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Original article

Synthesis of novel *N*-protected hydrophobic phenylalanines and their application in potential antibacterials

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ABSTRACT

An efficient synthesis of two new *N*-acetyl-4′-arylphenylalanines is described together with their incorporation into a number of cationic peptoid antibacterial agents, one of which had an MIC of 7.8 μg/mL against *Staphylococcus aureus*.

1. Introduction

With the increasing spread of antibacterial resistance [1–3], including resistance by pathogenic bacteria to vancomycin [4,5], there is a compelling imperative for new antibacterials [6,7]. In this context, we have undertaken a program investigating the design and synthesis of cyclic cationic peptoids linked by a hydrophobic scaffold as potential antibacterial agents, and thus far, have shown the binaphthyl [8] and carbazole scaffolds [9,10] within these cyclic peptoids to produce antibacterial agents, whilst the smaller indole based cyclic peptoids [11] failed to inhibit bacterial growth. Therefore, as part of this program targeting new peptoid derivatives as antibacterial agents and attempting to address the resistance mechanism against vancomycin, we investigated the synthesis of novel hydrophobic amino acids and their subsequent incorporation into acyclic cationic peptides. These peptides were designed to further explore the effect of hydrophobicity and the role of cationic residues within the peptide. The synthesis and methodology of the novel hydrophobic amino acids, their incorporation into cationic peptides and aspects of their in vitro antibacterial activity are reported in this paper [12].

2. Chemistry

The strategy employed to prepare the two hydrophobic amido acids proceeded via a common trimethylstannyl amido acid **5**, which was prepared from phenylalanine in four steps (Scheme 1). This common intermediate was then coupled to either 9-bromoanthracene or 9-bromophenanthrene via a Stille coupling [13] protocol followed by subsequent saponification to yield the hydrophobic amido acids **7a** and **7b** (Scheme 1).

Therefore, iodination of phenylalanine was performed as previously described [14] to produce *p*-iodophenylalanine **2**, which was isolated in quantitative yield. Esterification of **2** with MeOH/$SOCl_2$ afforded the methyl ester **3** as the hydrochloride salt in excellent yield, which was carried forward to the *N*-acetyl derivative **4** without further purification (Scheme 1). The key trimethylstannyl intermediate **5** was prepared following the procedure of Morera and Ortar [15] in 76% yield. This methodology was favoured over previously reported methods [16], due to the faster reaction time in preparing the aryltrimethylstannane over the aryltributylstannane, significantly decreasing the possibility of racemization at the α position of the amido ester.

The hydrophobic amido esters **6a** and **6b** were prepared via a Stille coupling methodology [14,15] in 67% and 59% yields,

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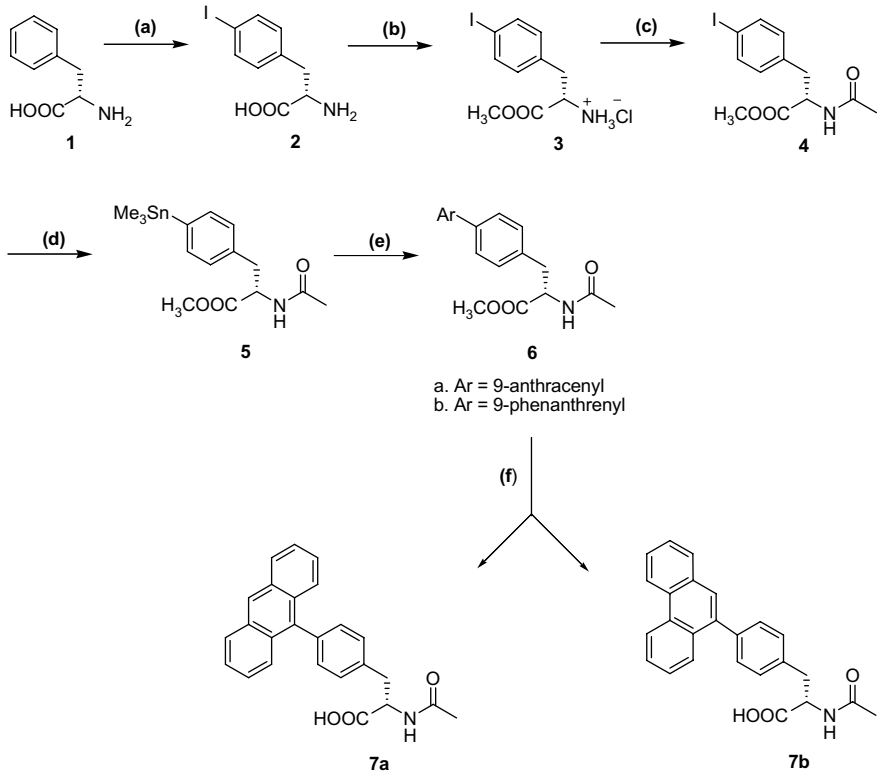
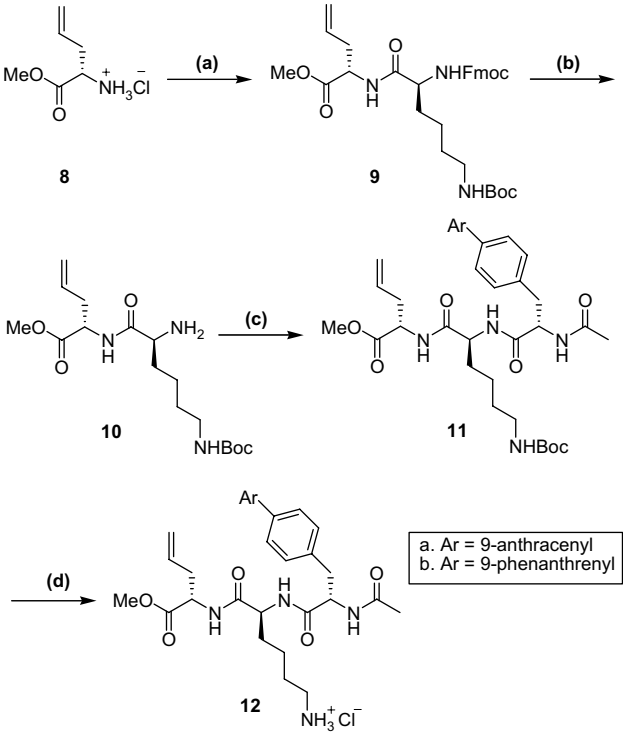


Scheme 1. *Reagents and conditions*: (a) $NaIO_3$, AcOH, H_2SO_4, 70 °C, 16 h, 100%; (b) $SOCl_2$, MeOH, 0 °C–RT, 16 h, 99%; (c) Ac_2O, $AcONa_{(aq)}$, 0 °C, 56%; (d) $(SnMe_3)_2$, $Pd(OAc)_2$, PPh_3, PhMe, 100 °C, 30 min, 76%; (e) *a*. 9-bromoanthracene, $Pd(OAc)_2$, P(*o*-tol)$_3$, DMF, 70 °C, 16 h, **6a**: 67%; *b*. 9-bromophenanthrene, $Pd(OAc)_2$, P(*o*-tol)$_3$, DMF, 70 °C, 16 h, **6b**: 59%; (f) LiOH, THF/H_2O, RT, 16 h, **7a**: 90%, **7b**: 55%.

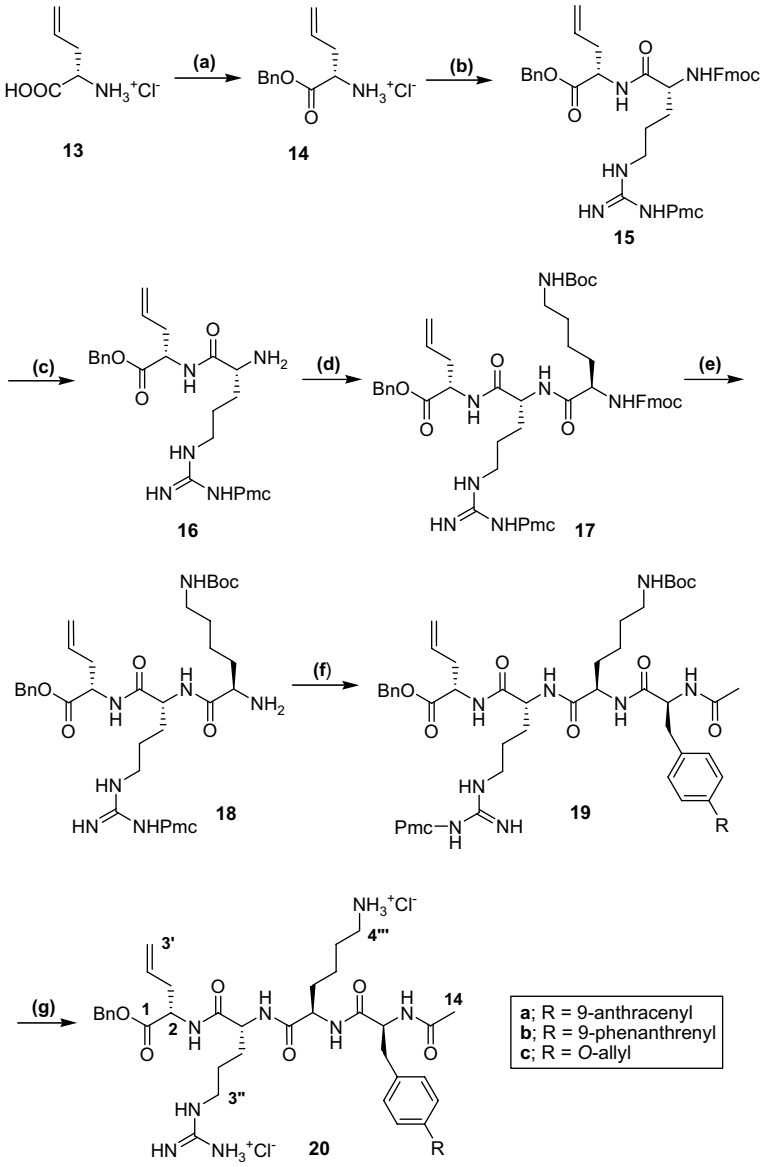
respectively (Scheme 1). The ligand of choice for this reaction was tri-*o*-tolylphosphine, as phenyl transfer to the amino acid was observed when triphenylphosphine was present as the ligand. It was found that increasing the temperature above 85 °C resulted in faster reaction times and also resulted in partial racemization of the α-stereocentre of the amido ester. However, at 70 °C, no racemization was observed. Partial racemization of these products formed at the higher temperature was detected from ^{1}H NMR analysis of their products **12a**, and **12b** (Scheme 2) that showed NMR signals for a minor diastereomer. The desired free acid form was obtained by saponification to afford **7a** and **7b** in 90% and 55% yields, respectively.

