Supporting Information for:
Chelation with a twist: A Bifunctional Chelator to Enable Room Temperature Radiolabeling and Targeted PET Imaging with Scandium-44.

Brett A. Vaughn[a], Shin Hye Ahn[a], Eduardo Alucio[b], Justin Devaraj[a], Aeli P. Olson[b], Jonathan Engle[b] and Eszter Boros *[a]
[a]Department of Chemistry, Stony Brook University, 100 Nicolls Road, Stony Brook, New York, 11790

[b]Medical Physics Department, University of Wisconsin-Madison, 1111 Highland Avenue, Madison, Wisconsin, 53705

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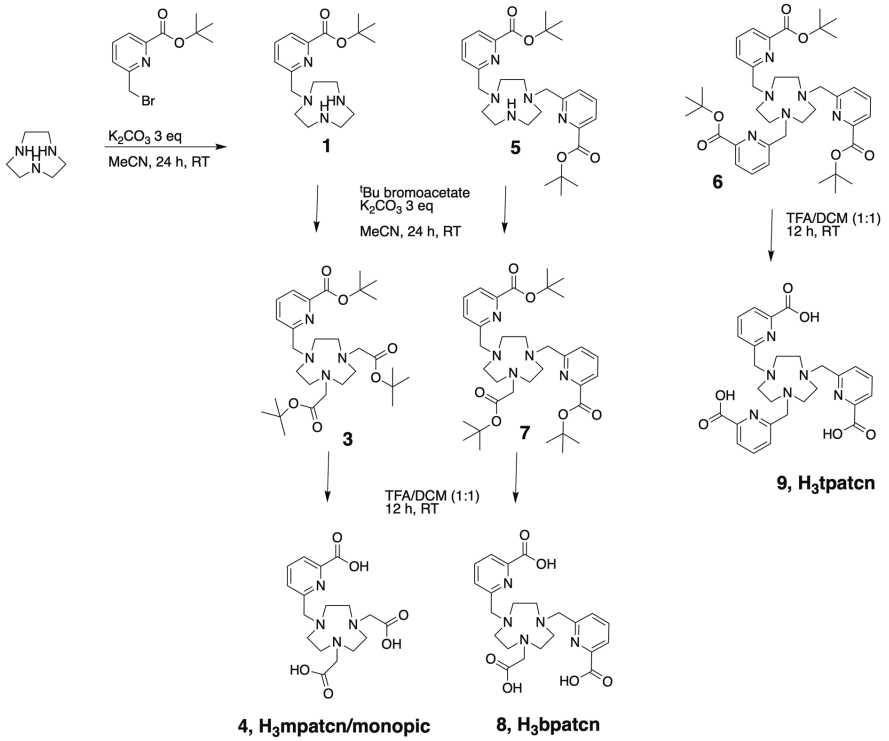
1. Chemical synthesis and characterization of non-functionalized and functionalized ligands

1.1 Synthesis protocols

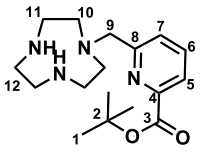
All starting materials were purchased from Acros Organics, Alfa Aesar, Macrocyclics, Sigma Aldrich, or TCI America and used without further purification. NMR spectra (^{1}H, ^{13}C, ^{45}Sc) were collected on a 700 MHz Advance III Bruker, 500 MHz or 400 MHz Bruker instrument at 25 °C and processed using TopSpin 3.5pl7. Chemical shifts are reported as parts per million (ppm). Mass spectrometry: low-resolution electrospray ionization (ESI) mass spectrometry and high-resolution (ESI) mass spectrometry was carried out at the Stony Brook University Institute for Chemical Biology and Drug Discovery (ICB&DD) Mass Spectrometry Facility with an Agilent LC/MSD and Agilent LC-UV-TOF spectrometers respectively. UV-VIS spectra were collected with the NanoDrop ^{1}C instrument (AZY1706045). Spectra were recorded from 190 to 850 nm in a quartz cuvette with 1 cm path length. HPLC: Preparative HPLC was carried out using a Shimadzu HPLC-20AR equipped with a Binary Gradient, pump, UV-Vis detector, manual injector on a Phenomenex Luna C18 column (250 mm×21.2 mm, 100 Å, AXIA packed). Method A (preparative purification method): A = 0.1% TFA in water, B = 0.1% TFA in MeCN. Gradient: 0-5 min: 95% A. 5-24 min: 5−95% B gradient. Method B (preparative purification method): A = 10^{-2} M ammonium formate in water, B = 10% 10 mM ammonium formate in water, 90% MeCN. Gradient: 0-5 min: 95% A. 5-24 min: 5−95% B gradient. RadioHPLC analysis was carried out using a Shimadzu HPLC-20AR equipped with a binary gradient, pump, UV-Vis detector, autoinjector and Laura radiodetector on a Gemini-NX C18 column (100 mm×3 mm, 110 Å, AXIA packed). Method C: A = 0.1% TFA in water, B = 0.1% TFA in MeCN with a flow rate of 0.8 mL/min, UV detection at 260 and 280 nm. Benzyl *tert*-butyl 2-



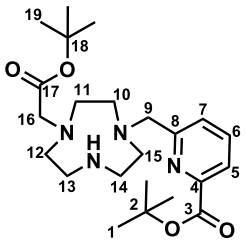
Scheme S1. Synthesis of H_3mpatcn, H_3bpatcn and H_3tpatcn.

(methylsulfonyloxy)glutarate and *tert*-Butyl 6-(bromomethyl)-2-pyridinecarboxylate were synthesized according to previously published procedures.[1-2]

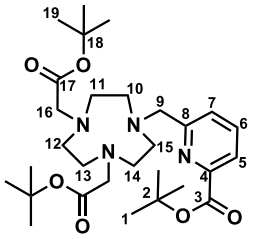
tert-Butyl 6-[(1,4,7-triazonan-1-yl)methyl]-2-pyridinecarboxylate (1). 1,4,7-Triazocyclonane (0.0380 g, 0.295 mmol, 1 eq), *tert*-butyl 6-(bromomethyl)-2-pyridinecarboxylate (0.0801 g, 0.295 mmol, 1 eq) was dissolved with K_2CO_3 (0.0409 g, 0.295 mmol, 1 eq) in acetonitrile (3.0 mL). The reaction mixture was stirred overnight at room temperature and subsequently filtered to remove solids. Solvent was removed *in vacuo* and **1** was purified using reverse-phase chromatography (Method **A**, product elutes at 35% B) and isolated as a yellow oil (0.0309 g, 0.097 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 7.6 Hz, 1H, H-5), 7.89 (t, J = 7.7 Hz, 1H, H-6), 7.40 (d, J = 7.7 Hz, 1H, H-7), 4.17 (s, 2H, H-9), 2.97-4.25 (m, 12H, H-10, H-11, H-12), 1.58 (s, 9H, H-1). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5 (C-3), 158.3 (C-4), 147.9 (C-8), 139.2 (C-6), 125.9 (C-7), 124.1 (C-5), 83.9 (C-2), 57.5 (C-9), 50.4 (C-10), 46.4 (C-12), 45.8 (C-11), 27.7 (C-1). Calculated monoisotopic mass for **1** ($C_{17}H_{28}N_4O_2$): 320.22; found: m/z = 321.2 $[M + H]^+$.



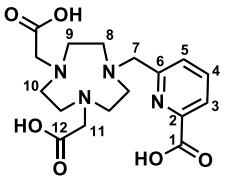
***tert*-Butyl 6-{[4-(*tert*-butoxycarbonylmethyl)-1,4,7-triazonan-1-yl]methyl}-2-pyridinecarboxylate (2).** Compound **1** (0.0517 g, 0.161 mmol, 1 eq), *tert*-butyl bromoacetate (0.0315 g, 0.161 mmol, 1 eq) was dissolved with K_2CO_3 (0.0224 g, 0.161 mmol, 1 eq) in acetonitrile (3.0 mL). The reaction mixture was stirred overnight at room temperature and subsequently filtered to remove solids. Solvent was removed *in vacuo* and **2** was purified using reverse-phase chromatography (Method **A**, product elutes at 35% B) and isolated as a yellow oil (0.0457 g, 0.101 mmol, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 7.3 Hz, 1H, H-7), 7.89 (t, J = 7.8 Hz, 1H, H-6), 7.44 (d, J = 7.7 Hz, 1H, H-5), 4.26 (s, 2H, H-16), 3.84 (s, 2H, H-9) 3.13-3.83 (m, 12H, H-10, H-11, H-12, H-13, H-14, H-15), 1.61 (s, 9H, H-1) 1.38 (s, 9H, H-19). ^{13}C NMR (175 MHz, $CDCl_3$): δ 164.0 (C-17), 157.6 (C-3) 161.4 (C-4), 147.7 (C-8), 138.8 (C-6), 126.1 (C-7), 124.1 (C-5), 83.9 (C-18), 83.7 (C-2), 58.6 (C-9), 58.5 (C-16), 55.0 (C-15), 53.5 (C-12) 52.5 (C-10), 50.8 (C-11), 45.3 (C-14), 45.1 (C-13), 27.9 (C-19), 27.8 (C-1). Calculated monoisotopic mass for **2** ($C_{23}H_{38}N_4O_4$): 434.29; found: m/z = 435.3 $[M + H]^+$.



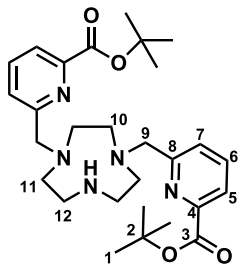
***tert*-Butyl 6-{[4,7-bis(*tert*-butoxycarbonylmethyl)-1,4,7-triazonan-1-yl]methyl}-2-pyridinecarboxylate (3).** Compound **1** (0.0517 g, 0.161 mmol, 1 eq), *tert*-butyl bromoacetate (0.0315 g, 0.161 mmol, 1 eq) was dissolved with K_2CO_3 (0.0224 g, 0.161 mmol, 1 eq) in acetonitrile (3.0 mL). The reaction mixture was stirred overnight at room temperature and subsequently filtered to remove solids. Solvent was removed *in vacuo* and **3** was purified using reverse-phase chromatography (Method **B**, product elutes at 95% B) and isolated as a yellow oil (0.0068 g, 0.013 mmol, 8%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 7.3 Hz, 1H, H-7), 7.92 (t, J = 7.8 Hz, 1H, H-6), 7.47 (d, J = 7.7 Hz, 1H, H-5), 4.88 (s, 2H, H-9), 4.22 (s, 4H, H-16), 3.09-3.68 (m, 12H, H-10, H-11, H-12, H-13, H-14, H-15), 1.53 (s, 18H, H-19), 1.43 (s, 9H, H-1). ^{13}C NMR (175 MHz, $CDCl_3$): δ 168.8 (C-17), 163.6 (C-3) 160.9 (C-4), 148.8 (C-8), 138.6 (C-6), 126.0 (C-7), 124.8 (C-5), 83.0 (C-18), 82.8 (C-2), 59.4 (C-9), 57.0 (C-16), 52.1 (C-15, C-10, C-11, C-14), 49.9 (C-12, C-13), 28.0 (C-1, C-19). Calculated monoisotopic mass for **3** ($C_{29}H_{48}N_4O_6$): 548.36; found: m/z = 549.5 $[M + H]^+$.



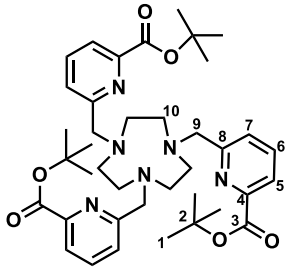
6-{[4,7-Bis(carboxymethyl)-1,4,7-triazonan-1-yl]methyl}-2-pyridinecarboxylic acid (4), H_3mpatcn. Compound **3** (0.0112 g, 0.020 mmol, 1 eq) was dissolved into as solution of 2:1 TFA and DCM (1 mL). The reaction mixture was stirred overnight at room temperature. Solvent was removed *in vacuo* and **4** was purified using reverse-phase chromatography (Method **B**, product elutes at 15% B) and isolated as an off-white solid (0.0067 g, 0.018 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (m, 1H, H-3), 8.04 (m, 1H, H-4), 7.82 (m, 1H, H-5), 4.45 (s, 2H, H-7), 3.68 (s, 4H, H-11), 3.01-3.27 (m, 12H, H-8, H-9, H-10). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0 (C-12), 166.0 (C-1), 154.7 (C-2), 147.9 (C-6), 138.7 (C-4), 127.4 (C-3), 124.5 (C-5), 59.0 (C-8), 54.7 (C-10), 50.6 (C-9), 50.0 (C-11), 48.8 (C-7). Calculated monoisotopic mass for **4** ($C_{17}H_{24}N_4O_6$): 380.17; found: *m*/*z* = 381.1 $[M + H]^+$.



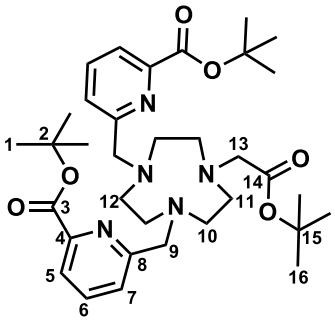
tert-butyl 6-{[4-({3-[(tert-butoxy)carbonyl]phenyl}methyl)-1,4,7-triazonan-1-yl]methyl}pyridine-2-carboxylate (5). 1,4,7-Triazocyclonane (0.0344 g, 0.267 mmol, 1 eq), *tert*-butyl 6-(bromomethyl)-2-pyridinecarboxylate (0.0725 g, 0.267 mmol, 1 eq) was dissolved with K_2CO_3 (0.0370 g, 0.267 mmol, 1 eq) in acetonitrile (3.0 mL). The reaction mixture was stirred overnight at room temperature and subsequently filtered to remove solids. Solvent was removed *in vacuo* and **5** was purified using reverse-phase chromatography (Method **A**, product elutes at 48% B) and isolated as a yellow oil (0.0457 g, 0.089 mmol, 33%). ^{1}H NMR (500 MHz, MeOD): δ 7.94 (t, *J* = 7.7 Hz, 2H, H-6), 7.86 (d, *J* = 7.6 Hz, 2H, H-5), 7.55 (d, *J* = 7.7 Hz, 2H, H-7), 4.64 (s, 4H, H-9), 3.57-3.92 (m, 12H, H-10, H-11, H-12), 1.55 (s, 18H, H-1). ^{13}C NMR (100 MHz, MeOD): δ 163.4 (C-3), 155.7 (C-4), 147.4 (C-8), 138.7 (C-6), 126.2 (C-7), 124.0 (C-5), 82.9 (C-2), 59.4 (C-9), 52.6 (C-10), 52.0 (C-12), 48.1 (C-11), 26.9 (C-1). Calculated monoisotopic mass for **5** ($C_{28}H_{41}N_5O_4$): 511.32; found: *m*/*z* = 512.4 $[M + H]^+$.



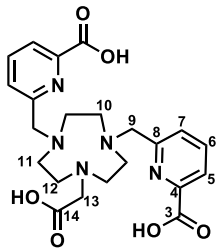
tert-butyl 6-[4,7-bis({6-[(tert-butoxy)carbonyl]pyridin-2-yl})-1,4,7-triazonan-1-yl]pyridine-2-carboxylate (6). 1,4,7-Triazocyclonane (0.0344 g, 0.267 mmol, 1 eq), *tert*-butyl 6-(bromomethyl)-2-pyridinecarboxylate (0.0725 g, 0.267 mmol, 1 eq) was dissolved with K_2CO_3 (0.0370 g, 0.267 mmol, 1 eq) in acetonitrile (3.0 mL). The reaction mixture was stirred overnight at room temperature and subsequently filtered to remove solids. Solvent was removed *in vacuo* and **6** was purified using reverse-phase chromatography (Method **A**, product elutes at 58% B) and isolated as a yellow oil (0.0272 g, 0.039 mmol, 15%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (m, 6H, H-5, H-6), 7.55 (m, 3H, H-7), 4.71 (s, 6H, H-9), 3.64-4.39 (m, 12H, H-10), 1.46 (s, 27H, H-1). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1 (C-3), 153.7 (C-4), 147.8 (C-8), 138.3 (C-6), 126.2 (C-7), 124.3 (C-5), 82.9 (C-2), 61.0 (C-9), 54.0 (C-10), 27.9 (C-1). Calculated monoisotopic mass for **6** ($C_{39}H_{54}N_6O_6$): 702.41; found: *m*/*z* = 703.5 $[M + H]^+$.



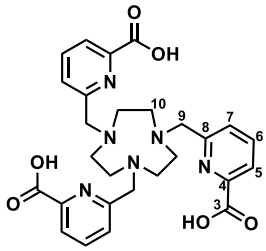
tert-butyl 6-({4-[2-(tert-butoxy)-2-oxoethyl]-7-({6-[(tert-butoxy)carbonyl]pyridin-2-yl}methyl)-1,4,7-triazonan-1-yl}methyl)pyridine-2-carboxylate (7). Compound **1** (0.0666 g, 0.130 mmol, 1 eq), *tert*-butyl bromoacetate (0.0253 g, 0.130 mmol, 1 eq) was dissolved with K_2CO_3 (0.0180 g, 0.130 mmol, 1 eq) in acetonitrile (3.0 mL). The reaction mixture was stirred overnight at room temperature and subsequently filtered to remove solids. Solvent was removed *in vacuo* and **7** was purified using reverse-phase chromatography (Method **A**, product elutes at 85% B) and isolated as a yellow oil (0.0160 g, 0.026 mmol, 20%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 7.4 Hz, 2H, H-7), 7.85 (t, J = 7.7 Hz, 2H, H-6), 7.57 (d, J = 7.7 Hz, 2H, H-5), 4.57 (s, 4H, H-9), 3.73 (s, 2H, H-13) 3.42-3.81 (m, 12H, H-10, H-11, H-12), 1.53 (s, 18H, H-1) 1.42 (s, 9H, H-16). ^{13}C NMR (175 MHz, $CDCl_3$): δ 168.0 (C-14), 163.4 (C-3), 148.3 (C-8), 138.4 (C-4), 128.7 (C-6), 126.5 (C-5), 124.4 (C-7), 83.3 (C-15), 82.9 (C-2), 60.6 (C-9), 58.0 (C-13), 55.6 (C-11), 53.4 (C-10), 52.6 (C-12), 27.9 (C-1), 27.9 (C-16). Calculated monoisotopic mass for **2** ($C_{34}H_{51}N_5O_6$): 625.38; found: m/z = 626.3 $[M + H]^+$.

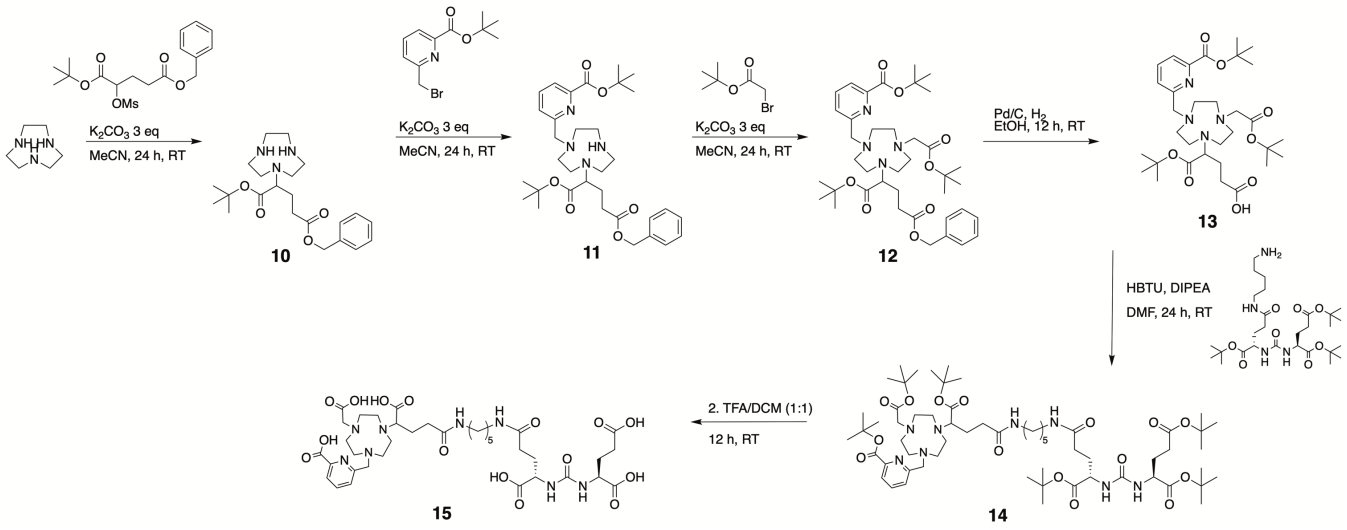


6-[4-(carboxymethyl)-7-(6-carboxypyridin-2-yl)-1,4,7-triazonan-1-yl]pyridine-2-carboxylic acid, H_3bptacn (8). Compound **7** (0.0200 g, 0.032 mmol, 1 eq) was dissolved into a solution of 2:1 TFA and DCM (1 mL). The reaction mixture was stirred overnight at room temperature. Solvent was removed *in vacuo* and **8** was purified using reverse-phase chromatography (Method **B**, product elutes at 14% B) and isolated as an off-white solid (0.0141 g, 0.031 mmol, 96%). ^{1}H NMR (700 MHz, MeOD): δ 8.04 (d, J = 7.7 Hz, 2H, H-7), 7.98 (t, J = 7.7 Hz, 2H, H-6), 7.69 (d, J = 7.9 Hz, 2H, H-5), 4.50 (s, 4H, H-9), 3.77 (s, 2H, H-13), 3.32-3.60 (m, 12H, H-10, H-11, H-12). ^{13}C NMR (175 MHz, MeOD): δ 171.1 (C-14), 166.0 (C-3), 155.1 (C-8), 147.4 (C-4), 138.6 (C-6), 126.9 (C-5), 124.3 (C-7), 59.6 (C-9), 55.6 (C-13), 51.7 (C-11), 51.1 (C-10), 50.5 (C-12). Calculated monoisotopic mass for **8** ($C_{22}H_{27}N_5O_6$): 457.20; found: m/z = 458.4 $[M + H]^+$.

