# Supporting Information 

## for

# Binaphthyl-anchored antibacterial tripeptide derivatives with hydrophobic C-terminal amino acid variations 

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## Experimental procedures and associated spectroscopic data (NMR and MS) for the syntheses of compounds $2 \mathrm{a}-\mathrm{b}$ and $2 \mathrm{~d}-\mathrm{g}$

## 1. General notes

Electrospray ionization (ESI) mass spectra were obtained on a VG Autospec spectrometer. High-resolution mass spectra (HRMS) were determined on a micromass QTof2 spectrometer with polyethylene glycol or polypropylene glycol as the internal standard. The $m / z$ values are stated with their peak intensity as a percentage in parentheses. Optical rotations were measured by using a Jasco polarimeter in a 10 mm path length cell. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained as specified on a Varian Mercury 300 MHz , Varian Inova 500 MHz or Varian Venus 500 MHz spectrometer. Spectra were recorded in the specified deuterated solvent, and referenced to the residual non-deuterated solvent signal. Chemical shifts ( $\delta$ ) in ppm were measured relative to the internal reference.

Proton and carbon assignments were determined through the interpretation of two dimensional spectra (COSY, gHSQC, gHMBC, ROESY, and TOCSY). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel $60 \mathrm{~F}_{254}$ precoated aluminium plates with a thickness of 0.2 mm . All column chromatography was performed under "flash" conditions on Merck silica gel 60 (230-400 mesh). Chromatography solvent mixtures were measured by volume. Analytical HPLC was performed on a Waters instrument equipped with a 1525 binary pump and a 2487 detector. Chromatographic separation was achieved with a C18 column ( $150 \times 4.60 \mathrm{~mm}, 5 \mu \mathrm{~m}$; Phenomenex), injection volume $20 \mu \mathrm{~L}$, flow rate $1.0 \mathrm{~mL} / \mathrm{min}$ and UV detection at 254 nm . Solvent was removed under reduced pressure with a Büchi rotary evaporator. Solvents were purified and dried based on standard techniques. All compounds were judged to be of greater than $95 \%$ purity based upon ${ }^{1} \mathrm{H}$ NMR and TLC analysis. Compounds for antibacterial testing were of $>96 \%$ purity by HPLC analysis. Starting materials and reagents were purchased from Sigma-Aldrich Pty Ltd, Auspep Pty Ltd or Bachem Ltd and were used as received.

## 2. General synthetic procedures [1]

## Protocol 1: Peptide coupling

To a solution of the acid in dichloromethane or acetonitrile ( $10 \mathrm{~mL} / 0.10 \mathrm{mmol}$ ) at rt was added EDCI (1.2 equiv), HOBt ( 1.2 equiv), and the amine ( 1 equiv). When the amine was a hydrochloride salt, DIPEA ( 1.2 equiv) was also added. After stirring of the mixture for $1-3 \mathrm{~h}$, the solvent was removed under reduced pressure, and then the resulting residue was subjected to silica gel column chromatography $\left(\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2} 1-4: 99-96\right.$ as the eluent) to afford a coupled product.

## Protocol 2: $N$-Fmoc deprotection

The Fmoc-protected amine was stirred in 1 equiv of piperidine/acetonitrile ( $5 \mathrm{~mL} / 0.10 \mathrm{mmol}$ ) overnight at rt, unless otherwise stated. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography with $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2} 2: 98$ and then $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2} 5-15: 95-85$ to yield the free amine.

## Protocol 3: $\boldsymbol{N}$-Boc, Pbf and Pmc deprotection

The $N$-Boc-, Pbf- or Pmc-protected amine was stirred for 1 h (for Boc) or overnight (for Pbf and Pmc ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2} /$ TFA $1: 1(6 \mathrm{~mL} / 0.10 \mathrm{mmol})$ solution at rt . The solvent was removed under reduced pressure, and the residue was resuspended in a minimal volume of methanol or $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The solution was then treated with an excess of $2 \mathrm{M} \mathrm{HCl} /$ ether ( $2 \mathrm{~mL} / 0.01 \mathrm{mmol}$ )
solution and the solvent evaporated. The product was purified by precipitation from $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ or MeOH and diethyl ether.

## 3. Protecting group abbreviations






## Benzyl 1-(tert-butoxycarbonylamino)cyclobutanecarboxylate

 added benzyl bromide ( $0.12 \mathrm{~mL}, 1.01 \mathrm{mmol}$ ). The resulting solution was heated under reflux overnight before being cooled, filtered and evaporated to dryness. The resulting residue was subjected to flash column chromatography over silica, eluting with ethyl acetate/hexane 5:95 to first remove benzyl bromide, then with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to yield the titled product ( $262 \mathrm{mg}, 92 \%$ ) as a white solid. ${ }^{1} \mathrm{H}$ NMR $\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 1.39(\mathrm{~s}, 9 \mathrm{H}), 1.90-2.09(\mathrm{~m}, 2 \mathrm{H}), 2.12-2.39(\mathrm{~m}$, $2 \mathrm{H}) 2.51-2.67(\mathrm{~m}, 2 \mathrm{H}), 5.18(\mathrm{~s}, 2 \mathrm{H}), 5.40(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH}), 7.25-7.40(\mathrm{~m}, 5 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 15.0,28.1,31.2,58.2,66.7,79.6,127.9,128.0,128.3,135.7,154.7$, 173.6; ESIMS $(\mathrm{m} / \mathrm{z}):[\mathrm{M}+\mathrm{Na}]^{+} 1204$ ( $80 \%$ ), $[\mathrm{M}+\mathrm{H}]^{+} 1182$ (100).

## Benzyl 1-amino-cyclobutanecarboxylate (4a)



This compound was prepared following protocol 3 and basification, by using the above protected amino acid ( $110 \mathrm{mg}, 0.36 \mathrm{mmol}$ ) to yield the titled product ( $67 \mathrm{mg}, 91 \%$ ) as a pale yellow oil. ${ }^{1} \mathrm{H}$ NMR $\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 1.79-2.10(\mathrm{~m}$, $\left.6 \mathrm{H} / \mathrm{NH}_{2}\right), 2.49-2.65(\mathrm{~m}, 2 \mathrm{H}), 5.18(\mathrm{~s}, 2 \mathrm{H}), 7.25-7.41(\mathrm{~m}, 5 \mathrm{H}) ;{ }^{13} \mathrm{C} \mathrm{NMR}\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 14.1, 34.0, 58.4, 66.5, 127.9, 128.1, 128.4, 135.8, 175.8; ESIMS $(\mathrm{m} / \mathrm{z}):[\mathrm{M}+\mathrm{H}]^{+} 206$ (100\%).

## Benzyl 1-((3R)-1-aza-6-(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5- <br> yl)sulfonyl]guanidino)-3-(9H-9-fluorenylmethoxycarbonylamido)-2oxohexanyl)cyclobutanecarboxylate (5a)

This compound was prepared following protocol 1, by using Fmoc- $(R)-\operatorname{Arg}(\mathrm{Pbf})-\mathrm{OH}$ ( $150 \mathrm{mg}, 0.23 \mathrm{mmol}$ ) and $\mathbf{4 a}(67 \mathrm{mg}, 0.33 \mathrm{mmol})$ to yield the Fmoc-protected product $(185 \mathrm{mg}, 96 \%)$ as a white foam. ${ }^{1} \mathrm{H}$ NMR $\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 1.37(\mathrm{~s}, 6 \mathrm{H}), 1.50-1.61(\mathrm{~m}$,

$3 \mathrm{H}), 1.80-2.00(\mathrm{~m}, 3 \mathrm{H}), 2.03(\mathrm{~s}, 3 \mathrm{H}), 2.09-2.32(\mathrm{~m}, 2 \mathrm{H})$, $2.50(\mathrm{~s}, 3 \mathrm{H}), 2.55-2.74(\mathrm{~m}, 2 \mathrm{H}), 2.58(\mathrm{~s}, 3 \mathrm{H}), 2.84(\mathrm{~s}, 2 \mathrm{H})$, 3.13-3.21 (m, 2H), 4.05-4.10 (m, 1H), 4.25-4.28 (m, 2H), 4.26-4.60 (m, 1H), $5.08(\mathrm{~s}, 2 \mathrm{H}), 6.17(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 2 \mathrm{H}$, $2 \mathrm{NH}), 6.36(\mathrm{~s}, 2 \mathrm{H}, \mathrm{NH}), 7.16-7.34(\mathrm{~m}, 9 \mathrm{H}), 7.51(\mathrm{~d}, J=$ 7.2 Hz, 2H), $7.69(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.93(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{NH})$; ${ }^{13} \mathrm{C} \operatorname{NMR}\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 12.3,15.4,17.9,19.2,25.2,28.4,31.1,31.3,43.0,46.9,53.3$, $53.9,58.3,64.8,66.85,66.9,86.2,117.4,119.8,124.6,125.0,126.8,126.9,127.3,127.5$, $127.7,128.0,128.28,128.3,132.1,132.6,135.5,138.2,141.03,141.05,143.5,143.7,156.3$, 156.4, 158.6, 172.0, 173.1; ESIMS $(m / z):[\mathrm{M}+\mathrm{H}]^{+} 836$ (100\%).

Benzyl 1-((3R)-3-amino-1-aza-6-(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-yl)sulfonyl]guanidino)-2-oxohexan)cyclobutanecarboxylate (6a)


This compound was prepared following protocol 2, by using 5a (185 $\mathrm{mg}, 0.22 \mathrm{mmol})$ to yield the product $\mathbf{6 a}(111 \mathrm{mg}, 82 \%) .{ }^{1} \mathrm{H}$ NMR $\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 1.46-3.51(\mathrm{~m}, 29 \mathrm{H}), 5.14-5.44(\mathrm{~m}, 3 \mathrm{H}), 6.20-$ $6.70(\mathrm{~m}, 3 \mathrm{H}, 3 \mathrm{NH}), 7.32-7.44(\mathrm{~m}, 5 \mathrm{H}), 8.08-8.19(\mathrm{~m}, 1 \mathrm{H}, \mathrm{NH})$; ${ }^{13} \mathrm{C}$ NMR $\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 12.5,15.4,18.0,19.3,25.3,26.6,28.6$, $31.5,40.7,43.2,54.0,58.1,67.0,86.4,114.5,124.6,127.9,128.5$, 132.1, 132.9, 135.6, 138.3, 156.4, 158.7, 173.2; ESIMS (m/z): $[\mathrm{M}+\mathrm{H}]^{+} 614$ (100\%); HRMSESI $m / z$ : calcd for $\mathrm{C}_{31} \mathrm{H}_{44} \mathrm{~N}_{5} \mathrm{O}_{6} \mathrm{~S} 614.3012$, found 614.3034 .

