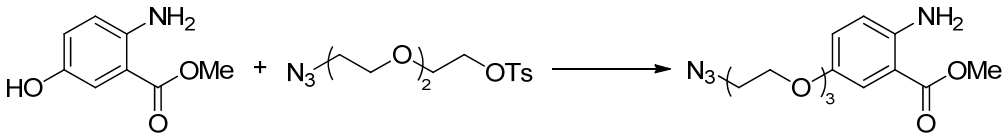
Supplementary Methods

Synthesis of Bodipy-ANA-12. All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out in oven dried or flamed vessels and performed under argon. Solvents were dried and purified by conventional methods prior use. Dichloromethane was distilled from CaH_2. Flash column chromatography was performed with Merck silica gel 60, 0.040-0.063 mm (230-400 mesh) (1). Merck aluminum backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualized by staining with $KMnO_4$.

NMR spectra were recorded at 300 MHz for ^1H. Conditions are specified for each spectrum (temperature 25°C unless specified). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Chemical shifts (δ) are given in ppm relative to the resonance of their respective residual solvent peak, $CHCl_3$ (7.27 ppm, ^1H).

Methyl 2-amino-5-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)benzoate (1):



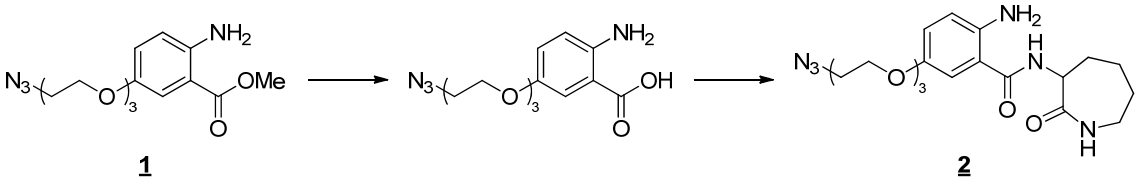
1

In a dry flask under argon, methyl 2-amino-5-hydroxybenzoate **[**500 mg, 2.99 mmol; synthesized according to (2)], 2-(2-azidoethoxy)ethyl 4-methylbenzenesulfonate [985 mg, 2.99 mmol; synthesized according to (3)], K_2CO_3 (413 mg, 2.99 mmol), molecular sieves 4Å (400 mg) were introduced in dried DMF (10 mL). The solution was stirred at 90°C for 7h. The reaction mixture was cooled to room temperature and H_2O (10 mL) was added. The suspension obtained was extracted with EtOAc (3 x 10 ml) and organic layer was washed with water (3 x 10 mL). The organic layer was dried over dry Na_2SO_4. After filtration and

evaporation, compound **X** was purified by flash chromatography (60:40 pentane-EtOAc) to give **1** (174 mg, 18 %) as a white solid.

Rf = 0.47 (90:10 CH_2Cl_2/MeOH); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.39 (d, *J* = 8.4 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.9 Hz, 1H), 5.45 (br s, 2H), 4.09 (m, 2H), 3.88 (s, 3H), 3.85 (3, 2H), 3.78-3.73 (m, 3H), 3.72-3.63 (m, 3H), 3.40 (m, 2H).

2-amino-5-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-N-(2-oxoazepan-3-yl)benzamide (2):



