

Solution-Phase Synthesis of a Library of Carbapeptide Analogues Based on Glycosylamino Acid Scaffolds and Their In Silico Screening and Antimicrobial Evaluation

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A well-organized and efficient approach toward the solution phase synthesis of a library of carbapeptide analogues based on glycosyl amino ester scaffold is described. The reported synthetic route involves a five step preparation of heptofuranuronamides **6a–h** and octopyranuronamide **7e** from glycosyl amino esters **1** and **7**, respectively. Coupling of glycosyl amino esters **1** or **7** with three different *N*-Fmoc protected amino acids afford the *N*-Fmoc protected intermediates **2a–c** and **7a**. Deprotection of Fmoc group in **2a–c** and **7a** with piperidine gave respective compounds **3a–c** and **7b** with free amine. Subsequent coupling of **3a–c** and **7b** with different aromatic acids furnishes respective heptofuranuronates **4a–h** and octopyranuronate **7c** in good yields. The latter, on ester hydrolysis by LiOH gave the corresponding glycopeptide analogues **5a–h** and **7d** with terminal carboxyl group. The carboxyl group in these compounds was amidated with oxalyl chloride/NH₄OH to afford heptofuranuronamides **6a–h** and octopyranuronamides **7e**. In vitro screening of all compounds displayed moderate antifungal, antitubercular, and general antibacterial activities. Reverse docking calculations involving over 841 protein drug targets have identified two potential targets for these compounds. These results will form the basis for synthesizing second-generation antimicrobial compounds.

Introduction

Naturally occurring glycosylated peptides play an important role in various biological processes and are therefore relevant lead molecules for the preparation of new drugs.¹ The ubiquitous nature of glycopeptides reflects their broad functions as biomarkers in intra- and intercellular communication events. The latter, in turn regulate many biological and pathological processes such as cell-cell recognition, fertilization, bacterial/viral infections,² inflammation,^{3,4} host immune responses,^{5–7} and tumor metastasis. Carbohydrates represent an attractive source of readily available, stereochemically defined, highly functionalized synthetic scaffolds, which if modified can demonstrate interesting properties.^{8–11} The molecular diversity of carbohydrates offers a valuable tool for drug discovery in the areas of biologically important glycoconjugates, and molecular scaffolds by investigating their structural and functional impact. Monosaccharides also provide rigid molecular systems (privileged structures), which can be used as molecular templates to display pharmacophoric groups in well defined spatial orientations. Therefore, in general glycosylation of

peptide not only affects its pharmacological parameters including the rate of circulation,¹² solubility,¹³ and immunogenicity, it also plays a vital role in the biological functions of peptides by modulating their folding and stability and serving as a recognition signal in cell–cell, cell matrix, and cell–pathogen interactions.^{5,14–16} The synthesis of glycopeptides is challenging because of the polyfunctionality of the target molecules. There are several reports toward the chemical synthesis of these complex natural structures^{17,18} and their unnatural analogues, generally defined as neoglycopeptides.^{19,20} A search for new, more stable glycopeptide mimics led to the development of *C*-linked isosteres,²¹ providing excellent chemical and enzymatic stability without negatively influencing the biological properties.²² Recently we have initiated a program on development of new antitubercular agents based on glycosyl amino acids.²³ These compounds were designed keeping in mind the roles of two enzymes D-alanine racemase and D-alanyl-alanine synthetase participating in initial steps in the biosynthesis of pentapeptide of mycobacterial cell wall.^{24–26} Several compounds based on simple amino acids and dipeptides were developed but were never advanced into clinical use due to their toxicity in humans.²⁷ We have also used glycosyl amino acids as scaffolds for solid phase combinatorial synthesis of a small library of glycoconjugates as potent inhibitors of filarial DNA topoisomerase-II.²⁸ These glycoconjugates have also dis-