Benzyl 1-((3R,6R)-3-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-yl)sulfonyl]guanidinopropyl)-9-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)-6-(4-(tert-butoxycarbonylamino)butyl)-1,4,7-triaza-2,5,8trioxononan)cyclobutanecarboxylate (8a)


This compound was prepared following protocol 1 , by using 7 ( $100 \mathrm{mg}, 0.16 \mathrm{mmol}$ ) and $\mathbf{6 a}(111 \mathrm{mg}$, $0.18 \mathrm{mmol})$ to yield the product ( $30 \mathrm{mg}, 16 \%$ ) as an off white solid. ${ }^{1} \mathrm{H}$ NMR $\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 0.48$ $(\mathrm{d}, J=6.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.53(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.74-$ $0.88(\mathrm{~m}, 2 \mathrm{H}), 0.94-0.99(\mathrm{~m}, 1 \mathrm{H}), 1.04-1.58(\mathrm{~m}, 8 \mathrm{H})$, $1.42(\mathrm{~s}, 9 \mathrm{H}), 1.44(\mathrm{~s}, 6 \mathrm{H}), 1.67-1.82(\mathrm{~m}, 1 \mathrm{H}), 1.74-$ $2.11(\mathrm{~m}, 4 \mathrm{H}), 2.07(\mathrm{~s}, 3 \mathrm{H}), 2.25-2.38(\mathrm{~m}, 2 \mathrm{H}), 2.49$ $(\mathrm{s}, 3 \mathrm{H}), 2.57(\mathrm{~s}, 3 \mathrm{H}), 2.66-2.74(\mathrm{~m}, 1 \mathrm{H}), 2.91(\mathrm{~s}, 2 \mathrm{H}), 2.92-3.08(\mathrm{~m}, 2 \mathrm{H}), 3.83-3.90(\mathrm{~m}, 1 \mathrm{H})$,
3.98-4.05 (m, 2H), 4.38 and $4.54(\mathrm{ABq}, J=14.7 \mathrm{~Hz}, 2 \mathrm{H}), 4.40-4.51(\mathrm{~m}, 1 \mathrm{H}), 4.69-4.79(\mathrm{~m}$, $1 \mathrm{H}, \mathrm{NH}$ ), 6.14-6.19 (m, 3H, 3NH), 7.10-7.38 (m, 12H), $7.43(\mathrm{~d}, J=9.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.65(\mathrm{br} \mathrm{s}$, $1 \mathrm{H}, \mathrm{NH}), 7.83-7.87(\mathrm{~m}, 2 \mathrm{H}), 7.94\left(\mathrm{dd}, J_{l}=9.0 \mathrm{~Hz}, J_{2}=2.7 \mathrm{~Hz}, 2 \mathrm{H}\right) ;{ }^{13} \mathrm{C} \mathrm{NMR}(75 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \delta 12.5,15.6,18.0,19.3,22.0,22.3,22.5,24.5,25.2,28.4,28.6,29.1,29.7,31.2,31.4$, $37.9,40.1,40.4,43.2,58.4,66.8,68.0,68.2,78.9,86.3,114.3,115.8,117.5,119.47,120.4$, $123.9,124.2,124.6,124.9,125.5,126.5,126.7,127.8,127.9,128.1,128.5,129.2,129.7$, $129.8,132.2,132.9,133.6,133.8,135.9,138.3,152.2,154.4,156.0,156.3,158.7,169.2$, 171.1, 171.3, 173.0; ESIMS (m/z): [M + Na] ${ }^{+} m / z 1261$ (100\%); [M + H] 1239 (65); HRMSESI $m / z$ : calcd for $\mathrm{C}_{69} \mathrm{H}_{88} \mathrm{~N}_{7} \mathrm{O}_{12} \mathrm{~S}$ 1238.6212, found 1238.6194.

Benzyl 1-((3R,6R)-6-butylamino-3-(3-guanidinopropyl)-9-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)-1,4,7-triaza-2,5,8-trioxononan)cyclobutanecarboxylate dihydrochloride (2a)


This compound was prepared following protocol 3 , by using 8a ( $30 \mathrm{mg}, 0.024 \mathrm{mmol}$ ) to yield the product ( $22 \mathrm{mg}, 96 \%$ ) as a pale yellow solid. ${ }^{1} \mathrm{H}$ NMR ( $\left.500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 0.55(\mathrm{~d}, J=6.5 \mathrm{~Hz}$, $3 \mathrm{H}), 0.58(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.92-1.05(\mathrm{~m}, 2 \mathrm{H})$, $1.11-1.30(\mathrm{~m}, 4 \mathrm{H}), 1.47-1.70(\mathrm{~m}, 7 \mathrm{H}), 1.99-2.05$ (m, 2H), 2.01-2.26 (m, 1H), 2.29-2.35 (m, 1H), 2.54-2.59 (m, 1H), 2.68-2.73 (m, 1H), 2.72$2.87(\mathrm{~m}, 2 \mathrm{H}), 3.05-3.11(\mathrm{~m}, 2 \mathrm{H}), 3.94-3.99(\mathrm{~m}, 1 \mathrm{H}), 4.11-4.16(\mathrm{~m}, 2 \mathrm{H}), 4.23-4.26(\mathrm{~m}, 1 \mathrm{H})$, 4.47 and $4.55(\mathrm{ABq}, J=14.5 \mathrm{~Hz}, 2 \mathrm{H}), 5.12$ and $5.15(\mathrm{ABq}, J=12.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.06\left(\mathrm{dd}, J_{l}=\right.$ $\left.14.5 \mathrm{~Hz}, J_{2}=8.5 \mathrm{~Hz}, 2 \mathrm{H}\right), 7.20-7.24(\mathrm{~m}, 2 \mathrm{H}), 7.30-7.37(\mathrm{~m}, 7 \mathrm{H}), 7.47(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H})$, $7.55(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.90(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 8.02\left(\mathrm{dd}, J_{1}=9.0 \mathrm{~Hz}, J_{2}=4.0 \mathrm{~Hz}, 2 \mathrm{H}\right)$; ${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) $\delta 16.4,22.6,22.8,23.0,25.6,26.1,27.7,30.0,32.1,32.3,39.3$, $40.3,42.0,53.6,54.2,59.6,68.0,69.0,69.2,116.0,116.9,120.6,121.8,124.8,125.2,126.0$, 126.4, 127.6, 129.2, 129.3, 129.6, 130.9, 131.4, 135.1, 135.3, 137.4, 154.1, 156.0, 158.6, 173.3, 173.7, 174.4; ESIMS $(\mathrm{m} / \mathrm{z}):[\mathrm{M}+\mathrm{H}]^{+} 886$ ( $80 \%$ ), $[\mathrm{M}+2 \mathrm{H}]^{2+} 443$ (100); HRMS-ESI $\mathrm{m} / \mathrm{z}$ : calcd for $\mathrm{C}_{51} \mathrm{H}_{64} \mathrm{~N}_{7} \mathrm{O}_{7}$ 886.4867, found 886.4881.

## Benzyl 1-(tert-butoxycarbonylamino)cyclopentanecarboxylate



To 1-(tert-butyloxycarbonyl)cyclopentanecarboxylic acid (120 mg, 0.523 mmol ) and potassium carbonate ( $178 \mathrm{mg}, 1.29 \mathrm{mmol}$ ) in acetone $(25 \mathrm{~mL})$ was added benzyl bromide $(0.1 \mathrm{~mL}, 0.92 \mathrm{mmol})$. The resulting solution was heated
under reflux overnight before being cooled, filtered and evaporated to dryness. The residue was purified by column chromatography, eluting with $5 \%$ ethyl acetate/hexane to first remove benzyl bromide, then with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to yield the title product ( $173 \mathrm{mg}, 96 \%$ ) as a white solid. ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.37$ ( $\mathrm{s}, 9 \mathrm{H}$ ), 1.72-1.75 (m, 4H), 1.81-1.98 (m, 2H), 2.18-2.23 $(\mathrm{m}, 2 \mathrm{H}), 5.08(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{NH}), 5.13(\mathrm{~s}, 2 \mathrm{H}), 7.26-7.32(\mathrm{~m}, 5 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 24.4,28.1,37.5,66.7,78.8,127.9,127.95,128.3,135.8,155.0,174.4 ;$ ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 320(50 \%),\left[\mathrm{M}-\mathrm{C}_{4} \mathrm{H}_{8}\right]^{+} 264(100) ;[\mathrm{M}-\mathrm{Boc}]^{+} 220(100)$

## Benzyl 1-aminocyclopentanecarboxylate (4b)



Compound 4b [2] was prepared following protocol 3 and basification, by using the above amino acid derivative ( $170 \mathrm{mg}, 0.532 \mathrm{mmol}$ ) to yield the title product ( $102 \mathrm{mg}, 87 \%$ ) as a pale yellowish oil. ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 1.50-1.61$ (m, 2H), 1.65-1.79 (m, 2H), 1.80-1.91 (m, 2H), 2.02-2.18 (m, 2H), 5.13 (s, 2H), 7.30-7.34 $(\mathrm{m}, 5 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(126 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 24.9,39.4,64.8,66.5,127.8,128.0,128.4,135.9$, 177.8; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 220(100 \%)$; HRMS-ESI $\mathrm{m} / \mathrm{z}$ : calcd for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{NO}_{2}$ 220.1338, found 220.1348.

## Benzyl 1-((3R)-1-aza-6-(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-

 yl)sulfonylguanidino)-3-(9H-9-fluorenylmethoxycarboxamido)-2oxohexan)cyclopentanecarboxylate (5b)

This compound was prepared following protocol 1, Fmoc( $R$ ) $-\mathrm{Arg}(\mathrm{Pbf})-\mathrm{OH}(296 \mathrm{mg}, 0.456 \mathrm{mmol})$ and $\mathbf{4 b}(100 \mathrm{mg}$, $0.456 \mathrm{mmol})$ to yield $\mathbf{5 b}(241 \mathrm{mg}, 61 \%)$ as a white foam. ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.41(\mathrm{~s}, 6 \mathrm{H}), 1.47-1.75(\mathrm{~m}$, $7 \mathrm{H}), 1.77-1.87(\mathrm{~m}, 1 \mathrm{H}), 1.95-2.16(\mathrm{~m}, 3 \mathrm{H}), 2.05(\mathrm{~s}, 3 \mathrm{H})$, 2.24-2.27 (m, 1H), $2.50(\mathrm{~s}, 3 \mathrm{H}), 2.57(\mathrm{~s}, 3 \mathrm{H}), 2.88(\mathrm{~s}, 2 \mathrm{H})$, 3.11-3.23 (m, 2H), 3.89-4.11 (m, 1H), 4.27-4.28 (m, 3H), 5.04-5.09 (m, 2H), 6.06 (br s, 1H, NH), 6.29 (s, 2H, 2NH), 7.20-7.37 (m, 5H), 7.52 (d, $J=7.5 \mathrm{~Hz}, 2 \mathrm{H}$ ), 7.71 (d, $J=7.5 \mathrm{~Hz}$, $2 \mathrm{H})$; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 850$ ( $100 \%$ ).