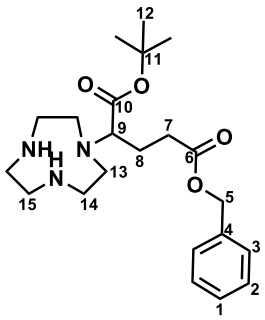


6-({4,7-bis[(6-carboxypyridin-2-yl)methyl]-1,4,7-triazonan-1-yl}methyl)pyridine-2-carboxylic acid, H_3tptacn (9). Compound **6** (0.0272 g, 0.039 mmol, 1 eq) was dissolved into a solution of 2:1 TFA and DCM (1 mL). The reaction mixture was stirred overnight at room temperature. Solvent was removed *in vacuo* and **9** was purified using reverse-phase chromatography (Method **B**, product elutes at 14% B) and isolated as an off-white solid (0.0198 g, 0.037 mmol, 94%). ^{1}H NMR (500 MHz, MeOD): δ 7.89 (t, 3H, H-6), 7.81 (d, 3H, H-5), 7.51 (d, 3H, H-7), 4.73 (s, 6H, H-9), 3.58-4.39 (m, 12H, H-10). ^{13}C NMR (175 MHz, MeOD): δ 165.6 (C-3), 154.2 (C-4), 146.7 (C-8), 138.5 (C-6), 126.2 (C-7), 124.3 (C-5), 60.1 (C-9), 52.7 (C-10). Calculated monoisotopic mass for **9** ($C_{27}H_{30}N_6O_6$): 534.22; found: m/z = 535.4 $[M + H]^+$.

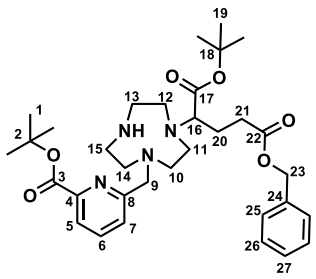




Scheme S2. Chemical synthesis of picaga-DUPA (**15**).



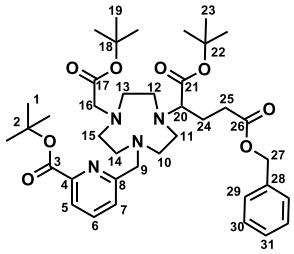
Benzyl *tert*-butyl 2-(1,4,7-triazonan-1-yl)glutarate (10). 1,4,7-Triazocyclonane (0.703 g, 0.546 mmol, 1 eq), benzyl *tert*-butyl 2- (methylsulfonyloxy)glutarate (0.2030 g, 0.546 mmol, 1 eq) was dissolved with K_2CO_3 (0.0759 g, 0.546 mmol, 1 eq) in acetonitrile (3.0 mL). The reaction mixture was stirred overnight at room temperature and subsequently filtered to remove solids. Solvent was removed *in vacuo* and **10** was purified using reverse-phase chromatography (Method **A**, product elutes at 28% B) and isolated as a white solid (0.1397 g, 0.346 mmol, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (br, 5H, H-1, H-2, H-3), 5.13 (m, 2H, H-5), 3.39 (m, 1H, H-9) 2.92-3.85 (m, 12H, H-13, H-14, H-15), 2.48 (m, 1H, H-7), 2.57 (m, 1H, H-7), 2.04 (m, 2H, H-8), 1.45 (s, 9H, H-12). ^{13}C NMR (175 MHz, $CDCl_3$): δ 172.7 (C-6), 172.5 (C-10), 135.7 (C-4), 128.6 (C-1), 128.4 (C-2), 128.4 (C-3), 83.8 (C-11), 66.6 (C-9), 45.5 (C-13, C-14, C15), 31.3 (C-8), 28.0 (C-12), 24.4 (C-7). Calculated monoisotopic mass for **10** ($C_{22}H_{35}N_3O_4$): 405.26; found: *m*/*z* = 406.2 $[M + H]^+$.



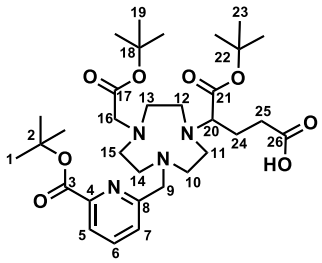
Benzyl *tert*-butyl 2-{4-[(6-*tert*-butoxycarbonyl-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}glutarate (11). Compound **10** (0.0271 g, 0.067 mmol, 1 eq), *tert*-butyl 6-(bromomethyl)-2-pyridinecarboxylate (0.0182 g, 0.067 mmol, 1 eq) was dissolved with K_2CO_3 (0.0093 g, 0.067 mmol, 1 eq) in acetonitrile (3.0 mL). The reaction mixture was stirred overnight at room temperature and subsequently filtered to remove solids. Solvent was removed *in vacuo* and **12** was purified using reverse-phase chromatography (Method **A**, product elutes at 35% B) and isolated as a yellow oil (0.0078 g, 0.013 mmol, 20%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (m, 1H, H-5), 7.81 (m, 1H, H-6), 7.36 (m, 6H, H-7, H-25, H-26, H-27), 5.09 (s, 2H, H-23), 4.16 (m, 2H, H-9),

2.78-3.63 (m, 13H, H-10, H-11, H-12, H-13, H-14, H-15, H-16), 2.49 (m, 2H, H-21), 2.07 (m, 1H, H-20), 1.91 (m, 1H, H-20), 1.59 (m, 9H, H-19), 1.43 (s, 9H, H-1). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6 (C-22), 171.5 (C-17), 163.6 (C-3), 158.2 (C-4), 157.3 (C-8), 148.2 (C-6), 138.4 (C-5), 135.7 (C-24), 128.6 (C-27), 128.4 (C-26), 126.8 (C-7), 125.6 (C-25), 83.4 (C-2), 82.4 (C-18), 66.6 (C-23), 65.3 (C-9), 58.8 (C-15) 50.9 (C-14), 49.6 (C-10, C-12), 47.7 (C-11), 45.6 (C-13), 39.9 (C-16), 32.8 (C-20), 31.1 (C-21), 28.1 (C-19), 27.9 (C-1). Calculated monoisotopic mass for **11** ($C_{33}H_{48}N_4O_6$): 596.36; found: *m*/*z* = 597.3 $[M + H]^+$.

Benzyl *tert*-butyl 2-{7-(*tert*-butoxycarbonylmethyl)-4-[(6-*tert*-butoxycarbonyl-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}glutarate (12). Compound **11** (0.0440 g, 0.101 mmol, 1 eq), *tert*-butyl 2-(methylsulfonyloxy)glutarate (0.0376 g, 0.101 mmol, 1 eq) was dissolved with K_2CO_3 (0.0140 g, 0.101 mmol, 1 eq) in acetonitrile (3.0 mL). The reaction mixture was stirred overnight at room temperature and subsequently filtered to remove solids. Solvent was removed *in vacuo* and **12** was purified using reverse-phase chromatography (Method **A**, product elutes at 95% B) and isolated as a yellow oil (0.0112 g, 0.016 mmol, 16%). NMR (400 MHz, $CDCl_3$): δ 7.98 (m, 1H, H-5), 7.87 (m, 1H, H-6), 7.65 (m, 1H, H-7), 7.33 (m, 5H, H-29, H-30, H-31), 5.05 (s, 2H, H-27), 4.61 (m, 2H, H-9), 2.63-3.67 (m, 15H, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-20), 2.52 (m, 2H, H-25), 2.01 (m, 2H, H-24), 1.37-1.70 (m, 27H, H-1, H-19, H-23). ^{13}C NMR (175 MHz, $CDCl_3$): δ 174.5 (C-26), 172.8 (C-21), 171.2 (C-17), 169.3 (C-3), 160.6 (C-4), 160.2 (C-8), 148.9 (C-6), 138.8 (C-5), 135.7 (C-28), 128.6 (C-31), 128.4 (C-30), 128.3 (C-29), 127.1 (C-7), 82.6 (C-27), 66.5 (C-9), 64.2 (C-16), 59.1 (C-20), 28.1 (C-1), 28.0 (C-19), 28.0 (C-23), 27.9 (C-24), 25.0 (C-25). Calculated monoisotopic mass for **12** ($C_{39}H_{58}N_4O_8$): 710.43; found: *m*/*z* = 711.4 $[M + H]^+$.

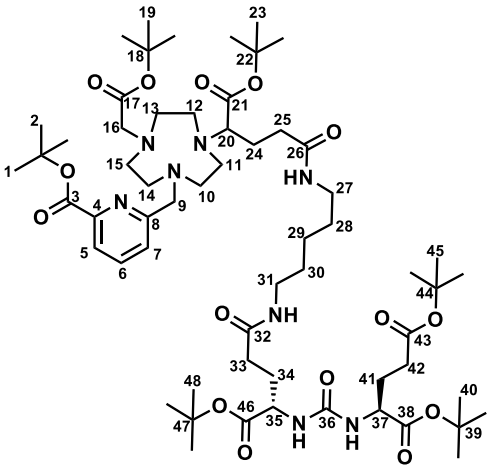


4-*tert*-Butoxycarbonyl-4-{7-(*tert*-butoxycarbonylmethyl)-4-[(6-*tert*-butoxycarbonyl-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}butyric acid (13). Compound **12** (0.0312 g, 0.044 mmol, 1 eq) was dissolved in EtOH (4 mL) and 10% Pd/C (0.0120 g) was added to the flask. After purging the flask with H_2, the reaction mixture was stirred for 3 h under H_2-pressure (1 atm). The reaction mixture was filtered through a PVDF filter, the solvent was evaporated *in vacuo*, and the desired product was obtained as a yellow oil (0.0272 g, 0.044 mmol, 99%) and used without further purification immediately for amidation with *tert*-butyl-protected DUPA fragment. Calculated monoisotopic mass for **13** ($C_{32}H_{52}N_4O_8$): 620.38; found: *m*/*z* = 621.3 $[M + H]^+$.

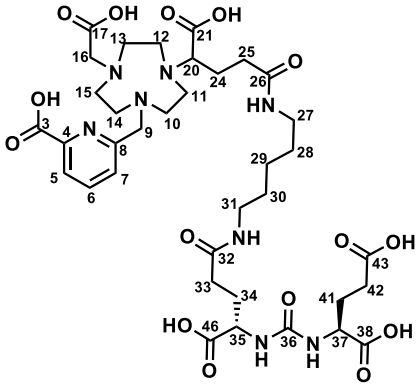


Di*tert*-butyl 2-{3-[(*R*)-4-oxo-1-*tert*-butoxycarbonyl-4-[5-(4-*tert*-butoxycarbonyl-4-{7-(*tert*-butoxycarbonylmethyl)-4-[(6-*tert*-butoxycarbonyl-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}butyrylamino)pentylamino]butyl]ureido}glutarate (14) Compound **13** (0.0272 g, 0.0483, 1.0 eq) and HBTU (0.0183 g, 0.0439, 1.1 eq) were dissolved in DMF (1 mL), DIPEA (0.0057 g, 0.0439 mmol, 1.1 eq) was added. Di*tert*-butyl 2-{3-[(*R*)-4-(5-aminopentylamino)-4-oxo-1-*tert* butoxycarbonylbutyl]

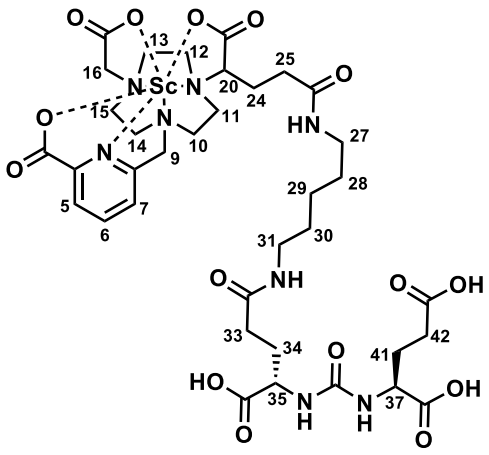
ureido}glutarate (0.0251 g, 0.0483 mmol, 1 eq) was added and reaction mixture was stirred overnight at room temperature. Solvent was removed *in vacuo* and product was purified by reverse-phase flash chromatography (Method **B**) to afford **14** (0.0045 g, 0.004 mmol, 9%) as an off-white solid. NMR (500 MHz, $CDCl_3$): δ 8.00 (d, 1H, H-5), 7.91 (t, 1H, H-6), 7.66 (d, 1H, H-7), 4.18 (m, 2H, H-35, H-37), 3.56 (m, 2H, H-16), 3.38 (m, 1H, H-20), 3.12 (m, 4H, H-27, H-31), 2.70-3.69 (m, 14H, H-9, H-10, H-11, H-12, H-13, H-14, H-15), 2.35 (m, 2H, H-25), 2.28 (m, 2H, H-42), 2.20 (m, 2H, H-33), 2.03 (m, 2H, H-34, H-41), 2.02 (m, 1H, H-24), 1.91 (m, 1H, H-24), 1.79 (m, 2H, H-34, H-41), 1.43 (m, 4H, H-28, H-30), 1.33-1.59 (m, 63H, H-1, H-19, H-23, H-40, H-45, H-48) 1.28 (m, 2H, H-29). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3 (C-26), 173.4, (C-32), 173.3 (C-38), 172.4 (C-46), 172.3 (C-43), 172.1 (C-21), 172.0 (C-17), 171.8 (C-36), 170.0(C-3), 148.9 (C-4), 138.9 (C-8), 124.8 (C-6), 116.8 (C-5), 115.1 (C-7), 82.7 (C-22), 82.5 (C-47), 81.8 (C-44), 81.7 (C-18), 81.5 (C-2), 81.4 (C-39), 64.1 (C-20), 58.7 (C-35), 58.2 (C-37), 53.2 (C-19), 52.8 (C-16), 39.5 (C-27), 38.9 (C-31), 32.1 (C-28, C-30), 31.1 (C-25), 28.7 (C-33), 28.6 (C-34), 28.5 (C-24), 27.9 (C-31), 27.1 (C-23), 27.1 (C-48), 27.0 (C-45), 27.0 (C-1), 26.9 (C-29) 25.7 (C-41), 25.6 (C-42), 23.8 (C-40). Calculated monoisotopic mass for **14** ($C_{60}H_{102}N_8O_{15}$): 1174.75; found: m/z = 1175.8 $[M + H]^+$.

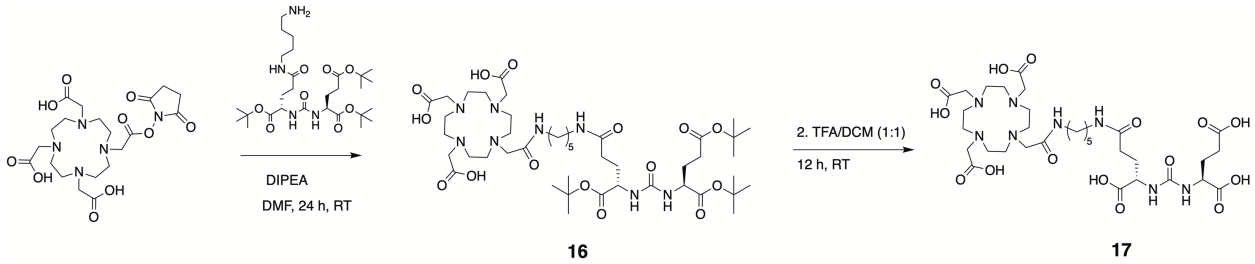


2-{3-[(*R*)-1-Carboxy-4-[5-(4-carboxy-4-{7-(carboxymethyl)-4-[(6-carboxy-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}butyrylamino)pentylamino]-4-oxobutyl]ureido}glutaric acid, picaga-DUPA (15) Compound **14** (0.0045 g, 0.004 mmol, 1 eq) was dissolved into a solution of 2:1 TFA and DCM (1 mL). The reaction mixture was stirred overnight at room temperature. Solvent was removed *in vacuo* and **15** was purified using reverse-phase chromatography (Method **B**, product elutes at 15% B) and isolated as an off-white solid (0.0034 g, 0.004 mmol, 99%). ^1H NMR (700 MHz, $CDCl_3$): δ 8.19 (d, 1H, H-5), 8.07 (m, 1H, H-6), 7.84 (m, 1H, H-7), 4.33 (m, 1H, H-35), 4.29 (m, 1H, H-37), 3.70 (m, 2H, H-16), 3.47 (m, 1H, H-20), 3.15 (m, 4H, H-27, H-31), 2.89-3.60 (m, 14H, H-9, H-10, H-11, H-12, H-13, H-14, H-15), 2.43 (m, 2H, H-25), 2.31 (m, 2H, H-42), 2.18 (m, 2H, H-33), 2.02 (m, 2H, H-24), 1.63 (m, 1H, H-24), 1.90 (m, 2H, H-34, H-41), 1.51 (m, 2H, H-34, H-41), 1.31 (m, 4H, H-28, H-30), 0.92 (m, 2H, H-29). ^{13}C NMR (175 MHz, $CDCl_3$): δ 175.0 (C-26), 174.5 (C-32), 174.4 (C-38), 173.6 (C-46), 173.5 (C-43), 166.0 (C-21), 160.5 (C-17), 160.3 (C-36), 158.7 (C-3), 131.2 (C-4), 131.0 (C-8), 126.8 (C-6), 117.0 (C-5), 115.4 (C-7), 67.7 (C-20), 58.8 (C-16), 52.2 (C-35), 52.2 (C-37), 38.9 (C-25), 31.9 (C-33), 29.7 (C-34), 28.6 (C-24), 28.5 (C-29), 25.3 (C-41), 23.8 (C-42). Calculated monoisotopic mass for **15** ($C_{36}H_{54}N_8O_{15}$): 838.37; found: m/z = 839.1 $[M + H]^+$.



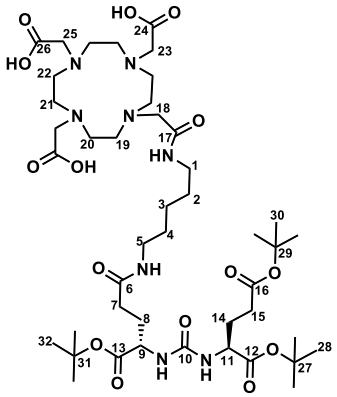
Scandium complexed 2-{3-[(*R*)-1-Carboxy-4-[5-(4-carboxy-4-{7-(carboxymethyl)-4-[(6-carboxy-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}butyrylamino)pentylamino]-4-oxobutyl]ureido}glutaric acid, Sc(picaga)-DUPA (18) Compound **15** (0.0033 g, 0.004 mmol, 1 eq) was dissolved into a solution of 0.25 M ammonium acetate pH 4.0 (1.0 mL). $ScCl_3 \cdot 6H_2O$ (0.0011 g, 0.004 mmol, 1.05 eq) was added to the vial and the mixture was complexed at 80 °C for 30 minutes. **18** was purified using reverse-phase chromatography (Method **C**, isomer A and B elute at 14% B and 15% B, respectively) and isolated separate stereoisomers as Sc(picaga)-DUPA A (0.0009 g, 0.001 mmol, 26%) and Sc(picaga)-DUPA B (0.0011 g, 0.001 mmol, 32%) as off-white solids. Isomer A: ^{1}H NMR (700 MHz, MeOD): δ 8.12 (m, 1H, H-6), 8.01 (m, 1H, H-5), 7.60 (m, 1H, H-7), 4.21 (m, 1H, H-35), 4.17 (m, 1H, H-37), 3.52 (m, 2H, H-16), 3.28 (m, 1H, H-20), 3.20 (m, 4H, H-27, H-31), 2.49-3.60 (m, 14H, H-9, H-10, H-11, H-12, H-13, H-14, H-15), 2.39 (m, H-34, H-41) 2.38 (m, 2H, H-33), 2.28 (m, 2H, H-42), 2.12 (m, 4H, H-25 H-34, H-41), 1.93 (m, 2H, H-34, H-41), 1.85 (m, 1H, H-34, H-41), 1.72 (m, 1H, H-24), 1.56 (m, 1H, H-24), 1.56 (m, 2H, H-28), 1.44 (m, 2H, H-30), 0.86 (m, 2H, H-29). Isomer B ^{1}H NMR (700 MHz, MeOD): δ 8.15 (m, 1H, H-6), 8.05 (m, 1H, H-5), 7.63 (m, 1H, H-7), 4.33 (m, 1H, H-35), 4.29 (m, 1H, H-37), 3.60 (m, 2H, H-16), 3.28 (m, 1H, H-20), 3.19 (m, 4H, H-27, H-31), 2.49-3.60 (m, 14H, H-9, H-10, H-11, H-12, H-13, H-14, H-15), 2.44 (m, H-34, H-41) 2.42 (m, 2H, H-33), 2.33 (m, 2H, H-42), 2.18 (m, 2H, H-34, H-41), 2.12 (m, 2H, H-25), 2.02 (m, 1H, H-24), 1.90 (m, 2H, H-34, H-41), 1.59 (m, 1H, H-24), 1.54 (m, 2H, H-28), 1.31 (m, 2H, H-30), 0.92 (m, 2H, H-29). Calculated monoisotopic mass for **20** ($C_{36}H_{51}N_8O_{15}Sc_1$): 880.30; found: m/z = 881.3 $[M + H]^+$.



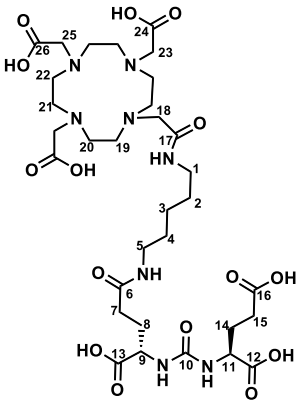


Scheme S3. Chemical synthesis of DOTA-DUPA (**17**).

