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Design and synthesis of diketopiperazine and acyclic analogs related to the caprazamycins and liposidomycins as potential antibacterial agents

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Abstract—A systematic simplification methodology of a class of 6′-*N*-alkyl-5′-*O*-aminoribosyl-glycyluridine antibiotics was shown to produce potential antibacterial agents having a novel mechanism of action. Diketopiperazines and acyclic analogs of the caprazamycins (CPZs) and liposidomycins (LPMs) were efficiently synthesized, and their antibacterial activity was evaluated. The diketopiperazine analog **11a** and the acyclic analogs **12a** and **16a** having a palmitoyl group as a lipophilic side chain exhibited moderate antibacterial activities with MICs of 12.5–50 μg/mL. This approach could provide ready access to a range of analogs for the development of potential antibacterial agents.

1. Introduction

The extensive use of antibiotics has raised a serious global public health problem. Since bacterial pathogens inevitably develop resistance to every new drugs launched in the clinic,[1] the need for new antibiotics is critical. The caprazamycins (CPZs) (Fig. 1, **1**) isolated from a culture broth of the Actinomycete strain *Streptomyces* sp. MK730-62F2 in 2003[2] constitute the newest member of the naturally occurring 6′-*N*-alkyl-5′-*O*-aminoribosyl-glycyluridine structure, which also includes the liposidomycins (LPMs, **2**),[3] the muraymycins (MRYs, **3**)[4], and FR-900493 (**4**).[5] CPZs have shown excellent anti-mycobacterial activity in vitro against drug-susceptible and multi drug-resistant *Mycobacterium tuberculosis* strains, and exhibit no significant toxicity in mice. With these excellent properties, CPZs are expected to be a promising lead for developing anti-tuberculosis agents. LPMs and MRYs are also known to exhibit antibacterial activity similar to that of the CPZs.[4] LPMs and MRYs prevent formation of bacterial cell wall peptidoglycan by strong inhibition of phospho-MurNAc-pentapeptide translocase (MraY, translocase I, Fig. 2). Peptide glycan biosynthesis consists of three stages, including the formation of uridine diphosphate *N*-acetylmuraminylpentapeptide (UDP-MurNAc-pentapeptide) in cytoplasm, the membrane-anchored synthesis of lipid I and lipid II, a precursor to the peptide glycan, and polymerization of the resulting lipid II by transpeptidation and transglycosidation. The second and the third stages are involved in a lipid cycle, and the MraY catalyzes the first step of the lipid-linked cycle of reactions, where UDP-MurNAc-pentapeptide is attacked by the undecaprenol monophosphate in the bacterial cell membrane providing lipid I. Lipid I anchored to the cell membrane is further glycosylated by *N*-acetylglucosamine to afford lipid II. MraY is one of the key enzymes for peptidoglycan biosynthesis and appears to be conserved in both Gram-negative and Gram-positive bacteria. The enzyme is highly conserved across bacterial species and is essential for the growth of the bacteria.[6] Attention therefore has been focused on MraY as a new target enzyme for the development of antibacterial agents. [7,8]

CPZs and LPMs consist of a uridine, an aminoribose, a fatty acyl side chain, and a characteristic diazepanone. It is suggested that their complex structures resemble the transition state of a MraY-catalyzed transfer reaction of a UDP-MurNAc-pentapeptide onto an undecaprenol monophosphate inside the bacterial cell membrane. Because of their molecular

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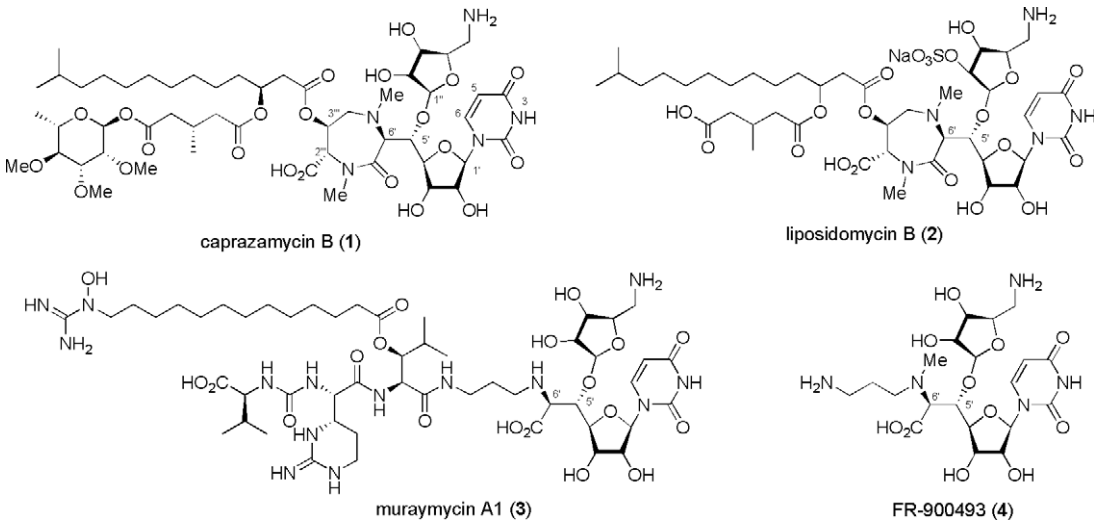


Figure 1. Structures of nucleoside antibiotics possessing a 6′-*N*-alkyl-5′-*O*-aminoribosyl-glycyluridine structures.

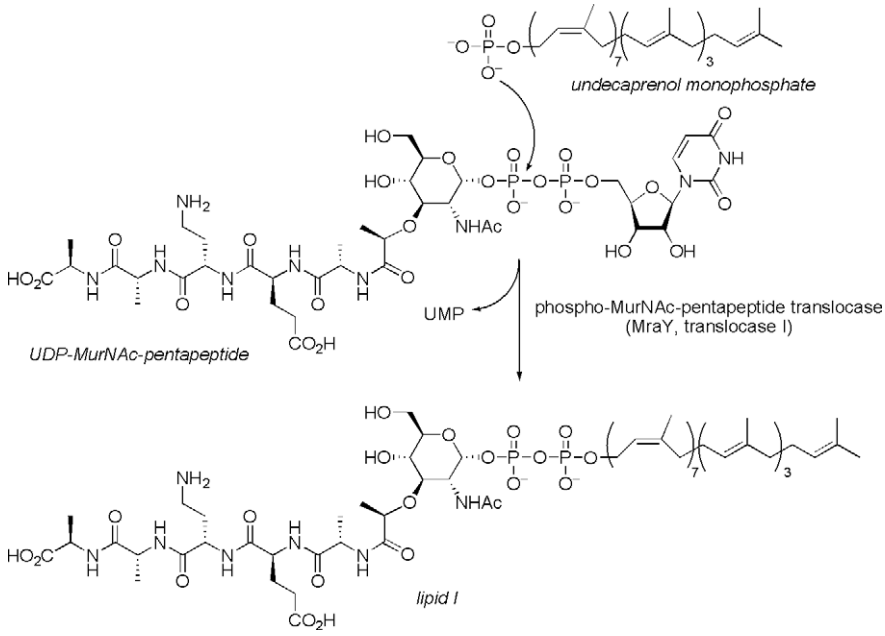


Figure 2. Formation of lipid/catalyzed by MraY (translocase I).

