Supporting Information

General consideration

Compound **1** was synthesized according to published procedure.[1] Cyclic RGDyK (RGD-containing peptide) and neurotensin peptide (NT) (Cys-Pro-Arg-Arg-Pro-Tyr-*tert*Leu-Leu) was purchased from CSBio. *N*-Succinimidyl-S-acetylthioacetate (SATA) and Hydroxylamine.HCl was purchased from Thermo Scientific. Glutamate-urea-lysine (GUL) (PSMA inhibitor) was purchased from FutureChem Co., Ltd. Di-*iso*-propylethylamine (DIEA) was purchased from Sigma-Aldrich. High-resolution mass spectrometry was performed by mass spectrometry core laboratory, department of chemistry, University of North Carolina at Chapel Hill.

Synthetic Methodology

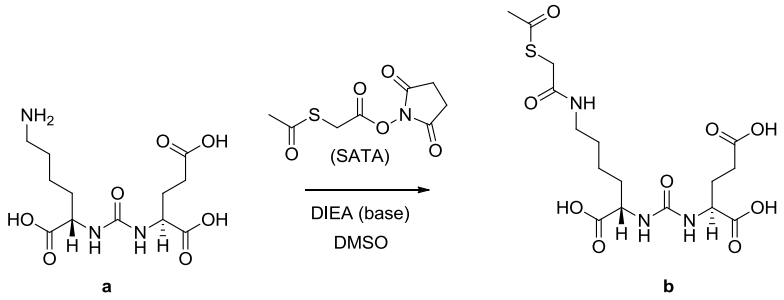
HPLC Methods

Method A: Phenomenex, Kinetex® 5µm EVO C18 100 Å, 250 x 4.6 mm LC Column. Solvent A: 0.1%TFA water; Solvent B: 0.1%TFA acetonitrile; 0 to 2 min: isocratic elution at 5% solvent B, 2 to 22 min, 5% to 95% solvent B. Flow rate: 1 mL/min, column temperature: 19 to 21 °C.

Method B: Phenomenex, Kinetex® 5µm EVO C18 100 Å, 250 x 4.6 mm LC Column. Solvent A: 0.1%TFA water; Solvent B: 0.1%TFA acetonitrile; 0 to 2 min: isocratic elution at 25% solvent B, 2 to 22 min, 25% to 40% solvent B. Flow rate: 1 mL/min, column temperature: 19 to 21 °C.

Synthesis of the precursors

Synthesis of (11S,15S)-2,5,13-trioxo-3-thia-6,12,14-triazaheptadecane-11,15,17-tricarboxylic acid (**b**)



To a solution mixture of Glutamate-urea-lysine (**a**) (2.0 mg, 6.26 µmol) and N-Succinimidyl-S-acetylthioacetate (SATA) (2.0 mg, 8.65 µmol) in DMSO (100 µL) was added Di-*iso*-propylethylamine (DIEA) (2 µL, 11.50 µmol). The resulting mixture was incubated at room temperature for 2 h. Following reaction, the mixture was purified by HPLC using **method A** to isolate chemically pure **b** (2.2 mg, 5.05 µmol). The identity of **b** was confirmed with high-resolution mass spectrometry. HRMS calculated for $C_{16}H_{26}N_3O_9S$ ($[M+H]^+$):436.1390, found: 436.1377.

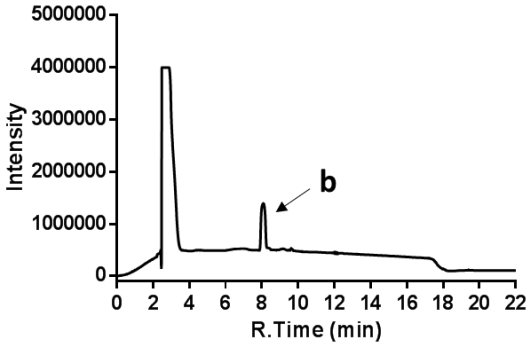
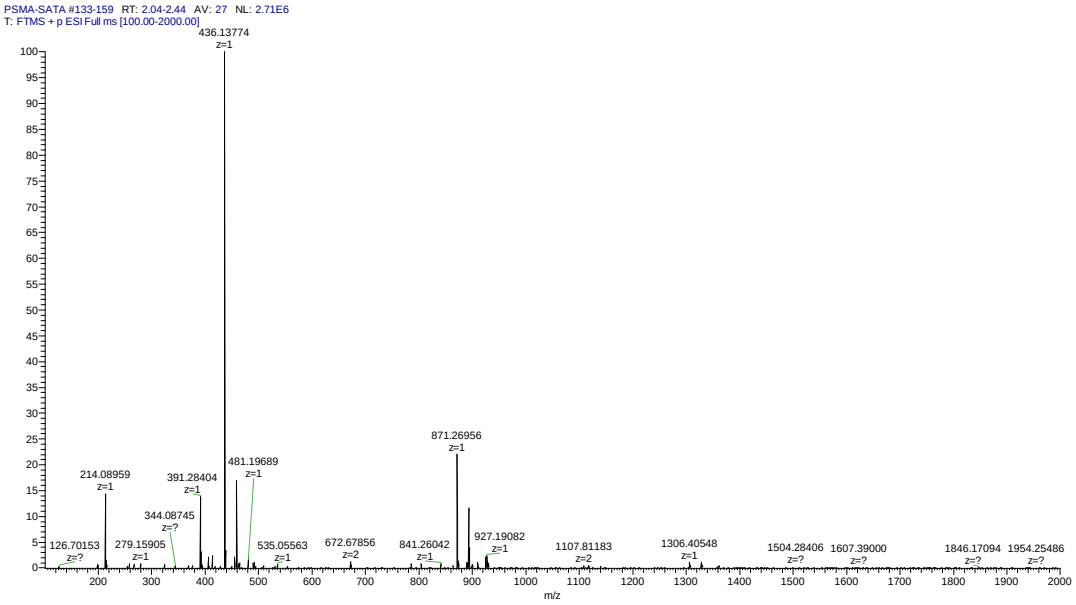


Figure S1. UV-HPLC profile (UV detection at 210 nm) of **b**.

