

**Electronic Supplementary Information (ESI) for:**

**<sup>t</sup>Bu<sub>4</sub>octapa-alkyl-NHS for Metalloradiopeptide Preparation**

Lily Li<sup>a,b</sup>, Hsiou-Ting Kuo<sup>c</sup>, Xiaozhu Wang<sup>a</sup>, Helen Merkens<sup>c</sup>, Nadine Colpo<sup>c</sup>, Valery Radchenko<sup>b,d</sup>, Paul Schaffer<sup>b</sup>, Kuo-Shyan Lin<sup>c</sup>, François Bénard<sup>c</sup>, Chris Orvig<sup>a\*</sup>

<sup>a</sup> Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia V6T 1Z1, Canada

<sup>b</sup> Life Sciences Division, TRIUMF, 4004 Wesbrook Mall, Vancouver, British Columbia V6T 2A3, Canada

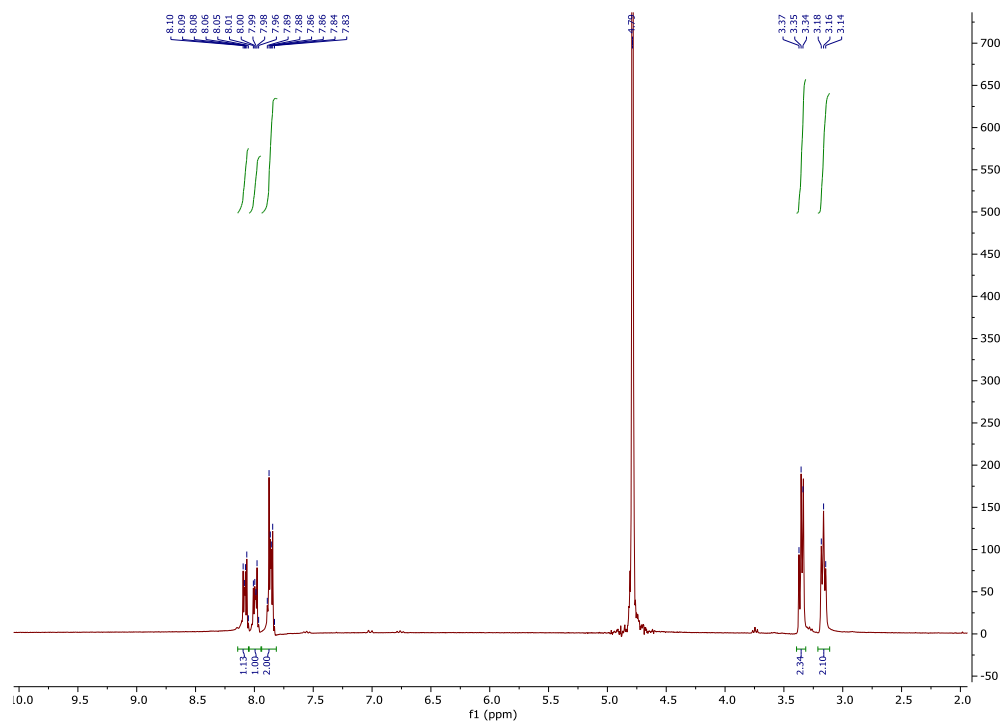
<sup>c</sup> Department of Molecular Oncology, BC Cancer, 675 West 10<sup>th</sup> Ave, Vancouver, British Columbia V5Z 1L3, Canada

<sup>d</sup> Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia V6T 1Z1, Canada

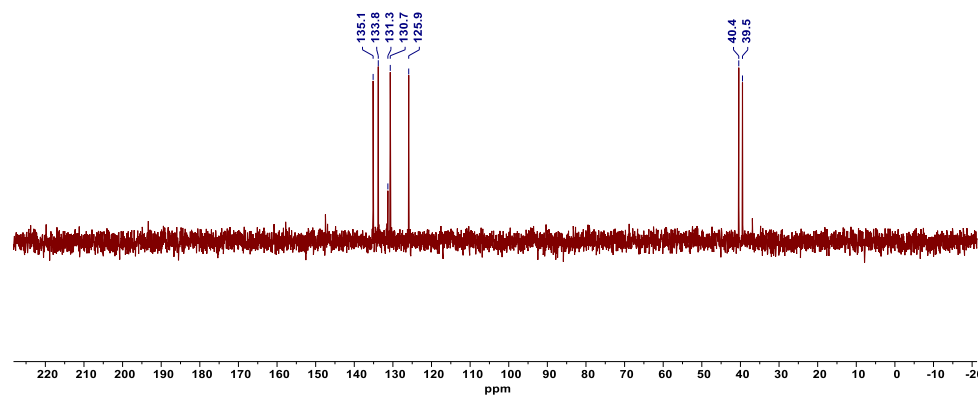
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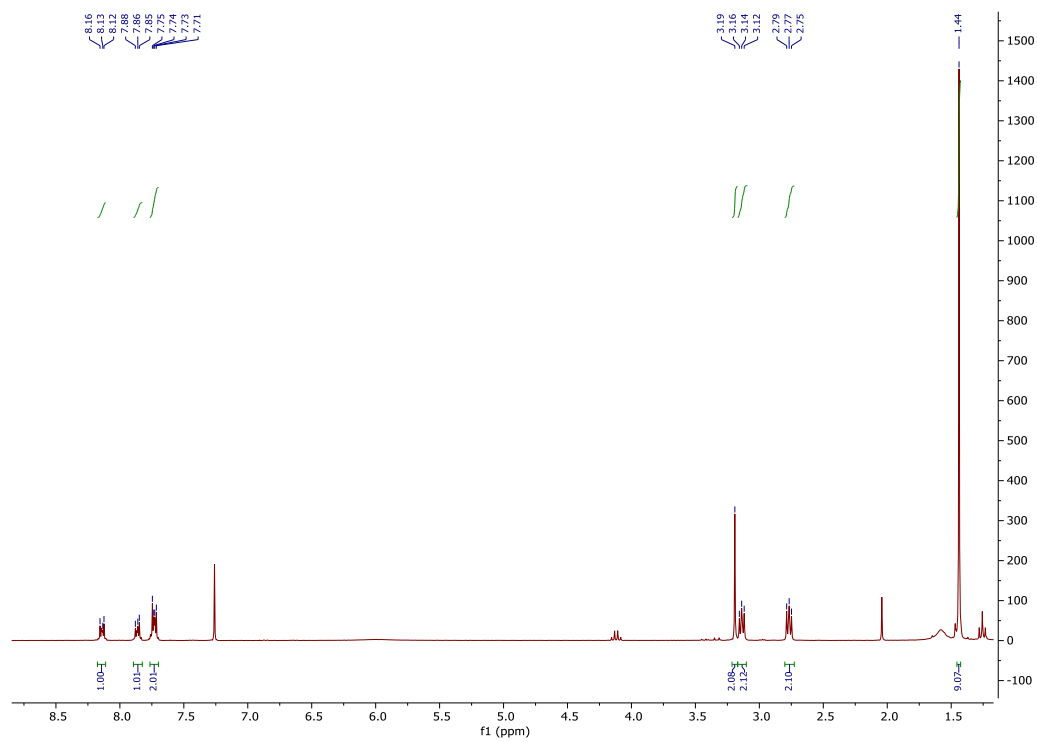
## NMR Spectra



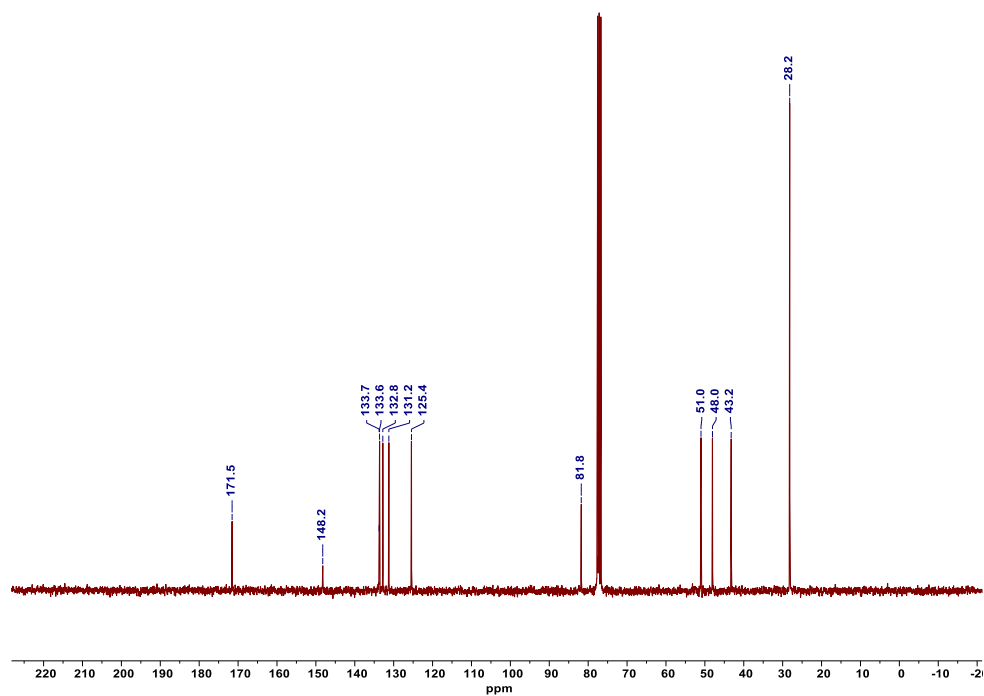
**Figure S1** Compound **1**  $^1\text{H}$  NMR spectrum (400 MHz, 298 K,  $\text{D}_2\text{O}$ ).