Benzyl 1-((3R)-3-amino-1-aza-6-(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-yl)sulfonyl]guanidino)-2-oxohexan)cyclopentanecarboxylate (6b)

This compound was prepared following protocol 2 , by using $\mathbf{5 b}$ ( $241 \mathrm{mg}, 0.279 \mathrm{mmol}$ ) to yield 6b ( $152 \mathrm{mg}, 85 \%$ ). ${ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 1.44$ (s, 6H), 1.42-2.11 (m,
$12 \mathrm{H} / \mathrm{NH}_{2}$ ), $1.44(\mathrm{~s}, 6 \mathrm{H}), 2.07(\mathrm{~s}, 3 \mathrm{H}), 2.16-2.29(\mathrm{~m}, 2 \mathrm{H}), 2.57(\mathrm{~s}, 3 \mathrm{H}), 2.63(\mathrm{~s}, 3 \mathrm{H}), 2.93$ (s, $2 \mathrm{H}), 3.13-3.21(\mathrm{~m}, 2 \mathrm{H}), 3.40-3.43(\mathrm{~m}, 1 \mathrm{H}), 3.98-4.06(\mathrm{~m}, 1 \mathrm{H}), 5.05$ and $5.09(\mathrm{ABq}, J=12.5 \mathrm{~Hz}, 2 \mathrm{H}), 6.37-6.49(\mathrm{~m}, 3 \mathrm{H}, 3 \mathrm{NH}), 7.45-7.31$ $(\mathrm{m}, 5 \mathrm{H}), 7.52(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 12.4,17.9$, $19.2,23.2,24.4,28.5,30.8,37.0,40.1,43.1,53.4,65.4,66.9,86.2$, 117.4, 124.5, 128.0, 128.1, 128.4, 132.1, 135.6, 138.1, 156.4, 158.6, 168.4, 173.4; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 628$ (100\%); HRMS-ESI $\mathrm{m} / \mathrm{z}:$ calcd for $\mathrm{C}_{32} \mathrm{H}_{46} \mathrm{~N}_{5} \mathrm{O}_{6} \mathrm{~S}$ 628.3169, found 628.3182 .

## Benzyl 1-((3R,6R)-3-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-

yl)sulfonyl]guanidinopropyl)-9-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)-6-(4-(tert-butoxycarbonylamino)butyl)-1,4,7-triaza-2,5,8trioxononan)cyclopentanecarboxylate (8b)


This compound was prepared following protocol 1 , by using 7 ( $100 \mathrm{mg}, 0.155 \mathrm{mmol}$ ) and $\mathbf{6 b}$ ( 141 mg , 0.224 mmol ) to yield the title product ( 123 mg , $63 \%$ ) as a white solid. ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 0.47(\mathrm{~d}, J=6.4 \mathrm{~Hz}, 3 \mathrm{H}), 0.52(\mathrm{~d}, J=6.4 \mathrm{~Hz}, 3 \mathrm{H})$, $0.75-0.82(\mathrm{~m}, 2 \mathrm{H}), 0.88-1.02(\mathrm{~m}, 1 \mathrm{H}), 1.06-1.54$ $(\mathrm{m}, 10 \mathrm{H}), 1.42(\mathrm{~s}, 9 \mathrm{H}), 1.43(\mathrm{~s}, 3 \mathrm{H}), 1.44(\mathrm{~s}, 3 \mathrm{H})$, 1.59-1.81 (m, 4H), 1.95-1.97 (m, 2H), 2.07 ( s , $3 \mathrm{H}), 2.11-2.15(\mathrm{~m}, 1 \mathrm{H}), 2.24-2.30(\mathrm{~m}, 1 \mathrm{H}), 2.50(\mathrm{~s}, 3 \mathrm{H}), 2.57(\mathrm{~s}, 3 \mathrm{H}), 2.81-2.99(\mathrm{~m}, 2 \mathrm{H})$, $2.91(\mathrm{~s}, 2 \mathrm{H}), 3.00-3.21(\mathrm{~m}, 2 \mathrm{H}), 3.84-3.87(\mathrm{~m}, 1 \mathrm{H}), 4.01-4.05(\mathrm{~m}, 2 \mathrm{H}), 4.38(\mathrm{~d}, J=14.5 \mathrm{~Hz}$, $2 \mathrm{H}), 4.54(\mathrm{~d}, J=15.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.07(\mathrm{~s}, 2 \mathrm{H}), 6.15(\mathrm{~d}, J=6.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{NH}), 6.25(\mathrm{br} \mathrm{s}, 2 \mathrm{H}$, 2 NH ), $7.11(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.15(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.21-7.36(\mathrm{~m}, 10 \mathrm{H}), 7.43(\mathrm{~d}, J=$ $9.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.84(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.85(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.93(\mathrm{~d}, J=6.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.94$ (d, $J=9.0 \mathrm{~Hz}, 1 \mathrm{H}$ ); ${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 12.4,17.9,19.3,22.0,22.2,22.4,23.2$, $24.4,24.46,24.5,25.3,28.4,28.5,29.1,31.1,36.9,37.1,37.9,40.0,43.2,52.8,53.4,65.9$, $66.8,67.9,68.2,78.8,86.3,114.2,115.8,117.4,119.3,120.3,123.8,124.1,124.5,124.9$, $125.4,126.5,126.6,127.8,127.9,128.0$, 128.4, 129.1, 129.7, 132.1, 132.9, 133.5, 133.8, $135.8,138.2,152.1,154.3,156.0,156.3,158.6,169.1,171.3,173.8 ; \operatorname{ESIMS}(m / z):[\mathrm{M}+\mathrm{Na}]^{+}$ 1275 (20\%); [M + H] 1253 (100).

Benzyl 1-((3R,6R)-6-butylamino-3-(3-guanidinopropyl)-9-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)- 1,4,7-triaza-2,5,8-trioxononan)cyclopentanecarboxylate dihydrochloride (2b)


This compound was prepared following protocol 3 , by using $\mathbf{8 b}$ ( $110 \mathrm{mg}, 0.088 \mathrm{mmol}$ ) to yield $\mathbf{2 b}$ ( $83 \mathrm{mg}, 97 \%$ ) as an off-white solid. ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) $\delta 0.51(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.57$ $(\mathrm{d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.94-0.97(\mathrm{~m}, 2 \mathrm{H}), 1.12-1.18$ $(\mathrm{m}, 2 \mathrm{H}), 1.20-1.28(\mathrm{~m}, 2 \mathrm{H}), 1.42-1.44(\mathrm{~m}, 1 \mathrm{H})$, $1.54-1.64(\mathrm{~m}, 5 \mathrm{H}), 1.66-1.85(\mathrm{~m}, 5 \mathrm{H}), 1.97-2.00(\mathrm{~m}, 2 \mathrm{H}), 2.10-2.13(\mathrm{~m}, 1 \mathrm{H}), 2.29-2.32(\mathrm{~m}$, $1 \mathrm{H}), 2.78-2.79(\mathrm{~m}, 2 \mathrm{H}), 3.07-3.08(\mathrm{~m}, 2 \mathrm{H}), 3.93-3.98(\mathrm{~m}, 1 \mathrm{H}), 4.11-4.16(\mathrm{~m}, 2 \mathrm{H}), 4.25-4.28$ $(\mathrm{m}, 1 \mathrm{H}), 4.45$ and $4.55(\mathrm{ABq}, J=14.7 \mathrm{~Hz}, 2 \mathrm{H}), 5.07$ and $5.12(\mathrm{ABq}, J=12.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.07$ $(\mathrm{t}, J=9.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.19-7.22(\mathrm{~m}, 2 \mathrm{H}), 7.29-7.35(\mathrm{~m}, 7 \mathrm{H}), 7.47(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.55(\mathrm{~d}, J$ $=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.89(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.92(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 8.01(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 1 \mathrm{H})$, $8.02(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $\left.126 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 22.6,22.8,23.0,25.4,25.6,26.1$, $27.7,30.0,32.2,37.6,38.0,39.3,40.4,41.9,53.4,54.0,67.2,68.0,69.0,69.2,116.0,116.9$, $120.5,121.8,124.8,125.2,125.9,126.4,127.5,127.6,129.1,129.2,129.25,129.6,130.7$, 130.9, 131.4, 135.0, 135.2, 137.3, 154.0, 155.9, 158.5, 170.7, 173.0, 173.7, 175.1; ESIMS $(m / z):[M+H]^{+} 900(5 \%) ; 451[M+2 H]^{2+}(100) ;$ HRMS-ESI $m / z$ : calcd for $\mathrm{C}_{52} \mathrm{H}_{66} \mathrm{~N}_{7} \mathrm{O}_{7}$ 900.5024, found 900.5042 .

## Benzyl 4-(tert-butoxycarbonylamino)tetrahydro-2H-pyran-4-carboxylate



Benzyl bromide ( $0.25 \mathrm{~mL}, 2 \mathrm{mmol}$ ) was added to a stirred suspension of 4-(tert-butoxycarbonylamino)tetrahydro- 2 H -pyran-4-carboxylic acid ( $245 \mathrm{mg}, 1.0 \mathrm{mmol}$ ) and anhydrous potassium carbonate $(345 \mathrm{mg}$, 2.5 mmol ) in anhydrous THF ( 30 mL ). The mixture was heated under reflux for 3 h . The mixture was cooled and poured into water ( 50 mL ) and extracted with EtOAc ( $3 \times 50 \mathrm{~mL}$ ). The combined organic layers were washed with sat. $\mathrm{NaHCO}_{3}$ and sat. NaCl solution and dried with anhydrous sodium sulfate. After evaporation of organic solvent, crude product was purified by column chromatography on silica gel using EtOAc/petroleum ether (0-20:100-80) to give the benzyl ester ( $230 \mathrm{mg}, 69 \%$ ). ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.38$ ( $\mathrm{s}, 9 \mathrm{H}$ ), 1.79-1.85 $(\mathrm{m}, 2 \mathrm{H}), 2.17-2.20(\mathrm{~m}, 2 \mathrm{H}), 3.61-3.64(\mathrm{~m}, 2 \mathrm{H}), 3.76-3.79(\mathrm{~m}, 2 \mathrm{H}), 4.70(\mathrm{bs}, 1 \mathrm{H}), 5.16(\mathrm{~s}$, 2H), 7.32-7.41 (m, 5H); ESIMS (m/z): $[\mathrm{M}+\mathrm{H}]^{+} 336(30 \%)$.

## Benzyl 4-aminotetrahydro-2H-pyran-4-carboxylate (4d)

The Boc-protected compound from above ( $213 \mathrm{mg}, 0.64 \mathrm{mmol}$ ) was added to a mixture of trifluoroacetic acid $/ \mathrm{CH}_{2} \mathrm{Cl}_{2} 3: 7,20 \mathrm{~mL}$. The solution was stirred at rt for 2 h . The solvent was evaporated under the reduced pressure and the residue was redissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$, and washed with sat. aq. $\mathrm{NaHCO}_{3}$, water, dried $\left(\mathrm{MgSO}_{4}\right)$ and filtered. The solvent was removed by rotary evaporation to give $\mathbf{4 d}$ $(120 \mathrm{mg}, 80 \%) .{ }^{1} \mathrm{H}$ NMR ( $\left.500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 1.43(\mathrm{~d}, J=14.0 \mathrm{~Hz} ; 2 \mathrm{H}), 1.79(\mathrm{br} \mathrm{s}, 2 \mathrm{H})$, 2.05-2.10 (m, 2H), 3.56-3.60 (m, 2H), 3.76-3.81 (m, 2H), 5.10 (s, 2H), 7.18-7.30 (m, 5H); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) $\delta$ 31.7, 56.6, 62.7, 68.5, 128.6, 128.7, 128.7, 135.0, 169.8; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 236$ (70\%).

