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Supporting Information

Di-macrocyclic terephthalamide ligands as chelators for the PET radionuclide zirconium-89†

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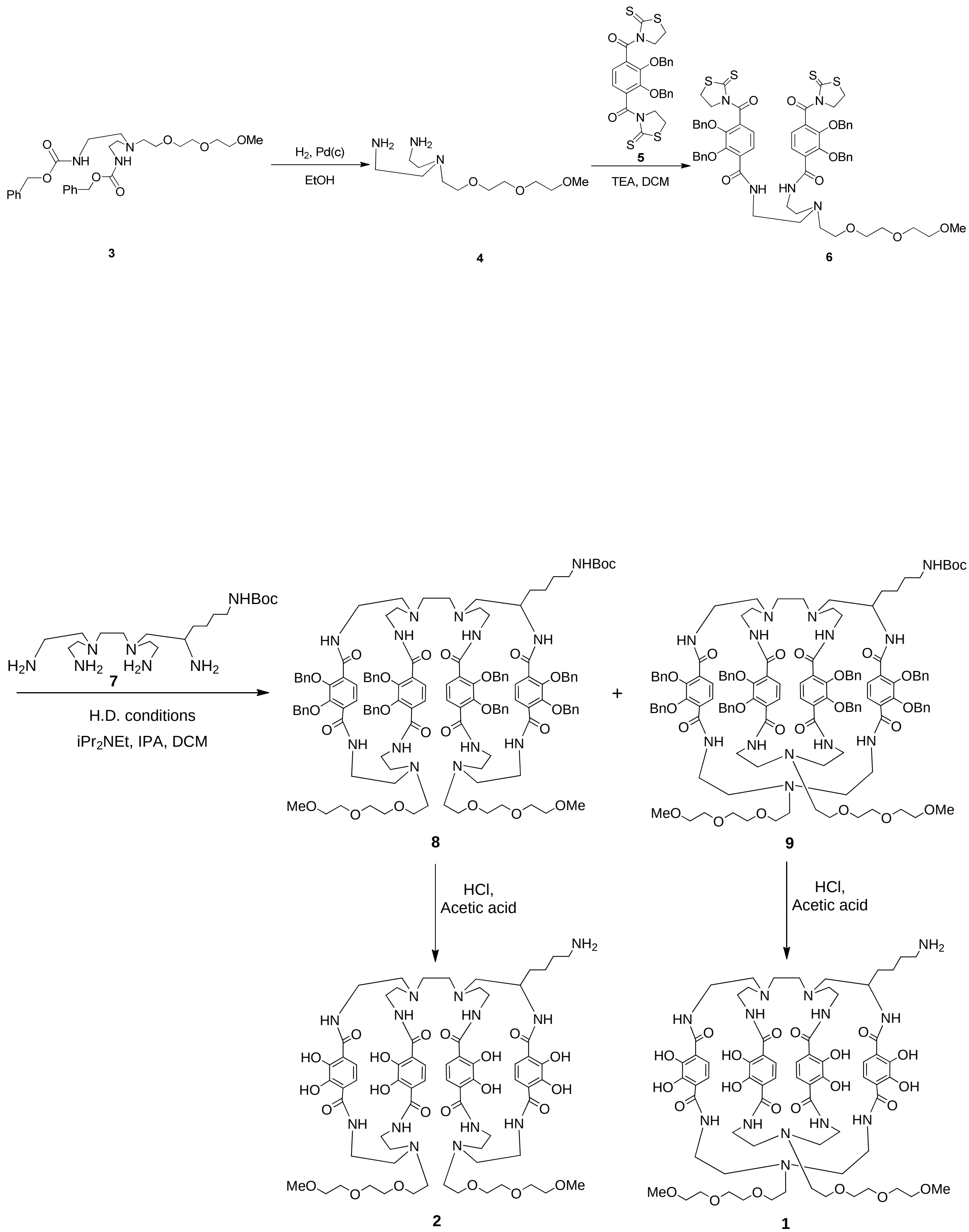
Table of Contents

MATERIALS AND METHODS

Zirconium-89 (^{89}Zr: ($t_{½}$ = 78.4 h, β^+: 22.8 %, $E_{\beta+max}$ = 901 keV; EC: 77%, E_γ = 909 keV) was purchased from Washington University School of Medicine (St. Louis, MO) or IBA Molecular, Inc. (Dulles, VA). Unless otherwise noted, all other chemicals were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO USA), and solutions were prepared using ultrapure water (18 MΩ-cm resistivity). Electrospray ionization (ESI) high-resolution mass spectra (HRMS) were obtained by the Mass Spectrometry Facility, College of Chemistry, University of California, Berkeley, CA. Flash chromatography was performed using EM Science Silica Gel 60 (230 - 400 mesh). NMR spectra were obtained using either Bruker AM-300 or AV-600 spectrometers operating at 300 (75) MHz and 600 (150) MHz for ^{1}H (or ^{13}C) respectively. ^{1}H (or ^{13}C) chemical shifts are reported in parts per million (ppm) relative to the solvent resonances, taken as δ 7.26 (δ 77.0) for $CDCl_3$. For the deprotected macrocycles **1** and **2**, the observed NMR spectra were very complicated due to the presence of differing conformers/isomers in solution, and are not reported.[3] Analytical HPLC was performed on an Agilent 1200 instrument (Agilent, Santa Clara, CA) equipped with a diode array detector (λ = 280 or 315 nm, 600 nm reference), a thermostat set at 25 °C, and a Zorbax Eclipse XDB-C18 column (4.6 x 150 mm, 5 µm, Agilent, Santa Clara, CA). The mobile phase of a binary gradient (Method 1: 2-40% B/20 min; solvent A, 0.1% TFA; solvent B, ACN or Method 2: 10-60% B) at a flow rate of 1 mL/min was used for analytical HPLC. All compounds (except **4** that was not analyzed) were ≥95% pure.

Radiochemistry reaction progress and purity were analyzed by using a Waters analytical HPLC (Milford, MA), which runs Empower software and is configured with a 1525 binary pump, 2707 autosampler, 2998 photodiode array detector, 2475 multichannel fluorescence detector, 1500 column heater, fraction collector, Grace Vydac 218MS C18 column (5 µm, 4.6 ×

250 mm, Grace Davidson, DeerField, IL) and a Carrol Ramsey 105-s radioactivity detector (Berkeley, CA). All ligands (**DFO**, **1**, and **2**) and associated ^{Nat}Zr-complexes were monitored at 220 nm using a mobile phase consisting of 0.01% TFA/H_2O (solvent A) and 0.01% TFA/acetonitrile (solvent B), and a gradient consisting of 0% B to 70% B in 20 min at a flow rate of 1.2 mL/min. In addition, radio-TLC was conducted on a Bioscan AR 2000 radio-TLC scanner equipped with a 10% methane:argon gas supply and a PC interface running Winscan v.3 analysis software (Eckert & Ziegler, Berlin, DE). Varian ITLC-SG strips were employed using a 50 mM DTPA (pH 7) solution as eluent, and the complex $^{89}Zr(Ox)_2$ as a standard control. Radioactive samples were counted using a Perkin Elmer 2480 Wizard® gamma counter (Waltham, MA).



Scheme S1. Synthesis of di-macrocyclic terephthalamide ligands 1 and 2

Ligand Synthesis

2,3-Dibenzyloxy-bis(2-mercaptothiazole)terephthalamide **(5)** and 5-amino-6-[(2-aminoethyl)-[2-[bis(2-aminoethyl)amino]ethyl]amino]hexylcarbamic acid tert-butyl ester **(7)** were prepared as previously described. [1]

N,N″-Bis(carbobenzyloxy)-N′-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-bis(2-aminoethyl)amine (3). N,N″-Di-Z-diethylenetriamine (1.00 g, 2.69 mmol), [2-[2-(2-methoxyethoxy)ethoxy]ethoxy] p-toluene sulfonate (1.529 g, 4.80 mmol), potassium carbonate (557 mg, 4.04 mmol), and sodium iodide (404 mg, 2.69 mmol) were dried together in vacuo. Anhydrous acetonitrile (15 mL) was added, and the resulting solution was heated at reflux for 28 hr. The residue was dissolved in dichloromethane (25 mL) and washed with 1 M sodium hydroxide (15 mL). The aqueous phase was extracted with dichloromethane (10 mL) and solvent was removed from the combined organic extracts under reduced pressure. The crude product was purified by silica gel chromatography using 1 – 2% methanol in dichloromethane as eluents. Fractions containing product were combined, solvent was removed under reduced pressure, and the residue dried in vacuo to provide N,N″-bis(carbobenzyloxy)-N′-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-bis(2-aminoethyl)amine **3** (1.028 g, 73.8%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (s, 10H, ArH), 5.05 (s, 4H, $PhCH_2O$), 3.50 (m, 4H, CH_2CH_2O), 3.42 (m, 6H, CH_2CH_2O), 3.29 (s, 3H, OMe), 3.21 (m, 4H, CH_2CH_2N), 2.62 (m, 6H, CH_2CH_2N). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 156.8, 136.9, 128.4, 128.1, 128.0, 71.8, 70.5, 70.3, 70.2, 70.0, 66.5, 58.9, 54.3, 53.3, 39.2. FTMS pESI: m/z calculated for $C_{27}H_{40}N_3O_7$ $[M+H]^+$, 518.2861, found, 518.2857.

