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Solution phase synthesis of a library of carbapeptide analogues based on glycosylamino acid scaffolds, their in silico screening and antimicrobial evaluation

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A well-organized and efficient approach towards 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/ NH_4OH to afford heptofuranuronamides **6a-h** and octopyranuronamides **7e**. *In vitro* screening of all compounds displayed moderate anti-fungal, anti-tubercular 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 bio-markers 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 towards 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 programme 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 displayed interesting antitubercular activities *in vitro* against sensitive and MDR strains of *M. 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 bio-evaluations necessitated a larger quantity of pure compounds. Therefore, we have developed a solution phase synthesis of pure carbapeptide 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 anti-fungal, anti-tubercular and general antibacterial activities. Reverse docking calculations involving over 841 protein drug targets suggest that binding to Penicillopepsin results in the observed anti-fungal activity. Observed anti-bacterial activities apparently arise largely due to binding to ATP/NAD binding sites of DNA helicase and gyrase. The compounds suggestedly also bind to lysA and dihydropicolinate reductase which results in the observed anti-tubercular activities.

Results and Discussion

Our objective was to develop simple, cost-effective and efficient chemical routes for solution-phase synthesis of a library of carbapeptide 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 i.e. 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-hydroxy benzotriazole (HOBT), 4-dimethylamino pyridine (DMAP) and diisopropylcarbodiimide (DIC) as coupling reagents in anhydrous CH_2Cl_2 under N_2 atmosphere for 5 hrs at 0 °C led to the formation of respective 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**) in good yield. Considering the lability of the Fmoc group towards 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. NH_4OH 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*-heptofuranuronamide (**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*-isopropylidene-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 SiO_2 (200-440 mesh). To evaluate the potential of this methodology, two different

glycosyl-β-amino 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).

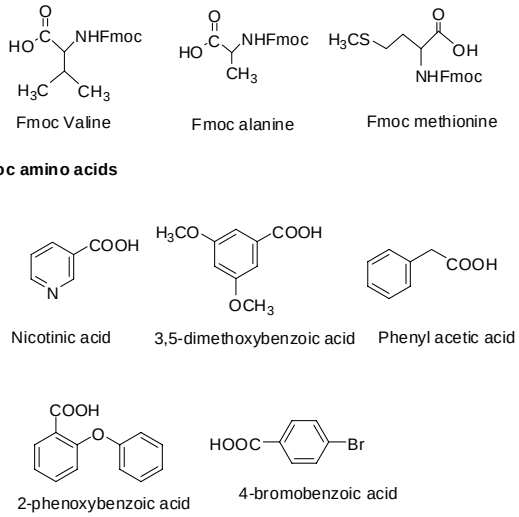
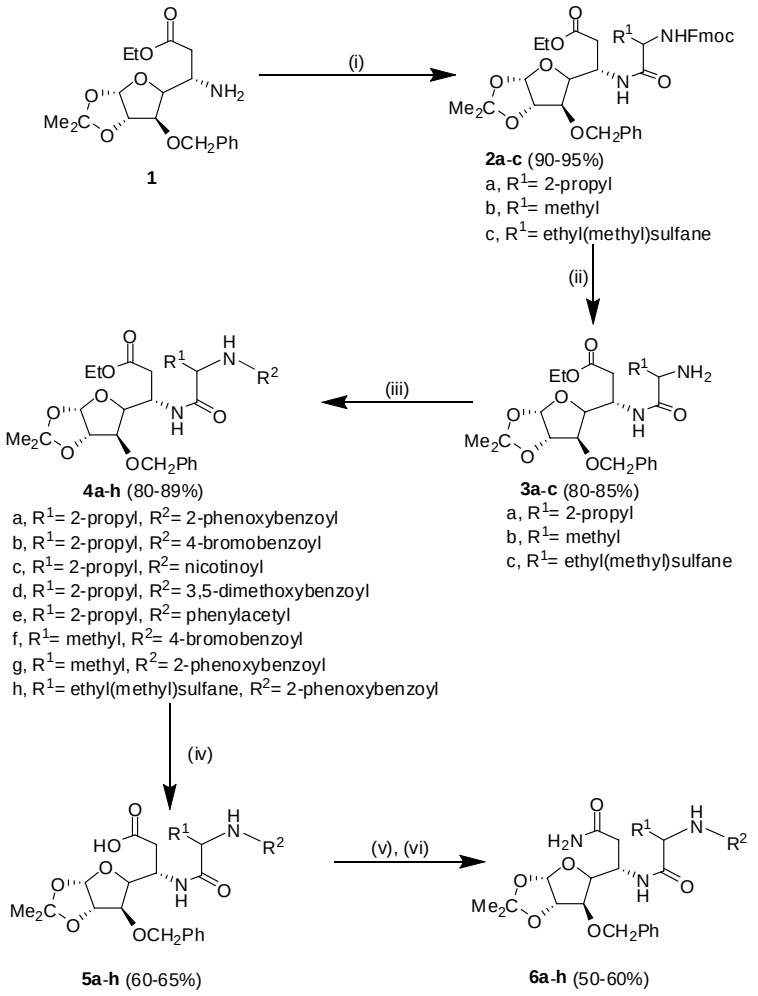


