Glycoconjugates of amines: alkylation of primary and secondary amines with *N*-chloroacetyl-β-glycopyranosylamines

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Efficient monoalkylation of a series of primary and secondary amines was demonstrated with the use of *N*-chloroacetylglycosylamines derived from D-glucose, D-galactose, D-mannose, *N*-acetyl-D-glucosamine, and lactose. The reaction was shown to be useful for incorporation of carbohydrate residues into physiologically active compounds. Glycoconjugates of some derivatives of piperazine, 2-phenylethylamine, tryptamine, and important biogenic amines (norephedrine, octopamine, dopamine) were prepared.

Key words: glycoconjugates, *N*-chloroacetylglycosylamines, piperazine, 2-phenylethylamine, tryptamine, norephedrine, octopamine, dopamine.

The introduction of mono- and oligosaccharide residues into the molecules of various physiologically active compounds and drugs presents considerable interest due to the possibility of controlled change of their interaction with receptors and of target-directed transport to particular cells, which contain specific carbohydrate-binding proteins (lectins) on their surface.

Modification of the initial compounds with glycosylamine derivatives appears to be a promising approach to this type of construction of drug precursors ("prodrugs"). The glycosylamines can be easily prepared from either monosaccharides[1–4] or complex oligosaccharides including the products of cleavage of natural *N*-glycoproteins.[5–7] The use of glycosylamines for the synthesis of glycoconjugates generally involves their *N*-acylation and subsequent modification based on reactions of functional groups present in the acyl residue (see reviews[8,9]).

A convenient variant of this approach is transformation of glycosylamines into *N*-haloacetylglycosylamines,[7,10,11] which are subsequently used to modify peptides and proteins at the SH groups.[10,11] The transformation of *N*-chloroacetylglycosylamines of oligosaccharides into *N*-glycylglycosylamines after the reaction with $(NH_4)_2CO_3$, and the use of the products for preparing various glycoconjugates containing fluorescent labels, biotin residues, palmitic acid, and also bovine serum albumin have been described.[7,12,13] However, the possibilities of using *N*-haloacetylglycosylamines for introduction of carbohydrate residues into other types of biologically active compounds still remain little studied.

In this work, we studied the reaction of some *N*-chloroacetyl-β-glycopyranosylamines **1a–e**, described in our previous publication,[4] with a number of primary and secondary amines (Scheme 1).

This reaction was used to alkylate a number of physiologically active compounds, which made it possible to prepare previously unknown glycoconjugates **2–8** (Scheme 2).

Scheme 1

$$\text{Sug}\beta1\text{-NHCOCH}_2\text{Cl} + \text{HNR}^1\text{R}^2 \longrightarrow \text{Sug}\beta1\text{-NHCOCH}_2\text{NR}^1\text{R}^2$$

1a–e

Sug = D-Gal(β1-4)D-Glc (**a**); D-GlcNAc (**b**); D-Gal (**c**); D-Man (**d**); D-Glc (**e**)

Alkylation of secondary amines was studied using morpholine and piperazine and its derivatives (*N*-methylpiperazine and 1,4-diazabicyclo[4.3.0]nonane). Piperazine is a well-known anthelminthic, and its structural fragment is a part of anesthetic, psychotropic, and antitumor drugs. Lectins specific to the residues of β-D-galactose and *N*-acetyl-D-glucosamine are widespread on the surface of animal cells.[14] Therefore, for the synthesis of glycoconjugates we used derivatives of these monosaccharides and the disaccharide lactose.

We found that secondary amines are smoothly alkylated upon treatment with chloroacetyl derivatives of glycosylamines (molar ratio 2 : 1) at 70 °C in MeOH or aqueous MeOH. The course of the reaction can be conveniently monitored by paper electrophoresis. After the reaction has been carried out for 3 h, the conversion of the alkylating reagent was 85–90%. Under the conditions chosen, we did not observe noticeable cleavage of the *N*-glycosylamide bond, whose lability in an alkaline medium has been noted previously for a glucose derivative.[15] The reaction products were separated from the initial *N*-chloroacetylglycosylamines by the cation exchange chromatography and additionally purified by crystallization or chromatography on Al_2O_3; the yields of conjugates **2**, **3c**, and **4** were about 65%.