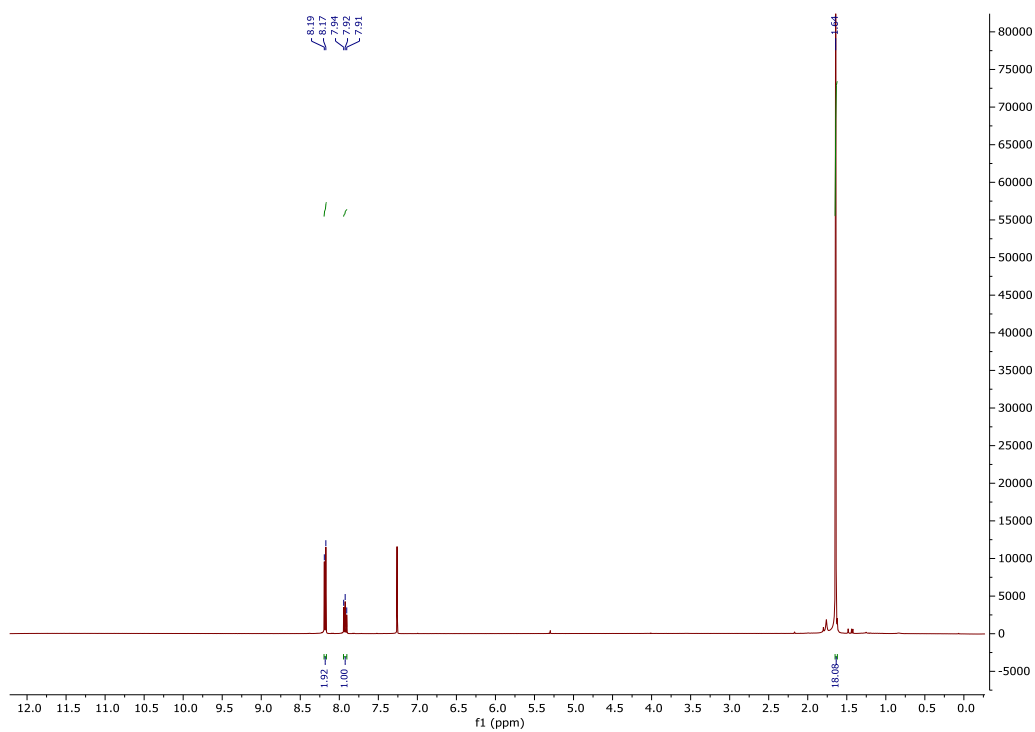
**Figure S2.** Compound **1**  $^{13}\text{C}$  NMR spectrum (100 MHz, 298 K,  $\text{D}_2\text{O}$ ).



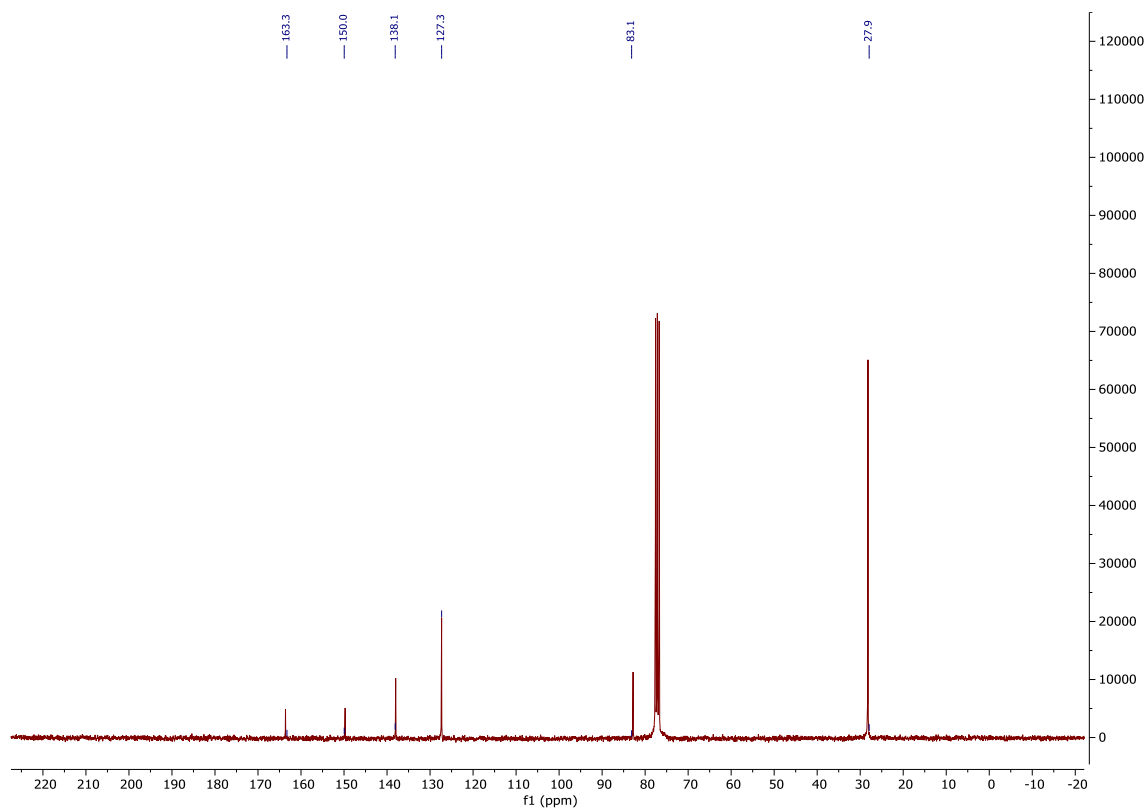
**Figure S3** Compound **2**  $^1\text{H}$  NMR spectrum (400 MHz, 298 K,  $\text{CDCl}_3$ ).