Full scan



Zoom Inset

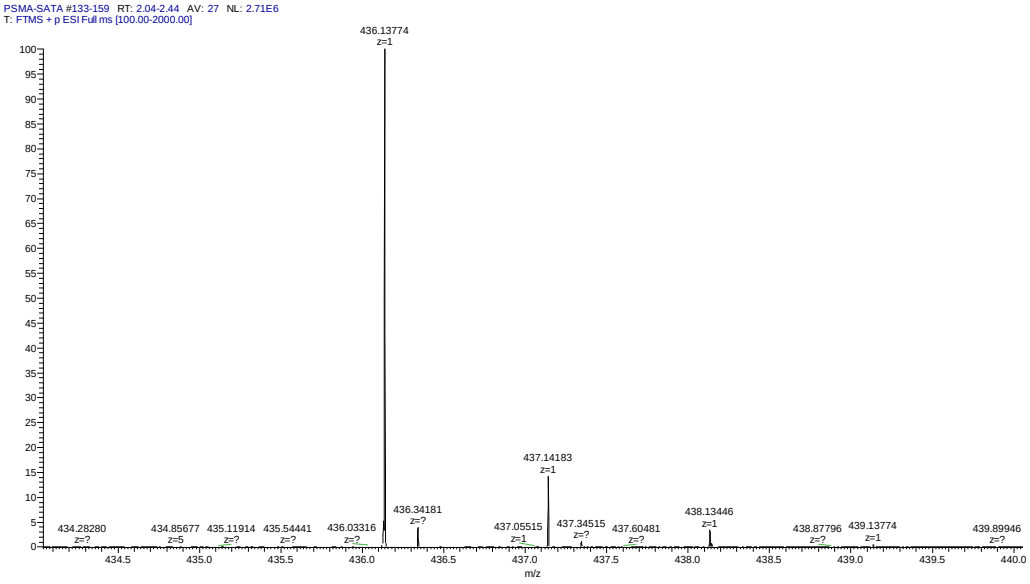
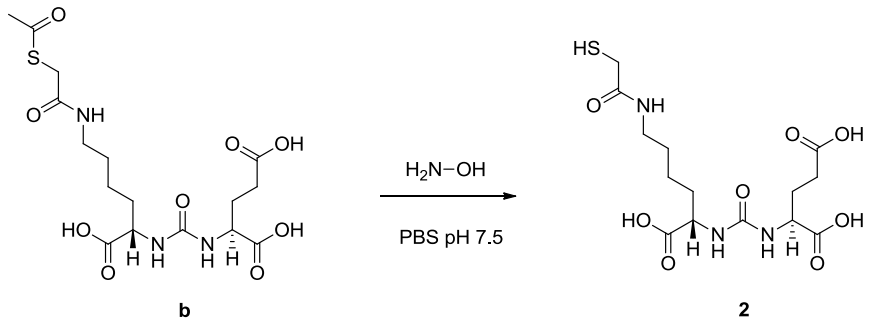


Figure S2. Positive-mode electrospray ionization (ESI^+) mass spectra of **b**.

Synthesis of (((S)-1-carboxy-5-(2-mercaptoacetamido)pentyl)carbamoyl)-L-glutamic acid (**2**)



To a solution of **b** (2.2 mg, 5.05 μmol) in phosphate buffer solution pH 7.5 (100 μL) was added hydroxylamine.HCl (1.0 mg, 14.40 μmol). The pH of the mixture was re-adjusted to pH 7.5 with 0.1 N NaOH. The resulting mixture was then incubated at room temperature for 2 h. Following reaction, the mixture was purified by HPLC using **method A** to isolate chemically pure **2** (1.9 mg, 4.83 μmol). The identity of **2** was confirmed with high-resolution mass spectrometry. HRMS calculated for $C_{14}H_{24}N_3O_8S$ ($[M+H]^+$):394.1284, found: 394.1276.

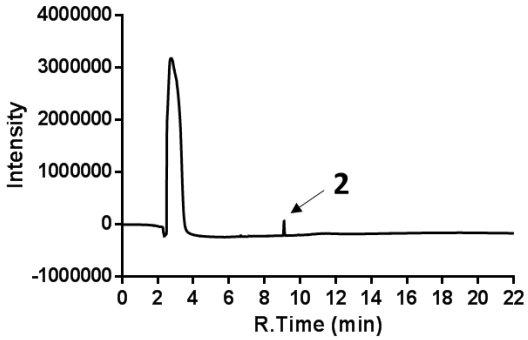
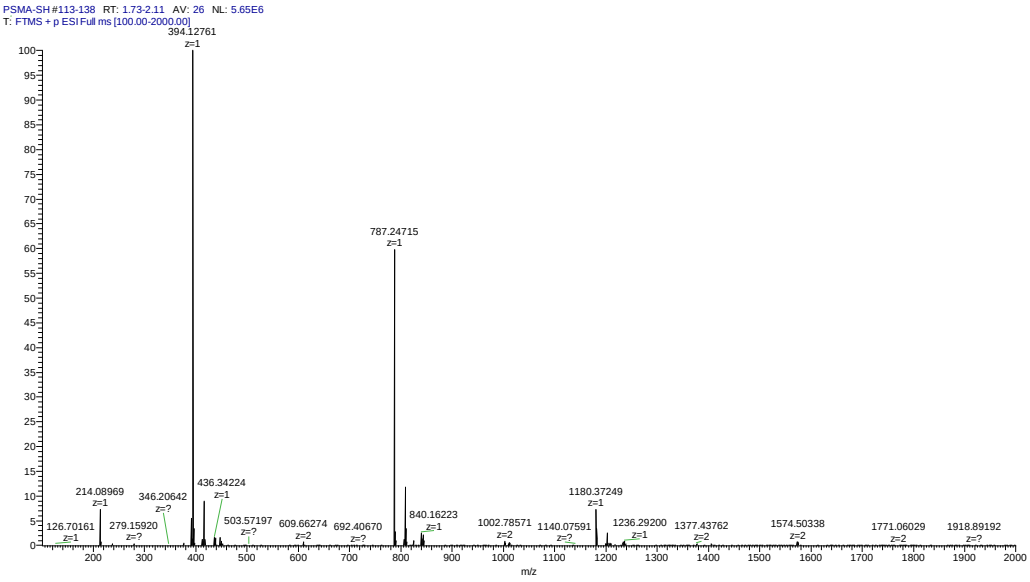


Figure S3. UV-HPLC profile (UV detection at 210 nm) of **2**.