N′-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-bis(2-aminoethyl)amine (4). N,N″-bis(carbo benzyloxy)-N′-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-bis(2-aminoethyl)amine (1.028 g, 1.99 mmol) was dissolved in ethyl alcohol (100 mL). Palladium on carbon (10% wet, 100 mg) was added, and the atmosphere was exchanged for hydrogen. After 19.5 hr, the solution was filtered through Celite® to remove catalyst, the Celite was washed with ethyl alcohol (100 mL), solvent was removed under reduced pressure, and the residue dried in vacuo to provide N′-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-bis(2-aminoethyl)amine **4** (481 mg, 97.1%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.58 (m, 6H, CH_2CH_2O), 3.49 (m, 4H, CH_2CH_2O), 3.33 (s, 3H, OMe), 2.70 (t, 4H, CH_2CH_2N), 2.62 (t, 2H, CH_2CH_2N), 2.51 (t, 4H, CH_2CH_2N), 1.83 (brs, 4H, NH_2). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 71.9, 70.6, 70.4, 70.3, 69.9, 59.0, 57.8, 53.7, 39.7. FTMS pESI: m/z calculated for $C_{11}H_{28}N_3O_3$ $[M+H]^+$, 250.2125, found, 250.2123.

N,N″-bis[2,3-dibenzyloxy-1-(2-mercaptothiazoleamido)-4-terephthalamido]-N′-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-bis(2-aminoethyl)amine (6). N′-[2-[2-(2-methoxyethoxy) ethoxy]ethoxy]-bis(2-aminoethyl)amine **4** (371 mg, 1.49 mmol) was dissolved in dichloromethane (30 mL) and added using a syringe pump (NE1000) to a solution of 2,3-dibenzyloxy-bis(2-mercaptothiazole)terephthalamide **5** (7.80 g, 13.4 mmol) in dichloromethane (75 mL) over a period of 20 hrs at a rate of 1.50 mL/hr. After a further 22 hr, solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography using 1 – 2% methanol in dichloromethane as eluents. Fractions containing product were combined, solvent was removed under reduced pressure, and the residue dried in vacuo to provide compound **6** (1.134 g, 65.0%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, 2H, ArH), 7.35 – 7.31 (m, 20H, ArH), 7.18 (d, 2H, ArH), 5.07 (s, 8H, $PhCH_2O$), 4.36 (t, 4H,

NCH_2CH_2S), 3.56 – 3.46 (m, 8H, CH_2CH_2O), 3.38 (t, 2H, CH_2CH_2O), 3.31 – 3.26 (m, 7H, CH_2CH_2N, OMe), 2.92 (t, 4H, NCH_2CH_2S), 2.59 (t, 2H, CH_2CH_2N), 2.47 (t, 4H, CH_2CH_2N). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 201.6, 167.1, 164.6, 150.3, 149.6, 137.3, 136.2, 133.5, 131.0, 129.1, 129.0, 128.9, 128.6, 128.2, 126.8, 124.7, 77.2, 76.4, 72.1, 70.8, 70.7, 70.6, 69.9, 59.3, 55.8, 53.7, 53.5, 38.1, 29.0. FTMS pESI: m/z calculated for $C_{61}H_{66}N_5O_{11}S_4$ $[M+H]^+$, 1172.3636, found, 1172.3621.

Benzyl and tert-butyloxycarbonyl-protected di-macrocycles (8) and (9). A solution of N,N″-bis[2,3-dibenzyloxy-1-(2-mercaptothiazoleamido)-4-terephthalamido]-N′-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-bis(2-aminoethyl)amine **6** (1.085 g, 925 μmol) in dichloromethane (50 mL) and a solution of 5-amino-6-[(2-aminoethyl)-[2-[bis(2-aminoethyl)amino]ethyl]amino]hexyl carbamic acid tert-butyl ester **7** (187 mg, 463 μmol) in dichloromethane, isopropyl alcohol (ca. 5%), and diisopropylethylamine (ca. 3%) (50 mL) were added dropwise to dichloromethane (2 L) over a period of four days using two syringe pumps at a rate of 0.5 mL/hr. After an additional two days of reaction, solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography using 0.1% triethylamine, 5 – 7.5% methanol in dichloromethane as eluents. The silica gel column was prepared so as to have a short section (ca. 1.25") of aluminum oxide (basic, Brockmann I) on its bottom. Di-macrocycle **8** eluted first, with 5% MeOH in dichloromethane. Fractions containing each product were combined, solvent was removed under reduced pressure, and the residues dried in vacuo to provide the protected di-macrocycles **8** and **9** (264 mg and 242 mg, respectively, 24.1%). Di-macrocycle **8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (m, 4H, ArH), 7.29 – 7.25 (m, 40H, ArH), 7.12 – 7.00 (m, 4H, ArH), 5.04 – 4.90 (m, 16H, $PhCH_2O$), 3.54 – 3.29 (m, 26H, CH_2CH_2O, OMe), 2.98 – 2.14 (m, 39H, CH_2CH_2N), 1.67 (m, 4H, CH_2), 1.38 (s, 9H, CH_3), 1.24 (m, 5H, CH, CH_2). ^{13}C NMR (600 MHz, $CDCl_3$): δ = 166.0, 165.8, 155.9, 150.3, 150.2, 136.5, 136.4, 131.8, 128.7, 128.6, 128.4, 128.3, 128.2, 127.8, 125.0, 124.8, 76.7, 76.5, 71.8, 70.5, 70.4, 70.2, 68.8, 68.7, 58.9, 52.4, 51.8, 47.1, 40.3, 37.1, 37.0, 33.6, 29.8, 28.4, 23.4. FTMS pESI: m/z calculated for $C_{129}H_{157}N_{13}O_{24}$ $[M+2H]^{2+}$, 1136.0727, found, 1136.0709. Di-macrocycle **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 – 7.57 (m, 4H, ArH), 7.33 – 7.25 (m, 40H, ArH), 7.20 – 6.96 (m, 4H, ArH), 5.29 – 4.93 (m, 16H, $PhCH_2O$), 3.66 – 3.27 (m, 26H, CH_2CH_2O, OMe), 2.92 – 2.51 (m, 39H, CH_2CH_2N), 1.95 – 1.81 (m, 4H, CH_2), 1.38 (s, 9H, CH_3), 1.24 (m, 5H, CH, CH_2). ^{13}C NMR (600 MHz, $CDCl_3$): δ = 165.7, 165.6, 165.5, 155.9, 150.3, 150.2, 149.9, 136.5, 136.4, 132.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 124.8, 124.6, 76.7, 76.6, 76.5, 76.3, 71.8, 70.5, 70.3, 70.1, 69.3, 58.9, 54.1, 53.9, 53.5, 53.4, 52.9, 52.3, 52.2, 37.8, 37.7, 37.6, 37.5, 29.6, 28.4, 23.4. FTMS pESI: m/z calculated for $C_{129}H_{157}N_{13}O_{24}$ $[M+2H]^{2+}$, 1136.0727, found, 1136.0705.

Di-macrocyclic terephthalamide ligand (1). Benzyl and tert-butyloxycarbonyl-protected di-macrocycle **9** (10 mg, 4.4 μmol) was dissolved in 12 N hydrochloric acid (0.5 mL, BDH Aristar Plus) and glacial acetic acid (0.5 mL, 99.99+%). The solution was stirred under inert atmosphere for 44 hr, whereupon HCl was removed with a stream of inert gas. Solvents were removed under reduced pressure and the residue was dried in vacuo. The residue was dissolved in methanol (2 x 200 μL) and transferred to an O-ring microcentrifuge tube. Ether (ca. 1.5 mL) was added, and the tube was placed at 4 °C overnight. The tube was centrifuged at 12,000 rpm for 3 minutes, decanted; the pellet was washed with ether (ca. 1.5 mL) and allowed to air dry. The pellet was dried in vacuo to provide di-macrocycle **1**, pentahydrochloride salt (6.75 mg, 94%). FTMS pESI: m/z calculated for $C_{68}H_{101}N_{13}O_{22}$ $[M+2H]^{2+}$, 725.8587, found, 725.8583. Analysis (C,H,N): Calc. for $C_{68}H_{99}N_{13}O_{22}.5(HCl).9(H_2O)$, 45.48, 6.85, 10.15; found, 45.62, 6.80, 10.04.

Di-macrocyclic terephthalamide ligand (2). Di-macrocycle **2** was formed from compound **8** following a similar procedure. FTMS pESI: m/z calculated for $C_{68}H_{101}N_{13}O_{22}$ $[M+2H]^{2+}$, 725.8587, found, 725.8590. Analysis (C,H,N): Calc. for $C_{68}H_{99}N_{13}O_{22}.5(HCl).9(H^2O)$, 45.48, 6.85, 10.15; found, 45.72, 6.91, 10.05. Tandem mass spectrometry performed on compound **2**, 484.33 MS1 peak $[M+3H]^{3+}$, revealed peaks at m/z 352.1688 $[M+2H]^{2+}$, 387.7056 $[M+2H]^{2+}$, 677.3151 $[M+H]^{+}$, and 748.3884 $[M+H]^{+}$, consistent with fragmentation across the ethylene diamine bridge. Cf. Figure S1. Similar fragmentation was not observed upon analysis of compound **1**.