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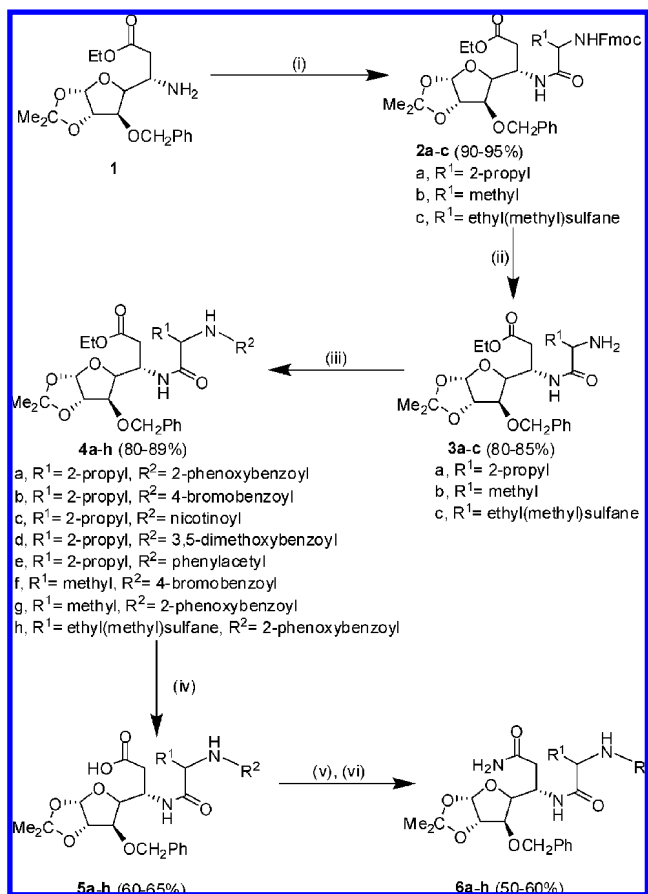
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played interesting antitubercular activities *in vitro* against sensitive and MDR strains of *Mycobacterium tuberculosis* H37 Rv in preliminary screening.²⁹ However, the solid phase synthesis of glycopeptide analogues afforded very small quantity with only 70–80% purity of the final compounds. The full characterization and detailed bioevaluations necessitated a larger quantity of pure compounds. Therefore, we have developed a solution phase synthesis of pure carbapetide analogues in quantities sufficient for detailed biological evaluations against several strains of bacteria and fungi. The compounds were tested in various *in vitro* screening models and were found to display moderate antifungal, antitubercular, and general antibacterial activities. Reverse docking calculations involving over 841 protein drug targets suggest that binding to Penicillopepsin results in the observed antifungal activity. Observed antibacterial activities apparently arise largely from the binding to ATP/NAD binding sites of DNA helicase and gyrase. The compounds are suggested to also bind to lysA and dihydropicolinate reductase, which results in the observed antitubercular activities.