The peptide fragment **10** was prepared by employing a well-established EDCI peptide coupling methodology and an Fmoc protection/deprotection protocol [8–11]. This fragment was coupled to **7a** and **7b** to give the protected tripeptoids **11a** and **11b**, respectively (Scheme 2). *N*-Boc deprotection of **11a** and **11b** by exposure to TFA, followed by anion exchange with HCl provided the hydrochloride salts **12a** and **12b**, respectively (Scheme 2).

This chemistry was further expanded to include the dicationic tetrapeptoids **20a** and **20b**, which also incorporated the hydrophobic amido acids **7a** and **7b** and the less hydrophobic *O*-allyltyrosine peptoid analogue **20c** (Scheme 3). Allyl glycine **13** was converted to its benzyl ester **14** which was coupled to Fmoc-D-arginine(Pmc)OH to give the dipeptide **15**. Selective base catalysed removal of the *N*-Fmoc protecting group of **15** gave the free amine **16** that was coupled to Fmoc-D-lysine(Boc)OH to give the protected tripeptoid **17**. *N*-Fmoc removal from **17** and coupling of the resulting amine **18** with **7a** or **7b** gave the protected tetrapeptoids **19a** and **19b**, respectively. Coupling of **18** with *N*-acetyl-*O*-allyl-L-tyrosine [17] gave the tetrapeptoid **19c**. Acid catalysed deprotection of **19a**, **19b** and **19c**, followed by anion exchange with HCl, gave the bis-hydrochloride salts of tetrapeptoids **20a**, **20b** and **20c**, respectively (Scheme 3).



Scheme 2. *Reagents and conditions*: (a) Fmoc-L-lysine(Boc)OH, EDCI, HOBt, CH_2Cl_2, DMAP, RT, 16 h, 87%; (b) 1% piperidine, MeCN, RT, 3 h, 100%; (c) **7a**, EDCI, HOBt, DMF, RT, 16 h, **11a**: 59%, **11b**: 50%; (d) TFA/CH_2Cl_2 (1:1), RT, 3 h, then HCl/ether, **12a**: 61%, **12b**: 69%.



Scheme 3. *Reagents and conditions*: (a) BnOH, $SOCl_2$, 16 h, RT, 68%; (b) Fmoc-D-arginine(Pmc)OH, EDCI, HOBt, DMF, 16 h, RT, 51%; (c) 1% piperidine, MeCN, RT, 3 h, 70%; (d) Fmoc-D-lysine(Boc)OH, EDCI, HOBt, DMF, 16 h, RT, 51%; (e) 1% piperidine, MeCN, RT, 3 h, 93%; (f) **7a** or **7b** or *N*-Ac-*O*-allyl-L-tyrosine, EDCI, HOBt, DMF, 16 h, RT, **19a**: 36%, **19b**: 80%, **19c**: 85%; (g) TFA/CH_2Cl_2 (1:1), RT, 3 h, then HCl/ether, **20a**: 88%, **20b**: 79%, **20c**: 85%.

2.1. In vitro antibacterial activity

The synthesized hydrophobic and cationic peptoids **12a**, **12b**, **20a**, **20b** and **20c** were tested against the Gram-positive bacterium *Staphylococcus aureus* (ATCC6538) and it showed MIC values of 31.3, 15.6, 15.6, 7.8 and >125 mg/mL, respectively. The positive control, vancomycin, showed an MIC value of 1.95 mg/mL. In stark contrast to **12a**, **12b** and **20a**, **20b** the less hydrophobic tetrapeptoid **20c** was not active (MIC > 125 mg/mL). 9-Phenanthrenyl peptoids, **12b** and **20b**, were more active than their respective 9-anthracenyl counterparts, **12a** and **20a**. The dicationic peptoids, **20a** and **20b** were more active than their respective monocationic analogues **12a** and **12b**. However, it should be noted that peptides **12a**, **12b** have a L-lysine residue whereas peptides **20a** and **20b** have a D-lysine residue. These differences limit further structure–activity comparisons to be made between the tripeptides **12a** and **12b** and tetrapeptides **20a** and **20b**. These biological results are consistent with the pharmacophore model proposed by Svendsen [12] for peptide compounds which indicates that two hydrophobic and two cationic sites are important for antibacterial activity. In our case the benzyl ester moiety in **20a** and **20b** would represent the second, albeit considerably smaller, hydrophobic group.

In contrast to the activity shown against *S. aureus*, the cationic peptoids **12a**, **12b**, **20a**, and **20b**, were not active against *Enterococcus faecalis* strains (both vancomycin sensitive and resistant strains); MIC values > 125 μg/mL were obtained against these strains and the same results were seen with the peptoid **20c**.

3. Conclusions

We have developed a useful method for preparing the novel biaryl hydrophobic amido acids **7a** and **7b** via Stille coupling reactions. This method could potentially be employed to prepare other novel biaryl phenylalanine derivatives. We have shown that incorporation of these hydrophobic amido acid residues into cationic peptides resulted in peptoids having significant

antibacterial activity against *S. aureus* when compared to a less hydrophobic, *O*-allyltyrosine analogue **20c**. These results highlight the importance of hydrophobicity within the peptoid for antibacterial activity and provide a platform for further development of antimicrobial agents with improved activity against *S. aureus*.

4. Experimental

4.1. Chemistry

Chemical ionization (CI) mass spectra were obtained on a Shimadzu QP-5000 mass spectrometer by a direct insertion technique (electron beam density, 70 eV). Electrospray ionization (ESI) mass spectra were obtained on a VG Quattro spectrometer. High-resolution mass spectra (HRMS) were determined on a VG Autospec spectrometer or on a micromass QTof2 spectrometer using polyethylene glycol as the internal standard. The *m*/*z* values are stated with their peak intensity percentages in parentheses. Optical rotations were measured using a Jasco DIP-370 digital polarimeter with a 10-mm path length. Proton and carbon nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$ solution at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR) unless otherwise stated, using a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer. TMS was used as the internal standard and all chemical shifts (δ) were measured relative to the internal standard. Analytical thin layer chromatography (TLC) was carried out on Merck Silica gel 60 F_{254} pre-coated aluminium plates with a 0.2-mm adsorbant thickness. All column chromatography was performed under 'flash' conditions on Merck Silica gel 60 (230–400 mesh). ^{1}H NMR assignments were achieved with the aid of gCOSY, and in some cases NOESY and TOCSY experiments. ^{13}C NMR assignments were based upon DEPT, gHSQC and sometimes gHMBC experiments. All compounds were homogeneous by TLC analysis and judged to be of >95% purity based upon ^{1}H NMR analysis. Compound numbering is based on that of compound **20** as shown in Scheme 3. All compounds were judged to be greater than 95% purity based upon ^{1}H NMR and TLC analyses. Solvent ratios are vol/vol.

4.2. General procedures

4.2.1. General synthetic procedure for N-*Boc and Pmc deprotection (procedure A)*

The *N*-Boc or Pmc protected amine was stirred for 3 h in 1:1 CH_2Cl_2/TFA (5 mL/0.1 mmol of substrate) solution at RT. The solvent was removed under reduced pressure, and the residue was resuspended in a minimal volume of methanol. The solution was then treated with an excess of 1 M HCl/ether solution and the solvent evaporated. The crude product was purified by precipitation from CH_2Cl_2 and/or MeOH by addition of diethyl ether.

4.2.2. General synthetic procedure for peptide coupling *(procedure B)*

To a solution of the acid (1 equiv.) in DMF (10 mL/1 mmol of substrate) at room temperature were added HOBt (1.1 equiv.), EDCI (1 equiv.) and the amine (1.2 equiv.). If the amine was a hydrochloride salt, DIPEA (1 equiv.) was also added. The mixture was allowed to stir for 16 h before dilution with EtOAc (30 mL) and washing with water (30 mL) and brine (30 mL). The organic fraction was dried ($MgSO_4$) and further purified by column chromatography if required.

4.2.3. General synthetic procedure for N-*Fmoc deprotection (procedure C)*

The Fmoc protected amine was stirred in 1% piperidine/acetonitrile (5 mL/1 mmol of substrate) for 3 h at RT. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (15:1, CH_2Cl_2/MeOH) to yield the free amine.

4.2.4. (*S*)-2-Amino-3-(4-iodophenyl)propanoic acid ***2***

To a solution of (*S*)-2-amino-3-phenylpropanoic acid (4.01 g, 24.3 mmol) in acetic acid (22 mL) were added sulfuric acid (2.9 mL, 5.14 mmol), iodine (2.47 g, 4.7 mmol) and sodium iodate (1.02 g, 5.14 mmol). The mixture was heated to 70 °C and allowed to stir at this temperature for 16 h before an additional portion of sodium iodate (1.02 g, 5.14 mmol) was added. The reaction was left for a further 2 h before being concentrated, dissolved in MeOH (20 mL) and treated with NaOH (60 mL). The mixture was left to precipitate out of the basic solution overnight and the resulting solid was filtered by vacuum filtration to yield the title compound **2** (7.07 g, 24.3 mmol, 100%) as a pink solid, which had spectral data in agreement with that reported [14]. $[\alpha]_D^{21}$ −10.6 (*c*. 0.3, HCl). Mp 258–260 °C (lit. 261–262 °C) [14].

4.2.5. Methyl (2S)-2-amino-3-(4-iodophenyl)propanoate hydrochloride ***3***

To a solution of **2** (2.00 g, 6.87 mmol) in MeOH (10 mL) at 0 °C was added thionyl chloride (2 mL) and the resulting solution was allowed to stir for 16 h whilst equilibrating to RT. The reaction was evaporated to dryness in vacuo to yield the title compound **3** (2.25 g, 6.80 mmol, 99%) as a white solid, which had spectral data in agreement with that reported [14]. $[\alpha]_D^{21}$ −9.3 (*c*. 0.15, HCl). Mp 195–198 °C (lit. 199.5–200.5 °C) [14].