Benzyl 4-(2-((R)-(9H-9-fluorenylmethoxycarboxamido))-5-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-yl)sulfonyl]guanidino)pentanamido)tetrahydro-2H-pyran-4-carboxylate (5d)

To a solution of Fmoc- $(R)$ - Arg (Pbf)-OH ( $324 \mathrm{mg}, 0.50 \mathrm{mmol}$ ) and $\mathbf{4 d}(100 \mathrm{mg}, 0.24 \mathrm{mmol})$ in $\mathrm{CH}_{3} \mathrm{CN}(20 \mathrm{~mL})$, was added $\mathrm{EDCI} \cdot \mathrm{HCl}(200 \mathrm{mg}, 1.0 \mathrm{mmol})$, and $\mathrm{HOBt}(54 \mathrm{mg}$, $0.5 \mathrm{mmol})$. The resulting mixture was stirred at rt for 16 h . The reaction mixture was diluted with EtOAc $(50 \mathrm{~mL})$ and the solution was washed sat. aq. $\mathrm{NaHCO}_{3}$, water, dried $\left(\mathrm{MgSO}_{4}\right)$
 and filtered. The solvent was removed by rotary evaporation. The residue was subjected to flash silica gel chromatography with $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2} 0-3: 100-97$ as eluent to afford the $\mathbf{5 d}$ ( $236 \mathrm{mg}, 65 \%$ ). ${ }^{1} \mathrm{H}$ NMR ( 500 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 1.37(\mathrm{~s}, 6 \mathrm{H}), 1.44-1.63(\mathrm{~m}, 3 \mathrm{H}), 1.74-1.87(\mathrm{~m}$, $1 \mathrm{H}), 1.87-2.18(\mathrm{~m}, 4 \mathrm{H}), 2.02(\mathrm{~s}, 3 \mathrm{H}), 2.48(\mathrm{~s}, 3 \mathrm{H}), 2.58(\mathrm{~s}$, $3 \mathrm{H}), 2.87(\mathrm{~s}, 2 \mathrm{H}), 3.19(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 3.46-3.72(\mathrm{~m}, 4 \mathrm{H}), 4.03-4.11(\mathrm{~m}, 1 \mathrm{H}), 4.20-4.38(\mathrm{~m}, 3 \mathrm{H})$, $5.01-5.12(\mathrm{~m}, 2 \mathrm{H}), 5.98(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{NH}), 6.20$ (br s, $2 \mathrm{H}, 2 \mathrm{NH}$ ), 7.13-7.37 (m, 9H), 7.45-7.58 ( $\mathrm{m}, 3 \mathrm{H} / \mathrm{NH}$ ), $7.73(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 12.8,18.3$, 19.7, 25.8, $28.8,29.8,32.4,32.5,40.8,43.4,47.2,53.8,55.0,57.2,63.5,63.6,67.4,67.5,86.7,118.0$, $120.2,125.1,125.4,127.3,128.0,128.3,128.5,128.8,132.5,132.9,135.8,138.6,141.5$, 144.0, 144.1, 156.7, 156.8, 159.2, 172.9, 173.4; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 866$ ( $100 \%$ ).

Benzyl 4-(2-((R)-amino)-5-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-yl)sulfonyl]guanidino)pentanamido)tetrahydro-2H-pyran-4-carboxylate (6d)


Piperidine ( 0.3 mL ) was added to a solution of $\mathbf{5 d}$ ( 200 mg , $0.23 \mathrm{mmol})$ in $\mathrm{CH}_{3} \mathrm{CN}(20 \mathrm{~mL})$. The mixture was stirred at rt for 3 h . After evaporation of solvent under reduced pressure, the residue was subjected to flash silica gel column chromatography using $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2} 0-5: 100-95$ to give $\mathbf{6 d}$ as a white foam ( $115 \mathrm{mg}, 78 \%$ ). ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.37(\mathrm{~s}, 6 \mathrm{H}), 1.48-1.50(\mathrm{~m}, 1 \mathrm{H}), 1.63-$ $1.66(\mathrm{~m}, 1 \mathrm{H}), 1.84-1.92(\mathrm{~m}, 2 \mathrm{H}), 2.00(\mathrm{~s}, 3 \mathrm{H}), 2.03-2.13(\mathrm{~m}, 4 \mathrm{H}), 2.42(\mathrm{~s}, 3 \mathrm{H}), 2.49(\mathrm{~s}, 3 \mathrm{H})$, $2.86(\mathrm{~s}, 2 \mathrm{H}), 3.06-3.09(\mathrm{~m}, 2 \mathrm{H}), 3.38-3.40(\mathrm{~m}, 1 \mathrm{H}), 3.50-3.57(\mathrm{~m}, 2 \mathrm{H}), 3.66-3.69(\mathrm{~m}, 2 \mathrm{H})$, 5.01 and $5.04(\mathrm{ABq}, J=12.5 \mathrm{~Hz}, 2 \mathrm{H}), 6.31(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{NH}), 6.32(\mathrm{br} \mathrm{s}, 2 \mathrm{H}, 2 \mathrm{NH}), 7.19-7.25$ (m, 5H), 7.85 (br s, $1 \mathrm{H}, \mathrm{NH}$ ); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 12.7,18.2,19.6,25.7,28.8$, $29.5,31.9,32.4,32.9,40.8,43.5,53.7,54.4,56.6,63.6,63.7,67.4,86.7,117.8,124.9,128.4$, $128.6,128.8,132.4,133.1,135.8,138.5,156.6,159.0,173.3,175.5 ; \operatorname{ESIMS}(\mathrm{m} / \mathrm{z}):[\mathrm{M}+\mathrm{H}]^{+}$ 644 (100\%).

## Benzyl 4-((3R,6R)-3-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-

yl)sulfonyl]guanidino)propyl)-6-(4-(tert-butoxycarbonylamino)butyl)-9-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)-1,4,7-triaza-2,5,8-trioxononane)tetrahydro-2H-pyran-4-carboxylate (8d)


To a solution of $7(100 \mathrm{mg}, 0.16 \mathrm{mmol})$ and $\mathbf{6 d}$ ( $100 \mathrm{mg}, 0.16 \mathrm{mmol}$ ) in $\mathrm{CH}_{3} \mathrm{CN}(20 \mathrm{~mL})$, was added EDCI $\cdot \mathrm{HCl}(100 \mathrm{mg}, 0.50 \mathrm{mmol})$ and HOBt ( 54 mg , 0.50 mmol ), and then the resulting mixture was stirred at rt for 16 h . The reaction mixture was diluted with EtOAc ( 50 mL ), and the EtOAc solution was washed sat. aq. $\mathrm{NaHCO}_{3}$ and water, dried $\left(\mathrm{MgSO}_{4}\right)$, and filtered. The solvent was removed by rotary evaporation. The residue was subjected to flash chromatography on silica gel with $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2} 0-1: 100-99$ as eluent to afford $\mathbf{8 d}(162 \mathrm{mg}, 80 \%)$. $[\alpha]^{24}{ }_{\mathrm{D}}=-15.2(c$ $0.2, \mathrm{MeOH}) ;{ }^{1} \mathrm{H}$ NMR ( $\left.500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 0.48(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.53(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H})$, $0.67-0.86(\mathrm{~m}, 3 \mathrm{H}), 0.87-1.02(\mathrm{~m}, 1 \mathrm{H}), 1.03-1.60(\mathrm{~m}, 9 \mathrm{H}), 1.42(\mathrm{~s}, 9 \mathrm{H}), 1.429(\mathrm{~s}, 3 \mathrm{H}), 1.433$ (s, 3H), 1.89-2.22 (m, 4H), 2.06 (s, 3H), 2.48 (s, 3H), 2.56 (s, 3H), 2.79-3.21 (m, 4H), 2.90 (s, 2H), 3.60-3.64 (m, 2H), 3.69-3.71 (m, 1H), 3.75-3.77 (m, 1H), 3.85-3.90 (m, 1H), 3.89-
$4.02(\mathrm{~m}, 1 \mathrm{H}), 3.99-4.03(\mathrm{~m}, 1 \mathrm{H}), 4.33-4.50(\mathrm{~m}, 1 \mathrm{H}), 4.36$ and $4.53(\mathrm{ABq}, J=14.5 \mathrm{~Hz}, 2 \mathrm{H})$, 4.71 (br s, 1H), $5.09(\mathrm{~s}, 2 \mathrm{H}), 6.09-6.10(\mathrm{~m}, 3 \mathrm{H}, 3 \mathrm{NH}), 7.05(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{NH}), 7.10(\mathrm{~d}, J=$ $8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.14(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.20-7.36(\mathrm{~m}, 10 \mathrm{H}), 7.43(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.85(\mathrm{t}$, $J=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.93(\mathrm{t}, J=10.0 \mathrm{~Hz}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 10.2,15.7,17.1$, 19.8, 20.1, 20.2, 22.2, 23.1, 26.2, 26.3, 27.0, 29.8, 30.1, 35.7, 37.9, 38.2, 40.1, 54.7, 61.0, 61.1, 64.7, 65.7, 66.0, 76.8, 84.1, 111.9, 113.5, 115.3, 117.1, 118.1, 121.6, 122.0, 122.4, $122.6,123.3,124.3,124.5,125.7,125.8,125.8,125.9,126.2,126.2,126.9,127.5,127.6$, $129.9,130.6,131.3,131.6,133.4,136.0,149.8,152.1,153.7,154.0,156.5,167.0,169.1$, 169.2, 170.5; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{Na}]^{+} 1290$ (100\%), $[\mathrm{M}+\mathrm{H}]^{+} 1268$ (40); HRMS-ESI $\mathrm{m} / \mathrm{z}:$ calcd for $\mathrm{C}_{70} \mathrm{H}_{90} \mathrm{~N}_{7} \mathrm{O}_{13} \mathrm{~S}$ 1268.6317, found 1268.6311.

Benzyl 4-((3R,6R)-3-guanidinopropyl-6-butylamino-9-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)-1,4,7-triaza-2,5,8-trioxononane)tetrahydro-2H-pyran-4-carboxylate dihydrochloride (2d)


The Boc-protected 8d ( $150 \mathrm{mg}, 0.12 \mathrm{mmol}$ ) was added to a mixture of trifluoroacetic acid and $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ 3:7 $(20 \mathrm{~mL})$, and the solution was stirred at rt. After 2 h , the solvent was evaporated under reduced pressure, HCl in ether ( 2 M solution, 3 mL ) was added, and after a few minutes shaking, the solvent was evaporated under reduced pressure. This process was repeated two more times. The dihydrochloride salt $\mathbf{2 d}$ ( 60 mg , $50 \%$ ) was obtained by precipitation using anhydrous ether followed by filtration and vacuum drying. $[\alpha]^{24}{ }_{\mathrm{D}}-21.6(c 0.2, \mathrm{MeOH}) ;{ }^{1} \mathrm{H}$ NMR ( $\left.500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 0.53(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H})$, $0.58(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.87-1.01(\mathrm{~m}, 2 \mathrm{H}), 1.03-1.33(\mathrm{~m}, 4 \mathrm{H}), 1.34-1.80(\mathrm{~m}, 7 \mathrm{H}), 1.95-$ $2.18(\mathrm{~m}, 4 \mathrm{H}), 2.62-2.89(\mathrm{~m}, 2 \mathrm{H}), 3.00-3.16(\mathrm{~m}, 2 \mathrm{H}), 3.67-3.73(\mathrm{~m}, 2 \mathrm{H}), 3.74-3.89(\mathrm{~m}, 2 \mathrm{H})$, 3.97-3.99 (m, 1H), 4.07-4.23 (m, 2H), 4.26-4.39 (m, 1H), 4.47 and $4.56(\mathrm{ABq}, J=14.5 \mathrm{~Hz}$, $2 \mathrm{H}), 5.10$ and $5.14(\mathrm{ABq}, J=12.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.07\left(\mathrm{dd}, J_{l}=15.5 \mathrm{~Hz}, J_{2}=8.5 \mathrm{~Hz}, 2 \mathrm{H}\right), 7.22(\mathrm{t}, J$ $=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 7.28-7.42(\mathrm{~m}, 7 \mathrm{H}), 7.48(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.56(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.91(\mathrm{~d}$, $J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 8.02-8.04(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $\left.125 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 21.4,21.7,22.1,24.5$, $25.1,26.8,28.9,31.3,31.9,32.6,38.2,39.6,41.0,52.3,53.1,56.8,63.2,63.5,67.1,68.0$, $114.9,115.9,119.4,120.7,123.7,124.1,124.8,125.2,126.4,126.5,128.0,128.2,128.3$, $128.5,129.6,129.8,130.3,133.9,134.1,136.1,152.9,154.8,157.4,171.9,172.7,173.1 ;$ ESIMS $(m / z):[M+H]^{+} 916(40 \%),[M+2 H]^{2+} 459$ (100); HRMS-ESI $m / z:$ calcd for $\mathrm{C}_{52} \mathrm{H}_{66} \mathrm{~N}_{7} \mathrm{O}_{8} 916.4973$, found 916.4982.