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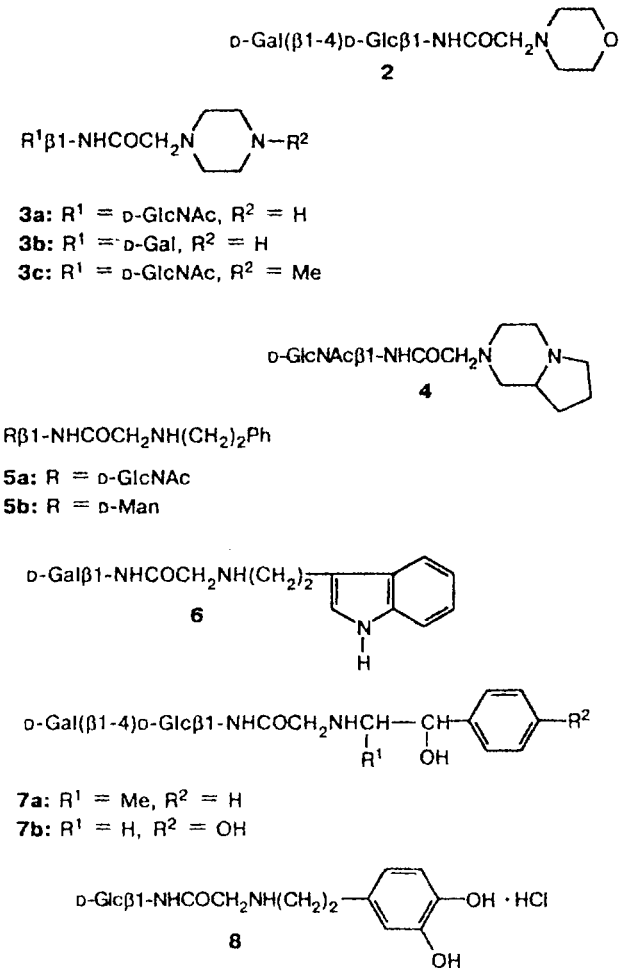
Scheme 2



In the preparation of derivatives **3a** and **3b** by alkylation of piperazine, the best results were obtained when a 10-fold molar excess of the base was used. Under these conditions, the amount of by-products resulting from bis-alkylation was ~10%.

The optimal conditions for the interaction of *N*-chloroacetylglycosylamines with primary amines were selected in relation to the reaction of the corresponding *N*-acetyl-β-D-glucosamine and β-D-mannose derivatives with 2-phenylethylamine. It was found that monoalkylation smoothly occurs at 70 °C only when MeOH—DMSO mixtures are used as solvents. To diminish the undesirable dialkylation, the reaction should be carried out in dilute solutions at a molar ratio of the amine to an alkylating reagent equal to 3 : 1. Under these conditions, the monoalkylation products **5a,b** were isolated in 65—70% yields, while the yield of the dialkyl derivative was no more than 10%.

These conditions proved to be applicable to the preparation of glycoconjugates **6**, **7a**, and **7b**, which are derivatives of important biogenic amines, 2-(indol-3-yl)ethylamine (tryptamine), (*1S,2R*)-2-amino-1-phenylpropan-1-ol (D-norephedrine), and DL-1-(4-hydroxyphenyl)-2-aminoethanol (DL-octopamine), respectively.

Some change in the reaction conditions was required in the synthesis of compound **8**, a derivative of 2-(3,4-dihydroxyphenyl)ethylamine (dopamine). In this case, the D-glucose derivative was used as the alkylating reagent, because it has been reported that the selectivity of interaction of the glucosylated analog of dopamine with various receptors changes compared to that for the non-glucosylated derivative[16] and that the penetration of glucosylated drugs through the blood-brain barrier is facilitated.[17] Due to the lability of the initial amine, the best results were achieved with a higher amine : alkylating reagent ratio, equal to 4 : 1, in more concentrated solutions, and with an increased content of DMSO in the solvent. As a result of these changes, the reaction time substantially decreased, and product **8** was isolated in 56% yield as the corresponding hydrochloride. Unlike the other glycoconjugates described here, compounds **7a,b** and **8** prepared from amino alcohols or amino phenols are purified most efficiently by gel chromatography.

