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Tetrahydrofuran amino acid containing gramicidin S analogues with improved biological profiles

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Gramicidin S (GS) is a cyclic cationic antimicrobial peptide (CAP) with wide spectrum of antibiotic activities whose usage was limited to topical applications only owing to its cytotoxic side effects. We have synthesized tetrahydrofuran amino acid (Taa) containing GS analogues, carried out conformational analysis and explored their structure activity relationships by evaluating the antitubercular, antibacterial and cytotoxic properties. Two of these analogues showed impressive as well as selective activity against *Mycobacterium tuberculosis* (MTB) devoid of toxicity towards the mammalian Vero cells or human RBCs, promising to be potential leads.

Introduction

Cationic antimicrobial peptides (CAPs) form part of the biological defence system against a wide-range of microorganisms and long have been pursued as a potential source of new antibiotics, especially because resistance to CAPs has been found to be rare.[1] Recently, there has been renewed interest in CAPs for the treatment of bacterial infections, especially multidrug-resistant (MDR) pathogens, including MTB.[2] Gramicidin S (GS, **1** in Fig.1), one of the most discussed CAPs which is produced non-ribosomally by *Bacillusbrevis*,[3] is active against Gram positive, Gram negative bacteria as well as fungi[4] and has also been tested against MTB in isolated reports.[4c,4f] We intended to take a relook at the GS-analogous CAPs for potential source of new antimicrobial, especially antitubercular drugs. Tuberculosis (TB) is the second leading cause of death, after the human immunodeficiency virus (HIV).[5] It is quite alarming that approximately 4% of new cases and 45% of the previously treated cases have multidrug-resistant TB (MDR-TB) and that number tripled between 2009 and 2013.[6] Even more disturbing is that 9% of those with MDR-TB[7] have extensively drug-resistant TB (XDR-TB)[8] and are resistant to rifampicin, isoniazid, fluoroquinolones and any of the second-line injectable drugs such as capreomycin, amikacin and kanamycin. The grim scenario warrants serious efforts to develop a pipeline of new drugs for effective treatment of TB with novel mechanisms of action.

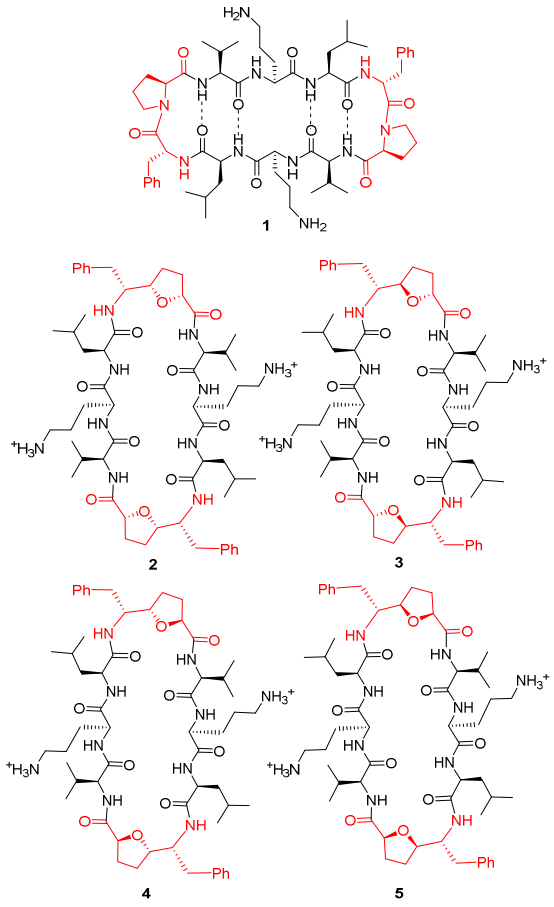

Figure 1. Structures of gramicidin S (GS, **1**) and its tetrahydrofuran amino acid (Taa) containing analogues (**2**-**5**).

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In spite of its existence for over seven decades, GS has remained limited to only topical antibacterial use due to its cytotoxicity. GS targets lipid bilayer localizing in the glycerol backbone region below polar head groups and above the hydrocarbon chains, where it perturbs lipid packing and induces pore formation causing extrusion of the intracellular contents.[9] Since its target is lipid bilayer as a whole and not any particular cellular component, it gains great interest in the design of novel antibiotics, especially because microbes, in order to develop resistance against GS, need to modify its cellular envelope which may be suicidal as it affects the 'fitness' of the microbe.

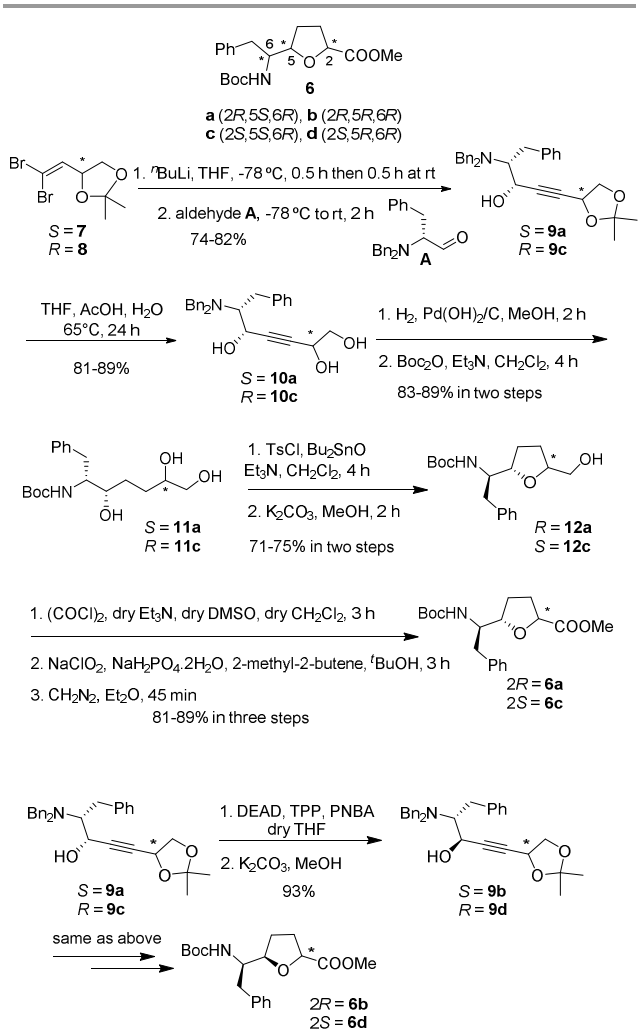
The C_2 symmetric cyclic decapeptide framework of GS adopts a β-pleated sheet structure where the two anti-parallel β-strands are held together by the type-II' β-turns on two sides induced by the D-Phe-Pro residues.[10] The important amphiphilic nature of the peptide comes from the orientation of the hydrophobic and hydrophilic units in the orthogonal positions. Several efforts[11] have been made to develop modified versions of GS by changing both the strand and turn regions in order to increase its therapeutic index by decreasing the cytotoxicity which helped in understanding the structure activity relationships of GS. The aim of the present study was to modify GS while maintaining structural integrity, which may retain its antimicrobial activity while minimizing the cytotoxicity taking advantage of the known differences in architecture between the bacterial and host cell membranes. We envisaged modifying the β-turn unit D-Phe-Pro of GS with a suitably functionalized tetrahydrofuran amino acid (Taa), a dipeptide isostere carrying a substituent at its C_6-position resembling the side chains of D-Phe residues of GS and a tetrahydrofuran ring to mimic its Pro-induced turn structure based on the known propensity of similar sugar amino acids (Saa) toward inducing turns in peptide backbones.[12] We chose to have an *R*-stereochemistry at C_6-position in the proposed analogues **2**-**5** (Fig.1) to mimic the orientation of the D-Phe side chain of GS and all possible stereocentres in the 2,5-positions of the tetrahydrofuran ring for structure activity relationship studies.[13]

Results and Discussion

Synthesis of the Taa Monomers 6a-d: The syntheses of the Taa monomers **6a-d** were carried out with slight modification of our earlier reported procedure[14] as shown in Scheme 1. The first step was the coupling of the D-phenylalanine derived amino aldehyde **A** with the chiral glyceraldehyde acetonide-derived substrates **7**/**8**. From the (*R*)-glyceraldehyde acetonide, compounds (2*R*,5*S*,6*R*)-**6a** and (2*R*,5*R*,6*R*)-**6b** and from the (*S*)-glyceraldehyde acetonide, the other two isomers (2*S*,5*S*,6*R*)-**6c** and (2S,5R,6R)-**6d** were synthesized. (*R*)/(*S*)-glyceraldehyde acetonide was converted to dibromoalkenes **7** and **8** through Corey-Fuchs reaction.[15] The dibromoalkene was treated with ^{n}BuLi at -78 °C in dry THF to form the Li-acetylide and coupled with *N*,*N*-dibenzyl-protected D-phenylalanine derived amino aldehyde **A** to prepare the acetonide-protected propargylic alcohols **9a**/**9c** in 74-82% yield.

Now to obtain (2*R*,5*S*,6*R*)/(2*S*,5*S*,6*R*)-Taa (**6a/6c**), we proceeded with the propargylic alcohols **9a**/**9c** obtained from the corresponding (*R*)/(*S*)-glyceraldehyde acetonides. But to synthesize the (2*R*,5*R*,6*R*)/(2*S*,5*R*,6*R*)-Taa (**6b/6d**), a Mitsunobu inversion[16] at C_5 centre was carried out on the propargylic alcohols **6a**/**6c** to give **9b**/**9d** (Scheme 1).

The acetonide protecting group was then removed by treatment with THF:AcOH:H_2O (1:8:1) at 65 °C for 6 h in 81-89% yields. The resulting alkynetriol **10a-d** was next hydrogenated with $Pd(OH)_2$ in MeOH to reduce the triple bond and deprotect the *N*,*N*-dibenzyl groups, simultaneously. The free amine was re-protected with Boc_2O and triethylamine in CH_2Cl_2 to prepare the *N*-Boc-protected triols **11a-d** in 83-89% yields. The primary hydroxyl was then selectively tosylated with the help of dibutyltin oxide catalyst and Et_3N in CH_2Cl_2.