(4-{2-[2-(5-{(*R*)-4-[3-(1,3-Di*tert*-butoxycarbonylpropyl)ureido]-4-*tert*-butoxycarbonylbutyrylamino}pentylamino)-2-oxoethylamino]-2-oxoethyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraaza-1-cyclododecyl)acetic acid (16). Di*tert*-butyl 2-{3-[(*R*)-4-(5-aminopentylamino)-4-oxo-1-*tert*-butoxycarbonylbutyl]ureido}glutarate (0.0100 g, 0.0175 mmol, 1 eq) was added to {4,10-bis(carboxymethyl)-7-[(2,5-dioxo-1-pyrrolidinyloxycarbonyl)methyl]-1,4,7,10-tetraaza-1-cyclododecyl}acetic acid·HPF_6·TFA (13.8 g, 0.0175 mmol, 1 eqand DIPEA (0.0023 g, 0.017 mmol, 1 eq) in 1 mL DMF. The reaction mixture was stirred for 2 h at room temperature. Subsequently, the mixture was concentrated *in vacuo* and **16** was purified using reverse-phase chromatography (Method **B**, product elutes at 60% B) and isolated as an off-white solid (0.0079 g, 0.008 mmol, 47%). ^{1}H NMR (700 MHz, MeOD): δ 4.22 (m, 1H, H-11), 4.15 (m, 1H, H-9), 3.27-3.38 (m, 22H, H-19, H-20, H-21, H-22, H-23, H-25), 3.12-3.26 (m, 6H, H-1, H-5, H-18), 2.31 (m, 4H, H-7, H-15), 2.09 (m, 2H, H-8, H-14), 1.84 (m, 2H, H-8, H-14), 1.54 (m, 4H, H-2, H-4), 1.49 (m, 18H, H-28, H-32, 1.47 (m, 9H, H-30), 1.37 (m, 2H, H-3). ^{13}C NMR (100 MHz, MeOD): δ 172.3 (C-6), 172.1 (C-12, C-13), 172.0 (C-16), 159.7 (C-17), 159.5 (C-24), 159.3 (C-26), 158.4 (C-10), 116.6 (C-23), 115.0 (C-25), 81.5 (C-27), 81.6 (C-31), 80.4 (C-29), 53.2 (C-9), 52.8 (C-18), 48.2 (C-11), 48.0 (H-19, H-20, H-21, H-22), 39.0 (C-1), 38.8 (C-5), 31.8 (C-2), 31.8 (C-4), 31.1 (C-15), 28.7 (C-8), 28.4 (C-14), 27.6 (C-7), 26.9 (C-28, C-32), 26.9 (C-30), 23.7 (C-3). Calculated monoisotopic mass for **16** ($C_{44}H_{78}N_8O_{15}$): 958.56; found: *m*/*z* = 959.5 $[M + H]^+$.



2-{3-[(*R*)-1-Carboxy-4-oxo-4-[5-(2-{2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraaza-1-cyclododecyl]acetylamino}acetylamino)pentylamino]butyl]ureido}glutaric acid (17). Compound **16** (0.0138 g, 0.0167 mmol, 1 eq) was dissolved into a solution of 2:1 TFA and DCM (1 mL). The reaction mixture was stirred overnight at room temperature. Solvent was removed *in vacuo* and **17** was purified using reverse-phase chromatography (Method **B**, product elutes at 15% B) and isolated as an off-white solid (0.0058 g, 0.007 mmol, 53%). ^{1}H NMR (400 MHz, D_2O): δ 4.20 (m, 1H, H-9), 4.10 (m, 1H, H-11), 3.54-4.00 (br, 8H, H-18, H-23, H-25,), 2.95-3.45 (m, 20H, H-1, H-5, H-19, H-20, H-21, H-22), 2.54 (m, 2H, H-15) 2.28 (m, 2H, H-7), 2.10 (m, 2H, H-8, H-14), 1.90 (m, 2H, H-8, H-14), 1.43 (m, 4H, H-2, H-4), 1.24 (m, 2H, H-3). ^{13}C NMR (100 MHz, MeOD): δ 175.0 (C-6), 174.6 (C-12, C-13), 174.5 (C-16), 173.5 (C-17), 161.4 (C-26), 161.2 (C-24), 158.7 (C-10), 81.3 (C-23), 78.1 (C-25), 52.2 (C-9), 52.2 (C-11), 49.3 (C-18), 49.3 (H-19), 48.5 (H-20), 48.1 (H-21), 48.1 (H-22), 38.6 (C-1), 33.9 (C-5), 33.8 (C-2), 31.8 (C-4), 29.7 (C-15), 28.6 (C-8), 28.4 (C-14), 27.4 (C-7), 23.7 (C-3). Calculated monoisotopic mass for **17** ($C_{32}H_{54}N_8O_{15}$): 790.37; found: m/z = 791.3 $[M + H]^+$.



1.2 NMR spectra

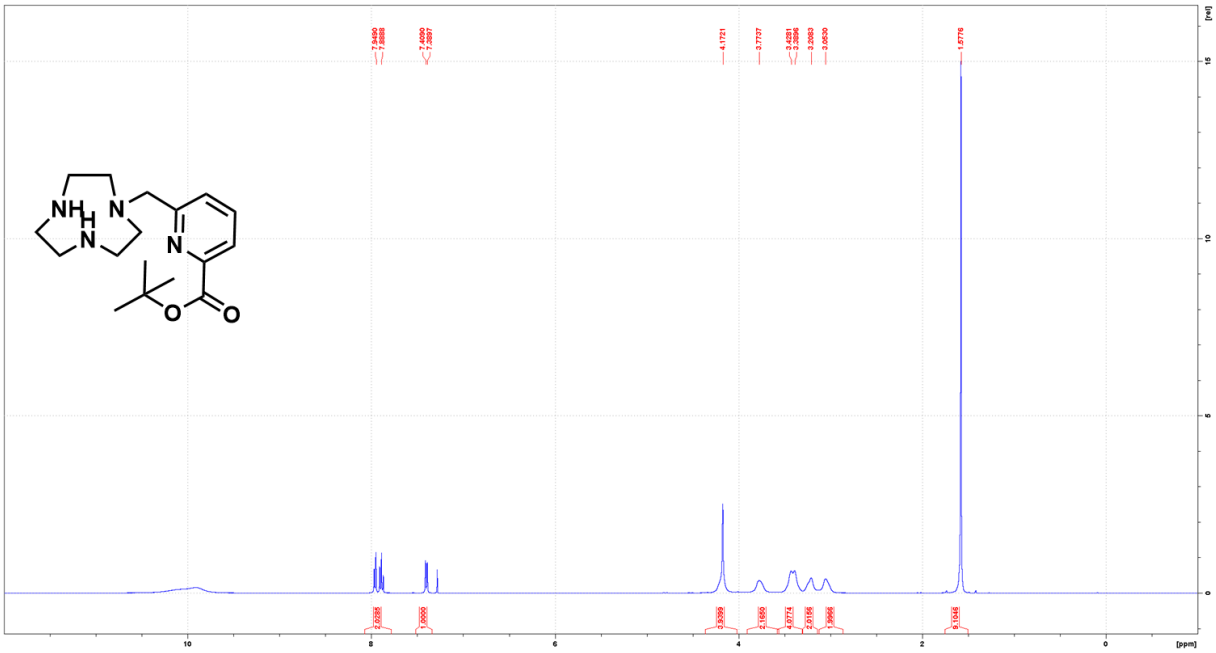


Figure S1. ^{1}H NMR of tert-butyl 6-[(1,4,7-triazonan-1-yl)methyl]-2-pyridinecarboxylate **(1)**.

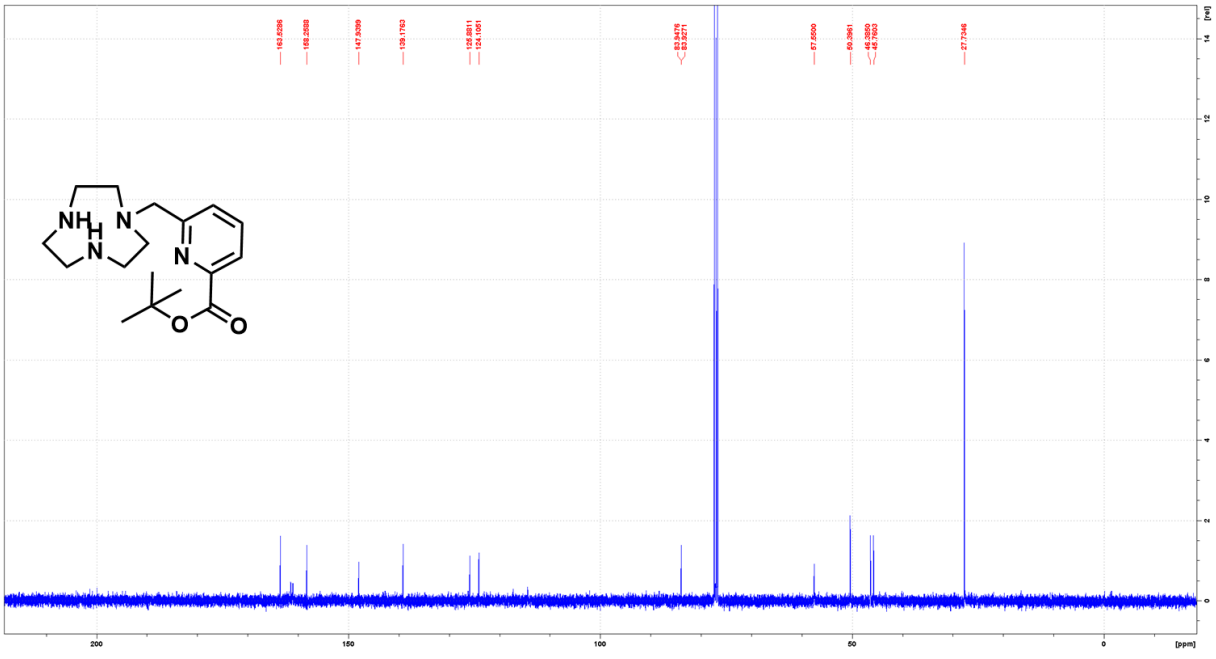


Figure S2. ^{13}C NMR of tert-butyl 6-[(1,4,7-triazonan-1-yl)methyl]-2-pyridinecarboxylate **(1)**.

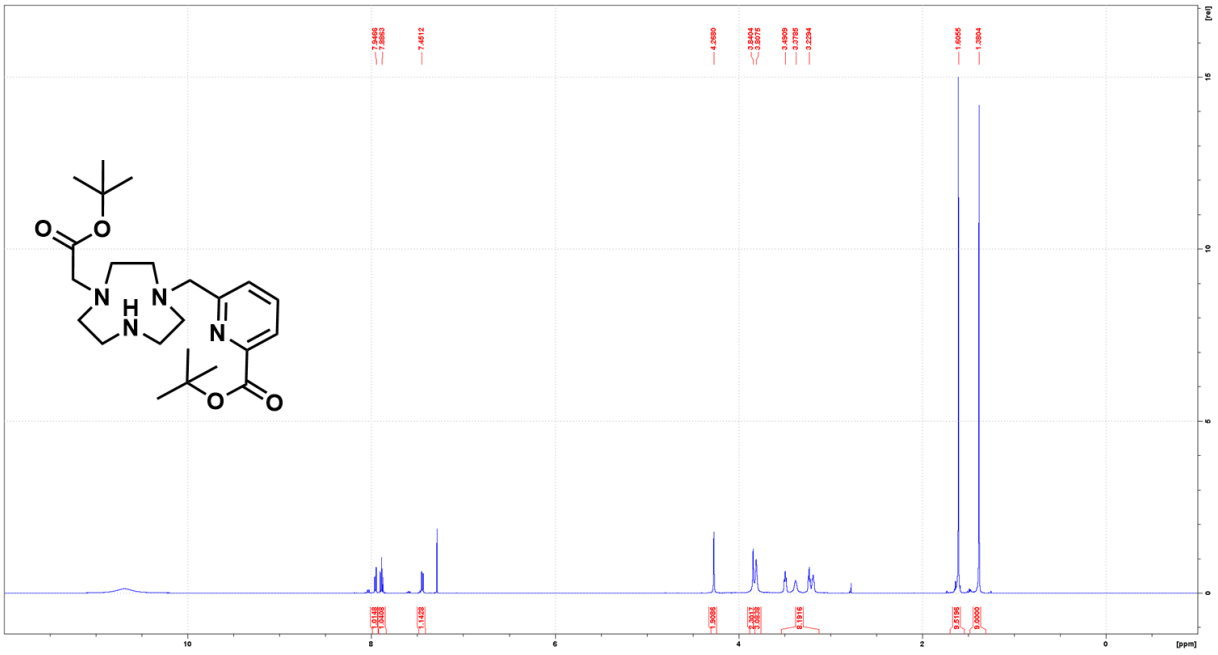


Figure S3. ^{1}H NMR of tert-butyl 6-{[4-(tert-butoxycarbonylmethyl)-1,4,7-triazonan-1-yl]methyl}-2-pyridinecarboxylate **(2)**.

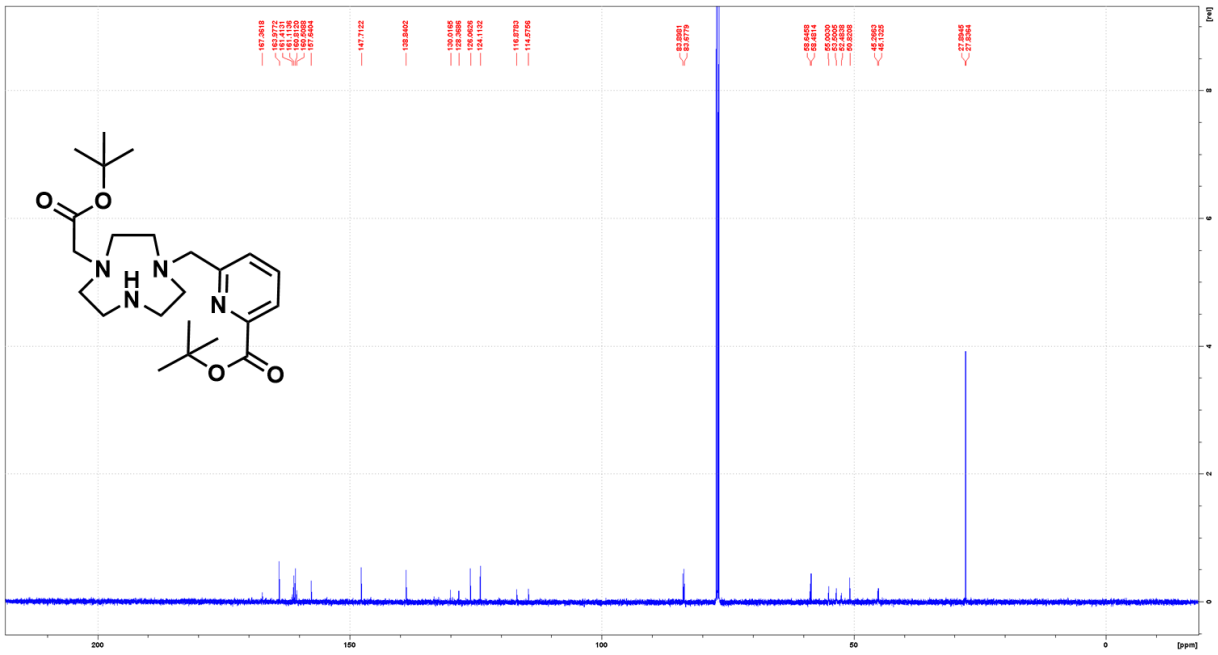


Figure S4. ^{13}C NMR of tert-butyl 6-{[4-(tert-butoxycarbonylmethyl)-1,4,7-triazonan-1-yl]methyl}-2-pyridinecarboxylate **(2)**.

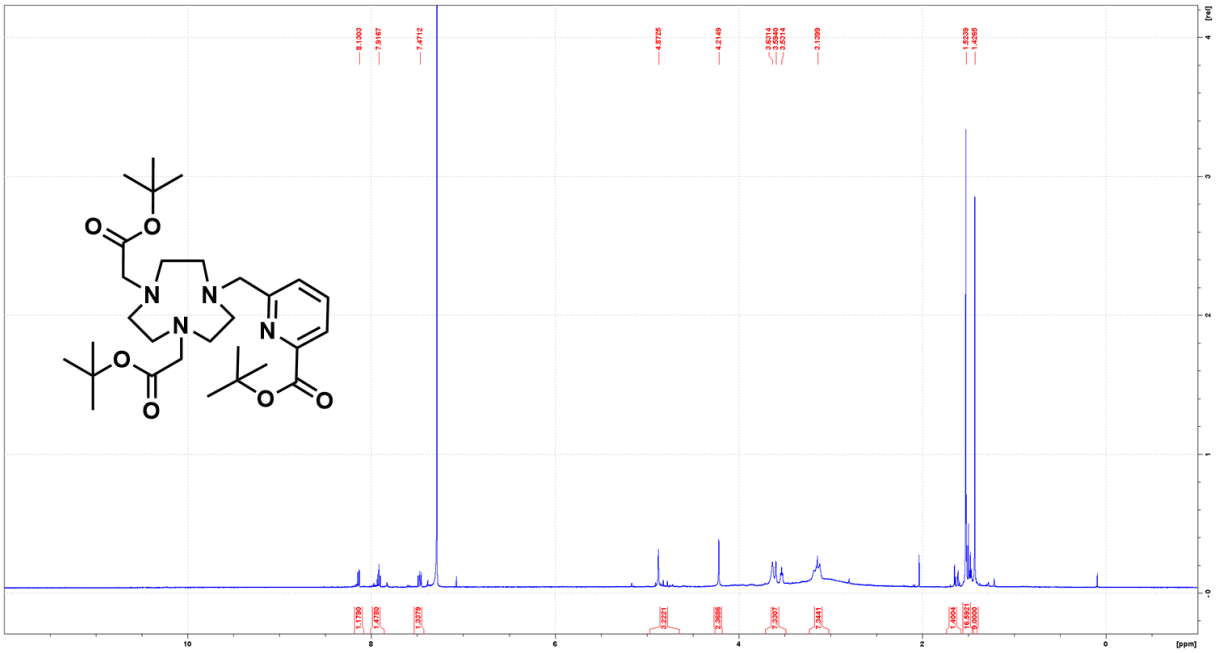


Figure S5. [1]H NMR of *tert*-butyl 6-{[4,7-bis(*tert*-butoxycarbonylmethyl)-1,4,7-triazonan-1-yl]methyl}-2-pyridinecarboxylate **(3)**.

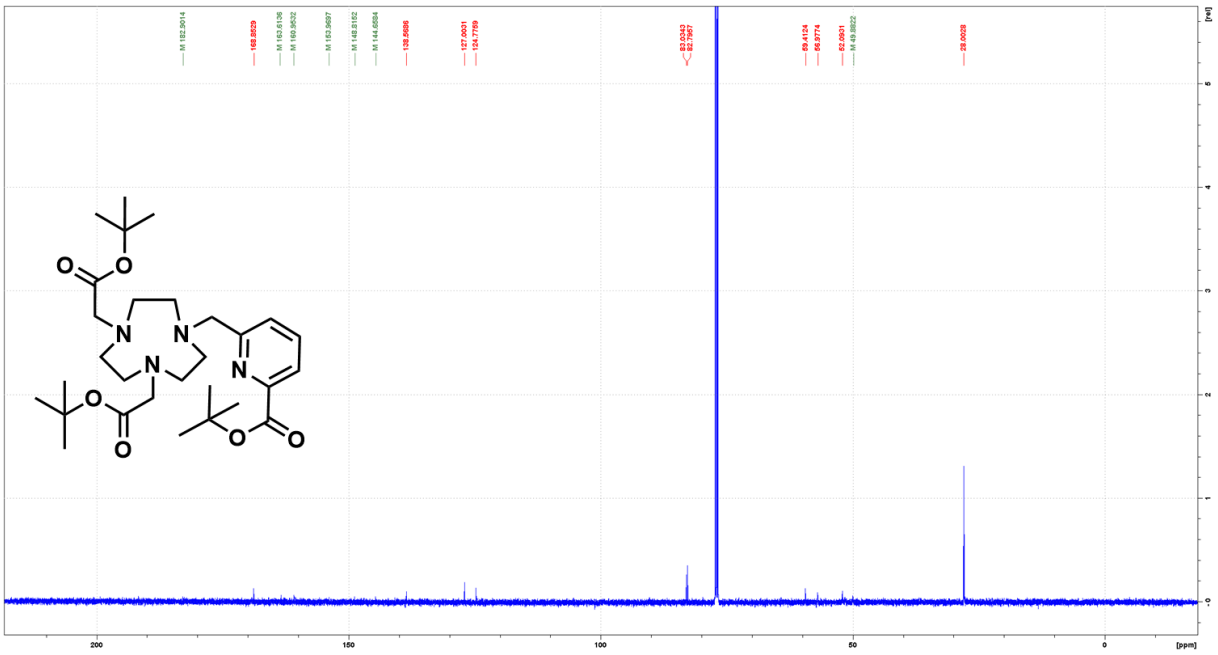


Figure S6. [13]C NMR of *tert*-butyl 6-{[4,7-bis(*tert*-butoxycarbonylmethyl)-1,4,7-triazonan-1-yl]methyl}-2-pyridinecarboxylate **(3)**.

