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Repurposing primaquine as a polyamine conjugate to become an antibiotic adjuvant

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ABSTRACT

In our search for new antibiotic adjuvants as a novel strategy to deal with the emergence of multi-drug resistant (MDR) bacteria, a series of succinylprimaquine-polyamine (SPQ-PA) conjugates and derivatives of a cationic amphiphilic nature have been prepared. Evaluation of these primaquine conjugates for intrinsic antimicrobial properties and the ability to restore the antibiotic activity of doxycycline identified two derivatives, SPQ-PA3-8-3 and SPQ-PA3-10-3 that exhibited intrinsic activity against the Gram-positive bacteria *Staphylococcus aureus* and the yeast *Cryptococcus neoformans*. None of the analogues were active against the Gram-negative bacterium *Pseudomonas aeruginosa*. However, in the presence of a sub-therapeutic amount of doxycycline (4.5 μM), both SPQ-PA3-4-3 and SPQ-PA3-10-3 compounds displayed potent antibiotic adjuvant properties against *P. aeruginosa*, with MIC's of 6.25 μM. A series of derivatives were prepared to investigate the structure-activity relationship that explored the influence of both a simplified aryl lipophilic substituent and variation of the length of the polyamine scaffold on observed intrinsic antimicrobial properties and the ability to potentiate the action of doxycycline against *P. aeruginosa*.

1. Introduction

The emergence of multi-drug resistant (MDR) bacteria has become a serious global issue triggering increased rates of morbidity and mortality in those affected, with associated negative impacts upon public health and the economy. The declining number of clinically effective agents available to treat these infections has critically compromised therapeutic options and has highlighted the urgent need for novel strategies with new mechanisms of action to combat the diversity of antimicrobial resistance mechanisms exhibited by these MDR pathogens.[1–4] The use of antibiotic adjuvants or potentiators which can breathe new life back into ineffective drugs is an attractive strategy which can be explored to subvert the drug-resistant phenotype.[5–8]

In recent years, the bacterial membrane has been receiving considerable interest as a non-specific anti-infectious target with potential for bactericidal activity. Progress in the investigation of membrane-active agents has determined that those that best disrupt membrane integrity are typically both lipophilic and positively charged. In particular, centrally positioned, positively charged diamines are able to interact electrostatically with the negatively charged lipids on the surfaces of bacterial membranes while the insertion of bulky terminal hydrophobic units into the lipid layer leads to increased membrane permeability, depolarization with disruption of the transmembrane proton gradient, loss of cell wall rigidity, integrity and lysis.[9] These attributes bestow the inherent capacity upon these agents to serve as chemosensitizers to enhance the effectiveness of other antibacterial agents. Reports have confirmed that natural polyamines[10–12] and polyamine derivatives such as the natural product ianthelliformisamine (**1**)[13], the (bis)thiourea analogue **2**[14], and acylpolyamines[15,16] can prejudice membrane integrity and sensitize bacteria to antibiotics (Fig. 1).

During our ongoing investigations into the biological activities of polyamine-containing compounds,[17–21] we found that a library of substituted indolglyoxylpolyamines exhibited mild to modest intrinsic antimicrobial activity.[21] The most active, 6-bromoindolglyoxylamidospermine (**3**), demonstrated good antimicrobial activity against two Gram-positive bacterial strains, *Staphylococcus intermedius* (MIC 3.13

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μM) and *Staphylococcus aureus* (MIC 6.25 μM), and moderate to strong antifungal activity towards *Candida albicans* (MIC 17.2 μM) and *Cryptococcus neoformans* (MIC 1.1 μM). This compound was then evaluated for the ability to enhance the antibiotic activity of doxycycline towards *Pseudomonas aeruginosa* ATCC 27853. Despite having no intrinsic antibiotic activity against *P. aeruginosa* itself, a combination of **3** at 6.25 μM with doxycycline at 4.5 μM, a concentration at which doxycycline alone is ineffective (MIC >45 μM), was able to restore the action of the antibiotic.

Mechanism of action studies were performed to measure permeabilization, characteristic of membrane perturbation, and to verify the loss of the bacterial transmembrane proton gradient force which enables pathogens like *P. aeruginosa* to actively pump antibiotics out of the cell via drug efflux systems. The results of these studies established that rapid disruption of the bacterial membrane and loss of integrity coupled with strong depolarization occurred indicating that **3** was also able to dissipate the proton concentration gradient and inhibit efflux pumps. Unfortunately, this lead compound also exhibited low selectivity with undesirable cytotoxicity to rat skeletal muscle (L6) and human embryonic kidney (HEK-293) cell lines.

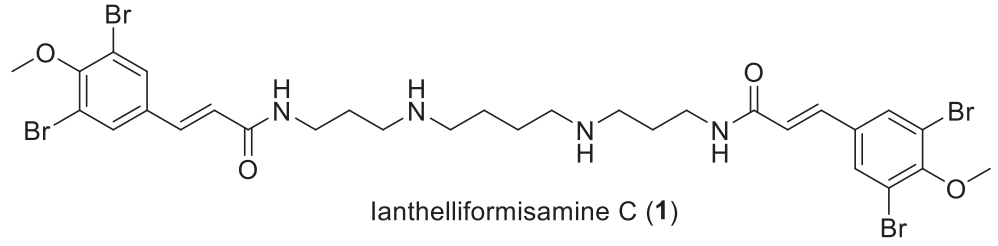
Intrigued by these findings we decided to test a primaquine-polyamine hybrid, which had previously been synthesized as a possible anti-malarial candidate, and had demonstrated modest results, but which had not displayed adequate *in vivo* activity. Herein we present these preliminary data, and the preparation of a library of analogues for a structure-activity relationship study that explores the influence on intrinsic antimicrobial and antibiotic adjuvant properties of both a simplified hydrophobic pendant substituent and the consequence of chain length of the polyamine core. In this way, we could span a wide range of lipophilicities and modifications in order to identify the minimum pharmacophore necessary for intrinsic antibiotic activity as well as for the ability to increase antibiotic susceptibility in resistant strains of pathogens.

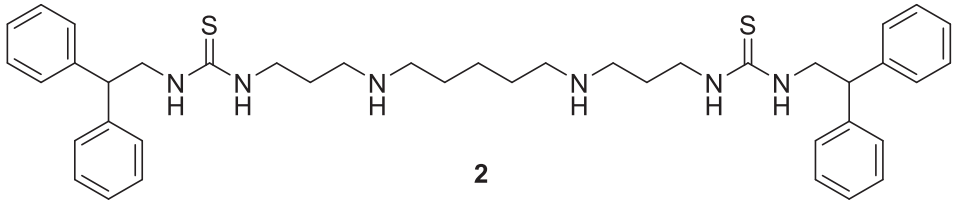
2. Chemistry

The preparation of the library of SPQ-PA analogues was straightforward and uncomplicated and all analogues follow the synthetic scheme shown in Scheme 1. The initial step was the synthesis of the Boc-protected polyamine scaffolds **4a-e** (Fig. 2) which has been previously described.[20,22-24] Five polyamines were prepared with chains of varying lengths, commencing with spermine (polyamine PA3-4-3) and continuing through PA3-6-3, PA3-7-3, PA3-8-3 and PA3-10-3 designed to examine the influence of chain length, lipophilicity, steric bulk and spatial positioning of the positive charges on bioactivity.

The library of SPQ-PA analogues was synthesized first. In order to couple a polyamine scaffold to primaquine it was necessary to convert the amine substituent into a carboxylic acid functionality. Thus, primaquine bisphosphate was first converted to the free base by dissolving it in CH_2Cl_2 and washing the organic layer with 1% aq. K_2CO_3, following which the resulting free-based amine was reacted with succinic anhydride in anhydrous CH_2Cl_2 to give the succinylprimaquine acid intermediate **5**. This intermediate was subsequently reacted with the Boc-protected polyamine scaffolds **4a-e** by HBTU/DIPEA or CDI-mediated coupling in DMF affording the Boc-protected diamides **6–10** in yields of 70−84%. Deprotection of the Boc-protected diamides was carried out using either TFA in CH_2Cl_2 or 4 M HCl in dioxane to yield the target analogues **11-15** as their di-TFA or di-HCl salts in 87–97% yield (Scheme 1).

We sought to compare the intrinsic antibiotic and antibiotic adjuvant activities of the SPQ-PA conjugates with a corresponding library of amine-polyamine conjugates comprising progressively simpler nitrogen-containing aryl groups. These analogues were prepared using the general scheme outlined in Scheme 1. The initial amido-acids were synthesized from the desired nitrogen-containing aromatic amine and succinic anhydride to produce an amido-acid fragment with a succinyl spacer as described above, capable of being coupled to a Boc-protected polyamine. The targeted conjugates were then prepared by HBTU, EDC.HCl-HOBt, or EDC·HCl-DMAP-mediated coupling of the capping amido-acids **16-22** with the Boc-protected polyamines **4a-e** to afford Boc-protected diamides **23-42** in yields of 24–100% (Scheme S1). Subsequent Boc deprotection was achieved using TFA in CH_2Cl_2 to give compounds **43-62** as their di-TFA salts (Fig. 3).





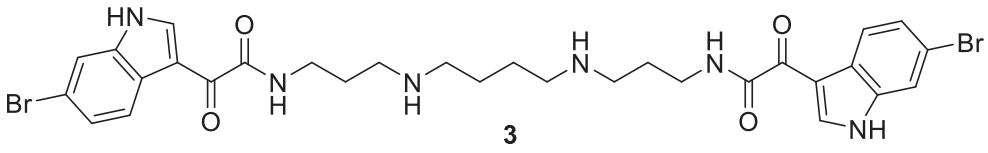
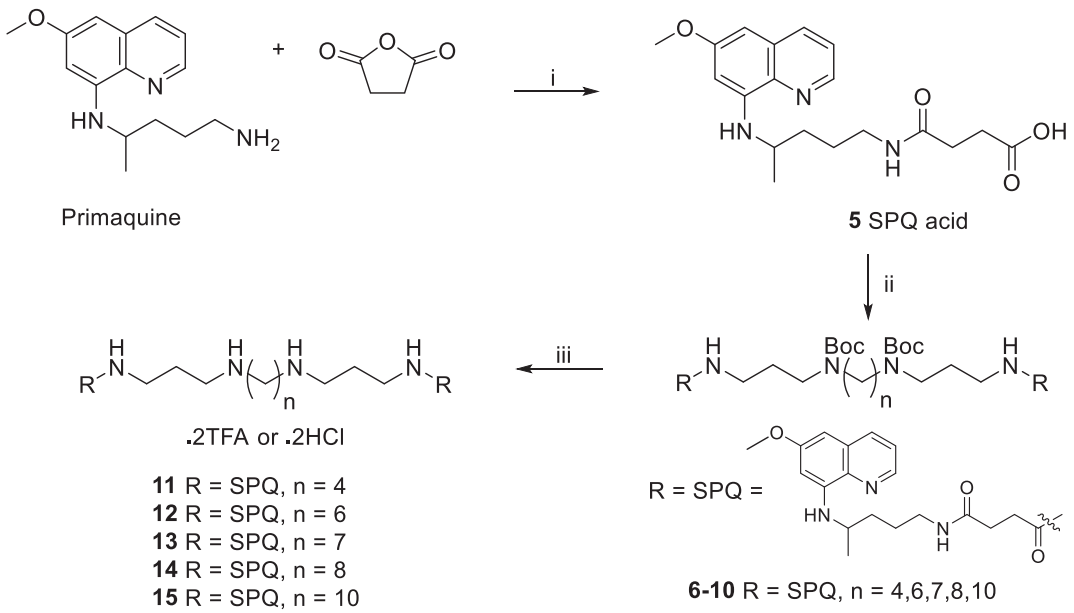


Fig. 1. Structures of polyamines **1**–**3**.



Scheme 1. General method for the preparation of the SPQ-PA conjugates **11-15.** Reagents and conditions: (i) CH_2Cl_2, N_2, rt, 12 h, (96% yield); (ii) **4a-e**, HBTU, DIPEA, DMF, (70-81% yield), or CDI, DMF, (76-84% yield), N_2, rt, 12 h; (iii) TFA/CH_2Cl_2, N_2, rt, 2 h, (92-97% yield), or 4M HCl in dioxane, N_2, rt, 4 h, (87% yield).

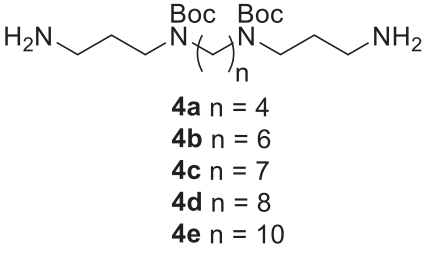


Fig. 2. Target polyamine scaffolds **4a-e.**

3. Biological results and discussion

3.1. Bioactivity of SPQ analogues

The intrinsic antimicrobial efficacy of the set of succinylprimaquine-polyamine (SPQ-PA) analogues **11-15** was evaluated against antibiotic resistant Gram-negative (*Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae* and *Acinetobacter baumannii*) and Gram-positive bacteria (Methicillin-resistant *Staphylococcus aureus* (MRSA)) as well as two yeast strains (*Candida albicans* and *Cryptococcus neoformans*) (Table 1).

Initial screening of the SPQ-PA conjugates showed that these compounds exhibited only modest or no intrinsic activity against the bacterial pathogens, except for derivatives **14** (SPQ-PA3-8-3) and **15** (SPQ-PA3-10-3) that revealed moderately potent MIC's of 13.7 and 3.3 μM respectively against *S. aureus*. However, all compounds except **11** (SPQ-PA3-4-3) demonstrated potent activities against the yeast *C. neoformans* (MIC 33.4, 1.8, 0.4, 1.7, 1.7 μM respectively for analogues **11-15**). Of note was the lack of efficacy against Gram-negative organisms, likely due to the presence of a second outer cellular membrane, which typically confers extra protection against many antimicrobials. We observed with some interest a clear structure-activity trend strongly indicating that progressive lengthening of the polyamine chain increased antibiotic activity, as only **14** with the octyl mid-section chain length (SPQ-PA3-8-3) and **15** with the decyl chain length (SPQ-PA3-10-3) demonstrated any activity against *S. aureus.* Compound **11** (SPQ-PA3-4-3) which possessed the least hydrophobic alkyl chain length with only four carbons was essentially inactive in all assays. Gratifyingly, we observed no cytotoxicity against rat skeletal muscle (L6) or human embryonic kidney (HEK-293) cell lines, and no hemolytic activity towards human erythrocytes in any of these compounds (data not shown). These results clearly illustrated a strong correlation of increasing antibacterial potency with the increasing lipophilicity of the polyamine scaffold whilst retaining selectivity towards bacterial membranes and sparing mammalian cells, the decyl chain length showing significantly more activity over the shorter acyl chains. This is consistent with previous reports affirming that the spacing between the positively charged groups is strongly linked to selectivity and intrinsic antibiotic activity.[12,15,16,25]

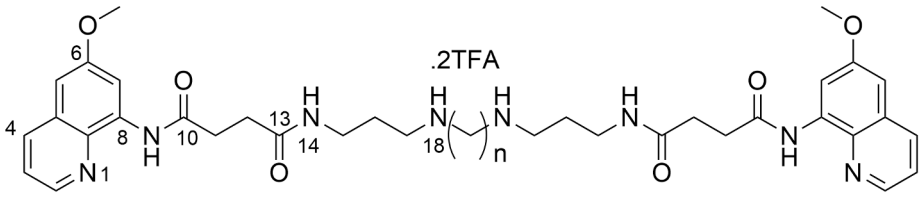
With the initial screening in hand, we then set about exploring the main objective of our investigation, which was to evaluate this set of compounds for their ability to act as adjuvants to overcome the resistance mechanisms of *P. aeruginosa* that enables it to evade the antibiotic efficacy of doxycycline.

As shown in Table 1, none of the SPQ analogues demonstrated any intrinsic activity against *P. aeruginosa,* so we found to our interest, that all analogues restored, to varying degrees, the susceptibility of *P. aeruginosa* to doxycycline when they were combined with just 4.5 μM doxycycline, a concentration at which doxycycline alone is ineffective (MIC >45 μM) (Table 2). Compounds **11** (SPQ-PA3-4-3) and **15** (SPQ-PA3-10-3) in particular, both exhibited significant MIC's of 6.25 μM demonstrating especially promising potential, followed by the intermediate chain lengths of **12**, **13**, and **14** with more modest MIC values of 25, 50, and 25 μM respectively.

Further investigation of the ability of compounds **11** and **15** to restore the antibiotic activity of doxycycline against other Gram-negative pathogens*, Escherichia coli, Klebsiella pneumoniae* and *Acinetobacter baumannii* was undertaken, and the results summarized in Table 3. As established for *P. aeruginosa*, neither of these conjugates exhibited any intrinsic antibiotic activity towards these bacteria, but did demonstrate some modest synergistic activity with doxycycline. Compound **15** with the decyl chain length was identified as the most effective adjuvant against *E. coli* requiring an MIC of 12.5 μM to restore the action of doxycycline at a fixed concentration of 4.5 μM, followed by **11** with a weaker MIC of 50 μM. No activity was observed towards *A. baumannii* and neither derivative demonstrated any substantial ability to sensitize *K. pneumoniae* to doxycycline, compound **15** exhibiting an MIC value of 50 μM, with compound **11** being completely inactive. This confirmed our observation that generally the longer chain lengths were optimal.

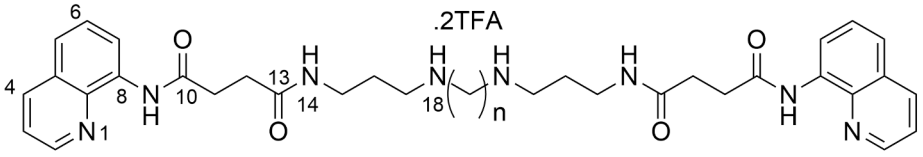
Notably however, the synergistic activity with doxycycline towards

Series 1

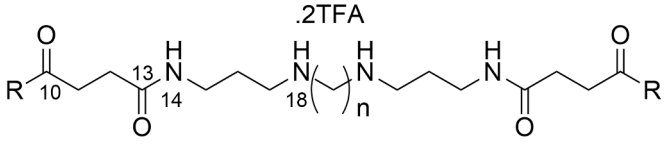


43 n = 4
44 n = 6
45 n = 7
46 n = 8
47 n = 10

Series 2

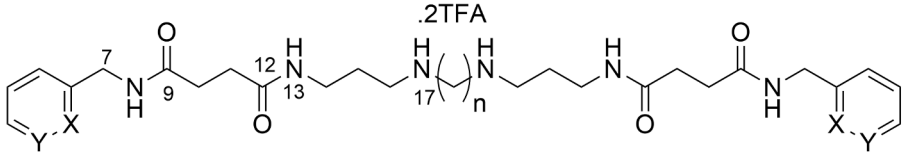


48 n = 4
49 n = 6
50 n = 7
51 n = 8
52 n = 10



53 R = 2-aminoquinoline, n = 4
54 R = 2-aminoquinoline, n = 10
55 R = 5-aminoquinoline, n = 4
56 R = 5-aminoquinoline, n = 10
57 R = 6-aminoquinoline, n = 4
58 R = 6-aminoquinoline, n = 10

Series 3



59 X = N, Y = CH, n = 4
60 X = N, Y = CH, n = 10
61 X = CH, Y = N, n = 4
62 X = CH, Y = N, n = 10

Fig. 3. Structures of the SPQ-PA derivatives **43-62.**

P. aeruginosa did not coincide with the general preference for increased spatial positioning between the positive charges as observed for the intrinsic biological activity. As the MIC_{50} values of 6.25 μM were comparable between the shortest spermine SPQ-PA3-4-3 (**11**) analogue and the longest SPQ-PA3-10-3 (**15**) scaffold, with weaker variable values being shown in the intermediate chain lengths, it became apparent that the potentiating activity was not completely lipophilicity-driven. The inference that interaction with membrane protein targets also plays a part is yet to be determined but cannot be discounted.

3.2. SAR design of series 1-3

Motivated by these results, we sought to prepare a series of novel conjugates that would enable us to optimize the molecules to gain

Table 1
Antibacterial and antifungal activities of SPQ-PA analogues **11-15** and derivatives **43-62.**

Compound	MIC (μM)						
	S. a[a]	*P. a*[b]	*E. c*[c]	*K. p*[d]	*A. b*[e]	*C. a*[f]	*C. n*[g]
11	>33.4	>33.4	>33.4	>33.4	>33.4	>33.4	33.4
12	28.0	>28.0	>28.0	>28.0	>28.0	>28.0	1.8
13	>27.7	>27.7	>27.7	>27.7	>27.7	>27.7	0.4
14	13.7	>27.4	>27.4	>27.4	>27.4	>27.4	1.7
15	3.3	>26.7	>26.7	>26.7	>26.7	26.7	1.7
43	>33.9	>33.9	>33.9	>33.9	>33.9	>33.9	>33.9
44	>33.0	>33.0	>33.0	>33.0	>33.0	>33.0	>33.0
45	>32.5	>32.5	>32.5	>32.5	>32.5	>32.5	>32.5
46	>32.0	>32.0	>32.0	>32.0	>32.0	>32.0	>32.0
47	3.9	>31.2	>31.2	>31.2	>31.2	>31.2	>31.2
48	>36.2	>36.2	>36.2	>36.2	>36.2	>36.2	>36.2
49	17.6	>35.1	>35.1	>35.1	>35.1	>35.1	>35.1
50	>34.6	>34.6	>34.6	>34.6	>34.6	>34.6	>34.6
51	>34.1	>34.1	>34.1	>34.1	>34.1	>34.1	>34.1
52	33.1	>33.1	>33.1	>33.1	>33.1	>33.1	>33.1
53	>36.2	>36.2	>36.2	>36.2	>36.2	>36.2	>36.2
54	>33.1	>33.1	>33.1	>33.1	>33.1	>33.1	>33.1
55	>36.2	>36.2	>36.2	>36.2	>36.2	>36.2	>36.2
56	>33.1	>33.1	>33.1	>33.1	>33.1	>33.1	>33.1
57	>36.2	>36.2	>36.2	>36.2	>36.2	>36.2	>36.2
58	>33.1	>33.1	>33.1	>33.1	>33.1	>33.1	>33.1
59	>39.5	>39.5	>39.5	>39.5	>39.5	>39.5	>39.5
60	>35.8	>35.8	>35.8	>35.8	>35.8	>35.8	>35.8
61	>39.5	>39.5	>39.5	>39.5	>39.5	>39.5	>39.5
62	>35.8	>35.8	>35.8	>35.8	>35.8	>35.8	>35.8

[a] *Staphylococcus aureus* ATCC 43300 (MRSA) with vancomycin (MIC 0.7 μM) used as positive controls and values presented as the mean (n = 2).
[b] *Pseudomonas aeruginosa* ATCC 27853 with colistin (MIC 0.2 μM) used as positive controls and values presented as the mean (n = 2).
[c] *Escherichia coli* ATCC 25922 with colistin (MIC 0.1 μM) used as positive controls and values presented as the mean (n = 2).
[d] *Klebsiella pneumoniae* ATCC 700603 with colistin (MIC 0.2 μM) as a positive control and values presented as the mean (n = 2).
[e] *Acinetobacter baumannii* ATCC 19606 with colistin (MIC 0.2 μM) as a positive control and values presented as the mean (n = 2).
[f] *Candida albicans* ATCC 90028 with fluconazole (MIC 0.4 μM) as a positive control and values presented as the mean (n = 2).
[g] *Cryptococcus neoformans* ATCC 208821 with fluconazole (MIC 26 μM) as a positive control and values presented as the mean (n = 2).