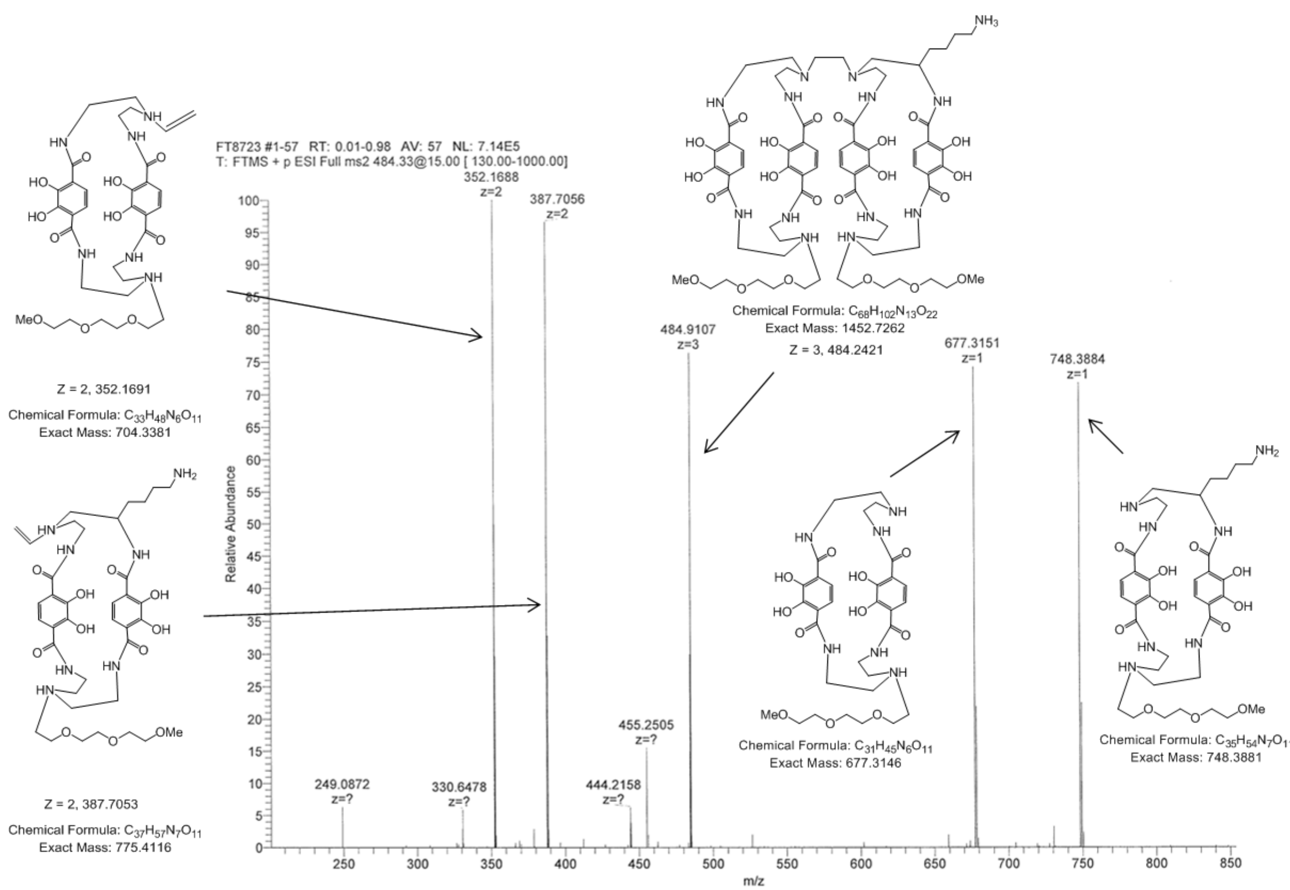
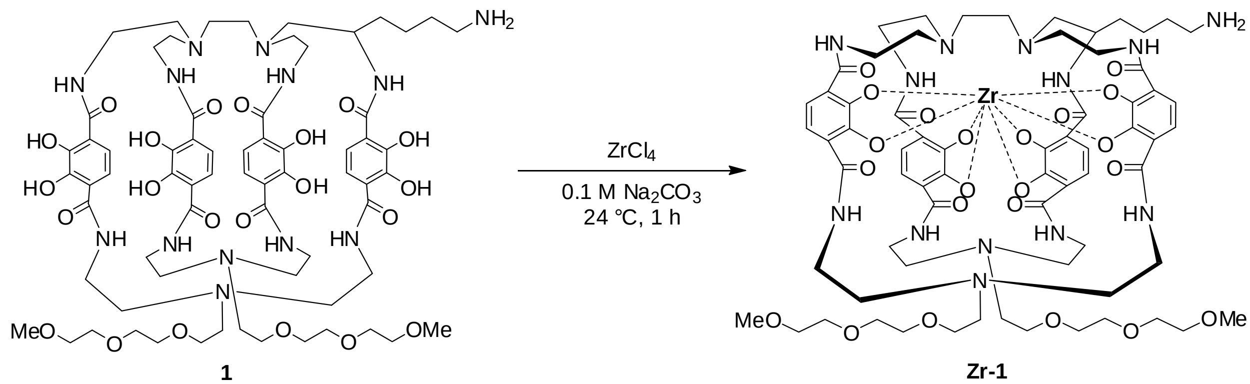


Figure S1. Mass spectrum of di-macrocyclic ligand 2.



Scheme S2. Synthesis of zirconium complex of di-macrocyclic terephthalamide ligand 1

Synthesis of Zr-1. To a solution of ligand **1** (0.5 mg, 0.31 µmol) and $ZrCl_4$ (0.11 mg, 0.46 µmol) in 0.5 mL of water was added 0.1 M Na_2CO_3 to adjust pH 7-7.5. The resulting solution was stirred for 1 h at room temperature. Then the mixture was lyophilized to give a white solid. Formation of **Zr-1** complex was confirmed by ESI-MS analysis. Calculated for $C_{68}H_{97}N_{13}O_{22}Zr$, 768.79 [$(MH_2)^{+2}$] Found: 768.78 [$(MH_2)^{+2}$].

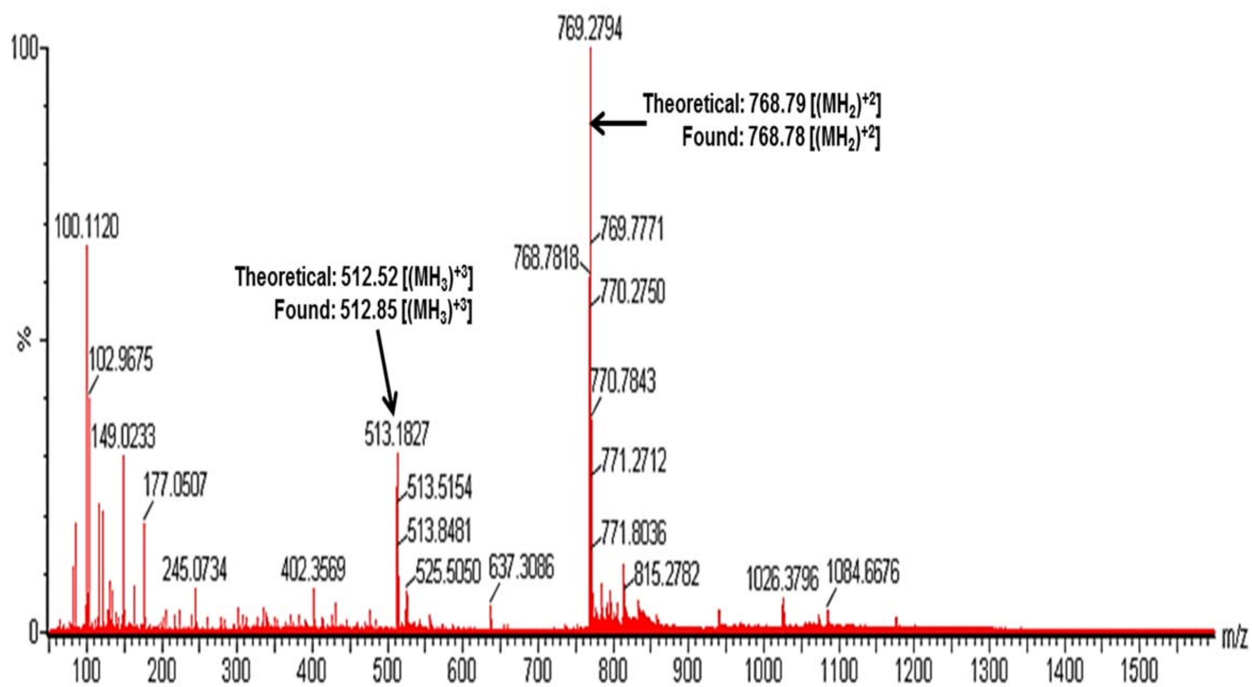
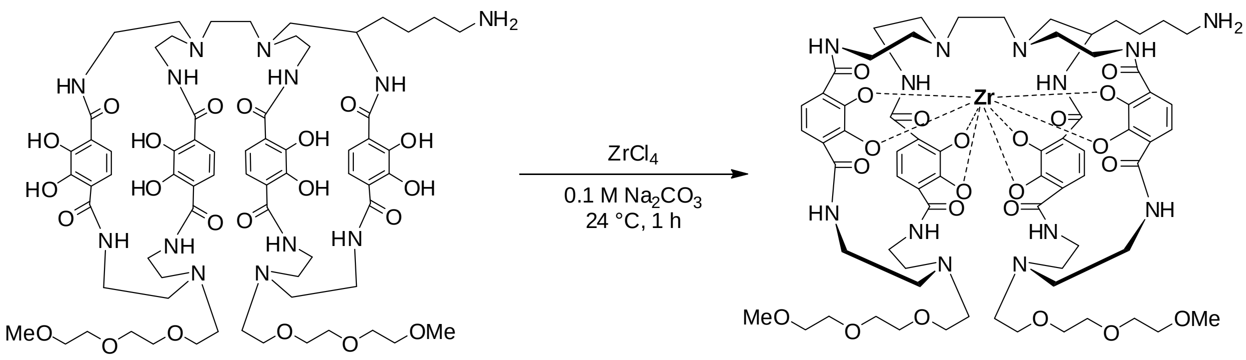


Figure S2. ESI-MS analysis of the Zr-1 complex



Scheme S3. Synthesis of zirconium complex of di-macrocyclic terephthalamide ligand 2

Synthesis of Zr-2. To a solution of ligand **2** (0.4 mg, 0.24 μmol) and $ZrCl_4$ (83.9 μg, 0.36 μmol) in 0.5 mL of water was added 0.1 M Na_2CO_3 to adjust pH 7-7.5. The resulting solution was stirred for 1 h at room temperature. Then the mixture was lyophilized to give a white solid. Formation of **Zr-2** complex was confirmed by ESI-MS analysis. Calculated for $C_{68}H_{97}N_{13}O_{22}Zr$, 768.79 [$(MH_2)^{+2}$] Found: 768.78 [$(MH_2)^{+2}$].