Results and Discussion

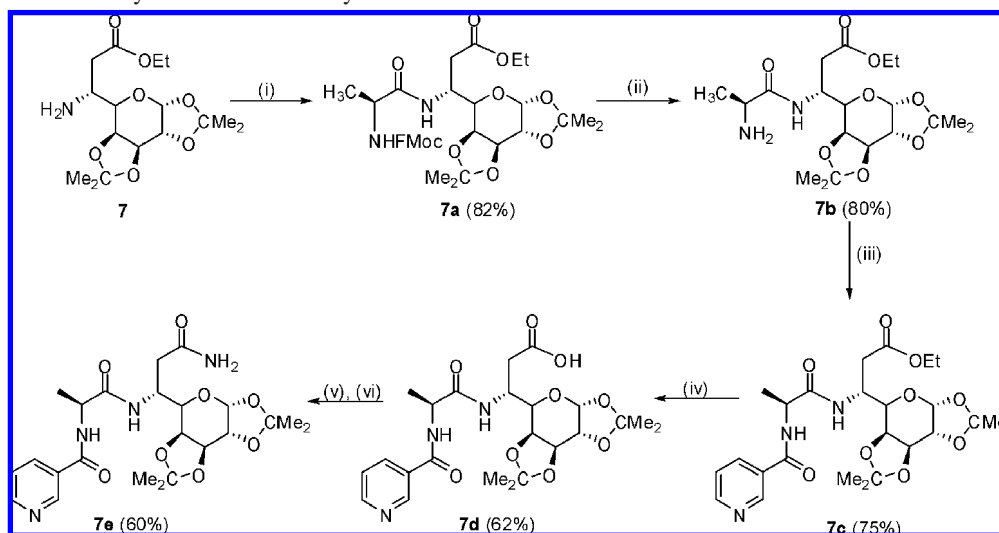
Our objective was to develop simple, cost-effective, and efficient chemical routes for solution-phase synthesis of a library of carbapetide analogues characterized by assembling a glycosyl- β -amino ester, natural amino acid, and aromatic acid connected via carboxamide linkages. The starting glycosyl- β -amino ester, that is, ethyl-5-amino-5,6-dideoxy-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronate (**1**)^{30a} and ethyl-6-amino-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene- β -L-*glycero*-D-*galacto*-octopyranuronate (**7**)^{30b} scaffolds were synthesized and characterized in our laboratory earlier. In a pilot experiment, coupling of Fmoc valine with the above amino ester **1**, using 1-hydroxybenzotriazole (HOBT), 4-dimethylamino pyridine (DMAP), and diisopropylcarbodiimide (DIC) as coupling reagents in anhydrous CH₂Cl₂ under N₂ atmosphere for 5 h at 0 °C led to the formation of ethyl-5,6-dideoxy-5-[*N*-{*N*-(Fmoc)-L-valin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronate (**2a**), respectively, in good yield. Considering the lability of the Fmoc group toward bases, we employed piperidine as base for deprotection of Fmoc group in **2a** to give the free amine derivative **3a**. The latter undergoes coupling with 2-phenoxybenzoic acid using the above coupling reagent to give ethyl-5,6-dideoxy-5-[*N*-{*N*-(2-phenoxybenzoyl)-L-valin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronate (**4a**) in good yield. The ester group in compound **4a** was hydrolyzed with aq. LiOH in THF to give respective acid ethyl-5,6-dideoxy-5-[*N*-{*N*-(2-phenoxybenzoyl)-L-valin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronic acid (**5a**) in moderate yield. The final step of synthesis was accomplished by reacting the amino acid derivative **5a** with oxalyl chloride, followed by the treatment of aq. NH₄OH to yield the respective ethyl-5,6-dideoxy-5-[*N*-{*N*-(2-phenoxybenzoyl)-L-valin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuramide (**6a**) (Scheme 1) in good yield. Similarly, we obtained ethyl-5,6-dideoxy-5-[*N*-{*N*-(4-bromobenzoyl)-L-valin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-iso-

Scheme 1. Solution-Phase Synthesis of Glycosyl Carboxamide Derivatives^a



^a Reagents and conditions: (i) R¹CH(NH-Fmoc)COOH, DIC, HOBT, DMAP, CH₂Cl₂, N₂ atm, 3–5 h, 0 °C; (ii) 10% piperidine in CH₃CN; (iii) R²COOH, DIC, HOBT, DMAP, CH₂Cl₂, N₂ atm, 3–5 h, 0 °C; (iv) LiOH·H₂O, H₂O/THF 1:1, 25 °C; (v) oxalyl chloride, THF, 0 °C, 2 h; (vi) NH₄OH solution, 0 °C, 2–4 h.

propylidene- β -L-*ido*-heptofuranuronamide (**6b**), ethyl-5,6-dideoxy-5-[*N*-{*N*-(nicotinoyl)-L-valin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronamide (**6c**), ethyl-5,6-dideoxy-5-[*N*-{*N*-(3,5-dimethoxybenzoyl)-L-valin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronamide (**6d**), ethyl-5,6-dideoxy-5-[*N*-{*N*-(phenylethanoyl)-L-valin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronamide (**6e**), ethyl-5,6-dideoxy-5-[*N*-{*N*-(4-bromobenzoyl)-L-alanin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronamide (**6f**), ethyl-5,6-dideoxy-5-[*N*-{*N*-(2-phenoxybenzoyl)-L-alanin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronamide (**6g**), ethyl-5,6-dideoxy-5-[*N*-{*N*-(2-phenoxybenzoyl)-L-methionin-1-yl}]amino-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronamide (**6h**) starting from ethyl-5-amino-5,6-dideoxy-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-*ido*-heptofuranuronate (**1**) (Scheme 1) and ethyl-6,7-dideoxy-6-[*N*-{*N*-(nicotinoyl)-L-alanin-1-yl}]amino-1,2:3,4-di-*O*-isopropylidene- β -L-*glycero*-D-*galacto*-octopyranuronamide (**7e**) from ethyl-6-amino-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene- β -L-*glycero*-D-*galacto*-octopyranuronate (**7**) (Scheme 2) by using different amino acid and aromatic acid. Purification of all the compounds was carried out by column chromatography over SiO₂ (200–440 mesh). To evaluate the potential of this methodology, two different glycosyl- β -amino

