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Guanidine Functionalized Anthranilamides as Effective Antibacterials with Biofilm Disruption Activity

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Abstract

We describe a library of amphiphilic anthranilamide compounds as antimicrobial peptide (AMP) mimics. These contain a hydrophobic naphthoyl side chain and different hydrophilic cationic groups such as amino, quaternary ammonium and guanidino groups. These are prepared via the ring-opening of different isatoic anhydrides. The antibacterial activity against *S. aureus* and *E. coli* of compounds containing guanidino cationic groups was greater than that for amino and quaternary ammonium cationic groups. The fluoro-substituted guanidinium compound **9b** showed a minimum inhibitory concentration (MIC) of 2.0 µM against *S. aureus*, and reduced established biofilms of *S. aureus* by 92% at 64 µM concentration. The bromo-substituted guanidinium compound **9d** exhibited good MIC against *S. aureus* (3.9 µM) and *E. coli* (15.6 µM) and disrupted established biofilms of *S. aureus* by 83% at 62.4 µM concentration. Cytoplasmic membrane permeability studies suggested that depolarization and disruption of the bacterial cell membrane could be a possible mechanism for antibacterial activity and the in vitro toxicity studies against MRC-5 human lung fibroblast cells showed that the potent compounds are non-toxic against mammalian cells.

Introduction

Multidrug-resistant bacteria pose an increasing threat to human health.[1] Resistant bacterial strains can complicate the treatment of urinary tract infections, pneumonia, and gastroenteritis, and can also contaminate medical devices.[2] Bacterial resistance to antibiotics can occur through several different mechanisms, such as altering the permeability of cell membranes, altering drug target binding sites, utilization of enzymes to destroy antibiotics, and use of efflux pumps to remove antibiotics.[3, 4]

Moreover, the existence of bacterial biofilms, which are clusters of bacterial cells encased in a self-produced matrix, increases the resistance of microbes to antibiotics and immune defenses.[5, 6] Biofilm-encased bacteria can be 10 to 1000 times more resistant to conventional antibiotics than planktonic cells.[7] Therefore, research and development of new antibacterial drugs must focus not only on planktonic bacteria but also on potential disruption of the biofilm.

In recent decades, cationic antimicrobial peptides (AMPs) have emerged as an alternative approach to small molecule antibiotics to combat bacteria resistance.[8-10] AMPs usually act against microbial membranes via non-receptor interactions, a principal role in the defence against local and systemic infections.[11]

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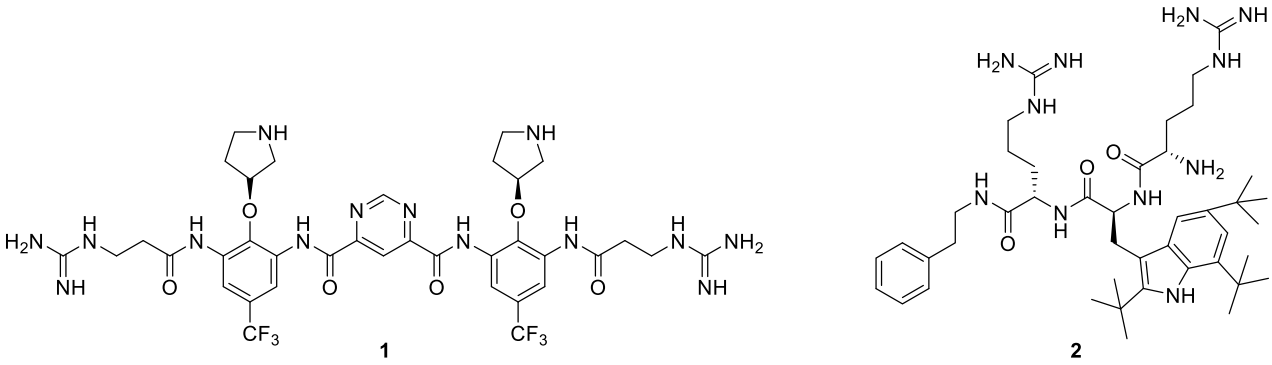

Fig. 1. Peptidomimetic compounds in clinical trials.

AMPs usually act against microbial membranes via non-receptor interactions, a principal role in the defence against local and systemic infections.[11] However, only a few naturally occurring AMPs have been used clinically, with the broad-spectrum Pexiganan (MSI-78)[12] being one notable example. The use of AMPs as antimicrobial agents is limited by their low proteolytic stability, poor oral bioavailability, and multistep synthesis.

Peptidomimetics are small protein-like molecules containing natural or unnatural amino acids to mimic the properties of natural peptides. The various types of peptidomimetics include α-peptides,[13] γ-AA peptides,[14-16] β-peptides,[17] peptoids,[18] β-turn mimetics,[19] and lipopeptides.[20] The peptidomimetics LTX-109 (**1**) and PMX-30063 (**2**) (Fig. 1) are currently undergoing human clinical trials.[21-23] Several research groups have studied small molecular mimics of AMPs, including arylamide foldamers[24], glyoxamides[25, 26], biphenyl backbone mimics[27], binaphthyl based dicationic peptoids[28], aryl-alkyl-lysines[29], xanthone[30, 31], and others.[32-38]

AMPs and their synthetic mimics possess an overall amphiphilic scaffold with both cationic and hydrophobic groups. The cationic charge enhances the specificity of the molecules for bacterial cells, due to the fact that the bacterial membranes contains a greater amount of anionic lipids compared to mammalian membranes.[39, 40] Meanwhile, the hydrophobicity of the molecules forms pore and it is important for the peptides partitioning into the lipid bilayer to cause bacterial death.[41]

In our previous research, we reported biphenyl backbone cationic peptidomimetic derivatives with good antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.[27] We also demonstrated the importance of having a tryptophan residue for antibacterial activity, as well as having simple amine or guanidine groups to mimic lysine and arginine amino acids.[27] Our group has also previously reported glyoxamide derivatives as antibacterial agents and biofilm disruptors by utilizing the ring-opening of isatins with amines.[25] However, the ring-opening of isatoic anhydrides to form carboxamides has not yet been explored as an avenue to generate peptidomimetics.

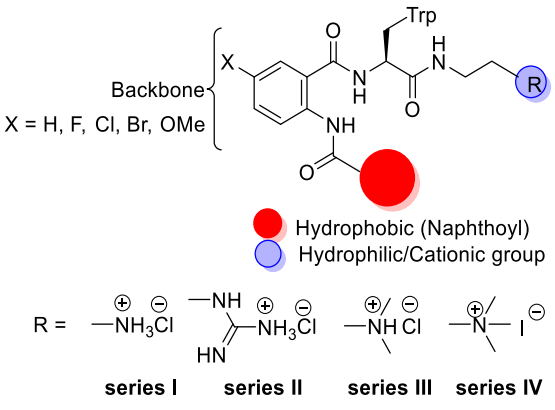

Fig. 2. Design of peptidomimetics based on the anthranilic acid scaffold.

In the present work, we describe the ring-opening of isatoic anhydrides to generate short cationic peptidomimetics based on the anthranilic acid (2-aminobenzoic acid) scaffold (Fig. 2).

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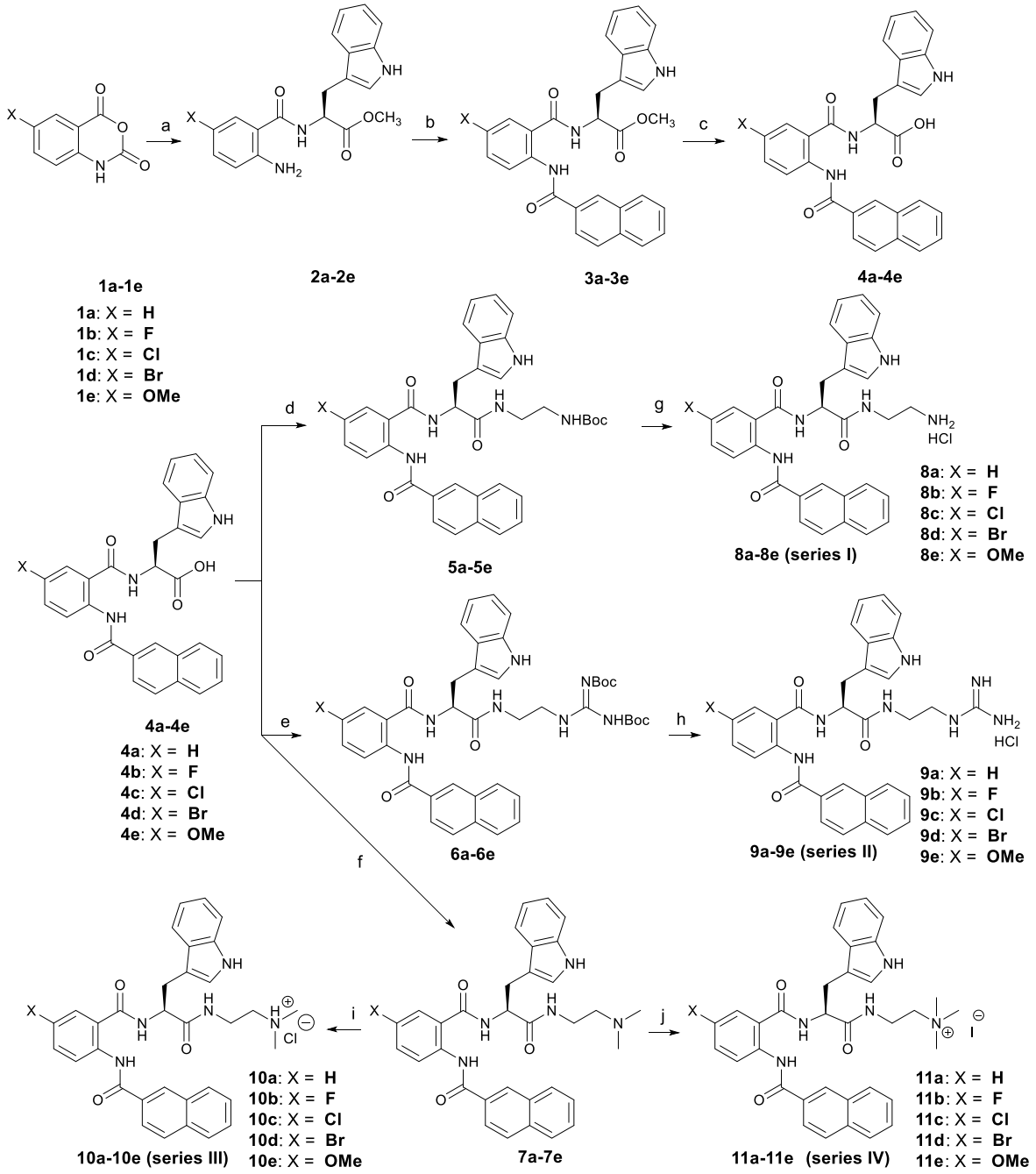

Scheme 1 General synthetic scheme to synthesize anthranilic acid-based peptidomimetics. Reaction conditions: a) isatoic anhydrides (1.0 equiv), methyl-*L*-tryptophanate (1.0 equiv), CH_3CN, reflux, 16 h; b) 2-naphthoyl chloride (1.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, rt, 4 h; c) 1 N $NaOH_{(aq)}$ (2.0 equiv), THF, MeOH, rt, overnight; d) N-Boc-1,2-diaminoethane, EDCI (1.2 equiv), HOBt (1.0 equiv), DIEA (2.5 equiv), DMF, rt, overnight; e) 1-(2-aminoethyl) 2,3-bis(*tert*-butoxycarbonyl)guanidine, EDCI (1.2 equiv), HOBt (1.0 equiv), DIEA (2.5 equiv), DMF, rt, overnight; f) *N*,*N*-dimethylethylenediamine, EDCI (1.2 equiv), HOBt (1.0 equiv), DIEA (2.5 equiv), DMF, rt, overnight; g) 4 N HCl in dioxane, CH_2Cl_2, rt, 4 h; h) TFA, CH_2Cl_2, rt, 8 h; 4 N HCl in dioxane, CH_2Cl_2, rt, 30 min; i) 4 N HCl in dioxane, CH_2Cl_2, rt, 30 min; j) CH_3I (2.0 equiv), CH_3CN, rt, overnight.

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The phenyl ring of the isatoic anhydrides was modified with electron-withdrawing halogen substitutions (F, Cl and Br) or an electron-donating OMe group to investigate the effect of electronic character on biological activity. Four series of compounds were synthesized containing different cationic groups, namely primary amine (series I), guanidine (series II), tertiary amine (series III) or quaternary ammonium salts (series IV), in order to understand the effect of the cationic functionality on the antimicrobial activities of these compounds. All of the compounds contained an *N*-naphthoyl substituent on the anthranilic acid backbone as the hydrophobic group. Moreover, due to the previously reported efficacy of tryptophan-containing peptidomimetics, all of the compounds in this study contained a tryptophan residue in the amine side chain.

The antibacterial activity of these compounds was measured against both Gram-positive and Gram-negative bacterial strains. We also investigated the mechanism of action of the active peptidomimetics using a membrane depolarization assay. Additionally, the ability of the active compounds to disrupt pre-formed biofilms of *S. aureus* and *E. coli* was evaluated. Finally, mammalian cell cytotoxicity was investigated for selected potent antimicrobial compounds to determine compound specificity.

Results and Discussion

Synthesis

The isatoic anhydrides **1a-e** were ring-opened with methyl-*L*-tryptophanate using acetonitrile as solvent to afford the corresponding substituted methyl (2-aminobenzoyl)-*L*-tryptophanate **2a-e** in 60-75% yields following trituration from acetonitrile and diethyl ether (Scheme 1). Treating **2a-2e** with 2-naphthoyl chloride and triethylamine as base furnished the *N*-naphthoyl compounds **3a-3e** in good yields (62-80%). The ester groups of **3a-3e** were hydrolyzed using sodium hydroxide and water yielding the key intermediate acids **4a-4e** in excellent yields (80-89%).

The acids **4a-4e** were treated with *N*-Boc-1,2-diaminoethane, 1-(2-aminoethyl)-2,3-bis(*tert*-butoxycarbonyl) guanidine, or *N,N*-dimethylethylenediamine under EDCI coupling conditions to afford the corresponding amides **5a-5e**, **6a-6e** and **7a-7e** respectively in moderate to good yields (50-61%). Compounds **5a-5e** were treated with 4 N HCl in dioxane to yield the primary ammonium hydrochloride salts **8a-8e** (series I) in good yields (75-81%). Treating compounds **6a-6e** with TFA and dichloromethane as solvent followed by 4 N HCl in dioxane gave the guanidinium hydrochloride **9a-9e** (series II) in moderate yields (45-59%). The compounds **7a-7e** were treated with 4 N HCl in dioxane to give the tertiary ammonium hydrochloride salts **10a-10e** (series III) in 90-91% yield. Finally, treatment of compounds **7a-7e** with methyl iodide in acetonitrile yielded the quaternary ammonium iodide salts **11a-11e** (series IV) in 90-94% yield.

Antibacterial activity

The antimicrobial activity of peptidomimetics **8a-11e** was examined by determination of their minimal inhibitory concentration (MIC) following a previously published protocol.[42] The activities were assessed against the Gram-positive *S. aureus* [SA38] and the Gram-negative bacterium and *E. coli* [K12]. The MIC values of these compounds **8a-11e** are presented in table 1.

We compared the MIC data of all our compounds with MSI-78 (Pexiganan) which has a 22-amino acid sequence. Based on the MIC data, a number of structure-activity relationships (SAR) studies could be determined. Most of the compounds showed good to excellent antibacterial activity against *S. aureus*, with MIC values ranging between 2.0 and 31.2 µM. The replacement of the H at the 5-position of isatoic anhydride with halogens such as F, Cl, Br or the electron-donating OCH_3 group both resulted in improvement of MIC values. Overall, the bromo-guanidinium compound **9d** displayed the best combination of activity against both *S. aureus* (3.9 µM) and *E. coli* (15.6 µM). Interestingly, the guanidinium compound **9b** containing the fluoro group that is widely used in medicinal chemistry[43] also showed excellent activity against *S. aureus* (2.0 µM), but was not as effective against *E. coli* (125 µM).