complexity, CPZs and LPMs are not suitable for use in preparing analogs for the study of a structure–activity relationship in a lead optimization process. Dini et al., in a structure–activity relationship of LPMs with quite simple analogs, found that the 3′-hydroxy group, the amino group of the ribose attached on the 5′-hydroxyl group, and the uracil moiety are crucial for MraY inhibitiocn.[9] Thus, the 5′-β-*O*-aminoribosyl-glycyluridine structure is predicted to be the pharmacophore of this class of natural products. Moreover, it suggests that the lipophilic moiety is necessary in order to penetrate inside the bacterial cell membrane to exhibit antibacterial activity. Considering these results, we speculated that the characteristic diazepanone ring systems of the CPZs and LPMs might play an important role as a scaffold on which to hang each of the aminoribosyluridine and the fatty acyl moieties. This would allow them to be placed in the right orientation to interact with the target MraY, and the diazepanone structure, which constitutes a molecular complexity of this class of natural products, could be replaced by a simpler scaffold. We selected a diketopiperazine structure to provide newly designed simple analogs of CPZs and LPMs in order to connect the aminoribosyluridine and the fatty acyl moieties with the simpler scaffold (Fig. 3). A diketopiperazine is synthetically readily accessible and is already used as a scaffold in medicinal chemistry.[10] Herein we describe the synthesis of simplified analogs, where the diazepanone was substituted by a diketopiperazine. Acyclic analogs, which are regarded as acyclic analogs of CPZs and LPMs, were also synthesized with the aim of better understanding the importance of the cyclic structure.

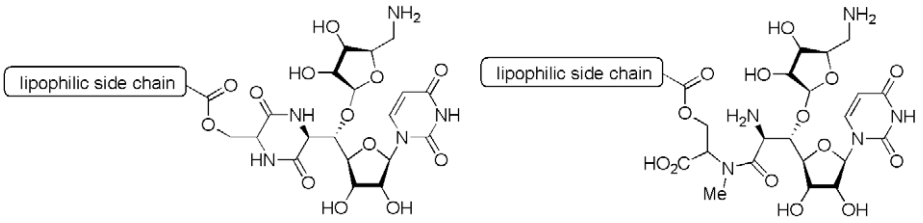


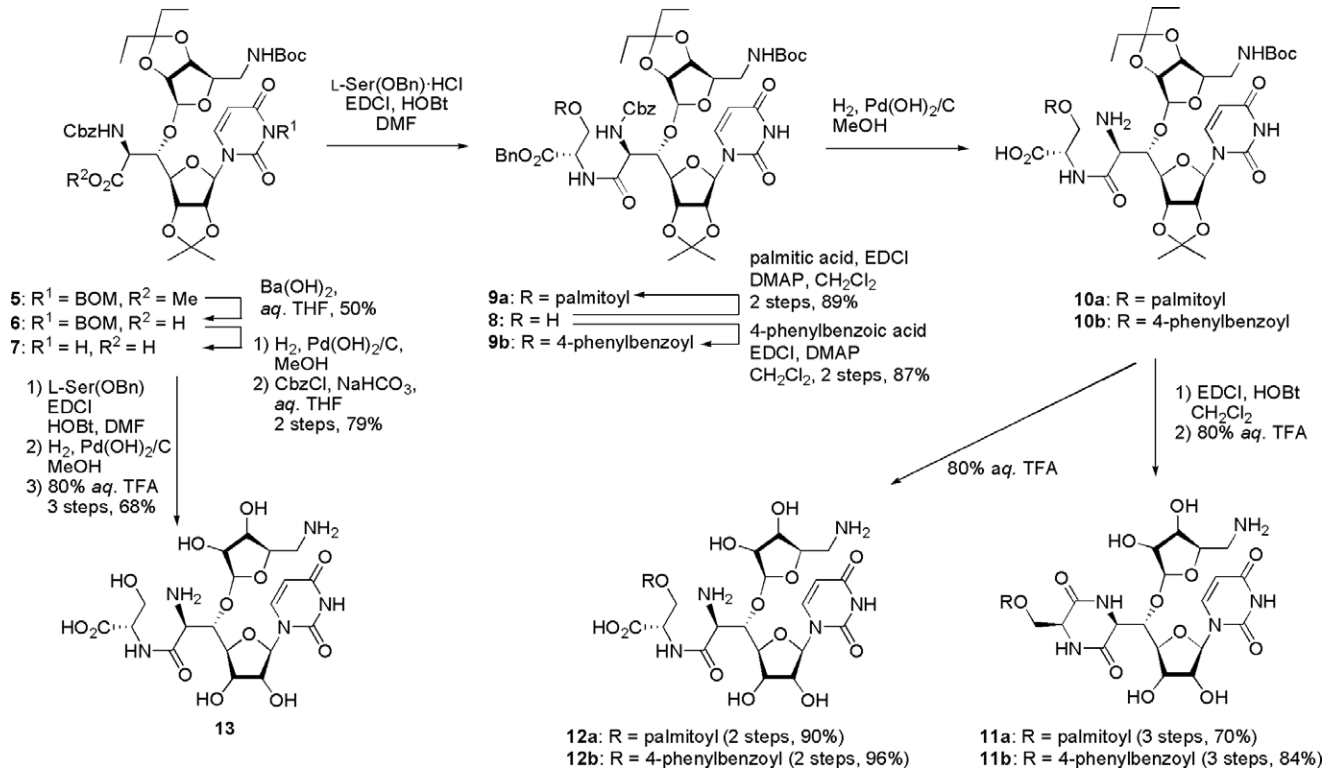
Figure 3. Structures of diketopiperazine and acyclic analogs.