Scheme 2. Solution-Phase Synthesis of Galactosyl Carboxamide Derivatives^a

^a Reagents and conditions: (i) CH₃CH(NHFmoc)COOH, DIC, HOBt, DMAP, CH₂Cl₂, N₂ atm, 3–5 h, 0 °C; (ii) 10% piperidine in CH₃CN; (iii) C₆H₄NCOOH, DIC, HOBt, DMAP, CH₂Cl₂, N₂ atm, 3–5 h, 0 °C; (iv) LiOH·H₂O, H₂O/THF 1:1, 25 °C; (v) oxalyl chloride, THF, 0 °C, 2 h; (vi) NH₄OH solution, 0 °C, 2–4 h.

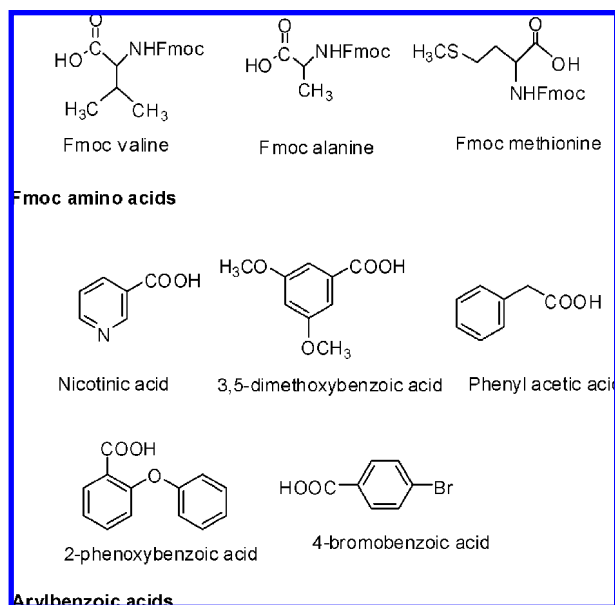


Figure 1. Different amino acids and aromatic acids used.

ester scaffolds with furanose and pyranose rings, three different Fmoc amino acids and five different aromatic acids (Figure 1) have been successfully used for library generation (Figure 2).

All of the above compounds were evaluated in vitro against different strains of bacteria and fungi including *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Candida albicans*, *Cryptococcus neoformans*, *Sporothrix schenckii*, *Trichophyton mentagrophytes*, *Aspergillus fumigatus*, *Candida parapsilosis*, and *M. tuberculosis H37 Rv*. While compounds **3a**, **3c**, **4g**, **5a**, **5b**, **5g**, **6a**, **6g**, **6h**, and **7h** displayed moderate inhibition with MIC 50 µg/mL against *Trichophyton mentagrophytes*, compounds **4g**, **5b**, **5f**, **5g**, and **6h** displayed MIC 50 µg/mL against *Pseudomonas aeruginosa*. However, only three compounds (**6c**, **6d** and **6e**) displayed moderate antitubercular activity with MIC 12.5 µg/mL. The in vitro activity against different strains of bacteria, fungi, and *M. tuberculosis*

indicate their nonspecificity toward *M. tuberculosis* and also that they are acting through different mode of action. The latter is substantiated by in silico screening involving the reverse docking approach with about 841 protein targets implemented in the potential drug target database.³¹ The evaluation suggests that the compounds should exhibit good binding with Penicillopepsin which is a member of the aspartic proteinase family of enzymes and plays an important role in common fungal infections,³² such as candidiasis. The antifungal activities of the compounds may also be corroborated as *Trichophyton rubrum*, *T. mentagrophytes*, and many other fungal strains secrete proteases like Penicillopepsin.³³ Two targets, the lysA gene and dihydropicolinate reductase³⁴ of *M. tuberculosis* both a part of the lysine biosynthetic pathway and absent in humans, were suggested for antitubercular activities in in silico screening studies. The calculations also suggest that the general antibacterial activities of the compounds can be ascribed to the binding of the compounds to the ATP/NAD binding sites of DNA helicase, DNA gyrase and aspartate semialdehyde dehydrogenase all from bacterial sources.