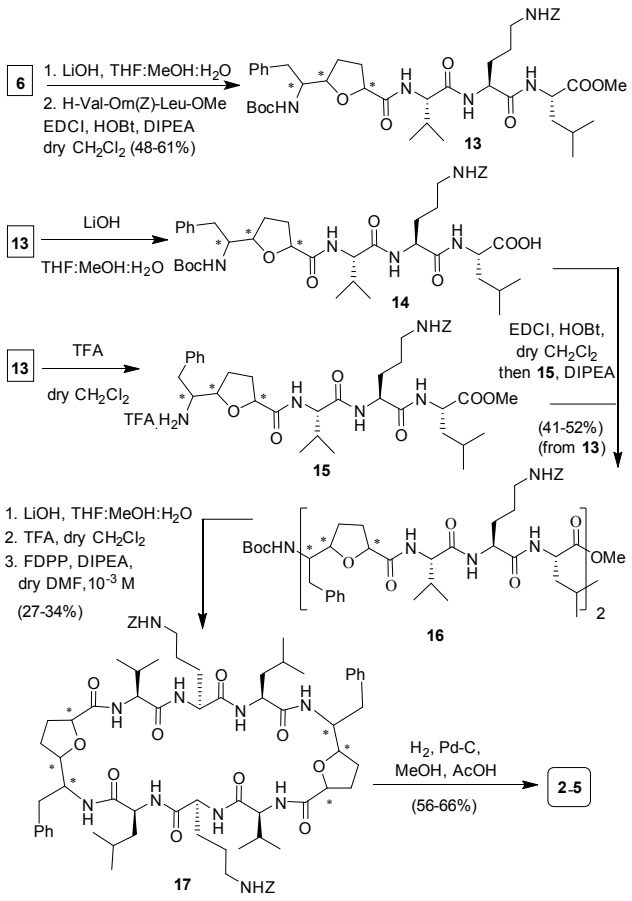


Scheme 1. Synthesis of the Taa monomers **6a-d**.

The tosyl compounds were next converted to the tetrahydrofuryl alcohols **12a-d** by treatment with K_2CO_3 in dry MeOH in 71-75% yields. The alcohol was then oxidized to aldehyde through Swern oxidation[17] and converted to the acid

by Pinnick oxidation.[18] The acid was converted to methyl ester with diazomethane for purification and characterization purposes to give **6a-d** in 81-89% yields.

Synthesis of the GS analogues 2-5: To prepare the cyclic GS analogues – **2** from **6a**, **3** from **6b**, **4** from **6c** and **5** from **6d** – we planned to prepare first the linear octapeptides, which could be assembled by combining two parts of tetrapeptides Taa-Val-Orn(Z)-Leu (Scheme 2). For the synthesis of the tetrapeptides **13**, the Taa ester **6** was hydrolyzed with LiOH in THF:MeOH:H_2O and coupled with tripeptide H-Val-Orn(Z)-Leu-OMe by using standard EDCI-HOBt coupling procedures to get the tetramers. Then, the two units of Boc-Taa-Val-Orn(Z)-Leu-OMe (**13**) were dimerized to form the linear octamers, Boc-Taa-Val-Orn(Z)-Leu-Taa-Val-Orn(Z)-Leu-OMe (**16**). The octamers were then hydrolyzed followed by Boc-deprotection and cyclized using pentafluorophenyl diphenylphosphinate (FDPP) in dry DMF under high dilution to get the desired side-chain protected 30-membered cyclic compounds **17**. Next, the Cbz-protected compounds were deprotected with hydrogen in presence of AcOH to yield the isomerically pure GS analogues **2-5**.



Scheme 2. Synthesis of the GS analogues **2-5**.

NMR studies of GS analogues 2-5: Subtle variations in the backbone often had their impact on the overall structural preferences which may further affect the activity.[19] Structural studies carried out by NMR in solution would be an excellent option for deriving the conformational preferences of the synthesized GS analogues (**2-5**, **17a-d**) and comparing the derived conformations with that of wild type GS. Solution conformational studies were carried out on 2-5 mM concentrations of the cyclic analogues in suitable solvents. Single set of resonances noticed in the ^{1}H-NMR spectra of **2-5** in DMSO-d_6, **17a-d** in $CDCl_3$ suggests that these analogues preferred to be in a single conformation in the NMR time scale.[20] Medium range nOes between ValNH↔TaaC5H, TaaC6H and LeuNH suggest their close proximity in these molecules (Fig.2). In addition, only minimum deviation in the chemical shift positions ($\Delta\delta/\Delta T$), from the variable temperature (VT) studies (Supporting Information), for ValNH and LeuNH compared to OrnNH and TaaNH, which show higher $\Delta\delta/\Delta T$ values, suggested their participation in H-bonding.[21] Analysis of the natural GS also showed nOes between ValNH↔D-PheCαH, D-PheCβH and LeuNH, suggesting their close proximity. Similarity in the nOe patterns and H-bonding of the amide protons of Val, Leu residues in the natural GS suggests that the analogues **2-5**, **17a-d** might have predisposed into similar conformations as that of natural GS.

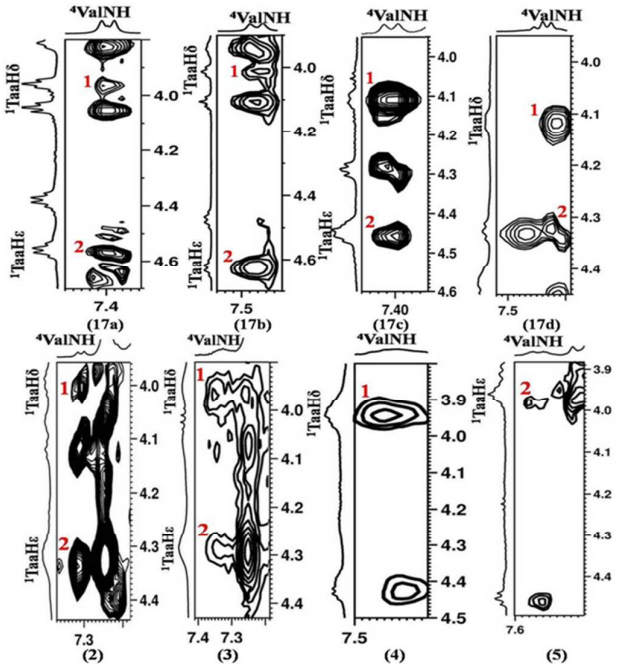


Figure 2: ROESY expansions of compounds **17a-d**, **2-5** showing characteristic nOes between ValNH↔TaaδH, ValNH↔TaaεH denoted as 1-2, respectively

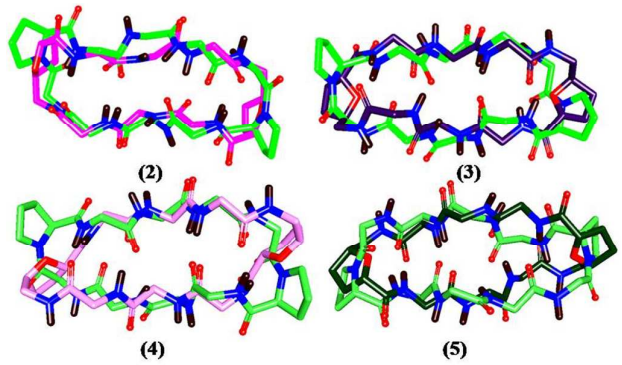


Figure 3: Superimposition of peptides **2-5** with natural GS (green); RMS deviations of backbone are - a) 0.8 Å for **2**, b) 1.53 Å for **3**, c) 1.60 Å for **4** and d) 1.48 Å for **5**. Side chains are removed for clarity after superposition of the structures.

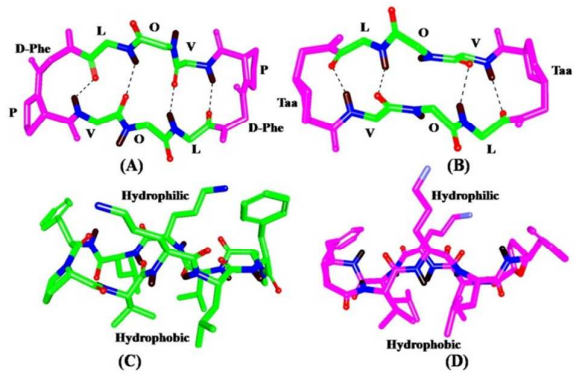


Figure 4: Top views of **A**) natural GS and **B**) peptide **2**, showing intramolecular H-bonding (black dotted lines). Side views of **C**) of natural GS and **D**) peptide **2**, showing hydrophobic and hydrophilic faces disposed in orthogonal orientations.

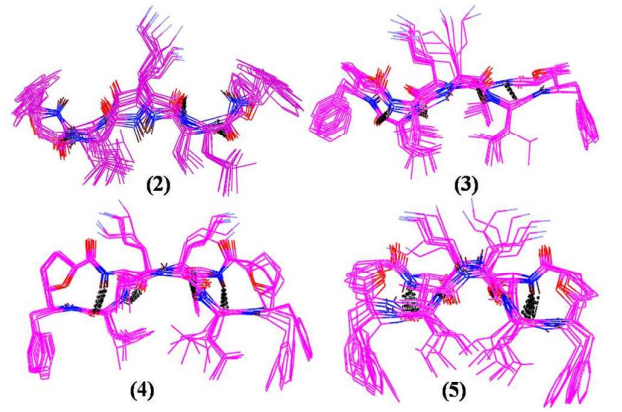


Figure 5: Top 10 minimum energy conformations from MD calculations are superimposed and are given as **2-5** respectively. The average pair-wise heavy atom rmsd values for 2-5 are 0.75 Å, 0.82 Å, 0.72 Å and 0.96 Å respectively.

Molecular dynamics simulations: The distance geometry calculations on **2-5**, **17a-d** were performed on Discovery studio 3.0 client program using CHARMm force field[22] with default parameters throughout the simulation.

The resulted structures of 1 nS simulations carried out using experimentally derived distance and dihedral restraints[23] displayed hydrophilic (Orn) residue orienting in orthogonal position to hydrophobic (Val, Leu) residues. Four H-bonds, one between each ValNH↔LeuCO and another between LeuNH↔ValCO in each half of the GS analogues, were observed in all of the studied compounds. The conformations of each analogue were compared with native GS to verify their structural similarities and further to correlate them with their biological activities. Figure 3 shows the superimposition of GS (green) and synthetic GS-analogues with average pair-wise heavy atom rmsd of about 0.8 Å, 1.53 Å, 1.6 Å, 1.48 Å for **2-5**, respectively.[24]

The structural variation was noticed at the turn regions where D-Phe-Pro was substituted with Taa. However, the rest of the backbone exhibited closer resemblances with GS suggesting the modification of the backbone did not alter the backbone structure to a greater extent. Similarly, the backbone structure and orthogonal pre-disposition of hydrophilic and hydrophobic residues in synthetic analogues were compared with natural GS and are shown for peptide **2** and natural GS (**1**) in Figure 4. Structure ensembles having 10 minimum energy structures of **2-5** derived from the restrained MD calculations converge well and are given in Figure 5.