The structures of the obtained compounds **2**—**8** were confirmed by the data of elemental analysis and NMR spectroscopy.

The results obtained demonstrate that alkylation of primary and secondary amines by *N*-chloroacetylglycosylamines can serve as a facile and convenient method for introducing carbohydrate residues into molecules of various drugs. The use of this reaction opens up broad opportunities for the preparation of glycoconjugates with a more complex structure of the carbohydrate fragment, which may be promising materials for the directed drug delivery to target cells.

Experimental

The ^1H and ^{13}C NMR spectra were recorded in D_2O at 300 K on a Bruker WM-250 spectrometer (operating at 250 MHz for ^1H and 75 MHz for ^{13}C). Optical rotation was measured on a Jasco DIP-360 polarimeter. Electrophoresis (30 V cm^{-1}, 30—60 min) was carried out on Filtrak FN 1 paper in pyridinium acetate buffer (0.05 *M* for Py, pH 4.5). The substances were detected by ninhydrin and by the sequence of reagents KIO_4—$AgNO_3$—KOH and Cl_2—KI—starch. The reactions were carried out in test tubes with screw caps, which were closed after air had been displaced by MeOH vapor. The elution of compounds in gel chromatography was monitored using the absorption at 206 nm. Column chromatography was carried out using neutral Al_2O_3. The water of crystallization was determined by the Fischer method.

***N*-Morpholinoacetyl-4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosylamine (2).** Morpholine (0.174 mL, 2 mmol) was added to a solution of *N*-chloroacetyl-4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosylamine monohydrate (**1a**) (0.43 g, 1 mmol) in 6 mL of 90% aqueous MeOH; the mixture was kept for 3 h at 70 °C and for 16 h at 0 °C. The precipitate formed was filtered off, washed with cold MeOH and ether,

and dissolved in 2 mL of H_2O. The solution was applied to a column (1×13 cm) packed with the Amberlite IRC-50 cation exchanger (H^+). The column was washed with 100 mL of H_2O and 100 mL of 0.5 *M* aqueous pyridine. The fractions that contained product **2**, according to the electrophoresis data, were combined and concentrated to dryness, and the residue was recrystallized from MeOH. Yield 0.29 g (63%), m.p. 214—216 °C, $[\alpha]_D^{20}$ +4.8° (*c* 1, H_2O). Found (%): C, 45.11; H, 7.11; N, 6.10; H_2O, 2.80. $C_{18}H_{32}N_2O_{12} \cdot 1/2\ H_2O$. Calculated (%): C, 45.27; H, 6.96; N, 5.87; H_2O, 1.89. ^1H NMR, δ: 2.62 (br.s, 4 H, CH_2NCH_2); 3.22 (br.s, 2 H, $COCH_2$); 3.42—3.97 (m, 16 H); 4.47 (d, 1 H, H(1) Gal, J = 8 Hz); 5.03 (d, 1 H, H(1) Glc, J = 9 Hz). ^{13}C NMR, δ: 54.5 (CH_2NCH_2); 61.7, 62.3, 62.9 (2 CH_2OH, $CO\underline{C}H_2$); 68.1 (CH_2OCH_2); 70.4, 72.8, 73.3, 74.4, 76.95, 77.2, 78.3, 79.6 (C(2)—C(5) Glc and Gal), 80.8 (C(1) Glc); 104.7 (C(1) Gal); 175.0 (CO).

