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Amino Acid Derivatives, V [1]: Synthesis and Antiviral Evaluation of α-Amino Acid Esters Bearing an α-D-Mannofuranoside Side Chain

Omar M. Ali and **Adel A.-H. Abdel-Rahman***

Department of Chemistry, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt

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Summary. D-Mannose was treated with dry acetone in the presence of conc. H_2SO_4 to afford 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside. Treating the latter with ethyl chloroacetate gave carboethoxymethyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside, which was hydrolyzed with $N_2H_4 \cdot H_2O$ to afford the acid hydrazide derivative. Treating of the acid hydrazide with acylated amino acides, *via* the azide-coupling method afforded the corresponding *O*-glycopeptides. Reaction of the glycopeptide methyl esters with $N_2H_4 \cdot H_2O$ afforded the corresponding hydrazides, which were coupled with the amino acid methyl esters to afford the dipeptides. Deprotection was carried out by using 70% *Ac*OH. The prepared *O*-glycopeptides were tested for antiviral activity against hepatitis B virus and showed moderate activities.

Keywords. Carbohydrates; Mannofuranosides; Amino acids; *O*-Glycopeptides; Antiviral activity.

Introduction

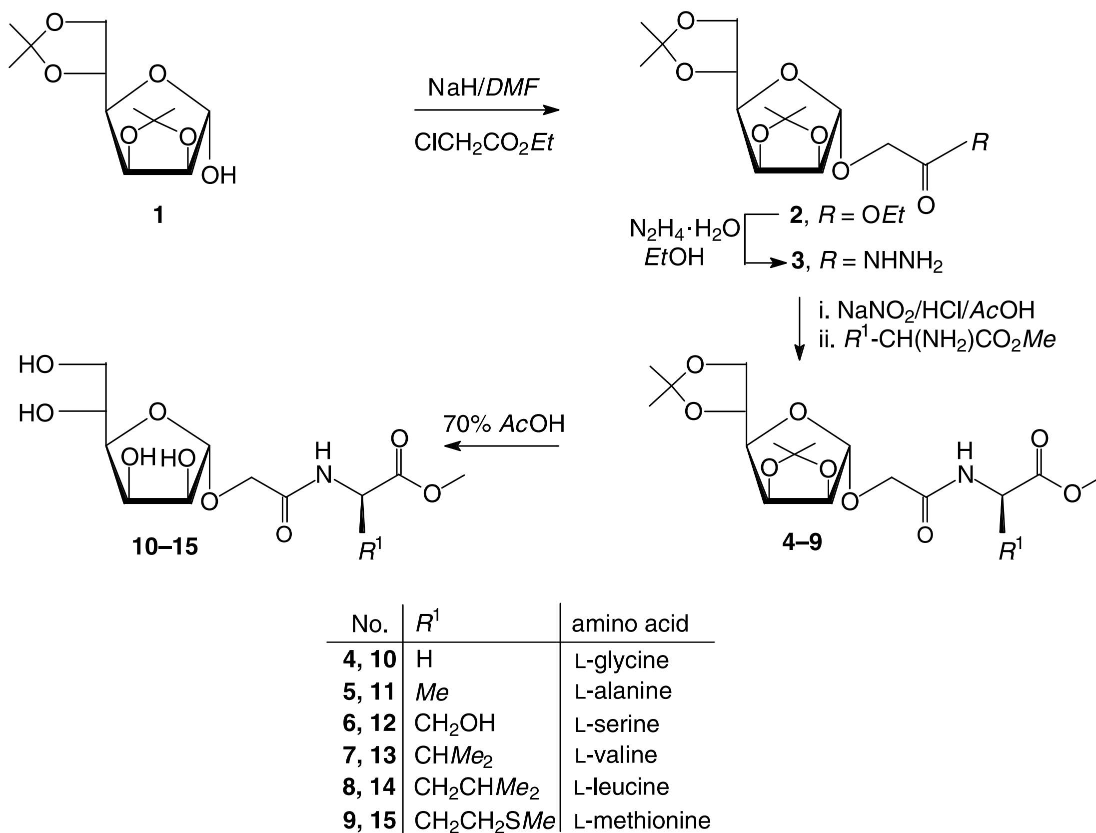
Carbohydrate moieties in glycopeptides play a crucial role in a number of biological processes including cell recognition [2], adhesion, infection, and tumor metastasis [3]. The conformation [4] and solubility [5] of proteins are influenced by the oligosaccharide chain that can also prohibit the proteolytic cleavage [6]. As a result, the synthesis of glycopeptides is an attractive goal for an understanding of the mutual interactions between both moieties and for their biological interest [7]. Thus, glycopeptides have attracted much attention in recent years. It is therefore desirable that a convenient and high yielding method is available for the routine synthesis of glyocopeptides [8]. Although a significant advancement has been made in the solid and solution phase glycopeptide synthesis during the last decade [9], limited availability of protected glycosylated amino acid derivatives has been impeding *O*-glycopeptide research. Our interest in the synthesis of such compounds was to shed some light on their antiviral properties as a part of our program aimed at the development of new α-amino acid derivatives as antiviral agents [1, 10].