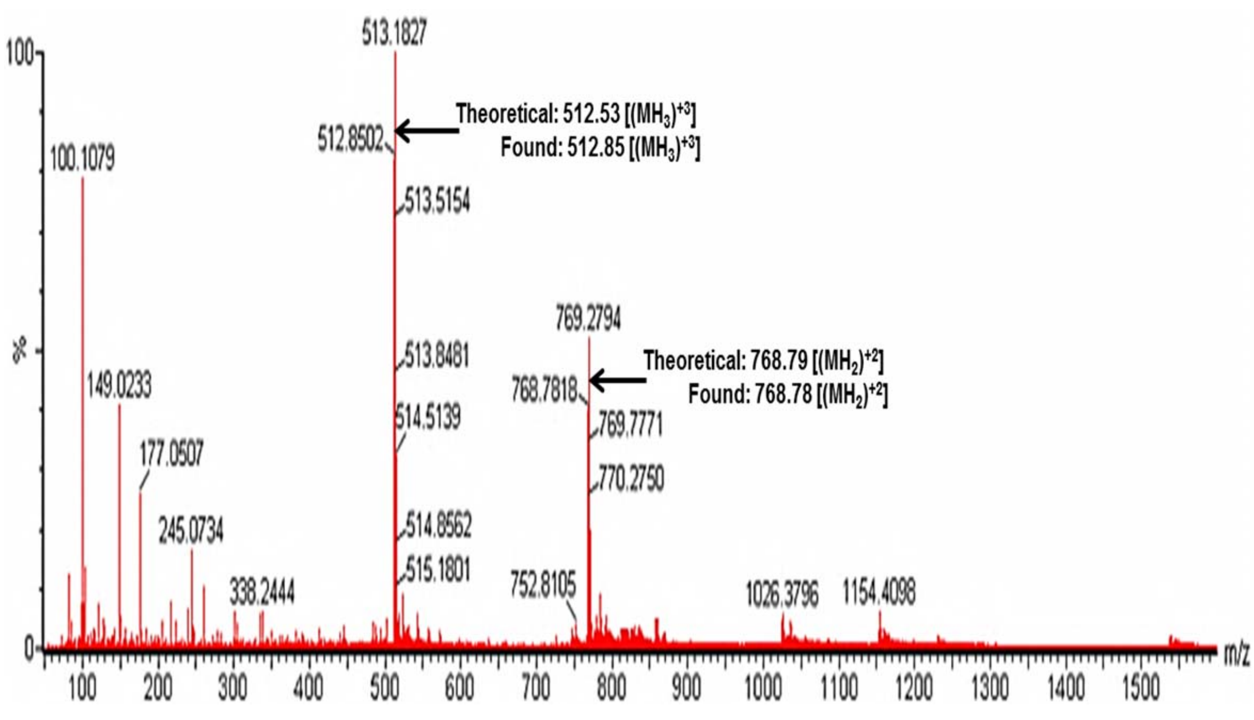
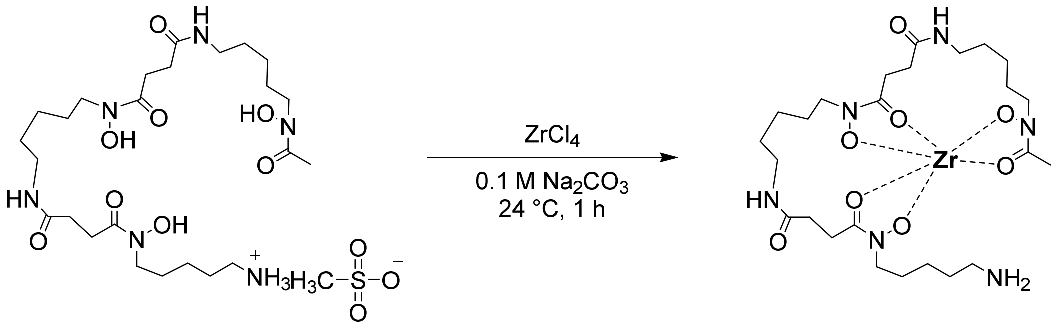


Figure S3. ESI-MS analysis of the Zr-2 complex



Scheme S4. Synthesis of zirconium complex of DFO

Synthesis of Zr-DFO. To a solution of DFO (1 mg, 1.52 μmol) and $ZrCl_4$ (0.53 mg, 2.28 μmol) in 0.6 mL of water was added 0.1 M Na_2CO_3 to adjust pH 7-7.5. The resulting solution was stirred for 1 h at room temperature. Then the mixture was lyophilized to give a white solid. Formation of Zr-DFO complex was confirmed by ESI-MS analysis. Calculated for $C_{25}H_{45}N_6O_8Zr$, 647.23 $[(M)^+]$ Found: 647.23 $[(M)^+]$.

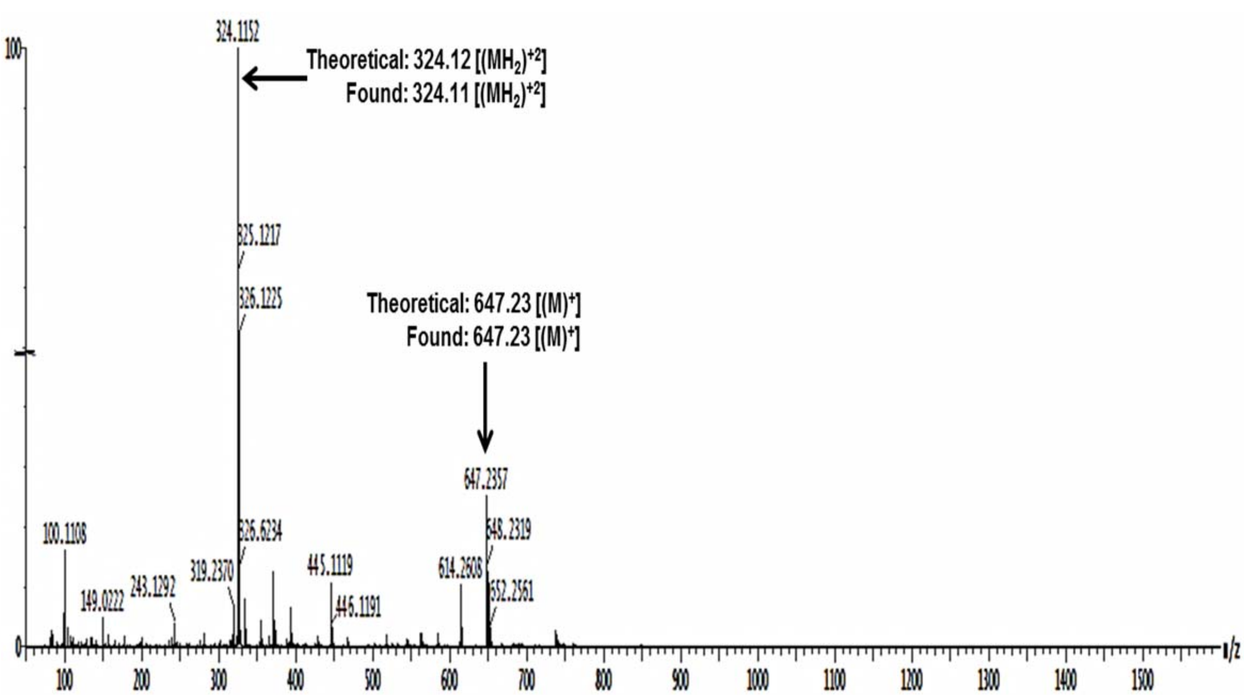


Figure S4. ESI-MS analysis of the Zr-DFO complex

Density Functional Theory (DFT) calculations

Ground state density functional theory calculations were performed at the Molecular Graphics and Computational Facility, College of Chemistry, University of California, Berkeley using Gaussian 09.[2] The ground state geometries of $[Zr\text{-}\mathbf{1}]^{4-}$ and $[Zr\text{-}\mathbf{2}]^{4-}$ were optimized using the B3LYP functional, treating the light atoms (H through O) with the 6-31G(d,p) basis set and the Zr atom with the effective core potential MWB28.[3] No solvent, symmetry constraints, or counter ions were included in the calculations. Crystal structures of the related H22 linked 2-hydroxyisophthalamide ligands bound to Tb^{III} were used as starting points for these terephthalamide Zr^{IV} complexes.[1c, 4] If the alkyl amine linker arm is neglected, both Zr complexes exhibit two-fold rotational symmetry, where the symmetry axis passes through the midpoint of the central ethylene unit and through the metal center. The optimized structures of $[Zr\text{-}\mathbf{1}]^{4-}$ and $[Zr\text{-}\mathbf{2}]^{4-}$ are shown below. In addition to geometry optimizations, frequency calculations were performed. The lack of any negative frequencies confirmed that the calculated structures are ground states.