2. Results and discussion

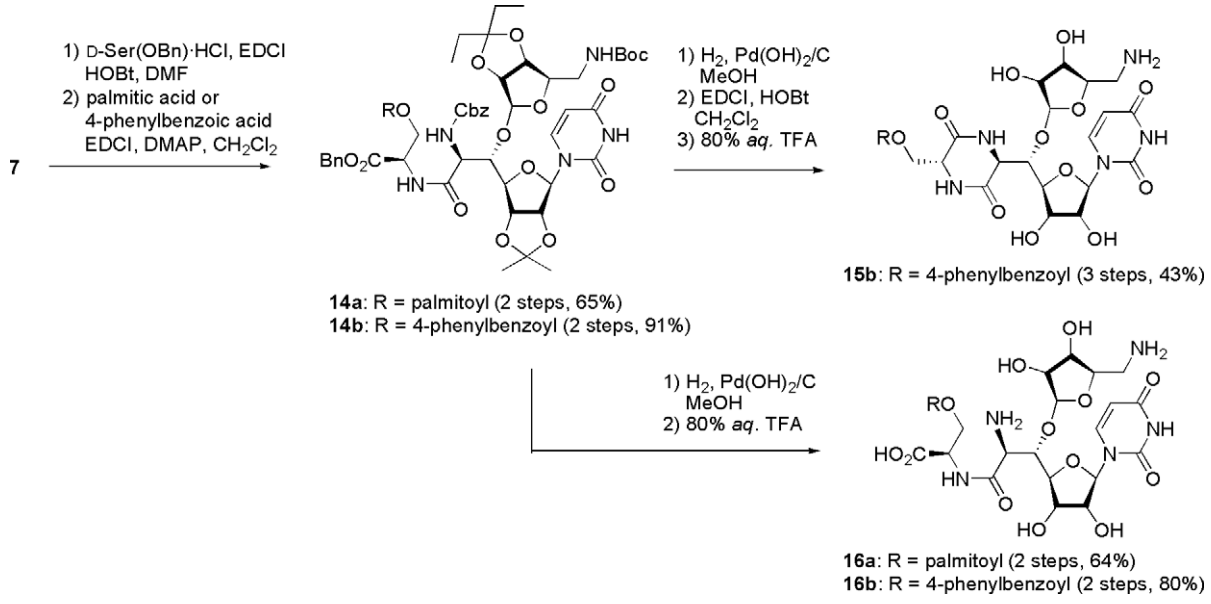
Recently, we have synthesized efficiently the key 5′-β-*O*-aminoribosyl-glycyluridine structure.[11] Our strategy included a sequential installation of L- or D-serine benzyl ester and an acyl side chain to the carboxylic acid derivative **7**, and a cyclization to set the diketopiperazine system. The synthesis of these analogs is summarized in Scheme 1. Initially, we attempted to prepare target molecules with the N^3-benzyloxymethyl (BOM)-protected derivative **6**, which was obtained by hydrolysis of an aminoriboside **5**[11] with $Ba(OH)_2$ in 50% yield. However, we had difficulty removing the BOM group by hydrogenolysis at the final deprotection stage, as observed in our recent FR-900493 synthesis.[12] Therefore we decided to synthesize the target compounds using substrates without the BOM protection at the N^3-position of the uracil moiety throughout the synthesis. Consequently, both the Cbz and the BOM groups of **6** were removed by catalytic hydrogenation, and the resulting free amine at the 6′-position was re-protected with a Cbz group to give **7** in 79% in two steps. Coupling of **7** with L-serine benzyl ester using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI) and 1-hydroxybenzotriazole (HOBt)[13] in DMF gave the amide **8** without any racemization at the 6′-position. The use of CH_2Cl_2 as a solvent in the coupling reaction gave no desired compounds because **7** was insoluble in that solvent. The amide **8** was then acylated with either palmitic acid or 4-phenylbenzoic acid with EDCI in the presence of DMAP in CH_2Cl_2 to give **9a** (89% in two steps) or **9b** (87% in two steps), respectively. Deprotection of both the Cbz group at the N^6′-position and the Bn group on the serine moiety of **9** was conducted by hydrogenolysis catalyzed by $Pd(OH)_2$/C in MeOH to provide the free amino acid **10**, the precursor for the cyclization reaction. Next, the cyclization to construct the diketopiperazine scaffold was examined. Treatment of **10** with either *N*,*N*′-dicyclohexylcarbodiimide (DCC) and HOBt or (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOPCl) in CH_2Cl_2 resulted in a complex mixture of products, and only a trace amount of the desired diketopiperazine derivative was obtained. However, the cyclization was successful when EDCI and HOBt were used in CH_2Cl_2 to give smoothly the diketopiperazine derivative, which was sequentially treated with 80% aqueous TFA to afford the target compound **11a** (70% in three steps from **9a**) or **11b** (84% in three steps from **9b**). These compounds were obtained efficiently in five steps with a minimum number of isolations from the key intermediate **7**. Compounds **12a** and **12b** were also designed and synthesized since they may also be regarded as acyclic analogs of CPZs and LPMs to understand the importance of the cyclic structure. These were obtained by simple treatment of the intermediates **10a** and **10b** with 80% aqueous TFA (**11a**: 90% in two steps from **9a**, **11b**: 96% in two steps from **9b**). In order to see the impact of the lipophilic side chain, the deacyl derivative **13** was prepared by the coupling of **7** with L-serine benzyl ester followed by global deprotection (three steps from **7**, 68%).

A variety of analogs could also be synthesized with this strategy using a variation of the condensed amino acids. By using D-serine benzyl ester in the first coupling reaction with **7**, the intermediates **14a** and **14b** were synthesized as shown in Scheme 2. Compounds **15a** and **15b** were prepared in a manner similar to the syntheses of **11a** and **11b**. However, the diketopiperazine derivatives with the *trans*-substituents tend to be less stable compared to those with the *cis*-substituents for promoting β-elimination of the acyloxy group. Transformation of **14a** and **14b** did proceed to give in moderate yield the corresponding protected diketopiperazine derivatives, deprotection of which afforded **15b** in moderate yield (43% in three steps from **14a**) or resulted in decomposition for **15a**. On the other hand, the synthesis of the acyclic analogs **16a** and **16b** was accomplished without any difficulty, and the same deprotection conditions as for the preparation of **12** were applied to provide **16a** (64% in two steps) and **16b** (80% in two steps), respectively.

The antibacterial activity of the synthesized compounds was evaluated against a range of Gram-positive bacterial strains, including *Mycobacterium* sp., and the minimum inhibitory concentrations (MIC, μg/mL) are summarized in Table 1. None of the newly synthesized analogs exhibited antibacterial activity against *Mycobacterium smegmatis*. However, the diketopiperazine analog **11a** and the acyclic analogs **12a** and **16a**, which possess a palmitoyl side chain, demonstrated moderate antibacterial activity (MIC = 12.5–50 μg/mL) against some strains including *Micrococcus* sp. or *Corynebacterium* sp. Since the acyclic analogs retain the amino and the carboxylic acid functionalities of the parent natural products, it is assumed that their reduced activity is due to the loss of conformational constraint, and the cyclic structure is crucial for MraY inhibition. Although the activity was moderate, the analogs still possess antibacterial activity, and the optimization of the bridging amino acid moiety might lead to better activity. On the other hand, the diketopiperazine analog **11a** exhibited antibacterial activity to a lesser extent than the acy-



Scheme 1. Synthesis of diketopiperazine and acyclic analogs containing L-serine moiety.



