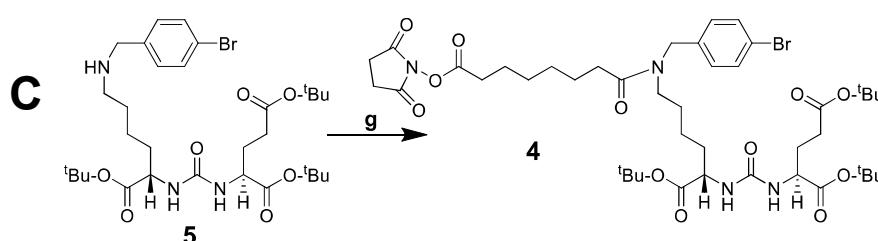
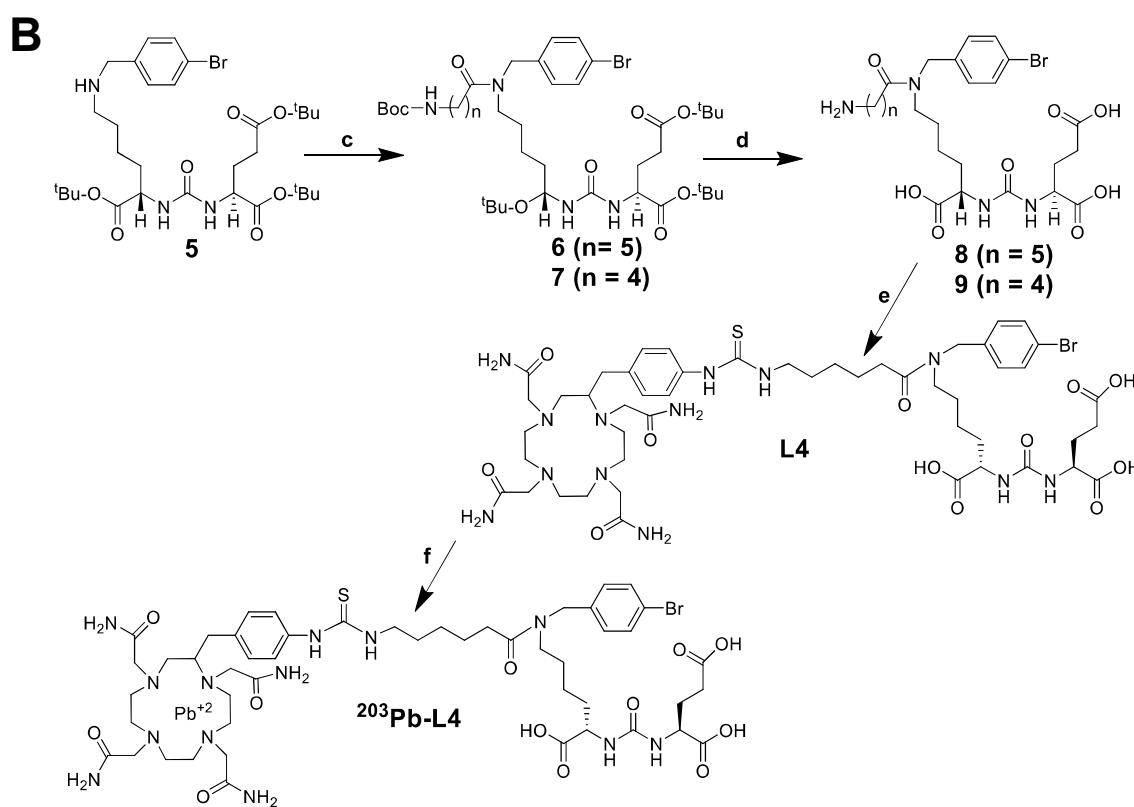
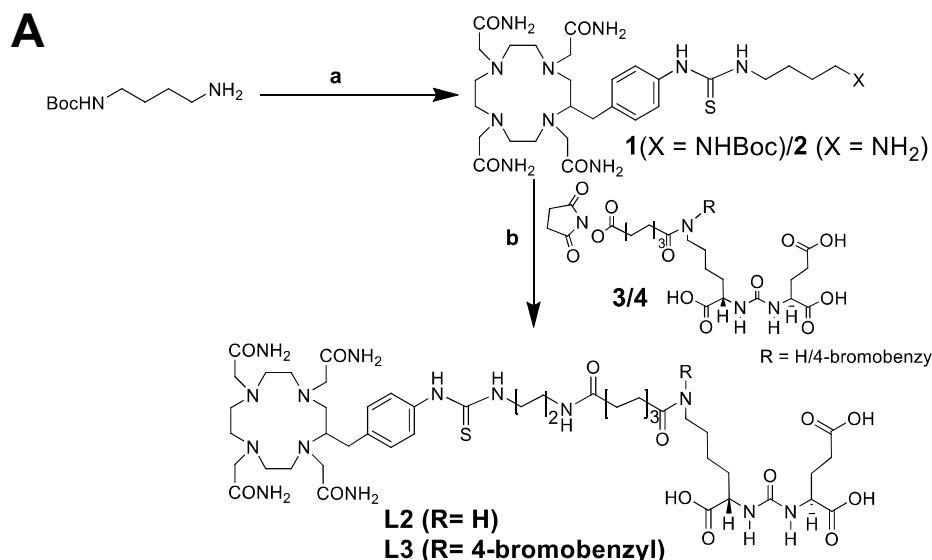
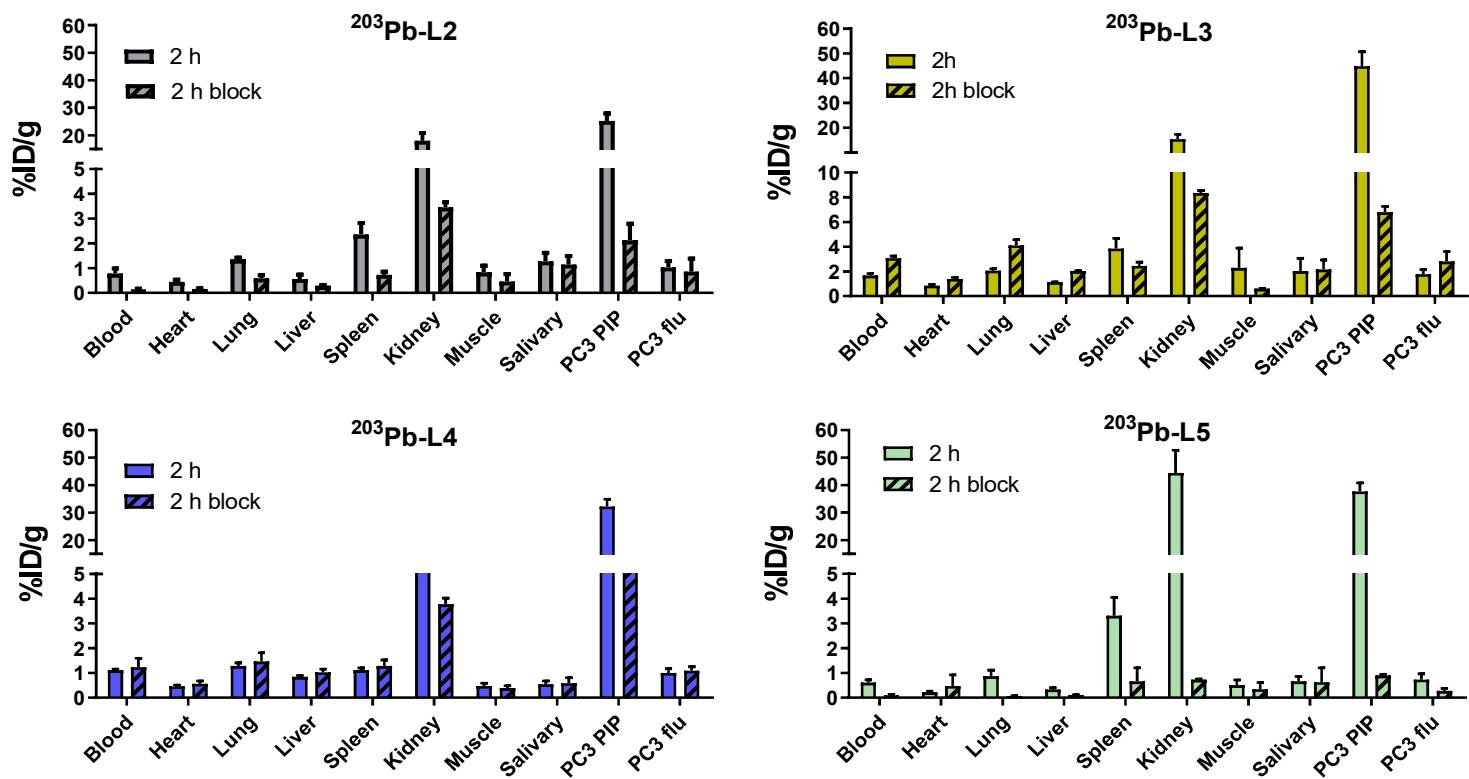


Supplemental Figure 1. A. Synthetic routes for ligands **L2 and **L3**. B. Synthetic scheme for the intermediate compound **4**. C. Synthetic schemes for ligand **L4** and **L5** and representative radiolabeling scheme of ^{203}Pb -**L4**.**



- a.** (i) DOTA-Bn-SCN, DMSO, Et_3N , 40°C , 4 h; (ii) TFA: CH_2Cl_2 (1:1), rt, 2 h; **b.** DMSO, DIEA, rt, 2 h; **c.** 6-(Boc-amino)hexanoic acid, DIPEA, TSTU, DMF, rt, 4 h; **d.** TFC: CH_2Cl_2 (1:1), rt, 2 h; **e.** TCMC-Bn-SCN, DMSO, DIPEA, rt; **f.** $\text{Pb}(\text{NO}_3)_2$, 0.2 M NaOAc , $\text{pH} \sim 4-5.5$, $40-50^\circ\text{C}$; **g.** Disuccinimidyl suberate, Et_3N , DMF, rt, 2 h.