Results and Discussion

Synthesis

D-Mannose was treated with dry acetone in the presence of conc. H_2SO_4 to afford 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (**1**) [11]. Treating of **1** with ethyl chloroacetate in the presence of NaH and dry *DMF* gave carboethoxymethyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (**2**) in 80% yield. The acid hydrazide derivative **3** was obtained in 95% yield by reacting of **2** with $N_2H_4 \cdot H_2O$ in ethanol at reflux temperature. This hydrazide was selected as a starting material for the coupling reaction with the appropriate acylated amino acides, *via* the azide-coupling method [12]. Thus, treatment of **3** at -5°C in *Ac*OH and 1 *N* HCl with $NaNO_2$ afforded the inseparable azide derivative. The yellow syrupy

* Corresponding author. E-mail: adelnassar63@hotmail.com



No.	R^1	amino acid
4, 10	H	L-glycine
5, 11	*Me*	L-alanine
6, 12	CH_2OH	L-serine
7, 13	$CHMe_2$	L-valine
8, 14	CH_2CHMe_2	L-leucine
9, 15	CH_2CH_2SMe	L-methionine

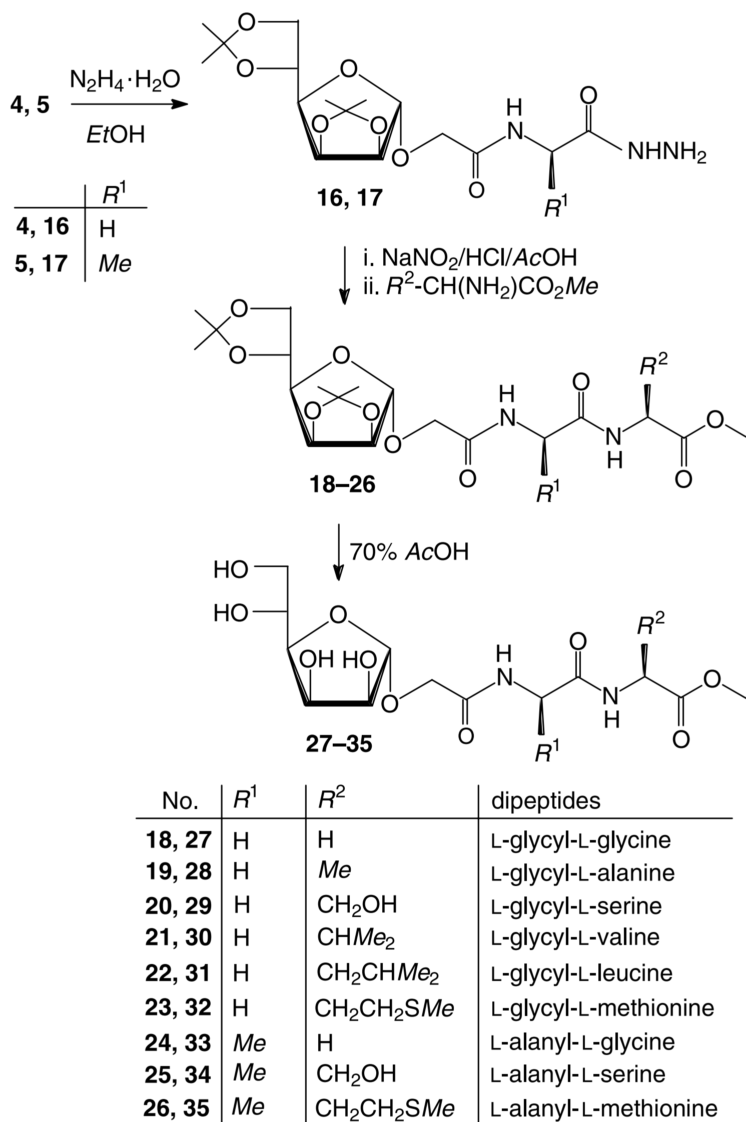
Scheme 1

azide compound was then treated, *in situ*, with the appropriate amino acid methyl esters in ethyl acetate containing Et_3N at 0°C to give, after neutralization, the desired *O*-glycopeptides **4**–**9** in 78–83% yields. The structures of **4**–**9** were assigned from their ^{1}H NMR and mass spectra. The ^{1}H NMR spectra showed four singlets at $\delta = 1.31$–1.33, 1.36–1.39, 1.41–1.44, and 1.46–1.49 ppm corresponding to four *Me* of the two isopropylidene groups. The singlet at $\delta = 5.01$–5.03 ppm is corresponding to H-1 of the sugar moiety, which is consistent with the α-configuration [13]. The protons of the side chain were fully analyzed as well as the remaining protons. Deprotection of compounds **4**–**9** was carried out by using 70% *Ac*OH at reflux temperature. The crude products were purified by silica gel column chromatography affording **10**–**15** in 78–89%. The structures of the deprotected derivatives were confirmed by their ^{1}H NMR and mass spectra, which showed the disappearance of the isopropylidene groups in all cases (Scheme 1).

Treating of **4** or **5** with $N_2H_4 \cdot H_2O$ in ethanol at reflux temperature afforded the corresponding hydrazides **16** and **17** in 92% yield. Treatment of **16** or **17** at −5°C in *Ac*OH and 1 *N* HCl with $NaNO_2$ afforded the inseparable azide derivatives. The yellow syrupy azide compounds were treated, as mentioned above, with the appropriate amino acid methyl esters in ethyl acetate containing Et_3N at 0°C to afford **18**–**26** in 80–86% yields. The structures of the protected dipeptide derivatives were confirmed by their ^{1}H NMR and mass spectra. Deprotection of compounds **18**–**26** was carried out by using 70% *Ac*OH at reflux temperature. The crude products were purified on silica gel column chromatography to give **27**–**35** in 80–87%. The structures of the deprotected derivatives were confirmed by their ^{1}H NMR and mass spectra, which showed the disappearance of the isopropylidene groups (Scheme 2).