Scheme 2. Synthesis of diketopiperazine and acyclic analogs containing D-serine moiety.

clic analogs **12a** and **16a** although **11a** does not have the amino and the carboxylic acid functionalities of the parent CPZs and LPMs. The amino and the carboxylic acid functionalities found in the parent natural products may play an important role in the interaction with MraY. Introduction of amino and carboxylic acid groups to the diketopiperazine scaffold may be effective in increasing the activity. Analogs **11b**, **12b**, **15b**, and **16b** possessing a *p*-phenylbenzoyl group as a compact lipophilic acyl side chain all showed no activity at >100 μg/mL against bacterial strains tested in this study. The lipophilic acyl group at the hydroxyl group of the serine moiety may be responsible for transporting the active structure to the target enzyme in the membrane. This was supported by a total loss of activity of the deacyl derivative **13**. In conjunction with the previous study,[7] the antibacterial activity of this class of antibiotics would be changed by the structural alteration of the acyl side chains. Antibacterial activity of the newly synthesized analogs against *M. tuberculosis* H37Rv was also

Table 1. Antibacterial activity of synthesized analogs

Test organisms	MIC (μg/mL)							
	11a	**11b**	**12a**	**12b**	**13**	**15b**	**16a**	**16b**
Staphylococcus aureus Smith	25	>100	25	>100	>100	>100	25	>100
Staphylococcus aureus MS9610 (MDR)	100	>100	50	>100	>100	>100	50	>100
Staphylococcus aureus MRSA No. 5 (MRSA)	100	>100	50	>100	>100	>100	50	>100
Micrococcus luteus FDA16	25	>100	50	>100	>100	>100	50	>100
Micrococcus luteus PCI 1001	50	100	25	50	> 100	>100	12.5	>100
Bacillus subtilis NRRL B-558	25	>100	25	>100	>100	>100	25	>100
Corynebacterium bovis 1810	50	>100	12.5	100	>100	>100	12.5	>100
Mycobacterium smegmatis ATCC607	100	100	100	100	100	>100	50	100
Enterococcus faecalis NCTC 12201 (VRE)	100	>100	50	>100	>100	>100	50	>100

evaluated (Table 2). The assay was performed by the Alamar blue assay, and the inhibition rate of the *M. tuberculosis* H37Rv at 6.25 μg/mL concentration is summarized in Table 2. The acyclic analogs exhibited moderate antibacterial activity. Different from the results obtained in Table 1, the 4-phenylbenzoyl derivatives showed similar potency to the corresponding palmitoyl derivatives.

In conclusion, simplification of a class of 6′-*N*-alkyl-5′-*O*-aminoribosyl-glycyluridine antibiotics, including CPZs and LPMs, based on the construction of the predicted pharmacophore of MraY inhibitors, was shown to produce potential antibacterial agents with a novel mechanism of action. Diketopiperazine and acyclic analogs of CPZs and LPMs were synthesized, and their antibacterial activity was evaluated. Some analogs exhibited moderate antibacterial activity against *Micrococcus* sp. or *Corynebacterium* sp. By altering the amino acids and/or the acyl side chains, a variety of analogs could be synthesized easily using our strategy. Therefore, this approach would provide ready access to a range of analogs for the development of antibacterial agents, and this study is underway.

3. Experimental

3.1. General experimental methods

NMR spectra were obtained on a JEOL EX270, JEOL GX270, JEOL AL400, or Bruker ARX-500, and were reported in parts per million (δ) relative to tetramethylsilane (0.00 ppm) as internal standard otherwise noted. Coupling constant (J) was reported in Hertz (Hz). Abbreviations of multiplicity were as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data were presented as follows; chemical shift (multiplicity, integration, coupling constant). Assignment was based on ^{1}H–^{1}H COSY, HMBC and HMQC NMR spectra. Optical rotations were recorded on JASCO DIP-370 digital polarimeter or JASCO P-1030 polarimeter. FAB-MS was obtained on a JEOL JMS-HX101 or JEOL JMS-700TZ. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60F254 plates. Normal-phase column chromatography was performed on Merck silica gel 5715 or Kanto Chemical silica gel 60N (neutral). Flash column chromatography was performed on Merck silica gel 60.

Table 2. Antibacterial activity (% inhibition) against *Mycobacterium tuberculosis* at 6.25 μg/mL

	11a	**11b**	**12a**	**12b**	**15b**	**16a**	**16b**
Mycobacterium tuberculosis	35	48	51	52	29	59	27

3.1.1. Carboxylic acid (7). A mixture of **6**[11] (10 mg, 0.011 mmol), 2,2,2-trichloroacetic acid (18 mg, 0.1 mmol), and 10% $Pd(OH)_2$/C (5 mg) in MeOH (1.5 mL) was vigorously stirred for 1 h under H_2 atmosphere. The catalyst was filtered off through Celite pad, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), to which saturated aqueous $NaHCO_3$ (10 mL) was added. The biphasic mixture was treated with CbzCl (6.3 μL, 0.044 mmol), and the whole mixture was vigorously stirred at room temperature for 30 min. The organic phase was separated, washed with brine, dried (Na_2SO_4), filtrated, and concentrated in vacuo. The residue was purified by silica gel column chromatography (1 × 5, 12% MeOH/$CHCl_3$) to afford **7** (6.9 mg, 79%) as a white foam: $[\alpha]_D^{21}$ +21.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (br d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.38–7.27 (m, 5H, phenyl), 5.74 (br s, 1H, H-1′), 5.65 (br d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.22 (s, 1H, H-1″), 5.16 (d, 1H, benzyl, J = 12.5 Hz), 5.11 (m, 1H, H-2′), 5.02 (d, 1H, benzyl, J = 12.5 Hz), 4.98 (m, 1H, H-3′), 4.90 (m, 1H, H-2″), 4.65 (m, 1H, H-6′), 4.56 (d, 1H, H-3″, $J_{3'',2''}$ = 5.8 Hz), 4.50 (m, 1H, H-5′), 4.18–4.11 (m, 2H, H-4′, H-4″), 3.13 (m, 2H, H-5″a, H-5″b), 1.60 (m, 4H, CH_2CH_3 × 2), 1.49 (s, 3H, acetonide), 1.48 (s, 9H, *tert*-butyl), 1.31 (s, 3H, acetonide), 0.79 (m, 6H, CH_2CH_3 × 2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 166.23, 158.54, 152.00, 138.25, 130.27, 129.68, 129.24, 128.70, 117.36, 115.63, 88.44, 87.87, 83.81, 83.38, 80.50, 57.39, 44.48, 30.53, 29.03, 28.59, 28.17, 27.78, 27.32, 25.78, 8.60, 7.89, 7.55; FABMS-LR (negative) *m*/*z* 789 $(M-H)^-$; FABMS-HR (NBA) calcd for $C_{37}H_{49}N_4O_{15}$ 789.3194, found 789.3194.