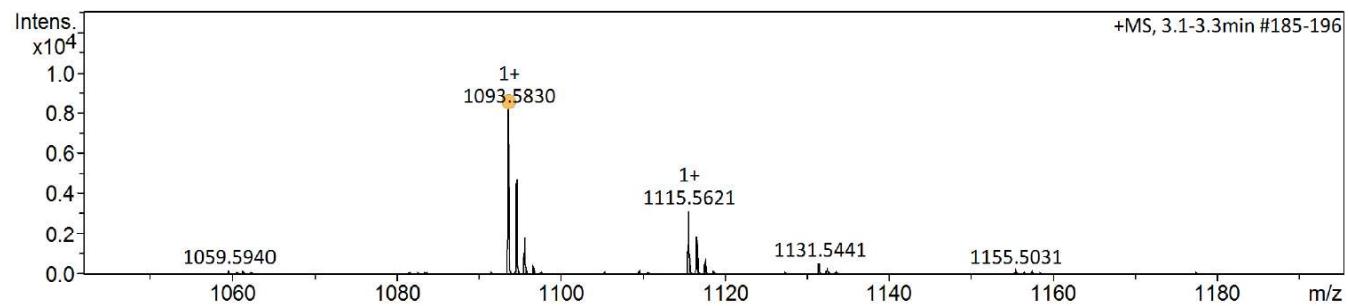
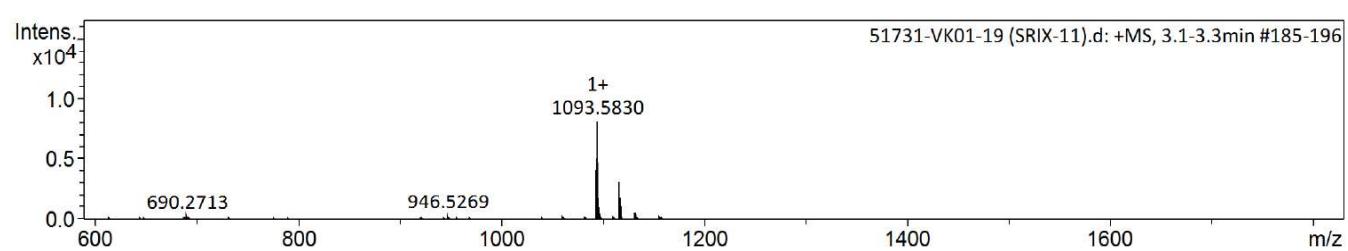
Supplemental Figure 2. PSMA binding specificity of the compounds were assessed by co-administration of ^{203}Pb -L2- ^{203}Pb -L5 with 50 nmol of ZJ43 for ^{203}Pb -L2, ^{203}Pb -L3 and ^{203}Pb -L4 and 100 nmol for ^{203}Pb -L5.



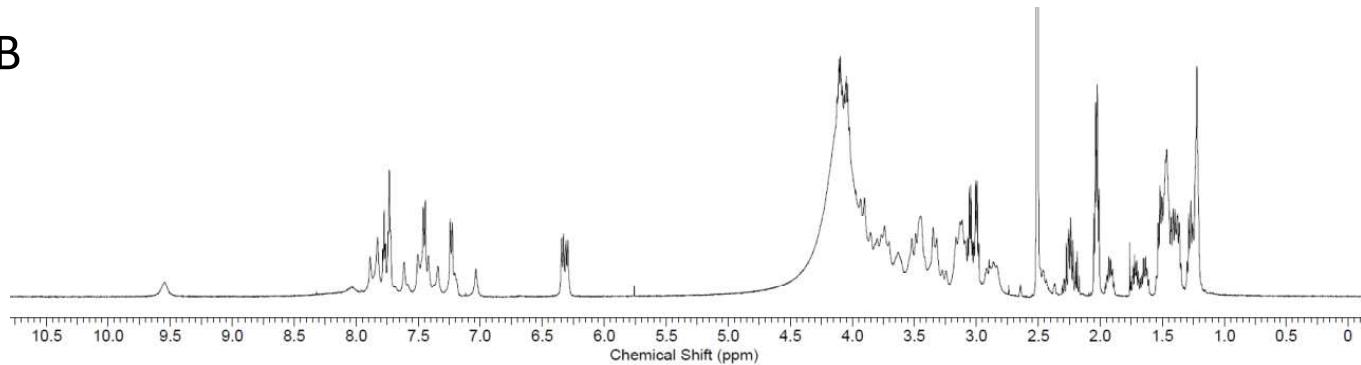
Comparison of time-dependent uptake of blood (A), kidney (B) and PSMA(+) tumor (C) of ^{203}Pb -L1- ^{203}Pb -L5.

Supplemental Figure 3. High resolution electrospray ionization mass spectrometry HR-ESI-MS (A) and ^1H NMR (B) of L2 in DMSO at room temperature.

A

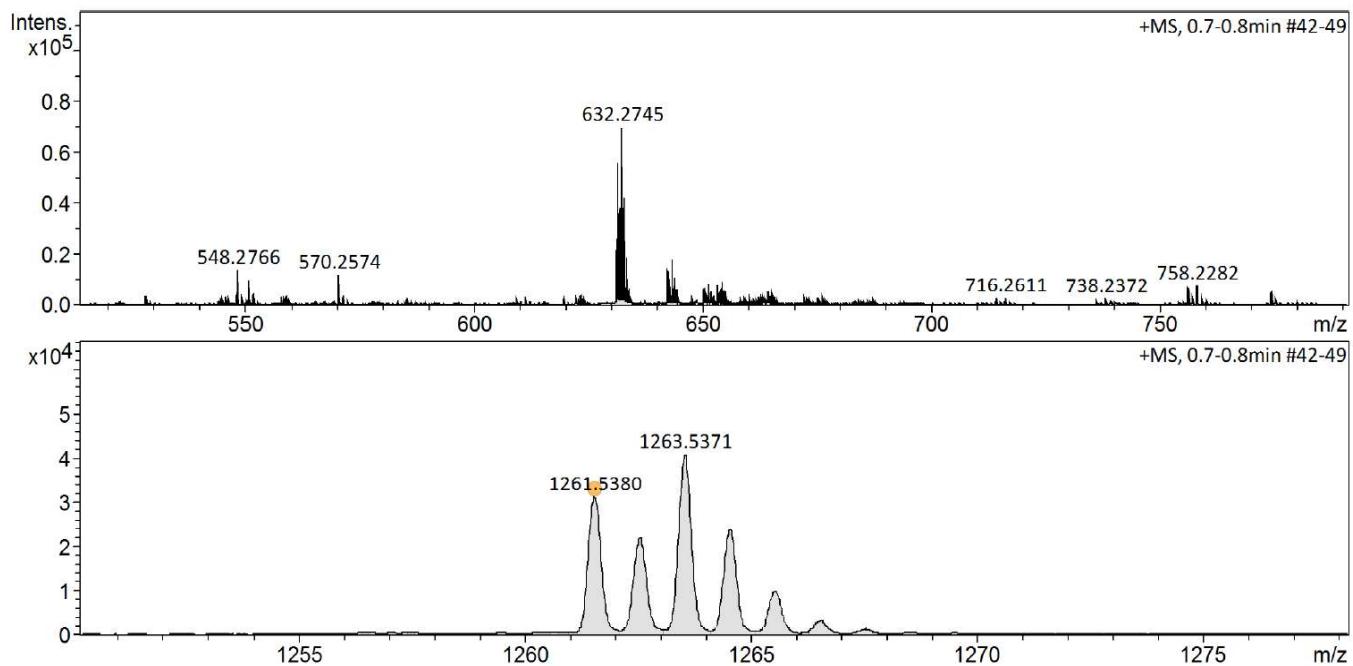


B

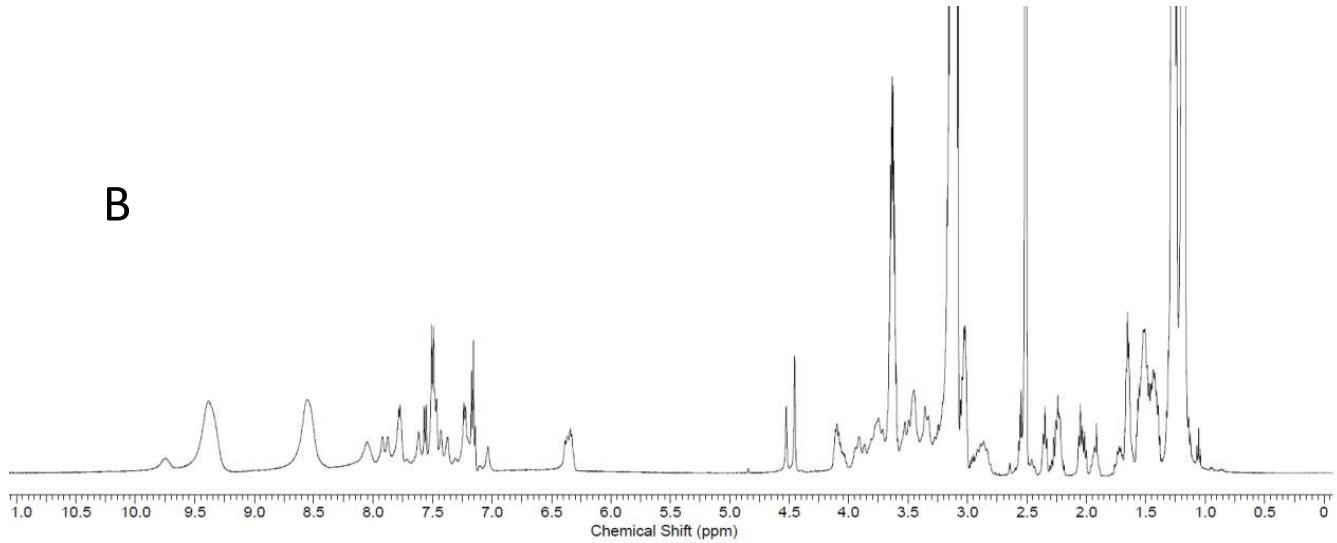


Supplemental Figure 4. High resolution electrospray ionization mass spectrometry (A) and ^1H NMR (B) of L3 in DMSO at room temperature.