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Table 1: Antibacterial activity (MIC) of compounds.

Cpd	X	MIC (μM)	
		S. aureus	*E. coli*
8a	H	31.2	125
8b	F	7.8	15.6
8c	Cl	3.9	31.2
8d	Br	3.9	>125
8e	OMe	31.2	125
9a	H	15.6	62.5
9b	F	2.0	125
9c	Cl	3.9	62.5
9d	Br	3.9	15.6
9e	OMe	7.8	62.5
10a	H	31.2	125
10b	F	125	>125
10c	Cl	15.6	>125
10d	Br	7.8	125
10e	OMe	62.5	>125
11a	H	31.2	>125
11b	F	125	>125
11c	Cl	15.6	>125
11d	Br	31.2	>125
11e	OMe	31.2	>125
MSI-78	n/a	3.2-6.45	3.2-6.45

MIC values for MSI-78 previously reported.[27, 44, 45]

The nature of the cationic moiety greatly influenced the antimicrobial activity of the compounds. The primary ammonium compounds (**8a-8e**, series I), which mimic a lysine residue, showed good activity ranging from (3.9 to 31.2 μM) against *S. aureus* and good activity against *E. coli (*15.6–31.2 μM). Compound **8b**, substituted with a fluoro moiety showed a four-fold increase in MIC (7.8 μM) against *S. aureus* compared to unsubstituted derivative **8a**. Compound **8d** with least electronegative atom bromo showed two-fold increase in MIC (7.8 μM) against *S. aureus* compared to fluoro substituted compound **8b**. Interestingly, against *E. coli* the fluoro substituted compound showed eight-fold increase in MIC (15.6 μM) activity compared to bromo compound **8d** (>125 μM). However, the MIC of chloro (31.2 μM) and OMe (125 μM) substituted compound against *E. coli* suggests that it could be the steric factor which influences the activity against Gram-negative bacterium.

The guanidinium compounds (**9a-9e**, series II), which mimic the arginine residue, showed excellent activity (2.0–15.6 μM) against *S. aureus* and good activity (15.6–62.5 μM) against *E. coli*. Compound **9b**, substituted with a fluoro moiety showed a two-fold increase in MIC (2.0 μM) against *S. aureus* compared to the chloro-substituted compound **9c** (3.9 μM) and the bromo substituted compound **9d** (3.9 μM). Interestingly, against *E. coli* the trend was reversed with MIC values of 125 μM for **9b** (fluoro), 62.5 μM for **9c** (chloro), and 15.6 μM for **9d** (bromo). This result suggests that electronic and/or steric factors may influence the activity of the halogenated guanidinium compounds against the two bacterial strains.

Interestingly, in the case of the tertiary ammonium compounds (series III) and the quaternary ammonium compounds (QACs; series IV), *S. aureus* (7.8–15.6 μM) was generally more sensitive than *E. coli (*>125 μM). This suggests the length of the alkyl chains in the QACs is important for the activity against *E. coli.* [46, 47] There was no marked difference in the activity between the tertiary and quaternary salts (**10a-10c**) and (**11a-11c**) against *S. aureus.*, Notably, the bulkier Br substituent (**10d**) of tertiary ammonium salt showed four-fold increase in activity (7.8 μM) compared to quaternary salt (**11d**).

Overall, peptidomimetics with primary ammonium and guanidinium cationic groups showed good to excellent antimicrobial activity against *S. aureus* irrespective of the

halogen substituents. This is likely due to the interaction of primary amines and guanidines to the phosphate groups in the lipids, through a combination of hydrogen bonding and electrostatic interactions. Against *E. coli* the activity depended on both the nature of the cationic group and the identity of the halogen (F, Cl, Br). The bulky and electron withdrawing Br substitution with a guanidine cationic group had broad-spectrum activity. The tertiary and quaternary ammonium salts were not active against *E. coli* and moderately active against *S. aureus*. Out of the four series, the guanidinium peptidomimetics (series II) generally showed the highest broad-spectrum activity.

Cytoplasmic permeability

The mode of action of cationic AMPs and their mimics is generally believed to occur through electrostatic interactions between the positively-charged compounds and the negatively-charged bacterial membrane.[48] To test this hypothesis, the effect of the antibacterial compounds on the bacterial cytoplasmic membrane was tested by using the membrane potential-sensitive dye diSC3-5 (3,3'-dipropylthiadicarbocyanine iodide). The dye readily partitions into the bacterial cell membrane and aggregates within the membrane, leading to self-quenching of fluorescence.[49] However, the alteration of membrane potential due to membrane destabilization or pore formation by compounds will lead to an increase in fluorescence due to release of the dye. The guanidine compounds (**9b, 9d**) showing excellent MIC values are selected to understand their mode of action. As shown in Fig. 3A-B, compounds **9b** and **9d** (added at 0.5×, 1×, 2× and 4× MIC) caused release of the dye from *S. aureus* in a time and concentration-dependent manner. In particular, compound **9d** showed an increase in fluorescence at 1x MIC levels within 3 min. However, **9b** did not show much increase in fluorescence at 1x MIC.

Against *E. coli*, the active compound **9d** showed an increase in fluorescence intensity even at sub-MIC levels within 3 min as shown in Fig. 3C. Similarly, **8b** and **8c** also perturbs the cell membrane led to similar disruption of diSC3-5 fluorescence intensity (supplementary material Fig. S1). Taken together, these results indicated that the isatoic anhydride-derived cationic peptidomimetic compounds can readily permeabilize the bacterial membrane, which may then result in bacterial cell death.

To further explore the mechanism responsible for cell killing, we analyzed the effect of the active peptidomimetics on bacterial cell viability as shown in Fig. 4 (A-C). The cell viability of compounds **9b** and **9d** against *S. aureus* and **9d** against *E. coli* generally resembled the results observed in membrane depolarization studies. The compound **9d** at 4x MIC showed almost 4 log reductions in bacterial numbers within 5 minutes and this result coincides with the dye release assay as well. Compounds **9b** showed < 1 log reduction in bacterial numbers at 4x MIC suggests the bacterial killing increases with concentration. Against *E. coli*, compound, **9d** reduced the bacterial numbers with increase in concentration and time. Overall, these results suggest that these peptidomimetic compounds could exert their bactericidal effect via their membrane depolarization activity.

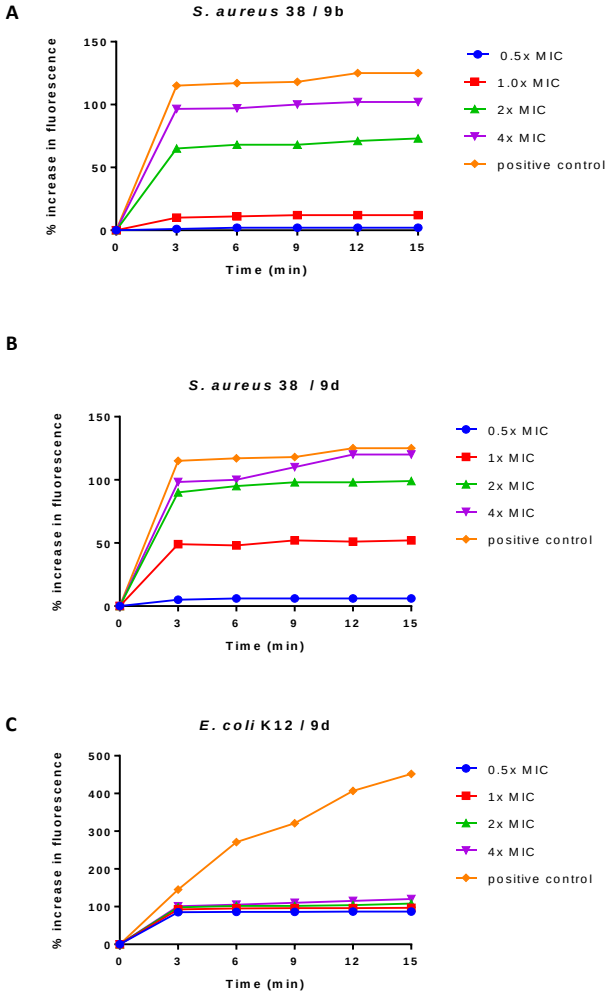

Fig. 3. *S. aureus* cytoplasmic membrane disruption promoted by **(A) 9b (1.0 µM, 2.0 µM, 4.0 µM, 8.0 µM) and (B) 9d (1.95 µM, 3.9 µM, 7.8 µM, 15.6 µM)** at different concentrations. **(C)** *E. coli* cytoplasmic membrane disruption promoted by **9d (7.8 µM, 15.6 µM, 31.2 µM, 62.4 µM)** at different concentrations. 20% DMSO was used as positive control.

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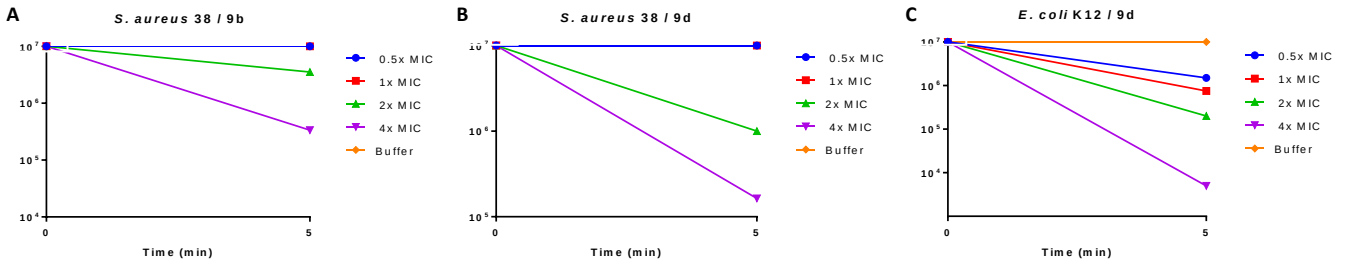

Fig. 4. *S. aureus* cell viability count in the presence of **9b (A), 9d (B),** and *E. coli* cell viability count in the presence of **9d (C)** at same concentrations used for cytoplasmic membrane disruption.

Anti-biofilm activity

The most active antibacterial peptidomimetics were tested against pre-formed biofilms of both bacterial strains using the crystal violet staining assay. The ability of compounds **9b** and **9d** to disrupt established *S. aureus* biofilms was measured at increasing MIC concentrations 1×, 2×, 4×, 8×, 16× and 32× (Fig. 5). The most active fluoro substituted compound **9b** showed 35% disruption at 1x MIC. Whereas **9d** with bromo substituent disrupted 58% of *S. aureus* biofilms at 1× MIC.

At the maximum concentration of 32× MIC, the compounds **9b** and **9d** disrupted *S. aureus* biofilms by 83-93%. Interestingly, the bromo quaternary ammonium compound **10d** showed 72% disruption at 1x MIC concentration despite having moderate MIC values compared to the fluoro guanidinium compound **9b** as shown in supplementary information Fig. S3.

Compound **9d** which showed good antibacterial activity against *E. coli* were also examined for their ability to disrupt established biofilms of *E. coli*. **9d** exhibited low levels of disruption against the established biofilm of *E. coli*. The bromo substituted guanidine compound **9d** disrupted 36% of the established biofilm of *E. coli* at 1x MIC concentration. Overall, these compounds are effectively disrupting the established biofilms of *S. aureus*.

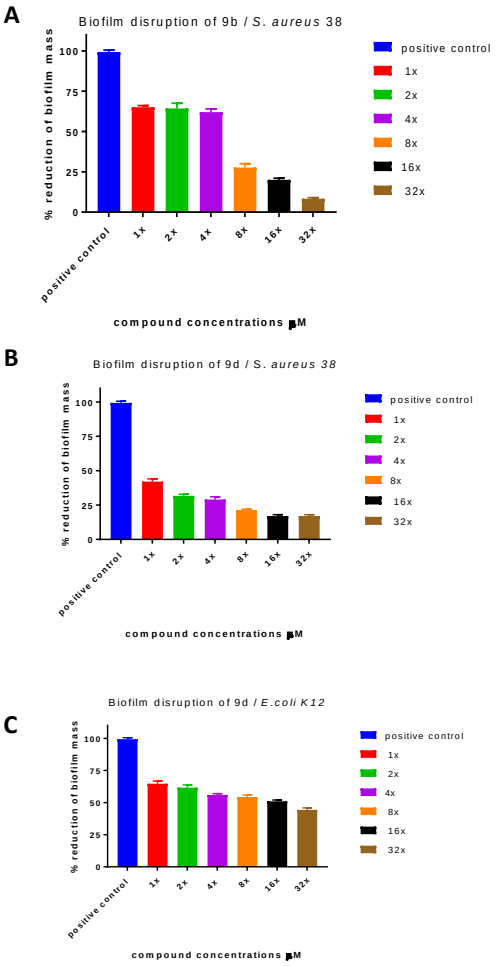

Fig. 5. Disruption of established biofilm of *S. aureus* after 24 h with 1× to 32× MIC concentrations of compounds **9b (A)** and **9d (B).** Disruption of established biofilm of *E. coli* after 24 h with 1× to 32× MIC concentrations of compound **9d (C)**. The positive control represents the pre-established biofilms without any compounds. Error bars indicate the standard error of the mean (SEM) of three independent experiments.

Cytotoxicity

The most active peptidomimetics (**8b-8d, 9b-9d, 10d, 11c**) were assessed for mammalian cell cytotoxicity against MRC-5 normal human lung fibroblasts using the Alamar Blue (Resazurin) assay.[50] The results showed that the guanidinium compounds with fluoro (**9b**) and bromo (**9d**) substituents were not cytotoxic at 50 µM. Even at 100 µM, **9b** and **9d** showed only 6.5% and 20% decrease in cell viability as shown in Table 2. These results indicate that compounds **9b** and **9d** are essentially non-toxic at the dosages needed to suppress *S. aureus* bacterial growth (MICs of 2.0 µM and 3.9 µM respectively).

Similarly, the chloro-substituted quaternary ammonium compound **11c** was not cytotoxic at 50 µM, which again was much higher than its MIC of 15.6 µM against *S. aureus*. All the primary ammonium compounds (**8b**-**8d**) with halogen substituents F (7.8 µM), Cl (3.9 µM), Br (3.9 µM) were cytotoxic at 50 µM concentration even though the MIC values are good against *S. aureus*.

Table 2 Percentage cell viability of MRC-5 after 72 h[a] incubation with 100 µM and 50 µM of compounds.

Compounds	MRC-5 cell viability after 72 h (% cell viability)	
	100 µM	50 µM
9b	99 ± 7	99 ± 3
9d	79 ± 14	93 ± 5
11c	0	97 ± 3
8b		0
8c		0
8d		0

[a] Data displayed are averages of three independent experiments with ± values representing standard deviation.