***N*-Piperazinoacetyl-2-acetamido-2-deoxy-β-D-glucopyranosylamine (3a) and *N*-piperazinoacetyl-β-D-galactopyranosylamine (3b).** Piperazine (0.87 g, 10 mmol) was added to a solution of *N*-chloroacetyl-2-acetamido-2-deoxy-β-D-glucopyranosylamine (**1b**) (0.3 g, 1 mmol) in 7 mL of MeOH or *N*-chloroacetyl-β-D-galactopyranosylamine (**1c**) (0.25 g, 1 mmol) in 12 mL of 70% aqueous MeOH. The mixture was heated for 3 h at 70 °C. The MeOH was evaporated, and the residue was dissolved in 20 mL of H_2O; 35 mL of the Dowex 50Wx8 cation exchanger (H^+) was added, and the mixture was stirred for 1 h. The resin was filtered off and washed with 400 mL of H_2O and 300 mL of 1.5 *M* NH_4OH. The alkaline fractions were concentrated to dryness, and the reaction products were isolated from the residue.

Compound **3a** was isolated by chromatography on a column (2.8×11 cm) packed with Al_2O_3 (propan-2-ol → MeOH) followed by crystallization (MeOH—propan-2-ol). Yield 0.2 g (58%), m.p. 218—219 °C, $[\alpha]_D^{20}$ +26.7° (*c* 1, H_2O). Found (%): C, 48.42; H, 7.55; N, 16.25. $C_{14}H_{26}N_4O_6$. Calculated (%): C, 48.54; H, 7.57; N, 16.17. ^1H NMR, δ: 2.05 (s, 3 H, CH_3CO); 2.58 (br.s, 4 H, $\underline{CH_2}N\underline{CH_2}$); 2.92 (br.s, 4 H, $\underline{CH_2}NH\underline{CH_2}$); 3.20 (s, 2 H, $COCH_2$); 3.51—3.98 (m, 6 H); 5.15 (d, 1 H, H(1), J = 9 Hz).

Compound **3b** was isolated by crystallization (MeOH—propan-2-ol). Yield 0.21 g (58%), m.p. 219—221 °C (decomp.), $[\alpha]_D^{20}$ +14.5° (*c* 1, H_2O). Found (%): C, 47.24; H, 7.63; N, 13.52. $C_{12}H_{23}N_3O_6$. Calculated (%): C, 47.20; H, 7.59; N, 13.76. ^1H NMR, δ: 2.60 (br.s, 4 H, $\underline{CH_2}N\underline{CH_2}$); 2.95 (br.s, 4 H, $\underline{CH_2}NH\underline{CH_2}$); 3.25 (br.s, 2 H, $COCH_2$); 3.66—3.87 (m, 5 H); 4.04 (m, 1 H, H(4)); 5.03 (d, 1 H, H(1), J = 9 Hz).

***N*-(4-Methylpiperazin-1-ylacetyl)-2-acetamido-2-deoxy-β-D-glucopyranosylamine (3c).** A mixture of *N*-chloroacetyl-2-acetamido-2-deoxy-β-D-glucopyranosylamine (**1b**) (0.45 g, 1.5 mmol) and *N*-methylpiperazine (0.3 mL, 3 mmol) in 5 mL of MeOH was heated for 3 h at 70 °C. The solvent was evaporated, and the residue was dissolved in 15 mL of H_2O; 12 mL of the Dowex 50Wx8 cation exchanger (H^+) was added, and the mixture was stirred for 1.5 h. The resin was filtered off, washed with 200 mL of H_2O and then with 200 mL of 1.5 *M* NH_4OH. The alkaline fractions were evaporated to dryness. Recrystallization of the residue (MeOH—acetone) gave compound **3c**. Yield 0.4 g (74%), m.p. 205—207 °C, $[\alpha]_D^{20}$ +24.7° (*c* 1, H_2O). Found (%): C, 47.64; H, 8.08; N, 15.37; H_2O, 4.56. $C_{15}H_{28}N_4O_6 \cdot H_2O$. Calculated (%): C, 47.61; H, 7.99; N, 14.81; H_2O, 4.76. ^1H NMR, δ: 2.06 (s, 3 H, CH_3CO); 2.30 (s, 3 H, NCH_3); 2.57 (br.s, 8 H, 4 CH_2); 3.19 (br.s, 2 H, $COCH_2$); 3.50—3.96 (m, 6 H); 5.13 (d, 1 H, H(1), J = 9.5 Hz).

