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Design and Solution Phase Synthesis of Membrane Targeting Lipopeptides with Selective Antibacterial Activity

Mohini M. Konai, Utsarga Adhikary, and Jayanta Haldar*[a]

Abstract: Designing selective antibacterial molecules remains an unmet goal in the field of membrane targeting agents. To this aim, herein we report the rational design and synthesis of a new class of lipopeptides which possess highly selective bacterial killing over mammalian cells. The selective interaction with bacterial over mammalian membranes was established through various spectroscopic as well as microscopic experiments including biophysical studies with the model membranes. A detailed antibacterial structure-activity relationship was delineated after preparing a series of molecules consisting of the peptide moieties with varied sequence of amino acids such as D-phenylalanine, D-leucine and D-lysine. Antibacterial activity was found to vary with the nature and positioning of hydrophobicity in the molecules as well as number of positive charges. Optimized lipopeptide, **9** did not show any hemolytic activity even at 1000 μg/mL and displayed >200-fold and >100-fold selectivity towards *S. aureus* and *E. coli* respectively. More importantly, compound **9** was found to display good antibacterial activity (MIC = 6.3-12.5 μg/mL) against the five top most critical bacteria according to WHO (World Health Organization) priority list. Therefore, altogether the results suggested that this new class of lipopeptides bear real promises for the development as future antibacterial agents.

Introduction

The ever emerging phenomenon of bacterial resistance has presented with an unprecedented challenge in global public health. Recently, the World Health Organization (WHO) has published for the first time a list of drug-resistant bacteria posing the greatest threat and against which new antibiotics are urgently needed.[1] In this catalogue, the Gram-negative bacteria *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacteriaceae (specifically *Klebsiella pneumoniae* and *Escherichia coli*) were deemed to be the most critical ones. Almost no treatment regimens exist to treat infections caused by multi-drug resistant strains of these deadly pathogens. Gram-positive bacteria, vancomycin-resistant *Enterococcus faecium* (VRE) and Methicillin-resistant *Staphylococcus aureus* (MRSA) are also a major cause of worry and were justifiably ranked next in the priority list. Therefore, it goes without saying that in order to tackle these drug-resistant bacteria, there is a critical need for new classes of broad-spectrum antibacterial agents with novel mechanism of action. To this end, the recent past has seen the emergence of numerous classes of membrane active molecules including even membrane active analogues of antibiotics, offering some hope.[2-30] By targeting the bacterial membrane, this class of compounds are typically advantageous over conventional antibiotics, as bacterial resistance development is much slower in the face of membrane disintegration. Living up to the promise of this class of molecules; lipopeptide antibiotics, such as daptomycin and colistin have already entered the clinic. However, the potential of this class of molecules is largely overshadowed by certain serious limitations. Firstly, lipopeptide antibiotics possess narrow spectrum of antibacterial activity. For example, daptomycin targets the membrane of Gram-positive bacteria in a calcium ion (Ca^{2+}) dependent manner and is active only against these bacteria.[31] The other class of FDA approved lipopeptide antibiotics, polymyxins (polymyxin B and colistin) specifically target the lipopolysaccharide (LPS) and are therefore effective only against Gram-negative bacteria.[32] Furthermore, issues such as toxicity and stability limit their broad-scale usages in clinic. To address the above-mentioned limitations, the scientific community responded with diverse classes of synthetic mimics of lipopeptides.[22-30] Even though many of these synthetic lipopeptides were potent against bacteria, a big caveat was their unimpressive selectivity towards bacteria over mammalian cells. Quite notably, the preparation of most of the existing lipopeptides require solid phase synthesis, which left considerable space for the development of new class of lipopeptides with simpler synthetic designs and more selective antibacterial activity. Towards this goal, herein we report the rational design and solution phase synthesis of a new class of lipopeptides in order to achieve antibacterial activity with superior selectivity towards bacterial killing. Other than above mentioned motives, our additional interest for developing amino acid based antibacterial agents was their high abundance due to naturally occurring starting material and non-toxic nature. All of these reasons make them attractive as starting materials in chemical syntheses. Indeed, amino acids have attracted enormous attention in diverse research areas in the field of medicinal chemistry owing to these several advantages.[33-35] Importantly, research from various groups including ours have already implicated the role of amino acids in dictating the antibacterial activity.[36-38] Moreover, to the best of our knowledge, solution phase synthesis of lipopeptide class of molecules that display antibacterial activity has rarely been reported in literature. Therefore, the highlight of this paper is the simple and flexible synthetic strategy, allowing the generation of series of lipopeptides via solution phase amide coupling reactions at relative ease. To this end, we synthesized a series of molecules consisting of nine compounds by varying all possible combinations of the amino acids D-phenylalaine, D-leucine and D-

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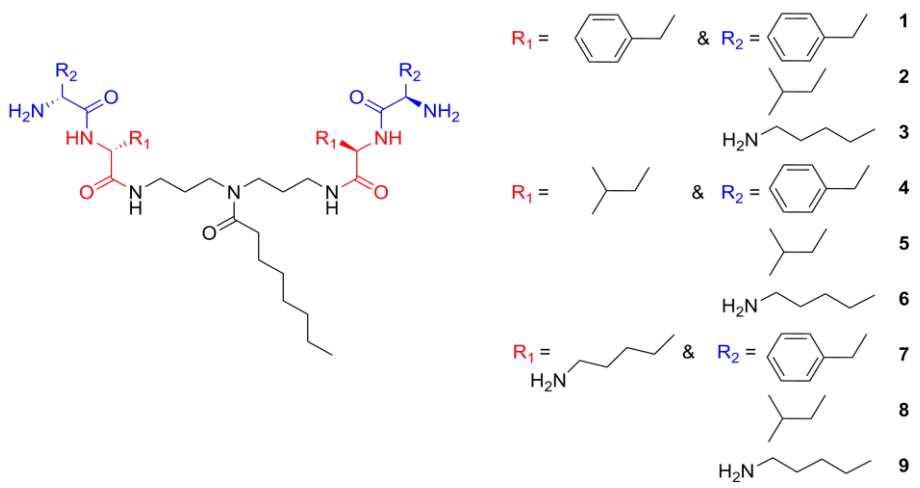
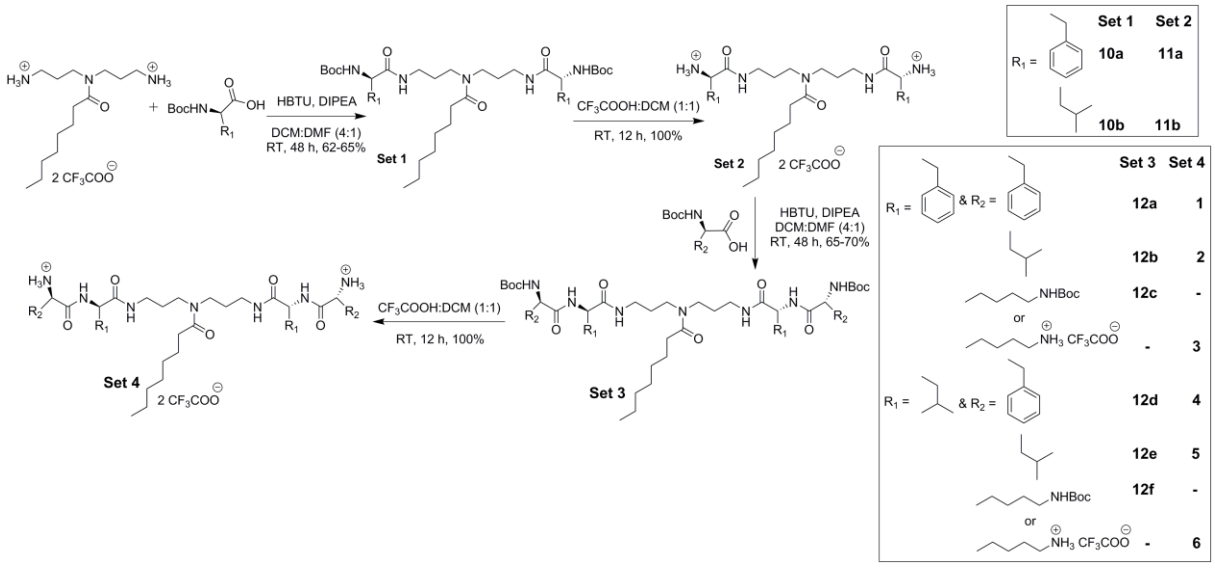


Figure 1. Chemical structure of lipopeptides.

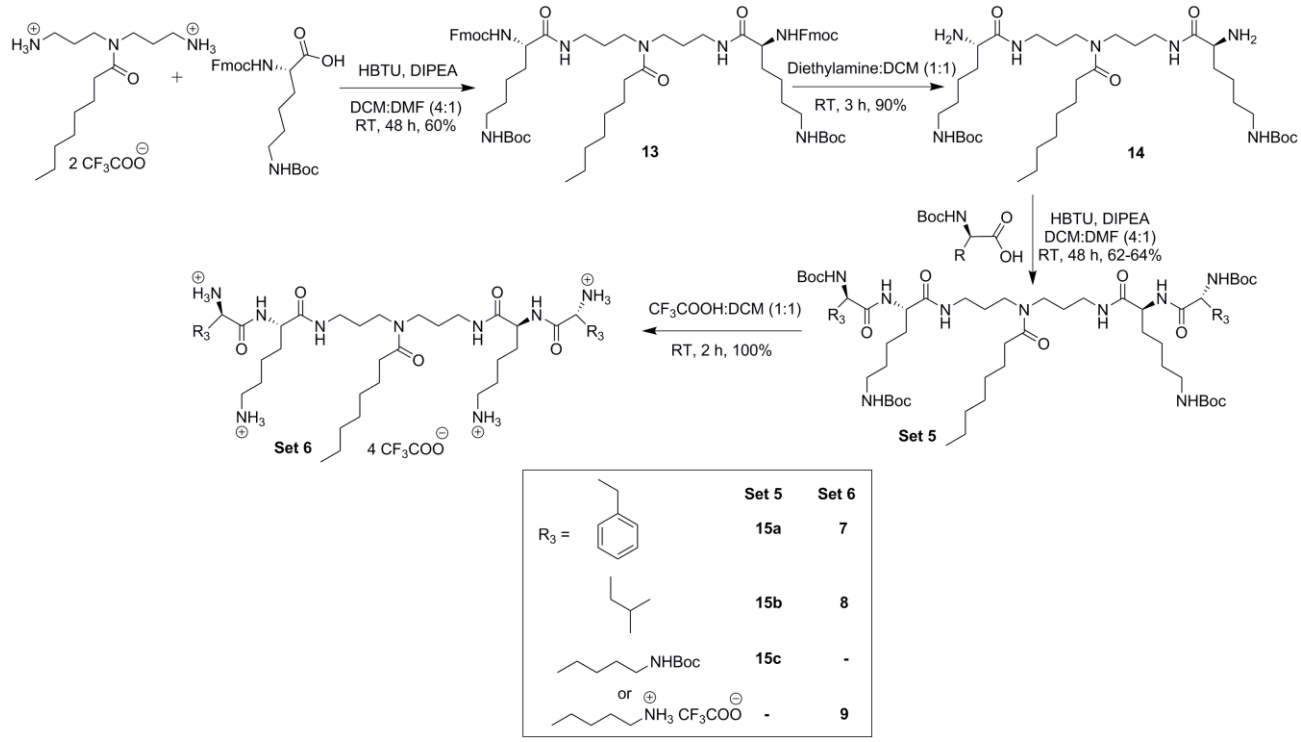
lysine in the peptide sequence. Following synthesis, all the lipopeptides were then tested for antibacterial activity against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria including the top most critical bacteria according to WHO priority list. We next evaluated the selectivity of the compounds by evaluating their toxicity against human red blood cells (hRBCs), as a model for mammalian cells. The effect of various structural parameters in the lipopeptides laid the framework for a structure-activity analysis, based on the number and position of positive charges, and the nature and positioning of hydrophobicity in the design scaffold. Finally, we investigated the mechanism of action of this series of lipopeptides by employing various spectroscopic and microscopic techniques as primarily acting through membrane disruption.