Table 2
Doxycycline potentiation activity (MIC) of SPQ-PA analogues **11-15** and derivatives **43-62** against *P. aeruginosa.*

Compound	MIC (μM) for potentiation[a]	Compound	MIC (μM) for potentiation[a]
11	6.25	**51**	200
12	25	**52**	100
13	50	**53**	566
14	25	**54**	517
15	6.25	**55**	300
43	200	**56**	517
44	300	**57**	566
45	300	**58**	517
46	300	**59**	617
47	300	**60**	559
48	566	**61**	617
49	100	**62**	559
50	200		

[a] MIC (μM) required to restore doxycycline activity at 2 μg/mL (4.5 μM) against *P. aeruginosa* ATCC 27853.

Table 3
Doxycycline potentiation activity (MIC) of SPQ-PA conjugates **11** and **15** against *E. coli, K. pneumoniae* and *A. baumannii.*

Compound	MIC (μM) for potentiation[a]		
	E. coli[b]	*K. pneumoniae*[c]	*A. baumannii*[d]
11	50	>200	>200
15	12.5	50	>200

[a] MIC (μM) required to restore doxycycline activity at 2 μg/mL (4.5 μM).
[b] *Escherichia coli* ATCC 25922.
[c] *Klebsiella pneumoniae* ATCC 700603.
[d] *Acinetobacter baumannii* AYE.

potency, pathogen selectivity and to identify the minimal motif required for activity (Fig. 3). The SAR of the SPQ-polyamine conjugates was explored in three series of compounds, designed to become progressively simpler as deconstruction progressed and functionalities were systematically removed in order to assess the importance and contribution of each feature. As cationic amphiphiles act by perturbing the bacterial membrane, some tolerance for rigid structural requirements may be expected, so any significant variation in activity could point to the possible participation of other membrane protein targets.[26]

In Series 1 the 6-methoxy-quinoline pendant group was retained but the role of the 4-amino-pentyl linker to the succinylpolyamine chain was investigated by omitting it completely so that the activity would report on the contribution of this functionality. As the pK_a of the aniline nitrogen at position eight on the quinoline moiety is very low (unmeasurable)[27] and therefore unprotonated at physiological pH, it has no influence on the number of cationic species. This series was synthesized as the polyamine 3-4-3, 3-6-3, 3-7-3, 3-8-3, and 3-10-3 configurations for close comparison with the SPQ analogues **11-15**. Thus, we could interrogate the influence on activity of increased chain length, and therefore increased lipophilicity confining the two positive charges of the polyamine core, whilst retaining the mandatory cationic amphiphilic nature.

In Series 2, we not only removed the 4-amino-pentyl motif, but also modified the quinoline ring by eliminating the electron-donating 6-methoxy substituent to determine whether stereoelectronic variation was permitted at this position, as well as exploring any positional bias of 2, 5, 6, and 8-quinoline regioisomers. The 8-substituted quinoline, as for Series 1, was synthesized with all five polyamine chain lengths, while the other regioisomers were prepared with the 3-4-3 and 3-10-3 chains only, keeping in mind the observed adjuvant activities of SPQ compounds **11** and **15**.

The final series (Series 3) was designed to assess the significance and requirement for steric hydrophobic bulk as a feature for activity by

substituting 2- and 3-subsituted pyridine rings in place of the quinoline moiety. The resulting analogues would represent the minimal possible pharmacophore in the series, sporting the least bulky possible nitrogen-containing aromatic end group, while also omitting the 4-amino-pentyl substituent, but retaining the essential cationic and lipophilic features of the polyamine scaffold for activity. These compounds were also prepared only with the 3-4-3 and 3-10-3 chains.

3.3. Biological activity of the SAR analogues

Examination of the intrinsic activity of these derivatives utilizing the same microorganisms and protocols applied for the SPQ-PA analogues, revealed that consistent with the original SPQ-PA results, none exhibited antibacterial properties except for **47** (Series 1) and **49** (Series 2) with MIC's of 3.9 and 17.6 μM respectively towards *S. aureus* (Table 1). Interestingly however, unlike the SPQ-PA analogues, there was no intrinsic activity observed against the yeast *C. neoformans*.

Conjugates **47** and **49** both maintained the 8-substituted quinoline core, indicating significant preference for this functionality. To our interest, compound **47** (Series 1) was identical to SPQ-PA3-10-3 (**15**) in structure, retaining all of the features except for the absence of the 4-amino-pentyl substituent, confirming that of all the polyamine scaffolds, the decyl chain length contributed most to the activity. Given the parity of activity, (MIC 3.9 μM vs 3.3 μM for **15**) it would be tempting to conclude that in addition to the extended length of hydrophobicity between the two charged (at physiological pH) nitrogens, the important feature was the pendant steric bulk, were it not for the fact that none of the other 3-10-3 quinoline regioisomers exhibited any intrinsic activity at all. Further analysis leads us to observe that the spatial positioning of the 8-substituted quinoline must also play a valid role in that it is oriented in such a fashion that insertion into the lipid bilayer is facilitated. Furthermore, the presence of the electron rich 6-methoxy substituent on the quinoline ring also appears to be of significance. Thus, there are four motifs that all contribute to the activity: decyl chain length between the charged nitrogens, pendant hydrophobic steric bulk, an 8-substituted quinoline and a 6-methoxy quinoline substituent. Compound **49**, (Series 2) with much more modest activity (MIC 17.6 μM) and incorporating the shorter PA3-6-3 scaffold also retained the 8-quinoline substituted structure but lacked the 6-methoxy moiety and the 4-amino-pentyl substituent. Only compound **52** (PA3-10-3) in Series 2 exhibited some very weak haemolytic activity towards rat red blood cells with an HC_{50} (concentration at which 50% of red blood cells were lysed) of 30.5 μM. Otherwise no haemolytic or cytotoxic activity was observed (data not shown).

Finally, the extended set of analogues were evaluated for their ability to act as adjuvants for doxycycline against *P. aeruginosa*, *E. coli, K. pneumoniae* and *A. baumannii*. We were surprised to discover that unlike the SPQ-PA analogues, all of these compounds were completely ineffective at restoring the action of doxycycline not only against *P. aeruginosa* (Table 2) but also against the other Gram-negative pathogens (data not shown). Clearly, although the 4-amino-pentyl substituent was relatively inessential for intrinsic bioactivity, it was crucial for the mission of acting as an antibiotic adjuvant.

4. Conclusions

Our initial screening identified SPQ-PA3-10-3 (**15**) as a strongly active antimicrobial agent with excellent selectivity against the Gram-positive pathogen *S. aureus* and against the yeast *C. neoformans* which was also able to potently enhance the antibiotic susceptibility of *P. aeruginosa* to doxycycline. SPQ-PA3-4-3 (**11**), with the spermine scaffold, was even more interesting in that it was devoid of any intrinsic antibiotic activity in itself but was equipotent with **15** at enhancing the activity of doxycycline against *P. aeruginosa*.

Although SAR experiments failed to produce positive results in our attempts to simplify and enhance synergizing antibiotic activity, instead indeed, abrogating it altogether, they clearly showed that the 4-amino-pentyl substituent on the quinoline ring of the SPQ-PA analogues **11-15** is critical for potentiating activity. Whether this is due to the lengthening of the alkyl chain, therefore increasing the lipophilicity outside of the positively charged nitrogen core or even the presence of a methyl group remains to be explored further. It may also allude to the possibility that these molecules are also interacting with other protein targets in the bacterial membranes, thereby augmenting the proposed cationic amphiphilic effect in their mode of action. In addition, the SAR experiments indicated that the decyl chain length between the positive charges, the 8-substituted quinoline ring and the electron rich 6-methoxy quinoline substituent all appear to be mandatory features for intrinsic antibiotic activity.

It has become evident through these investigations that there is more structural specificity and considerably less flexibility in structural constraints allowed in these molecules than has previously been considered. Following our previous investigations that demonstrated convincingly that this type of small cationic amphiphile disrupts lipid membranes, and a report that confirms that primaquine itself is also capable of intercalating and perturbing lipid bilayers,[28] there is reasonable evidence to support the conclusion that the SPQ-PA analogues are also membrane disruptors. However, although this mode of action may be pivotal to the synergistic activity, it is clear that other factors are in play. Whether in addition, membrane proteins are actively involved remains interesting and unexplored territory for the focus of future investigations.

5. Experimental

5.1. General remarks

Infrared spectra were run as dry films on an ATR crystal and acquired with a Perkin-Elmer 100 Fourier Transform infrared spectrometer equipped with a Universal ATR Sampling Accessory. Mass spectra were acquired on a Bruker micrOTOF Q II mass spectrometer. Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 298 K on a Bruker AVANCE AVIII 400 MHz spectrometer at 400.13 and 100.62 MHz, or on a Bruker AVANCE AVIII-HD 500 MHz spectrometer at 500.13 and 125.76 MHz respectively using standard pulse sequences. Proto-deutero solvent signals were used as internal references (DMSO-d_6: δ_H 2.50, δ_C 39.52; $CDCl_3$: δ_H 7.26, δ_C 77.16; CD_3OD: δ_H 3.31, δ_C 49.00). For ^{1}H NMR, the data are quoted as position (δ), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*, Hz), and assignment to the atom. The ^{13}C NMR data are quoted as position (δ), and assignment to the atom. Flash column chromatography was carried out using Davisil silica gel (40–60 μm), Merck silica gel (15–40 μm) or Merck Diol bonded silica (40–63 μM) or Merck C_8 reversed-phase (40–63 μM) solid support. Thin layer chromatography was conducted on Merck DC-plastikfolien Kieselgel 60 F254 plates. Reversed-phase analytical thin layer chromatography (TLC) was carried out on 0.2 mm thick plates of DC-Kieselgel 60 RP-18 $F_{254}S$ (Merck). Analytical reversed phase C_{18} HPLC was run on a Waters 600 HPLC photodiode array system using an Alltech 3μm Econosphere Rocket^{TM} column (33 × 7 mm), eluting with a gradient from aqueous trifluoroacetic acid (0.05%) through to MeCN. All solvents used were of analytical grade or better and/or purified according to standard procedures. Chemical reagents used were purchased from standard chemical suppliers and used as purchased. All samples were determined to >95% purity. Protected polyamines di-*tert*-butyl butane-1,4-diylbis((3-aminopropyl)carbamate) (**4a**), di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl)carbamate) (**4b**), di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl)carbamate) (**4c**), di-*tert*-butyl octane-1,8-diylbis((3-aminopropyl)carbamate) (**4d**), and di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl)carbamate) (**4e**) were synthesized by literature procedures.[20,22-24]

5.2. Synthesis

5.2.1. Synthesis of SPQ polyamines **5-15**

5.2.1.1. General procedure A: synthesis of amido-acids. To a stirred solution of succinic anhydride (1.1 equiv.) in anhydrous CH_2Cl_2 was added the amine (1 equiv.) at room temperature. The reaction mixture was stirred under N_2 atmosphere for 20 h followed by solvent removal *in vacuo*. The product was purified by washing the solid with cold CH_2Cl_2 or EtOH.

*5.2.1.2. 4-((6-Methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanoic acid (**5**).* Primaquine bisphosphate (700 mg, 1.54 mmol) was dissolved in CH_2Cl_2 (30 mL) and washed with 1% K_2CO_3 (30 mL). The organic layer was separated, dried ($MgSO_4$) and solvent removed *in vacuo* to afford the free-based product which was used without purification. Following general procedure A, succinic anhydride was added to the free-based primaquine (320 mg, 1.24 mmol) and was stirred under nitrogen at room temperature for 24 h, followed by removal of the solvent *in vacuo* to afford **5** as a yellow solid (420 mg, 96% yield) which was used without purification. R_f (2% MeOH/CH_2Cl_2) 0.32; m.p. 141–143 °C (Lit. 142-145 °C[29]); IR (ATR) ν_{max} 3455, 3268, 2928, 1710, 1671, 1646, 1615, 1584, 1563, 1524, 1452, 1386, 1227, 826, 786 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 8.48 (1H, dd, J = 4.3, 1.9 Hz, H-2), 8.01 (1H, dd, J = 8.4, 1.8 Hz, H-4), 7.35 (1H, dd, J = 8.4, 4.3 Hz, H-3), 6.44 (1H, d, J = 2.5 Hz, H-5), 6.31 (1H, d, J = 2.5 Hz, H-7), 3.86 (3H, s, OMe), 3.67–3.61 (1H, m, H-10), 3.23–3.17 (2H, m, H_2-13), 2.56 (2H, t, J = 7.2 Hz, H_2-16 or H_2-17), 2.43 (2H, t, J = 7.2 Hz, H_2-16 or H_2-17), 1.73–1.59 (4H, m, H_2-11, H_2-12), 1.28 (3H, d, J = 6.7 Hz, 10-Me); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.3 (C-18), 174.5 (C-15), 161.0 (C-6), 146.2 (C-8), 145.3 (C-2), 136.5 (C-8a), 136.4 (C-4), 131.6 (C-4a), 123.0 (C-3), 98.4 (C-7), 93.1 (C-5), 55.6 (OMe), 48.9 (C-10), 40.3 (C-13), 34.9 (C-11), 31.7, 30.5 (C-16, C-17), 27.1 (C-12), 20.7 (10-Me); HRESIMS $[M+H]^+$ m/z 360.1926 (calcd for $C_{19}H_{26}N_3O_4$, 360.1918).

5.2.2. General procedure B: diamide bond formation

To a solution of SPQ acid (**5**) or the relevant acid (2.2 equiv.) and either CDI (2.4 equiv.), HBTU (2.2 equiv.), or EDC·HCl/HOBt (2.2 equiv.) with DIPEA (7 equiv.) stirred in dry DMF (3 mL) at 0 °C for 15 min under N_2 was added the appropriate Boc-protected polyamine **4a-e** (1 equiv.). The mixture was allowed to come to room temperature and stirred for a further 24 h under N_2. The reaction mixture was poured into CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ (2 × 30 mL) followed by H_2O (2 × 30 mL), then dried *in vacuo* and purified by silica gel flash column chromatography (6–8% MeOH/CH_2Cl_2) to afford the desired products.

*5.2.2.1. Di-tert-butyl butane-1,4-diylbis((3-(4-((4-((6-methoxyquinolin-8-yl) amino)pentyl)amino)-4-oxobutanamido)propyl)carbamate) (**6**).* Following general procedure B, 4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanoic acid (**5**) (97 mg, 0.27 mmol) and di-*tert*-butyl butane-1,4-diylbis((3-aminopropyl)carbamate) (**4a**) (50 mg, 0.12 mmol) with CDI afforded **6**, (114 mg, 84%) as a green gum. R_f (5% MeOH/CH_2Cl_2) 0.33; IR (ATR) ν_{max} 3299, 2966, 2931, 1642, 1616, 1518, 1454, 1419, 1387, 1219, 1155, 822, 790, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.52 (2H, dd, J = 4.3, 1.3 Hz, H-2), 7.91 (2H, dd, J = 8.4, 1.7 Hz, H-4), 7.29 (2H, dd, J = 8.4, 4.3 Hz, H-3), 6.95 (2H, br s, NH-19), 6.54 (2H, br s, NH-14), 6.33 (2H, d, J = 2.4 Hz, H-5), 6.26 (2H, d, J = 2.4 Hz, H-7), 5.99 (2H, br s, NH-9), 3.88 (6H, s, OMe), 3.60 (2H, br m, H-10), 3.28–3.07 (16H, m, H_2-13, H_2-20, H_2-22, H_2-24), 2.52–2.44 (8H, m, H_2-16, H_2-17), 1.73–1.56 (12H, m, H_2-11, H_2-12, H_2-21), 1.46–1.41 (4H, m, H_2-25), 1.43 (18H, s, *t*-Bu), 1.27 (6H, d, J = 6.6 Hz, 10-Me); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.4 (C-15, C-18), 159.5 (C-6), 156.3 (C-26), 145.0 (C-8), 144.4 (C-2), 135.4 (C-8a), 134.9 (C-4), 130.0 (C-4a), 122.0 (C-3), 96.9 (C-7), 91.8 (C-5), 79.8 (C-27), 55.3 (OMe), 47.9 (C-10), 47.0 (C-24), 43.8 (C-22), 39.6 (C-13), 36.2 (C-20), 34.1 (C-11), 32.0 (C-16, C-17), 28.5 (*t*-Bu), 28.0 (C-21), 26.4 (C-12), 26.1 (C-25), 20.7 (C-10Me); HRESIMS $[M+H]^+$ m/z 1085.6800 (calcd for $C_{58}H_{89}N_{10}O_{10}$, 1085.6758).

*5.2.2.2. Di-tert-butyl hexane-1,6-diylbis((3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanamido)propyl)carbamate) (**7**).* Following general procedure B, 4-((6-methoxyquinolin-8-yl)amino)pentyl) amino)-4-oxobutanoic acid (**5**) (127 mg, 0.36 mmol) and di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl)carbamate) (**4b**) (70 mg, 0.16 mmol) with HBTU and DIPEA afforded **7**, (147 mg, 81%) as a yellow gum. R_f (5% MeOH/CH_2Cl_2) 0.27; IR(ATR) ν_{max} 3305, 2971, 2932, 1739, 1650, 1617, 1510, 1454, 1421, 1388, 1366, 1218, 1161, 823, 792 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.52 (2H, dd, J = 4.4, 1.5 Hz, H-2), 7.91 (2H, dd, J = 8.4, 1.6 Hz, H-4), 7.29 (2H, dd, J = 8.4, 4.4 Hz, H-3), 6.98 (2H, br s, NH-19), 6.49 (2H, br s, NH-14), 6.33 (2H, d, J = 2.4 Hz, H-5), 6.26 (2H, d, J = 2.4 Hz, H-7), 5.98 (2H, br s, NH-9), 3.88 (6H, s, OMe), 3.63–3.57 (2H, m, H-10), 3.30–3.01 (16H, m, H_2-13, H_2-20, H_2-22, H_2-24), 2.53–2.44 (8H, m, H_2-16, H_2-17), 1.73–1.57 (12H, m, H_2-11, H_2-12, H_2-21), 1.51–1.40 (4H, m, H_2-25), 1.44 (18H, s, *t*-Bu), 1.28 (6H, d, J = 6.6 Hz, 10-Me), 1.26–1.23 (4H, m, H_2-26); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4 (C-15, C-18), 159.5 (C-6), 156.5 (C-27), 145.0 (C-8), 144.4 (C-2), 135.4 (C-8a), 134.9 (C-4), 130.0 (C-4a), 122.0 (C-3), 96.9 (C-7), 91.8 (C-5), 79.7 (C-28), 55.3 (OMe), 47.9 (C-10), 47.1 (C-24), 43.6 (C-22), 39.6 (C-13), 36.1 (C-20), 34.1 (C-11), 32.1 (C-16, C-17), 28.5 (*t*-Bu), 27.9 (C-21), 26.7 (C-26), 26.4 (C-25, C-12), 20.6 (C-10Me); HRESIMS $[M+H]^+$ m/z 1113.7077 (calcd for $C_{60}H_{93}N_{10}O_{10}$, 1113.7071).

*5.2.2.3. Di-tert-butyl heptane-1,7-diylbis((3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanamido)propyl)carbamate) (**8**).* Following general procedure B, 4-((6-methoxyquinolin-8-yl)amino) pentyl)amino)-4-oxobutanoic acid (**5**) (100 mg, 0.28 mmol) and di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl)carbamate) (**4c**) (63 mg, 0.14 mmol) with CDI afforded **8**, (122 mg, 76%) as a green gum. R_f (5% MeOH/CH_2Cl_2) 0.30; IR (ATR) ν_{max} 3302, 2929, 1642, 1618, 1518, 1454, 1419, 1387, 1365, 1219, 1157, 821, 791, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.52 (2H, dd, J = 4.4, 1.5 Hz, H-2), 7.91 (2H, dd, J = 8.3, 1.5 Hz, H-4), 7.29 (2H, dd, J = 8.4, 4.4 Hz, H-3), 6.97 (2H, br s, NH-19), 6.49 (2H, br s, NH-14), 6.33 (2H, d, J = 2.5 Hz, H-5), 6.27 (2H, d, J = 2.5 Hz, H-7), 5.99 (2H, br s, NH-9), 3.88 (6H, s, OMe), 3.64–3.57 (2H, m, H-10), 3.30–3.02 (16H, m, H_2-13, H_2-20, H_2-22, H_2-24), 2.53–2.44 (8H, m, H_2-16, H_2-17), 1.73–1.56 (12H, m, H_2-11, H_2-12, H_2-21), 1.51–1.41 (4H, m, H_2-25), 1.44 (18H, s, *t*-Bu), 1.31–1.19 (6H, m, H_2-26, H_2-27), 1.28 (6H, d, J = 6.5 Hz, 10-Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4 (C-15, C-18), 159.5 (C-6), 156.5 (C-28), 145.0 (C-8), 144.4 (C-2), 135.4 (C-8a), 134.9 (C-4), 130.0 (C-4a), 122.0 (C-3), 96.9 (C-7), 91.8 (C-5), 79.7 (C-29), 55.3 (OMe), 47.9 (C-10), 47.1 (C-24), 43.6 (C-22), 39.6 (C-13), 36.0 (C-20), 34.1 (C-11), 32.0 (C-16, C-17), 29.2 (C-27), 28.5 (*t*-Bu), 27.9 (C-21), 26.9 (C-25, C-26), 26.4 (C-12), 20.6 (C-10Me); HRESIMS $[M+H]^+$ m/z 1127.7271 (calcd for $C_{61}H_{95}N_{10}O_{10}$, 1127.7227).