A

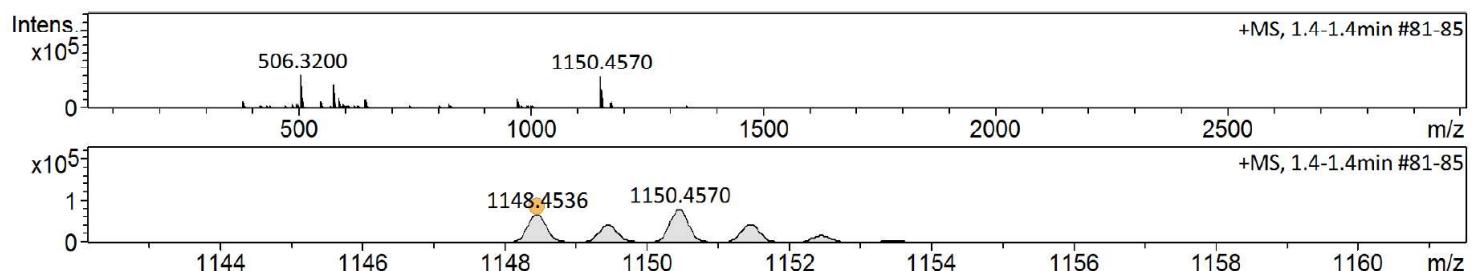


B

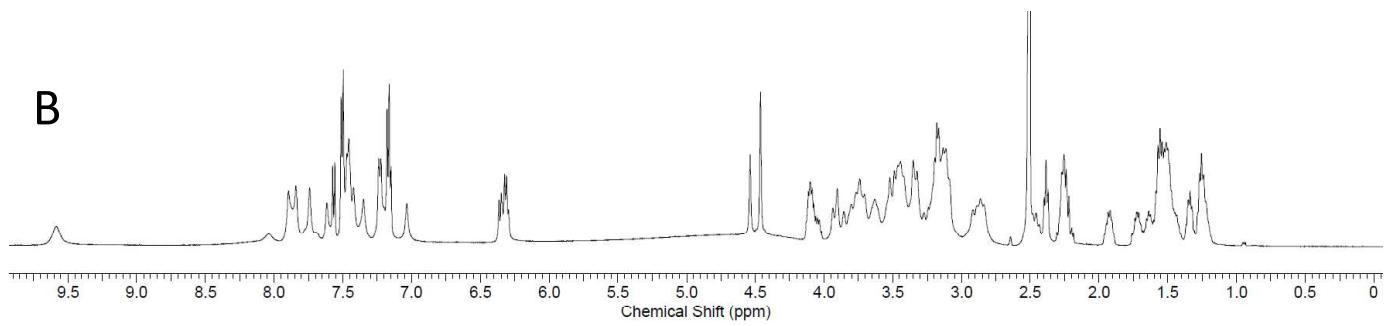


Supplemental Figure 5. High resolution electro-spray ionization mass spectrometry MS HR-ESI-MS (A) and ^1H NMR (B) of L4 in DMSO at room temperature.

A

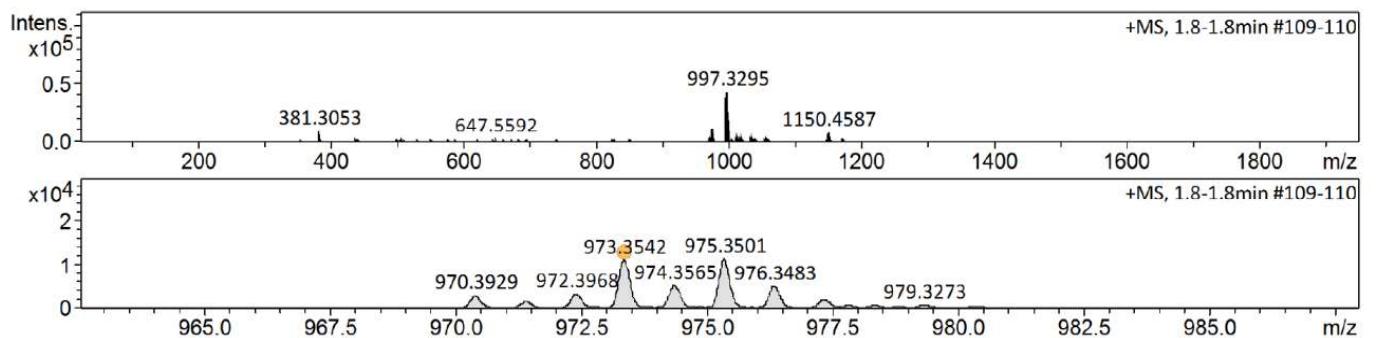


B

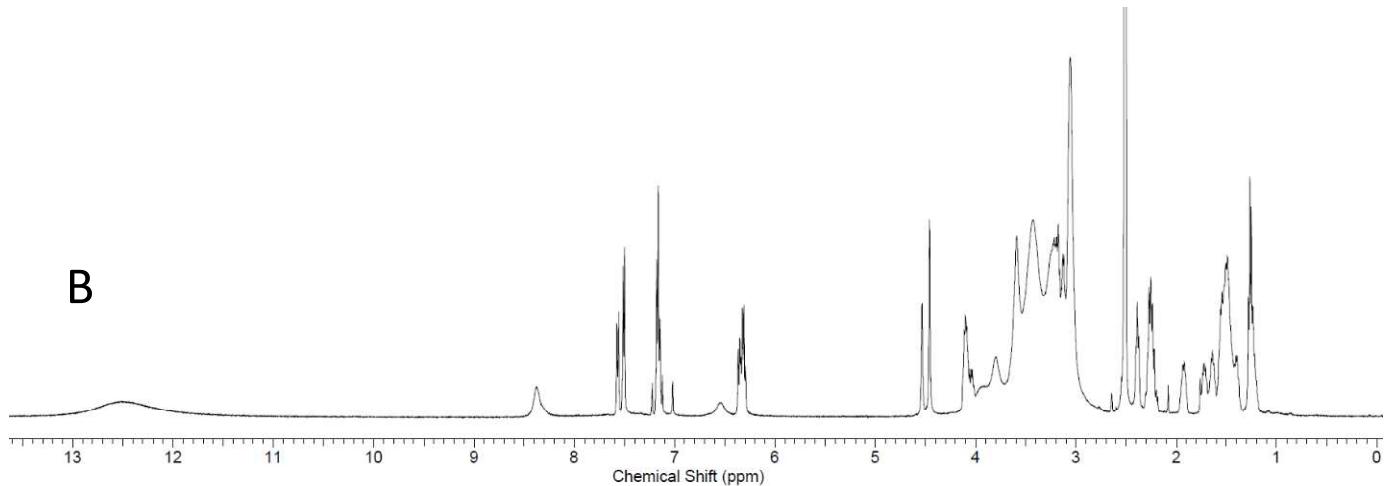


Supplemental Figure 6. High resolution electrospray ionization mass spectrometry MS HR-ESI-MS (A) and ^1H NMR (B) of L5 in DMSO at room temperature.

A

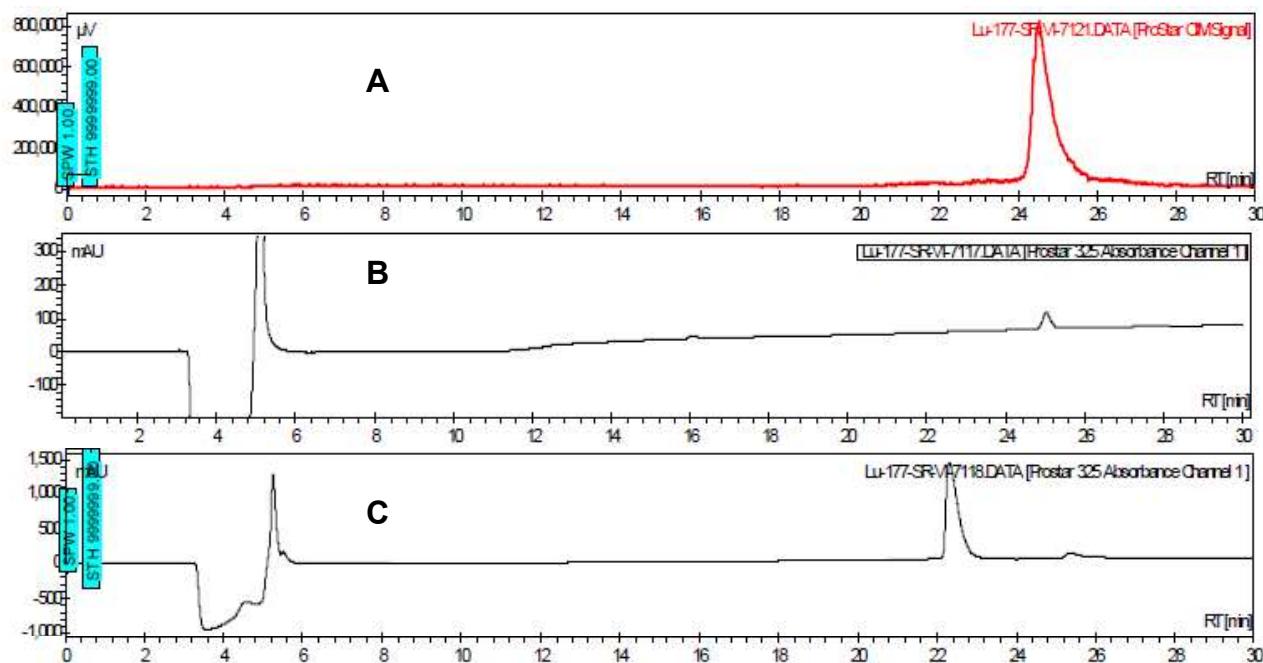


B



Supplemental Figure 7. HPLC chromatogram for $^{203}\text{Pb-L1}$.