Full scan



Zoom Inset

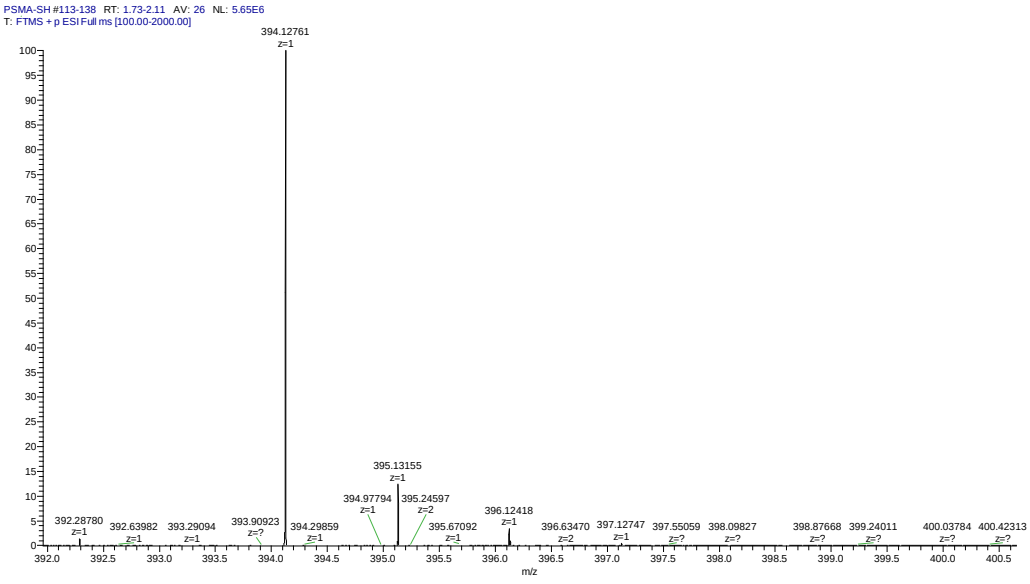
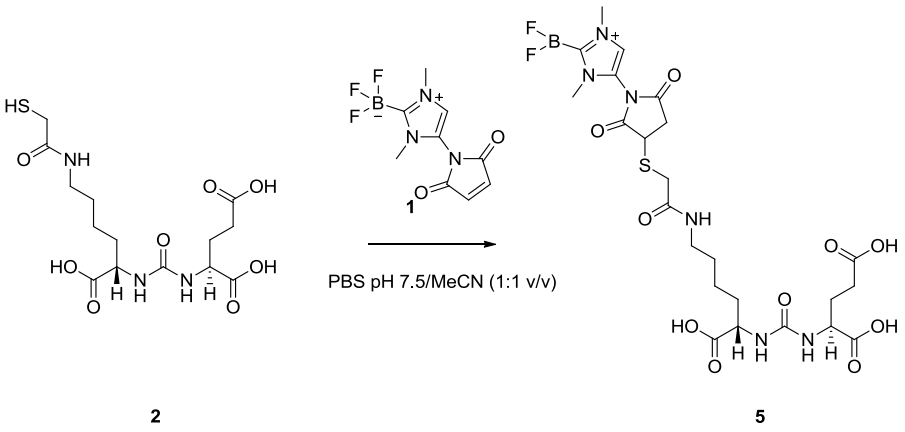


Figure S4. Positive-mode electrospray ionization (ESI^+) mass spectra of **2**.

Synthesis of NHC-BF_3 conjugated glutamate-urea-lysine (**5**)



To a solution of **2** (1.9 mg, 4.83 μmol) in phosphate buffer solution pH 7.5 (50 μL) was added a solution of **1** (2.0 mg, 7.72 μmol) in MeCN (50 μL). The solution mixture was incubated at room temperature for 2h. Following reaction, the mixture was purified by HPLC using **method B** to isolate chemically pure **5** (2.3 mg, 3.53 μmol). The identity of **5** was confirmed with high-resolution mass spectrometry. HRMS calculated for $C_{23}H_{33}BF_3N_6O_{10}S$ ($[M+H]^+$): 653.2024, found: 653.1999.

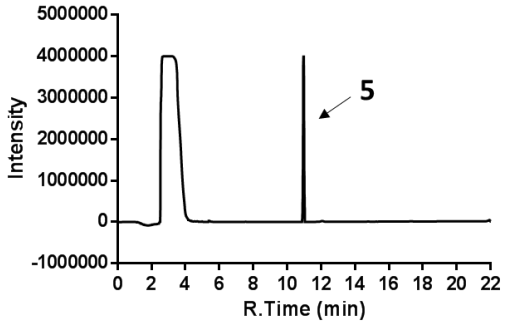
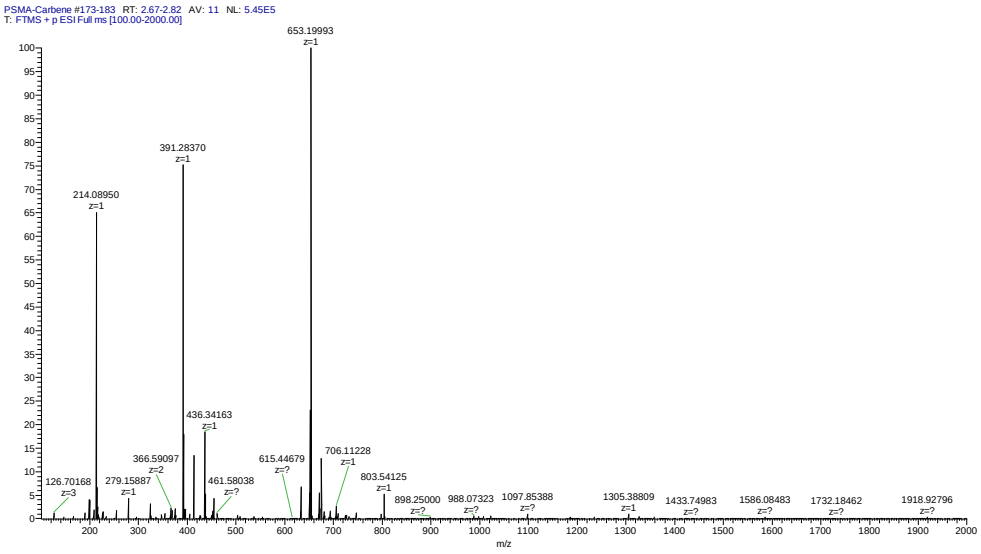


Figure S5. UV-HPLC profile (UV detection at 210 nm) of **5**.

Full scan



Zoom inset

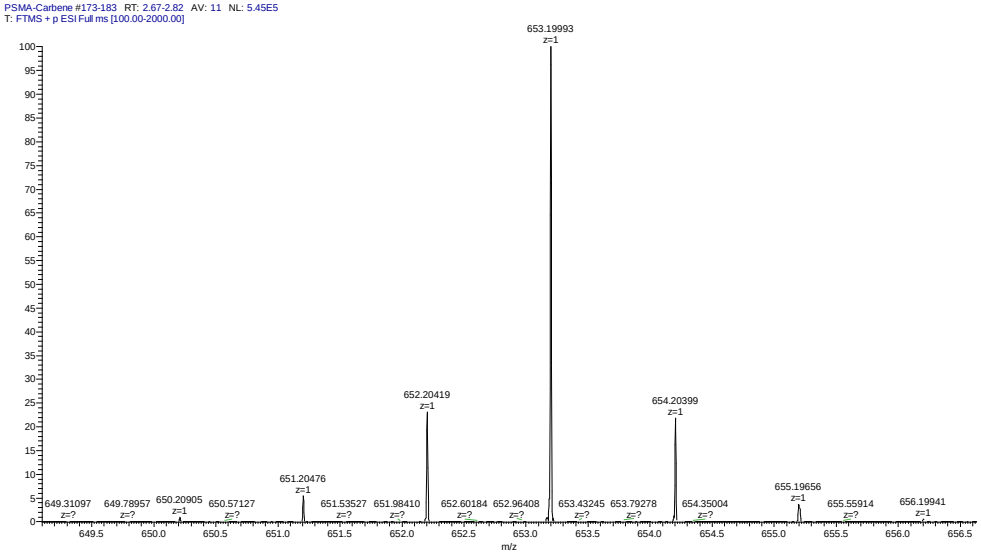
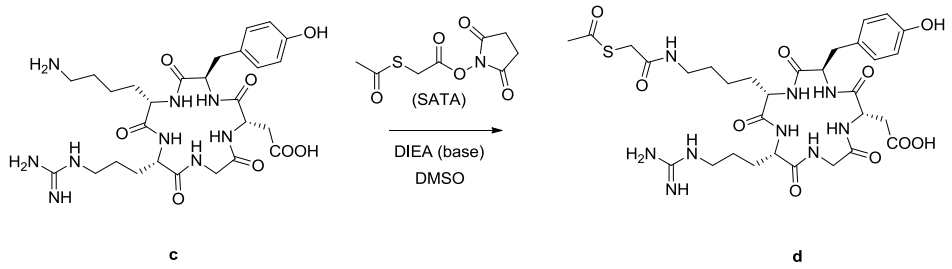


Figure S6. Positive-mode electrospray ionization (ESI^+) mass spectra of **5**.