*5.2.2.4. Di-tert-butyl octane-1,8-diylbis((3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanamido)propyl)carbamate (**9**).* Following general procedure B, 4-((6-methoxyquinolin-8-yl)amino) pentyl)amino)-4-oxobutanoic acid (**5**) (148 mg, 0.42 mmol) and di-*tert*-butyl octane-1,8-diylbis((3-aminopropyl)carbamate) (**4d**) (87 mg, 0.19 mmol) with HBTU and DIPEA afforded **9**, (170 mg, 78%) as a yellow gum. R_f (5% MeOH/CH_2Cl_2) 0.24; IR (ATR) ν_{max} 3306, 2929, 2858, 1643, 1616, 1521, 1454, 1420, 1387, 1365, 1219, 1158, 822, 792, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.52 (2H, dd, J = 4.3, 1.5 Hz, H-2), 7.91 (2H, dd, J = 8.5, 1.5 Hz, H-4), 7.29 (2H, dd, J = 8.5, 4.3 Hz, H-3), 6.97 (2H, br s, NH-19), 6.48 (2H, br s, NH-14), 6.33 (2H, d, J = 2.5 Hz, H-5), 6.27 (2H, d, J = 2.5 Hz, H-7), 5.99 (2H, br s, NH-9), 3.88 (6H, s, OMe), 3.60 (2H, br m, H-10), 3.30–3.04 (16H, m, H_2-13, H_2-20, H_2-22, H_2-24), 2.52–2.43 (8H, m, H_2-16, H_2-17), 1.72–1.56 (12H, m, H_2-11, H_2-12, H_2-21), 1.51–1.42 (4H, m, H_2-25), 1.44 (,18H, s, *t*-Bu), 1.30–1.20

(8H, m, H_2-26, H_2-27), 1.28 (6H, d, $J = 6.6$ Hz, 10-Me); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4 (C-15, C-18), 159.5 (C-6), 156.5 (C-28), 145.0 (C-8), 144.4 (C-2), 135.4 (C-8a), 134.9 (C-4), 130.0 (C-4a), 122.0 (C-3), 96.9 (C-7), 91.8 (C-5), 80.0 (C-29), 55.3 (OMe), 47.9 (C-10), 47.1 (C-24), 43.5 (C-22), 39.6 (C-13), 36.0 (C-20), 34.1 (C-11), 32.0 (C-16, C-17), 29.4 (C-27), 28.5 (*t*-Bu), 27.9 (C-21), 26.9 (C-25, C-26), 26.4 (C-12), 20.6 (C-10Me); HRESIMS $[M+Na]^+$ *m/z* 1163.7193 (calcd for $C_{62}H_{96}N_{10}NaO_{10}$, 1163.7203).

*5.2.2.5. Di-tert-butyl decane-1,10-diylbis((3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanamido)propyl)carbamate) (**10**).* Following general procedure B, 4-((6-methoxyquinolin-8-yl)amino) pentyl)amino)-4-oxobutanoic acid (**5**) (114 mg, 0.32 mmol) and di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl)carbamate) (**4e**) (71 mg, 0.15 mmol) with HBTU and DIPEA afforded **10**, (120 mg, 70%) as a yellow gum. R_f (5% MeOH/CH_2Cl_2) 0.28; IR (ATR) ν_{max} 3306, 2928, 2856, 1645, 1616, 1524, 1455, 1420, 1388, 1365, 1219, 1159, 822, 792 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (2H, dd, $J = 4.4$, 1.5 Hz, H-2), 7.91 (2H, dd, $J = 8.4$, 1.5 Hz, H-4), 7.29 (2H, dd, $J = 8.4$, 4.4 Hz, H-3), 7.00 (2H, br s, NH-19), 6.54 (2H, br s, NH-14), 6.33 (2H, d, $J = 2.4$ Hz, H-5), 6.27 (2H, d, $J = 2.4$ Hz, H-7), 6.00 (2H, br s, NH-9), 3.88 (6H, s, OMe), 3.63–3.57 (2H, m, H-10), 3.29–3.04 (16H, m, H_2-13, H_2-20, H_2-22, H_2-24), 2.54–2.44 (8H, m, H_2-16, H_2-17), 1.74–1.57 (12H, m, H_2-11, H_2-12, H_2-21), 1.51–1.41 (4H, m, H_2-25), 1.44 (18H, s, *t*-Bu), 1.32–1.19 (12H, m, H_2-26, H_2-27, H_2-28), 1.28 (,6H, d, $J = 6.5$ Hz, 10-Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4 (C-15, C-18), 159.5 (C-6), 156.6 (C-29), 145.0 (C-8), 144.4 (C-2), 135.4 (C-8a), 134.9 (C-4), 130.0 (C-4a), 122.0 (C-3), 96.9 (C-7), 91.8 (C-5), 79.6 (C-30), 55.3 (OMe), 47.9 (C-10), 47.1 (C-24), 43.5 (C-22), 39.6 (C-13), 36.0 (C-20), 34.1 (C-11), 32.0 (C-16, C-17), 29.6 (C-28), 29.4 (C-27), 28.5 (*t*-Bu), 27.8 (C-21), 26.9 (C-25, C-26), 26.3 (C-12), 20.6 (C-10Me); HRESIMS $[M+Na]^+$ *m/z* 1191.7559 (calcd for $C_{64}H_{100}N_{10}NaO_{10}$, 1191.7516).

5.2.3. General procedure C: Boc deprotection

A solution of the *tert*-butyl-carbamate derivative was stirred either in CH_2Cl_2 (2 mL) with TFA (0.2 mL) at room temperature under N_2 for 2 h, or alternatively in dioxane (2 mL) with 4 M HCl in dioxane (2 mL) for 4 h followed by solvent removal *in vacuo*. The crude product was purified using C_8 reversed-phase flash column chromatography eluting with 25–70% MeOH/H_2O (0.05% TFA or aq. HCl) to afford the corresponding polyamine conjugate as the acid salt.

*5.2.3.1. N^1,N^4-Bis(3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl) amino)-4-oxobutanamido)propyl)butane-1,4-diaminium 2,2,2-trifluoroacetate (**11**).* Following general procedure C, di-*tert*-butyl butane-1,4-diylbis((3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanamido)propyl)carbamate) (**6**) (12 mg, 0.01 mmol) was treated with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **11** (9 mg, 93%) as an orange oil. R_f (75% MeOH/H_2O/0.05%TFA, C_{18}) 0.52; IR (ATR) ν_{max} 3322, 2962,1594, 1453, 1385, 1294, 1201, 1172, 1015, 760 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz, * = reduced in intensity due to deuterium exchange[30]) δ 8.62 (2H, d, $J = 4.5$ Hz, H-2), 8.35 (2H, d, $J = 8.7$ Hz, H-4), 7.57 (2H, dd, $J = 8.7$, 4.5 Hz, H-3), 6.70 (0.04H*, br s, H-5), 6.56 (1H*, br s, H-7), 3.91 (6H, s, OMe), 3.71–3.68 (2H, m, H-10), 3.28 (4H, t, $J = 6.3$ Hz, H_2-20), 3.19 (4H, t, $J = 6.3$ Hz, H_2-13), 3.01–2.98 (8H, m, H_2-22, H_2-24), 2.52–2.44 (8H, m, H_2-16, H_2-17), 1.87–1.81 (4H, m, H_2-21), 1.78–1.61 (12H, m, H_2-11, H_2-12, H_2-25), 1.30 (6H, d, $J = 6.4$ Hz, 10-Me); ^{13}C NMR (CD_3OD, 125 MHz, * = reduced in intensity due to deuterium exchange[30]) δ 176.2 (C-18), 174.5 (C-15), 161.5 (C-6), 143.8 (C-2), 143.4 (C-8), 140.0 (C-4), 133.1 (C-8a), 132.4 (C-4a), 123.1 (C-3), 102.4 (C-7), 95.0* (C-5), 56.0 (OMe), 50.1 (C-10), 48.1 (C-24), 46.1 (C-22), 40.3 (C-13), 36.6 (C-20), 34.5 (C-11), 31.9, 31.8 (C-16, C-17), 27.7 (C-21), 27.1 (C-12), 24.3 (C-25), 20.2 (C-10Me); HRESIMS $[M+2H]^{2+}$ *m/z* 443.2902 (calcd for $C_{48}H_{74}N_{10}O_6$, 443.2891).

*5.2.3.2. N^1,N^6-Bis(3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl) amino)-4-oxobutanamido)propyl)butane-1,6-diaminium 2,2,2-trifluoroacetate (**12**).* Following general procedure C, di-*tert*-butyl hexane-1,6-diylbis((3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanamido)propyl)carbamate) (**7**) (140 mg, 0.13 mmol) was treated with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **12** (138 mg, 97%) as a yellow oil. R_f (75% MeOH/H_2O/0.05%TFA, C_{18}) 0.28; IR (ATR) ν_{max} 3383, 2940 2866, 1598, 1428, 1389, 1151, 1038, 812, 796, 782, 701 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz, * = reduced in intensity due to deuterium exchange[30]) δ 8.52 (2H, dd, $J = 4.4$, 1.5 Hz, H-2), 8.11 (2H, dd, $J = 8.4$, 1.5 Hz, H-4), 7.41, (2H, dd, $J = 8.4$, 4.4 Hz, H-3), 6.51 (0.10H*, br s, H-5), 6.37 (2H, s, H-7), 3.87 (6H, s, OMe), 3.67–3.61 (2H, m, H-10), 3.27 (4H, t, $J = 6.3$ Hz, H_2-20), 3.18 (4H, t, $J = 6.2$ Hz, H_2-13), 2.96 (4H, t, $J = 6.4$ Hz, H_2-22), 2.89 (4H, t, $J = 7.6$ Hz, H_2-24), 2.51–2.43 (8H, m, H_2-16, H_2-17), 1.85–1.80 (4H, m, H_2-21), 1.72–1.57 (12H, m, H_2-11, H_2-12, H_2-25), 1.37–1.34 (4H, m, H_2-26), 1.27 (6H, d, $J = 6.2$ Hz, 10-Me); ^{13}C NMR (CD_3OD, 125 MHz, * = reduced in intensity due to deuterium exchange[30]) δ 176.1 (C-18), 174.4 (C-15), 161.1 (C-6), 145.2 (C-8), 144.8 (C-2), 137.5 (C-4), 135.2 (C-8a), 131.8 (C-4a), 123.0 (C-3), 99.6 (C-7), 93.7* (C-5), 56.8 (OMe), 49.3 (C-10), 48.8 (C-24), 46.0 (C-22), 40.3 (C-13), 36.6 (C-20), 34.8 (C-11), 31.9, 31.7 (C-16, C-17), 27.7 (C-21), 27.1, 27.0, 26.9 (C-12, C-25, C-26), 20.6 (C-10Me); HRESIMS $[M+H]^+$ *m/z* 913.6029 (calcd for $C_{50}H_{77}N_{10}O_6$, 913.6022).

*5.2.3.3. N^1,N^7-Bis(3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl) amino)-4-oxobutanamido)propyl)heptane-1,7-diaminium chloride (**13**).* Following general procedure C, di-*tert*-butyl heptane-1,7-diylbis((3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanamido) propyl)carbamate) (**8**) (100 mg, 0.09 mmol) was treated in dioxane with 4M HCl in dioxane. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 60% MeOH/40% H_2O (0.05% aq. HCl) to afford **13** (77 mg, 87%) as a yellow oil. R_f (75% MeOH/H_2O/0.05% TFA, C_{18}) 0.42; IR (ATR) ν_{max} 3317, 2944, 1629, 1595, 1473, 1454, 1425, 1387, 1202, 1173, 1021, 833, 795, 710 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz, * = reduced in intensity due to deuterium exchange[30]) δ 8.85 (2H, dd, $J = 8.3$, 1.2 Hz, H-4), 8.79 (2H, dd, $J = 5.2$, 1.2 Hz, H-2), 7.91 (2H, dd, $J = 8.3$, 5.2 Hz, H-3), 7.03 (0.14H*, br s, H-5), 6.88 (1.3H*, br s, H-7), 3.98 (6H, s, OMe), 3.82–3.78 (2H, m, H-10), 3.37 (4H, t, $J = 6.4$ Hz, H_2-20), 3.33 (4H, H_2-13, obsc. solvent), 3.06 (4H, t, $J = 7.5$ Hz, H_2-22), 3.00 (4H, t, $J = 7.7$ Hz, H_2-24), 2.76–2.68 (8H, m, H_2-16, H_2-17), 2.00–1.68 (16H, m, H_2-11, H_2-12, H_2-21, H_2-25), 1.45–1.39 (6H, m, H_2-26, H_2-27), 1.35 (6H, d, $J = 6.4$ Hz, 10-Me); ^{13}C NMR (CD_3OD, 100 MHz, * = reduced in intensity due to deuterium exchange[30]) δ 176.7 (C-18), 176.2 (C-15), 162.6 (C-6), 145.7 (C-4), 140.8 (C-2), 140.1 (C-8), 133.7 (C-4a), 127.5 (C-8a), 123.1 (C-3), 106.8 (C-7), 97.1* (C-5), 56.6 (OMe), 51.3 (C-10), 49.1 (C-24), 46.4 (C-22), 41.3 (C-13), 37.8 (C-20), 34.0 (C-11), 31.3, 31.0 (C-16, C-17), 29.4 (C-27), 27.2, 27.1, 27.1 (C-21, C-25, C-26), 26.5 (C-12), 19.7 (C-10Me); HRESIMS $[M+2H]^{2+}$ *m/z* 464.3127 (calcd for $C_{51}H_{80}N_{10}O_6$, 464.3126).

*5.2.3.4. N^1,N^8-Bis(3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl) amino)-4-oxobutanamido)propyl)octane-1,8-diaminium 2,2,2-trifluoroacetate (**14**).* Following general procedure C, di-*tert*-butyl octane-1,8-diylbis((3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanamido)propyl)carbamate) (**9**) 160 mg, 0.14 mmol) was treated with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **14** (83 mg, 97%) as a yellow oil. R_f (75% MeOH/H_2O/0.05%TFA, C_{18}) 0.44; IR (ATR) ν_{max} 3302, 2936, 2862, 1643, 1597, 1455, 1426, 1387, 1172, 1051, 831, 798,

719 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz, * = reduced in intensity due to deuterium exchange[30]) δ 8.52 (2H, dd, J = 4.3, 1.2 Hz, H-2), 8.11 (2H, dd, J = 8.4, 1.8 Hz, H-4), 7.41 (2H, dd, J = 8.4, 4.3 Hz, H-3), 6.51 (0.08H*, br s, H-5), 6.37 (1.7H*, br s, H-7), 3.87 (6H, s, OMe), 3.67–3.60 (2H, m, H-10), 3.27 (4H, t, J = 6.1 Hz, H_2-20), 3.18 (4H, t, J = 6.9 Hz, H_2-13), 2.97 (4H, t, J = 7.1 Hz, H_2-22), 2.87 (4H, t, J = 7.8 Hz, H_2-24), 2.50 (4H, t, J = 6.7 Hz, H_2-16 or H_2-17), 2.45 (4H, t, J = 6.7 Hz, H_2-16 or H_2-17), 1.85–1.80 (4H, m, H_2-21), 1.74–1.58 (12H, m, H_2-11, H_2-12, H_2-25), 1.36–1.25 (8H, m, H_2-26, H_2-27), 1.27 (6H, d, J = 6.7 Hz, 10-Me); ^{13}C NMR (CD_3OD, 125 MHz, * = reduced in intensity due to deuterium exchange[30]) δ 176.2 (C-18), 174.4 (C-15), 161.1 (C-6), 145.3 (C-8), 144.8 (C-2), 137.5 (C-4), 135.3 (C-8a), 131.8 (C-4a), 123.0 (C-3), 99.5 (C-7), 93.4* (C-5), 55.8 (OMe), 49.3 (C-10), 49.0 (C-24), 46.0 (C-22), 40.3 (C-13), 36.6 (C-20), 34.8 (C-11), 31.9, 31.7 (C-16, C-17), 29.9 (C-27), 27.7 (C-21), 27.4, 27.2, 27.1 (C-12, C-25, C-26), 20.6 (C-10Me); HRESIMS $[M+Na]^+$ *m/z* 963.6141 (calcd for $C_{52}H_{80}N_{10}NaO_6$, 963.6155).

*5.2.3.5. N^1,N^{10}-Bis(3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl) amino)-4-oxobutanamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**15**).* Following general procedure C, di-*tert*-butyl decane-1,10-diylbis((3-(4-((4-((6-methoxyquinolin-8-yl)amino)pentyl)amino)-4-oxobutanamido)propyl)carbamate) (**10**) 80 mg, 0.07 mmol) was treated with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **15** (75 mg, 92%) as a yellow oil. R_f (75% MeOH/H_2O/0.05%TFA, C_{18}) 0.29; IR (ATR) ν_{max} 3370, 2935, 2860, 1775, 1644, 1597, 1549, 1455, 1427, 1387, 1171, 1060, 831, 797, 720 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz, * = reduced in intensity due to deuterium exchange[30]) δ 8.52 (2H, dd, J = 4.3, 1.8 Hz, H-2), 8.10 (2H, dd, J = 8.2, 1.8 Hz, H-4), 7.40 (2H, dd, J = 8.2, 4.3 Hz, H-3), 6.50 (0.10H*, br s, H-5), 6.36 (2H, br s, H-7), 3.87 (6H, s, OMe), 3.66–3.61 (2H, m, H-10), 3.28 (4H, t, J = 5.8 Hz, H_2-20), 3.18 (4H, t, J = 6.2 Hz, H_2-13), 2.97 (4H, t, J = 7.2 Hz, H_2-22), 2.87 (4H, t, J = 7.7 Hz, H_2-24), 2.50 (4H, m, H_2-16 or H_2-17), 2.45 (4H, m, H_2-16 or H_2-17), 1.85–1.80 (4H, m, H_2-21), 1.74–1.58 (12H, m, H_2-11, H_2-12, H_2-25), 1.33–1.23 (12H, m, H_2-26, H_2-27, H_2-28), 1.28 (6H, d, J = 6.2 Hz, 10-Me); ^{13}C NMR (CD_3OD, 125 MHz, * = reduced in intensity due to deuterium exchange[30]) δ 176.2 (C-18), 174.4 (C-15), 161.1 (C-6), 145.4 (C-8), 144.9 (C-2), 137.3 (C-4), 135.6 (C-8a), 131.7 (C-4a), 123.0 (C-3), 99.3 (C-7), 93.5* (C-5), 55.8 (OMe), 49.2 (C-10), 49.1 (C-24), 46.0 (C-22), 40.4 (C-13), 36.6 (C-20), 34.9 (C-11), 31.8, 31.6 (C-16, C-17), 27.7 (C-21), 30.4, 30.2, 27.5, 27.3, 27.2 (C-12, C-25, C-26, C-27, C-28), 20.6 (C-10Me); HRESIMS $[M+Na]^+$ *m/z* 991.6462 (calcd for $C_{54}H_{84}N_{10}NaO_6$, 991.6468).

*5.2.4. Synthesis of analogues **16-62***

*5.2.4.1. 4-((6-Methoxyquinolin-8-yl)amino)-4-oxobutanoic acid (**16**).* Following general procedure A, succinic anhydride was added to 8-amino-6-methoxyquinoline (300 mg, 1.72 mmol) under N_2 atmosphere at room temperature. The mixture was stirred for 18 h, the solvent removed *in vacuo* and the solid washed with cold EtOH (50 mL) to afford **16** as a brown solid (120 mg, 25%). R_f (10% MeOH/CH_2Cl_2) 0.37; m.p. 148-150 °C ; IR (ATR)) ν_{max} 3568, 3482, 3340, 3062, 2969, 2932, 1981, 1681, 1525, 1167, 850, 830 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.15 (1H, br s, OH), 10.10 (1H, br s, NH-9), 8.74 (1H, dd, J = 4.2, 1.6 Hz, H-2), 8.30 (1H, d, J = 2.9 Hz, H-7), 8.27 (1H, dd, J = 8.5, 1.6 Hz, H-4), 7.57 (1H, dd, J = 8.5, 4.2 Hz, H-3), 7.06 (1H, d, J = 2.5 Hz, H-5), 3.88 (3H, br s, OMe), 2.82 (2H, t, J = 6.6 Hz, H_2-11 or H_2-12), 2.57 (2H, t, J = 6.6 Hz, H_2-11 or H_2-12); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8 (C-13), 170.9 (C-10), 157.5 (C-6), 146.1 (C-2), 135.5 (C-8a), 135.3 (C-4), 134.5 (C-8), 128.9 (C-4a), 122.5 (C-3), 108.8 (C-7), 99.6 (C-5), 55.5 (OMe), 31.5, 28.8 (C-11, C-12); (+)-HRESIMS *m/z* 297.0854 $[M+Na]^+$ (calcd for $C_{14}H_{14}N_2NaO_4$, 297.0846).

