Supporting Information for

Role of the capping bond effect on pyclen $^{nat}Y^{3+}/^{90}Y^{3+}$ chelates: full control of the regiospecific *N*-functionalisation makes the difference

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33 pages

Summary

- Materials and methods

Reagents were purchased from ACROS Organics and from Aldrich Chemical Co and used without further purification. Pyclen·3HCl was provided by Guerbet (Aulnay-sous-bois, France). All solvents were dried and distilled prior to use according to standard methods. Pyclen-Boc (**5**)[1] and methyl 6-(chloromethyl)picolinate[2] were synthesised as previously described. Analytic HPLC was performed on a Prominence Shimadzu HPLC/LCMS-2020 equipped with a UV SPD-20 A detector. The chromatographic system employs semi-preparative HPLC (VisionHT C18 HL 5µm 250 × 10 mm) with either H_2O - MeCN (v/v) or H_2O (0.1% HCl) - MeCN as eluents at a flow rate of 5 mL/min and UV detection at 254 and 350 nm. The following method was used: 100% H_2O for 5 minutes, up to 90% MeCN in 20 minutes and 90% MeCN for 5 minutes.

NMR spectra were recorded at the "Services communs" of the University of Brest. ^1H and ^{13}C NMR spectra were recorded using Bruker Avance 500 (500 MHz), Bruker Avance 400 (400 MHz), or BrukerAMX-3 300 (300 MHz) spectrometers. HRMS analyses were realised on a HRMS Q-Tof MaXis, sources ESI, APCI, APPI, nano-ESI (at the Institute of Organic and Analytic Chemistry – ICOA in Orléans).

- Synthesis of **L1** and NMR spectra

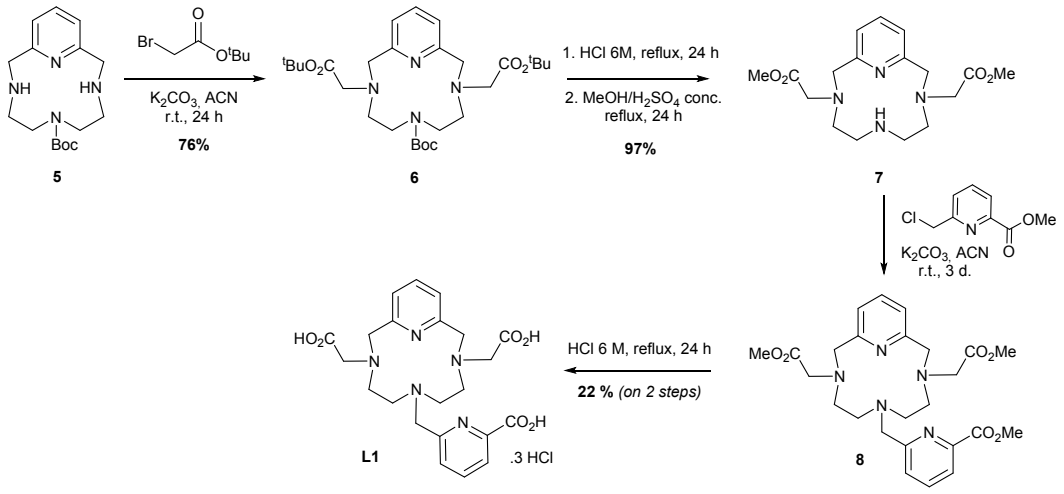


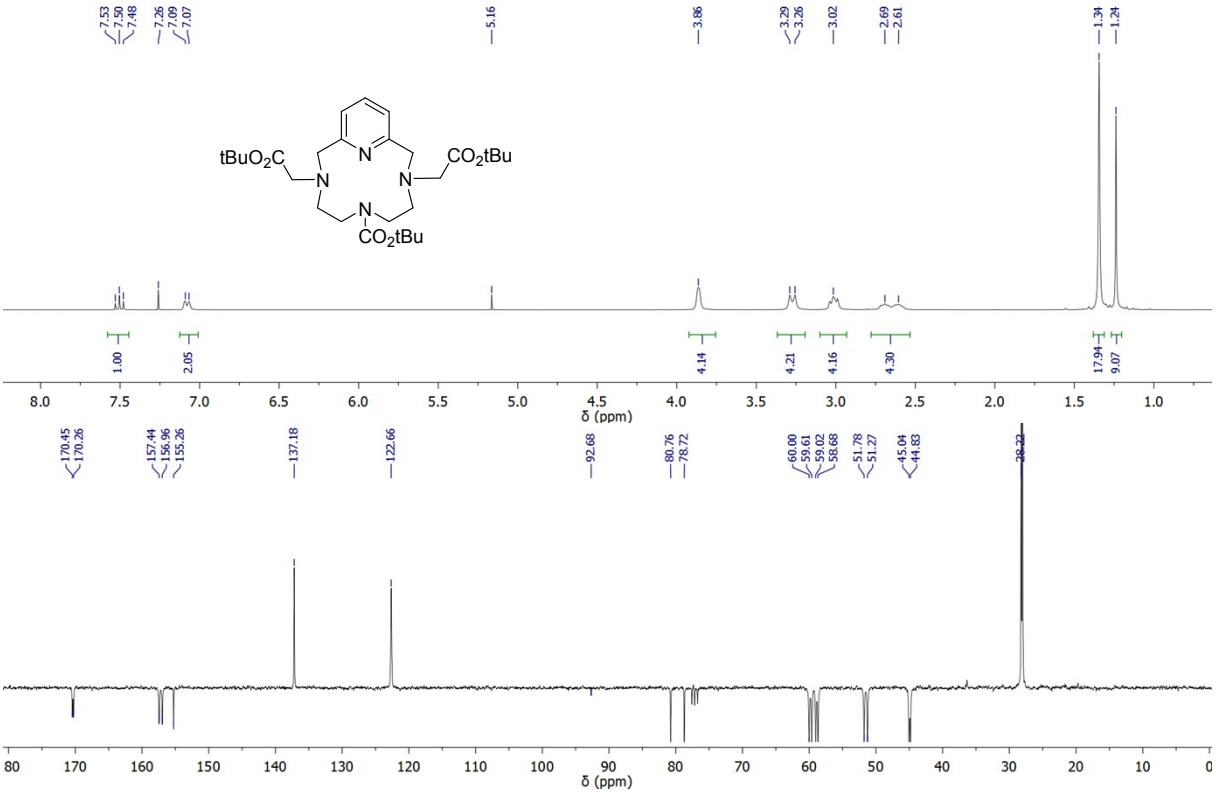
Figure S1. Synthetic route for the synthesis of **L1**.

. Compound 6.

A solution of *tert*-butyl bromoacetate (1.022 g, 5.24 mmol) in dry acetonitrile (50 mL) was added to a solution of compound **5** (0.803 g, 2.62 mmol) and K_2CO_3 (1.45 g, 10.5 mmol) in dry acetonitrile (150 mL). The reaction mixture was stirred at r.t. for 24h. The solvent was evaporated and the residue was taken up in dichloromethane, filtered and concentrated. The crude product was purified by column chromatography using silica gel (CH_2Cl_2/MeOH: 100/0 to 98/2) yielding compound **6** as a yellow oil (1.06 g, 76 %).

^1H NMR (300 MHz, $CDCl_3$): δ 7.5 (t, 1H, ^3J = 7.5 Hz), 7.08 (d, 2H, ^3J = 7.5 Hz), 3.86 (s, br, 4H), 3.27 (d, 4H, ^3J = 9.4 Hz), 3.01 (m, 4H), 2.75-2.55 (m, 4H), 1.34 (s, 18H), 1.24 (s, 9H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 170.45, 170.27, 157.44, 156.97, 155.26, 137.18, 122.67, 122.61, 80.75, 78.71, 59.99, 59.60, 59.02, 58.67, 51.77, 51.27, 45.04, 44.81, 28.21, 28.03.



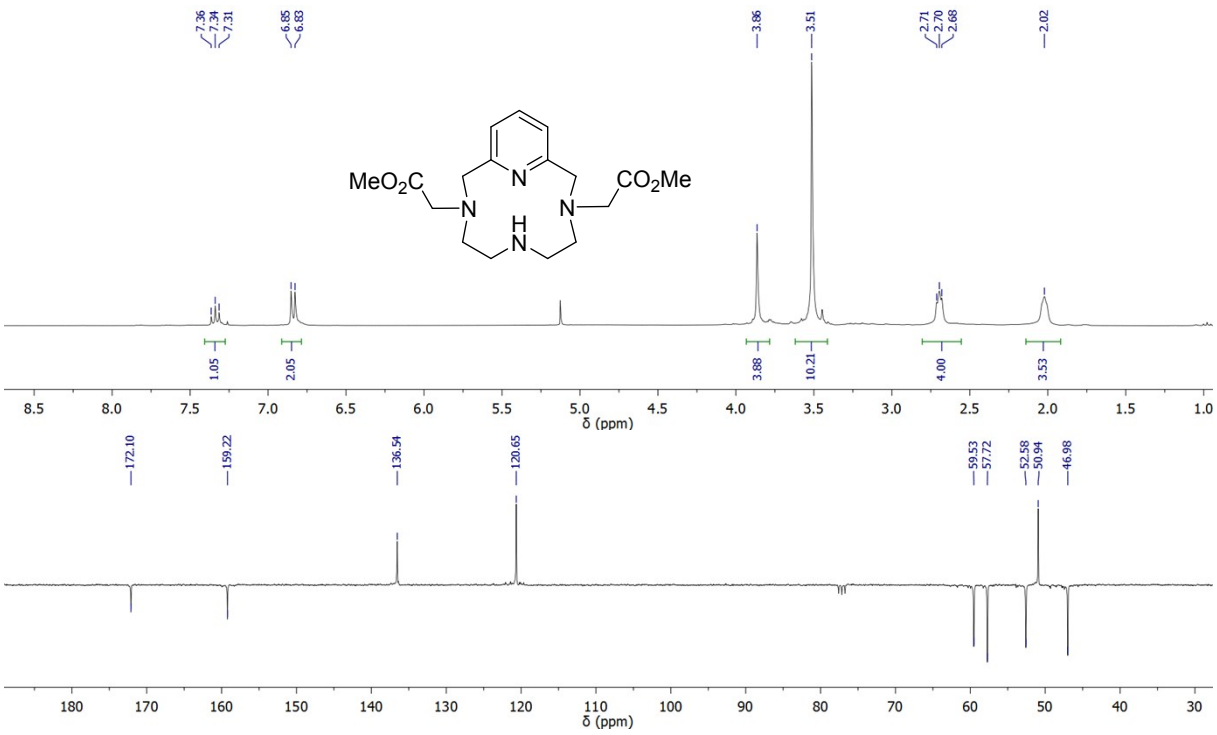
^{1}H and ^{13}C NMR spectra of compound **6** (300MHz, $CDCl_3$, 298K)

. Compound 7

Compound **6** (1.06 g, 1.98 mmol) was dissolved in hydrochloric acid (20 mL, 6 M) and the mixture was refluxed overnight. After cooling to r.t., the solvent was evaporated. The resulting solid was dissolved in MeOH and concentrated sulfuric acid (5 mL) was slowly added. The mixture was heated to reflux overnight. After cooling to r.t., the solvent was evaporated, water (10 mL) was added and the pH was adjusted to **7** with K_2CO_3. Water was evaporated and the residue was taken up in dichloromethane. Magnesium sulfate was added and the organic layer was filtered and concentrated. Compound **7** was obtained as a yellow oil (0.67 g, 97 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (t, 1H, ^{3}J = 7.5 Hz), 6.84 (d, 2H, ^{3}J = 7.5 Hz), 3.86 (s, 4H), 3.51 (s, 10H), 2.69 (m, 4H), 2.02 (m, 4H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 172.12, 159.24, 136.56, 120.66, 59.54, 57.73, 52.59, 50.95, 46.99.



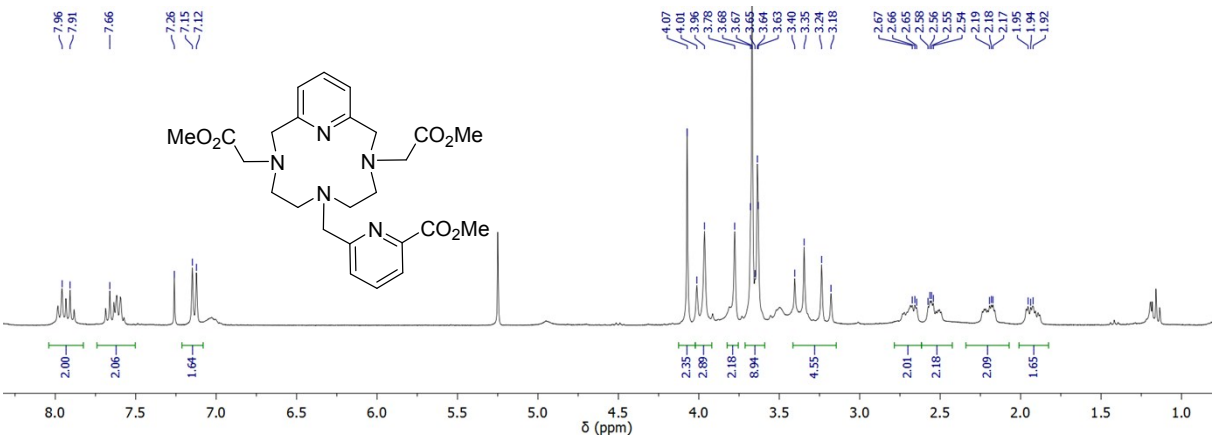
^{1}H and ^{13}C NMR spectra of compound **7** (300MHz, $CDCl_3$, 298K)

. Compound 8

6-Chloromethylpyridine-2-carboxylic acid methylester (0.353 g, 1.9 mmol) was added to a solution of **7** (0.67 mg, 1.9 mmol) in acetonitrile (50 mL) in the presence of K_2CO_3 (0.524 g, 3.8 mmol). The reaction mixture was stirred at r.t. for 2 days and the solvent was evaporated. The residue was taken up in dichloromethane and the salts were removed by filtration. The filtrate was concentrated. The product was engaged in the next step without further purification.

NMR: ^{1}H and ^{13}C NMR spectra couldn't be described because of their complexity.

ESI-HR-MS (positive, H_2O) *m/z* calcd. for $[C_{25}H_{34}N_5O_6]^+$, 500.2504; found 500.2502 $[M + H]^+$, calcd. for $[C_{25}H_{33}N_5O_6Na]^+$, 522.2323; found 522.2319 $[M + Na]^+$, calcd. for $[C_{25}H_{35}N_5O_6]^{2+}$, 250.6288; found 250.6288 $[M + 2H]^{2+}$.