Conclusion

A library of amphiphilic compounds derived from 5-substitituted isatoic anhydride was prepared. These peptidomimetic compounds contain a hydrophobic naphthoyl group and different hydrophilic groups, including containing primary ammonium, guanidinium, tertiary ammonium or quaternary ammonium, as a source of cationic charge. In the antibacterial assay, the primary ammonium compounds (**8b-8d**) and guanidinium compounds (**9b-9d**) showed excellent antibacterial activity against *S. aureus* compared to the tertiary and quaternary ammonium counterparts. Additionally, the nature of the substituents (such as fluoro, chloro, bromo) in the aromatic ring also influenced biological activity. For instance, the bromo-substituted primary ammonium compound **8d** showed a four-fold increase in antibacterial activity compared to the corresponding fluoro compound **8b** against *E. coli*, however interestingly this trend was reversed for the bromo (**9d**) and fluoro (**9b**) guanidinium compounds. The methoxy substituted compounds are not as effective antibacterials as the halo derivatives. Cytoplasmic membrane permeability studies of active and non-toxic compounds **9b** and **9d** suggested that depolarization and disruption of the bacterial cell membrane could be a possible mechanism for antibacterial activity. In addition, these compounds showed effective biofilm disruption. The most active compounds **9b** (MIC: 2.0 µM) and **9d** (MIC: 3.9 µM) showed the highest biofilm disruption activity of 92% and 83% respectively at concentrations of 64 µM and 62.4 µM in established *S. aureus* biofilms. Furthermore, *in vitro* toxicity assays against human MRC-5 fibroblast cells demonstrated that the guanidine containing compounds **9b** and **9d** were highly selective for bacterial cells over mammalian cells. Overall, this work suggests that anthranilic acid-based peptidomimetics bearing primary ammonium or guanidinium cationic groups could be a new avenue for the development of membrane-disrupting antibacterial agents with biofilm disruption activity.

Experimental

Chemistry

All chemical reagents were purchased from commercial sources (Combi-Blocks, Chem-Impex and Sigma Aldrich) and used without further purification. Solvents were commercial and used as obtained. Reactions were performed using oven-dried glassware under an atmosphere of nitrogen and in anhydrous conditions (as required). Room temperature refers to the ambient temperature. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) plates pre-coated with Merck silica gel 60 F254. Visualization was accomplished with UV light, a ninhydrin staining solution in n-butanol. Flash chromatography and silica pipette plugs were performed under positive air pressure using Silica Gel 60 of 230–400 mesh (40–63 µm) and using Grace Davison LC60A 6-µm for reverse phase chromatography. Infrared spectra were recorded using a Cary 630 ATR spectrophotometer. High-resolution mass spectrometry was performed by the Bioanalytical Mass Spectrometry facility, UNSW (The

supplementary HRMS data reports both the measured and calculated mass. The calculated mass is below the found mass). Proton and Carbon NMR spectra were recorded in the solvents specified using a Bruker DPX 300 or a Bruker Avance 400 or 600 MHz spectrometer as designated. Chemical shifts (δ) are quoted in parts per million (ppm), to the nearest 0.01 ppm and internally referenced relative to the solvent nuclei. ^{1}HNMR spectral data are reported as follows [chemical shift in ppm; multiplicity in br, broad; s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; sept, septet; m, multiplet; or as a combination of these (*e.g*. dd, dt *etc*.)]; coupling constant (*J*) in hertz, integration, proton count and assignment.

The compound *L*-tryptophan methyl ester and 1-(2-aminoethyl)2,3-Bis(tert-butoxycarbonyl) guanidine was synthesized by using the previously reported procedure[27].

General Procedure (A) for the synthesis of compounds 2a-2e from Isatoic anhydrides. The suspension of isatoic anhydride (1 mmol) and *L*-tryptophan methyl ester (1 mmol) in anhydrous acetonitrile (20 mL) was refluxed under an argon atmosphere for 16 h. After completion of the reaction the mixture was concentrated in *vacuo* to yield the crude compound, which was subjected to trituration using acetonitrile and diethyl ether. The solid was filtered out and dried under *vacuo*.

Methyl (2-aminobenzoyl)-*L*-tryptophanate (**2a**). The title compound **2a** was prepared from compound **1a** (2.0 g, 12.26 mmol) and *L*-tryptophan methyl ester (2.67 g, 12.26 mmol) according to the general procedure **A**. The product **2a** was obtained as a grey solid (2.89 g, 69%); mp 139.0–140.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 400 MHz, DMSO-d$_6$: δ 10.84 (s, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 7.57-7.50 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), (7.14 (td, *J* = 4.0, 10.6 Hz, 1H), 7.07 (td, *J* = 1.2, 10.8 Hz, 1H), 7.00 (td, *J* = 0.8, 11.0 Hz, 1H), 6.67 (dd, *J* = 1.2, 8.2 Hz, 1H), 6.52-6.48 (m, 1H), 6.35 (br s, 2H), 4.66-4.60 (m, 1H), 3.26-3.23 (m, 2H), 3.63 (s, 3H) ;^{13}C NMR (100 MHz, DMSO-d_6): δ173.3, 169.4, 150.2, 136.5, 132.4, 128.9, 127.5, 124.1, 121.5, 118.9, 118.5, 116.8, 114.8, 114.1, 111.9, 110.5, 53.9, 52.3, 26.9; IR (ATR): ν_{max} 3420, 3326, 3239, 2950, 2341, 2114, 1920, 1739, 1640, 1508, 1433, 1233, 1176, 1133, 1017, 901, 742; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}N_3O_3$ [M + H]$^+$: 338.1499; found: 338.1494.

Methyl (2-amino-5-fluorobenzoyl)-*L*-tryptophanate (**2b**). The title compound **2b** was prepared from compound **1b** (2.0 g, 11.04 mmol) and *L*-tryptophan methyl ester (2.41 g, 11.04 mmol) according to the general procedure **A**. The product **2b** was obtained as a grey solid (2.43 g, 62%); mp 151.5–152.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 400 MHz, DMSO-d$_6$: δ 10.86 (s, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 0.80, 9.2 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.10-6.98 (m, 3H), 6.70 (dd, *J* = 4.0, 7.6 Hz, 1H), 6.25 (br s, 2H), 4.66-4.60 (m, 1H), 3.64 (s, 3H) 3.27-3.19 (m, 2H),;^{13}C NMR (100 MHz, DMSO-d_6): δ 173.2, 169.4, 150.2, 136.5, 132.4, 128.9, 127.5, 124.1, 121.4, 118.9, 118.4, 116.8, 114.8, 114.1, 111.9, 110.5, 53.9, 52.3, 26.9 ; IR (ATR): ν_{max} 3415, 3327, 3233, 3057, 2937, 2341, 2109, 1739, 1642, 1563, 1510, 1421, 1234, 1203, 1126, 1017, 946, 891, 826, 745; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}FN_3O_3$ [M + H]$^+$: 356.1405; found: 356.1400.

Methyl (2-amino-5-chlorobenzoyl)-*L*-tryptophanate (**2c**). The title compound **2c** was prepared from compound **1c** (2.0 g, 10.15 mmol) and *L*-tryptophan methyl ester (2.21 g, 10.15 mmol) according to the general procedure **A**. The product **2c** was obtained as a grey solid (2.8 g, 75%); mp 135.6–136.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.67 (d, *J* = 8.0 Hz, 1H), 7.59-7.55 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.20-7.15 (m, 2H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 12.0 Hz, 1H), 6.49 (br s, 2H), 4.65-4.59 (m, 1H), 3.64 (s, 3H), 3.21-3.18 (m, 2H) ;^{13}C NMR (100 MHz, DMSO-d_6): δ 173.0, 168.2, 149.2, 136.5, 132.2, 128.1, 127.5, 124.0, 121.4, 118.9, 118.5, 118.4, 118.0, 114.8, 111.9, 110.5, 54.0, 52.3, 26.9 ; IR (ATR): vmax 3417, 3326, 3259, 2938, 2341, 2097, 1890, 1726, 1572, 1508, 1423, 1230, 1174, 1101, 1017, 897, 822, 742; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}ClN_3O_4$ Na [M + Na]$^+$: 394.0929; found: 394.0929.

Methyl (2-amino-5-bromobenzoyl)-*L*-tryptophanate (**2d**). The title compound **2d** was prepared from compound **1d** (2.0 g, 8.30 mmol) and *L*-tryptophan methyl ester (1.81 g, 8.30 mmol) according to the general procedure **A**. The product **2d** was obtained as a grey solid (2.48 g, 72%); mp 212.5–213.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 8.68 (d, *J* = 8.0 Hz, 1H), 7.71 (br s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.27 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.20 (br s, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 12.0 Hz, 1H), 6.52 (br s, 2H), 4.63 (q, *J* = 8.0 Hz, 1H), 3.63 (s, 3H), 3.26-3.22 (m, 2H) ;^{13}C NMR (100 MHz, DMSO-d_6): δ 173.0, 168.2, 149.5, 136.5, 134.9, 130.9, 127.5, 124.0, 121.4, 118.9, 118.4, 115.4, 111.9, 110.5, 105.2, 54.0, 52.3, 26.9 ; IR (ATR): ν_{max} 3471, 3319, 2298, 2112, 1629, 1521, 1362, 1248, 1161, 1097, 1040, 817, 734; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}BrN_3O_3$ [M + H]$^+$: 416.0604; found: 416.0602.

Methyl (2-amino-5-methoxybenzoyl)-*L*-tryptophanate (**2e**). The title compound **2e** was prepared from compound **1e** (2.0 g, 10.36 mmol) and *L*-tryptophan methyl ester (2.26 g, 10.36 mmol) according to the general procedure **A**. The product **2e** was obtained as a grey solid (2.28 g, 60%); mp 144.0–144.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 1.6 Hz, 1H), 7.08-7.06 (m, 2H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.84 (dd, *J* = 4.0, 8.0 Hz, 1H), 6.63 (d, *J* = 12.0 Hz, 1H), 5.89 (br s, 2H), 4.65-4.59 (m, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.29-3.18 (m, 2H) ;^{13}C NMR (100 MHz, DMSO-d_6): δ 173.2,

169.1, 149.6, 144.4, 136.5, 127.5, 124.1, 121.4, 120.4, 118.9, 118.4, 118.1, 114.4, 112.6, 111.9, 110.5, 56.0, 54.0, 52.3, 27.0 ; IR (ATR): ν_{max} 3416, 3334, 3227, 2990, 2833, 2631, 1639, 1569, 1509, 1741, 1485, 1423, 1343, 1236, 1174, 1146, 1043, 1019, 834, 754; HRMS (ESI): *m/z* calcd for $C_{20}H_{21}N_3O_4$ Na [M + Na]$^+$: 390.1424; found: 390.1424.

General Procedure (B) for the synthesis of compounds 3a-3e. To a suspension of the anthranilate (1 mmol) in anhydrous dichloromethane (15 mL) triethylamine (3 mmol) was added at 0 ° C and stirred for 5 min. 2-naphthoyl chloride (1.2 mmol) in dichloromethane (15 mL) was added dropwise for 10 min. The reaction mixture was warmed to room temperature and stirred for 6 h. After completion, the reaction mixture was diluted with dichloromethane and washed with water, saturated sodium bicarbonate and then saturated brine solution. The organic layer was separated, dried over sodium sulfate, filtered and evaporated under reduced pressure. The crude compound was triturated with diethylether and the solid was filtered and dried under *vacuo*.

Methyl (2-(2-Naphthamido)benzoyl)-*L*-tryptophanate (**3a**). The title compound **3a** was prepared from compound **2a** (1.5 g, 4.44 mmol) and 2- naphthoyl chloride (1.01 g, 5.33 mmol) according to the general procedure **B**. The product **3a** was obtained as a off-white solid (1.41 g, 65%); mp 173.9–174.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.22 (s, 1H), 8.87 (d, *J* = 8.0 Hz, 1H), 8.58 (s, 1H), 8.20 (br s, 1H), 8.11-8.09 (m, 1H), 8.05-8.02 (m, 1H), 7.99-7.97 (m, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.62-7.52 (m, 4H), 7.37-7.31 (m, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.03-7.01 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.20-5.18 (m, 1H), 3.77 (s, 3H), 3.51-3.47 (m, 2H) ;^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 168.7, 165.6, 140.1, 136.1, 134.9, 133.0, 132.7, 132.0, 129.4, 128.6, 128.4, 127.8, 127.7, 127.5, 126.8, 126.7, 123.7, 122.9, 122.8, 122.4, 121.6, 119.88, 119.87, 118.5, 111.4, 109.8, 53.4, 52.6, 27.6 ; IR (ATR): ν_{max} 3308, 3050, 2945, 2319, 2112, 1909, 1733, 1661, 1585, 1516, 1430, 1299, 1218, 1092, 1027, 858, 811, 754, 667; HRMS (ESI): *m/z* calcd for $C_{30}H_{25}N_3O_4$ Na [M + Na]$^+$: 514.1737; found: 514.1736.

Methyl (2-(2-Naphthamido)-5-fluorobenzoyl)-*L*-tryptophanate (**3b**). The title compound **3b** was prepared from compound **2b** (1.5 g, 4.22 mmol) and 2- naphthoyl chloride (0.965 g, 5.06 mmol) according to the general procedure **B**. The product **3b** was obtained as an off-white solid (1.43 g, 67%); mp 125.1–125.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.97 (s, 1H), 10.85 (br s, 1H), 9.30 (d, *J* = 8.0 Hz, 1H), 8.60 (dd, *J* = 4.0, 16.0 Hz, 1H), 8.46 (br s, 1H), 8.09-8.00 (m, 3H), 7.88 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.66-7.57 (m, 3H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.52-7.47 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 4.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 8.0 Hz, 1H), 4.77-4.75 (m, 1H), 3.62 (s, 3H), 3.31-3.27 (m, 2H) ;^{13}C NMR (100 MHz, DMSO-d_6): δ 172.3, 168.0, 164.9, 158.7, 136.5, 136.0, 134.9, 132.6, 132.1, 129.5, 129.1, 128.6, 128.2, 128.1, 127.58, 127.5, 124.2, 123.6, 123.3, 122.5, 121.4, 119.8, 118.9, 118.4, 115.6, 115.4, 111.9, 110.1, 54.4, 52.5, 26.9, 31.4, 22.5, 14.4 ; IR (ATR): ν_{max} 3308, 3054, 2949, 1904, 1734, 1647, 1605, 1510, 1410,1351, 1301, 1205, 1116, 1009, 960, 822, 740; HRMS (ESI): *m/z* calcd for $C_{30}H_{24}FN_3O_4$ Na [M + Na]$^+$: 532.1643; found: 532.1639.

Methyl (2-(2-Naphthamido)-5-chlorobenzoyl)-*L*-tryptophanate (**3c**). The title compound **3c** was prepared from compound **2c** (1.5 g, 4.03 mmol) and 2- naphthoyl chloride (0.923 g, 4.84 mmol) according to the general procedure **B**. The product **3c** was obtained as a grey solid (1.48 g, 70%); mp 208.6–209.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s, 1H), 10.87 (s, 1H), 9.41 (d, *J* = 8.0 Hz, 1H), 8.65 (d, *J* = 12.0 Hz, 1H), 8.46 (s, 1H), 8.10-8.01 (m, 3H), 7.89-7.86 (m, 2H), 7.70-7.58 (m, 4H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 4.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 12.0 Hz, 1H), 4.80-4.77 (m, 1H), 3.64 (s, 3H), 3.30-3.28 (m, 2H) ;^{13}C NMR (100 MHz, DMSO-d_6): δ 172.3, 168.0, 165.0, 138.5, 136.5, 134.9, 132.69, 132.6, 131.9, 129.5, 129.2, 128.7, 128.6, 128.3, 128.2, 127.6, 127.5, 127.2, 124.1, 123.6, 122.7, 122.2, 121.5, 118.9, 118.4, 111.9, 110.1, 54.5, 52.5, 26.9; IR (ATR): ν_{max} 3308, 3054, 2947, 2341, 2111, 1917, 1735, 1668, 1628, 1584, 1512, 1436, 1303, 1207, 1096, 1008, 912, 960, 824, 735; HRMS (ESI): *m/z* calcd for $C_{30}H_{24}ClN_3O_4$ Na [M + Na]$^+$: 548.1348; found: 548.1346.