Antibacterial, antitubercular and host cell cytotoxic activities: Antibacterial activity of GS and peptides **2-5** is depicted in Table 1 and their haemolytic activities against human RBC are shown in Figure 6. The anti-tubercular as well as cytotoxic (against Vero cells) activities of these peptides is depicted in Table 2.

Table 1. Antibacterial activities of GS and its analogues **2-5**.

	MIC (μM)			
Peptide	*E. coli* ATCC 25922	*S. aureus* ATCC25923	*B. subtilis* ATCC6633	*P. auroginosa* ATCCBAA427
GS	17.5	8.8	35	44
2	18	11	37	37
3	200	150	180	>200
4	>200	>200	>200	>200
5	70	50	140	140

As expected, GS exhibited lowest MICs against the Gram-positive as well as Gram-negative bacteria and MTB. Nonetheless, it was also highly toxic for hRBCs (50% haemolysis at 40 μM, Fig. 6) and mammalian cells Vero (CC_{50} = 10 μM, Table 2). Peptide **2** with (2*R*,5*S*,6*R*)-Taa, which had the best structural fit with GS, showed a much reduced toxicity while retaining its antibacterial activity. It was nearly 5 times less haemolytic than GS at 45 μM concentration (Fig.6), though comparably active against the bacteria (Table 1). The other 2,5-*cis*Taa containing analogue **5** showed only a moderate antibacterial activity, much lower than that of **2**. Both the 2,5-

trans Taa containing analogues (**3** and **4**) did not show any antibacterial or haemolytic activity. Against MTB, peptides **2** and **3** showed good activity (Table 2), though both were considered cytotoxic with a selectivity index (SI) of ≤ 10 against Vero cells.

Table 2. Anti-tubercular activities of GS and its analogues **2**-**5**.

Peptide	MIC (μM)*	CC_{50} (μM)**	MBC (μM)***	% ↓ in I/C CFU#
GS	0.7	10	ND##	ND
2	3.12	29	ND	ND
3	6.25	40	ND	ND
4	6.25	151	12.5	67
5	6.25	134	12.5	75

* Minimum Inhibitory Concentration for *M. tuberculosis* H37Ra (ATCC 25177);
** Concentration needed for 50% cytotoxicity of Vero cells (ATCC CRL-1586);
*** Minimum Bactericidal Concentration (MBC);
# % reduction in intracellular (I/C) Colony Forming Units (CFU);
Not determined (ND), as these peptides were considered cytotoxic (Selectivity Index ≤ 10).

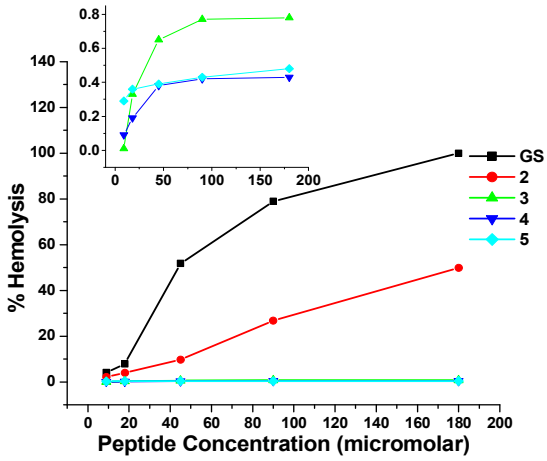


Figure 6. Haemolysis of hRBC by GS and its analogues **2**-**5** (inset: expansion of data for **3**-**5**).

The most promising anti-tubercular activity was exhibited by peptides **4** and **5** (MIC = 6.25 μM, SI > 20, no haemolytic activity). More significantly, their activities were bactericidal (MBC = 12.5 μM) and they were also able to kill MTB within mouse macrophages (> 65% reduction in CFU), a model that mimics growth environment of a natural infection with MTB.
Of particular interest was the observation that both peptides (**4** and **5**) targeted MTB 'selectively', as they did not show any significant activity against either Gram positive or Gram negative bacteria. Though we are unable to confirm at present, it is possible that these analogs, based on the known mechanism of action of GS,[25] are able to disrupt the cell envelope architecture of MTB by targeting its unique and vital component - the mycolic acids.[26] Another important aspect of this activity profile is that these analogs, considering that they share the unique mechanism of action of GS, are also likely to show activity against the MDR strains of MTB.

Conclusions

The most important drawback with GS, for which it could never be developed for therapeutic purposes, is its cytotoxicity. In this study we have synthesized 'Taa' with either '6*R*' or '6*S*' stereocentres and all possible combinations in the 2,5-positions of the THF ring and incorporated them in the D-Phe-Pro segment, responsible for inducing β-turns, on the either side of GS. Of these, the conformational preferences of '6*R*' analogues resembled those of GS. The Taa based peptides **4** and **5**, that we synthesized, could be termed 'non-toxic' with high selectivity index compared to GS. Peptides **2** and **3** were also less cytotoxic than GS. In summary, the results of this study suggest that the newly developed GS analogues are of high specificity towards MTB with minimal toxicity for mammalian cells. Further studies on these analogues in mimicked prokaryotic and eukaryotic cell membranes to decipher the reasons for the observed preferences are in progress.

Experimental Section

General Experimental Procedures: All reactions were carried out in oven or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)-heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. IR spectra were recorded as neat liquids or KBr pellets. Mass spectra were obtained under ESI-QqQ and ESI-Q-TOF techniques. ^{1}H NMR spectra were recorded on 500, 400 and 300 MHz spectrometers in appropriate solvents and calibrated using residual undeuterated solvent as an internal reference, and the chemical shifts are shown in δ ppm scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded on 125, 100, and 75 MHz spectrometers with complete proton decoupling. Optical rotations were measured using sodium (589 nm, D line) lamp and are reported as follows: $[\alpha]_D^T$ (c = g/100 mL, solvent).

General procedure for Taa preparation

Preparation of 9a and 9c: To a stirred solution of the dibromo compound **7**/**8** (1 eq.) in dry THF (100 mL) at –78 °C, ^{n}BuLi (1.95 eq., 2.0 M in hexane) was added. Stirring continued at –78 °C for 30 minutes and then at room temperature for another 30 minutes, re-cooled to –78 °C and (*R*)-2-

(dibenzylamino)-3-phenylpropanal (**A**, 1 eq.) dissolved in dry THF (100 mL) was added. After 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with brine (200 mL) and dried (Na_2SO_4). The solvent was removed in rotary evaporator and purified by column chromatography (SiO_2, 10-15% EtOAc in petroleum ether eluant) to afford compound **9a/9c** as yellow color syrup.

Data for **9a**: scale of reaction 10 g, 35.2 mmol, yield = 13.1 g, 82%; R_f = 0.45 (silica gel, 25% EtOAc in petroleum ether); $[\alpha]_D^{23}$ = -27.2 (*c* = 1.7, $CHCl_3$); IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.19 (m, 15H, ArH), 4.75 (dd, *J* = 11.4, 6.3 Hz, 1H), 4.27 (d, *J* = 13.2 Hz, 2H), 4.10 (dd, *J* = 8.0, 6.5 Hz, 2H), 3.85 (dd, *J* = 8.0, 6.3 Hz, 1H), 3.50 (d, *J* = 13.3 Hz, 2H), 3.20-3.10 (m, 2H), 3.04-2.95 (m, 1H), 1.33 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.0 (2C), 138.6, 129.2 (2C), 129.1 (4C), 128.6 (2C), 128.5 (4C), 127.5 (2C), 126.5, 110.3, 85.8, 84.6, 69.9, 65.7, 62.6, 60.5, 55.1 (2C), 31.8, 26.1, 26.0; MS (ESI-QqQ): *m/z* (%) 478 $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{30}H_{34}NO_3$ 456.2533 $[M+H]^+$, found 456.2534.

Data for **9c**: scale of reaction 10 g, 35.2 mmol, yield = 11.8 g, 74%; R_f = 0.45 (silica gel, 25% EtOAc in petroleum ether); $[\alpha]_D^{23}$ = -57.0 (*c* = 1.2, $CHCl_3$); IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.19 (m, 15H), 4.75 (dd, *J* = 6.2, 5.3 Hz, 1H), 4.27 (d, *J* = 13.1 Hz, 2H), 4.13-4.05 (m, 2H), 3.91 (dd, *J* = 8.0, 6.3 Hz, 1H), 3.54 (d, *J* = 13.1 Hz, 2H), 3.19 (t, *J* = 4.2 Hz, 2H), 3.03-2.92 (m, 1H), 1.49 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0 (2C), 138.7, 129.3 (2C), 129.2 (4C), 128.7 (2C), 128.6 (4C), 127.2 (2C), 126.0, 112.0, 88.1, 85.0, 73.7, 70.4, 68.6, 62.4, 54.2 (2C), 32.9, 26.2, 26.0; MS (ESI-QqQ): *m/z* (%) 478 $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{30}H_{34}NO_3$ 456.2533 $[M+H]^+$, found 456.2524.

Preparation of 9b and 9d: To a stirred solution of the propargylic alcohol **9a/9c** (1 eq.) in dry THF (110 mL) at 0 °C, TPP (2eq.) and PNBA (2 eq.) were added. Stirring continued at 0 °C for 5 minutes and then, at 0 °C, DEAD (2 eq.) was added drop by drop. Next, it was stirred at room temperature for another 1.5 h, re-cooled to 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was removed in rotary evaporator and purified by column chromatography (SiO_2, 6% EtOAc in petroleum ether eluant) to afford the PNB-esters as yellow color syrup.

Data for **9a**-PNB ester: scale of reaction 10 g, 21.9 mmol, yield = 12.3 g, 93%; R_f = 0.45 (silica gel, 10% EtOAc in petroleum ether); $[\alpha]_D^{27}$ = +40.0 (*c* = 1.35, $CHCl_3$); IR (KBr): ν_{max} 3433, 2962, 1724, 1637, 1530, 1383, 1215, 848, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.25 (*J* = 8.8 Hz, 2H), 8.04 (*J* = 8.8 Hz, 2H), 7.24-7.20 (m, 15H, ArH), 5.91 (dd, *J* = 4.7, 1.5 Hz, 1H), 4.74 (dt, *J* = 6.0, 1.3 Hz, 1H), 4.10 (dd, *J* = 8.1, 6.6 Hz, 1H), 3.87 (d, *J* = 13.8 Hz, 2H), 3.85 (m, 1H), 3.76 (d, *J* = 13.8 Hz, 2H), 3.59-3.49 (m, 1H), 3.25 (dd, *J* = 14.1, 6.9 Hz, 1H), 3.05 (dd, *J* = 14.1, 6.9 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.5, 150.8, 139.3 (2C), 139.2, 135.2, 131.1(2C), 129.3 (2C), 128.8 (4C), 128.5 (2C), 128.3 (4C), 127.2 (2C), 126.4, 123.6 (2C), 110.7, 85.5, 81.9, 69.5, 66.1, 65.6, 61.9, 54.7 (2C), 33.4, 26.3, 26.0; MS (ESI-QqQ): *m/z* (%) 627 $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{37}H_{37}N_2O_6$ 605.2646 $[M+H]^+$, found 605.2623.