*5.2.4.2. 4-Oxo-4-(quinolin-8-ylamino)butanoic acid (**17**).* Following general procedure A, quinolin-8-amine (200 mg, 1.39 mmol) and succinic anhydride were reacted in CH_2Cl_2 (10 mL). After solvent removal *in vacuo*, the solid was washed with cold CH_2Cl_2 (25 mL) and cold EtOH (50 mL) to afford **17** as a brown-purple solid (272 mg, 80%). R_f (10% MeOH/CH_2Cl_2) 0.58; m.p. 143–145 °C; IR (ATR) ν_{max} 3439, 3072, 2931, 2436, 1962, 1710, 1684, 1527, 1490, 1262, 825, 710 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.15 (1H, br s, OH), 10.13 (1H, br s, NH-9), 8.93 (1H, dd, J = 4.0, 1.5 Hz, H-2), 8.61 (1H, dd, J = 7.5, 1.0 Hz, H-7), 8.40 (1H, dd, J = 7.5, 1.0 Hz, H-4), 7.67–7.62 (2H, m, H-3, H-6), 7.56 (1H, t, J = 8.0 Hz, H-5), 2.83 (2H, t, J = 6.5 Hz, H_2-11 or H_2-12), 2.58 (2H, t, J = 6.8 Hz, H_2-11 or H_2-12); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8 (C-13), 170.6 (C-10), 148.9 (C-2), 138.0 (C-8a), 136.5 (C-4), 134.6 (C-8), 127.8 (C-4a), 126.9 (C-5), 122.1 (C-3), 121.7 (C-6), 116.5 (C-7), 31.5, 28.9 (C-11, C-12); (+)-HRESIMS *m/z* 267.0737 $[M+Na]^+$ (calcd for $C_{13}H_{12}N_2NaO_3$, 267.0740).

*5.2.4.3. 4-Oxo-4-(quinolin-2-ylamino)butanoic acid (**18**).* Following general procedure A, quinolin-2-amine (200 mg, 1.39 mmol) and succinic anhydride were reacted in CH_2Cl_2 (10 mL). After solvent removal *in vacuo*, the impure solid was washed with cold CH_2Cl_2 (25 mL) and cold EtOH (50 mL) to afford **18** as a white solid (266 mg, 78%). R_f (10% MeOH/CH_2Cl_2) 0.39; m.p 190.5–192 °C; IR (ATR) ν_{max} 3227, 3027, 2927, 2429, 1902, 1700, 1599, 1505, 1120, 847, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.12 (1H, br s, OH), 10.84 (1H, br s, NH-9), 8.34–8.26 (2H, m, H-3, H-4), 7.90 (1H, dd, J = 8.5, 1.0 Hz, H-5), 7.80 (1H, d, J = 8.3 Hz, H-8), 7.72–7.69 (1H, m, H-7), 7.50–7.45 (1H, m, H-6), 2.70 (2H, t, J = 6.7 Hz, H_2-11 or H_2-12), 2.54 (2H, t, J = 6.7 Hz, H_2-11 or H_2-12); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7 (C-13), 171.6 (C-10), 151.6 (C-2), 146.3 (C-8a), 138.2 (C-4), 129.9 (C-7), 127.7 (C-5), 126.8 (C-8), 125.5 (C-4a), 124.8 (C-6), 114.2 (C-3), 31.0, 28.5 (C-11, C-12); (+)-HRESIMS *m/z* 267.0733 $[M+Na]^+$ (calcd for $C_{13}H_{12}N_2NaO_3$, 267.0740).

*5.2.4.4. 4-Oxo-4-(quinolin-5-ylamino)butanoic acid (**19**).* Following general procedure A, quinolin-5-amine (200 mg, 1.39 mmol) and succinic anhydride were reacted in CH_2Cl_2 (10 mL). After solvent removal *in vacuo*, the solid was washed with cold CH_2Cl_2 (25 mL) and cold EtOH (50 mL) to afford **19** as a white solid (212 mg, 62%). R_f (10% MeOH/CH_2Cl_2) 0.13; m.p 143–145 °C; IR (ATR) ν_{max} 3273, 2450, 1890, 1655, 1538, 1335, 1187, 813 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.18 (1H, br s, OH), 10.08 (1H, br s, NH-9), 8.91 (1H, dd, J = 4.0, 1.5 Hz, H-2), 8.50 (1H, br d, J = 8.4 Hz, H-4), 7.86–7.84 (1H, m, H-8), 7.73–7.72 (2H, m, H-6, H-7), 7.56–7.53 (1H, m, H-3), 2.73 (2H, t, J = 6.5 Hz, H_2-11 or H_2-12), 2.59 (2H, t, J = 6.7 Hz, H_2-11 or H_2-12); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.9 (C-13), 171.0 (C-10), 150.4 (C-2), 148.1 (C-8a), 134.1 (C-5), 131.6 (C-4), 129.0 (C-7), 126.0 (C-8), 122.9 (C-4a) 121.5 (C-6), 120.8 (C-3), 30.7, 29.0 (C-11, C-12); (+)-HRESIMS *m/z* 245.0917 $[M+H]^+$ (calcd for $C_{13}H_{13}N_2O_3$, 245.0921).

*5.2.4.5. 4-Oxo-4-(quinolin-6-ylamino)butanoic acid (**20**).* Following general procedure A, quinolin-6-amine (200 mg, 1.39 mmol) and succinic anhydride were reacted in CH_2Cl_2 (10 mL). After solvent removal *in vacuo*, the solid was washed with cold CH_2Cl_2 (25 mL) and cold EtOH (50 mL) to afford **20** as a white solid (272 mg, 80%). R_f (10% MeOH/CH_2Cl_2) 0.13; m.p. 209–211 °C; IR (ATR) ν_{max} 3289, 3218, 3181, 3098, 2955, 2928, 2369, 1881, 1722, 1680, 1565, 1390, 875, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.30 (1H, br s, NH-9), 8.76 (1H, dd, J = 4.0, 1.5 Hz, H-2), 8.37 (1H, d, J = 2.5 Hz, H-5), 8.26 (1H, dd, J = 8.5, 1.1 Hz, H-4), 7.95 (1H, d, J = 9.0 Hz, H-8), 7.78 (1H, dd, J = 9.0, 2.5 Hz, H-7), 7.48–7.45 (1H, m, H-3), 2.64 (2H, t, J = 6.3 Hz, H_2-11 or H_2-12), 2.56 (2H, t, J = 6.25 Hz, H_2-11 or H_2-12); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.0 (C-13), 170.8 (C-10), 148.8 (C-2), 144.5 (C-8a), 137.2 (C-6), 135.4 (C-4), 129.4 (C-8), 128.3 (C-4a), 123.2 (C-7), 121.7 (C-3), 114.6 (C-5), 31.4, 29.2 (C-11, C-12); (+)-HRESIMS *m/z* 245.0925 $[M+H]^+$

(calcd for $C_{13}H_{13}N_2O_3$, 245.0921).

*5.2.4.6. 4-Oxo-4-(pyridin-2-ylamino)butanoic acid (**21**).* Following general procedure A, succinic anhydride in anhydrous CH_2Cl_2 (5 mL) was reacted with 2-aminomethylpyridine (300 mg, 2.77 mmol). After solvent removal *in vacuo*, the solid was washed with cold EtOH (50 mL) to afford **21** as a white solid (289 mg, 54%). R_f (10% MeOH/CH_2Cl_2) 0.08; m.p 157–158.5 °C; IR (ATR) ν_{max} 3724, 3580, 3343, 3105, 2925, 2085, 1715, 1651, 1533, 1164, 823, 793, 757 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.09 (1H, br s, OH), 8.49–8.47 (1H, m, H-6), 8.45 (1H, t, J = 5.9 Hz, NH-8), 7.73 (1H, ddd, J = 7.6, 7.6, 1.8 Hz, H-4), 7.28 (1H, d, J = 7.6 Hz, H-3), 7.24 (1H, dd, J = 7.6, 4.8 Hz, H-5), 4.34 (2H, d, J = 6.0 Hz, H_2-7), 2.49–2.46 (2H, m, H_2-10 or H_2-11), 2.44–2.40 (2H, m, H_2-10 or H_2-11); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.9 (C-12), 171.2 (C-9), 158.8 (C-2), 148.7 (C-6), 136.6 (C-4), 122.0 (C-5), 120.8 (C-3), 44.2 (C-7), 30.0, 29.1 (C-10, C-11); (+)-HRESIMS *m/z* 231.0748 $[M+Na]^+$ (calcd for $C_{10}H_{12}N_2NaO_3$, 231.0740).

*5.2.4.7. 4-Oxo-4-(pyridin-3-ylamino)butanoic acid (**22**).* Following general procedure A, succinic anhydride in anhydrous CH_2Cl_2 (7 mL) was reacted with 3-aminomethylpyridine (300 mg, 2.77 mmol). After solvent removal *in vacuo*, the solid was washed with cold EtOH (50 mL) to afford **22** as a white solid (400 mg, 74%). R_f (10% MeOH/CH_2Cl_2) 0.07; m.p 180–182 °C; IR (ATR) ν_{max} 3649, 3344, 3063, 2926, 2498, 1969, 1714, 1648, 1532, 1489, 1164, 823, 793 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.07 (1H, br s, OH), 8.47 (1H, d, J = 1.9 Hz, H-2), 8.45–8.40 (2H, m, NH-8, H-6), 7.64 (1H, dt, J = 7.8, 1.9 Hz, H-4), 7.33 (1H, dd, J = 7.8, 4.8 Hz, H-5), 4.39 (2H, d, J = 5.9 Hz, H_2-7), 2.48–2.45 (2H, m, H_2-10 or H_2-11), 2.40–2.36 (2H, m, H_2-10 or H_2-11); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8 (C-12), 171.2 (C-9), 148.6 (C-2), 148.0 (C-6), 135.0 (C-3), 134.9 (C-4), 123.4 (C-5), 39.7 (C-7), 29.9, 29.0 (C-10, C-11); (+)-HRESIMS *m/z* 231.0747 $[M+Na]^+$ (calcd for $C_{10}H_{12}N_2NaO_3$, 231.0740).

*5.2.4.8. Di-tert-butyl butane-1,4-diylbis((3-(4-((6-methoxyquinolin-8-yl) amino)-4-oxobutanamido)propyl)carbamate) (**23**).* Following general procedure B, reaction of 4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanoic acid (**16**) (75 mg, 0.27 mmol) with di-*tert*-butyl butane-1,4-diylbis((3-aminopropyl)carbamate) (**4a**) (50 mg, 0.12 mmol), EDC·HCl, HOBt and DIPEA afforded **23** as a pale brown oil (36 mg, 32%). R_f (10% MeOH/CH_2Cl_2) 0.57 ; IR (ATR) ν_{max} 3334, 3085, 2968, 2927, 2856, 1664, 1628, 1523, 1418, 1156, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (2H, br s, NH-9), 8.62 (2H, dd, J = 4.4, 1.5 Hz, H-2), 8.49–8.43 (2H, m, H-7), 8.00 (2H, dd, J = 8.4, 1.5 Hz, H-4), 7.37 (2H, dd, J = 8.4, 4.4 Hz, H-3), 7.02–6.88 (2H, m, NH-14), 6.76 (2H, d, J = 2.5 Hz, H-5), 3.90 (6H, br s, OMe), 3.30–3.16 (8H, m, H_2-15, H_2-17), 3.16–3.05 (4H, m, H_2-19), 2.92 (4H, t, J = 6.9 Hz, H_2-11 or H_2-12), 2.67 (4H, t, J = 6.9 Hz, H_2-11 or H_2-12), 1.71–1.59 (4H, m, H_2-16), 1.49–1.42 (4H, m, H_2-20), 1.44 (18H, br s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C-13), 170.9 (C-10), 158.5 (C-6), 156.3 (C-21), 145.7 (C-2), 135.4 (C-4), 135.0 (C-8, C-8a), 129.0 (C-4a), 122.2 (C-3), 109.1 (C-7), 99.8 (C-5), 79.8 (C-22), 55.6 (OMe), 46.9 (C-19), 43.6 (C-17), 36.1 (C-15), 33.2, 31.6 (C-11, C-12), 28.5 (C-20, *t*-Bu), 27.9 (C-16); (+)-HRESIMS *m/z* 937.4785 $[M+Na]^+$ (calcd for $C_{48}H_{66}N_8NaO_{10}$, 937.4794).

*5.2.4.9. Di-tert-butyl hexane-1,6-diylbis((3-(4-((6-methoxyquinolin-8-yl) amino)-4-oxobutanamido)propyl)carbamate) (**24**).* Following general procedure B, reaction of 4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanoic acid (**16**) (70 mg, 0.26 mmol) with di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl)carbamate) (**4b**) (50 mg, 0.12 mmol), EDC·HCl, HOBt and DIPEA afforded **24** as a pale brown oil (61 mg, 56%). R_f (10% MeOH/CH_2Cl_2) 0.67 ; IR (ATR) ν_{max} 3334, 3073, 2978, 2928, 2857, 1662, 1628, 1523, 1418, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (2H, br s, NH-9), 8.61 (2H, dd, J = 4.4, 1.5 Hz, H-2), 8.48–8.43 (2H, m, H-7), 7.99 (2H, dd, J = 8.5, 1.5 Hz, H-4), 7.37 (2H, dd, J = 8.5, 4.4 Hz, H-3), 7.08–7.00 (2H, m, NH-14), 6.75 (2H, d, J = 2.5 Hz, H-5), 3.89 (6H, br s, OMe), 3.29–3.19 (8H, m, H_2-15, H_2-17), 3.13–3.03 (4H, m, H_2-19), 2.92 (4H, t, J = 6.8 Hz, H_2-11 or H_2-12), 2.68 (4H, t, J = 6.8 Hz, H_2-11 or H_2-12), 1.71–1.60 (4H, m, H_2-16), 1.51–1.42 (4H, m, H_2-20), 1.44 (18H, br s, *t*-Bu), 1.28–1.19 (4H, m, H_2-21); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C-13), 170.9 (C-10), 158.4 (C-6), 156.4 (C-22), 145.7 (C-2), 135.4, 135.0 (C-8, C-8a, C-4), 128.9 (C-4a), 122.1 (C-3), 109.1 (C-7), 99.7 (C-5), 79.6 (C-23), 55.6 (OMe), 47.0 (C-19), 43.6 (C-17), 36.1 (C-15), 33.2, 31.5 (C-11, C-12), 28.5 (C-20, *t*-Bu), 27.8 (C-16), 26.7 (C-21); (+)-HRESIMS *m/z* 965.5107 $[M+Na]^+$ (calcd for $C_{50}H_{70}N_8NaO_{10}$, 965.5107).

*5.2.4.10. Di-tert-butyl heptane-1,7-diylbis((3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)carbamate) (**25**).* Following general procedure B, reaction of 4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanoic acid (**16**) (68 mg, 0.25 mmol) with di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl)carbamate) (**4c**) (50 mg, 0.11 mmol), EDC·HCl, HOBt and DIPEA, afforded **25** as a pale brown oil (45 mg, 42%). R_f (10% MeOH/CH_2Cl_2) 0.67; IR (ATR) ν_{max} 3334, 3078, 2970, 2927, 2855, 1667, 1627, 1523, 1418, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (2H, br s, NH-9), 8.62 (2H, dd, J = 4.4, 1.5 Hz, H-2), 8.50–8.45 (2H, m, H-7), 8.01 (2H, dd, J = 8.5, 1.5 Hz, H-4), 7.38 (2H, dd, J = 8.5, 1.5 Hz, H-3), 7.00–6.88 (2H, m, NH-14), 6.77 (2H, d, J = 2.5 Hz, H-5), 3.91 (6H, br s, OMe), 3.29–3.19 (8H, m, H_2-15, H_2-17), 3.13–3.04 (4H, m, H_2-19), 2.92 (4H, t, J = 6.8 Hz, H_2-11 or H_2-12), 2.67 (4H, t, J = 6.8 Hz, H_2-11 or H_2-12), 1.70–1.60 (4H, m, H_2-16), 1.51–1.43 (4H, m, H_2-20), 1.44 (18H, br s, *t*-Bu), 1.32–1.15 (6H, m, H_2-21, H_2-22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (C-13), 170.8 (C-10), 158.4 (C-6), 156.4 (C-23), 145.6 (C-2), 135.4, 135.0, 134.9 (C-8, C-8a, C-4), 128.9 (C-4a), 122.1 (C-3), 109.0 (C-7), 99.7 (C-5), 79.5 (C-24), 55.6 (OMe), 47.0 (C-19), 43.4 (C-17), 35.9 (C-15), 33.1, 31.5 (C-11, C-12), 29.1 (C-21 or C-22), 28.5 (C-20, *t*-Bu), 27.7 (C-16), 26.8 (C-21 or C-22); (+)-HRESIMS *m/z* 979.5262 $[M+Na]^+$ (calcd for $C_{51}H_{72}N_8NaO_{10}$, 979.5264).

*5.2.4.11. Di-tert-butyl octane-1,8-diylbis((3-(4-((6-methoxyquinolin-8-yl) amino)-4-oxobutanamido) propyl)carbamate) (**26**).* Following general procedure B, reaction of 4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanoic acid (**16**) (66 mg, 0.24 mmol) with di-*tert*-butyl octane-1,8-diylbis ((3-aminopropyl)carbamate) (**4d**) (50 mg, 0.11 mmol), EDC·HCl, HOBt and DIPEA afforded **26** as a pale brown oil (41 mg, 39%). R_f (10% MeOH/CH_2Cl_2) 0.57; IR (ATR)) ν_{max} 3334, 3085, 2968, 2927, 2855, 1667, 1652, 1523, 1417, 1155, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (2H, br s, NH-9), 8.62 (2H, dd, J = 4.4, 1.5 Hz, H-2), 8.49–8.45 (2H, m, H-7), 8.00 (2H, dd, J = 8.5, 1.5 Hz, H-4), 7.37 (2H, dd, J = 8.5, 4.4 Hz, H-3), 6.99–6.90 (2H, m, NH-14), 6.77 (2H, d, J = 2.5 Hz, H-5), 3.91 (6H, br s, OMe), 3.30–3.19 (8H, m, H_2-15, H_2-17), 3.13–3.04 (4H, m, H_2-19), 2.92 (4H, t, J = 7.0 Hz, H_2-11 or H_2-12), 2.68 (4H, t, J = 7.0 Hz, H_2-11 or H_2-12), 1.71–1.60 (4H, m, H_2-16), 1.51–1.43 (4H, m, H_2-20), 1.46 (18H, br s, *t*-Bu), 1.31–1.16 (8H, m, H_2-21, H_2-22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (C-13), 170.8 (C-10), 158.4 (C-6), 156.4 (C-23), 145.6 (C-2), 135.4, 135.0 (C-8, C-8a), 134.9 (C-4), 128.9 (C-4a), 122.1 (C-3), 109.0 (C-7), 99.7 (C-5), 79.5 (C-24), 55.6 (OMe), 47.0 (C-19), 43.4 (C-17), 36.0 (C-15), 33.1, 31.5 (C-11, C-12), 29.3 (C-21 or C-22), 28.5 (C-20, *t*-Bu), 27.8 (C-16), 26.8 (C-21 or C-22); (+)-HRESIMS *m/z* 993.5419 $[M+Na]^+$ (calcd for $C_{52}H_{74}N_8NaO_{10}$, 993.5420).

*5.2.4.12. Di-tert-butyl decane-1,10-diylbis((3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)carbamate) (**27**).* Following general procedure B, reaction of 4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanoic acid (**16**) (62 mg, 0.23 mmol) with di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl)carbamate) (**4e**) (50 mg, 0.10 mmol), EDC·HCl, HOBt, and DIPEA, afforded **27** as a pale brown oil (52 mg, 51%). R_f (10% MeOH/CH_2Cl_2) 0.47; IR (ATR)) ν_{max} 3334, 3073, 2975, 2926, 2854, 1667, 1628, 1524, 1418, 1155 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 9.87 (2H, br s, NH-9), 8.62 (2H, dd, J = 4.4, 1.4 Hz, H-2), 8.50–8.45 (2H, m, H-7), 8.01 (2H, dd, J = 8.5, 1.5 Hz, H-4), 7.38 (2H, dd, J = 8.5, 4.4 Hz, H-3), 6.98–6.90 (2H, m, NH-14), 6.78 (2H, d, J = 2.8 Hz, H-5), 3.91 (6H, s, OMe), 3.30–3.19 (8H, m, H_2-15, H_2-17), 3.08 (4H, t, J = 6.6 Hz, H_2-19), 2.92 (4H, t, J = 6.6 Hz, H_2-11 or H_2-12), 2.68 (4H, t, J = 6.6 Hz, H_2-11 or H_2-12), 1.70–1.60 (4H, m, H_2-16), 1.51–1.45 (4H, m, H_2-20), 1.45 (18H, br s, *t*-Bu), 1.30–1.17 (12H, m, H_2-21, H_2-22, H_2-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (C-13), 170.8 (C-10), 158.4 (C-6), 156.5 (C-24), 145.6 (C-2), 135.4, 135.0, 134.9 (C-8, C-8a, C-4), 128.9 (C-4a), 122.1 (C-3), 109.0 (C-7), 99.7 (C-5), 79.5 (C-25), 55.6 (OMe), 47.0 (C-19), 43.4 (C-17), 35.9 (C-15), 33.2, 31.6 (C-11, C-12), 29.5 (C-21 or C-22 or C-23), 29.3 (C-21 or C-22 or C-23), 28.5 (C-20, *t*-Bu), 27.7 (C-16), 26.9 (C-21 or C-22 or C-23); (+)-HRESIMS *m/z* 1021.5727 $[M+Na]^+$ (calcd for $C_{54}H_{78}N_8NaO_{10}$, 1021.5733).