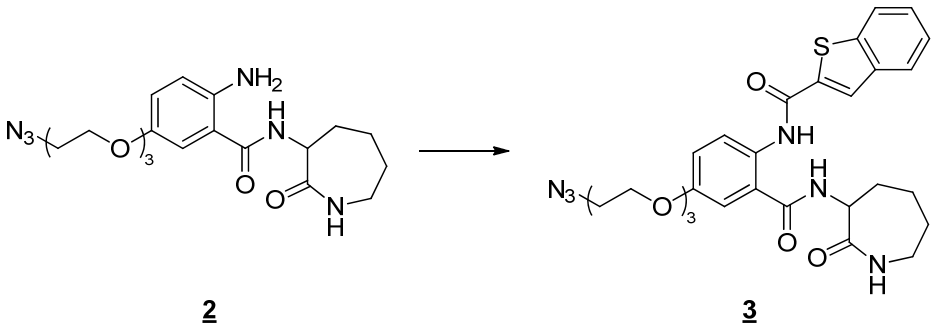
1 **2**

In a dry flask under argon, **1** (174 mg, 0.536 mmol) and LiOH (27 mg, 1.12 mmol) were introduced in mixture of DME/H_2O (2:1) (7.5 mL). The solution was stirred at 90°C for 24h. The reaction mixture was cooled to room temperature and concentrated. The residue was filtered over silica pad with DCM/MeOH (90/10) as eluent. After concentration a white solid was obtained (120 mg). The residue was dissolved under argon in 5 mL of DCM and (DL)-α-amino-ε-caprolactam hydrochloride (77 mg, 0.464 mmol), EDCI (82 µL, 0.464 mmol), HOBt (62.3 mg, 0.464 mmol), DIEA (152 µL, 0.851 mmol) and molecular sieves 4Å (400 mg) were added. The reaction mixture was stirred at room temperature for 12h then 5 mL of an aqueous saturated $NaHCO_3$ solution was added and the aqueous layer was extracted three times with CH_2Cl_2. The organic layer was washed with 10 mL of 5% aqueous citric acid solution then dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (100:0 at 90:10 EtOAc-MeOH) to give **2** (81 mg, 36%) as a white solid.

Rf = 0.08 (AcOEt); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.03 (br s, 1H), 7.52 (m, 1H), 7.05 (d, *J* = 2.9 Hz, 1H), 6.90 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 6.08 (br t, *J* = 5.5

Hz, 1H), 5.19 (br s, 1H), 4.68 (ddd, *J* = 11.3, 5.5, 1.4 Hz, 1H), 4.09 (m, 2H), 3.84 (m, 2H), 3.37-3.27 (m, 2H), 2.21 (m, 1H), 2.07 (m, 1H), 1.90 (m, 2H), 1.59 (m, 1H), 1.47 (m, 1H).

N-(4-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-2-((2-oxoazepan-3-yl)carbamoyl)phenyl)benzo[*b*]thiophene-2-carboxamide (3):

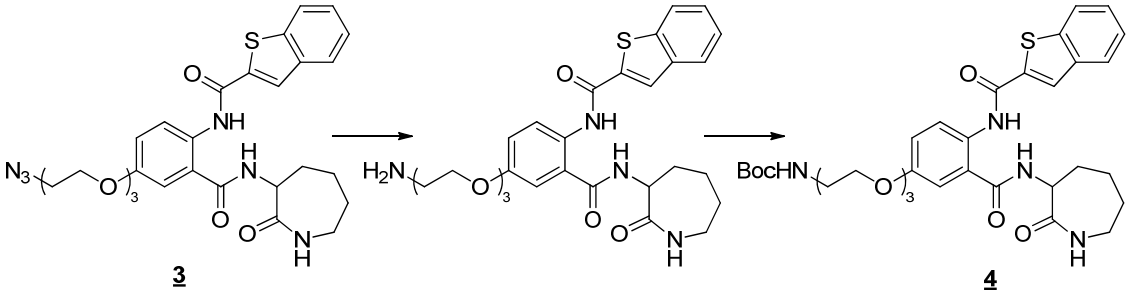


2 **3**

In a dry flask under argon, benzo[*b*]thiophene-2-carboxylic acid (41 mg, 0.232 mmol) was introduced in 5 mL of CH_2Cl_2. Then oxalyl chloride (21 µL, 0.238 mmol) was added follow by three drops of DMF. The mixture was stirred for 6 h then **2** (81 mg, 0.193 mmol) and Et_3N (47 µL, 0.333 mmol) were added. 5 mL of 1M aqueous HCl solution were added and the aqueous layer was extracted three times with CH_2Cl_2. The organic layer was washed with 10 mL of an aqueous satured $NaHCO_3$ solution then dried over Na_2SO_4, filtered and concentrated. The residue was purified by recristallisation (90/10 pentane/CH_2Cl_2) to give **3** (86 mg, 77%) as a white solid.