Results and Discussion

Rational Design and Synthesis: Our reported design scaffold consisting of a norspermidine backbone to which amino acids were symmetrically coupled on both ends, along with the presence of a central aliphatic long chain.[8] As a next step towards fine-tuning our design, the central goal in this research undertaking was to increase the selectivity by rational chemical modifications. Lessons learnt from our previous studies



Scheme 1. Synthesis of lipopeptides **1-6**.



Scheme 2. Synthesis of lipopeptides **7-9**.

indicated that the hydrophobicity of the central aliphatic chain is one of the main factors that dictate the antibacterial potency of a candidate molecule. This increase in activity with increasing hydrophobicity however comes at a price; indeed in many cases, highly active molecules are also highly toxic towards mammalian cells. To address this issue, we rationally incorporated aliphatic chains of comparatively lower length (i.e. octanoyl moiety) in the new design. This aliphatic moiety was flanked by two dipeptide moieties on either end of the molecule to afford the final lipopeptides (Figure 1). For interrogating the role of positive charges, and the nature and spatial positioning of hydrophobic moiety in the lipopeptides, amino acids with various structural features were incorporated in the peptide sequence. These included amino acids with hydrophobic side chains such as phenylalanine (aromatic hydrophobicity) and leucine (aliphatic hydrophobicity) and an amino acid with a positively charged side chain, lysine, which we conjectured, would introduce distinct properties in the molecular scaffold. We rationally incorporated only D-amino acids in our lipopeptides; given the observation made by others and us that D-amino acid containing small molecules are stable in presence of proteases than their L counterparts even while retaining their antibacterial activity. We therefore synthesized a series of lipopeptides consisting of nine compounds by varying all possible combination of the amino acids D-phenylalanine, D-leucine and D-lysine in the peptide sequence. Preparation of this class of lipopeptides (compounds **1-9**) was achieved by following a simple solution-based synthetic strategy. Starting from a precursor amine, compounds **1-6** were prepared through a sequence of reactions consisting of four steps (Scheme1). In the first step, two amine groups of the precursor amine (lipidated norspermidine derivative) were coupled with the carboxylic acid group of either Boc-D-Phe-OH or Boc-D-Leu-OH. After that, the Boc-groups of the resulting compounds were removed by using excess of 50% of trifluoroacetic acid (TFA) in DCM. In the third step, another amide coupling reaction was performed to incorporate the second amino acid. In the final step, all the Boc-groups were deprotected by using excess of 1:1 (TFA:DCM) to achieve the lipopeptides **1-6**. The remaining lipopeptides **7-9** were prepared by following a similar synthetic strategy, but involving orthogonal protection and deprotection chemistry (Scheme 2). In the first step of reactions, the carboxylic acid group of Fmoc-D-Lys (Boc)-OH was coupled with two primary amine groups of the precursor amine. In the next step, the Fmoc-groups were selectively removed by using excess amount of 50% diethyl amine (in DCM). The resulting compound was then subjected to conjugation with a second amino acid by an amide coupling reaction. After that, the Boc groups were removed (using 50% TFA in DCM) to achieve the lipopeptides **7-9**. The final compounds were then characterized by ^{1}H-NMR, ^{13}C-NMR and HR-MS (Supporting Information Figure S1-S28).

Selective Antibacterial Activity: We initially determined the toxicity of this class of lipopeptides as a first approximation of how selective these would be as antibacterial agents. Toxicity

Table 1 Hemolytic and antibacterial activity of the lipopeptides.

Lipopeptides	Charges	HC_{50} (μg/mL)	MIC (μg/mL)		Selectivity ratio (HC_{50}/MIC_{SA})
		hRBCs	*S. aureus*	*E. coli*	
1	2	540	15	>100	36
2	2	360	32	>100	11.3
3	4	>1000	30	>100	>33.3
4	2	320	27	>100	11.9
5	2	630	50	>100	12.6
6	4	>1000	95	>100	>10.5
7	4	>1000	7.3	50	>137
8	4	>1000	10.5	100	>95.2
9	6	>1000	5.0	11.2	>200

MIC_{SA} corresponds to antibacterial activity against *S. aureus*

studies were performed against human erythrocytes (hRBCs) as model mammalian cells. Briefly, we determined the HC_{50} (concentration corresponding to 50% lysis of the hRBCs) values for all the compounds (**1-9**) to quantify hemolytic activity. We observed that all the compounds possess low toxicity as evidenced by high HC_{50} values ranging from 320 μg/mL to >1000 μg/mL (Table 1). A general observation from this dataset suggests that hemolytic activity is strongly dependent on positive charges present in the lipopeptides. Indeed, lipopeptides with only two charges (**1, 2, 4** and **5**) showed higher toxicity, with HC_{50} ranging between 320 μg/mL to 640 μg/mL, whereas those bearing higher number of charges (**3, 6, 7, 8** and **9**) are evidently less toxic, as apparent from their high HC_{50} values of >1000 μg/mL. This was not surprising because a high hemolysis is usually related with higher hydrophobicity.[37] Here too, the result suggested that molecules with higher density of positive charges are better suited as selective antibacterial candidates. To obtain definitive proof of functional relevance, we tested all the lipopeptides (**1-9**) against various pathogenic bacteria including clinically isolated strains. Encouragingly, general observations suggested that the antibacterial efficacy of this class of lipopeptides was also charge-dependent. Additionally, we found that spatial positioning of the amino acid residues play an important role in directing antibacterial activity. Two-charge bearing compounds **1** and **4**, where phenylalanine is present at the end of the design, showed moderate antibacterial efficacy with MIC values of 15 μg/mL and 27 μg/mL against *S. aureus*, respectively (Table 1). Intriguingly, the other two-charge comprising compounds, where the phenylalanine moiety is either present at the middle of the molecule (compound **2**) or completely absent (compound **5**), resulted in compromised activity against this bacterial strain (MIC values of **2** and **5** were 32 and 50 μg/mL respectively). This could indicate that the presence of phenylalanine as well as its spatial positioning in the lipopeptide is important to achieve more potent antibacterial activity. We next analysed the activity of the lipopeptides bearing four positive charges. Overall, an improvement in antibacterial activity was noticed compared to two-charge bearing compounds, although compounds **3** and **6**, where the lysine residue was present at the end of the molecules, displayed lesser activity with the MIC values of 30 μg/mL and 95 μg/mL respectively. However, compounds **7** and **8**, with lysine moieties occupying an interior position showed drastic improvement in antibacterial efficacy. Compounds **7** and **8** displayed similar antibacterial activity with the MIC values of 7.3 μg/mL and 10.5 μg/mL. Finally, compound **9**, which consisted of six charges

Table 2 Minimum inhibitory concentration (μg/mL) against critical strains of bacteria.

Bacterial strains	9	Meropenum	Vancomycin	Methicillin
A. baumannii-MTCC	12.5	<1.6	ND	ND
A. baumannii-R676	12.5	>100	ND	ND
P. aeruginosa-MTCC	6.3	<1.6	ND	ND
P. aeruginosa-R590	12.5	>100	ND	ND
K. pneumoniae-ATCC	12.5	<1.6	ND	ND
E. coli-R3336	12.5	>100	ND	ND
VRSA-AB267	6.3	ND	>100	ND
MRSA-ATCC	6.3	ND	1.6	>50
MRSA-R3890	6.3	ND	1.6	>50

owing to the presence of a lysine-lysine amino acid pair on either side of the design, displayed the best efficacy with the MIC value of 5 μg/mL. More importantly, this compound also displayed potent activity against the Gram-negative bacteria, *E. coli*, with the MIC value of 11.2 μg/mL (Table 1). Altogether, this analytical exercise revealed a lead compound, **9**, which displayed potent activity against both *S. aureus* and *E. coli*. On computing the selectivity ratios (HC_{50}/MIC) we observed that the two-charge bearing compounds were less selective compared to four- and six-charge comprising compounds (Figure 2a). This was in direct agreement with prior experiments which showed that these compounds are not only more active but also less toxic than compounds with lower number of charges. Among four-charge containing compounds, compound **7** and **8** displayed a selectivity ratio of >150 and >100 respectively. The best selectivity however, was observed for compound **9**, bearing six positive charges. It displayed >200 fold selectivity towards *S. aureus* (Table 1).

Activity against Critical Bacteria: In order to assess the potential of this class of lipopeptides in the face of the most threatening infections, we next tested the antibacterial activity of compound **9** against five top most critical bacteria according to WHO priority list. It can be seen from table 2 that lead compound **9** was active against these deadly bacteria, including various clinical

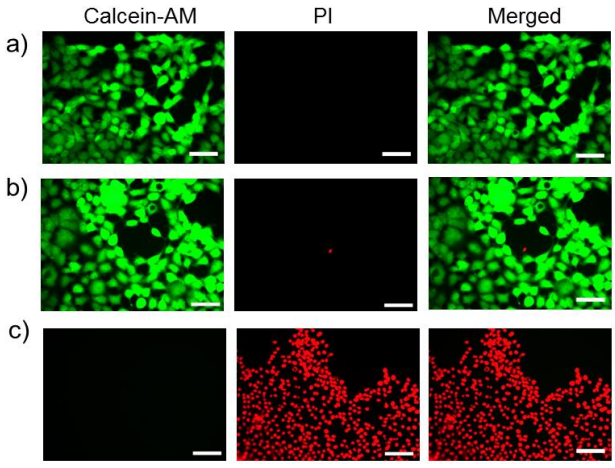


Figure 2. Fluorescence microscopy images of HEK cells; a) Untreated, b) Treated with compound **9** (31.25 μg/mL) and c) Treated with Triton-X. Scale bar: 50μm.

isolates. The antibiotic meropenem remained inactive against all the clinical isolates of Gram-negative bacteria even at 100 µg/mL and methicillin did not display any activity at 50 µg/mL against the MRSA strains, whereas the lipopeptide **9** displayed the activity against these clinical isolates with the MIC values in the concentration ranged 6.3-12.5 µg/mL depending on bacterial strain. Therefore, collectively the results suggested that lipopeptide **9** not only possessed broad spectrum of antibacterial activity but also retained activity against clinically circulating bacterial strains that mounted antibiotic-resistance.