^{1}H and ^{13}C NMR spectra of compound **8** (300MHz, $CDCl_3$, 298K)

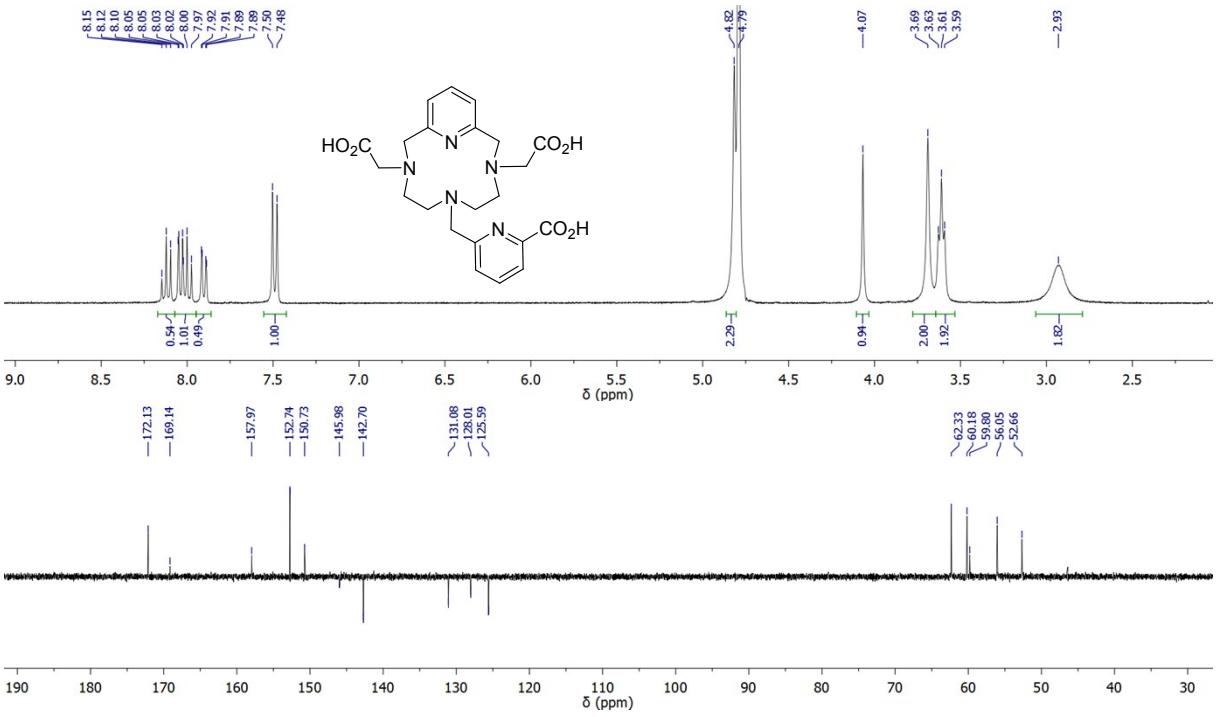
. Ligand L1

Hydrochloric acid (20 mL, 6 M) was added to compound **8** and the mixture was refluxed overnight. The solvent was evaporated and the crude product was purified by HPLC (C18, H_2O 0.1% HCl /ACN: 100/0 to 10/90) to yield **L1** as a colourless oil (0.237 g, 22% calcd. from **7** for 3 HCl).

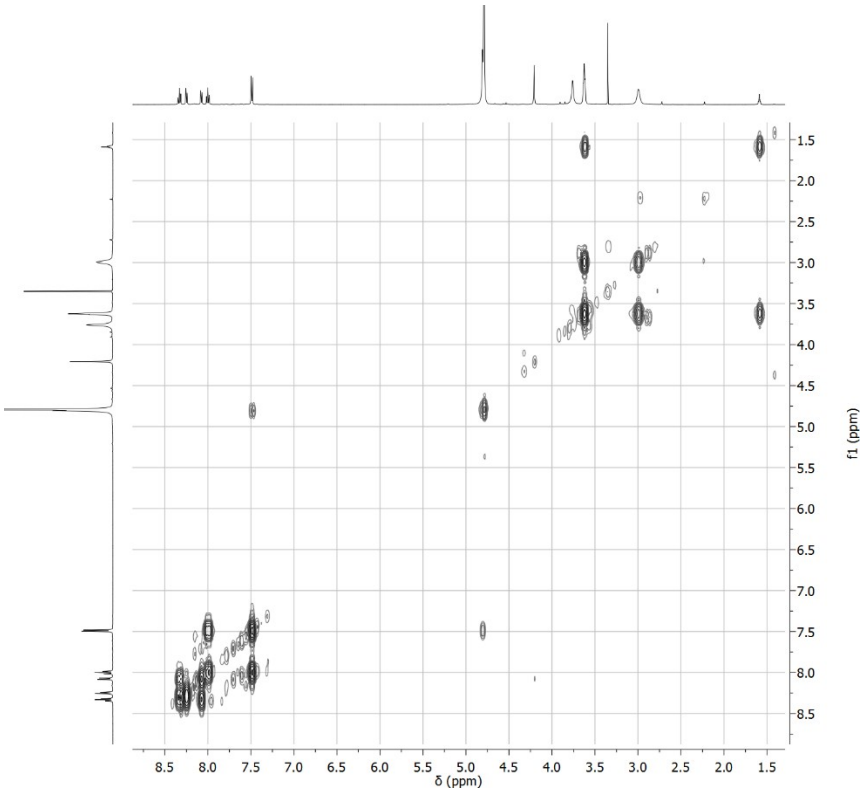
^{1}H NMR (500.25 MHz, D_2O): δ 8.12 (t, 1H, ^{3}J = 7.8 Hz), 8.04 (d, 1H, ^{3}J = 7.8 Hz), 7.99 (d, 1H, ^{3}J = 7.8 Hz), 7.90 (t, 1H, ^{3}J = 7.8 Hz), 7.49 (d, 2H, ^{3}J = 7.8 Hz), 4.82 (s, 4H), 4.07 (s, 2H), 3.69 (s, 4H), 3.61 (m, 4H), 2.93 (s, br, 4H).

^{13}C NMR (125.79 MHz, D_2O): δ 172.17, 168.64, 157.78, 152.89, 150.25, 146.36, 142.80, 131.30, 128.33, 125.60, 62.35, 60.08, 59.47, 56.09, 52.88.

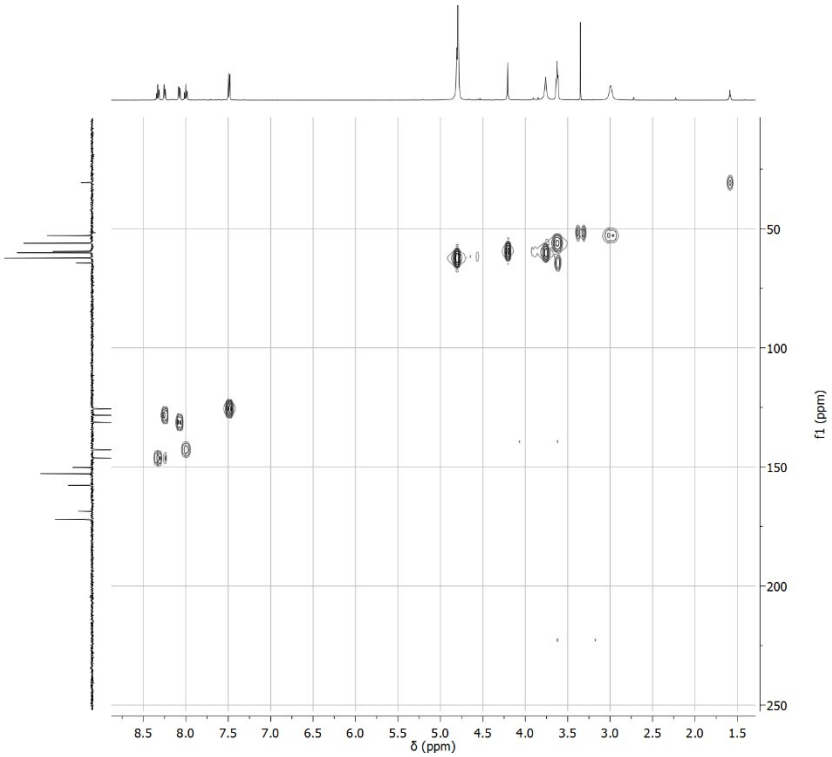
ESI-HR-MS (positive, H_2O) *m/z* calcd. for $[C_{22}H_{28}N_5O_6]^+$, 458.2034; found 458.2032 $[M + H]^+$, calcd. for $[C_{22}H_{29}N_5O_6]^{2+}$, 229.6053; found 229.6054 $[M + 2H]^{2+}$.



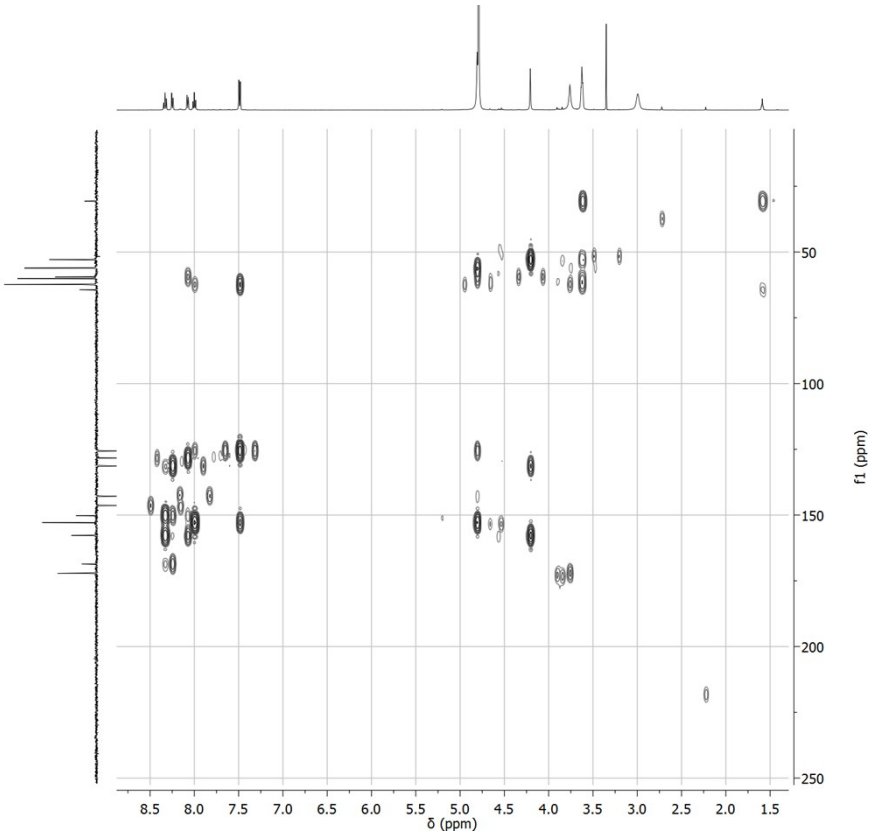
^{1}H and ^{13}C NMR spectra of **L1** (300MHz, D_2O, 298K)



^{1}H-^{1}H COSY experiment of **L1** (D_2O, 500 MHz, 298K)



^{1}H-^{13}C HMQC experiment of **L1** (D_2O, 500 MHz, 298K)



^{1}H-^{13}C HMBC experiment of **L1** (D_2O, 500 MHz, 298K)

- Synthesis of **L2** and NMR spectra

. Pyclen base

Pyclen·3HCl (10 g, 31.36 mmol) was dissolved in water (10 mL) and a concentrated solution of NaOH (10 M, 20 mL) was added. The mixture was stirred for 1h and concentrated under vacuum. The white powder was dried at 100ºC overnight. Acetonitrile was added, the mixture was filtered and the filtrate was concentrated to yield pyclen base as a white powder (5.88 g, 91 %).

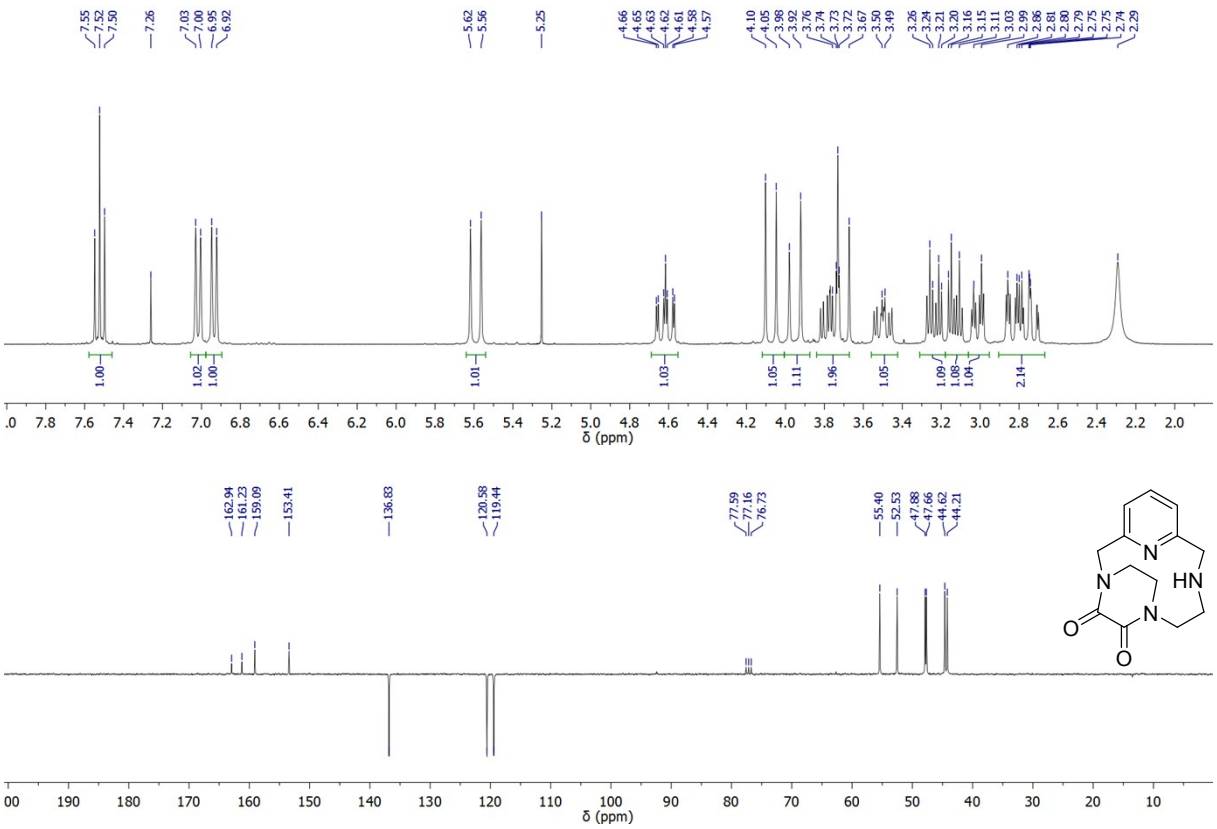
. Pyclen oxalate (1)

A solution of diethyloxalate (4.21 g, 28.49 mmol) in MeOH (100 mL) was added to a solution of pyclen base (5.88 g, 28.49 mmol) in MeOH (200 mL). The reaction mixture was stirred at r.t. overnight and then concentrated. The residue was taken in dichloromethane, filtered and concentrated to remove the remaining pyclen. The solid was dissolved in a small amount of methanol. A large amount of ethyl acetate was then added. Crystals were formed and filtered to yield compound **1** (6.28 g, 85 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (t, 1H, ^{3}J = 7.7 Hz), 7.02 (d, 1H, ^{3}J = 7.9 Hz), 6.93 (d, 1H, ^{3}J = 7.5 Hz), 5.59 (d, 1H, ^{2}J = 16.2 Hz), 4.62 (ddd, 1H, ^{2}J = 13.9 Hz, ^{3}J = 11.1 Hz, ^{3}J = 2.5 Hz), 4.08 (d, 1H, ^{2}J = 16.6 Hz), 3.95 (d, 1H, ^{2}J = 17.3 Hz), 3.77 (ddd, 1H, ^{2}J = 13.9 Hz, ^{3}J = 10.6 Hz, ^{3}J = 4.52 Hz), 3.70 (d, 1H, ^{2}J = 17.3 Hz), 3.5 (ddd, 1H, ^{2}J = 12.4 Hz, ^{3}J = 10.6 Hz, ^{3}J = 4.5 Hz), 3.24 (dt, 1H, ^{2}J = 13.9 Hz, ^{3}J = 4.4 Hz), 3.13 (dt, 1H, ^{2}J = 12.4 Hz, ^{3}J = 4.1 Hz), 3.01 (dt, 1H, ^{2}J = 12.2 Hz, ^{3}J = 3.2 Hz), 2.83 (dt, 1H, ^{2}J = 13.9 Hz, ^{3}J = 3.0 Hz), 2.74 (td, 1H, ^{2}J = 11.7 Hz, ^{3}J = 2.3 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 162.96, 161.23, 159.10, 153.42, 136.83, 120.58, 119.44, 55.40, 52.53, 47.89, 47.66, 44.61, 44.20.