Data for **9c**-PNB ester: scale of reaction 10 g, 21.9 mmol, yield = 12.3 g, 93%; R_f = 0.45 (silica gel, 10% EtOAc in petroleum ether); $[\alpha]_D^{23}$ = +19.0 (*c* = 1.92, $CHCl_3$); IR (KBr): ν_{max} 3433, 2962, 1724, 1637, 1530, 1383, 1215, 848, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (*J* = 8.8 Hz, 2H), 8.03 (*J* = 8.8 Hz, 2H), 7.25-7.10 (m, 15H), 5.91 (d, *J* = 3.8 Hz, 1H), 4.73 (t, *J* = 6.2 Hz, 1H), 4.11 (t, *J* = 8.0 Hz, 1H), 3.89 (d, *J* = 14.2 Hz, 1H), 3.87 (d, *J* = 13.9 Hz, 2H), 3.76 (d, *J* = 13.8 Hz, 2H), 3.54 (dd, *J* = 11.7, 6.7 Hz, 1H), 3.24 (dd, *J* = 14.2, 7.1 Hz, 1H), 3.03 (dd, *J* = 14.1, 6.8 Hz, 1H), 1.43 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 150.7, 139.3 (3C), 135.1, 131.0 (2C), 129.2 (2C), 128.9 (4C), 128.5 (2C), 128.3 (4C), 127.1 (2C), 126.4, 123.5 (2C), 110.6, 85.5, 81.9, 69.8, 66.0, 65.6, 61.9, 54.6 (2C), 33.4, 26.3, 26.0; MS (ESI-QqQ): *m/z* (%) 627 $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{37}H_{37}N_2O_6$ 605.2646 $[M+H]^+$, found 605.2656.

To a stirred solution of the above PNB ester (1 eq.) in dry MeOH (100 mL), dry K_2CO_3 (2 eq.) was added at 0 °C and stirred for 30 min at room temperature. Then, the reaction mixture was cooled to 0 °C, neutralized with saturated solution of 1 N HCl and extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was removed in rotary evaporator and purified by column chromatography (SiO_2, 10-15% EtOAc in petroleum ether eluant) to afford compound **9b/9d** as yellow color syrup.

Data for **9b**: scale of reaction 12.3 g, 20.3 mmol, yield = 8.5 g, 92%; R_f = 0.45 (silica gel, 25% EtOAc in petroleum ether); $[\alpha]_D^{27}$ = -32.0 (*c* = 2.18, $CHCl_3$); IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.22 (m, 15H), 4.77 (t, *J* = 6.2 Hz, 1H), 4.28 (d, *J* = 13.2 Hz, 2H), 4.04 (dd, *J* = 8.1, 6.6 Hz, 1H), 4.06 (d, *J* = 3.9 Hz, 1H), 3.85 (dd, *J* = 7.8, 6.3 Hz, 1H), 3.50 (d, *J* = 13.2 Hz, 2H), 3.20-3.10 (m, 2H), 2.94 (dd, *J* = 11.4, 9.3 Hz, 1H), 1.33 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.0 (2C), 138.7, 129.3 (6C), 128.7 (2C), 128.6 (4C), 127.6 (2C), 126.6, 110.4, 85.9, 84.6, 70.0, 65.8, 62.7, 60.6, 55.2 (2C), 31.9, 26.2, 26.1; MS (ESI-QqQ): *m/z* (%) 478 $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{30}H_{34}NO_3$ 456.2533 $[M+H]^+$, found 456.2536.

Data for **9d**: scale of reaction 12.3 g, 20.3 mmol, yield = 8.4 g, 91%; R_f = 0.45 (silica gel, 25% EtOAc in petroleum ether); $[\alpha]_D^{24}$ = -53.0 (*c* = 1.89, $CHCl_3$);IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.32-7.20 (m, 15H), 4.74 (t, *J* = 6.2 Hz, 1H), 4.26 (d, *J* = 13.1 Hz, 2H), 4.10 (dd, *J* = 8.0, 6.3, 1H), 3.91 (dd, *J* = 7.9, 6.2 Hz, 1H), 3.50 (d, *J* = 13.2 Hz, 2H), 3.19-3.12 (m, 1H), 2.99-2.86 (m, 1H), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 138.9 (2C), 138.6, 129.2 (6C), 128.7 (2C), 128.6 (4C), 127.6 (2C), 126.6, 110.4, 85.8, 84.6, 70.0, 65.8, 62.6, 60.5, 55.1 (2C), 31.8, 26.3, 26.1; MS (ESI-QqQ): *m/z* (%) 479 $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{30}H_{34}NO_3$ 456.2533 $[M+H]^+$, found 456.2539.

Preparation of 10a-d: To a stirred solution of the compound **9a-d** (1 eq.) in THF (15 mL) and water (15 mL), AcOH (120 mL) was added at room temperature and heated for 24 h at 65 °C. Then, the reaction mixture was concentrated under reduced pressure, diluted with EtOAc (250 mL), cooled to 0 °C and neutralized with saturated solution of $NaHCO_3$. The aqueous

layer was extracted with EtOAc (250 mL). The combined organic layers were washed with brine (200 mL) and dried (Na_2SO_4). The solvent was removed in rotary evaporator and purified by column chromatography (SiO_2, 60% EtOAc in petroleum ether eluant) to afford compound **10a-d** as yellow color syrup.

Data for **10a**: scale of reaction 13.1 g, 28.8 mmol, yield = 10.6 g, 89%; R_f = 0.4 (silica gel, 70% EtOAc in petroleum ether); $[\alpha]_D^{27}$ = -26.6 (*c* = 1.96, $CHCl_3$); IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.27 (m, 15H, ArH), 4.42 (t, *J* = 2.2 Hz, 1H), 4.22 (d, *J* = 13.3 Hz, 2H), 4.05 (d, *J* = 3.0 Hz, 1H), 3.66-3.59 (m, 5H), 3.48 (d, *J* = 13.3 Hz, 2H), 3.17-3.07 (m, 2H), 2.96-2.89 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.0 (2C), 138.7, 129.4 (2C), 129.3 (4C), 128.65 (2C), 128.6 (4C), 127.6 (2C), 126.6, 85.8, 85.3, 66.5, 63.4, 62.5, 60.6, 55.1 (2C), 31.9; MS (ESI-QqQ): *m/z* (%) 416, (100) $[M+H]^+$, HRMS (ESI-Q-TOF): calcd. for $C_{27}H_{30}NO_3$ 416.2220 $[M+H]^+$, found 416.2222.

Data for **10b**: scale of reaction 8.5 g, 18.7 mmol, yield = 6.9 g, 89%; R_f = 0.4 (silica gel, 70% EtOAc in petroleum ether); $[\alpha]_D^{26}$ = -32.6 (*c* = 0.83, $CHCl_3$); IR (KBr): ν_{max} 3401, 3019, 2968, 2400, 1720, 1601, 1522, 1421, 1215, 1074, 928, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.16 (m, 15H), 4.40 (t, *J* = 4.1 Hz, 1H), 4.20 (d, *J* = 13.3 Hz, 2H), 4.07-4.06 (m, 1H), 3.65-3.56 (m, 2H), 3.51-3.44 (m, 5H), 3.15-3.06 (m, 2H), 2.95-2.86 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.0 (2C), 138.7, 129.3 (2C), 129.1 (4C), 128.6 (6C), 127.4 (2C), 126.4, 85.6, 85.3, 66.3, 63.2, 62.3, 60.5, 54.9 (2C), 31.9; MS (ESI-QqQ): *m/z* (%) 416 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{27}H_{30}NO_3$ 416.2220 $[M+H]^+$, found 416.2223.

Data for **10c**: scale of reaction 11.8 g, 26.1 mmol, yield = 8.9 g, 83%; R_f = 0.4 (silica gel, 70% EtOAc in petroleum ether); $[\alpha]_D^{26}$ = -33.4 (*c* = 1.31, $CHCl_3$);IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27-7.16 (m, 15H), 4.40 (dd, *J* = 5.9, 4.3 Hz, 1H), 4.19 (d, *J* = 13.3 Hz, 2H), 4.06 (t, *J* = 10.3 Hz, 1H), 3.66-3.55 (m, 2H), 3.48 (d, *J* = 13.3 Hz, 2H), 3.15-3.05 (m, 2H), 2.96-2.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0 (2C), 138.7, 129.3 (2C), 129.1 (4C), 128.6 (2C), 128.5 (4C), 127.4 (2C), 126.4, 85.6, 85.3, 66.3, 63.2, 62.3, 60.5, 54.9 (2C), 31.9; MS (ESI-QqQ): *m/z* (%) 416 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{27}H_{30}NO_3$ 416.2220 $[M+H]^+$, found 416.2222.

Data for **10d**: scale of reaction 8.4 g, 18.4 mmol, yield = 6.4 g, 84%; R_f = 0.4 (silica gel, 70% EtOAc in petroleum ether); $[\alpha]_D^{24}$ = -48.5 (*c* = 2.08, $CHCl_3$); IR (KBr): ν_{max} 3401, 3019, 2968, 2400, 1720, 1601, 1522, 1421, 1215, 1074, 928, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33-7.16 (m, 15H), 4.41 (br, 1H), 4.22 (d, *J* = 13.3 Hz, 2H), 4.07 (d, *J* = 3.3 Hz, 1H), 3.63 (dd, *J* = 12.3, 7.6 Hz, 2H), 3.50 (d, *J* = 13.3 Hz, 2H), 3.15-3.03 (m, 2H), 2.97-2.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9 (2C), 138.5, 129.2 (2C), 129.1 (4C), 128.6 (6C), 127.5 (2C), 126.5, 85.7, 85.3, 66.3, 63.3, 62.3, 60.5, 54.9 (2C), 31.8; MS (ESI-QqQ): *m/z* (%) 416 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{27}H_{30}NO_3$ 416.2220 $[M+H]^+$, found 416.2225.