*5.2.4.13. Di-tert-butyl butane-1,4-diylbis((3-(4-oxo-4-(quinolin-8-ylamino) butanamido)propyl)carbamate) (**28**).*

To a solution of 4-oxo-4-(quinolin-8-ylamino)butanoic acid (**17**) (76 mg, 0.31 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added EDC·HCl (67 mg, 0.35 mmol) and DMAP (76 mg, 0.63 mmol) and the reaction was left to stir for 10 min under nitrogen atmosphere at 0 °C. Then di-*tert*-butyl butane 1,4-diylbis((3-aminopropyl)carbamate) (**4a**) (50 mg, 0.13 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added and the reaction was left to stir under nitrogen atmosphere at room temperature for 12 h. CH_2Cl_2 (30 mL) was added and the mixture was washed with saturated $NaHCO_3$ (2 × 20 mL) and deionised water (2 × 30 mL). The organic layer was collected, dried with $MgSO_4$and the solvent removed *in vacuo*. The crude oil was purified with silica gel flash column chromatography (10% MeOH/CH_2Cl_2) to afford **28** as a brown oil (67 mg, 63%). R_f (5% MeOH/CH_2Cl_2) 0.42; IR (ATR) ν_{max} 3345, 2929, 1684, 1527, 1487, 1163, 827, 793 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (2H, br s, NH-9), 8.80 (2H, dd, J =4.5, 2.0 Hz, H-2), 8.73 (2H, d, J = 6.5 Hz, H-7), 8.14 (2H, dd, J = 8.0, 1.5 Hz, H-4), 7.51–7.47 (4H, m, H-5, H-6), 7.47–7.43 (2H, m, H-3), 6.89 (2H, br s, NH-14), 3.24–3.10 (12H, m, H_2-15, H_2-17, H_2-19), 2.93 (4H, t, J = 7.0 Hz, H_2-11 or H_2-12), 2.68 (4H, br s, H_2-11 or H_2-12), 1.64 (4H, br s, H_2-16), 1.43 (18H, br s, *t*-Bu), 1.42 (4H, br s, H_2-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C-13), 170.9 (C-10), 156.4 (C-21), 148.3 (C-2), 138.5 (C-8a), 136.4 (C-4), 134.6 (C-8), 128.1 (C-4a), 127.4 (C-5), 121.7 (C-3, C-6), 116.6 (C-7), 80.0 (C-22), 47.0 (C-19), 43.8 (C-17), 36.3 (C-15), 33.1 (C-12), 31.7 (C-11), 28.5 (*t*-Bu), 27.9 (C-16), 26.1 (C-20); (+)-HRESIMS *m/z* 877.4608 $[M+Na]^+$ (calcd for $C_{46}H_{62}N_8NaO_8$, 877.4583).

*5.2.4.14. Di-tert-butyl hexane-1,6-diylbis((3-(4-oxo-4-(quinolin-8-ylamino) butanamido)propyl) carbamate) (**29**).* Following general procedure B, reaction of 4-oxo-4-(quinolin-8-ylamino)butanoic acid (**17**) (62 mg, 0.26 mmol) with di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl)carbamate) (**4b**) (50 mg, 0.12 mmol), EDC·HCl, HOBt and DIPEA afforded **29** as a black gum (36 mg, 35%). R_f (10% MeOH/CH_2Cl_2) 0.43; IR (ATR) ν_{max} 3318, 3072, 2970, 2928, 2857, 1660, 1523, 1418, 1156, 826, 791, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (2H, br s, NH-9), 8.79 (2H, dd, J = 4.2, 1.5 Hz, H-2), 8.73 (2H, d, J = 6.5 Hz, H-7), 8.13 (2H, dd, J = 8.4, 1.5 Hz, H-4), 7.52–7.46 (4H, m, H-5, H-6), 7.43 (2H, dd, J = 8.4, 4.2 Hz, H-3), 7.01–6.92 (2H, m, NH-14), 3.30–3.19 (8H, m, H_2-15, H_2-17), 3.13–3.03 (4H, m, H_2-19), 2.93 (4H, t, J = 6.9 Hz, H_2-11 or H_2-12), 2.69 (4H, t, J = 6.9 Hz, H_2-11 or H_2-12), 1.71–1.60 (4H, m, H_2-16), 1.52–1.44 (4H, m, H_2-20), 1.44 (18H, br s, *t*-Bu), 1.28–1.19 (4H, m, H_2-21); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C-13), 170.8 (C-10), 156.4 (C-22), 148.3 (C-2), 138.4 (C-8a), 136.3 (C-4), 134.6 (C-8), 128.0 (C-4a), 127.3, 121.7, 121.5 (C-3, C-5, C-6), 116.5 (C-7), 79.6 (C-23), 47.0 (C-19), 43.6 (C-17), 36.0 (C-15), 33.2, 31.6 (C-11, C-12), 28.5 (C-20, *t*-Bu), 27.8 (C-16), 26.7 (C-21); (+)-HRESIMS *m/z* 883.5058 $[M+H]^+$ (calcd for $C_{48}H_{67}N_8O_8$, 883.5076).

*5.2.4.15. Di-tert-butyl heptane-1,7-diylbis((3-(4-oxo-4-(quinolin-8-ylamino) butanamido) propyl)carbamate) (**30**).* Following general procedure B, reaction of 4-oxo-4-(quinolin-8-ylamino)butanoic acid (**17**) (60 mg, 0.26 mmol) with di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl)carbamate) (**4c**) (50 mg, 0.11 mmol), EDC·HCl, HOBt and DIPEA afforded **30** as a black gum (32 mg, 32%). R_f (10% MeOH/CH_2Cl_2) 0.40; IR (ATR) ν_{max} 3298, 2927, 2855, 1652, 1498, 1424, 1318, 1155, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (2H, br s, NH-9), 8.79 (2H, dd, J = 4.2, 1.5 Hz, H-2), 8.73 (2H, d, J = 6.8 Hz, H-7), 8.13 (2H, dd, J = 8.5, 1.5 Hz, H-4), 7.52–7.46 (4H, m, H-5, H-6), 7.43 (2H, dd, J = 8.5, 4.2 Hz, H-3), 7.01–6.89 (2H, m, NH-14), 3.32–3.16 (8H, m, H_2-15, H_2-17), 3.14–3.02 (4H, m, H_2-19), 2.93 (4H, t, J = 7.0 Hz, H_2-11 or H_2-12), 2.69 (4H, t, J = 7.0 Hz, H_2-11 or H_2-12), 1.72–1.60 (4H, m, H_2-16), 1.52–1.44 (4H, m, H_2-20), 1.44 (18H, br s, *t*-Bu), 1.32–1.16 (6H, m, H_2-21, H_2-22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C-13), 170.8 (C-10), 156.5 (C-23), 148.3 (C-2), 138.4 (C-8a), 136.3 (C-4), 134.6 (C-8), 128.0 (C-4a), 127.3, 121.7, 121.5 (C-3, C-5, C-6), 116.5 (C-7), 79.6 (C-24), 47.0 (C-19), 43.5 (C-17), 36.0 (C-15), 33.2, 31.7 (C-11, C-12), 29.2 (C-21 or C-22), 28.5 (C-20, *t*-Bu), 27.8 (C-16), 26.9 (C-21 or C-22); (+)-HRESIMS *m/z* 939.5694 $[M+H]^+$ (calcd for $C_{52}H_{75}N_8O_8$, 939.5702).

*5.2.4.16. Di-tert-butyl octane-1,8-diylbis((3-(4-oxo-4-(quinolin-8-ylamino) butanamido) propyl)carbamate) (**31**).* Following general procedure B, reaction of 4-oxo-4-(quinolin-8-ylamino)butanoic acid (**17**) (59 mg, 0.24 mmol) with di-*tert*-butyl octane-1,8-diylbis((3-aminopropyl)carbamate) (**4d**) (50 mg, 0.11 mmol), EDC·HCl, HOBt and DIPEA afforded **31** as a black gum (30 mg, 30%). R_f (10% MeOH/CH_2Cl_2) 0.40; IR (ATR) ν_{max} 3334, 3073, 2969, 2927, 2856, 1661, 1523, 1418, 1155, 826, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (2H, br s, NH-9), 8.79 (2H, dd, J = 4.2, 1.5 Hz, H-2), 8.73 (2H, dd, J = 6.5 Hz, H-7), 8.13 (2H, dd, J = 8.5, 1.5 Hz, H-4), 7.52–7.46 (4H, m, H-5, H-6), 7.43 (2H, dd, J = 8.5, 4.2 Hz, H-3), 7.00–6.90 (2H, m, NH-14), 3.32–3.14 (8H, m, H_2-15, H_2-17), 3.14–3.03 (4H, m, H_2-19), 2.93 (4H, t, J = 7.0 Hz, H_2-11 or H_2-12), 2.69 (4H, t, J = 7.0 Hz, H_2-11 or H_2-12), 1.72–1.59 (4H, m, H_2-16), 1.52–1.44 (4H, m, H_2-20), 1.44 (18H, br s, *t*-Bu), 1.31–1.16 (8H, m, H_2-21, H_2-22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C-13), 170.8 (C-10), 156.5 (C-23), 148.3 (C-2), 138.4 (C-8a), 136.3 (C-4), 134.6 (C-8), 128.0 (C-4a), 127.4, 121.7, 121.5 (C-3, C-5, C-6), 116.5 (C-7), 79.6 (C-24), 47.1 (C-19), 43.5 (C-17), 36.0 (C-15), 33.2, 31.7 (C-11, C-12), 29.4 (C-21 or C-22), 28.5 (C-20, *t*-Bu), 27.8 (C-16), 26.9 (C-21 or C-22); (+)-HRESIMS *m/z* 933.5198 $[M+Na]^+$ (calcd for $C_{50}H_{70}N_8NaO_8$, 933.5209).

*5.2.4.17. Di-tert-butyl decane-1,10-diylbis((3-(4-oxo-4-(quinolin-8-ylamino) butanamido)propyl)carbamate) (**32**).* To a solution of 4-oxo-4-(quinolin-8-ylamino)butanoic acid (**17**) (63 mg, 0.26 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added EDC·HCl (55 mg, 0.29 mmol) and DMAP (63 mg, 0.52 mmol). The reaction was left to stir for 10 min under nitrogen atmosphere at 0 °C. Then di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl)carbamate) (**4e**) (50 mg, 0.10 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added and the reaction was left to stir under nitrogen atmosphere at room temperature for 12 h. CH_2Cl_2 (30 mL) was added and the mixture was washed with saturated $NaHCO_3$ (2 × 20 mL) and deionised water (2 × 30 mL). The organic layer was collected, dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude oil was purified with silica gel flash column chromatography (10% MeOH/CH_2Cl_2) to afford **32** as a brown oil (88 mg, 91%). R_f (5% MeOH/CH_2Cl_2) 0.36; IR (ATR) ν_{max} 3342, 2927, 2856, 1669, 1524, 1419, 1158, 827, 793 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (2H, br s, NH-9), 8.79 (2H, dd, J = 4.5, 2.0 Hz, H-2), 8.73 (2H, d, J = 6.5 Hz, H-7), 8.14 (2H, dd, J = 8.0, 1.5 Hz, H-4), 7.53–7.46 (4H, m, H-5, H-6), 7.45–7.42 (2H, m, H-3), 6.96 (2H, br s, NH-14), 3.26–3.21 (8H, m, H_2-15, H_2-17), 3.11–3.04 (4H, m, H_2-19) 2.93 (4H, t, J = 7.0 Hz, H_2-11 or H_2-12), 2.72–2.65 (4H, m, H_2-11 or H_2-12), 1.64 (4H, br s, H_2-16), 1.45 (22H, br s, H_2-20, *t*-Bu), 1.24 (12H, br s, H_2-21, H_2-22, H_2-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C-13), 170.8 (C-10), 156.5 (C-24), 148.3 (C-2), 138.5 (C-8a), 136.4 (C-4), 134.6 (C-8), 128.0 (C-4a), 127.4, 121.7, 121.5 (C-3, C-5, C-6), 116.6 (C-7), 79.6 (C-25), 47.1 (C-19), 43.5 (C-17), 36.0 (C-15), 33.3, 31.7 (C-11, C-12), 29.5 (C-23), 29.4 (C-22), 28.5 (C-20, *t*-Bu), 27.8 (C-16), 26.9 (C-21); (+)-HRESIMS *m/z*

961.5521 $[M+Na]^+$ (calcd for $C_{52}H_{74}N_8NaO_8$, 961.5522).

*5.2.4.18. Di-tert-butyl butane-1,4-diylbis((3-(4-oxo-4(quinolin-2-ylamino) butanamido)propyl)carbamate) (**33**).* To a solution of 4-oxo-4-(quinoline-2-ylamino) butanoic acid (**18**) (62 mg, 0.26 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added EDC·HCl (55 mg, 0.29 mmol) and DMAP (62 mg, 0.51 mmol) and the reaction was left to stir for 10 min under nitrogen atmosphere at 0 °C. Then di-*tert*-butyl butane- 1,4-diylbis ((3-aminopropyl)carbamate) (**4a**) (41 mg, 0.04 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added and the reaction was left to stir under nitrogen atmosphere at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with saturated $NaHCO_3$ (2 × 20 mL) and deionised water (2 × 30 mL) and the organic layer was collected, dried with $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified with silica gel flash column chromatography (10% MeOH/CH_2Cl_2) to afford **33** as a colourless oil (55 mg, 51%). R_f (5% MeOH/CH_2Cl_2) 0.31; IR (ATR) ν_{max} 3300, 2928, 1662, 1600, 1500, 1426, 1319, 1163, 832, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (2H, br s, NH-9), 8.36 (2H, d, $J = 8.5$ Hz, H-3), 8.10 (2H, d, $J = 9.0$ Hz, H-4), 7.80 (2H, d, $J = 8.5$ Hz, H-8), 7.74–7.72 (2H, m, H-5), 7.64–7.59 (2H, m, H-7), 7.43–7.39 (2H, m, H-6), 7.02 (2H, br s, NH-14), 3.27–3.09 (12H, m, H_2-15, H_2-17, H_2-19), 2.85–2.84 (4H, m, H_2-11 or H_2-12), 2.67–2.66 (4H, m, H_2-11 or H_2-12), 1.66 (4H, br s, H_2-16), 1.43 (18H, br s, *t*-Bu), 1.42 (4H, br s, H_2-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C-13), 171.7 (C-10), 156.3 (C-21), 151.1 (C-2), 146.7 (C-8a), 138.3 (C-4), 129.8 (C-7), 127.5 (C-5, C-8), 126.2 (C-4a), 125.0 (C-6), 114.5 (C-3), 79.7 (C-22), 46.8 (C-19), 43.6 (C-17), 36.1 (C-15), 32.9, 31.2 (C-11, C-12), 28.4 (*t*-Bu), 27.8 (C-16), 26.0 (C-20); (+)-HRESIMS *m/z* 855.4769 $[M+H]^+$ (calcd for $C_{46}H_{63}N_8O_8$, 855.4763).

*5.2.4.19. Di-tert-butyl decane-1,10-diylbis((3-(4-oxo-4-(quinolin-2-ylamino) butanamido)propyl)carbamate) (**34**).* To a solution of 4-oxo-4-(quinoline-2-ylamino) butanoic acid (**18**) (63 mg, 0.26 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added EDC·HCl (55 mg, 0.29 mmol) and DMAP (63 mg, 0.52 mmol). The reaction was left to stir for 10 min under nitrogen atmosphere at 0 °C. Then di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl)carbamate) (**4e**) (50 mg, 0.10 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added and the reaction was left to stir under nitrogen atmosphere at room temperature for 12 h. CH_2Cl_2 (30 mL) was added and the mixture was washed with saturated $NaHCO_3$ (2 × 20 mL) and deionised water (2 × 30 mL). The organic layer was collected, dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified with silica gel flash column chromatography (10% MeOH/CH_2Cl_2) to afford **34** as a pale yellow oil (102 mg, 100%). R_f (5% MeOH/CH_2Cl_2) 0.42; IR (ATR) ν_{max} 3298, 2929, 2856, 1669, 1500, 1426, 1320, 1165, 832, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (2H, br s, NH-9), 8.37 (2H, d, $J = 8.7$ Hz, H-3), 8.10 (2H, d, $J = 9.0$ Hz, H-4), 7.81 (2H, d, $J = 8.4$ Hz, H-8), 7.73 (2H, dd, $J = 8.3$, 1.0 Hz, H-5), 7.64–7.60 (2H, m, H-7), 7.43–7.39 (2H, m, H-6), 7.02 (2H, br s, NH-14), 3.28–3.24 (8H, m, H_2-15, H_2-17), 3.08 (4H, br s, H_2-19) 2.85 (4H, t, $J = 6.0$ Hz, H_2-11 or H_2-12), 2.66 (4H, s, H_2-11 or H_2-12), 1.66 (4H, br s, H_2-16), 1.43 (22H, br s, H_2-20, *t*-Bu), 1.24 (12H, br s, H_2-21, H_2-22, H_2-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C-13), 171.7 (C-10), 156.3 (C-24), 151.2 (C-2), 146.7 (C-8a), 138.3 (C-4), 129.8 (C-7), 127.5 (C-5, C-8), 126.3 (C-4a), 125.0 (C-6), 114.5 (C-3), 79.6 (C-26), 47.1 (C-19), 43.4 (C-17), 36.0 (C-15), 33.0, 31.3 (C-11, C-12), 29.5 (C-23), 29.3 (C-22), 28.5 (C-20, *t*-Bu), 27.7 (C-16), 26.9 (C-21); (+)-HRESIMS *m/z* 939.5684 $[M+H]^+$ (calcd for $C_{52}H_{75}N_8O_8$, 939.5702).

*5.2.4.20. Di-tert-butyl butane-1,4-diylbis((3-(4-oxo-4-(quinolin-5-ylamino) butanamido)propyl)carbamate) (**35**).* To a solution of 4-oxo-4-(quinolin-5-ylamino)butanoic acid (**19**) (76 mg, 0.31 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added EDC·HCl (67 mg, 0.35 mmol) and DMAP (76 mg, 0.63 mmol) and the reaction was left to stir for 10 min under nitrogen atmosphere at 0 °C. Then di-*tert*-butyl butane- 1,4-diylbis((3-aminopropyl)carbamate) (**4a**) (50 mg, 0.13 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added and the reaction was left to stir under nitrogen atmosphere at room temperature for 12 h. CH_2Cl_2 (30 mL) was added and the mixture was washed with saturated $NaHCO_3$ (2 × 20 mL) and deionised water (2 × 30 mL). The organic layer was collected, dried with $MgSO_4$ and the solvent removed *in vacuo.* The crude product was purified with silica gel flash column chromatography (10% MeOH/CH_2Cl_2) to afford **35** as a pale yellow oil (86 mg, 80%). R_f (10% MeOH/CH_2Cl_2) 0.56; IR (ATR) ν_{max} 3289, 2925, 1661, 1539, 1260, 1160, 801, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.34 (2H, br s, NH-9), 8.86 (2H, d, $J = 3.0$ Hz, H-2), 8.41 (2H, s, H-4), 7.95–7.87 (4H, m, H-6, H-8), 7.64–7.62 (2H, m, H-7), 7.37–7.36 (2H, m, H-3), 7.24 (2H, br s, NH-14), 3.25–3.06 (12H, m, H_2-15, H_2-17, H_2-19), 2.85 (4H, t, $J = 6.0$ Hz, H_2-11 or H_2-12), 2.70 (4H, br s, H_2-11 or H_2-12), 1.61 (4H, br s, H_2-16), 1.42 (18H, br s, *t*-Bu), 1.39 (4H, br s, H_2-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (C-13), 171.9 (C-10), 156.5 (C-21), 150.2 (C-2), 148.5 (C-8a), 133.4 (C-5), 130.8 (C-4), 129.4 (C-7), 126.5 (C-8), 122.6 (C-4a), 120.9 (C-3), 120.6 (C-6), 80.0 (C-22), 46.9 (C-19), 43.7 (C-17), 36.3 (C-15), 33.0, 31.9 (C-11, C-12), 28.5 (*t*-Bu), 27.9 (C-16), 26.0 (C-20); (+)-HRESIMS *m/z* 877.4602 $[M+Na]^+$ (calcd for $C_{46}H_{62}N_8NaO_8$, 877.4583).

*5.2.4.21. Di-tert-butyl decane-1,10-diylbis((3-(4-oxo-4-(quinolin-5-ylamino) butanamido)propyl)carbamate) (**36**).* To a solution of 4-oxo-4-(quinolin-5-ylamino)butanoic acid (**19**) (63 mg, 0.26 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added EDC·HCl (55 mg, 0.29 mmol) and DMAP (63 mg, 0.52 mmol). The reaction was left to stir for 10 min under nitrogen atmosphere at 0 °C then di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl) carbamate) (**4e**) (50 mg, 0.10 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added and the reaction was left to stir under nitrogen atmosphere at room temperature for 12 h. CH_2Cl_2 (30 mL) was added and the mixture was washed with saturated $NaHCO_3$ (2 × 20 mL) and deionised water (2 × 30 mL). The organic layer was collected, dried with $MgSO_4$ and the solvent removed *in vacuo.* The crude oil was purified with silica gel flash column chromatography (15% MeOH/CH_2Cl_2) to afford **36** as a pale yellow oil (70 mg, 72%). R_f (5% MeOH/CH_2Cl_2) 0.08; IR (ATR) ν_{max} 3287, 2928, 1663, 1542, 1419, 1158, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (2H, br s, NH-9), 8.87 (2H, d, $J = 3.0$ Hz, H-2), 8.44 (2H, d, $J = 7.5$ Hz, H-4), 7.98 (2H, s, H-6), 7.90 (2H, d, $J = 8.5$ Hz, H-8), 7.64 (2H, t, $J = 8.0$ Hz, H-7), 7.39–7.34 (2H, m, H-3), 7.32 (2H, br s, NH-14), 3.26–3.21 (8H, m, H_2-15, H_2-17), 3.07 (4H, t, $J = 7.2$ Hz, H_2-19), 2.85 (4H, t, $J = 6.0$ Hz, H_2-11 or H_2-12), 2.71 (4H, br s, H_2-11 or H_2-12), 1.62 (4H, br s, H_2-16), 1.43 (22H, br s, H_2-20, *t*-Bu), 1.24 (12H, br s, H_2-21, H_2-22, H_2-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (C-13), 171.8 (C-10), 156.7 (C-24), 150.2 (C-2), 148.6 (C-8a), 133.4 (C-5), 130.7 (C-4), 129.4 (C-7), 126.5 (C-8), 122.6 (C-4a), 120.9 (C-3), 120.5 (C-6), 79.9 (C-25), 47.2 (C-19), 43.4 (C-17), 36.1 (C-15), 33.1, 32.0 (C-11, C-12), 29.5 (C-23), 29.4 (C-22), 28.5 (C-20, *t*-Bu), 27.8 (C-16), 26.9 (C-21); (+)-HRESIMS *m/z* 961.5519 $[M+Na]^+$ (calcd for $C_{52}H_{74}N_8NaO_8$, 961.5522).