3.1.2. *O*-Palmitoyl-L-serylamide (9a). A solution of **7** (44 mg, 0.056 mmol), L-Ser(OBn) (22.4 mg, 0.056 mmol), and HOBt (30.8 mg, 0.17 mmol) in DMF (560 μL) was treated with EDCI (30.8 mg, 0.17 mmol) at room temper-

ature for 12 h. The reaction mixture was partitioned between AcOEt and 0.3 N aqueous HCl, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue in CH_2Cl_2 (1.4 mL) was treated with palmitic acid (28 mg, 0.11 mmol), DMAP (2.8 mg, 0.017 mmol), and EDCI (30.8 mg, 0.17 mmol) at room temperature for 2 h. The reaction mixture was partitioned between AcOEt and 0.3 N aqueous HCl, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2×15 cm, 33–50% AcOEt/hexane) to give **9a** (61.5 mg, 89% in two steps) as a colorless glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.02 (br s, 1H, NH-3), 7.42–7.27 (m, 12H, phenyl, NHCO, H-6), 5.87 (m, 1H, NHCbz), 5.69 (d, 1H, H-5, $J_{5,6} = 8.0$ Hz), 5.68 (s, 1H, H-1′), 5.64 (br s, 1H, NHBoc), 5.24–5.09 (m, 5H, benzyl × 4, H-1″), 4.84 (m, 3H, H-2′, H-3′, H-9′), 4.58 (m, 3H, H-2″, H-3″, H-6′), 4.46 (m, 2H, H-10′a, H-5′), 4.34 (dd, 1H, H-10′b, $J_{10'b,10'a} = 11.4$, $J_{10'b,9'} = 2.9$ Hz), 4.26 (dd, 1H, H-4′, $J_{4',5'} = 4.2$, $J_{4',3'} = 6.4$ Hz), 4.22 (m, 1H, H-4″), 3.32 (m, 1H, H-5″a), 3.07 (m, 1H, H-5″b), 2.14 (m, 2H, H-1‴), 1.62 (m, 2H, CH_2CH$_3$), 1.53 (m, 2H, CH_2CH$_3$), 1.48 (m, 5H, acetonide, H-2‴a, H-2‴b), 1.43 (s, 9H, *tert*-butyl), 1.31 (s, 3H, acetonide), 1.25 (m, 26H, palmitoyl), 0.85 (m, 9H, CH$_2$CH_3 × 2, palmitoyl terminal-Me); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.30, 169.05, 162.71, 156.06, 150.08, 141.88, 136.07, 134.88, 128.59, 128.53, 128.49, 128.35, 128.18, 117.10, 114.78, 110.86, 102.83, 93.58, 86.62, 85.93, 84.06, 81.84, 79.49, 77.76, 67.73, 67.29, 63.44, 55.26, 52.39, 43.39, 33.69, 31.88, 29.65, 29.63, 29.61, 29.60, 29.46, 29.31, 29.25, 29.07, 28.97, 28.36, 27.02, 25.36, 24.65, 22.64, 14.07, 8.32, 7.41; FABMS-LR *m*/*z* 1228 (MNa^+); FABMS-HR (NBA) calcd for $C_{63}H_{91}N_5O_{18}Na$ 1228.6257, found 1228.6255.

3.1.3. *O*-4-Phenylbenzoyl-L-serylamide (9b). Compound **9b** was prepared from **7** (50 mg, 0.063 mmol) and 4-phenylbenzoic acid instead of palmitic acid as described above for the synthesis of **9a**. Purification by silica gel column chromatography (1×15 cm, 33-50% AcOEt/hexane) afforded **9b** (63.6 mg, 87% in two steps) as a colorless glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.18 (br s, 1H, NH-3), 7.92-7.23 (m, 21H, phenyl, H-6, CONH), 5.87 (br s, 1H, CbzNH), 5.65 (d, 1H, H-5, $J_{5,6} = 8.0$ Hz), 5.63 (s, 1H, H-1′), 5.55 (m, 1H, BocNH), 5.28 (d, 1H, benzyl, $J = 12.1$ Hz), 5.23 (s, 1H, H-1″), 5.15 (m, 2H, benzyl × 2), 5.04 (d, 1H, benzyl, $J = 12.2$ Hz), 4.98 (m, 1H, H-9′), 4.85 (m, 2H, H-2′, H-3′), 4.67 (m, 2H, H-10′a, H-10′b), 4.62 (m, 1H, H-6′), 4.55 (m, 1H, H-2″), 4.49 (m, 2H, H-3″, H-5′), 4.27 (m, 1H, H-4′), 4.12 (m, 1H, H-4″), 3.27 (m, 1H, H-5″a), 2.98 (m, 1H, H-5″b), 1.59 (m, 2H, CH_2CH$_3$), 1.47 (m, 2H, CH_2CH$_3$), 1.40 (s, 12H, *tert*-butyl, acetonide), 1.29 (s, 3H, acetonide), 0.79 (m, 6H, CH$_2$CH_3 × 2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.11, 165.78, 162.82, 156.05, 150.09, 146.01, 141.80, 139.79, 136.03, 134.80, 130.17, 128.93, 128.55, 128.47, 128.35, 128.26, 128.12, 127.86, 127.20, 127.06, 117.01, 114.80, 110.98, 102.80, 93.80, 86.56, 85.90, 83.99, 81.79, 80.81, 79.49, 77.67, 67.85, 67.28, 64.19, 55.36, 52.48, 43.32, 29.63, 29.39, 28.91, 28.33, 27.03, 25.36, 8.27, 7.39; FABMS-LR *m*/*z* 1170 (MNa^+); FABMS-HR (NBA) calcd for $C_{60}H_{69}N_5O_{18}Na$ 1170.4536, found 1170.4534.

3.1.4. *O*-Palmitoyl diketopiperazine (11a). A mixture of **9a** (13 mg, 0.011 mmol) and 10% $Pd(OH)_2$/C (5 mg) in MeOH (1 mL) was vigorously stirred for 1 h under H_2 atmosphere. The catalyst was filtered off through Celite pad, and the filtrate was concentrated in vacuo to give the free amino acid **10a**. The amino acid **10a** in CH_2Cl_2 (1 mL) was treated with EDCI (8.6 mg, 0.043 mmol) and HOBt (5.8 mg, 0.043 mmol) at room temperature for 24 h. The reaction mixture was partitioned between AcOEt and 0.3 N aqueous HCl, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was treated with aqueous 80% TFA at room temperature for 1 h. The reaction mixture was concentrated in vacuo, and the residue was purified by C18 reverse phase column chromatography (1×10 cm, 0.5% aqueous TFA–MeOH) to afford **11a** (6.6 mg, 70% in three steps) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.77 (d, 1H, H-6, $J_{6,5} = 8.0$ Hz), 5.74 (s, 1H, H-1′), 5.69 (d, 1H, H-5, $J_{5,6} = 8.0$ Hz), 5.29 (s, 1H, H-1″), 4.42–4.16 (m, 8H, H-2′, H-3′, H-4′, H-5′, H-6′, H-9′, H-12′a, H-12′b), 4.02 (m, 2H, H-3″, H-4″), 3.94 (m, 1H, H-2″), 3.18 (m, 2H, H-5″a, H-5″b), 2.42 (m, 2H, $COCH_2$), 1.56 (m, 2H, $COCH_2CH_2$), 1.31 (m, 24H, palmitoyl), 0.91 (m, 3H, palmitoyl terminal-Me); ^{13}C NMR (CD_3OD, 125 MHz) δ 175.08, 167.59, 167.24, 166.16, 151.96, 109.93, 102.59, 93.91, 83.87, 80.63, 79.82, 76.13, 74.88, 73.70, 71.14, 66.58, 57.41, 55.57, 43.96, 34.77, 33.06, 30.79, 30.75, 30.64, 30.52, 30.46, 30.22, 25.87, 23.72, 14.42; FABMS-LR *m*/*z* 756 (MH^+); FABMS-HR (NBA) calcd for $C_{35}H_{58}N_5O_{13}$ 756.4031, found 756.4037.