Preparation of 11a-d: To a solution of **10a**-**d** (1 eq.) in MeOH (125 mL), $Pd(OH)_2/C$ was added and hydrogenated using H_2 filled balloons under atmospheric pressure. After completion of reaction, the reaction mixture was filtered through a short pad of Celite and the filter cake was washed with MeOH. The filtrate and washings were combined, concentrated in vacuo and dried. The residue was dissolved in dry CH_2Cl_2 (100 mL) under nitrogen atmosphere, basified with Et_3N (2 eq.) and Boc_2O (1.5 eq.) was added. After being stirred at room temperature for 4 h, the reaction mixture was quenched with NH_4Cl, and then MeOH was evaporated and extracted with EtOAc (2 × 500 mL). The organic extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 80% EtOAc in petroleum ether eluant) afforded compound **11a**-**d** as white solid.

Data for **11a**: scale of reaction 10.6 g, 25.6 mmol, yield = 7.6g, 88%; R_f = 0.4 (silica gel, EtOAc); $[\alpha]_D^{26}$ = +5.3 (*c* = 0.54, MeOH); IR (KBr): ν_{max} 3401, 3019, 2968, 2400, 1720, 1601, 1522, 1421, 1215, 1074, 928, 669 cm^{-1}; ^1H NMR (300 MHz, CD_3OD+$CDCl_3$): δ 7.30-7.19 (m, 5H), 3.73-3.36 (m, 6H), 2.96 (dd, *J* = 13.8, 3.3 Hz, 1H), 2.67 (t, *J* = 10.9 Hz, 1H), 1.71-1.59 (m, 4H), 1.32 (s, 9H); ^{13}C NMR (50 MHz, CD_3OD+$CDCl_3$): δ 156.3, 140.6, 129.1 (2C), 128.1 (2C), 126.0, 79.3, 73.4, 71.8, 66.3, 56.3, 35.4, 29.5, 29.3, 28.0 (3C); MS (ESI-QqQ): m/z (%) 362 (100) $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{18}H_{29}NO_5Na$ 362.1938 $[M+Na]^+$, found 362.1939.

Data for **11b**: scale of reaction 6.9 g, 1.6 mmol, yield = 5.3 g, 95%; R_f = 0.4 (silica gel, EtOAc); $[\alpha]_D^{26}$ = +6.5 (*c* = 1.25, MeOH); IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CD_3OD): δ 7.27-7.20 (m, 5H), 3.73-3.34 (m, 5H), 2.96 (dd, *J* = 13.7, 2.7 Hz, 1H), 2.68 (t, J = 10.9, 1H), 1.67-1.53 (m, 4H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD): δ 158.3, 140.6, 130.4 (2C), 129.1 (2C), 126.9, 79.8, 74.8, 73.1, 67.4, 58.3, 37.4, 30.8, 30.6, 28.7 (3C); MS (ESI-QqQ): m/z (%) 340 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{18}H_{29}NO_5Na$ 362.1938 $[M+Na]^+$, found 362.1929.

Data for **11c**: scale of reaction 8.9 g, 21.6 mmol, yield = 5.9 g, 81%; R_f = 0.4 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +16.2 (*c* = 1.34, MeOH); IR (KBr): ν_{max} 3401, 3019, 2968, 2400, 1720, 1601, 1522, 1421, 1215, 1074, 928, 669 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 7.34-7.17 (m, 5H), 3.77-3.36 (m, 5H), 2.97-2.91 (m, 1H), 2.79-2.72 (m, 1H), 1.74-1.68 (m, 2H), 1.54-1.50 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD): δ 158.1, 140.6, 130.5 (2C), 129.2 (2C), 127.1, 79.9, 75.3, 73.7, 67.4, 58.2, 37.4, 31.05, 31.0, 28.8 (3C); MS (ESI-QqQ): *m/z* (%) 362 (100) $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{18}H_{29}NO_5Na$ 362.1938 $[M+Na]^+$, found 362.1938.

Data for **11d**: scale of reaction 6.4 g, 15.4 mmol, yield = 4.2 g, 81%; R_f = 0.4 (silica gel, EtOAc); $[\alpha]_D^{23}$ = +6.2 (*c* = 1.43, MeOH); IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.24-7.18 (m, 5H), 3.66 (dd, *J* = 10.1, 6.0 Hz, 2H), 3.54-3.43 (m, 3H), 3.33 (br, 1H), 3.07 (dd, *J* = 13.6, 3.0 Hz, 1H), 2.59 (dd, *J* = 13.3, 10.7 Hz, 1H), 1.83-1.80 (m, 2H), 1.46 (m, 2H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD): δ 158.0, 140.5, 130.4 (2C), 129.1 (2C), 126.9, 79.8, 75.2, 73.6, 67.4, 58.1, 37.4, 30.95, 30.9, 28.7 (3C); MS (ESI-QqQ): m/z (%) 340 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{18}H_{29}NO_5Na$ 362.1938 $[M+Na]^+$, found 362.1945.

Preparation of 12a-d: To a solution of **11a**-**d** (1 eq.) in dry CH_2Cl_2 (65 mL), Bu_2SnO (0.2 eq.) was added followed by Et_3N (2 eq.) and TsCl (1.1 eq.) at 0 °C. After completion of the reaction, the reaction mixture was filtered through a short pad of Celite

and the filter cake was washed with CH_2Cl_2. The filtrate and washings were combined and diluted with EtOAc (250 mL), washed with water, brine, dried (Na_2SO_4) and concentrated in *vacuo*. Purification by flash column chromatography (SiO_2, EtOAc) afforded the tosylated compound as white solid.

To a solution of the tosylated compound in dry MeOH (50 mL), K_2CO_3 (2 eq.) was added at 0 °C. After completion of the reaction in 2 h, the reaction mixture was filtered through Celite. The reaction mixture was taken in EtOAc (500 mL) and washed with 1 N HCl (100 mL), water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated in *vacuo*. Purification by column chromatography (SiO_2, 80% EtOAc in petroleum ether eluant) afforded compound **12a**-**d** as white solid.

Data for **12a**: scale of reaction 7.6 g, 22.4 mmol, yield = 5.4 g, 75%; R_f = 0.4 (silica gel, 60% EtOAc in petroleum ether eluant); $[\alpha]_D^{27}$ = +4.0 (*c* = 0.69, $CHCl_3$); IR (KBr): ν_{max} 3437, 3019, 2973, 1709, 1502, 1216, 928, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.21 (m, 5H), 4.42 (d, *J* = 7.6 Hz, 1H), 4.11-4.03 (m, 1H), 3.94 (br, 1H), 3.84 (dd, *J* = 12.7, 6.5 Hz, 1H), 3.72 (dd, *J* = 11.5, 3.1 Hz, 1H), 3.53-3.45 (m, 1H), 2.91 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.09 (dd, *J* = 13.8, 7.4 Hz, 1H), 1.97-1.69 (m, 4H), 1.36 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.7, 137.7, 129.5 (2C), 128.4 (2C), 126.4, 81.0, 80.0, 79.5, 65.5, 54.5, 37.5, 28.5 (3C), 27.9, 26.9; MS (ESI-QqQ): *m/z* (%) 344 (100), $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{18}H_{27}NO_4Na$ 344.1832 $[M+Na]^+$, found 344.1836.

Data for **12b**: scale of reaction 5.3 g, 15.7 mmol, yield = 3.7 g, 75%; R_f = 0.4 (silica gel, EtOAc); $[\alpha]_D^{27}$ = +4.5 (*c* = 1.46, $CHCl_3$); IR (KBr): ν_{max} 3437, 3019, 2973, 1709, 1502, 1216, 928, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.20 (m, 5H), 4.47 (d, *J* = 8.8 Hz, 1H), 4.08-4.01 (m, 1H), 3.92 (br, 1H), 3.84 (dd, *J* = 12.3, 6.0 Hz, 1H), 3.71 (dd, *J* = 11.5, 2.9 Hz, 1H), 3.50 (dd, *J* = 11.5, 5.8 Hz, 1H), 2.91 (dd, *J* = 14.0, 5.1 Hz, 1H), 2.79 (dd, *J* = 13.5, 7.2 Hz, 1H), 1.99-1.68 (m, 4H), 1.36 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.7, 137.8, 129.4 (2C), 128.4 (2C), 126.3, 81.0, 80.0, 79.4, 65.2, 54.3, 37.5, 28.3 (3C), 27.8, 26.9; MS (ESI-QqQ): *m/z* (%) 322 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{18}H_{27}NO_4Na$ 344.1832 $[M+Na]^+$, found 344.1836.

Data for **12c**: scale of reaction 5.9 g, 17.5 mmol, yield = 4.1 g, 73%; R_f = 0.4 (silica gel, 60% EtOAc in petroleum ether eluant); $[\alpha]_D^{27}$ = +13.0 (*c* = 0.65, $CHCl_3$); IR (KBr): ν_{max} 3437, 3019, 2973, 1709, 1502, 1216, 928, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.18 (m, 5H), 4.46 (b, 1H), 4.20-4.12 (m, 1H), 3.87 (m, 2H), 3.66 (dd, *J* = 11.5, 3.3 Hz, 1H), 3.50 (dd, *J* = 11.5, 6.1 Hz, 1H), 2.98 (dd, *J* = 14.1, 3.9 Hz, 1H), 2.79 (m, 1H), 2.06-1.95 (m, 2H), 1.82-1.63 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 137.8, 129.6 (2C), 128.4 (2C), 126.3, 80.7, 79.9, 79.3, 65.0, 54.3, 37.1, 28.8, 28.3 (3C), 27.4; MS (ESI-QqQ): *m/z* (%) 344 (100), $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{18}H_{27}NO_4Na$ 344.1832 $[M+Na]^+$, found 344.1831.

Data for **12d**: scale of reaction 4.2 g, 12.4 mmol, yield = 3.0 g, 75%; R_f = 0.4 (silica gel, EtOAc); $[\alpha]_D^{25}$ = +13.4 (*c* = 1.58, $CHCl_3$); IR (KBr): ν_{max} 3437, 3019, 2973, 1709, 1502, 1216, 928, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.19 (m, 5H), 4.57 (d, *J* = 8.3 Hz, 1H), 4.15 (br, 1H), 3.88 (m, 2H), 3.64 (d, *J* = 9.9 Hz, 1H), 3.49 (dd, *J* = 10.9, 5.7 Hz, 1H), 2.98 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.77 (m, 1H), 2.53 (m, 1H), 2.00 (t, *J* = 3.6 Hz, 2H), 1.80-1.65 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 138.0, 129.5 (2C), 128.3 (2C), 126.2, 80.8, 80.0, 79.2, 64.9, 54.3, 37.0, 28.7, 28.3 (3C), 27.3; MS (ESI-QqQ): *m/z* (%) 322 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{18}H_{27}NO_4Na$ 344.1832 $[M+Na]^+$, found 344.1838.