4.2.6. Methyl (2S)-2-acetamido-3-(4-iodophenyl)propanoate ***4***

To a solution of **3** (2.25 g, 6.80 mmol) in 10% HCl (10 mL) at 0 °C was added 4 M sodium acetate (115 mL) and the resulting solution was allowed to stir whilst equilibrating to 0 °C. Acetic anhydride (50 mL) was added and the reaction allowed to proceed with vigorous stirring. After 1 h the product was collected by vacuum filtration, dissolved in ethyl acetate (30 mL) and washed with 2 M sodium bicarbonate (2 × 30 mL). The organic layer was dried and evaporated to yield the title compound **4** (1.31 g, 3.79 mmol, 56%) as a white solid. Mp 118–120 °C. $[\alpha]_D^{27}$ +93.8 (*c*. 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.61 (d, J = 8.4 Hz, 2H, ArH2′ and ArH6′); 6.84 (d, J = 8.1 Hz, 2H, ArH3′ and ArH5′); 5.92 (d, J = 7.2 Hz, 1H, NH); 4.87 (m, 1H, H2); 3.73 (s, 3H, OCH_3); 3.11 (dd, J = 6.0, 13.8 Hz, 1H, $H3_a$); 3.03 (dd, J = 5.4, 13.8 Hz, 1H, $H3_b$); 1.99 (s, 3H, $NCOCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 171.8, C1; 169.5, NCO; 137.6, ArCH2′ and ArCH6′; 135.5, ArC4′; 131.2, ArCH3′ and ArCH5′; 94.1, ArC1′; 52.9, C2; 52.4, OCH_3; 37.4, C3; 23.1, $NCOCH_3$. Mass spectrum (CI+) *m*/*z*: 348 (100%) [MH^+]. HRMS calcd for $C_{12}H_{15}NO_3I$, 348.0097; found, 348.0104.

4.2.7. Methyl (2S)-2-acetamido-3-(4-trimethylstannylphenyl)propanoate ***5***

A solution of **4** (590 mg, 1.7 mmol), hexamethyldistannane (781 mg, 2.38 mmol), palladium acetate (20 mg, 0.085 mmol), and triphenylphosphine (45 mg, 0.17 mmol) in toluene (7 mL) was flushed with nitrogen for 15 min and then heated at 100 °C for 30 min under N_2. The brown mixture was filtered through a short pad of silica, diluted with diethyl ether (40 mL) and washed twice with water. The organic layer was dried and evaporated to yield the title compound **5** (497 mg, 1.29 mmol, 76%) as a clear oil. $[\alpha]_D^{27}$ +13.7 (*c*. 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.41 (d, J = 7.5 Hz, 2H, ArH2′ and ArH6′); 7.07 (d, J = 7.8 Hz, 2H, ArH3′ and ArH5′); 6.25 (d, J = 7.8 Hz, 1H, NH); 4.87 (m, 1H, H2); 3.72 (s, 3H, OCH_3); 3.12 (dd, J = 5.7, 14.1 Hz, 1H, $H3_a$); 3.04 (dd, J = 6.0, 13.9 Hz, 1H, $H3_b$); 1.98 (s, 3H, $NCOCH_3$); 0.27 (t, J = 27.6 Hz, 9H, $Sn(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.1, C1; 169.7, NCO; 140.6, ArC4′; 135.9, ArCH2′ and ArCH6′; 135.9, ArC1′; 128.7, ArCH3′ and ArCH5′;

53.0, C2; 52.1, OCH_3; 37.5, C3; 23.9, $NCOCH_3$; −9.7, $Sn(CH_3)_3$. Mass spectrum (CI+) *m*/*z*: 386 (50%) [MH^+], 382 (10%) [MH^+] (^{112}Sn), 85 (100%). HRMS calcd for $C_{15}H_{24}NO_3Sn$ (^{112}Sn), 382.0754; found, 382.0756.

4.2.8. Methyl (2S)-2-acetamido-3-(4-[9-anthracenyl]phenyl)-propanoate **6a**

A solution of **5** (192 mg, 0.50 mmol), 9-bromoanthracene (141 mg, 0.55 mmol), palladium acetate (6 mg, 0.025 mmol), and tri-*o*-tolylphosphine (15 mg, 0.05 mmol) in DMF (2 mL) was flushed with N_2 for 15 min, then heated to 70 °C and allowed to stir for 16 h. The reaction was diluted with diethyl ether (20 mL) and washed with water (5 × 20 mL), dried and evaporated. The crude product was purified by flash column chromatography (15% EtOAc/hexane then 5% MeOH/CH_2Cl_2) to yield the title compound **6a** (133 mg, 0.33 mmol, 67%) as an orange oil. $[\alpha]_D^{27}$ +66.9 (*c*. 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 8.48 (s, 1H, ArH10″); 8.03 (dd, *J* = 0.9, 8.7 Hz, 2H, ArH3″ and ArH6″); 7.63 (dd, *J* = 0.6, 9.0 Hz, 2H, ArH8″ and ArH1″); 7.45 (m, 2H, ArH4″ and ArH5″); 7.36 (m, 6H, ArH2″ and ArH7″, 4 × ArH′); 5.40 (d, *J* = 7.8 Hz, 1H, NH); 5.04 (m, 1H, H2); 3.79 (s, 3H, OCH_3); 3.32 (dd, *J* = 5.7, 13.8 Hz, 1H, $H3_a$); 3.25 (dd, *J* = 6.3, 13.8 Hz, 1H, $H3_b$); 2.08 (s, 3H, $COCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 172.2, C1; 169.8, *C*OCH_3; 137.4, ArC9″; 136.4, ArC4′; 135.2, ArC1′; 132.0, ArC8a″ and ArC9a″; 131.9, ArCH2″ and ArCH7″; 131.3, ArCH2′ and ArCH6′; 129.2, ArCH3′ and ArCH5′; 128.3, ArCH4″ and ArCH5″; 126.5, ArC4a″ and ArC10a″; 125.3, ArCH8″ and ArCH1″; 125.0, ArCH3″ and ArCH6″, ArCH10″; 53.3, C2; 52.3, OCH_3; 37.8, C3; 23.1, $COCH_3$. Mass spectrum (CI+) *m*/*z*: 398 (100%) [MH^+]. HRMS calcd for $C_{26}H_{23}NO_3$, 397.1678; found, 397.1675.

4.2.9. Methyl (2S)-2-acetamido-3-(4-[9-phenanthrenyl]phenyl)propanoate **6b**

A solution of **5** (259 mg, 0.67 mmol), 9-bromophenanthrene (190 mg, 0.74 mmol), palladium acetate (8 mg, 0.034 mmol), and tri-*o*-tolylphosphine (20 mg, 0.067 mmol) in DMF (2 mL) was flushed with N_2 for 15 min, then heated to 70 °C and allowed to stir for 16 h. The reaction was diluted with diethyl ether (20 mL) and washed with water (5 × 20 mL), dried and evaporated. The crude product was purified by flash column chromatography (15% EtOAc/hexane then 5% MeOH/CH_2Cl_2) to yield the title compound **6b** (157 mg, 0.40 mmol, 59%) as a clear oil. $[\alpha]_D^{27}$ +94.6 (*c*. 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 8.77 (d, *J* = 9.0 Hz, 1H, ArH4″); 8.71 (d, *J* = 8.1 Hz, 1H, ArH3″); 7.89 (m, 2H, ArH1″ and ArH10″); 7.61 (m, 5H, ArH7″, ArH6″, ArH5″, ArH2″ and ArH1″); 7.48 (d, *J* = 8.4 Hz, 2H, ArH2′ and ArH6′); 7.26 (d, *J* = 8.1 Hz, 2H, ArH3′ and ArH5′); 6.25 (d, *J* = 7.5 Hz, 1H, NH); 5.00 (m, 1H, H2); 3.79 (s, 3H, OCH_3); 3.30 (dd, *J* = 5.7, 13.8 Hz, 1H, $H3_a$); 3.20 (dd, *J* = 6.0, 13.8 Hz, 1H, $H3_b$); 2.05 (s, 3H, $COCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 172.1, C1; 169.7, *C*OCH_3; 139.5, ArC4′; 138.2, ArC1′; 135.0, ArC9″; 131.4, ArC4b″; 130.9, ArC9a″; 130.6, ArC4a″; 130.1, ArCH2′ and ArCH6′; 129.9, ArC10a″; 129.1, ArCH3′ and ArCH5′; 128.5, ArCH1″; 127.4, ArCH7″; 126.8, ArCH6″; 126.7, ArCH1″; 126.5, ArCH5″; 126.4, ArCH10″; 126.3, ArCH2″; 122.9, ArCH4″; 122.4, ArCH3″; 53.2, C2; 52.3, OCH_3; 37.6, C3; 23.0, $COCH_3$. Mass spectrum (CI+) *m*/*z*: 398 (100%) [MH^+]. HRMS (EI) calcd for $C_{26}H_{23}NO_3$, 397.1678; found, 397.1680.

4.2.10. (2S)-2-Acetamido-3-(4-[9-anthracenyl]phenyl)propanoic acid **7a**

To a solution of **6a** (80 mg, 0.20 mmol) in THF/water, 2:1 (3 mL) was added lithium hydroxide monohydrate (17 mg, 0.40 mmol) and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 mL) and the THF was removed by evaporation. The aqueous layer was washed with CH_2Cl_2 (40 mL) to remove unreacted starting material. The aqueous phase was acidified with 10% HCl and the resulting precipitate was extracted with CH_2Cl_2 (3 × 40 mL). The combined organics were dried and evaporated to yield the title compound **7a** (69 mg, 0.18 mmol, 90%) as a white solid. Mp 76 °C. $[\alpha]_D^{20}$ +29.7 (*c*. 0.1, EtOH). ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 8.47 (s, 1H, ArH10″); 8.02 (d, *J* = 8.4 Hz, 2H, ArH3″ and ArH6″); 7.59 (d, *J* = 8.7 Hz, 2H, ArH8″ and ArH1″); 7.45 (m, 2H, ArH4″ and ArH5″); 7.35 (m, 6H, ArH2″ and ArH7″, 4 × ArH′); 6.27 (d, *J* = 6.6 Hz, 1H, NH); 5.00 (m, 1H, H2); 3.39 (dd, *J* = 4.8, 12.9 Hz, 1H, $H3_a$); 3.26 (dd, *J* = 6.3, 14.4 Hz, 1H, $H3_b$); 2.07 (s, 3H, $COCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 174.2, C1; 171.2, *C*OCH_3; 137.5, ArC9″; 136.4, ArC4′; 135.0, ArC1′; 131.4, ArC8a″; 131.2, ArC9a″; 130.1, ArCH2″ and ArCH7″; 129.3, ArCH2′ and ArCH6′; 128.8, ArCH3′ and ArCH5′; 128.3, ArCH4″ and ArCH5″; 126.6, ArC4a″ and ArC10a″; 125.3, ArCH8″ and ArCH1″; 125.0, ArCH3″ and ArCH6″, ArC10″; 53.5, C2; 37.3, C3; 22.9, $COCH_3$. Mass spectrum (ESI+) *m*/*z*: 383 (70%) [MH^+]. HRMS calcd for $C_{25}H_{22}NO_3$, 384.1600; found, 384.1610.