Testing

A preliminary viral screening against HBV (Hep G2 2.2.15 cell method) [14–16] indicated that compounds **11**, **13**–**15**, and **33**–**35** are active against



No.	R^1	R^2	dipeptides
18, 27	H	H	L-glycyl-L-glycine
19, 28	H	*Me*	L-glycyl-L-alanine
20, 29	H	CH_2OH	L-glycyl-L-serine
21, 30	H	CH*Me*$_2$	L-glycyl-L-valine
22, 31	H	CH_2CH*Me*$_2$	L-glycyl-L-leucine
23, 32	H	CH_2CH_2S*Me*	L-glycyl-L-methionine
24, 33	*Me*	H	L-alanyl-L-glycine
25, 34	*Me*	CH_2OH	L-alanyl-L-serine
26, 35	*Me*	CH_2CH_2S*Me*	L-alanyl-L-methionine

Scheme 2

HBV replication with IC_{50} 80–90 μM and CC_{50} 82–92 μM, while compounds **10**, **12**, and **16**–**32** showed moderate viral replication inhibition and moderate cytotoxicity. The drug Lamivudine, which is a potent selective inhibitor of HBV replication [17], was used as a standard for the comparative studies.

Conclusions

New α-amino acid derivatives bearing an α-D-mannofuranoside side chain (*O*-glycopeptides) were synthesized in order to increase the number of tested compounds screened for anti-HBV activity.

Experimental

Melting points were determined using a *Kofler* block instrument. TLC was performed on plastic plates Silica Gel 60 F_{254} (E. Merck, layer thickness 0.2 mm). IR spectra were recorded with a Perkin-Elmer model 1720 FTIR (KBr), ^{1}H NMR spectra were recorded with *Bruker* AC 250 FT NMR spectrometer at 250 MHz with *TMS* as an internal standard. MALDI-MS were measured with a KRATOS Analytical Compact, using 2,5-dihydroxybenzoic acid (*DHB*) as matrix. The $(M+Na)^+$ and $(M+K)^+$ ions were peak-matched using ions derived from the 2,5-dihydroxybenzoic acid matrix. The microanalyses were performed at the microanalytical unit, Tokyo University, Japan, and were found to agree favorably with the calculated values. Viral screening against HBV was conducted at the National Liver Institute, Menoufia University, Egypt. Petroleum ether (*PE*), ethyl acetate (*EE*).

Carboethoxymethyl 2,3:5,6-di-O-isopropylidene-α-D-mannofuranoside (**2**, $C_{16}H_{26}O_8$)
Sodium hydride (1.03 g, 43.0 mmol) was added to a solution of 10.40 g **1** [11] (40.0 mmol) in 100 cm^3 dry *DMF*. The mixture was stirred for 10 min until the evolution of hydrogen was ceased. Ethyl chloroacetate (4.90 g, 40.0 mmol) was added, and the mixture was stirred at room temperature for 24 h (TLC). The salt was removed by filtration, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using *PE*:*EE* = 5:1 to afford 11.07 g **2** (80%) as oil. ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.29$ (t, $J = 7.1$ Hz, CH_3CH_2O), 1.33 (s, CH_3), 1.37 (s, CH_3), 1.42 (s, CH_3), 1.45 (s, CH_3), 3.98–4.09 (m, CH_3CH_2O, CH_2), 4.11 (d, $J = 3.7$ Hz, H-4), 4.20–4.24 (m, H-6), 4.37–4.43 (m, H-5), 4.71 (d, $J = 5.9$ Hz, H-2), 4.81 (dd, $J = 3.5$, 5.8 Hz, H-3), 5.08 (s, H-1) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 369 [$(M + Na)^+$, 55].

Acetylhydrazine 2,3:5,6-di-O-isopropylidene-α-D-mannofuranoside (**3**, $C_{14}H_{24}N_2O_7$)
A mixture of 3.46 g **2** (10 mmol) and 1.25 g $N_2H_4 \cdot H_2O$ (25 mmol) in 30 cm^3 ethanol was heated under reflux for 3 h. The excess of ethanol was removed under reduced pressure and the resulting precipitate was filtered off, washed with ethanol, and recrystallized from ethanol to give 3.15 g **3** (95%). Mp 133–135°C; IR (KBr): $\bar{\nu} = 3305$, 3210 (NH), 1660–1685 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 1.33$ (s, CH_3), 1.37 (s, CH_3), 1.45 (s, CH_3), 1.46 (s, CH_3), 3.80 (br, s, NH_2), 3.99–4.16 (m, H-4, H-6, CH_2), 4.38–4.44 (m, H-5), 4.65 (d, $J = 5.8$ Hz, H-2), 4.80 (dd, $J = 3.5$, 5.8 Hz, H-3), 5.00 (s, H-1), 7.51 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 355 [$(M + Na)^+$, 62].

*General Procedure for the Preparation of 2,3:5,6-Di-O-isopropylidene-α-D-mannofuranoside Bearing Amino Acid Esters **4–9***
A solution of 0.26 g **3** (0.80 mmol) in 6 cm^3 HO*Ac*, 3 cm^3 1 *N* HCl, and 25 cm^3 H_2O was cooled in an ice-bath (−5°C). $NaNO_2$ (0.87 g, 12.60 mmol) in 3 cm^3 cold H_2O was added with stirring. After stirring at −5°C for 15 min, the yellow syrup was formed. The azide was taken in 30 cm^3 cold ethyl acetate, washed with 30 cm^3 $NaHCO_3$ (3%), 30 cm^3 H_2O, and dried (Na_2SO_4). A solution of the appropriate amino acid methyl ester hydrochloride (0.90 mmol) in 20 cm^3 ethyl acetate containing 0.2 cm^3 *Et*$_3$N was stirred at 0°C for 20 min, filtered, and the filtrate was added to the azide solution. The mixture was kept at −5°C for 12 h, then at room temperature for another 12 h, followed by washing with 30 cm^3 0.5 *N* HCl, 30 cm^3 $NaHCO_3$ (3%), 30 cm^3 H_2O, and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography using *PE*:*EE* = 5:1 to afford **4–9** in 78–83% yields.

