pharmaceuticals

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Structure–Activity Relationship Studies of Indolglyoxyl-Polyamine Conjugates as Antimicrobials and Antibiotic Potentiators

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Abstract: Antibiotic resistance is a growing global health threat, requiring urgent attention. One approach to overcome antibiotic resistance is to discover and develop new antibiotic enhancers, molecules that work with legacy antibiotics to enhance their efficacy against resistant bacteria. Our previous screening of a library of purified marine natural products and their synthetic analogues led to the discovery of an indolglyoxyl-spermine derivative that exhibited intrinsic antimicrobial properties and was also able to potentiate the action of doxycycline towards the difficult to treat, Gram-negative bacterium *Pseudomonas aeruginosa*. A set of analogues have now been prepared, exploring the influence of indole substitution at the 5- and 7- positions and length of the polyamine chain on biological activity. While limiting cytotoxicity and/or hemolytic activities were observed for many analogues, two 7-methyl substituted analogues (**23b** and **23c**) were found to exhibit strong activity towards Gram-positive bacteria with no detectable cytotoxicity or hemolytic properties. Different molecular attributes were required for antibiotic enhancing properties, with one example identified, a 5-methoxy-substitiuted analogue (**19a**), as being a non-toxic, non-hemolytic enhancer of the action of two tetracycline antibiotics, doxycycline and minocycline, towards *P. aeruginosa*. These results provide further stimulation for the search for novel antimicrobials and antibiotic enhancers amongst marine natural products and related synthetic analogues.

Keywords: indole; potentiator; antimicrobial; polyamine; antibiotics; antifungal agents; structure–activity relationships

Citation: Cadelis, M.M.; Liu, T.; Sue, K.; Rouvier, F.; Bourguet-Kondracki, M.-L.; Brunel, J.M.; Copp, B.R. Structure–Activity Relationship Studies of Indolglyoxyl-Polyamine Conjugates as Antimicrobials and Antibiotic Potentiators. *Pharmaceuticals* **2023**, *16*, 823. https://doi.org/10.3390/ph16060823

Academic Editor: Noelia Duarte

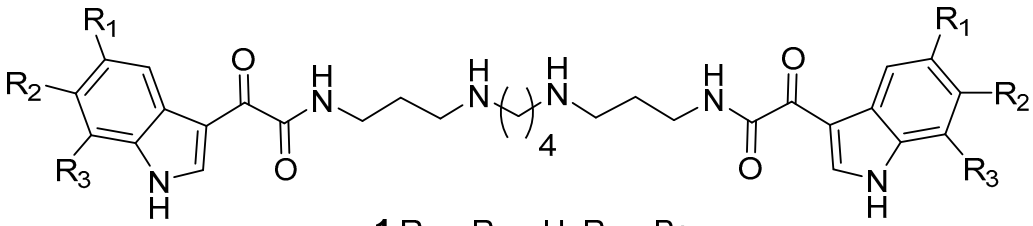
Received: 4 May 2023
Revised: 25 May 2023
Accepted: 29 May 2023
Published: 31 May 2023

1. Introduction

The global increase in microbial antibiotic resistance is a growing health threat, requiring urgent attention. With only limited numbers of new antibiotics being approved for clinical use [1–3] the search is on for novel strategies that can prove effective against drug-resistant pathogens. One option for treatment is to restore the antibiotic action of legacy antibiotics, requiring the discovery of antibiotic adjuvants or enhancers [4–8]. Marine natural products represent an excellent reservoir of small drug-like molecules from which to discover both new classes of antimicrobial agents [9–11] as well as antibiotic enhancers [8,12–14].

Our screening of a library of marine natural product-related α,ω-disubstituted spermine analogues for antimicrobial and antibiotic enhancing properties identified the 6-bromoindolglyoxyl derivative **1** (Figure 1) as a moderately active antimicrobial towards the Gram-positive bacteria *Staphylococcus aureus* ATCC 25923 (MIC 6.25 μM) and the fungus

Cryptococcus neoformans (MIC 1.1 μM). In addition, the combination of **1** with doxycycline exhibited a strong antibiotic enhancement effect towards the Gram-negative bacterium *Pseudomonas aeruginosa* [15]. Interest in these activities was somewhat tempered by the observation of associated cytotoxicity (human embryonic kidney cell line HEK293, IC_{50} 5.1 μM; rat skeletal myoblast cell line L6, IC_{50} 7.7 μM), prompting the search for less toxic analogues. Subsequent studies identified the requirement of substitution on the indole ring for activity, with **2** being inactive as an antimicrobial or antibiotic enhancer, and that some examples of 5- and 7- substituted analogues (**3**–**8**), notably including halogen, methoxy or methyl functionality, exhibited more modest antimicrobial activities (Table 1), were moderate to excellent antibiotic enhancers (Table 2) and were generally less cytotoxic and non-hemolytic (Table 3) [16].



1 $R_1 = R_3 = H$, $R_2 = Br$
2 $R_1 = R_2 = R_3 = H$
3 $R_1 = Br$, $R_2 = R_3 = H$
4 $R_1 = OMe$, $R_2 = R_3 = H$
5 $R_1 = Me$, $R_2 = R_3 = H$
6 $R_1 = R_2 = H$, $R_3 = F$
7 $R_1 = R_2 = H$, $R_3 = OMe$
8 $R_1 = R_2 = H$, $R_3 = Me$

Figure 1. Structures of indolglyoxyl spermine derivatives.

Taken together, these studies enabled the identification of the structural requirements for antibiotic enhancement properties amongst a limited set of indolglyoxyl-spermine conjugates, summarized in Figure 2.

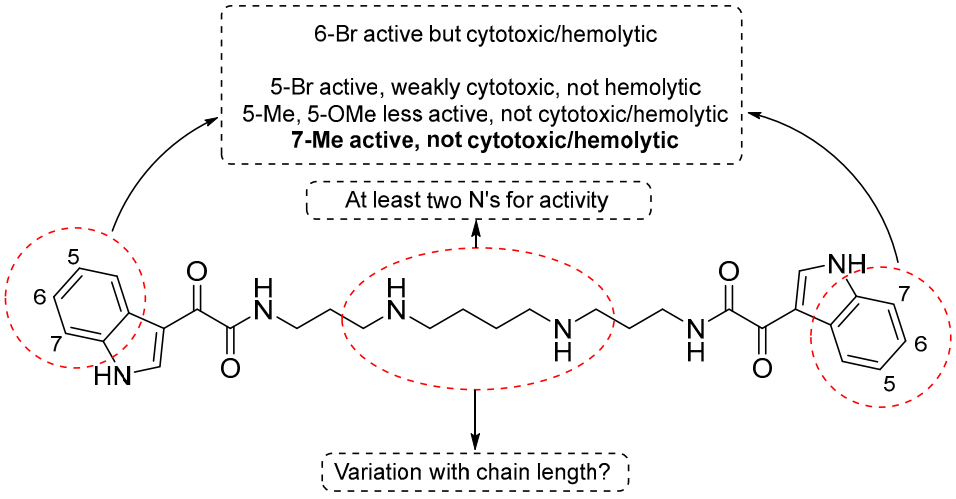


Figure 2. Antibiotic enhancement structure–activity relationship for indolglyoxyl spermine derivatives.

A component of the structure–activity relationship yet to be addressed in this compound series is the effect, if any, of variation in the polyamine (PA) chain length on intrinsic antimicrobial, antibiotic enhancement and cytotoxicity/hemolysis biological activities. Previous studies investigating disubstituted polyamine-bearing arylacyl [17] head groups

identified that changes in the chain length of the core polyamine fragment can lead to wide variation in antimicrobial and/or antibiotic enhancing properties. Herein we report details on the synthesis of a new set of indolglyoxyl-polyamine conjugates that vary in substitution at the 5- and 7- positions on the indole ring and that vary in polyamine chain length, and the abilities of these analogues to exhibit intrinsic antimicrobial properties and to potentiate the activity of doxycycline towards the Gram-negative bacteria *Pseudomonas aeruginosa*.

2. Results and Discussion

2.1. Chemistry

The Boc-protected polyamine scaffolds used in this study were the five examples **9a–e** covering core chain lengths of 6, 7, 8, 10 and 12 methylenes (Figure 3). The preparation of **9a–e** has been previously described [18–21].

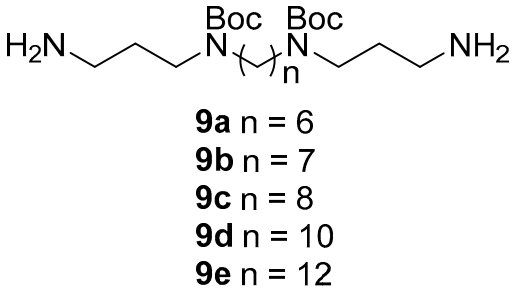


Figure 3. Polyamine scaffolds **9a–e**.

The indole-3-glyoxyl head groups used in the current study (**10–16**) (Figure 4) were the same set previously explored in analogues **2–8** [16]. Syntheses of **10–15**, as either the glyoxylic acid or glyoxylchloride, have been previously reported [22–25].

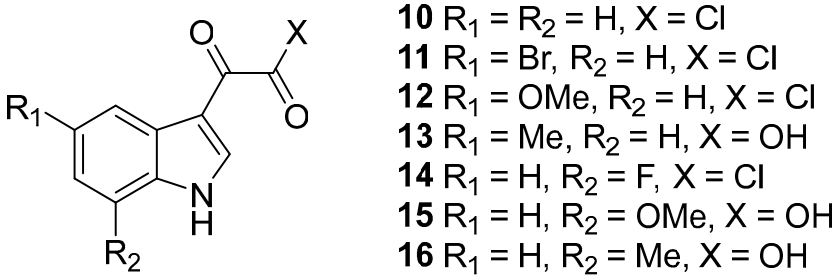
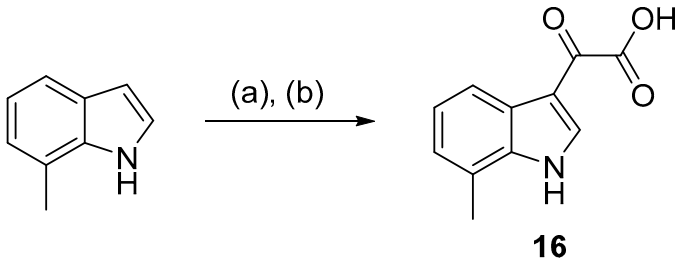


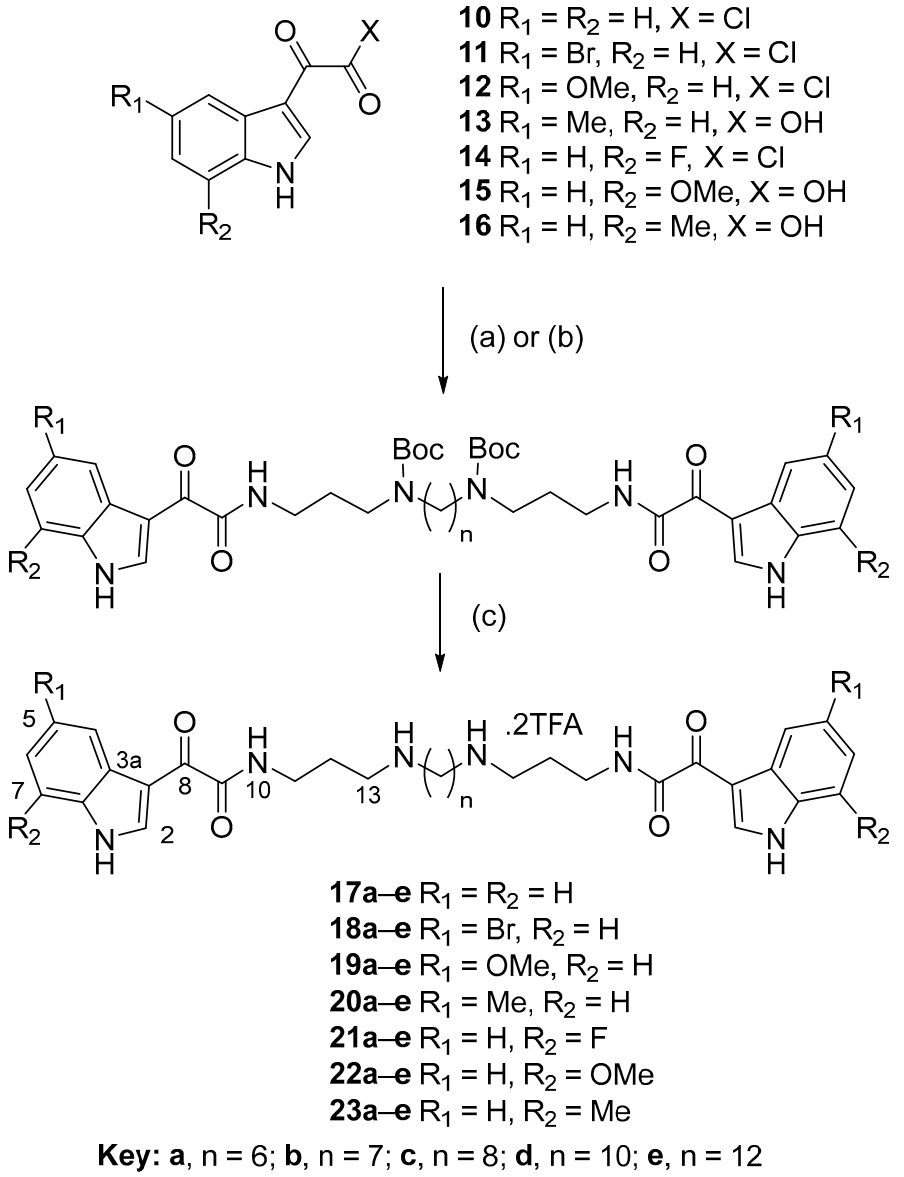
Figure 4. Indole-3-glyoxyl head groups **10–16**.