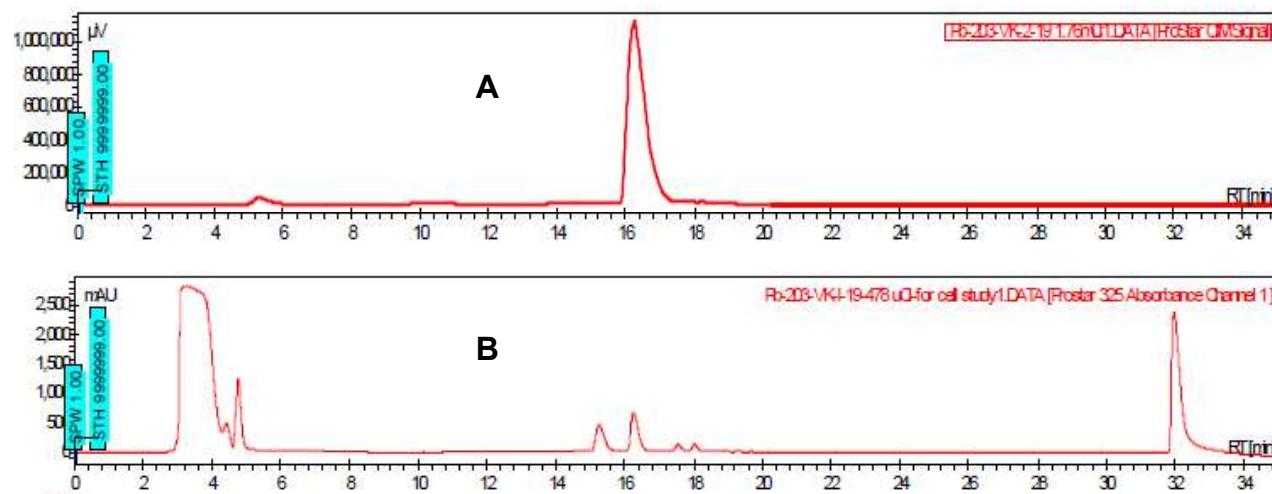
A. Radioactive peak at 24-25 min; B. UV peak (254 nm) associated with radioactive peak; C. UV peak (254 nm) at 22-24 min is for L1.



HPLC Method for $^{203}\text{Pb-L1}$

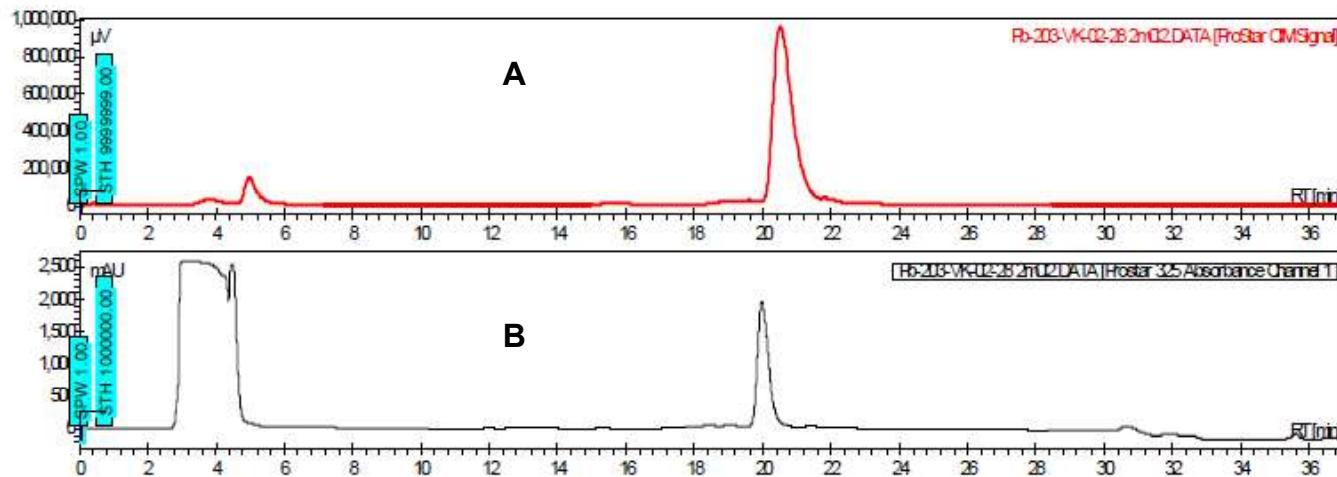
Min	Flow (mL/min)	Solvent A (10 mM ammonium acetate, pH 4.5)	Solvent B Acetonitrile
0	1	88	12
5	1	88	12
25	1	68	32
30	1	5	95
35	1	88	12

Supplemental Figure 8. HPLC chromatogram for ^{203}Pb -L2. A. Radioactive peak; B. UV peak (254 nm) at 16-17 min is associated with the radioactive peak and UV peak (254 nm) at 15.1-15.8 min is for unreacted L2.



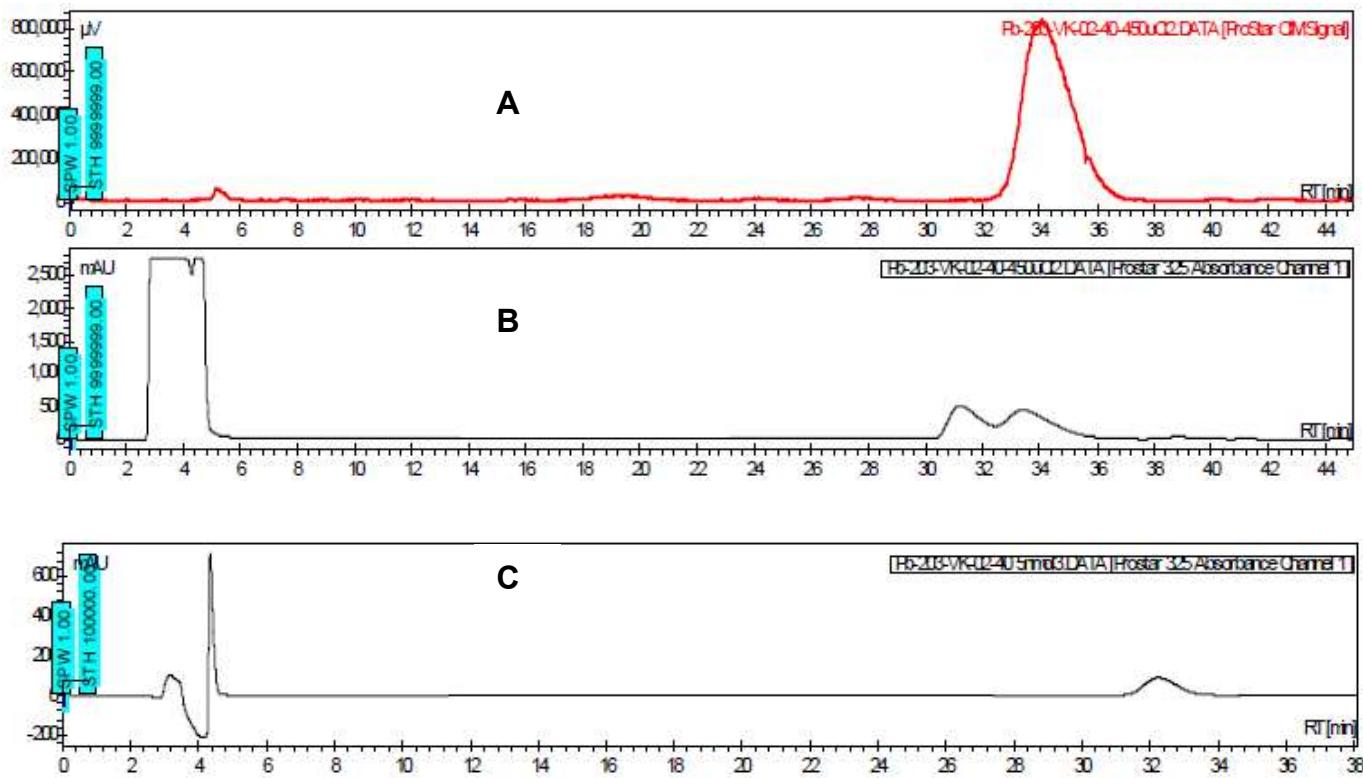
HPLC Method for ^{203}Pb -L2			
Min	Flow (mL/min)	Solvent A (10 mM ammonium acetate, pH 4.5)	Solvent B Acetonitrile
0	1	88	12
5	1	88	12
25	1	68	32
30	1	5	95
35	1	88	12

Supplemental Figure 9. HPLC chromatogram for ^{203}Pb -L3. A. Radioactive peak at 22-22 min; B. UV peak (254 nm) showing cold stable Pb-L2 peak



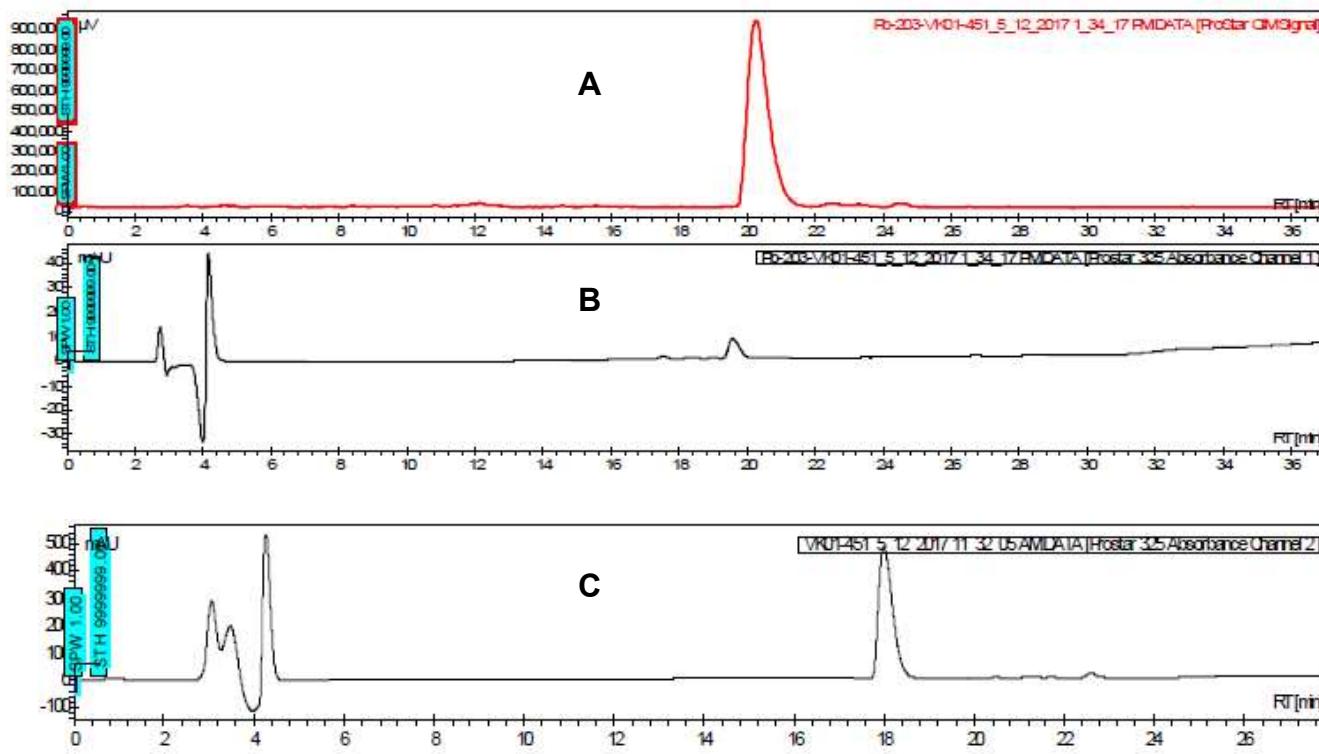
HPLC Method for ^{203}Pb -L3			
Min	Flow (mL/min)	Solvent A (10 mM ammonium acetate, pH 4.5)	Solvent B Acetonitrile
0	1	88	12
5	1	88	12
25	1	68	32
30	1	5	95
35	1	88	12

