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Glycosyl derivatives of 2-bromosugar of selected non-steroidal anti-inflammatory drugs. Synthesis and QSAR data

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Abstract

On the basis of molecular modeling and calculation of physicochemical SAR data we obtained new derivatives of 2-bromosugars **5a**–**d** and **6** for widely used non-steroidal anti-inflammatory drugs (NSAIDs). Compounds **5a**–**d** and **6** were synthesized as stable, crystalline compounds from the reaction of phosphoroates **1**–**3** with salicylic acid (**4a**), aspirin (**4b**), diclofenac (**4c**) and indomethacin (**4d**) in an aprotic solvent. The reaction took place in the presence of silver carbonate as the activator of leaving groups with high stereoselectivity and good yields. The structures of the new derivatives of **5a**–**d** and **6** for NSAIDs were established by spectroscopic methods ^{1}H and ^{13}C NMR, and elemental analyses.

Keywords: Glycosyl; 2-Bromosugars; Non-steroidal anti-inflammatory; QSAR

1. Introduction

Since the term prodrug was introduced by Albert et al. [1], scientific research has aimed not only at the synthesis of new drugs, but also at obtaining new derivatives of well known drugs to improve their pharmacokinetic properties. In the group of non-steroidal anti-inflammatory drugs (NSAIDs) widely used in the therapy, current research aims at obtaining new prodrugs causing weaker adverse effects, in particular less ulcerogenic and less irritating to gastric mucosa. The derivatives of carboxylic acids constitute a large group of these compounds; they are weak acids of pK_a between 3 and 5. The synthesis of prodrugs for aspirin by Hansen and Senning (1983) [2] prompted rapid development in the field of synthesis of new NSAIDs derivatives. One of the trends in this group is the exchange of carboxylic group for ester derivatives, for example 2-formylphenyl esters [3], morpholinoalkyl esters (HCl salts) [4,5], butyl, octyl and farnesil esters [7–9], omega-(*N*,*N*,*N*-trialkylammonium)alkyl esters [10] and orthoesters [11,12]. The obtained derivatives are more lipophilic [4] and far less irritating to the gastric mucosa than their parent prodrugs [3,5,6,9].

Our interest so far has centred on the synthesis of glycosyl esters of 2,3,4,6-tetra-*O*-acetyl-β-D-hexopyranose, 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucose, and 2,3,4-tri-*O*-acetyl-β-D-xylose for selected NSAIDs, e.g. salicylic acid, aspirin, indomethacin [13,14] and diclofenac [15] using glycosyl phosphoroates as effective glycosyl donors.

2. Experimental

2.1. Chemistry

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker AC 200 (200.11 and 50.33 MHz, respectively). The ^{1}H and ^{13}C chemical shifts are reported in parts per million (δ) downfield from Me_4Si (1%) as the internal standard. Melting points were determined with a Boetius PHMK 05 apparatus and are uncorrected. Specific rotations were measured in chloroform: Polamat A polarimeter. Elemental analyses were carried out by Microanalytical Laboratory, Institute of Chemistry, Medical University of Łódź.

Phosphoroates of 2-bromosugar used as glycosyl donors of **1**–**3** were prepared according to Refs. [16,17]. All non-steroidal anti-inflammatory drugs **4a**–**d** were

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used after drying over P_2O_5. Reactions were performed in dry benzene.

*2.1.1. General procedure for the synthesis of glycosyl esters of 2-bromosugars having β-D-gluco **5a–d** and α-D-manno **6** configuration*

Stoichiometric amounts of glycosyl derivatives **1–3** (1 mmol) in benzene solution containing molecular sieves (4 Å) were mixed with appriopriate acid **4a–d** (1 mmol) in benzene solution and Ag_2CO_3 (0.5 mmol). The mixture was heated at reflux in the dark (for specific conditions, see Table 2). When reaction was stopped (monitored by ^1H and ^{13}C NMR), precipitated silver phosphoroacid salt and molecular sieves were removed by filtration (through Celite 535). The filtrate was washed with water and aqueous sodium carbonate and again with water. After drying with $MgSO_4$, organic solvent evaporated in vacuo. Syrup or semicrystalline residue obtained by crystallization from ethanol afforded pure derivatives of glycosyl esters **5a–d** and **6**.