In terms of structure activity relationship, generally presence of an aromatic ring as R² substituent in compounds **4a–h**, **5a–h**, and **6a–h** (Scheme 1) renders the antibacterial activity, while replacement of methyl group with isopropyl moiety as R¹ substituent result in loss of antibacterial activity.

Conclusion

We have developed an efficient and simple approach for the solution phase synthesis of glycopeptide analogues with carboxyl and carboxamide terminal groups using DIC, HOBt and DMAP as coupling reagents. The glycoconjugates were obtained in good yield and high purity. The compounds were screened in vitro against different strains of bacteria, *M. tuberculosis* H37 Rv, and fungi. Few of the compounds displayed moderate inhibitory activities against the pathogens. The reverse docking approach of in silico screening with these compounds on various targets revealed the

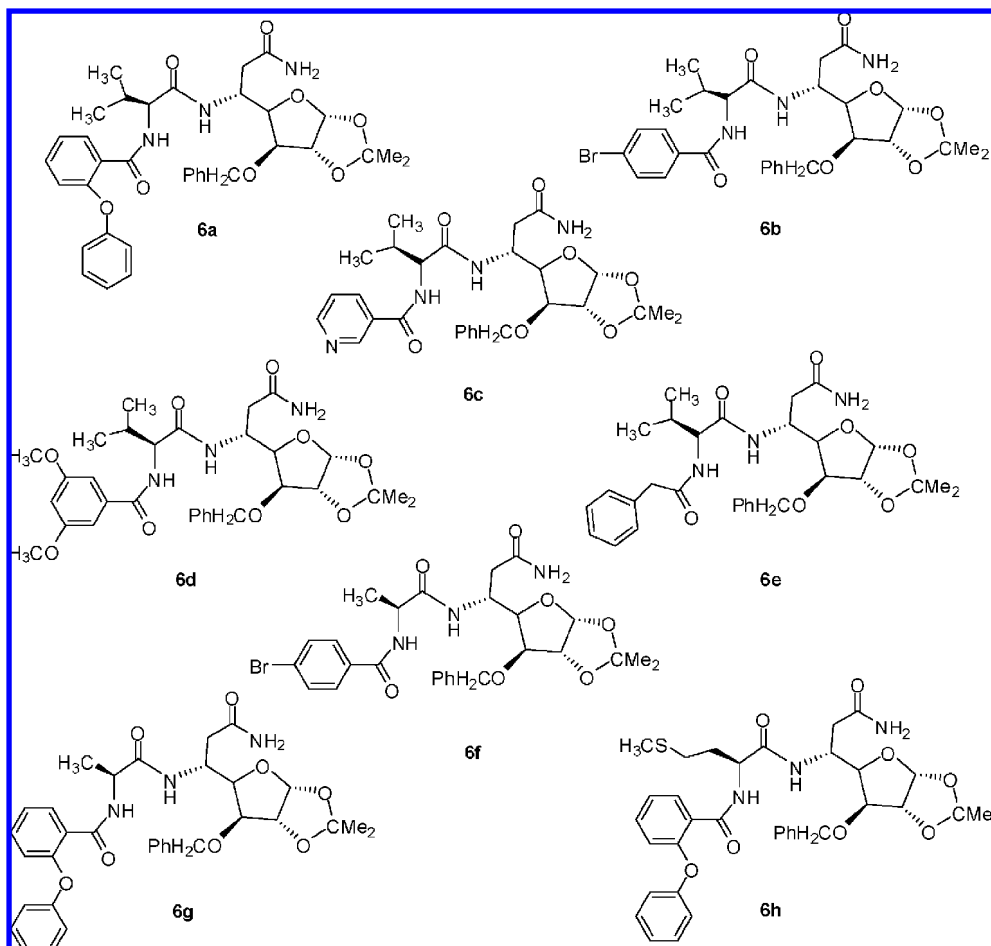


Figure 2. Library of carbapeptide analogues 6a–h.