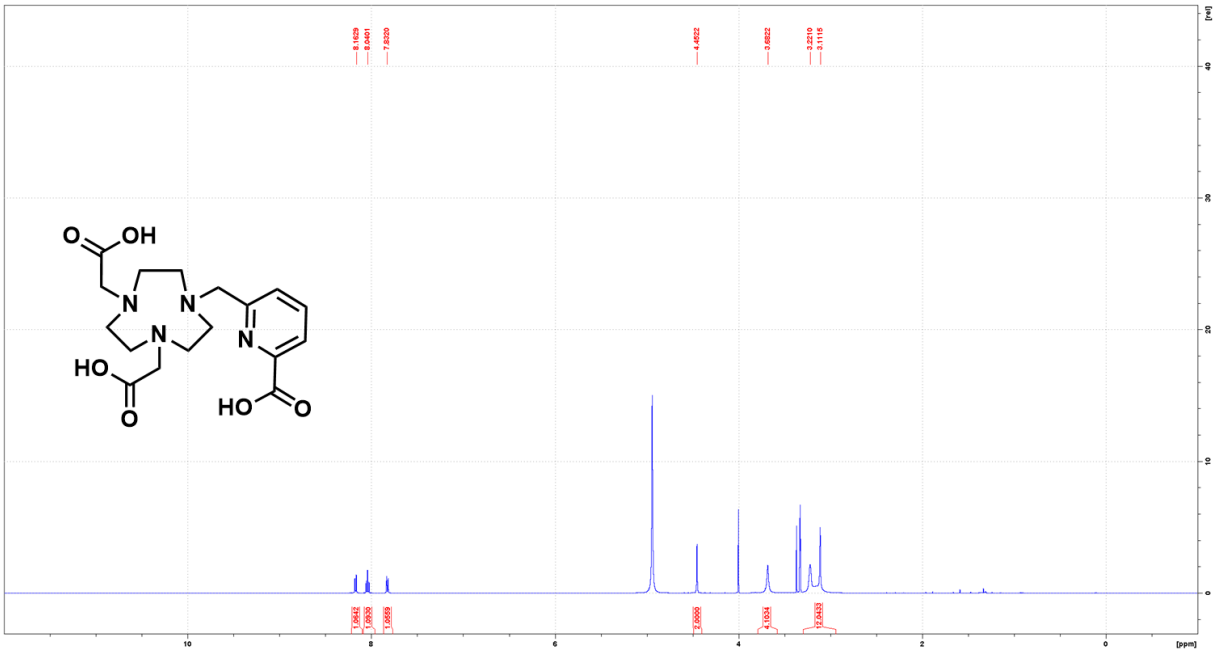


Figure S7. [1]H NMR of 6-{[4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl]methyl-2-pyridinecarboxylic acid **(4)**.

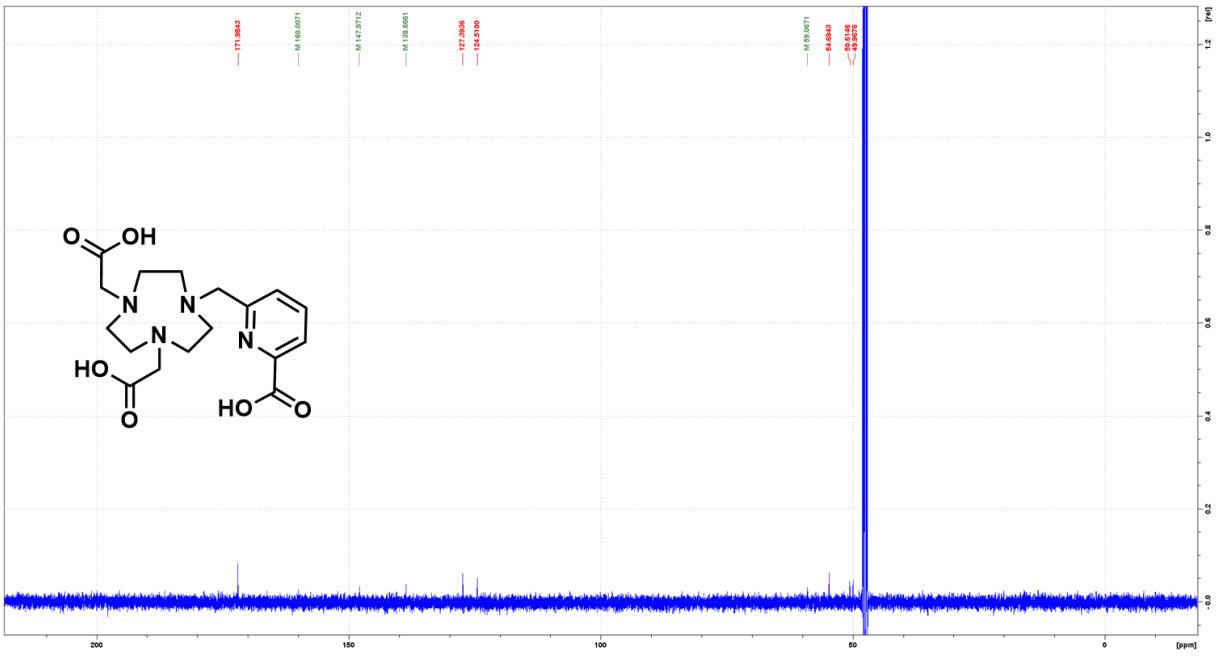


Figure S8. [13]C NMR of 6-{[4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl]methyl}-2-pyridinecarboxylic acid **(4)**.

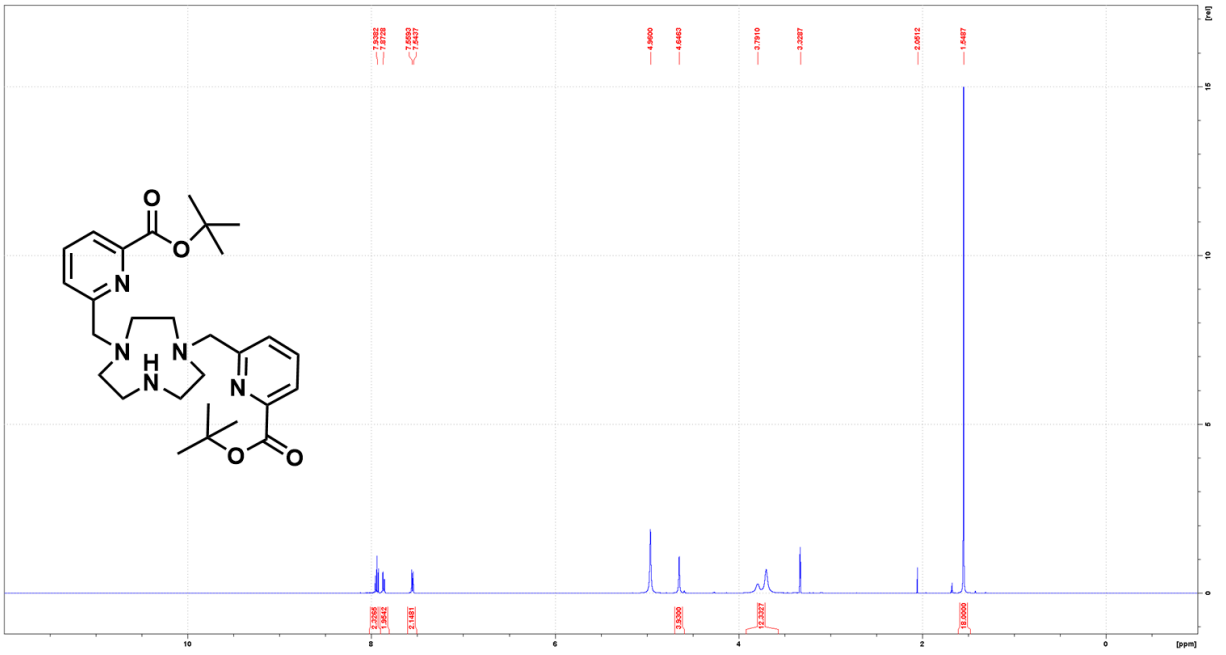


Figure S9. ^{1}H NMR of tert-butyl 6-{[4-({3-[(tert-butoxy)carbonyl]phenyl}methyl)-1,4,7-triazonan-1-yl]methyl}pyridine-2-carboxylate (**5**).

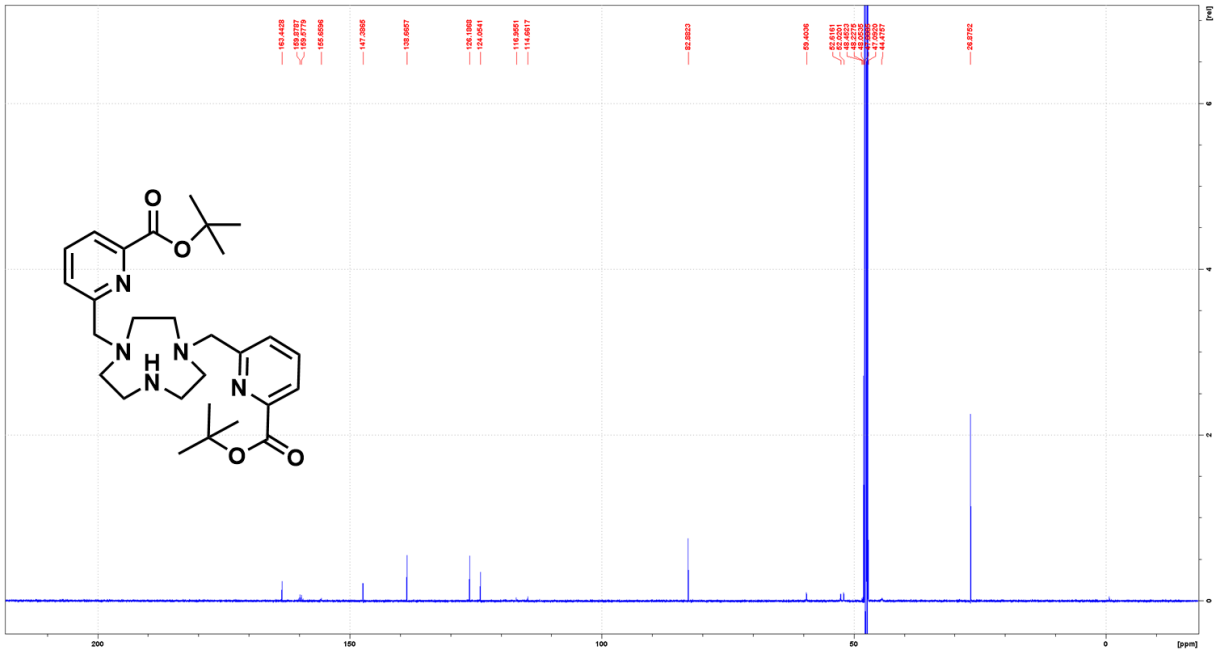


Figure S10. ^{13}C NMR of tert-butyl 6-{[4-({3-[(tert-butoxy)carbonyl]phenyl}methyl)-1,4,7-triazonan-1-yl]methyl}pyridine-2-carboxylate (**5**).

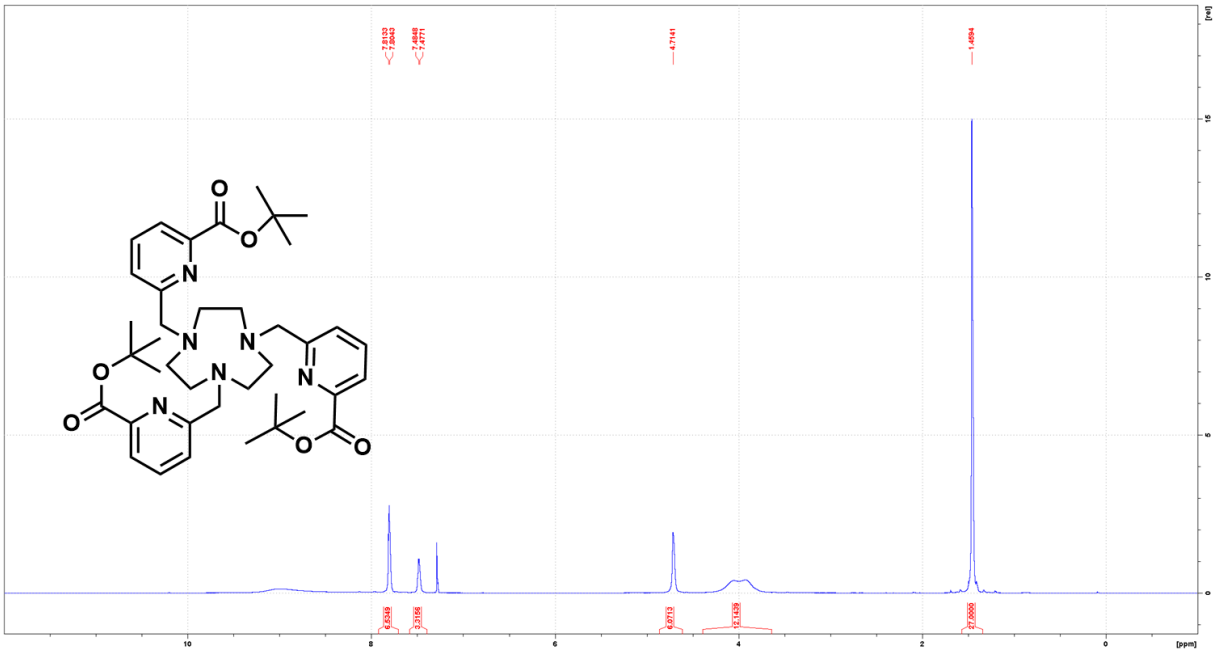


Figure S11. ^{1H} NMR of tert-butyl 6-[4,7-bis({6-[(tert-butoxy)carbonyl]pyridin-2-yl})-1,4,7-triazonan-1-yl]pyridine-2-carboxylate **(6)**.

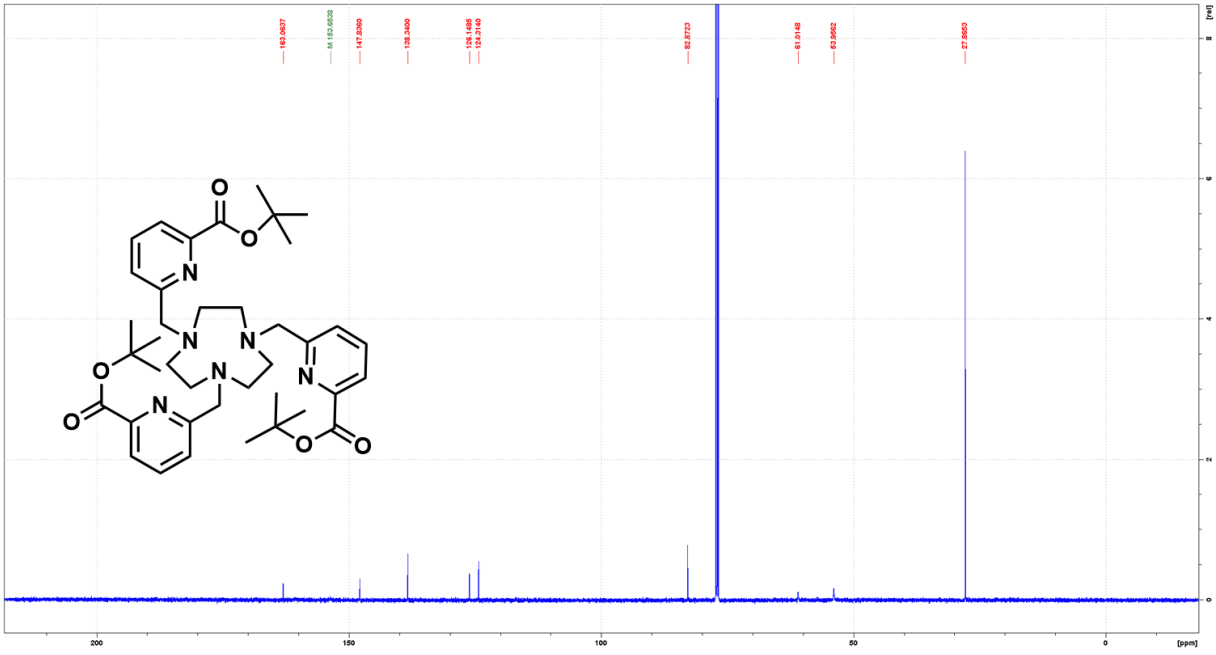


Figure S12. ^{13}C NMR of tert-butyl 6-[4,7-bis({6-[(tert-butoxy)carbonyl]pyridin-2-yl})-1,4,7-triazonan-1-yl]pyridine-2-carboxylate **(6)**.

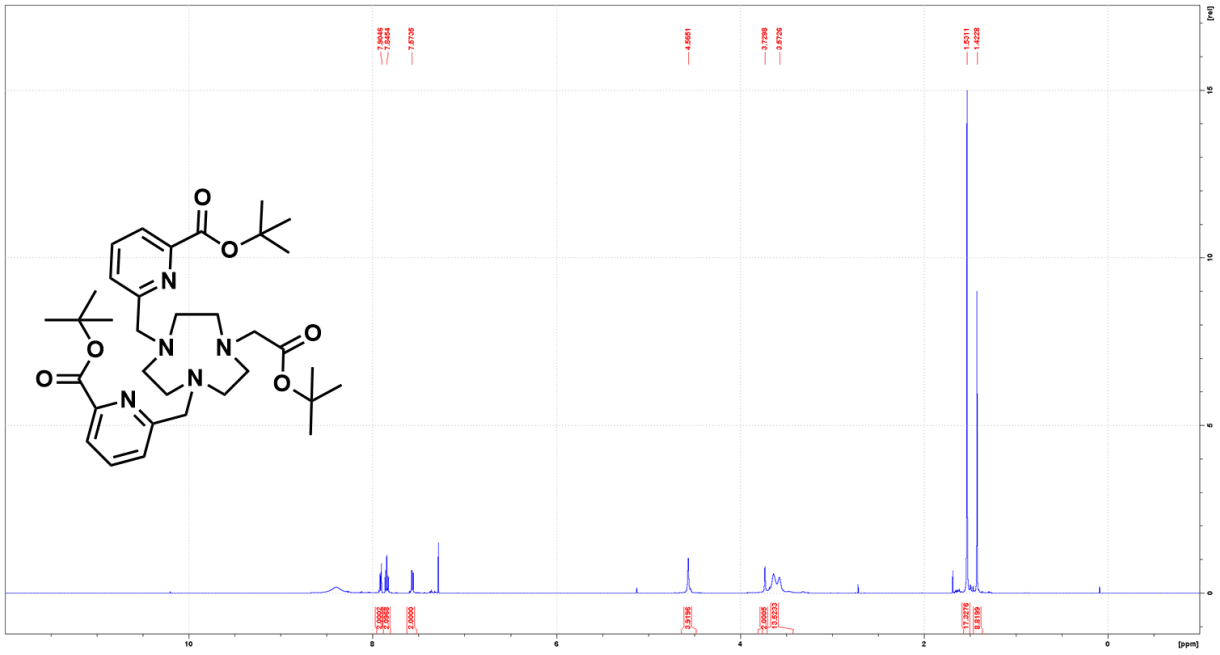


Figure S13. ^{1}H NMR of tert-butyl 6-({4-[2-(tert-butoxy)-2-oxoethyl]-7-({6-[(tert-butoxy)carbonyl]pyridin-2-yl}methyl)-1,4,7-triazonan-1-yl}methyl)pyridine-2-carboxylate (**7**).

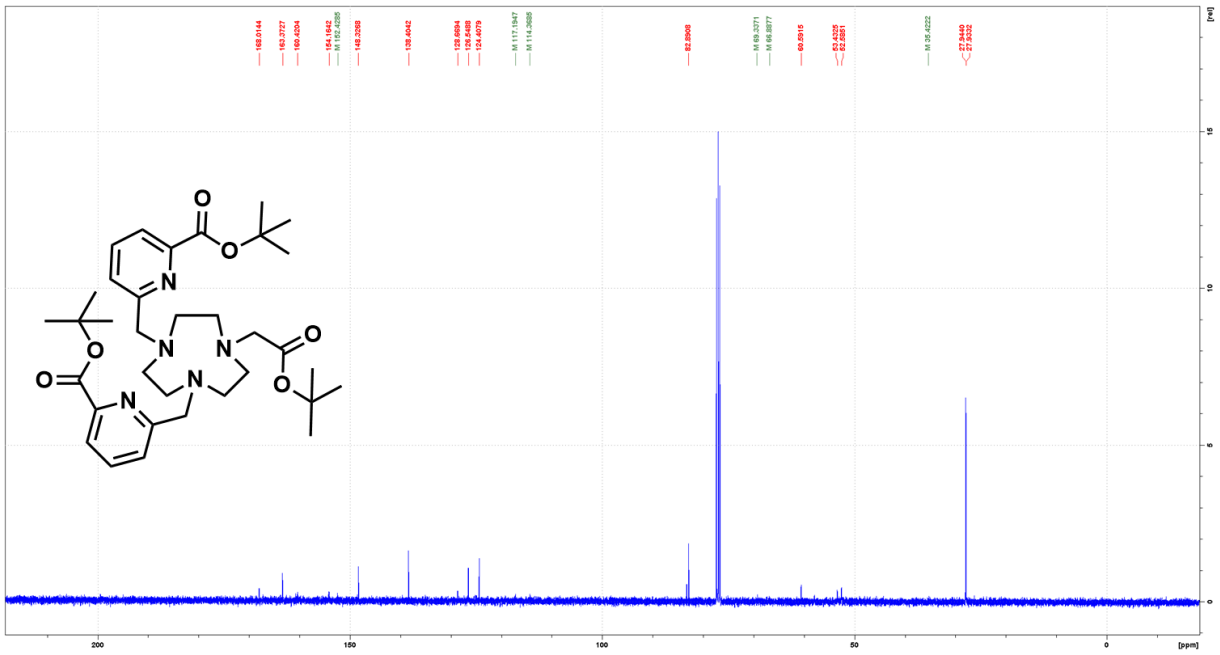


Figure S14. ^{13}C NMR of tert-butyl 6-({4-[2-(tert-butoxy)-2-oxoethyl]-7-({6-[(tert-butoxy)carbonyl]pyridin-2-yl}methyl)-1,4,7-triazonan-1-yl}methyl)pyridine-2-carboxylate (**7**).