4.2.11. (2S)-2-Acetamido-3-(4-[9-phenanthrenyl]phenyl)propanoic acid **7b**

To a solution of **6b** (124 mg, 0.31 mmol) in THF/water, 2:1 (9 mL) was added lithium hydroxide monohydrate (26 mg, 0.62 mmol) and the resulting suspension was allowed to stir for 16 h. The reaction mixture was diluted with water (30 mL) and the THF was removed by evaporation. The aqueous layer was washed with CH_2Cl_2 (40 mL) to remove unreacted starting material. The aqueous phase was acidified with 10% HCl and the resulting precipitate was extracted with CH_2Cl_2 (3 × 40 mL). The combined organics were dried and evaporated to yield the title compound **7b** (65 mg, 0.17 mmol, 55%) as a white solid. Mp 128–132 °C. $[\alpha]_D^{20}$ +36.8 (*c*. 0.1, EtOH). ^1H NMR (CD_3OD, 300 MHz) *δ*: 8.71 (d, *J* = 8.1 Hz, 1H, ArH4″); 8.66 (d, *J* = 8.4 Hz, 1H, ArH3″); 7.79 (s, 1H, ArH1″); 7.76 (s, 1H, ArH10″); 7.51 (m, 5H, ArH7″, ArH6″, ArH5″, ArH2″ and ArH1″); 7.32 (m, 2H, Ar′H); 4.76 (dd, *J* = 5.1, 9.0 Hz, 1H, H2); 3.29 (dd, *J* = 4.8, 13.5 Hz, 1H, $H3_a$); 3.03 (dd, *J* = 8.7, 13.5 Hz, 1H, $H3_b$); 1.95 (s, 3H, $COCH_3$). ^{13}C NMR (CD_3OD, 75 MHz) *δ*: 174.8, C1; 173.2, *C*OCH_3; 140.5, ArC4′; 139.7, ArC1′; 137.7, ArC9″; 132.9, ArC4b″; 132.2, ArC8a″; 131.9, ArC4a″; 131.2, ArC10a″; 131.1, ArCH2′ and ArCH6′; 130.2, ArCH3′ and ArCH5′; 129.6, ArCH1″; 128.3, ArCH3″; 127.9, ArCH6″; 127.7, ArCH1″; 127.7, ArCH5″; 127.6, ArCH10″; 127.5, ArCH2″; 124.0, ArCH4″; 123.5, ArCH3″; 55.2, C2; 38.2, C3; 22.4, $COCH_3$. Mass spectrum (ESI+) *m*/*z*: 384 (50%) [MH^+]. HRMS calcd for $C_{25}H_{22}NO_3$, 384.1600; found, 384.1628.

4.2.12. Methyl (2S,5S)-2-allyl-3-aza-9-(tert-butoxycarboxamido)-5-(9H-9-fluorenylmethyloxycarboxamido)-4-oxononanoate **9**

To a solution of **8** [18] (430 mg, 2.61 mmol) and Fmoc-L-lysine(Boc)OH (1.22 g, 2.61 mmol) in CH_2Cl_2 (10 mL) were added EDCI (500 mg, 2.61 mmol) and a catalytic quantity of DMAP. The resulting mixture was allowed to stir at RT for 16 h. The reaction was diluted with CH_2Cl_2 (25 mL), then the organic layer was washed with brine (2 × 25 mL) and water (2 × 25 mL) and dried, before being concentrated. The crude product was purified by flash column chromatography (25:1 CH_2Cl_2/MeOH) to afford the title compound **9** (1.31 g, 2.27 mmol, 87%) as a cream coloured solid. Mp 123–126 °C. ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 7.76 (d, *J* = 7.6 Hz, 2H, ArH1″ and ArH8″); 7.59 (d, *J* = 7.6 Hz, 2H, ArH4″ and ArH5″); 7.40 (t, *J* = 7.6 Hz, 2H, ArH3″ and ArH6″); 7.31 (ddd, *J* = 9.0, 7.2, 1.2 Hz, 2H, ArH2″ and ArH7″); 6.46 (br s, 1H, NH); 5.64 (m, 1H, H2′); 5.44 (s, 1H, NH); 5.10 (m, 2H, H3′); 4.65 (m, 1H, H2); 4.39 (d, *J* = 7.2 Hz, 2H, O*CH*$_2$–H9″); 4.22 (m, 1H, H5); 4.17 (br s, 1H, H9″); 3.74 (s, 3H, OCH_3); 3.11 (m, 2H, H9); 2.55 (m, 2H, H1′); 1.85 (m, 2H, H7); 1.65 (m, 2H, H6); 1.50 (m, 2H, H8); 1.44 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 171.9, C4; 171.6, C1; 156.2, NCO_2; 143.7, ArC8a″ and ArC9a″; 142.7, ArC4a″ and ArC4b″; 131.9, C2′; 127.7, ArCH3″ and ArCH6″; 127.0, ArCH2″ and ArCH7″; 125.0, ArCH1″ and ArCH8″;

119.9, C3′; 119.3, ArCH4″ and ArCH5″; 79.1, *C*(CH$_3$)$_3$; 67.0, *C*H$_2$–C9″; 54.5, C5; 52.4, OCH$_3$; 50.6, C2; 47.0, C9″; 39.8, C9; 36.1, C1′; 32.0, C6; 29.9, C8; 28.3, C(*C*H$_3$)$_3$; 22.2, C7. Mass spectrum (ESI+) *m*/*z*: 580.5 (10%) [MH$^+$], 130.5 (100%) [MH$^+$ (less allylglgly)]. HRMS calcd for $C_{32}H_{42}N_3O_7$, 580.3023; found, 580.3025.

4.2.13. Methyl (2*S*,5*S*)-2-allyl-5-amino-3-aza-9-(tert-butoxycarboxamido)-4-oxononanoate **10**

The title compound was synthesized using the general *N*-Fmoc deprotection procedure (procedure C), from **9** (1.27 g, 2.19 mmol) to yield **10** (778 mg, 2.18 mmol, 100%) as a cream oil. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 7.81 (d, J = 8.0 Hz, 1H, NH); 5.69 (m, 1H, H2′); 5.11 (m, 2H, H3′); 4.76 (br s, 1H, NH); 4.67 (m, 1H, H2); 3.75 (s, 3H, OCH$_3$); 3.39 (dd, J = 4.6, 7.6 Hz, 1H, H5); 3.12 (d, J = 6.3 Hz, 2H, H9); 2.54 (m, 2H, H1′); 1.52 (m, 8H, H6, H7, H8 and NH$_2$); 1.44 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 174.8, C4; 172.1, C1; 156.0, NCO$_2$; 132.2, C2′; 118.9, C3′; 78.9, *C*(CH$_3$)$_3$; 54.8, C5; 52.2, C2; 51.1, OCH$_3$; 40.0, C9; 36.4, C1′; 34.4, C6; 29.7, C8; 28.3, C(*C*H$_3$)$_3$; 22.6, C7. Mass spectrum (ESI+) *m*/*z*: 358.5 (85%) [MH$^+$], 258.4 (100%) [MH$^+$ (less Boc)]. HRMS calcd for $C_{17}H_{32}N_3O_5$, 358.2342; found, 358.2339.

4.2.14. Benzyl (2*S*)-2-amino-4-pentenoate hydrochloride **14**

To a solution of **13** (225 mg, 1.96 mmol) in benzyl alcohol (5 mL) was added thionyl chloride (2 mL) and the resulting mixture was allowed to stir for 16 h before addition of diethyl ether (30 mL) and extraction with water (3 × 30 mL). The aqueous layer was concentrated, diluted with 2 M sodium bicarbonate (20 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were dried and acidified with 1 M HCl/diethyl ether (2 mL) and evaporated. The crude product was dissolved in a minimal volume of MeOH and precipitated with diethyl ether to yield the title compound **14** (322 mg, 1.34 mmol, 68%) as a white solid. $[\alpha]_D^{20}$ −40.6 (*c*. 0.1, H_2O). Mp 186–191 °C. ^{1}H NMR (D_2O, 300 MHz) δ: 7.28 (m, 5H, ArH); 5.51 (m, 1H, H4); 5.11 (m, 4H, H5 and ArCH$_2$); 4.08 (t, J = 5.4 Hz, 1H, H2); 2.55 (m, 2H, H3). ^{13}C NMR (D_2O, 75 MHz) δ: 172.1, C1; 137.3, C4; 132.5, ArC1′; 131.7, ArC4′; 131.6, ArCH′; 131.4, ArCH′; 124.4, C5; 71.3, ArCH$_2$; 54.9, C2; 36.8, C3. Mass spectrum (CI+) *m*/*z*: 205 (25%) [MH$^+$]. HRMS calcd for $C_{12}H_{16}NO_2$, 206.1181; found, 206.1169.