***N*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-2-(1,4-diazabicyclo[4.3.0]non-4-yl)acetamide (4).** Compound **4** was prepared similarly to **3c** from 1,4-diazabicyclo[4.3.0]nonane (0.375 g, 3 mmol)[18] and purified by chromatography on a column (2.5×8 cm) packed with Al_2O_3 (propan-2-ol → MeOH) followed by crystallization (MeOH—ether). Yield 0.5 g (65%), m.p. 150—151 °C, $[\alpha]_D^{20}$ +21.7° (*c* 1, H_2O). Found (%): C, 50.40; H, 7.87; N, 14.52; H_2O, 4.56. $C_{17}H_{30}N_4O_6 \cdot H_2O$. Calculated (%): C, 50.48; H, 7.97; N, 13.85; H_2O, 4.45. ^1H NMR, δ: 1.38 (m, 1 H); 1.71—1.97 (m, 3 H); 2.02 (s, 3 H, CH_3CO); 2.05—2.47 (m, 5 H); 2.71—3.06 (m, 4 H); 3.20 (s, 2 H, $COCH_2$); 3.47—3.59 (m, 2 H, H(4,5) GlcN); 3.65 (t, 1 H, H(3) GlcN); 3.77 (dd, 1 H, H(6a) GlcN); 3.84—3.94 (m, 2 H, H(2b,6b) GlcN); 5.10 (d, 1 H, H(1) GlcN, J = 9.5 Hz). ^{13}C NMR, δ: 21.5 (CH_2); 23.1 (CH_3); 27.8 (CH_2); 51.2 (CH_2); 52.5 (CH_2); 53.3 (CH_2); 55.3 (C(2) GlcN); 57.6 (CH_2); 61.3 (CH_2); 61.6 (CH_2); 63.1 (NCH); 70.7 (C(4) GlcN); 75.3 (C(3) GlcN); 78.8 (C(5) GlcN); 79.4 (C(1) GlcN); 174.6 (CO); 175.7 (CO).

***N*-(*N*-Phenethylglycyl)-2-acetamido-2-deoxy-β-D-glucopyranosylamine (5a) and *N*-(*N*-phenethylglycyl)-β-D-mannopyranosylamine (5b).** 2-Phenylethylamine (0.4 mL, 3 mmol) and 10 mL MeOH were added to a solution of *N*-chloroacetyl-2-acetamido-2-deoxy-β-D-glucopyranosylamine (**1b**) (0.3 g, 1 mmol) or *N*-chloroacetyl-β-D-mannopyranosylamine (**1d**) (0.25 g, 1 mmol) in 2 mL of DMSO, and the mixture was heated for 10 h at 70 °C. The MeOH was evaporated, and the residue was diluted with 25 mL of toluene. The resulting oily product was washed 3 times with toluene and ether, and dissolved in 10 mL of H_2O. The solution was stirred for 1.5 h with 10 mL of the Dowex 50Wx8 cation exchanger (H^+). The resin was filtered off, washed with 150 mL of H_2O, 150 mL of 1.5 *M* NH_4OH, and 150 mL of 1.5 *M* NH_4OH containing 6% Py. The alkaline fractions were concentrated to dryness, and the reaction products were isolated from the residue.

Compound **5a** was isolated by crystallization (MeOH—propan-2-ol). Yield 0.28 g (71%), m.p. 223—225 °C, $[\alpha]_D^{20}$ +21.4° (*c* 1, H_2O). Found (%): C, 55.41; H, 7.11; N, 11.02; H_2O, 2.12. $C_{18}H_{27}N_3O_6 \cdot 1/2\ H_2O$. Calculated (%): C, 55.37; H, 7.23; N, 10.76; H_2O, 2.31. ^1H NMR, δ: 1.95 (s, 3 H, CH_3CO); 2.84 (m, 4 H, CH_2CH_2); 3.34 (br.s, 2 H, $COCH_2$); 3.49—3.60 (m, 2 H, GlcN); 3.66 (t, 1 H, H(3) GlcN); 3.75—3.95 (m, 3 H, GlcN); 5.12 (d, 1 H, H(1) GlcN, J = 9.5 Hz); 7.32—7.50 (m, 5 H, Ar).