Toxicity against HEK Cells: To further validate the selectivity of this class of lipopeptides, toxicity of optimized lipopeptide **9** was investigated against HEK cells by performing live-dead assay using dual staining with Calcein-AM and PI dyes. The results suggested that even after 24 h exposure in presence of compound **9** (31.25 µg/mL), all the cells were alive as in the untreated case (Figure 2), which further showcased the non-toxic nature of the lead candidate.

Membrane Targeting Mechanism of Action: We next investigated a possible membrane targeting mechanism of action of compound **9** by assessing its effect on bacterial membrane permeability and membrane potential employing complementary spectroscopic techniques. First, membrane permeabilization was studied using the dye propidium iodide (PI), a robust fluorescent readout for compromised bacterial membranes. We clearly demonstrated that compound **9** is capable of causing membrane permeabilization of both *S. aureus* and *E. coli* even at a low concentration of 5 µg/mL (Figure 3a and 3b). From this study we could also account for the observed lower activity against *E. coli* from the rather modest increase in fluorescence intensity compared to *S. aureus*. Next, other spectroscopic studies were performed to observe the effect of compound **9** on membrane potential using the dye $DiSC_3(5)$. Sensitive to membrane potential, this dye can

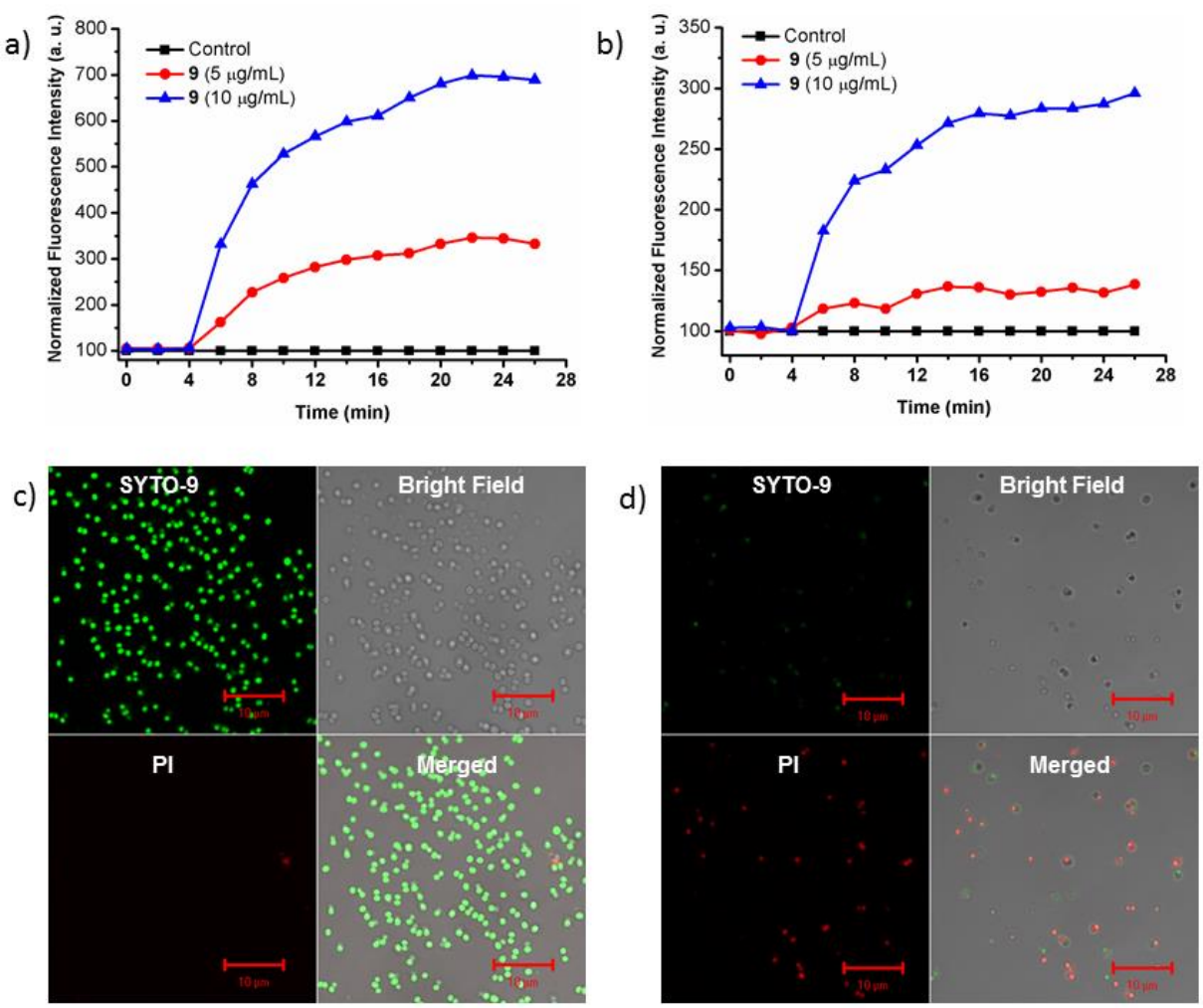


Figure 3. Membrane active mechanism of action; a) Membrane permeabilization of *S. aureus*, b) Membrane permeabilization of *E. coli,* Confocal laser-scanning microscopy images of *S. aureus*; c) Untreated, d) Treated with compound **9** (31.25 µg/mL). Scale bar: 10µm.

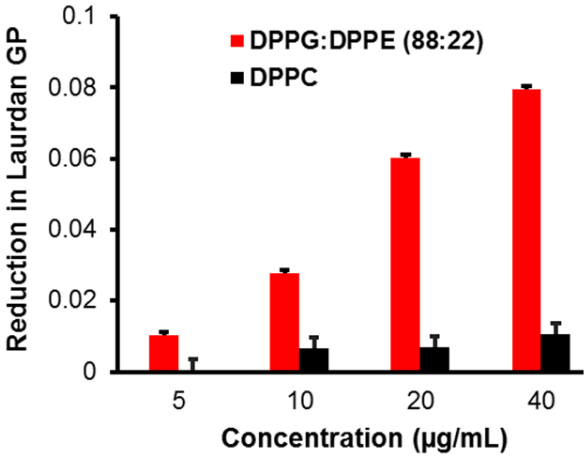


Figure 4. Reduction in laurdan GP after treated with **9.**

distribute itself inside the bacterial cells but can leak out into external media upon disruption of normal membrane potential, resulting in an increase in fluorescence intensity. We observed that compound **9** could indeed disrupt the membrane potential of both *S. aureus* and *E. coli* significantly even at concentrations as low as 5 µg/mL (Supporting Information Figure S29). Finally, to definitively confirm the membrane targeting mechanism of action, we resorted to visualizing the effect of the compound on *S. aureus* using confocal laser-scanning microscopy (CLSM). To this end, we performed a live-dead assay by dual staining with SYTO-9 and PI dyes in order to visualize live and dead cells simultaneously. Our experiments confirmed that bacterial cell membranes were indeed compromised due to compound exposure. Under conditions of no treatment, we observed no signal from the PI channel, which meant that all the *S. aureus* cells were alive. This was cross validated by corresponding SYTO-9 staining. In comparison, compound treated images clearly suggested the presence of dead cells as observed from the more abundant red fluorescence in PI channel, with only a few SYTO-9 stained live cells (Figure 3d).

Membrane Hydration Studies: Selective bacterial killing of compound **9** was further established by performing biophysical studies. Laurdan (6-Dodecanoyl-2-dimethylaminonaphthalene) dye encapsulated liposomes were prepared by using the DPPG:DPPE (88:12) and DPPC lipids, which mimic the membrane of the bacterial and mammalian cells respectively. As the fluorescence of laurdan dye is sensitive towards dipole moment of the lipid environment, an increase in dipole moment due to hydration induces a perturbation in its fluorescence in the lipid bilayer. This change in dipole moment is brought about by the exposure of membrane interacting agents. This allows for the quantification of the extent of interaction of the agent by calculating the general polarization (GP) at various concentrations. The difference in GP values of untreated and compound treated samples is a direct measure of the effect of a compound on the model membrane. Figure 4 clearly suggests a stronger interaction of compound **9** with the bacterial model membrane over the mammalian model membrane. This is evident from the remarkable attenuation of laurdan GP for bacterial model membrane with increasing compound concentration, an effect much less pronounced for the mammalian model membrane. Taken together, the above results establish membrane disruption as the mechanism of action of compound **9**.

Conclusions

In summary, a new class of lipopeptides was rationally designed and prepared by using simple solution phase amide coupling reaction. Structure-activity relationship within this class of compounds suggested that both nature and positioning of hydrophobicity as well as positive charge density play an important role in dictating antibacterial activity and toxicity. The lead compound **9** displayed potent antibacterial activity with high selectivity towards pathogenic bacteria including clinical isolates of both Gram-negative and Gram-positive bacteria through membrane targeted mechanism of action. Therefore, this class of synthetic lipopeptides possess potential for further development as broad-spectrum antibacterial agents.

Experimental Section

Synthesis Protocols and Characterization

General protocol for synthesizing 10a and 10b: At first, 2.4 equivalents of Boc-D-Phe-OH or Boc-D-Leu-OH were dissolved in dry DCM and anhydrous DMF in 4:1 ratio and the solution containing RB was placed at 0-5 ºC ice bath. 4 equivalents of DIPEA were then added to the reaction mixture followed by 2.4 equivalents of HBTU and allowed to stir for 10-15 min. After that, 1 equivalent of precursor amine was added drop wise by dissolving it in dry DCM in presence of additional 2 equivalents of DIPEA. The reaction mixture containing RB was then brought to RT and allowed to stir for 48h. At the end of the reaction, solvent was removed under reduce pressure by using rotary evaporator and crude residue was diluted in ethyl acetate. The reaction mixture was then washed by using 1N HCl (3 times) and saturated Na_2CO_3 solution (3 times) respectively. Finally, the ethyl acetate layer was collected through anhydrous Na_2SO_4 and column chromatography was performed on silica gel (60-120 mesh) with various ratios of MeOH and $CHCl_3$ as eluent to achieve pure **10a** and **10b**.

***N,N*-bis-[3-(*N*-Boc-^{D}Phe)amidopropyl]octanamide (10a):** Yield-65%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.242-6.996 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH(NHBoc)-CH_2-Ph*H*)$_2$, 12H),

5.401-5.271 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(*NH*Boc)-CH_2-Ph)$_2$, 2H), 4.357-4.318 (t, *J* = 7.8 Hz, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*(NHBoc)-CH_2-Ph)$_2$, 2H), 3.382-2.869 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH(NHBoc)-*CH_2*-Ph)$_2$, 12H), 2.215-2.184 (t, *J* = 6.2 Hz, CH_3-$(CH_2)_4$-CH_2-*CH_2*- of R group, 2H), 1.738-1.597 (m, CH_3-$(CH_2)_4$-*CH_2*-CH_2-CO-N(-CH_2-*CH_2*-CH_2-NH-CO-CH(NHBoc)-CH_2-Ph)$_2$, 6H), 1.349 (s, R-CO-NH(-CH_2-CH_2-CH_2-NH-CO-CH(NH-COO-C*$(CH_3)_3$*)-CH_2-Ph)$_2$, 18H), 1.274 (bs, CH_3-*$(CH_2)_4$*-CH_2-CH_2- of R group, 8H), 0.886-0.852 (t, *J* = 6.8 Hz, *CH_3*-$(CH_2)_4$-CH_2-CH_2- of R group, 3H); HRMS (m/z): 752.49110 [$(M+H)^+$] (Observed), 752.49662 [$(M+H)^+$] (Calculated).