3.1.5. *O*-4-Phenylbenzoyl diketopiperazine (11b). Compound **11b** was prepared from **9b** (41 mg, 0.036 mmol) as described above for the synthesis of **11a**. Purification by C18 reverse phase column chromatography (1×10 cm, 0.5% aqueous TFA–MeOH) afforded **11b** (9.4 mg, 84% in three steps) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 8.15 (d, 2H, *o*-phenyl, $J = 8.4$ Hz), 7.78 (d, 2H, *m*-phenyl, $J = 8.4$ Hz), 7.73 (d, 1H, H-6, $J_{6,5} = 8.1$ Hz), 7.68 (d, 2H, *o*-phenyl, $J = 7.4$ Hz), 7.46 (t, 2H, *m*-phenyl, $J = 7.4$ Hz), 7.39 (t, 1H, *p*-phenyl, $J = 7.4$ Hz), 5.77 (d, 1H, H-1′, $J_{1',2'} = 2.6$ Hz), 5.67 (d, 1H, H-5, $J_{5,6} = 8.1$ Hz), 5.00 (d, 1H, H-1″, $J_{1'',2''} = 2.0$ Hz), 4.84 (m, 1H, H-12′a), 4.60 (dd, 1H, H-12′b, $J_{12'b,9'} = 3.7$, $J_{12'b,12'a} = 11.2$ Hz), 4.46 (m, 1H, H-9′), 4.41 (d, 1H, H-6′, $J_{6',5'} = 5.7$ Hz), 4.32 (dd, 1H, H-4′, $J_{4',5'} = 4.6$, $J_{4',3'} = 7.5$ Hz), 4.20 (m, 2H, H-5′, H-2′), 4.10 (dd, 1H, H-3′, $J_{3',2'} = 5.7$, $J_{3',4'} = 7.5$ Hz), 4.00–3.95 (m, 3H, H-2″, H-3″, H-4″), 3.21 (m, 2H, H-5″a, H-5″b); FABMS-LR *m*/*z* 698 (MH^+); FABMS-HR (NBA) calcd for $C_{32}H_{36}N_5O_{13}$ 698.2310, found 698.2304.

3.1.6. *O*-Palmitoyl-L-serylamide (12a). A mixture of **9a** (25 mg, 0.021 mmol) and 10% $Pd(OH)_2$/C (15 mg) in MeOH (1 mL) was vigorously stirred under H_2 atmosphere for 1 h. The catalyst was filtered off through Celite pad, and the filtrate was concentrated in vacuo. The

residue was treated with aqueous 80% TFA (1 mL) at room temperature for 50 min. The solution was concentrated in vacuo, and the residue was purified by C18 reverse phase column chromatography (1 × 10 cm, 0.5% aqueous TFA–MeOH) to afford **11a** (18.7 mg, 90% in two steps) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.68 (d, 1H, H-6, $J_{6,5}$ = 8.3 Hz), 5.81 (s, 1H, H-1′), 5.73 (d, 1H, H-5, $J_{5,6}$ = 8.3 Hz), 5.16 (s, 1H, H-1″), 4.61 (m, 1H, H-10′a), 4.51 (m, 1 H, H-3′), 4.42 (m, 1 H, H-3″), 4.37 (m, 1 H, H-10′b), 4.32 (m, 1 H, H-9′), 4.27 (m, 1 H, H-6′), 4.24 (m, 1 H, H-5′), 4.19 (m, 1 H, H-2′), 4.04 (m, 3 H, H-4′, H-2″, H-4″), 3.18 (m, 2 H, H-5″a, H-5″b), 2.32 (t, 2 H, $COCH_2$, J = 9.2 Hz), 1.59 (m, 2H, $COCH_2CH_2$), 1.28 (m, 24H, palmitoyl), 0.89 (m, 3H, palmitoyl terminal-Me); ^{13}C NMR (CD_3OD, 125 MHz) δ 175.05, 173.63, 172.43, 168.43, 165.90, 155.01, 151.93, 142.50, 111.37, 111.24, 102.86, 93.23, 91.98, 85.48, 84.82, 81.02, 78.52, 78.27, 76.45, 76.36, 74.61, 73.48, 73.07, 73.00, 72.73, 71.15, 70.46, 65.16, 62.23, 56.36, 55.19, 43.46, 38.99, 34.84, 33.10, 31.87, 30.83, 30.79, 30.66, 30.50, 30.28, 25.93, 23.77, 14.49; FABMS-LR *m*/*z* 774 (MH^+); FABMS-HR (NBA) calcd for $C_{35}H_{60}N_5O_{14}$ 774.4137, found 774.4128.

3.1.7. *O*-4-Phenylbenzoyl-L-serylamide (12b). Compound **12b** was prepared from **9b** (23 mg, 0.020 mmol) as described above for the synthesis of **12a**. Purification by C18 reverse phase column chromatography (1 × 10 cm, 0.5% aqueous TFA–MeOH) afforded **12b** (18.0 mg, 96% in two steps) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 8.10 (d, 2H, *o*-phenyl, J = 8.3 Hz), 7.72 (d, 2H, *m*-phenyl, J = 8.3 Hz), 7.66 (m, 3H, *o*′-phenyl, H-6, J = 7.3, $J_{6,5}$ = 8.1 Hz), 7.47 (t, 2H, *m*′-phenyl, J = 7.2 Hz), 7.39 (t, 1H, *p*′-phenyl, J = 7.2 Hz), 5.80 (d, 1H, H-1′, $J_{1',2'} = 3.0$ Hz), 5.77 (d, 1H, H-5, $J_{5,6}$ = 8.1 Hz), 5.18 (s, 1H, H-1″), 4.78 (m, 1H, H-9′), 4.71 (dd, 1H, H-10′a, $J_{10'a,10'b} = 11.7$, $J_{10',9'} = 2.0$ Hz), 4.63 (dd, 1H, H-10′b, $J_{10'b,10'a} = 11.7$, $J_{10'b,9'} = 5.6$ Hz), 4.55 (m, 1H, H-6′), 4.34 (m, 1H, H-5′), 4.26–4.21 (m, 2H, H-3′, H-4′), 4.19 (dd, 1H, H-2′, $J_{2',1'} = 3.0$, $J_{2',3'} = 7.6$ Hz), 4.07 (m, 3H, H-2′, H-3″, H-4″), 3.20 (m, 2H, H-5″a, H-5″b); ^{13}C NMR (CD_3OD, 125 MHz) δ 168.72, 167.7, 166.69, 152.13, 147.54, 141.11, 131.48, 130.21, 129.79, 129.53, 128.32, 128.20, 111.57, 103.06, 93.51, 85.71, 81.26, 78.45, 76.58, 74.80, 73.71, 73.26, 70.67, 66.12, 62.45, 56.57, 43.75; FABMS-LR *m*/*z* 716 (MH^+); FABMS-HR (NBA) calcd for $C_{32}H_{38}N_5O_{14}$ 716.2416, found 716.2404.