Methyl (2-(2-Naphthamido)-5-bromobenzoyl)-*L*-tryptophanate (**3d**). The title compound **3d** was prepared from compound **2d** (1.5 g, 3.60 mmol) and 2- naphthoyl chloride (0.824 g, 4.32 mmol) according to the general procedure **B**. The product **3d** was obtained as an off-white solid (1.27 g, 62%); mp 216.6–217.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s, 1H), 10.86 (s, 1H), 9.42 (d, *J* = 8.0 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.45 (s, 1H), 8.09-7.88 (m, 4H), 7.88-7.78 (m, 2H), 7.67-7.57 (m, 3H), 7.30-7.23 (m, 2H), 7.05-6.94 (m, 2H), 4.80-4.75 (m, 1H), 3.63 (s, 3H), 3.31-3.30 (m, 2H) ;^{13}C NMR (100 MHz, DMSO-d_6): δ 172.3, 167.9, 165.0, 138.9, 136.5, 135.6, 134.9, 132.6, 132.0, 131.4, 129.6, 129.2, 128.7, 128.3, 128.2, 127.6, 127.5, 124.2, 123.6, 123.0, 122.4, 121.5, 118.9, 118.5, 115.1, 111.9, 110.2, 54.5, 52.6, 26.9 ; IR (ATR): ν_{max} 3448, 3286, 2341, 2105, 1918, 1736, 1649, 1594, 1509, 1430, 1392, 1299, 1098, 972, 912, 823, 739; HRMS (ESI): *m/z* calcd for $C_{30}H_{24}BrN_3O_4$ Na [M + Na]$^+$: 592.0842; found: 592.0842.

Methyl (2-(2-Naphthamido)-5-methoxybenzoyl)-*L*-tryptophanate (**3e**). The title compound **3e** was prepared from compound **2e** (1.0 g, 4.08 mmol) and 2- naphthoyl chloride (0.933 g, 4.89 mmol) according to the general procedure **B**. The product **3e** was obtained as a grey solid (1.59 g, 75%); mp 178.9–179.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.77 (s, 1H), 8.74 (d, *J* = 8.0 Hz, 1H), 8.55 (s, 1H), 8.18 (br s, 1H), 8.07-7.91 (m, 4H), 7.62-7.57 (m, 3H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.12-7.07 (m, 2H), 7.01 (br s, 1H), 6.82-6.78 (m, 2H), 5.16 (q, *J* = 4.0 Hz, 1H), 3.77 (s, 3H),

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3.68 (s, 3H), 3.55-3.42 (m, 2H) ;^{13}C NMR (100 MHz, DMSO-d_6): δ 171.9, 168.4, 165.3, 154.9, 136.1, 134.9, 133.1, 132.8, 132.1, 129.3, 128.6, 128.2, 127.76, 127.7, 127.5, 126.6, 123.6, 123.3, 122.8 122.4, 121.5, 119.9, 118.4, 118.1, 112.1, 111.4, 109.7, 55.6, 53.5, 52.6, 27.5 ; IR (ATR): ν_{max} 3330, 2990, 2941, 1742, 1662, 1595, 1509, 1438, 1356, 1310, 1208, 1096, 1032, 902, 866, 813, 760, 684; HRMS (ESI): *m/z* calcd for $C_{31}H_{27}N_3O_5$ Na [M + Na]$^+$: 544.1843; found: 544.1841.

General Procedure (C) for the hydrolysis of esters 4a-4e. To the solution of methyl ester (1 mmol) in THF (2.0 mL) and MeOH (2.0 mL) 1 N $NaOH_{(aq)}$ (2 mmol) was added and stirred at room temperature for 8 h. After completion, the reaction mixture was acidified with 1.5 N HCl and then extracted with ethylacetate. The organic layer was washed with water, and saturated brine. The organic layer was separated and dried over sodium sulfate, filtered and evaporated under reduced pressure to yield the product.

(2-(2-Naphthamido)benzoyl)-*L*-tryptophan (**4a**). The title compound **4a** was prepared from compound **3a** (1.0 g, 2.03 mmol) according to the general procedure **C**. The product **4a** was obtained as an off-white solid (0.825 g, 85%); mp 216.0–217.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.86 (br s, 1H), 12.32 (s, 1H), 10.82 (s, 1H), 9.11 (d, *J* = 8.0 Hz, 1H), 8.65 (d, *J* = 8.0 Hz, 1H), 8.46 (br s, 1H), 8.09-8.01 (m, 3H), 7.89 (dd, *J* = -4.0, -12.0 Hz, 1H), 7.84 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.67-7.57 (m, 4H), 7.30-7.19 (m, 3H), 7.03-6.95 (m, 2H), 4.76-4.72 (m, 1H), 3.32-3.27 (m, 2H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.5, 169.3, 164.9, 139.7, 136.5, 134.8, 132.9, 132.6, 132.3, 129.6, 129.1, 128.9, 128.6, 128.2, 128.1, 127.5, 124.0, 123.6, 123.3, 121.4, 120.7, 120.5, 118.8, 118.5, 111.9, 110.7, 54.3, 26.8 ; IR (ATR): ν_{max} 3508, 3071, 2564, 2445, 2188, 2067, 1984, 1728, 1629, 1526, 1434, 1328, 1219, 746; HRMS (ESI): *m/z* calcd for $C_{29}H_{23}N_3O_4$ Na [M + Na]$^+$: 500.1581; found: 500.1573.

(2-(2-Naphthamido)-5-fluorobenzoyl)-*L*-tryptophan (**4b**). The title compound **4b** was prepared from compound **3b** (1.0 g, 1.96 mmol) according to the general procedure **C**. The product **4b** was obtained as an off-white solid (0.77 g, 80%); mp 171.9–172.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.80 (br s, 1H), 12.11 (s, 1H), 10.84 (d, *J* = 4.0 Hz, 1H), 9.19 (d, *J* = 8.0 Hz, 1H), 8.64 (dd, *J* = 8.0, 10.0 Hz, 1H), 8.46 (d, *J* = 4.0 Hz, 1H), 8.08-8.06 (m, 2H), 8.02-8.00 (m, 1H), 7.88 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.69-7.60 (m, 4H), 7.51-7.47 (m, 1H), 7.30-7.24 (m, 2H), 7.05-6.94 (m, 2H), 4.76-4.70 (m, 1H), 3.37-3.27 (m, 2H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 168.0, 164.9, 156.3, 136.5, 136.2, 134.9, 132.6, 132.1, 129.6, 129.1, 128.6, 128.2, 128.1, 127.5, 124.1, 123.6, 123.0, 122.4, 122.3, 121.4, 119.7, 119.5, 118.5, 115.3, 111.9, 110.6, 79.6, 54.4, 26.9 ; IR (ATR): ν_{max} 3296, 3053, 2921, 2341, 2106, 1918, 1718, 1640, 1604, 1509, 1409, 1305, 1203, 1094, 1010, 948, 864, 821, 739; HRMS (ESI): *m/z* calcd for $C_{29}H_{22}FN_3O_4$ Na [M + Na]$^+$: 518.1487; found: 518.1479.

(2-(2-Naphthamido)-5-chlorobenzoyl)-*L*-tryptophan (**4c**). The title compound **4c** was prepared from compound **3c** (1.0 g, 1.90 mmol) according to the general procedure **C**. The product **4c** was obtained as an off-white solid (0.86 g, 89%); mp 222.3–222.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.86 (br s, 1H), 12.23 (s, 1H), 10.85 (br s, 1H), 9.30 (d, *J* = 8.0 Hz, 1H), 8.67 (d, *J* = 8.0 Hz, 1H), 8.45 (br s, 1H), 8.09-8.01 (m, 3H), 7.92-7.86 (m, 2H), 7.69-7.62 (m, 4H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 4.0 Hz, 1H), 7.06-6.96 (m, 2H), 4.78-4.72 (m, 1H), 3.40-3.25 (m, 2H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 168.0, 165.0, 138.6, 136.5, 134.9, 132.6, 132.0, 129.6, 129.2, 128.7, 128.6, 128.3, 128.1, 127.5, 127.1, 124.0, 123.6, 122.5, 122.1, 121.4, 118.8, 118.5, 111.9, 110.6, 60.2, 54.4, 49.0, 26.9, 21.5, 21.3 ; IR (ATR): ν_{max} 3392, 3316, 3056, 2930, 2342, 2097, 1912, 1725, 1662, 1589, 1521, 1452, 1305, 1396, 1222, 1092, 999, 884, 810, 648, 735; HRMS (ESI): *m/z* calcd for $C_{29}H_{22}ClN_3O_4$ Na [M + Na]$^+$: 534.1191; found: 534.1190.

(2-(2-Naphthamido)-5-bromobenzoyl)-*L*-tryptophan (**4d**). The title compound **4d** was prepared from compound **3d** (1.0 g, 1.75 mmol) according to the general procedure **C**. The product **4d** was obtained as an off-white solid (0.799 g, 82%); mp 193.6–194.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.0 (br s, 1H), 12.25 (s, 1H), 10.85 (br s, 1H), 9.30 (d, *J* = 12.0 Hz, 1H), 8.62 (d, *J* = 12.0 Hz, 1H), 8.45 (br s, 1H), 8.10-8.01 (m, 4H), 7.87 (dd, *J* = 4.0, 12.0 Hz, 1H), 7.79 (dd, *J* = 4.0, 12.0 Hz, 1H), 7.70-7.62 (m, 3H), 7.30-7.23 (m, 2H), 7.06-6.94 (m, 2H), 4.77-4.70 (m, 1H), 3.29-3.21 (m, 2H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 167.8, 165.0, 139.0, 136.5, 135.5, 134.9, 132.6, 132.0, 131.4, 129.6, 129.2, 128.7, 128.3, 128.1, 127.6, 127.5, 124.0, 123.6, 122.7, 122.4, 121.4, 118.8, 118.6, 115.0, 111.9, 110.7, 54.5, 26.9 ; IR (ATR): ν_{max} 3382, 3313, 3052, 2928, 2342, 2110, 1907, 1737, 122, 1580, 1501, 1437, 1388, 1308, 1162, 1072, 1092, 912, 818, 736; HRMS (ESI): *m/z* calcd for $C_{29}H_{22}BrN_3O_4$ Na [M + Na]$^+$: 578.0686; found: 578.0686.

(2-(2-Naphthamido)-5-methoxybenzoyl)-L-tryptophan (**4e**). The title compound **4e** was prepared from compound **3e** (1.0 g, 1.91 mmol) according to the general procedure **C**. The product **4e** was obtained as an off-white solid (0.78 g, 81%); mp 150.8–151.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.96 (s, 1H), 10.86 (s, 1H), 9.10 (d, *J* = 8.0 Hz, 1H), 8.52 (d, *J* = 12.0 Hz, 1H), 8.45 (br s, 1H), 8.11-7.97 (m, 3H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.68-7.62 (m, 3H), 7.31-7.18 (m, 4H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 8.0 Hz, 1H), 4.75-4.74 (m, 1H), 3.83 (s, 3H), 3.28-3.22 (m, 2H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 168.9, 164.5, 154.9, 136.5, 134.8, 132.8, 132.7, 132.4, 129.5, 129.1, 128.5, 128.1, 128.0, 127.6, 127.4, 125.6, 124.1, 123.6, 122.6, 122.3, 121.4, 118.8, 118.5, 118.4, 113.8, 111.9, 110.7, 56.0, 54.3, 26.9 ; IR (ATR): ν_{max} 3491, 3430, 3254, 2917, 2734, 2540, 2082, 1919, 1707, 1647, 1600, 1520, 1451, 1432, 1345, 1097, 1044, 926, 864, 823, 737, 682; HRMS (ESI): *m/z* calcd for $C_{30}H_{25}N_3O_5$ Na [M + Na]$^+$: 530.1686; found: 530.1686.

General Procedure (D) for the synthesis of amides 5a-5e, 6a-6e, **7a-7e.** To the stirred solution of an acid (1.0 mmol), amine (1.0 mmol), HOBt (1.0 mmol), DIEA (2.5 mmol) in DMF (5 – 10 mL) EDCI (1.2 mmol) was added portion-wise. The

reaction was stirred for 16 h before the solvent was removed under reduced pressure and the resultant residue subjected to flash chromatography (2-5% MeOH/CH_2Cl_2 as the eluent) to afford the desired compounds.

***tert*-Butyl (*S*)-(2-(2-(2-(2-naphthamido)benzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate** (**5a**). The title compound **5a** was prepared from compound **4a** (0.1 g, 0.2094 mmol) and *N*-Boc-1,2-diaminoethane (33 mg, 0.2094 mmol) according to the general procedure **D**. The product **5a** was obtained as an off-white solid (91 mg, 70%); mp 223.7–225.1 °C; 400 MHz, DMSO-d_6: δ 12.30 (s, 1H), 10.78 (s, 1H), 8.92 (d, *J* = 8.0 Hz, 1H), 8.60 (d, *J* = 8.0 Hz, 1H), 8.46 (s, 1H), 8.26 (t, *J* = 4.0 Hz, 1H), 8.07-8.00 (m, 3H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.71-7.56 (m, 4H), 7.28-7.20 (m, 3H), 7.04-6.95 (m, 2H), 6.77 (t, *J* = 4.0 Hz, 1H), 4.76-4.73 (m, 1H), 3.29-3.01 (m, 6H), 1.33 (s, 9H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.7, 169.1, 165.0, 156.1, 139.6, 136.5, 134.8, 132.7, 132.6, 132.3, 129.5, 129.0, 128.5, 128.3, 128.1, 127.6, 127.5, 124.1, 123.7, 123.2, 121.3, 121.2, 120.8, 118.9, 118.6, 111.8, 110.9, 78.1, 54.9, 40.0, 39.4, 28.6, 27.8 ; IR (ATR): ν_{max} 3300, 3054, 2112, 1656, 1568, 1516, 1447, 1232, 1165, 971, 911, 862; HRMS (ESI): *m/z* calcd for $C_{36}H_{37}N_5O_5Na$ [M + Na]$^+$: 642.2687; found: 642.2678.

***tert*-Butyl (*S*)-(2-(2-(2-(2-naphthamido)-5-fluorobenzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate** (**5b**). The title compound **5b** was prepared from compound **4b** (0.1 g, 0.2018 mmol) and *N*-Boc-1,2-diaminoethane (32 mg, 0.2018 mmol) according to the general procedure **D**. The product **5b** was obtained as an off-white solid (91 mg, 71%); mp 241.4–242.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (s, 1H), 10.79 (s, 1H), 9.03 (d, *J* = 4.0 Hz, 1H), 8.58-8.55 (m, 1H), 8.45 (s, 1H), 8.25 (s, 1H), 8.06-8.00 (m, 3H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.69-7.62 (m, 4H), 7.47 (t, *J* = 4.0 Hz, 1H), 7.27-7.22 (m, 2H), 7.03-6.94 (m, 2H), 6.78 (br s, 1H), 4.73-4.69 (m, 1H), 3.17-3.00 (m, 6H), 1.33 (s, 9H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 167.8, 165.0, 158.7, 156.3, 156.1, 136.5, 136.0, 134.8, 132.6, 132.1, 129.5, 129.0, 128.5, 128.3, 128.1, 127.6, 127.5, 124.1, 123.7, 123.2, 121.3, 119.4, 119.2, 118.9, 118.6, 115.8, 115.5, 111.8, 110.9, 78.1, 55.0, 40.0, 39.5, 28.6, 27.8 ; IR (ATR): ν_{max} 3304, 3057, 2928, 1657, 1596, 1520, 1285, 1232, 1168, 1094, 946, 866, 757, 724, 660; HRMS (ESI): *m/z* calcd for $C_{36}H_{36}FN_5O_5Na$ [M + Na]$^+$: 660.2593; found: 660.2590.