*2.1.2. 1-O-(2-Hydroxybenzoyl)-3,4,6-tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranose (**5a**)*

The derivative **1** (0.518 g, 1 mmol), salicylic acid (**4a**) (0.138 g, 1 mmol) and Ag_2CO_3 (0.137g, 0.5 mmol) were condensed (for reaction conditions see Table 2, entry 1).The glycosyl derivative **5a** was obtained (0.320 g) with 65% yield. Physical data are presented in Table 2, entry 1. ^1H NMR ($CDCl_3$): δ 2.03, 2.05, 2.10 (3s, 9H, OAc), 3.90–4.04 (m, 1H, H-5), 4.08–4.14 (m, 2H, H-6a, H-6b), 4.34 (dd, $J_{1,2} = 8.6$ Hz, $J_{2,3} = 9.0$ Hz, 1H, H-2), 5.08 (t, $J_{3,4} = 10.0$ Hz, $J_{4,5} = 9{,}4$ Hz, 1H, H-4), 5.39 (dd, $J_{2,3} = 8.5$ Hz, $J_{3,4} = 9{,}1$ Hz, 1H, H-3), 6.03 (d, $J_{1,2} = 9{,}0$ Hz, 1H, H-1), 6.90–7.00 (m, 2H, H-aromat), 7.77–7.89 (m, 1H, H-aromat), 10.23 (s,1H,OH).^{13}C NMR ($CDCl_3$): δ 20.88 (s, $2 \times CH_3CO$), 20.47(s, CH_3CO), 47.19 (C-2), 61.26 (C-6), 68.42 (C-4), 72.32 (C-5), 74.15 (C-3), 93.52 (C-1), 117.55, 117.66, 119.38, 119.56, 130.13, 136.70 (6s, C-aromat.), 162.06 [O*C*(O)Ph], 169.28, 169.40, 169.86 [O*C*(O)CH_3].

*2.1.3. 1-O-(2-Acetyloxybenzoyl)-3,4,6-tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranose (**5b**)*

The derivative **2** (0.502 g, 1 mmol), acetylsalicylic acid (**4b**) (0.170 g, 1 mmol) and Ag_2CO_3 (0.137 g, 0.5 mmol) were condensed (for reaction conditions, see Table 2, entry 2). The glycosyl derivative **5b** (0.325 g) with 61% yield was obtained. Physical data are presented in Table 2, entry 2. ^1H NMR ($CDCl_3$): δ 2.03, 2.06, 2.07 (3s, 9H, OAc), 2.10 (s, 3H, Ph-OCO*C*H_3), 3.89–4.00 (m, 1H, H-5), 4.02–4.15 (m, 2H, H-6a, H-6b), 4.32 (dd, $J_{1,2} = 7.6$ Hz, $J_{2,3} = 8.0$ Hz, 1H, H-2), 5.07 (dd, $J_{2,3} = 9.2$ Hz, $J_{4,5} = 9.1$ Hz, 1H, H-4), 5.39 (dd, $J_{2,3} = J_{4,5} = 9.2$ Hz, 1H, H-3), 5.99 (d, $J_{1,2} = 9.1$ Hz, 1H, H-1), 6.91–7.13 (m, 1H, H-aromat.), 7.37–7.43 (m, 1H, H-aromat.), 7.57–7.70 (m, 1H, H-aromat.), 8.05–8.27 (m, 1H, H-aromat.). ^{13}C NMR: δ 20.23 (s, $2 \times CH_3CO$), 20.23, 20.65 (2s, $2 \times CH_3CO$), 47.30 (C-2), 61.09 (C-6), 68.29 (C-4), 72.49 (C-5), 74.05 (C-3), 93.19 (C-1), 123.88, 125.86 (2s, 2C-aromat.), 128.04 (s, 2C-aromat.), 131.74, 134.59 (2s, C-aromat.), 161.45 [O*C*(O)Ph], 169.17, 169.17, 169.24, 169.52, 170.18 [O*C*(O)CH_3].