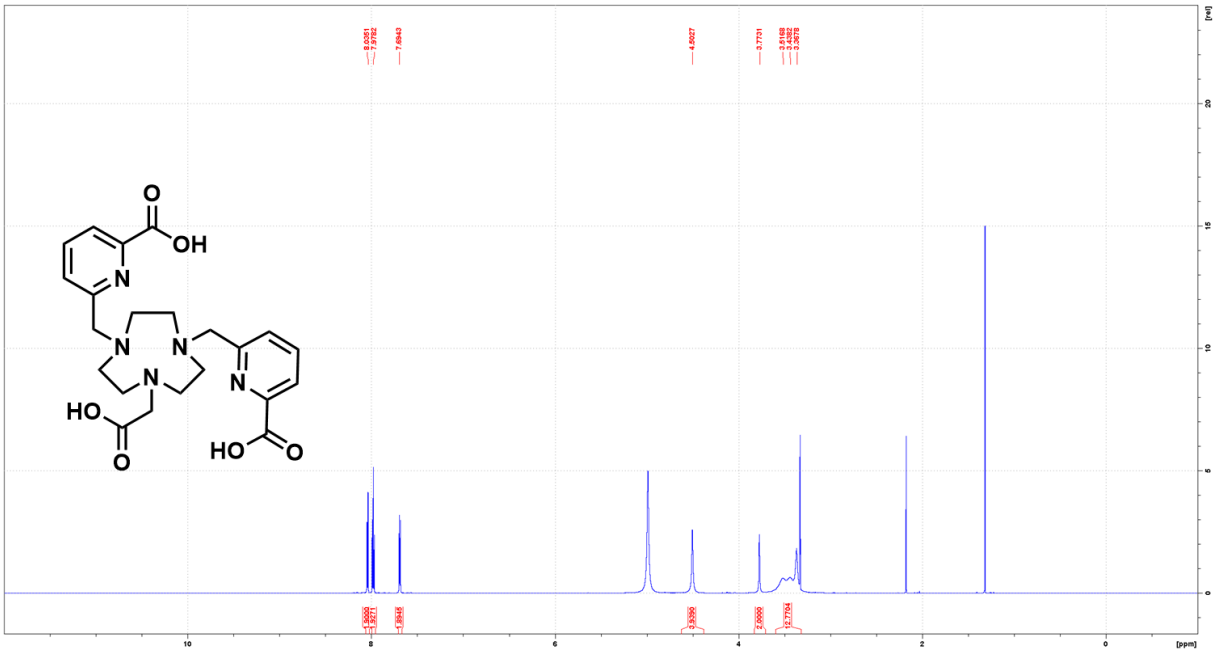


Figure S15. ^{1}H NMR of 6-[4-(carboxymethyl)-7-(6-carboxypyridin-2-yl)-1,4,7-triazonan-1-yl]pyridine-2-carboxylic acid, H_3bptacn **(8)**.

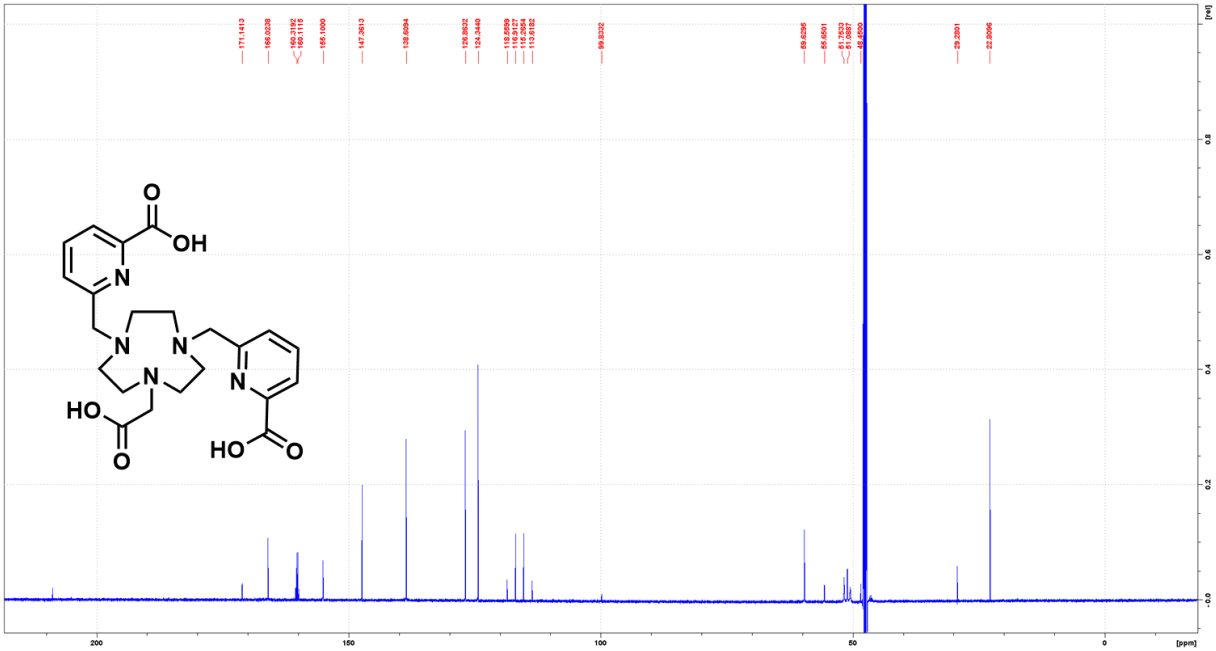


Figure S16. ^{13}C NMR of tert-Butyl 6-[(1,4,7-triazonan-1-yl)methyl]-2-pyridinecarboxylate **(8)**.

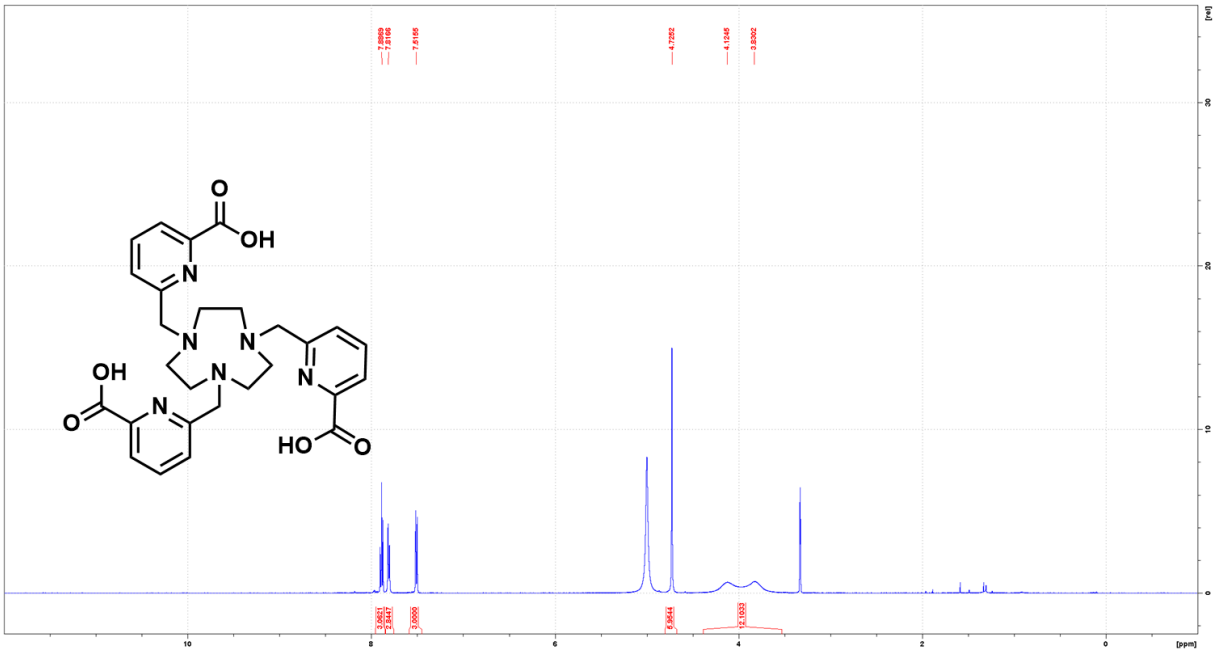


Figure S17. ^{1}H NMR of 6-({4,7-bis[(6-carboxypyridin-2-yl)methyl]-1,4,7-triazonan-1-yl}methyl)pyridine-2-carboxylic acid, H_3tptacn **(9)**.

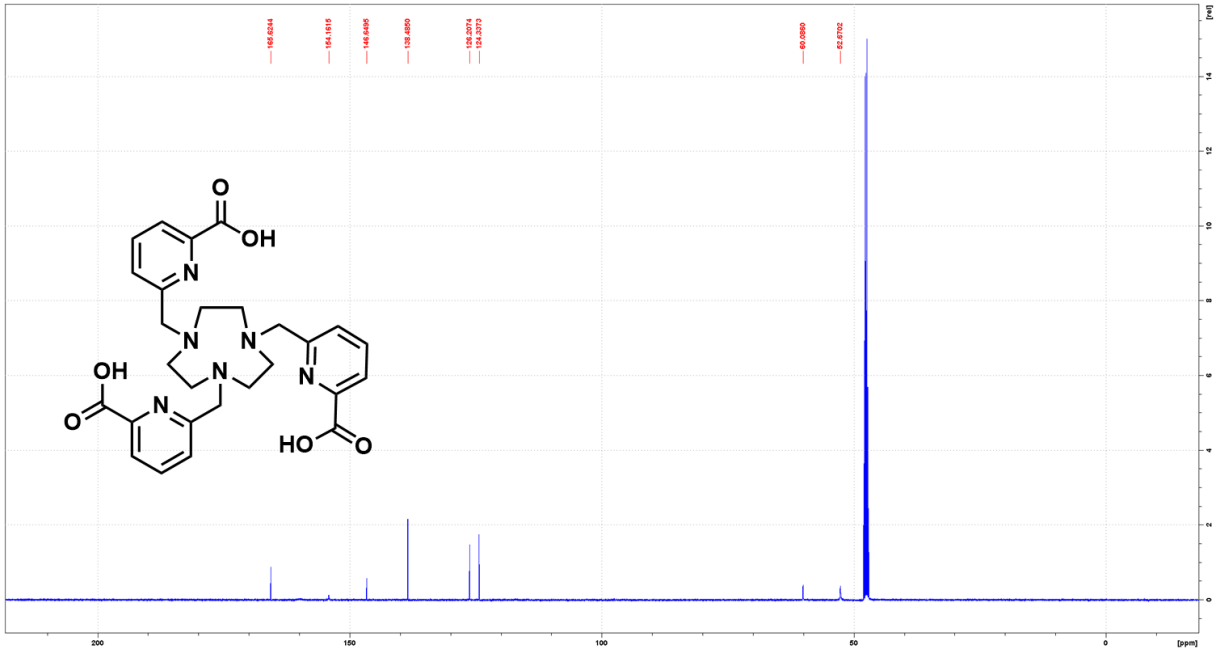


Figure S18. ^{13}C NMR of 6-({4,7-bis[(6-carboxypyridin-2-yl)methyl]-1,4,7-triazonan-1-yl}methyl)pyridine-2-carboxylic acid, H_3tptacn **(9)**.

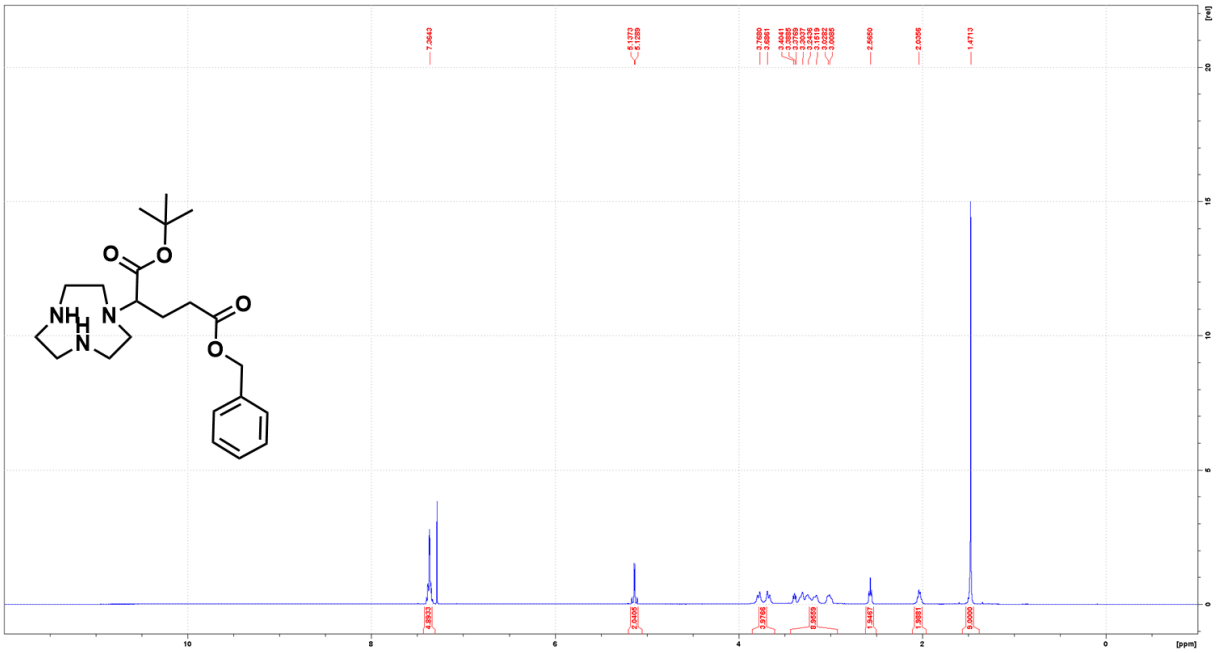


Figure S19. ^{1}H NMR of benzyl *tert*-butyl 2-(1,4,7-triazonan-1-yl)glutarate **(10)**.

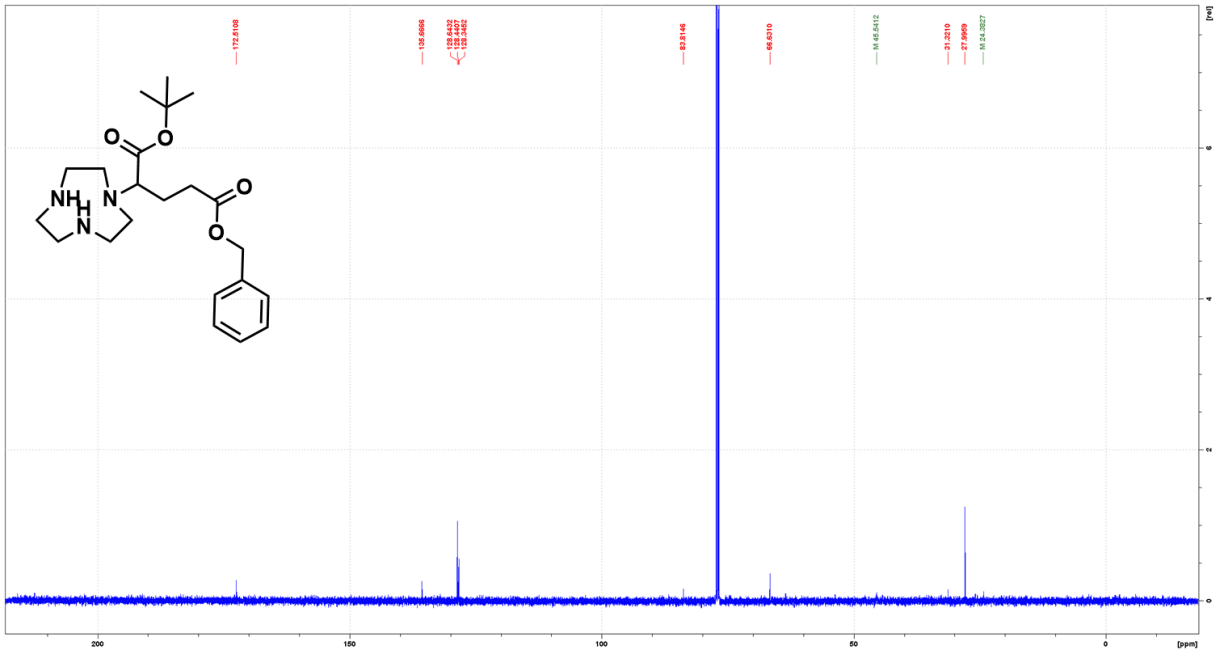


Figure S20. ^{13}C NMR of benzyl *tert*-butyl 2-(1,4,7-triazonan-1-yl)glutarate **(10)**.

Figure S21. ^{1}H NMR of benzyl *tert*-butyl 2-{4-[(6-*tert*-butoxycarbonyl-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}glutarate (**11**).

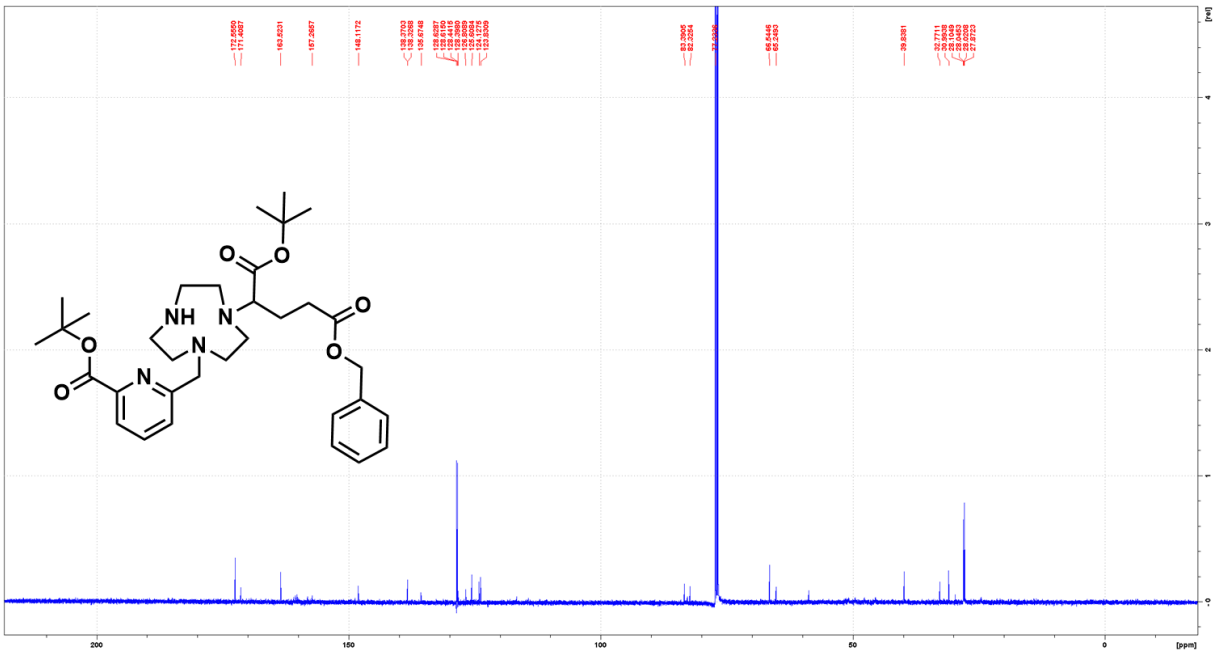


Figure S22. ^{13}C NMR of benzyl *tert*-butyl 2-{4-[(6-*tert*-butoxycarbonyl-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}glutarate (**11**).

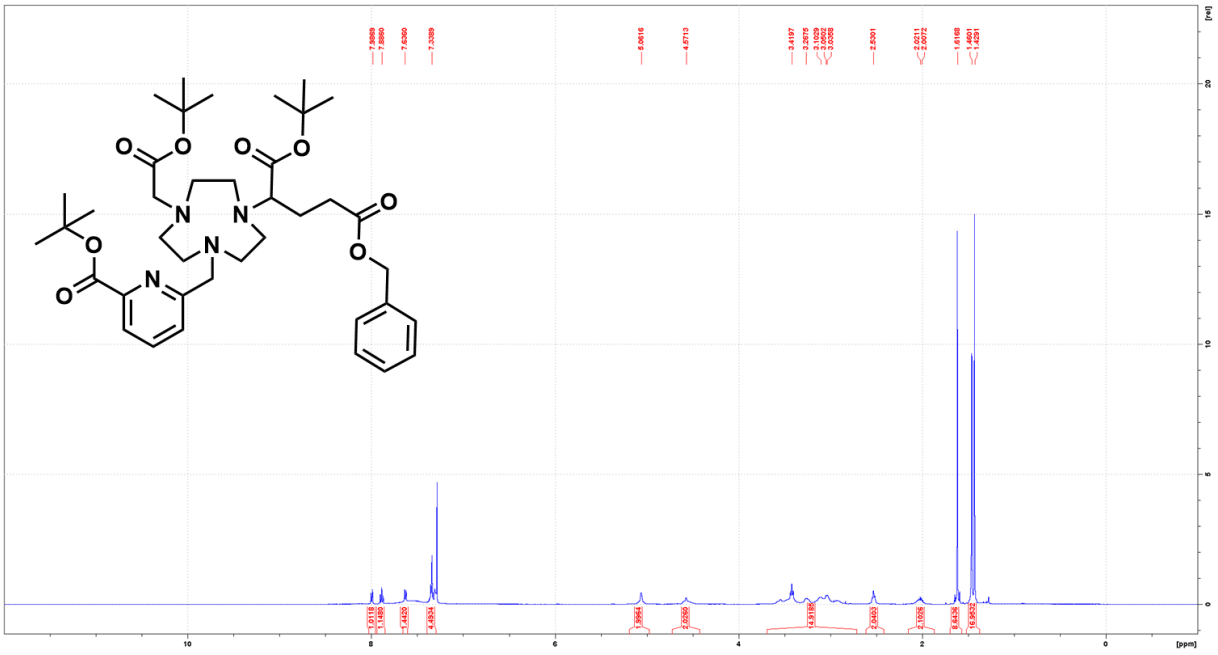


Figure S23. ^{1}H NMR of benzyl *tert*-butyl 2-{7-(*tert*-butoxycarbonylmethyl)-4-[(6-*tert*-butoxycarbonyl-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}glutarate **(12)**.