**Figure S4.** Compound **2**  $^{13}\text{C}$  NMR spectrum (100 MHz, 298 K,  $\text{CDCl}_3$ ).

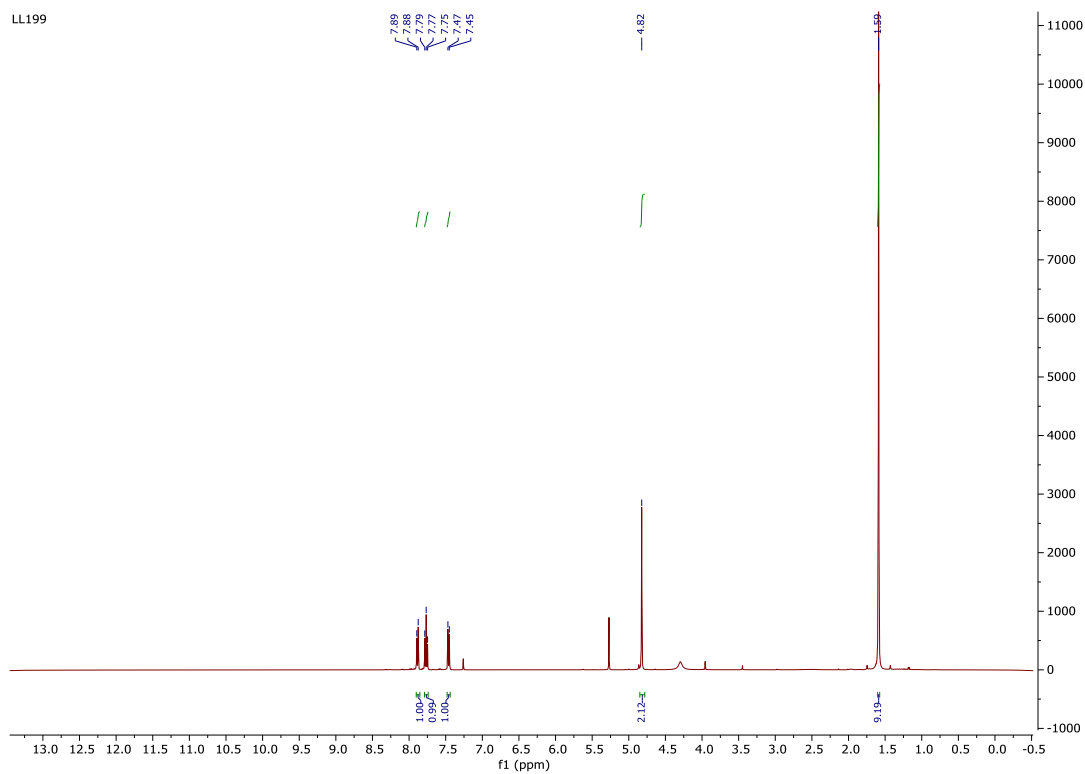


**Figure S5.** Compound 3  $^1\text{H}$  NMR spectrum (400 MHz, 298 K,  $\text{CDCl}_3$ ).

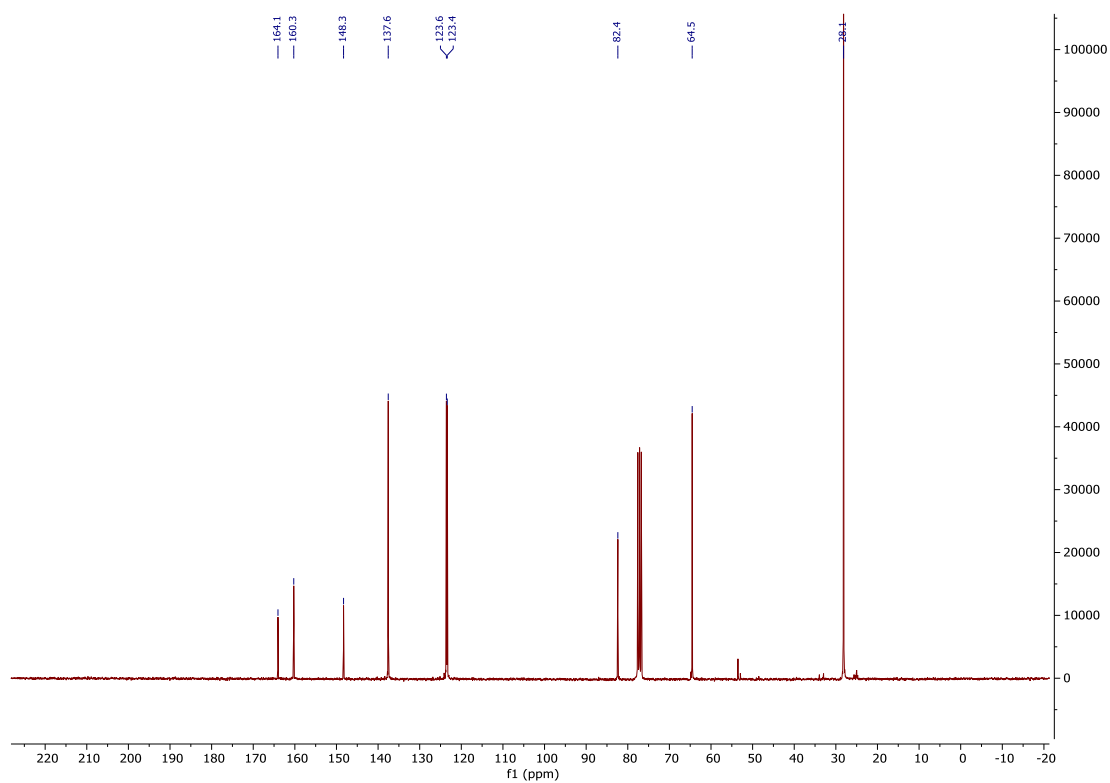


**Figure S6.** Compound 3  $^{13}\text{C}$  NMR spectrum (100 MHz, 298 K,  $\text{CDCl}_3$ ).

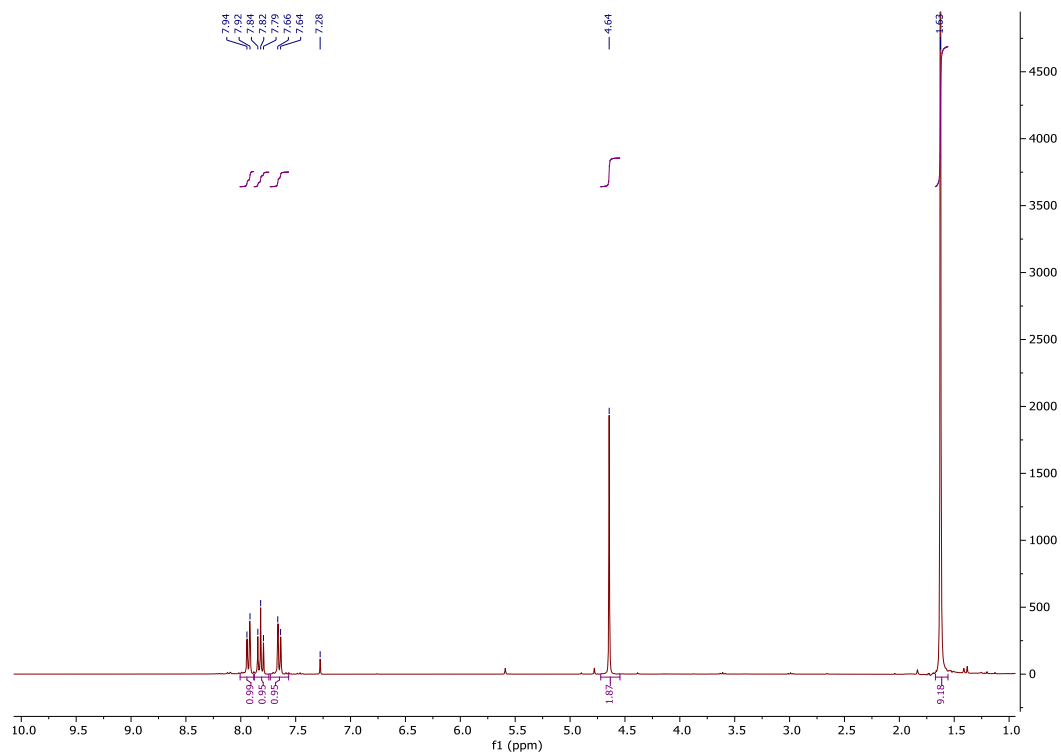
LL199



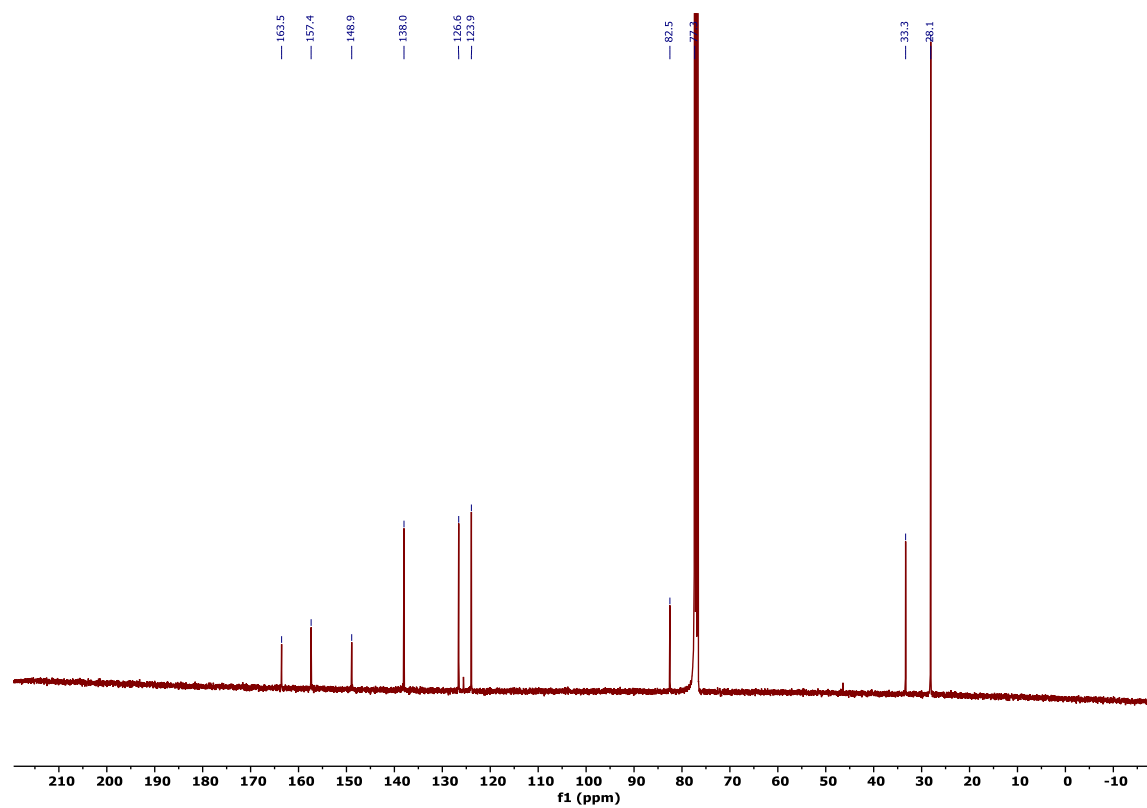
**Figure S7.** Compound 4 <sup>1</sup>H NMR spectrum (400 MHz, 298 K, CDCl<sub>3</sub>).



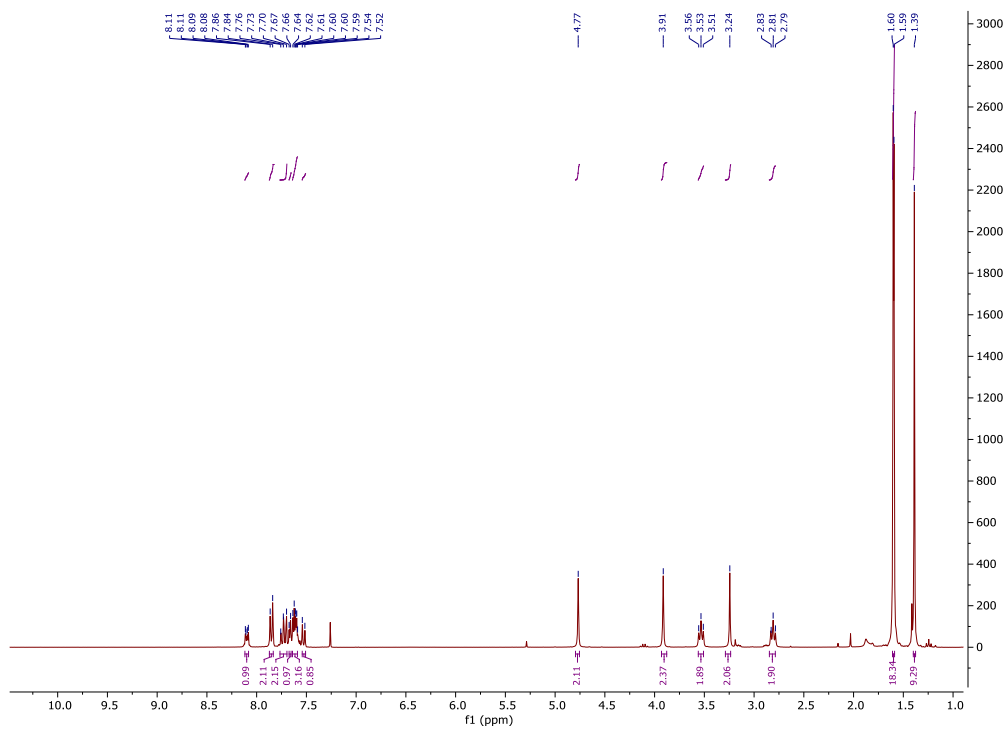
**Figure S8.** Compound 4 <sup>13</sup>C NMR spectrum (100 MHz, 298 K, CDCl<sub>3</sub>).