In the case of the 7-methyl analogue **16,** it was prepared using the two-step protocol shown in Scheme 1. Reaction of 7-methyl-1*H*-indole with excess oxalyl chloride afforded the oxalylchloride intermediate which was not isolated but hydrolyzed by heating with saturated aq. $NaHCO_3$ solution to afford 2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**16**) (Figure S1) in 95% yield over two steps.



Scheme 1. Synthesis of 2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**16**). Reagents and conditions: (**a**) oxalyl chloride, Et_2O, 0 °C, 1.5 h; and (**b**) saturated aq. $NaHCO_3$, reflux, 2 h (95% over two steps).

The reaction of indole-3-glyoxyl chlorides **10**–**12** and **14** directly with Boc-protected polyamines **9a**–**e**, or glyoxylic acids **13**, **15** and **16** with **9a**–**e** utilizing the coupling reagent PyBOP (benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate) afforded a set of intermediate products that were then deprotected with 2,2,2-trifluoroacetic acid (TFA) to afford the desired compounds as their di-TFA salts (Scheme 2, Figures S2–S30).



Scheme 2. Synthetic route to target indolglyoxylpolyamine conjugates **17**–**23**. *Reagents and conditions*: (**a**) for glyoxylchlorides **10**–**12**, **14**: DMF, DIPEA, polyamine **9a**–**e**, r.t., 48 h (16–56%); (**b**) for glyoxylic acids **13**, **15**, **16**: DMF, PyBOP, DIPEA, polyamine **9a**–**e**, r.t., N_2, 24 h (13–97%); and (**c**) TFA (0.2 mL) in CH_2Cl_2 (2 mL), N_2, 2 h (19–100%).

2.2. Biological Evaluation

The antimicrobial activity of the series was evaluated against a range of bacterial strains (*S. aureus*, MRSA, *P. aeruginosa* and *Escherichia coli*) and the fungus *Candida albicans* (Table 1). Cytotoxicity towards HEK293 (human kidney epithelial cell line, IC_{50}) and hemolytic activity against human red blood cells (HC_{10}) were also determined.

Table 1. Antimicrobial (MIC), cytotoxicity (IC_{50}) and hemolytic (HC_{10}) activities (μM) of analogues **2–8**, **17–23**.

Compound	*S. a* [a]	*MRSA* [b]	*P. a* [c]	*E. c* [d]	*C. a* [e]	*Cyto.* [f]	*Hem.* [g]
2	>100 [h]	41.4	>100 [h]	>100 [h]	>41.4 [h]	>41 [h]	>41
3	3.125 [h]	4.32	50 [h]	25 [h]	>34.4 [h]	14 [h]	>34
4	100 [h]	38.4	>200 [h]	>200 [h]	>38.4 [h]	>38 [h]	>38
5	25 [h]	20.0	100 [h]	200 [h]	>40.0 [h]	>40 [h]	>40
6	25 [h]	19.8	200 [h]	200 [h]	>39.6 [h]	19 [h]	>40
7	15 [h]	38.4	>200 [h]	>200 [h]	38.4 [h]	27 [h]	>38
8	25 [h]	20.0	>200 [h]	>200 [h]	>40.0 [h]	>40 [h]	>40
17a	12.5	>40	>200	50	>40	n.d [i]	n.d
17b	25	39	>200	25	>39	31	>39
17c	25	39	100	12.5	>39	10	>39
17d	14.6	18.7	117	117	37	4.9	>37
17e	25	9.04	>200	>200	36	5.6	>36
18a	1.56	4.17	50	6.25	16.7	8.9	>33
18b	6.4	4.1	51	51	16	13	>33
18c	25	8.1	>200	>200	32	18	>32
18d	6.16	7.88	200	98	32	16	>32
18e	5.99	3.84	96	24	31	8.6	20
19a	29	>37	>200	>200	>37	>37	>37
19b	57	37	>200	>200	37	>37	>37
19c	>100	>36	>100	>100	36	18	26
19d	12.5	17.4	>200	50	35	6.8	>35
19e	12.5	34	>200	100	34	8.6	>34
20a	12.5	≤0.30	200	50	>39	>39	n.d.
20b	6.25	≤0.30	200	50	>38	n.d.	>38
20c	3.125	4.7	800	12.5	>37	>37	n.d.
20d	3.125	≤0.28	800	12.5	9.0	>36	n.d.
20e	3.125	n.d.	800	12.5	2.2	n.d.	2.0
21a	7.5	19.1	240	240	>38	12	>38 [e]
21b	7.3	18.8	>200	>200	38	11	>38
21c	29	18.5	>200	>200	>37	9.2	>37
21d	3.125	4.48	>200	6.25	36	4.7	>36
21e	27.2	4.34	>220	>220	35	6.4	>35
22a	50	>37	800	400	>37	>37	>37
22b	25	>37	800	200	>37	8.9	>37
22c	25	4.5	800	200	>36	n.d.	>36
22d	25	≤0.27	800	50	17	>35	8.4
22e	3.125	≤0.26	800	12.5	≤0.26	n.d.	0.93
23a	30.2	≤0.30	>240	60	>39	>39	>39
23b	14.8	≤0.30	>240	120	>38	>38	>38
23c	7.3	≤0.29	>230	29	>37	>37	>37
23d	7.1	≤0.28	>230	14.1	18	>36	n.d.
23e	6.85	≤0.27	>220	13.7	≤0.27	>35	8.4

[a] *S. aureus* ATCC 25923 with streptomycin (MIC 21.5 μM) and chloramphenicol (MIC 1.5–3 μM) used as positive controls and values presented as the mean (n = 3); [b] MRSA ATCC 43300 with vancomycin (MIC 0.7 μM) used as a positive control and values presented as the mean (n = 2); [c] *P. aeruginosa* ATCC 27853 with streptomycin

(MIC 21.5 μM) and colistin (MIC 1 μM) used as positive controls and values presented as the mean (n = 3); [d] *E. coli* ATCC 25922 with streptomycin (MIC 21.5 μM) and colistin (MIC 2 μM) used as positive controls and values presented as the mean (n = 3); [e] *C. albicans* ATCC 90028 with fluconazole (MIC 0.4 μM) as a positive control and values presented as the mean (n = 2); [f] Concentration of compound at 50% cytotoxicity on HEK293 (human embryonic kidney cells) with tamoxifen as the positive control (IC_{50} 24 μM) and values presented as the mean (n = 2); [g] Concentration of compound at 10% hemolytic activity on human red blood cells with melittin as the positive control (HC_{10} 0.95 μM) and values presented as the mean (n = 2); [h] Data taken from Cadelis et al. [16]; [i] n.d., not determined.

In general, the compound set exhibited more pronounced activity towards the Gram-positive bacteria *S. aureus* ATCC 25923 and MRSA, with only poor or no activity towards Gram-negative bacteria *P. aeruginosa* and *E. coli* and the fungus *C. albicans*. Amongst the more active examples identified were the 5-bromo substituted analogues **18a–e** with *S. aureus* and MRSA MIC 1.6–7.8 μM, 5-methyl analogues **20a–d** (MIC $\leq$ 0.28–6.25 μM), 7-methoxy analogue **22e** (MIC $\leq$ 0.26–3.125 μM), and 7-methyl substituted variants **23c–e** (MIC $\leq$ 0.27–7.3 μM). In many cases, those analogues that exhibited good levels of antimicrobial activity also unfortunately demonstrated cytotoxicity and/or hemolytic activity. There were some examples identified, however, that were devoid of these detrimental properties including the 7-methyl substituted analogues **23b** (MIC MRSA $\leq$ 0.30 μM, cytotoxicity IC_{50} > 38 μM, hemolysis HC_{10} > 38 μM) and **23c** (MIC MRSA $\leq$ 0.29 μM, cytotoxicity IC_{50} > 37 μM, hemolysis HC_{10} > 37 μM). Overall, the discovery of Gram-positive antibacterial activity for **23b** and **23c** with low to no cytotoxicity and hemolytic activity suggests a narrow structure–activity requirement of 7-methyl substitution and polyamine mid-chain length of 7 (PA3-7-3) or 8 (PA3-8-3) carbons for optimal activity.

The set of compounds were next evaluated for the ability to potentiate the activity of the antibiotic doxycycline towards the Gram-negative bacteria *P. aeruginosa* ATCC 27853 (Table 2). In these assays, doxycycline is present at a concentration of 2 μg/mL (4.5 μM), well below the observed MIC of 20 μg/mL (50 μM) towards this drug-resistant human pathogen.

Table 2. Doxycycline potentiation activity (MIC, μM) of analogues **2**–**8**, **17**–**23**.

Compound	Conc (μM) for Potentiation [a]	Compound	Conc (μM) for Potentiation [a]
2	>50 [b]	**20a**	12.5
3	3.125 [b]	**20b**	12.5
4	12.5 [b]	**20c**	400
5	6.25 [b]	**20d**	400
6	3.125 [b]	**20e**	400
7	3.75 [b]	**21a**	3.7
8	6.25 [b]	**21b**	7.3
17a	12.5	**21c**	58
17b	100	**21d**	100
17c	50	**21e**	>200
17d	58	**22a**	100
17e	6.25	**22b**	100
18a	6.5	**22c**	200
18b	12.9	**22d**	400
18c	>200	**22e**	400
18d	25	**23a**	60
18e	24	**23b**	240
19a	7.3	**23c**	230
19b	114	**23d**	230

Table 2. *Cont.*

Compound	Conc (μM) for Potentiation [a]	Compound	Conc (μM) for Potentiation [a]
19c	25	**23e**	220
19d	>200		
19e	>200		

[a] Concentration (μM) required to restore doxycycline activity at 2 μg/mL (4.5 μM) against *P. aeruginosa* ATCC 27853; [b] Data taken from Cadelis et al. [16].

Strong antibiotic enhancing activities were observed for the PA3-6-3 analogues **18a** (5-bromo, MIC 6.5 μM), **19a** (5-methoxy, MIC 7.3 μM) and **21a** (7-fluoro, MIC 3.7 μM), the 7-fluoro substituted PA3-7-3 analogue **21b** (MIC 7.3 μM), and the unsubstituted indolglyoxyl-PA3-12-3 analogue **17e** (MIC 6.25 μM).

A closer investigation of the ability of the 5-methoxy-indolglyoxyl-PA3-6-3 analogue **19a** to enhance the action of other antibiotics towards *P. aeruginosa* identified it to be capable of reactivating another tetracycline antibiotic minocycline (MIC 14.5 μM), was only a weak activator of chloramphenicol (MIC 58 μM) and could not restore the activity of erythromycin or nalidixic acid (Table 3).

Table 3. Antibiotic potentiating activity of **19a**.

Antibiotic	Concentration (μM) for Potentiation against *P. aeruginosa* [a]
No antibiotic	>200
Minocycline	14.5
Erythromycin	>200
Chloramphenicol	58
Nalidixic acid	>200

All values presented as the mean (n = 3). [a] Concentration (μM) of compound **19a** required to restore antibiotic activity at 2 μg/mL concentration of antibiotic. *P. aeruginosa* ATCC 27853 against minocycline (MIC 70 μM), erythromycin (MIC >200 μM), chloramphenicol (MIC >200 μM) and nalidixic acid (MIC >200 μM).

The spectrum of antibiotic potentiating activity of the 7-fluoro analogue **21a** was also investigated, evaluating its ability to enhance other antibiotics against other Gram-negative bacteria (Table 4). The polyamine-conjugate was able to restore the action of doxycycline against *E. coli* (MIC 1.56 μM) and to a lesser degree against *Acinetobacter baumannii* (MIC 12.5 μM). Of the other combinations examined, **21a** was also found to weakly enhance the action of chloramphenicol and nalidixic acid towards *P. aeruginosa*. We have observed similar levels of drug-organism antibiotic enhancement for other examples of indolglyoxyl-polyamines [16].