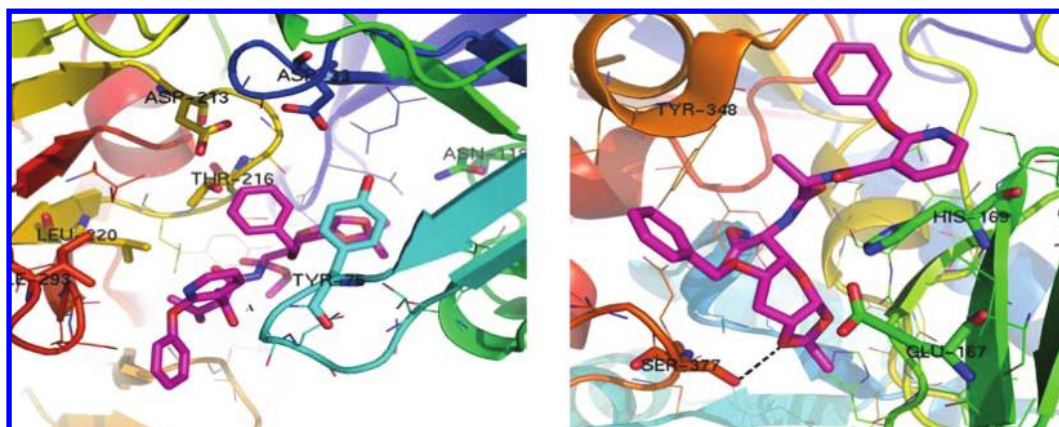


Figure 3. Interactions of compound 6g with (left panel) Penicillopepsin from *Penicillium janthinellum* and (right panel) dihydropicolinate reductase from *Mycobacterium tuberculosis*. The hydrogen bonding interactions are marked and interacting residues are labeled for clarity.

probable targets for these glycoconjugates. These findings encourage us to generate a number of compounds to establish inhibition pathways and find out structure–activity relationships (SARs).

Experimental Section

General. Commercially available reagent grade chemicals were used as received. TLC was carried out with E. Merck Kieselgel 60 F₂₅₄. Spots were visualized under UV light or visualized by spraying with a 20% aq. KMnO₄ or with an ethanolic H₂SO₄, followed by heating at 120 °C

for 5 min. Column chromatography was performed on silica gel (230–400 mesh, E. Merck). [α]_D values were measured at 25 °C on a Rudolph Autopol III polarimeter in MeOH. IR spectra were recorded as thin films or in KBr solution with a Perkin-Elmer Spectrum RX-1 (4000–450 cm⁻¹) spectrophotometer. The ¹H (200 and 300 MHz), and ¹³C NMR (50 MHz) spectra were recorded on a Bruker DRX-300 in CDCl₃. Chemical shift values are reported in parts per million relative to TMS as internal reference, unless otherwise stated: s (singlet), d (doublet), t (triplet), m (multiplet); *J* in hertz. FAB mass spectra

were performed using a mass Spectrometer Jeol SX-102, and ESI mass spectra were performed with a Quattro II (Micromass). Elemental analyses were performed on a Perkin-Elmer 2400 II elemental analyzer.

Ethyl-5,6-dideoxy-5-[N-{N-(Fmoc)-L-valin-1-yl}]amino-3-O-benzyl-1,2-O-isopropylidene- β -L-ido-heptofuranuronate (2a). The coupling of glycosyl amino ester (1, 4.0 g, 10.96 mmol) with Fmoc valine (3.8 g, 11.20 mmol) using HOBt (1.5 g, 11.10 mmol), DMAP (1.34 g, 10.97 mmol), and DIC (1.72 mL, 10.99 mmol) as described above gave compound **2a** as a pale yellow powder (yield 95%). $[\alpha]^{25}_{\text{D}} = -36.71$ (c, 0.08, MeOH). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.76 (d, $J = 7.4$ Hz, 2H), 7.61 (d, $J = 7.32$ Hz, 2H), 7.41–7.28 (m, 9H), 6.47 (d, $J = 7.89$ Hz, 1H), 5.90 (d, $J = 3.39$ Hz, 1H), 5.50 (d, $J = 7.89$ Hz, 1H), 4.71 (d, $J = 12.0$ Hz, 1H), 4.58–4.57 (m, 2H), 4.46–4.33 (m, 4H), 4.24–4.22 (m, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.89 (m, 1H), 3.86 (d, $J = 3.24$ Hz, 1H), 2.57 (m, 2H), 2.04 (m, 1H), 1.46 and 1.31 (s, 6H), 1.24 (t, $J = 7.1$ Hz, 3H), 0.92 (m, 6H). $^{13}\text{C NMR}$: δ 171.4, 170.7, 157.0, 144.4, 144.3, 141.7, 137.2, 129.1, 128.6, 128.5, 128.0, 127.5, 125.6, 120.3, 112.0, 110.0, 105.2, 82.4, 81.9, 79.8, 71.9, 67.4, 60.9, 52.0, 47.7, 46.0, 36.3, 31.7, 27.2, 26.8, 19.5, 18.10, 14.56. IR (Neat): ν_{max} cm^{-1} 3309, 3069, 2962, 2884, 1727, 1666. ESMS ($\text{C}_{39}\text{H}_{46}\text{N}_2\text{O}_9$): 687 (M + H) $^+$.