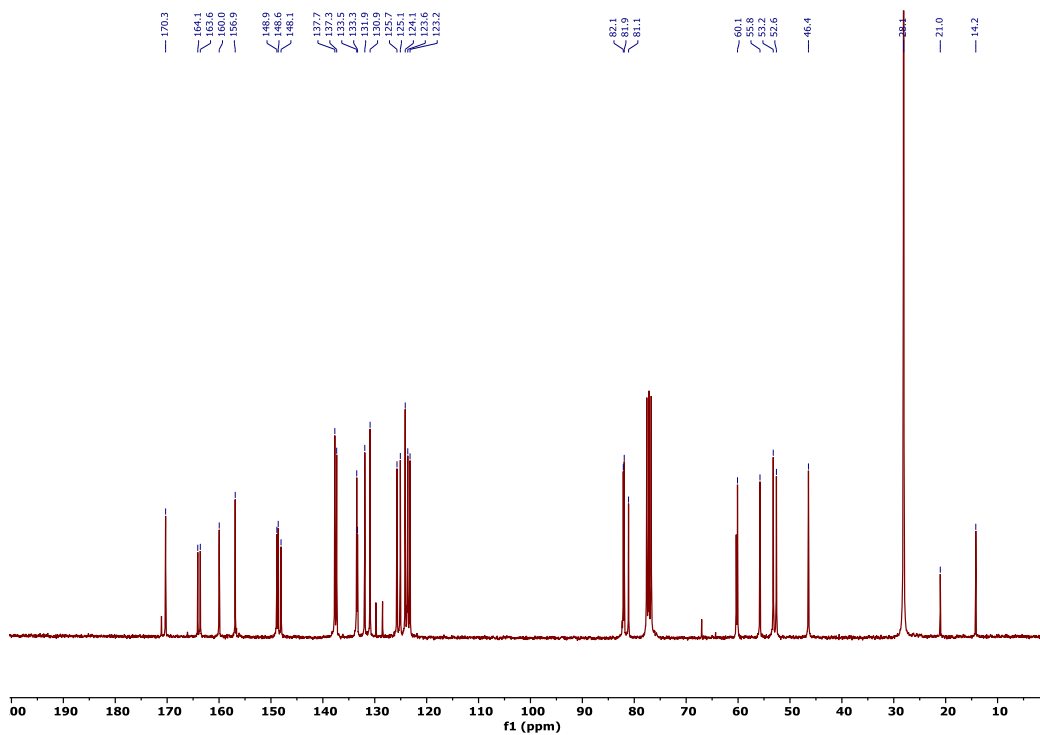
**Figure S9.** Compound **5**  $^1\text{H}$  NMR spectrum (400 MHz, 298 K,  $\text{CDCl}_3$ ).