3.1.8. L-Serylamide (13). A solution of **7** (16 mg, 0.02 mmol), L-Ser(Bn) (8 mg, 0.02 mmol), and HOBt (11 mg, 0.06 mmol) in DMF (200 μL) was treated with EDCI (11 mg, 0.06 mmol) at room temperature for 12 h. The reaction mixture was partitioned between AcOEt and 0.3 N aqueous HCl, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was treated with 80% aqueous TFA (1 mL) at room temperature for 30 min. The mixture was concentrated in vacuo, and the residue was purified by C18 reverse phase column chromatography (1 × 10 cm, 0.5% aqueous TFA–MeOH) to afford **13** (8.8 mg, 68% in three steps) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.68 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.80 (s, 1H, H-1′), 5.72 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.16 (s, 1H, H-1″), 4.48 (m, 2H, H-3′, H-6′), 4.35 (m, 1H, H-3″), 4.31–4.23 (m, 2H, H-10′a, H-10′b), 4.19 (m, 1H, H-2′), 4.06 (m, 3H, H-2″, H-4″, H-9′), 3.89 (m, 1H, H-4′), 3.20 (m, 2H, H-5″a, H-5″b); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.45, 168.36, 165.91, 154.97, 151.90, 142.46, 111.53, 111.40, 102.76, 93.00, 91.82, 84.93, 84.41, 80.92, 78.65, 78.44, 76.38, 76.22, 74.50, 73.35, 72.75, 71.02, 70.31, 62.81, 62.09, 57.36, 56.04, 43.20, 38.80, 31.68; FABMS-LR (negative) *m*/*z* 534 $(M-H)^-$; FABMS-HR (NBA) calcd for $C_{19}H_{28}N_5O_{13}$ 534.1684, found 534.1680.

3.1.9. *O*-Palmitoyl-D-serylamide (14a). Compound **14a** was prepared from **7** (53 mg, 0.10 mmol) as described above for the synthesis of **9a**. Purification by silica gel column chromatography (1 × 10 cm, 33–50% AcOEt/hexane) afforded **14a** (15.6 mg, 65% in two steps) as a colorless glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.98 (br s, 1H, NH-3), 7.36–7.33 (m, 11H, phenyl, NHCO), 7.25 (d, 1H, H-6, $J_{6,5}$ = 8.2 Hz), 5.76 (br s, 1H, NHCbz), 5.70 (d, 1H, H-5, $J_{5,6}$ = 8.2 Hz), 5.66 (br s, 1H, NHBoc), 5.60 (br s, 1H, H-1′), 5.26-5.07 (m, 5H, benzyl × 4, H-1″), 4.90 (m, 1H, H-9′), 4.86 (m, 2H, H-2′, H-3′), 4.57–4.45 (m, 5H, H-10′a, H-10′b, H-2″, H-3″, H-6′), 4.35 (m, 1H, H-5′), 4.18 (m, 2H, H-4″, H-4′), 3.30 (m, 1H, H-5″a), 2.91 (m, 1H, H-5″b), 2.15 (m, 2H, H-1‴), 1.62 (m, 4H, CH_2CH_3 × 2), 1.52 (m, 2H, H-2‴a, H-2‴b), 1.50 (s, 3H, acetonide), 1.48 (s, 9H, *tert*-butyl), 1.30 (s, 3H, acetonide), 1.25 (m, 26H, palmitoyl), 0.89–0.79 (m, 9H, CH_2CH_3 × 2, palmitoyl terminal-Me); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.07, 173.64, 169.37, 163.05, 156.39, 150.28, 142.30, 136.92, 135.19, 128.88, 128.83, 128.77, 128.58, 117.12, 115.05, 110.09, 103.08, 87.38, 86.36, 84.23, 82.28, 79.78, 68.03, 67.67, 63.49, 55.70, 52.56, 43.73, 34.07, 33.98, 32.15, 29.92, 29.88, 29.83, 29.75, 29.69, 29.58, 29.52, 29.49, 29.35, 28.65, 27.26, 25.00, 24.90, 22.91, 14.33, 8.57, 7.62; FABMS-LR *m*/*z* 1228 (MNa^+); FABMS-HR (NBA) calcd for $C_{63}H_{91}N_5O_{18}Na$ 1228.6257, found 1228.6255.

3.1.10. *O*-4-Phenylbenzoyl-D-serylamide (14b). Compound **14b** was prepared from **7** (28 mg, 0.035 mmol) and 4-phenylbenzoic acid instead of palmitic acid as described above for the synthesis of **9a**. Purification by silica gel column chromatography (1 × 15 cm, 33–50% AcOEt/hexane) afforded **14b** (36.8 mg, 91% in two steps) as a colorless glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.58 (br s, 1H, NH-3), 7.96–7.22 (m, 20H, phenyl, H-6), 7.02 (m, 1H, NHCO), 5.80 (m, 1H, NHCbz), 5.79 (m, 1H, NHBoc), 5.54 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.28 (m, 2H, benzyl × 2), 5.24 (s, 1H, H-1′), 5.20 (s, 1H, H-1″), 5.35 (d, 1H, benzyl, J = 15 Hz), 5.05 (d, 1H, benzyl, J = 15 Hz), 4.99 (m, 1H, H-9′), 4.86 (m, 1H, H-2′), 4.82 (m, 2H, H-6′, H-2″), 4.52 (m, 2H, H-3″, H-5′), 4.22 (m, 1H, H-4′), 4.11 (m, 1H, H-4″), 3.38 (m, 1H, H-5″a), 2.96 (m, 1H, H-5″b), 1.57 (m, 2H, CH_2CH_3), 1.44 (m, 14H, *tert*-butyl, CH_2CH_3, acetonide), 1.27 (s, 3H, acetonide), 0.80 (m, 6H, CH_2CH_3 × 2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.19, 165.66, 165.58, 156.08, 149.70, 145.86, 142.83, 139.62, 136.51, 134.81, 130.29,

128.98, 128.58, 128.53, 128.47, 128.33, 128.13, 127.92, 127.15, 127.01, 116.82, 114.78, 102.66, 87.13, 86.11, 83.94, 82.04, 67.95, 67.30, 63.96, 55.46, 52.39, 29.47, 28.91, 28.39, 26.99, 25.27, 8.29, 7.32; FABMS-LR *m/z* 1170 (MNa^+); FABMS-HR (NBA) calcd for $C_{60}H_{69}N_5O_{18}Na$ 1170.4535, found 1170.4531.