***N,N*-bis-[3-(*N*-Boc-^{D}Leu)amidopropyl]octanamide (10b):** Yield-62%; ^{1}H-NMR (400 MHz, $CDCl_3$); δ/ppm: 7.668-7.569 (d, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH(NHBoc)-$CH_2CH(CH_3)_2)_2$, 2H), 5.339-5.212 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(*NH*Boc)-$CH_2CH(CH_3)_2)_2$, 2H), 4.223-4.206 (d, *J* = 6.8 Hz, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*(NHBoc)-$CH_2CH(CH_3)_2)_2$, 2H), 3.679-2.888 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH(NHBoc)-$CH_2CH(CH_3)_2)_2$, 8H), 2.326-2.207 (m, CH_3-$(CH_2)_4$-CH_2-*CH_2*- of R group, 2H), 1.864-1.478 (m, CH_3-$(CH_2)_4$-*CH_2*-CH_2-CO-N(-CH_2-*CH_2*-CH_2-NH-CO-CH(NHBoc)-*CH_2CH*$(CH_3)_2)_2$, 12H), 1.404 (s, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(NH-COO-C*$(CH_3)_3$*)-$CH_2CH(CH_3)_2)_2$, 18H), , 1.265 (bs, CH_3-*$(CH_2)_4$*-CH_2-CH_2- of R group, 8H), 0.907-0.839 (m, *CH_3*-$(CH_2)_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(NHBoc)-CH_2CH*$(CH_3)_2)_2$*, 15H); HRMS (m/z): 684. 52044 [$(M+H)^+$] (Observed), 684. 52752 [$(M+H)^+$] (Calculated).

General protocol for synthesizing 11a and 11b: At first, **10a** or **10b** was dissolved in excess of in 1:1 of DCM (dichloromethane) and TFA (trifluoroacetic acid). At the end of 2h of stirring, the reaction solvent and unused TFA were removed by using rotary evaporator to afford pure **11a** and **11b** with 100% yield.

***N,N*-bis-[3-(^{D}Phe)amidopropyl]octanamide bis(trifluoroacetate) (11a):** ^{1}H-NMR (400 MHz, DMSO-d_6) δ/ppm: 8.473-8.231 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH(*NH_3^+*)-CH_2-Ph)$_2$, 8H), 7.339-7.219 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(NH_3^+)-CH_2-Ph*H*)$_2$, 10H), 3.938 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*(NH_3^+)-CH_2-Ph)$_2$, 2H), 3.187-2.889 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH(NH_3^+)-*CH_2*-Ph)$_2$, 12H), 2.200-2.165 (t, *J* = 7.0 Hz, CH_3-$(CH_2)_4$-CH_2-*CH_2*- of R group, 2H), 1.526-1.445 (m, CH_3-$(CH_2)_4$-*CH_2*-CH_2-CO-N(-CH_2-*CH_2*-CH_2-NH-CO-CH(NH_3^+)-CH_2-Ph)$_2$, 6H), 1.221 (bs, CH_3-*$(CH_2)_4$*-CH_2-CH_2- of R group , 8H), 0.864-0.830 (t, *J* = 6.8 Hz, *CH_3*-$(CH_2)_4$-CH_2-CH_2- of R group, 3H); HRMS (m/z): 552.39456 [$(M+H)^+$] (Observed), 552.39137 [$(M+H)^+$] (Calculated).

***N,N*-bis-[3-(^{D}Leu)amidopropyl]octanamide (11b):** ^{1}H-NMR (400 MHz, DMSO-d_6); δ/ppm: 8.687-8.189 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH(*NH_3^+*)-CH_2-$CH(CH_3)_2)_2$, 8H), 3.733-3.698 (t, *J* = 7.0 Hz, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*(NH_3^+)-CH_2-$CH(CH_3)_2)_2$, 2H), 3.253-3.992 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH(NH_3^+)-CH_2-$CH(CH_3)_2)_2$, 8H), 2.262-2.223 (t, *J* = 7.8 Hz, CH_3-$(CH_2)_4$-CH_2-*CH_2*- of R group, 2H), 1.685-1.464 (m, CH_3-$(CH_2)_4$-*CH_2*-CH_2-CO-N(-CH_2-*CH_2*-CH_2-NH-CO-CH(NH_3^+)-*CH_2*-*CH*$(CH_3)_2)_2$, 12H), 1.243 (bs, CH_3-*$(CH_2)_4$*-CH_2-CH_2- of R group, 8H), 0.906-0.834 (m, *CH_3*-$(CH_2)_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(NH_3^+)-CH_2-CH(*CH_3*$)_2)_2$, 15H); HRMS (m/z): 484.41843 [$(M+H)^+$] (Observed), 484.42267 [$(M+H)^+$] (Calculated).

General protocol for synthesizing 12a-12f: Briefly, 2.4 equivalents Boc-protected amino acids such as; Boc-D-Phe-OH, Boc-D-Leu-OH or Boc-D-Lys (Boc)-OH was dissolved in dry DCM and anhydrous DMF (4:1) at 0-5 ºC ice bath. After that, 4 equivalents of DIPEA were added followed by 2.4 equivalents of HBTU and allowed reaction mixture to stir for 10-15 min. Now, 1 equivalent of **11a** or **11b** was added drop wise to the reaction mixture after dissolving it in dry DCM in presence of additional 2 equivalents of DIPEA. The RB containing reaction mixture was then brought to RT and kept for stirring. At the end of 48h, reaction solvent was removed by using rotary evaporator. The crude reaction mixture was diluted in ethyl acetate and then washed by using 1N HCl (3 times) followed by saturated Na_2CO_3 solution (3 times). Finally, the ethyl acetate layer was collected through anhydrous Na_2SO_4 and pure **12a-12f** was achieved by performing column chromatography on silica gel (60-120 mesh) with various ratios of MeOH and $CHCl_3$ as eluent.

***N,N*-bis-[3-(*N*-Boc-^{D}Phe-*N*-Boc-^{D}Phe)amidopropyl]octanamide (12a):** Yield-66%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.335-6.354 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH-(CH_2-Ph*H*)-*NH*-CO-CH(NHBoc)-CH_2-Ph*H*)$_2$, 24H), 5.011-4.854 (d, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH(*NH*Boc)-CH_2-Ph)$_2$, 2H), 4.667-4.614 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*-(CH_2-Ph)-NH-CO-CH(NHBoc)-CH_2-Ph)$_2$, 2H), 4.316-4.197 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-*CH*(NHBoc)-CH_2-Ph)$_2$, 2H), 3.252-2.907 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH-(*CH_2*-

Ph)-NH-CO-CH(NHBoc)-$\underline{CH_2}$-Ph)$_2$, 16H), 2.242-2.204 (t, *J* = 7.6 Hz, CH_3-$(CH_2)_4$-CH_2-$\underline{CH_2}$- of R group, 2H), 1.650-1.577 (m, CH_3-$(CH_2)_4$-$\underline{CH_2}$-CH_2-CO-N(-CH_2-$\underline{CH_2}$-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH(NHBoc)-CH_2-Ph)$_2$, 6H), 1.342 (s, CH_3-$(CH_2)_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH(NH-COO C$\underline{(CH_3)_3}$)-CH_2-Ph)$_2$, 18H), 1.281-1.251 (m, CH_3-$\underline{(CH_2)_4}$-CH_2-CH_2- of R group , 8H), 0.884-0.850 (t, *J* = 6.8 Hz, $\underline{CH_3}$-$(CH_2)_4$-CH_2-CH_2- of R group, 3H). HRMS (m/z): 1046.62798 [(M+H)$^+$] (Observed), 1046.63305 [(M+H)$^+$] (Calculated).

***N,N*-bis-[3-(*N*-Boc-^{D}Phe-*N*-Boc-^{D}Leu)amidopropyl]octanamide (12b):** Yield-68%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.296-6510 (m, R-CO-N(-CH_2-CH_2-CH_2-$\underline{NH}$-CO-CH-(CH_2-Ph$\underline{H}$)-$\underline{NH}$-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 14H), 4.909-4.797 (d, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH($\underline{NH}$Boc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 4.689-4.659 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-$\underline{CH}$(CH_2-Ph)-NH-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 4.061-3.925 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-$\underline{CH}$(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 3.242-3.033 (m, R-CO-N(-$\underline{CH_2}$-CH_2-$\underline{CH_2}$-NH-CO-CH-($\underline{CH_2}$-Ph)-NH-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 12H), 2.247-2.209 (t, *J* = 7.6 Hz, CH_3-$(CH_2)_4$-CH_2-$\underline{CH_2}$- of R group, 2H), 1.667-1.494 (m, CH_3-$(CH_2)_4$-$\underline{CH_2}$-CH_2-CO-N(-CH_2-$\underline{CH_2}$-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH(NHBoc)-$\underline{CH_2}$-$\underline{CH}$-(CH_3)$_2$)$_2$, 12H), 1.412 (s, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH(NH-COO-C$\underline{(CH_3)_3}$)-CH_2-CH-(CH_3)$_2$)$_2$, 18H), 1.282 (bs, CH_3-$\underline{(CH_2)_4}$-CH_2-CH_2- of R group , 8H), 0.923-0.855 (m, $\underline{CH_3}$-$(CH_2)_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH(NHBoc)-CH_2-CH-$\underline{(CH_3)_2}$)$_2$, 15H). HRMS (m/z): 978.66302 [(M+H)$^+$] (Observed), 978.66435 [(M+H)$^+$] (Calculated).

***N,N*-bis-[3-(*N*-Boc-^{D}Phe-*N,N´*-Di-Boc-^{D}Lys)amidopropyl]octanamide (12c):** Yield-65%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.310-7.085 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph$\underline{H}$)-$\underline{NH}$-CO-CH(NHBoc)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 12H), 6.677-6.487 (d, R-CO-N(-CH_2-CH_2-CH_2-$\underline{NH}$-CO-CH-(CH_2-Ph)-NH-CO-CH(NHBoc)-CH_2-CH_2-CH_2-CH_2 NHBoc)$_2$, 2H), 5.619-5.328 (d, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH($\underline{NH}$Boc)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 2H), 4.770 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH(NHBoc)-CH_2-CH_2-CH_2-CH_2-$\underline{NH}$Boc)$_2$, 2H), 4.700-4.654 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-$\underline{CH}$(CH_2-Ph)-NH-CO-CH(NHBoc)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 2H), 3.983-3.884 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-Ph)-NH-CO-$\underline{CH}$(NHBoc)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 2H), 3.323-3.079 (m, R-CO-N(-$\underline{CH_2}$-CH_2-$\underline{CH_2}$-NH-CO-CH($\underline{CH_2}$-Ph)-NH-CO-CH(NHBoc)-CH_2-CH_2-CH_2-$\underline{CH_2}$-NHBoc)$_2$, 16H), 2.256-2.219 (t, CH_3-$(CH_2)_4$-CH_2-$\underline{CH_2}$- of R group, 2H), 1.720-1.579 (m, CH_3-$(CH_2)_4$-$\underline{CH_2}$-CH_2-CO-N(-CH_2-$\underline{CH_2}$-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH(NHBoc)-$\underline{CH_2}$-CH_2-$\underline{CH_2}$-CH_2-NHBoc)$_2$, 14H), 1.468-1.206 (m, CH_3-$\underline{(CH_2)_4}$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-Ph)-NH-CO-CH(NH-COO-C$\underline{(CH_3)_3}$)-CH_2-$\underline{CH_2}$-CH_2-CH_2-NH-COO-C$\underline{(CH_3)_3}$)$_2$, 48H), 0.890-0.856 (t, *J* = 6.8 Hz, $\underline{CH_3}$-$(CH_2)_4$-CH_2-CH_2- of R group, 3H). HRMS (m/z): 1208.79098 [(M+H)$^+$] (Observed), 1208.79101 [(M+H)$^+$] (Calculated).