Table 4. Antibiotic potentiating activity of **21a**.

Antibiotic	Concentration (μM) for Potentiation [a]			
	P. aeruginosa [b]	*E. coli* [c]	*K. pneumoniae* [d]	*A. baumannii* [e]
No antibiotic	200	>200	>200	100
Doxycycline	3.125	1.56	200	12.5
Erythromycin	100	200	>200	100
Chloramphenicol	25	>200	>200	200
Nalidixic acid	25	200	>200	200

All values presented as the mean (n = 3). [a] Concentration (μM) of compound **21a** required to restore antibiotic activity at 2 μg/mL concentration of antibiotic; [b] *P. aeruginosa* ATCC 27853 against doxycycline (MIC 50 μM), erythromycin (MIC > 200 μM), chloramphenicol (MIC > 200 μM) and nalidixic acid (MIC > 200 μM); [c] *E. coli* ATCC 25922 against doxycycline (MIC 25 μM), erythromycin (MIC >200 μM), chloramphenicol (MIC > 200 μM) and nalidixic acid (MIC > 200 μM); [d] *Klebsiella pneumoniae* ST258 against doxycycline (MIC 25 μM), erythromycin (MIC > 200 μM), chloramphenicol (MIC 50 μM) and nalidixic acid (MIC 100 μM); [e] *A. baumannii* AYE against doxycycline (MIC 12.5 μM), erythromycin (MIC 200 μM), chloramphenicol (MIC > 200 μM) and nalidixic acid (MIC > 200 μM).

3. Materials and Methods

3.1. Chemistry: General Remarks

Infrared spectra were recorded on a Perkin-Elmer spectrometer 100 Fourier-transform infrared spectrometer (Perkin-Elmer, MA, USA) equipped with a universal ATR accessory. Mass spectra were acquired on a Bruker micrOTOF Q II spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 298 K on a Bruker (Karlsruhe, Germany) AVANCE 400 spectrometer using standard pulse sequences. Proto-deutero solvent signals were used as internal references (DMSO-d_6: δ_H 2.50, δ_C 39.52). For ^{1}H NMR, the data are quoted as position (δ), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, dt = doublet of triplet, tt = triplet of triplet, m = multiplet), 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) or Merck LiChroprep RP-8 (40–63 μm) (Merck Millipore, Darmstadt, Germany). Thin-layer chromatography was conducted on Merck DC Kieselgel 60 RP-18 F254S plates. 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. Protected polyamines di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl)carbamate) (**9a**), di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl)carbamate) (**9b**), di-*tert*-butyl octane-1,8-diylbis((3-aminopropyl)carbamate) (**9c**), di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl)carbamate) (**9d**), and di-*tert*-butyl dodecane-1,12-diylbis((3-aminopropyl)carbamate) (**9e**) [18–21], 2-(1*H*-indol-3-yl)-2-oxoacetyl chloride (**10**) [22], 2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetyl chloride (**11**) [16], 2-(5-methoxy-1*H*-indol-3-yl)-2-oxoacetyl chloride (**12**) [23], 2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**13**) [24], 2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetyl chloride (**14**) [5], 2-(7-methoxy-1*H*-indol-3-yl)-2-oxoacetic acid (**15**) [25], and polyamine conjugates (**17c**/**17e**/**19c**/**19e**/**22c**/**22e**) [25] were synthesized using procedures from the literature.

3.1.1. General Procedure A—Coupling of 3-Indolglyoxylyl Chlorides with Boc-Protected Polyamine

To a solution of 3-indolglyoxylyl chloride (2 equiv.) in DMF (1 mL) was added DIPEA (6 equiv.) and Boc-protected polyamine **9a**–**e** (1 equiv.) in DMF (1 mL). The reaction mixture was stirred for 48 h before solvent removal under reduced pressure. The crude product was purified using silica gel flash column chromatography (3% MeOH:CH_2Cl_2).

3.1.2. General Procedure B—Boc Deprotection

A solution of *tert*-butyl-carbamate derivative in CH_2Cl_2 (2 mL) and TFA (0.2 mL) was stirred at room temperature under N_2 for 2 h followed by solvent removal under reduced pressure. The crude product was purified using C_8 reversed-phase flash column chromatography (0%–50% MeOH/H_2O (+0.05% TFA)) to afford the product as a di-TFA salt.

3.1.3. General procedure C—Coupling of Indole-Oxoacetic Acids with Boc-Protected Polyamine

To a solution of indole-oxoacetic acid (2 equiv.) and PyBOP (2 equiv.) in DMF (1 mL) was added DIPEA (3.5 equiv.) and Boc-protected polyamine **9a**–**e** (1 equiv.) in DMF (1 mL). The reaction mixture was stirred for 24 h under N_2 at room temperature before the solvent was removed under reduced pressure. The crude product was purified using silica gel flash column chromatography (1–4% MeOH:CH_2Cl_2).

3.2. Synthesis of Compounds

3.2.1. 2-(7-Methyl-1*H*-indol-3-yl)-2-oxoacetic Acid (**16**)

Oxalyl chloride (0.69 mL, 8.0 mmol) was added dropwise at 0 °C to 7-methyl-1*H*-indole (0.35 g, 2.7 mmol) in anhydrous diethyl ether (10 mL) and the solution stirred for 1.5 h. Saturated aq. $NaHCO_3$ (10 mL) was then added, and the solution heated at reflux for 2 h. After cooling to room temperature, 10% aq. HCl was added to adjust the pH to 1.

The resulting yellow precipitate was filtered, washed with cold diethyl ether (10 mL) and dried under vacuum, affording 2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**16**) as a yellow solid (0.52 g, 95%). The product was used in the next step without further purification. R_f (MeOH:10% HCl, 3:1) 0.57; m.p. 206 °C (decomp); IR ν_{max} (ATR) 3320, 2944, 2832, 1625, 1448, 1112, 1028 cm^{-1}; ^{1}H NMR, (DMSO-d_6, 400 MHz) δ 12.37 (1H, br s, NH-1), 8.37 (1H, d, *J* = 3.4 Hz, H-2), 8.01 (1H, d, *J* = 7.9 Hz, H-4), 7.16 (1H, t, *J* = 7.6 Hz, H-5), 7.08 (1H, d, *J* = 7.3 Hz, H-6), 2.51 (3H, s, Me), OH not observed; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 180.9 (C-8), 165.3 (C-9), 137.5 (C-2), 136.1 (C-7a), 125.4 (C-3a), 124.3 (C-6), 122.9 (C-5), 122.1 (C-7), 118.7 (C-4), 112.7 (C-3), 16.7 (Me); (−)-HRESIMS $[M-H]^-$ *m/z* 202.0514 (calcd for $C_{11}H_8NO_3$, 202.0510).

3.2.2. N^1,N^6-Bis(3-(2-(1*H*-indol-3-yl)-2-oxoacetamido)propyl)hexane-1,6-diaminium 2,2,2-trifluoroacetate (**17a**)

Using general procedure A, 2-(1*H*-indol-3-yl)-2-indoloxoacetyl chloride (**10**) (0.048 g, 0.24 mmol) was reacted with di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl)carbamate) (**9a**) (0.050 g, 0.12 mmol) and DIPEA (0.13 mL, 0.74 mmol) to afford di-*tert*-butyl hexane-1,6-diylbis((3-(2-(1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow gum (0.045 g, 48%). Using general procedure B, a sub-sample of this product (0.040 g, 0.05 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **17a** as a pale-yellow oil (0.018 g, 45%). R_f (MeOH/10% HCl, 7:3) 0.63; IR (ATR) ν_{max} 3389, 2949, 2838, 1713, 1663, 1342, 1333, 1204, 1031 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.26 (2H, br s, NH-1), 8.89 (2H, t, *J* = 6.0 Hz, NH-10), 8.76 (2H, d, *J* = 3.3 Hz, H-2), 8.32 (4H, br s, NH_2-14), 8.24–8.22 (2H, m, H-4), 7.55–7.53 (2H, m, H-7), 7.28–7.25 (4H, m, H-5, H-6), 3.35–3.26 (4H, obscured, H_2-11), 2.96–2.86 (8H, m, H_2-13, H_2-15), 1.88–1.81 (4H, m, H_2-12), 1.58–1.53 (4H, m, H_2-16), 1.33–1.30 (4H, m, H_2-17); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.8 (C-9), 138.5 (C-2), 136.3 (C-7a), 126.2 (C-3a), 123.6 (C-6), 123.7 (C-5), 121.2 (C-4), 112.6 (C-7), 112.1 (C-3), 46.7 (C-15), 44.8 (C-13), 35.8 (C-11), 25.7, 25.5, 25.4 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 573.3190 (calcd for $C_{32}H_{41}N_6O_4$, 573.3184).

3.2.3. N^1,N^7-Bis(3-(2-(1*H*-indol-3-yl)-2-oxoacetamido)propyl)heptane-1,7-diaminium 2,2,2-trifluoroacetate (**17b**)

Using general procedure A, 2-(1*H*-indol-3-yl)-2-oxoacetyl chloride (**10**) (0.072 g, 0.35 mmol) was reacted with di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl)carbamate) (**9b**) (0.078 g, 0.17 mmol) and DIPEA (0.18 mL, 1.03 mmol) to afford di-*tert*-butyl heptane-1,7-diylbis((3-(2-(1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow oil (0.046 g, 33%). Using general procedure B, a sub-sample of this product (0.010 g, 0.013 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **17b** as an orange oil (0.011 g, 100%). R_f (MeOH/10% HCl, 7:3) 0.64; IR (ATR) ν_{max} 3269, 2865, 1677, 1627, 1495, 1438 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.36 (2H, s, NH-1), 8.87 (2H, t, *J* = 6.1 Hz, NH-10), 8.76 (2H, s, H-2), 8.65 (4H, br s, NH_2-14), 8.24–8.22 (2H, m, H-4), 7.57–7.53 (2H, m, H-7), 7.29–7.23 (2H, m, H-5, H-6), 3.31 (4H, m, H_2-11), 2.92–2.88 (8H, m, H_2-13, H_2-15), 1.88–1.85 (4H, m, H_2-12), 1.57 (4H, br s, H_2-16), 1.28–1.23 (6H, m, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.8 (C-8), 163.8 (C-9), 138.5 (C-2), 136.3 (C-7a), 126.2 (C-3a), 123.5 (C-6), 122.6 (C-5), 121.3 (C-4), 112.6 (C-7), 112.1 (C-3), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 28.0 (C-18), 25.8, 25.7, 25.4 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 587.3344 (calcd for $C_{33}H_{43}N_6O_4$, 587.3340).

3.2.4. N^1,N^{10}-Bis(3-(2-(1*H*-indol-3-yl)-2-oxoacetamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**17d**)

Using general procedure A, 2-(1*H*-indol-3-yl)-2-oxoacetyl chloride (**10**) (0.073 g, 0.36 mmol) was reacted with di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl)carbamate) (**9d**) (0.084 g, 0.17 mmol) and DIPEA (0.19 mL, 1.1 mmol) to afford di-*tert*-butyl decane-1,10-diylbis((3-(2-(1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a dark yellow oil (0.056 g, 40%). Using general procedure B, a sub-sample of this product (0.016 g, 0.019 mmol) was reacted

with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **17d** as a yellow oil (0.011 g, 66%). R_f (MeOH/10% HCl, 7:3) 0.60; IR (ATR) ν_{max} 3410, 2844, 2677, 1630, 1494, 1441 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.29 (2H, s, NH-1), 8.89 (2H, t, *J* = 6.0 Hz, NH-10), 8.76 (2H, d, *J* = 2.6 Hz, H-2), 8.41 (4H, br s, NH_2-14), 8.24–8.22 (2H, m, H-4), 7.55–7.53 (2H, m, H-7), 7.29–7.25 (4H, m, H-5, H-6), 3.30–3.27 (4H, obscured, H_2-11), 2.98–2.84 (8H, m, H_2-13, H_2-15), 1.88–1.81 (4H, m, H_2-12), 1.57–1.53 (4H, m, H_2-16), 1.24 (12H, br s, H_2-17, H_2-18, H_2-19); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.7 (C-9), 138.5 (C-2), 136.2 (C-7a), 126.2 (C-3a), 123.5 (C-6), 122.6 (C-5), 121.2 (C-4), 112.6 (C-7), 112.1 (C-3), 46.8 (C-15), 44.7 (C-13), 35.8 (C-11), 28.7, 28.5 (C-18, C-19), 25.9, 25.7, 25.5 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 629.3804 (calcd for $C_{36}H_{49}N_6O_4$, 629.3810).