**Figure S10.** Compound **5**  $^{13}\text{C}$  NMR spectrum (100 MHz, 298 K,  $\text{CDCl}_3$ ).

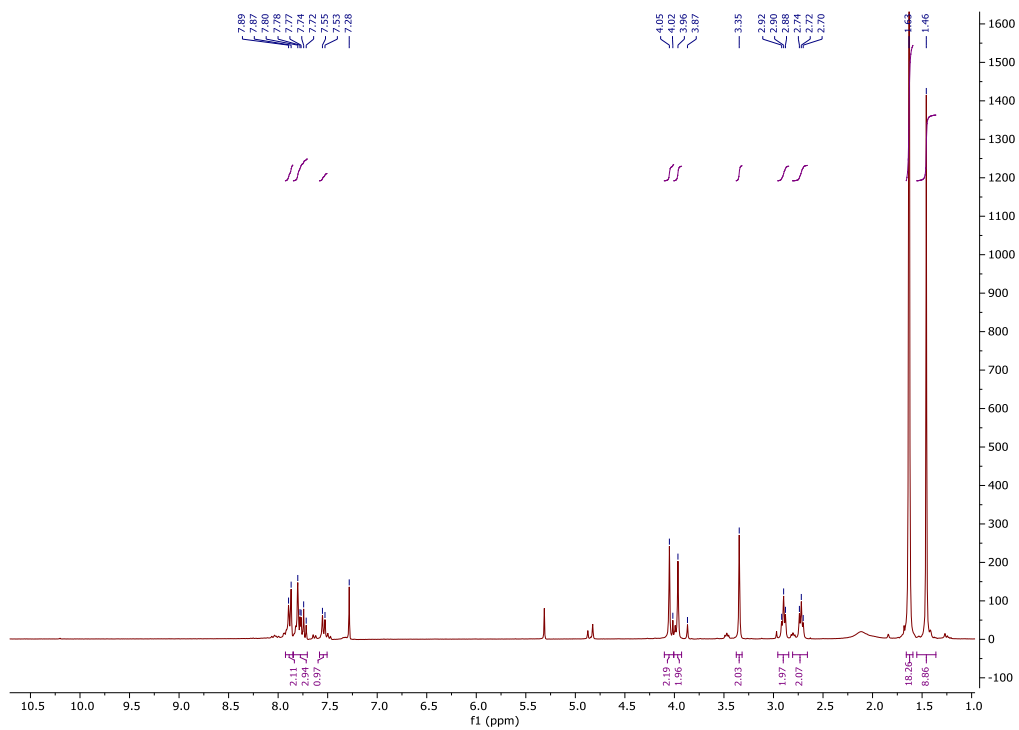


**Figure S11.** Compound **6**  $^1\text{H}$  NMR spectrum (400 MHz, 298 K,  $\text{CDCl}_3$ ).

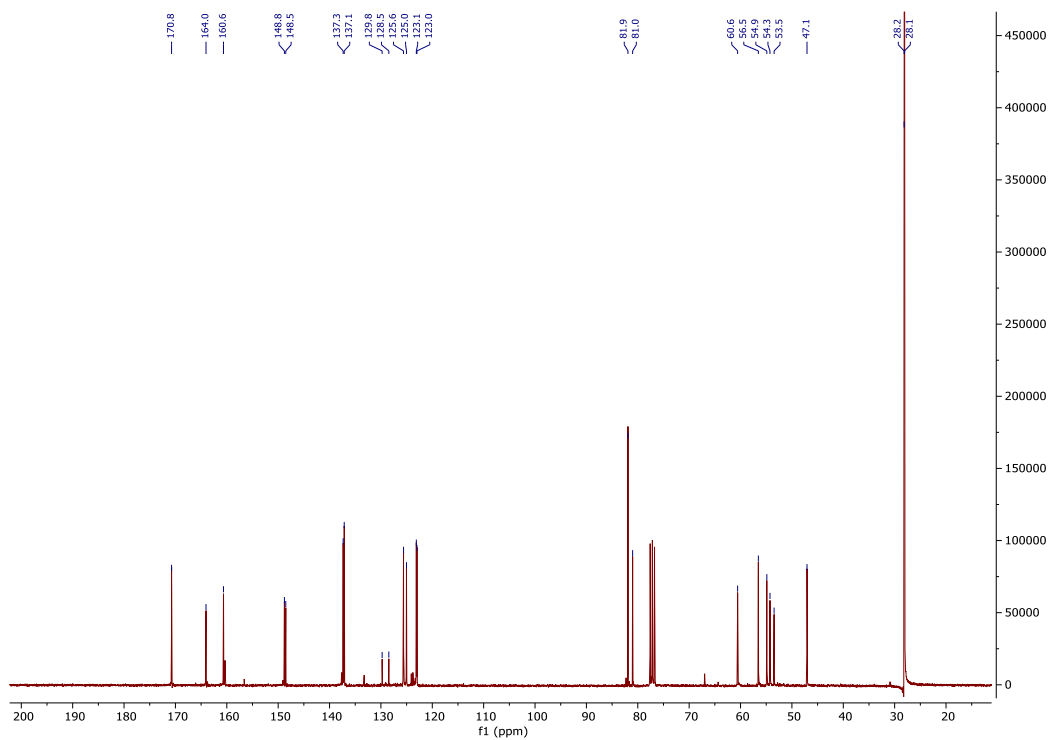


**Figure S12.** Compound **6**  $^{13}\text{C}$  NMR spectrum (100 MHz, 298 K,  $\text{CDCl}_3$ ).

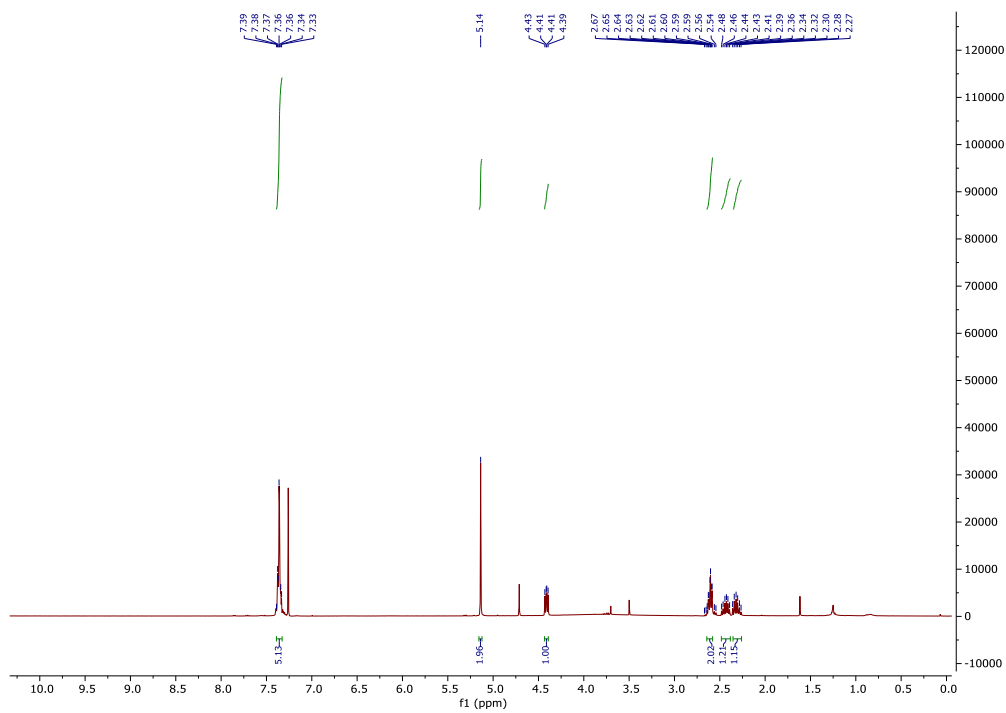




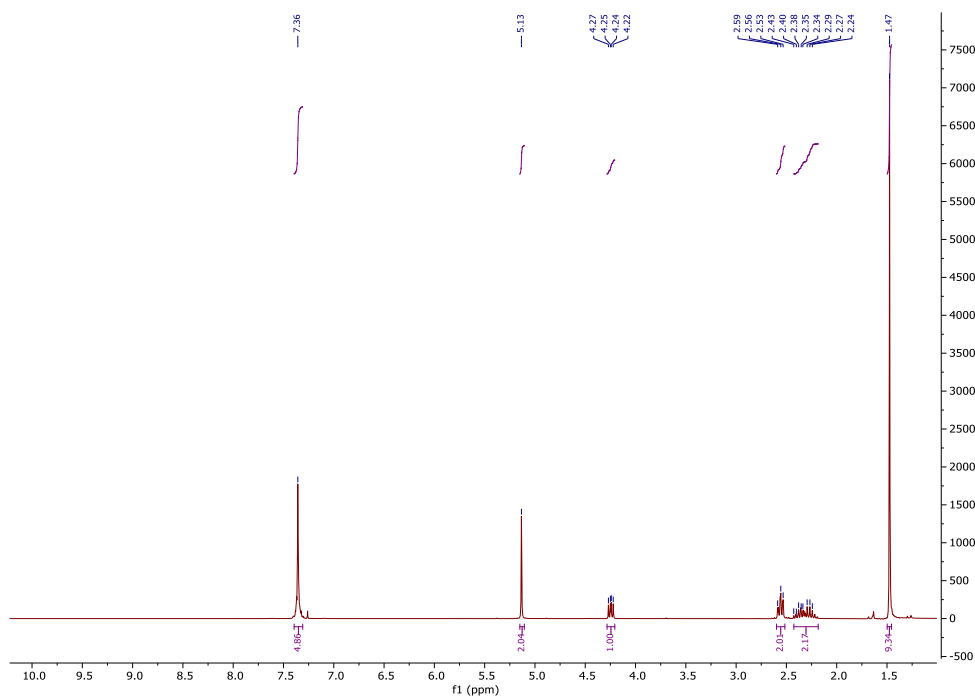
**Figure S13.** Compound 7  $^1\text{H}$  NMR spectrum (400 MHz, 298 K,  $\text{CDCl}_3$ ).



**Figure S14.** Compound 7  $^{13}\text{C}$  NMR spectrum (100 MHz, 298 K,  $\text{CDCl}_3$ ).



**Figure S15.** Compound **8**  $^1\text{H}$  NMR spectrum (400 MHz, 298 K,  $\text{CDCl}_3$ ).



**Figure S16.** Compound **9**  $^1\text{H}$  NMR spectrum (400 MHz, 298 K,  $\text{CDCl}_3$ ).

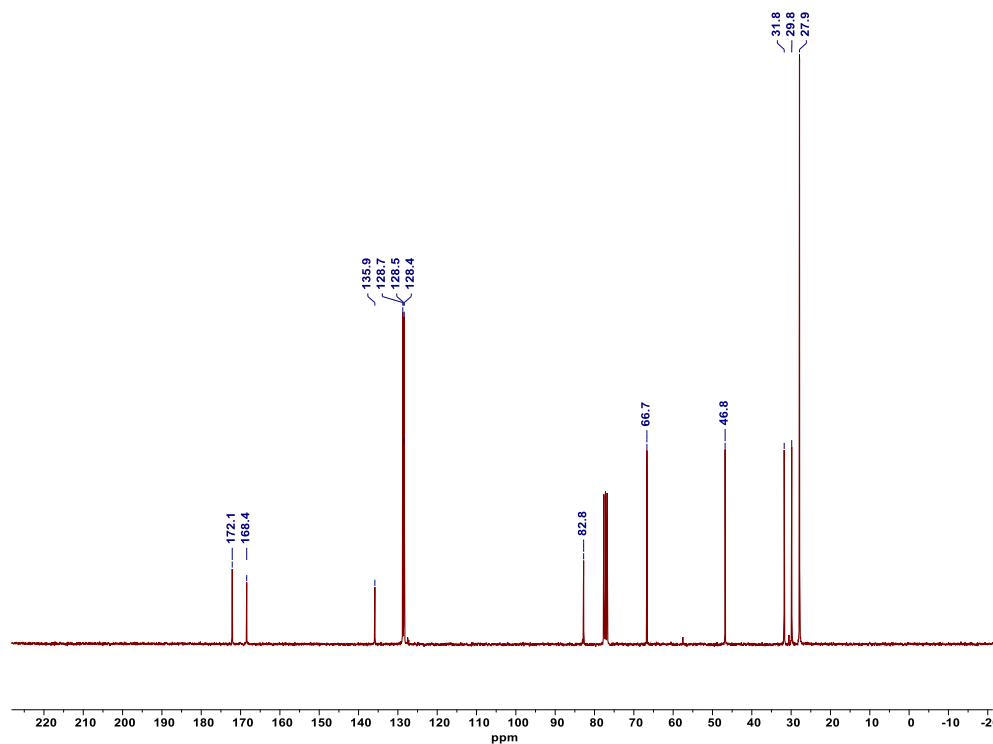


Figure S17. Compound 9 <sup>13</sup>C NMR spectrum (100 MHz, 298 K, CDCl<sub>3</sub>).

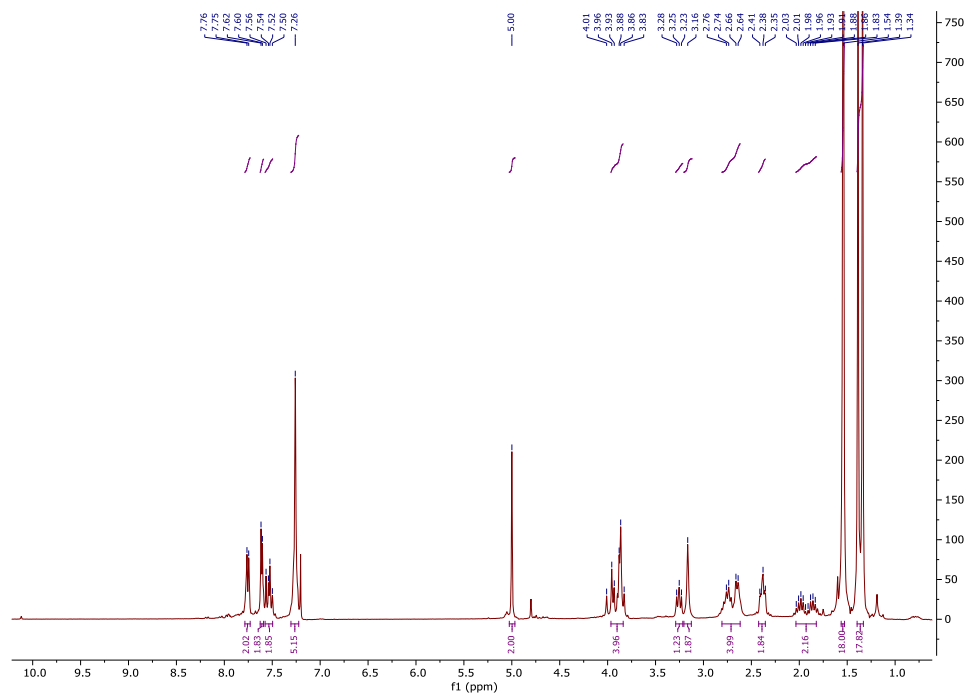
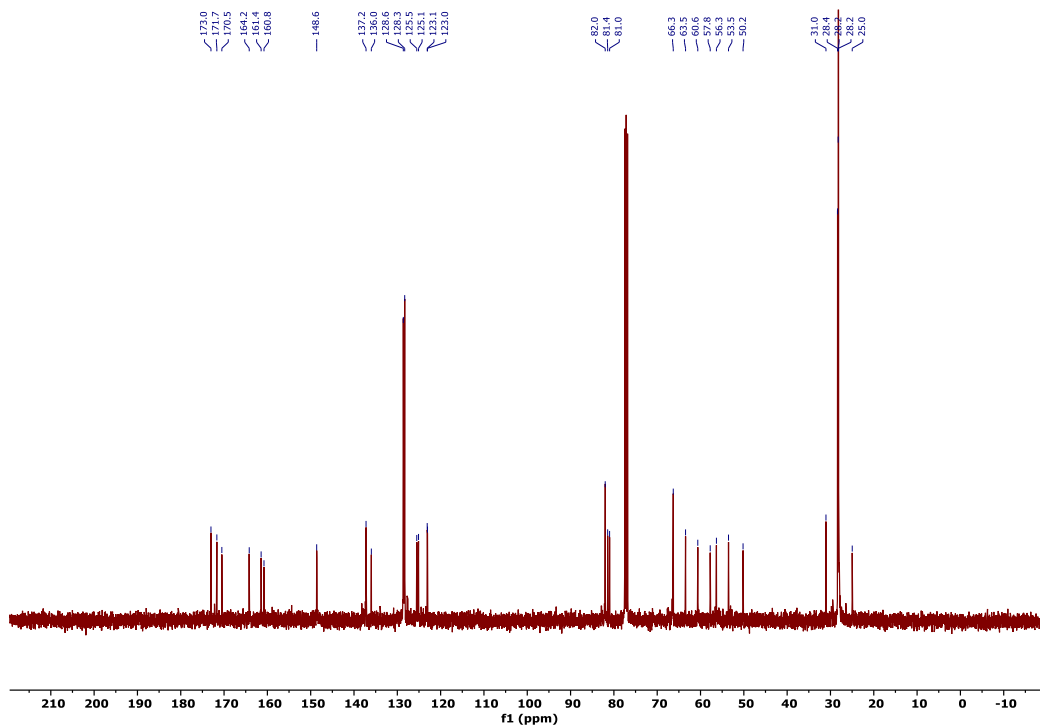
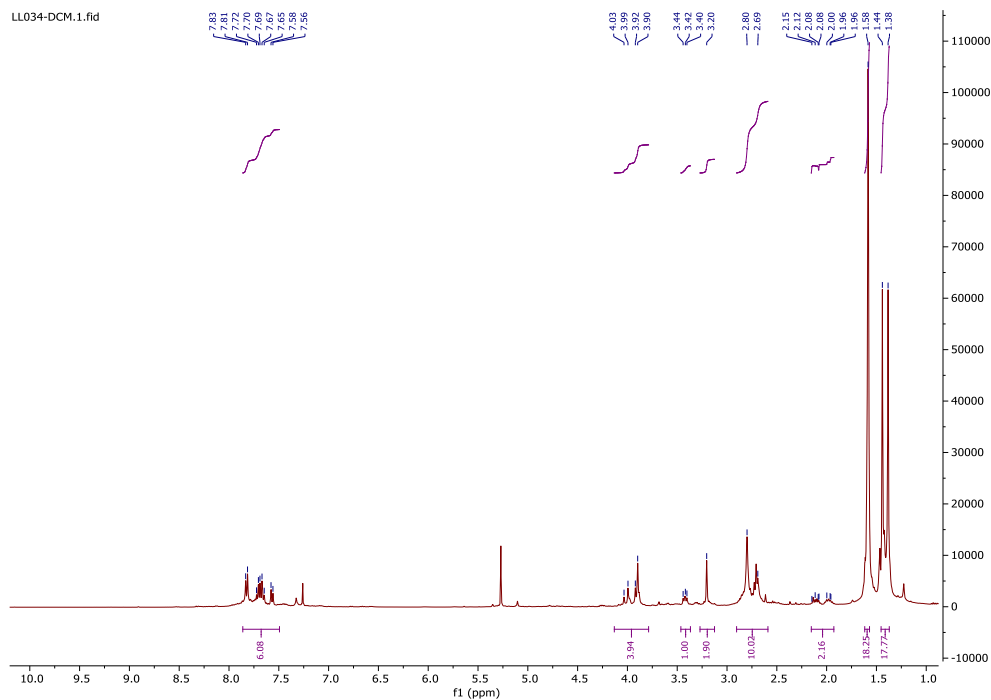