Synthesis of 2-((2S,5R,8S,11S)-8-(4-(2-(acetylthio)acetamido)butyl)-11-(3-guanidinopropyl)-5-(4-hydroxybenzyl)-3,6,9,12,15-pentaoxo-1,4,7,10,13-pentaazacyclopentadecan-2-yl)acetic acid (**d**)



To a solution mixture of c(RGDyK)(**c**) (2.0 mg, 3.23 μmol) and N-Succinimidyl-S-acetylthioacetate (SATA) (1.5 mg, 4.33 μmol) in DMSO (50 μL) was added Di-*iso*-propylethylamine (DIEA) (1 μL, 5.75 μmol). The resulting mixture was incubated at room temperature for 2 h. Following reaction, the mixture was purified by HPLC using **method A** to isolate chemically pure **d** (2.1 mg, 2.85 μmol). The identity of **d** was confirmed with high-resolution mass spectrometry. HRMS calculated for $C_{31}H_{46}N_9O_{10}S$ ($[M+H]^+$):736.3088, found: 736.3045.

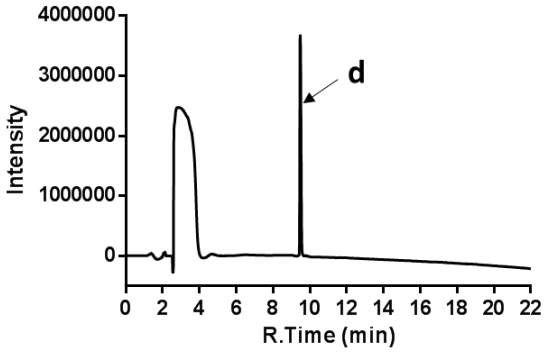
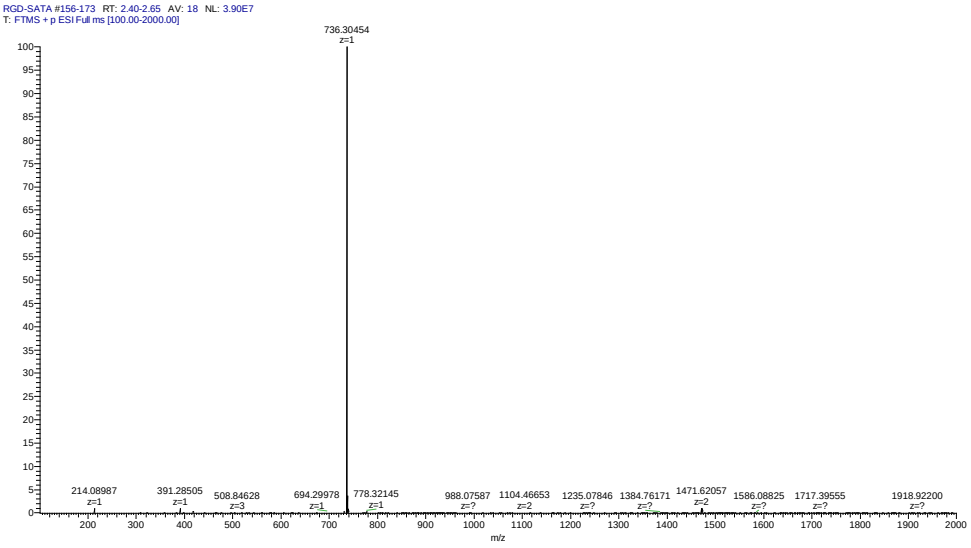


Figure S7. UV-HPLC profile (UV detection at 210 nm) of **d**.

Full scan



Zoom inset

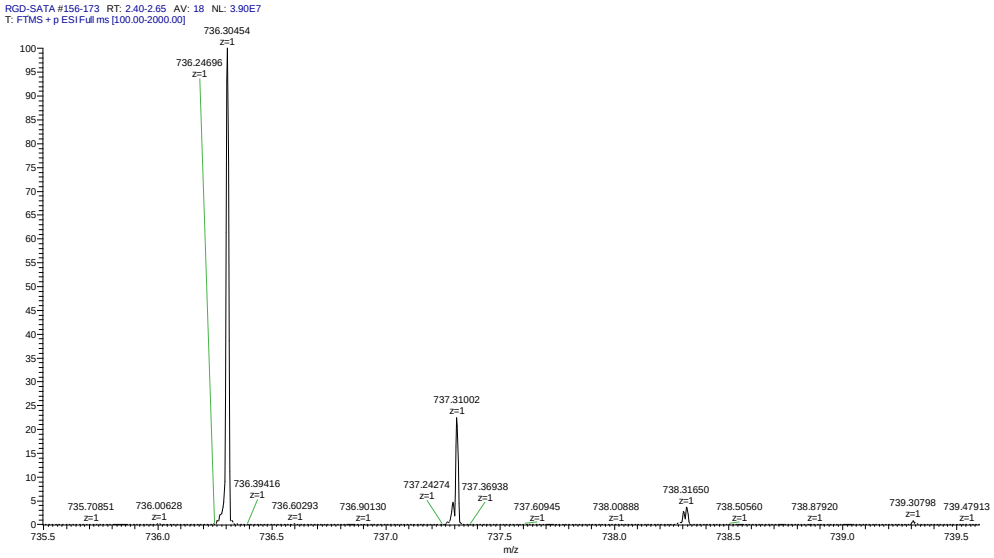
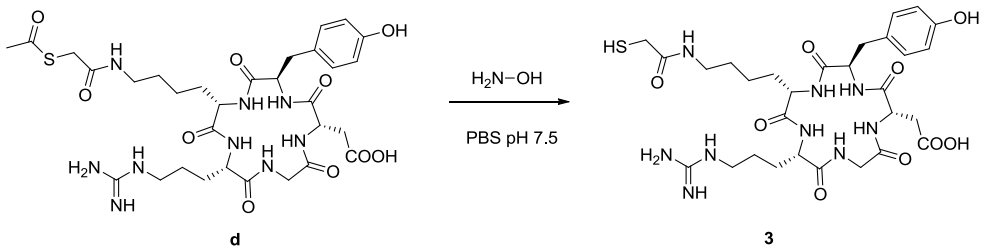


Figure S8. Positive-mode electrospray ionization (ESI^+) mass spectra of **d**.