3.2.5. N^1,N^6-Bis(3-(2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetamido)propyl)hexane-1,6-diaminium 2,2,2-trifluoroacetate (**18a**)

Using general procedure A, 2-(5-bromo-1*H*-indol-3-yl)-2-indoloxoacetyl chloride (**11**) (0.067 g, 0.24 mmol) was reacted with di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl)carbamate) (**9a**) (0.050 g, 0.12 mmol) and DIPEA (0.13 mL, 0.74 mmol) to afford di-*tert*-butyl hexane-1,6-diylbis((3-(2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a pale yellow gum (0.030 g, 27%). Using general procedure B, this product (0.030 g, 0.03 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **18a** as a pale-yellow oil (0.006 g, 19%). R_f (MeOH/10% HCl, 7:3) 0.38; IR (ATR) ν_{max} 3434, 1672, 1627, 1433, 1293, 1202, 1137, 1028, 721 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.48 (2H, br s, NH-1), 8.91 (2H, t, *J* = 6.0 Hz, NH-10), 8.80 (2H, s, H-2), 8.45 (4H, br s, NH_2-14), 8.35 (2H, d, *J* = 2.0 Hz, H-4), 7.53 (2H, d, *J* = 8.5 Hz, H-7), 7.42 (2H, dd, *J* = 8.5, 2.0 Hz, H-6), 3.34–3.29 (4H, obscured, H_2-11), 2.97–2.86 (8H, m, H_2-13, H_2-15), 1.85 (4H, tt, *J* = 8.5, 8.5 Hz, H_2-12), 1.56 (4H, br s, H_2-16), 1.31 (4H, br s, H_2-17); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.3 (C-9), 139.5 (C-2), 135.1 (C-7a), 128.0 (C-3a), 126.1 (C-6), 123.3 (C-4), 115.4 (C-5), 114.7 (C-7), 111.6 (C-3), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 25.7, 25.5, 25.4 (C-12, C-16, C-17); (+)-HRESIMS $[M+Na]^+$ *m/z* 751.1230 (calcd for $C_{32}H_{38}{}^{79}Br_2N_6NaO_4$, 751.1213), 753.1199 (calcd for $C_{32}H_{38}{}^{79}Br^{81}BrN_6NaO_4$, 753.1196), 755.1197 (calcd for $C_{32}H_{38}{}^{81}Br_2N_6NaO_4$, 755.1183).

3.2.6. N^1,N^7-Bis(3-(2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetamido)propyl)heptane-1,7-diaminium 2,2,2-trifluoroacetate (**18b**)

Using general procedure A, 2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetyl chloride (**11**) (0.089 g, 0.31 mmol) was reacted with di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl)carbamate) (**9b**) (0.069 g, 0.15 mmol) and DIPEA (0.16 mL, 0.92 mmol) to afford di-*tert*-butyl heptane-1,7-diylbis((3-(2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as an orange oil (0.027 g, 17%). Using general procedure B, a sub-sample of this product (0.010 g, 0.010 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **18b** as a yellow oil (0.009 g, 80%). R_f (MeOH/10% HCl, 7:3) 0.35; IR (ATR) ν_{max} 3422, 2955, 2839, 1680, 1434 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.48 (2H, d, *J* = 2.8 Hz, NH-1), 8.91 (2H, t, *J* = 6.0 Hz, NH-10), 8.80 (2H, d, *J* = 2.8, H-2), 8.44 (4H, br s, NH_2-14), 8.35 (2H, d, *J* = 2.0 Hz, H-4), 7.53 (2H, d, *J* = 8.8 Hz, H-7), 7.42 (2H, dd, *J* = 8.8, 2.0 Hz, H-6), 3.30 (4H, dt, *J* = 6.4, 6.4 Hz, H_2-11), 2.93–2.89 (8H, m, H_2-13, H_2-15), 1.88–1.81 (4H, m, H_2-12), 1.56 (4H, br s, H_2-16), 1.29–1.23 (6H, m, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.3 (C-9), 139.5 (C-2), 135.1 (C-7a), 128.0 (C-3a), 126.1 (C-6), 123.3 (C-4), 115.4 (C-5), 114.7 (C-7), 111.6 (C-3), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 28.0 (C-18), 25.8, 25.7, 25.4 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 743.1570 (calcd for $C_{33}H_{41}{}^{79}Br_2N_6O_4$, 743.1551), 745.1555 (calcd for $C_{33}H_{41}{}^{79}Br^{81}BrN_6O_4$, 745.1533), 747.1544 (calcd for $C_{33}H_{41}{}^{81}Br_2N_6O_4$, 747.1521).

3.2.7. N^1,N^8-Bis(3-(2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetamido)propyl)octane-1,8-diaminium 2,2,2-trifluoroacetate (**18c**)

Using general procedure A, 2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetyl chloride (**11**) (0.072 g, 0.25 mmol) was reacted with di-*tert*-butyl octane-1,8-diylbis((3-aminopropyl)carbamate) (**9c**) (0.055 g, 0.12 mmol) and DIPEA (0.12 mL, 0.66 mmol) to afford di-*tert*-butyl octane-

1,8-diylbis((3-(2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a brown oil (0.035 g, 30%). Using general procedure B, a sub-sample of this product (0.020 g, 0.021 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **18c** as a brown oil (0.0048 g, 23%). R_f (MeOH/10% HCl, 7:3) 0.32; IR (ATR) ν_{max} 3056, 2163, 1978, 1711, 1677, 1433, 1360, 1265, 1203, 1141, 1058, 738, 704 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.46 (2H, s, NH-1), 8.93 (2H, t, *J* = 6.1 Hz, NH-10), 8.82 (2H, br s, H-2), 8.37 (2H, d, *J* = 2.0 Hz, H-4), 8.36 (4H, br s, NH_2-14), 7.55 (2H, d, *J* = 8.9 Hz, H-7), 7.44 (2H, dd, *J* = 8.6, 1.8 Hz, H-6), 3.30 (4H, obscured, H_2-11), 2.94–2.89 (8H, m, H_2-13, H_2-15), 1.86–1.83 (4H, m, H_2-12), 1.55–1.53 (4H, br s, H_2-16), 1.26–1.23 (8H, m, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.3 (C-9), 139.5 (C-2), 135.0 (C-7a), 128.0 (C-3a), 126.1 (C-6), 123.3 (C-4), 115.4 (C-5), 114.8 (C-7), 111.6 (C-3), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 28.3 (C-18), 25.8, 25.7, 25.5 (C-12, C-16, C-17); (+)-HRESIMS $[M+Na]^+$ *m/z* 779.1548 (calcd $C_{34}H_{42}{}^{79}Br_2N_6NaO_4$, 779.1526), 781.1513 (calcd $C_{34}H_{42}{}^{79}Br^{81}BrN_6NaO_4$, 781.1509), 783.1497 (calcd $C_{34}H_{42}{}^{81}Br_2N_6NaO_4$, 783.1497).

3.2.8. N^1,N^{10}-Bis(3-(2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**18d**)

Using general procedure A, 2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetyl chloride (**11**) (0.083 g, 0.29 mmol) was reacted with di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl)carbamate) (**9d**) (0.068 g, 0.14 mmol) and DIPEA (0.15 mL, 0.86 mmol) to afford di-*tert*-butyl decane-1,10-diylbis((3-(2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as an orange oil (0.042 g, 30%). Using general procedure B, a sub-sample of this product (0.026 g, 0.026 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **18d** as a brown oil (0.007 g, 34%). R_f (MeOH/10% HCl, 7:3) 0.34; IR (ATR) ν_{max} 3023, 1676, 1438, 1203, 1030, 721 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.46 (2H, d, *J* = 2.1 Hz, NH-1), 8.91 (2H, t, *J* = 5.9 Hz, NH-10), 8.80 (2H, s, H-2), 8.35 (4H, br s, NH_2-14), 8.35 (2H, d, *J* = 2.0 Hz, H-4), 7.53 (2H, d, *J* = 8.6 Hz, H-7), 7.42 (2H, dd, *J* = 8.5, 2.1 Hz, H-6), 3.30 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.97–2.84 (8H, m, H_2-13, H_2-15), 1.84 (4H, tt, *J* = 7.6, 7.6 Hz, H_2-12), 1.55 (4H, br s, H_2-16), 1.24 (12H, br s, H_2-17, H_2-18, H_2-19); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.3 (C-9), 139.5 (C-2), 135.1 (C-7a), 128.0 (C-3a), 126.1 (C-6), 123.3 (C-4), 115.4 (C-5), 114.7 (C-7), 111.6 (C-3), 46.8 (C-15), 44.7 (C-13), 35.8 (C-11), 28.7, 28.5 (C-18, C-19), 25.9, 25.6, 25.5 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 785.2001 (calcd for $C_{36}H_{47}{}^{79}Br_2N_6O_4$, 785.2020), 787.1988 (calcd for $C_{36}H_{47}{}^{79}Br^{81}BrN_6O_4$, 787.2003), 789.1973 (calcd for $C_{36}H_{47}{}^{81}Br_2N_6O_4$, 789.1992).

3.2.9. N^1,N^{12}-Bis(3-(2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetamido)propyl)dodecane-1,12-diaminium 2,2,2-trifluoroacetate (**18e**)

Using general procedure A, 2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetyl chloride (**11**) (0.081 g, 0.28 mmol) was reacted with di-*tert*-butyl dodecane-1,12-diylbis((3-aminopropyl)carbamate) (**9e**) (0.073 g, 0.14 mmol) and DIPEA (0.15 mL, 0.86 mmol) to afford di-*tert*-butyl dodecane-1,12-diylbis((3-(2-(5-bromo-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a dark orange oil (0.047 g, 33%). Using general procedure B, a sub-sample of this product (0.014 g, 0.014 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **18e** as a yellow oil (0.011 g, 76%). R_f (MeOH/10% HCl, 7:3) 0.35; IR (ATR) ν_{max} 3402, 2981, 2036, 1681, 1654, 1385 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.50 (2H, d, *J* = 2.3 Hz, NH-1), 8.91 (2H, t, *J* = 6.0 Hz, NH-10), 8.80 (2H, d, *J* = 2.4, H-2), 8.44 (4H, br s, NH_2-14), 8.35 (2H, d, *J* = 1.7 Hz, H-4), 7.53 (2H, d, *J* = 8.6 Hz, H-7), 7.41 (2H, dd, *J* = 8.6, 1.8 Hz, H-6), 3.30 (4H, dt, *J* = 6.3, 6.3 Hz, H_2-11), 2.98–2.84 (8H, m, H_2-13, H_2-15), 1.86–1.82 (4H, m, H_2-12), 1.55 (4H, br s, H_2-16), 1.27–1.23 (16H, m, H_2-17, H_2-18, H_2-19, H_2-20); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.4 (C-9), 139.5 (C-2), 135.1 (C-7a), 128.0 (C-3a), 126.1 (C-4), 123.3 (C-6), 115.4 (C-5), 114.7 (C-7), 111.6 (C-3), 46.8 (C-15), 44.7 (C-13), 35.8 (C-11), 28.9, 28.8, 28.5 (C-18, C-19, C-20), 25.9, 25.6, 25.5 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 813.2336 (calcd for $C_{38}H_{51}{}^{79}Br_2N_6O_4$, 813.2333), 815.2315 (calcd for $C_{38}H_{51}{}^{79}Br^{81}BrN_6O_4$, 815.2317), 817.2308 (calcd for $C_{38}H_{51}{}^{81}Br_2N_6O_4$, 817.2306).

3.2.10. N^1,N^6-Bis(3-(2-(5-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)hexane-1,6-diaminium 2,2,2-trifluoroacetate (**19a**)

Using general procedure A, 2-(5-methoxy-1*H*-indol-3-yl)-2-indoloxoacetyl chloride (**12**) (0.057 g, 0.24 mmol) was reacted with di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl) carbamate) (**9a**) (0.050 g, 0.12 mmol) and DIPEA (0.13 mL, 0.74 mmol) to afford di-*tert*-butyl hexane-1,6-diylbis((3-(2-(5-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as an orange oil (0.025 g, 24%). Using general procedure B, a sub-sample of this product (0.018 g, 0.022 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **19a** as a pale orange oil (0.016 g, 86%). R_f (MeOH/10% HCl, 7:3) 0.74; IR (ATR) ν_{max} 3422, 1691, 1628, 1485, 1274, 1201, 1052, 1026, 1006, 823, 760, 734 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 12.18 (2H, br s, NH-1), 8.86 (2H, t, *J* = 5.8 Hz, NH-10), 8.69 (2H, d, *J* = 3.5 Hz, H-2), 8.44 (4H, br s, NH_2-14), 7.74 (2H, d, *J* = 2.6 Hz, H-4), 7.44 (2H, d, *J* = 8.8 Hz, H-7), 6.91 (2H, dd, *J* = 8.8, 2.6 Hz, H-6), 3.79 (6H, s, OMe), 3.30 (4H, dt, *J* = 6.8, 6.8 Hz, H_2-11), 2.97–2.86 (8H, br m, H_2-13, H_2-15), 1.84 (4H, br s, H_2-12), 1.56 (4H, br s, H_2-16), 1.31 (4H, br s, H_2-17); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 181.5 (C-8), 163.8 (C-9), 156.0 (C-5), 138.4 (C-2), 131.0 (C-7a), 127.2 (C-3a), 113.3 (C-7), 112.8 (C-6), 112.0 (C-3), 103.5 (C-4), 55.3 (OMe), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 25.7, 25.5, 25.4 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 633.3396 (calcd for $C_{34}H_{45}N_6O_6$, 633.3395).