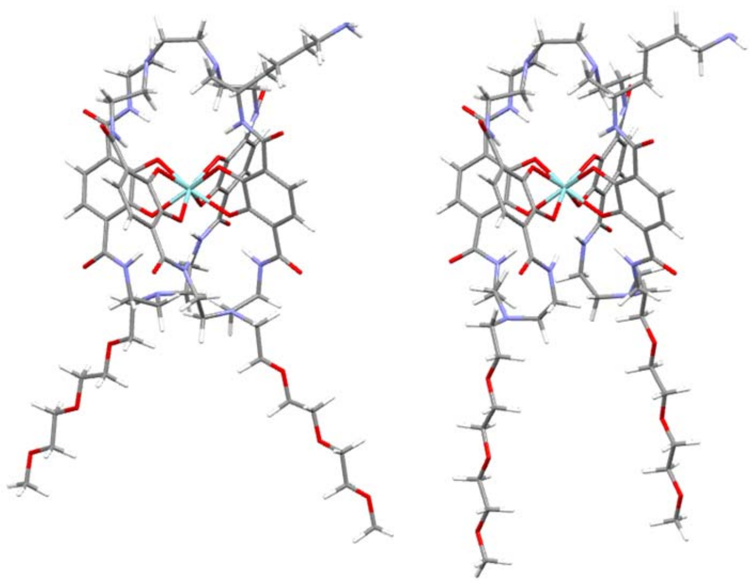


Figure S5. Side on view of $[Zr\text{-}\mathbf{1}]^{4-}$ (left) and $[Zr\text{-}\mathbf{2}]^{4-}$ (right).

Final Coordinates

Compound 1				Compound 2			
Atom Type	x (Å)	y (Å)	z (Å)	Atom Type	x (Å)	y (Å)	z (Å)
C	-13.895	-4.869	2.499	C	-13.812	-5.551	2.713
C	-9.393	-5.320	4.028	C	-9.285	-5.332	4.241
C	-15.246	-4.232	2.861	C	-8.285	-5.743	5.358
N	-15.462	-4.053	4.282	C	-15.249	-5.039	2.933
N	-9.006	-6.142	6.330	N	-15.534	-4.627	4.291
C	-16.488	-3.260	4.726	N	-8.896	-5.662	6.684
H	-13.790	-5.783	3.108	C	-16.577	-3.784	4.575
H	-13.976	-5.208	1.455	H	-13.610	-6.320	3.479
C	-8.310	-6.607	7.417	H	-13.812	-6.077	1.747
O	-17.267	-2.727	3.911	C	-8.207	-5.898	7.848
H	-16.030	-4.880	2.434	O	-17.333	-3.378	3.672
H	-15.353	-3.262	2.360	H	-15.925	-5.856	2.625
H	-14.916	-4.528	5.006	H	-15.459	-4.198	2.263
O	-7.117	-6.963	7.315	H	-15.019	-4.983	5.102
H	-9.892	-5.687	6.575	O	-6.977	-6.111	7.842
C	-16.577	-3.039	6.194	H	-9.862	-5.348	6.825
C	-9.079	-6.727	8.683	C	-16.708	-3.354	5.997
C	-17.619	-2.183	6.649	C	-9.027	-5.963	9.090
C	-8.448	-7.425	9.752	C	-17.748	-2.434	6.310
C	-17.744	-1.846	7.973	C	-8.375	-6.420	10.271
C	-16.801	-2.304	8.937	C	-17.877	-1.897	7.569
C	-9.098	-7.655	10.938	C	-16.958	-2.217	8.606
O	-14.717	-4.447	6.867	C	-9.069	-6.638	11.438
C	-10.441	-7.224	11.135	O	-14.853	-4.638	6.891
C	-15.736	-3.128	8.516	C	-10.471	-6.414	11.513
H	-18.306	-1.805	5.897	C	-15.917	-3.128	8.327
C	-11.103	-6.539	10.095	H	-18.421	-2.159	5.503
H	-7.433	-7.772	9.582	C	-11.140	-5.932	10.370
H	-18.554	-1.217	8.330	H	-7.308	-6.611	10.201
O	-11.056	-5.503	7.992	H	-18.664	-1.188	7.809
O	-14.755	-3.545	9.301	O	-11.136	-5.226	8.138
H	-8.616	-8.172	11.763	O	-14.960	-3.464	9.180
O	-12.365	-6.146	10.141	H	-8.577	-7.005	12.334
C	-10.339	-0.284	9.382	O	-12.445	-5.712	10.302
C	-15.425	-9.696	7.044	C	-10.784	0.128	8.882
C	-16.336	-9.430	8.039	C	-15.501	-9.710	7.456
C	-14.343	-8.809	6.793	C	-16.305	-9.441	8.537
C	-10.580	-0.134	8.037	C	-14.455	-8.822	7.079
C	-11.342	-1.098	7.322	C	-10.962	0.082	7.520
O	-15.001	-6.201	9.236	C	-11.654	-1.001	6.910
O	-12.048	-3.508	9.947	O	-14.965	-6.132	9.460
O	-13.290	-6.725	7.404	O	-12.325	-3.101	9.789

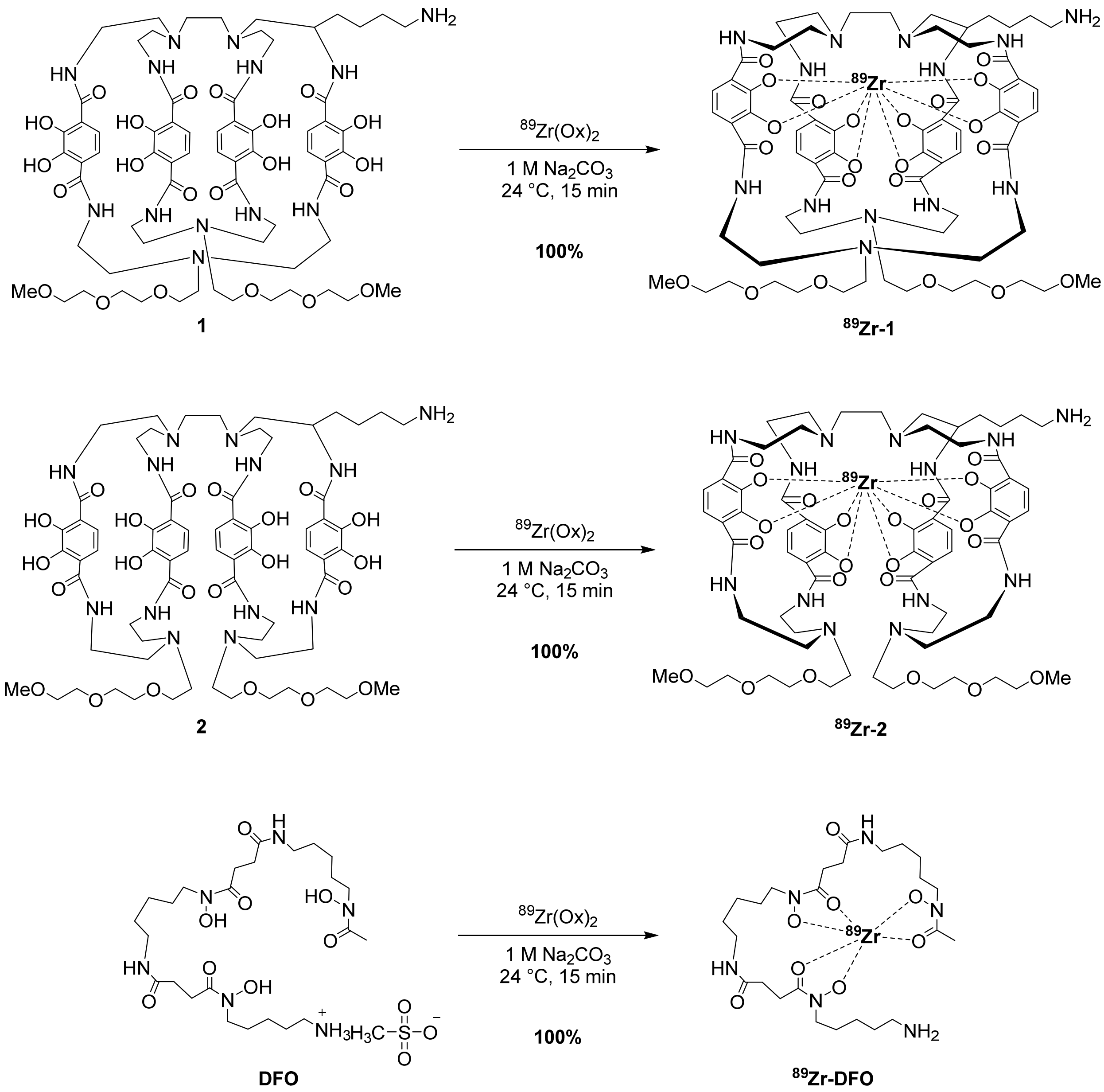
O	-12.505	-3.210	7.445	O	-13.319	-6.736	7.589
H	-9.776	0.456	9.944	O	-12.732	-3.139	7.262
H	-15.498	-10.588	6.427	H	-10.302	0.972	9.365
H	-17.157	-10.108	8.254	H	-15.625	-10.612	6.863
H	-10.208	0.724	7.482	H	-17.077	-10.133	8.859
H	-8.800	-4.947	3.182	H	-10.606	0.878	6.872
H	-9.831	-4.434	4.517	H	-8.692	-5.024	3.369
C	-10.820	-1.411	10.107	H	-9.809	-4.427	4.589
C	-11.549	-2.411	9.420	H	-7.464	-5.006	5.315
C	-16.250	-8.254	8.838	C	-11.256	-0.917	9.727
C	-15.206	-7.330	8.594	C	-11.874	-2.050	9.142
C	-11.606	-0.879	5.868	C	-16.155	-8.241	9.289
C	-13.368	-9.141	5.711	C	-15.173	-7.298	8.896
O	-13.626	-9.911	4.771	C	-11.892	-0.965	5.437
O	-10.899	-0.152	5.150	C	-13.604	-9.182	5.907
C	-12.434	-3.383	3.870	O	-13.935	-10.004	5.037
H	-11.357	-3.392	4.046	O	-11.166	-0.346	4.643
H	-12.873	-3.959	4.690	C	-12.578	-3.705	3.840
C	-12.887	-1.913	4.010	H	-11.514	-3.625	4.077
H	-12.277	-1.252	3.387	H	-13.040	-4.168	4.715
H	-13.935	-1.808	3.708	C	-13.117	-2.264	3.725
C	-11.407	-6.741	4.412	H	-12.527	-1.676	3.015
H	-12.412	-6.603	4.007	H	-14.159	-2.275	3.390
H	-11.397	-6.172	5.345	C	-11.159	-6.829	4.787
C	-11.257	-8.240	4.756	H	-12.043	-6.182	4.849
H	-10.217	-8.452	5.026	H	-10.676	-6.752	5.758
H	-11.531	-8.875	3.908	C	-11.631	-8.289	4.679
N	-12.139	-8.544	5.865	H	-10.755	-8.952	4.599
H	-12.144	-7.825	6.593	H	-12.264	-8.486	3.804
N	-12.727	-1.520	5.397	N	-12.400	-8.528	5.884
H	-13.097	-2.202	6.063	H	-12.357	-7.776	6.582
N	-10.403	-6.219	3.475	N	-13.020	-1.644	5.034
N	-12.723	-3.998	2.566	H	-13.403	-2.229	5.778
C	-10.907	-5.882	2.151	N	-10.193	-6.388	3.780
H	-11.625	-6.664	1.877	N	-12.766	-4.531	2.641
H	-10.079	-5.967	1.424	C	-10.738	-6.225	2.436
C	-11.554	-4.482	1.845	H	-11.367	-7.101	2.243
H	-10.777	-3.714	1.944	H	-9.901	-6.291	1.717
H	-11.800	-4.526	0.768	C	-11.533	-4.946	1.987
C	-11.047	-7.466	12.468	H	-10.854	-4.085	2.011
C	-17.288	-8.077	9.885	H	-11.747	-5.131	0.917
C	-17.033	-1.934	10.355	C	-11.166	-6.751	12.795
C	-10.514	-1.454	11.560	C	-17.008	-8.070	10.490
O	-18.166	-8.934	10.111	C	-17.112	-1.517	9.919
O	-9.908	-0.534	12.145	C	-11.155	-0.713	11.192
O	-10.408	-7.959	13.422	O	-17.794	-8.954	10.899