## Benzyl 2-(4-(tert-butoxycarbonylamino) tetrahydro-2H-pyran-4-yl)acetate



Benzyl bromide ( $0.25 \mathrm{~mL}, 2 \mathrm{mmol}$ ) was added to a stirred suspension of 2-(4-(tert-butoxycarbonylamino)tetrahydro-2H-pyran-4-yl)acetic $\operatorname{acid}(259 \mathrm{mg}, 1.0 \mathrm{mmol})$ and anhydrous $\mathrm{K}_{2} \mathrm{CO}_{3}(345 \mathrm{mg}, 2.5 \mathrm{mmol})$ in anhydrous THF ( 30 mL ). The mixture was then heated under reflux for 3 h before being cooled, poured into water ( 50 mL ) and extracted with $\mathrm{EtOAc}(3 \times 50 \mathrm{~mL})$. The combined organic layers were washed with sat. $\mathrm{NaHCO}_{3}$ and sat. NaCl solution and dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$. After evaporation of the solvent, the residue was subjected to silica gel column chromatography with EtOAc/petroleum ether 0-20:100-80 to give the title compound ( $220 \mathrm{mg}, 63 \%$ ). ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.38(\mathrm{~s}, 9 \mathrm{H}), 1.61-1.71(\mathrm{~m}, 2 \mathrm{H}), 1.99-2.09(\mathrm{~m}$, $2 \mathrm{H}), 2.80(\mathrm{~s}, 2 \mathrm{H}), 3.62-3.70(\mathrm{~m}, 4 \mathrm{H}), 4.42(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{NH}), 5.16(\mathrm{~s}, 2 \mathrm{H}), 7.21-7.32(\mathrm{~m}, 5 \mathrm{H})$; ${ }^{13} \mathrm{C}_{\mathrm{NMR}}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 28.6,35.7,42.2,51.3,63.5,66.4,128.5,128.6,128.9,136.1$, 156.6, 170.7; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 350(30 \%)$.

## Hydrochloride salt of benzyl 2-(4-aminotetrahydro-2H-pyran-4-yl)acetate (4e)



The above Boc-protected compound ( $220 \mathrm{mg}, 0.63 \mathrm{mmol}$ ) was added to a mixture of trifluoroacetic acid and $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ 3:7 ( 20 mL ), and the solution stirred at rt for 2 h . The solvent was then evaporated under the reduced pressure, and HCl in ether ( 2 M solution, 3 mL ) was added. After a few minutes shaking, the solvent was evaporated under reduced pressure. This process was repeated two more times. The HCl salt of $\mathbf{4 e}(180 \mathrm{mg}, 100 \%)$ was obtained by precipitation using anhydrous ether. ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.90-1.94(\mathrm{~m}, 2 \mathrm{H}), 2.21-2.24(\mathrm{~m}, 2 \mathrm{H}), 3.02$ (s, 2H), 3.60-3.64 (m, 2H), 3.98-4.02 (m, 2H), 5.18 (s, 2H), 7.33-7.36 (m, 5H), 8.83, (br s, $3 \mathrm{H}, \mathrm{NH}_{3}{ }^{+}$); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 33.9,39.8,53.7,62.8,67.5,128.5,128.7,128.8$, 134.9, 170.3; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 250(70 \%)$.

## Benzyl 2-(4-(3-amino-6-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-

 yl)sulfonyl]guanidino)-1-aza-2-oxohexan)tetrahydro-2H-pyran-4-yl)acetate (6e)

The title compound was prepared in two steps. The initial coupling reaction following protocol 1 , by using $\mathbf{4 e}(162 \mathrm{mg}, 0.6 \mathrm{mmol})$ and Fmoc- $(R)-\operatorname{Arg}(\mathrm{Pbf})-\mathrm{OH}(453 \mathrm{mg}, 0.75 \mathrm{mmol})$ to yield the Fmoc protected precursor 5e as a white foamy solid ( $300 \mathrm{mg}, 57 \%$ ); ESIMS $(\mathrm{m} / \mathrm{z}):[\mathrm{M}+\mathrm{H}]^{+} 881(100 \%)$. Piperidine $(0.5 \mathrm{~mL})$, was added to a solution of $\mathbf{5 e}(300 \mathrm{mg}, 0.34 \mathrm{mmol})$ in $\mathrm{CH}_{3} \mathrm{CN}(20 \mathrm{~mL})$. The
mixture was stirred at rt for 3 h . After evaporation of the solvent under reduced pressure, the residue was subjected to flash silica gel column chromatography with $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ (0-5:100-95 to give 6e as a white foam ( $165 \mathrm{mg}, 78 \%$ ). ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.41$ (s, $6 \mathrm{H}), 1.50-1.53(\mathrm{~m}, 2 \mathrm{H}), 1.64-1.69(\mathrm{~m}, 4 \mathrm{H}), 1.77-2.00\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{NH}_{2}\right), 2.04(\mathrm{~s}, 3 \mathrm{H}), 2.14-2.18$ $(\mathrm{m}, 2 \mathrm{H}), 2.43(\mathrm{~s}, 3 \mathrm{H}), 2.53(\mathrm{~s}, 3 \mathrm{H}), 2.84(\mathrm{~s}, 2 \mathrm{H}), 2.90(\mathrm{~s}, 2 \mathrm{H}), 3.12-3.13(\mathrm{~m}, 2 \mathrm{H}), 3.20-3.30$ (m, 1H), 3.50-3.54 (m, 2H), 3.65-3.67 (m, 2H), 5.01 (s, 2H), 6.41 (br s, 3H, 3NH), 7.24-7.28 (m, 5H), 7.45 (br s, $1 \mathrm{H}, \mathrm{NH}$ ); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 12.8,18.2,19.6,25.9,28.9$, $32.1,35.2,35.3,41.0,42.6,43.5,52.0,53.8,55.1,63.6,66.5,86.7,117.8,125.0,128.6,128.7$, 128.9, 132.4, 133.2, 136.1, 138.5, 156.7, 159.0, 170.6, 175.6; ESIMS (m/z): $[\mathrm{M}+\mathrm{H}]^{+} 658$ (100\%).

## Benzyl 2-(4-((3R,6R)-3-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-

 yl)sulfonyl]guanidino)propyl)-6-(4-(tert-butoxycarbonylamino)butyl)-9-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)-1,4,7-triaza-2,5,8-trioxononane)tetrahydro-2H-pyran-4-yl)acetate (8e)

To a solution of $\mathbf{7}(160 \mathrm{mg}, 0.25 \mathrm{mmol})$ and $\mathbf{8 e}$ ( $150 \mathrm{mg}, 0.23 \mathrm{mmol}$ ) in $\mathrm{CH}_{3} \mathrm{CN}(20 \mathrm{~mL}$ ), was added EDCI $\cdot \mathrm{HCl}(100 \mathrm{mg}, 0.50 \mathrm{mmol})$ and HOBt ( $54 \mathrm{mg}, 0.50 \mathrm{mmol}$ ) and the resulting mixture was stirred at rt for 16 h . The reaction mixture was diluted with EtOAc ( 50 mL ) and the EtOAc solution was washed with sat. aq. $\mathrm{NaHCO}_{3}$ and water, dried $\left(\mathrm{MgSO}_{4}\right)$, and filtered. The solvent was removed by rotary evaporation and the residue subjected to flash column chromatography on silica gel with $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2} 0-1: 100-99$ as eluent to afford $\mathbf{8 e}(235 \mathrm{mg}, 85 \%) .[\alpha]^{24}{ }_{\mathrm{D}}$ $-17.6(c 0.3, \mathrm{MeOH}) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 0.43(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.48(\mathrm{~d}, J=$ $6.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.68-0.82(\mathrm{~m}, 2 \mathrm{H}), 0.84-0.96(\mathrm{~m}, 1 \mathrm{H}), 1.02-1.42(\mathrm{~m}, 24 \mathrm{H}), 1.60-1.67(\mathrm{~m}, 2 \mathrm{H})$, $1.70-1.82(\mathrm{~m}, 1 \mathrm{H}), 2.00(\mathrm{~s}, 3 \mathrm{H}), 2.15-2.22(\mathrm{~m}, 2 \mathrm{H}), 2.43(\mathrm{~s}, 3 \mathrm{H}), 2.51(\mathrm{~s}, 3 \mathrm{H}), 2.74-2.90(\mathrm{~m}$, $6 \mathrm{H}), 2.97-3.14(\mathrm{~m}, 2 \mathrm{H}), 3.49-3.55(\mathrm{~m}, 2 \mathrm{H}), 3.63-3.66(\mathrm{~m}, 2 \mathrm{H}), 3.80-3.84(\mathrm{~m}, 2 \mathrm{H}), 3.94-3.98$ $(\mathrm{m}, 1 \mathrm{H}), 4.15-4.26(\mathrm{~m}, 1 \mathrm{H}), 4.33$ and $4.47(\mathrm{ABq}, J=14.5 \mathrm{~Hz}, 2 \mathrm{H}), 4.58-4.69(\mathrm{~m}, 1 \mathrm{H}), 4.98$ (s, 2H), 6.01-6.02 (m, 3H, 3NH), 6.39 (br s, 1H, NH), 6.82 (br s, 1H, NH), 7.05-7.09 (m, $2 \mathrm{H}), 7.17-7.31(\mathrm{~m}, 10 \mathrm{H}), 7.38(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.79(\mathrm{t}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.86-7.91(\mathrm{~m}$, $2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 12.5,18.0,19.4,22.1,22.4,22.6,24.5,26.0,28.5,28.6$, $28.6,29.2,31.3,34.5,34.7,38.0,40.2,40.5,42.6,43.2,52.5,53.5,63.2,63.3,66.2,68.1$,
$78.9,114.3,115.7,117.5,119.3,120.5,123.9,124.2,124.7,124.9,125.6,126.6,126.7,128.0$, 128.1, 128.2, 128.5, 129.2, 129.8, 129.9, 132.2, 133.0, 133.6, 133.8, 135.9, 138.3, 152.2, 154.5, 156.0, 156.4, 158.7, 169.2, 170.3, 171.4, 171.7; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{Na}]^{+} 1305$ (50\%), $[\mathrm{M}+\mathrm{H}]^{+} 1282(10) ;$ HRMS-ESI $m / z: \mathrm{C}_{71} \mathrm{H}_{92} \mathrm{~N}_{7} \mathrm{O}_{13}$ S; calc. 1282.6474, found 1282.6482.