***tert*-Butyl (*S*)-(2-(2-(2-(2-naphthamido)-5-chlorobenzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate** (**5c**). The title compound **5c** was prepared from compound **4c** (0.1 g, 0.1953 mmol) and *N*-Boc-1,2-diaminoethane (31 mg, 0.1953 mmol) according to the general procedure **D**. The product **5c** was obtained as an off-white solid (89 mg, 69%); mp 189.6–191.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.19 (s, 1H), 10.80 (s, 1H), 9.13 (d, *J* = 8.0 Hz, 1H), 8.61 (d, *J* = 8.0 Hz, 1H), 8.44 (s, 1H), 8.25 (t, *J* = 8.0 Hz, 1H), 8.07-8.02 (m, 3H), 7.90-7.71 (m, 2H), 7.69-7.61 (m, 4H), 7.26-7.21 (m, 2H), 7.03-6.94 (m, 2H), 6.78 (t, *J* = 4.0 Hz, 1H), 4.76-4.71 (m, 1H), 3.29-3.01 (m, 6H), 1.33 (s, 9H), ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 167.8, 165.0, 156.1, 138.5, 136.5, 134.9, 132.6, 132.3, 132.0, 129.5, 129.1, 128.8, 128.6, 128.4, 128.1, 127.6, 127.5, 127.1, 124.0, 123.6, 122.7, 122.5, 121.3, 118.9, 118.6, 111.8, 110.9, 78.1, 40.0, 39.4, 28.6, 27.8 ; IR (ATR): ν_{max} 3298, 3054, 2342, 2112, 1910, 1655, 1584, 1506, 1451, 1392, 1301, 1230, 1166, 1096, 970, 913, 826, 734; HRMS (ESI): *m/z* calcd for $C_{36}H_{36}ClN_5O_5Na$ [M + Na]$^+$: 676.2297; found: 676.2295.

***tert*-Butyl (*S*)-(2-(2-(2-(2-naphthamido)-5-bromobenzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate** (**5d**). The title compound **5d** was prepared from compound **4d** (0.1 g, 0.1797 mmol) and a *N*-Boc-1,2-diaminoethane (28 mg, 0.1797 mmol) according to the general procedure **D**. The product **5d** was obtained as an off-white solid (81 mg, 65%); mp 189.5–190.9 °C; ^{1}H NMR 400 MHz, DMSO-d_6: δ 12.22 (s, 1H), 10.80 (s, 1H), 9.16 (d, *J* = 8.0 Hz, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 8.43 (s, 1H), 8.27 (br s, 1H), 8.06-8.00 (m, 4H), 7.86-7.61 (m, 5H), 7.26-7.21 (m, 2H), 7.03-6.95 (m, 2H), 6.78 (br s, 1H), 4.75-4.71 (m, 1H), 3.29-3.01 (m, 6H), 1.33 (s, 9H), ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 167.7, 165.0, 156.1, 138.9, 136.5, 135.2, 134.9, 132.6, 132.0, 131.6, 129.5, 129.1, 128.6, 128.4, 128.1, 127.6, 127.5, 124.0, 123.6, 122.9, 122.7, 121.3, 118.9, 118.6, 115.0, 111.8, 110.9, 78.1, 55.1, 40.0, 39.4, 28.6, 27.8 ; IR (ATR): ν_{max} 3390, 1740, 1636, 1578, 1498, 1437, 1388, 1299, 1225, 1164, 1093, 1010, 912, 819; HRMS (ESI): *m/z* calcd for $C_{36}H_{36}BrN_5O_5$ Na [M + Na]$^+$: 720.1792; found: 720.1792.

***tert*-Butyl (*S*)-(2-(2-(2-(2-naphthamido)-5-methoxybenzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate** (**5e**). The title compound **5e** was prepared from compound **4e** (0.1 g, 0.197 mmol) and *N*-Boc-1,2-diaminoethane (31 mg, 0.197 mmol) according to the general procedure **D**. The product **5e** was obtained as an off-white solid (77 mg, 60%); mp 244.1–244.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.87 (s, 1H), 10.83 (s, 1H), 8.95 (d, *J* = 8.0 Hz, 1H), 8.44-8.40 (m, 2H), 8.28 (br s, 1H), 8.06-7.99 (m, 3H), 7.88-7.86 (m, 1H), 7.71-7.60 (m, 3H), 7.29-7.24 (m, 3H), 7.17 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.04-6.44 (m, 2H), 6.78 (t, *J* = 8.0 Hz, 1H), 4.74-4.68 (m, 1H), 3.82 (s, 3H), 3.34-3.01 (m, 6H), 1.33 (s, 9H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.7, 168.7, 164.7, 156.0, 155.0, 136.5, 134.7, 132.6, 132.5, 132.4, 129.5, 128.9, 128.4, 128.1, 127.6, 127.4, 124.2, 123.7, 123.3, 122.8, 121.3, 118.9, 118.6, 118.1, 113.9, 111.8, 110.9, 78.1, 55.9, 54.8, 40.0, 39.4, 28.6, 27.8 ; IR (ATR): ν_{max} 3302, 2288, 1655, 1592, 1519, 1455, 1271, 1225, 1166, 1095, 1042, 991, 859, 819, 735; HRMS (ESI): *m/z* calcd for $C_{37}H_{39}N_5O_6$ Na [M + Na]$^+$: 672.2793; found: 672.2791.

(*S*)-*N*-(2-((1-((2-diBocguanidinoethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**6a**). The title compound **6a** was prepared from compound **4a** (0.2 g, 0.4188 mmol) and amine (126 mg, 0.4188 mmol) according to the general procedure **D**. The product **6a** was

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obtained as an off-white solid (0.172 mg, 54%); mp 243.8–245.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.56 (s, 1H), 11.35 (br s, 1H), 8.91 (dd, *J* = 4.0, 8.0 Hz, 1H), 8.63 (br s, 1H), 8.44 (br s, 1H), 8.22 (br s, 1H), 8.14 (dd, *J* = 4.0, 8.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.99-7.92 (m, 2H), 7.70-7.55 (m, 6H), 7.36-7.31 (m, 2H), 7.19-7.09 (m, 4H), 4.92-4.91 (m, 1H), 3.50-3.21 (m, 6H), 1.57 (s, 9H), 1.52 (s, 9H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.8, 168.5, 165.6, 157.0, 152.8, 140.3, 136.0, 134.9, 132.9, 132.8, 132.3, 129.4, 128.4, 128.3, 127.7, 127.6, 127.1, 126.5, 123.8, 123.1, 122.8, 122.2, 121.4, 119.7, 119.6, 118.8, 111.1, 110.4, 84.0, 80.5, 60.4, 54.5, 41.1, 40.2, 29.08, 28.2, 28.0, 21.0, 14.2 ; IR (ATR): ν_{max} 3280, 2972, 2330, 2113, 1719, 1615, 1507, 1430, 1304, 1925, 1128, 1047, 880, 739; HRMS (ESI): *m/z* calcd for $C_{42}H_{47}N_7O_7$ [M +H]$^+$: 762.3610; found: 762.3605.

(*S*)-*N*-(4-fluoro-2-((1-((2-diBocguanidinoethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**6b**). The title compound **6b** was prepared from compound **4b** (0.2 g, 0.4039 mmol) and amine (122 mg, 0.4039 mmol) according to the general procedure **D**. The product **6b** was obtained as an off-white solid (160 mg, 52%); mp 208.4–209.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.30 (s, 1H), 11.35 (s, 1H), 8.88 (dd, *J* = 4.0, 8.0 Hz, 1H), 8.60 (br s, 2H), 8.46 (br s, 1H), 8.21 (br s, 1H), 8.11 (dd, *J* = 4.0, 8.0 Hz, 1H), 8.05-8.03 (m, 1H), 7.98-7.92 (m, 2H), 7.76 (br s, 1H), 7.68-7.56 (m, 3H), 7.31-7.28 (m, 2H), 7.25-7.09 (m, 5H), 4.90-4.89 (m, 1H), 3.49-3.21 (m, 6H), 1.57 (s, 9H), 1.53 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 167.3, 165.4, 156.5, 152.8, 136.4, 136.0, 134.9, 132.7, 132.0, 129.3, 128.5, 128.3, 127.8, 127.7, 127.5, 126.6, 123.7, 123.4, 123.3, 123.1, 122.2, 119.7, 119.5, 118.7, 113.8, 113.6, 111.2, 110.3, 84.1, 54.6, 41.3, 40.3, 29.0, 28.2, 28.0 ; IR (ATR): ν_{max} 3278, 2974, 2327, 2119, 1908, 1719, 1607, 1509, 1409, 1322, 1226, 1128, 1047, 958, 809, 738; HRMS (ESI): *m/z* calcd for $C_{42}H_{46}FN_7O_7$ [M + H]$^+$: 780.3516; found: 780.3498.

(*S*)-*N*-(4-chloro-2-((1-((2-diBocguanidinoethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**6c**). The title compound **6c** was prepared from compound **4c** (0.2 g, 0.3906 mmol) and amine (118 mg, 0.3906 mmol) according to the general procedure **D**. The product **6c** was obtained as an off-white solid (155 mg, 54%); mp 235.1–236.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.39 (s, 1H), 11.35 (s, 1H), 8.88 (d, *J* = 9.0 Hz, 1H), 8.59 (br s, 1H), 8.46 (t, *J* = 3.0 Hz, 1H), 8.28 (br s, 1H), 8.04-8.01 (m, 1H), 7.98-7.91 (m, 2H), 7.76-7.69 (m, 1H), 7.66-7.55 (m, 3H), 7.51-7.48 (m, 2H), 7.35-7.28 (m, 2H), 7.18-7.09 (m, 3H), 4.94-4.87 (m, 1H), 3.45-3.37 (m, 6H), 1.56 (s, 9H), 1.52 (s, 9H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 167.3, 165.5, 162.7, 157.3, 152.9, 138.8, 136.0, 135.0, 132.76, 132.7, 131.9, 129.3, 128.5, 128.4, 127.9, 127.7, 127.5, 126.9, 126.6, 123.7, 123.1, 122.7, 122.3, 121.1, 119.7, 118.7, 111.2, 110.3, 83.8, 80.0, 54.6, 41.5, 40.06, 29.0, 28.3, 28.0 IR (ATR): ν_{max} 3277, 2977, 1728, 1615, 1502, 1397, 1305, 1226, 1128, 1048, 912, 807, 739; HRMS (ESI): *m/z* calcd for $C_{42}H_{46}ClN_7O_7$ Na [M + Na]$^+$: 818.3039; found: 818.3042.

(*S*)-*N*-(4-bromo-2-((1-((2-diBocguanidinoethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**6d**). The title compound **6d** was prepared from compound **4d** (0.2 g, 0.3594 mmol) and amine (108 mg, 0.3594 mmol) according to the general procedure **D**. The product **6d** was obtained as an off-white solid (150 mg, 50%); mp 259.5–260.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.37 (s, 1H), 11.33 (s, 1H), 8.80 (dd, *J* = 4.0, 1.8 Hz, 1H), 8.57 (br s, 1H), 8.43 (t, *J* = 4.0 Hz, 1H), 8.23 (br s, 1H), 8.09-8.06 (m, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.95-7.89 (m, 2H), 7.73 (t, *J* = 4.0 Hz, 1H), 7.58-7.54 (m, 5H), 7.33-7.28 (m, 2H), 7.16-7.07 (m, 3H), 4.90-4.85 (m, 1H), 3.45-3.25 (m, 6H), 1.54 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 167.2, 165.5, 162.7, 157.3, 152.9, 139.3, 136.0, 135.6, 135.0, 132.7, 131.9, 129.8, 129.3, 128.5, 128.4, 127.9, 127.7, 127.5, 126.6, 123.7, 123.1, 123.0, 122.3, 121.5, 119.8, 118.7, 115.3, 111.2, 110.3, 83.8, 80.0, 54.6, 41.5, 40.0, 29.0, 28.3, 28.0 ; IR (ATR): ν_{max} 3413, 3353, 3276, 2984, 2763, 1769, 1679, 1646, 1551, 1459, 1405 1328, 1256, 1128, 1019, 831, 801; HRMS (ESI): *m/z* calcd for $C_{42}H_{46}BrN_7O_7$ [M + H]$^+$: 840.2715; found: 840.2712.

(*S*)-*N*-(4-methoxy-2-((1-((2-diBocguanidinoethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**6e**). The title compound **6e** was prepared from compound **4e** (0.2 g, 0.394 mmol) and amine (119 mg, 0.394 mmol) according to the general procedure **D**. The product **6e** was obtained as an off-white solid (159 mg, 51%); mp 249.1–249.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1H), 11.48 (s, 1H), 10.80 (s, 1H), 8.95 (d, *J* = 8.0 Hz, 1H), 8.44-8.38 (m, 4H), 8.04-8.02 (m, 3H), 7.87-7.84 (m, 1H), 7.72-7.61 (m, 3H), 7.29-7.25 (m, 3H), 7.16 (dd, *J* = 4.0, 12.0 Hz, 1H), 7.02-6.96 (m, 2H), 4.74-4.68 (m, 1H), 3.83 (s, 3H), 3.40-3.27 (m, 2H), 3.26-3.17 (m, 4H), 1.41 (s, 9H), 1.35 (s, 9H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.0, 168.7, 164.6, 163.5, 156.0, 154.9, 152.3, 136.5, 134.7, 132.68, 132.6, 132.4, 129.4, 128.9, 128.4, 128.1, 127.6, 127.4, 124.1, 123.7, 123.1, 122.7, 121.3, 118.9, 118.6, 118.1, 113.9, 111.7, 111.0, 83.2, 78.6, 55.9, 54.9, 40.5, 38.4 28.4, 28.0, 27.8; IR (ATR): ν_{max} 3292, 2976, 2088, 1720, 1612, 1517, 1412, 1326, 1227, 1132, 1047, 740; HRMS (ESI): *m/z* calcd for $C_{43}H_{49}N7O_8$ Na [M + Na]$^+$: 814.3535; found: 814.3533.

(*S*)-*N*-(2-((1-((2-(dimethylamino)ethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**7a**). The title compound **7a** was prepared from compound **4a** (0.2 g, 0.4188 mmol) and *N*,*N*-dimethylethylenediamine (37 mg, 0.4188 mmol) according to the general procedure **D**. The product **7a** was obtained as an off-white solid (158 mg, 69%); mp 87.0–88.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.28 (s, 1H), 10.80 (s, 1H), 8.94 (d, *J* = 12.0 Hz, 1H), 8.57 (d, *J* = 6.0 Hz, 1H), 8.47 (s, 1H), 8.09-8.01 (m, 4H), 7.89 (d, *J* = 12.0 Hz, 1H), 7.80 (d, *J* = 12.0 Hz, 1H), 7.71-7.56 (m, 4H), 7.29-7.25

(m, 2H), 7.05-6.96 (m, 2H), 4.74-4.71 (m, 1H), 3.20-3.16 (m, 4H), 2.23-2.18 (m, 2H), 2.02 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.4, 169.1, 165.0, 139.5, 136.5, 134.8, 132.6, 132.3, 129.5, 129.0, 128.5, 128.2, 128.1, 127.6, 127.5, 124.2, 123.7, 123.3, 121.4, 121.3, 120.9, 118.9, 118.6, 111.7, 110.9, 58.4, 54.9, 45.4, 37.4, 27.7 ; IR (ATR): ν_{max} 3282, 3053, 2942, 2341, 2110, 1921, 1638, 1594, 1507, 1441, 1304, 1229, 1041, 1096, 862, 911, 740; HRMS (ESI): *m/z* calcd for $C_{33}H_{33}N_5O_3$ $[M + H]^+$: 548.2656; found: 548.2647.