Ethyl-5,6-dideoxy-5-(N-L-valin-1-yl)-amino-3-O-benzyl-1,2-O-isopropylidene- β -L-ido-heptofuranuronate (3a). Deprotection of Fmoc group in the above compound **2a** (4.5 g, 6.6 mmol) with piperidine (0.97 mL, 9.80 mmol) in acetonitrile (10 mL) as described above gave compound **3a** as a light yellow oil (yield: 82%). $[\alpha]^{25}_{\text{D}} = -19.18$ (c, 0.08, MeOH). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.58 (d, $J = 7.98$ Hz, 1H), 7.32–7.24 (m, 5H), 5.88 (d, $J = 3.69$ Hz, 1H), 4.63 (d, $J = 11.4$ Hz, 1H), 4.55–4.48 (m, 2H), 4.46–4.33 (m, 2H), 4.09 (q, $J = 7.1$ Hz, 2H), 3.87 (d, $J = 2.91$ Hz, 1H), 3.60 (br s, 2H), 2.93 (t, $J = 7.1$ Hz, 1H), 2.53 (m, 2H), 2.15 (m, 1H), 1.43 and 1.27 (s, 6H), 1.22 (t, $J = 7.1$ Hz, 3H), 0.90 and 0.77 (d, $J = 6.9$ and 6.8 Hz, 6H). $^{13}\text{C NMR}$: δ 173.2, 171.3, 170.8, 137.0, 128.4, 128.0, 111.6, 104.7, 82.3, 82.1, 79.3, 71.8, 60.2, 51.4, 45.3, 36.5, 30.9, 26.9, 26.4, 19.5, 16.3, 14.2. IR (Neat): ν_{max} cm^{-1} 3377, 3020, 2361, 1728, 1662. ESMS ($\text{C}_{24}\text{H}_{36}\text{N}_2\text{O}_7$): 465 (M + H) $^+$.

Ethyl-5,6-dideoxy-5-[N-{N-(2-phenoxybenzoyl)-L-valin-1-yl}]amino-3-O-benzyl-1,2-O-isopropylidene- β -L-ido-heptofuranuronate (4a). The coupling of compound **3a** (1.0 g, 2.15 mmol) with 2-phenoxy benzoic acid (0.97 g, 4.52 mmol) using DIC (0.34 mL, 2.17 mmol), DMAP (0.26 g, 2.15 mmol), and HOBt (0.29 g, 2.15 mmol) as described above yielded compound **4a** as a white powder (yield: 85%). $[\alpha]^{25}_{\text{D}} = +25.68$ (c, 0.08, MeOH). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.20–8.17 (m, 2H), 7.39–7.28 (m, 8H), 7.21–7.16 (m, 2H), 7.07 (d, $J = 7.68$ Hz, 2H), 6.87 (d, $J = 8.16$ Hz, 1H), 6.57 (d, $J = 8.37$ Hz, 1H), 5.87 (d, $J = 3.78$ Hz, 1H), 4.67 (d, $J = 12.0$ Hz, 1H), 4.56–4.55 (m, 2H), 4.44–4.36 (m, 3H), 4.05 (q, $J = 7.1$ Hz, 2H), 3.86 (d, $J = 3.24$ Hz, 1H), 2.53 (m, 2H), 2.16 (m, 1H), 1.45 and 1.27 (s, 6H), 1.21 (t, $J = 7.1$ Hz, 3H), 0.89 and 0.83 (d, $J = 6.78$ and 6.8 Hz, 6H). $^{13}\text{C NMR}$: δ 171.9, 171.4, 170.7, 164.9, 156.0, 137.3, 133.1, 132.7, 130.5, 129.0, 128.5, 128.3, 124.9, 124.4,

119.8, 118.9, 112.0, 105.2, 82.4, 82.1, 79.8, 71.9, 60.9, 59.4, 45.9, 36.3, 31.1, 27.3, 26.8, 19.6, 18.1, 14.6. IR (Neat): ν_{max} cm^{-1} 3425, 3020, 2361, 1725, 1654. ESMS ($\text{C}_{37}\text{H}_{44}\text{N}_2\text{O}_9$): 661 (M + H) $^+$.