## Benzyl 2-(4-((3R,6R)-3-guanidinopropyl-6-butylamino-9-((S)-2'-(3-methylbutoxy)-1,1'-

 binaphth-2-yloxy)-1,4,7-triaza-2,5,8-trioxononane)tetrahydro-2H-pyran-4-yl)acetate dihydrochloride (2e)

Boc-protected 8e ( $200 \mathrm{mg}, 0.156 \mathrm{mmol}$ ) was added to a mixture of trifluoroacetic acid and $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ 3:7 ( 20 mL ). The solution was stirred at rt for 2 h , before the solvent was evaporated under reduced pressure. HCl in ether ( 2 M solution, 3 mL ) was added and after a few minutes shaking, the solvent was evaporated under reduced pressure. This process was repeated two more times. The dihydrochloride salt $\mathbf{2 e}$ ( 80 mg , $51 \%$ ) was obtained by precipitation using anhydrous ether followed by filtration and vacuum drying. $[\alpha]^{24}{ }_{\mathrm{D}}-19.7(c 0.2, \mathrm{MeOH}) ;{ }^{1} \mathrm{H}$ NMR ( $\left.500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 0.48(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H})$, 0.53 (d, $J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.85-1.03(\mathrm{~m}, 2 \mathrm{H}), 1.04-1.34(\mathrm{~m}, 5 \mathrm{H}), 1.42-1.88(\mathrm{~m}, 8 \mathrm{H}), 2.16-$ $2.40(\mathrm{~m}, 2 \mathrm{H}), 2.68-2.88(\mathrm{~m}, 3 \mathrm{H}), 3.01-3.03(\mathrm{~m}, 1 \mathrm{H}), 3.09(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 3.53-3.84(\mathrm{~m}, 4 \mathrm{H})$, $3.90-4.04(\mathrm{~m}, 1 \mathrm{H}), 4.08-4.33(\mathrm{~m}, 3 \mathrm{H}), 4.47$ and $4.57(\mathrm{ABq}, J=14.5 \mathrm{~Hz}, 2 \mathrm{H}), 5.01-5.20(\mathrm{~m}$, 2 H ), 6.70 (br s, 1H, NH), 7.06 (t, $J=8.0 \mathrm{~Hz}, 2 \mathrm{H}$ ), $7.16-7.44(\mathrm{~m}, 9 \mathrm{H}), 7.48(\mathrm{~d}, J=8.0 \mathrm{~Hz}$, $1 \mathrm{H}), 7.56(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.91(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 8.02(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 8.12(\mathrm{br} \mathrm{s}$, $1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) $\delta 21.4,21.7,22.1,24.5,25.1,26.6,28.8,31.3,34.5,34.7$, $38.2,39.6,40.9,42.5,52.3,52.6,53.9,63.2,63.3,66.1,67.9,68.1,114.8,115.8,119.4,120.7$, 123.7, 124.1, 124.8, 125.3, 126.4, 126.5, 128.0, 128.1, 128.5, 129.6, 129.7, 130.3, 134.0, 134.1, 136.4, 152.9, 154.8, 157.4, 170.5, 172.0, 172.9; MS (ESI, +ve) $\mathrm{m} / \mathrm{z} 930$ (40\%) $[\mathrm{M}+\mathrm{H}]^{+} ; 466(100)[\mathrm{M}+2 \mathrm{H}]^{2+} ;$ HRMS-ESI $m / z:$ calcd for $\mathrm{C}_{53} \mathrm{H}_{68} \mathrm{~N}_{7} \mathrm{O}_{8} 930.5129$, found 930.5133.

## Benzyl 1-((tert-butoxycarbonylamino)methyl)cyclohexanecarboxylate



Benzyl bromide ( $0.25 \mathrm{~mL}, 2 \mathrm{mmol}$ ) was added to a stirred suspension of 1-((tert-butoxycarbonylamino)methyl)cyclohexanecarboxylic acid ( $257 \mathrm{mg}, 1.0 \mathrm{mmol}$ ) and anhydrous $\mathrm{K}_{2} \mathrm{CO}_{3}(345 \mathrm{mg}, 2.5 \mathrm{mmol})$ in anhydrous THF ( 30 mL ). The mixture was heated under reflux for 3 h before being cooled,
poured into water ( 50 mL ) and extracted with EtOAc ( $3 \times 50 \mathrm{~mL}$ ). The combined organic layers were washed with sat. $\mathrm{NaHCO}_{3}$ and sat. NaCl solution, and dried $\left(\mathrm{Na}_{2} \mathrm{SO}_{4}\right)$. After evaporation of the organic solvent, the residue was subjected to silica gel column chromatography with $0-20 \% \mathrm{EtOAc} /$ petroleum ether 0-20:100-80 to give the benzyl ester $(238 \mathrm{mg}, 69 \%)$ as a colorless oil. ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.30-1.65(\mathrm{~m}, 8 \mathrm{H}), 1.41(\mathrm{~s}$, 9H), 1.92-2.01 (m, 2H), 3.31 (br s, 2H), 4.70 (br s, 1H, NH), 5.18 (s, 2H), 7.21-7.42 (m, 5H); ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 348(30 \%)$.

## Hydrochloride salt of benzyl 1-(aminomethyl)cyclohexanecarboxylate (4f)



The above NBoc compound ( $230 \mathrm{mg}, 0.69 \mathrm{mmol}$ ) was added to a mixture of trifluoroacetic acid and $\mathrm{CH}_{2} \mathrm{Cl}_{2} 3: 7(20 \mathrm{~mL})$, and the solution was stirred at rt for 2 h . The solvent was then evaporated under reduced pressure, HCl in ether ( 2 M solution, 3 mL ) was added, and after a few minutes shaking, the solvent was evaporated under reduced pressure. This process was repeated two more times. The HCl salt of $\mathbf{4 f}(200 \mathrm{mg}, 100 \%)$ was obtained by precipitation using anhydrous ether. ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.41-1.59(\mathrm{~m}, 6 \mathrm{H}), 1.57-1.58(\mathrm{~m}, 2 \mathrm{H}), 2.11-$ $2.14(\mathrm{~m}, 2 \mathrm{H}), 3.13(\mathrm{~s}, 2 \mathrm{H}), 5.27(\mathrm{~s}, 2 \mathrm{H}), 7.27-7.38(\mathrm{~m}, 5 \mathrm{H}), 8.49\left(\mathrm{br} \mathrm{s}, 3 \mathrm{H}, \mathrm{NH}_{3}{ }^{+}\right) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 22.3,25.4,31.6,45.6,45.9,67.5,128.4,128.5,128.8,136.1,174.4$; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 248(70 \%)$.

## Benzyl 1-((4R)-2-aza-7-((2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-

yl)sulfonylguanidino))-4-(9H-9-fluorenylmethoxycarboxamido)-3oxoheptan)cyclohexanecarboxylate (5f)


To a solution of $\mathrm{Fmoc}-(R)-\operatorname{Arg}(\mathrm{Pbf})-\mathrm{OH}$ (453 mg, 0.75 mmol ) and $4 \mathbf{f}(200 \mathrm{mg}, 0.7 \mathrm{mmol})$ in $\mathrm{CH}_{3} \mathrm{CN}$ $(20 \mathrm{~mL})$, was added EDCI $\cdot \mathrm{HCl}(200 \mathrm{mg}, 1.0 \mathrm{mmol})$, HOBt ( $108 \mathrm{mg}, 0.8 \mathrm{mmol}$ ), and DIPEA ( 0.35 mL , 0.2 mmol ) and the resulting mixture was stirred at rt for 16 h . The reaction was diluted with EtOAc ( 50 mL ) and the EtOAc solution was washed with sat. aq. $\mathrm{NaHCO}_{3}$ and water, dried $\left(\mathrm{MgSO}_{4}\right)$, and filtered. The solvent was removed by rotary evaporation, and the residue was then subjected to flash silica gel chromatography with MeOH in $\mathrm{CH}_{2} \mathrm{Cl}_{2} \mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}(0-3: 100-97)$ as eluent to afford 5 f ( $490 \mathrm{mg}, 75 \%$ ). ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.10-1.19(\mathrm{~m}, 6 \mathrm{H}), 1.44(\mathrm{~s}, 6 \mathrm{H})$, $1.24-1.32(\mathrm{~m}, 5 \mathrm{H}), 1.36-1.44(\mathrm{~m}, 1 \mathrm{H}), 1.98-2.05(\mathrm{~m}, 2 \mathrm{H}), 2.09(\mathrm{~s}, 3 \mathrm{H}), 2.53$ (s, 3H), 2.61 (s,

3H), 2.93 (s, 2H), 3.22-3.24 (m, 3H), 3.25-3.31 (m, 1H), 4.16-4.19 (m, 2H), 4.36-4.37 (m, 2 H ), 5.07 and $5.11(\mathrm{ABq}, J=12.5 \mathrm{~Hz}, 2 \mathrm{H}), 5.68$ (br s, $1 \mathrm{H}, \mathrm{NH}$ ), 5.81 (br s, $1 \mathrm{H}, \mathrm{NH}$ ), 6.14 (br $\mathrm{s}, 2 \mathrm{H}, 2 \mathrm{NH}$ ), 6.70 (br s, 1H, NH), 7.27-7.32 (m, 7H), 7.37-7.40 (m, 2H), 7.52-7.62 (m, 2H), 7.75 (d, $J=7.5 \mathrm{~Hz}, 2 \mathrm{H}$ ); ${ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 12.7$, 18.2, 19.6, 22.9, 25.9, 28.9, $32.0,32.4,40.9,43.5,46.5,48.1,54.6,66.9,86.6,117.7,124.9,128.4,128.5,128.8,132.4$, 133.3, 136.3, 138.5, 156.7, 158.9, 175.6, 175.7; ESIMS (m/z): $[\mathrm{M}+\mathrm{Na}]^{+} 900$ (100\%).

Benzyl 1-((4R)-2-aza-7-((2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-
yl)sulfonylguanidino))-4-(9H-9-fluorenylmethoxycarboxamido)-3oxoheptan)cyclohexanecarboxylate (6f)


Piperidine ( $0.5 \mathrm{~mL}, 5.06 \mathrm{mmol}$ ) was added to a solution of $\mathbf{5 f}$ ( $380 \mathrm{mg}, 0.34 \mathrm{mmol}$ ) in $\mathrm{CH}_{3} \mathrm{CN}(20 \mathrm{~mL}$ ) and the mixture was stirred at rt for 3 h . After evaporation of solvent under reduced pressure, the residue was subjected to flash silica gel column chromatography with $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}(0-5: 100-95)$ to give $6 f$ as a white foam ( $184 \mathrm{mg}, 83 \%$ ). ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 1.21-1.30(\mathrm{~m}, 5 \mathrm{H})$, $1.35-1.74\left(\mathrm{~m}, 9 \mathrm{H} / \mathrm{NH}_{2}\right), 1.42(\mathrm{~s}, 6 \mathrm{H}), 1.99-2.01(\mathrm{~m}, 2 \mathrm{H}), 2.05(\mathrm{~s}, 3 \mathrm{H}), 2.47(\mathrm{~s}, 3 \mathrm{H}), 2.54(\mathrm{~s}$, $3 \mathrm{H}), 2.91(\mathrm{~s}, 2 \mathrm{H}), 3.12-3.14(\mathrm{~m}, 2 \mathrm{H}), 3.21-3.37(\mathrm{~m}, 3 \mathrm{H}), 5.06(\mathrm{~s}, 2 \mathrm{H}), 6.40(\mathrm{br} \mathrm{s}, 3 \mathrm{H}, 3 \mathrm{NH})$, $7.24-7.30(\mathrm{~m}, 5 \mathrm{H}), 7.56(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{NH}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 12.7,18.2,19.6,25.7$, $28.8,29.5,31.9,32.4,32.9,40.8,43.5,53.7,54.4,56.6,63.6,63.7,67.4,86.7,117.8,124.9$, 128.4, 128.6, 128.8, 132.4, 133.1, 135.8, 138.5, 156.6, 159.0, 173.3, 175.5; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 644$ (100\%).