4.2.15. Benzyl (2*S*,5*R*)-2-allyl-3-aza-5-(9H-9-fluorenylmethyloxycarboxamido)-4-oxo-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl)guanidino]octanoate **15**

The title compound was synthesized using the general peptide coupling procedure (procedure B), from **14** (155 mg, 0.65 mmol) and Fmoc-D-arginine(Pmc)OH (431 mg, 0.65 mmol) to afford **15** (280 mg, 0.33 mmol, 51%) as a white solid. Mp 78–74 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 7.69 (d, J = 7.5 Hz, 2H, ArH1″ and ArH8″); 7.51 (d, J = 7.5 Hz, 2H, ArH4″ and ArH5″); 7.28 (m, 9H, ArH); 6.33 (m, 3H, NH); 5.68 (m, 1H, H2′); 5.61 (m, 1H, NH); 4.99 (m, 4H, ArCH$_2$ and H3′); 4.58 (m, 1H, H2); 4.24 (m, 3H, O*CH*$_2$–H9″and H5); 4.05 (dd, J = 7.2, 7.2 Hz, 1H, H9″); 3.20 (m, 2H, H8); 2.57 (s, 3H, 7‴-CH$_3$); 2.54 (s, 3H, 5‴-CH$_3$); 2.52 (m, 4H, H3‴ and H1′); 2.05 (s, 3H, 8‴-CH$_3$); 1.85 (m, 2H, H6); 1.69 (dd, J = 6.3, 6.3 Hz, H4‴); 1.58 (m, 2H, H7); 1.22 (s, 6H, 2 × 2‴-CH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 172.2, C1; 171.4, C4; 156.4, ArC6‴; 156.3, NCO$_2$; 153.5, ArC8a‴; 143.7, CN$_3$; 143.6, ArC8a″ and ArC9a″; 141.0, ArC4a″ and ArC4b″; 135.3, ArC7‴; 135.1, ArC5‴; 134.8, C2′; 128.5, ArC; 128.4, ArC; 128.3, ArC; 128.2, ArC; 127.6, ArCH2″ and ArCH7″; 127.0, ArCH3″ and ArCH6″; 125.1, ArCH4″ and ArCH5″; 124.0, ArC8‴; 119.8, ArCH1″ and ArCH8″; 119.0, C3′; 117.9, ArC4a‴; 73.5, C2‴; 67.0, ArCH$_2$; 66.7, *C*H$_2$–C9″; 54.7, C5; 53.8; 53.4, C2; 46.8, C9″; 39.0, C8; 35.7, C1′; 32.6, C4‴; 29.8, C6; 26.6, 2″-CH$_3$; 22.4, C7; 21.3, C3‴; 18.5, C7‴–CH$_3$; 17.5, C5‴–CH$_3$; 12.0, C8‴–CH$_3$. Mass spectrum (ESI+) *m*/*z*: 850 (100%) [MH$^+$]. HRMS calcd for $C_{47}H_{56}N_5O_8S$, 850.3850; found, 850.3855.

4.2.16. Benzyl (2*S*,5*R*)-2-allyl-5-amino-3-aza-8-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonamido)guanidino]-4-oxooctanoate **16**

The title compound was synthesized using the general *N*-Fmoc deprotection procedure (procedure C), from **15** (278 mg, 0.33 mmol) to yield **16** (144 mg, 0.23 mmol, 70%) as a cream semi-solid. Mp 66–68 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 7.85 (d, J = 7.8 Hz, 1H, NH); 7.60 (d, J = 7.8 Hz, 1H, NH); 7.32 (m, 5H, ArH); 6.33 (m, 2H, NH$_2$); 5.63 (s, 1H, H2′); 5.14 (m, 4H, ArCH$_2$ and H3′); 4.56 (m, 1H, H2); 3.40 (m, 1H, H5); 3.16 (m, 2H, H8); 3.09 (m, 2H, H1′); 2.61 (t, J = 6.9 Hz, 2H, H4″); 2.56 (s, 3H, 7″-CH$_3$); 2.55 (s, 3H, 5″-CH$_3$); 2.09 (s, 3H, 8″-CH$_3$); 1.78 (t, J = 7.2 Hz, 2H, H3″); 1.68 (m, 4H, H6 and NH$_2$); 1.54 (m, 2H, H7); 1.29 (s, 6H, 2 × 2″-CH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 171.4, C1; 171.2, C4; 156.2, ArC6″; 153.4, ArC8a″; 146.0, CN$_3$; 135.2, ArC7″; 135.1, ArC5″; 134.7, C2′; 128.5, ArC; 128.3, ArC; 128.3, ArC; 128.2, ArC; 123.9, ArC8″; 119.2, C3′; 117.8, ArC4a″; 73.5, C2″; 67.1, ArCH$_2$; 54.2, C5; 53.4, C2; 40.8, C8; 35.9, C1′; 32.7, C4″; 30.8, C6; 29.3, C7; 26.6, 2″-CH$_3$; 21.3, C3″; 18.4, C7″–CH$_3$; 17.4, C5″–CH$_3$; 12.0, C8″–CH$_3$. Mass spectrum (ESI+) *m*/*z*: 628 (100%) [MH$^+$]. HRMS calcd for $C_{32}H_{46}N_5O_6S$, 628.3169; found, 628.3157.

4.2.17. Benzyl (2*S*,5*R*,8*R*)-2-allyl-3,6-diaza-12-(tert-butoxycarboxamido)-8-(9H-9-fluorenylmethyloxycarboxamido)-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonamido}guanidino]propyl)-4,7-dioxododecanoate **17**

The title compound was synthesized using the general peptide coupling procedure (procedure B), from **16** (200 mg, 0.32 mmol) and Fmoc-D-lysine(Boc)OH (151 mg, 0.32 mmol) to afford **17** (202 mg, 0.19 mmol, 59%) as a white solid. Mp 116 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 7.72 (d, J = 7.8 Hz, 2H, ArH1‴ and ArH8‴); 7.55 (d, J = 7.8 Hz, 2H, ArH4‴ and ArH5‴); 7.45 (m, 1H, NH); 7.29 (m, 11H, ArH); 6.25 (m, 3H, NH); 5.64 (m, 1H, H2′); 5.03 (m, 4H, ArCH$_2$, H3′); 4.59 (m, 1H, H2); 4.51 (m, 1H, H5); 4.29 (m, 1H, H8); 4.20 (m, 2H, O*CH*$_2$–H9‴); 3.98 (m, 1H, H9‴); 3.18 (m, 2H, H3″); 3.05 (m, 2H, H12); 2.55 (s, 3H, 7‴-CH$_3$); 2.52 (s, 3H, 5‴-CH$_3$); 2.50 (m, 4H, H4‴ and H1′); 2.03 (s, 3H, 8‴-CH$_3$); 1.95 (m, 4H, H1″ and H9); 1.74 (m, 2H, H3‴); 1.67 (m, 4H, H2″ and H10); 1.59 (m, 2H, H11); 1.41 (s, 6H, 2 × 2‴-CH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 173.0, C1; 171.7, C4; 170.7, C7; 156.8, ArC6‴; 156.2, NCO$_2$; 153.5, NCO$_2$; 144.0, CN$_3$; 143.5, ArC8a‴ and ArC9a‴; 141.1, ArC4a‴ and ArC4b‴; 135.3, ArC7‴; 135.2, ArC5‴; 134.8, C2′; 128.4, ArC; 128.2, ArC; 128.1, ArC; 127.5, ArC; 126.9, ArCH2‴ and ArCH7‴; 125.2, ArCH3‴ and ArCH6‴; 125.0, ArCH4‴ and ArCH5‴; 124.0, ArC8‴; 119.8, ArC1‴ and ArC8‴; 118.9, C3′; 117.9, ArC4a‴; 79.0, *C*(CH$_3$)$_3$; 73.5, C2‴; 67.2, *C*H$_2$–C9‴; 67.0, ArCH$_2$; 55.4, C5; 53.0, C2; 52.0, C8; 46.7, C9‴; 40.6, C3″; 39.9, C12; 35.8, C1′; 32.5, C3‴; 31.8, C2″; 29.4, C9; 28.3, C(*C*H$_3$)$_3$; 26.6, C10; 25.3, 2‴-CH$_3$; 22.6, C11; 21.2, C4‴; 17.5, C7‴–CH$_3$; 15.2, C5‴–CH$_3$; 12.0, C8‴–CH$_3$. Mass spectrum (ESI+) *m*/*z*: 1078 (10%) [MH$^+$]; 288 (100%). HRMS calcd for $C_{58}H_{76}N_7O_{11}S$, 1078.5324; found, 1078.5333.

4.2.18. Benzyl (2*S*,5*R*,8*R*)-2-allyl-8-amino-3,6-diaza-12-(tert-butoxycarboxamido)-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonamido}guanidino]propyl)-4,7-dioxododecanoate **18**

The title compound was synthesized using the general *N*-Fmoc deprotection procedure (procedure C), from **17** (202 mg, 0.19 mmol) to yield **18** (157 mg, 0.18 mmol, 93%) as a cream oil. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 8.00 (d, J = 7.2 Hz, 1H, NH); 7.58 (d, J = 7.2 Hz, 1H, NH); 7.32 (m, 5H, ArH); 6.44 (m, 3H, NH); 5.63 (m, 1H, H2′); 5.09 (m, 4H, ArCH$_2$ and H3′); 4.61 (m, 2H, H2 and H5); 3.36 (m, 1H, H8); 3.22 (m, 2H, H3″); 3.05 (m, 2H, H12); 2.62 (m, 2H, H4‴); 2.58 (s, 3H, 7‴-CH$_3$); 2.56 (s, 3H, 5‴-CH$_3$); 2.47 (m, 2H, H1′); 2.15 (m, 2H, H1″); 2.10 (s, 3H, 8‴-CH$_3$); 1.89 (m, 2H, H9); 1.80 (t, J = 6.3 Hz, H3‴); 1.72 (m, 4H, H2″ and H10); 1.58 (m, 4H, H11 and NH$_2$); 1.42 (s, 9H, C(CH$_3$)$_3$); 1.31 (s, 6H, 2 × 2‴-CH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ; 175.7, C1; 171.6, C4; 171.3, C7; 156.2, ArC6‴ and NCO$_2$; 153.4, ArC8‴; 135.2, ArC7‴; 135.1, ArC5‴; 133.3, ArC; 132.2,

C2′; 128.4, ArC; 128.2, ArC; 128.0, ArC; 123.8, ArC8‴; 118.9, C3′; 117.8, ArC4a‴; 78.9, *C*(CH$_3$)$_3$; 73.5, C2‴; 66.9, ArCH$_2$; 54.8, C8; 53.3, C2; 51.8, C5; 40.3, C3″; 40.0, C12; 35.9, C1′; 34.5, C2″; 32.6, C4‴; 29.6, C9; 28.3, C(*C*H$_3$)$_3$; 26.6, 2‴-CH$_3$; 25.4, C10; 22.6, C11; 21.3, C4‴; 18.4, 7‴-CH$_3$; 17.4, 5‴-CH$_3$; 15.3, C1″; 12.0, 8‴-CH$_3$. Mass spectrum (ESI+) *m*/*z*: 856 (100%) [MH$^+$]. HRMS calcd for $C_{43}H_{66}N_7O_9S$, 856.4643; found, 856.4655.