Compound **5b** was isolated by chromatography on a column (1.4×12 cm) with Al_2O_3 (acetone → propan-2-ol → MeOH). The yield of the amorphous compound was 0.22 g (65%), $[\alpha]_D^{20}$ −24.8° (*c* 1, H_2O). Found (%): C, 56.71; H, 7.20; N, 8.23. $C_{16}H_{24}N_2O_6$. Calculated (%): C, 56.46; H, 7.11; N, 8.23. ^1H NMR, δ: 2.90 (m, 4 H, CH_2CH_2); 3.46 (br.s, 2 H, $COCH_2$); 3.48 (m, 1 H, H(5) Man); 3.62 (t, 1 H, H(4) Man); 3.68—3.78 (m, 2 H, Man); 3.88—3.98 (m, 2 H, Man); 5.24 (br.s, 1 H, H(1) Man); 7.30—7.48 (m, 5 H, Ar).

***N*-{*N*-[2-(Indol-3-yl)ethyl]glycyl}-β-D-galactopyranosylamine (6)** was synthesized similarly to compound **5** from *N*-chloroacetyl-β-D-galactopyranosylamine (**1c**) (0.25 g, 1 mmol) and tryptamine (0.48 g, 3 mmol) in a mixture of 2 mL of DMSO and 18 mL of MeOH over a period of 30 h; prior to the treatment with the cation exchanger, the aqueous solution was decolorized by carbon. Product **6** was crystallized from H_2O. Yield 0.2 g (54%), m.p. 142—143 °C, $[\alpha]_D^{20}$ +15.4° (*c* 1, CH_3OH). Found (%): C, 54.90; H, 7.17; N, 10.58; H_2O, 3.55. $C_{18}H_{25}N_3O_6 \cdot H_2O$. Calculated (%): C, 54.40; H, 6.85; N, 10.57; H_2O, 4.53. ^1H NMR (CD_3OD), δ: 2.95 (br.s, 4 H, CH_2CH_2); 3.54—3.68 (m, 3 H, Gal);

3.71—3.78 (m, 2 H, Gal); 3.94 (m, 1 H, H(4) Gal); 4.92 (d, 1 H, H(1) Gal, J = 9 Hz); 6.99—7.15 (m, 2 H, Ar); 7.12 (s, 1 H, Ar); 7.37 (d, 1 H, Ar, J = 8 Hz); 7.58 (d, 1 H, Ar, J = 8 Hz). ^{13}C NMR (CD_3OD), δ: 26.7 (CH_2Ar); 51.2 (NCH_2); 53.0 (NCH_2); 62.8 (C(6) Gal); 70.7 (C(4) Gal); 71.8 (C(2) Gal); 76.0 (C(3) Gal); 78.5 (C(5) Gal); 81.6 (C(1) Gal); 112.5, 113.8, 119.6, 119.8, 122.6, 123.8, 129.0, 138.5 (8 C, Ar); 175.4 (CO).

***N*-{*N*-[(*1S,2R*)-1-Hydroxy-1-phenylprop-2-yl]glycyl}-4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosylamine (7a) and *N*-{*N*-[DL-2-hydroxy-2-(4-hydroxyphenyl)ethyl]glycyl}-4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosylamine (7b)** was synthesized similarly to **5** from *N*-chloroacetyl-4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosylamine monohydrate (**1a**) (0.22 g, 0.5 mmol) and D-norephedrine hydrochloride (0.28 g, 1.5 mmol) or DL-octopamine hydrochloride (0.28 g, 1.5 mmol) in the presence of Et_3N (0.11 mL, 1.5 mmol) in a mixture of 1 mL of DMSO and 5 mL of MeOH. The reaction duration was 22 h. The residue obtained after concentration of the alkaline fractions resulting from ion exchange chromatography was treated with acetone (5×15 mL) in order to remove the initial amine (in the case of DL-octopamine, hot acetone was used) and dissolved in 5 mL of H_2O. The solution was applied to a column (4×100 cm) with Sephadex G-25 (fine), and the column was washed with water (1 L) and then with 0.1 *M* AcOH. The fractions containing the products were combined, concentrated to dryness, dissolved in H_2O, and lyophilized, and the amorphous residue was dried *in vacuo* over KOH.