O	-18.062	-1.338	10.739
C	-10.623	-2.715	13.647
H	-10.413	-1.706	14.015
H	-9.700	-3.301	13.795
C	-12.975	-6.941	13.888
H	-14.011	-7.310	13.866
H	-12.419	-7.563	14.596
C	-16.271	-2.322	12.653
H	-17.103	-1.643	12.862
H	-15.389	-1.938	13.186
C	-18.265	-6.630	11.588
H	-19.112	-6.079	11.145
H	-18.662	-7.602	11.900
H	-12.761	-6.644	11.770
H	-16.545	-6.220	10.315
H	-15.288	-2.852	10.816
H	-11.360	-3.313	11.685
N	-12.363	-7.104	12.598
N	-17.242	-6.910	10.608
N	-16.046	-2.297	11.234
N	-10.937	-2.566	12.245
C	-10.395	-6.230	8.862
C	-14.247	-7.628	7.552
C	-15.664	-3.576	7.135
C	-11.802	-2.239	8.006
C	-16.546	-3.737	13.208
H	-15.671	-4.356	12.988
H	-16.600	-3.661	14.318
C	-17.754	-5.856	12.814
H	-16.748	-6.219	13.046
H	-18.388	-6.122	13.686
N	-17.695	-4.407	12.613
C	-18.978	-3.727	12.752
H	-18.945	-2.770	12.220
H	-19.744	-4.335	12.260
C	-19.427	-3.500	14.206
H	-19.348	-4.427	14.799
H	-18.799	-2.740	14.699
O	-20.788	-3.056	14.199
C	-21.276	-2.740	15.472
H	-21.257	-3.613	16.150
H	-20.684	-1.943	15.955
C	-11.752	-3.354	14.473
H	-12.707	-3.009	14.064
H	-11.698	-2.960	15.509
C	-13.033	-5.471	14.359

O	-10.682	0.326	11.704
O	-10.581	-7.258	13.769
O	-17.986	-0.657	10.128
H	-12.873	-6.115	11.917
H	-16.183	-6.230	10.741
H	-15.488	-2.543	10.543
H	-12.029	-2.530	11.443
N	-12.503	-6.460	12.812
N	-16.856	-6.885	11.161
N	-16.213	-1.898	10.881
N	-11.669	-1.720	11.965
C	-10.414	-5.685	9.139
C	-14.279	-7.625	7.805
C	-15.818	-3.748	7.021
C	-12.086	-2.075	7.712
C	-15.993	-1.179	12.113
H	-16.843	-0.510	12.271
H	-15.966	-1.882	12.958
C	-11.843	-1.589	13.390
H	-11.480	-2.497	13.894
H	-11.207	-0.758	13.708
C	-14.659	-0.392	12.068
H	-14.847	0.593	11.628
H	-13.977	-0.907	11.383
C	-13.308	-1.376	13.868
H	-13.893	-2.260	13.590
H	-13.286	-1.374	14.970
N	-14.057	-0.202	13.404
C	-13.347	1.070	13.533
H	-14.012	1.859	13.161
H	-12.417	1.115	12.938
C	-12.973	1.430	14.965
H	-12.369	2.354	14.949
H	-12.353	0.647	15.426
O	-14.141	1.641	15.763
C	-13.849	1.935	17.099
H	-13.254	1.137	17.577
H	-13.271	2.872	17.203
Zr	-13.334	-4.772	8.560
C	-13.421	-6.875	13.846
H	-12.844	-7.375	14.628
H	-13.902	-6.001	14.309
C	-17.516	-6.615	12.413
H	-18.029	-5.642	12.366
H	-18.284	-7.386	12.529
C	-14.514	-7.803	13.262

H	-13.615	-4.910	13.621	H	-14.152	-8.836	13.290
H	-13.621	-5.440	15.305	H	-14.654	-7.557	12.203
N	-11.735	-4.818	14.456	C	-16.592	-6.561	13.662
C	-10.779	-5.418	15.379	H	-15.901	-5.720	13.545
H	-10.528	-6.429	15.041	H	-17.233	-6.297	14.519
H	-9.852	-4.835	15.340	N	-15.785	-7.735	14.013
C	-11.244	-5.455	16.845	C	-16.516	-9.001	14.014
H	-11.616	-4.469	17.171	H	-15.805	-9.795	14.273
H	-12.065	-6.177	16.982	H	-16.955	-9.259	13.033
O	-10.136	-5.838	17.667	C	-17.649	-9.060	15.031
C	-10.468	-5.969	19.021	H	-18.200	-10.006	14.891
H	-10.840	-5.021	19.449	H	-18.368	-8.241	14.876
H	-11.256	-6.726	19.181	O	-17.142	-8.999	16.366
Zr	-13.224	-4.908	8.554	C	-18.149	-9.006	17.338
C	-9.202	-6.392	19.752	H	-18.854	-8.166	17.207
H	-8.414	-5.639	19.594	H	-18.748	-9.936	17.311
H	-8.839	-7.347	19.343	C	-15.178	2.079	17.825
C	-8.399	-6.916	21.914	H	-15.780	2.864	17.342
H	-7.574	-6.186	21.849	H	-15.742	1.137	17.757
H	-8.000	-7.890	21.587	C	-16.081	2.558	19.958
C	-8.879	-7.017	23.354	H	-16.713	3.384	19.589
H	-9.284	-6.043	23.677	H	-16.695	1.644	19.942
H	-9.697	-7.752	23.420	C	-15.636	2.853	21.383
C	-22.712	-2.268	15.295	H	-14.994	3.749	21.391
H	-23.306	-3.060	14.813	H	-15.035	2.012	21.763
H	-22.733	-1.387	14.636	C	-16.479	3.291	23.531
C	-24.573	-1.494	16.531	H	-15.864	4.198	23.660
H	-24.669	-0.586	15.912	H	-17.422	3.429	24.069
H	-25.251	-2.253	16.106	H	-15.934	2.448	23.986
C	-24.988	-1.184	17.962	O	-14.914	2.413	19.185
H	-24.882	-2.090	18.581	O	-16.791	3.052	22.182
H	-24.318	-0.417	18.383	C	-17.463	-8.886	18.692
O	-9.504	-6.520	21.139	H	-16.750	-9.715	18.819
O	-7.783	-7.404	24.167	H	-16.895	-7.946	18.737
O	-26.332	-0.732	17.952	C	-17.940	-8.806	21.007
O	-23.244	-1.951	16.578	H	-17.361	-7.876	21.130
C	-8.135	-7.532	25.522	H	-17.266	-9.645	21.251
H	-7.236	-7.832	26.069	C	-19.122	-8.805	21.964
H	-8.505	-6.583	25.945	H	-19.717	-9.721	21.816
H	-8.914	-8.297	25.677	H	-19.776	-7.946	21.742
C	-26.802	-0.408	19.237	C	-19.653	-8.687	24.249
H	-27.838	-0.071	19.134	H	-20.293	-9.585	24.215
H	-26.779	-1.277	19.917	H	-19.182	-8.630	25.235
H	-26.213	0.399	19.702	H	-20.302	-7.806	24.118
C	-8.381	-5.932	5.030	O	-18.463	-8.923	19.706
H	-7.598	-5.162	5.142	O	-18.626	-8.733	23.291

C	-7.697	-7.206	4.456	C	-7.656	-7.132	5.109
H	-8.156	-7.453	3.490	H	-7.015	-7.330	5.970
H	-7.899	-8.044	5.127	H	-8.454	-7.883	5.095
C	-6.178	-7.053	4.314	C	-6.857	-7.229	3.801
H	-5.795	-6.781	5.303	H	-7.536	-7.086	2.953
H	-5.944	-6.225	3.626	H	-6.119	-6.413	3.753
C	-5.481	-8.328	3.822	C	-6.130	-8.573	3.613
H	-5.749	-9.155	4.496	H	-5.730	-8.652	2.592
H	-5.840	-8.613	2.823	H	-6.862	-9.388	3.722
C	-3.958	-8.203	3.787	C	-4.981	-8.809	4.594
H	-3.612	-7.882	4.785	H	-5.349	-8.700	5.624
H	-3.669	-7.407	3.086	H	-4.217	-8.032	4.451
N	-3.323	-9.457	3.329	N	-4.339	-10.121	4.346
H	-2.319	-9.403	3.497	H	-3.666	-10.295	5.091
H	-3.654	-10.211	3.931	H	-5.053	-10.839	4.468



Scheme S5. Radiochemical Synthesis of ^{89}Zr-1, ^{89}Zr-2, and ^{89}Zr-DFO

Radiolabeling of di-macrocyclic terephthalamide ligands (1 and 2) and DFO with ^{89}Zr.