ESI-HR-MS (positive, H_2O) *m/z* calcd. for $[C_{13}H_{17}N_4O_2]^+$, 261.1346; found 261.1346 $[M + H]^+$.



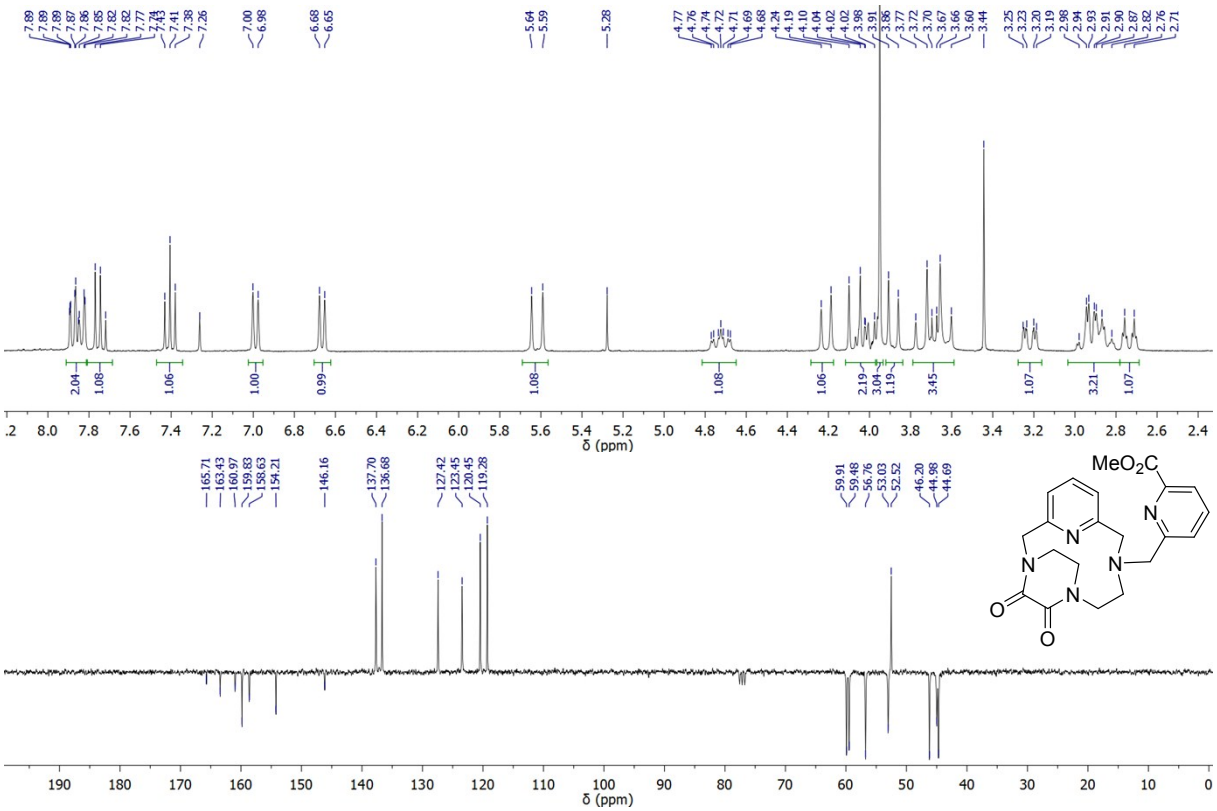
^{1}H and ^{13}C NMR spectra of compound **1** (300MHz, $CDCl_3$, 298K)

. Compound 2

6-Chloromethylpyridine-2-carboxylic acid methylester (711 mg, 3.85 mmol) was added to a solution of compound **9** (1.0 g, 3.85 mmol) in acetonitrile (300 mL) in the presence of K_2CO_3 (1.5 g, 12 mmol). The reaction mixture was refluxed for four days, then filtered and concentrated. The crude product was purified by column chromatography using neutral alumina (CH_2Cl_2/MeOH 98/2) yielding compound **2** as a yellow oil (1.56 g, 99 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90-7.80 (m, 2H), 7.72 (t, 1H, ^{3}J = 7.91 Hz), 7.38 (t, 1H, ^{3}J = 7.72 Hz), 6.97 (d, 1H, ^{3}J = 7.91 Hz), 6.65 (d, 1H, ^{3}J = 7.54 Hz), 5.59 (d, 1H, ^{2}J = 16.20 Hz), 4.70 (m, 1H), 4.19 (d, 1H, ^{2}J = 14.3 Hz), 4.12-3.92 (m, 2H), 3.93 (s, 3H), 3.86 (d, 1H, ^{2}J = 14.3 Hz), 3.77-3.54 (m, 3H), 3.20 (m, 1H), 2.99-2.76 (m, 3H), 2.72 (m, 1H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 165.71, 163.43, 160.97, 159.82, 158.63, 154.21, 146.15, 137.69, 136.67, 127.42, 123.44, 120.45, 119.28, 59.90, 59.47, 56.75, 53.02, 52.51, 46.19, 44.97, 44.68.



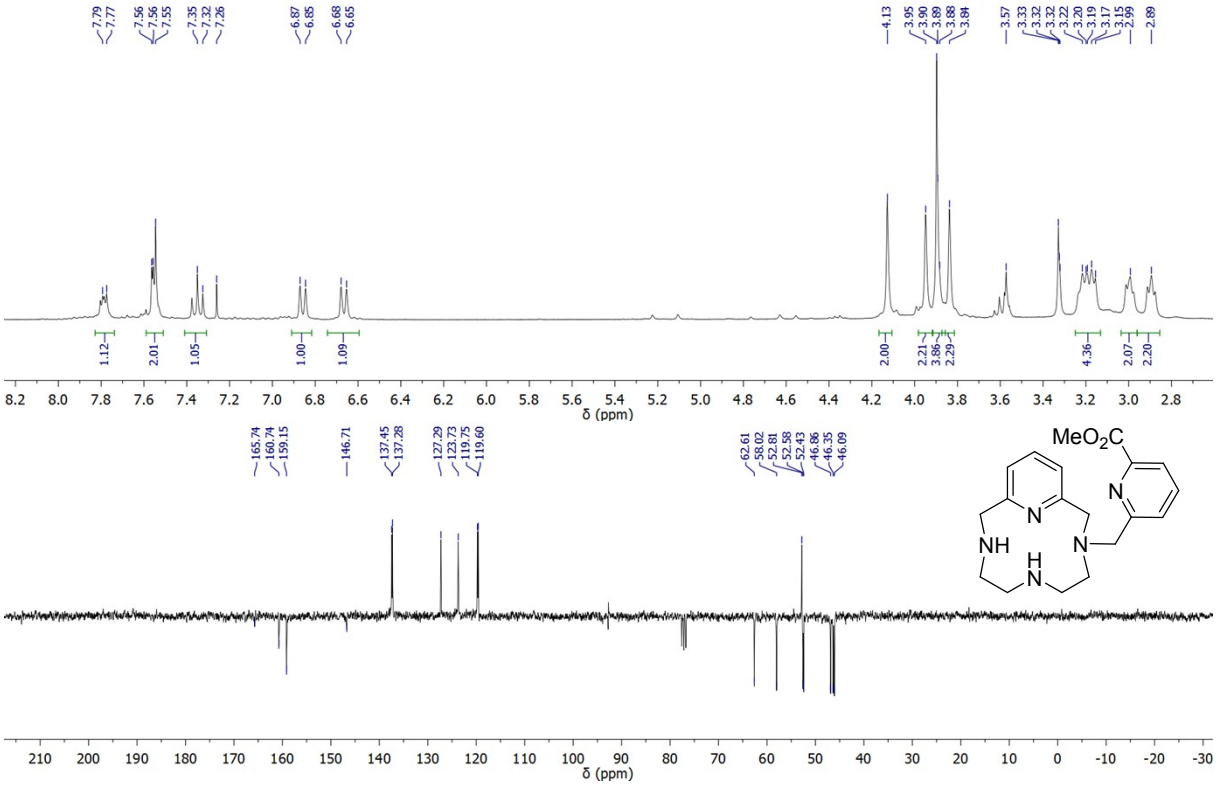
^{1}H and ^{13}C NMR spectra of compound **2** (300MHz, $CDCl_3$, 298K)

. Compound 3

Compound **2** (1.34 g, 3.27 mmol) was dissolved in MeOH (40 mL) and concentrated sulfuric acid was slowly added (1 mL). The mixture was refluxed for 24h. After cooling to r.t., the solvent was evaporated. 20 mL of water were added and the pH was adjusted to 7 using K_2CO_3. Water was evaporated and the residue was taken up in dichloromethane. Magnesium sulfate was added and the organic layer was filtered and then concentrated. The crude product was purified by column chromatography using neutral alumina (CH_2Cl_2/MeOH: 98/2 to 95/5) yielding compound **3** as a yellow oil (0.727 g, 63 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (m, 1H), 7.55 (m, 2H), 7.35 (t, 1H, ^{3}J = 7.8 Hz), 6.85 (d, 1H, ^{3}J = 7.8 Hz), 6.66 (d, 1H, ^{3}J = 7.5 Hz), 4.13 (s, 2H), 3.95 (s, 2H), 3.89 (s, 3H), 3.84 (s, 2H), 3.19 (m, 4H), 2.98 (m, 2H), 2.89 (m, 2H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 165.74, 160.74, 159.15, 146.71, 137.45, 137.28, 127.29, 123.73, 119.75, 119.60, 62.61, 58.02, 52.81 52.58, 52.43, 46.86, 46.35, 46.09.



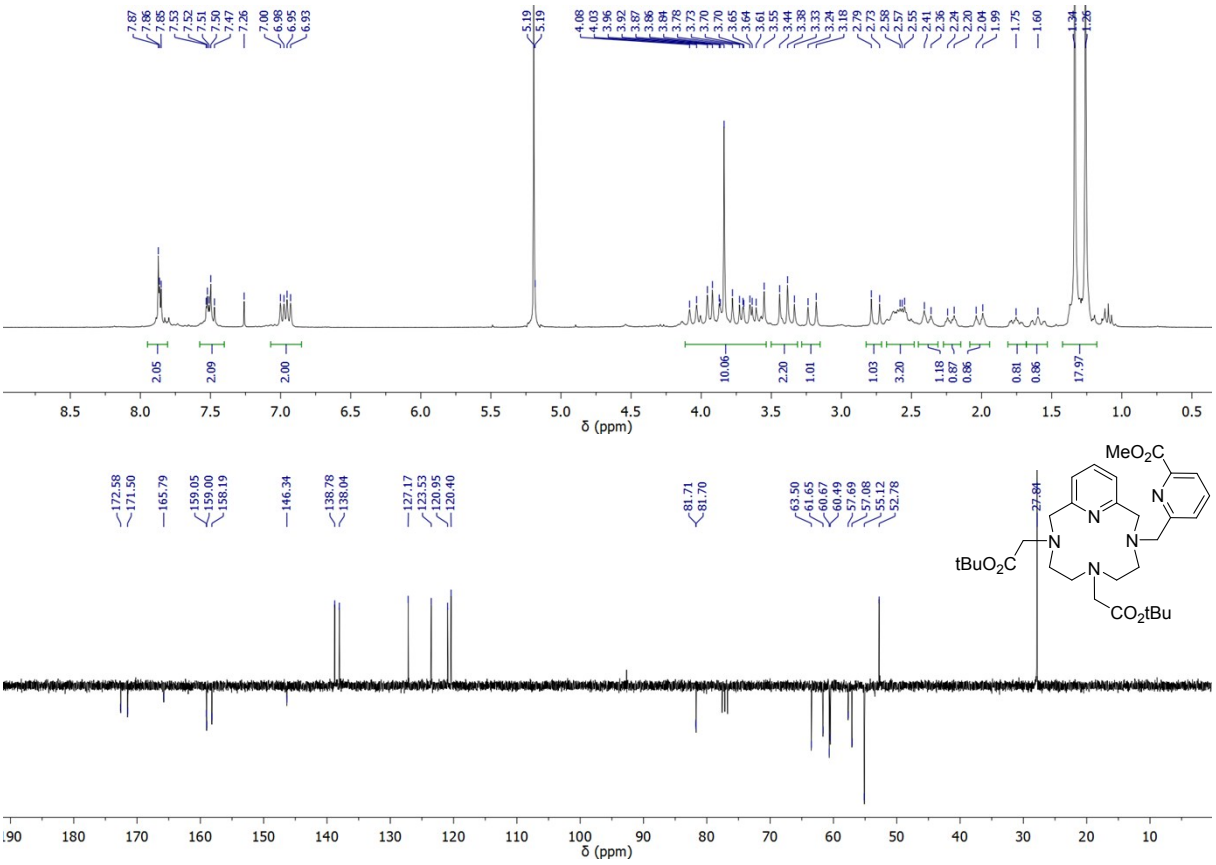
^{1}H and ^{13}C NMR spectra of compound **3** (300MHz, $CDCl_3$, 298K)

. Compound 4

A solution of *tert*-butyl bromoacetate (0.774 g, 4.09 mmol) in acetonitrile (150 mL) was added to a mixture of compound **3** (0.706 g, 1.99 mmol) and K_2CO_3 (0.850 g, 6.15 mmol) in acetonitrile (150 mL). The reaction mixture was refluxed for two days. The solvent was evaporated, the residue was taken up in dichloromethane, filtered and concentrated. The crude product was purified by column chromatography using neutral alumina (CH_2Cl_2/MeOH: 98/2 to 95/5) yielding **4** as a yellow oil (0.821 g, 71 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ the ^{1}H NMR spectrum couldn't be described because of its complexity.