(*S*)-*N*-(2-((1-((2-(dimethylamino)ethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)-4-fluorophenyl)-2-naphthamide (**7b**). The title compound **7b** was prepared from compound **4b** (0.2 g, 0.4036 mmol) and *N*,*N*-dimethylethylenediamine (36 mg, 0.4036 mmol) according to the general procedure **D**. The product **7b** was obtained as an off-white solid (161 mg, 71%); mp 148.4–149.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s, 1H), 10.81 (s, 1H), 9.03 (d, *J* = 8.0 Hz, 1H), 8.53 (q, *J* = 8.0 Hz, 1H), 8.45 (br s, 1H), 8.09-8.01 (m, 4H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.70-7.61 (m, 4H), 7.49-7.44 (m, 1H), 7.28-7.24 (m, 2H), 7.04-6.94 (m, 2H), 4.75-4.69 (m, 1H), 3.29-3.26 (m, 1H), 3.18-3.10 (m, 3H), 2.22-2.10 (m, 2H), 2.03 (s, 6H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.2, 167.8, 165.0, 156.3, 136.5, 135.8, 134.8, 132.6, 132.1, 129.5, 129.0, 128.6, 128.3, 128.1, 127.6, 127.5, 124.2, 123.7, 121.3, 118.9, 118.6, 111.8, 110.8, 58.4, 55.0, 45.5, 37.4, 27.7 ; IR (ATR): ν_{max} 3390, 3318, 3050, 2918, 2599, 2119, 1724, 1639, 1589, 1520, 1447, 1326, 1213, 1154, 1094, 897, 759; HRMS (ESI): *m/z* calcd for $C_{33}H_{32}FN_5O_3$ $[M + H]^+$: 566.2562; found: 566.2559.

(*S*)-*N*-(4-chloro-2-((1-((2-(dimethylamino)ethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**7c**). The title compound **7c** was prepared from compound **4c** (0.2 g, 0.3906 mmol) and *N*,*N*-dimethylethylenediamine (35 mg, 0.3906 mmol) according to the general procedure **D**. The product **7c** was obtained as an off-white solid (158 mg, 70%); mp 131.2–132.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.25 (s, 1H), 8.83 (d, *J* = 8.0 Hz, 1H), 8.55 (br s, 1H), 8.22 (br s, 1H), 8.07-8.01 (m, 2H), 7.97-7.90 (m, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.62-7.48 (m, 5H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H),7.21-7.15 (m, 3H), 6.59 (br s, 1H), 4.98-4.96 (m, 1H),3.52-3.47 (m, 1H), 3.36-3.27 (m, 2H), 3.19-3.16 (m, 2H), 2.35-2.16 (m, 6H), 2.08 (s, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 167.6, 165.5, 138.7, 136.2, 135.0, 132.79, 132.7, 131.8, 129.4, 128.6, 128.3, 127.96, 127.9, 127.7, 127.4, 127.0, 126.7, 123.6, 123.2, 122.8, 122.4, 121.1, 119.9, 118.9, 111.3, 110.7, 57.1, 54.6, 44.4, 36.3, 28.9; IR (ATR): ν_{max} 3275, 3053, 2933, 2320, 2105, 2105, 1908, 1651, 1581, 1500, 1430, 1396, 1297, 1227, 104, 1038, 912, 823, 736; HRMS (ESI): *m/z* calcd for $C_{33}H_{32}ClN_5O_3$ $[M + H]^+$: 582.2266; found: 582.2264.

(*S*)-*N*-(4-bromo-2-((1-((2-(dimethylamino)ethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**7d**). The title compound **7d** was prepared from compound **4d** (0.2 g, 0.3594 mmol) and *N*,*N*-dimethylethylenediamine (30 mg, 0.3594 mmol) according to the general procedure **D**. The product **7d** was obtained as an off-white solid (146 mg, 65%); mp 114.9–116.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 12.26 (s, 1H), 8.80 (d, *J* = 8.0 Hz, 1H), 8.57 (br s, 1H), 8.17 (br s, 1H), 8.09-8.03 (m, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.67-7.56 (m, 4H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.35-7.33 (m, 1H), 7.23-7.15 (m, 3H), 6.25 (br s, 1H), 4.97-4.91 (m, 1H), 3.51-3.10 (m, 1H), 3.31-3.24 (m, 2H), 3.19-3.12 (m, 1H), 2.22-2.19 (m, 1H), 2.08-2.06 (m, 1H), 2.00 (s, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 167.4, 165.5, 139.2, 136.2, 135.7, 135.0, 132.7, 131.8, 129.7, 129.4, 128.6, 128.4, 127.9, 127.7, 127.4, 126.7, 123.6, 123.1, 122.5, 121.4, 120.0, 118.8, 115.3, 111.3, 110.7, 57.1, 54.6, 44.6, 36.7, 29.0 ; IR (ATR): ν_{max} 3055, 2934, 2319, 1736, 1637, 1580, 1431, 1389, 1303, 1223, 1177, 912, 819; HRMS (ESI): *m/z* calcd for $C_{33}H_{32}BrN_5O_3$ $[M + H]^+$: 625.1761; found: 626.1759.

(*S*)-*N*-(2-((1-((2-(dimethylamino)ethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)-4-methoxyphenyl)-2-naphthamide (**7e**). The title compound **7e** was prepared from compound **4e** (0.2 g, 0.394 mmol) and *N*,*N*-dimethylethylenediamine (32 mg, 0.394 mmol) according to the general procedure **D**. The product **7e** was obtained as an off-white solid (154 mg, 68%); mp 98.8–99.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H), 10.84 (s, 1H), 8.95 (d, *J* = 8.0 Hz, 1H), 8.45 (s, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 8.10-8.00 (m, 4H), 7.89-7.86 (m, 1H), 7.71-7.61 (m, 3H), 7.30-7.24 (m, 3H), 7.16 (dd, *J* = 4.0, 12.0 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 12.0 Hz, 1H), 4.74-4.68 (m, 1H), 3.82 (s, 3H), 3.27-3.21 (m, 2H), 3.17-3.10 (m, 3H), 2.26-2.23 (m, 2H), 2.00 (s, 6H); ^{13}C NMR (10 MHz, DMSO-d_6): δ 171.4, 168.7, 164.7, 155.0, 136.5, 134.8, 132.6, 132.4, 132.3, 129.5, 128.9, 128.4, 128.16, 128.1, 127.6, 127.4, 124.2, 123.7, 123.6, 122.9, 121.3, 118.9, 118.7, 118.1, 113.8, 111.8, 110.9, 58.4, 55.9, 54.9, 45.5, 37.4, 27.7 ; IR (ATR): ν_{max} 3281, 3056, 2937, 2317, 2098, 1908, 1649, 1595, 1516, 145, 1224, 1097, 1036, 910, 820, 741; HRMS (ESI): *m/z* calcd for $C_{34}H_{35}N_5O_4$ $[M + H]^+$: 578.2762; found: 578.2759.

General Procedure (E) for the *N*-Boc deprotection of compounds 8a-8e. To a solution of **5a-5e** (0.1 mmol) in dichloromethane (4.0 mL) was added HCl in dioxane (4 N solution) (1.0 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h. After completion of the reaction, solvent was removed under reduced pressure and treated with diethylether and the solid filtered out and dried under high vacuum to yield the product.

(*S*)-*N*-(2-((1-((2-aminoethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**8a**). The title compound **8a** was prepared from compound **5a** (0.05 g, 0.08 mmol) according to the general procedure **E**. The product **8a** was obtained as a grey solid (33 mg, 79%);

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mp 249.4–250.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.28 (s, 1H), 10.82 (s, 1H), 9.05 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 8.49-8.46 (m, 2H), 8.09-8.02 (m, 6H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.72-7.56 (m, 4H), 7.27-7.18 (m, 3H), 7.03-6.94 (m, 2H), 4.82-4.77 (m, 1H), 3.42-3.38 (m, 1H), 3.25-3.19 (m, 3H), 2.88-2.83 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.2, 169.0, 165.0, 139.6, 136.5, 134.8, 132.7, 132.6, 132.3, 129.5, 129.18, 129.1, 128.5, 128.3, 128.1, 127.7, 127.5, 124.1, 123.6, 123.3, 121.3, 121.2, 120.9, 118.9, 118.6, 111.8, 110.9, 54.8, 38.8, 37.0, 27.7 ; IR (ATR): ν_{max} 3236, 3048, 2341, 2109, 1919, 1638, 1597, 1505, 1403, 1396, 1227, 1095, 911, 863, 821, 741; HRMS (ESI): *m/z* calcd for $C_{31}H_{29}N_5O_3$ [M + H]$^+$: 520.2343; found: 520.2335.

(*S*)-*N*-(2-((1-((2-aminoethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)-4-fluorophenyl)-2-naphthamide (**8b**). The title compound **8b** was prepared from compound **5b** (0.075 g, 0.117 mmol) according to the general procedure **E**. The product **8b** was obtained as an off-white solid (51 mg, 80%); mp 229.7–230.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1H), 10.83 (s, 1H), 9.18 (d, *J* = 8.0 Hz, 1H), 8.56-8.53 (m, 1H), 8.45 (s, 1H), 8.49-8.45 (m, 2H), 8.08-8.01 (m, 6H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.75-7.62 (m, 4H), 7.47-7.45 (m, 1H), 7.26-7.23 (m, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 4.80-4.75 (m, 1H), 3.41-3.17 (m, 4H), 2.88-2.84 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.0, 167.8, 165.0, 158.7, 156.3, 136.5, 135.9, 134.8, 132.6, 132.1, 129.5, 129.1, 128.6, 128.3, 128.1, 127.7, 127.5, 124.1, 123.6, 123.29, 123.2, 123.1, 121.3, 119.4, 119.2, 118.9, 118.6, 115.9, 115.7, 111.8, 110.8, 66.8, 54.8, 38.8, 37.0, 27.6 ; IR (ATR): ν_{max} 3054, 2610, 2113, 1910, 1705, 1658, 1596, 1539, 1385, 1308, 1203, 811; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}FN_5O_3$ [M + H]$^+$: 538.2249; found: 538.2242.

(*S*)-*N*-(2-((1-((2-aminoethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)-4-chlorophenyl)-2-naphthamide (**8c**). The title compound **8c** was prepared from compound **5c** (0.075 g, 0.116 mmol) according to the general procedure **E**. The product **8c** was obtained as an off-white solid (54 mg, 75%); mp 119.3–120.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (s, 1H), 10.84 (s, 1H), 9.25 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 8.50 (t, 1H), 8.44 (s, 1H), 8.09-8.02 (m, 6H), 7.96-7.95 (m, 1H), 7.84 (d, *J* = 4.0 Hz, 1H), 7.73-7.62 (m, 4H), 7.26-7.22 (m, 2H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 8.0 Hz, 1H), 4.82-4.76 (m, 1H), 3.23-3.17 (m, 4H), 2.88-2.84 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.9, 167.8, 165.0, 138.4, 136.5, 134.9, 132.6, 132.3, 132.0, 129.6, 129.1, 128.9, 128.6, 128.4, 128.1, 127.7, 127.5, 127.5, 127.1, 124.0, 123.6, 122.8, 122.6, 121.3, 118.9, 118.6, 111.8, 110.9, 66.8, 55.0, 38.7, 37.0, 27.6 ; IR (ATR): ν_{max} 3278, 3052, 2938, 2111, 1581, 1500, 1429, 1395, 1297, 1157, 1222, 1010, 912, 923, 733; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}ClN_5O_3$ [M + H]$^+$: 554.1953; found: 554.1951.

(*S*)-*N*-(2-((1-((2-aminoethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)-4-bromophenyl)-2-naphthamide (**8d**). The title compound **8d** was prepared from compound **5d** (0.075 g, 0.107 mmol) according to the general procedure **E**. The product **8d** was obtained as an off-white solid (45 mg, 70%); mp 131.9–132.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (s, 1H), 10.83 (s, 1H), 9.25 (d, *J* = 8.0 Hz, 1H), 8.55-8.44 (m, 3H), 8.08-8.02 (m, 7H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.78-7.62 (m, 4H), 7.25-7.21 (m, 2H), 7.02-6.94 (m, 2H), 4.79-4.77 (m, 1H), 3.40-3.34 (m, 3H), 3.22-3.16 (m, 1H), 2.87-2.83 (m, 2H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.0, 167.7, 165.0, 138.8, 136.5, 135.3, 134.9, 132.6, 132.0, 131.6, 129.6, 129.1, 128.6, 128.4, 128.1, 127.7, 127.5, 124.0, 123.6, 123.0, 122.8, 121.3, 118.9, 118.7, 115.1, 111.8, 110.9, 66.8, 55.3, 55.0, 38.7, 37.0, 27.6, 15.6 ; IR (ATR): ν_{max} 3639, 3359, 2996, 2619, 1795, 1691, 1608, 1552; 1462, 1411, 1347, 1257, 1208, 1106, 1061, 931, 838, 805; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}BrN_5O_3$ [M + H]$^+$: 598.1448; found: 598.1444.

(*S*)-*N*-(2-((1-((2-aminoethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)-4-methoxyphenyl)-2-naphthamide (**8e**). The title compound **8e** was prepared from compound **5e** (0.075 g, 0.115 mmol) according to the general procedure **E**. The product **8e** was obtained as an off-white solid (44 mg, 69%); mp 129.7–130.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.88 (s, 1H), 10.85 (s, 1H), 9.09 (d, *J* = 8.0 Hz, 1H), 8.45-8.39 (m, 3H), 8.07-7.61 (m, 9H), 7.34-7.15 (m, 4H), 7.03-6.94 (m, 2H), 4.77 (br s, 1H), 3.84 (s, 3H), 3.22-3.17 (m, 4H), 2.85 (t, *J* = 12.0 Hz, 2H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.1, 168.6, 164.7, 155.0, 136.5, 134.7, 132.6, 132.5, 132.4, 129.5, 129.0, 128.4, 128.1, 127.7, 127.5, 124.2, 123.7, 123.2, 122.8, 121.3, 118.9, 118.7, 118.3, 113.8, 111.8, 110.9, 56.0, 54.8, 38.9, 37.3, 27.7 ; IR (ATR): ν_{max} 3262, 3055, 2952, 2341, 1645, 1597, 1506, 1430, 1364, 1234, 1201, 132, 1036, 913, 823; HRMS (ESI): *m/z* calcd for $C_{32}H_{31}N_5O_4$ [M + H]$^+$: 550.2449; found: 550.2443.

General Procedure (F) for the *N*-Boc deprotection of compounds 9a-9e. To a solution of **6a-6e** (0.1 mmol) in dichloromethane (1 mL) was added TFA (1 mL). The reaction mixture was warmed to room temperature and stirred for 8 h. After completion of the reaction, excess solvent was removed under reduced pressure and treated with excess HCl in dioxane (4 N solution) to exchange the TFA anion with HCl. The gummy liquid was concentrated under reduced pressure to yield the gummy solid. The gummy solid was dissolved in minimum amount of MeOH (≤10 drops) and diethylether (5-10 mL) was added to get precipitation of the product.

(*S*)-*N*-(2-((1-((2-guanidinoethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**9a**). The title compound **9a** was prepared from compound **6a** (0.1 g, 0.131 mmol) according to the general procedure **F**. The product **9a** was obtained as an off-white solid (44 mg, 59%); mp 180.8–181.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.25 (s, 1H), 10.80 (s, 1H), 8.97 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 4.0 Hz, 1H), 8.45 (br s, 1H), 8.39 (t, *J* = 4.0 Hz, 1H), 8.06-8.02 (m, 3H),

7.88-7.82 (m, 2H), 7.70-7.63 (m, 3H), 7.59-7.55 (m, 2H), 7.28-6.98 (m, 8H), 4.80-4.76 (m, 1H), 3.29-3.18 (m, 6H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.4, 169.1, 165.0, 158.8, 157.4, 139.6, 136.5, 134.8, 132.8, 132.6, 132.3, 129.5, 129.09, 129.0, 128.07, 128.6, 128.3, 128.1, 127.6, 127.5, 124.1, 123.6, 123.3, 121.4, 121.2, 120.9, 118.8, 118.6, 111.8, 110.8, 54.8, 40.8, 38.5, 27.8 ; IR (ATR): ν_{max} 3293, 2340, 2113, 1903, 1654, 1518, 1431, 1309, 1180, 1127, 912, 837, 742; HRMS (ESI): *m/z* calcd for $C_{32}H_{31}N_7O_3$ [M + H]$^+$: 562.2561; found: 562.2554.