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-glycine methyl ester (**4**, $C_{17}H_{27}NO_9$)
Colorless oil (80%); $R_f = 0.22$ (*PE*:*EE* = 2:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.32$ (s, CH_3), 1.36 (s, CH_3), 1.42 (s, CH_3), 1.47 (s, CH_3), 3.72 (s, OCH_3), 4.11–4.29 (m, H-4, H-6, NHCH_2), 4.43–4.60 (m, H-5, OCH_2), 4.75 (d, $J = 5.9$ Hz, H-2), 4.90 (dd, $J = 3.5$, 5.8 Hz, H-3), 5.01 (s, H-1), 7.20 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 412 [$(M + Na)^+$, 42], 428 [$(M + K)^+$, 30].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-alanine methyl ester (**5**, $C_{18}H_{29}NO_9$)
Colorless oil (80%); $R_f = 0.23$ (*PE*:*EE* = 2:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.34$–1.38 (m, 3CH_3), 1.44 (s, CH_3), 1.49 (s, CH_3), 3.68 (s, OCH_3), 4.15 (d, $J = 3.7$ Hz, H-4), 4.23–4.29 (m, H-6), 4.34–4.40 (m, H-5), 4.56 (s, OCH_2), 4.62 (m, CH), 4.76 (d, $J = 5.9$ Hz, H-2), 4.88 (dd, $J = 3.5$, 5.8 Hz, H-3), 5.03 (s, H-1), 7.08 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 426 [$(M + Na)^+$, 19], 442 [$(M + K)^+$, 43].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-serine methyl ester (**6**, $C_{18}H_{29}NO_{10}$)
Colorless oil (78%); $R_f = 0.15$ (*PE*:*EE* = 2:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.33$ (s, CH_3), 1.39 (s, CH_3), 1.42 (s, CH_3), 1.46 (s, CH_3), 3.60 (m, CH), 3.70 (s, OCH_3), 4.17 (d, $J = 3.7$ Hz, H-4), 4.25–4.32 (m, H-6), 4.40–4.56 (m, H-5, CH), 4.66–4.71 (m, H-2, OCH_2), 4.87 (dd, $J = 3.5$, 5.8 Hz, H-3), 5.03 (s, H-1), 7.22 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 442 [$(M + Na)^+$, 33], 458[$(M + K)^+$, 26].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-valine methyl ester (**7**, $C_{20}H_{33}NO_9$)
Colorless oil (83%); $R_f = 0.22$ (*PE*:*EE* = 2:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.80$ (d, $J = 4.6$ Hz, 2CH_3), 1.31 (s, CH_3), 1.39 (s, CH_3), 1.41 (s, CH_3), 1.44 (s, CH_3), 3.57 (s, OCH_3), 4.19 (d, $J = 3.7$ Hz, H-4), 4.25–4.35 (m, H-6), 4.37–4.50 (m, H-5, CH, OCH_2), 4.75 (d, $J = 5.9$ Hz, H-2), 4.89 (dd, $J = 3.5$, 5.8 Hz, H-3), 5.01 (s, H-1), 5.59 (d, $J = 7.2$ Hz, CH), 7.04 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 454 [$(M + Na)^+$, 45].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-leucine methyl ester (**8**, $C_{21}H_{35}NO_9$)
Colorless oil (79%); $R_f = 0.22$ (*PE*:*EE* = 2:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.85$ (d, $J = 4.6$ Hz, 2CH_3), 1.09 (m, CH), 1.31 (s, CH_3), 1.37 (s, CH_3), 1.42 (s, CH_3), 1.48 (s, CH_3), 2.09 (m, CH_2), 3.58 (s, OCH_3), 4.15 (d, $J = 3.7$ Hz, H-4), 4.27–4.34 (m, H-6), 4.37–4.49 (m, H-5, CH, OCH_2), 4.70 (d, $J = 5.9$ Hz, H-2), 4.88 (dd, $J = 3.5$, 5.8 Hz, H-3), 5.02 (s, H-1), 7.20 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 468 [$(M + Na)^+$, 40].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-methionine methyl ester (**9**, $C_{20}H_{33}NO_9S$)
Yellow oil (79%); $R_f = 0.24$ (*PE*:*EE* = 2:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.32$ (s, CH_3), 1.39 (s, CH_3), 1.43 (s, CH_3), 1.48 (s, CH_3), 2.41 (s, SCH_3), 2.69 (t, $J = 7.3$ Hz, CH_2), 2.85 (m, CH_2), 3.69 (s, OCH_3), 4.19 (d, $J = 3.7$ Hz, H-4), 4.29–4.39 (m, H-6), 4.48–4.68 (m, H-5, CH, OCH_2), 4.75 (d, $J = 5.9$ Hz, H-2), 4.87 (dd, $J = 3.5$, 5.8 Hz, H-3), 5.01 (s, H-1), 7.65 (br, s,

NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 486 [(M + Na)$^+$, 32].

General Procedure for the Preparation of α-D-mannofuranoside Bearing Amino Acid Esters ***10–15***

Compounds **4–9** (3 mmol) were dissolved in 5 cm^3 70% *Ac*OH and heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was coevaporated two times with 3 cm^3 H_2O and two times with 3 cm^3 ethanol. The residual was purified by silica gel column chromatography using 10% *Me*OH in $CHCl_3$ to give **10–15** in 78–89% yields.