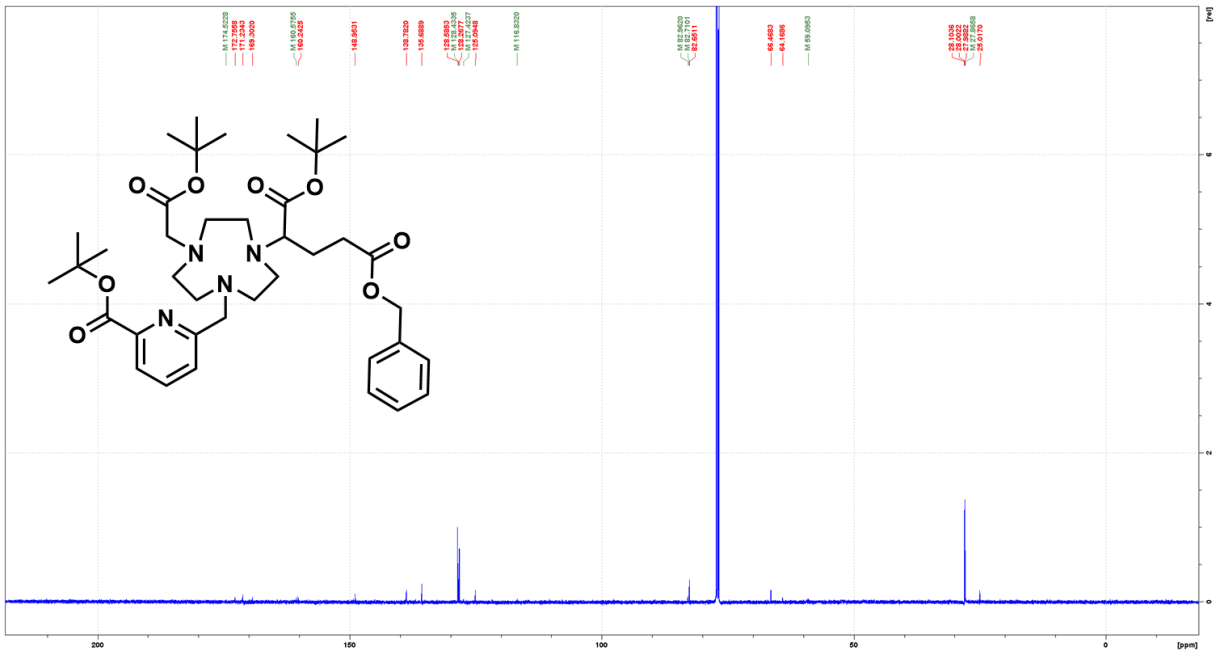


Figure S24. ^{13}C NMR of benzyl *tert*-butyl 2-{7-(*tert*-butoxycarbonylmethyl)-4-[(6-*tert*-butoxycarbonyl-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}glutarate **(12)**.

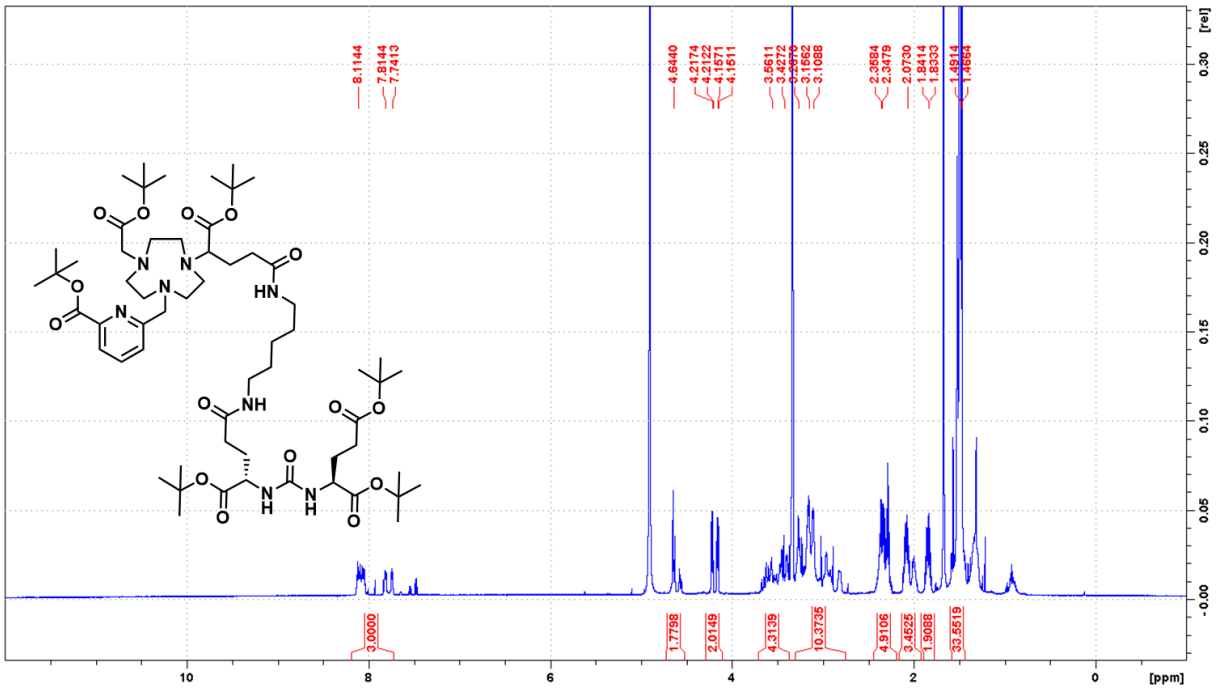


Figure S25. ^{1}H NMR of di*tert*-butyl 2-{3-[(*R*)-4-oxo-1-*tert*-butoxycarbonyl-4-[5-(4-*tert*-butoxycarbonyl-4-{7-(*tert*-butoxycarbonylmethyl)-4-[(6-*tert*-butoxycarbonyl-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}butyrylamino)pentylamino]butyl]ureido}glutarate **(14)**

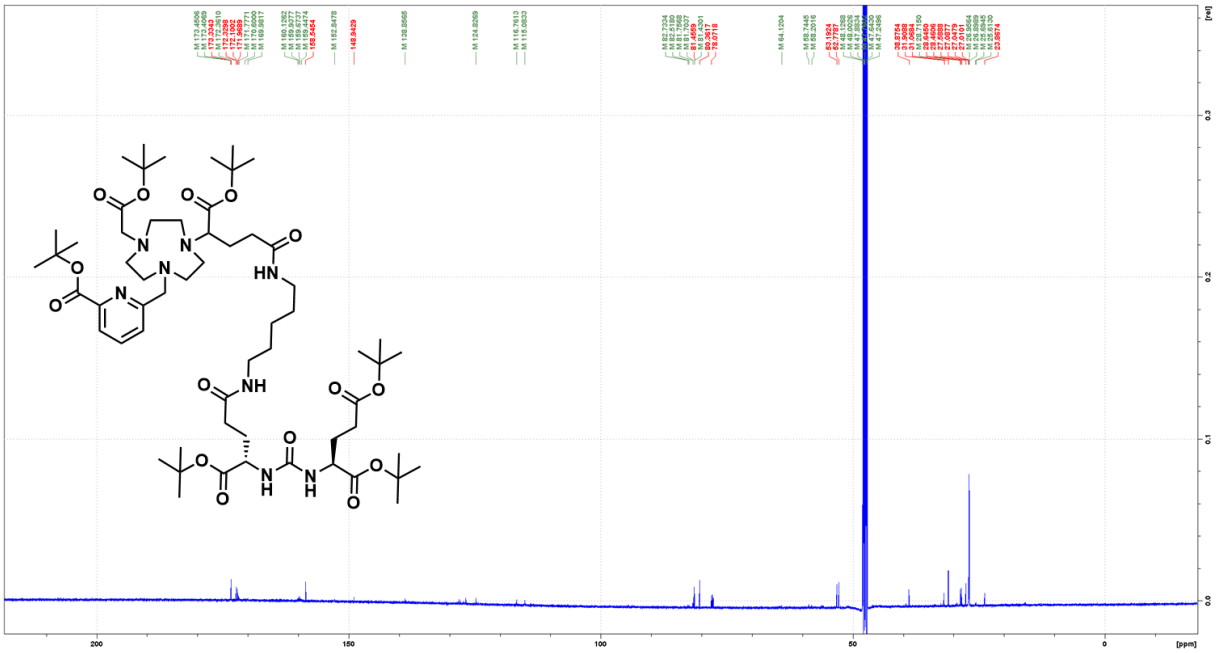


Figure S26. ^{13}C NMR of di*tert*-butyl 2-{3-[(*R*)-4-oxo-1-*tert*-butoxycarbonyl-4-[5-(4-*tert*-butoxycarbonyl-4-{7-(*tert*-butoxycarbonylmethyl)-4-[(6-*tert*-butoxycarbonyl-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}butyrylamino)pentylamino]butyl]ureido}glutarate **(14)**.

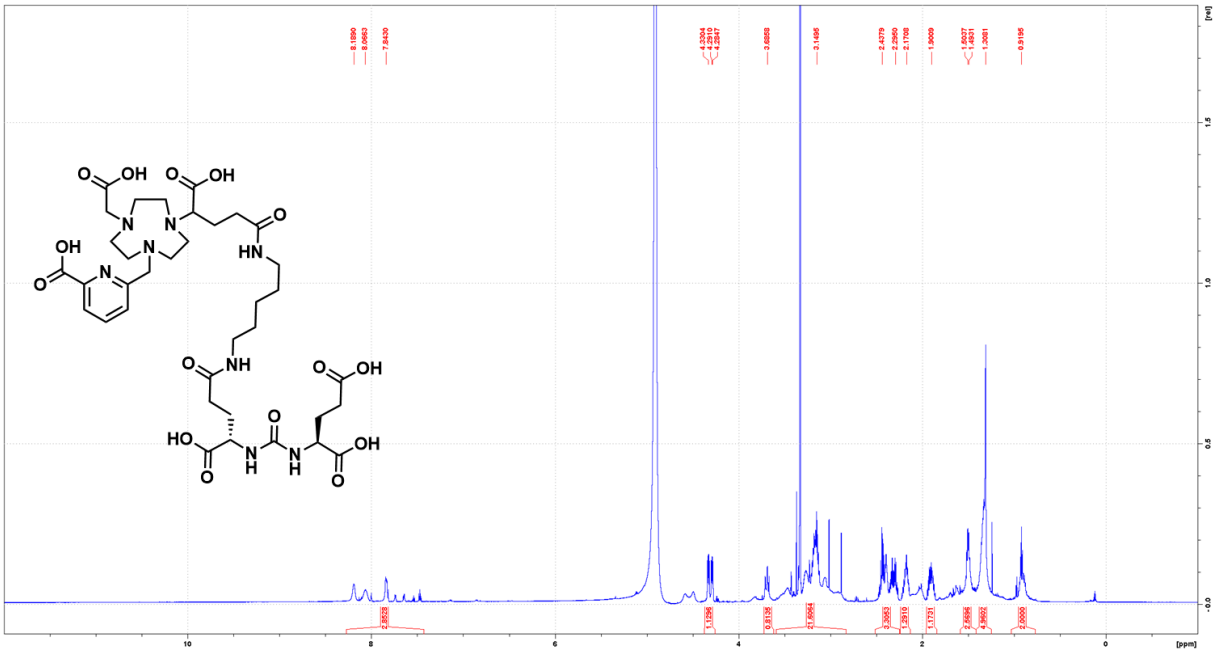


Figure S27. ^{1}H NMR of 2-{3-[(*R*)-1-carboxy-4-[5-(4-carboxy-4-{7-(carboxymethyl)-4-[(6-carboxy-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}butyrylamino)pentylamino]-4-oxobutyl]ureido}glutaric acid, picaga-DUPA (**15**).

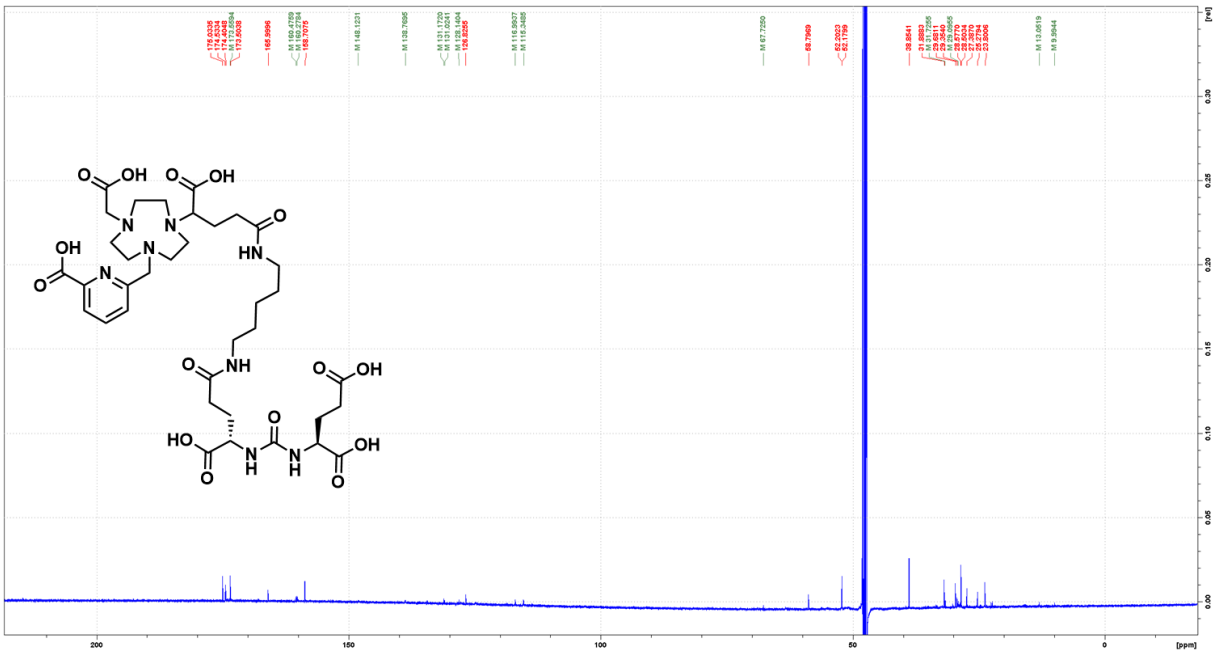


Figure S28. ^{13}C NMR of 2-{3-[(*R*)-1-carboxy-4-[5-(4-carboxy-4-{7-(carboxymethyl)-4-[(6-carboxy-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}butyrylamino)pentylamino]-4-oxobutyl]ureido}glutaric acid, picaga-DUPA (**15**).

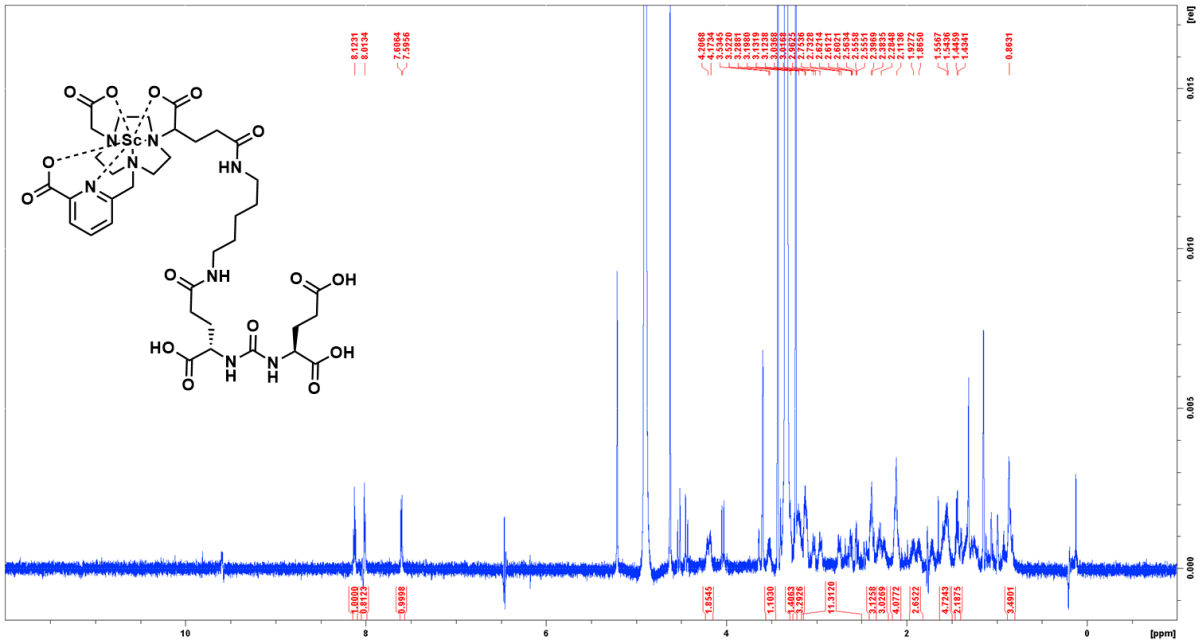


Figure S29. ^{1}H NMR of scandium complexed 2-{3-[(*R*)-1-carboxy-4-[5-(4-carboxy-4-{7-(carboxymethyl)-4-[(6-carboxy-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}butyrylamino)pentylamino]-4-oxobutyl]ureido}glutaric acid, Sc(picaga)-DUPA A (**18A**).

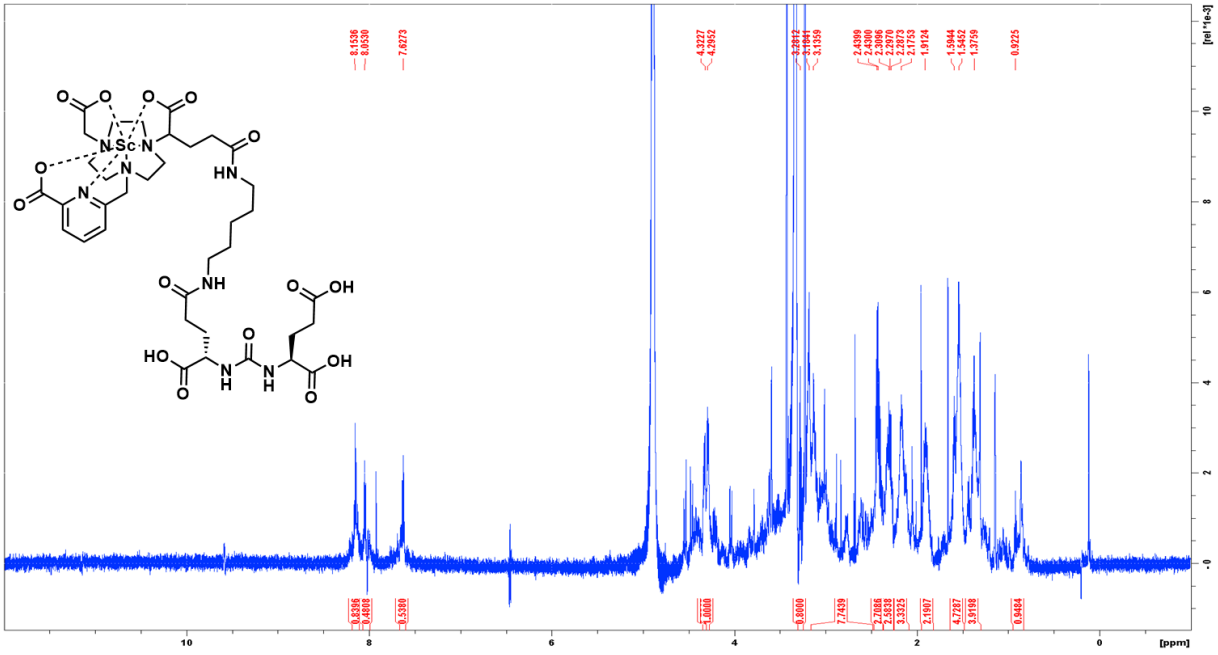


Figure S30. ^{1}H NMR of scandium complexed 2-{3-[(*R*)-1-carboxy-4-[5-(4-carboxy-4-{7-(carboxymethyl)-4-[(6-carboxy-2-pyridyl)methyl]-1,4,7-triazonan-1-yl}butyrylamino)pentylamino]-4-oxobutyl]ureido}glutaric acid, Sc(picaga)-DUPA B (**18B**).

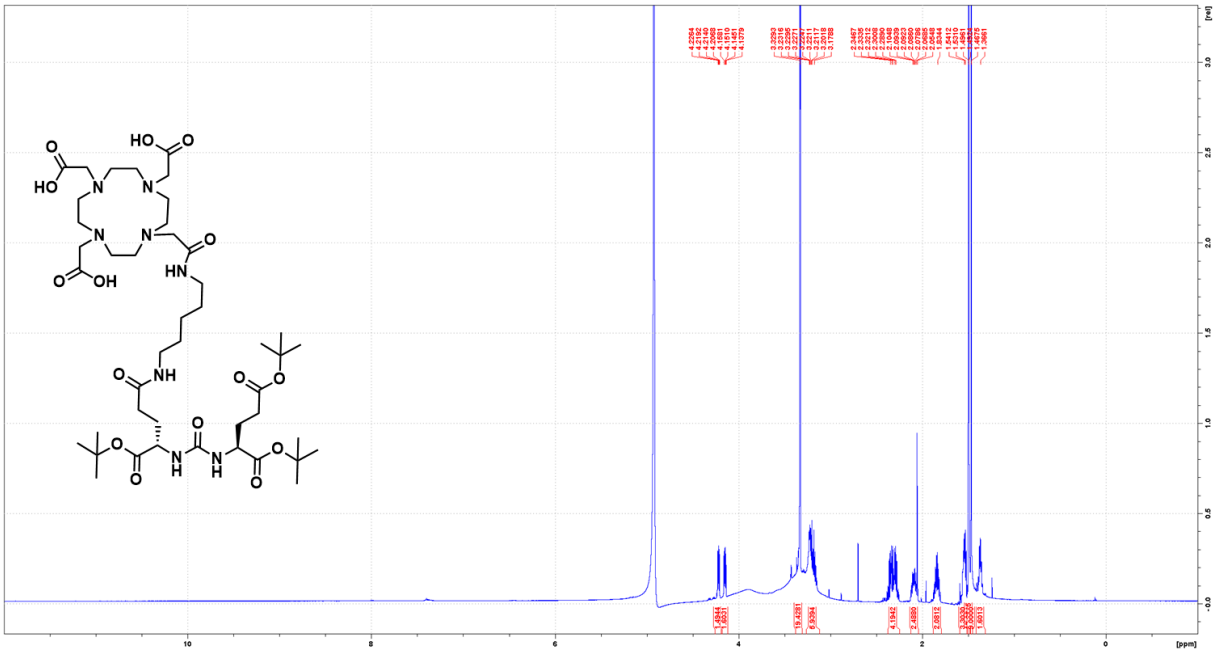


Figure S31. ^{1}H NMR of (4-{2-[2-(5-{(*R*)-4-[3-(1,3-di*tert*-butoxycarbonylpropyl)ureido]-4-*tert*-butoxycarbonylbutyrylamino}pentylamino)-2-oxoethylamino]-2-oxoethyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraaza-1-cyclododecyl)acetic acid (**16**).