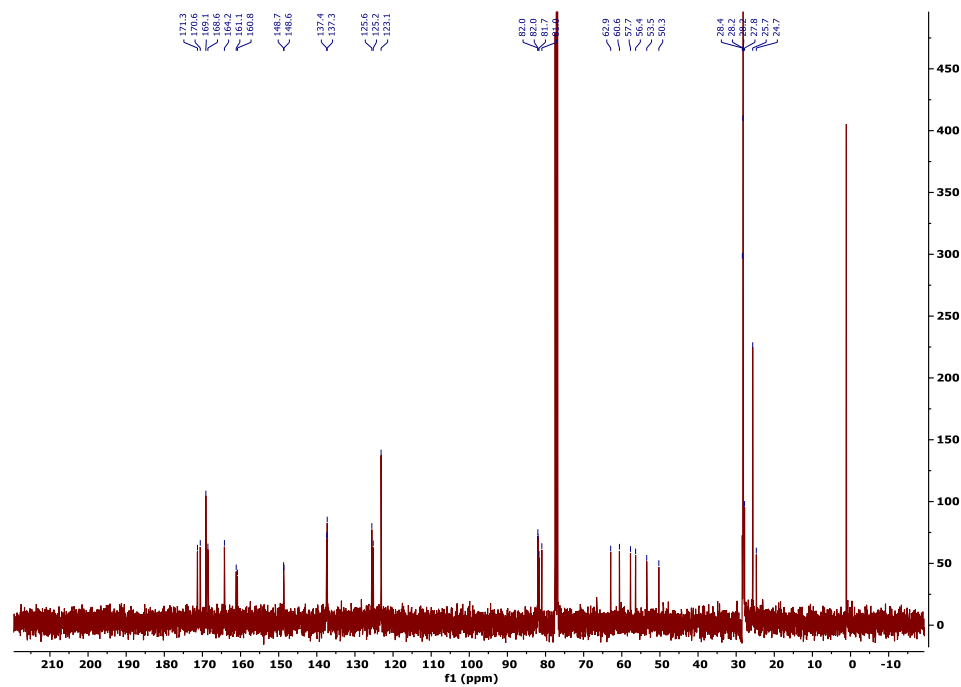
Figure S18. Compound 10 <sup>1</sup>H NMR spectrum (400 MHz, 298 K, CDCl<sub>3</sub>).



**Figure S19.** Compound **10**  $^{13}\text{C}$  NMR spectrum (100 MHz, 298 K,  $\text{CDCl}_3$ ).



**Figure S20.** Compound **12**  $^1\text{H}$  NMR (400 MHz, 298 K,  $\text{CDCl}_3$ ).



**Figure S21.** Compound **12**  $^{13}\text{C}$  NMR spectrum (100 MHz, 298 K,  $\text{CDCl}_3$ ).

## Mass Spectra

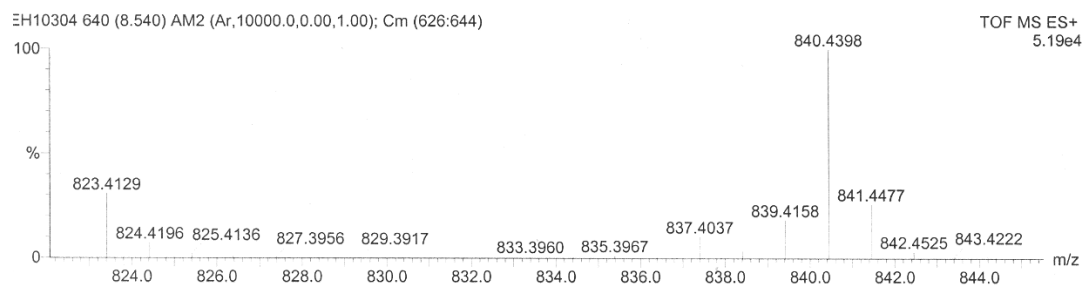


Figure S22.  $t\text{Bu}_4\text{octapa-alkyl-NHS}$  high-resolution mass spectrum.

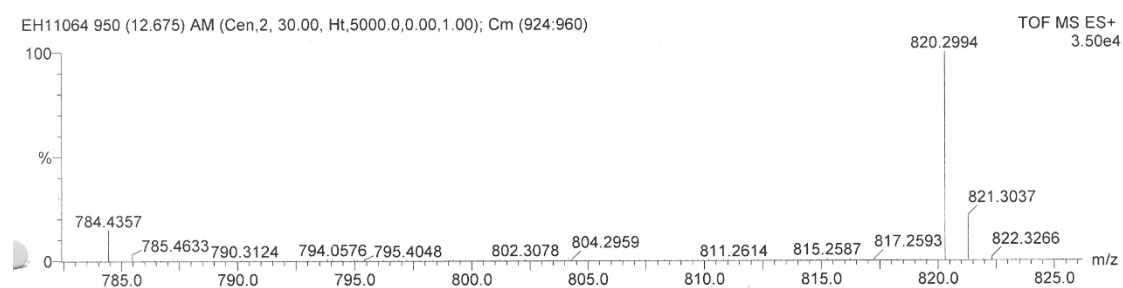


Figure S23.  $\text{H}_4\text{octapa-PSMA-ureido}$  high-resolution mass spectrum.