Synthesis of 2-((2S,5R,8S,11S)-11-(3-guanidinopropyl)-5-(4-hydroxybenzyl)-8-(4-(2-mercaptoacetamido)butyl)-3,6,9,12,15-pentaoxo-1,4,7,10,13-pentaazacyclopentadecan-2-yl)acetic acid (**3**)



To a solution of **d** (2.1 mg, 2.85 μmol) in phosphate buffer solution pH 7.5 (100 μL) was added hydroxylamine.HCl (1.0 mg, 14.40 μmol). The pH of the mixture was re-adjusted to pH 7.5 with 0.1 N NaOH. The resulting mixture was then incubated at room temperature for 2 h. Following reaction, the mixture was purified by HPLC using **method A** to isolate chemically pure **3** (1.8 mg, 2.60 μmol). The identity of **3** was confirmed with high-resolution mass spectrometry. HRMS calculated for $C_{29}H_{44}N_9O_9S$ ($[M+H]^+$):694.2983, found: 694.2944.

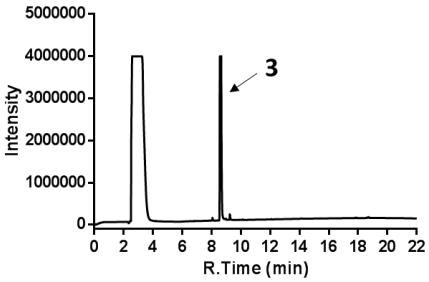
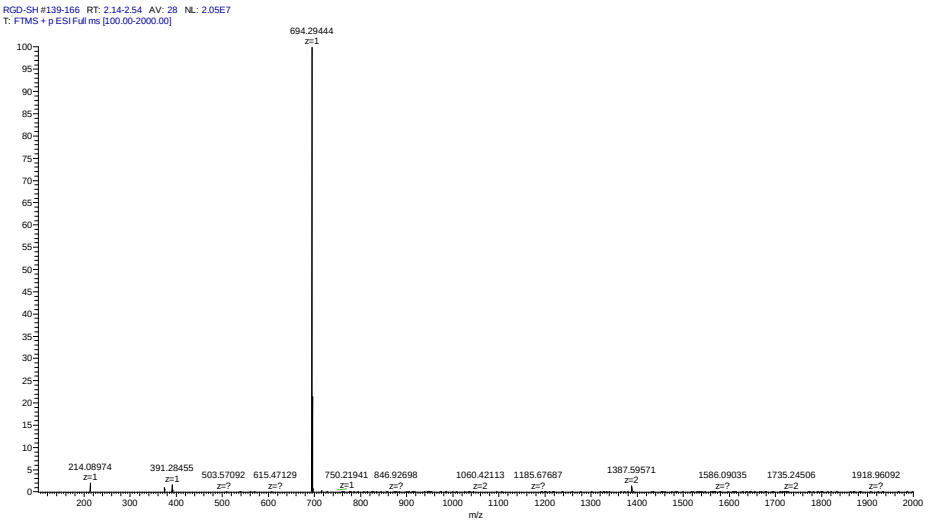


Figure S9. UV-HPLC profile (UV detection at 210 nm) of **3**.

Full scan



Zoom inset

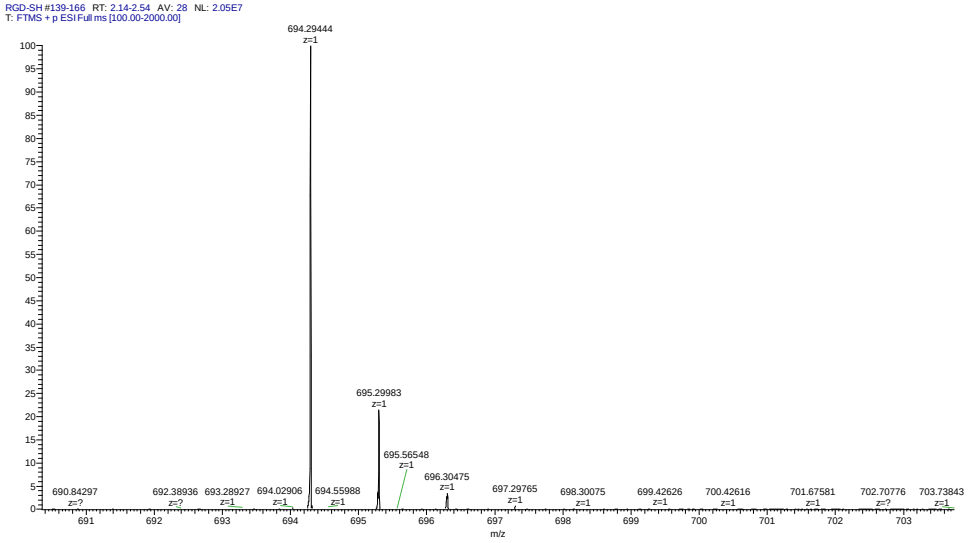
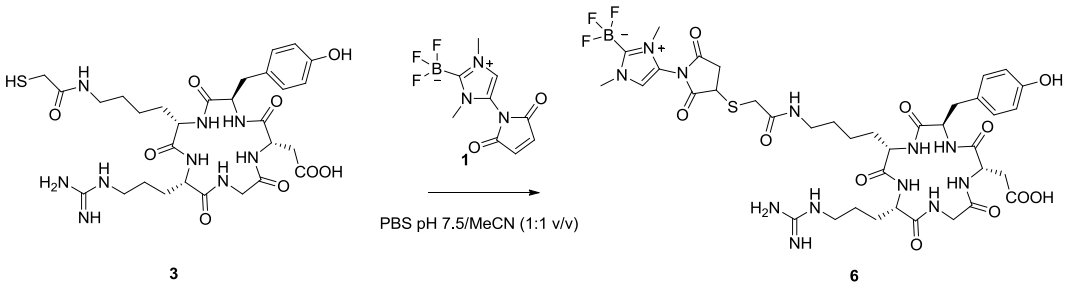


Figure S10. Positive-mode electrospray ionization (ESI^+) mass spectra of **3**.

Synthesis of NHC-BF_3 conjugated cyclic Arg-Gly-Asp-containing peptide (**6**)



To a solution of **3** (1.8 mg, 2.60 μmol) in phosphate buffer solution pH 7.5 (50 μL) was added a solution of **1** (2.0 mg, 7.72 μmol) in MeCN (50 μL). The solution mixture was incubated at room temperature for 2h. Following reaction, the mixture was purified by HPLC using **method A** to isolate chemically pure **6** (2.0 mg, 2.10 μmol). The identity of **6** was confirmed with high-resolution mass spectrometry. HRMS calculated for $C_{38}H_{53}BF_3N_{12}O_{11}S$ ($[M+H]^+$): 953.3723, found: 953.3689.