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 172.58, 171.50, 165.79, 159.05, 159.00, 158.19, 146.34, 138.78, 138.04, 127.17, 123.53, 120.95, 120.40, 81.71, 81.70, 63.50, 61.65, 60.67, 60.49, 57.69, 57.08, 55.12, 52.78, 27.84.



^{1}H and ^{13}C NMR spectra of compound **4** (300MHz, $CDCl_3$, 298K)

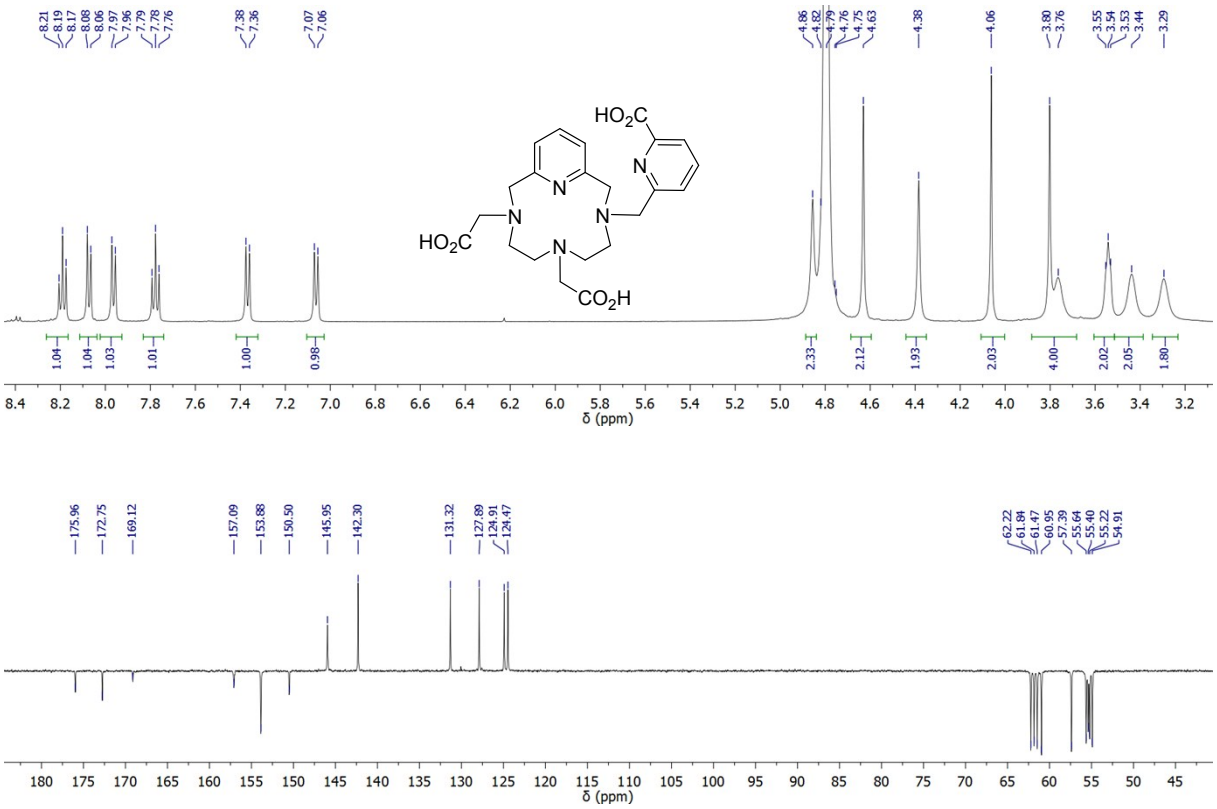
. Ligand L2

Hydrochloric acid (20 mL, 6 M) was slowly added to compound **4** (0.821 g, 1.41 mmol). The reaction mixture was refluxed for 24h and then concentrated. The crude product was purified using HPLC-C18 (H_2O 0.1% HCl/acetonitrile: 90/10 to 5/95) and the ligand **L2** was obtained as a colorless oil (0.346 g, 43 % calcd. for 3 HCl).

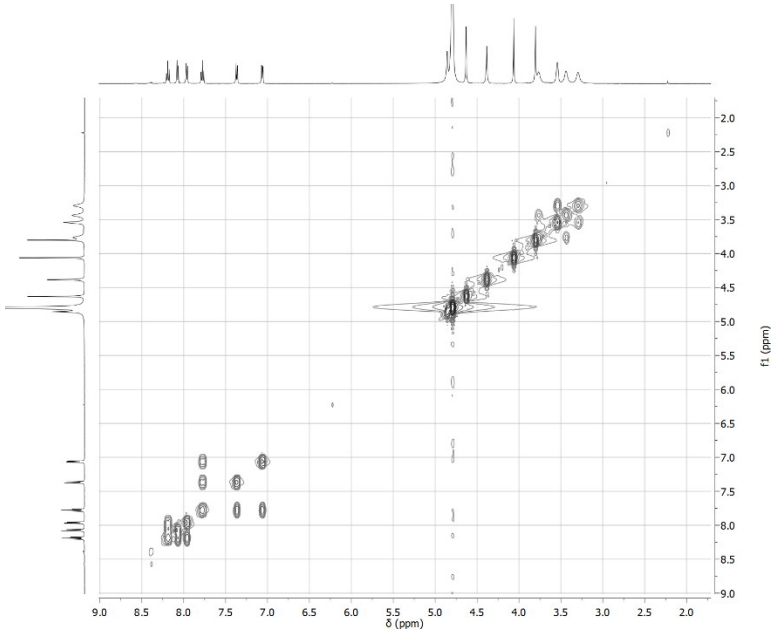
^{1}H NMR (500 MHz, D_2O): δ 8.19 (t, 1H, ^{3}J = 7.9Hz), 8.07 (d, 1H, ^{3}J = 7.9Hz), 7.96 (d, 1H, ^{3}J = 7.9Hz), 7.78 (t, 1H, ^{3}J = 7.9Hz), 7.37 (d, 1H, ^{3}J = 7.9Hz), 7.06 (d, 1H, ^{3}J = 7.9Hz), 4.86 (s, 2H), 4.63 (s, 2H), 4.38 (s, 2H), 4.06 (s, 2H), 3.80 (s, 2H), 3.77 (m, 2H), 3.54 (m, 2H), 3.44 (m, 2H), 3.29 (m, 2H).

^{13}C NMR (125.77 MHz, D_2O): δ 175.98, 172.77, 169.14, 157.10, 153.90, 153.90, 150.52, 145.97, 142.32, 131.34, 127.90, 124.93, 124.48, 62.23, 61.85, 61.47, 60.96, 57.39, 55.64, 55.40, 55.23, 54.91.

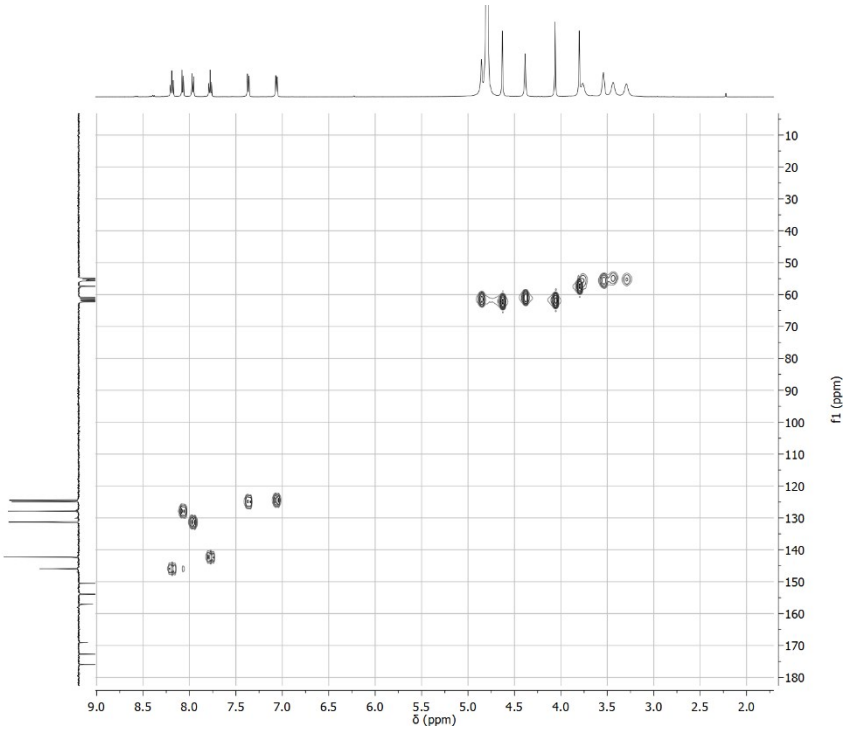
ESI-HR-MS (positive, H_2O) *m/z* calcd. for $[C_{22}H_{28}N_5O_6]^+$, 458.2034; found 458.2035 $[M + H]^+$, calcd. for $[C_{22}H_{29}N_5O_6]^{2+}$, 229.6053; found 229.6057 $[M + 2H]^{2+}$.



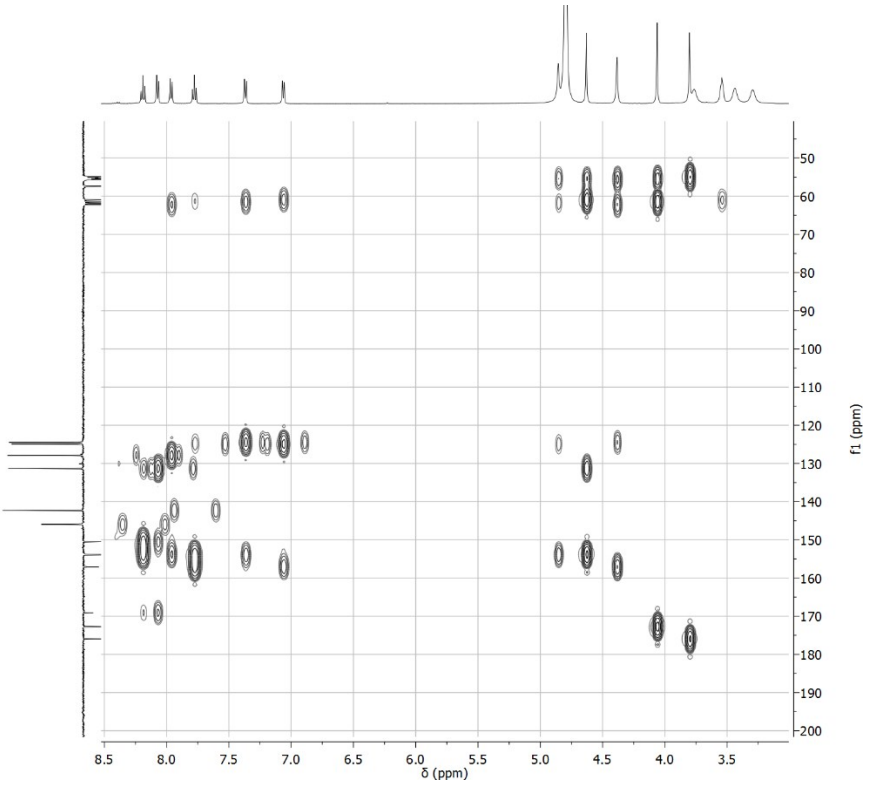
^{1}H and ^{13}C NMR spectra of **L2** (300MHz, D_2O, 298K)



^{1}H-^{1}H COSY experiment of **L2** (D_2O, 500 MHz, 298K)



^{1}H-^{13}C HMQC experiment of **L2** (D_2O, 500 MHz, 298K)



^{1}H-^{13}C HMBC experiment of **L2** (D_2O, 500 MHz, 298K)

- General procedure for preparation of [YL] chelates and NMR spectra

L·3HCl was dissolved in H_2O (5 mL) and the pH adjusted to 5 with a solution of KOH 1 M. A solution of $YCl_3 \cdot 6H_2O$ (~1.5 equiv.) in H_2O (2 mL) was added to the ligand solution. The mixture was refluxed overnight and then concentrated. The complex was obtained after purification by HPLC-C18 (H_2O/acetonitrile 100/0 to 10/90).

. [YL2(H_2O)] **complex**

L2.3HCl (30.0 mg, 0.053 mmol), $YCl_3.6H_2O$ (24.0 mg, 0.079 mmol)

Yield: 28.0 mg, 94%

^{1}H NMR (500.25 MHz, D_2O): δ 8.13 (t, 1H, ^3J = 7.8 Hz), 7.86 (d, 1H, ^3J = 7.8 Hz), 7.81 (t, 1H, ^3J = 7.8 Hz), 7.75 (d, 1H, ^3J = 7.8 Hz), 7.36 (d, 1H, ^3J = 7.8 Hz), 7.13 (d, 1H, ^3J = 7.8 Hz), 4.83 (d, 1H, ^2J = 16.0 Hz), 4.49 (d, 1H, ^2J = 14.7 Hz), 4.29 (d, 1H, ^2J = 14.7 Hz), 4.15 (d, 1H, ^2J = 16.0 Hz), 4.10 (m, 3H), 3.88 (d, 1H, ^2J = 16.7 Hz), 3.54 (d, 1H, ^2J = 16.2 Hz), 3.47 (m, 1H), 3.10 (d, 1H, ^2J = 16.7 Hz), 3.07 (m, 1H), 2.94 (m, 1H), 2.89 (m, 1H), 2.68 (m, 1H), 2.60 (m, 2H), 1.89 (m, 1H).

^{13}C NMR (125.79 MHz, D_2O): δ 183.42, 182.93, 174.79, 162.30, 160.81, 159.29, 153.07, 144.78, 143.34, 129.50, 126.38, 123.75, 122.63, 66.34, 65.80, 65.52, 65.01, 64.27, 63.93, 60.16, 59.54, 59.46,

ESI-HR-MS (positive, H_2O) *m/z* calcd. for $[C_{22}H_{25}YN_5O_6]^+$, 544.0858; found 544.0859 $[M + H]^+$, calcd. for $[C_{22}H_{26}YN_5O_6]^{2+}$, 272.5465; found 272.5469 $[M + 2H]^{2+}$.