Compound **7a** was obtained in a yield of 0.16 g (61%), $[\alpha]_D^{20}$ +5.2° (*c* 1, H_2O). Found (%): C, 51.42; H, 6.67; N, 5.23. $C_{23}H_{36}N_2O_{12}$. Calculated (%): C, 51.87; H, 6.81; N, 5.26. ^{1}H NMR, δ: 1.18 (d, 3 H, CH_3); 3.10 (m, 1 H, NCH); 3.48 (br.s, 2 H, $COCH_2$); 3.40—4.05 (m, 12 H, Glc, Gal); 4.55 (d, 1 H, H(1) Gal, J = 8 Hz); 4.70 (d, 1 H, CHAr, J = 6 Hz); 5.03 (d, 1 H, H(1) Glc, J = 9 Hz); 7.46—7.58 (m, 5 H, Ar).

Compound **7b** was obtained as the corresponding acetate by precipitation with ether from a solution in MeOH. Yield 0.21 g (79%) $[\alpha]_D^{20}$ +4.5° (*c* 1, H_2O). Found (%): C, 48.10; H, 6.34; N, 4.51. $C_{21}H_{34}N_2O_{13} \cdot CH_3COOH$. Calculated (%): C, 48.48; H, 6.44; N, 4.71. ^{1}H NMR, δ: 1.90 (s, 3 H, CH_3CO); 2.88 (m, 2 H, NCH_2); 3.38 (br.s, 2 H, $COCH_2$); 3.47—3.94 (m, 13 H); 4.44 (d, 1 H, H(1) Gal, J = 8 Hz); 4.98 (d, 1 H, H(1) Glc, J = 9 Hz); 6.89 (d, 2 H, Ar, J = 8 Hz); 7.32 (d, 2 H, Ar, J = 8 Hz).

***N*-{*N*-[2-(3,4-Dihydroxyphenyl)ethyl]glycyl}-β-D-glucopyranosylamine hydrochloride (8).** Triethylamine (0.147 mL, 2 mmol) was added to a solution of *N*-chloroacetyl-β-D-glucopyranosylamine (**1e**) (0.13 g, 0.5 mmol) and dopamine (0.38 g, 2 mmol) in a mixture of 1.3 mL of DMSO and 2.6 mL of MeOH. The mixture was heated for 2.5 h at 70 °C and poured in 45 mL of toluene, and the precipitate was washed with toluene (3×15 mL) and ether and dissolved in 3 mL of H_2O. To the solution, 4 mL of 0.5 *M* HCl was added, and the solution was applied to a column (5×90 cm) with Sephadex G-15. The column was washed with H_2O (1.5 L) and then with 0.1 *M* AcOH. The fractions containing the reaction products were combined, concentrated *in vacuo*, and lyophilized, and the amorphous residue was dried over P_2O_5. The yield of product **8** was 0.115 g (56%); $[\alpha]_D^{20}$ −9.6° (*c* 1, H_2O). Found (%): C, 46.60; H, 6.64; N, 6.23, Cl, 9.07. $C_{16}H_{24}N_2O_8 \cdot HCl$. Calculated (%): C, 47.00; H, 6.16; N, 6.85, Cl, 8.67. ^{1}H NMR, δ: 2.95 (t, 2 H, CH_2Ar, J = 7 Hz); 3.36 (t, 2 H, NCH_2, J = 7 Hz); 3.39—3.59 (m, 4 H, Glc); 3.73 (dd, 1 H, H(6a) Glc); 3.89 (dd, 1 H, H(6b) Glc); 3.98 (br.s, 2 H, $COCH_2$); 5.03 (d, 1 H, H(1), J = 9); 6.77 (d, 1 H, Ar, J = 8); 6.86 (s, 1 H, Ar); 6.42 (d, 1 H, Ar, J = 8).

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