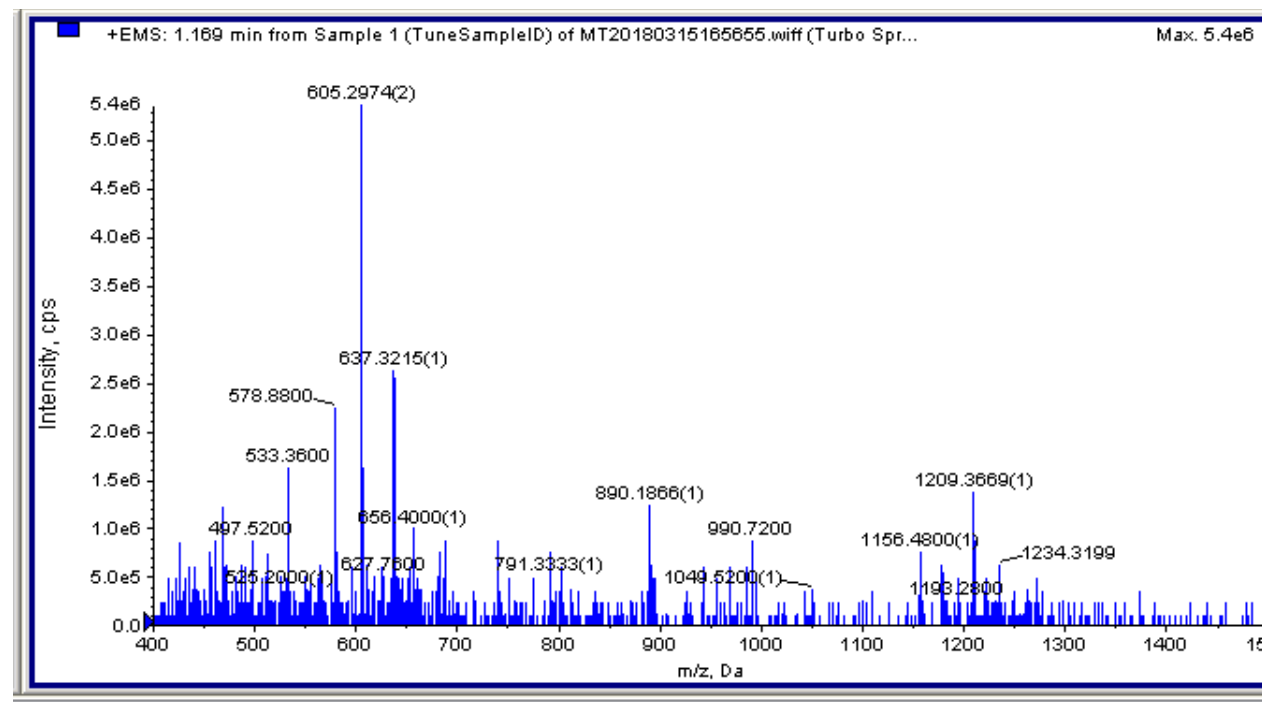
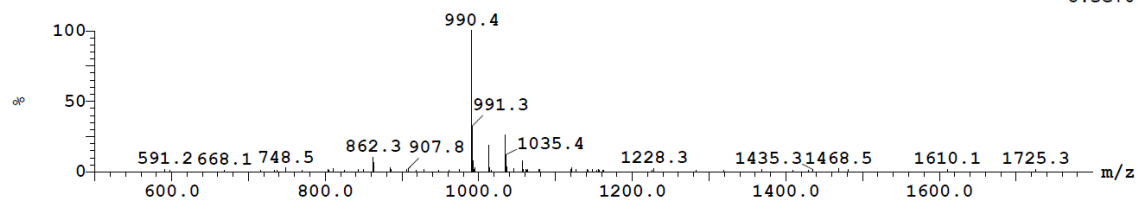


Figure S24.  $\text{H}_4\text{octapa-alkyl-PSMA617}$  high-resolution mass spectrum.

1: (Time: 1.20) Combine (33:50-(13:27+79:89))

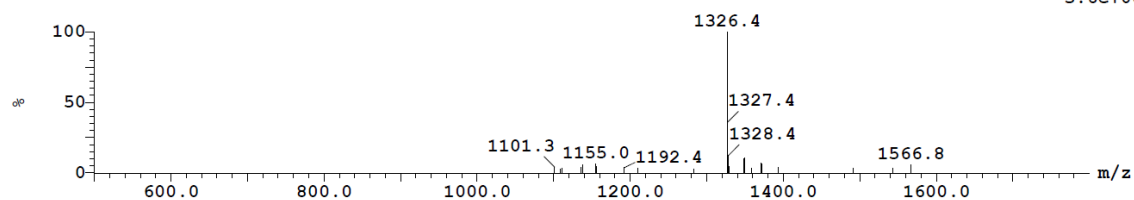
3: MS ES-  
8.3e+004



**Figure S25.** [<sup>nat</sup>Lu][Lu(octapa-alkyl-PSMA-ureido)] low-resolution mass spectrum.

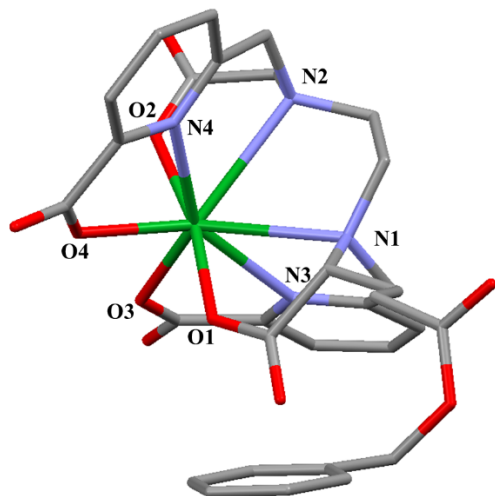
1: (Time: 1.20) Combine (33:49-(13:26+79:89))

4: MS ES-  
3.6e+004

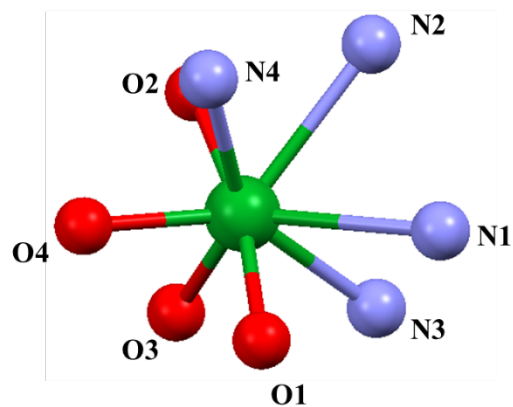


**Figure S26.** [<sup>nat</sup>Lu][Lu(octapa-alkyl-PSMA617)] low-resolution mass spectrum.

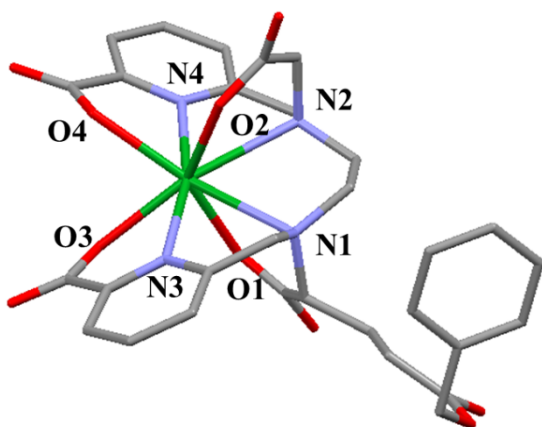
## DFT calculations



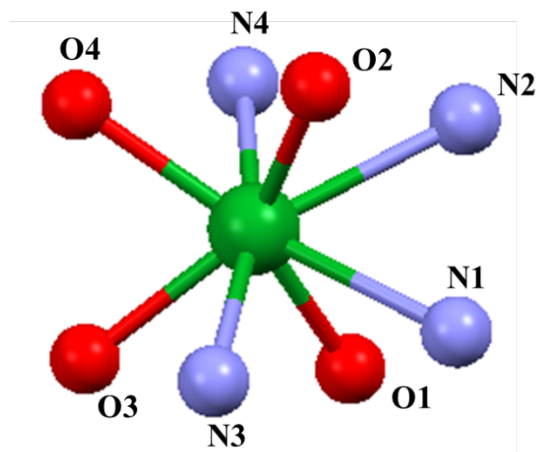
R-DBTA



R-DBTA



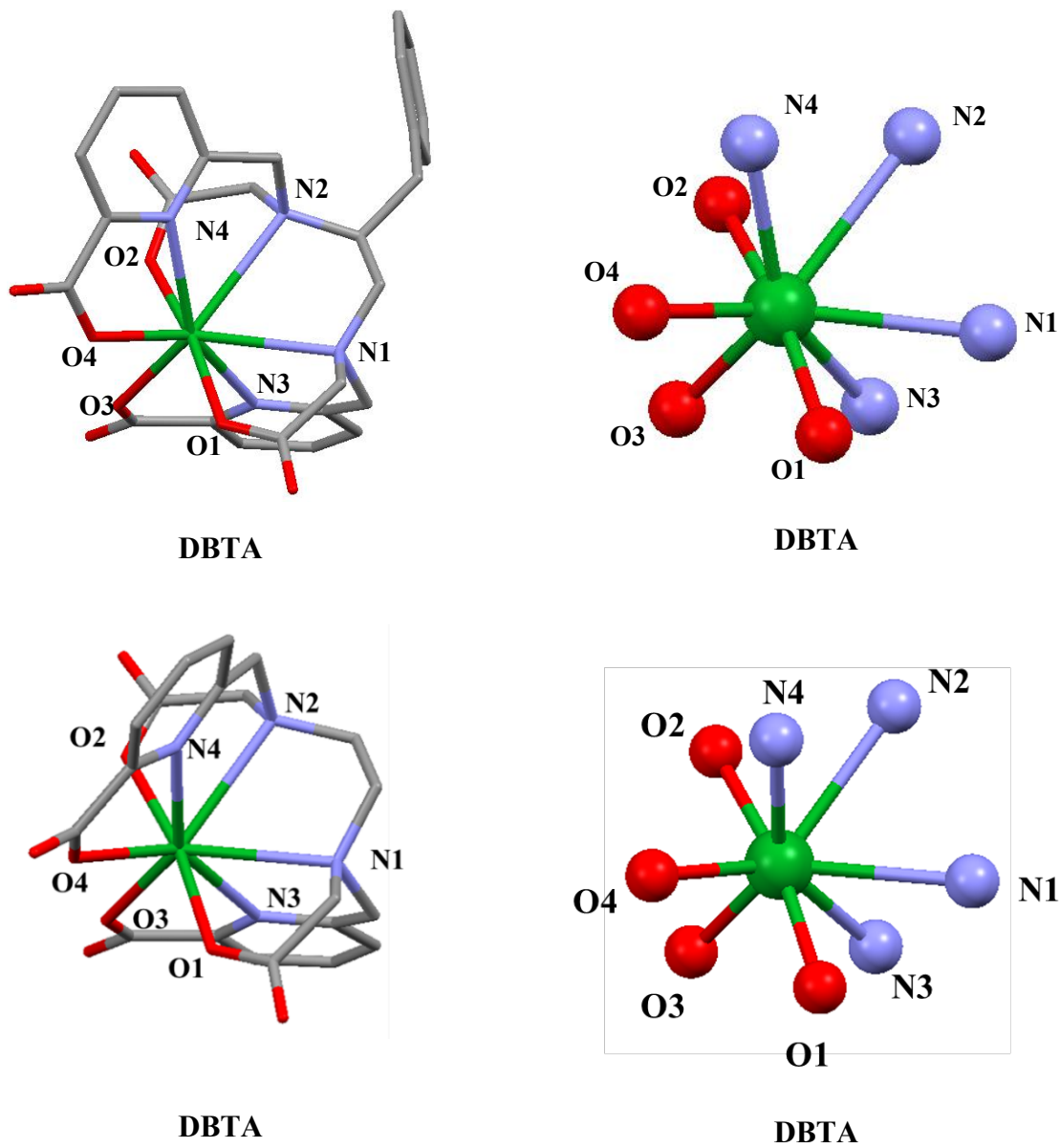
R-DSA



R-DSA

**Figure S27.** DFT-calculated structures of R-DBTA, R-DSA geometries of [Lu(octapa-alkyl-benzyl-ester)]<sup>-</sup>.





**Figure S28.** DFT-calculated structures for  $[\text{Lu}(\text{S-benzyl-octapa})]^-$  (top) and  $[\text{Lu}(\text{octapa})]^-$  (bottom).