Preparation of 6a-d: To a solution of oxalyl chloride (1.5 eq.) in dry CH_2Cl_2 (60 mL), dry DMSO (3.2 eq.) was added drop by drop at -78 °C under nitrogen atmosphere. After 15 minutes, compound **12a**-**d** (1 eq.) in dry CH_2Cl_2 (30 mL) was added with stirring at the same temperature. After 30 min, Et_3N (5 eq.) was added at -78 °C under nitrogen atmosphere. After continuing the reaction for 45 min at the same temperature, the reaction mixture was brought to 0 °C in 30 min. Then, the reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2 × 250 ml). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in *vacuo*. The crude aldehyde was directly used for the next reaction.

To a solution of the aldehyde in 2-methyl-2-butene (2 eq.) and ^{t}BuOH (45 mL), the mixture of $NaClO_2$ (2 eq.) and NaH_2PO_4 (2 eq.), dissolved in minimum amount of water, was added and stirring continued for 3 h at room temperature. The solvents of reaction mixture were evaporated under vacuum; the residue was diluted with EtOAc (500 mL), washed with 1 N HCl (100 mL), water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated in *vacuo*. Crude acid was dissolved in Et_2O (50 mL) and treated with excess CH_2N_2 in ether at 0 °C. Then the solvent was evaporated and purification by column chromatography (SiO_2, 35% EtOAc in petroleum ether eluant) afforded methyl ester **6a**-**d**.

Data for **6a**: scale of reaction 5.4 g, 16.8 mmol, yield = 4.7 g, 81%; R_f = 0.4 (silica gel, 50% EtOAc in petroleum ether eluant); $[\alpha]_D^{25}$ = +1.5 (*c* = 0.76, $CHCl_3$); IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.17 (m, 5H), 4.73 (br, 1H), 4.52 (dd, *J* = 8.2, 5.2 Hz, 1H), 4.01-3.90 (m, 2H), 3.77 (s, 3H), 2.99 (br, 1H), 2.79 (d, *J* = 4.8 Hz, 1H), 2.10-2.07 (m, 2H), 2.03-1.87 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.7, 155.7, 137.9, 129.6 (2C), 128.3(2), 126.2, 82.1, 79.1, 77.4, 53.8, 52.1, 36.7, 30.0, 28.3 (3C), 27.5; MS (ESI-QqQ): *m/z* (%) 372 (100), $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{19}H_{27}NO_5Na$ 372.1781 $[M+Na]^+$, found 372.1784.

Data for **6b**: scale of reaction 3.7 g, 11.5 mmol, yield = 3.4 g, 85%; R_f = 0.4 (silica gel, 50% EtOAc in petroleum ether eluant); $[\alpha]_D^{23}$ = +4.6 (*c* = 1.27, $CHCl_3$); IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.17 (m, 5H), 4.75 (br, 1H), 4.57-4.49 (m, 1H), 4.01-3.90 (m, 1H), 3.77 (s, 3H), 3.00 (d, *J* = 2.6 Hz, 1H), 2.79 (d, *J* = 4.8 Hz, 1H), 2.33-1.85 (m, 4H), 1.36 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.7, 155.7, 138.0, 129.6 (2C), 128.3 (2C), 126.2, 82.2, 79.1, 77.4, 54.1, 52.0, 37.0, 30.2, 28.3 (3C), 27.5; MS (ESI-QqQ): *m/z* (%) 350 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{19}H_{27}NO_5Na$ 372.1781 $[M+Na]^+$, found 372.1781.

Data for **6c**: scale of reaction 4.1 g, 12.7 mmol, yield = 3.9 g, 89%; R_f = 0.4 (silica gel, 50% EtOAc in petroleum ether eluant); $[\alpha]_D^{23}$ = +2.9 (*c* = 1.05, $CHCl_3$); IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28-7.20 (m, 5H), 4.60 (dd, *J* = 8.0, 5.0 Hz, 1H), 4.45 (d, *J* = 7.7 Hz, 1H), 4.06 (t, *J* = 6.7 Hz,

1H), 3.86 (m, 1H), 3.75 (s, 3H), 3.00 (dd, *J* = 13.9, 4.0 Hz, 1H), 2.80-2.76 (m, 3H), 2.32 (dd, *J* = 15.1, 8.8 Hz, 1H), 2.07-1.84 (m, 1H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 155.3, 137.5, 129.6 (2C), 128.2 (2C), 126.2, 81.8, 79.3, 77.1, 54.1, 52.0, 37.0, 29.8, 28.2 (3C), 27.9; MS (ESI-QqQ): *m/z* (%) 372 (100), $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{19}H_{27}NO_5Na$ 372.1781 $[M+Na]^+$, found 372.1784.

Data for **6d**: scale of reaction 3.0 g, 9.3 mmol, yield = 2.9 g, 89%; R_f = 0.4 (silica gel, 50% EtOAc in petroleum ether eluant); $[\alpha]_D^{25}$ = +1.5 (*c* = 2.0, $CHCl_3$); IR (KBr): ν_{max} 3302, 2980, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.19 (m, 5H), 4.60 (dd, *J* = 8.0, 5.0 Hz, 1H), 4.44 (d, *J* = 9.1 Hz, 1H), 4.07 (dd, *J* = 13.3, 6.7 Hz, 1H), 3.86 (br, 1H), 3.75 (s, 3H), 3.00 (dd, *J* = 13.9, 6.7 Hz, 1H), 2.79-2.77 (m, 1H), 2.31 (dd, *J* = 15.3, 8.8 Hz, 1H), 2.07-1.96 (m, 2H), 1.83 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 155.4, 137.6, 129.6 (2C), 128.3 (2C), 126.3, 81.8, 79.3, 77.2, 54.2, 52.0, 37.0, 29.8, 28.2 (3C), 27.9; MS (ESI-QqQ): *m/z* (%) 372 (100), $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{19}H_{27}NO_5Na$ 372.1781 $[M+Na]^+$, found 372.1790.

General procedure for the tetrapeptide preparation (13a-d):

To a stirring solution of **6a**-**d** (1 eq.) in THF:MeOH:H_2O (3:1:1, 15 mL) at 0 °C, LiOH.H_2O (3 eq.) was added and stirred at room temperature for 1 h. The reaction mixture was then acidified to pH 2 with 1 N HCl and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to get the acid intermediate. The crude acid was used in the next reaction without further purification.

To a stirred solution of Boc-Val-Orn(Cbz)-Leu-OMe (1.2 eq.) in dry dichloromethane (10 mL) at 0 °C was added trifluoroacetic acid (5 mL) and stirred for 2 h at room temperature. The reaction mixture was then concentrated in *vacuo* to get the trifluoroacetate salt.

To a stirring solution of the crude acid in dry dichloromethane (15 mL) at 0 °C was sequentially added HOBt.H_2O (1.5 eq.) and EDCI (1.5 eq.). After 10 min, the above-prepared trifluoroacetate salt was dissolved in dichloromethane (6 mL) and added to the reaction mixture followed by the addition of DIPEA (5 eq.). After stirring for 12 h at room temperature, the reaction mixture was diluted with EtOAc (125 mL), washed with 1 N HCl solution (2 x 20 mL), saturated $NaHCO_3$ solution (2 x 20 mL), water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by silica gel column chromatography (SiO_2 100-200 mesh, 0.8% MeOH in chloroform) afforded compound **13a**-**d** as white solid.

Data for **13a**: scale of reaction 1 g, 2.9 mmol, yield = 1.2 g, 51%; R_f = 0.45 (SiO_2, 80% EtOAc in petroleum ether); IR (KBr): ν_{max} 3312, 3019, 1720, 1657, 1539, 1285, 1165, 1073, 758, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (br, 1H), 7.35-7.20 (m, 10H), 7.07 (br, 1H), 7.00 (br, 1H), 6.69 (br, 1H), 5.22 (br, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 5.06 (d, *J* = 12.1 Hz, 1H), 4.74 (m, 1H), 4.53 (m, 1H), 4.44 (m, 1H), 4.20 (t, *J* = 9.4 Hz, 1H), 4.11-3.92 (m, 2H), 3.69 (s, 3H), 3.52-3.47 (m, 1H), 3.22-3.12 (m, 1H), 2.96-2.84 (m, 1H), 2.70-2.62 (m, 1H), 2.24-2.14 (m, 2H), 1.89-1.83 (m, 2H), 1.69-1.60 (m, 2H), 1.43-1.36 (m, 6H), 1.25 (s, 9H), 0.98-0.86 (m, 12H); MS (ESI-QqQ): *m/z* (%) 832 (100) $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{43}H_{64}N_5O_{10}$ 810.4648 $[M+H]^+$, found 810.4638.

Data for **13b**: scale of reaction 1 g, 2.9 mmol, yield = 1.3 g, 56%; R_f = 0.45 (SiO_2, 80% EtOAc in petroleum ether); IR (KBr): ν_{max} 3312, 3019, 1720, 1657, 1539, 1285, 1165, 1073, 758, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (br, 1H), 7.27-7.11 (m, 10H), 7.01 (br, 1H), 6.86 (br, 1H), 5.33 (br, 1H), 5.19 (br, 1H), 5.04 (d, *J* = 12.5 Hz, 1H), 4.99 (d, *J* = 12.0 Hz, 1H), 4.68-4.62 (m, 1H), 4.49-4.43 (m, 1H), 4.39-4.30 (m, 1H), 4.22-4.11 (m,1H), 4.00-3.98 (m, 1H), 3.95-3.84 (m, 1H), 3.61 (s, 3H), 3.36-3.30 (m, 1H), 3.20-2.99 (m, 1H), 2.90-2.78 (m, 1H), 2.62-2.58 (m, 1H), 2.20-2.06 (m, 3H), 1.97-1.89 (m, 1H), 1.82 (m, 2H), 1.56-1.50 (m, 6H), 1.18 (s, 9H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J*= 6.5 Hz, 3H);MS (ESI-QqQ): *m/z* (%) 832 (100) $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{43}H_{64}N_5O_{10}$ 810.4648 $[M+H]^+$, found 810.4642.