*5.2.4.22. Di-tert-butyl butane-1,4-diylbis((3-(4-oxo-4-(quinolin-6-ylamino) butanamido)propyl)carbamate) (**37**).* To a solution of 4-oxo-4-(quinolin-6-ylamino)butanoic acid (**20**) (76 mg, 0.31 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added EDC·HCl (67 mg, 0.35 mmol) and DMAP (76 mg, 0.63 mmol) and the reaction was left to stir for 10 min under nitrogen atmosphere at 0 °C. Then di-*tert*-butyl butane- 1,4-diylbis((3-aminopropyl)carbamate) (**4a**) (50 mg, 0.13 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added and the reaction was left to stir under nitrogen atmosphere at room temperature for 12 h. CH_2Cl_2 (30 mL) was added and the mixture was washed with saturated $NaHCO_3$ (2 × 20 mL) and deionised water (2 × 30 mL). The organic layer was collected, dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude oil was purified with silica gel flash column chromatography (10% MeOH/CH_2Cl_2) to afford **37** as a pale yellow oil (74 mg, 69%). R_f (10% MeOH/CH_2Cl_2) 0.55; IR (ATR) ν_{max} 3280, 2928, 1665, 1559, 1421, 1165, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (2H, br s, NH-9), 8.86 (2H, dd, J =4.0, 2.5 Hz, H-2), 8.31 (2H, s, H-5), 8.00–7.94 (4H, m, H-4, H-8), 7.62 (2H, dd, $J = 9.0$, 6.5 Hz, H-

7), 7.33–7.28 (2H, m, H-3), 7.21 (2H, br s, NH-14), 3.26–3.08 (12H, m, H_2-15, H_2-17, H_2-19), 2.79 (4H, t, J = 5.5 Hz, H_2-11 or H_2-12), 2.70 (4H, t, J = 5.5 Hz, H_2-11 or H_2-12), 1.66 (4H, br s, H_2-16), 1.43 (18H, br s, *t*-Bu), 1.41 (4H, br s, H_2-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (C-13), 171.4 (C-10), 156.5 (C-21), 149.1 (C-2), 145.3 (C-8a), 136.7 (C-6), 136.0 (C-4), 129.8 (C-8), 128.9 (C-4a), 123.5 (C-7), 121.5 (C-3), 115.8 (C-5), 80.0 (C-22), 47.0 (C-19), 43.8 (C-17), 36.3 (C-15), 33.1, 31.7 (C-11, C-12), 28.5 (*t*-Bu), 27.9 (C-16), 26.1 (C-20); (+)-HRESIMS *m/z* 877.4560 $[M+Na]^+$ (calcd for $C_{46}H_{62}N_8NaO_8$, 877.4564).

*5.2.4.23. Di-tert-butyl decane-1,10-diylbis((3-(4-oxo-4-(quinolin-6-ylamino) butanamido)propyl)carbamate) (**38**).*

To a solution of 4-oxo-4-(quinolin-6-ylamino)butanoic acid (**20**) (63 mg, 0.26 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added EDC·HCl (55 mg, 0.29 mmol) and DMAP (63 mg, 0.52 mmol). The reaction was left to stir for 10 min under nitrogen atmosphere at 0 °C, then di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl)carbamate) (**4e**) (50 mg, 0.10 mmol) dissolved in anhydrous CH_2Cl_2 (1.5 mL) was added and the reaction was left to stir under nitrogen atmosphere at room temperature for 12 h. CH_2Cl_2 (30 mL) was added and the mixture was washed with saturated $NaHCO_3$ (2 × 20 mL) and deionised water (2 × 30 mL). The organic layer was collected, dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude oil was purified with silica gel flash column chromatography (15% MeOH/CH_2Cl_2) to afford **38** as a pale yellow oil (94 mg, 97%). R_f (5% MeOH/CH_2Cl_2) 0.08; IR (ATR) ν_{max} 3299, 2928, 2856, 1657, 1554, 1419, 1158, 881, 836, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (2H, br s, NH-9), 8.76 (2H, d, J = 3.0 Hz, H-2), 8.32 (2H, s, H-5), 8.01 (2H, d, J = 8.0 Hz, H-4), 7.95 (2H, d, J = 9.0 Hz, H-8), 7.62 (2H, dd, J = 9.0, 2.5 Hz, H-7), 7.31–7.28 (4H, m, H-3, NH-14), 3.27–3.25 (8H, m, H_2-15, H_2-17), 3.08 (4H, t, J = 7.5 Hz, H_2-19), 2.81–2.78 (4H, m, H_2-11 or H_2-12), 2.70 (4H, s, H_2-11 or H_2-12), 1.66 (4H, br s, H_2-16), 1.45 (22H, br s, H_2-20, *t*-Bu), 1.23 (12H, br s, H_2-21, H_2-22, H_2-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C-13), 171.4 (C-10), 156.8 (C-24), 149.1 (C-2), 145.4 (C-8a), 136.7 (C-6), 135.9 (C-4), 129.8 (C-8), 128.9 (C-4a), 123.5 (C-7), 121.5 (C-3), 115.8 (C-5), 79.9 (C-25), 47.2 (C-19), 43.5 (C-17), 36.2 (C-15), 33.2, 31.7 (C-11, C-12), 29.5 (C-23), 29.4 (C-22), 28.5 (C-20, *t*-Bu), 27.8 (C-16), 26.9 (C-21); (+)-HRESIMS *m/z* 961.5522 $[M+Na]^+$ (calcd for $C_{52}H_{74}N_8NaO_8$, 961.5522).

*5.2.4.24. Di-tert-butyl butane-1,4-diylbis((3-(4-oxo-4-((pyridin-2-ylmethyl) amino)butanamido)propyl)carbamate) (**39**).* Following general procedure B, 4-oxo-4-(pyridin-2-ylamino)butanoic acid (**21**) (54 mg, 0.26 mmol), di-*tert*-butyl butane-1,4-diylbis((3-aminopropyl)carbamate) (**4a**) (49 mg, 0.12 mmol), EDC·HCl, HOBt and DIPEA afforded **39** as an orange oil (38 mg, 40%). R_f (10% MeOH/CH_2Cl_2) 0.33; IR (ATR) ν_{max} 3288, 3075, 2973, 2929, 1652, 1544, 1418, 1160 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (2H, d, J = 6.0 Hz, H-6), 8.42 (2H, t, J = 5.9 Hz, NH-8), 7.80 (2H, br s, NH-13), 7.72 (2H, ddd, J = 7.5, 7.5, 1.8 Hz, H-4), 7.27 (2H, d, J = 7.5 Hz, H-3), 7.23 (2H, dd, J = 7.5, 5.0 Hz, H-5), 4.33 (4H, d, J = 6.0 Hz, H-7), 3.13–3.05 (8H, m, H_2-16, H_2-18), 3.00 (4H, dt, J = 6.7, 6.2 Hz, H_2-14), 2.44–2.38 (4H, m, H_2-10 or H_2-11), 2.36–2.30 (4H, m, H_2-10 or H_2-11), 1.62–1.51 (4H, m, H_2-15), 1.43–1.34 (4H, m, H_2-19), 1.37 (18H, m, *t*-Bu); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6 (C-12), 171.1 (C-9), 158.8 (C-2), 154.6 (C-20), 148.7 (C-6), 136.6 (C-4), 121.9 (C-5), 120.8 (C-3), 78.2 (C-21), 46.2 (C-18), 44.4 (C-16), 44.1 (C-7), 36.3 (C-14), 30.7 (C-10, C-11), 28.0 (C-15, *t*-Bu), 25.1 (C-19); (+)-HRESIMS $[M+Na]^+$ *m/z* 805.4608 (calcd for $C_{40}H_{62}N_8NaO_8$, 805.4580).

*5.2.4.25. Di-tert-butyl decane-1,10-diylbis((3-(4-oxo-4-((pyridin-2-ylmeth yl)amino)butanamido)propyl)carbamate) (**40**).*

Following general procedure B, 4-oxo-4-(pyridin-2-ylamino)butanoic acid (**21**) (48 mg, 0.23 mmol), di-*tert*-butyl decane-1,10-diylbis((3-amino propyl)carbamate) (**4e**) (49 mg, 0.10 mmol), HBTU and DIPEA afforded **40** as an orange gum (23 mg, 35%). R_f (10% MeOH/CH_2Cl_2) 0.40; IR (ATR) ν_{max} 3286, 3075, 2927, 2856, 1652, 1418, 1156, 1025 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (2H, d, J = 5.0 Hz, H-6), 8.41 (2H, t, J = 6.0 Hz, NH-8), 7.82–7.76 (2H, m, NH-13), 7.72 (2H, ddd, J = 7.8, 7.8, 2.0 Hz, H-4), 7.27 (2H, d, J = 7.8 Hz, H-3), 7.23 (2H, dd, J = 7.8, 5.0 Hz, H-5), 4.33 (4H, d, J = 6.0 Hz, H-7), 3.13–3.04 (8H, m, H_2-16, H_2-18), 3.00 (4H, dt, J = 6.8, 6.1 Hz, H_2-14), 2.44–2.38 (4H, m, H_2-10 or H_2-11), 2.36–2.30 (4H, m, H_2-10 or H_2-11), 1.61–1.52 (4H, m, H_2-15), 1.46–1.34 (4H, m, H_2-19), 1.37 (18H, br s, *t*-Bu), 1.28–1.13 (12H, m, H_2-20, H_2-21, H_2-22); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 171.1 (C-9, C-12), 158.8 (C-2), 154.6 (C-23), 148.7 (C-6), 136.6 (C-4), 121.9 (C-5), 120.8 (C-3), 78.1 (C-24), 46.3 (C-18), 44.3 (C-16), 44.1 (C-7), 36.3 (C-14), 30.7 (C-10, C-11), 28.9 (C-20 or C-21 or C-22), 28.7 (C-20 or C-21 or C-22), 28.3 (C-15), 28.0 (*t*-Bu), 27.6 (C-19), 26.2 (C-20 or C-21 or C-22); (+)-HRESIMS $[M+Na]^+$ *m/z* 889.5488 (calcd for $C_{46}H_{74}N_8NaO_8$, 889.5522).

*5.2.4.26. Di-tert-butyl butane-1,4-diylbis((3-(4-oxo-4-((pyridin-3-ylmethyl) amino)butanamido)propyl)carbamate) (**41**).* Following general procedure B, 4-oxo-4-(pyridin-3-ylamino)butanoic acid (**22**) (54 mg, 0.26 mmol), di-*tert*-butyl butane-1,4-diylbis((3-aminopropyl)carbamate) (**4a**) (49 mg, 0.12 mmol), EDC·HCl, HOBt and DIPEA afforded **41** as an orange oil (29 mg, 31%). R_f (10% MeOH/CH_2Cl_2) 0.33; IR (ATR) ν_{max} 3277, 2934, 2252, 2126, 1652, 1419, 1162, 1024, 1005 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (2H, d, J = 1.7 Hz, H-2), 8.43 (2H, dd, J = 4.7, 1.5 Hz, H-6), 8.04 (2H, t, J = 7.0 Hz, NH-8), 7.89–7.82 (2H, m, NH-13), 7.63 (2H, dt, J = 7.8, 1.9 Hz, H-4), 7.32 (2H, dd, J = 7.8, 4.7 Hz, H-5), 4.27 (4H, d, J = 6.0 Hz, H_2-7), 3.14–3.05 (8H, m, H_2-16, H_2-18), 3.00 (4H, dt, J = 6.7, 6.1 Hz, H_2-14), 2.40–2.35 (4H, m, H_2-10 or H_2-11), 2.35–2.29 (4H, m, H_2-10 or H_2-11), 1.56 (4H, tt, J = 6.9, 6.7 Hz, H_2-15), 1.44–1.34 (4H, m, H_2-19), 1.37 (18H, br s, *t*-Bu); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6 (C-9), 171.1 (C-12), 154.6 (C-20), 148.6 (C-2), 148.0 (C-6), 135.1 (C-3), 134.9 (C-4), 123.3 (C-5), 78.2 (C-21), 46.3 (C-18), 44.5 (C-16), 39.7 (C-7), 36.3 (C-14), 30.7 (C-10, C-11), 28.7 (C-15), 28.0 (*t*-Bu), 25.4 (C-19); (+)-HRESIMS $[M+Na]^+$ *m/z* 805.4599 (calcd for $C_{40}H_{62}N_8NaO_8$, 805.4583).

*5.2.4.27. Di-tert-butyl decane-1,10-diylbis((3-(4-oxo-4-((pyridin-3-ylmeth yl)amino)butanamido)propyl)carbamate) (**42**).*

Following general procedure B, 4-oxo-4-(pyridin-3-ylamino)butanoic acid (**22**) (54 mg, 0.26 mmol), di-*tert*-butyl decane-1,10-diylbis((3-amino propyl)carbamate) (**4e**) (56 mg, 0.12 mmol), EDC·HCl, HOBt and DIPEA afforded **42** as an orange oil (21 mg, 24%). R_f (10% MeOH/CH_2Cl_2) 0.33; IR (ATR) ν_{max} 3288, 2928, 2856, 2254, 1652, 1579, 1418, 1024, 1003 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (2H, d, J = 1.5 Hz, H-2), 8.43 (2H, d, J = 4.8 Hz, H-6), 8.39 (2H, t, J = 6.0 Hz, NH-8), 7.79 (2H, t, J = 5.2 Hz, NH-13), 7.62 (2H, dt, J = 7.9, 2.0 Hz, H-4), 7.32 (2H, dd, J = 7.9, 4.8 Hz, H-5), 4.27 (4H, d, J = 5.8 Hz, H_2-7), 3.12–3.04 (8H, m, H_2-16, H_2-18), 3.00 (4H, dt, J = 6.2, 6.8 Hz, H_2-14), 2.40–2.34 (4H, m, H_2-10 or H_2-11), 2.34–2.29 (4H, m, H_2-10 or H_2-11), 1.62–1.51 (4H, m, H_2-15), 1.46–1.35 (4H, m, H_2-19), 1.37 (18H, br s, *t*-Bu), 1.29–1.13 (12H, m, H_2-20, H_2-21, H_2-22); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 171.1 (C-9, C-12), 154.6 (C-23), 148.6 (C-2), 148.0 (C-6), 135.1 (C-3), 134.9 (C-4), 123.3 (C-5), 78.1 (C-24), 46.3 (C-18), 44.3 (C-16), 39.7 (C-7), 36.3 (C-14), 30.7 (C-10, C-11), 28.2 (C-15), 28.9 (C-20 or C-21 or C-22), 28.7 (C-20 or C-21 or C-22), 28.0 (*t*-Bu), 27.7 (C-19), 26.2 (C-20 or C-21 or C-22); (+)-HRESIMS $[M+Na]^+$ *m/z* 899.5535 (calcd for $C_{46}H_{74}N_8NaO_8$, 889.5522).

*5.2.4.28. N^1,N^4-Bis(3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutana-mido)propyl)butane-1,4-diaminium 2,2,2-trifluoroacetate (**43**).*

Following general procedure C, di-*tert*-butyl butane-1,4-diylbis((3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)carbamate) (**23**) (15 mg, 0.016 mmol) was reacted with TFA in CH_2Cl_2. Purification was achieved by C_8 reversed-phase column chromatography eluting with 30% MeOH/H_2O (0.05% TFA), affording **43** as a clear oil (11 mg, 73%). R_f (70% MeOH/30% 1M HCl, C_{18}) 0.80; IR (ATR) ν_{max} 3334, 3072, 2955, 2844, 1677, 1638, 1531, 1203, 1159, 1133, 721 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (2H, br s, NH-9), 8.74 (2H, dd, J = 4.2, 1.5 Hz, H-2), 8.46–8.34 (4H, m, NH_2-18), 8.30–8.28 (2H, m, H-7),

8.30–8.26 (2H, m, H-4), 8.12 (2H, t, $J = 5.8$ Hz, NH-14), 7.57 (2H, dd, $J = 8.4$, 4.2 Hz, H-3), 7.06 (2H, d, $J = 2.8$ Hz, H-5), 3.87 (6H, br s, OMe), 3.14 (4H, dt, $J = 6.4$, 6.2 Hz, H_2-15), 2.91–2.80 (8H, m, H_2-17, H_2-19), 2.85–2.80 (4H, m, H_2-11 or H_2-12), 2.50–2.45 (4H, m, H_2-11 or H_2-12), 1.71 (4H, tt, $J = 7.4$, 7.0 Hz, H_2-16), 1.60–1.50 (4H, m, H_2-20); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0 (C-13), 171.2 (C-10), 157.4 (C-6), 146.1 (C-2), 135.4, 135.3, 134.5 (C-8, C-8a, C-4), 128.9 (C-4a), 122.5 (C-3), 108.8 (C-7), 99.6 (C-5), 55.5 (OMe), 46.1 (C-19), 44.5 (C-17), 35.5 (C-15), 31.9, 30.1 (C-11, C-12), 26.2 (C-16), 22.6 (C-20); (+)-HRESIMS $[M+H]^+$ *m/z* 715.3952 (calcd for $C_{38}H_{51}N_8O_6$, 715.3926).

*5.2.4.29. N^1,N^6-Bis(3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)hexane-1,6-diaminium 2,2,2-trifluoroacetate (**44**).* Following general procedure C, di-*tert*-butyl hexane-1,6-diylbis((3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)carbamate) (**24**) (20 mg, 0.02 mmol) was reacted with TFA in CH_2Cl_2. Purification was achieved by C_8 reversed-phase column chromatography eluting with 30% MeOH/H_2O (0.05% TFA), affording **44** as a clear oil (11 mg, 55%). R_f (70% MeOH/30% 1M HCl, C_{18}) 0.80; IR (ATR) ν_{max} 3346, 3074, 2941, 2859, 1673, 1627, 1527, 1199, 1175, 1129, 1025, 720 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (2H, br s, NH-9), 8.74 (2H, dd, $J = 4.2$, 1.6 Hz, H-2), 8.38–8.30 (4H, m, NH_2-18), 8.29–8.28 (2H, m, H-7), 8.29–8.25 (2H, m, H-4), 8.15 (2H, t, $J = 6.0$ Hz, NH-14), 7.57 (2H, dd, $J = 8.4$, 4.2 Hz, H-3), 7.06 (2H, d, $J = 2.8$ Hz, H-5), 3.87 (6H, br s, OMe), 3.15 (4H, dt, $J = 6.3$, 6.0 Hz, H_2-15), 2.92–2.80 (4H, m, H_2-17), 2.86–2.81 (4H, m, H_2-11 or H_2-12), 2.79–2.69 (4H, m, H_2-19), 2.50–2.45 (4H, m, H_2-11 or H_2-12), 1.71 (4H, tt, $J = 7.0$, 7.0 Hz, H_2-16), 1.48–1.37 (4H, m, H_2-20), 1.15–1.07 (4H, m, H_2-21); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2 (C-13), 171.3 (C-10), 157.5 (C-6), 146.1 (C-2), 135.43 (C-8), 135.37 (C-4), 134.5 (C-8a), 128.9 (C-4a), 122.6 (C-3), 108.8 (C-7), 99.6 (C-5), 55.5 (OMe), 46.7 (C-19), 44.4 (C-17), 35.4 (C-15), 31.9, 30.1 (C-11, C-12), 26.3 (C-16), 25.3, 25.3 (C-20, C-21); (+)-HRESIMS $[M+H]^+$ *m/z* 743.4236 (calcd for $C_{40}H_{55}N_8O_6$, 743.4239).

*5.2.4.30. N^1,N^7-Bis(3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)heptane-1,7-diaminium 2,2,2-trifluoroacetate (**45**).* Following general procedure C, di-*tert*-butyl heptane-1,7-diylbis((3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)carbamate) (**25**) (20 mg, 0.02 mmol) was reacted with TFA in CH_2Cl_2. Purification was achieved by C_8 reversed-phase column chromatography eluting with 30% MeOH/H_2O (0.05% TFA), affording **45** as a clear oil (15 mg, 75%). R_f (70% MeOH/30% 1M HCl, C_{18}) 0.80; IR (ATR) ν_{max} 3331, 3072, 2938, 2850, 1674, 1634, 1528, 1200, 1177, 1132, 720 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (2H, br s, NH-9), 8.74 (2H, dd, $J = 4.4$, 1.5 Hz, H-2), 8.40–8.30 (4H, m, NH_2-18), 8.30–8.28 (2H, m, H-7), 8.28–8.25 (2H, m, H-4), 8.16 (2H, t, $J = 5.8$ Hz, NH-14), 7.57 (2H, dd, $J = 8.4$, 4.4 Hz, H-3), 7.06 (2H, d, $J = 2.8$ Hz, H-5), 3.87 (6H, br s, OMe), 3.15 (4H, dt, $J = 6.4$, 6.2 Hz, H_2-15), 2.92–2.81 (4H, m, H_2-17), 2.87–2.81 (4H, m, H_2-11 or H_2-12), 2.79–2.71 (4H, m, H_2-19), 2.50–2.45 (4H, m, H_2-11 or H_2-12), 1.71 (4H, tt, $J = 7.0$, 6.5 Hz, H_2-16), 1.51–1.38 (4H, m, H_2-20), 1.12–1.04 (6H, m, H_2-21, H_2-22); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2 (C-13), 171.3 (C-10), 157.5 (C-6), 146.1 (C-2), 135.4 (C-8 or C-8a), 135.3 (C-4), 134.5 (C-8 or C-8a), 128.9 (C-4a), 122.5 (C-3), 108.8 (C-7), 99.5 (C-5), 55.5 (OMe), 46.7 (C-19), 44.4 (C-17), 35.3 (C-15), 31.9, 30.1 (C-11, C-12), 26.2 (C-16), 25.6 (C-21, C-22), 25.4 (C-20); (+)-HRESIMS $[M+H]^+$ *m/z* 757.4411 (calcd for $C_{41}H_{57}N_8O_6$, 757.4396).