4.2.19. Methyl (2S,5S,8S)-2-allyl-8-(4-[9-anthracenyl]benzyl)-3,6,9-triaza-5-(4-[tert-butoxycarboxamido]butyl)-4,7,10-trioxoundecanoate **11a**

The title compound was synthesized using the general peptide coupling procedure (procedure B), from **10** (35 mg, 0.098 mmol) and **7a** (20 mg, 0.052 mmol) to afford the title compound **11a** (22 mg, 0.030 mmol, 59%) as a cream solid. Mp 128 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 8.49 (s, 1H, ArH10‴); 8.04 (d, J = 8.7 Hz, 2H, ArH2‴ and ArH6‴); 7.64 (d, J = 8.4 Hz, 2H, ArH3‴ and ArH5‴); 7.38 (m, 8H, ArH‴); 6.72 (d, J = 7.2 Hz, 1H, NH); 6.48 (d, J = 7.2 Hz, 1H, NH); 6.37 (br s, 1H, NH); 5.59 (m, 1H, H2′); 5.06 (m, 2H, H3′); 4.82 (m, 1H, H8); 4.60 (dd, J = 6.9, 14.1 Hz, 1H, H2); 4.45 (m, 1H, H5); 3.73 (s, 3H, OCH$_3$); 3.24 (m, 2H, ArCH$_2$); 3.08 (m, 2H, H4″); 2.47 (m, 2H, H1′); 2.07 (s, 3H, H11); 1.93 (m, 2H, H1″); 1.68 (m, 2H, H3″); 1.50 (m, 2H, H2″); 1.44 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 171.9, OCH$_3$; 171.3, C4; 171.1, C10; 170.4, C7; 156.2, NCOOC; 137.3, ArC9″; 136.5, ArC4‴; 135.7, ArC1‴; 131.9, ArC8a‴; 131.4, ArC9a‴; 131.3, C2′; 130.1, ArCH2‴ and ArCH7‴; 129.2, ArCH4‴ and ArCH6‴; 129.1, ArCH2‴ and ArCH6‴; 128.3, ArCH3‴ and ArCH5‴; 126.8, ArCH10‴; 126.5, ArCH4a‴ and ArC10a‴; 125.3, ArCH8‴ and ArCH1‴; 123.4, ArCH3‴ and ArCH6‴; 119.2, C3′; 79.0, *C*(CH$_3$)$_3$; 54.4, C8; 52.9, OCH$_3$; 52.4, C2; 51.8, C5; 40.0, C4″; 38.2, ArCH$_2$; 36.1, C1′; 32.2, C1″; 29.7, C3″; 29.3, C2″; 28.4, C(*C*H$_3$)$_3$; 23.1, C11. Mass spectrum (ESI+) *m*/*z*: 745 (50%) [MNa$^+$], 723 (20%) [MH$^+$], 623 (100%) [M − Boc]. HRMS calcd for $C_{44}H_{49}N_4O_7$, 745.3601; found, 745.3590.

4.2.20. Methyl (2S,5S,8S)-2-allyl-3,6,9-triaza-5-(4-[tert-butoxycarboxamido]butyl)-4,7,10-trioxo-8-(4-[9-phenanthrenyl]benzyl)undecanoate **11b**

The title compound was synthesized using the general peptide coupling procedure (procedure B), from **10** (28 mg, 0.078 mmol) and **7b** (15 mg, 0.039 mmol) to afford **11b** (14 mg, 0.019 mmol, 50%) as a cream solid. Mp 132–134 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 8.76 (d, J = 8.1 Hz, 1H, ArH4‴); 8.71 (d, J = 8.4 Hz, 1H, ArH3‴); 7.88 (m, 2H, ArH1‴ and ArH10‴); 7.60 (m, 5H, ArH7‴, ArH6‴, ArH5‴, ArH2‴ and ArH1‴); 7.45 (d, J = 7.8 Hz, 2H, ArH2‴ and ArH6‴); 7.33 (d, J = 7.8 Hz, 2H, ArH3‴ and ArH5‴); 7.10 (d, J = 8.4 Hz, 1H, NH); 6.94 (d, J = 8.7 Hz, 1H, NH); 6.74 (d, J = 8.1 Hz, 1H, NH); 5.61 (m, 1H, H2′); 5.06 (m, 2H, H3′); 4.90 (m, 1H, H8); 4.57 (m, 2H, H2 and H5); 3.72 (s, 3H, OCH$_3$); 3.20 (m, 2H, ArCH$_2$); 3.08 (m, 2H, H4″); 2.47 (m, 2H, H1′); 2.04 (s, 3H, H11); 1.92 (m, 2H, H1″); 1.68 (m, 2H, H3″); 1.48 (m, 2H, H2″); 1.42 (s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 171.9, OCH$_3$; 171.4, C4; 171.0, C10; 170.4, C7; 156.1, NCOOC; 139.4, ArC4‴; 138.3, ArC1‴; 135.6, ArC9‴; 132.0, ArC4b‴; 131.5, ArC8a‴; 131.0, ArC4a‴; 130.6, ArC10a‴; 130.2, ArCH2‴ and ArCH6‴; 129.9, ArCH3‴ and ArCH5‴; 129.2, ArCH1‴; 128.6, ArCH3‴; 127.5, ArCH6‴; 126.8, ArCH1‴; 126.6, ArCH5‴; 126.5, ArCH10‴; 122.8, ArCH2‴; 122.5, ArCH4‴; 119.3, ArCH3‴; 79.1, *C*(CH$_3$)$_3$; 54.4, C8; 52.9, OCH$_3$; 52.4, C2; 51.8, C5; 40.0, C4″; 38.0, ArCH$_2$; 36.1, C1′; 32.1, C1″; 29.7, C3″; 29.3, C2″; 28.4, C(*C*H$_3$)$_3$; 23.1, C11. Mass spectrum (ESI+) *m*/*z*: 745 (60%) [MNa$^+$], 723 (20%) [MH$^+$], 623 (100%) [M − Boc]. HRMS calcd for $C_{42}H_{51}N_4O_7$, 723.3758; found, 723.3767.

4.2.21. Methyl (2S,5S,8S)-2-allyl-5-(4-aminobutyl)-8-(4-[9-anthracenyl]benzyl)-3,6,9-triaza-5-butylamino-4,7,10-trioxoundecanoate hydrochloride **12a**

The title compound was synthesized using the general *N*-Boc deprotection procedure (procedure A), from **11a** (20 mg, 0.028 mmol) to yield **12a** (13 mg, 0.017 mmol, 61%) as a light yellow solid. Mp 194–202 °C. ^{1}H NMR (CD$_3$OD, 300 MHz) δ: 8.53 (s, 1H, ArH10‴); 8.26 (m, 3H, exchanging NH's); 8.06 (d, J = 8.1 Hz, 2H, ArH2‴ and ArH6‴); 7.64 (d, J = 9.0 Hz, 2H, ArH3‴ and ArH5‴); 7.38 (m, 8H, ArH‴); 5.68 (m, 1H, H2′); 5.02 (m, 2H, H3′); 4.67 (m, 1H, H8); 4.45 (m, 2H, H2 and H5); 3.69 (s, 3H, OCH$_3$); 2.93 (m, 4H, H4″ and ArCH$_2$); 2.44 (m, 2H, H1′); 2.00 (s, 3H, H11); 1.69 (m, 4H, H1″ and H3″); 1.50 (m, 2H, H2″). ^{13}C NMR (CD$_3$OD, 75 MHz) δ: 174.4, C7; 173.7, C1; 173.6, C4; 173.5, C10; 138.7, ArC4‴; 137.8, ArC1‴; 137.7, ArC9‴; 134.1, C2′; 132.9, ArCH2‴ and ArCH6‴; 132.4, ArC4a‴ and ArC10a‴; 131.5, ArC8a‴ and ArC9a‴; 130.4, ArCH4‴ and ArCH5‴; 130.1, ArCH3‴ and ArCH5‴; 129.5, ArCH10‴; 127.7, ArCH8‴ and ArCH1‴; 126.5, ArCH2‴ and ArCH7‴; 126.2, ArCH3‴ and ArCH6‴; 118.8, C3′; 56.7, C5; 53.8, OCH$_3$; 53.6, C8; 52.7, C2; 40.5, C4″; 38.6, ArCH$_2$; 36.6, C1′; 32.8, C1″; 28.1, C3″; 23.4, C11; 22.4, C2″. Mass spectrum (ESI+) *m*/*z*: 623 (100%) [M$^+$]. HRMS calcd for $C_{37}H_{43}N_4O_5$, 623.3233; found, 623.3215.

4.2.22. Methyl (2S,5S,8S)-2-allyl-5-(4-aminobutyl)-3,6,9-triaza-5-butylamino-4,7,10-trioxo-8-(4-[9-[phenanthrenyl]benzyl)undecanoate hydrochloride **12b**

The title compound was synthesized using the general *N*-Boc deprotection procedure (procedure A), from **11b** (24 mg, 0.033 mmol) to yield **12b** (15 mg, 0.023 mmol, 69%) as a light yellow solid. Mp 198 °C. ^{1}H NMR (CD$_3$OD, 300 MHz) δ: 8.84 (d, J = 7.8 Hz, 1H, ArH4‴); 8.78 (d, J = 8.1 Hz, 1H, ArH5‴); 8.30 (d, J = 7.2 Hz, 1H, exchanging NH); 8.15 (d, J = 8.1 Hz, 1H, exchanging NH); 7.90 (m, 2H, ArH1‴ and ArH10‴); 7.60 (m, 5H, ArH7‴, ArH6‴, ArH5‴, ArH2‴ and ArH1‴); 7.45 (d, J = 8.4 Hz, 2H, ArH2‴ and ArH6‴); 7.40 (d, J = 8.7 Hz, 2H, ArH3‴ and ArH5‴); 5.68 (m, 1H, H2′); 4.98 (m, 2H, H3′); 4.61 (m, 1H, H8); 4.40 (m, 2H, H2 and H5); 3.67 (s, 3H, OCH$_3$); 2.93 (t, J = 7.5 Hz, 2H, H4″); 2.40 (m, 2H, H1′); 1.99 (s, 3H, H11); 1.83 (m, 4H, H1″ and ArCH$_2$); 1.69 (m, 2H, H3″); 1.49 (m, 2H, H2″). ^{13}C NMR (CD$_3$OD, 75 MHz) δ: 173.7, C7; 173.6, C1; 173.5, C4; 173.4, C10; 140.7, ArC4‴; 139.8, ArC1‴; 137.5, ArC9‴; 134.0, C2′; 133.0, ArC8a‴"; 132.3, ArC4b‴; 132.0, ArC4a‴; 131.3, ArCH2‴ and ArCH6‴; 131.2, ArC10a‴; 130.3, ArCH3‴ and ArCH5‴; 129.7, ArCH1‴; 128.5, ArCH7‴; 128.0, ArCH6‴; 127.9, ArCH1‴; 127.8, ArCH5‴; 127.7, ArCH10‴; 127.6, ArCH2‴; 124.2, ArC4‴; 124.1, ArCH3‴; 118.8, C3′; 56.7, C5; 53.7, OCH$_3$; 53.6, C8; 52.7, C2; 40.5, C4″; 38.5, ArCH$_2$; 36.5, C1′; 32.8, C1″; 28.0, C3″; 23.3, C11; 22.4, C2″. Mass spectrum (ESI+) *m*/*z*: 623 (100%) [MH$^+$]. HRMS calcd for $C_{37}H_{43}N_4O_5$, 623.3233; found, 623.3262.