*2.1.4. 1-O-[o-(2,6-Dichloroanilino)phenacetyl]-3,4,6-tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranose (**5c**)*

Derivative **2** (0.502 g, 1 mmol), diclofenac (**4c**) (0.292 g, 1 mmol) and Ag_2CO_3 (1.137 g, 0,5 mmol) were condensed (for reaction conditions, see Table 2, entry 3). The glycosyl derivative **5c** (0.415 g) with 63% yield was obtained. Physical data are presented in Table 2, entry 3. ^1H NMR ($CDCl_3$): δ 1.16 (s, 1H, NH), 1.92, 1.96, 1.99 (3s, 9H, OAc), 3.78 (s, O*C*H_2Ph), 3.80–3.89 (m, 1H, H-5), 3.94–4.01 (m, 2H, H-6a, H-6b), 4.25 (dd, $J_{1,2} = 8.0$ Hz, $J_{2,3} = 8.5$ Hz, 1H, H-2), 4.94 (dd, $J_{3,4} = 9.4$ Hz, $J_{4,5} = 9.2$ Hz, 1H, H-4), 5.24 (dd, $J_{2,3} = 9.3$ Hz, $J_{3,4} = 10.0$ Hz, 1H, H-3), 5.79 (d, $J_{1,2} = 9.1$ Hz, 1H, H-1), 6.22–6.50 (m, 1H, H-aromat.), 6.87–7.05 (m, 2H, H-aromat.). ^{13}C NMR ($CDCl_3$): δ 20.48 (s, 2*C*H_3CO), 20.60 (s, *C*H_3CO), 37.88 (O*C*H_2Ph), 47.43 (C-2), 61.26 (C-6), 68.39 (C-4), 72.87 (C-5), 74.23 (C-3), 93.49 (C-1), 118.85 (s, 2C-aromat.), 122.42 (s, 2C-aromat.), 123.99 (s, 2C-aromat.), 128.26 (s, 2C-aromat.), 128.80 (s, 3 C-aromat.), 130.99 (s, C-aromat.), 169.38 [O*C*(O)Ph], 169.94 [$2 \times$ O*C*(O)CH_3], 170.09 [O*C*(O)CH_3].

*2.1.5. 1-O-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl-acetyl]-3,4,6-tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranose (**5d**)*

Derivative **1** (0.518 g, 1 mmol), indomethacin (**4d**) (0.629 g, 1 mmol) and Ag_2CO_3 (0.137 g, 0.5 mmol) were condensed (reaction conditions see Table 2, entry 4) to give the glycosyl derivative **5d** (0.525 g) with 74% yield. Physical data are presented in Table 2, entry 4. ^1H NMR ($CDCl_3$): δ 1.55 (s, 3H, CH_3), 2.02, 2.06, 2.08 (3s, 9H, OAc), 2.38 (s, 1H, O*C*H_2Ph), 3.77–3.85 (m, 1H, H-5), 3.90–3.95 (m, 1H, H-6a), 4.11–4.28 (m, 1H, H-6b), 4.32 (dd, $J_{1,2} = J_{2,3} = 11.7$ Hz, 1H, H-2), 5.03 (t, $J_{3,4} = 9.3$ Hz, $J_{4,5} = 10.0$ Hz, 1H, H-4), 5.32 (dd, $J_{2,3} = 9.2$ Hz, $J_{3,4} = 9.1$ Hz, 1H, H-3), 5.82 (d, $J_{1,2} = 9.1$ Hz, 1H, H-1), 6.63–6.70 (m, 1H, H-aromat.), 6.84–6.88 (m, 1H, H-aromat.), 6.90–6.93 (m, 1H, H-aromat.), 7.44–7.48 (m, 2H, H-aromat.). ^{13}C NMR ($CDCl_3$): δ 13.39 (s, CH_3), 20.51 (s, $2 \times CH_3CO$), 20.65 (s, *C*H_3CO), 29.87 (O*C*H_2Ph), 47.61 (C-2), 55.69 (OCH_3), 61.33 (C-6), 68.50 (C-4), 72.98 (C-5), 74.30 (C-3), 93.56 (C-1), 101.12, 111.29, 111.82, 114.95 (4s, 4C-aromat.), 129.12 (s, 4C-aromat.), 131.19 (s, 4C-aromat.), 139.34, 156.06 (2s, 2C-aromat.), 168.00 [O*C*(O)CH_2], 169.44 (s, 2CH_3CO), 170.48 (s, CH_3*C*O).