Supplemental Figure 10. HPLC chromatogram for $^{203}\text{Pb-L4}$. A. Radioactive peak at 32-36 min; B. UV peak (254 nm) showing unreacted L4 at 30-32 min and UV-peak associated with the radiolabeled peak at 32-36 min; C. UV peak (254 nm) at 32-34 min for cold Pb-L4.



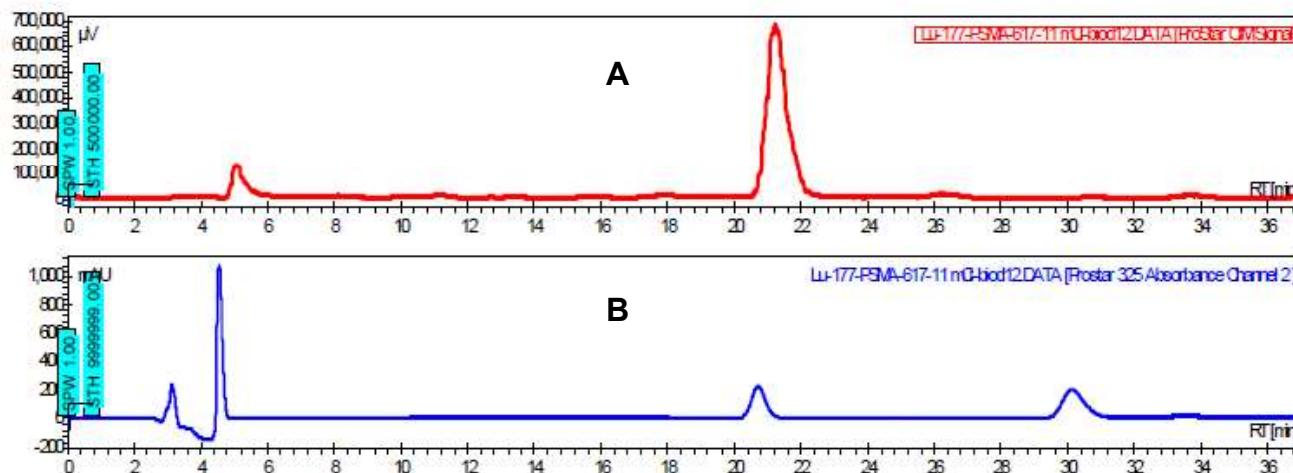
HPLC Method for $^{203}\text{Pb-L4}$			
Min	Flow (mL/min)	Solvent A (10 mM ammonium acetate, pH 4.5)	Solvent B Acetonitrile
0	1	77	23
5	1	77	23
25	1	57	43
30	1	5	95
35	1	77	23

Supplemental Figure 11. HPLC chromatogram for ^{203}Pb -L5. A. Radioactive peak at 20-22 min; B. UV peak (254 nm) at 19.8-20.8 was associated with the radiolabeled peak; C. UV peak (254 nm) at 17.8-18.4 min was for L5.



HPLC Method for ^{203}Pb -L5			
Min	Flow (mL/min)	Solvent A (10 mM ammonium acetate, pH 4.5)	Solvent B Acetonitrile
0	1	88	12
5	1	88	12
25	1	68	32
30	1	5	95
35	1	88	12

Supplemental Figure 12. HPLC chromatogram for ^{177}Lu -PSMA-617. A. Radioactive peak at 20-22 min; B. UV peak (254 nm) at 20-22 min associated with the radiolabeled peak and for peak at 29.8-30.8 min was related to the unlabeled PSMA-617.



HPLC Method for ^{177}Lu -PSMA-617 (isocratic)			
Min	Flow (mL/min)	Solvent A (10 mM ammonium acetate, pH 4.5)	Solvent B Acetonitrile
0	1	78	22
5	1	78	22
45	1	78	22

SUPPLEMENTAL TABLE 1. Tissue biodistribution of $^{203}\text{Pb-L1}$ in male NOD-SCID mice bearing PSMA(+) PC3 PIP and PSMA(-) PC3 flu tumors in either flank. Data are shown as %ID/g, expressed as mean \pm SEM (n = 4)

Tissue	1 h	2 h	4 h	24 h
Blood	0.60 \pm 0.05	0.31 \pm 0.04	0.24 \pm 0.02	0.21 \pm 0.02
Heart	0.30 \pm 0.03	0.14 \pm 0.06	0.09 \pm 0.01	0.07 \pm 0.01
Lung	1.20 \pm 0.19	0.64 \pm 0.14	0.28 \pm 0.04	0.16 \pm 0.01
Liver	1.09 \pm 0.07	1.01 \pm 0.21	0.92 \pm 0.09	0.64 \pm 0.04
Stomach	0.30 \pm 0.04	0.15 \pm 0.03	0.13 \pm 0.03	0.07 \pm 0.01
Pancreas	0.49 \pm 0.09	0.29 \pm 0.05	0.24 \pm 0.05	0.09 \pm 0.06
Spleen	5.07 \pm 1.68	1.59 \pm 0.58	0.72 \pm 0.16	0.24 \pm 0.02
Fat	0.77 \pm 0.29	0.31 \pm 0.22	0.31 \pm 0.18	0.05 \pm 0.06
Kidney	75.2 \pm 9.94	39.4 \pm 7.28	22.8 \pm 6.22	7.01 \pm 0.80
Muscle	0.22 \pm 0.14	0.22 \pm 0.07	0.06 \pm 0.02	0.04 \pm 0.03
Small intestine	0.31 \pm 0.05	0.23 \pm 0.04	0.15 \pm 0.04	0.04 \pm 0.03
Salivary gland	1.78 \pm 0.69	0.93 \pm 0.07	0.29 \pm 0.02	0.10 \pm 0.05
Bladder	5.96 \pm 2.24	10.4 \pm 3.21	1.94 \pm 0.49	0.31 \pm 0.16
PSMA(+) PC3 PIP tumor	41.9 \pm 7.60	38.1 \pm 6.30	34.7 \pm 7.37	27.9 \pm 7.01
PSMA(-) PC3 flu tumor	0.43 \pm 0.11	0.29 \pm 0.14	0.20 \pm 0.06	0.14 \pm 0.01

SUPPLEMENTAL TABLE 2. Tissue biodistribution of ^{203}Pb -L2 in male NOD-SCID mice bearing PSMA(+) PC3 PIP and PSMA(-) PC3 flu tumors in either flank. Data are shown as %ID/g, expressed as mean \pm SEM (n = 4).

Tissue	0.5 h	1 h	2 h	4 h	24 h	2 h Block
Blood	2.39 \pm 0.33	0.77 \pm 0.25	0.78 \pm 0.42	0.04 \pm 0.01	0.01 \pm 0.00	0.14 \pm 0.05
Heart	1.07 \pm 0.16	0.43 \pm 0.16	0.44 \pm 0.17	0.06 \pm 0.03	0.02 \pm 0.00	0.15 \pm 0.07
Lung	2.58 \pm 0.67	1.23 \pm 0.61	1.34 \pm 0.17	0.19 \pm 0.09	0.06 \pm 0.01	0.58 \pm 0.26
Liver	0.63 \pm 0.04	0.42 \pm 0.15	0.57 \pm 0.34	0.17 \pm 0.04	0.12 \pm 0.01	0.29 \pm 0.06
Stomach	1.00 \pm 0.19	1.44 \pm 1.65	1.48 \pm 1.27	0.09 \pm 0.04	0.05 \pm 0.02	0.54 \pm 0.50
Pancreas	0.54 \pm 0.07	0.37 \pm 0.23	0.60 \pm 0.50	0.09 \pm 0.06	0.02 \pm 0.01	0.20 \pm 0.09
Spleen	3.79 \pm 0.86	1.88 \pm 1.15	2.36 \pm 0.94	0.34 \pm 0.08	0.23 \pm 0.04	0.73 \pm 0.23
Fat	0.76 \pm 0.14	1.62 \pm 2.13	1.50 \pm 1.44	0.09 \pm 0.05	0.08 \pm 0.02	0.10 \pm 0.04
Kidney	33.81 \pm 6.90	22.99 \pm 11.92	18.05 \pm 5.55	3.76 \pm 1.03	3.11 \pm 0.79	3.45 \pm 0.41
Muscle	0.71 \pm 0.32	1.07 \pm 0.72	0.84 \pm 0.51	0.08 \pm 0.04	0.04 \pm 0.034	0.46 \pm 0.61
Small intestine	0.98 \pm 0.35	1.00 \pm 1.09	1.03 \pm 0.83	0.16 \pm 0.18	0.04 \pm 0.01	0.33 \pm 0.12
Large intestine	1.70 \pm 1.51	0.93 \pm 0.56	4.02 \pm 5.60	0.23 \pm 0.15	0.07 \pm 0.017	4.90 \pm 8.07
Saliv glands	1.26 \pm 0.17	5.29 \pm 8.69	0.76 \pm 0.23	0.12 \pm 0.03	0.05 \pm 0.01	0.28 \pm 0.15
Bladder	38.22 \pm 12.05	53.46 \pm 35.17	15.88 \pm 7.79	2.39 \pm 2.55	0.52 \pm 0.19	4.01 \pm 2.74
PSMA(+) PC3 PIP tumor	18.55 \pm 3.40	22.46 \pm 8.12	25.24 \pm 5.35	11.63 \pm 4.19	8.54 \pm 2.06	2.12 \pm 1.33
PSMA(-) PC3 flu tumor	1.26 \pm 0.20	1.49 \pm 1.19	1.03 \pm 0.51	0.14 \pm 0.04	0.08 \pm 0.02	0.86 \pm 1.06

SUPPLEMENTAL TABLE 3. Tissue biodistribution of $^{203}\text{Pb-L3}$ in male NOD-SCID mice bearing PSMA(+) PC3 PIP and PSMA(-) PC3 flu tumors in either flank. Data are shown as %ID/g, expressed as mean \pm SEM (n = 4).

