3} or CH\textsubscript{2})}</td>
<td>ν\textsubscript{C=O or ν\textsubscript{ring}}</td>
<td>ν\textsubscript{C-O}</td>
<td>ν\textsubscript{C-N}</td>
<td>ν\textsubscript{M-O}</td>
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<td>1283</td>
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<td>1286</td>
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<td>1584 1538 1498</td>
<td>1346</td>
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<td>-</td>
<td>1591 1544 1504</td>
<td>1348</td>
<td>1285</td>
<td>529 485 450</td>
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\textsuperscript{w} = weak
### Table S.4. Cytotoxicity data (MTT assay) for the free ligands in MG-63 cells, n = 3.

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<th>Compound</th>
<th>Functional group</th>
<th>EC$_{50}$ MG-63 Cell (µM)</th>
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<td>H2•HCl</td>
<td>propyl-OH</td>
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<td>H3•HCl</td>
<td>butyl-OH</td>
<td>&gt; 1268</td>
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<tr>
<td>H4</td>
<td>isopropyl-OH</td>
<td>&gt; 2729</td>
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<tr>
<td>H6</td>
<td>secbutyl-OH</td>
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<tr>
<td>H8</td>
<td>ethyl-carboxylate</td>
<td>&gt; 5071</td>
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<tr>
<td>H$_5$XT•HCl</td>
<td>phosphinate-EDTA derivative</td>
<td>&gt; 562</td>
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<tr>
<td>HL1</td>
<td>methyl</td>
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### Table S.5. Cytotoxicity data (MTT assay) for the Ln$^{3+}$ complexes in MG-63 cells, n = 3.

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<th>Compound</th>
<th>Functional group</th>
<th>EC$_{50}$ MG-63 Cell (µM)</th>
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</thead>
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<td>Eu(1)$_3$</td>
<td>ethyl-OH</td>
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<tr>
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<td>&gt; 1400</td>
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<td>La(2)$_3$</td>
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<td>propyl-OH</td>
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<td>La(3)$_3$</td>
<td>butyl-OH</td>
<td>&gt; 131</td>
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<tr>
<td>La(4)$_3$</td>
<td>isopropyl-OH</td>
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<tr>
<td>Eu(4)$_3$</td>
<td>isopropyl-OH</td>
<td>&gt; 136</td>
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<td>Gd(4)$_3$</td>
<td>isopropyl-OH</td>
<td>&gt; 676</td>
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<td>Na$_3$[La(7)$_3$]</td>
<td>methyl-carboxylate</td>
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<tr>
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<td>&gt; 1209</td>
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<td>K$_2$[Lu(XT)]</td>
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<td>methyl</td>
<td>&gt; 102</td>
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**Figure S.1.** The stepwise acid dissociation (pK$_{an}$) equilibria of the 3-hydroxy-4-pyridinones, where pK$_{an}$ = -logK$_{an}$.
**Figure S.2.** Speciation diagrams for solutions containing 1 mM M$^{3+}$ and 3 mM HLL: a) La$^{3+}$; b) Gd$^{3+}$. 
Figure S.3. Speciation diagrams for solutions containing 1 mM La$^{3+}$ and 1 mM H$_3$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$^{3+}$. 
References