O-(α-D-Mannofuranosyl)-acetyl L-glycine methyl ester (**10**, $C_{11}H_{19}NO_9$)

White foam (85%); R_f = 0.18 (*PE*:*EE* = 1:1); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): δ = 3.33 (br, s, OH), 3.60–3.70 (m, OCH_3, H-4), 3.90–4.35 (m, H-2, H-3, H-5, H-6, NHC*H*$_2$, 3OH), 4.55 (s, OCH_2), 5.01 (s, H-1), 7.00 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 332 [(M + Na)$^+$, 23].

O-(α-D-Mannofuranosyl)-acetyl L-alanine methyl ester (**11**, $C_{12}H_{21}NO_9$)

White foam (89%); R_f = 0.19 (*PE*:*EE* = 1:1); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): δ = 1.30 (d, J = 7.2 Hz, CH_3), 3.46–3.67 (m, OCH_3, OH, H-4), 3.89–4.30 (m, H-2, H-3, H-5, H-6, 3OH), 4.53 (s, OCH_2), 4.64 (m, CH), 5.03 (s, H-1), 6.89 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 346 [(M + Na)$^+$, 23].

O-(α-D-Mannofuranosyl)-acetyl L-serine methyl ester (**12**, $C_{12}H_{21}NO_{10}$)

White foam (78%); R_f = 0.10 (*PE*:*EE* = 1:1); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): δ = 3.40–3.56 (m, CH, OH), 3.64–3.72 (m, OCH_3, H-4), 4.00–4.50 (m, H-2, H-3, H-5, H-6, CH, 3OH), 4.56 (s, OCH_2), 5.02 (s, H-1), 7.00 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 362 [(M + Na)$^+$, 20].

O-(α-D-Mannofuranosyl)-acetyl L-valine methyl ester (**13**, $C_{14}H_{25}NO_9$)

White foam (81%); R_f = 0.19 (*PE*:*EE* = 1:1); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): δ = 0.90 (d, J = 4.6 Hz, 2CH_3), 3.32 (br, s, OH), 3.54 (s, OCH_3), 3.72 (m, H-4), 4.85–4.05 (m, H-5, H-6, 3OH), 4.20–4.56 (m, H-2, H-3, CH, OCH_2), 5.01 (s, H-1), 5.44 (m, CH), 7.03 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 374 [(M + Na)$^+$, 32].

O-(α-D-Mannofuranosyl)-acetyl L-leucine methyl ester (**14**, $C_{15}H_{27}NO_9$)

White foam (83%); R_f = 0.19 (*PE*:*EE* = 1:1); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): δ = 0.84 (d, J = 4.6 Hz, 2CH_3), 1.22 (m, CH), 2.12 (m, CH_2), 3.35 (br, s, OH), 3.54 (s, OCH_3), 3.80 (m, H-4), 4.07–4.37 (m, H-2, H-3, H-5, H-6, 3OH), 4.40–4.56 (m, CH, OCH_2), 5.01 (s, H-1), 7.04 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 388 [(M + Na)$^+$, 32].

O-(α-D-Mannofuranosyl)-acetyl L-methionine methyl ester (**15**, $C_{14}H_{25}NO_9S$)

Pale yellow foam (78%); R_f = 0.20 (*PE*:*EE* = 1:1); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): δ = 2.45 (s, SCH_3), 2.70 (t, J = 7.3 Hz, CH_2), 2.93 (m, CH_2), 3.40 (br, s, OH), 3.59 (s, OCH_3), 3.78 (m, H-4), 3.90–4.09 (m, H-5, H-6, 3OH), 4.28–4.58 (m, H-2, H-3, CH, OCH_2), 5.01 (s, H-1), 7.05 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 406 [(M + Na)$^+$, 17].

General Procedure for the Preparation of the Hydrazides ***16*** *and* ***17***

A mixture of **4** or **5** (10 mmol) and 1.25 g $N_2H_4 \cdot H_2O$ (25 mmol) in 30 cm^3 ethanol was heated under reflux for 3 h. The excess of ethanol was removed under reduced pressure and the resulting precipitate was filtered off, washed with ethanol, and recrystallized from ethanol to give **16** and **17** in 92% yields.

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-glycine hydrazide (**16**, $C_{16}H_{27}N_3O_8$)

White powder (92%); mp 155–156°C; R_f = 0.08 (*PE*:*EE* = 1:1); IR (KBr): $\bar{\nu}$ = 3325, 3215 (NH), 1665–1690 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): δ = 1.30 (s, CH_3), 1.37 (s, CH_3), 1.43 (s, CH_3), 1.49 (s, CH_3), 3.90 (br, s, NH_2), 4.18–4.33 (m, H-4, H-6, NHC*H*$_2$), 4.45–4.57 (m, H-5, OCH_2), 4.73 (d, J = 5.9 Hz, H-2), 4.93 (dd, J = 3.5, 5.8 Hz, H-3), 5.11 (s, H-1), 7.33 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 412 [(M + Na)$^+$, 31].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-alanine hydrazide (**17**, $C_{17}H_{29}N_3O_8$)

White powder (92%); mp 173–173°C; R_f = 0.09 (*PE*:*EE* = 1:1); IR (KBr): $\bar{\nu}$ = 3320, 3210 (NH), 1670–1685 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): δ = 1.35–1.39 (m, 3CH_3), 1.42 (s, CH_3), 1.47 (s, CH_3), 3.88 (br, s, NH_2), 4.19 (m, H-4), 4.27–4.33 (m, H-6), 4.38–4.42 (m, H-5), 4.58 (s, OCH_2), 4.65 (m, CH), 4.76 (m, H-2), 4.88 (m, H-3), 5.10 (s, H-1), 7.02 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 426 [(M + Na)$^+$, 27].