Tissue	0.5 h	1 h	2 h	4 h	24 h	2h Block
Blood	9.43 \pm 0.86	4.42 \pm 0.69	1.66 \pm 0.36	0.33 \pm 0.10	0.05 \pm 0.00	3.07 \pm 0.35
Heart	5.07 \pm 4.04	1.70 \pm 0.13	0.86 \pm 0.15	0.20 \pm 0.03	0.12 \pm 0.01	1.40 \pm 0.24
Lung	5.76 \pm 3.04	4.13 \pm 1.20	2.07 \pm 0.31	0.72 \pm 0.23	0.25 \pm 0.08	4.10 \pm 0.94
Liver	2.19 \pm 0.45	1.57 \pm 0.18	1.13 \pm 0.07	0.69 \pm 0.10	0.93 \pm 0.19	2.03 \pm 0.05
Stomach	3.24 \pm 1.59	2.09 \pm 1.54	1.63 \pm 1.88	0.34 \pm 0.23	0.77 \pm 0.86	0.85 \pm 0.05
Pancreas	2.54 \pm 1.94	0.85 \pm 0.15	0.64 \pm 0.18	0.19 \pm 0.09	0.10 \pm 0.02	1.00 \pm 0.54
Spleen	5.73 \pm 2.60	4.60 \pm 1.70	3.86 \pm 1.65	1.15 \pm 0.30	0.86 \pm 0.50	2.46 \pm 0.58
Fat	1.27 \pm 0.72	1.12 \pm 0.40	1.50 \pm 1.16	0.19 \pm 0.08	0.28 \pm 0.14	0.83 \pm 0.245
Kidney	56.73 \pm 21.55	22.16 \pm 14.46	15.41 \pm 3.78	6.44 \pm 1.76	4.61 \pm 0.47	8.35 \pm 0.39
Muscle	1.27 \pm 0.47	1.23 \pm 0.56	2.29 \pm 3.19	0.13 \pm 0.02	0.14 \pm 0.09	0.61 \pm 0.07
Small intestine	1.81 \pm 0.25	1.50 \pm 0.78	0.77 \pm 0.35	0.42 \pm 0.29	0.36 \pm 0.32	1.00 \pm 0.21
Large intestine	4.40 \pm 2.88	1.14 \pm 0.65	2.03 \pm 2.04	0.55 \pm 0.46	0.40 \pm 0.50	2.16 \pm 1.55
Salivary glands	4.38 \pm 2.82	1.77 \pm 0.16	0.94 \pm 0.12	0.29 \pm 0.04	0.22 \pm 0.06	1.63 \pm 0.51
Bladder	28.82 \pm 18.62	24.86 \pm 30.96	13.13 \pm 1.59	3.38 \pm 1.92	0.75 \pm 0.17	23.51 \pm 7.72
PSMA(+) PC3 PIP tumor	28.25 \pm 6.16	37.48 \pm 8.98	44.92 \pm 11.71	24.87 \pm 7.44	24.17 \pm 9.30	6.79 \pm 0.94
PSMA(-) PC3 flu tumor	2.44 \pm 0.50	1.35 \pm 0.91	1.77 \pm 0.78	0.45 \pm 0.07	0.26 \pm 0.03	2.80 \pm 1.63

SUPPLEMENTAL TABLE 4. Tissue biodistribution of ^{203}Pb -L4 in male NOD-SCID mice bearing PSMA(+) PC3 PIP and PSMA(-) PC3 flu tumors in either flank. Data are shown as %ID/g, expressed as mean \pm SEM ($n = 4$).

	0.5h	1h	2h	4h	24h	2h Block
Blood	7.09 \pm 0.90	3.96 \pm 0.78	1.16 \pm 0.08	0.31 \pm 0.12	0.07 \pm 0.07	1.24 \pm 0.72
Heart	2.80 \pm 0.66	1.40 \pm 0.33	0.47 \pm 0.08	0.17 \pm 0.05	0.08 \pm 0.02	0.56 \pm 0.24
Lung	5.15 \pm 0.50	3.15 \pm 0.44	1.28 \pm 0.25	0.54 \pm 0.16	0.30 \pm 0.27	1.46 \pm 0.71
Liver	1.82 \pm 0.15	1.24 \pm 0.20	0.84 \pm 0.10	0.57 \pm 0.08	0.59 \pm 0.11	1.03 \pm 0.24
Stomach	1.57 \pm 0.21	1.64 \pm 1.24	2.58 \pm 3.37	0.37 \pm 0.26	0.09 \pm 0.02	0.44 \pm 0.12
Pancreas	1.02 \pm 0.13	0.71 \pm 0.24	0.35 \pm 0.18	0.10 \pm 0.03	0.05 \pm 0.02	0.34 \pm 0.16
Spleen	4.89 \pm 0.38	2.85 \pm 0.76	1.11 \pm 0.18	0.67 \pm 0.23	0.50 \pm 0.18	1.29 \pm 0.49
Fat	2.27 \pm 0.72	3.47 \pm 4.14	1.50 \pm 1.92	0.25 \pm 0.22	0.15 \pm 0.07	0.63 \pm 0.24
Kidney	35.87 \pm 8.51	20.31 \pm 2.96	10.29 \pm 2.10	6.02 \pm 1.45	2.61 \pm 0.47	3.78 \pm 0.49
Muscle	1.09 \pm 0.33	0.99 \pm 0.56	0.47 \pm 0.23	0.26 \pm 0.22	0.19 \pm 0.21	2.39 \pm 4.18
Sm Intestine	1.33 \pm 0.23	0.95 \pm 0.60	1.93 \pm 3.19	0.12 \pm 0.06	0.09 \pm 0.02	0.73 \pm 0.40
Lrg Intestine	1.44 \pm 0.35	2.67 \pm 3.29	0.55 \pm 0.27	0.45 \pm 0.31	0.09 \pm 0.02	2.59 \pm 3.87
Sal Glnds	2.17 \pm 0.25	1.32 \pm 0.42	0.43 \pm 0.06	0.28 \pm 0.18	0.11 \pm 0.02	1.16 \pm 1.40
Bladder	18.79 \pm 6.37	52.30 \pm 36.76	33.61 \pm 33.85	7.82 \pm 5.31	0.37 \pm 0.22	30.85 \pm 31.13
PSMA(+) PC3 PIP tumor	27.27 \pm 3.43	31.10 \pm 8.26	32.19 \pm 5.42	27.66 \pm 9.38	16.44 \pm 8.72	6.22 \pm 1.70
PSMA(-) PC3 flu tumor	2.13 \pm 0.40	2.06 \pm 0.48	1.00 \pm 0.34	0.61 \pm 0.41	0.21 \pm 0.06	1.10 \pm 0.32

SUPPLEMENTAL TABLE 5. Tissue biodistribution of ^{203}Pb -L5 in male NOD-SCID mice bearing PSMA(+) PC3 PIP and PSMA(-) PC3 flu tumors in either flank. Data are shown as %ID/g, expressed as mean \pm SEM (n = 4).

	30 min	1 h	2 h	2 h blocking	4 h	24 h
Blood	1.76 \pm 0.16	0.67 \pm 0.21	0.47 \pm 0.31	1.34 \pm 2.59	2.02 \pm 3.12	0.02 \pm 0.01
Heart	0.72 \pm 0.13	0.30 \pm 0.10	0.22 \pm 0.10	0.48 \pm 0.89	0.81 \pm 1.23	0.02 \pm 0.02
Lung	2.42 \pm 0.47	1.30 \pm 0.46	0.87 \pm 0.50	1.37 \pm 2.58	2.64 \pm 3.84	0.07 \pm 0.06
Liver	0.89 \pm 0.10	0.43 \pm 0.13	0.33 \pm 0.14	0.69 \pm 1.17	1.09 \pm 1.53	0.07 \pm 0.05
Stomach	0.92 \pm 0.18	0.44 \pm 0.23	0.33 \pm 0.11	0.59 \pm 0.97	1.09 \pm 1.61	0.03 \pm 0.02
Pancreas	1.01 \pm 0.50	0.52 \pm 0.13	0.53 \pm 0.16	0.45 \pm 0.69	0.76 \pm 0.97	0.01 \pm 0.01
Spleen	7.54 \pm 1.81	5.97 \pm 2.18	3.31 \pm 1.48	0.66 \pm 1.09	3.77 \pm 3.41	0.17 \pm 0.21
Fat	0.55 \pm 0.04	0.47 \pm 0.14	0.47 \pm 0.42	0.25 \pm 0.35	0.47 \pm 0.58	0.01 \pm 0.01
Kidney	82.23 \pm 13.53	63.78 \pm 7.36	44.46 \pm 16.38	5.46 \pm 9.47	38.90 \pm 18.03	5.30 \pm 5.34
Muscle	0.50 \pm 0.08	0.29 \pm 0.10	0.51 \pm 0.42	0.35 \pm 0.53	0.47 \pm 0.67	0.01 \pm 0.00
Small Intestine	0.74 \pm 0.09	0.43 \pm 0.16	0.48 \pm 0.31	0.86 \pm 1.57	1.16 \pm 1.75	0.03 \pm 0.02
Salivary Glands	1.29 \pm 0.21	0.78 \pm 0.30	0.66 \pm 0.40	0.63 \pm 1.17	1.29 \pm 1.76	0.03 \pm 0.03
Lacrimal Gland	2.33 \pm 0.89	1.87 \pm 0.67	0.61 \pm 0.29	0.72 \pm 1.03	1.35 \pm 1.77	0.06 \pm 0.03
Bladder	23.92 \pm 11.98	30.69 \pm 21.82	23.54 \pm 6.77	24.72 \pm 24.95	18.03 \pm 12.10	0.26 \pm 0.08
Bone	0.97 \pm 0.51	0.38 \pm 0.18	2.50 \pm 3.65	0.73 \pm 0.82	1.47 \pm 1.13	0.04 \pm 0.01
PSMA(+) PC3 PIP tumor	36.53 \pm 1.93	45.37 \pm 9.30	37.67 \pm 6.26	1.80 \pm 1.82	55.81 \pm 22.42	42.61 \pm 12.97
PSMA(-) PC3 flu tumor	1.94 \pm 1.31	0.91 \pm 0.35	0.74 \pm 0.46	1.11 \pm 1.68	1.86 \pm 2.56	0.05 \pm 0.03