Data for **13c**: scale of reaction 1 g, 2.9 mmol, yield = 1.1 g, 49%; R_f = 0.45 (SiO_2, 80% EtOAc in petroleum ether); IR (KBr): ν_{max} 3312, 3019, 1720, 1657, 1539, 1285, 1165, 1073, 758, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.19 (m, 11H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 5.07 (d, *J* = 12.2 Hz, 1H), 5.04 (br, 1H), 4.68 (br, 1H), 4.56-4.52 (m, 1H), 4.50 (dd, *J* = 7.8, 6.2 Hz, 1H), 4.47-4.44 (m, 1H), 4.23 (t, *J* = 8.1 Hz, 1H), 4.01-3.95 (m,1H), 3.89 (m, 1H), 3.70 (s, 3H), 3.52-3.47 (m, 1H), 3.17-3.14 (m, 1H), 2.99 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.82 (br, 1H), 2.40-2.29 (m, 1H), 2.18-2.11 (m, 1H), 2.09-2.02 (m, 1H), 1.97-1.93 (m, 2H), 1.88-1.81 (m, 2H), 1.68-1.54 (m, 6H), 1.25 (s, 9H), 0.98-0.86 (m, 12H); MS (ESI-QqQ): *m/z* (%) 832 (100) $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{43}H_{64}N_5O_{10}$ 810.4648 $[M+H]^+$, found 810.4644.

Data for **13d**: scale of reaction 1 g, 2.9 mmol, yield = 1.2 g, 52%; R_f = 0.45 (SiO_2, 80% EtOAc in petroleum ether); IR (KBr): ν_{max} 3312, 3019, 1720, 1657, 1539, 1285, 1165, 1073, 758, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.21 (m, 11H), 6.99 (br, 1H), 6.86 (d, *J* = 6.9 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 5.16 (br, 1H), 4.67 (d, *J* = 3.9 Hz, 1H), 4.56-4.48 (m, 3H), 4.26 (dd, *J* = 8.3, 1.2 Hz, 1H), 3.97-3.95 (m, 1H), 3.89-3.88 (m, 1H), 3.70 (s, 3H), 3.47-3.45 (m, 1H), 3.15 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.99 (dd, *J* = 14.0, 4.2 Hz, 1H), 2.81 (m, 1H), 2.40-2.31 (m, 1H), 2.16-2.01 (m, 2H), 1.97-1.82 (m, 4H), 1.71-1.56 (m, 5H), 1.35 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 6H), 0.90 (d, *J* = 6.7 Hz, 6H); MS (ESI-QqQ): *m/z* (%) 832 (100) $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{43}H_{64}N_5O_{10}$ 810.4648 $[M+H]^+$, found 810.4642.

General procedure for the octapeptide preparation (16a-d):

To a stirring solution of **13a**-**d** (1 eq.) in THF:MeOH:H_2O (3:1:1, 10 mL) at 0 °C, LiOH.H_2O (3 eq.) was added and stirred at room temperature for 1 h. The reaction mixture was then acidified to pH 2 with 1 N HCl and was extracted with EtOAc (2 x 125 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to get the acids **14a**-**d**. The crude acid was used in the next reaction without further purification.

To a stirred solution of **13a**-**d** (1 eq.) in dry dichloromethane (6 mL) at 0 °C was added trifluoroacetic acid (3.0 mL) and stirred for 2 h at room temperature. The reaction mixture was then concentrated in *vacuo* to get the trifluoroacetate salts **15a**-**d**.

To the stirred solution of the above-prepared crude acids **14a-d** in dry dichloromethane (6 mL) at 0 °C were sequentially added HOBt.H_2O (1.5 eq.) and EDCI (1.5 eq.). After 10 min, the above-prepared trifluoroacetate salts **15a-d** were dissolved in dichloromethane (3 mL) and added to the reaction mixture followed by the addition of DIPEA (5 eq.). After stirring for 12 h at room temperature, the reaction mixture was diluted with EtOAc (250 mL), washed with 1 N HCl solution (2 x 50 mL), saturated $NaHCO_3$ solution (2 x 50 mL), water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by silica gel column chromatography (SiO_2 100-200 mesh, 1.6% MeOH in chloroform) afforded compounds **16a-d** as white solids.

Data of **16a**: scale of reaction 600 mg, 0.75 mmol, yield = 580 mg, 52%; R_f = 0.5 (SiO_2, 8% MeOH in chloroform); IR (KBr): ν_{max} 3429, 3019, 2929, 2400, 1638, 1526, 1385, 1156, 1094, 928, 669 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, J = 7.6 Hz, 1H), 8.19 (d, J = 7.7 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.9 Hz, 1H), 7.53 (d, J = 7.1 Hz, 1H), 7.49 (d, J = 9.0 Hz, 1H), 7.42-7.40 (m, 1H), 7.36-7.35 (m, 1H), 7.34-7.28 (m, 12H), 7.24-7.12 (m, 13H), 6.75 (d, J = 9.0 Hz, 1H), 5.00 (s, 2H), 4.99 (s, 2H), 4.32-4.26 (m, 8H), 4.18-4.10 (m, 2H), 3.95-3.93 (m, 1H), 3.83-3.80 (m, 2H), 3.65-3.63 (m, 1H), 3.58 (s, 3H), 2.61-2.54 (m, 2H), 2.12-2.04 (m, 2H), 2.01-1.94 (m, 3H), 1.81 (m, 4H), 1.72-1.58 (m, 6H), 1.55-1.39 (m, 3H), 1.24 (s, 9H), 1.13-1.03 (m, 3H), 0.88-0.78 (m, 18H), 0.71 (d, J= 6.4 Hz, 3H), 0.67 (d, J = 6.4 Hz, 3H); MS (ESI-QqQ): *m/z* (%) 1487 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{80}H_{115}N_{10}O_{17}$ 1487.8436 $[M+H]^+$, found 1487.8417.

Data of **16b**: scale of reaction 650 mg, 0.80 mmol, yield = 582 mg, 49%; R_f = 0.5 (SiO_2, 8% MeOH in chloroform); IR (KBr): ν_{max} 3429, 3019, 2929, 2400, 1638, 1526, 1385, 1156, 1094, 928, 669 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, J = 6.4 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H), 8.10 (d, J = 9.7 Hz, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.78 (br, 1H), 7.58 (d, J = 9.9 Hz, 1H), 7.50 (d, J = 9.3 Hz, 1H), 7.32-7.13 (m, 21H), 6.77 (d, J = 9.5 Hz, 1H), 5.00 (s, 2H), 4.98 (s, 2H), 4.35-4.28 (m, 7H), 4.13-4.12 (m, 1H), 3.94-3.92 (m, 1H), 3.83 (m, 2H), 3.64 (m, 1H), 3.58 (s, 3H), 3.13-3.10 (m, 1H), 3.05-2.95 (m, 5H), 2.56 (m, 2H), 2.08 (m, 2H), 1.99 (m, 2H), 1.81 (m, 4H), 1.70-1.43 (m, 13H), 1.24 (s, 9H), 1.12 (m, 4H), 1.03 (m, 2H), 0.84-0.79 (m, 18H), 0.69 (d, J = 5.9 Hz, 3H), 0.68 (d, J = 5.9 Hz, 3H); MS (ESI-QqQ): *m/z* (%) 1487 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{80}H_{114}N_{10}O_{17}Na$ 1509.8256 $[M+Na]^+$, found 1509.8260.

Data of **16c**: scale of reaction 550 mg, 0.68 mmol, yield = 474 mg, 47%; R_f = 0.5 (SiO_2, 8% MeOH in chloroform); IR (KBr): ν_{max} 3429, 3019, 2929, 2400, 1638, 1526, 1385, 1156, 1094, 928, 669 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.26 (d, J = 7.5 Hz, 1H), 8.20 (d, J = 7.5 Hz, 2H), 8.13 (d, J = 7.6 Hz, 1H), 7.95-7.93 (m, 1H), 7.90 (d, J = 9.1 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.34-7.14 (m, 24H), 6.78 (d, J = 9.7 Hz, 1H), 5.00 (s, 2H), 4.98 (s, 2H), 4.46-4.41 (m, 2H), 4.28-4.21 (m, 6H), 4.17-4.10 (m, 1H), 3.98-3.90 (m, 3H), 3.59 (s, 3H), 3.05-2.93 (m, 6H), 2.59 (dd, J = 14.8, 6.5 Hz, 1H), 2.19-2.16 (m, 2H), 2.00-1.94 (m, 2H), 1.86-1.71 (m, 6H), 1.63-1.43 (m, 10H), 1.27 (s, 9H), 0.89-0.67 (m, 24H); MS (ESI-QqQ): *m/z* (%) 1487 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{80}H_{115}N_{10}O_{17}$ 1487.8436 $[M+H]^+$, found 1487.8359.

Data of **16d**: scale of reaction 600 mg, 0.74 mmol, yield = 561 mg, 51%; R_f = 0.5 (SiO_2, 8% MeOH in chloroform); IR (KBr): ν_{max} 3429, 3019, 2929, 2400, 1638, 1526, 1385, 1156, 1094, 928, 669 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.26 (d, J = 7.6 Hz, 1H), 8.23-8.13 (m, 3H), 8.07-8.04 (m, 1H), 7.98-7.90 (m, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.78 (t, J = 7.9 Hz, 1H), 7.47 (d, J = 9.1 Hz, 2H), 7.34-7.16 (m, 24H), 6.79 (d, J = 9.5 Hz, 1H), 5.01 (s, 2H), 5.00 (s, 2H), 4.43 (m, 1H), 4.34-4.26 (m, 6H), 4.18-4.11 (m, 2H), 3.97-3.91 (m, 2H), 3.60 (s, 3H), 3.00-2.98 (m, 7H), 2.67-2.57 (m, 2H), 2.29-2.28 (m, 1H), 2.20-2.17 (m, 3H), 2.00-1.91 (m, 4H), 1.84-1.72 (m, 2H), 1.64-1.43 (m, 8H), 1.24 (s, 9H), 0.89-0.67 (m, 24H); MS (ESI-QqQ): *m/z* (%) 1487 (100) $[M+H]^+$, HRMS (ESI-Q-TOF): calcd. for $C_{80}H_{115}N_{10}O_{17}$ 1487.8436 $[M+H]^+$, found 1487.8409.

General procedure for cyclization (17a-d): To the stirred solution of **16a-d** (1 eq.) in THF:MeOH:H_2O (3:1:1, 5 mL) at 0 °C, LiOH.H_2O (3 eq.) was added and stirred at room temperature for 1 h. The reaction mixture was then acidified to pH 2 with 1 N HCl. The reaction mixture was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to get the crude acid, which was used in the next reaction without further purification.

To a stirred solution of the hydrolyzed product in dry dichloromethane (3 mL) at 0 °C was added trifluoroacetic acid (1.5 mL) and stirred for 2 h at room temperature. The reaction mixture was then concentrated in *vacuo* to get the trifluoroacetate salt.