3.2.11. N^1,N^7-Bis(3-(2-(5-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)heptane-1,7-diaminium 2,2,2-trifluoroacetate (**19b**)

Using general procedure A, 2-(5-methoxy-1*H*-indol-3-yl)-2-oxoacetyl chloride (**12**) (0.079 g, 0.33 mmol) was reacted with di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl) carbamate) (**9b**) (0.070 g, 0.15 mmol) and DIPEA (0.16 mL, 0.92 mmol) to afford di-*tert*-butyl heptane-1,7-diylbis((3-(2-(5-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow oil (0.004 g, 33%). Using general procedure B, a sub-sample of this product (0.017 g, 0.02 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **19b** as a yellow oil (0.014 g, 80%). R_f (MeOH/10% HCl, 7:3) 0.72; IR (ATR) ν_{max} 3318, 2981, 1678, 1621, 1486, 1438 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.22 (2H, d, *J* = 2.2 Hz, NH-1), 8.86 (2H, t, *J* = 6.0 Hz, NH-10), 8.69 (2H, d, *J* = 3.3 Hz, H-2), 8.51 (4H, br s, NH_2-14), 7.75 (2H, d, *J* = 2.5 Hz, H-4), 7.44 (2H, d, *J* = 8.8 Hz, H-7), 6.90 (2H, dd, *J* = 8.8, 2.5 Hz, H-6), 3.79 (6H, s, OMe), 3.30 (4H, dt, *J* = 6.4, 6.4 Hz, H_2-11), 2.98–2.89 (8H, m, H_2-13, H_2-15), 1.89–1.88 (4H, m, H_2-12), 1.56 (4H, br s, H_2-16), 1.29 (6H, br s, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.6 (C-8), 163.9 (C-9), 156.0 (C-5), 138.4 (C-2), 131.0 (C-7a), 127.2 (C-3a), 113.3 (C-7), 112.8 (C-6), 112.0 (C-3), 103.5 (C-4), 55.3 (OMe), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 28.0 (C-18), 25.8, 25.7, 25.4 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 647.3554 (calcd for $C_{35}H_{47}N_6O_6$, 647.3552).

3.2.12. N^1,N^{10}-Bis(3-(2-(5-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**19d**)

Using general procedure A, 2-(5-methoxy-1*H*-indol-3-yl)-2-oxoacetyl chloride (**12**) (0.081 g, 0.34 mmol) was reacted with di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl) carbamate) (**9d**) (0.076 g, 0.16 mmol) and DIPEA (0.17 mL, 0.97 mmol) to afford di-*tert*-butyl decane-1,10-diylbis((3-(2-(5-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow oil (0.033 g, 23%). Using general procedure B, a sub-sample of this product (0.016 g, 0.018 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **19d** as a dark orange oil (0.014 g, 85%). R_f (MeOH/10% HCl, 7:3) 0.76; IR (ATR) ν_{max} 3364, 2946, 2833, 1579, 1419 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.24 (2H, s, NH-1), 8.85 (2H, t, *J* = 6.0 Hz, NH-10), 8.68 (2H, d, *J* = 3.0 Hz, H-2), 8.54 (4H, br s, NH_2-14), 7.75 (2H, d, *J* = 1.9 Hz, H-4), 7.44 (2H, d, *J* = 8.7 Hz, H-7), 6.90 (2H, dd, *J* = 8.8, 1.9 Hz, H-6), 3.79 (6H, s, OMe), 3.29 (4H, dt, *J* = 6.2, 6.2 Hz, H_2-11), 2.97–2.85 (8H, br m, H_2-13, H_2-15), 1.86–1.81 (4H, m, H_2-12), 1.55 (4H, br m, H_2-16), 1.24 (12H, br s, H_2-17, H_2-18, H_2-19); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.6 (C-8), 163.9 (C-9), 156.0 (C-5), 138.4 (C-2), 131.0 (C-7a), 127.2 (C-3a), 113.3 (C-7), 112.8 (C-6), 112.0 (C-3), 103.5 (C-4), 55.3 (OMe), 46.8 (C-15), 44.7 (C-13), 35.8 (C-

11), 28.7, 28.5 (C-18, C-19), 25.9, 25.7, 25.5 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 689.4040 (calcd for $C_{38}H_{53}N_6O_6$, 689.4021).

3.2.13. N^1,N^6-Bis(3-(2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)hexane-1,6-diaminium 2,2,2-trifluoroacetate (**20a**)

Using general procedure C, 2-(5-methyl -1*H*-indol-3-yl)-2-oxoacetic acid (**13**) (0.070 g, 0.34 mmol) was reacted with di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl) carbamate) (**9a**) (0.072 g, 0.17 mmol), PyBOP (0.178 g, 0.34 mmol) and DIPEA (0.09 mL, 0.52 mmol). Purification by column chromatography afforded di-*tert*-butyl hexane-1,6-diylbis((3-(2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetamido) propyl) carbamate) as a yellow oil (0.054 g, 39%). Using general procedure B, a sub-sample of this product (0.025 g, 0.031 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **20a** as a brown gum (0.021 g, 81%). R_f (MeOH/10% HCl, 3:1) 0.59; IR (ATR) ν_{max} 3325, 2945, 1678, 1448, 1113, 1021 cm^{-1}; ^1H NMR, (DMSO-d_6, 400 MHz) δ 12.20 (2H, d, *J* = 2.8 Hz, NH-1), 8.85 (2H, t, *J* = 6.1 Hz, H-10), 8.69 (2H, d, *J* = 3.3 Hz, H-2), 8.49 (4H, br s, H-14), 8.03 (2H, s, H-4), 7.41 (2H, d, *J* = 8.2 Hz, H-7), 7.09 (2H, dd, *J* = 8.4, 1.4 Hz, H-6), 3.30 (4H, dt, *J* = 6.6, 6.6 Hz, H_2-11), 2.97–2.85 (8H, m, H_2-13, H_2-15), 2.42 (6H, s, Me), 1.88–1.81 (4H, m, H_2-12), 1.56 (4H, br s, H_2-16), 1.30 (4H, br s, H_2-17); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 164.0 (C-9), 138.5 (C-2), 134.6 (C-7a), 131.6 (C-5), 126.5 (C-3a), 125.0 (C-6), 121.1 (C-4), 112.3 (C-7), 111.8 (C-3), 46.7 (C-15), 44.8 (C-13), 35.8 (C-11), 25.8, 25.5, 25.4 (C-12, C-16, C-17), 21.4 (Me); (+)-HRESIMS $[M+H]^+$ *m/z* 601.3511 (calcd for $C_{34}H_{45}N_6O_4$, 601.3497).

3.2.14. N^1,N^7-Bis(3-(2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)heptane-1,7-diaminium 2,2,2-trifluoroacetate (**20b**)

Using general procedure C, 2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**13**) (0.080 g, 0.39 mmol) was reacted with di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl) carbamate) (**9b**) (0.085 g, 0.19 mmol), PyBOP (0.204 g, 0.39 mmol) and DIPEA (0.1 mL, 0.57 mmol). Purification by column chromatography afforded di-*tert*-butyl heptane-1,7-diylbis((3-(2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetamido) propyl) carbamate) as a yellow oil (0.079 g, 51%). Using general procedure B, a sub-sample of this product (0.045 g, 0.055 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **20b** as a brown gum (0.024 g, 52%). R_f (MeOH/10% HCl, 3:1) 0.53; IR (ATR) ν_{max} 3306, 2943, 1653, 1448, 1118, 1022, 739 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.24 (2H, d, *J* = 2.7 Hz, NH-1), 8.85 (2H, t, *J* = 6.2 Hz, NH-10), 8.70 (2H, d, *J* = 3.5 Hz, H-2), 8.55 (4H, br s, NH-14), 8.04 (2H, br s, H-4), 7.42 (2H, d, *J* = 8.1 Hz, H-7), 7.09 (2H, dd, *J* = 8.43 and 1.4, H-6), 3.29 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.97–2.85 (8H, m, H_2-13, H_2-15), 2.42 (6H, s, Me), 1.89–1.82 (4H, m, H_2-12), 1.60–1.52 (4H, br m, H_2-16), 1.28 (6H, br s, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.9 (C-9), 138.5 (C-2), 134.6 (C-7a), 131.6 (C-5), 126.5 (C-3a), 124.9 (C-6), 121.1 (C-4), 112.3 (C-7), 111.8 (C-3), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 28.0 (C-18), 25.8, 25.7, 25.4, (C-12, C-16, C-17), 21.4 (Me); (+)-HRESIMS $[M+H]^+$ *m/z* 615.3664 (calcd for $C_{35}H_{47}N_6O_4$, 615.3653).

3.2.15. N^1,N^8-Bis(3-(2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)octane-1,8-diaminium 2,2,2-trifluoroacetate (**20c**)

Using general procedure C, 2-(5-methyl -1*H*-indol-3-yl)-2-oxoacetic acid (**13**) (0.080 g, 0.39 mmol) was reacted with di-*tert*-butyl octane-1,8-diylbis((3-aminopropyl)carbamate) (**9c**) (0.088 g, 0.19 mmol), PyBOP (0.204 g, 0.39 mmol) and DIPEA (0.1 mL, 0.57 mmol). Purification by column chromatography afforded di-*tert*-butyl octane-1,8-diylbis((3-(2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow oil (0.054 g, 34%). Using general procedure B, a sub-sample of this product (0.030 g, 0.036 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **20c** as a brown gum (0.030 g, 97%). R_f (MeOH/10% HCl, 3:1) 0.50; IR (ATR) ν_{max} 3307, 2943, 1676, 1448, 1116, 1022, 713 cm^{-1}; ^1H NMR, (DMSO-d_6, 400 MHz) δ 12.25 (2H, d, *J* = 3.0 Hz, NH-1), 8.85 (2H, t, *J* = 6.1 Hz, NH-10), 8.70 (2H, d, *J* = 3.2 Hz, H-2), 8.55 (4H, br s, NH-14), 8.04 (2H, br s,

H-4), 7.42 (2H, d, *J* = 8.1 Hz, H-7), 7.09 (2H, dd, *J* = 8.3, 1.5 Hz, H-6), 3.29 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.94–2.85 (8H, br s, H_2-13, H_2-15), 2.42 (6H, s, Me), 1.89–1.82 (4H, br s, H_2-12), 1.56 (4H, br s, H_2-16), 1.26 (6H, br s, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.9 (C-9), 138.4 (C-2), 134.6 (C-7a), 131.5 (C-5), 126.5 (C-3a), 124.9 (C-6), 121.1 (C-4), 112.3 (C-7), 111.8 (C-3), 46.8 (C-15), 44.7 (C-13), 35.8 (C-11), 28.3 (C-18), 25.8, 25.7, 25.5 (C-12, C-16, C-17), 21.4 (Me); (+)-HRESIMS $[M+H]^+$ *m/z* 629.3818 (calcd for $C_{36}H_{49}N_6O_4$, 629.3810).

3.2.16. N^1,N^{10}-Bis(3-(2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**20d**)

Using general procedure C, 2-(5-methyl -1*H*-indol-3-yl)-2-oxoacetic acid (**13**) (0.070 g, 0.34 mmol) was reacted with di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl) carbamate) (**9d**) (0.081 g, 0.17 mmol), PyBOP (0.179 g, 0.34 mmol) and DIPEA (0.09 mL, 0.50 mmol). Purification by column chromatography afforded di-*tert*-butyl decane-1,10-diylbis((3-(2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow oil (0.087 g, 60%). Using general procedure B, a sub-sample of this product (0.043 g, 0.050 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **20d** as a white gum (0.044 g, 99%). R_f (MeOH/10% HCl, 3:1) 0.44; IR (ATR) ν_{max} 3307, 2944, 1678, 1449, 1115, 1021 cm^{-1}; ^{1}H NMR, (DMSO-d_6, 400 MHz) δ 12.24 (2H, d, *J* = 3.0 Hz, NH-1), 8.85 (2H, t, *J* = 6.1 Hz, NH-10), 8.70 (2H, d, *J* = 3.4 Hz, H-2), 8.52 (4H, br s, NH-14), 8.04 (2H, br s, H-4), 7.42 (2H, d, *J* = 8.2 Hz, H-7), 7.09 (2H, dd, *J* = 8.3, 1.5 Hz, H-6), 3.30 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.97–2.85 (8H, br m, H_2-13, H_2-15), 2.42 (6H, s, Me), 1.89–1.82 (4H, m, H_2-12), 1.57–1.52 (4H, m, H_2-16), 1.24 (12H, br s, H_2-17, H_2-18, H_2-19); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.9 (C-9), 138.5 (C-2), 134.6 (C-7a), 131.5 (C-5), 126.6 (C-3a), 124.9 (C-6), 121.1 (C-4), 112.3 (C-7), 111.8 (C-3), 46.8 (C-15), 44.7 (C-13), 35.8 (C-11), 28.7, 28.5 (C-18, C-19), 25.9, 25.7, 25.5 (C-12, C-16, C-17), 21.4 (Me), (+)-HRESIMS $[M+H]^+$ *m/z* 657.4125 (calcd for $C_{38}H_{53}N_6O_4$, 657.4123).