4.2.23. Benzyl (2S,5R,8R,11S)-2-allyl-11-(4-[9-anthracenyl]benzyl)-3,6,9,12-tetraaza-8-(4-[tert-butoxycarboxamido]butyl)-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl}guanidino]propyl)-4,7,10,13-tetraoxotetradecanoate **19a**

The title compound was synthesized using the general peptide coupling procedure (procedure B), from **18** (40 mg, 0.045 mmol) and **7a** (17 mg, 0.045 mmol) to afford **19a** (20 mg, 0.016 mmol, 36%) as a white solid. Mp 108–110 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 8.48 (s, 1H, ArH10‴′); 8.03 (m, 2H, ArH); 7.58 (m, 2H, ArH); 7.44 (m, 2H, ArH); 7.30 (m, 11H, ArH); 6.82 (br s, 1H, NH); 6.36 (br s, 2H, NH$_2$); 5.77 (m, 1H, H2′); 5.12 (m, 4H, H3′ and PhCH$_2$O); 4.85 (m, 1H, H11); 4.59 (m, 1H, H2); 4.44 (m, 1H, H5); 4.31 (m, 1H, H8); 3.19 (m, 2H, 11-CH$_2$); 2.95 (m, 4H, H4‴ and H3″); 2.56 (s, 3H, 7‴-CH$_3$); 2.54 (s, 3H, 5‴-CH$_3$); 2.52 (m, 4H, H4‴ and H1′); 2.06 (s, 3H, 8‴-CH$_3$); 1.97 (m, 2H, H3‴); 1.94 (s, 3H, H14); 1.74 (m, 4H, H1″ and H1‴); 1.71 (m, 2H, H3‴); 1.62 (m, 2H, H2″); 1.38 (m, 2H, H2‴); 1.36 (s, 9H, C(CH$_3$)$_3$); 1.23 (s, 6H, 2 × 2‴-CH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 173.0, C13; 172.2, C1; 172.0, C4; 171.8, C7; 170.6, C10; 156.3, ArC6‴; 156.2, NCO$_2$; 153.6, ArC8a‴; 142.8, CN$_3$; 140.0, ArC; 139.9, ArC; 136.5, ArC7‴; 135.4, ArC5‴; 133.2, ArC; 132.5, C2′; 131.5, ArC; 131.3, 2 × ArCH; 130.1, ArCH; 129.2, ArCH; 128.1, ArCH; 127.9, ArCH; 127.6,

ArCH; 127.5, ArCH; 126.6, ArC; 125.3, ArCH; 125.1, ArCH; 124.1, ArC; 123.5, ArC8‴; 119.0, C3′; 118.0, ArC4a‴; 79.0, *C*(CH_3)$_3$; 73.7, C2‴; 67.0, CH_2-ester; 57.7, C11; 54.6, C2; 53.2, C5; 52.3, C8; 40.7, C3″; 39.8, C4‴; 37.5, C1′; 36.0, C2″; 32.7, C4‴; 29.7, C1‴; 29.3, 11-CH_2; 28.4, C(*C*H_3)$_3$; 27.1, C1″; 26.7, 2‴-CH_3; 25.3, C2‴; 22.9, C14; 22.8, C3‴; 21.4, C3‴; 18.6, 7‴-CH_3; 17.5, 5‴-CH_3; 12.1, 8‴-CH_3. Mass spectrum (ESI+) *m*/*z*: 1221 (10%) [MH^+]; 282 (100%). HRMS calcd for $C_{68}H_{85}N_8O_{11}S$, 1221.6059; found, 1221.6089.

4.2.24. Benzyl (2*S*,5R,8R,11*S*)-2-allyl-3,6,9,12-tetraaza-8-(4-[tert-butoxycarboxamido]butyl)-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonyl}guanidino]propyl)-4,7,10,13-tetraoxo-11-(4-[9-phenanthrenyl]benzyl)tetradecanoate **19b**

The title compound was synthesized using the general peptide coupling procedure (procedure B), from **18** (38 mg, 0.044 mmol) and **7b** (16 mg, 0.042 mmol) to afford **19b** (41 mg, 0.034 mmol, 80%) as a white solid. Mp 108 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 8.72 (m, 2H, ArH); 7.58 (m, 16H, ArH); 6.40 (br s, 2H, NH); 5.71 (m, 1H, H2′); 5.13 (m, 2H, PhCH_2O); 5.03 (m, 2H, H3′); 4.83 (m, 1H, H11); 4.60 (m, 1H, H2); 4.59 (m, 1H, H5); 4.29 (m, 1H, H8); 3.12 (m, 2H, 11-CH_2); 2.94 (m, 4H, H4‴ and H3″); 2.56 (s, 3H, 7‴-CH_3); 2.54 (s, 3H, 5‴-CH_3); 2.53 (m, 4H, H4‴ and H1′); 2.07 (s, 3H, 8‴-CH_3); 1.91 (s, 3H, H14); 1.82 (m, 4H, H1″ and H1‴); 1.72 (t, *J* = 6.6 Hz, 2H, H3‴); 1.62 (m, 4H, H2″ and H3‴); 1.39 (m, 2H, H2‴); 1.34 (s, 9H, C(CH_3)$_3$); 1.23 (s, 6H, 2 × 2‴-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 173.0, C13; 172.4, C1; 172.0, 171.9, C10, C4; 171.7, C7; 156.3, ArC6‴; 156.1, NCO_2; 153.6, CN_3; 139.3, ArC8a‴; 138.2, ArC; 135.3, ArC and ArC7‴; 134.7, ArC5‴; 133.2, C2′; 132.7, ArC; 132.5, ArC; 131.4, ArC; 130.8, ArC; 130.6, ArCH; 130.2, ArCH; 129.8, ArC; 129.2, ArC; 128.6, ArCH; 128.5, ArCH; 128.3, ArCH; 128.1, ArCH; 127.4, ArCH; 126.8, ArCH; 126.6, 2 × ArCH; 126.4, ArCH; 126.2, ArCH; 124.0, ArCH; 122.9, ArC8‴; 122.4, ArCH; 118.9, C3′; 118.0, ArC4a‴; 78.9, *C*(CH_3)$_3$; 73.6, C2‴; 66.9, CH_2-ester; 55.4, C11; 54.5, C8; 53.2, C5; 52.2, C2; 40.6, C3″; 39.8, C4‴; 37.6, 11-CH_2; 36.0, C4‴; 32.6, H1′; 30.6, H1″; 29.6, C1‴; 29.4, H14; 28.3, C(*C*H_3)$_3$; 26.7, 2‴-CH_3; 25.4, C2″; 22.9, C3‴; 22.8, C2‴; 21.5, 7‴-CH_3; 18.6, 5‴-CH_3; 17.5, C3‴; 12.1, 8‴-CH_3. Mass spectrum (ESI+) *m*/*z*: 1221 (100%) [MH^+]. HRMS calcd for $C_{68}H_{85}N_8O_{11}S$, 1221.6059; found, 1221.6045.

4.2.25. Benzyl (2*S*,5R,8R,11*S*)-2-allyl-11-(4-allyloxybenzyl)-3,6,9,12-tetraaza-8-(4-[tert-butoxycarboxamido]butyl)-5-([{2,2,5,7,8-pentamethyl-3,4-dihydro-2H-6-chromenylsulfonamido}guanidino]propyl)-4,7,10,13-tetraoxotetradecanoate **19c**

The title compound was synthesized using the general peptide coupling procedure (procedure B), from *N*-acetyl-*O*-allyl-L-tyrosine [17] (60 mg, 0.069 mmol) and **16** (18 mg, 0.068 mmol) to afford **19c** (65 mg, 0.058 mmol, 85%) as a white solid. Mp 94–102 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.76 (br s, 1H, NH); 7.54 (br s, 1H, NH); 7.41 (br s, 1H, NH); 7.31 (m, 5H, ArH); 7.09 (d, *J* = 8.7 Hz, 2H, ArH2‴″ and ArH6‴″); 6.77 (d, *J* = 8.4 Hz, 2H, ArH3‴″ and ArH5‴″); 6.39 (br s, 3H, 3 × NH); 6.02 (m, 1H, H2‴″); 5.70 (m, 1H, H2′); 5.39 (dd, *J* = 1.5, 17.1 Hz, 1H, $H3_a$‴″); 5.26 (dd, *J* = 1.2, 10.5 Hz, 1H, $H3_b$‴″); 5.06 (m, 2H, H3′); 5.05 (m, 2H, PhCH_2O); 4.65 (dd, *J* = 6.9, 13.5 Hz, 1H, H11); 4.57 (dd, *J* = 8.1, 13.5 Hz, 1H, H2); 4.50 (m, 1H, H5); 4.45 (d, *J* = 5.4 Hz, 2H, H1‴″); 4.41 (m, 1H, H8); 4.14 (br s, 1H, NH); 3.15 (m, 2H, H3″); 2.92 (m, 4H, H4‴ and 11-CH_2); 2.58 (m, 4H, H1′ and H4‴); 2.53 (s, 3H, 7‴-CH_3); 2.52 (s, 3H, 5‴-CH_3); 2.08 (s, 3H, H14); 1.94 (m, 4H, H1″ and H1‴); 1.84 (s, 3H, 8‴-CH_3); 1.78 (m, 2H, H3‴); 1.69 (m, 4H, H2″ and H2‴); 1.55 (m, 2H, H3‴); 1.40 (s, 9H, C(CH_3)$_3$); 1.30 (s, 6H, 2 × 2‴-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 172.2, C1; 172.0, C4; 171.6, C7; 157.5, C10; 156.2, C13 and NCO_2; 156.1, ArC6‴; 153.5, ArC8a‴; 135.3, ArC7‴; 134.7, ArC5‴; 133.1, C2‴″; 132.5, C2′; 130.5, ArC4‴″, 130.2, ArCH2‴″ and ArCH6‴″; 128.5, ArC1‴″; 128.4, ArCH; 128.3, ArCH; 128.2, ArCH; 128.1, ArC; 124.0, ArC8‴; 118.8, C3′; 118.0, C3‴″; 117.6, ArC4a‴; 114.7, ArCH3‴″ and ArCH5‴″; 78.9, *C*(CH_3)$_3$; 73.7, C2‴; 68.7, C1‴″; 66.9, ArCH_2; 55.6, C11; 54.5, C5; 53.1, C8; 52.2, C2; 41.2, C3″; 40.0, C4‴″; 37.2, 11-CH_2; 35.9, C1′; 34.0, C4‴; 32.7, C2‴″; 31.1, C2′; 29.4, C1‴″; 28.4, C(*C*H_3)$_3$; 26.7, 2‴-CH_3; 22.9, C3‴″; 22.6, C14; 21.4, C3‴; 18.5, 7‴-CH_3; 17.5, 5‴-CH_3; 12.1, 8‴-CH_3. Mass spectrum (ESI+) *m*/*z*: 1101 (30%) [MH^+]; 288 (100%). HRMS calcd for $C_{57}H_{81}N_8O_{12}S$, 1101.5695; found, 1101.5731.