***N,N*-bis-[3-(*N*-Boc-^{D}Leu-*N*-Boc-^{D}Phe)amidopropyl]octanamide (12d):** Yield-68%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.326-7.183 and 6.630-6.390 (m, R-CO-N(-CH_2-CH_2-CH_2-$\underline{NH}$-CO-CH(CH_2-CH-(CH_3)$_2$)-$\underline{NH}$-CO-CH(NHBoc)-CH_2-Ph$\underline{H}$)$_2$, 14H), 5.011-4.931 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH-(CH_3)$_2$)-NH-CO-CH($\underline{NH}$Boc)-CH_2-Ph)$_2$, 2H), 4.491-4.306 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-$\underline{CH}$(CH_2-CH-(CH_3)$_2$)-NH-CO-$\underline{CH}$(NHBoc)-CH_2-Ph)$_2$, 4H), 3.411-2.988 (m, R-CO-N(-$\underline{CH_2}$-CH_2-$\underline{CH_2}$-NH-CO-CH(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NHBoc)-$\underline{CH_2}$-Ph)$_2$, 12H), 2.288-2.250 (t, *J* = 7.6 Hz, CH_3-$(CH_2)_4$-CH_2-$\underline{CH_2}$- of R group, 2H), 1.667-1.443 (m, CH_3-$(CH_2)_4$-$\underline{CH_2}$-CH_2-CO-N(-CH_2-$\underline{CH_2}$-CH_2-NH-CO-CH($\underline{CH_2}$-$\underline{CH}$-(CH_3)$_2$)$_2$-NH-CO-CH(NHBoc)-CH_2-Ph)$_2$, 12H), 1.402 (s, CH_3-$(CH_2)_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NHCOO-C$\underline{(CH_3)_3}$)-CH_2-Ph)$_2$, 18H), 1.274 (bs, CH_3-$\underline{(CH_2)_4}$-CH_2-CH_2- of R group , 8H), 0.910-0.856 (m, $\underline{CH_3}$-$(CH_2)_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH-$\underline{(CH_3)_2}$)-NH-CO-CH(NHBoc)-CH_2-Ph)$_2$, 15H). HRMS (m/z): 978.66022 [(M+H)$^+$] (Observed), 978.66435 [(M+H)$^+$] (Calculated).

***N,N*-bis-[3-(*N*-Boc-^{D}Leu-*N*-Boc-^{D}Leu)amidopropyl]octanamide (12e):** Yield-70%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.571-7.462 (d, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH-(CH_3)$_2$)-$\underline{NH}$-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 6.739-6.537 (m, R-CO-N(-CH_2-CH_2-CH_2-$\underline{NH}$-CO-CH(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 4.929-4.881 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH-(CH_3)$_2$)-NH-CO-CH($\underline{NH}$Boc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 4.557-4.490 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-$\underline{CH}$(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 4.082-4.050 (t, *J* = 6.4 Hz, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH-(CH_3)$_2$)-NH-CO-$\underline{CH}$(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 3.650-2.986 (m, R-

CO-N(-*CH₂*-CH₂-*CH₂*-NH-CO-CH(CH₂-CH-(CH₃)₂)-NH-CO-CH(NHBoc)-CH₂-CH-(CH₃)₂)₂, 8H), 2.265-2.234 (t, *J* = 6.2 Hz, CH₃-(CH₂)₄-CH₂-*CH₂*- of R group, 2H), 1.745-1.435 (m, CH₃-(CH₂)₄-*CH₂*-CH₂-CO-N(-CH₂-*CH₂*-CH₂-NH-CO-CH(*CH₂*-*CH*-(CH₃)₂)-NH-CO-CH(NHBoc)-*CH₂*-*CH*-(CH₃)₂)₂, 18H), 1.429 (s, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH(CH₂-CH-(CH₃)₂)-NH-CO-CH(NH-COO-C*(CH₃)₃*)-CH₂-CH-(CH₃)₂)₂, 18H), 1.282 (bs, CH₃-*(CH₂)₄*-CH₂-CH₂- of R group , 8H), 0.954-0.853 (m, *CH₃*-(CH₂)₄-CH₂-CH₂-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH-(CH₂-CH-*(CH₃)₂*)-NH-CO-CH(NHBoc)-CH₂-CH-*(CH₃)₂*)₂, 27H). HRMS (m/z): 910.68365 [(M+H)⁺] (Observed), 910.69565 [(M+H)⁺] (Calculated).

***N,N*-bis-[3-(*N*-Boc-^{D}Leu-*N,N´*-Di-Boc-^{D}Lys)amidopropyl]octanamide (12f):** Yield-66%; ^{1}H-NMR (400 MHz, CDCl₃) δ/ppm: 7.544-7.449 (d, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH(CH₂-CH-(CH₃)₂)-*NH*-CO-CH(NHBoc)-CH₂-CH₂-CH₂-CH₂-NHBoc)₂, 2H), 6.636-6.488 (d, R-CO-N(-CH₂-CH₂-CH₂-*NH*-CO-CH(CH₂-CH-(CH₃)₂)-NH-CO-CH(NHBoc)-CH₂-CH₂-CH₂-CH₂-NHBoc)₂, 2H), 5.503-5.268 (d, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH(CH₂-CH-(CH₃)₂)-NH-CO-CH(*NH*Boc)-CH₂-CH₂-CH₂-CH₂-NHBoc)₂, 2H), 4.860 (s, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH(CH₂-CH-(CH₃)₂)-NH-CO-CH(NHBoc)-CH₂-CH₂-CH₂-CH₂-*NH*Boc)₂, 2H), 4.514-4.483 (m, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-*CH*(CH₂-CH-(CH₃)₂)-NH-CO-CH(NHBoc)-CH₂-CH₂-CH₂-CH₂-NHBoc)₂, 2H), 4.053-3.982 (m, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH(CH₂-CH-(CH₃)₂)-NH-CO-*CH*(NHBoc)-CH₂-CH₂-CH₂-CH₂-NHBoc)₂, 2H), 3.400-3.091 (m, R-CO-N(-*CH₂*-CH₂-*CH₂*-NH-CO-CH(CH₂-CH-(CH₃)₂)-NH-CO-CH(NHBoc)-CH₂-CH₂-CH₂-*CH₂*-NHBoc)₂, 12H), 2.283-2.245 (t, *J* = 7.6 Hz, CH₃-(CH₂)₄-CH₂-*CH₂*- of R group, 2H), 1.778-1.488 (m, CH₃-(CH₂)₄-*CH₂*-CH₂-CO-N(-CH₂-*CH₂*-CH₂-NH-CO-CH(*CH₂*-*CH*-(CH₃)₂)-NH-CO-CH(NHBoc)-*CH₂*-*CH₂*-*CH₂*-CH₂-NHBoc)₂, 24H), 1.436 (s, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH(CH₂-CH-(CH₃)₂)-NH-CO-CH(NH-COO-C*(CH₃)₃*)-CH₂-CH₂-CH₂-CH₂-NH-COO-C*(CH₃)₃*)₂, 36H), 1.292 (bs, CH₃-*(CH₂)₄*-CH₂-CH₂-of R group, 8H), 0.890-0.856 (t, *J* = 6.8 Hz, *CH₃*-(CH₂)₄-CH₂-CH₂- of R group, 3H). HRMS (m/z): 1140.80527 [(M+H)⁺] (Observed), 1140.82231 [(M+H)⁺] (Calculated).

General protocol for synthesizing 1-6: At first, **12a-12f** were dissolved in excess amount of 1:1 (DCM:TFA) and kept for stirring at RT. At the end 2h, the reaction solvent and unused TFA were removed to afford pure **1-6** with 100% yield.

***N,N*-bis-[3-(^{D}Phe-^{D}Phe)amidopropyl]octanamide bis(trifluoroacetate) (1):** ^{1}H-NMR (400 MHz, DMSO-d₆) δ/ppm: 8.850-8.800 (m, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH-(CH₂-Ph)-*NH*-CO-CH(NH₃⁺)-CH₂-Ph)₂, 2H), 8.175-8.004 (m, R-CO-N(-CH₂-CH₂-CH₂-*NH*-CO-CH-(CH₂-Ph)-NH-CO-CH(*NH₃⁺*)-CH₂-Ph)₂, 8H), 7.293-7.199 (m, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH-(CH₂-Ph*H*)-NH-CO-CH(NH₃⁺)-CH₂-Ph*H*)₂, 20H), 4.548-4.467 (m, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-*CH*-(CH₂-Ph)-NH-CO-CH(NH₃⁺)-CH₂-Ph)₂, 2H), 4.050-4.019 (t, *J* = 6.2 Hz, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH-(CH₂-Ph)-NH-CO-*CH*(NH₃⁺)-CH₂-Ph)₂, 2H), 3.139-2.831 (m, R-CO-N(-*CH₂*-CH₂-*CH₂*-NH-CO-CH-(*CH₂*-Ph)-NH-CO-CH(NH₃⁺)-*CH₂*-Ph)₂, 16H), 2.209-2.177 (t, *J* = 6.4 Hz, CH₃-(CH₂)₄-CH₂-*CH₂*- of R group, 2H), 1.563-1.454 (m, CH₃-(CH₂)₄-*CH₂*-CH₂-CO-N(-CH₂-*CH₂*-CH₂-NH-CO-CH-(CH₂-Ph)-NH-CO-CH(NH₃⁺)-CH₂-Ph)₂, 6H), 1.234-1.203 (m, CH₃-*(CH₂)₄*-CH₂-CH₂- of R group , 8H), 0.839-0.805 (t, *J* = 6.8 Hz, *CH₃*-(CH₂)₄-CH₂-CH₂- of R group, 3H). ^{13}C-NMR (100 MHz, DMSO-d₆) δ/ppm: 171.80, 167.79, 167.58, 135.01, 129.42, 128.47, 127.09, 53.62, 44.97, 42.76, 37.14, 36.28, 32.06, 31.29, 29.03, 28.70, 28.35, 27.27, 25.08, 22.09, 13.94. HRMS (m/z): 846.50588 [(M+H)⁺] (Observed), 846.52819 [(M+H)⁺] (Calculated). 423.75794 [(M+2H)²⁺]/2 (Observed), 423.76746 [(M+2H)²⁺]/2 (Calculated).