3.2.17. N^1,N^{12}-Bis(3-(2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)dodecane-1,12-diaminium 2,2,2-trifluoroacetate (**20e**)

Using general procedure C, 2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**13**) (0.070 g, 0.34 mmol) was reacted with di-*tert*-butyl dodecane-1,12-diylbis((3-aminopropyl)carbamate) (**9e**) (0.086 g, 0.17 mmol), PyBOP (0.179 g, 0.34 mmol) and DIPEA (0.09 mL, 0.50 mmol). Purification by column chromatography afforded di-*tert*-butyl dodecane-1,12-diylbis((3-(2-(5-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow oil (0.092 g, 62%). Using general procedure B, a sub-sample of this product (0.045 g, 0.051 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **20e** as a white gum (0.039 g, 84%). R_f (MeOH/10% HCl, 3:1) 0.41; IR (ATR) ν_{max} 3307, 2944, 1678, 1452, 1113, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.24 (2H, d, *J* = 2.9 Hz, NH-1), 8.85 (2H, t, *J* = 6.3 Hz, NH-10), 8.70 (2H, d, *J* = 3.3 Hz, H-2), 8.51 (4H, br s, NH-14), 8.04 (2H, br s, H-4), 7.42 (2H, d, *J* = 8.3 Hz, H-7), 7.09 (2H, dd, *J* = 8.4, 1.5 Hz, H-6), 3.29 (4H, dt, *J* = 6.4, 6.4 Hz, H_2-11), 2.97–2.85 (8H, br m, H_2-13, H_2-15), 2.42 (6H, s, Me), 1.89–1.82 (4H, m, H_2-12), 1.57–1.52 (4H, m, H_2-16), 1.31–1.22 (16H, br m, H_2-17, H_2-18, H_2-19, H_2-20); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.9 (C-9), 138.5 (C-2), 134.6 (C-7a), 131.5 (C-5), 126.6 (C-3a), 124.9 (C-6), 121.1 (C-4), 112.3 (C-7), 111.8 (C-3), 46.8 (C-15), 44.7 (C-13), 35.8 (C-11), 29.0, 28.9, 28.6 (C-18, C-19, C-20), 25.9, 25.7, 25.5 (C-12, C-16, C-17), 21.4 (Me); (+)-HRESIMS $[M+H]^+$ *m/z* 685.4453 (calcd for $C_{40}H_{57}N_6O_4$, 685.4436).

3.2.18. N^1,N^6-Bis(3-(2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetamido)propyl)hexane-1,6-diaminium 2,2,2-trifluoroacetate (**21a**)

Using general procedure A, 2-(7-fluoro-1*H*-indol-3-yl)-2-indoloxoacetyl chloride (**14**) (0.053 g, 0.24 mmol) was reacted with di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl) carbamate) (**9a**) (0.050 g, 0.12 mmol) and DIPEA (0.13 mL, 0.74 mmol) to afford di-*tert*-butyl hexane-1,6-diylbis((3-(2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a

yellow gum (0.016 g, 16%). Using general procedure B, this product (0.016 g, 0.02 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **21a** as a pale yellow oil (0.006 g, 35%). R_f (MeOH/10% HCl, 7:3) 0.76; IR (ATR) ν_{max} 3434, 1672, 1627, 1433, 1293, 1202, 1137, 1028, 721 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 12.88 (2H, br s, NH-1), 8.95 (2H, t, *J* = 5.6 Hz, NH-10), 8.77 (2H, s, H-2), 8.42 (4H, br s, NH_2-14), 8.04 (2H, d, *J* = 8.0 Hz, H-4), 7.25 (2H, ddd, *J* = 8.0, 8.0, 5.0 Hz, H-5), 7.14 (2H, dd, *J* = 11.2, 8.0 Hz, H-6), 3.38–3.29 (4H, m, H_2-11), 2.97–2.91 (8H, m, H_2-13, H_2-15), 1.85 (4H, tt, *J* = 7.3, 7.3 Hz, H_2-12), 1.55 (4H, br s, H_2-16), 1.31 (4H, br s, H_2-17); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 181.9 (C-8), 163.4 (C-9), 149.2 (d, $^1J_{CF}$ = 245.4 Hz, C-7), 138.8 (C-2), 129.8 (d, $^3J_{CF}$ = 4.5 Hz, C-3a), 124.0 (d, $^2J_{CF}$ = 13.4 Hz, C-7a), 123.4 (d, $^3J_{CF}$ = 5.9 Hz, C-5), 117.4 (d, $^4J_{CF}$ = 2.7 Hz, C-4), 112.8 (C-3), 108.7 (d, $^2J_{CF}$ = 15.9 Hz, C-6), 46.7 (C-15), 44.7 (C-13), 35.9 (C-11), 25.7, 25.5, 25.4 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 609.2987 (calcd for $C_{32}H_{39}F_2N_6O_4$, 609.2995).

3.2.19. N^1,N^7-Bis(3-(2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetamido)propyl)heptane-1,7-diaminium 2,2,2-trifluoroacetate (**21b**)

Using general procedure A, 2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetyl chloride (**14**) (0.080 g, 0.36 mmol) was reacted with di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl)carbamate) (**9b**) (0.079 g, 0.18 mmol) and DIPEA (0.19 mL, 1.1 mmol) to afford di-*tert*-butyl heptane-1,7-diylbis((3-(2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a dark yellow oil (0.058 g, 39%). Using general procedure B, a sub-sample of this product (0.013 g, 0.016 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **21b** as an orange oil (0.013 g, 96%). R_f (MeOH/10% HCl, 7:3) 0.75; IR (ATR) ν_{max} 3401, 2930, 1675, 1635, 1458 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.91 (2H, br d, *J* = 2.1 Hz, NH-1), 8.94 (2H, t, J = 6.1 Hz, NH-10), 8.77 (2H, d, J = 3.0 Hz, H-2), 8.51 (4H, br s, NH_2-14), 8.04 (2H, d, *J* = 7.9 Hz, H-4), 7.25 (2H, ddd, *J* = 8.1, 8.1, 5.0 Hz, H-5), 7.31 (2H, dd, *J* = 11.3, 7.3 Hz, H-6), 3.30 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.98–2.86 (8H, br m, H_2-13, H_2-15), 1.89–1.82 (4H, br m, H_2-12), 1.56 (4H, br s, H_2-16), 1.31–1.26 (6H, m, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.9 (C-8), 163.4 (C-9), 149.2 (d, $^1J_{CF}$ = 245 Hz, C-7), 138.8 (C-2), 129.9 (d, $^3J_{CF}$ = 4.4 Hz, C-3a), 123.4 (d, $^3J_{CF}$ = 6.0 Hz, C-5), 124.0 (d, $^2J_{CF}$ = 13.2 Hz, C-7a), 117.4 (br s, C-4), 112.8 (C-3), 108.6 (d, $^2J_{CF}$ = 15.5 Hz, C-6), 46.7 (C-15), 44.7 (C-13), 35.9 (C-11), 28.0 (C-18), 25.8, 25.7, 25.4 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 623.3161 (calcd for $C_{33}H_{41}F_2N_6O_4$, 623.3152).

3.2.20. N^1,N^8-Bis(3-(2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetamido)propyl)octane-1,8-diaminium 2,2,2-trifluoroacetate (**21c**)

Using general procedure A, 2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetyl chloride (**14**) (0.063 g, 0.28 mmol) was reacted with di-*tert*-butyl octane-1,8-diylbis((3-aminopropyl)carbamate) (**9c**) (0.056 g, 0.12 mmol) and DIPEA (0.13 mL, 0.75 mmol) to afford di-*tert*-butyl octane-1,8-diylbis((3-(2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a brown oil (0.064 g, 56%). Using general procedure B, a sub-sample of this product (0.034 g, 0.041 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **21c** as a brown oil (0.030 g, 85%). R_f (MeOH/10% HCl, 7:3) 0.70; IR (ATR) ν_{max} 3430, 1689, 1656, 1050, 1023, 1002, 930, 823, 760 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.89 (2H, d, *J* = 2.8 Hz, NH-1), 8.94 (2H, t, *J* = 6.1 Hz, NH-10), 8.77 (2H, d, *J* = 3.2 Hz, H-2), 8.46 (4H, br s, NH_2-14), 8.04 (2H, d, *J* = 7.8 Hz, H-4), 7.25 (2H, ddd, *J* = 8.0, 8.0, 4.7 Hz, H-5), 7.14 (2H, ddd, *J* = 11.0, 7.9, 1.0 Hz, H-6), 3.30 (4H, dt, *J* = 6.4, 6.4 Hz, H_2-11), 2.98–2.84 (4H, br m, H_2-13, H_2-15), 1.85 (4H, tt, *J* = 6.5, 6.5 Hz, H_2-12), 1.55 (4H, tt, *J* = 6.8, 6.8 Hz, H_2-16), 1.26 (8H, br s, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.9 (C-8), 163.4 (C-9), 149.2 ($^1J_{CF}$ = 245 Hz, C-7), 138.8 (C-2), 129.8 (d, $^3J_{CF}$ = 4.6 Hz, C-3a), 124.0 (d, $^2J_{CF}$ = 13.3 Hz, C-7a), 123.4 (d, $^3J_{CF}$ = 5.3 Hz, C-5), 117.4 (d, $^3J_{CF}$ = 3.5 Hz, C-4), 112.8 (C-3), 108.7 (d, $^2J_{CF}$ = 16.0 Hz, C-6), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 28.3 (C-18), 25.8, 25.6, 25.5 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 637.3313 (calcd $C_{34}H_{43}F_2N_6O_4$, 637.3308).

3.2.21. N^1,N^{10}-Bis(3-(2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**21d**)

Using general procedure A, 2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetyl chloride (**14**) (0.080 g, 0.35 mmol) was reacted with di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl)carbamate) (**9d**) (0.084 g, 0.17 mmol) and DIPEA (0.19 mL, 1.1 mmol) to afford di-*tert*-butyl decane-1,10-diylbis((3-(2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a dark yellow oil (0.072 g, 49%). Using general procedure B, a sub-sample of this product (0.023 g, 0.027 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **21d** as an orange oil (0.018 g, 76%). R_f (MeOH/10% HCl, 7:3) 0.73; IR (ATR) ν_{max} 3405, 2944, 2857, 1674, 1632, 1505, 1439 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.92 (2H, s, NH-1), 8.93 (2H, t, *J* = 6.1 Hz, NH-10), 8.78 (2H, d, *J* = 3.4 Hz, H-2), 8.49 (4H, br s, NH_2-14), 8.04 (2H, d, *J* = 7.9 Hz, H-4), 7.24 (2H, dd, *J* = 8.0, 8.0, 5.0 Hz, H-5), 7.13 (2H, dd, *J* = 11.2, 8.0 Hz, H-6), 3.30 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.98–2.84 (8H, m, H_2-13, H_2-15), 1.89–1.82 (4H, m, H_2-12), 1.57–1.52 (4H, br m, H_2-16), 1.23 (12H, br s, H_2-17, H_2-18, H_2-19); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.9 (C-8), 163.4 (C-9), 149.3 (d, $^1J_{CF}$ = 245 Hz, C-7), 138.8 (C-2), 129.8 (d, $^3J_{CF}$ = 4.5 Hz, C-3a), 124.1 (d, $^2J_{CF}$ = 13.2 Hz, C-7a), 123.4 (d, $^3J_{CF}$ = 5.9 Hz, C-5), 117.4 (d, $^3J_{CF}$ = 3.1 Hz, C-4), 112.8 (C-3), 108.7 (d, $^2J_{CF}$ = 15.8 Hz, C-6), 46.8 (C-15), 44.7 (C-13), 35.9 (C-11), 28.7, 28.5 (C-18, C-19), 25.9, 25.6, 25.5 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 665.3639 (calcd for $C_{36}H_{47}F_2N_6O_4$, 665.3621).