*5.2.4.31. N^1,N^8-Bis(3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)octane-1,8-diaminium 2,2,2-trifluoroacetate (**46**).* Following general procedure C, di-*tert*-butyl octane-1,8-diylbis((3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)carbamate) (**26**) (20 mg, 0.02 mmol) was reacted with TFA in CH_2Cl_2. Purification was achieved by C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA), affording **46** as a yellow oil (12 mg, 59%). R_f (70% MeOH/30% 1M HCl, C_{18}) 0.80; IR (ATR) ν_{max} 3330, 3072, 2937, 2858, 1674, 1631, 1530, 1201, 1179, 1133, 721 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (2H, br s, NH-9), 8.74 (2H, d, $J = 4.2$ Hz, H-2), 8.36–8.27 (4H, m, NH_2-18), 8.30–8.27 (2H, m, H-7), 8.30–8.25 (2H, m, H-4), 8.16 (2H, t, $J = 5.8$ Hz, NH-14), 7.57 (2H, dd, $J = 8.4$, 4.2 Hz, H-3), 7.06 (2H, d, $J = 2.8$ Hz, H-5), 3.87 (6H, br s, OMe), 3.16 (4H, dt, $J = 6.2$, 6.2 Hz, H_2-15), 2.92–2.81 (4H, m, H_2-17), 2.87–2.81 (4H, m, H_2-11 or H_2-12), 2.79–2.70 (4H, m, H_2-19), 2.50–2.45 (4H, m, H_2-11 or H_2-12), 1.71 (4H, tt, $J = 6.5$, 6.5 Hz, H_2-16), 1.49–1.38 (4H, m, H_2-20), 1.11–1.00 (8H, m, H_2-21, H_2-22); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3 (C-13), 171.3 (C-10), 157.5 (C-6), 146.1 (C-2), 135.4 (C-4), 135.3 (C-8), 134.5 (C-8a), 128.9 (C-4a), 122.5 (C-3), 108.7 (C-7), 99.5 (C-5), 55.5 (OMe), 46.8 (C-19), 44.4 (C-17), 35.3 (C-15), 31.9, 30.0 (C-11, C-12), 28.2 (C-21 or C-22), 26.3 (C-16), 25.7 (C-21 or C-22), 25.4 (C-20); (+)-HRESIMS $[M+H]^+$ *m/z* 771.4594 (calcd for $C_{42}H_{59}N_8O_6$, 771.4550).

*5.2.4.32. N^1,N^{10}-Bis(3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**47**).* Following general procedure C, di-*tert*-butyl decane-1,10-diylbis((3-(4-((6-methoxyquinolin-8-yl)amino)-4-oxobutanamido)propyl)carbamate) (**27**) (20 mg, 0.020 mmol) was reacted with TFA in CH_2Cl_2. Purification was achieved by C_8 reversed-phase column chromatography eluting with 30% MeOH/H_2O (0.05% TFA), affording **47** as a clear oil (12 mg, 59%). R_f (60% MeOH/40% 1M HCl, C_{18}) 0.74; IR (ATR) ν_{max} 3332, 3061, 2933, 2856, 1669, 1628, 1526, 1454, 1423, 1198, 1175, 1157, 1128, 833, 798, 719 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (2H, br s, NH-9), 8.74 (2H, dd, $J = 4.2$, 1.5 Hz, H-2), 8.40–8.30 (4H, m, NH_2-18), 8.29 (2H, d, $J = 2.5$ Hz, H-7), 8.27 (2H, dd, $J = 8.4$, 1.5 Hz, H-4), 8.17 (2H, t, $J = 5.9$ Hz, NH-14), 7.57 (2H, dd, $J = 8.4$, 4.2 Hz, H-3), 7.06 (2H, d, $J = 2.5$ Hz, H-5), 3.87 (6H, br s, OMe), 3.16 (4H, dt, $J = 6.4$, 6.2 Hz, H_2-15), 2.91–2.81 (4H, m, H_2-17), 2.86–2.82 (4H, m, H_2-11 or H_2-12), 2.80–2.73 (4H, m, H_2-19), 2.50–2.46 (4H, m, H_2-11 or H_2-12), 1.72 (4H, tt, $J = 7.2$, 6.8 Hz, H_2-16), 1.49–1.42 (4H, m, H_2-20), 1.31–1.06 (12H, m, H_2-21, H_2-22, H_2-23); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3 (C-13), 171.3 (C-10), 157.5 (C-6), 146.0 (C-2), 135.42, 135.36, 134.5 (C-8, C-8a, C-4), 128.9 (C-4a), 122.5 (C-3), 108.8 (C-7), 99.6 (C-5), 55.5 (OMe), 46.8 (C-19), 44.4 (C-17), 35.3 (C-15), 31.9, 30.0 (C-11, C-12), 28.6 (C-21 or C-22 or C-23), 28.4 (C-21 or C-22 or C-23), 26.3 (C-16), 25.8 (C-21 or C-22 or C-23), 25.4 (C-20); (+)-HRESIMS $[M+H]^+$ *m/z* 799.4933 (calcd for $C_{44}H_{63}N_8O_6$, 799.4870).

*5.2.4.33. N^1,N^4-Bis(3-(4-oxo-4-(quinolin-8-ylamino)butanamido)propyl) butane-1,4-diaminium 2,2,2-trifluoroacetate (**48**).* Following general procedure C, di-*tert*-butyl butane-1,4-diylbis((3-(4-oxo-4-(quinolin-8-ylamino)butanamido)propyl)carbamate) (**28**) (34 mg, 0.04 mmol) was treated with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phased column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **48** as a purple oil (20 mg, 57%). R_f (90% MeOH/10% 1M HCl, C_{18}) 0.24; IR (ATR) ν_{max} 3336, 3055, 2839, 1675, 1528, 1201, 1130, 830, 799, 721 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 8.94 (2H, dd, $J = 4.5$, 1.5 Hz, H-2), 8.49–8.45 (4H, m, H-4, H-7), 7.73 (2H, dd, $J = 8.0$, 1.0 Hz, H-5), 7.67–7.64 (2H, m, H-3), 7.60 (2H, t, $J = 8.0$ Hz, H-6) 3.34–3.30 (4H, m, H_2-15), 2.97–2.92 (8H, m, H_2-11 or H_2-12, H_2-17), 2.80 (4H, br s, H_2-19) 2.68–2.65 (4H, m, H_2-11 or H_2-12), 1.88–1.82 (4H, m, H_2-16), 1.58–1.55 (4H, m, H_2-20); ^{13}C NMR (100 MHz, CD_3OD) δ 176.3 (C-13), 173.5 (C-10), 149.2 (C-2), 140.2 (C-4), 138.8 (C-8a), 134.5 (C-8), 130.0 (C-4a), 128.7 (C-6), 124.6 (C-5), 123.2 (C-3), 121.2 (C-7), 48.0 (C-19), 46.0 (C-17), 36.6 (C-15), 32.8, 31.5 (C-11, C-12), 27.7 (C-16), 24.1 (C-20); (+)-HRESIMS *m/z* 655.3713 $[M+H]^+$ (calcd for $C_{36}H_{47}N_8O_4$, 655.3715).

*5.2.4.34. N^1,N^6-Bis(3-(4-oxo-4-(quinolin-8-ylamino)butanamido)propyl) hexane-1,6-diaminium 2,2,2-trifluoroacetate (**49**).* Following general procedure C, di-*tert*-butyl hexane-1,6-diylbis((3-(4-oxo-4-(quinolin-8-ylamino)butanamido)propyl)carbamate) (**29**) (20 mg, 0.02 mmol) was reacted with TFA in CH_2Cl_2. Purification was achieved by C_8 reversed-phase column chromatography eluting with 30% MeOH/H_2O (0.05% TFA), affording **49** as a clear oil (9 mg, 58%). R_f (70% MeOH/30% 1M HCl, C_{18}) 0.83; IR (ATR) ν_{max} 3332, 3060, 2941, 2851, 1671, 1525, 1199, 1174, 1126, 827, 797, 719 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.10 (2H, br s, NH-9), 8.93 (2H, dd, J = 4.2, 1.6 Hz, H-2), 8.59 (2H, dd, J = 7.8, 1.3 Hz, H-7), 8.41 (2H, dd, J = 8.4, 1.6 Hz, H-4), 8.37–8.27 (4H, m, NH_2-18), 8.16 (2H, t, J = 5.9 Hz, NH-14), 7.86–7.62 (4H, m, H-3, H-5), 7.55 (2H, dd, J = 8.6, 7.8 Hz, H-6), 3.15 (4H, dt, J = 6.5, 6.2 Hz, H_2-15), 2.91–2.82 (4H, m, H_2-17), 2.86–2.82 (4H, m, H_2-11 or H_2-12), 2.76–2.69 (4H, m, H_2-19), 2.51–2.48 (4H, m, H_2-11 or H_2-12), 1.71 (4H, tt, J = 7.0, 6.8 Hz, H_2-16), 1.46–1.36 (4H, m, H_2-20), 1.12–1.04 (4H, m, H_2-21); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2 (C-13), 171.0 (C-10), 148.8 (C-2), 138.0 (C-8a), 136.6 (C-4), 134.5 (C-8), 127.8 (C-4a), 126.9 (C-6), 122.1 (C-3), 121.7 (C-5), 116.4 (C-7), 46.6 (C-19), 44.4 (C-17), 35.4 (C-15), 31.9, 30.2 (C-11, C-12), 26.2 (C-16), 25.3 (C-21), 25.3 (C-20); (+)-HRESIMS *m/z* 683.4015 $[M+H]^+$ (calcd for $C_{38}H_{51}N_8O_4$, 683.4028).

*5.2.4.35. N^1,N^7-Bis(3-(4-oxo-4-(quinolin-8-ylamino)butanamido)propyl) heptane-1,7-diaminium 2,2,2-trifluoroacetate (**50**).* Following general procedure C, di-*tert*-butyl heptane-1,7-diylbis((3-(4-oxo-4-(quinolin-8-ylamino)butanamido)propyl)carbamate) (**30**) (20 mg, 0.02 mmol) was reacted with TFA in CH_2Cl_2. Purification was achieved by C_8 reversed-phase column chromatography eluting with 30% MeOH/H_2O (0.05% TFA), affording **50** as a clear oil (11 mg, 70%). R_f (70% MeOH/30% 1M HCl, C_{18}) 0.83; IR (ATR) ν_{max} 3332, 3061, 2939, 2859, 1671, 1525, 1199, 1175, 1127, 828, 797, 719 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.11 (2H, br s, NH-9), 8.93 (2H, dd, J = 4.2, 1.6 Hz, H-2), 8.60 (2H, dd, J = 7.8, 1.2 Hz, H-7), 8.40 (2H, dd, J = 8.4, 1.6 Hz, H-4), 8.38–8.30 (4H, m, NH_2-18), 8.17 (2H, t, J = 6.0 Hz, NH-14), 7.68–7.62 (4H, m, H-3, H-5), 7.55 (2H, dd, J = 8.6, 7.8 Hz, H-6), 3.15 (4H, dt, J = 6.3, 6.3 Hz, H_2-15), 2.91–2.81 (4H, m, H_2-17), 2.87–2.82 (4H, m, H_2-11 or H_2-12), 2.78–2.69 (4H, m, H_2-19), 2.51–2.47 (4H, m, H_2-11 or H_2-12), 1.71 (4H, tt, J = 7.0, 6.7 Hz, H_2-16), 1.46–1.36 (4H, m, H_2-20), 1.09–1.00 (6H, m, H_2-21, H_2-22); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3 (C-13), 171.0 (C-10), 148.8 (C-2), 138.0 (C-8a), 136.6 (C-4), 134.6 (C-8), 127.8 (C-4a), 126.9 (C-6), 122.1 (C-3), 121.7 (C-5), 116.4 (C-7), 46.7 (C-19), 44.4 (C-17), 35.4 (C-15), 31.9, 30.2 (C-11, C-12), 27.9 (C-21 or C-22), 26.2 (C-16), 25.6 (C-21 or C-22), 25.3 (C-20); (+)-HRESIMS *m/z* 697.4159 $[M+H]^+$ (calcd for $C_{39}H_{53}N_8O_4$, 697.4184).

*5.2.4.36. N^1,N^8-Bis(3-(4-oxo-4-(quinolin-8-ylamino)butanamido)propyl) octane-1,8-diaminium 2,2,2-trifluoroacetate (**51**).* Following general procedure C, di-*tert*-butyl octane-1,8-diylbis((3-(4-oxo-4-(quinolin-8-ylamino)butanamido)propyl)carbamate) (**31**) (20 mg, 0.02 mmol) was reacted with TFA in CH_2Cl_2. Purification was achieved by C_8 reversed-phase column chromatography eluting with 30% MeOH/H_2O (0.05% TFA), affording **51** as a clear oil (8 mg, 53%). R_f (70% MeOH/30% 1M HCl, C_{18}) 0.83; IR (ATR) ν_{max} 3316, 3263, 3097, 2934, 2858, 2443, 1671, 1523, 1198, 1163, 1127, 829, 797, 717 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.11 (2H, br s, NH-9), 8.93 (2H, dd, J = 4.2, 1.7 Hz, H-2), 8.60 (2H, dd, J = 7.8, 1.2 Hz, H-7), 8.40 (2H, dd, J = 8.2, 1.7 Hz, H-4), 8.37–8.27 (4H, m, NH_2-18), 8.17 (2H, t, J = 6.0 Hz, NH-14), 7.67–7.64 (2H, m, H-5), 7.66–7.62 (2H, m, H-3), 7.55 (2H, dd, J = 8.8, 7.8 Hz, H-6), 3.16 (4H, dt, J = 6.5, 6.0 Hz, H_2-15), 2.92–2.81 (4H, m, H_2-17), 2.88–2.81 (4H, m, H_2-11 or H_2-12), 2.78–2.68 (4H, m, H_2-19), 2.50–2.46 (4H, m, H_2-11 or H_2-12), 1.71 (4H, tt, J = 7.0, 7.0 Hz, H_2-16), 1.48–1.37 (4H, m, H_2-20), 1.09–1.00 (8H, m, H_2-21, H_2-22); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3 (C-13), 171.0 (C-10), 148.8 (C-2), 138.0 (C-8a), 136.6 (C-4), 134.6 (C-8), 127.8 (C-4a), 126.9 (C-6), 122.1 (C-3), 121.7 (C-5), 116.4 (C-7), 46.8 (C-19), 44.4 (C-17), 35.3 (C-15), 31.9, 30.1 (C-11, C-12), 28.2 (C-21 or C-22), 26.3 (C-16), 25.7 (C-21 or C-22), 25.4 (C-20); (+)-HRESIMS *m/z* 711.4333 $[M+H]^+$ (calcd for $C_{40}H_{55}N_8O_4$, 711.4341).

*5.2.4.37. N^1,N^{10}-Bis(3-(4-oxo-4-(quinolin-8-ylamino)butanamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**52**).* Following general procedure C, di-tert-butyl decane-1,10-diylbis((3-(4-oxo-4-(quinolin-8-ylamino)butanamido)propyl)carbamate) (**32**) (41 mg, 0.04 mmol) was treated with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 30% MeOH/H_2O (0.05% TFA) to afford **52** as a purple oil (40 mg, 93%). R_f (90% MeOH/10% 1M HCl, C_{18}) 0.73; IR (ATR) ν_{max} 2935, 1680, 1528, 1201, 1132, 829, 798, 721 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.92 (2H, dd, J = 4.5, 1.5 Hz, H-2), 8.53 (2H, dd, J = 7.5, 1.0 Hz, H-7), 8.43 (2H, dd, J = 8.5, 1.5 Hz, H-4), 7.70 (2H, dd, J = 8.5, 1.5 Hz, H-5), 7.65–7.57 (2H, m, H-3, H-6), 3.37–3.34 (4H, m, H_2-15), 3.03 (4H, t, J = 6.7 Hz, H_2-17), 2.97–2.94 (4H, m, H_2-11 or H_2-12), 2.79 (4H, t, J = 7.7 Hz, H_2-19), 2.69–2.66 (4H, m, H_2-11 or H_2-12), 1.91–1.85 (4H, m, H_2-16), 1.51–1.43 (4H, m, H_2-20), 1.00–0.93 (12H, m, H_2-21, H_2-22, H_2-23); ^{13}C NMR (100 MHz, CD_3OD) δ 176.5 (C-13), 173.3 (C-10), 149.6 (C-2), 139.4 (C-8a), 139.0 (C-4), 135.2 (C-8), 129.9 (C-4a), 128.4 (C-6), 124.0 (C-5), 123.2 (C-3), 119.5 (C-7), 49.1 (C-19), 45.9 (C-17), 36.4 (C-15), 32.8, 31.3 (C-11, C-12), 30.2 (C-23), 30.0 (C-22), 27.9 (C-16), 27.3 (C-21), 27.2 C-20); (+)-HRESIMS *m/z* 739.4675 $[M+H]^+$ (calcd for $C_{42}H_{59}N_8O_4$, 739.4653).

*5.2.4.38. N^1,N^4-Bis(3-(4-oxo-4-(quinolin-2-ylamino)butanamido)propyl) butane-1,4-diaminium 2,2,2-trifluoroacetate (**53**).* Following general procedure C, di-*tert*-butyl butane-1,4-diylbis((3-(4-oxo-4(quinoline-2-ylamino)butanamido)propyl)carbamate) (**33**) (15 mg, 0.02 mmol) was reacted with TFA in CH_2Cl_2. Purification was achieved by C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA), affording **53** as a clear oil in quantitative yield. R_f (70% MeOH/30% 1M HCl, C_{18}) 0.77; IR (ATR) ν_{max} 3387, 3282, 3064, 2847, 1673, 1500, 1427, 1199, 1175, 1127, 1024, 719 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.85 (2H, br s, NH-9), 8.51–8.40 (4H, m, NH_2-18), 8.33 (2H, d, J = 9.0 Hz, H-4), 8.26 (2H, d, J = 9.0 Hz, H-3), 8.11 (2H, t, J = 5.8 Hz, NH-14), 7.90 (2H, d, J = 8.4 Hz, H-5), 7.80 (2H, d, J = 8.4 Hz, H-8), 7.71 (2H, ddd, J = 8.4, 7.5, 1.5 Hz, H-7), 7.48 (2H, ddd, J = 8.4, 7.5, 1.5 Hz, H-6), 3.13 (4H, dt, J = 6.5, 5.8 Hz, H_2-15), 2.92–2.81 (8H, m, H_2-17, H_2-19), 2.72 (4H, t, J = 6.8 Hz, H_2-11 or H_2-12), 2.44 (4H, t, J = 6.8 Hz, H_2-11 or H_2-12), 1.71 (4H, tt, J = 7.2, 6.8 Hz, H_2-16), 1.62–1.53 (4H, m, H_2-20); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.04, 171.98 (C-10, C-13), 151.6 (C-2), 146.2 (C-8a), 138.3 (C-4), 130.0 (C-7), 127.7 (C-5), 126.8 (C-8), 125.5 (C-4a), 124.9 (C-6), 114.2 (C-3), 46.1 (C-19), 44.5 (C-17), 35.5 (C-15), 31.4, 29.8 (C-11, C-12), 26.1 (C-16), 22.6 (C-20); (+)-HRESIMS *m/z* 655.3736 $[M+H]^+$ (calcd for $C_{36}H_{47}N_8O_4$, 655.3715).

*5.2.4.39. N^1,N^{10}-Bis(3-(4-oxo-4-(quinolin-2-ylamino)butanamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**54**).* Following general procedure C, di-*tert*-butyl decane-1,10-diylbis((3-(4-oxo-4-(quinolin-2-ylamino)butanamido)propyl)carbamate) (**34**) (15 mg, 0.02 mmol) was reacted with TFA in CH_2Cl_2. Purification was achieved by C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) affording **54** as a white gum (12 mg, 78%). R_f (70% MeOH/30% 1M HCl, C_{18}) 0.77; IR (ATR) ν_{max} 3315, 3054, 2930, 2856, 1617, 1427, 1198, 1173, 1126, 719 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.91 (2H, br s, NH-9), 8.45–8.36 (4H, m, NH_2-18), 8.33 (2H, d, J = 9.0 Hz, H-4), 8.26 (2H, d, J = 9.0 Hz, H-3), 8.15 (2H, t, J = 5.8 Hz, NH-14), 7.90 (2H, dd, J = 8.2, 1.6 Hz, H-5), 7.80 (2H, d, J = 8.2 Hz, H-8), 7.70 (2H, ddd, J = 8.2, 6.8, 1.6 Hz, H-7), 7.48 (2H, ddd, J = 8.2, 6.8, 1.6 Hz, H-6), 3.15 (4H, dt, J = 6.5, 5.8 Hz, H_2-15), 2.88 (4H, tt, J = 7.2, 6.0

Hz, H_2-17), 2.82–2.75 (4H, m, H_2-19), 2.75–2.70 (4H, m, H_2-11 or H_2-12), 2.45 (4H, t, J = 6.6 Hz, H_2-11 or H_2-12), 1.72 (4H, tt, J = 6.8, 7.2 Hz, H_2-16), 1.47 (4H, tt, J = 7.5, 7.0 Hz, H_2-20), 1.16–0.99 (12H, m, H_2-21, H_2-22, H_2-23); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 172.2 (C-10, C-13), 151.6 (C-2), 146.0 (C-8a), 138.5 (C-4), 130.1 (C-7), 127.8 (C-5), 126.6 (C-8), 125.5 (C-4a), 124.9 (C-6), 114.2 (C-3), 46.9 (C-19), 44.4 (C-17), 35.4 (C-15), 31.4, 29.7 (C-11, C-12), 28.7 (C-21 or C-22 or C-23), 28.5 (C-21 or C-22 or C-23), 26.2 (C-16), 25.9 (C-21 or C-22 or C-23), 25.5 (C-20); (+)-HRESIMS *m/z* 739.4648 $[M+H]^+$ (calcd for $C_{42}H_{59}N_8O_4$, 739.4654).

*5.2.4.40. N^1,N^4-Bis(3-(4-oxo-4-(quinolin-5-ylamino)butanamido)propyl) butane-1,4-diaminium 2,2,2-trifluoroacetate (**55**).* Following general procedure C, di-*tert*-butyl butane-1,4-diylbis((3-(4-oxo-4(quinoline-5-ylamino)butanamido)propyl)carbamate) (**35**) (16 mg, 0.02 mmol) was treated with TFA in CH_2Cl_2. The crude product was purified with C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **55** as an orange oil (14 mg, 82%). R_f (90% MeOH/10% 1M HCl, C_{18}) 0.64; IR (ATR) ν_{max} 3285, 1675, 1540, 1202, 1131, 801, 722 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 9.20–9.15 (4H, m, H-2, H-4), 8.08–8.03 (6H, m, H-6, H-7, H-8), 7.99–7.97 (2H, m, H-3), 3.35–3.30 (4H, m, H_2-15), 3.02 (4H, t, J = 7.5 Hz, H_2-17), 2.92 (8H, t, J = 6.5 Hz, H_2-11 or H_2-12, H_2-19), 2.67 (4H, t, J = 6.8 Hz, H_2-11 or H_2-12), 1.91–1.85 (4H, m, H_2-16), 1.70–1.66 (4H, m, H_2-20); ^{13}C NMR (100 MHz, CD_3OD) δ 175.8 (C-13), 174.4 (C-10), 147.2 (C-2), 142.3 (C-8a), 141.6 (C-4), 136.5 (C-5), 135.2 (C-7), 125.7 (C-4a), 125.6 (C-8), 122.4 (C-3), 120.5 (C-6), 48.0 (C-19), 46.3 (C-17), 36.9 (C-15), 32.2, 31.4 (C-11, C-12), 27.6 (C-16), 24.2 (C-20); (+)-HRESIMS *m/z* 655.3700 $[M+H]^+$ (calcd for $C_{36}H_{47}N_8O_4$, 655.3715).