Benzyl 1-((4R,7R)-4-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-
yl)sulfonyl]guanidinopropyl)-10-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)-7-(4-(tert-butoxycarbonylamino)butyl)-2,5,8-triaza-3,6,9-trioxodecan)cyclohexanecarboxylate (8f)

To a solution of $7(192 \mathrm{mg}, 0.30 \mathrm{mmol})$ and $\mathbf{6 f}(150 \mathrm{mg}, 0.23 \mathrm{mmol})$ in $\mathrm{CH}_{3} \mathrm{CN}(20 \mathrm{~mL})$, was added EDCI $\cdot \mathrm{HCl}(100 \mathrm{mg}, 0.50 \mathrm{mmol})$ and $\mathrm{HOBt}(54 \mathrm{mg}, 0.50 \mathrm{mmol})$, and the resulting mixture was stirred at rt for 16 h . The reaction was diluted with $\mathrm{EtOAc}(50 \mathrm{~mL})$ and the EtOAc solution was washed with sat. aq. $\mathrm{NaHCO}_{3}$ and water, dried $\left(\mathrm{MgSO}_{4}\right)$, and filtered. The solvent was removed by rotary evaporation and the residue was subjected to flash chromatography on silica gel with $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2} 0-1: 100-99$ as eluent to afford $\mathbf{8 f}$ ( 244 mg , $83 \%) .[\alpha]^{24}{ }_{\mathrm{D}}-18.3$ (c 0.5, MeOH); ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 0.49(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 3 \mathrm{H}$ ),

0.53 (d, J=7.0 Hz, 3H), 0.80-0.81 (m, 2H), 0.89$0.95(\mathrm{~m}, 2 \mathrm{H}), 1.09-1.61(\mathrm{~m}, 16 \mathrm{H}), 1.42(\mathrm{~s}, 9 \mathrm{H})$, $1.428(\mathrm{~s}, 3 \mathrm{H}), 1.43(\mathrm{~s}, 3 \mathrm{H}), 1.69-1.80(\mathrm{~m}, 1 \mathrm{H})$, $1.94-2.05(\mathrm{~m}, 2 \mathrm{H}), 2.07(\mathrm{~s}, 3 \mathrm{H}), 2.50(\mathrm{~s}, 3 \mathrm{H}), 2.57$ (s, 3H), 2.86-3.20 (m, 4H), 2.92 ( $\mathrm{s}, 2 \mathrm{H}$ ), 3.27 (dd, $\left.J_{1}=13.5 \mathrm{~Hz}, J_{2}=6.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 3.48\left(\mathrm{dd}, J_{1}=\right.$ $\left.13.0 \mathrm{~Hz}, J_{2}=6.5 \mathrm{~Hz}, 1 \mathrm{H}\right), 3.86-3.90(\mathrm{~m}, 1 \mathrm{H})$, $3.90-4.00(\mathrm{~m}, 1 \mathrm{H}), 4.01-4.04(\mathrm{~m}, 1 \mathrm{H}), 4.22-4.32$ $(\mathrm{m}, 1 \mathrm{H}), 4.41$ and $4.50(\mathrm{ABq}, J=14.5 \mathrm{~Hz}, 2 \mathrm{H}), 4.63-4.72(\mathrm{~m}, 1 \mathrm{H}, \mathrm{NH}), 5.08(\mathrm{~s}, 2 \mathrm{H}), 6.10-$ $6.11(\mathrm{~m}, 3 \mathrm{H}, 2 \mathrm{NH}), 6.55(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{NH}), 6.82(\mathrm{br} \mathrm{d}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{NH}), 7.13\left(\mathrm{dd}, J_{I}=\right.$ $\left.12.5 \mathrm{~Hz}, J_{2}=8.5 \mathrm{~Hz}, 2 \mathrm{H}\right), 7.20-7.37(\mathrm{~m}, 10 \mathrm{H}), 7.44(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.86(\mathrm{t}, J=8.5 \mathrm{~Hz}$, $2 \mathrm{H}), 7.94(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(125 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 13.7,19.2,20.5,23.3,23.5$, 23.7, 23.9, 23.9, 25.7, 26.8, 29.7, 29.8, 30.2, 30.9, 32.5, 32.8, 32.9, 39.1, 41.2, 41.5, 44.4, 47.7, 49.2, 53.7, 67.7, 69.2, 69.3, 80.0, 87.5, 115.5, 117.0, 118.6, 120.4, 121.7, 124.9, 125.3, 125.7, 126.1, 126.7, 127.7, 127.8, 129.1, 129.2, 129.3, 129.7, 130.3, 130.9, 131.0, 133.3, $134.2,134.8,135.0,137.5,139.4,153.4,155.6,157.2,157.5,159.8,170.2,172.5,172.9$, 176.5; ESIMS $(m / z):[M+H]^{+} 1280(40 \%) ;$ HRMS-ESI $m / z: \quad$ calcd for $\mathrm{C}_{72} \mathrm{H}_{94} \mathrm{~N}_{7} \mathrm{O}_{12} \mathrm{~S}$ 1280.6681, found 1280.6675 .

Benzyl 1-((4R,7R)-7-butylamino-4-(3-guanidinopropyl)-10-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)-2,5,8-triaza-3,6,9-
 trioxodecan)cyclohexanecarboxylate dihydrochloride (2f)

Compound $\mathbf{8 f}(200 \mathrm{mg}, 0.16 \mathrm{mmol})$ was added to a mixture of trifluoroacetic acid and $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3: 7$, 20 mL ) and the solution was stirred at rt for 2 h . The solvent was then evaporated under the reduced pressure, HCl in ether ( 2 M solution, 3 mL ) was added, and after a few minutes shaking, the solvent was evaporated under reduced pressure. This process was repeated two more times. The salt $\mathbf{2 f}(110 \mathrm{mg}, 70 \%)$ was obtained by precipitation using anhydrous ether followed filtration and vacuum drying. $[\alpha]^{24}{ }_{D}-20.1$ (c $0.2, \mathrm{MeOH}) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 0.51(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.56(\mathrm{~d}, J=6.5 \mathrm{~Hz}$, $3 \mathrm{H}), 0.85-1.05(\mathrm{~m}, 2 \mathrm{H}), 1.13-1.78(\mathrm{~m}, 19 \mathrm{H}), 2.00-2.17$ (m, 2H), 2.70-2.91 (m, 2H), 3.07$3.21(\mathrm{~m}, 2 \mathrm{H}), 3.21-3.24(\mathrm{~m}, 1 \mathrm{H}), 3.46-3.49(\mathrm{~m}, 1 \mathrm{H}), 3.95-3.98(\mathrm{~m}, 1 \mathrm{H}), 4.11-4.15(\mathrm{~m}, 2 \mathrm{H})$, $4.27(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.46$ and $4.55(\mathrm{ABq}, J=14.5 \mathrm{~Hz}, 2 \mathrm{H}), 5.11(\mathrm{~s}, 2 \mathrm{H}), 7.04-7.08(\mathrm{~m}, 2 \mathrm{H}), 7.20-$
$7.23(\mathrm{~m}, 2 \mathrm{H}), 7.31-7.40(\mathrm{~m}, 7 \mathrm{H}), 7.45(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.55(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.89-7.95$ $(\mathrm{m}, 3 \mathrm{H} / \mathrm{NH}), 8.02(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) $\delta 21.3,21.5,22.0,22.7$, 24.3, 24.7, 25.1, 25.4, 26.5, 29.0, 31.0, 31.6, 31.7, 38.0, 39.1, 40.7, 52.3, 53.1, 66.5, 67.8, $68.0,114.7,115.7,119.7,120.4,120.5,123.5,123.9,124.7,125.1,126.2,126.3,127.8,128.0$, $128.3,129.4,129.6,130.1,132.3,133.8,134.0,136.4,143.3,152.8,154.7,157.3,171.9$, 172.7, 175.1; ESIMS $(\mathrm{m} / \mathrm{z}):[\mathrm{M}+\mathrm{H}]^{+} 928(40 \%),[\mathrm{M}+2 \mathrm{H}]^{2+} 465$ (100); HRMS-ESI $\mathrm{m} / \mathrm{z}$ : calcd for $\mathrm{C}_{54} \mathrm{H}_{70} \mathrm{~N}_{7} \mathrm{O}_{7} 928.5337$, found 928.5343.

## Benzyl 2-(tert-butoxycarbonylamino)-2-ethylbutanoate



To 2-(tert-butoxycarbonylamino)-2-ethylbutanoic acid (165 mg, $0.71 \mathrm{mmol})$ and $\mathrm{K}_{2} \mathrm{CO}_{3}(400 \mathrm{mg}, 2.87 \mathrm{mmol})$ in acetone ( 25 mL ) was added benzyl bromide ( $0.2 \mathrm{~mL}, 1.68 \mathrm{mmol}$ ). The mixture was heated under reflux overnight before being cooled, filtered and evaporated to dryness. The resulting residue was dried overnight under vacuum to yield the protected acid ( $182 \mathrm{mg}, 80 \%$ ) as a colorless oil. ${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 0.71(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.75(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H})$, $1.42(\mathrm{~s}, 9 \mathrm{H}), 1.74-1.86(\mathrm{~m}, 2 \mathrm{H}), 2.16-2.56(\mathrm{~m}, 2 \mathrm{H}), 5.17$ (s, 2H), 5.50 (br s, 1H, NH), 7.29$7.36(\mathrm{~m}, 5 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.1,28.2,33.3,64.6,67.0,78.8,128.2,128.3$, 128.4, 135.3, 153.7, 173.7.

## Benzyl 2-amino-2-ethylbutanoate (4g)



This compound was prepared following protocol 3 and basification, by using the above protected amino acid ( $180 \mathrm{mg}, 0.56 \mathrm{mmol}$ ) to yield $\mathbf{4 g}$ $(116 \mathrm{mg}, 94 \%)$ as a light brown oil. ${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 0.83(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H})$, $0.85(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H}), 1.55-1.67(\mathrm{~m}, 2 \mathrm{H}), 1.76-1.89(\mathrm{~m}, 2 \mathrm{H}), 2.47\left(\mathrm{br} \mathrm{s}, 2 \mathrm{H}, \mathrm{NH}_{2}\right), 5.15(\mathrm{~s}$, 2H), 7.32-7.40 (m, 5H); ${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.1,32.1,62.1,66.7,128.1,128.2$, 128.4, 135.8, 176.4; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 222$ ( $100 \%$ ).