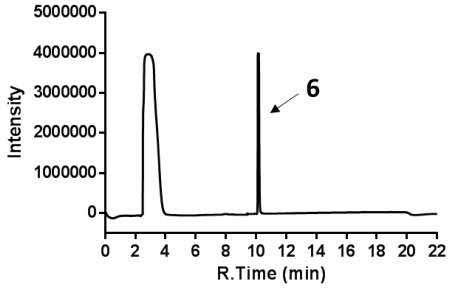
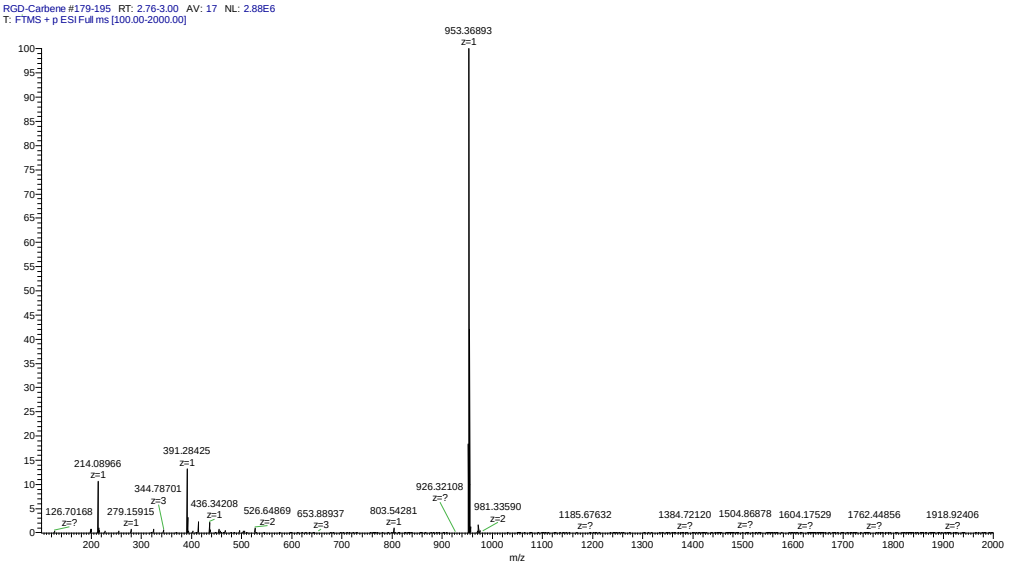


Figure 11. UV-HPLC profile (UV detection at 210 nm) of **6**.

Full scan



Zoom inset

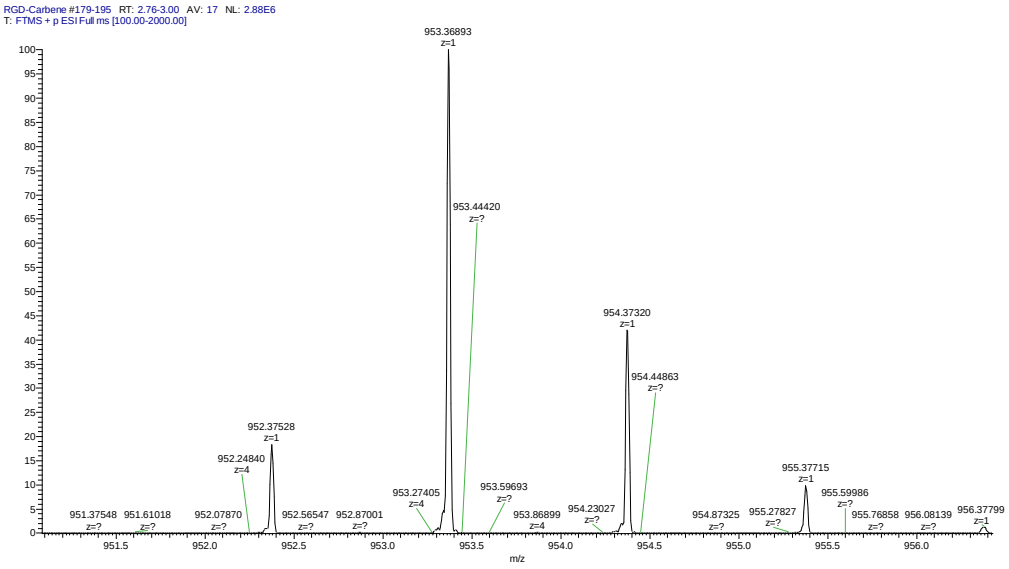
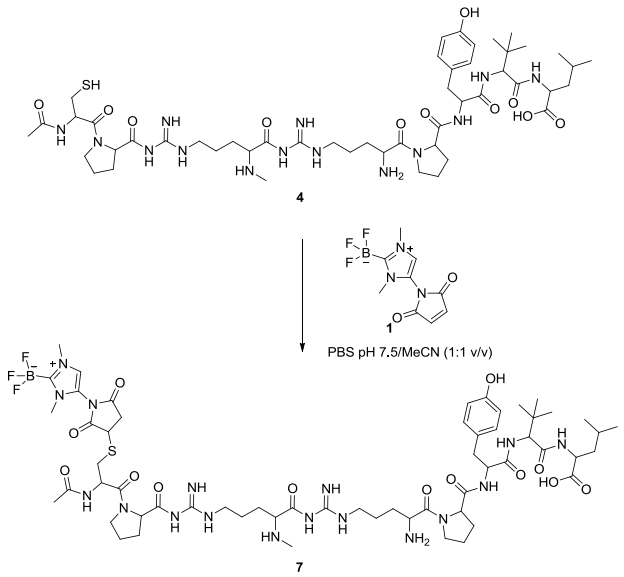


Figure S12. Positive-mode electrospray ionization (ESI^+) mass spectra of **6**.

Synthesis of NHC-BF_3 conjugated neurotensin peptide (**7**)



To a solution of neurotensin peptide **4** (3 mg, 2.80 μmol) in phosphate buffer solution pH 7.5 (50 μL) was added a solution of **1** (2.0 mg, 7.72 μmol) in MeCN (50 μL). The solution mixture was incubated at room temperature for 2h. Following reaction, the mixture was purified by HPLC using **method B** to isolate chemically pure **7** (2.5 mg, 1.88 μmol). The identity of **6** was confirmed with high-resolution mass spectrometry. HRMS calculated for $C_{58}H_{90}BN_{17}O_{13}SF_3$ ($[M]^+$): 1332.6670, found: 1332.6725, calculated for $C_{58}H_{91}BN_{17}O_{13}SF_3$ ($[M+H]^{2+}$) m/z : 666.8374, found 666.8360.