The complexation of ^{89}Zr with di-macrocyclic terephthalamide ligands (**1** and **2**) and DFO was achieved by reacting 10 µg (10 µL,1.0 mg/mL in water) of each ligand with an aliquot of $^{89}Zr(Ox)_2$ (0.6 mCi, 22.2 MBq) that was diluted in 100 µL of water and pH adjusted to 7-7.5 using 1 M Na_2CO_3. The reactions were incubated at 24ºC for 15 min in a thermomixer (550 rpm). Formation of ^{89}Zr-**1**, ^{89}Zr-**2**, and ^{89}Zr-**DFO** complexes was monitored by radio-TLC using Varian ITLC-SG strips and 50 mM DTPA (pH 7) as the mobile phase. In this system, free ^{89}Zr forms a complex with DTPA and eluted with the solvent front, while ^{89}Zr-ligand complex remained at the origin (Fig. S6). The identity of each radioactive complex was further confirmed by comparing its radio-HPLC elution profile to the UV-HPLC spectrum of its nonradioactive ^{Nat}Zr-complex (Figs. S7 – S9).

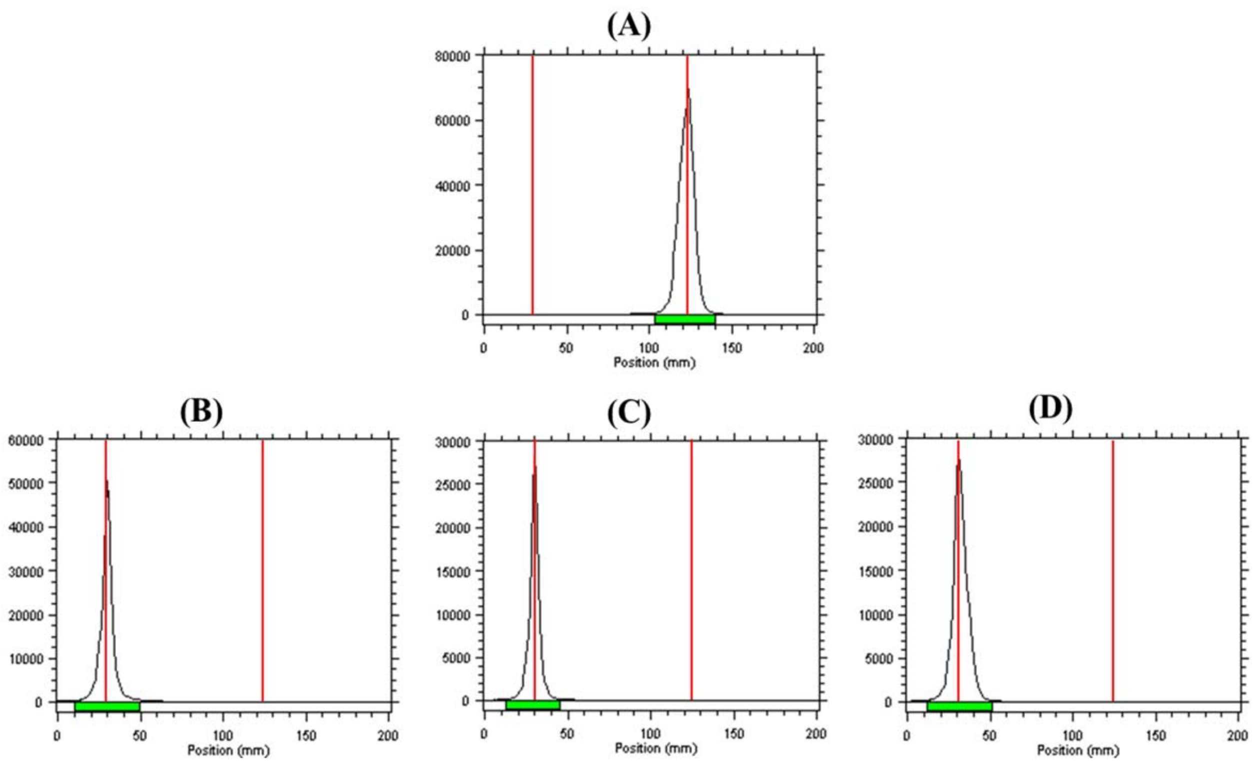


Figure S6. Radio-ITLC of $^{89}Zr(Ox)_2$ (A), ^{89}Zr-1 (B), ^{89}Zr-2 (C), and ^{89}Zr-DFO (D)

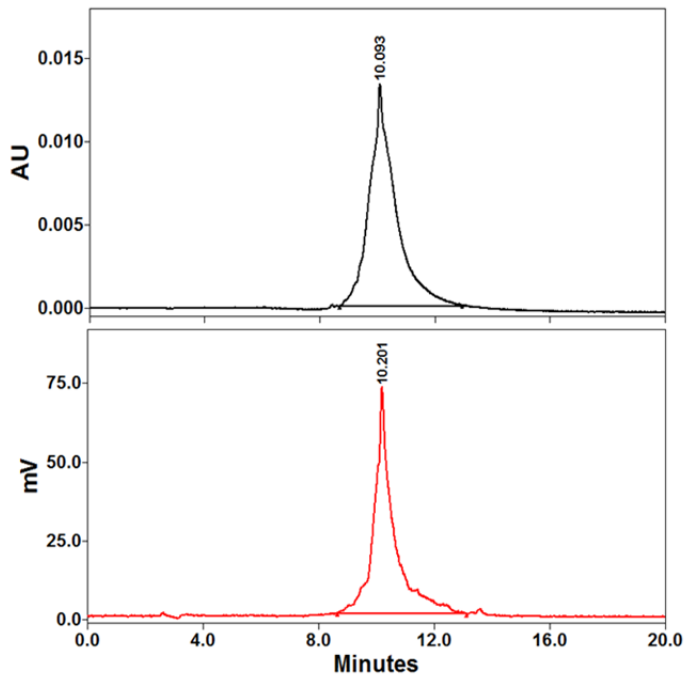


Figure S7. UV-HPLC chromatogram (220 nm) of nonradioactive ^{Nat}Zr-1 complex (top) compared with radio-HPLC chromatogram of ^{89}Zr-1 (bottom)

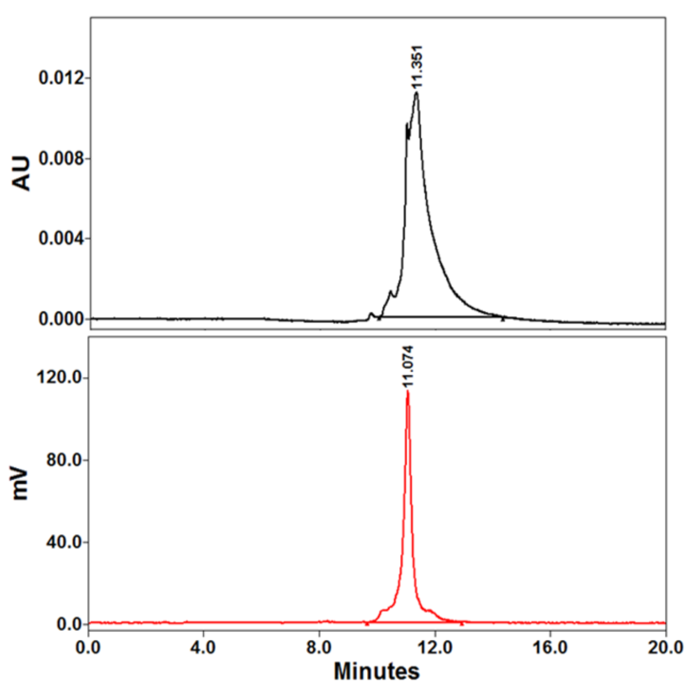


Figure S8. UV-HPLC chromatogram (220 nm) of nonradioactive ^{Nat}Zr-2 complex (top) compared with radio-HPLC chromatogram of ^{89}Zr-2 (bottom)