***N,N*-bis-[3-(^{D}Phe-^{D}Leu)amidopropyl]octanamide bis(trifluoroacetate) (2):** ^{1}H-NMR (400 MHz, DMSO-d₆) δ/ppm: 8.805-8.769 (t, *J* = 7.2 Hz, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH-(CH₂-Ph)-*NH*-CO-CH(NH₃⁺)-CH₂-CH-(CH₃)₂)₂, 2H), 8.175-7.981 (m, R-CO-N(-CH₂-CH₂-CH₂-*NH*-CO-CH-(CH₂-Ph)-NH-CO-CH(*NH₃⁺*)-CH₂-CH-(CH₃)₂)₂, 8H), 7.290-7.178 (m, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH-(CH₂-Ph*H*)-NH-CO-CH(NH₃⁺)-CH₂-CH-(CH₃)₂)₂, 10H), 4.536-4.454 (m, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-*CH*-(CH₂-Ph)-NH-CO-CH(NH₃⁺)-CH₂-CH-(CH₃)₂)₂, 2H), 3.771 (bs, R-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH-(CH₂-Ph)-NH-CO-*CH*(NH₃⁺)-CH₂-CH-(CH₃)₂)₂, 2H), 3.091-2.838 (m, R-CO-N(-*CH₂*-CH₂-*CH₂*-NH-CO-CH-(*CH₂*-Ph)-NH-CO-CH(NH₃⁺)-CH₂-CH-(CH₃)₂)₂, 12H), 2.200-2.164 (t, *J* = 7.2 Hz, CH₃-(CH₂)₄-CH₂-*CH₂*- of R group, 2H), 1.623-1.449 (m, CH₃-(CH₂)₄-*CH₂*-CH₂-CO-N(-CH₂-*CH₂*-CH₂-NH-CO-CH-(CH₂-Ph)-NH-CO-CH(NH₃⁺)-*CH₂*-*CH*-(CH₃)₂)₂, 12H), 1.232 (bs, CH₃-*(CH₂)₄*-CH₂-CH₂- of R group , 8H), 0.878-0.820 (m, *CH₃*-(CH₂)₄-CH₂-CH₂-CO-N(-CH₂-CH₂-CH₂-NH-CO-CH-(CH₂-Ph)-NH-CO-CH(NH₃⁺)-CH₂-CH-*(CH₃)₂*)₂, 15H). ^{13}C-NMR (100 MHz, DMSO-d₆) δ/ppm: 171.93, 170.04, 168.88, 137.47, 129.16, 128.23, 126.49, 54.64, 50.82, 45.08, 42.76, 37.93, 36.19, 32.12, 31.24, 28.77, 28.68, 27.46, 25.14, 23.46, 22.78, 22.07, 21.76, 13.96. HRMS (m/z): 778.53923 [(M+H)⁺] (Observed), 778.55949

[(M+H)$^+$] (Calculated). 389.77317 [(M+2H)$^{2+}$]/2 (Observed), 389.78311 [(M+2H)$^{2+}$]/2 (Calculated).

***N,N*-bis-[3-(^{D}Phe-^{D}Lys)amidopropyl]octanamide tetrakis(trifluoroacetate) (3):** ^{1}H-NMR (400 MHz, DMSO-d_6) δ/ppm: 8.731-8.680 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-*NH*-CO-CH(NH_3^+)-CH_2-CH_2-CH_2-CH_2-NH_3^+)$_2$, 2H), 8.253-7.859 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH-(CH_2-Ph)-NH-CO-CH(*NH_3^+*)-CH_2-CH_2-CH_2-CH_2-*NH_3^+*)$_2$, 14H), 7.293-7.190 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph*H*)-NH-CO- CH_2-CH_2-CH_2-CH_2-NH_3^+)$_2$, 10H), 4.528-4.447 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*-(CH_2-Ph)-NH-CO-CH(NH_3^+)-CH_2-CH_2-CH_2-CH_2-NH_3^+)$_2$, 2H), 3.755 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-*CH*(NH_3^+)-CH_2-CH_2-CH_2-CH_2-NH_3^+)$_2$, 2H), 3.120-2.740 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH-(*CH_2*-Ph)-NH-CO-CH(NH_3^+)-CH_2-CH_2-CH_2-*CH_2*-NH_3^+)$_2$, 16H), 2.221-2.183 (m, CH_3-(CH_2)$_4$-CH_2-*CH_2*- of R group, 2H), 1.706-1.317 (m, CH_3-(CH_2)$_4$-*CH_2*-CH_2-CO-N(-CH_2-*CH_2*-CH_2-NH-CO-CH-(CH_2-Ph)-NH-CO-CH(NH_3^+)-*CH_2*-*CH_2*-*CH_2*-CH_2-NH_3^+)$_2$, 18H), 1.223 (bs, CH_3-*(CH_2)$_4$*-CH_2-CH_2- of R group, 8H), 0.849-0.815 (t, *J* = 6.8 Hz, *CH_3*-(CH_2)$_4$-CH_2-CH_2- of R group, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ/ppm: 171.99, 170.60, 168.49, 137.38, 129.17, 128.22, 126.52, 54.68, 51.90, 38.55, 36.49, 36.21, 32.14, 31.23, 30.54, 28.78, 28.67, 28.52, 26.44, 25.14, 22.06, 21.03, 13.96. HRMS (m/z): 808.58202 [(M+H)$^+$] (Observed), 808.58129 [(M+H)$^+$] (Calculated). 404.79507 [(M+2H)$^{2+}$]/2 (Observed), 404.79401 [(M+2H)$^{2+}$]/2 (Calculated).

***N,N*-bis-[3-(^{D}Leu-^{D}Phe)amidopropyl]octanamide bis(trifluoroacetate) (4):** ^{1}H-NMR (400 MHz, DMSO-d_6) δ/ppm: 8.675-8.635 (t, *J* = 8.0 Hz, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH-(CH_3)$_2$)-*NH*-CO-CH(NH_3^+)-CH_2-Ph)$_2$, 2H), 8.137-7.977 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH-(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(*NH_3^+*)-CH_2-Ph)$_2$, 8H), 7.293-7.227 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NH_3^+)-CH_2-Ph*H*)$_2$, 10H), 4.324-4.277 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*-(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NH_3^+)-CH_2-Ph)$_2$, 2H), 4.006 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH-(CH_3)$_2$)-NH-CO-*CH*(NH_3^+)-CH_2-Ph)$_2$, 2H), 3.234-2.899 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH-(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NH_3^+)-*CH_2*-Ph)$_2$, 12H), 2.251-2.214 (t, *J* = 7.2 Hz, CH_3-(CH_2)$_4$-CH_2-*CH_2*- of R group, 2H), 1.636-1.443 (m, CH_3-(CH_2)$_4$-*CH_2*-CH_2-CO-N(-CH_2-*CH_2*-CH_2-NH-CO-CH-(*CH_2*-*CH*-(CH_3)$_2$)-NH-CO-CH(NH_3^+)-CH_2-Ph)$_2$, 12H), 1.216 (bs, CH_3-*(CH_2)$_4$*-CH_2-CH_2- of R group , 8H), 0.906-0.815 (m, *CH_3*-(CH_2)$_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH-*(CH_3)$_2$*)-NH-CO-CH(NH_3^+)-CH_2-Ph)$_2$, 15H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ/ppm: 171.94, 171.02, 167.67, 134.81, 129.55, 128.50, 127.14, 53.21, 51.38, 45.12, 41.50, 36.96, 36.37, 32.09, 31.22, 28.78, 28.66, 27.55, 25.10, 24.15, 22.87, 22.06, 21.88, 13.94. HRMS (m/z): 778.53750 [(M+H)$^+$] (Observed), 778.55949 [(M+H)$^+$] (Calculated). 389.77402 [(M+2H)$^{2+}$]/2 (Observed), 389.78311 [(M+2H)$^{2+}$]/2 (Calculated).

***N,N*-bis-[3-(^{D}Leu-^{D}Leu)amidopropyl]octanamide bis(trifluoroacetate) (5):** ^{1}H-NMR (400 MHz, DMSO-d_6) δ/ppm: 8.646-8.595 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH-(CH_3)$_2$)-*NH*-CO-CH(NH_3^+)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 8.195-8.005 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH-(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(*NH_3^+*)-CH_2-CH-(CH_3)$_2$)$_2$, 8H), 4.346-4.258 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*-(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NH_3^+)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 3.796 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH-(CH_3)$_2$)-NH-CO-*CH*(NH_3^+)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 3.515-2.927 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH-(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NH_3^+)-CH_2-CH-(CH_3)$_2$)$_2$, 8H), 2.234-2.200 (t, *J* = 6.8 Hz, CH_3-(CH_2)$_4$-CH_2-*CH_2*- of R group, 2H), 1.667-1.416 (m, CH_3-(CH_2)$_4$-*CH_2*-CH_2-CO-N(-CH_2-*CH_2*-CH_2-NH-CO-CH-(*CH_2*-*CH*-(CH_3)$_2$)-NH-CO-CH(NH_3^+)-*CH_2*-*CH*-(CH_3)$_2$)$_2$, 18H), 1.240 (bs, CH_3-*(CH_2)$_4$*-CH_2-CH_2- of R group , 8H), 0.901-0.832 (m, *CH_3*-(CH_2)$_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH-*(CH_3)$_2$*)-NH-CO-CH(NH_3^+)-CH_2-CH-*(CH_3)$_2$*)$_2$, 27H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ/ppm: 173.60, 172.43, 169.58, 52.48, 51.66, 45.89, 41.30, 40.75, 36.96, 32.77, 31.79, 29.19, 25.79, 24.79, 24.17, 23.40, 23.18, 22.66, 22.44, 22.34, 22.30, 22.24, 14.55. HRMS (m/z): 710.57239 [(M+H)$^+$] (Observed), 710.59079 [(M+H)$^+$] (Calculated). 355.79120 [(M+2H)$^{2+}$]/2 (Observed), 355.79876 [(M+2H)$^{2+}$]/2 (Calculated).