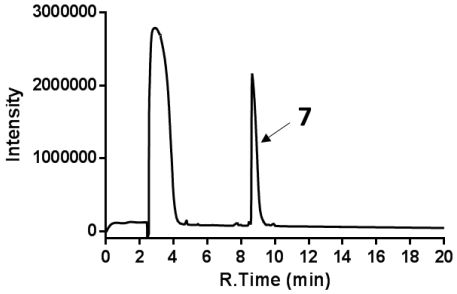
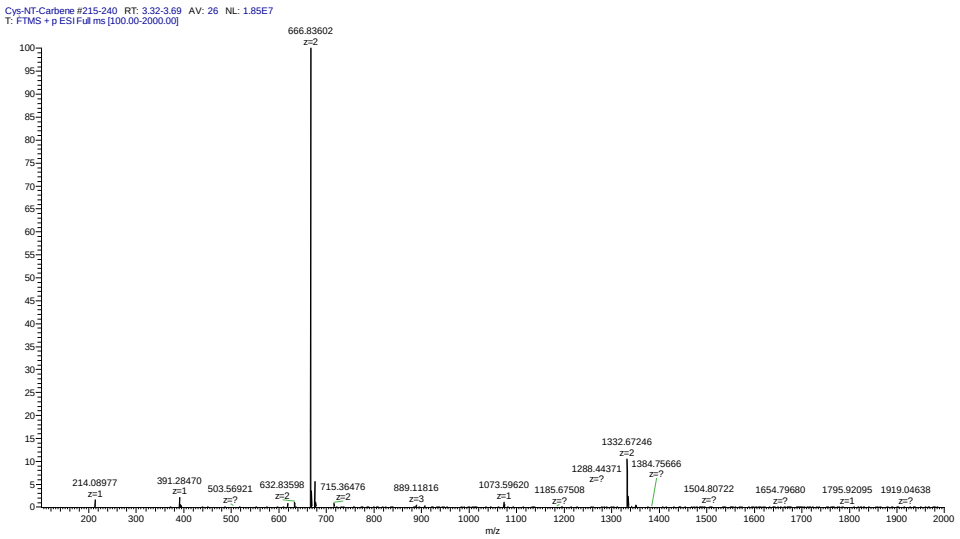


Figure 13. UV-HPLC profile (UV detection at 210 nm) of **7**.

Full scan



Zoom inset

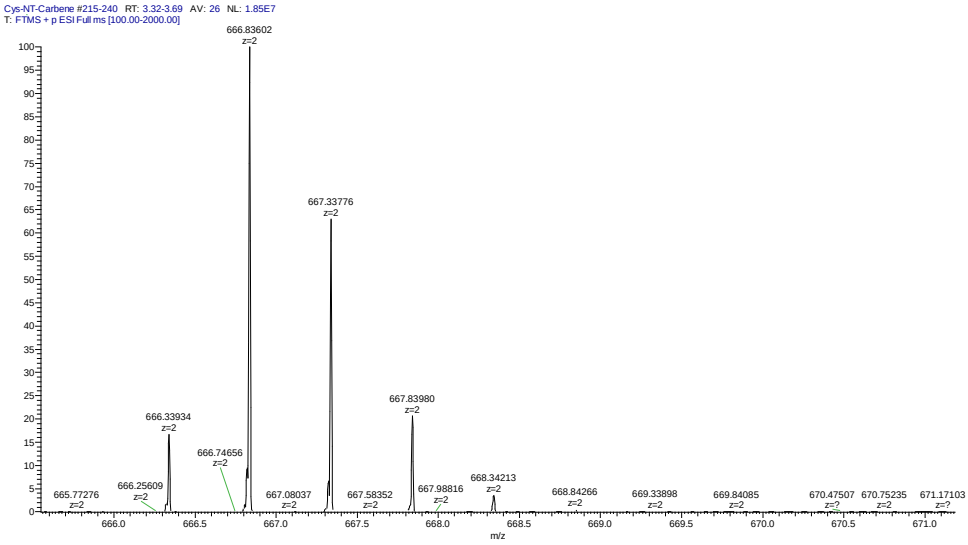


Figure S14. Positive-mode electrospray ionization (ESI^+) mass spectra of **7**.

Radiochemistry experiments

All chemicals are analytical grade and used without further purification. Analytical reversed-phase high-performance liquid chromatography (HPLC) was accomplished on a SHIMADZU chromatography system (Model CBM-20A). The λ absorbance detector and the model 2200 scaler ratemeter radiation detector were added to the HPLC system. HPLC was performed on a Phenomenex, Kinetex® 5µm EVO C18 100 Å, 250 x 4.6 mm LC Column with a flow of 1 ml/min.

Radiochemistry

The radiolabeling reactions were performed using the following protocol. The lyophilized **5**, **6** or **7** powder (~ 0.30 µmol) was mixed with $SnCl_4$ (1 µL) in 25 µL of anhydrous MeCN. The resulting solution was then combined with [^{18}F]-TBAF in MeCN. After incubating at 70 °C for 10 min, the reaction was quenched by adding 1 mL of water. The mixture was passed through a Sep-Pak light alumina N cartridge. An aliquot of aqueous fraction was analyzed by HPLC using **method A** for [^{18}F]-**6** and **method B** for [^{18}F]-**5** and [^{18}F]-**7**. The identity of [^{18}F]-NHC-BF_3 conjugates (**[^{18}F]-5**, **[^{18}F]-6,** and **[^{18}F]-7**) was confirmed by the comparison of their retention times with those of reference compounds (**5**, **6** and **7**) (Figure S15).

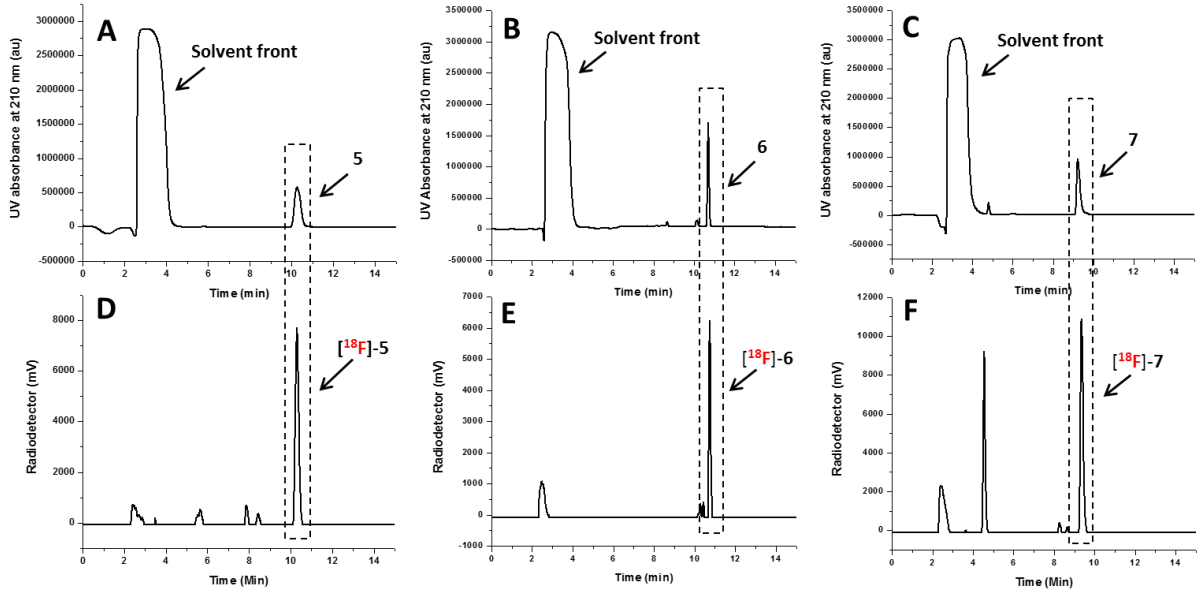


Figure S15. UV HPLC profiles of **5** (**A**), **6** (**B**), and **7** (**C**) as the reference compounds and radio HPLC profiles of the crude **[^{18}F]-5** (**D**), **[^{18}F]-6** (**E**) and **[^{18}F]-7** (**F**) obtained after passing through Sep-Pak alumina N cartridge.