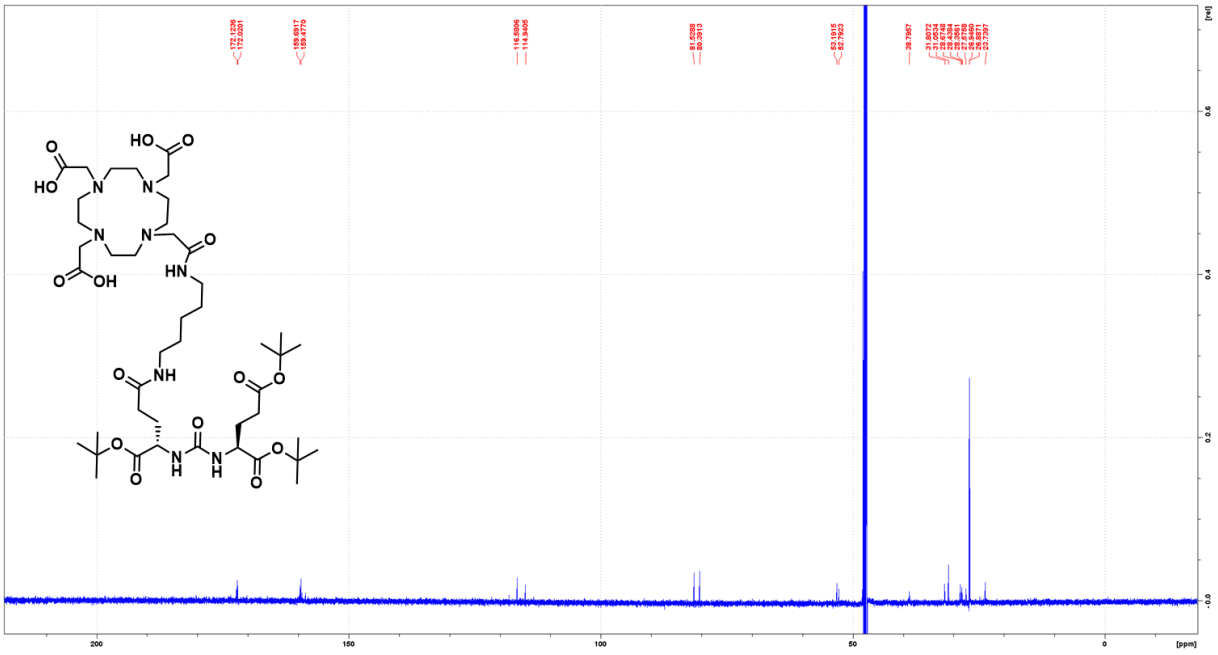


Figure S32. ^{13}C NMR of (4-{2-[2-(5-{(*R*)-4-[3-(1,3-di*tert*-butoxycarbonylpropyl)ureido]-4-*tert*-butoxycarbonylbutyrylamino}pentylamino)-2-oxoethylamino]-2-oxoethyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraaza-1-cyclododecyl)acetic acid (**16**).

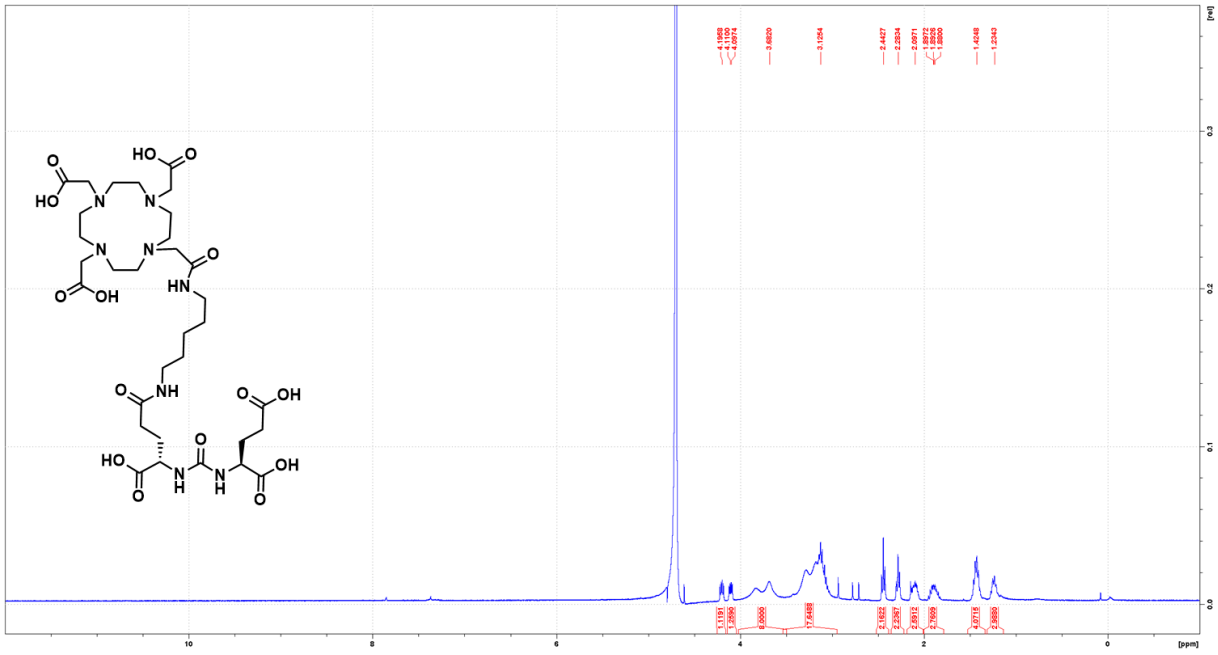


Figure S33. ^{1}H NMR of 2-{3-[(*R*)-1-carboxy-4-oxo-4-[5-(2-{2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraaza-1-cyclododecyl]acetylamino}acetylamino)pentylamino]butyl]ureido}glutaric acid (**17**).

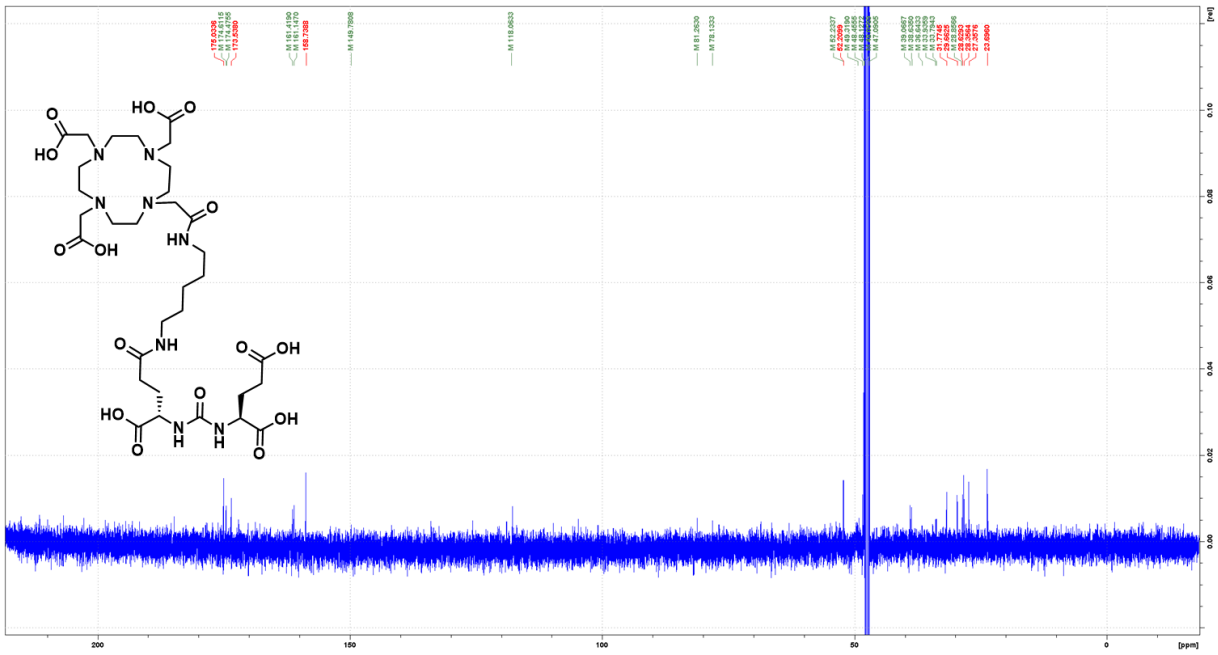


Figure S34. ^{13}C NMR of 2-{3-[(*R*)-1-carboxy-4-oxo-4-[5-(2-{2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraaza-1-cyclododecyl]acetylamino}acetylamino)pentylamino]butyl]ureido}glutaric acid (**17**).

1.3 Ligand stock concentration determination (titration)

In order to determine the concentration of H_3mpatcn and picaga-DUPA samples used for radiolabeling experiments, a spectrophotometric titration was carried out with Cu^{2+}. The formation of $[Cu(mpatcn)]^-$ or $[Cu(picaga\text{-}DUPA)]^-$ was monitored at 300 nm using a 1 cm path length cuvette and a NanoDrop spectrophotometer. The pH was adjusted to 5.5 using 0.25 M ammonium acetate buffer. 100 µM ligand stock solutions were titrated with addition of 5 µM Cu^{2+} aliquots (as determined by ICP-OES) to determine the concentration of ligand by equivalents of Cu^{2+}. The titration endpoint was determined when no further change to the absorbance intensity at 300 nm, diagnostic of complex formation, was detected. Analysis reveals a 33-40% w/w content of ligand, indicating that the final products following deprotection are isolated as H_3mpatcn·4TFA salt and picaga-DUPA·9TFA·$2H_2O$ salt.

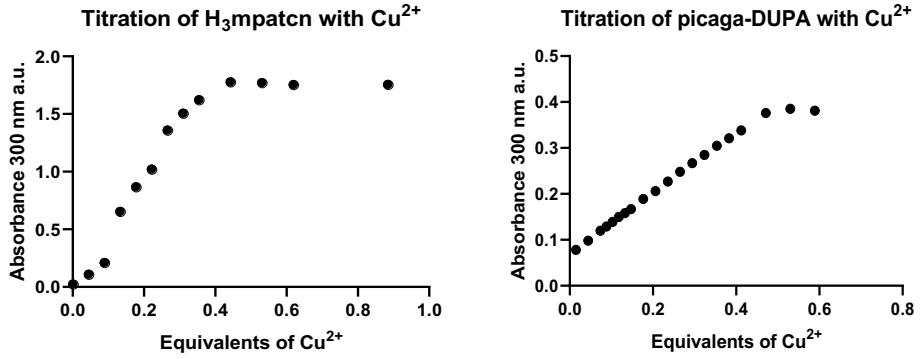


Figure S35. UV-vis titration to endpoint to determine ligand concentrations of H_3mpatcn and picaga-DUPA.

2. Characterization of non-radioactive Sc complexes

2.1 ^{1}H and ^{45}Sc spectral data

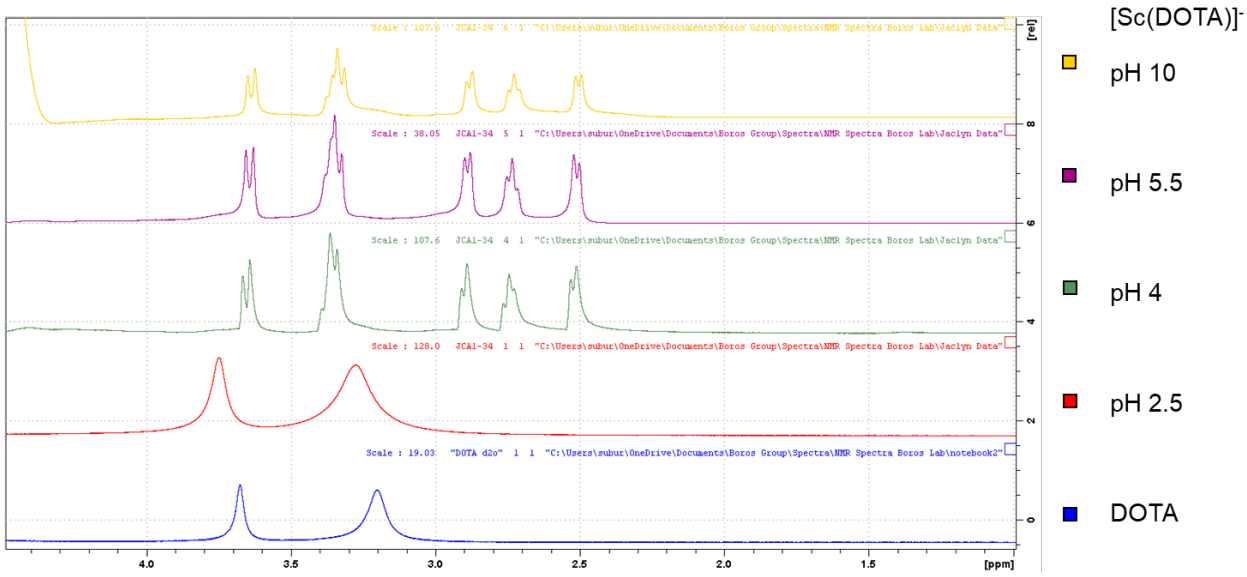


Figure S36. ^{1}H NMR of $[Sc(DOTA)]^{-}$ in dependence of pH.

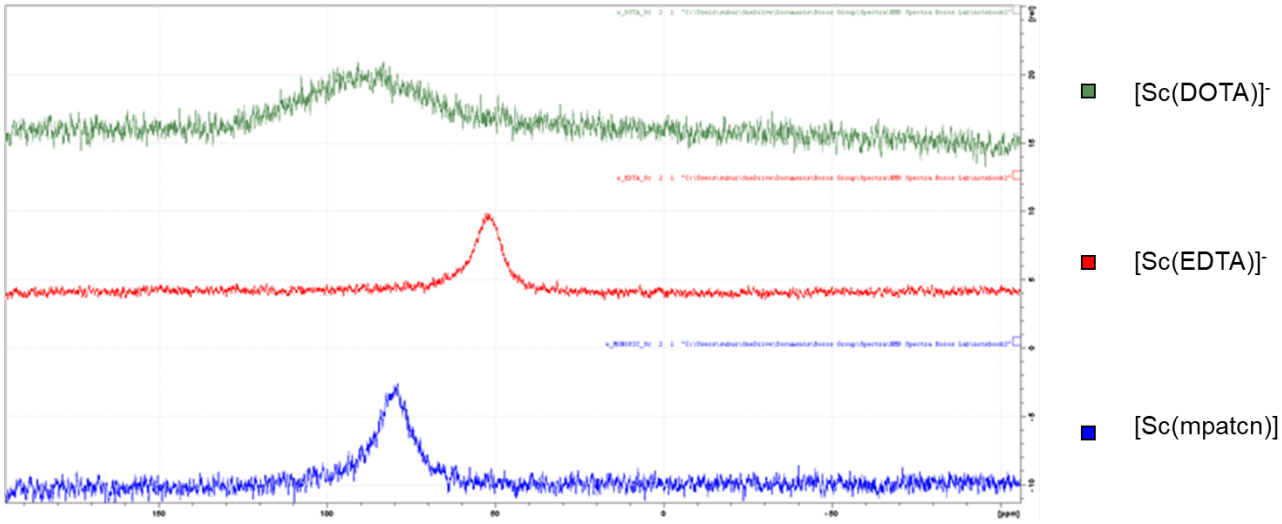


Figure S37. ^{45}Sc NMR of representative Sc-complexes.

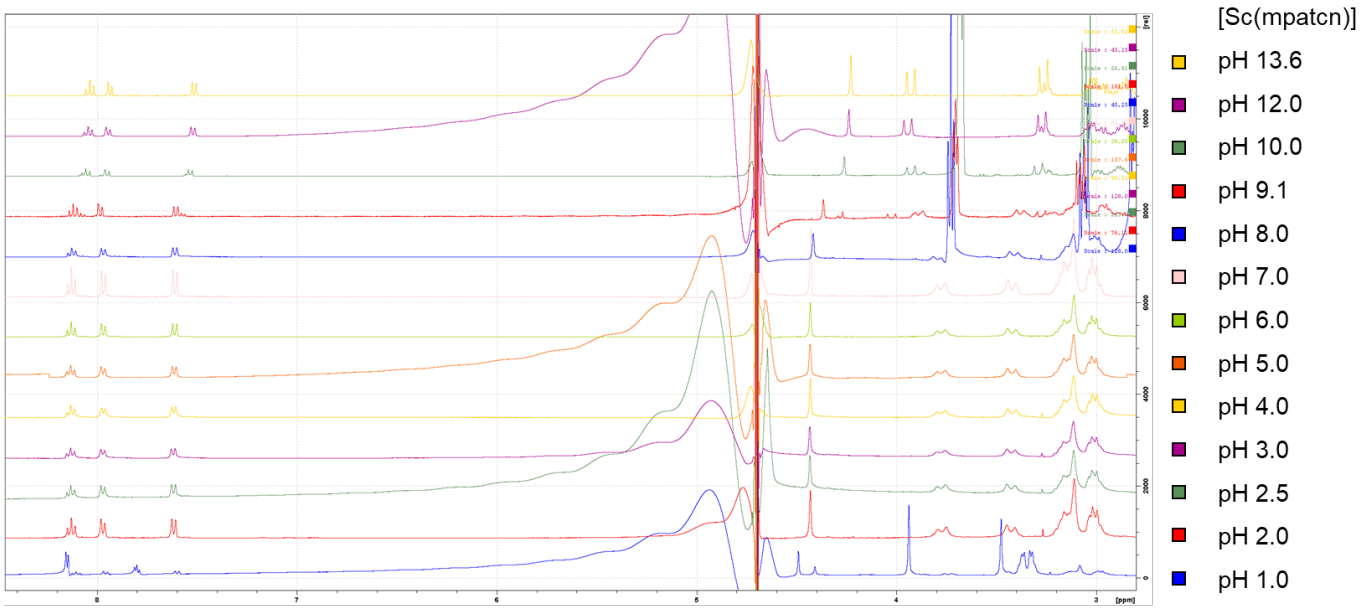


Figure S38. Spectral characterization of the pH-dependent speciation of the [Sc(mpatcn)]-complex.

Table S1. Chemical shift analysis of H_3mpatcn, Sc(mpatcn) and $[Sc(mpatcn)(OH)]^-$ complexes separated by picolinate ring protons, picolinate methylene protons, and acetate methylene protons.

	Chemical shift (ppm)				
	δ(^{1}H) Picolinate aromatic	δ(^{1}H) picolinate methylene	δ(^{1}H) acetate methylene	macrocycle ring	δ(^{45}Sc)
$ScCl_3$					1.3
H_3mpatcn	8.17 (d, 1H, H-5), 8.04 (t, 1H, H-6), 7.82 (d, 1H, H-7)	4.42 (s, 2H, H-9)	3.68 (s, 4H, H-16)	2.94-3.30 (m, 12H, H-10, H-11, H-12, H-13, H-14, H-15)	
[Sc(mpatcn)]	8.13 (t, 1H, H-6), 7.97 (d, 1H, H-5), 7.61 (d, 1H, H-7)	4.43 (s, 2H, H-9)	3.78 (m, 2H, H-16), 3.42 (m, 2H, H-16)	2.95-3.24 (m, 12H, H-10, H-11, H-12, H-13, H-14, H-15)	80.1
$[Sc(mpatcn)OH]^-$	8.04 (t, 1H, H-6), 7.94 (d, 1H, H-5), 7.51 (d, 1H, H-7)	4.23 (s, 2H, H-9)	3.93 (m, 2H, H-16), 3.19-3.30 (m, 2H, H-10, H-11, H-12, H13, H-14, H-15)	3.19-3.30 (m, 2H, H-19), 2.74-3.09 (m, 10H, H-10, H-11, H-12, H-13, H-14, H-15)	89.8

Table S2. Fraction of total pH-dependent speciation of the Sc(mpatcn)-complex based on integration of picolinate ring protons, picolinate methylene protons, and acetate methylene protons.