To a stirred solution of the salt in dry dimethyl formamide (1 x 10^{-3} M) at 0 °C was added FDPP (6 eq.) followed by the addition of DIPEA (10 eq.). After being stirred for 72 h at room temperature, the solvent was evaporated under reduced pressure and the product was dissolved in EtOAc (125 mL). The organic layer was washed with 1 N NaOH (2 x 50 mL), water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO_2 100-200 mesh, 1.3% MeOH in chloroform) afforded the cyclised compounds **17a-d** as white solids.

Data for **17a**: scale of reaction 580 mg, 0.39 mmol, yield = 169 mg, 32%; R_f = 0.5 (SiO_2, 6% MeOH in chloroform); ^1H NMR (500 MHz, $CDCl_3$): Table S7 (Supporting Information); MS (ESI-QqQ): *m/z* (%) 1377 (100) $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{74}H_{103}N_{10}O_{14}$ 1355.7650 $[M+H]^+$, found 1355.7557.

Data for **17b**: scale of reaction 582 mg, 0.39 mmol, yield = 158 mg, 30%; R_f = 0.5 (SiO_2, 6% MeOH in chloroform); ^1H NMR (500 MHz, $CDCl_3$): Table S8 (Supporting Information); MS (ESI-QqQ): *m/z* (%) 1377 (100) $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{74}H_{103}N_{10}O_{14}$ 1355.7650 $[M+H]^+$, found 1355.7650.

Data for **17c**: scale of reaction 474 mg, 0.32 mmol, yield = 130 mg, 30%; R_f = 0.5 (SiO_2, 6% MeOH in chloroform); ^1H NMR (500 MHz, $CDCl_3$): Table S9 (Supporting Information); MS (ESI-QqQ): *m/z* (%) 1377 (100) $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{74}H_{102}N_{10}O_{14}Na$ 1377.7469 $[M+Na]^+$, found 1377.7465.

Data for **17d**: scale of reaction 581 mg, 0.38 mmol, yield = 165 mg, 32%; R_f = 0.5 (SiO_2, 1.3% MeOH in chloroform); ^1H NMR

(500 MHz, $CDCl_3$): Table S10 (Supporting Information); MS (ESI-QqQ): *m/z* (%) 1377 (100) $[M+Na]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{74}H_{103}N_{10}O_{14}$ 1355.7650 $[M+H]^+$, found 1355.7634.

General procedure for the deprotection of Cbz (2-5): To the compounds **17a**-**d** (1 eq.) in MeOH (5 mL) was added $Pd(OH)_2$, followed by the addition of AcOH (4 eq.). The reaction was continued for 1 h. After completion of the reaction, the reaction mixture was filtered through Celite and concentrated. Then, the compound was passed through a pad of Sephadex LH-20 to get pure compounds **2**-**5** after concentration.

Data for **2**: scale of reaction 50 mg, 0.04 mmol, 26 mg, yield = 66%; ^1H NMR (500 MHz, DMSO-d_6): Table S11 (Supporting Information); MS (ESI-QqQ): *m/z* (%) 1087 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{58}H_{91}N_{10}O_{10}$ 1087.6914 $[M+H]^+$, found 1087.6942.

Data for **3**: scale of reaction 50 mg, 0.04 mmol, yield = 22 mg, 56%; ^1H NMR (500 MHz, DMSO-d_6): Table S12 (Supporting Information); MS (ESI-QqQ): *m/z* (%) 1087 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{58}H_{91}N_{10}O_{10}$ 1087.6914 $[M+H]^+$, found 1087.6942.

Data for **4**: scale of reaction 50 mg, 0.04 mmol, yield = 25 mg, 64%; ^1H NMR (500 MHz, DMSO-d_6): Table S13 (Supporting Information); MS (ESI-QqQ): *m/z* (%) 1087 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{58}H_{91}N_{10}O_{10}$ 1087.6914 $[M+H]^+$, found 1087.6938.

Data for **5**: scale of reaction 50 mg, 0.04 mmol, yield = 22 mg, 56%; ^1H NMR (500 MHz, DMSO-d_6): Table S14 (Supporting Information); MS (ESI-QqQ): *m/z* (%) 1087 (100) $[M+H]^+$; HRMS (ESI-Q-TOF): calcd. for $C_{58}H_{91}N_{10}O_{10}$ 1087.6914 $[M+H]^+$, found 1087.6932.

Assays for cytotoxicity against mammalian cells:

Cytotoxicity of Vero cells: Cytotoxicity of peptides against a mammalian cell line Vero (ATCC No. CRL-1586) was determined as follows. Cells, propagated in Minimal Essential Medium containing 10% fetal bovine serum (MEM-FBS) and antibiotics (Gentamycin, 50 mg/L; Amphotericin-B, 125 µg/L), were plated in 96-well culture plates (20,000 cells/200µl/well) and incubated in a CO_2 incubator (37 °C, 5% CO_2) overnight to allow their adherence. The supernatant was replaced with fresh medium containing different concentrations of peptides or a standard toxicant (saturosporine) or DMSO (vehicle). After further 24 h incubation, 20 µl MTS reagent (Promega Kit) was added and absorbance (OD) was read after 2 h at 490 nm. Growth inhibition for each concentration of the peptide was calculated as follows: 100 - [OD of test well ÷ OD of reference (DMSO) well x 100]. A peptide was considered as potentially toxic if it's CC_{50} (concentration causing 50% inhibition of Vero cell growth) was ≤ 10x MIC for *M. tuberculosis* (see below).[27]

Hemolysis of human RBCs. Hemolytic activity of peptides against human red blood cells (hRBCs) in PBS was examined by a standard procedure.[28] In brief, fresh hRBCs collected in the presence of an anti-coagulant from a healthy volunteer were washed (x3) with PBS. Freshly dissolved peptides in water were added to the suspension of RBCs (6% v/v, in PBS) to the final volume of 200 µL and incubated at 37 °C for 35 minutes. The samples were centrifuged (10 min at 2000 r.p.m.) and released hemoglobin was determined by measuring the absorbance (A_{sample}) of the supernatant at 540 nm. Absorbance of hRBC in PBS (A_{blank}) and in 0.2% (final concentration) Triton X-100 (A_{triton}) were used as negative and positive controls respectively. The percentage of hemolysis was calculated according to the following equation.

Percentage of hemolysis = $[(A_{sample}-A_{blank})/(A_{triton}-A_{blank})] \times 100$.

Assays for activity against Mycobacterium tuberculosis: These assays were performed with *M. tuberculosis* H37Ra (ATCC No. 25177). Standard anti-TB drugs (isoniazid and rifampicin) were used as positive controls and the vehicle (DMSO) alone was the negative control.

Minimum Inhibitory Concentration (MIC): Log-phase culture of *M. tuberculosis* in Sauton's broth was diluted in the same medium to get an OD of 0.005 at 580 nm. This working dilution was dispensed (190 µL/well) in 96-well white culture plates. Later, 10 µL of appropriately diluted standard drugs or peptides or vehicle were also dispensed in respective wells (final volume 200 µL/well) and the plates were incubated in a CO_2 incubator for 5 days. On 6th day, 15 µL Resazurin (Sigma-Aldrich, 0.33 mg/mL in water) was added to each well and plates were further incubated overnight. Viable and multiplying bacteria change the colour of redox dye (Resazurin) from blue to fluorescent pink.[29] Fluorescence was read on a plate reader (BMG Plorastar Galaxy) at 544 nm excitation and 590 nm emission wavelengths. Percent inhibition of growth at each dilution of the standard drug or peptide was calculated as follows: 100 - [FU with drug or peptide ÷ FU with DMSO x 100] (FU= fluorescence units). The lowest concentration of a peptide/drug which produced ≥ 90 % inhibition of FU was its MIC.

Minimum Bactericidal Concentration (MBC): MBC of peptides was determined as follows.[30] To each assay tube containing 2.5 mL Middlebrook 7H9 broth, 50 µL inoculum containing 10^5 *M. tuberculosis* was added and incubated (37 °C, up to 14 days) with 1x, 2x or 4x MIC of peptides and standard drugs or the vehicle. Colony Forming Units (CFUs) were counted on days 0, 7 and 14. If a molecule caused ≥ 99% reduction in CFU of the inoculum (i.e., day-0 CFU), it was considered as `bactericidal` and corresponding concentration was its MBC. If a molecule did not kill the inoculum but only prevented its multiplication (i.e., reduction in day-7 or day-14 CFU), it was considered as `bacteriostatic`.

Activity against intracellular infection: The effect of peptides or standard drugs or vehicle on the survival and multiplication of *M. tuberculosis* within mouse bone-marrow derived macrophages was evaluated as follows.[31] For preparation of macrophages, Swiss mice were euthanized and femurs dissected out. The bones were trimmed at both ends and marrow flushed out with MEM-FBS, antibiotics, 15% L929 fibroblast conditioned medium and nonessential amino acids. Washed cells, reconstituted in the same medium were dispensed in 24-well culture plates (106 cells/well). Five-day old cultures of bone-marrow derived macrophages were infected with *M. tuberculosis* (5x106 bacilli/well) in antibiotic-

free medium. After 3 h, the wells were washed (to remove extracellular bacteria) and replenished with fresh antibiotic-free medium containing 1x, 2x or 4x MIC of drugs and peptides or the vehicle. In order to determine the number of bacilli phagocytosed during the 3 h infection period (0 day count), vehicle-treated cells were lysed with 0.1% saponin and suitably diluted lysates were plated on Middlebrook 7H10 agar. Cells in remaining wells, after further 5 days of incubation were similarly washed, lysed and plated. All CFUs were determined after 4 weeks of incubation at 37 ˚C and results were recorded as % inhibition of CFU with respect to day-0 or day-5 CFUs of vehicle-treated macrophages.

Assay for activity against Gram positive and Gram negative bacteria: The Gram-positive bacteria *Bacillus subtilis* ATCC 6633 and *Staphylococcus aureus* ATCC 9144, and Gram-negative bacteria *Escherichia coli* ATCC 10536 and *Psuedomonas aurogenosa* were used in these assays. Antibacterial activity was assayed in 96-well culture plate (final volume 100 µL final/well) under aerobic conditions. In brief, mid-log phase bacteria were washed (x3) with PBS and re-suspended as such to gain nearly 105 CFU/mL. 50 µL bacterial suspensions, with 105 CFU/mL, were added to 50 µL of water containing two fold serially diluted different peptides in each well and incubated for 3 h at 37 °C. Later, bacterial suspensions were diluted 1:100 with PBS and 10 µL of each diluted suspension was spotted onto LB agar plates. The plates were incubated at 37 °C for 18-24 h. Antibacterial activities of the peptides were expressed in terms of MICs which indicate the peptide concentrations that resulted in 100% inhibition of microbial growth (absence of any visible bacterial colony).

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