3.2.22. N^1,N^{12}-Bis(3-(2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetamido)propyl)dodecane-1,12-diaminium 2,2,2-trifluoroacetate (**21e**)

Using general procedure A, 2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetyl chloride (**14**) (0.076 g, 0.034 mmol) was reacted with di-*tert*-butyl dodecane-1,12-diylbis((3-aminopropyl)carbamate) (**9e**) (0.087 g, 0.17 mmol) and DIPEA (0.18 mL, 1.0 mmol) to afford di-*tert*-butyl dodecane-1,12-diylbis((3-(2-(7-fluoro-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a dark orange oil (0.047 g, 31%). Using general procedure B, a sub-sample of this product (0.045 g, 0.050 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **21e** as an orange oil (0.026 g, 56%). R_f (MeOH/10% HCl, 7:3) 0.70; IR (ATR) ν_{max} 3342, 2929, 1676, 1632, 1506, 1459 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.94 (2H, d, *J* = 2.7 Hz, NH-1), 8.93 (2H, t, *J* = 6.9 Hz, NH-10), 8.78 (2H, d, *J* = 3.4 Hz, H-2), 8.57 (4H, br s, NH_2-14), 8.04 (2H, d, *J* = 8.5 Hz, H-4), 7.24 (2H, ddd, *J* = 7.8, 7.8, 5.0 Hz, H-5), 7.13 (2H, dd, *J* = 11.2, 8.0 Hz, H-6), 3.30 (4H, dt, *J* = 6.4, 6.4 Hz, H_2-11), 2.94–2.84 (8H, m, H_2-13, H_2-15), 1.90–1.83 (4H, m, H_2-12), 1.56 (4H, br s, H_2-16), 1.27–1.22 (16H, m, H_2-17, H_2-18, H_2-19, H_2-20); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.9 (C-8), 163.4 (C-9), 149.1 (d, $^1J_{CF}$ = 241 Hz, C-7), 138.9 (C-2), 129.9 (d, $^3J_{CF}$ = 4.2 Hz, C-3a), 124.1 (d, $^2J_{CF}$ = 14.0 Hz, C-7a), 123.4 (d, $^3J_{CF}$ = 6.1 Hz, C-5), 117.4 (d, $^3J_{CF}$ = 3.1 Hz, C-4), 112.8 (C-3), 108.6 (d, $^2J_{CF}$ = 16.1 Hz, C-6), 46.8 (C-15), 44.7 (C-13), 35.9 (C-11), 28.9, 28.8, 28.5 (C-18, C-19, C-20), 25.9, 25.6, 25.5 (C-12, C-16, C-17); (+)-HRESIMS $[M+Na]^+$ *m/z* 715.3747 (calcd for $C_{38}H_{50}F_2N_6NaO_4$, 715.3754).

3.2.23. N^1,N^6-Bis(3-(2-(7-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)hexane-1,6-diaminium 2,2,2-trifluoroacetate (**22a**)

Following general procedure C, 2-(7-methoxy-1*H*-indol-3-yl)-2-oxoacetic acid (**15**) (0.050 g, 0.23 mmol) was reacted with di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl) carbamate) (**9a**) (0.047 g, 0.11 mmol), PyBOP (0.119 g, 0.23 mmol) and DIPEA (0.06 mL, 0.34 mmol). Purification by column chromatography afforded di-*tert*-butyl hexane-1,6-diylbis((3-(2-(7-methoxy-1*H*-indol-3-yl)-2-oxoacetamido) propyl) carbamate) as a yellow oil (0.020 g, 22%). Using general procedure B, a sub-sample of this product (0.016 g, 0.019 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **22a** as a black gum (0.013 g, 79%). R_f (MeOH/10% HCl, 3:1) 0.68; IR (ATR) ν_{max} 3317, 2944, 1622, 1449, 1115, 1022, 721 cm^{-1}; ^1H NMR, (DMSO-d_6, 400 MHz) δ 12.45 (2H, d, *J* = 2.0 Hz, NH-1), 8.89 (2H, t, *J* = 5.5 Hz, NH-10), 8.62 (2H, d, *J* = 3.5 Hz, H-2), 8.38 (4H, br s, NH-14), 7.80 (2H, d, *J* = 7.9 Hz, H-4), 7.19 (2H, t, *J* = 7.6 Hz, H-5), 6.86 (2H, d, *J* = 8.2 Hz, H-6), 3.95 (6H, s, OMe), 3.29 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.92–2.88 (8H, m, H_2-13,

H_2-15), 1.87–1.82 (4H, m, H_2-12), 1.55 (4H, br s, H_2-16), 1.31 (4H, br s, H_2-17); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.7 (C-9), 146.4 (C-7), 137.4 (C-2), 127.8 (C-3a), 126.1 (C-7a), 123.5 (C-5), 113.7 (C-4), 112.6 (C-3), 104.4 (C-6), 55.4 (OMe), 46.6 (C-15), 44.7 (C-13), 35.8 (C-11), 25.7, 25.5, 25.4 (C-12, C-16, C-17); (+)-HRESIMS *m/z* $[M+H]^+$ 633.3408 (calcd for $C_{34}H_{45}N_6O_6$, 633.3395).

3.2.24. N^1,N^7-Bis(3-(2-(7-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)heptane-1,7-diaminium 2,2,2-trifluoroacetate (**22b**)

Using general procedure C, 2-(7-methoxy-1*H*-indol-3-yl)-2-oxoacetic acid (**15**) (0.086 g, 0.39 mmol) was reacted with di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl) carbamate) (**9b**) (0.088 g, 0.19 mmol), PyBOP (0.213 g, 0.41 mmol) and DIPEA (0.09 mL, 0.52 mmol). Purification by column chromatography afforded di-*tert*-butyl heptane-1,7-diylbis((3-(2-(7-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow oil (0.066 g, 41%). Using general procedure B, a sub-sample of this product (0.030 g, 0.035 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **22b** as a black gum (0.028 g, 90%). R_f (MeOH/10% HCl, 3:1) 0.58; IR (ATR) ν_{max} 3317, 2943, 1675, 1432, 1132, 1022, 721 cm^{-1}; ^{1}H NMR, (DMSO-d_6, 400 MHz) δ 12.45 (2H, d, *J* = 3.4 Hz, NH-1), 8.89 (2H, t, *J* = 6.2 Hz, NH-10), 8.62 (2H, d, *J* = 3.3 Hz, H-2), 8.35 (4H, br s, NH-14), 7.80 (2H, d, *J* = 7.7 Hz, H-4), 7.19 (2H, t, *J* = 7.9 Hz, H-5), 6.86 (2H, d, *J* = 7.9 Hz, H-6), 3.95 (6H, s, H_3-19), 3.29 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.96–2.84 (8H, br m, H_2-13, H_2-15), 1.87–1.82 (4H, m, H_2-12), 1.55 (4H, br s, H_2-16), 1.28 (6H, br s, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.8 (C-8), 163.7 (C-9), 146.4 (C-7), 137.4 (C-2), 127.8 (C-3a), 126.1 (C-7a), 123.6 (C-5), 113.7 (C-4), 112.6 (C-3), 104.4 (C-6), 55.4 (C-19), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 28.0 (C-18), 25.8, 25.7, 25.4 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 647.3550 (calcd for $C_{35}H_{47}N_6O_6$, 647.3552).

3.2.25. N^1,N^{10}-Bis(3-(2-(7-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**22d**)

Using general procedure C, 2-(7-methoxy-1*H*-indol-3-yl)-2-oxoacetic acid (**15**) (0.070 g, 0.32 mmol) was reacted with di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl) carbamate) (**9d**) (0.078 g, 0.16 mmol), PyBOP (0.170 g, 0.32 mmol) and DIPEA (0.08 mL, 0.47 mmol). Purification by column chromatography afforded di-*tert*-butyl decane-1,10-diylbis((3-(2-(7-methoxy-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow oil (0.091 g, 65%). Using general procedure B, a sub-sample of this product (0.022 g, 0.025 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **22d** as a black gum (0.022 g, 98%). R_f (MeOH/10% HCl, 3:1) 0.47; IR (ATR) ν_{max} 3308, 2944, 1679, 1449, 1114, 1021 cm^{-1}; ^{1}H NMR, (DMSO-d_6, 400 MHz) δ 12.45 (2H, d, *J* = 3.2 Hz, NH-1), 8.89 (2H, t, *J* = 6.1 Hz, NH-10), 8.62 (2H, d, *J* = 3.4 Hz, H-2), 8.39 (4H, br s, NH-14), 7.80 (2H, d, *J* = 7.7 Hz, H-4), 7.19 (2H, t, *J* = 7.9 Hz, H-5), 6.86 (2H, d, *J* = 7.7 Hz, H-6), 3.95 (6H, s, OMe), 3.29 (4H, dt, *J* = 6.7, 6.7 Hz, H_2-11), 2.96–2.85 (8H, m, H_2-13, H_2-15), 1.87–1.80 (4H, m, H_2-12), 1.56–1.53 (4H, m, H_2-16), 1.24 (12H, br s, H_2-17, H_2-18, H_2-19); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.7 (C-9), 146.4 (C-7), 137.4 (C-2), 127.8 (C-3a), 126.1 (C-7a), 123.6 (C-5), 113.8 (C-4), 112.7 (C-3), 104.4 (C-6), 55.4 (OMe), 46.8 (C-15), 44.7 (C-13), 35.8 (C-11), 28.7, 28.5 (C-18, C-19), 25.9, 25.7, 25.5 (C-12, C-16, C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 689.4010 (calcd for $C_{38}H_{53}N_6O_6$, 689.4021).

3.2.26. N^1,N^6-Bis(3-(2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)hexane-1,6-diaminium 2,2,2-trifluoroacetate (**23a**)

Using general procedure C, 2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**16**) (0.080 g, 0.39 mmol) was reacted with di-*tert*-butyl hexane-1,6-diylbis((3-aminopropyl) carbamate) (**9a**) (0.083 g, 0.19 mmol), PyBOP (0.204 g, 0.39 mmol) and DIPEA (0.1 mL, 0.57 mmol). Purification by column chromatography afforded di-*tert*-butyl hexane-1,6-diylbis((3-(2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetamido) propyl) carbamate) as a yellow oil (0.019 g, 13%). Using general procedure B, a sub-sample of this product (0.010 g, 0.013 mmol) was reacted

with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **23a** as a brown gum (0.010 g, 97%). R_f (MeOH/10% HCl, 3:1) 0.34; IR (ATR) ν_{max} 3316, 2944, 1668, 1449, 1115, 1022, 721 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.34 (2H, d, *J* = 2.9 Hz, NH-1), 8.89 (2H, t, *J* = 6.1 Hz, NH-10), 8.73 (2H, d, *J* = 3.6 Hz, H-2), 8.45 (4H, br s, NH-14), 8.06 (2H, d, *J* = 7.8 Hz, H-4), 7.16 (2H, t, *J* = 7.8 Hz, H-5), 7.07 (2H, d, *J* = 7.3 Hz, H-6), 3.30 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.92–2.88 (8H, m, H_2-13, H_2-15), 2.51 (6H, s, Me), 1.88–1.80 (4H, m, H_2-12), 1.56 (4H, m, H_2-16), 1.31 (4H, br s, H_2-17); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.8 (C-9), 138.0 (C-2), 135.7 (C-7a), 126.0 (C-3a), 124.1 (C-6), 122.8 (C-5), 121.9 (C-7), 118.8 (C-4), 112.5 (C-3), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 25.7, 25.5, 25.4 (C-12, C-16, C-17), 16.6 (Me); (+)-HRESIMS $[M+H]^+$ *m/z* 601.3486 (calcd for $C_{34}H_{45}N_6O_4$, 601.3497).