4.2.26. Benzyl (2*S*,5R,8R,11*S*)-2-allyl-8-(4-aminobutyl)-11-(4-[9-anthracenyl]benzyl)-3,6,9,12-tetraaza-5-(3-guanidinopropyl)-4,7,10,13-tetraoxotetradecanoate **20a**

The title compound was synthesized using the general *N*-Boc deprotection procedure (procedure A), from **19a** (20 mg, 0.016 mmol) to yield **20a** (13 mg, 0.014 mmol, 88%) as a white solid. Mp 218–220 °C. ^{1}H NMR (CD_3OD, 300 MHz) *δ*: 7.68 (m, 17H, ArH); 5.77 (m, 1H, H2′); 5.15 (m, 4H, H3′ and PhCH_2O); 4.82 (m, 1H, H11); 4.42 (m, 1H, H2); 4.25 (m, 1H, H5); 4.07 (m, 1H, H8); 3.18 (m, 2H, 11-CH_2); 2.88 (m, 4H, H4‴″ and H3″); 2.55 (m, 2H, H1′); 1.95 (s, 3H, H14); 1.85 (m, 2H, H1″); 1.65 (m, 2H, H1‴); 1.53 (m, 2H, H2″); 0.94 (m, 2H, H2‴). ^{13}C NMR (CD_3OD, 75 MHz) *δ*: 175.2, C13; 174.4, C1; 174.2, C4; 174.1, C10; 172.5, C7; 158.6, CN_3; 140.0, ArC; 139.9, ArC; 138.1, ArC; 137.4, ArC; 134.3, C2′; 133.2, ArC; 131.5, ArC; 131.3, ArCH; 130.1, ArCH; 129.2, ArC; 128.1, ArC; 127.9, ArCH; 127.6, ArCH; 127.5, ArCH; 126.6, ArCH; 125.9, ArCH; 125.8, ArCH; 125.6, ArCH; 124.2, ArCH; 119.1, C3′; 68.1, CH_2-ester; 57.9, C11; 55.3, C8; 54.7, C5; 54.2, C2; 42.1, C3″; 40.3, C4‴; 38.1, 11-CH_2; 36.7, C1′; 31.4, C1″: 29.4, C1‴; 27.3, C14; 26.5, C2″; 23.6, C3‴; 22.5, C2‴. Mass spectrum (ESI+) *m*/*z*: 855 (50%) [M^{2+}]; 428 (100%). HRMS calcd for $C_{49}H_{59}N_8O_6$, 855.4558; found, 855.4539.

4.2.27. Benzyl (2*S*,5R,8R,11*S*)-2-allyl-8-(4-aminobutyl)-3,6,9,12-tetraaza-5-(3-guanidinopropyl)-4,7,10,13-tetraoxo-11-(4-[9-phenanthrenyl]benzyl)tetradecanoate **20b**

The title compound was synthesized using the general *N*-Boc deprotection procedure (procedure A), from **19b** (42 mg, 0.034 mmol) to yield **20b** (25 mg, 0.027 mmol, 79%) as a white solid. Mp 215–220 °C. ^{1}H NMR (CD_3OD, 300 MHz) *δ*: 8.82 (m, 2H, ArH); 7.60 (m, 16H, ArH); 5.81 (m, 1H, H2′); 5.15 (m, 4H, Ph*C*H_2O and H3′); 4.58 (m, 1H, H11); 4.43 (m, 1H, H2); 4.35 (dd, *J* = 4.8, 9.0 Hz, 1H, H5); 4.17 (dd, *J* = 4.8, 9.6 Hz, 1H, H8); 3.17 (m, 4H, H4‴″ and H3″); 2.72 (m, 2H, 11-ArCH_2); 2.59 (m, 1H, H1′); 1.96 (s, 3H, H14); 1.80 (m, 4H, H1″ and H1‴); 1.65 (m, 2H, H3‴); 1.51 (m, 2H, H2″); 1.22 (m, 2H, H2‴). ^{13}C NMR (CD_3OD, 75 MHz) *δ*: 175.2, C13; 174.4, C1; 174.2, C4; 174.1, C10; 172.5, C7; 158.6, CN_3; 140.7, ArC; 139.6, ArC; 137.4, ArC; 137.2, ArC; 134.3, C2′; 132.9, ArC; 132.1, ArC; 131.3, ArCH; 130.5, ArCH; 129.7, ArC; 129.6, ArC; 129.4, 2 × ArCH; 128.5, ArCH; 128.1, ArCH; 127.9, ArCH; 127.8, ArCH; 127.6, ArCH; 124.2, ArCH; 123.7, ArCH; 12.4, ArCH; 122.1, ArCH; 121.8, ArCH; 119.0, C3′; 68.0, CH_2-ester; 57.7, C11; 55.2, C8; 54.7, C5; 54.0, C2; 42.0, C3″; 40.1, C4‴; 38.1, 11-CH_2; 36.6, C1′; 31.3, C1″; 29.6, C1‴; 27.8, C14; 26.4, C2″; 23.8, C3‴; 22.6, C2‴. Mass spectrum (ESI+) *m*/*z*: 855 (30%) [M^{2+}], 428 (100%). HRMS calcd for $C_{49}H_{59}N_8O_6$, 855.4558; found, 855.4528.

4.2.28. Benzyl (2*S*,5R,8R,11*S*)-2-allyl-11-(4-allyloxybenzyl)-8-(4-aminobutyl)-3,6,9,12-tetraaza-5-(3-[guanidino]propyl)-4,7,10,13-tetraoxotetradecanoate hydrochloride **20c**

The title compound was synthesized using the general *N*-Boc deprotection procedure (procedure A), from **19c** (65 mg, 0.059 mmol) to yield **20c** (39 mg, 0.048 mmol, 82%) as a cream solid. Mp 108 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.35 (m, 5H, ArH); 7.16 (d, *J* = 8.7 Hz, 2H, ArH2‴ and ArH6‴); 6.87 (d, *J* = 8.7 Hz, 2H, ArH3‴ and ArH5‴); 6.02 (m, 1H, H2‴); 5.78 (m, 1H, H2′); 5.39 (dd, *J* = 1.8, 17.1 Hz, 1H, $H3_a$‴″); 5.24 (dd, *J* = 1.8, 10.5 Hz, 1H, $H3_b$‴″); 5.10 (m, 4H, H3′ and PhCH_2O); 4.52 (m, 2H, H1‴″); 4.39 (m, 2H, H13 and H2); 4.24 (dd, *J* = 4.8, 9.0 Hz, 1H, H5); 3.98 (dd, *J* = 3.9, 9.9 Hz, 1H, H8); 3.16 (m, 2H, H3″); 2.94 (m, 2H, 11-CH_2); 2.84 (m, 2H, H4‴); 2.55 (m, 2H, H1′); 1.94 (s, 3H, H14); 1.87 (m, 2H, H1″); 1.73 (m, 2H, H1‴); 1.54 (m, 4H, H2″ and H2‴); 1.03 (m, 2H, H3‴). ^{13}C NMR

($CDCl_3$, 75 MHz) δ: 175.4, C1; 174.4, C4; 174.2, C7; 172.5, C10; 159.0, C13; 158.5, NCO; 137.2, ArC4‴′; 134.9, C2‴′′; 134.3, C2′; 131.5, ArC; 130.0, ArCH2‴′ and ArCH6‴′; 129.6, ArCH; 129.4, ArCH; 129.4, ArCH; 128.5, ArC1‴; 119.0, C3′; 117.6, C3‴′′; 115.9, ArCH3‴ and ArCH5‴′; 69.8, C1‴′′; 67.9, CH_2-ester; 57.8, C11; 55.3, C5; 54.8, C8; 54.0, C2; 41.9, C3‴; 40.3, C4‴′; 37.4, 11-CH_2; 36.5, C1′; 31.2, C1‴′; 29.5, C2‴; 28.0, C2‴′; 26.5, C14; 23.8, C3‴′; 22.5, C1‴. Mass spectrum (ESI+) *m*/*z*: 735 [M^{2+}] (70%), 368 (100%). HRMS calcd for $C_{38}H_{55}N_8O_7$, 735.4194; found, 735.4200.

4.3. In vitro antimicrobial activity

Antibacterial testing against *S. aureus* ATCC6538P was performed at Avexa Corporation, Melbourne, Australia. Assay procedure: a standardised inoculate for assays was prepared in 1/10 dilution of seed culture. To a 96-well microtitre plate was added 50 μL of liquid medium [Mueller–Hinton broth medium (MHB) and Mueller–Hinton agar medium (MHA)]. The peptoid compounds were dissolved in a 50% MeOH/H_2O solution for a final concentration of 1 mg/mL. Test solution (50 μL) was added into the top row of the plate. A dilution series was continued until it reached the last row of the plate, the excess was discarded. The plates (2 peptoid samples were tested per plate) were incubated at 37 °C and shaken at 100 rpm for 18 h.

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