SUPPLEMENTAL TABLE 6. Murine organ absorbed dose coefficients of $^{212}\text{Pb-L1}$ - $^{212}\text{Pb-L5}$ determined from the corresponding murine biodistribution data. Only α -particle deposition was considered.

Tissue	$^{203}\text{Pb-L1}$ (mGy/kBq)	$^{203}\text{Pb-L2}$ (mGy/kBq)	$^{203}\text{Pb-L3}$ (mGy/kBq)	$^{203}\text{Pb-L4}$ (mGy/kBq)	$^{203}\text{Pb-L5}$ (mGy/kBq)
Blood	0.167	0.135	0.528	0.435	0.389
Heart	0.063	0.081	0.297	0.194	0.178
Lung	0.205	0.234	0.615	0.504	0.610
Liver	0.526	0.138	0.663	0.457	0.278
Stomach	0.072	0.190	0.727	0.348	0.243
Pancreas	0.129	0.086	0.193	0.105	0.192
Spleen	0.540	0.431	1.040	0.575	1.273
Fat	0.144	0.203	0.300	0.351	0.140
Kidneys	12.711	4.409	5.800	4.193	15.180
Muscle	0.074	0.130	0.279	0.202	0.127
Small intestine	0.033	0.158	0.347	0.230	0.262
Large intestine	N/A	0.375	0.507	0.271	N/A
Salivary glands	0.241	0.281	0.347	0.211	0.316
Urinary bladder	1.448	4.128	3.143	5.571	5.766
PSMA(+) PC3 PIP tumor	23.111	8.014	18.269	14.958	30.997
PSMA(+) PC3 flu tumor	0.126	0.191	0.385	0.370	0.443
Bone	N/A	N/A	N/A	N/A	0.442
Lacrimal gland	N/A	N/A	N/A	N/A	0.407

SUPPLEMENTAL TABLE 7. Selected Human organ absorbed dose coefficients of $^{212}\text{Pb-L1}$ - $^{212}\text{Pb-L5}$ estimated based on the murine biodistribution data using OLINDA/EXM version 1 (1).

	Absorbed Dose Coefficient (mGy/MBq)			
	Alpha	Beta	Photon	Total
$^{212}\text{Pb-L1}$				
Kidneys	4.31	0.48	0.05	4.84
Spleen	0.18	0.02	0.01	0.21
Liver	0.18	0.02	0.01	0.21
Salivary glands (44.5 g)	N/A	N/A	N/A	0.09
PIP-Tumor (1 gram)	N/A	N/A	N/A	9.36
$^{212}\text{Pb-L2}$	Alpha	Beta	Photon	Total
Kidneys	1.50	0.17	0.02	1.69
Spleen	0.15	0.02	0.01	0.17
Liver	0.05	0.01	0.00	0.06
Salivary glands (44.5 g)	N/A	N/A	N/A	0.11
PIP-Tumor (1 gram)	N/A	N/A	N/A	2.99
$^{212}\text{Pb-L3}$	Alpha	Beta	Photon	Total
Kidneys	1.97	0.22	0.03	2.22
Spleen	0.35	0.04	0.01	0.40
Liver	0.23	0.03	0.01	0.26
Salivary glands (44.5 g)	N/A	N/A	N/A	0.13
PIP-Tumor (1 gram)	N/A	N/A	N/A	6.81
$^{212}\text{Pb-L4}$	Alpha	Beta	Photon	Total
Kidneys	1.42	0.16	0.02	1.60
Spleen	0.20	0.02	0.01	0.22
Liver	0.16	0.02	0.01	0.18
Salivary glands (44.5 g)	N/A	N/A	N/A	0.08
PIP-Tumor (1 gram)	N/A	N/A	N/A	5.58
$^{212}\text{Pb-L5}$	Alpha	Beta	Photon	Total
Kidneys	5.15	0.58	0.06	5.79
Spleen	0.43	0.05	0.01	0.49
Liver	0.09	0.01	0.01	0.11
Salivary glands (44.5 g)	N/A	N/A	N/A	0.12
PIP-Tumor (1 gram)	N/A	N/A	N/A	11.60

SUPPLEMENTAL TABLE 8. Blood chemistry in CD-1 mice (n = 7) at 7 months after single administration of 3.7 MBq ^{212}Pb -L2.

	Mouse number	Complete Blood Counts	Creatinine	Alanine Aminotransferase (U/L)	Aspartate Aminotransferase (U/dL)	Blood urea nitrogen (mg/dL)
^{212}Pb -L2			(0.2-0.9)	(26-77)	(54-269)	(8-33)
3.7 MBq	1	Died				
	2	Normal	1.4	47	112	258
	3	Normal	0.8	20	43	67
	4	Normal	0.6	78	96	49
	5	Died				
	6	Normal	1.8	24	41	196
	7	Normal	1.3	63	86	68
Control	15	Normal	0.4	90	125	25

SUPPLEMENTAL TABLE 9. Selected chemistry panel (metabolic profile) and lipid profile of the mice administered with a single dose of $^{212}\text{Pb-L2}$ and control (saline treatment) at one-year post-treatment ($n = 3$).

	Control	Control	Control	0.74 MBq	0.74 MBq	0.74 MBq	0.74 MBq	1.5 MBq	1.5 MBq
Body Weight	55.0	54.8	45.6	47.9	59.4	53.2	50.3	49.4	54.7
Chemistry									
Na	156	157	150	163	163	150	149	154	161
Cl	119	118	113	127	126	116	110	118	125
K	13.6	11.6	11.3	10	11.5	11.9	10.5	8.7	10.9
Blood urea nitrogen (mg/dL)	19	23	18	14	16	18	11	24	44
Creatinine (mg/dL)	0.3	0.2	0.3	0.1	0.2	0.2	0.3	0.2	0.3
Aspartate Aminotransferase (U/L)	247	123	73	116	86	85	82	84	75
Alanine Aminotransferase (U/dL)	72	94	42	79	48	51	23	37	30
Cholesterol (mg/dL)	236	137	210	154	237	214	158	149	170
Triglycerides (mg/dL)	233	109	182	91	177	129	132	95	166
High-density lipoprotein (mg/dL)	114	72	111	86	105	117	86	80	85
Total protein (g/dL)	6.6	6.4	6	NA	5.4	NA	5.6	6.3	6.2
Albumin g/dL	3.2	3	2.6	3.1	2.7	NA	2.7	3	3
Total Bilirubin (mg/dL)	0.3	0.1	0.2	0.1	0.2	NA	0.2	0.2	0.3

SUPPLEMENTAL TABLE 10. Complete blood counts of the mice (n = 3) administered with a single dose of $^{212}\text{Pb-L2}$ and control (saline treatment) at one-year post-treatment.

	control	control	control	$^{212}\text{Pb-L2}$ (0.74 MBq)	$^{212}\text{Pb-L2}$ (0.74 MBq)	$^{212}\text{Pb-L2}$ (0.74 MBq)	$^{212}\text{Pb-L2}$ (1.5 MBq)	$^{212}\text{Pb-L2}$ (1.5 MBq)	
Red blood cells (M/ μL)	10.97	9.35	11.6	5.06	6.37	9.19	8.82	7.84	6.28
Hemoglobin (g/dL)	16.3	13.2	17.9	8	9.9	13.9	13	10.8	8.7
Hematocrit %	54.8	42.4	61.5	26.4	31.8	45.9	42.2	35.6	26.4
Platelets (K/ μL)	1845	2784	1453	1228	1415	1456	1431	1282	1732
White blood cells (K/ μL)	5.51	8.76	27.33	41.8	8.7	9.39	12.52	16.27	10.11
Neutrophils (K/ μL)	3.94	6.3	10.45	9.66	4.75	4.06	7.06	7.31	5.55
Lymphocytes (K/ μL)	1.36	2.01	15.66	17.54	3.62	5	4.78	7.94	3.83
Monocytes (K/ μL)	0.21	0.44	0.85	14.59	0.31	0.27	0.5	0.93	0.66
Reticulocytes (K/ μL)	571.5	373.1	641.5	181.1	250.3	405.3	508.9	327.7	304.6
Urine									
Sp. gravity	1.051	1.035	1.035	>1.060	>1.060	1.047	1.032	1.047	1.044
Protein	2	1.6	1.8	2.1	2.7	1.8	1.7	1.6	1.4

SUPPLEMENTARY TABLE 11. Selected perfused organ weight of the mice (n = 3) administered with a single dose of $^{212}\text{Pb-L2}$ after 13 months post-administration.

	control	control	control	$^{212}\text{Pb-L2}$ (0.74 MBq)	$^{212}\text{Pb-L2}$ (0.74 MBq)	$^{212}\text{Pb-L2}$ (0.74 MBq)	$^{212}\text{Pb-L2}$ (0.74 MBq)	$^{212}\text{Pb-L2}$ (1.5 MBq)	$^{212}\text{Pb-L2}$ (1.5 MBq)
Body Weight	55.012	54.763	45.638	47.908	59.358	53.238	50.26	49.419	54.697
Organ Weights(g) perfused									
Liver g	2.689	2.811	2.881	3.272	3.383	3.016	2.27	2.053	2.446
Liver %	4.89	5.13	6.31	6.83	5.70	5.67	4.52	4.15	4.47
Spleen g	0.137	0.115	0.244	0.494	0.148	0.157	0.162	0.18	0.172
Spleen %	0.25	0.21	0.53	1.03	0.25	0.29	0.32	0.36	0.31
Heart	0.381	0.38	0.566	0.397	0.399	0.351	0.43	0.388	0.283
Right Kidney	0.516	0.526	0.486	0.567	0.668	0.547	0.49	0.413	0.573
Left Kidney	0.501	0.502	0.448	0.576	0.694	0.517	0.459	0.416	0.361

SUPPLEMENTAL EXPERIMENTAL METHODS

Chemistry

Ligand L1 (2) and L5 (3) and intermediates 3 (4) and 4 (3) were synthesized following our previous reports.