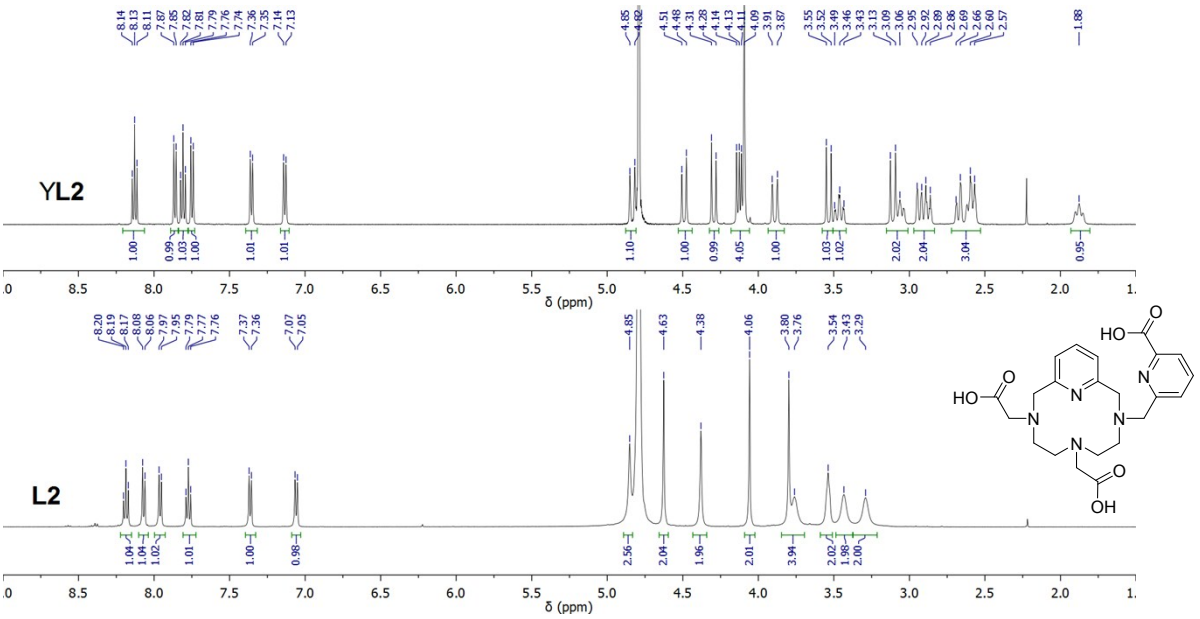
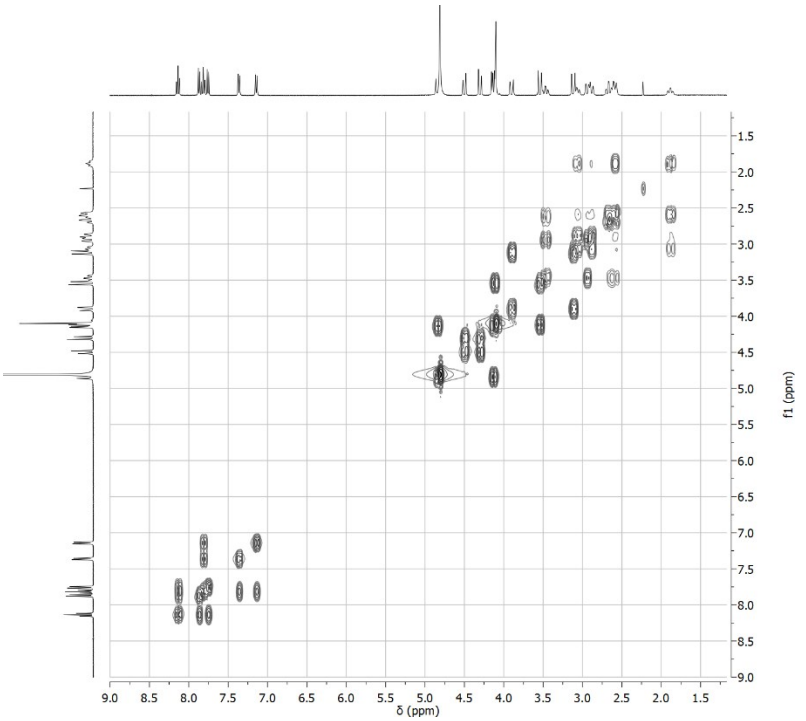
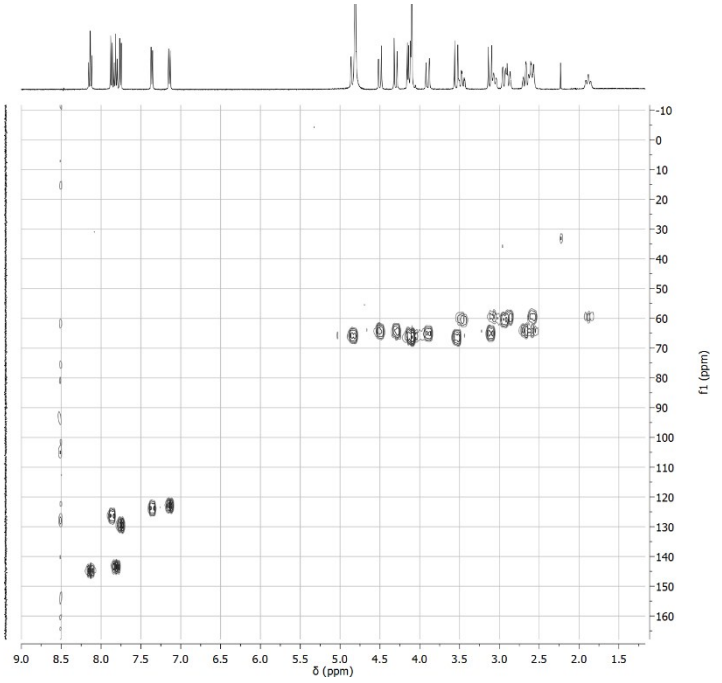


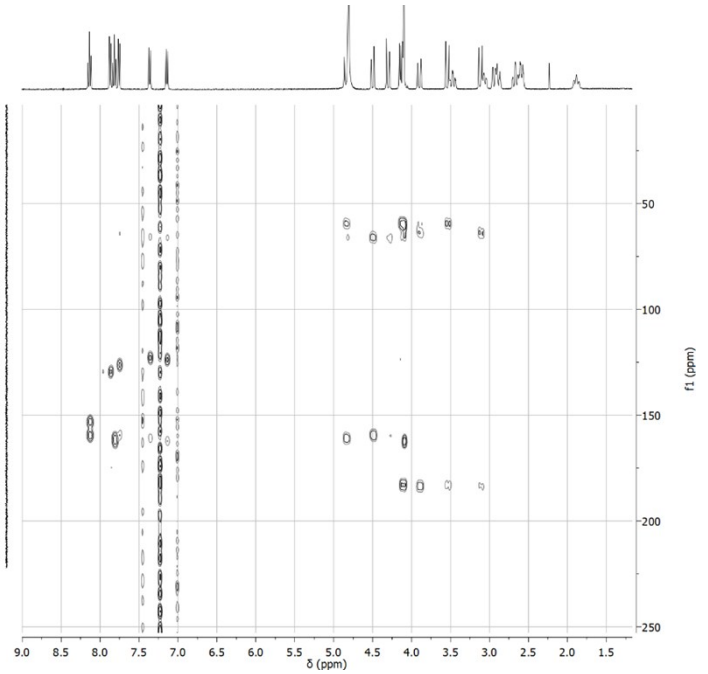
Figure S2. ^{1}H NMR spectra (298 K, D_2O, 500 MHz) of **L2** and its Yttrium (III) complex Y**L2**.



^{1}H-^{1}H COSY experiment of Y**L2** (D_2O, 500 MHz, 298K)



^{1}H-^{13}C HMQC experiment of Y**L2** (D_2O, 500 MHz, 298K)



^{1}H-^{13}C HMBC experiment of Y**L2** (D_2O, 500 MHz, 298K)

. [**YL1**(H_2O)] **complex**

L1.3HCl (27.2 mg, 0.048 mmol), $YCl_3.6H_2O$ (25.0 mg, 0.082 mmol)

Yield: 24.5 mg, 91%

^{1}H NMR (500.25 MHz, D_2O, 328 K): δ 8.19 (t, 1H, ^{3}J = 7.78 Hz), 8.11 (d, 1H, ^{3}J = 7.78 Hz), 8.01 (t, 1H, ^{3}J =7.78 Hz), 7.69 (d, 1H, ^{3}J = 7.78 Hz), 7.44 (d, 2H, ^{3}J =7.78 Hz), 4.58 (d, 2H, ^{2}J = 17.40 Hz), 4.21 (s, 2H), 4.11 (d, 2H, ^{2}J = 17.40 Hz), 3.56 (d, 2H, J = 16.02 Hz), 3.04 (m, 2H), 2.74 (m, 6H), 2.16 (s, br, 2H).

^{13}C NMR (125.79 MHz, D_2O, 328 K): δ 181.79, 161.70, 160.97, 153.24, 144.85, 144.06, 127.82, 126.72, 123.72, 67.19, 66.24, 66.24, 65.40, 62.66, 60.32.

ESI-HR-MS (positive, H_2O) *m/z* calcd. for $[C_{22}H_{25}YN_5O_6]^{+}$, 544.0858; found 544.0858 [M + H]$^{+}$, calcd. for $[C_{22}H_{26}YN_5O_6]^{2+}$, 272.5465; found 272.5469 [M + 2H]$^{2+}$.

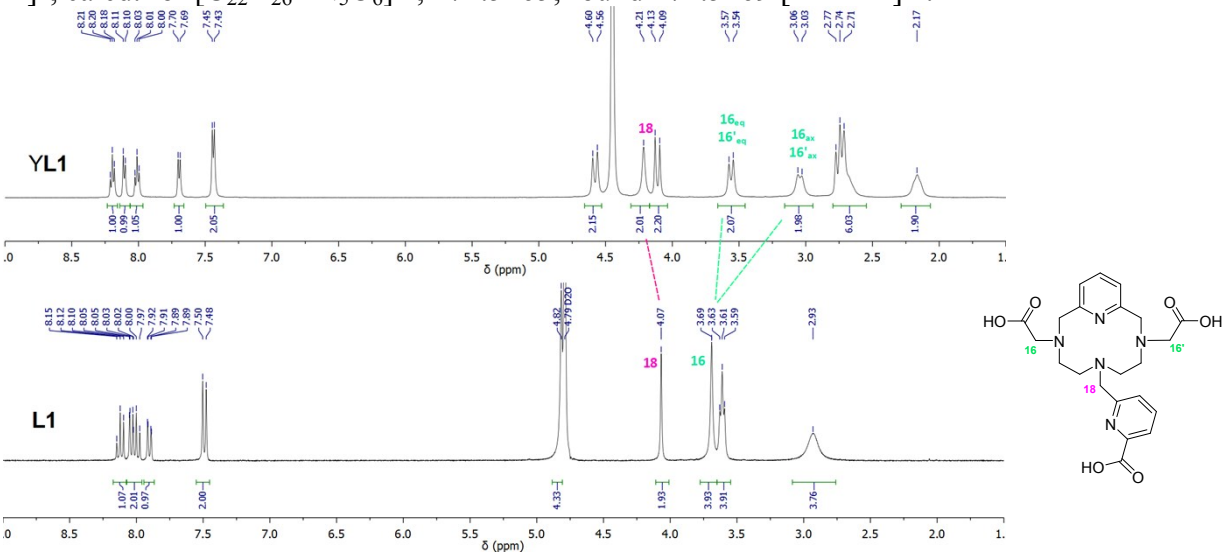
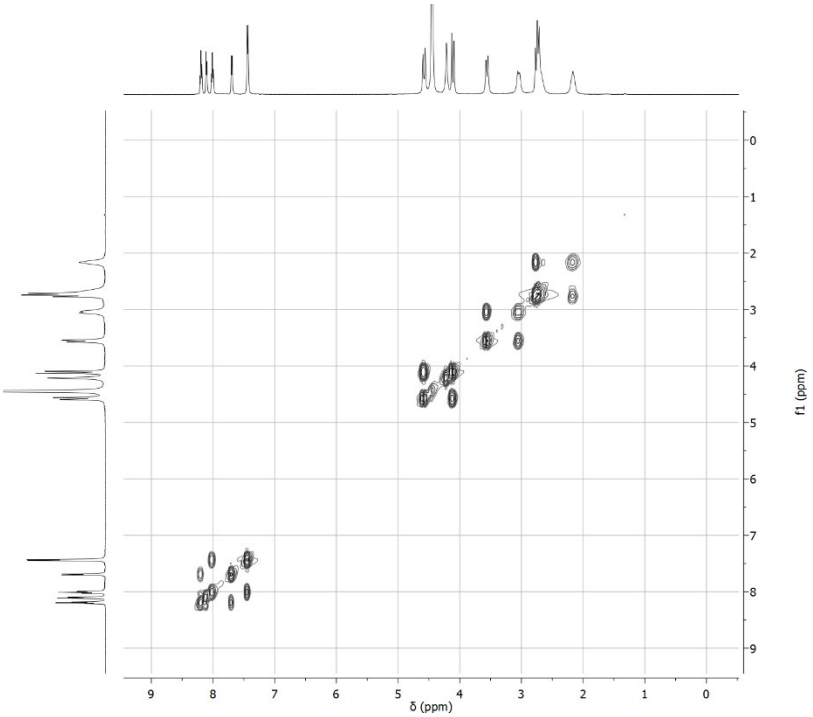
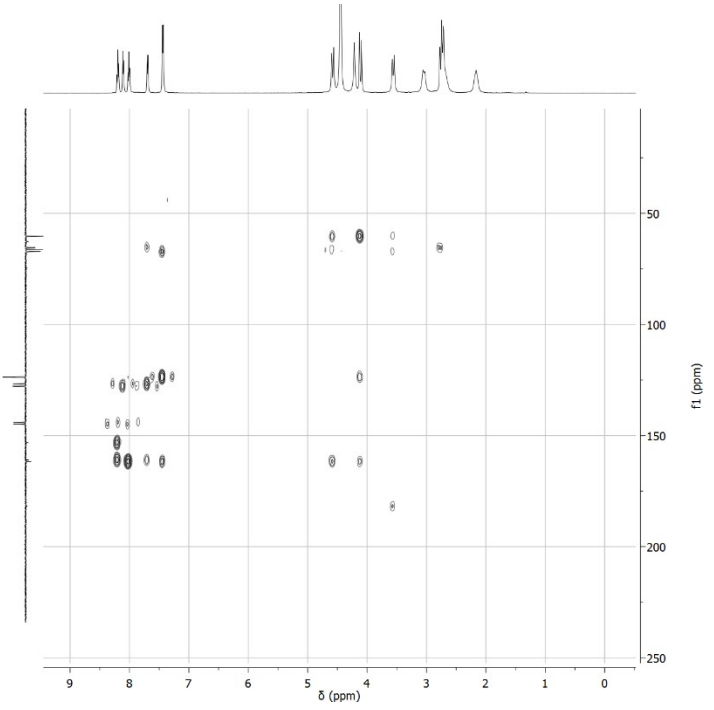