Rf = 0.31 (90:10 CH_2Cl_2/MeOH); **^{1}H NMR** ($CDCl_3$-CD_3OD, 300 MHz) δ 8.61 (d, *J* = 9.2 Hz, 1H), 7.95 (s, 1H), 7.88 (m, 2H), 7.40 (m, 2H), 7.22 (br d, *J* = 2.7 Hz, 1H), 7.10 (dd, *J* = 9.2, 2.7 Hz, 1H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.16 (t, *J* = 4.4 Hz, 2H), 3.86 (t, *J* = 4.4 Hz, 2H), 3.74 (m, 2H), 3.67 (m, 4H), 3.37 (m, 3H), 3.30 (m, 1H), 2.18 (m, 1H), 2.08 (m, 1H), 1.91 (m, 2H), 1.61 (m, 1H), 1.43 (m, 1H). **HRMS-ESI** (m/z): $M^{\bullet+}$ calcd 580.2104; found 580.2108 (Δ = 0.8 ppm).

tert-butyl(2-(2-(2-(4-(benzo[b]thiophene-2-carboxamido)-3-((2-oxoazepan-3-yl)carbamoyl) phenoxy)ethoxy)ethoxy)ethyl)carbamate (4):

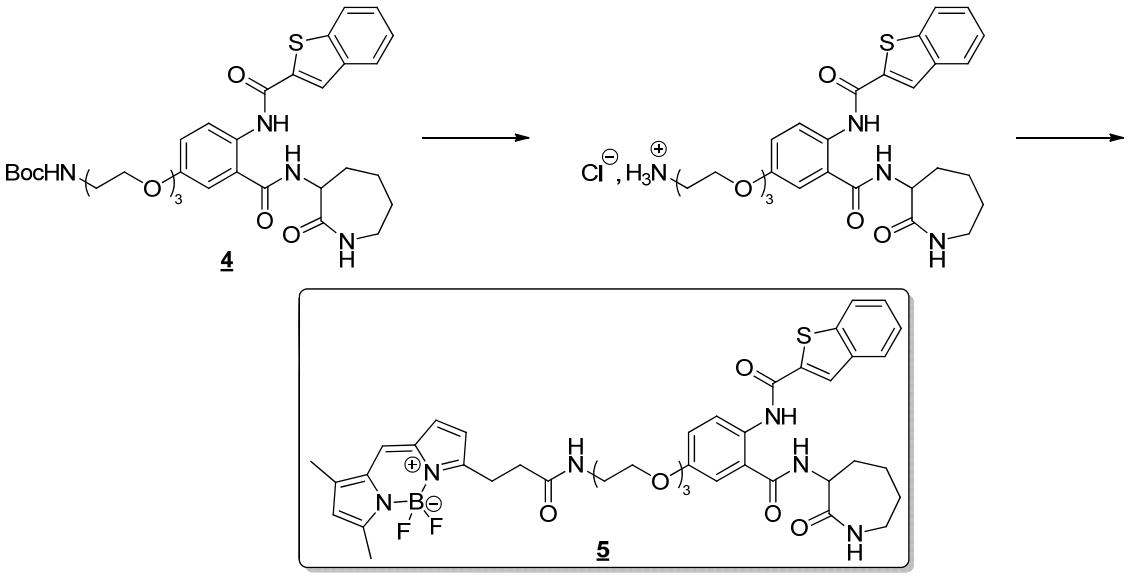


3 **4**

In a Parr flask under inert atmosphere, to a solution of **3** (78 mg, 0.134 mmol) in MeOH (20 mL) were added palladium catalyst (Pd/C 10%, 15% w/w) and 60 µL of 10% aqueous HCl solution. The mixture was set under 5 bar of hydrogen and was shaken overnight. Then, 5 mg of LiOH were added to neutralize the mixture and the residue was filtered over a Celite® pad. The solvent was removed, the residue was solubilized in 10 mL of MeOH then Boc_2O (35 mg, 0.161 mmol) and Et_3N (20 µL, 0.147 mmol) were added. The reaction mixture was stirred at room temperature for 3h. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (95:5 at 90:10 CH_2Cl_2-MeOH) to give **4** (28 mg, 32%) as a white solid.