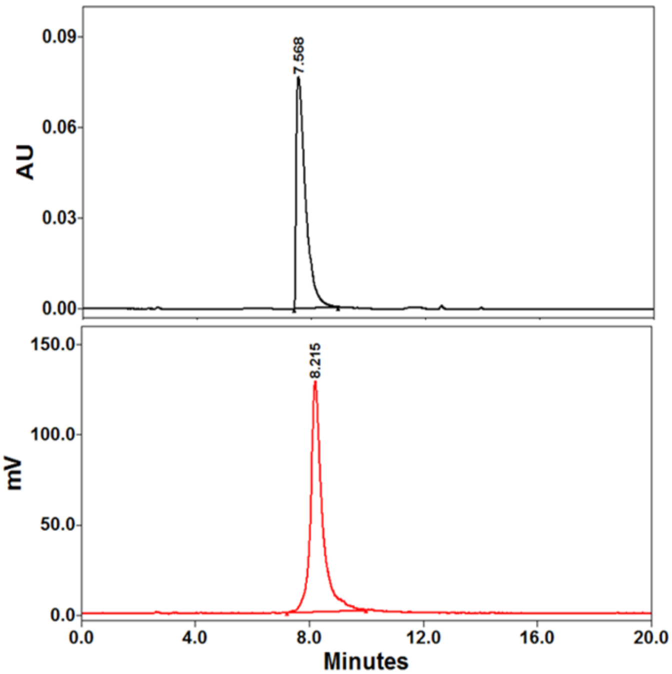


Figure S9. UV-HPLC chromatogram (220 nm) of nonradioactive ^{Nat}Zr-DFO complex (top) compared with radio-HPLC chromatogram of ^{89}Zr-DFO (bottom)

***In vitro* serum stability and DTPA challenge study**. *In vitro* stability was carried out by adding 10 μL of each ^{89}Zr-labeled complex (50 μCi, 1.85 MBq) to 500 μL DTPA (50 mM, pH7), or human serum. The solutions (n=12) were incubated at 37 °C for 7 days and were analyzed daily for 1 week by radio-TLC using Varian ITLC-SG strips and 50 mM DTPA (pH 7) as the mobile phase and gamma counting using an energy window of 500-1500 keV and standard protocols. [5]

Determination of partition coefficients (logP). The partition coefficient (LogP) for each complex was determined by adding 5 μL of each ^{89}Zr-labeled complex (approx. 5 μCi; 0.19 MBq) to a mixture of 500 μL of octanol and 500 μL of water. [6] The resulting solutions (n = 4) were vigorously vortexed for 5 min at room temperature, then centrifuged for 5 min to ensure complete separation of layers. From each of the four sets, 50 μL aliquot was removed from each phase into screw tubes and counted separately in a gamma counter. Each organic phase was washed with water to remove any radioactivity remaining in the organic phase before gamma counting. The partition coefficient was calculated as a ratio of counts in the octanol fraction to counts in the water fraction. The logP values were reported in an average of four measurements.

Biodistribution Studies. Biodistribution studies were conducted using a modified literature procedure. [7] Briefly, female NIH Swiss mice (6-8 wk old, n=6) were injected with each ^{89}Zr-labeled complex (0.55 MBq (15 μCi)/mouse) via the tail vein, and sacrificed at 2, 4, 24, 48, 72 h post-injection. Organs and tissues of interest were excised, weighted, and counted on a Perkin Elmer 2480 Wizard® gamma counter (Waltham, MA). The percent injected dose per gram (%ID/g) and percent injected dose per organ (%ID/organ) were calculated by comparison to a weighed, counted standard for each group (Tables S1 – S3).

Statistical Methods. All of the data are presented as mean±SD or mean (95% Confidence Interval). For statistical classification a student's t test (two-tailed, unpaired) was performed using GraphPad Prism (San Diego, CA). Any $p<0.05$ was considered significant.

Table S1. Biodistribution (%ID/g) of ^{89}Zr-1 in selected organs at 2, 4, 24, 48, and 72 h p.i.

Tissue/Organ	2 h	4 h	24 h	48 h	72 h
Blood	0.049 ± 0.018	0.023 ± 0.006	0.003 ± 0.002	0.002 ± 0.001	0.002 ± 0.002
Heart	0.067 ± 0.011	0.058 ± 0.014	0.046 ± 0.007	0.035 ± 0.004	0.039 ± 0.008
Lung	0.216 ± 0.095	0.148 ± 0.039	0.073 ± 0.011	0.055 ± 0.014	0.052 ± 0.008
Liver	0.566 ± 0.050	0.595 ± 0.109	0.449 ± 0.037	0.427 ± 0.057	0.382 ± 0.075
Small intestine	0.147 ± 0.030	0.133 ± 0.075	0.038 ± 0.004	0.028 ± 0.001	0.023 ± 0.004
Large intestine	1.816 ± 0.367	1.072 ± 0.426	0.040 ± 0.006	0.028 ± 0.003	0.025 ± 0.003
Kidney	11.628 ± 1.367	12.545 ± 2.812	8.214 ± 1.018	6.811 ± 0.599	4.767 ± 0.762
Spleen	0.158 ± 0.021	0.165 ± 0.037	0.128 ± 0.018	0.114 ± 0.005	0.128 ± 0.030
Pancreas	0.033 ± 0.008	0.039 ± 0.011	0.024 ± 0.004	0.019 ± 0.004	0.021 ± 0.003
Stomach	0.074 ± 0.047	0.097 ± 0.042	0.015 ± 0.005	0.013 ± 0.004	0.011 ± 0.002
Muscle	0.036 ± 0.022	0.023 ± 0.010	0.016 ± 0.007	0.008 ± 0.007	0.011 ± 0.008
Fat	0.028 ± 0.008	0.022 ± 0.007	0.019 ± 0.006	0.021 ± 0.012	0.015 ± 0.008
Bone	0.128 ± 0.027	0.099 ± 0.014	0.100 ± 0.030	0.067 ± 0.013	0.074 ± 0.022

Table S2. Biodistribution (%ID/g) of ^{89}Zr-2 in selected organs at 2, 4, 24, 48, and 72 h p.i.

Tissue/Organ	2 h	4 h	24 h	48 h	72 h
Blood	0.166 ± 0.094	0.051 ± 0.013	0.010 ± 0.003	0.006 ± 0.002	0.004 ± 0.002
Heart	0.229 ± 0.026	0.186 ± 0.029	0.147 ± 0.040	0.143 ± 0.020	0.138 ± 0.014
Lung	0.221 ± 0.049	0.181 ± 0.031	0.101 ± 0.020	0.083 ± 0.013	0.084 ± 0.021
Liver	1.367 ± 0.134	1.240 ± 0.185	1.244 ± 0.180	1.080 ± 0.161	0.953 ± 0.076
Small intestine	0.330 ± 0.172	0.184 ± 0.031	0.132 ± 0.025	0.088 ± 0.013	0.067 ± 0.006
Large intestine	0.905 ± 0.379	0.396 ± 0.159	0.146 ± 0.094	0.114 ± 0.027	0.091 ± 0.017
Kidney	54.241 ± 6.279	51.745 ± 4.931	46.095 ± 7.788	33.167 ± 4.874	24.375 ± 8.640
Spleen	0.634 ± 0.071	0.541 ± 0.089	0.644 ± 0.091	0.624 ± 0.070	0.509 ± 0.071
Pancreas	0.108 ± 0.030	0.076 ± 0.021	0.067 ± 0.008	0.066 ± 0.010	0.071 ± 0.007
Stomach	0.188 ± 0.134	0.075 ± 0.036	0.067 ± 0.009	0.056 ± 0.020	0.033 ± 0.004
Muscle	0.105 ± 0.048	0.049 ± 0.008	0.039 ± 0.014	0.031 ± 0.006	0.039 ± 0.026
Fat	0.105 ± 0.055	0.055 ± 0.014	0.056 ± 0.029	0.054 ± 0.022	0.074 ± 0.026
Bone	0.392 ± 0.057	0.293 ± 0.080	0.274 ± 0.100	0.278 ± 0.086	0.246 ± 0.032

Table S3. Biodistribution (%ID/g) of ^{89}Zr-DFO in selected organs at 2, 4, 24, 48, and 72 h p.i.

Tissue/Organ	2 h	4 h	24 h	48 h	72 h
Blood	0.009 ± 0.003	0.005 ± 0.001	0.001 ± 0.001	0.001 ± 0.001	0.000 ± 0.001
Heart	0.020 ± 0.003	0.019 ± 0.003	0.014 ± 0.002	0.010 ± 0.002	0.009 ± 0.004
Lung	0.060 ± 0.009	0.038 ± 0.006	0.024 ± 0.006	0.019 ± 0.005	0.017 ± 0.004
Liver	0.234 ± 0.023	0.163 ± 0.051	0.081 ± 0.012	0.070 ± 0.007	0.066 ± 0.009
Small intestine	0.357 ± 0.175	0.130 ± 0.080	0.013 ± 0.002	0.008 ± 0.001	0.006 ± 0.001
Large intestine	0.877 ± 0.435	1.020 ± 0.207	0.024 ± 0.004	0.009 ± 0.002	0.008 ± 0.001
Kidney	2.051 ± 0.238	1.848 ± 0.382	1.340 ± 0.137	0.957 ± 0.216	0.689 ± 0.098
Spleen	0.037 ± 0.005	0.036 ± 0.004	0.036 ± 0.007	0.030 ± 0.008	0.027 ± 0.007
Pancreas	0.015 ± 0.005	0.013 ± 0.002	0.012 ± 0.002	0.009 ± 0.003	0.007 ± 0.002
Stomach	0.140 ± 0.124	0.055 ± 0.038	0.014 ± 0.005	0.005 ± 0.003	0.005 ± 0.002
Muscle	0.011 ± 0.001	0.008 ± 0.003	0.006 ± 0.002	0.004 ± 0.001	0.004 ± 0.002
Fat	0.013 ± 0.003	0.009 ± 0.002	0.007 ± 0.002	0.005 ± 0.008	0.008 ± 0.004
Bone	0.051 ± 0.017	0.058 ± 0.008	0.082 ± 0.016	0.092 ± 0.011	0.078 ± 0.014

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