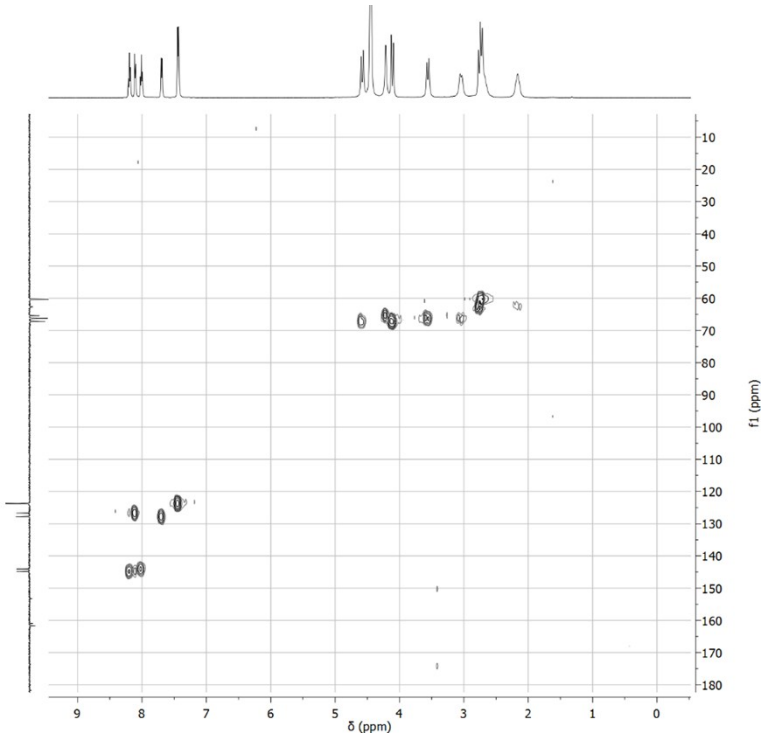
Figure S3. ^{1}H NMR spectra (D_2O, 500 MHz) of **L1** (298 K) and its Yttrium (III) complex Y**L1** (328 K).



^{1}H-^{1}H COSY experiment of Y**L1** (D_2O, 500 MHz, 328K)



^{1}H-^{13}C HMBC experiment of Y**L1** (D_2O, 500 MHz, 328K)



^{1}H-^{13}C HMQC experiment of Y**L1** (D_2O, 500 MHz, 328K)

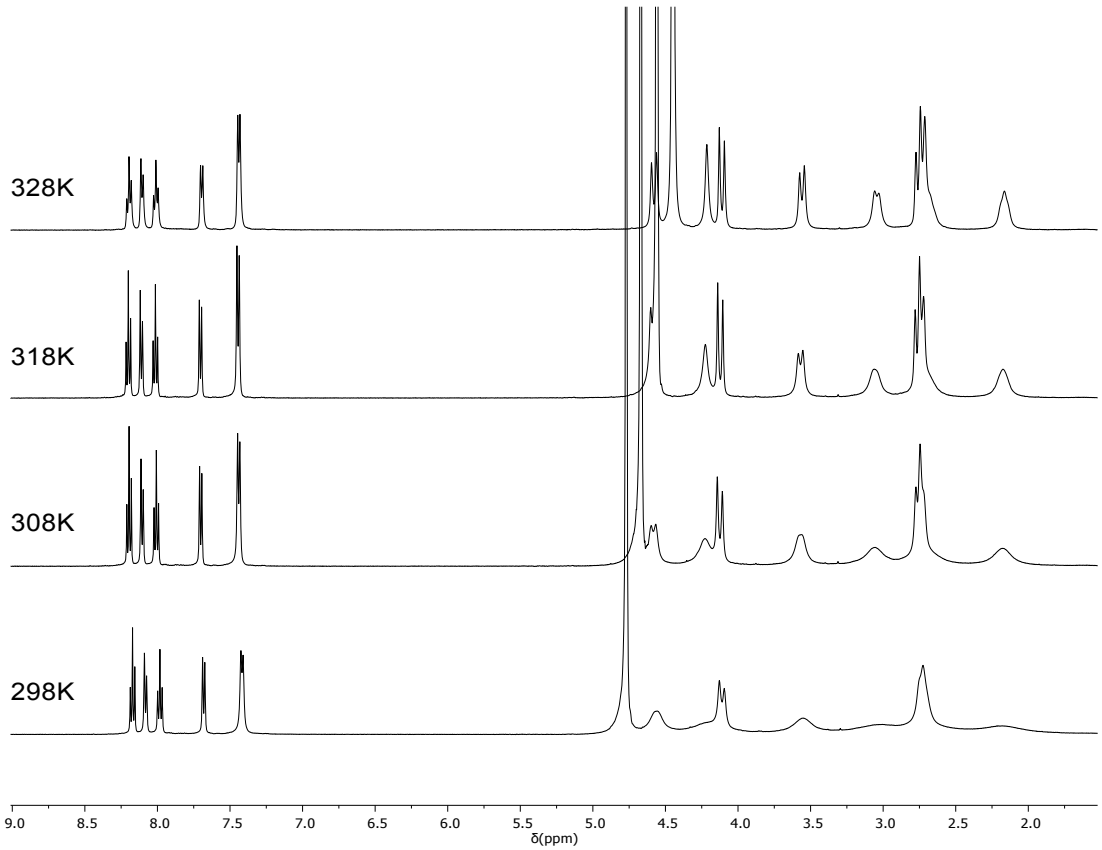


Figure S4. ^{1}H NMR spectra (D_2O, 500 MHz) of Y**L1** at 328, 318, 308 and 298 K.

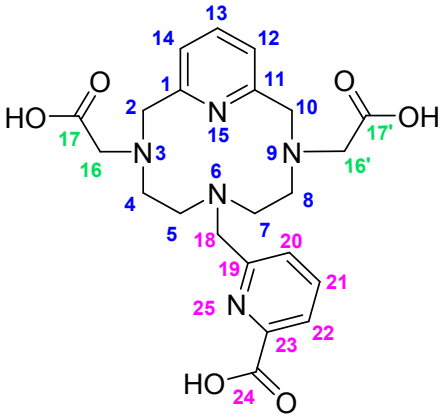


Table S1. ^{1}H and ^{13}C NMR assignments of **L1**.

	δ^{1}H	δ^{13}C
1+11	-	152.89
2+10	4.81 (s, 4H)	62.35
3	-	-
4+8	3.63 (m, 4H)	56.09
5+7	2.99 (s, br, 4H)	52.88
6	-	-
13	8.00 (t, 1H, ^{3}J = 7.8 Hz)	142.80
12+14	7.49 (d, 2H, ^{3}J = 7.8 Hz)	125.60
15	-	-
16+16'	3.76 (s, 4H)	60.08
17+17'	-	172.17
18	4.20 (s, 2H)	59.47
19	-	157.78
20	8.07 (d, 1H, ^{3}J = 7.8 Hz)	131.30
21	8.33 (t, 1H, ^{3}J = 7.8 Hz)	146.36
22	8.25 (d, 1H, ^{3}J = 7.8 Hz)	128.33
23	-	150.25
24	-	168.64
25	-	-

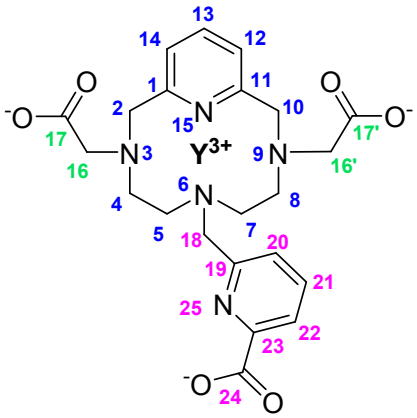


Table S2. ^{1}H and ^{13}C NMR assignments of Y**L1**.

	δ^{1}H	δ^{13}C
1	-	161.70
2eq	4.58 (d, 2H, ^{2}J = 17.4 Hz)	67.19
2ax	4.11 (d, 2H, ^{2}J = 17.4 Hz)	67.19
3	-	-
4a	2.74 (m, 6H)	60.32
4b	2.16 (s, br, 2H)	60.32
5a	2.74 (m, 6H)	62.66
5b	2.74 (m, 6H)	62.66
6	-	-
7a	2.74 (m, 6H)	62.66
7b	2.74 (m, 6H)	62.66
8a	2.74 (m, 6H)	60.32
8b	2.16 (s, br, 2H)	60.32
9	-	-
10eq	4.58 (d, 2H, ^{2}J = 17.4 Hz)	67.19
10ax	4.11 (d, 2H, ^{2}J = 17.4 Hz)	67.19
11	-	161.70
12	7.44 (d, 2H, ^{3}J = 7.8 Hz)	123.72
13	8.01 (t, 1H, ^{3}J =7.8 Hz)	144.06
14	7.44 (d, 2H, ^{3}J =7.8 Hz)	123.72
15	-	-
16eq	3.56 (d, 2H, J = 16.0 Hz)	66.24
16ax	3.04 (m, 2H)	66.24
16'eq	3.56 (d, 2H, J = 16.0 Hz)	66.24
16'ax	3.04 (m, 2H)	66.24
17	-	181.79
18	4.21 (s, 2H)	65.40
19	-	160.97
20	7.69 (d, 1H, ^{3}J = 7.8 Hz)	127.82
21	8.19 (t, 1H, ^{3}J = 7.8 Hz)	144.85
22	8.11 (d, 1H, ^{3}J = 7.8 Hz)	126.72
23	-	153.24
24		Not detected
25	-	-

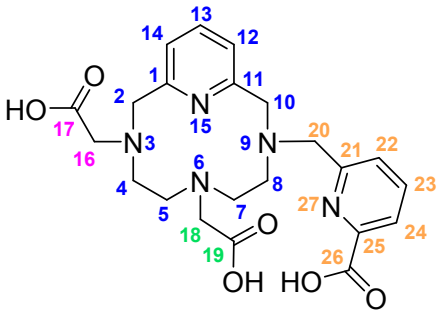


Table S3. ^{1}H and ^{13}C NMR assignments of **L2**.

	δ^{1}H	δ^{13}C
1	-	153.91
2	4.86 (s, 2H)	61.47
3	-	-
4	3.77 (m, 2H)	55.41
5	3.44 (m, 2H)	54.92
6	-	-
7	3.29 (m, 2H)	55.24
8	3.54 (m, 2H)	55.65
9	-	-
10	4.38 (s, 2H)	60.97
11	-	157.12
12	7.06 (d, 1H, ^{3}J = 7.9Hz)	124.49
13	7.78 (t, 1H, ^{3}J = 7.9Hz)	142.33
14	7.37 (d, 1H, ^{3}J = 7.9Hz)	124.93
15	-	-
16	4.06 (s, 2H)	61.85
17	-	172.77
18	3.80 (s, 2H)	57.41
19	-	175.98
20	4.63 (s, 2H)	62.23
21	-	153.91
22	7.96 (d, 1H, ^{3}J = 7.9Hz)	131.35
23	8.19 (t, 1H, ^{3}J = 7.9Hz)	145.97
24	8.07 (d, 1H, ^{3}J = 7.9Hz)	127.90
25	-	150.53
26	-	169.14
27	-	-

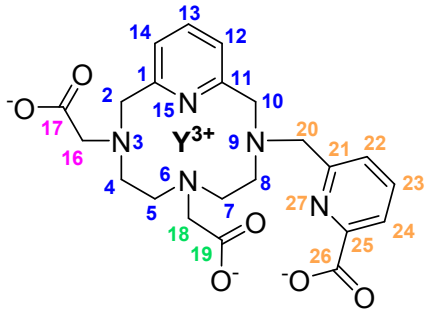


Table S4. ^{1}H and ^{13}C NMR assignments of Y**L2**.

	δ^{1}H	δ^{13}C
1	-	160.81
2a	4.83 (d, 1H, ^{2}J = 16.0 Hz)	65.52
2b	4.15 (d, 1H, ^{2}J = 16.0 Hz)	65.52
3	-	-
4eq	3.07 (m,1H), 2.60 (m, 2H) / 1.89 (m, 1H), 2.89 (m, 1H)	59.54 / 59.46
4ax	3.07 (m,1H), 2.60 (m, 2H) / 1.89 (m, 1H), 2.89 (m, 1H)	59.54 / 59.46
5eq	3.07 (m,1H), 2.60 (m, 2H) / 1.89 (m, 1H), 2.89 (m, 1H)	59.54 / 59.46
5ax	3.07 (m,1H), 2.60 (m, 2H) / 1.89 (m, 1H), 2.89 (m, 1H)	59.54 / 59.46
6	-	-
7a	2.68 (m, 1H)	63.93
7b	2.60 (d, 1H, ^{3}J =)	63.93
8ax	3.47 (m, 1H)	60.16
8eq	2.94 (m, 1H)	60.16
9	-	-
10eq	4.10 (m, 3H)	65.80
10ax	4.10 (m, 3H)	65.80
11	-	162.30
12	7.13 (d, 1H, ^{3}J = 7.8 Hz)	122.63
13	7.81 (t, 1H, ^{3}J = 7.8 Hz)	143.34
14	7.36 (d, 1H, ^{3}J = 7.8 Hz)	123.75
15	-	-
16eq	4.10 (m, 3H)	66.34
16ax	3.54 (d, 1H, ^{2}J = 16.2 Hz)	66.34
17	-	182.93
18eq	3.88 (d, 1H, ^{2}J = 16.7 Hz)	65.01
18ax	3.10 (d, 1H, ^{2}J = 16.7 Hz)	65.01
19	-	183.42
20eq	4.49 (d, 1H, ^{2}J = 14.7 Hz)	64.27
20ax	4.29 (d, 1H, ^{2}J = 14.7 Hz)	64.27
21	-	159.29
22	7.75 (d, 1H, ^{3}J = 7.8 Hz)	129.50
23	8.13 (t, 1H, ^{3}J = 7.8 Hz)	144.78
24	7.86 (d, 1H, ^{3}J = 7.8 Hz)	126.38
25	-	153.07
26	-	174.79
27	-	-

- Thermodynamic Stability Studies

The protonation constants of the ligands were determined by pH-potentiometric titrations carried out with a Methrohm 888 Titrando titration workstation using a Metrohm-6.0233.100 combined electrode. The titrated solutions (6.00 mL) were thermostated at 25°C and the ionic strength in the samples were set to 0.15 M NaCl. The samples were stirred and kept under inert gas atmosphere (N_2) to avoid the effect of CO_2. For the pH-calibration of the electrode standard buffers (KH-phthalate (pH=4.005) and borax (pH=9.177)) were used. The concentrations of the ligands were determined by pH-potentiometric titration from the titration data obtained in the presence and absence of large Ca^{2+} excess. In the pH-potentiometric titrations of the ligands 237-303 mL–pH data pairs were recorded in the pH range of 1.7-11.9. The calculation of $[H^+]$ from the measured pH values was performed with the use of the method proposed by Irving et al.[3] by titrating a 0.01 M HCl solution (I=0.15 M NaCl) with a standardized NaOH solution. The differences between the measured and calculated pH values were used to obtain the $[H^+]$ concentrations from the pH-data obtained in the titrations. The ion product of water was determined from the same experiment in the pH range 11.4–11.9. The protonation and stability constants were calculated from the titration data with the PSEQUAD program.[4]

The stability constants of the Gd^{3+} complexes were determined by measuring the longitudinal relaxation times of the "out-of-cell" samples prepared in strongly acidic solutions. The measurements were performed with a Bruker Minispec MQ20 NMR analyzer (20 MHz, 25 ^oC) using the inversion recovery method (180° - τ - 90°) at 14 different τ values by averaging 4-5 identical readouts. Altogether 12-13 different samples were prepared containing the ligand and Gd^{3+} at 2 mM concentration. The HCl concentration was varied in the concentration range 5.78-70.85 mM and 6.20-175.0 mM for the **L1** and **L2** systems, respectively. The realxivities of the samples were measured after 4 weeks and then after 8 weeks again. Since the two measurements returned identical results, it was concluded that the samples have attained the equilibrium. By fitting the relaxivity and acid concentration data including the relaxivity of the free (uncomplexed) Gd^{3+} ion (which is being equal to 13.172 $mM^{-1}s^{-1}$ at 20 MHz and 25 ^oC), it was possible to calculate the stability of the Gd**L1** and Gd**L2** complexes as well as their relaxivities.