*5.2.4.41. N^1,N^{10}-Bis(3-(4-oxo-4-(quinolin-5-ylamino)butanamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**56**).* Following general procedure C, di-tert-butyl decane-1,10-diylbis((3-(4-oxo-4-(quinolin-5-ylamino)butanamido)propyl)carbamate) (**36**) (31 mg, 0.03 mmol) was treated with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the product was purified with C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **56** as a yellow oil (31 mg, 97%). R_f (90% MeOH/10% 1M HCl, C_{18}) 0.79; IR (ATR) ν_{max} 3279, 1677, 1538, 1202, 1133, 802, 721 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 9.17–9.14 (4H, m, H-2, H-4), 8.06–8.03 (6H, m, H-6, H-7, H-8), 7.98–7.95 (2H, m, H-3), 3.35–3.30 (4H, m, H_2-15), 3.02 (4H, t, J = 7.5 Hz, H_2-17), 2.92 (4H, t, J = 6.5 Hz, H_2-11 or H_2-12), 2.86 (4H, t, J = 8.0 Hz, H_2-19), 2.69–2.66 (4H, m, H_2-11 or H_2-12), 1.91–1.84 (4H, m, H_2-16), 1.59–1.55 (4H, m, H_2-20), 1.20 (12H, br s, H_2-21, H_2-22, H_2-23); ^{13}C NMR (100 MHz, CD_3OD) δ 175.9 (C-13), 174.4 (C-10), 148.3 (C-2), 143.7 (C-8a), 140.0 (C-4), 136.1 (C-5), 134.0 (C-7), 125.6 (C-4a), 125.0 (C-8), 122.4, (C-3), 122.2 (C-6), 49.1 (C-19), 46.1 (C-17), 36.8 (C-15), 32.1, 31.3 (C-11, C-12), 30.3 (C-23), 30.1 (C-22), 27.7 (C-16), 27.4 (C-20), 27.2 (C-21); (+)-HRESIMS *m/z* 739.4657 $[M+H]^+$ (calcd for $C_{42}H_{59}N_8O_4$, 739.4653).

*5.2.4.42. N^1,N^4-Bis(3-(4-oxo-4-(quinolin-6-ylamino)butanamido)propyl) butane-1,4-diaminium 2,2,2-trifluoroacetate (**57**).* Following general procedure C, di-*tert*-butyl butane-1,4-diylbis((3-(4-oxo-4-(quinolin-6-ylamino)butanamido)propyl)carbamate) (**37**) (18 mg, 0.02 mmol) was treated with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **57** as an orange oil (15 mg, 83%). R_f (90% MeOH/10% 1M HCl, C_{18}) 0.53; IR (ATR) ν_{max} 3287, 3082, 2823, 1672, 1558, 1200, 1131, 835, 800, 721 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 9.03 (2H, dd, J = 5.5, 1.5 Hz, H-2), 8.98 (2H, d, J = 8.5 Hz, H-4), 8.67 (2H, d, J = 1.5 Hz, H-5), 8.20–8.14 (4H, m, H-7, H-8), 7.99–7.96 (2H, m, H-3), 3.35–3.30 (4H, m, H_2-15), 3.05 (4H, t, J = 7.1 Hz, H_2-17), 2.98–2.85 (4H, m, H_2-19), 2.83 (4H, t, J = 6.5 Hz, H_2-11 or H_2-12), 2.63 (4H, t, J = 6.7 Hz, H_2-11 or H_2-12), 1.93–1.86 (4H, m, H_2-16), 1.73–1.69 (4H, m, H_2-20); ^{13}C NMR (100 MHz, CD_3OD) δ 176.0 (C-13), 173.7 (C-10), 146.6 (C-4), 144.4 (C-2), 141.4 (C-6), 136.7 (C-8a), 131.5 (C-4a), 129.4 (C-7), 123.3 (C-3), 123.0 (C-8), 116.5 (C-5), 48.0 (C-19), 46.1 (C-17), 36.7 (C-15), 32.7, 31.2 (C-11, C-12), 27.7 (C-16), 24.2 (C-20); (+)-HRESIMS *m/z* 655.3703 $[M+H]^+$ (calcd for $C_{36}H_{47}N_8O_4$, 655.3715).

*5.2.4.43. N^1,N^{10}-Bis(3-(4-oxo-4-(quinolin-6-ylamino)butanamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**58**).* Following general procedure C, di-*tert*-butyl decane-1,10-diylbis((3-(4-oxo-4-(quinolin-6-ylamino)butanamido)propyl)carbamate) (**38**) (33 mg, 0.04 mmol) was treated with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **58** as a yellow oil (29 mg, 85%). R_f (90% MeOH/10% 1M HCl, C_{18}) 0.73; IR (ATR) ν_{max} 3273, 1679, 1538, 1202, 1133, 800, 723 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 9.04 (2H, dd, J = 5.0, 1.0 Hz, H-2), 8.97 (2H, d, J = 8.0 Hz, H-4), 8.70 (2H, d, J = 2.0 Hz, H-5), 8.21–8.14 (4H, m, H-7, H-8), 7.99–7.96 (2H, m, H-3), 3.36–3.30 (4H, m, H_2-15), 3.05 (4H, t, J = 7.0 Hz, H_2-17), 2.86 (8H, t, J = 6.5 Hz, H_2-11 or H_2-12, H_2-19), 2.66–2.62 (4H, m, H_2-11 or H_2-12), 1.93–1.86 (4H, m, H_2-16), 1.61–1.54 (4H, m, H_2-20), 1.20–1.08 (12H, m, H_2-21, H_2-22, H_2-23); ^{13}C NMR (100 MHz, CD_3OD) δ 176.1 (C-13), 173.7 (C-10), 146.0 (C-4), 144.8 (C-2), 141.2 (C-6), 137.4 (C-8a), 131.4 (C-4a), 129.1 (C-7), 123.6 (C-8), 123.3 (C-3), 116.5 (C-5), 49.0 (C-19), 46.0 (C-17), 36.6 (C-15), 32.5, 31.0 (C-11, C-12), 30.2 (C-23), 30.1 (C-22), 27.7 (C-16), 27.4 (C-20), 27.2 (C-21); (+)-HRESIMS *m/z* 739.4656 $[M+H]^+$ (calcd for $C_{42}H_{59}N_8O_4$, 739.4653).

*5.2.4.44. N^1,N^4-Bis(3-(4-oxo-4-((pyridin-2-ylmethyl)amino)butanamido) propyl)butane-1,4-diaminium 2,2,2-trifluoroacetate (**59**).* Following general procedure C, di-*tert*-butyl butane-1,4-diylbis((3-(4-oxo-4-((pyridin-2-ylmethyl)amino)butanamido)propyl)carbamate) (**39**) (38 mg, 0.05 mmol) was treated with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **59** as a colourless oil (38 mg, 100%). R_t = 4.80 mins; IR (ATR) ν_{max} 3301, 2935, 2818, 2127, 1671, 1645, 1196, 1177, 1122 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66–8.62 (2H, m, H-6), 8.63–8.57 (12H, m, NH-8, NH_2-17), 8.10–8.04 (4H, m, H-4, NH-13), 7.56–7.51 (4H, m, H-5, H-3), 4.46 (4H, d, J = 5.7 Hz, H_2-7), 3.12 (4H, dt, J = 6.6, 6.2 Hz, H_2-14), 2.93–2.84 (8H, m, H_2-16, H_2-18), 2.46 (4H, t, J = 6.8 Hz, H_2-10 or H_2-11), 2.36 (4H, t, J = 6.8 Hz, H_2-10 or H_2-11), 1.71 (4H, tt, J = 7.5, 6.6 Hz, H_2-15), 1.64–1.58 (4H, m, H_2-19); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.1, 172.0 (C-9, C-12), 157.1 (C-2), 145.8 (C-6), 140.6 (C-4), 123.4 (C-5), 122.6 (C-3), 46.1 (C-18), 44.6 (C-16), 42.6 (C-7), 35.6 (C-14), 30.4 (C-10, C-11), 26.1 (C-15), 22.7 (C-19); (+)-HRESIMS *m/z* 607.3715 $[M+Na]^+$ (calcd for $C_{30}H_{48}N_8NaO_4$, 607.3969).

*5.2.4.45. N^1,N^{10}-Bis(3-(4-oxo-4-((pyridin-2-ylmethyl)amino)butanamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**60**).* Following general procedure C, di-*tert*-butyl decane-1,10-diylbis((3-(4-oxo-4-((pyridin-2-ylmethyl)amino)butanamido)propyl)carbamate) (**40**) (20 mg, 0.02 mmol) was reacted with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 25% MeOH/H_2O (0.05% TFA) to afford **60** as a clear oil (8 mg, 40%). R_t = 5.36 mins; IR (ATR) ν_{max} 3285, 2931, 2850, 1668, 1198, 1175, 1128, 1025, 719 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64–8.61 (2H, m, H-6), 8.58 (2H, t, J = 5.8 Hz, NH-8), 8.49–8.31 (4H, m, NH-17), 8.08–8.02 (4H, m, NH-13, H-4), 7.55–7.49 (4H, m, H-3, H-5), 4.44 (4H, d, J = 5.7 Hz, H_2-7), 3.12 (4H, dt, J = 6.1, 6.4 Hz, H_2-14), 2.93–2.78 (8H, m, H_2-16, H_2-18), 2.49–2.42 (4H, m, H_2-10 or H_2-11), 2.39–2.30 (4H, m, H_2-10 or H_2-11), 1.70 (4H, tt, J = 7.3, 6.4 Hz, H_2-15), 1.59–1.49 (4H, m, H_2-19), 1.33–1.21 (12H, m, H_2-20, H_2-21, H_2-22); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.1, 172.0 (C-9, C-12), 157.2 (C-2), 146.0 (C-6), 140.2 (C-4), 123.2, 122.4 (C-5, C-

3), 46.8 (C-18), 44.5 (C-16), 42.7 (C-7), 35.5 (C-14), 30.4 (C-10, C-11), 28.7 (C-20 or C-21 or C-22), 28.4 (C-20 or C-21 or C-22), 26.1 (C-15), 25.9 (C-19), 25.5 (C-20 or C-21 or C-22); (+)-HRESIMS *m/z* 667.4654 $[M+H]^+$ (calcd for $C_{36}H_{59}N_8O_4$, 667.4647).

*5.2.4.46. N^1,N^4-Bis(3-(4-oxo-4-((pyridin-3-ylmethyl)amino)butanamido) propyl)butane-1,4-diaminium 2,2,2-trifluoroacetate (**61**).* Following general procedure C, di-*tert*-butyl butane-1,4-diylbis((3-(4-oxo-4-((pyridin-3-ylmethyl)amino)butanamido)propyl)carbamate) (**41**) (29 mg, 0.04 mmol) was reacted with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 50% MeOH/H_2O (0.05% TFA) to afford **61** as a clear oil (38 mg, 100%). R_t = 4.73 mins; IR (ATR) ν_{max} 3278, 3061, 2824, 2130, 1668, 1549, 1197, 1175, 1025 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.75–8.67 (4H, m, H-2, H-6), 8.66–8.56 (6H, m, NH-8, NH_2-17), 8.17 (2H, d, *J* = 7.9 Hz, H-4), 8.05 (2H, t, *J* = 5.8 Hz, NH-13), 7.80 (2H, dd, *J* = 7.9, 5.6 Hz, H-5), 4.39 (4H, d, *J* = 5.8 Hz, H_2-7), 3.11 (4H, dt, *J* = 6.4, 6.2 Hz, H_2-14), 2.94–2.83 (8H, m, H_2-16, H_2-18), 2.45–2.39 (4H, m, H_2-10, or H_2-11), 2.38–2.33 (4H, m, H_2-10 or H_2-11), 1.71 (4H, tt, *J* = 7.5, 6.4 Hz, H_2-15), 1.64–1.58 (4H, m, H_2-19); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 171.9 (C-9, C-12), 143.3, 143.1 (C-2, C-6), 141.2 (C-4), 138.2 (C-3), 125.7 (C-5), 46.1 (C-18), 44.6 (C-16), 39.1 (C-7), 35.6 (C-14), 30.4 (C-10, C-11), 26.1 (C-15), 22.7 (C-19); (+)-HRESIMS *m/z* 585.3864 $[M + H]^+$ (calcd for $C_{30}H_{49}N_8O_4$, 585.3861).

*5.2.4.47. N^1,N^{10}-Bis(3-(4-oxo-4-((pyridin-3-ylmethyl)amino)butanamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**62**).* Following general procedure C, di-*tert*-butyl decane-1,10-diylbis((3-(4-oxo-4-((pyridin-3-ylmethyl)amino)butanamido)propyl)carbamate) (**42**) (21 mg, 0.02 mmol) with TFA in CH_2Cl_2. The solvent was removed *in vacuo* and the crude product was purified with C_8 reversed-phase column chromatography eluting with 25% MeOH/H_2O (0.05% TFA) to afford **62** as a clear oil (16 mg, 76%). R_t = 5.55 mins; IR (ATR) ν_{max} 3283, 3062, 2933, 2859, 1670, 1551, 1199, 1178, 1129 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.75–8.67 (4H, m, H-2, H-6), 8.61–8.53 (2H, m, NH-8), 8.46–8.32 (4H, m, NH_2-17), 8.28–8.11 (2H, m, H-4), 8.03 (2H, t, *J* = 5.8 Hz, NH-13), 7.89–7.75 (2H, m, H-5), 4.42–4.37 (4H, m, H_2-7), 3.11 (4H, dt, *J* = 6.5, 6.0 Hz, H_2-14), 2.92–2.79 (8H, m, H_2-16, H_2-18), 2.45–2.40 (4H, m, H_2-10 or H_2-11), 2.38–2.33 (4H, m, H_2-10 or H_2-11), 1.70 (4H, tt, *J* = 7.4, 6.5 Hz, H_2-15), 1.59–1.49 (4H, m, H_2-19), 1.31–1.21 (12H, m, H_2-20, H_2-21, H_2-22); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 171.9 (C-9, C-12), 143.2*, 142.3* (C-2, C-6), 141.4* (C-4), 139.3 (C-3), 125.7 (C-5), 46.8 (C-18), 44.5 (C-16), 39.8 (C-7), 35.5 (C-14), 30.3 (C-10, C-11), 28.7 (C-20 or C-21 or C-22), 28.5 (C-20 or C-21 or C-22), 26.1 (C-15), 25.9 (C-19), 25.5 (C-20 or C-21 or C-22); (+)-HRESIMS *m/z* 667.4641 $[M+H]^+$ (calcd for $C_{36}H_{59}N_8O_4$, 667.4654).

* assigned by HSQC

5.3. Antimicrobial assays

Antimicrobial evaluation against *Staphylococcus aureus* (ATCC 43300), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 700603), *Acinetobacter baumannii* (ATCC 19606), *Candida albicans* (ATCC 90028), and *Cryptococcus neoformans* (ATCC 208821) was undertaken at the Community for Open Antimicrobial Drug Discovery at The University of Queensland (Australia) according to their standard protocols.[31] For antimicrobial assays, the tested strains were cultured in either Luria broth (LB) (In Vitro Technologies, USB75852), nutrient broth (NB) (Becton Dickson, 234000), or Mueller Hinton Broth (MHB) at 37 °C overnight. A sample of culture was then diluted 40-fold in fresh MHB and incubated at 37 °C for 1.5−2 h. The compounds were serially diluted 2-fold across the wells of 96-well plates (Corning 3641, nonbinding surface), with compound concentrations ranging from 0.015 to 64 μg/mL, plated in duplicate. The resultant mid log phase cultures were diluted to the final concentration of 1 × 106 CFU/mL; then, 50 μL was added to each well of the compound containing plates giving a final compound concentration range of 0.008 to 32 μg/mL and a cell density of 5 × 105 CFU/mL. All plates were then covered and incubated at 37 °C for 18 h. Resazurin was added at 0.001% final concentration to each well and incubated for 2 h before MICs were read by eye.

For the antifungal assay, fungi strains were cultured for 3 days on YPD agar at 30 °C. A yeast suspension of 1×10^6 to 5×10^6 CFU/mL was prepared from five colonies. These stock suspensions were diluted with yeast nitrogen base (YNB) (Becton Dickinson, 233520) broth to a final concentration of 2.5×10^3 CFU/mL. The compounds were serially diluted 2-fold across the wells of 96-well plates (Corning 3641, nonbinding surface), with compound concentrations ranging from 0.015 to 64 μg/mL and final volumes of 50 μL, plated in duplicate. Then, 50 μL of the fungi suspension that was previously prepared in YNB broth to the final concentration of 2.5×10^3 CFU/mL was added to each well of the compound-containing plates, giving a final compound concentration range of 0.008 to 32 μg/mL. Plates were covered and incubated at 35 °C for 36 h without shaking. *C. albicans* MICs were determined by measuring the absorbance at OD_{530}. For *C. neoformans*, resazurin was added at 0.006% final concentration to each well and incubated for a further 3 h before MICs were determined by measuring the absorbance at $OD_{570-600}$.

Colistin and vancomycin were used as positive bacterial inhibitor standards for Gram-negative and Gram-positive bacteria, respectively. Fluconazole was used as a positive fungal inhibitor standard for *C. albicans* and *C. neoformans*. The antibiotics were provided in 4 concentrations, with 2 above and 2 below its MIC value, and plated into the first 8 wells of column 23 of the 384-well NBS plates. The quality control (QC) of the assays was determined by the antimicrobial controls and the Z'-factor (using positive and negative controls). Each plate was deemed to fulfil the quality criteria (pass QC), if the Z'-factor was above 0.4, and the antimicrobial standards showed full range of activity, with full growth inhibition at their highest concentration, and no growth inhibition at their lowest concentration.

The susceptibility of bacterial strains *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 13443) and *Acinetobacter baumannii* (AYE) to antibiotics and compounds was determined in microplates using the standard broth dilution method in accordance with the recommendations of the Comité de l'AntibioGramme de la Société Française de Microbiologie (CA-SFM). Briefly, the minimal inhibitory concentrations (MICs) were determined with an inoculum of 10^5 CFU in 200 μL of MHB containing two-fold serial dilutions of each drug. The MIC was defined as the lowest concentration of drug that completely inhibited visible growth after incubation for 18 h at 37 °C. To determine all MICs, the measurements were independently repeated in triplicate.

5.4. Determination of the MICs of antibiotics in the presence of synergising compounds

Briefly, restoring enhancer concentrations were determined with an inoculum of $5x10^5$ CFU in 200 μL of MHB containing two-fold serial dilutions of each derivative in the presence of doxycycline at 2 μg/mL. The lowest concentration of the polyamine adjuvant that completely inhibited visible growth after incubation for 18 h at 37 °C was determined. These measurements were independently repeated in triplicate.

5.5. Cytotoxicity assays

The L6 cell line cytotoxicity assays were performed in 96-well microtiter plates, each well containing 100 μL of RPMI 1640 medium supplemented with 1% L-glutamine (200 mM) and 10% fetal bovine serum, and 4×10^4 L6 cells (a primary cell line derived from rat skeletal myoblasts). Serial drug dilutions of seven 3-fold dilution steps covering a

range from 90 to 0.123 μg/mL were prepared. After 72 h of incubation, the plates were inspected under an inverted microscope to assure growth of the controls and sterile conditions. Alamar Blue solution (10 μL) was then added to each well and the plates incubated for another 2 h. Then the plates were read with a Spectramax Gemini XS microplate fluorometer using an excitation wavelength of 536 nm and an emission wavelength of 588 nm. Data were analyzed using the microplate reader software Softmax Pro. Podophyllotoxin was the reference drug used.[32]

HEK293 cells were counted manually in a Neubauer haemocytometer and plated at a density of 5,000 cells/well into each well of the 384-well plates containing the 25x (2 μL) concentrated compounds. The medium used was Dulbecco's modified eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS). Cells were incubated together with the compounds for 20 h at 37 °C, 5% CO_2. To measure cytotoxicity, 5 μL (equals 100 μM final) of resazurin was added to each well after incubation, and incubated for further 3 h at 37 °C with 5% CO_2. After final incubation fluorescence intensity was measured as Fex 560/10 nm, em 590/10 nm ($F_{560/590}$) using a Tecan M1000 Pro monochromator plate reader. CC_{50} values (concentration at 50% cytotoxicity) were calculated by normalizing the fluorescence readout, with 74 μg/mL tamoxifen as negative control (0%) and normal cell growth as positive control (100%). The concentration-dependent percentage cytotoxicity was fitted to a dose response function (using Pipeline Pilot) and CC_{50} values determined.

5.6. Haemolytic assays

Human whole blood was washed three times with 3 volumes of 0.9% NaCl and then resuspended in same to a concentration of 0.5×10^8 cells/mL, as determined by manual cell count in a Neubauer haemocytometer. The washed cells were then added to the 384-well compound-containing plates for a final volume of 50 μL. After a 10 min shake on a plate shaker the plates were then incubated for 1 h at 37 °C. After incubation, the plates were centrifuged at 1,000g for 10 min to pellet cells and debris, 25 μL of the supernatant was then transferred to a polystyrene 384-well assay plate. Haemolysis was determined by measuring the supernatant absorbance at 405 mm (OD_{405}). The absorbance was measured using a Tecan M1000 Pro monochromator plate reader. HC_{10} and HC_{50} (concentration at 10% and 50% haemolysis, respectively) were calculated by curve fitting the inhibition values *vs.* log (concentration) using a sigmoidal dose-response function with variable fitting values for top, bottom and slope.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2021.116110.

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