(*S*)-*N*-(4-fluoro-2-((1-((2-guanidinoethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**9b**). The title compound **9b** was prepared from compound **6b** (0.1 g, 0.128 mmol) according to the general procedure **F**. The product **9b** was obtained as gummy solid (40 mg, 54%); ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.05 (s, 1H), 10.80 (s, 1H), 9.25 (d, *J* = 6.0 Hz, 1H), 8.70 (br s, 1H), 8.58-8.56 (m, 2H), 8.47-8.43 (m, 2H), 8.35 (s, 1H), 8.06-8.01 (m, 3H), 7.85 (d, *J* = 6.0 Hz, 1H), 7.69-7.62 (m, 7H), 7.48-7.44 (m, 1H), 7.26-7.22 (m, 2H), 7.00 (t, *J* = 12.0 Hz, 1H), 6.95 (t, *J* = 12.0 Hz, 1H), 4.78-4.75 (m, 1H), 3.27-3.23 (m, 2H), 3.17-3.13 (m, 4H) ; ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.9, 167.9, 166.5, 165.0, 157.8, 156.7, 136.5, 136.0, 134.8, 132.6, 132.1, 129.5, 129.0, 128.6, 128.3, 128.1, 127.6, 127.5, 124.1, 123.6, 123.19, 123.1, 121.3, 118.8, 118.6, 115.6, 111.8, 110.9, 54.9, 40.5, 38.5, 27.7; IR (ATR): ν_{max} 3750, 3716, 3320, 2947, 2836, 2462, 2139, 2048, 1976, 1919, 1890, 1786, 1669, 1519, 1449, 1400, 1312, 1268, 1204, 1142, 1022, 799, 738; HRMS (ESI): *m/z* calcd for $C_{32}H_{30}FN_7O_3$ [M + H]$^+$: 580.2467; found: 580.2461.

(*S*)-*N*-(4-chloro-2-((1-((2-guanidinoethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**9c**). The title compound **9c** was prepared from compound **6c** (0.1 g, 0.125 mmol) according to the general procedure **F**. The product **9c** was obtained as an off-white solid (34 mg, 46%); mp 117.8–118.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (s, 1H), 10.81 (s, 1H), 9.15 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 6.0 Hz, 1H), 8.43 (s, 1H), 8.38-8.37 (m, 2H), 8.06-8.02 (m, 3H), 7.91-7.90 (m, 1H), 7.84-7.83 (m, 1H), 7.70-7.64 (m, 4H), 7.46 (t, *J* = 6.0 Hz, 1H), 7.26-6.96 (m, 8H), 4.79-4.75 (m, 1H), 3.29-3.17 (m, 6H) ; ^{13}C NMR (150 MHz, DMSO-d_6): δ 172.4, 169.1, 165.0, 158.8, 157.4, 139.6, 136.5, 134.8, 132.8, 132.6, 132.3, 129.5, 129.09, 129.0, 128.6, 128.3, 128.1, 127.6, 127.5, 124.1, 123.6, 123.3, 121.4, 121.2, 120.9, 118.8, 118.6, 111.8, 110.8, 54.8, 40.8, 38.5, 27.8; IR (ATR): ν_{max} 3310, 3067, 2905, 2664, 2352, 1656, 1507, 1431, 1306, 1198, 1132, 915, 744; HRMS (ESI): *m/z* calcd for $C_{32}H_{30}ClN_7O_3$ [M + H]$^+$: 596.2171; found: 596.2167.

(*S*)-*N*-(4-bromo-2-((1-((2-guanidinoethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)phenyl)-2-naphthamide (**9d**). The title compound **9d** was prepared from compound **6d** (0.1 g, 0.118 mmol) according to the general procedure **F**. The product **9d** was obtained as gummy solid (34 mg, 45%);^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (s, 1H), 10.81 (br s, 1H), 9.17 (d, *J* = 8.0 Hz, 1H), 8.53 (d, *J* = 8.0 Hz, 1H), 8.42-8.38 (m, 2H), 8.05-8.02 (m, 3H), 7.83-7.76 (m, 2H), 7.70-7.62 (m, 4H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.26-7.20 (m, 5H), 7.02-6.96 (m, 3H), 4.78-4.73 (m, 1H), 3.28-3.25 (m, 2H), 3.21-3.13 (m, 4H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.2, 167.8, 165.1, 157.3, 138.8, 136.5, 135.3, 134.9, 132.6, 132.0, 131.6, 129.5, 129.1, 128.7, 128.4, 128.1, 127.6, 127.5, 124.0, 123.6, 123.5, 123.0, 122.9, 121.4, 118.7, 115.1, 111.8, 110.8, 55.0, 40.8, 38.5, 27.7 ; IR (ATR): ν_{max} 3889, 3761, 3824, 3390, 2940, 2825, 2437, 2257, 2180, 2092, 2092, 2139, 2127, 2040, 2003, 1966, 1942, 1860, 1655, 1447, 1406, 1113, 995, 824, 761; HRMS (ESI): *m/z* calcd for $C_{32}H_{30}BrN_7O_3$ [M + H]$^+$: 640.1666; found: 640.1662.

(*S*)-*N*-(2-((1-((2-guanidinoethyl)amino)-3-(*1H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)-4-methoxyphenyl)-2-naphthamide (**9e**). The title compound **9e** was prepared from compound **6e** (0.1 g, 0.126 mmol) according to the general procedure **F**. The product **9e** was obtained as gummy solid (36 mg, 49%);^{1}H NMR (600 MHz, DMSO-d_6): δ 11.87 (s, 1H), 10.82 (s, 1H), 9.13 (d, *J* = 12.0 Hz, 1H), 8.62 (br s, 1H), 8.48-8.41 (m, 4H), 8.05-8.00 (m, 3H), 7.86 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.70-7.61 (m, 6H), 7.30-7.22 (m, 3H), 7.16 (dd, *J* = 6.0, 12.0 Hz, 1H), 7.03-6.94 (m, 2H), 4.77-4.74 (m, 1H), 3.82 (s, 3H), 3.26-3.14 (m, 6H) ; ^{13}C NMR (150 MHz, DMSO-d_6): δ 172.1, 168.7, 167.6, 164.7, 157.8, 155.0, 136.5, 134.7, 132.6, 132.5, 129.5, 128.9, 128.4, 128.16, 128.1, 127.6, 127.4, 124.1, 123.7, 123.2, 122.8, 121.3, 118.7, 118.2, 113.9, 111.8, 110.9, 55.9, 54.8, 40.7, 38.5, 27.7 ; IR (ATR): ν_{max} 3732, 3350, 3150, 2955, 2526, 2313, 1680, 1537, 1355, 1262, 1201, 1135, 984, 826, 730; HRMS (ESI): *m/z* calcd for $C_{33}H_{33}N_7O_4$ [M + H]$^+$: 592.2667; found: 592.2662.

General Procedure (G) for the synthesis of compounds **10a-10e**.To a solution of **7a-7e** (0.1 mmol) in DCM was added 4 N HCl/dioxane (1.0 mL) The reaction mixture was stirred at room temperature for 15 min. After completion of the reaction, solvent was removed under reduced pressure and treated with diethylether and compound was dried under high vacuum to yield the product.

(*S*)-2-(2-(2-(2-naphthamido)benzamido)-3-(*1H*-indol-3-yl)propanamido)-N,N-dimethylethan-1-aminium chloride (**10a**). The title compound **10a** was prepared from compound **7a** (0.05 g, 0.094 mmol) according to the general procedure **G**. The product **10a** was obtained as an white solid (62 mg, 90%); mp 234.4–234.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.3 (s, 1H), 10.83 (s, 1H), 10.33 (br s, 1H), 9.11 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 8.51-8.46 (m, 2H), 8.09-8.02 (m, 3H), 7.89-7.89 (t, *J* = 8.0 Hz, 2H), 7.71-7.56 (m, 4H), 7.28-7.18 (m, 3H), 7.04-6.95 (m, 2H), 4.79-4.75 (m, 1H), 3.49-3.36 (m, 3H), 3.26-3.20 (m, 1H), 3.07-3.06 (m, 2H), 2.68 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 172.1, 169.1, 165.0, 139.7, 136.5, 134.8, 132.7, 132.6, 132.4, 129.6, 129.2, 129.1, 128.6, 128.3, 128.1, 127.7, 127.5, 124.1, 123.7, 123.3, 121.3, 121.1,

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120.9, 118.9, 118.6, 111.8, 110.9, 55.8, 54.9, 42.6, 34.6, 27.6 ; IR (ATR): ν_{max} 3231, 3049, 2961, 2650, 2455, 2342, 2109, 1922, 1637, 1595, 1508, 1428, 1302, 910, 863, 822, 743; HRMS (ESI): *m/z* calcd for $C_{33}H_{33}N_5O_3$ $[M + H]^+$: 548.2656; found: 548.2647.

(*S*)-2-(2-(2-(2-naphthamido)-5-fluorobenzamido)-3-(1*H*-indol-3-yl)propanamido)-*N,N*-dimethylethan-1-aminium chloride (**10b**). The title compound **10b** was prepared from compound **7b** (0.05 g, 0.08 mmol) according to the general procedure **G**. The product **10b** was obtained as an white solid (47 mg, 89%); ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.06 (s, 1H), 10.83 (s, 1H), 10.37 (br s, 1H), 9.22 (d, *J* = 6.0 Hz, 1H), 8.55 (q, *J* = 6.0 Hz, 1H), 8.50 (t, *J* = 6.0 Hz, 1H), 8.45 (s, 1H), 8.08-8.05 (m, 2H), 8.03 (d, *J* = 6.0 Hz, 1H), 7.86 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.74 (dd, *J* = 6.0, 12.0 Hz, 1H), 7.70-7.62 (m, 3H), 7.47 (td, *J* = 6.0, 12.0 Hz, 1H), 7.27-7.24 (m, 2H), 7.01 (t, *J* = 6.0 Hz, 1H), 6.96 (t, *J* = 6.0 Hz, 1H), 4.77-4.74 (m, 1H), 3.50-3.37 (m, 3H), 3.22-3.18 (m, 3H), 2.68 (s, 6H) ; ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.9, 167.8, 165.0, 136.5, 136.0, 134.8, 132.6, 132.1, 129.5, 129.1, 128.6, 128.3, 128.1, 127.6, 127.5, 124.1, 123.7, 123.18, 123.14, 121.3, 119.4, 119.3, 118.8, 118.7, 115.9, 115.7, 111.8, 110.8, 55.8, 55.0, 42.7, 34.6, 27.5 ; IR (ATR): ν_{max} 3217, 3053, 2962, 2593, 2464, 2111, 1902, 1654, 1599, 1518, 1409, 1290, 1246, 940, 869, 824, 752; HRMS (ESI): *m/z* calcd for $C_{33}H_{32}FN_5O_3$ $[M + H]^+$: 566.2562; found: 566.2555.

(*S*)-2-(2-(2-(2-naphthamido)-5-chlorobenzamido)-3-(1*H*-indol-3-yl)propanamido)-*N,N*-dimethylethan-1-aminium chloride (**10c**). The title compound **10c** was prepared from compound **7c** (0.05 g, 0.085 mmol) according to the general procedure **G**. The product **10c** was obtained as an white solid (48 mg, 91%); mp 200.3–202.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.27 (s, 1H), 8.86 (d, *J* = 9.0 Hz, 1H), 8.50 (s, 1H), 8.21 (br s, 1H), 8.10-7.90 (m, 4H), 7.80 (d, *J* = 6.0 Hz, 1H), 7.64-7.44 (m, 5H), 7.35-7.30 (m, 1H), 7.24-7.13 (m, 3H), 6.23 (br s, 1H), 4.93-4.92(m, 1H), 3.49 (dd, *J* = 6.0, 15.0 Hz, 1H), 3.32-3.10 (m, 3H), 2.25-2.20 (m, 3H), 1.99 (s, 6H) ; ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.5, 167.5, 165.5, 138.8, 136.2, 135.0, 132.7, 131.8, 129.4, 128.6, 128.3, 127.9, 127.7, 127.4, 126.9, 126.7, 123.6, 123.1, 122.8, 122.5, 121.13, 121.1, 120.0, 118.8, 111.3, 110.7, 57.0, 54.6, 44.6, 36.7, 29.0 ; IR (ATR): ν_{max} 3272, 3052, 2938, 2320, 2110, 1907, 1639, 1580, 1498, 1428, 1296, 1224, 1095, 912, 822, 738; HRMS (ESI): *m/z* calcd for $C_{33}H_{32}ClN_5O_3$ $[M + H]^+$: 582.2266; found: 582.2262.

(*S*)-2-(2-(2-(2-naphthamido)-5-bromobenzamido)-3-(1*H*-indol-3-yl)propanamido)-*N,N*-dimethylethan-1-aminium (**10d**). The title compound **10d** was prepared from compound **7d** (0.05 g, 0.08 mmol) according to the general procedure **G**. The product **10d** was obtained as an white solid (47 mg, 90%); mp 156.8–157.5 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.19 (s, 1H), 10.84 (s, 1H), 10.22 (br s, 1H), 9.28 (d, *J* = 12.0 Hz, 1H), 8.54 (d, *J* = 6.0 Hz, 1H), 8.48 (t, *J* = 6.0 Hz, 1H), 8.44 (br s, 1H), 8.08-8.02 (m, 4H), 7.85 (dd, *J* = 1.8, 9.0 Hz, 1H), 7.78 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.71-7.63 (m, 3H), 7.26-7.22 (m, 2H), 7.02-6.95 (m, 2H), 4.78-4.74 (m, 1H), 3.47-3.36 (m, 3H), 3.21-3.01 (m, 3H), 2.67 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.9, 167.8, 165.1, 138.8, 136.5, 135.3, 134.9, 132.6, 132.0, 131.6, 129.6, 129.1, 128.7, 128.4, 128.1, 127.69, 127.6, 124.1, 123.6, 123.0, 122.9, 121.3, 118.9, 118.7, 115.1, 111.8, 110.8, 55.9, 55.1, 42.8, 34.7, 27.5; IR (ATR): ν_{max} 3230, 3051, 2646, 2320, 2106, 1906, 1638; 1578, 1499, 1428, 1391, 1297, 1224, 1094, 1010, 912, 820, 738; HRMS (ESI): *m/z* calcd for $C_{33}H_{32}BrN_5O_3$ $[M + H]^+$: 626.1761; found: 626.1758.