3.1.11. *O*-4-Phenylbenzoyl diketopiperazine (15b). Compound **15b** was prepared from **14b** (13 mg, 0.012 mmol) as described above for the synthesis of **11a**. Purification by C18 reverse phase column chromatography (1 × 10 cm, 0.5% aqueous TFA–MeOH) afforded **15b** (3.7 mg, 43% in three steps) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 8.05 (d, 2H, *o*-phenyl, J = 8.2 Hz), 7.73 (d, 2H, *m*-phenyl, J = 8.2 Hz), 7.66 (m, 3H, *o*-phenyl, H-6), 7.46 (t, 2H, *m*-phenyl, J = 7.3 Hz), 7.39 (t, 1H, *p*-phenyl, J = 7.3 Hz), 5.72 (s, 1H, H-1′), 5.69 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.35 (s, 1H, H-1″), 4.74 (dd, 1H, H-12′a, $J_{12'a,12'b} = 11.6$, $J_{12'a,9'} = 3.0$ Hz), 4.67 (dd, 1H, H-12′b, $J_{12'b,12'a} = 11.6$, $J_{12'b,9'} = 2.7$ Hz), 4.47 (m, 2H, H-6′, H-9′), 4.38 (m, 1H, H-4′), 4.21 (m, 3H, H-5′, H-2′, H-3′), 4.07 (m, 1H, H-4″), 4.00 (m, 1H, H-2″), 3.95 (m, 1H, H-3″), 3.24 (m, 1H, H-5″a), 3.16 (m, 1H, H-5″b); FABMS-LR *m/z* 698 (MH^+); FABMS-HR (NBA) calcd for $C_{32}H_{36}N_5O_{13}$ 698.2309, found 698.2324.

3.1.12. *O*-Palmitoyl-D-serylamide (16a). Compound **16a** was prepared from **14a** (26 mg, 0.022 mmol) as described above for the synthesis of **12a**. Purification by C18 reverse phase column chromatography (1 × 10 cm, 0.5% aqueous TFA–MeOH) afforded **13a** (13.7 mg, 64% in two steps) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.62 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz), 5.74 (d, 1H, H-1′, $J_{1',2'} = 1.9$ Hz), 5.73 (d, 1H, H-5, $J_{5,6}$ = 8.1 Hz), 5.33 (s, 1H, H-1″), 4.52 (m, 2H, H-10′, H-6′), 4.40 (m, 2H, H-10′b, H-9′), 4.17 (dd, 1H, H-2′, $J_{2',1'} = 1.9$, $J_{2',3'} = 5.5$ Hz), 4.13 (m, 1H, H-5′), 4.07 (m, 2H, H-3′, H-3″), 4.01 (dd, 1H, H-2″, $J_{2'',1''} = 2.2$, $J_{2'',3''} = 7.8$ *Hz*), 3.98 (m, 1H, H-4″), 3.68 (m, 1H, H-4′), 3.15 (dd, 1H, H-5″a, $J_{5''a,5''b} = 13.3$, $J_{5''a,4''} = 3.2$ Hz), 2.96 (dd, 1H, H-5″b, $J_{5''b,5''a} = 13.3$, $J_{5''b,4''} = 5.9$ Hz), 2.32 (t, 2H, $COCH_2$, J = 7.5 Hz), 1.61 (m, 2H, $COCH_2CH_2$), 1.27 (m, 24 H, palmitoyl), 0.89 (m, 3H, palmitoyl terminal-Me); ^{13}C NMR (CD_3OD, 125 MHz) δ 175.31, 175.34, 169.01, 165.89, 151.90, 142.55, 112.24, 112.19, 102.77, 93.33, 92.12, 85.28, 81.31, 79.46, 76.61, 76.48, 74.62, 73.49, 72.87, 72.79, 71.06, 70.37, 65.18, 62.24, 56.76, 55.10, 43.06, 34.92, 33.10, 31.87, 30.83, 30.80, 30.69, 30.51, 30.29, 26.00, 23.78, 14.49; FABMS-LR *m/z* 774 (MH^+); FABMS-HR (NBA) calcd for $C_{35}H_{60}N_5O_{14}$ 774.4136, found 774.4144.

3.1.13. *O*-4-Phenylbenzoyl-D-serylamide (16b). Compound **16b** was prepared from **14b** (17 mg, 0.015 mmol) as described above for the synthesis of **12a**. Purification by C18 reverse phase column chromatography (1 × 10 cm, 0.5% aqueous TFA–MeOH) afforded **16b** (11.7 mg, 80% in two steps) as a TFA salt: ^{1}H NMR (CD_3OD, 500 MHz) δ 8.13 (d, 2H, *o*-phenyl, J = 8.4 Hz), 7.75 (d, 2H, *m*-phenyl, J = 8.4 Hz), 7.67 (d, 2H, *o*′-phenyl, J = 7.4 Hz), 7.65 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz), 7.46 (t, 2H, *m*′-phenyl, J = 7.4 Hz), 7.39 (t, 1H, *p*′-phenyl, J = 7.4 Hz), 5.75 (s, 1H, H-1′), 5.69 (d, 1H, H-5, $J_{5,6}$ = 8.1 Hz), 5.03 (s, 1H, H-1″), 4.82 (m, 1H, H-9′), 4.74 (dd, 1H, H-10′a, $J_{10'a,9'} = 3.8$, $J_{10'a,10'b} = 11.4$ Hz), 4.69 (dd, 1H, H-10′b, $J_{10'b,10'a} = 11.4$, $J_{10'b,9'} = 6.1$ Hz), 4.36 (m, 2H, H-5′, H-6′), 4.23 (m, 2H, H-3′, H-4′), 4.16 (m, 1H, H-2′), 4.05 (m, 3H, H-2′, H-3″, H-4″), 3.15 (m, 2H, H-5″a, H-5″b); ^{13}C NMR (CD_3OD, 125 MHz) δ 175.05, 173.63, 172.43, 168.43, 165.90, 155.01, 151.93, 142.50, 111.37, 111.24, 102.86, 93.23, 91.98, 85.48, 84.82, 81.02, 78.52, 78.27, 76.45, 76.36, 74.61, 73.48, 73.07, 73.00, 72.73, 71.15, 70.46, 65.16, 62.23, 56.36, 55.19, 43.46, 38.99, 34.84, 33.10, 31.87, 30.83, 30.79, 30.66, 30.50, 30.28, 25.93, 23.77, 14.49; FABMS-LR *m/z* 716 (MH^+); FABMS-HR (NBA) calcd for $C_{32}H_{38}N_5O_{14}$ 716.2415, found 716.2411.

3.2. Antibacterial activity and determination of minimum inhibitory concentration (MIC)

The minimum inhibitory concentrations (MIC) of synthesized compounds were examined by serial agar dilution method using Muller–Hinton (MH) agar (Difco) containing 5% sheep blood for *Enterococcus faecalis*, MH agar containing 5% glycerol for *M. smegmatis*, and MH agar for other bacteria. The MIC was observed after 18 hours incubation at 37 °C in 5% CO_2 for *E. faecalis*, 42 h incubation at 37 °C for *M. smegmatis*, and 18 h incubation at 37 °C for other bacteria.

3.3. Antibacterial activity against *M. tuberculosis*

The initial screen is conducted against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using the microplate Alamar blue assay (MABA). Compounds are tested in 10 twofold dilutions, usually from 100 to 0.19 μg/mL. Compounds exhibiting autofluorescence are sent for testing in an alternative assay at the University of Illinois at Chicago.

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