***N,N*-bis-[3-(^{D}Leu-^{D}Lys)amidopropyl]octanamide tetrakis(trifluoroacetate) (6):** ^{1}H-NMR (400 MHz, DMSO-d_6) δ/ppm: 8.588-8.537 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH-(CH_3)$_2$)-*NH*-CO-CH(NH_3^+)-CH_2-CH_2-CH_2-CH_2-NH_3^+)$_2$, 2H), 8.241-7.903 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH-(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(*NH_3^+*)-CH_2-CH_2-CH_2-CH_2-*NH_3^+*)$_2$, 14H), 4.323-4.236 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*-(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NH_3^+)-CH_2-CH_2-CH_2-CH_2-NH_3^+)$_2$, 2H), 3.799 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH-(CH_3)$_2$)-NH-CO-*CH*(NH_3^+)-CH_2-CH_2-CH_2-CH_2-NH_3^+)$_2$, 2H), 3.217-2.749 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH-(CH_2-CH-(CH_3)$_2$)-NH-CO-CH(NH_3^+)-CH_2-CH_2-CH_2-*CH_2*-NH_3^+)$_2$, 12H),

2.246-2.200 (m, CH_3-$(CH_2)_4$-CH_2-$\underline{CH_2}$- of R group, 2H), 1.698-1.348 (m, CH_3-$(CH_2)_4$-$\underline{CH_2}$-CH_2-CO-N(-CH_2-$\underline{CH_2}$-CH_2-NH-CO-CH-($\underline{CH_2}$-$\underline{CH}$-$(CH_3)_2$)-NH-CO-CH(NH_3^+)-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-CH_2-NH_3^+)$_2$, 24H), 1.242 (bs, CH_3-$\underline{(CH_2)_4}$-CH_2-CH_2- of R group, 8H), 0.899-0.832 (t, $\underline{CH_3}$-$(CH_2)_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH-$\underline{(CH_3)_2}$)-NH-CO-CH(NH_3^+)-CH_2-CH_2-CH_2-CH_2-NH_3^+)$_2$, 15H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ/ppm: 171.80, 171.49, 168.34, 51.89, 51.59, 45.12, 42.81, 41.05, 38.57, 36.50, 32.10, 31.26, 30.48, 28.70, 26.41, 25.13, 24.19, 22.92, 22.09, 21.69, 21.06, 13.98. HRMS (m/z): 740.59400 [$(M+H)^+$] (Observed), 740.61259 [$(M+H)^+$] (Calculated). 370.80232 [$(M+2H)^{2+}$]/2 (Observed), 370.80966 [$(M+2H)^{2+}$]/2 (Calculated).

Protocol for synthesizing 13: At first, 2.4 equivalents of Fmoc-D-Lys (Boc)-OH was dissolved in dry DCM and anhydrous DMF (4:1) at 0-5 ºC ice bath. 4 equivalents of DIPEA were then added to the solution followed by 2.4 equivalents of HBTU. After that, the reaction mixture allowed stirring for 10-15 min. To the reaction mixture then, 1 equivalent of precursor amine was added drop wise after dissolving it in dry DCM in presence of additional 2 equivalents of DIPEA. The reaction mixture was then brought to RT and allowed to stir for 48h. At the end of the reaction, solvent was removed by using rotary evaporator. The crude reaction mixture was diluted in ethyl acetate and then washed by using 1N HCl (3 times). At the end, the ethyl acetate layer was collected by passing through anhydrous Na_2SO_4 and the compound was purified by performing column chromatography on silica gel (60-120 mesh) with various ratios of MeOH and $CHCl_3$ as eluent. Yield-60%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.747-7.088 (m, R-CO-N(-CH_2-CH_2-CH_2-$\underline{NH}$-CO-CH(NH-COO-CH_2-*Fl*-*Ar*-$\underline{H}$)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 18H), 5.923-5.877 (d, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH($\underline{NH}$Fmoc)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 2H), 4.855 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(NHFmoc)-CH_2-CH_2-CH_2-CH_2-$\underline{NH}$Boc)$_2$, 2H), 4.368-4.169 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-$\underline{CH}$(NH-COO-$C\underline{H_2}$-*Fl*-$\underline{H_9}$)-CH_2-CH_2-CH_2-NHBoc)$_2$, 8H), 3.426-3.068 (m, R-CO-N(-$C\underline{H_2}$-CH_2-$C\underline{H_2}$-NH-CO-CH(NHFmoc)-CH_2-CH_2-CH_2-$C\underline{H_2}$-NHBoc)$_2$, 12H), 2.259-2.221 (t, *J* = 7.6 Hz, CH_3-$(CH_2)_4$-CH_2-$C\underline{H_2}$- of R group, 2H), 2.046-1.544 (m, CH_3-$(CH_2)_4$-$C\underline{H_2}$-CH_2-CO-N(-CH_2-$C\underline{H_2}$-CH_2-NH-CO-CH(NHFmoc)-$C\underline{H_2}$-$C\underline{H_2}$-$\underline{CH_2}$-CH_2-NHBoc)$_2$, 18H), 1.424 (s, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(NHFmoc)-CH_2-CH_2-CH_2-NH-COO-C($C\underline{H_3}$)$_3$)$_2$, 18H), 1.238 (bs, CH_3-$(C\underline{H_2})_4$-CH_2-CH_2- of R group, 8H), 0.891-0.856 (t, *J* = 7.0 Hz, $C\underline{H_3}$-$(CH_2)_4$-CH_2-CH_2- of R group, 3H); HRMS (m/z): 1158.67996 [$(M+H)^+$] (Observed), 1158.68548 [$(M+H)^+$] (Calculated).

Protocol for synthesizing 14: Fmoc group of compound **13** was selectively deprotected to achieve compound **14**. Briefly, compund **13** was dissolved in excess amount of 1:1 of Diethylamine and DCM and allowed to stir at RT. At the end of 3h, the reaction mixture was evaporated to dryness and the crude product was dissolved in minimum volume of $CHCl_3$ and MeOH mixture. After that, pure compound **14** was isolated through precipitation by adding diethyl ether to the crude reaction mixture. Yield: 90%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.675-7.235 (m, R-CO-N(-CH_2-CH_2-CH_2-$\underline{NH}$-CO-CH($\underline{NH_2}$)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 6H), 4.569 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(NH_2)-CH_2-CH_2-CH_2-$\underline{NH}$Boc)$_2$, 2H), 4.186-4.151 (t, *J* = 7.0 Hz, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-$C\underline{H}$(NH_2)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 2H), 3.410-3.061 (m, R-CO-N(-$C\underline{H_2}$-CH_2-$C\underline{H_2}$-NH-CO-CH(NH_2)-CH_2-CH_2-CH_2-$C\underline{H_2}$-NHBoc)$_2$, 12H), 2.258-2.222 (t, *J* = 7.2 Hz, CH_3-$(CH_2)_4$-CH_2-$C\underline{H_2}$- of R group, 2H), 1.801-1.542 (m, CH_3-$(CH_2)_4$-$C\underline{H_2}$-CH_2-CO-N(-CH_2-$C\underline{H_2}$-CH_2-NH-CO-CH(NH_2)-$C\underline{H_2}$-$C\underline{H_2}$-$\underline{CH_2}$-CH_2-NHBoc)$_2$, 18H), 1.241 (bs, CH_3-$\underline{(CH_2)_4}$-CH_2-CH_2- of R group, 8H), 0.886-0.853 (t, *J* = 6.6 Hz, $C\underline{H_3}$-$(CH_2)_4$-CH_2-CH_2- of R group, 3H); HRMS (m/z): 714.54903 [$(M+H)^+$] (Observed), 714.54932 [$(M+H)^+$] (Calculated).

General protocol for synthesizing 15a-15c: Briefly, 2.4 equivalents of Boc-D-Phe-OH, Boc-D-Leu-OH or Boc-D-Lys (Boc)-OH was dissolved in dry DCM and anhydrous DMF (4:1) at 0-5 ºC ice bath. To this solution, 4 equivalents of DIPEA were then added followed by 2.4 equivalents of HBTU and kept for stirring. At the end of 10-15 min, 1 equivalent of **14** was added drop wise to the reaction mixture after dissolving it in dry DCM in presence of additional 2 equivalents of DIPEA. The RB containing reaction mixture was then brought to RT and allowed to stir for 48h. At the end, the reaction solvent was removed by using rotary evaporator and the crude reaction mixture was diluted in ethyl acetate and then washed by using 1N HCl (3 times). Finally, the ethyl acetate layer was collected through anhydrous Na_2SO_4 and pure **15a-12c** was achieved by performing column chromatography on silica gel (60-120 mesh) with various ratios of MeOH and $CHCl_3$ as eluent.

***N,N*-bis-[3-(Nε-Boc-^{D}Lys-N-Boc-^{D}Phe)amidopropyl]octanamide (15a):** Yield-62%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.289-7.086 (m, R-CO-N(-CH_2-CH_2-

CH_2-NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-NHBoc)-*NH*-CO-CH(NHBoc)-CH_2-Ph*H*)$_2$, 12H), 6.677-6.487 (d, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH-(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-CH(NHBoc)-CH_2-Ph)$_2$, 2H), 5.620-5.329 (d, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-CH(*NH*Boc)-CH_2-Ph)$_2$ 2H), 4.767 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-*NH*Boc)-NH-CO-CH(NHBoc)-CH_2-Ph)$_2$, 2H), 4.685-4.654 (t, *J* = 6.2 Hz, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-*CH*(NHBoc)-CH_2-Ph)$_2$ 2H), 3.983-3.884 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*-(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-CH(NHBoc)-CH_2-Ph)$_2$, 2H), 3.323-3.079 (m, R-CO-N(-*CH*$_2$-CH_2-*CH*$_2$-NH-CO-CH(CH_2-CH_2-CH_2-*CH*$_2$-NHBoc)-NH-CO-CH(NHBoc)-*CH*$_2$-Ph)$_2$, 16H), 2.257-2.219 (t, *J* = 7.6 Hz, CH_3-(CH_2)$_4$-CH_2-*CH*$_2$- of R group, 2H), 1.720-1.580 (m, CH_3-(CH_2)$_4$-*CH*$_2$-CH_2-CO-N(-CH_2-*CH*$_2$-CH_2-NH-CO-CH-(*CH*$_2$-*CH*$_2$-*CH*$_2$-CH_2-NHBoc)-NH-CO-CH(NHBoc)-CH_2-Ph)$_2$, 18H), 1.479-1.276 (m, CH_3-*(CH$_2$)$_4$*-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-NH-COO-C*(CH$_3$)$_3$*)-NH-CO-CH(NH-COO-C*(CH$_3$)$_3$*)-CH_2-Ph)$_2$, 44H), 0.890-0.856 (t, *J* = 6.8 Hz, *CH*$_3$-(CH_2)$_4$-CH_2-CH_2- of R group, 3H). HRMS (m/z): 1208.79084 [(M+H)$^+$] (Observed), 1208.79101 [(M+H)$^+$] (Calculated).

***N,N*-bis-[3-(Nε-Boc-^{D}Lys-N-Boc-^{D}Leu)amidopropyl]octanamide (15b):** Yield-64%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.545-7.449 (d, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-NHBoc)-*NH*-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 6.636-6.488 (d, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 5.503-5.268 (d, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-CH(*NH*Boc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 4.861 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-*NH*Boc)-NH-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 4.514-4.483 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 4.400-3.983 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-*CH*(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 3.457-3.092 (m, R-CO-N(-*CH*$_2$-CH_2-*CH*$_2$-NH-CO-CH(CH_2-CH_2-CH_2-*CH*$_2$-NHBoc)-NH-CO-CH(NHBoc)-CH_2-CH-(CH_3)$_2$)$_2$, 12H), 2.283-2.245 (t, *J* = 7.6 Hz, CH_3-(CH_2)$_4$-CH_2-*CH*$_2$- of R group, 2H), 1.778-1.488 (m, CH_3-(CH_2)$_4$-*CH*$_2$-CH_2-CO-N(-CH_2-*CH*$_2$-CH_2-NH-CO-CH(*CH*$_2$-*CH*$_2$-*CH*$_2$-CH_2-NHBoc)-NH-CO-CH(NHBoc)-*CH*$_2$-*CH*-(CH_3)$_2$)$_2$, 24H), 1.436 (s, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-NH-COO-C*(CH$_3$)$_3$*)-NH-CO-CH(NH-COO-C*(CH$_3$)$_3$*)-CH_2-CH-(CH_3)$_2$)$_2$, 36H), 1.283 (bs, CH_3-*(CH$_2$)$_4$*-CH_2-CH_2-of R group, 8H), 0.937-0.872 (m, *CH*$_3$-(CH_2)$_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-CH(NHBoc)-CH_2-CH-*(CH$_3$)$_2$*)$_2$, 15H). HRMS (m/z): 1140.80527 [(M+H)$^+$] (Observed), 1140.82231 [(M+H)$^+$] (Calculated).