Rf = 0.40 (90:10 CH_2Cl_2/MeOH); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.65 (d, *J* = 9.1 Hz, 1H), 7.96 (s, 1H), 7.88 (m, 2H), 7.41 (m, 2H), 7.24 (m, 1H), 7.10 (dd, *J* = 9.1, 2.7 Hz, 1H), 4.72 (dd, *J* = 10.8, 5.5 Hz, 1H), 4.18 (br t, *J* = 4.6 Hz, 2H), 3.86 (br t, *J* = 4.6 Hz, 2H), 3.71 (m, 2H), 3.64 (m, 2H), 3.54 (br t, *J* = 4.6 Hz, 2H), 3.31 (m, 4H), 2.20 (m, 1H), 2.07 (m, 2H), 1.91 (m, 2H), 1.58 (m, 1H), 1.42 (s, 9H). **HRMS-ESI** (m/z): $[M+H]^+$ calcd 655.2802; found 655.2835 (Δ = 1.2 ppm).

2-(3-((2-(2-(2-(4-(benzo[b]thiophene-2-carboxamido)-3-((2-oxoazepan-3-yl)carbamoyl)phenoxy) ethoxy)ethoxy)ethyl)amino)-3-oxopropyl)-5,5-difluoro-7,9-dimethyl-5H-dipyrrolo[1,2-c:2',1'-f] [1,3,2]diazaborinin-4-ium-5-uide (5): Bodipy-ANA-12



In a dry flask under argon, to a solution of **4** (28 mg, 0.043 mmol) in CH_2Cl_2 (3 mL) was added 200 μL of a solution of HCl in diethyl ether (C = 2 M). The reaction mixture was stirred for 10h then the solvent was evaporated under reduced pressure. The residue was solubilized in 3 mL of CH_2Cl_2 and the solution was filtered. Then the filtrate was concentrated under reduced pressure to give the free ammonium (17 mg, 67% crude yield) as a white solid.

In a dry flask under argon, to a solution of free ammonium (3.8 mg, 0.0065 mmol) in CH_2Cl_2 (1.5 mL) were added 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-propionic acid succinimidyl ester (BODIPY® FL, SE, Invitrogen; 2.1 mg, 0.0054 mmol) and Et_3N (1 □L, 0.0065 mmol). The reaction mixture was stirred at room temperature for 12h then the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (97:3 at 95:5 CH_2Cl_2-MeOH) to give **5** (3.2 mg, 72%) as a red solid.

Rf = 0.19 (95:5 CH_2Cl_2/MeOH); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 12.12 (s, 1H), 8.65 (d, *J* = 8.9 Hz, 1H), 7.97 (s, 1H), 7.91 (m, 2H), 7.79 (m, 2H), 7.43 (m, 2H), 7.23 (br d, *J* = 2.9 Hz, 1H), 7.07 (m, 2H), 6.87 (br d, *J* = 4.1 Hz, 1H), 6.69 (m, 2H), 6.19 (m, 1H), 6.10 (m, 1H), 4.72 (dd, *J* = 10.9, 5.7 Hz, 1H), 4.16 (br t, *J* = 4.6 Hz, 2H), 3.85 (br t, *J* = 4.7 Hz, 2H), 3.70 (m, 2H), 3.64 (m, 2H), 3.55 (m, 2H), 3.47 (m, 2H), 3.37 (m, 2H), 3.29 (t, *J* = 7.6 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.55 (s, 3H), 2.36 (t, *J* = 7.6 Hz, 1H), 2.24 (s, 3H), 2.21 (m, 1H), 2.07 (m, 2H), 1.93 (m, 2H); **LRMS-ESI (**m/z) 851.4 (M+Na), 829.4 (M+H), 809.4 (M-F).

Supplementary References

1. Clark Still, W., Kahn, M., and Mitra, A. 1978. Rapid chromatographic technique for preparative separations with moderate resolution. *Journal of Organic Chemistry* 43:2923-2925.
2. Hara, O., Sugimoto, K., and Hamada, Y. 2004. Synthetic studies on bradykinin antagonist martinellines: construction of a pyrrolo[3,2-c]quinoline skeleton using silicon-tether RCM reaction and allylic amination *Tetrahedron* 60:9381-9390.
3. Legeay, J.-C., Vanden, J.-J., and Bazureau, J.-P. 2007. Sequential synthesis of a new analogue of amlodipine bearing a short amino polyethyleneglycol chain *Tetrahedron* 63:12081-12086.