(*S*)-2-(2-(2-(2-naphthamido)-5-methoxybenzamido)-3-(1*H*-indol-3-yl)propanamido)-*N,N*-dimethylethan-1-aminium (**10e**). The title compound **10e** was prepared from compound **7e** (0.05 g, 0.09 mmol) according to the general procedure **G**. The product **10e** was obtained as an white solid (47 mg, 90%); mp 201.6–201.9 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.90 (s, 1H), 10.86 (s, 1H), 10.33 (br s, 1H), 9.16 (d, *J* = 6.0 Hz, 1H), 8.49 (t, *J* = 6.0 Hz, 1H), 8.44 (s, 1H), 8.41 (d, *J* = 6.0 Hz, 1H), 8.10-8.04 (m, 1H), 8.01 (d, *J* = 12.0 Hz, 1H), 7.87 (d, *J* = 3.6 Hz, 1H), 7.71 (d, *J* = 6.0 Hz, 1H), 7.67-7.62 (m, 2H), 7.37 (d, *J* = 6.0 Hz, 1H), 7.29-7.25 (m, 2H), 7.17 (dd, *J* = 3.0, 9.0 Hz, 1H), 7.04-7.00 (m, 1H), 6.97-6.94 (m, 1H), 4.78-4.74 (m, 1H), 3.84 (s, 3H), 3.52-3.49 (m, 1H), 3.40-3.37 (m, 2H), 3.25-3.20 (m, 1H), 3.11-3.05 (m, 2H), 2.68 (br s, 6H) ; ^{13}C NMR (150 MHz, DMSO-d_6): δ 172.1, 168.7, 164.7, 155.0, 136.5, 134.7, 132.68, 132.6, 132.5, 129.5, 129.0, 128.4, 128.16, 128.1, 127.7, 127.5, 124.2, 123.7, 123.0, 122.8, 121.3, 118.9, 118.7, 118.4, 113.8, 111.8, 110.8, 56.0, 55.8, 54.9, 42.6, 34.6, 27.5; IR (ATR): ν_{max} 3242, 3050, 2958, 2674, 2467, 2342, 2113, 1907, 1639, 1595, 1594, 1509, 1454, 1434, 1222, 109, 1032, 910, 819, 742; HRMS (ESI): *m/z* calcd for $C_{34}H_{35}N_5O_4$ $[M + H]^+$: 578.2762; found: 578.2760.

General Procedure (H) for the synthesis of compounds 11a-11e. To a solution of **7a-7e** (0.1 mmol) in CH_3CN (1.0 mL) was added CH_3I (0.1 mmol) The reaction mixture was stirred at room temperature for 8 h. After completion of the reaction, the solvent was removed under reduced pressure and treated with diethylether and compound was dried under high vacuum to yield the product.

(*S*)-2-(2-(2-(2-naphthamido)benzamido)-3-(1*H*-indol-3-yl)propanamido)-*N,N,N*-trimethylethan-1-aminium iodide (**11a**). The title compound **11a** was prepared from compound **7a** (0.05 g, 0.094 mmol) according to the general procedure **H**. The product **11a** was obtained as an white solid (58 mg, 90%); mp 240.3–240.6 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.28 (s, 1H), 10.83 (s, 1H), 9.05 (d, *J* = 6.0 Hz, 1H), 8.59 (d, *J* = 6.0 Hz, 1H), 8.48-8.45 (m, 2H), 8.09-8.03 (m, 3H), 7.90-7.86 (m, 2H), 7.70-7.59 (m, 4H), 7.31-7.22 (m, 3H), 7.06-6.98 (m, 2H), 4.74-4.70 (m, 1H), 3.50-3.48 (m, 3H), 3.30-3.17 (m, 3H), 2.97 (s, 9H) ; ^{13}C NMR (150 MHz, DMSO-d_6): δ 172.3, 169.2, 165.1, 139.6, 136.5, 134.8, 132.9, 132.6, 132.4, 129.5, 129.17, 129.1, 128.6, 128.3, 128.1, 127.6, 127.5, 124.2,

123.6, 123.3, 121.4, 121.08, 121.0, 118.7, 111.9, 110.6, 64.0, 55.0, 52.9, 33.8, 27.4; IR (ATR): ν_{max} 3244, 3050, 2341, 2109, 1650, 1596, 1506, 149, 1301, 1228, 1094, 1009, 954, 912, 865, 823, 746; HRMS (ESI): *m/z* calcd for $C_{34}H_{36}N_5O_3$ $[M]^+$: 562.2813; found: 562.2816.

(*S*)-2-(2-(2-(2-naphthamido)-5-fluorobenzamido)-3-(1*H*-indol-3-yl)propanamido)-N,N,N-trimethylethan-1-aminium iodide (**11b**). The title compound **11b** was prepared from compound **7b** (0.05 g, 0.08 mmol) according to the general procedure **H**. The product **11b** was obtained as an white solid (52 mg, 92%); mp 182.1–182.0 °C; ^{1}H NMR (600 MHz, DMSO-d_6): 12.04 (s, 1H), 10.84 (s, 1H), 9.12 (d, *J* = 12.0 Hz, 1H), 8.54-8.47 (m, 3H), 8.07-8.02 (m, 3H), 7.87 (d, *J* = 12.0 Hz, 1H), 7.68-7.64 (m, 4H), 7.48 (t, *J* = 12.0 Hz, 1H), 7.30-7.25 (m, 2H), 7.04-6.98 (m, 2H), 4.71 (br m, 1H), 3.48-3.31 (m, 2H), 3.20-3.14 (m, 4H), 2.98 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 172.1, 167.9, 165.1, 158.8, 156.4, 136.5, 135.9, 134.8, 132.6, 132.2, 129.5, 129.1, 128.6, 128.3, 128.2, 127.6, 127.5, 124.2, 123.7, 123.4, 123.3, 123.0, 121.4, 119.6, 119.4, 118.7, 115.8, 115.6, 111.9, 110.5, 64.0, 55.1, 53.0, 33.8, 27.4; IR (ATR): ν_{max} 3345, 3244, 2112, 1904, 1605, 1665, 1520, 1434, 1307, 1233, 1019, 1092, 956, 870, 826, 754; HRMS (ESI): *m/z* calcd for $C_{34}H_{35}FN_5O_3$ $[M]^+$: 580.2718; found: 580.2712.

(*S*)-2-(2-(2-(2-naphthamido)-5-chlorobenzamido)-3-(1*H*-indol-3-yl)propanamido)-N,N,N-trimethylethan-1-aminium iodide (**11c**). The title compound **11c** was prepared from compound **7c** (0.05 g, 0.085 mmol) according to the general procedure **H**. The product **11c** was obtained as an white solid (56 mg, 91%); mp 194.1–194.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (s, 1H), 10.84 (s, 1H), 9.22 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 8.48-8.45 (m, 2H), 8.09-8.02 (m, 3H), 7.94 (d, *J* = 4.0 Hz, 1H), 7.87-7.84 (m, 1H), 7.70-7.62 (m, 4H), 7.29-7.23 (m, 2H), 7.05-6.96 (m, 2H), 4.74-4.68 (m, 1H), 3.49-3.46 (m, 2H), 3.30-3.14 (m, 4H), 2.97 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 172.0, 168.0, 165.1, 138.5, 136.5, 134.9, 132.6, 132.5, 132.1, 129.6, 129.1, 128.8, 128.7, 128.4, 128.2, 127.6, 127.5, 127.2, 124.2, 123.6, 122.8, 122.6, 121.4, 118.7, 111.9, 110.6, 64.0, 55.2, 52.9, 33.8, 27.4; IR (ATR): ν_{max} 3626, 3429, 3242, 3055, 2778, 2320, 1649, 1598, 1429, 1504, 1292, 1103, 1007, 957, 825, 747; HRMS (ESI): *m/z* calcd for $C_{34}H_{35}ClN_5O_3$ $[M]^+$: 596.2423; found: 596.2418.

(*S*)-2-(2-(2-(2-naphthamido)-5-bromobenzamido)-3-(1*H*-indol-3-yl)propanamido)-*N,N,N*-trimethylethan-1-aminium iodide (**11d**) The title compound **11d** was prepared from compound **7d** (0.05 g, 0.08 mmol) according to the general procedure **H**. The product **11d** was obtained as an white solid (55 mg, 90%); mp 231.6–231.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.20 (s, 1H), 10.85 (s, 1H), 9.24 (d, *J* = 8.0 Hz, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.48 (s, 2H), 8.09-8.02 (m, 4H), 7.86 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.80 (dd, *J* = 2.0, 9.0 Hz, 1H), 7.70-7.62 (m, 3H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 4.0 Hz, 1H), 7.06-6.97 (m, 2H), 4.74-4.69 (m, 1H), 3.50-3.58 (m, 2H), 3.30-3.27 (m, 4H), 2.98 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.1, 167.9, 165.1, 138.9, 136.5, 135.4, 134.9, 132.6, 132.1, 131.6, 129.6, 129.1, 128.7, 128.4, 128.2, 127.6, 127.5, 124.1, 123.6, 123.0, 122.8, 121.4, 118.8, 115.1, 111.9, 110.6, 64.0, 55.2, 52.9, 33.8, 27.4 ; IR (ATR): ν_{max} 3622, 3508, 3427, 3238, 3039, 2913, 2763, 1783, 1603, 1679, 1543, 1427, 1359, 1278, 1233, 1103, 1058, 963, 827, 762; HRMS (ESI): *m/z* calcd for $C_{34}H_{35}BrN_5O_3$ $[M]^+$: 640.1918; found: 640.1912.

(*S*)-2-(2-(2-(2-naphthamido)-5-methoxybenzamido)-3-(1*H*-indol-3-yl)propanamido)-*N,N,N*-trimethylethan-1-aminium iodide (**11e**). The title compound **11e** was prepared from compound **7e** (0.05 g, 0.09 mmol) according to the general procedure **H**. The product **11e** was obtained as an white solid (62 mg, 90%); mp 168.9–171.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.85 (s, 1H), 10.86 (s, 1H), 9.04 (d, *J* = 8.0 Hz, 1H), 8.48-8.45 (m, 2H), 8.39 (d, *J* = 8.0 Hz, 1H), 8.09-8.02 (m, 3H), 7.89-7.86 (m, 1H), 7.69-7.62 (m, 3H), 7.32-7.27 (m, 3H), 7.20 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.99 (t, *J* = 4.0 Hz, 1H), 4.72-4.67 (m, 1H), 3.84 (s, 3H), 3.49-3.47 (m, 2H), 3.26-3.15 (m, 4H), 2.97 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.2, 168.8, 164.8, 155.0, 136.5, 134.7, 132.6, 132.55, 132.5, 129.5, 129.0, 128.5, 128.1, 127.5, 124.3, 123.7, 123.2, 123.0, 121.4, 118.8, 118.2, 114.1, 111.9, 110.6, 65.3, 64.0, 56.0, 55.0, 52.9, 33.7, 27.4, 15.6; IR (ATR): ν_{max} 3310, 2341, 1599, 1654, 1519, 1430, 1235, 1095, 1038, 956, 818, 742; HRMS (ESI): *m/z* calcd for $C_{35}H_{38}N_5O_4$ $[M]^+$: 592.2918; found: 592.2912.

Minimum inhibitory concentration (MIC)

The antimicrobial activity of the compounds was evaluated by a broth microdilution assay using the procedure described by Clinical and Laboratory Standards Institute (CLSI).[51] Briefly, bacteria were grown to mid-log phase in Muller Hinton broth (MHB) with shaking at 120 rpm and incubated at 37°C for 12-16 h. Following incubation, bacteria were washed three times in PBS pH 7.4 at 3500 g for 10 min. After washing, bacteria were diluted with fresh MHB. The turbidity of the bacterial suspensions were adjusted so that OD_{660nm} was 0.1, which gave 1×10^8 CFU/ml, and then further diluted to achieve 5×10^5 CFU/ml as a final bacterial concentration. Each compound was diluted (250-3.9 µM) through two-fold dilution. Wells in microtiter plates were loaded with 100 µl of inoculum containing 5×10^5 CFU/ml bacteria. Wells without any compound and containing only bacteria were used as negative controls (i.e. no inhibition of growth). Wells with media only was set as blank. The microtiter plate was wrapped with paraffin to prevent evaporation and incubated with shaking at 120 rpm at 37°C for 18-24 h. After incubation, spectrophotometric reading was taken. The well at the lowest concentration without any bacterial growth and showing zero spectrophotometric reading was regarded as the MIC of the compounds. We compared the MIC data of

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all our compounds with **MSI-78** (also known as pexiganan), which is an antibiotic currently in Phase-III clinical trials and has the amino acid sequence of Gly-Ile-Gly-Lys-Phe-Leu-Lys-Lys-Ala-Lys-Lys-Phe-Gly-Lys-Ala-Phe-Val-Lys-Ile-Leu-Lys-Lys-NH_2. Each experiment was performed in triplicate and was repeated in three independent experiments.

Cytoplasmic membrane permeability assay

The method was adopted from Wu *et al.*[52] with slight modification. Bacterial cytoplasmic membrane permeability was determined using membrane potential sensitive dye diSC3-5 (3,3'-dipropylthiadicarbocyanine iodide) which penetrates inside bacterial cells depending on the membrane potential gradient of the cytoplasmic membrane. Bacteria were grown in MHB to mid-log phase by incubating with shaking at 37 °C for 18-24 h. Following incubation bacteria were washed with 5 mM HEPES containing 20 mM glucose pH 7.2 and resuspended in the same buffer to an OD_{600} 0.5-0.6 which gave 1×10^7 CFU/ml. The dye diSC3-5 was added at 4 µM to the bacterial suspension. The suspensions were incubated at room temperature for 1 h in the dark for maximum dye take-up by the bacterial cells. Then 100 mM KCl was added to balance the K+ outside and inside the bacterial cell to prevent further uptake or outflow of the dye. For Gram-negative bacteria, 0.5 mM EDTA was used to destabilize the lipopolysaccharides-Mg^{2+}-Ca^{2+} complex to help in dye penetration without affecting bacterial growth. 100 µl of bacterial suspension was added in 96-well microtiter plate and with equal volume of antimicrobial compounds. DMSO (20%) was set as a positive control while dye and only bacterial cells were set as negative control. Fluorescence was measured with a luminescence spectrophotometer at 3 min intervals at an excitation wavelength of 621m and an emission wavelength of 670 nm.

Viable cell count assay

The number of viable cells was confirmed by serially diluting aliquots of bacteria in D/E neutralizing broth (Remel, Lenexa, KS, USA) and plating these onto Tryptic Soy Agar (Oxoid, Basingstoke, UK) containing phosphatidylcholine (0.7 g /L) and Tween 80 (5 ml/L). The plates were incubated at 37 °C overnight and numbers of live bacteria were enumerated and expressed as CFU/ml. The experiment was performed in triplicate.

Toxicity assay

Normal human lung fibroblasts MRC-5 were cultured in minimal essential medium (MEM, Invitrogen) supplemented with 10% foetal calf serum (FCS), 1% L-glutamine–penicillin–streptomycin, 2% sodium bicarbonate, 1% non-essential amino acids (NEAA) and 1% sodium pyruvate. The cell line was maintained at 37 °C in 5% CO_2 as an adherent monolayer and was passaged upon reaching confluence by standard cell culture techniques. MRC-5 cells were seeded at 2×10^4 cells per well in 96-well plates to ensure full confluence (quiescence). Cells were treated 24 h after seeding with 0.1 to 1000 µM of compounds. After 72 h drug incubation, the treated media was replaced with fresh media containing 10% Alamar Blue and the cells were incubated for another 6 h. The metabolic activity was detected by spectrophotometric analysis by assessing the absorbance of Alamar blue as previously described by Pasquier *et al*. [53] Cell proliferation was determined and expressed as a percentage of untreated control cells. The determination of IC_{50} values was performed using GraphPad Prism 6 (San Diego, CA, USA). Each experiment was performed in triplicate and was repeated in three independent experiments.

Biofilm inhibition assay

Bacterial cultures (*S. aureus* and *E. coli*) were grown in MHB media overnight at 37 °C with shaking at 120 rpm. Cultures were diluted (1:20) in MHB medium and 200 µl aliquots were dispensed to flat bottom 96-well plate wells (Sarstedt Australia). Cultures were supplemented with varying concentrations of synthetic compounds dissolved in DMSO. Biofilm was grown in 96-well plate for 24 h followed by addition of synthetic compounds and incubated further for 24 h. Plates were sealed with self-adhesive microplate sealers (TopSeal-A, PerkinElmer) to allow air diffusion and to prevent condensation. Biofilms adhered on polystyrene substratum were quantified by crystal violet staining as described previously.[54] The experiment was performed in triplicate.

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