Table S5. Protonation constants of the ligands **L1** and **L2** (25°C, 0.15 M NaCl) and comparison with related compounds from literature.

	L1[a]	***L2***[a]	***pcta***[b]	**dota**[d]
log β_{01}	9.69(2)	10.43(1)	11.36	12.60
(log K_1^H)				
log β_{02}	17.32(2)	16.90(1)	18.71	22.30
(log K_2^H)	7.63	6.47	7.35	9.70
log β_{03}	21.34 (3)	21.03(2)	22.54	26.80
(log K_3^H)	4.02	4.13	3.83	4.50
log β_{04}	23.69(3)	23.74(2)	24.66	30.94
(log K_4^H)	2.35	2.71	2.12	4.14
log β_{05}	-	25.13(2)	25.95	33.26
(log K_5^H)		1.39	1.29	2.32

[a] This work (25°C, 0.15 M NaCl); [b] Ref. 5 (25°C, 1.0 M KCl); [d] Ref. 6 (25°C, 0.1 M Me_4NNO_3);

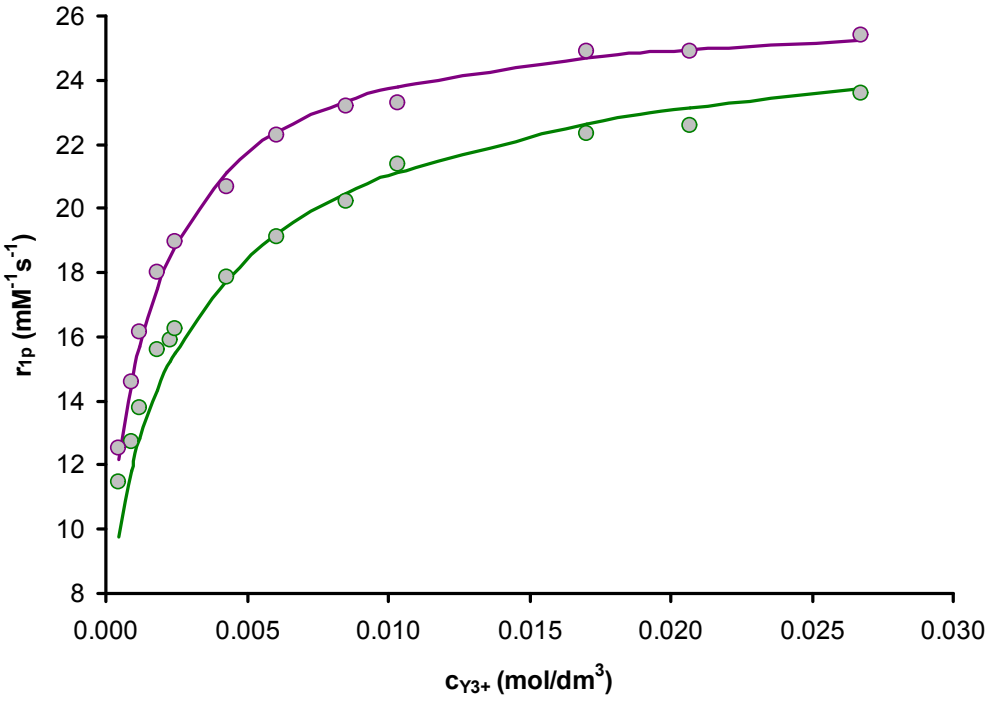


Figure S5. Determination of the Y**L1** (green line) and Y**L2** (blue line) stabilities by following the competition between Gd^{3+} and Y^{3+} *via* ^{1}H-relaxometry (cGd^{3+}=2.005 mM, $c_{DMP\ buffer}$ =0.050 M with pH =4.70; 20 MHz, 298 K).

The Y**L1** and Y**L2** complex stabilities were determined by competition titration with Gd^{3+} at pH = 4.70 in 50 mM DMP buffer in 0.15 M NaCl at 25 °C. The samples were prepared by mixing the two metal ions together and then the buffered ligand solution was added to the mixture. The samples were set aside at 25°C for 8 weeks, and their relaxivities were recorded. A second measurement of the relaxivities was performed after another 8 weeks, which evidenced no significant changes of the relaxivities, indicating that thermodynamic equilibrium was attained during this period of time (16 weeks).

- Dissociation kinetics

The acid-assisted dissociation of the yttrium(III) complexes was studied under pseudo-first order conditions without control of the ionic strength by following the shift of the π–π* transition band either of the ligand or of the complex in the UV range. Concentrated aqueous solutions of HCl were added to an aqueous solution of the preformed complex.

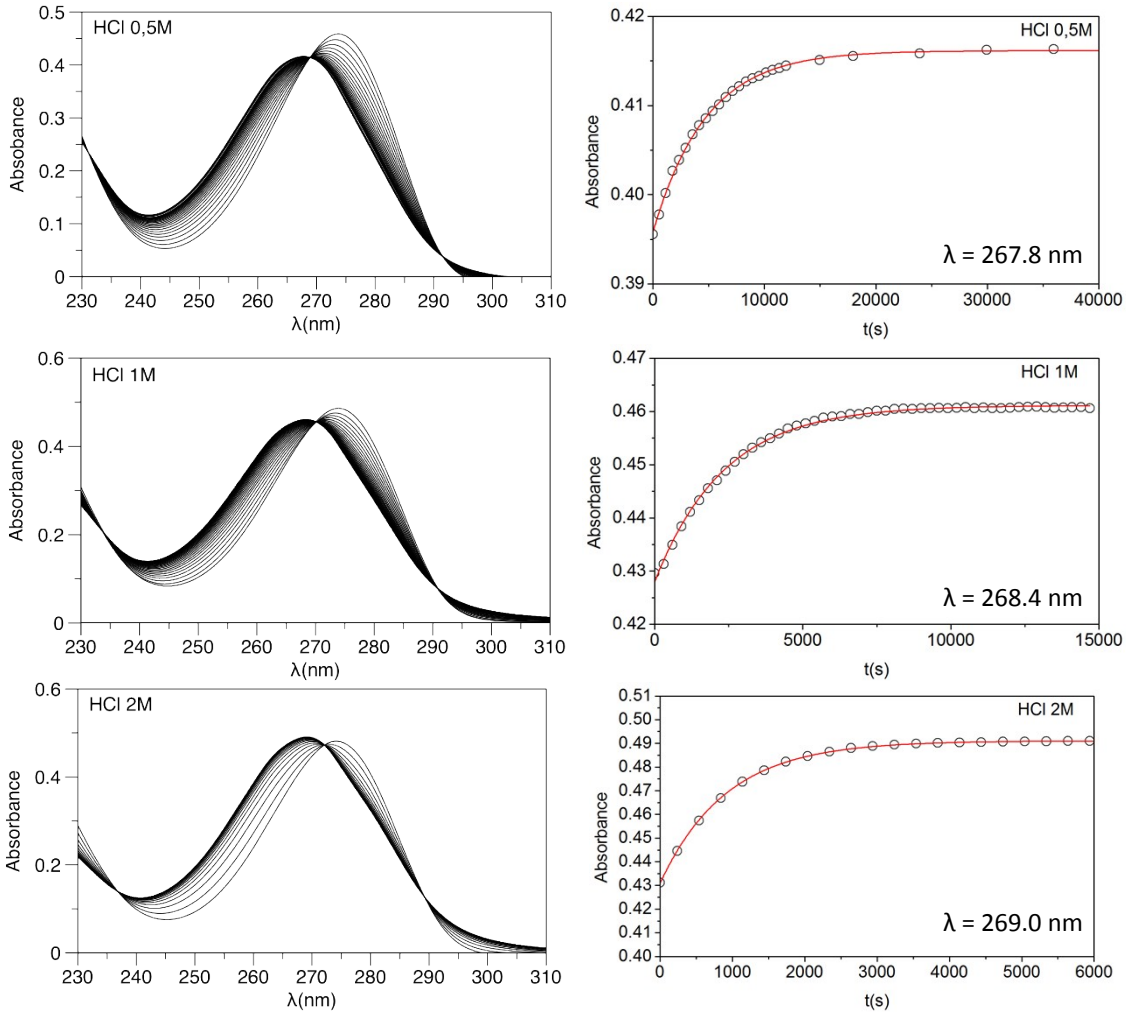


Figure S6. Acid assisted dissociation of the Yttrium(III) complex **YL1** for $C_{YL} = 4 \times 10^{-5}$ M in 0.5, 1 and 2 M HCl (in the quartz cell) followed in the UV range at 25°C (with each λmax).

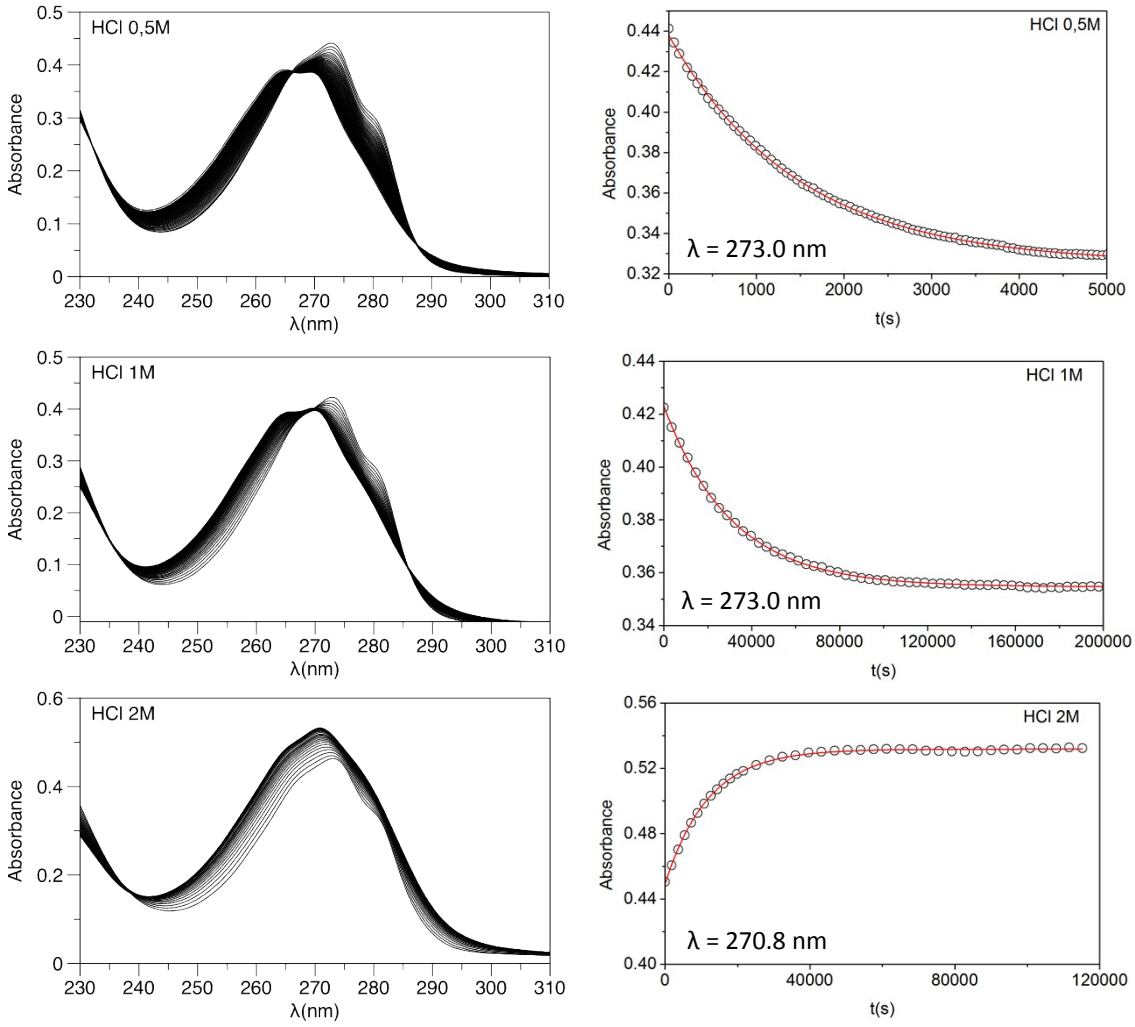


Figure S7. Acid assisted dissociation of the Yttrium(III) complex **YL2** for $C_{YL} = 1 \times 10^{-4}$ M in 0.5, 1 and 2 M HCl (in the quartz cell) followed in the UV range at 25°C (with each λmax).

-DFT calculations

Geometry optimisations of the Y**L1**$(H_2O)\cdot 2H_2O$ and Y**L2**$(H_2O)\cdot 2H_2O$ systems were carried out using DFT with the hybrid meta-GGA approximation (TPSSh exchange-correlation functional)[7] and the Gaussian 09 package (Revision D.01).[8] In these calculations we employed the quasi-relativistic effective core potential ECP28MWB[9] and the related (8s7p6d2f1g)/[6s5p3d2f1g]-GTO valence basis set for Y.[9,10] For the ligand atoms the standard 6-31G(d,p) basis set was selected. No symmetry constraints have been imposed during the optimisations, while the default values for the integration grid (75 radial shells and 302 angular points) and the SCF energy convergence criteria (10^{-8}) were used. The stationary points found on the potential energy surfaces were tested to represent true energy minima via frequency analysis. Bulk solvent effects (water) were considered with the integral equation formalism variant of the polarizable continuum model (IEFPCM),[11] using the universal force field radii (UFF)[12] scaled by a factor of 1.1 to define the solute cavities.