Figure 1. Different amino acids and aromatic acids used

Scheme 1. Solution phase synthesis of glycosyl carboxamide derivatives[a]



[a]Reagents and conditions: (i) $R^1CH(NHFmoc)COOH$, DIC, HOBt, DMAP, CH_2Cl_2, N_2 atm, 3-5 hrs, 0°C (ii) 10% piperidine in CH_3CN (iii) R^2COOH, DIC, HOBt, DMAP, CH_2Cl_2, N_2 atm, 3-5 hrs, 0°C (iv) $LiOH.H_2O$, H_2O:THF:: 1:1, 25 °C.(v) Oxalyl Chloride, THF, 0°C, 2 hrs (vi) NH_4OH solution, 0 °C, 2-4 hrs.

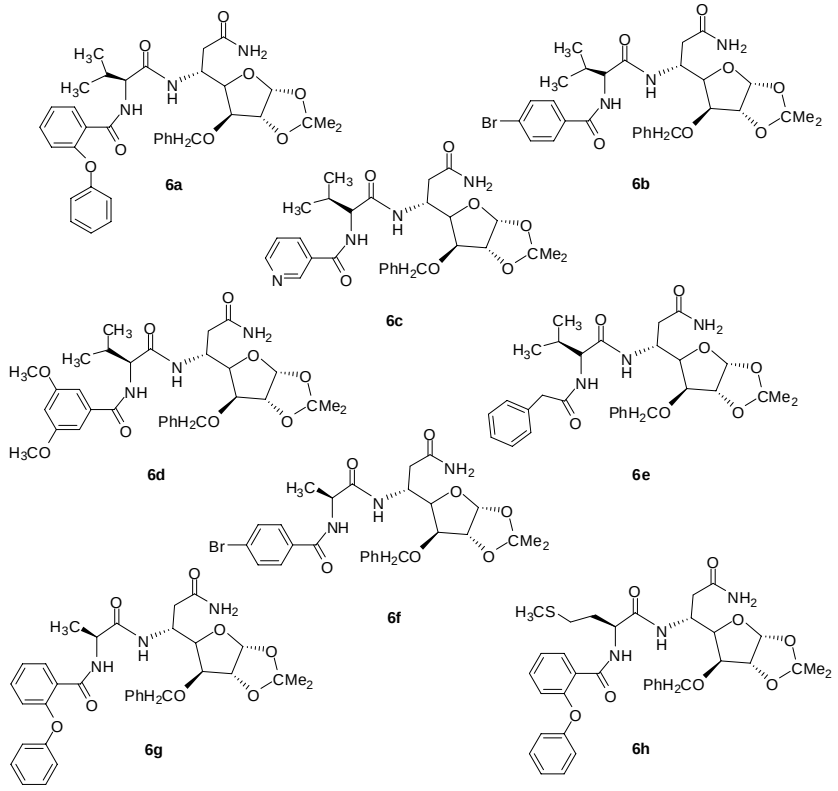
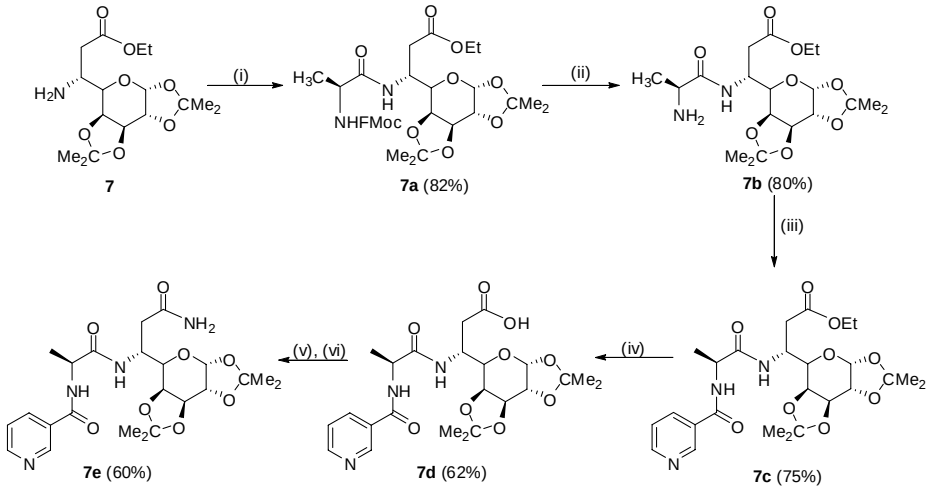


Figure 2. Library of carbapeptide analogues 6a-h

Scheme 2. Solution phase synthesis of galactosyl carboxamide derivatives[a]



[a]Reagents and conditions: (i) $CH_3CH(NHFmoc)COOH$, DIC, HOBt, DMAP, CH_2Cl_2, N_2 atm, 3-5 hrs, 0°C (ii) 10% piperidine in CH_3CN (iii) C_6H_4NCOOH, DIC, HOBt, DMAP, CH_2Cl_2, N_2 atm, 3-5 hrs, 0°C (iv) $LiOH.H_2O$, H_2O:THF:: 1:1, 25 °C.(v) Oxalyl Chloride, THF, 0°C, 2 hrs (vi)NH_4OH solution, 0 °C, 2-4 hrs.