## Radiolabeling, Human Serum Challenge and Lanthanum Competition

**Table S1.** % Intact of [ $^{177}\text{Lu}$ ][Lu(L)] where L = octapa-alkyl-PSMA-ureido and octapa-alkyl-PSMA617 in human serum at 37°C.

Day	[ $^{177}\text{Lu}$ ][Lu(octapa-alkyl-PSMA-ureido)]		[ $^{177}\text{Lu}$ ][Lu(octapa-alkyl-PSMA617)]	
	% Intact	SD	% Intact	SD
0.04	91	2	91	8
1	50	5	18	10
3	48	8	12	5
7	45	3	4	1

**Table S2.** Radiochemical yield of [ $^{177}\text{Lu}$ ][Lu(L)] where L = octapa-alkyl-PSMA-ureido and octapa-alkyl-PSMA617 at pH=7, 15 min.

-log[M]	[ $^{177}\text{Lu}$ ][Lu(octapa-alkyl-PSMA-ureido)]		[ $^{177}\text{Lu}$ ][Lu(octapa-alkyl-PSMA617)]	
	RCY %	SD	RCY %	SD
4	100	0	99	0
5	96	3	99	0
6	94	1	98	1
7	8	4	2	1

**Table S3.** Lanthanum competition study of [ $^{177}\text{Lu}$ ][Lu(octapa)]<sup>-</sup> (La:L 0:1 and 3:1).

Day	0:1		3:1	
	% Intact	SD	% Intact	SD
0.04	99	1	98	0
1	99	2	88	5
5	99	1	45	25
7	99	0	51	14

**Table S4.** Lanthanum competition study of [ $^{177}\text{Lu}$ ][Lu(octapa-alkyl-PSMA-ureido)] (La:L 0:1 and 3:1).

Day	0:1		3:1	
	% Intact	SD	% Intact	SD
0.04	91	1	60	23
1	80	2	55	5
5	79	3	25	5
7	75	2	17	6

**Table S5.** Lanthanum competition study of [<sup>177</sup>Lu][Lu(octapa-alkyl-PSMA617)] (La:L 0:1 and 3:1).

Day	0:1		3:1	
	% Intact	SD	% Intact	SD
0.04	95	1	96	2
1	88	5	85	10
5	57	6	54	18
7	57	2	39	11

**Table S6.** Lanthanum competition study of [<sup>177</sup>Lu][Lu(pypa)]<sup>-</sup> (La:L 0:1 and 3:1).

Day	0:1		3:1	
	% Intact	SD	% Intact	SD
0.04	99	0	99	0
1	99	1	99	0
5	99	0	97	1
7	99	0	97	2

**Table S7.** Lanthanum competition study of [<sup>177</sup>Lu][Lu(pypa-C7-PSMA-ureido)] (La:L 0:1 and 3:1).

Day	0:1		3:1	
	% Intact	SD	% Intact	SD
0.04	99	1	98	3
1	99	1	93	1
5	99	0	92	2
7	99	0	92	2

**Table S8.** Lanthanum competition study of [<sup>177</sup>Lu][Lu(pypa-C7-PSMA617)] (La:L 0:1 and 3:1).

Day	0:1		3:1	
	% Intact	SD	% Intact	SD
0.04	99	0	99	0
1	97	0	96	0
5	99	0	91	4
7	99	0	86	3

## Ex Vivo Biodistribution Studies

**Table S9.** *Ex Vivo* biodistribution data of [<sup>177</sup>Lu][Lu(octapa-alkyl-PSMA-ureido)] at different p.i. timepoints (n = 5)..

Organs	1 h		4 h		24 h	
	% ID/g	SD	% ID/g	SD	% ID/g	SD
<b>Blood</b>	0.917	0.156	0.237	0.151	0.056	0.036
<b>Fat</b>	0.512	0.090	0.494	0.430	0.375	0.295
<b>Seminal</b>	3.633	4.378	0.175	0.170	0.151	0.204
<b>Testes</b>	0.502	0.167	0.225	0.060	0.099	0.069
<b>Intestine</b>	0.470	0.098	0.182	0.069	0.160	0.061
<b>Stomach</b>	0.106	0.034	0.102	0.040	0.486	0.878
<b>Spleen</b>	9.605	5.149	3.993	2.762	1.526	1.102
<b>Liver</b>	0.377	0.044	0.235	0.092	0.425	0.431
<b>Pancreas</b>	0.624	0.117	0.333	0.143	0.755	1.334
<b>Adrenal</b>	5.828	2.605	2.969	1.830	1.168	1.040
<b>Kidney</b>	74.946	9.322	59.493	14.766	49.450	4.392
<b>Lung</b>	2.006	0.514	0.941	0.184	0.450	0.193
<b>Heart</b>	0.432	0.124	0.181	0.045	0.119	0.099
<b>Tumor</b>	4.917	0.881	3.446	0.954	3.800	2.203
<b>Muscle</b>	0.305	0.062	0.125	0.085	0.092	0.046
<b>Bone</b>	0.561	0.111	0.667	0.382	0.623	0.230
<b>Brain</b>	0.027	0.002	0.034	0.030	0.012	0.004
<b>Tail</b>	0.841	0.056	0.526	0.166	0.672	0.351
<b>Salivary</b>	6.683	1.126	2.690	0.862	1.040	1.041
<b>Lacrimal</b>	0.690	0.252	0.267	0.122	0.082	0.067

**Table S10.** Tumor-to-background ratios of [<sup>177</sup>Lu][Lu(octapa-alkyl-PSMA-ureido)] at different p.i. timepoints (n = 5).

	1 h	4 h	24 h
<b>Tumor/bone</b>	8.76	5.17	6.10
<b>Tumor/muscle</b>	16.10	27.67	41.35
<b>Tumor/blood</b>	5.36	14.55	68.20
<b>Tumor/kidney</b>	0.07	0.06	0.08

**Table S11.** *Ex Vivo* biodistribution data of [<sup>177</sup>Lu][Lu(octapa-alkyl-PSMA617)] different p.i. timepoints (n = 5).

Organs	1 h		4 h		24 h	
	% ID/g	SD	% ID/g	SD	% ID/g	SD
Blood	1.539	0.367	0.949	0.254	0.079	0.014
Fat	1.405	0.760	0.810	0.662	0.133	0.086
Seminal	0.663	0.650	0.136	0.032	0.046	0.016
Testes	0.810	0.230	0.600	0.242	0.143	0.048
Intestine	1.121	0.135	0.571	0.385	0.671	0.443
Stomach	0.205	0.080	0.527	0.765	1.427	1.494
Spleen	24.962	13.045	6.543	7.009	2.025	1.926
Liver	0.630	0.161	0.496	0.142	0.450	0.079
Pancreas	0.879	0.253	0.494	0.296	0.082	0.018
Adrenal	8.030	3.379	11.140	8.293	2.972	2.048
Kidney	143.245	17.248	183.057	51.772	26.025	10.940
Lung	3.586	1.502	1.829	0.888	0.354	0.052
Heart	0.904	0.432	0.431	0.104	0.154	0.029
Tumor	13.468	1.080	16.994	2.042	10.721	1.275
Muscle	0.472	0.120	0.311	0.156	0.150	0.013
Bone	0.643	0.285	1.330	0.568	3.617	2.061
Brain	0.033	0.005	0.046	0.043	0.016	0.004
Tail	1.848	0.456	1.556	0.561	1.404	0.226
Salivary	8.897	2.904	5.582	3.431	1.386	0.579
Lacrimal	0.090	0.116	0.057	0.071	0.058	0.104

Organs	72h	
	% ID/g	SD
Blood	0.014	0.006
Fat	0.122	0.130
Seminal	0.034	0.014
Testes	0.115	0.055
Intestine	0.301	0.239
Stomach	0.727	0.885
Spleen	0.586	0.242
Liver	0.270	0.129
Pancreas	0.044	0.017
Adrenal	1.528	0.796
Kidney	7.221	3.433
Lung	0.175	0.075
Heart	0.103	0.070
Tumor	12.267	4.632
Muscle	0.114	0.069
Bone	2.128	1.148
Brain	0.012	0.005
Tail	1.251	0.650
Salivary	0.591	0.228
Lacrimal	0.053	0.050

**Table S12.** Tumor-to-background ratios of [<sup>177</sup>Lu][Lu(octapa-alkyl-PSMA617)] at different p.i. timepoints (n = 5).

	<b>1 h</b>	<b>4 h</b>	<b>24 h</b>	<b>72 h</b>
<b>Tumor/bone</b>	20.94	12.78	2.96	5.76
<b>Tumor/muscle</b>	28.53	54.64	71.47	107.69
<b>Tumor/blood</b>	8.75	17.91	135.66	907.86
<b>Tumor/kidney</b>	0.09	0.09	0.41	1.70