General Procedure for the Preparation of the Glycopeptides ***18–26***

A solution of **16** or **17** (0.80 mmol) in 6 cm^3 HO*Ac*, 3 cm^3 1 *N* HCl, and 25 cm^3 H_2O was cooled in an ice-bath (−5°C). $NaNO_2$ (0.87 g, 12.60 mmol) in 3 cm^3 cold H_2O was added with stirring. After stirring at −5°C for 15 min, the yellow syrup was formed. The azide was taken in 30 cm^3 cold ethyl acetate, washed with 30 cm^3 $NaHCO_3$ (3%), 30 cm^3 H_2O, and dried (Na_2SO_4). A solution of the appropriate amino acid methyl ester hydrochloride (0.90 mmol) in 20 cm^3 ethyl acetate containing 0.2 cm^3 *Et*$_3$N was stirred at 0°C for 20 min, filtered, and the filtrate was added to the azide solution. The mixture was kept at −5°C for 12 h, then at room temperature for another 12 h, followed by washing with 30 cm^3 0.5 *N* HCl, 30 cm^3 $NaHCO_3$ (3%), 30 cm^3 H_2O, and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography using *PE*:*EE* = 5:1 to afford **18–26** in 80–86% yields.

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-glycyl-L-glycine methyl ester (**18**, $C_{19}H_{30}N_2O_{10}$)
White foam (85%); $R_f = 0.27$ (*PE*:*EE* = 1:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.33$ (s, CH_3), 1.35 (s, CH_3), 1.42 (s, CH_3), 1.48 (s, CH_3), 3.67 (s, OCH_3), 4.11–4.33 (m, H-4, H-6, NHCH_2), 4.43–4.60 (m, H-5, NHCH_2), 4.69 (s, OCH_2), 4.77 (d, $J = 5.9$ Hz, H-2), 4.92 (dd, $J = 3.5$, 5.8 Hz, H-3), 5.07 (s, H-l), 6.60 (br, s, NH), 6.80 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 469 [(M + Na)$^+$, 29].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-glycyl-L-alanine methyl ester (**19**, $C_{20}H_{32}N_2O_{10}$)
White foam (86%); $R_f = 0.28$ (*PE*:*EE* = 1:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.32$ (s, CH_3), 1.35 (s, CH_3), 1.40 (d, $J = 7.2$ Hz, CH_3), 1.44 (s, CH_3), 1.49 (s, CH_3), 3.70 (s, OCH_3), 4.17–4.33 (m, H-4, H-6, NHCH_2), 4.43–4.52 (m, H-5, CH), 4.60 (s, OCH_2), 4.76 (m, H-2), 4.90 (m, H-3), 5.05 (s, H-1), 7.60 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 483 [(M + Na)$^+$, 23].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-glycyl-L-serine methyl ester (**20**, $C_{20}H_{32}N_2O_{11}$)
White foam (80%); $R_f = 0.18$ (*PE*:*EE* = 1:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.32$ (s, CH_3), 1.35 (s, CH_3), 1.44 (s, CH_3), 1.49 (s, CH_3), 3.65 (s, OCH_3), 4.15–4.31 (m, H-4, H-6, NHCH_2), 4.40–4.60 (m, H-5, 2OCH_2, CH), 4.72 (m, H-2), 4.90 (m, H-3), 5.05 (s, H-1), 5.70 (br, s, OH), 6.85 (br, s, NH), 6.95 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 499 [(M + Na)$^+$, 18].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-glycyl-L-valine methyl ester (**21**, $C_{22}H_{36}N_2O_{10}$)
White foam (86%); $R_f = 0.28$ (*PE*:*EE* = 1:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.90$ (d, $J = 4.6$ Hz, 2CH_3), 1.33 (s, CH_3), 1.37 (s, CH_3), 1.43 (s, CH_3), 1.48 (s, CH_3), 2.50 (m, CH), 3.70 (s, OCH_3), 4.14–4.35 (m, H-4, H-6, NHCH_2), 4.40–4.54 (m, H-5, CH), 4.64 (s, OCH_2), 4.70 (m, H-2), 4.90 (m, H-3), 5.06 (s, H-1), 7.30 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 511 [(M + Na)$^+$, 14].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-glycyl-L-leucine methyl ester (**22**, $C_{23}H_{38}N_2O_{10}$)
White foam (86%); $R_f = 0.29$ (*PE*:*EE* = 1:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.95$ (d, $J = 4.5$ Hz, 2CH_3), 1.25 (m, CH), 1.31 (s, CH_3), 1.35 (s, CH_3), 1.42 (s, CH_3), 1.49 (s, CH_3), 1.70 (m, CH_2), 3.68 (s, OCH_3), 4.10–4.28 (m, H-4, H-6, NHCH_2), 4.45–4.65 (m, H-5, CH, OCH_2), 4.77 (m, H-2), 4.90 (m, H-3), 5.06 (s, H-1), 6.90 (br, s, NH), 7.30 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 525 [(M + Na)$^+$, 15].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-glycyl-L-methionine methyl ester (**23**, $C_{22}H_{36}N_2O_{10}S$)
Pale yellow foam (80%); $R_f = 0.29$ (*PE*:*EE* = 1:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.34$ (s, CH_3), 1.37 (s, CH_3), 1.42 (s, CH_3), 1.48 (s, CH_3), 1.99 (s, SCH_3), 2.15 (m, CH_2), 2.65 (m, CH_2), 3.68 (s, OCH_3), 4.19–4.35 (m, H-4, H-6, NHCH_2), 4.45–4.65 (m, H-5, OCH_2, CH), 4.75 (m, H-2), 4.90 (m, H-3), 5.03 (s, H-1), 6.95 (br, s, NH), 7.40 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 543 [(M + Na)$^+$, 22].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-alanyl-L-glycine methyl ester (**24**, $C_{20}H_{32}N_2O_{10}$)
White foam (86%); $R_f = 0.27$ (*PE*:*EE* = 1:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.35$–1.30 (m, 3CH_3), 1.43 (s, CH_3), 1.48–1.52 (m, 2CH_3), 3.58 (s, OCH_3), 3.99 (m, NHCH_2), 4.15 (m, H-4), 4.20–4.27 (m, H-6), 4.30–4.40 (m, H-5), 4.57 (s, OCH_2), 4.73 (m, H-2), 4.80–4.88 (m, H-3, CH), 5.03 (s, H-1), 6.77 (br, s, NH) 7.45 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 483 [(M + Na)$^+$, 33].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-alanyl-L-serine methyl ester (**25**, $C_{21}H_{34}N_2O_{11}$)
White foam (80%); $R_f = 0.20$ (*PE*:*EE* = 1:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.35$–1.39 (m, 3CH_3), 1.43 (s, CH_3), 1.49 (s, CH_3), 3.58–3.70 (m, CH_2OH, OCH_3), 4.15–4.19 (m, H-4, CH), 4.25–4.30 (m, H-6), 4.40–4.55 (m, H-5, OCH_2), 4.79 (m, H-2), 4.88 (m, H-3), 5.03 (s, H-l), 5.45 (m, CH), 5.60 (br, s, OH), 6.79 (br, s, NH), 6.95 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 513 [(M + Na)$^+$, 43].