(15S,19S)-6,9,17-Trioxo-1-((4-((1,4,7,10-tetrakis(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-2-yl)methyl)phenyl)amino)-1-thioxo-2,5,10,16,18-pentaazahenicosane-15,19,21-tricarboxylic acid (L2). Ligand **L2** was synthesized following the scheme described in Supplemental Figure 1A, as following a method previously reported by us (2). Briefly, commercially available N-Boc-1,4-diaminobutane (81.4 mg, 0.43 mmol in 0.5 mL DMSO) was mixed with S-2-(4-Isothiocyanatobenzyl)-1,4,7,10-tetraaza-1,4,7,10-tetra(2-carbamoylmethyl)cyclododecane] (*p*-SCN-Bn-TCMC) (300 mg, 0.43 mmol in 1.5 mL DMSO) and DIEA (376 μ L, 2.16 mmol) and stirred at 40°C for 4 h. The solvent was evaporated, and the residue was purified by reverse phase C₁₈ flash chromatography (5.5 g, Agilent SF10) using water and acetonitrile (80/20, respectively, and with 0.1% TFA in each solvent). The pulled fractions containing compound **1** were lyophilized. ¹H NMR (DMSO-*d*₆) δ : 9.61 (bs, 1H), 8.06-6.82 (m, 13H), 4.00-3.14 (m, 24H, merged with water peak), 2.93-2.74 (m, 6H), 1.56-1.38 (13H). ESI-MS 736.42 [M+H]⁺. Compound **1** was then treated with ice-cold TFA/CH₂Cl₂ (50/50) solution and left stirring at ambient temperature for 2 h. After solvent removal, the residue was dried under vacuum and purified by C₁₈ flash chromatography (90/10 water/acetonitrile) to obtain compound **2** in moderate yield. ESI-MS: 636.36 [M+1]⁺. To a solution of compound **2** (200 mg, 0.31 mmol in 1 mL DMSO) was added **3** (4) (198 mg, 0.34 mmol in 1 mL DMSO) and TEA (318 mg, 3.15 mmol), which was left stirring at ambient temperature for 2 h. After evaporation of solvent, the residue was dissolved in water and purified by HPLC to obtain **L2**. Elemental Anal. (C₄₈H₈₀N₁₄O₁₃S, 3.5CF₃COOH·H₂O) C, H, N, calculated: 43.74%, H 5.71%, N 12.98% S 2.12%; Found C 43.79%, H 5.64%, N 12.73% S 1.90%.

(21S,25S)-16-(4-Bromobenzyl)-8,15,23-trioxo-1-((4-((1,4,7,10-tetrakis(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-2-yl)methyl)phenyl)amino)-1-thioxo-2,7,16,22,24-pentaazaheptacosane-21,25,27-tricarboxylic acid. (L3). L3 was synthesized following the same method as L2 by using the intermediate compound 4 as shown in Supplemental Fig. 1C.

Di-tert-butyl (((S)-6-(N-(4-bromobenzyl)-8-((2,5-dioxopyrrolidin-1-yl)oxy)-8-oxooctanamido)-1-(tert-butoxy)-1-oxohexan-2-yl)carbamoyl)-L-glutamate (Compound 4). Compound 5, urea-lysine intermediate di-tert-butyl-(((S)-1-(tert-butoxy)-6-((4-bromobenzyl)amino)-1-oxohexan-2-yl)carbamoyl)-L-glutamate was synthesized following a literature method after minor modification (5). Compound 4 was synthesized following a route as shown in Fig. 1C. A solution of 5 (0.190 g, 0.29 mmol), Et₃N (0.029 g, 0.29 mmol) and DMF (1 mL) was added dropwise to a stirred solution of disuccinimidyl suberate (0.223 g, 0.61 mmol) in DMF (1 mL). The reaction mixture was stirred overnight, concentrated and purified by flash column chromatography eluting with 30% acetonitrile/CH₂Cl₂ provided 0.120 g (46%) of oily material, compound 4. ESMS *m/z* 911.3 (M + H)⁺.

(((2S)-6-(N-(4-Bromobenzyl)-6-(3-((4-((1,4,7,10-tetrakis(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-2-yl)methyl)phenyl)thioureido)hexanamido)-1-hydroxyhexan-2-yl)carbamoyl)-L-glutamic acid (L4). L4 was synthesized following a scheme as shown in Fig. 2B. A mixture of 6-(Boc-amino)hexanoic acid (0.09 g, 0.40 mmol), TSTU (0.121 g, 0.40 mmol) and DIPEA (0.103 g, 0.80 mmol) were stirred in DMF (1 mL) at RT for 1 h. Compound 5 (0.264 g, 0.40 mmol) was added dropwise after dilution with DMF (1 mL). The reaction mixture was stirred for 4 h, concentrated and purified by C₁₈ column chromatography eluting with 100% acetonitrile (in 0.1% TFA) provided 0.151 g (44%) of oily material. ¹H NMR (500 MHz, DMSO-*d*6) δ ppm 7.95 (s, 1H), 7.40 (d, *J* = 10 Hz, 1H), 7.34 (d, *J* = 10 Hz, 1H), 7.24 (s, 1H), 7.04 (d, *J* =

5 Hz, 1H), 6.97 (d, J = 10 Hz, 1H), 5.48-5.44 (m, 1H), 4.87-4.83 (m, 1H), 4.48-4.36 (m, 2H), 4.26-4.21 (m, 2H), 3.66-3.63 (m, 1H), 3.12-2.95 (m, 4H), 2.90 (s, 1H), 2.81 (s, 1H), 2.73 (s, 2H), 2.33-2.27 (s, 1H), 2.26-2.23 (m, 3H), 2.00-1.98 (m, 1H), 1.77 (m, 1H), 1.66-1.60 (m, 2H), 1.37 (s, 36H), 1.26-1.07 (m, 2H); ESMS m/z : 843.1 ($M + H$)⁺. A cold solution of 50% TFA/CH₂Cl₂ (2 mL) was added to that oily material (0.145 g, 0.17 mmol) and stirred at RT for 2 h. The reaction mixture was concentrated and purified by C₁₈ column chromatography eluting with 40% acetonitrile/water (0.1 % TFA in each) and lyophilized to provide 0.067 g (67%) of white solid product as compound 8. ¹H NMR (500 MHz, DMSO- δ) δ ppm 7.55 (d, J = 5.0 Hz, 1H), 7.48 (d, J = 5.0 Hz, 1H), 7.19-7.15 (m, 2H), 4.62-4.53 (m, 2H), 4.33-4.27 (m, 2H), 3.40 (s, 1H), 2.98-2.92 (m, 2H), 2.83 (s, 1H), 2.56 (s, 1H), 2.44 (s, 3H), 2.16 (bs, 1H), 1.93-1.84 (m, 2H), 1.74 (s, 2H), 1.67-1.60 (m, 5H), 1.41-1.40 (m, 2H); ESMS m/z : 574.1 ($M + H$)⁺. A reaction mixture of TCMC-Bn-SCN (0.101 g, 0.12 mmol in 200 μ L DMSO), 8 (0.069 g, 0.08 mmol in 100 μ L DMSO) and DIPEA (0.102 g, 0.79 mmol) were stirred at RT for 3 h. The reaction mixture was concentrated and purified by HPLC to provide the desired ligand L4.

(14S,18S)-9-(4-Bromobenzyl)-2,8,16-trioxo-1-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)-3,9,15,17-tetraazaicosane-14,18,20-tricarboxylic acid (L5).

L5 was synthesized following the same scheme as used for L4, shown in Fig. 2B. A mixture of Boc-5-amino valeric acid (0.087 g, 0.40 mmol), TSTU (0.121 g, 0.40 mmol) and DIPEA (0.103 g, 0.80 mmol) were stirred in DMF (1 mL) at RT for 1 h. Compound 5 (0.264 g, 0.40 mmol) was added dropwise after dilution with DMF (1 mL). The reaction mixture was stirred for 4 h, concentrated and purified by C₁₈ column chromatography eluting with 100% acetonitrile (in 0.1% TFA) provided 0.151 g (44%) of oily material. ESMS m/z : 828.1 ($M + H$). A cold solution of 50% TFA/CH₂Cl₂ (2 mL) was added to the oily material (0.14 g, 0.17 mmol) and stirred at RT for 2 h. The reaction mixture was concentrated and purified by C₁₈ column chromatography eluting with 40% acetonitrile/water (0.1 % TFA in each) and lyophilized to provide 0.06 g of white solid

product as compound 9. ESMS *m/z*: 560.5 (M + H)⁺. A reaction mixture of DOTA-NHS-ester (0.090 g, 0.12 mmol in 200 μL DMSO), 9 (0.069 g, 0.08 mmol in 100 μL DMSO) and DIPEA (0.102 g, 0.79 mmol) were stirred at RT for 3 h. The reaction mixture was concentrated and purified by HPLC to provide the desired ligand L5.

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