Ethyl-5,6-dideoxy-5-[N-{N-(2-phenoxybenzoyl)-L-valin-1-yl}]amino-3-O-benzyl-1,2-O-isopropylidene- β -L-ido-heptofuranuronic Acid (5a). Hydrolysis of compound **4a** (0.8 g, 1.21 mmol) with LiOH (0.09 g, 2.19 mmol) as described above gave compound **5a** as a white powder (yield: 62%). $[\alpha]^{25}_{\text{D}} = +28.49$ (c, 0.08, MeOH). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.37 (d, $J = 6.6$ Hz, 1H), 8.17 (d, $J = 6.9$ Hz, 1H), 8.00 (bs, 1H), 7.40–7.06 (m, 12H), 6.85 (d, $J = 7.86$ Hz, 1H), 5.87 (d, $J = 3.69$ Hz, 1H), 4.64–4.39 (m, 6H), 3.91 (d, $J = 2.04$ Hz, 1H), 2.30 (m, 2H), 1.96 (m, 1H), 1.47 and 1.31 (s, 7H), 0.92 and 0.86 (d, $J = 6.66$ and 6.72 Hz, 6H). $^{13}\text{C NMR}$: δ 165.4, 156.2, 155.7, 137.6, 133.2, 132.9, 130.5, 128.9, 128.2, 125.1, 123.9, 120.0, 111.9, 105.3, 82.4, 82.4, 81.0, 72.1, 59.4, 45.9, 36.3, 31.7, 27.4, 26.9, 19.5, 18.5. IR (Neat): ν_{max} cm^{-1} 3409, 3020, 2361, 1641, 1527. ESMS ($\text{C}_{35}\text{H}_{40}\text{N}_2\text{O}_9$): 639 (M + Li) $^+$.

Ethyl-5,6-dideoxy-5-[N-{N-(2-phenoxybenzoyl)-L-valin-1-yl}]amino-3-O-benzyl-1,2-O-isopropylidene- β -L-ido-heptofuranuronamide (6a). Reaction of compound **5a** (0.70 g, 1.10 mmol) with oxalyl chloride (0.12 mL, 1.37 mmol) and NH_4OH (0.5 mL) in THF (10 mL) as described above gave **6a** as a white powder (yield: 60%). $[\alpha]^{25}_{\text{D}} = +33.68$ (c, 0.08, MeOH). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.57 (d, $J = 8.88$ Hz, 1H), 8.19 (q, $J = 6.24$ and 1.62, 1H), 7.42–7.28 (m, 10H), 7.20–7.09 (m, 4H), 6.90 (d, $J = 7.98$ Hz, 1H), 5.90 (d, $J = 3.87$ Hz, 1H), 4.98 (m, 1H), 4.70–4.58 (m, 3H), 4.49–4.45 (m, 2H), 3.86 (d, $J = 3.12$ Hz, 1H), 2.57 (m, 2H), 2.06 (m, 1H), 1.44 (s, 3H), 1.31 (bs, 4H), 0.96 and 0.89 (d, $J = 6.72$ and 6.75 Hz, 6H). IR (Neat): ν_{max} cm^{-1} 3397, 3020, 2361, 1722, 1597. ESMS ($\text{C}_{35}\text{H}_{41}\text{N}_3\text{O}_8$): 632 (M + H) $^+$. Elemental analysis for $\text{C}_{35}\text{H}_{41}\text{N}_3\text{O}_8$: Calcd. C, 66.54; H, 6.54; N, 6.65. Found: C, 66.51; H, 6.59; N, 6.61.

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Supporting Information Available. General procedures for synthesis of library of carbapeptide analogues and their data (IR, ESMS, and ^1H and ^{13}C NMR) for the compounds. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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