O-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-acetyl L-alanyl-L-methionine methyl ester (**26**, $C_{23}H_{38}N_2O_{10}S$)
Pale yellow foam (80%); $R_f = 0.30$ (*PE*:*EE* = 1:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.34$–1.39 (m, 3CH_3), 1.43–1.50 (m, 2CH_3), 2.01 (s, SCH_3), 2.17 (m, CH_2), 2.55 (m, CH_2), 3.68 (s, OCH_3), 4.16 (m, H-4), 4.20–4.30 (m, H-6), 4.35–4.40 (m, H-5), 4.55 (s, OCH_2), 4.70–4.79 (m, H-2, CH), 4.80–4.88 (m, H-3, CH), 5.13 (s, H-1), 6.71 (br, s, NH) 7.00 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 557 [(M + Na)$^+$, 28].

General Procedure for the Preparation of the Deprotected Glycopeptides ***27–35***
Compounds **18–26** (3 mmol) were dissolved in 5 cm^3 70% *Ac*OH and heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was coevaporated two times with 3 cm^3 H_2O and two times with 3 cm^3 ethanol. The residual was purified by silica gel column chromatography using 10% *Me*OH in $CHCl_3$ to afford **27–35** in 80–87% yields.

O-(α-D-Mannofuranosyl)-acetyl L-glycyl-L-glycine methyl ester (**27**, $C_{13}H_{22}N_2O_{10}$)
White powder (84%); mp 190–192°C; $R_f = 0.19$ (*PE*:*EE* = 1:2); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 3.37$ (br, s, OH), 3.65 (s, OCH_3), 3.75 (m, H-4), 3.90–4.07 (m, H-5, H-6, NHCH_2, 3OH), 4.13–4.40 (m, H-2, H-3, NHCH_2), 4.58 (s, OCH_2), 5.02 (s, H-1), 6.80 (br, s, NH), 6.95 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 389 [(M + Na)$^+$, 40].

O-(α-D-Mannofuranosyl)-acetyl L-glycyl-L-alanine methyl ester (**28**, $C_{14}H_{24}N_2O_{10}$)
White powder (86%); mp 183–184°C; $R_f = 0.20$ (*PE*:*EE* = 1:2); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 1.44$ (d, J = 7.2 Hz, CH_3), 3.39 (br, s, OH), 3.70–3.75 (m, OCH_3, H-4), 3.90–4.08 (m, H-5, H-6, NHCH_2, 3OH), 4.19–4.28 (m, H-2, H-3), 4.40–4.50 (m, CH), 4.62 (s, OCH_2), 5.02 (s, H-1), 7.50 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 403 [(M + Na)$^+$, 39].

O-(α-D-Mannofuranosyl)-acetyl L-glycyl-L-serine methyl ester (**29**, $C_{14}H_{24}N_2O_{11}$)
White powder (80%); mp 208–210°C; $R_f = 0.14$ (*PE*:*EE* = 1:2); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 3.40$ (br, s, OH), 3.65–3.75 (m, OCH_3, H-4), 3.95–4.18 (m, H-5, H-6, NHCH_2, 3OH), 4.20–4.60 (m, H-2, H-3, 2OCH_2, CH), 5.01 (s, H-1), 5.73 (br, s, OH), 6.90 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 419 [(M + Na)$^+$, 33].

O-(α-D-Mannofuranosyl)-acetyl L-glycyl-L-valine methyl ester (**30**, $C_{16}H_{28}N_2O_{10}$)
White powder (87%); mp 196–198°C; $R_f = 0.18$ (*PE*:*EE* = 1:2); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 0.95$ (d, J = 4.6 Hz, 2CH_3), 2.55 (m, CH), 3.33 (br, s, OH), 3.70–3.79 (m, OCH_3, H-4), 3.88–4.05 (m, H-5, H-6, NHCH_2, 3OH), 4.20–4.30 (H-2, H-3), 4.40–4.45 (m, CH), 4.56 (s, OCH_2), 5.00 (s, H-1), 7.20 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 431 [(M + Na)$^+$, 30].