***N,N*-bis-[3-(*Nε*-Boc-^{D}Lys-*N,N´*-Di-Boc-^{D}Lys)amidopropyl]octanamide (15c):** Yield-63%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm: 7.545-7.449 (d, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-NHBoc)-*NH*-CO-CH(NHBoc)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 2H), 6.636-6.488 (d, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-CH(NHBoc)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 2H), 5.503-5.268 (d, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-CH(*NH*Boc)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 2H), 4.861 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-*NH*Boc)-NH-CO-CH(NHBoc)-CH_2-CH_2-CH_2-CH_2-*NH*Boc)$_2$, 4H), 4.514-4.483 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-CH(NHBoc)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 2H), 4.40-3.983 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-NHBoc)-NH-CO-*CH*(NHBoc)-CH_2-CH_2-CH_2-CH_2-NHBoc)$_2$, 2H), 3.457-3.092 (m, R-CO-N(-*CH*$_2$-CH_2-*CH*$_2$-NH-CO-CH(CH_2-CH_2-CH_2-*CH*$_2$-NHBoc)-NH-CO-CH(NHBoc)-CH_2-CH_2-CH_2-*CH*$_2$-NHBoc)$_2$, 16H), 2.283-2.245 (t, CH_3-(CH_2)$_4$-CH_2-*CH*$_2$- of R group, 2H), 1.778-1.488 (m, CH_3-(CH_2)$_4$-*CH*$_2$-CH_2-CO-N(-CH_2-*CH*$_2$-CH_2-NH-CO-CH(*CH*$_2$-*CH*$_2$-*CH*$_2$-CH_2-NHBoc)-NH-CO-CH(NHBoc)-*CH*$_2$-*CH*$_2$-*CH*$_2$-CH_2-NHBoc)$_2$, 30H), 1.436 (s, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH(CH_2-CH_2-CH_2-CH_2-NH-COO-C*(CH$_3$)$_3$*)-NH-CO-CH(NH-COO-C*(CH$_3$)$_3$*)-CH_2-CH_2-CH_2-CH_2-NH-COO-C*(CH$_3$)$_3$*)$_2$, 54H), 1.283 (bs, CH_3-*(CH$_2$)$_4$*-CH_2-CH_2-of R group, 8H), 0.882-0.852 (t, *J* = 6.0 Hz, *CH*$_3$-(CH_2)$_4$-CH_2-CH_2- of R group, 3H). HRMS (m/z): 1370.94867 [(M+H)$^+$] (Observed), 1370.94897 [(M+H)$^+$] (Calculated).

***N,N*-bis-[3-(^{D}Lys-^{D}Phe)amidopropyl]octanamide tetrakis(trifluoroacetate) (7):** ^{1}H-NMR (400 MHz, DMSO-d_6) δ/ppm: 8.731-8.679 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-NH_3^+)-*NH*-CO-CH(NH_3^+)-CH_2-Ph)$_2$, 2H), 8.253-7.859 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH-(CH_2-CH_2-CH_2-CH_2-*NH*$_3^+$)-NH-CO-CH(*NH*$_3^+$)-CH_2-Ph)$_2$, 14H), 7.273-7.184 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-NH_3^+)-NH-CO-CH_2-Ph*H*)$_2$, 10H), 4.527-4.447 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*-(CH_2-CH_2-CH_2-CH_2-NH_3^+)-NH-CO-CH(NH_3^+)-CH_2-Ph)$_2$, 2H), 3.755 (bs, R-CO-N(-CH_2-CH_2-CH_2-

NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-NH_3^+)-NH-CO-*CH*(NH_3^+)-CH_2-Ph)$_2$, 2H), 3.120-2.669 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH-(CH_2-CH_2-CH_2-*CH_2*-NH_3^+)-NH-CO-CH(NH_3^+)-*CH_2*-Ph)$_2$, 16H), 2.221-2.183 (t, *J* = 7.6 Hz, CH_3-(CH_2)$_4$-CH_2-*CH_2*- of R group, 2H), 1.706-1.317 (m, CH_3-(CH_2)$_4$-*CH_2*-CH_2-CO-N(-CH_2-*CH_2*-CH_2-NH-CO-CH-(*CH_2*-*CH_2*-*CH_2*-CH_2-NH_3^+)-NH-CO-CH(NH_3^+)-CH_2-Ph)$_2$, 18H), 1.227 (bs, CH_3-*(*CH_2*)$_4$*-CH_2-CH_2- of R group, 8H), 0.849-0.815 (t, *J* = 6.8 Hz, *CH_3*-(CH_2)$_4$-CH_2-CH_2- of R group, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ/ppm: 170.33, 168.51, 137.38, 129.28, 128.23, 126.54, 54.69, 51.92, 38.57, 31.24, 30.57, 28.79, 28.69, 26.45, 25.15, 22.07, 21.04, 13.97. HRMS (m/z): 808.58203 [(M+H)$^+$] (Observed), 808.58129 [(M+H)$^+$] (Calculated). 404.79551 [(M+2H)$^{2+}$]/2 (Observed), 404.79401 [(M+2H)$^{2+}$]/2 (Calculated).

***N,N*-bis-[3-(^{D}Lys-^{D}Leu)amidopropyl]octanamide tetrakis(trifluoroacetate) (8):** ^{1}H-NMR (400 MHz, DMSO-d_6) δ/ppm: 8.588-8.536 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-NH_3^+)-*NH*-CO-CH(NH_3^+)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 8.240-7.903 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH-(CH_2-CH_2-CH_2-CH_2-*NH_3^+*)-NH-CO-CH(*NH_3^+*)-CH_2-CH-(CH_3)$_2$)$_2$, 14H), 4.323-4.236 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*-(CH_2-CH_2-CH_2-CH_2-NH_3^+)-NH-CO-CH(NH_3^+)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 3.798 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-NH_3^+)-NH-CO-*CH*(NH_3^+)-CH_2-CH-(CH_3)$_2$)$_2$, 2H), 3.217-2.749 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH-(CH_2-CH_2-CH_2-*CH_2*-NH_3^+)-NH-CH(NH_3^+)-CH_2-CH-(CH_3)$_2$)$_2$, 12H), 2.245-2.199 (m, CH_3-(CH_2)$_4$-CH_2-*CH_2*- of R group, 2H), 1.698-1242 (m, CH_3-*(*CH_2*)$_4$*-*CH_2*-CH_2-CO-N(-CH_2-*CH_2*-CH_2-NH-CO-CH-(*CH_2*-*CH_2*-*CH_2*-CH_2-NH_3^+)-NH-CH(NH_3^+)-*CH_2*-*CH*-(CH_3)$_2$)$_2$, 32H), 0.899-0.850 (m, *CH_3*-(CH_2)$_4$-CH_2-CH_2-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-NH_3^+)-NH-CO-CH(NH_3^+)-CH_2-CH-*(CH_3)$_2$*)$_2$, 15H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ/ppm: 171.98, 171.50, 168.35, 51.89, 51.50, 45.12, 42.82, 41.19, 38.58, 36.16. 32.10, 31.26, 30.51, 28.80, 26.41, 25.13, 24.19, 22.98, 22.09, 21.70, 21.05, 13.98. HRMS (m/z): 740.61199 [(M+H)$^+$] (Observed), 740.61259 [(M+H)$^+$] (Calculated).

***N,N*-bis-[3-(^{D}Lys-^{D}Lys)amidopropyl]octanamide tetrakis(trifluoroacetate) (9):** ^{1}H-NMR (400 MHz, DMSO-d_6) δ/ppm: 8.787-7.887 (m, R-CO-N(-CH_2-CH_2-CH_2-*NH*-CO-CH-(CH_2-CH_2-CH_2-CH_2-*NH_3^+*)-*NH*-CO-CH(*NH_3^+*)-CH_2-CH_2-CH_2-CH_2-*NH_3^+*)$_2$, 22H), 4.211-4.197 (m, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-*CH*-(CH_2-CH_2-CH_2-CH_2-NH_3^+)-NH-CO-CH(NH_3^+)-CH_2-CH_2-CH_2-CH_2-NH_3^+)$_2$, 2H), 3.839 (bs, R-CO-N(-CH_2-CH_2-CH_2-NH-CO-CH-(CH_2-CH_2-CH_2-CH_2-NH_3^+)-NH-CO-*CH*(NH_3^+)-CH_2-CH_2-CH_2-CH_2-NH_3^+)$_2$, 2H), 3.213-2.757 (m, R-CO-N(-*CH_2*-CH_2-*CH_2*-NH-CO-CH-(CH_2-CH_2-CH_2-*CH_2*-NH_3^+)-NH-CH(NH_3^+)-CH_2-CH_2-CH_2-*CH_2*-NH_3^+)$_2$, 16H), 2.233-2.217 (t, *J* = 6.4 Hz, CH_3-(CH_2)$_4$-CH_2-*CH_2*- of R group, 2H), 1.711-1242 (m, CH_3-*(*CH_2*)$_4$*-*CH_2*-CH_2-CO-N(-CH_2-*CH_2*-CH_2-NH-CO-CH-(*CH_2*-*CH_2*-*CH_2*-CH_2-NH_3^+)-NH-CH(NH_3^+)-*CH_2*-*CH_2*-*CH_2*-CH_2-NH_3^+)$_2$, 38H), 0.857-0.841 (t, *CH_3*-(CH_2)$_4$-CH_2-CH_2- of R group, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ/ppm: 172.63, 168.90, 168.53, 52.11, 46.23, 44.24, 38.46, 37.37, 32.21, 31.29, 30.34, 29.06, 29.01, 28.88, 28.69, 26.52, 24.93, 22.08, 21.20, 13.94. HRMS (m/z): 770.63381 [(M+H)$^+$] (Observed), 770.63439 [(M+H)$^+$] (Calculated). 385.82142 [(M+2H)$^{2+}$]/2 (Observed), 385.82056 [(M+2H)$^{2+}$]/2 (Calculated).

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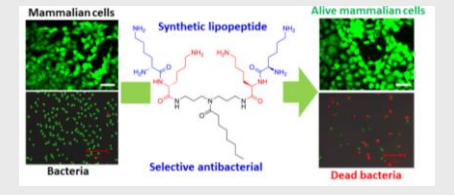

Text for Table of Contents

*Mohini M. Konai, Utsarga Adhikary and, Jayanta Haldar**

Page No. – Page No.

Design and Solution Phase Synthesis of Membrane Targeting Lipopeptides with Selective Antibacterial Activity