	Total (mpatcn) fraction (%)		
pH	H_3(mpatcn)	[Sc(mpatcn)]	$[Sc(mpatcn)OH]^-$
1.15	75.6±4.8	24.4±4.8	
2	0.4±0.6	99.4±0.2	
2.5		100.0±0.0	
3		100.0±0.0	
4		100.0±0.0	
5		100.0±0.0	
6		100.0±0.0	
7		100.0±0.0	
8		100.0±0.0	
9.1		88.6±7.7	11.4±7.7
10		1.4±0.4	98.6±0.4
12			100.0±0.0
13.5			100.0±0.0

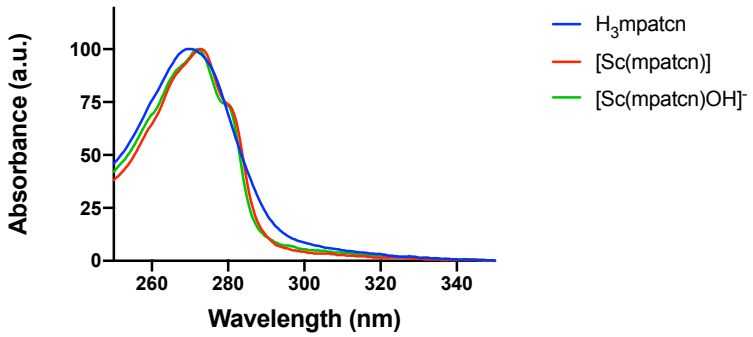


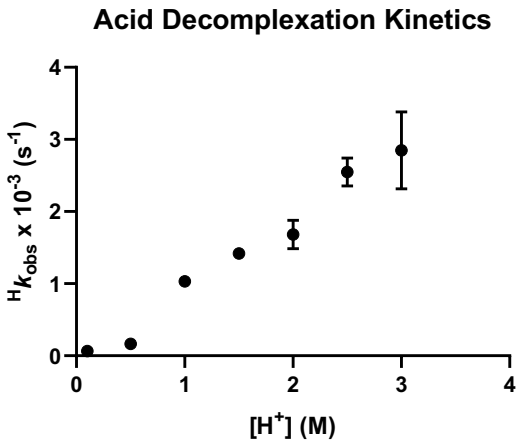
Figure S39. UV-Vis absorbance spectra of 0.1 mM H_3mpatcn, [Sc(mpatcn)], and [Sc(mpatcn)OH]$^-$.

2.2 Dissociation kinetics in acidic media

Solutions of $ScCl_3$ were prepared by dissolving $ScCl_3 \cdot 6H_2O$ in 0.2 M HCl at a concentration of 35 mM. The solutions of the [Sc(mpatcn)] complex for kinetic measurements were prepared by mixing the ligand (L) and $ScCl_3$ stock solutions to give a final 1:1 L:Sc molar ratio and adjustment of the pH to 5.5. Complex formation was confirmed using ^{1}H and ^{45}Sc NMR spectroscopy. Dissociation of [Sc(mpatcn)] complex was followed by using UV-Vis spectrophotometry. Decomplexation was quantified by plotting the change in absorbance over time at 284 nm. Complex concentration was 0.1 mM and experiments were carried in aq. HCl (0.1–3.0 M).[3]

Table S3. Dissociation rate constants measured.

$[H^+]$ conc.	**$^{H}k_{obs}$ (s^{-1})**	**$t_{1/2}$ (min)**
3 M	$2.8\times10^{-3} \pm 0.53\times10^{-4}$	4.1±0.8
2.5 M	$2.5\times10^{-3} \pm 1.9\times10^{-4}$	4.6±0.3
2 M	$1.7\times10^{-3} \pm 2.0\times10^{-4}$	6.9±0.9
1.5 M	$1.4\times10^{-3} \pm 4.1\times10^{-5}$	8.1±0.2
1 M	$1.0\times10^{-3} \pm 6.2\times10^{-5}$	11.2±0.7
0.5 M	$1.7\times10^{-4} \pm 2.0\times10^{-5}$	70.1±8.4
0.1 M	$6.5\times10^{-5} \pm 9.2\times10^{-6}$	179.6±27.5



2.3 Diastereomer separation and stability assessment

The Sc(picaga)-DUPA complex forms two distinct stereoisomers. In order to determine if the two isomers are in dynamic equilibrium, separation of the two species was carried out using method C. The observed peak ratio 38:62. Following chromatographic separation, the two isolated isomer fractions were reinjected after 40 minutes and 18 hours. No interconversion or isomerization of the two was observed. Corresponding HPLC traces are provided in figure S38. Corresponding ^{1}H NMR spectra are provided in figures S29 and S30.

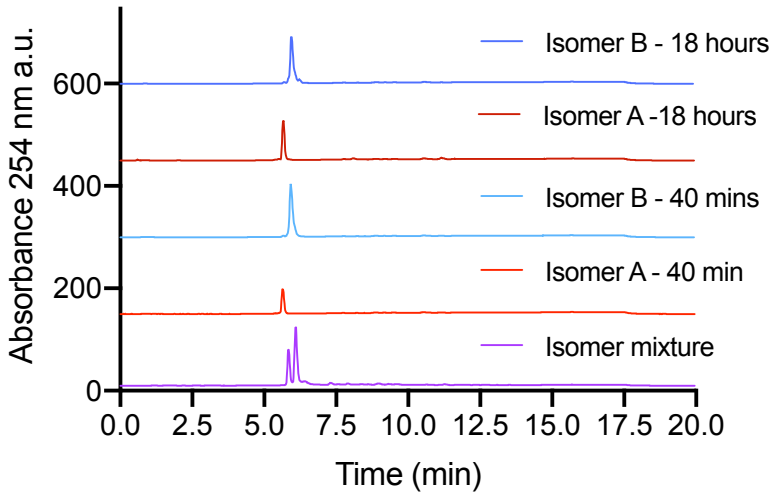


Figure S40. Stacked HPLC traces of isomer mixture, isolated isomer A and B after 40 mins and 18 hours, showing no indication for isomerization.

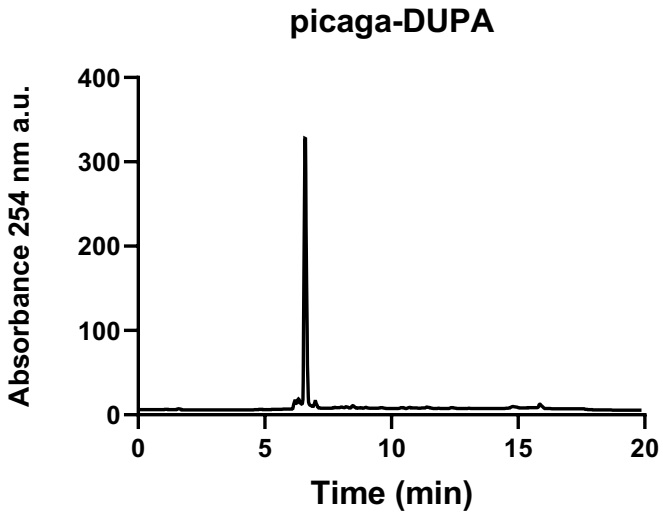


Figure S41. HPLC trace of picaga-DUPA.

3. Radiochemistry

Table S4. Summary of apparent molar activities at 25 and 80 °C and HPLC retention time of ^{44}Sc-complexes.

Ligand	Apparent molar activity, 25 °C [MBq/nmol]	Apparent molar activity, 80 °C [MBq/nmol]	HPLC retention time [min]
DOTA	0.06	0.06	3.71
H_3mpatcn	0.03	0.06	5.01
DOTA-DUPA	< 0.01	0.65	9.24
Picaga-DUPA	0.06	0.06	10.41/10.95
Unchelated ^{44}Sc	n/A	n/A	2.99

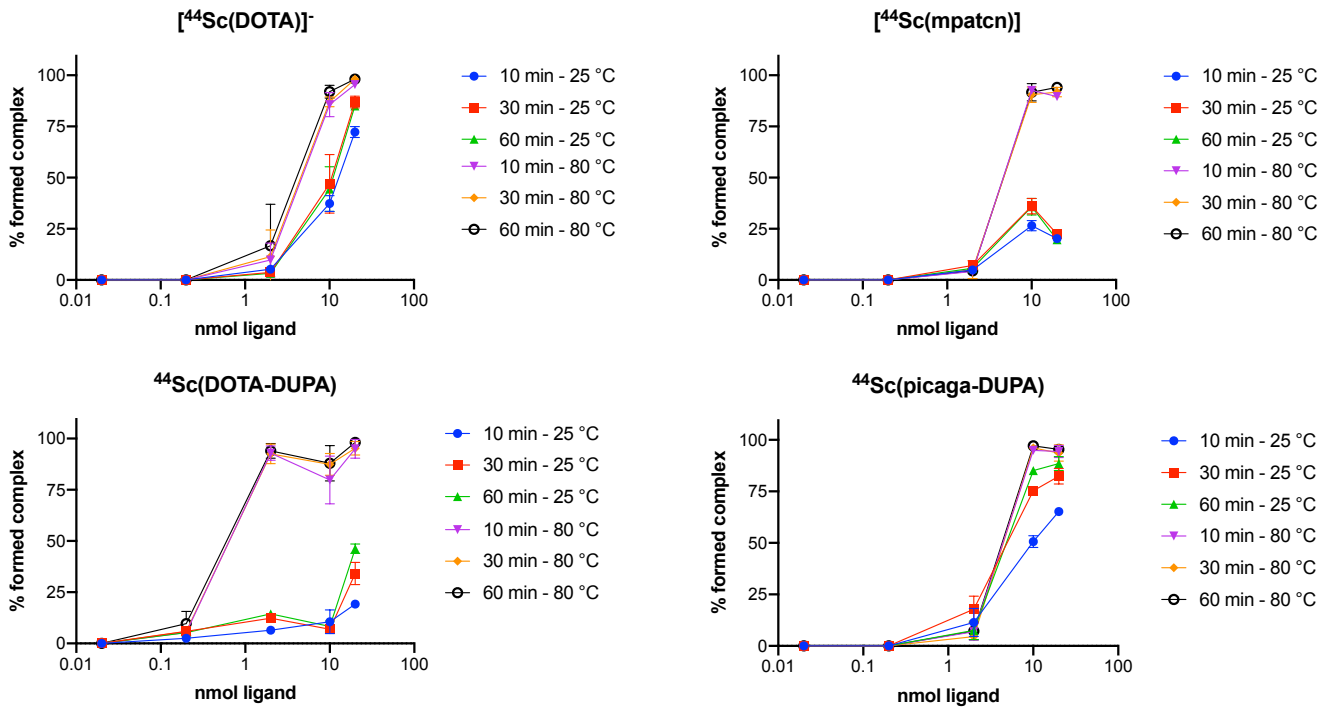


Figure S42. Time and temperature-dependent radiolabeling plots of DOTA, H_3mpatcn, DOTA-DUPA and picaga-DUPA (n=3 experiments per concentration and time point).

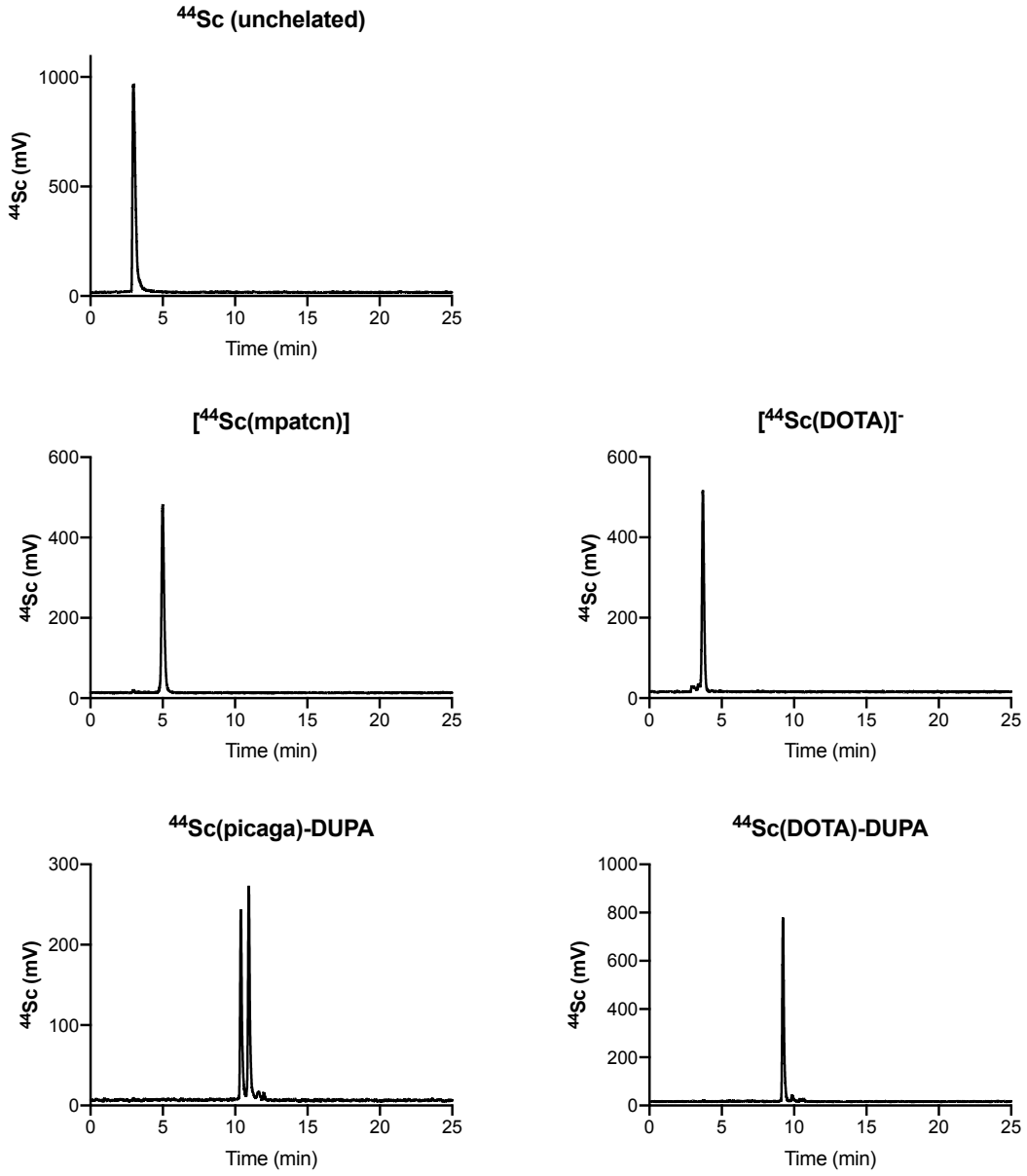


Figure S43. Crude radio-HPLC chromatograms of $[^{44}Sc(DOTA)]^-$, $^{44}Sc(mpatcn)$, $^{44}Sc(DOTA)$-DUPA, $^{44}Sc(picaga)$-DUPA.

Table S5. Time-dependent complex stability in rat plasma (experiments carried out in duplicate)

Stability in rat plasma, 37 °C [% intact complex±stdev]				
Ligand	**10 min**	**30 min**	**60 min**	**120 min**
H_3mpatcn	98.1±1.4	97.0±3.4	95.5±0.4	94.2±1.6
DOTA	99.8±3.1	95.7±0.5	95.8±0.6	95.8±2.8
picaga-DUPA	99.3±0.1	97.7±1.1	97.5±0.4	96.0±0.5
DOTA-DUPA	98.4±0.1	97.0±1.4	96.4±0.1	97.6±1.0

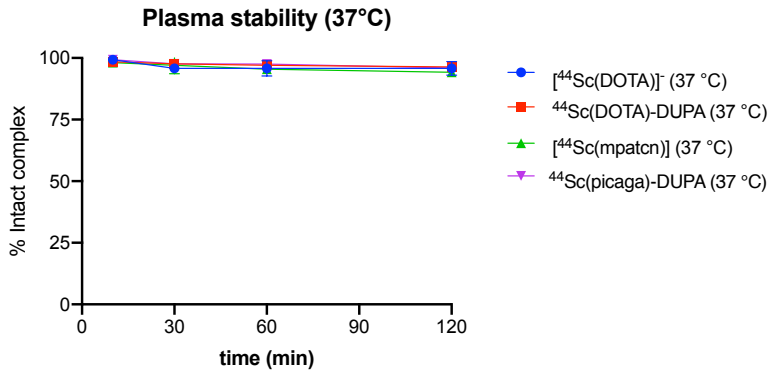


Figure S44. Time-dependent plasma stability of compounds investigated.

4. Displacement assay

4.1 Displacement assay curves for compounds tested – Synthesis of MIP-1427

Stock solutions of Sc(picaga)-DUPA and Sc(DOTA)-DUPA in H_2O were prepared and concentrations were determined by ICP (Agilent 5110 ICP-OES, Danbury, CT). A 6-point standard curve with respect to scandium was used (R^2 of 0.9998). Stock solutions were serially diluted 10x, resulting in stocks with concentrations as follows: 1 mM–10 pM Sc(picaga)-DUPA, 1 mM–10 pM Sc(DOTA)-DUPA, and 1 mM–0.01 nM (DCFPyL). N-{[(1S)-1-carboxy-5-{[(6-fluoro-3-pyridinyl)carbonyl]amino}-pentyl]carbamoyl}-L-glutamic acid (DCFPyL) was provided by Dr. Peter Smith-Jones (Facility for Experimental Radiopharmaceutical Manufacturing, School of Medicine, Stony Brook University), and was used as a standard and measured alongside each compound.

$^{99m}Tc(CO)_3$-MIP-1427 was synthesized according to literature procedure.[4] Sodium pertechnetate, $Na[^{99m}TcO_4]$, was eluted from a $^{99}Mo/^{99m}Tc$ sterile generator (Triad Isotopes) as a 1.0 mL saline solution (0.9% v/v) and added to a sealed vial containing boranocarbonate (4 mg), sodium tartrate (7 mg), and sodium borate decahydrate (7 mg). The sealed vial was heated to 100 °C for 40 minutes to form the $[^{99m}Tc(H_2O)_3(CO)_3]^+$ intermediate, which was subsequently neutralized to pH 7 with 1 M HCl (150–180 µL). 1,5-di-tert-butyl (2S)-2-({[(2S)-1-(tert-butoxy)-4-{[(2S)-1-(tert-butoxy)-6-[({1-[2-(tert-butoxy)-2-oxoethyl]-1H-imidazol-2-yl}methyl)({1-[(tert-butoxy)carbonyl]-1H-imidazol-2-yl}methyl)amino]-1-oxohexan-2-yl]carbamoyl}-1-oxobutan-2-yl]carbamoyl}amino)pentanedioate (protected MIP-1427, 0.1 mg in 1 mL, 1:1 CH_3CN:water) was added, the vial was sealed, and the mixture was heated at 100 °C for 30 min. The solvent was removed and the tert-butyl ester protecting groups were removed by treatment with 1.5 mL of 2:1 TFA:DCM for 45 minutes at room temperature. After concentrating the reaction mixture under reduced pressure, the deprotected $^{99m}Tc(CO)_3$-MIP-1427 was purified by HPLC using Method C (t_R= 10.0 min). The solvent was removed and the purified complex was reconstituted in PBS (pH 7.4).

The K_i values were calculated using equation 2 below,[5] where the K_i value of DCFPyL was given as 1.1 nM.

$$K_i = \frac{IC_{50}}{1+\frac{[S]}{K_M}} \qquad (1)$$

The binding curves of each displacement experiment are provided below in Figures S1A, S1B and S1C. The K_i was determined by nonlinear regression analysis using GraphPad Prism software.

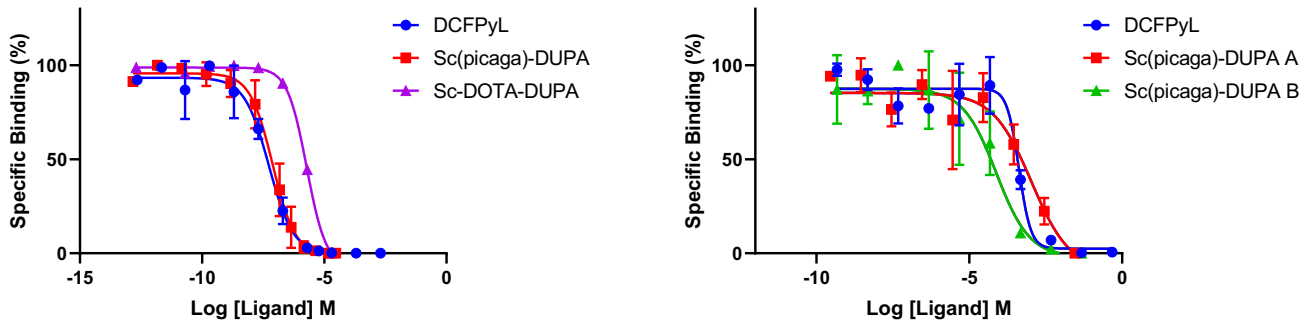


Figure S45. Displacement assay curves obtained with concentration dependent challenge of MIP-1427 with Sc-complexes and DCFPyL. A) Sc-PICAGA-DUPA, Sc-DOTA-DUPA, and DCFPyL. B) Sc-PICAGA-DUPA separated stereoisomers A and B and DCFPyL

5. Animal studies

5.1 Tabulated biodistribution data

Table S6. All organs were harvested 2 h post injection.

Organ	^{44}Sc(picaga)-DUPA (n=3)	^{44}Sc(DOTA)-DUPA (n=4)	MIP-1427 (n=3)
Blood	0.263 ± 0.085	0.248 ± 0.033	0.653 ± 0.491
Heart	0.230 ± 0.062	0.168 ± 0.062	1.160 ± 0.275
Liver	2.510 ± 2.338	0.390 ± 0.187	1.213 ± 0.482
Spleen	0.510 ± 0.079	0.263 ± 0.083	31.090 ± 12.603
Kidney	9.473± 8.223	4.508± 5.152	96.225 ± 2.906
Sm Int	0.390 ± 0.070	0.255± 0.111	1.407± 1.018
Muscle	0.130 ± 0.035	0.140 ± 0.029	0.710 ± 0.342
Bone	0.330 ± 0.026	0.220 ± 0.109	0.803 ± 0.306
Tumor +	13.827± 0.565	2.783 ± 1.318	21.207 ± 6.177
Tumor -	0.157± 0.047	0.428 ± 0.154	n/A*

* *study did not include PSMA- tumor implantation.*

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