O-(α-D-Mannofuranosyl)-acetyl L-glycyl-L-leucine methyl ester (**31**, $C_{17}H_{30}N_2O_{10}$)
White powder (85%); mp 203–205°C; $R_f = 0.19$ (*PE*:*EE* = 1:2); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 0.92$ (d, J = 4.5 Hz, 2CH_3), 1.33 (m, CH), 1.77 (m, CH_2), 3.38 (br, s, OH), 3.69–3.76 (m, OCH_3, H-4), 3.95–4.08 (m, H-5, H-6, NHCH_2, 3OH), 4.22–4.35 (m, H-2, H-3), 4.45–4.50 (m, CH, OCH_2), 5.02 (s, H-1), 6.99 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 445 [(M + Na)$^+$, 43].

O-(α-D-Mannofuranosyl)-acetyl L-glycyl-L-methionine methyl ester (**32**, $C_{16}H_{28}N_2O_{10}S$)
Pale yellow powder (81%); mp 183–185°C; $R_f = 0.21$ (*PE*:*EE* = 1:2); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 2.11$ (s, SCH_3), 2.22 (m, CH_2), 2.60 (m, CH_2), 3.40 (br, s, OH), 3.65–3.75 (m, OCH_3, H-4), 3.99–4.25 (m, H-5, H-6, NHCH_2, 3OH), 4.22–4.39 (m, H-2, H-3), 4.49–4.58 (m, OCH_2, CH), 5.02 (s, H-1), 6.95 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 463 [(M + Na)$^+$, 27].

O-(α-D-Mannofuranosyl)-acetyl L-alanyl-L-glycine methyl ester (**33**, $C_{14}H_{24}N_2O_{10}$)
White powder (87%); mp 167–169°C; $R_f = 0.18$ (*PE*:*EE* = 1:2); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 1.35–1.30$ (m, 3CH_3), 1.48–1.52 (m, CH_3), 3.40 (br, s, OH), 3.60–3.76 (m, OCH_3, H-4), 3.96–4.12 (m, H-5, H-6, NHCH_2, 3OH), 4.20–4.36 (m, H-2, H-3), 4.55 (s, OCH_2), 4.80–4.85 (m, CH), 5.01 (s, H-1), 6.80 (br, s, NH), 7.15 (br, s, NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 403 [(M + Na)$^+$, 25].

O-(α-D-Mannofuranosyl)-acetyl L-alanyl-L-serine methyl ester (**34**, $C_{15}H_{26}N_2O_{11}$)
White powder (82%); mp 232–234°C; $R_f = 0.15$ (*PE*:*EE* = 1:2); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 1.35–1.38$ (m, CH_3), 3.38–3.68 (m, H-4, OH, CH_2OH, OCH_3), 3.90–4.12 (m, H-5, H-6, 3OH), 4.19 (m, CH), 4.27–4.39 (m, H-2, H-3), 4.55 (s, OCH_2), 5.02 (s, H-l), 5.48 (m, CH), 5.63 (br, s, OH), 6.90 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 433 [(M + Na)$^+$, 10].

O-(α-D-Mannofuranosyl)-acetyl L-alanyl-L-methionine methyl ester (**35**, $C_{17}H_{30}N_2O_{10}S$)
Pale yellow powder (80%); mp 161–162°C; $R_f = 0.20$ (*PE*:*EE* = 1:2); ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 1.37$ (m, CH_3), 2.11 (s, SCH_3), 2.22 (m, CH_2), 2.66 (m, CH_2), 3.42–3.68 (m, H-4, OCH_3, OH), 3.88–4.00 (m, H-5, H-6, 3OH), 4.15–4.30 (m, H-2, H-3), 4.59 (s, OCH_2), 4.72 (m, CH), 4.84 (m, CH), 5.03 (s, H-1), 6.94 (br, s, 2NH) ppm; MS (MALDI, positive mode, Matrix: *DHB*): m/z (%) = 477 [(M + Na)$^+$, 17].

Preparation and Culture of Hep G2 2.2.15 Cells
The required cell line was made by transfection of Hep G2-cells with a plasmid containing multiple tandem copies of the HBV genome (subtype ayw) [14]. The 2.2.15 cell line was maintained in RPMI-1640 (Glutamax) culture media containing 100 IU/cm^3 nystatin and 380 μg/cm^3 G418 (geneticin). The transferred HEP G2-2.2.15 cell line was kept in tissue culture flask at 37°C + 5% CO_2. Subcultures were set up after a week by aspiration of the media from culture flask and washing the cells twice by PBS. A 10% versene/trypsin solution was added and the cells were incubated for 1 min at 37°C.

Cytotoxicity Assay
A colorimetric assay for living cells utilized the colorless substrate 3-(3,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (*MTT*) that is modified to colored product by any living cells, but not by dead cells or tissue culture medium. The cytotoxic effect of the compounds was accessed by culturing the Hep G2-2.2.15 cells in the presence of compounds using a *MTT*-assay [15, 16].

Calculation of IC_{50} and CC_{50}
The 50% inhibitory concentration of antiviral drugs (IC_{50}) was determined by interpolation from the plots of amount of *DNA* copies versus antiviral drug concentration. The 50% cytotoxic effect (CC_{50}) was calculated from the average viability of the cells with concentration of drugs [16].

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