Table S1. radiosynthesis table for **[^{18}F]-5**, **[^{18}F]-6**, and **[^{18}F]-7**.

Entry	cpd	Radiochemical yield determination [a]			Specific activity determination [b]		
		Starting ^{18}F-activity (GBq)	^{18}F-activity of the isolated product (GBq)	Radiochemical yield (%)	^{18}F-Activity of the product at the end of synthesis (EOS) (GBq)	Amount of cpd (μmol)	Specific activity (GBq/μmol)
1	**5**	5.92	1.75	29.6	0.078	0.013	6.0
2	**6**	5.62	1.44	25.6	0.096	0.027	3.5
3	**7**	5.85	1.25	21.4	0.085	0.025	3.4

[a]Radiochemical yield (RCY) is determined by dividing the ^{18}F-activity of the isolated product by the starting ^{18}F activity. [b]A fraction of isolated ^{18}F-product was re-injected to HPLC for specific activity determination. Then, the specific activity (SA) is determined by dividing the isolated product activity by the amount of the product (based on the integration of UV-HPLC profile and compare it with the standard calibration curve). The radiochemical yields were decay corrected. The specific activities were measured at the end of synthesis (EOS).

In vitro stability test

After HPLC purification, a fraction of purified **[^{18}F]-5**, **[^{18}F]-6,** or **[^{18}F]-7** were re-injected into the HPLC to confirm that only single radio peak was obtained at the starting point. Then, the probes were adjusted to pH 7 with 0.1N NaOH. Then, 10X PBS was added to each solution to reconstruct the solution to 1X PBS. After 1 hour and 2 hours incubation at room temperature, a fraction of each probe (0.0019 GBq) was injected into the HPLC. The radio purity was calculated based on the integration of the product peak and other minor peaks.

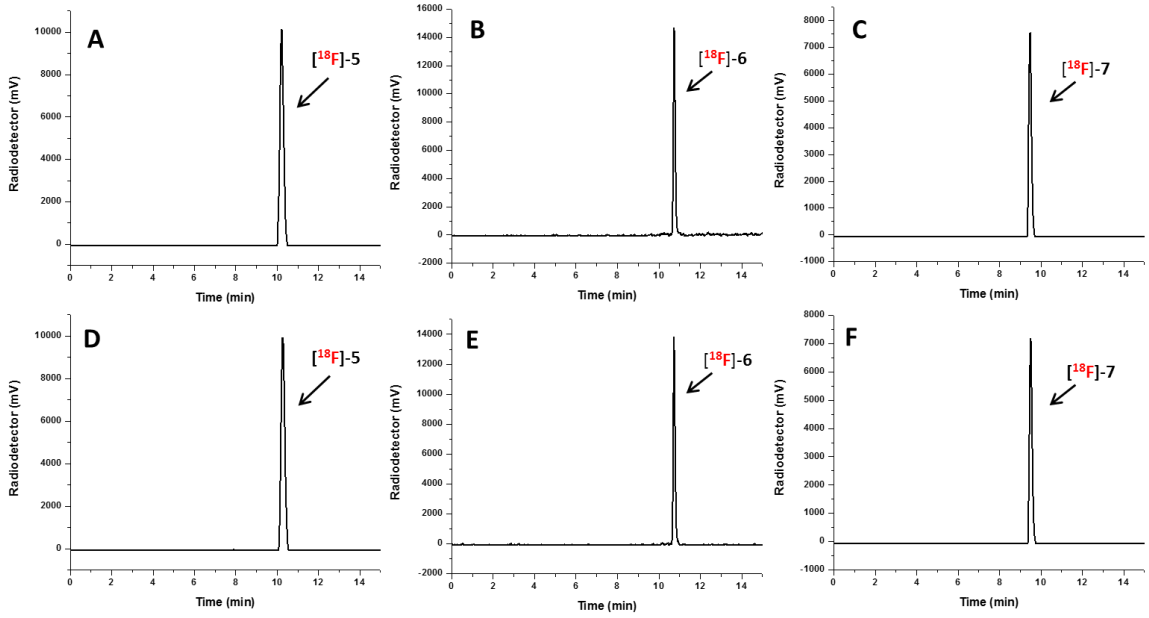


Figure S16. Radio-HPLC profiles of **[^{18}F]-5**, **[^{18}F]-6**, and **[^{18}F]-7** after incubation in phosphate buffer solution (PBS) pH=7.5 for 1 hour (**A**, **B**, and **C**) and 2 hours (**D**, **E**, and **F**)

***In vivo* PET/CT Imaging**

For PET image acquiring, each nude mice was injected with 0.0037 GBq of **[^{18}F]-5**, **[^{18}F]-6,** or **[^{18}F]-7** in 1X PBS pH 7.5 (300 μL) *via* the tail vein. At each post-injection time point, the mice were anesthetized using isoflurane (2% in oxygen), then placed on the imaging cradle with body temperature maintained. The static PET/CT acquisition were then achieved and reconstructed for analysis.

PET quantifications

For each microPET scan, regions of interest (ROIs) were drawn over the normal tissues and major organs using AMIDE 0.9.0 software on decay-corrected coronal images. The average radioactivity concentration (accumulation) within an organ was obtained from the mean pixel values within the multiple region of interest volume, which were converted to counts/mL/min using a conversion factor. Assuming a tissue density of 1 g/mL, the ROIs were converted to counts/g/min and then divided by the administered activity to obtain an imaging derived %ID/g.

Table S2. PET quantification (%ID/g) of **[^{18}F]-6** in nude mice bearing U87MG at 0.5 h post-injection.

Organs	**[^{18}F]-6** (%ID/g) (n=3)
Tumor	1.50 ± 0.01
Liver	1.189 ± 0.04
Kidneys	2.77 ± 0.23
Muscle	0.15 ± 0.01

Table S3. PET quantification (%ID/g) of **[^{18}F]-7** in nude mice bearing PANC1 at 1 h post-injection.

Organs	**[^{18}F]-7** (%ID/g) (n=3)
Tumor	0.54 ± 0.03
Liver	0.086 ± 0.006
Kidneys	0.94 ± 0.10
Muscle	0.059 ± 0.006

1 K. Chansaenpak, M. Wang, Z. Wu, R. Zaman, Z. Li and F. P. Gabbai, *Chem. Commun.*, 2015, **51**, 12439-12442.