## Benzyl (5R)-3-aza-2,2-diethyl-5-(9H-9-fluorenylmethoxycarboxamido)-8-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-yl)sulfonyl]guanidino)-4oxooctanoate ( 5 g )

To a solution of Fmoc- $(R)-\operatorname{Arg}(\mathrm{Pbf})-\mathrm{OH}(600 \mathrm{mg}, 0.92 \mathrm{mmol})$ and $\mathbf{4 g}(210 \mathrm{mg}, 0.95 \mathrm{mmol})$ in acetonitrile ( 25 mL ) was added DIPEA ( 0.4 mL ), followed by BOP reagent ( 600 mg , $1.36 \mathrm{mmol})$. The reaction mixture was stirred at rt for 3 h before the solvent was evaporated. The residue was subjected to column flash chromatography $\left(\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}(5: 95)\right.$ to yield $\mathbf{5 g}$

(402 mg, 50\%) as an off-white foam. ${ }^{1} \mathrm{H}$ NMR ( 300 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 0.63-0.68(\mathrm{~m}, 6 \mathrm{H}), 1.41(\mathrm{~s}, 6 \mathrm{H}), 1.50-1.70(\mathrm{~m}$, $3 \mathrm{H}), 1.75-1.89(\mathrm{~m}, 3 \mathrm{H}), 2.06(\mathrm{~s}, 6 \mathrm{H}), 2.11-2.24(\mathrm{~m}, 2 \mathrm{H})$, $2.50(\mathrm{~s}, 3 \mathrm{H}), 2.57(\mathrm{~s}, 3 \mathrm{H}), 2.89(\mathrm{~s}, 2 \mathrm{H}), 3.12-3.27(\mathrm{~m}, 2 \mathrm{H})$, 4.11-4.15 (m, 1H), 4.15-4.24 (m, 1H), 4.26-4.34 (m, 1H), $5.13(\mathrm{~s}, 2 \mathrm{H}), 5.97(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{NH}), 6.08$ (br s, 1 H , NH), 6.23 (s, 2H, 2NH), 7.12 (br s, 1H, NH), 7.20-7.38 $(\mathrm{m}, 9 \mathrm{H}), 7.54(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.72(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}) ; \operatorname{ESIMS}(\mathrm{m} / \mathrm{z}):[\mathrm{M}+\mathrm{H}]^{+} 852$ (100\%).

## Benzyl (5R)-5-amino-3-aza-2,2-diethyl-8-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-yl)sulfonyl]guanidino)-4-oxooctanoate ( 6 g )



This compound was prepared following protocol 2, by using 5 g (402 mg, 0.47 mmol ) to yield $\mathbf{6 g}(187 \mathrm{mg}, 63 \%) .{ }^{1} \mathrm{H}$ NMR (500 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 0.66-0.71(\mathrm{~m}, 6 \mathrm{H}), 1.33(\mathrm{~s}, 3 \mathrm{H}), 1.34(\mathrm{~s}, 3 \mathrm{H}), 1.45(\mathrm{~s}, 9 \mathrm{H})$, $1.57-1.67(\mathrm{~m}, 3 \mathrm{H}), 1.80-1.89(\mathrm{~m}, 3 \mathrm{H}), 2.08(\mathrm{~s}, 3 \mathrm{H}), 2.13-2.19(\mathrm{~m}$, $2 \mathrm{H}), 2.49(\mathrm{~s}, 3 \mathrm{H}), 2.56(\mathrm{~s}, 3 \mathrm{H}), 2.94(\mathrm{~s}, 2 \mathrm{H}), 3.05-3.25(\mathrm{~m}, 2 \mathrm{H}), 3.57-$ $3.66(\mathrm{~m}, 1 \mathrm{H}), 5.15(\mathrm{~s}, 2 \mathrm{H}), 6.42(\mathrm{~s}, 2 \mathrm{H}, 2 \mathrm{NH}), 6.52(\mathrm{br} \mathrm{s}, 1 \mathrm{H}, \mathrm{NH})$, 7.29-7.35 (m, 5H), $7.96(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH}) ;$ ESIMS $(\mathrm{m} / \mathrm{z}):[\mathrm{M}+\mathrm{H}]^{+} 630$ (100\%).

Benzyl (5R,8R)-2,2-diethyl-5-(3-[(2,3-dihydro-2,2,4,6,7-pentamethyl-2H-1-benzofuran-5-yl)sulfonyl]guanidinopropyl)-11-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)-8-(4-(tert-butoxycarbonylamino)butyl)-3,6,9-triaza


## 4,7,10-trioxoundecanoate ( 8 g )

To a solution of $7(50 \mathrm{mg}, 0.078 \mathrm{mmol})$ and $\mathbf{6 g}$ ( $48 \mathrm{mg}, 0.076 \mathrm{mmol}$ ) in acetonitrile ( 10 mL ) was added HOBt ( $30 \mathrm{mg}, 0.222 \mathrm{mmol}$ ), followed by EDCI ( $30 \mathrm{mg}, 0.156 \mathrm{mmol}$ ). The mixture was stirred at rt for 3 days before the solvent was removed. The residue was subjected to radial chromatography $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2} 1-2: 99-98$ to yield $\mathbf{8 g}(54 \mathrm{mg}, 55 \%)$ as an off-white solid. ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{~Hz}, \mathrm{CDCl}_{3}\right) \delta 0.50(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 3 \mathrm{H})$, $0.54(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.64-0.71(\mathrm{~m}, 6 \mathrm{H}), 0.80-0.89(\mathrm{~m}, 3 \mathrm{H}), 0.94-0.96(\mathrm{~m}, 1 \mathrm{H}), 1.11-$ $1.59(\mathrm{~m}, 12 \mathrm{H}), 1.33(\mathrm{~s}, 3 \mathrm{H}), 1.34(\mathrm{~s}, 3 \mathrm{H}), 1.41(\mathrm{~s}, 9 \mathrm{H}), 1.79-1.87(\mathrm{~m}, 3 \mathrm{H}), 2.07(\mathrm{~s}, 3 \mathrm{H}), 2.26-$
$2.35(\mathrm{~m}, 2 \mathrm{H}), 2.49(\mathrm{~s}, 3 \mathrm{H}), 2.55(\mathrm{~s}, 3 \mathrm{H}), 2.90-2.97(\mathrm{~m}, 2 \mathrm{H}), 2.92(\mathrm{~s}, 3 \mathrm{H}), 3.08-3.20(\mathrm{~m}, 2 \mathrm{H})$, $3.88-3.93(\mathrm{~m}, 1 \mathrm{H}), 4.05-4.09(\mathrm{~m}, 2 \mathrm{H}), 4.25-4.32(\mathrm{~m}, 1 \mathrm{H}), 4.41$ and $4.49(\mathrm{ABq}, J=12.0 \mathrm{~Hz}$, $2 \mathrm{H}), 4.74-4.76(\mathrm{~m}, 1 \mathrm{H}, \mathrm{NH}), 5.19(\mathrm{~s}, 2 \mathrm{H}), 6.18-6.20(\mathrm{~m}, 3 \mathrm{H}, 3 \mathrm{NH}), 7.12(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H})$, $7.16(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.20-7.37(\mathrm{~m}, 10 \mathrm{H}), 7.44(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.83(\mathrm{~d}, J=7.5 \mathrm{~Hz}$, $1 \mathrm{H}), 7.87(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.92(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.94(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.3,12.4,17.9,19.3,21.6,22.1,22.3,22.6,24.5,25.6,27.4,27.5,28.4$, $28.5,29.1,31.0,37.9,40.0,40.4,43.2,52.7,53.5,65.6,67.4,68.0,68.2,78.9,86.2,114.2$, $115.8,117.3,119.3,120.4,123.8,124.1,124.5,124.9,125.5,126.6,127.9,128.0,128.2$, $128.5,128.6,129.1,129.6,129.8,132.2,133.1,133.6,133.8,135.3,138.3,152.2,154.4$, 156.2, 158.6, 169.1, 170.2, 171.5, 173.6; ESIMS ( $\mathrm{m} / \mathrm{z}$ ): $[\mathrm{M}+\mathrm{H}]^{+} 1254$ ( $100 \%$ ).

Benzyl (5R,8R)-2,2'-diethyl-8-butylamino-5-(3-guanidinopropyl)-11-((S)-2'-(3-methylbutoxy)-1,1'-binaphth-2-yloxy)-3,6,9-triaza-4,7,10-trioxoundecanoate dihydrochloride (2g)


This compound was prepared following protocol 3, by using $\mathbf{8 g}$ ( $54 \mathrm{mg}, 0.043 \mathrm{mmol}$ ) to yield $\mathbf{2 g}$ ( $37 \mathrm{mg}, 88 \%$ ) as an off-white solid. ${ }^{1} \mathrm{H}$ NMR $\left(300 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 0.53(\mathrm{~d}, J=6.1 \mathrm{~Hz}, 3 \mathrm{H})$, $0.58(\mathrm{~d}, J=6.3 \mathrm{~Hz}, 3 \mathrm{H}), 0.73-0.80(\mathrm{~m}, 6 \mathrm{H}), 0.91-$ $0.98(\mathrm{~m}, 2 \mathrm{H}), 1.08-1.30(\mathrm{~m}, 5 \mathrm{H}), 1.49-1.69(\mathrm{~m}$, 7H), 1.77-2.19 (m, 5H), 2.74-2.80 (m, 2H), 3.10-3.15 (m, 2H), 3.93-4.01 (m, 1H), 4.13-4.22 $(\mathrm{m} 2 \mathrm{H}), 4.26-4.30(\mathrm{~m}, 1 \mathrm{H}), 4.45$ and $4.56(\mathrm{ABq}, J=14.7,2 \mathrm{H}), 5.18(\mathrm{~s}, 2 \mathrm{H}), 7.07\left(\mathrm{dd}, J_{l}=\right.$ $\left.8.4 \mathrm{~Hz}, J_{2}=4.5 \mathrm{~Hz}, 2 \mathrm{H}\right), 7.19-7.25(\mathrm{~m}, 2 \mathrm{H}), 7.31-7.40(\mathrm{~m}, 7 \mathrm{H}), 7.48(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H})$, $7.55(\mathrm{~d}, J=9.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.91(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 2 \mathrm{H}), 8.01\left(\mathrm{dd}, J_{1}=9.0 \mathrm{~Hz}, J_{2}=7.2 \mathrm{~Hz}, 2 \mathrm{H}\right)$; ${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) $\delta 8.3,8.4,22.6,22.8,23.2,25.6,26.3,27.4,27.8,28.0,30.0$, $32.5,39.3,40.4,41.9,53.3,54.4,65.6,68.3,69.0,69.2,116.0,116.9,120.5,124.8,125.2$, $126.0,126.4,127.5,127.6,129.1,129.3,129.49,129.5,129.6,130.7,130.8,130.9,131.4$, $135.1,135.2,137.1,154.0,155.9,158.5,170.7,172.7,173.1,174.6$; ESIMS $(\mathrm{m} / \mathrm{z}):[\mathrm{M}+\mathrm{H}]^{+}$ $902(15 \%) ;[\mathrm{M}+2 \mathrm{H}]^{2+} 452$ (100); HRMS-ESI $m / z$ : calcd for $\mathrm{C}_{52} \mathrm{H}_{68} \mathrm{~N}_{7} \mathrm{O}_{7} 902.5180$, found 902.5220.

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