3.2.27. N^1,N^7-Bis(3-(2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)heptane-1,7-diaminium 2,2,2-trifluoroacetate (**23b**)

Using general procedure C, 2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**16**) (0.070 g, 0.34 mmol) was reacted with di-*tert*-butyl heptane-1,7-diylbis((3-aminopropyl) carbamate) (**9b**) (0.075 g, 0.17 mmol), PyBOP (0.178 g, 0.34 mmol) and DIPEA (0.09 mL, 0.52 mmol). Purification by column afforded di-*tert*-butyl heptane-1,7-diylbis((3-(2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetamido) propyl) carbamate) as a yellow oil (0.066 g, 48%). Using general procedure B, a sub-sample of this product (0.030 g, 0.036 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **23b** as a brown gum (0.022 g, 71%). R_f (MeOH/10% HCl, 3:1) 0.34; IR (ATR) ν_{max} 3326, 2944, 1678, 1449, 1114, 1022 cm^{-1}; ^1H NMR, (DMSO-d_6, 400 MHz) δ 12.35 (2H, d, *J* = 2.8 Hz, NH-1), 8.89 (2H, t, *J* = 6.1 Hz, NH-10), 8.73 (2H, d, *J* = 3.4 Hz, H-2), 8.46 (4H, br s, NH-14), 8.06 (2H, d, *J* = 7.9 Hz, H-4), 7.16 (2H, t, *J* = 7.5 Hz, H-5), 7.07 (2H, d, *J* = 7.1 Hz, H-6), 3.30 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.97–2.85 (8H, br m, H_2-13, H_2-15), 2.51 (6H, s, Me), 1.88–1.81 (4H, m, H_2-12), 1.56 (4H, br s, H_2-16), 1.28 (6H, br s, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.8 (C-9), 138.1 (C-2), 135.7 (C-7a), 126.0 (C-3a), 124.1 (C-6), 122.8 (C-5), 121.9 (C-7), 118.8 (C-4), 112.4 (C-3), 46.7 (C-15), 44.7 (C-13), 35.8 (C-11), 28.0 (C-18), 25.8, 25.7, 25.4 (C-12, C-16, C-17), 16.6 (Me); (+)-HRESIMS $[M+H]^+$ *m/z* 615.3644 (calcd for $C_{35}H_{47}N_6O_4$, 615.3653).

3.2.28. N^1,N^8-Bis(3-(2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)octane-1,8-diaminium 2,2,2-trifluoroacetate (**23c**)

Using general procedure C, 2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**16**) (0.070 g, 3.4 mmol) was reacted with di-*tert*-butyl octane-1,8-diylbis((3-aminopropyl)carbamate) (**9c**) (0.077 g, 0.17 mmol), PyBOP (0.178 g, 0.34 mmol) and DIPEA (0.09 mL, 0.52 mmol). Purification by column chromatography afforded di-*tert*-butyl octane-1,8-diylbis((3-(2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow oil (0.102 g, 73%). Using general procedure B, a sub-sample of this product (0.080 g, 0.097 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **23c** as a yellow oil (0.036 g, 44%). R_f (MeOH/10% HCl, 3:1) 0.34; IR (ATR) ν_{max} 3325, 2944, 1678, 1448, 1116, 1021 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.35 (2H, d, *J* = 2.5 Hz, NH-1), 8.89 (2H, t, *J* = 6.0 Hz, NH-10), 8.74 (2H, d, *J* = 3.3 Hz, H-2), 8.47 (4H, br s, NH-14), 8.06 (2H, d, *J* = 7.8 Hz, H-4), 7.16 (2H, t, *J* = 7.5 Hz, H-5), 7.07 (2H, d, *J* = 7.1 Hz, H-6), 3.30 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.98–2.85 (8H, br m, H_2-13, H_2-15), 2.51 (6H, s, Me), 1.88–1.81 (4H, m, H_2-12), 1.56 (4H, br s, H_2-16), 1.26 (8H, br s, H_2-17, H_2-18); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.8 (C-9), 138.1 (C-2), 135.7 (C-7a), 126.1 (C-3a), 124.1 (C-6), 122.8 (C-5), 121.9 (C-7), 118.8 (C-4), 112.5 (C-3), 46.8 (C-15), 44.7 (C-13), 35.8 (C-11), 28.3 (C-18), 25.8, 25.7, 25.5 (C-12, C-16, C-17), 16.6 (Me); (+)-HRESIMS $[M+H]^+$ *m/z* 629.3812 (calcd for $C_{36}H_{49}N_6O_4$, 629.3810).

3.2.29. N^1,N^{10}-Bis(3-(2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)decane-1,10-diaminium 2,2,2-trifluoroacetate (**23d**)

Using general procedure C, 2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**16**) (0.070 g, 3.4 mmol) was reacted with di-*tert*-butyl decane-1,10-diylbis((3-aminopropyl) carbamate) (**9d**) (0.081 g, 0.17 mmol), PyBOP (0.179 g, 0.34 mmol) and DIPEA (0.09 mL, 0.52 mmol).

Purification by column chromatography afforded di-*tert*-butyl decane-1,10-diylbis((3-(2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a white solid (0.080 g, 55%). Using general procedure B, a sub-sample of this product (0.030 g, 0.035 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **23d** as a brown oil (0.029 g, 94%). R_f (MeOH/10% HCl, 3:1) 0.26; IR (ATR) ν_{max} 3312, 2944, 1678, 1449, 1117, 1021 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.35 (2H, d, *J* = 3.0 Hz, NH-1), 8.90 (2H, t, *J* = 6.1 Hz, NH-10), 8.73 (2H, d, *J* = 3.5 Hz, H-2), 8.44 (4H, br s, NH-14), 8.06 (2H, d, *J* = 7.8 Hz, H-4), 7.16 (2H, t, *J* = 7.5 Hz, H-5), 7.07 (2H, d, *J* = 7.2 Hz, H-6), 3.29 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.97–2.85 (8H, m, H_2-13, H_2-15), 2.51 (6H, s, Me), 1.87–1.81 (4H, m, H_2-12), 1.56–1.50 (4H, br m, H_2-16), 1.24 (12H, br s, H_2-17, H_2-18, H_2-19); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.8 (C-9), 138.1 (C-2), 135.7 (C-7a), 126.1 (C-3a), 124.2 (C-6), 122.9 (C-5), 122.0 (C-7), 118.9 (C-4), 112.5 (C-3), 46.8 (C-15), 44.7 (C-13), 35.8 (C-11), 28.8, 28.5 (C-18, C-19), 26.0, 25.7, 25.5 (C-12, C-16, C-17), 16.6 (Me), (+)-HRESIMS $[M+H]^+$ *m/z* 657.4130 (calcd for $C_{38}H_{53}N_6O_4$, 657.4123).

3.2.30. N^1,N^{12}-Bis(3-(2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)dodecane-1,12-diaminium 2,2,2-trifluoroacetate (**23e**)

Using general procedure C, 2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetic acid (**16**) (0.070 g, 0.34 mmol) was reacted with di-*tert*-butyl octane-1,8-diylbis((3-aminopropyl)carbamate) (**9e**) (0.086 g, 0.17 mmol), PyBOP (0.179 g, 0.34 mmol) and DIPEA (0.09 mL, 0.52 mmol). Purification by column chromatography afforded di-*tert*-butyl dodecane-1,12-diylbis((3-(2-(7-methyl-1*H*-indol-3-yl)-2-oxoacetamido)propyl)carbamate) as a yellow oil (0.145 g, 97%). Using general procedure B, a sub-sample of this product (0.084 g, 0.095 mmol) was reacted with TFA (0.2 mL) in CH_2Cl_2 (2 mL) to afford the di-TFA salt **23e** as a brown oil (0.057 g, 66%). R_f (MeOH/10% HCl, 3:1) 0.23; IR (ATR) ν_{max} 3325, 2944, 1676, 1448, 1114, 1020 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.39 (2H, d, *J* = 2.7 Hz, NH-1), 8.90 (2H, t, *J* = 6.0 Hz, NH-10), 8.74 (2H, d, *J* = 3.2 Hz, H-2), 8.51 (4H, br s, NH-14), 8.07 (2H, d, *J* = 7.8 Hz, H-4), 7.16 (2H, t, *J* = 7.4 Hz, H-5), 7.07 (2H, d, *J* = 7.6 Hz, H-6), 3.30 (4H, dt, *J* = 6.5, 6.5 Hz, H_2-11), 2.98–2.85 (8H, m, H_2-13, H_2-15), 2.51 (6H, s, Me), 1.85 (4H, tt, *J* = 6.5, 6.5 Hz, H_2-12), 1.55 (4H, br m, H_2-16), 1.22 (16H, br s, H_2-17, H_2-18, H_2-19, H_2-20); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.7 (C-8), 163.8 (C-9), 138.1 (C-2), 135.7 (C-7a), 126.1 (C-3a), 124.1 (C-6), 122.8 (C-5), 122.0 (C-7), 118.8 (C-4), 112.5 (C-3), 46.8 (C-15), 44.7 (C-13), 35.8 (C-11), 29.0, 28.9, 28.6 (C-18, C-19, C-20), 25.9, 25.7, 25.5 (C-12, C-16, C-17), 16.6 (Me); (+)-HRESIMS $[M+H]^+$ *m/z* 685.4421 (calcd for $C_{40}H_{57}N_6O_4$, 685.4436).

3.3. Antimicrobial Assays

The susceptibility of bacterial strains *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853) to antibiotics and compounds was determined according to previously reported protocols [17]. Additional antimicrobial evaluation against MRSA (ATCC 43300) and *C. albicans* (ATCC 90028) was undertaken at the Community for Open Antimicrobial Drug Discovery at The University of Queensland (Australia) according to their standard protocols as reported previously [17,26].

3.4. Determination of the MICs of Antibiotics in the Presence of Synergizing Compounds

Antibiotic enhancing activities were determined according to previously reported protocols [14,17].

3.5. Cytotoxicity Assays

Cytotoxicity assays were conducted according to previously reported protocols [17,26].

3.6. Hemolytic Assay

Hemolysis assays were conducted according to previously reported protocols [17,26].

4. Conclusions

Our original screening for antimicrobial and antibiotic enhancing compounds from a library of marine natural products and their synthetic analogues identified a 6-bromoindolglyoxylamido-spermine conjugate as an active lead compound. Due to associated cytotoxicity and hemolytic properties, further efforts to explore the structure–activity relationship have investigated variation of substitution on the indole ring, and changes in the chain length of the polyamine fragment. While many analogues that were active as Gram-positive antibacterials were also associated with variable levels of cytotoxicity and/or hemolytic properties, the current study has identified two 7-methyl substituted analogues (**23b** and **23c**) with excellent anti-MRSA activity that are non-cytotoxic and non-hemolytic. This result defines a very narrow range of structural features required for optimal antibacterial properties. From the same set of analogues, only one example (**19a**), a 5-methoxy-PA3-6-3 conjugate, was non-toxic while also exhibiting strong tetracycline antibiotic enhancing activity towards *P. aeruginosa*. Further studies will be required to refine the mechanism of antibiotic enhancement.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ph16060823/s1. Figure S1. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **16**; Figure S2. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **17a**; Figure S3. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **17b**; Figure S4. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **17d**; Figure S5. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **18a**; Figure S6. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **18b**; Figure S7. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **18c**; Figure S8. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **18d**; Figure S9. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **18e**; Figure S10. ^{1}H (DMSO-d_6, 500 MHz) and ^{13}C (DMSO-d_6, 125 MHz) NMR spectra for **19a**; Figure S11. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **19b**; Figure S12. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **19d**; Figure S13. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **20a**; Figure S14. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **20b**; Figure S15. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **20c**; Figure S16. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **20d**; Figure S17. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **20e**; Figure S18. ^{1}H (DMSO-d_6, 500 MHz) and ^{13}C (DMSO-d_6, 125 MHz) NMR spectra for **21a**; Figure S19. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **21b**; Figure S20. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **21c**; Figure S21. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **21d**; Figure S22. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **21e**; Figure S23. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **22a**; Figure S24. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **22b**; Figure S25. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **22d**; Figure S26. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **23a**; Figure S27. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **23b**; Figure S28. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **23c**; Figure S29. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **23d**; Figure S30. ^{1}H (DMSO-d_6, 400 MHz) and ^{13}C (DMSO-d_6, 100 MHz) NMR spectra for **23e**.

Author Contributions: Conceptualization, B.R.C.; methodology, M.M.C., T.L., F.R. and K.S.; formal analysis, B.R.C. and J.M.B.; investigation, M.M.C., T.L., F.R., K.S., M.-L.B.-K., J.M.B. and B.R.C.; resources, B.R.C., M.-L.B.-K. and J.M.B.; data curation, B.R.C.; writing—original draft preparation, B.R.C. and M.M.C.; writing—review and editing, B.R.C., M.M.C., M.-L.B.-K. and J.M.B.; supervision, B.R.C., M.M.C. and J.M.B.; project administration, B.R.C. and M.M.C.; funding acquisition, B.R.C., M.M.C., M.-L.B.-K. and J.M.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Catalyst: Seeding Dumont d'Urville NZ-France Science and Technology Support Programme (19-UOA-057-DDU) provided by the New Zealand Ministry of Business, Innovation and Employment and administered by the Royal Society Te Apārangi, and the Auckland Medical Research Foundation (1116001).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article or Supplementary Material.

Acknowledgments: We thank Michael Schmitz, Tony Chen and Mansa Nair for their assistance with the NMR and mass spectrometric data and Hugo Gordon for technical support. Some of the antimicrobial screening was performed by CO-ADD (The Community for Antimicrobial Drug Discovery), funded by the Wellcome Trust (UK) and The University of Queensland (Australia).

Conflicts of Interest: The authors declare no conflict of interest.

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