Table S6. Optimised Cartesian coordinates (Å) obtained for the Y**L1**(H_2O)·$2H_2O$ system.

Center Number	Atomic Number		Coordinates (Angstroms) X	Y	Z
1	6	0	0.025125	-2.971691	-0.804376
2	1	0	-0.263140	-4.033637	-0.794222
3	1	0	1.113019	-2.930860	-0.868114
4	6	0	-0.627092	-2.299634	-2.012209
5	1	0	-0.357436	-2.848015	-2.925458
6	1	0	-1.713676	-2.366131	-1.912396
7	6	0	-1.351721	-0.129609	-2.875758
8	1	0	-2.309935	-0.515391	-2.527294
9	1	0	-1.296456	-0.337716	-3.954758
10	6	0	-1.282659	1.382576	-2.681478
11	1	0	-0.325402	1.754414	-3.056786
12	1	0	-2.068060	1.849403	-3.294729
13	6	0	-2.782620	1.888883	-0.776279
14	1	0	-3.453576	2.396170	-1.484105
15	1	0	-2.772606	2.472034	0.151095
16	6	0	-3.311388	0.512883	-0.458979
17	6	0	-4.658942	0.196177	-0.630385
18	1	0	-5.346749	0.942587	-1.012343
19	6	0	-5.090054	-1.095725	-0.325850
20	1	0	-6.130503	-1.374889	-0.455398
21	6	0	-4.156300	-2.029888	0.114335
22	1	0	-4.444751	-3.053931	0.326356
23	6	0	-2.822644	-1.635831	0.269650
24	6	0	-1.803535	-2.624922	0.776124
25	1	0	-2.053037	-3.628833	0.406713
26	1	0	-1.903814	-2.661890	1.864311
27	6	0	0.446274	-2.657420	1.611440
28	1	0	1.500382	-2.532322	1.343524
29	1	0	0.301946	-3.700936	1.922728
30	6	0	0.110460	-1.714800	2.785304
31	6	0	0.992080	-0.720492	-2.914362
32	1	0	1.065939	0.313951	-3.265636
33	1	0	0.975794	-1.363479	-3.805670
34	6	0	2.227595	-0.981894	-2.090829
35	6	0	3.412897	-1.455740	-2.663557
36	1	0	3.432788	-1.741652	-3.709756
37	6	0	4.557666	-1.545803	-1.869593
38	1	0	5.486972	-1.916804	-2.289801
39	6	0	4.492008	-1.136116	-0.536963
40	1	0	5.351793	-1.151804	0.122105
41	6	0	3.270553	-0.683955	-0.039757
42	6	0	3.119676	-0.148666	1.371497
43	6	0	-0.799706	3.207763	-1.197591
44	1	0	-1.215479	3.727642	-0.331393
45	1	0	-1.034923	3.808393	-2.086301
46	6	0	0.714661	3.148803	-0.976679
47	7	0	-0.391217	-2.294249	0.445883
48	7	0	-0.270430	-0.854148	-2.145072
49	7	0	-1.388795	1.851214	-1.270312
50	7	0	-2.409731	-0.380000	0.010199
51	7	0	2.155035	-0.637817	-0.794185
52	8	0	-0.527404	2.162440	1.617905
53	8	0	1.930456	0.259132	1.656671
54	8	0	4.113233	-0.127274	2.115427
55	8	0	1.217026	1.988547	-0.759738
56	8	0	1.342501	4.231086	-0.941869
57	39	0	0.061479	0.275703	0.294277
58	8	0	-0.530453	-0.637493	2.434819
59	8	0	0.439860	-2.026232	3.933838
60	1	0	0.186036	2.851074	1.731875
61	1	0	-0.861994	1.952495	2.537600
62	8	0	-1.328827	1.304107	4.003077
63	8	0	1.409859	4.060200	1.824238

64	1	0	1.001585	4.874054	2.155856
65	1	0	1.577122	4.239226	0.868087
66	1	0	-2.296229	1.248640	4.020197
67	1	0	-1.031351	0.435313	3.604159

E(RTPSSh) = -1846.01497720 Hartre
Zero-point correction = 0.532692
Thermal correction to Energy = 0.568636
Thermal correction to Enthalpy = 0.569580
Thermal correction to Gibbs Free Energy = 0.467755
Sum of electronic and zero-point Energies = -1845.482285
Sum of electronic and thermal Energies = -1845.446341
Sum of electronic and thermal Enthalpies = -1845.445397
Sum of electronic and thermal Free Energies = -1845.547222

Table S7. Optimised Cartesian coordinates (Å) obtained for the Y**L2**(H_2O)·2H_2O system.

Center Number	Atomic Number		Coordinates (Angstroms) X	Y	Z
1	6	0	-1.625631	0.581607	2.798656
2	1	0	-2.298117	1.189023	3.423277
3	1	0	-0.830465	0.196918	3.436080
4	6	0	-2.442039	-0.568223	2.203145
5	1	0	-2.916214	-1.121050	3.027169
6	1	0	-3.249012	-0.158623	1.591365
7	6	0	-2.569719	-2.196177	0.385253
8	1	0	-3.328343	-1.478990	0.067840
9	1	0	-3.099278	-3.023885	0.878744
10	6	0	-1.833265	-2.755460	-0.831246
11	1	0	-1.107600	-3.504714	-0.506410
12	1	0	-2.562191	-3.263221	-1.480121
13	6	0	-1.926303	-0.945478	-2.520567
14	1	0	-2.623659	-1.580469	-3.084653
15	1	0	-1.262282	-0.457799	-3.242502
16	6	0	-2.682097	0.137442	-1.794537
17	6	0	-3.945941	0.543393	-2.225775
18	1	0	-4.412317	0.050288	-3.071709
19	6	0	-4.593546	1.571549	-1.541340
20	1	0	-5.579064	1.905015	-1.849254
21	6	0	-3.963904	2.144626	-0.438898
22	1	0	-4.443657	2.928639	0.137086
23	6	0	-2.696597	1.683931	-0.067743
24	6	0	-1.969340	2.315257	1.092088
25	1	0	-2.692390	2.704844	1.821934
26	1	0	-1.424075	3.180379	0.699043
27	6	0	0.102091	2.255682	2.313507
28	1	0	0.747824	1.596881	2.904289
29	1	0	-0.280412	3.042951	2.978102
30	6	0	0.910046	2.857201	1.178441
31	6	0	1.570235	4.088863	1.245235
32	1	0	1.492638	4.704748	2.134663
33	6	0	2.325320	4.504468	0.144833
34	1	0	2.842853	5.457951	0.171259
35	6	0	2.416047	3.683714	-0.983629
36	1	0	3.010274	3.955676	-1.847830
37	6	0	1.720610	2.476134	-0.976171
38	6	0	1.811259	1.441710	-2.085074
39	6	0	-0.914910	-2.495610	2.163244
40	1	0	-0.748758	-3.395234	1.565627
41	1	0	-1.496618	-2.794811	3.046456
42	6	0	0.471063	-2.002794	2.596990
43	6	0	-0.030540	-2.443962	-2.409561
44	1	0	0.299446	-1.785502	-3.215656

45	1	0	-0.413044	-3.368033	-2.865011
46	7	0	-0.987997	1.419227	1.748514
47	7	0	-1.656958	-1.502077	1.341296
48	7	0	-1.069020	-1.742335	-1.617157
49	7	0	-2.055170	0.707212	-0.740911
50	7	0	0.978849	2.093792	0.077182
51	8	0	0.984633	0.455896	-1.981037
52	8	0	2.687666	1.564249	-2.961333
53	39	0	0.224942	-0.253278	0.064965
54	8	0	0.820652	-0.836540	2.187365
55	8	0	1.190052	-2.759083	3.283418
56	6	0	1.199345	-2.742469	-1.547235
57	8	0	2.695891	-0.117752	0.338527
58	8	0	2.188128	-3.274828	-2.096419
59	8	0	1.130118	-2.361688	-0.322054
60	1	0	3.163253	-0.460709	-0.469770
61	1	0	2.963778	-0.722145	1.078426
62	8	0	3.858732	-0.980815	-1.986120
63	8	0	3.636305	-1.727425	2.425961
64	1	0	3.443280	-0.317046	-2.572404
65	1	0	3.346591	-1.810224	-2.119011
66	1	0	3.892975	-1.041445	3.060156
67	1	0	2.793395	-2.090839	2.802549

E(RTPSSh) = -1846.02620537 Hartree
Zero-point correction = 0.534017
Thermal correction to Energy = 0.569446
Thermal correction to Enthalpy = 0.570390
Thermal correction to Gibbs Free Energy = 0.471303
Sum of electronic and zero-point Energies = -1845.492188
Sum of electronic and thermal Energies = -1845.456759
Sum of electronic and thermal Enthalpies = -1845.455815
Sum of electronic and thermal Free Energies = -1845.554902

- Materials and Methods for ^{90}Y radiolabelling

Yttrium-90 chloride was provided by PerkinElmer Life Sciences (Waltham, MA, USA), in 0.05 M HCl solution. The activity of the ^{90}Y solution was between 40.90 µCi and 1.96 mCi (1.51-72.52 MBq). Human serum was obtained from Biopredic International (Saint-Grégoire, France). Other chemicals (HPLC solvents, buffer solutions) were used as received from suppliers.
Experiments were performed in borosilicated sealed glass flasks. Sealed flasks were heated on a Bioblock heating block (ThermoFischer, Waltham, MA, USA), able to heat until 6 flasks. Activities were measured with a CRC-127R (Capintec Inc., Ramsey, NJ, USA) dose calibrator. Quality controls were carried out by TLC on Whatman 1 paper (GE Healthcare, Maidstone, UK) eluted in MeOH with 0.1 % NEt_3. Radiochemical purities (RCP) were determined with a Cyclone Storage Phosphorimager (PerkinElmer, Waltham, MA, USA), using the Optiquant software. HPLC analyses were performed on HPLC Dionex Ultimate 3000 (Sunnyvale, CA, USA) equipped with a diode array detector and a radiochromatographic *ƒ*Lumo (Berthold Technologies GmbH, Bad Wildbad, Germany) detector piloted by the Chromeleon software. The chromatographic analytic system employs a Accucore C_{18} 100 x 3 mm, 2.6 µ column with A= H_2O/TFA 0.1 %; B= MeOH as eluents; 0-3 min: 100 % A, 3-20 min: 0-90 % B, 20-25 min: 90 % B, 25-26 min: 90-0 % B, 26-30 min: 100 % A, at a flow rate of 0.4 mL/min.

^{90}Y radiolabelling of L1 and L2

Several parameters such as concentration of ligands, volume and pH of the reaction mixture, incubation time, and temperature were varied extensively to obtain an optimised protocol. A 0.5 mL amount of an yttrium-90 chloride solution in 0.1 M HCl solution (pH = 3) or in acetate buffer 3M (pH = 4.65-9) were added to 0.5 mL of a ligand solution (C = 0.01-1 mM) in ethanol. The resulting solution was heated at 20-100°C for 15-60 min.

Inertness of ^{90}YL1 and ^{90}YL2 in serum and transchelation studies

For the stability studies, ^{90}Y**L** complexes were synthesized by using 1 mM ligand **L1** or **L2** solutions at pH = 5.2 and at 80°C, for 15 min. Aliquots of ^{90}Y**L** solutions (0.5 mL) were alternatively mixed with i) 1 mL of healthy human serum solution, or ii) 0.5 mL of a 100 mM EDTA solution. The mixtures were incubated at 37°C under slight stirring and analyzed on TLC after 0, 1, 24, 48 and 72 min, for i) and after 0, 1, 2, 4, 24, 48 and 72 h for ii).

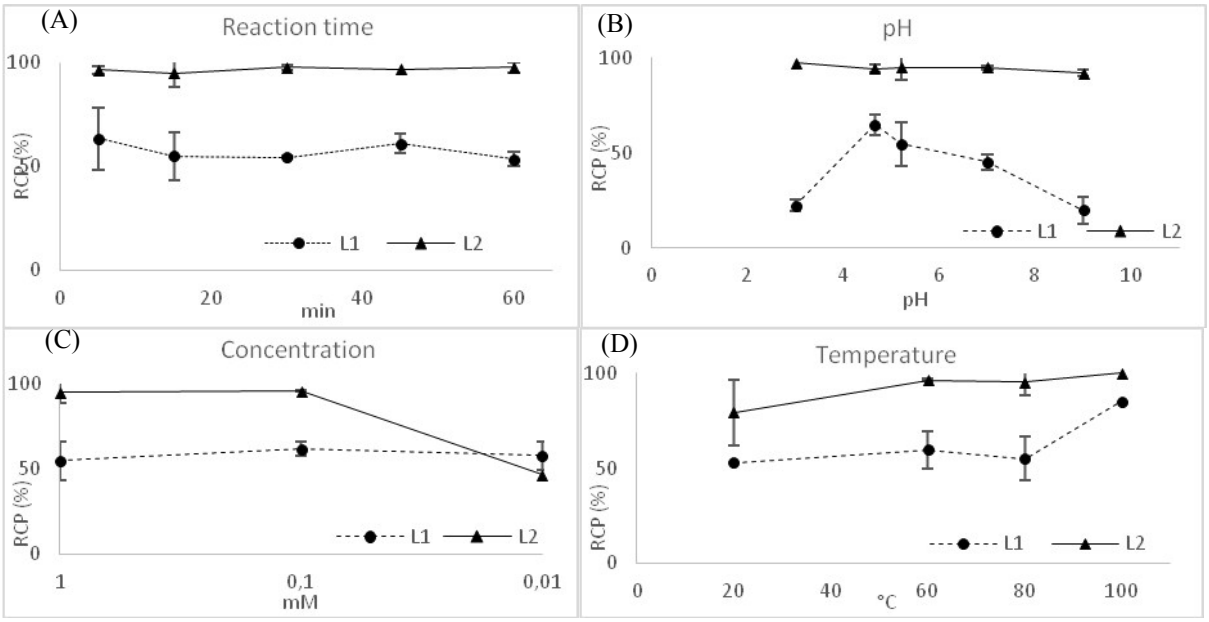


Figure S8. (A) Radiolabelling reaction times (80°C, pH 5.2, 10^{-3}M), (B) Influence of pH (15 min, 80 °C, pH = 5.2, 10^{-3} M), (C) Influence of ligand concentration (15 min, 80 °C, pH = 5.2), (D) Influence of temperature (15 min, pH = 5.2, 10^{-3} M).

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