All of the above compounds were evaluated *in vitro* against different strains of bacteria and fungi including *E. coli*, *Pseudomonas aeruginosa*, *Staphylcoccus aureus*, *Klebsiella pneumonia*, *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 non-specificity towards *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 *Trychophyton rubrum, T. mentagrophytes* and many other fungal strains secrete proteases like Penicillopepsin.[33] Two targets, the lysA gene and dihydropicolinate reductase[34] of *M. tuberculosis* both a part of the lysine biosynthetic pathway and absent in humans, were suggested for anti-tubercular 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 R^2 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 R^1 substituent result in loss of antibacterial activity.

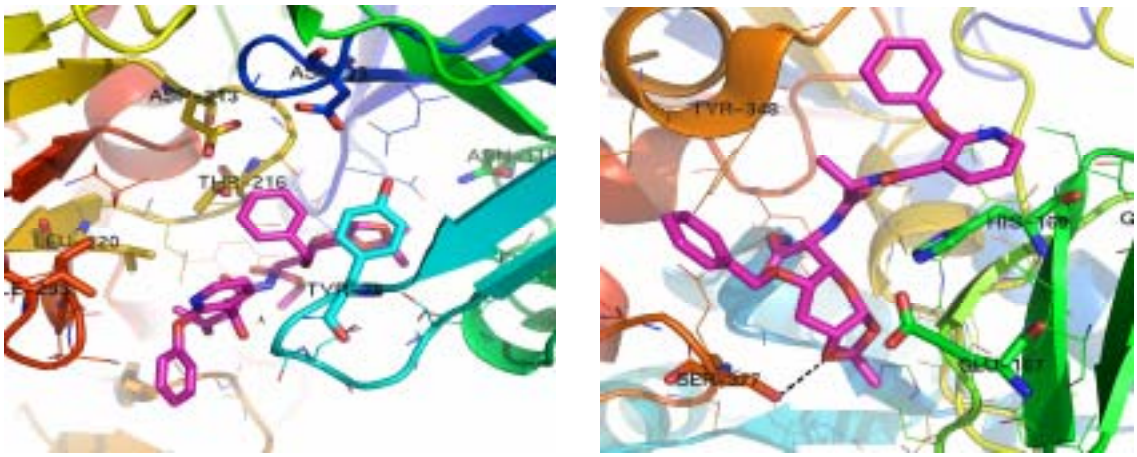


Figure 3. Interactions of compound **6g** with: *Left panel*: Penicillopepsin from *Penicillium janthinellum* and *Right panel*: Diaminopimelate reductase from *Mycobacterium tuberculosis.* The hydrogen bonding interactions are marked and interacting residues are labeled for clarity.

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 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

General: Commercially available reagent grade chemicals were used as received. TLC was carried out with E. Merck Kieselgel 60 F_{254}, Spots were visualized under UV light and/or visualized by spraying with a 20% aq. $KMnO_4$ or by spraying with a ethanolic H_2SO_4 followed by heating at 120°C for 5 min. Column chromatography was performed on silica gel (230–400 mesh, E. Merck). $[\alpha]_D$ 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 300MHz) and ^{13}C NMR (50MHz) spectra were recorded on a Brucker DRX-300 in $CDCl_3$. Chemical shift values are reported in ppm 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 with 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**) It was obtained by 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%). $[\alpha]^{25}_D$ = -36.71 (c, 0.08, MeOH); ^1H 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}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 ($C_{39}H_{46}N_2O_9$): 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%). $[\alpha]^{25}_{D}$ = -19.18 (c, 0.08, MeOH); ^{1}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}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 ($C_{24}H_{36}N_2O_7$): 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**) It was obtained by 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%). $[\alpha]^{25}_{D}$ = +25.68 (c, 0.08, MeOH); ^{1}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}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, 124.0, 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 ($C_{37}H_{44}N_2O_9$): 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%). $[\alpha]^{25}_{D}$ = +28.49 (c, 0.08, MeOH); ^{1}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}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 ($C_{35}H_{40}N_2O_9$): 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 (0.5ml) in THF (10ml) as described above gave **6a** as a white powder (yield: 60%). $[\alpha]^{25}_{D}$ = +33.68 (c, 0.08, MeOH); ^{1}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 ($C_{35}H_{41}N_3O_8$): 632 $(M+H)^+$; Elemental analysis for $C_{35}H_{41}N_3O_8$: 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, ^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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