*2.1.6. 1-O-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl-acetyl]-3,4,6-tri-O-acetyl-2-bromo-2-deoxy-α-D-mannopyranose (**6**)*

Derivative **3** (0.585 g, 1 mmol), indomethacin (**4d**) (0.629 g, 1 mmol) and Ag_2CO_3 (0.137 g, 0.5 mmol) were condensed (for reaction conditions see Table 2, entry 5) to give the glycosyl derivative **6** (0.520 g) with 74% yield. Physical data are presented in Table 2, entry 5. ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 3H, CH_3), 2.00, 2.01, 2.04 (3s, 9H, OAc), 2.34 (s, 2H, CH_3), 3.73 (d, $J_{H,H} < 1$ Hz, 3H, OCH_3), 3.75–3.88 (m, 1H, H-5), 4.00–4.22 (m, 2H, H-6a, H-6b), 4.39 (dd, $J_{1,2} = J_{2,3} < 1$ Hz, H-2), 5.02 (dd, $J_{3,4} = 9.0$ Hz, $J_{4,5} = 9.3$ Hz, 1H, H-4), 5.22 (dd, $J_{2,3} = J_{3,4} = 9.3$ Hz, 1H, H-3), 6.23 (d, $J_{1,2} = 1.3$ Hz, 1H, H-1), 6.83, 6.92–6.96, 7.27–7.25, 7.34–7.42, 7.45–7.48 (dd, 3 × m, 1H, 2H, 2H, 2H, H-aromat.). ^{13}C NMR ($CDCl_3$): δ 13.34 (s, CH_3), 20.74, 20.77, 20.84 (3s, CH_3CO), 30.11 (CH_2), 47.44 (C-2), 61.38 (C-6), 67.44 (C-4), 69.16 (C-5), 71.25 (C-3), 93.33 (C-1), 111.49, 114.83 (2s, 2C-aromat.), 128.17 (s, 5C-aromat.), 128.98, 130.36 (2s, 2C-aromat.), 131.01 (s, 2C-aromat.), 133.67, 135.99, 139.09 (3s, 3C-aromat.), 168.01 [$OC(O)CH_2$], 169.68, 170.24, 170.41 (CH_3CO).

2.2. Computational calculations

The calculations for the present work were obtained using the semiempirical AM1 method supplied by the code HyperChem Release 5.1 (Hypercube, Inc.). The Polak–Ribiere algorithm was employed for geometry optimization. The convergence criteria were adopted at energy gradient of 0.01 kcal mol^{-1} A^{-1} for the compounds **5a**–**d** and **6**. Partial charges on the atoms were determined using single-point AM1 calculations.

3. Results and discussion

As a continuation of our studies on the development of new prodrugs for NSAIDs, basing on molecular modelling and calculation of physicochemical data, we have designed a series of glycosyl ester derivatives for drugs of carboxyl acids structure. In order to increase their lipophilic properties, we chose derivatives with the structure of 2-bromosugars, which contain acetyl protective groups in the sugar molecule. Lipophilic property is an important factor affecting the distribution and further changes of a molecule in the body. Increased lipophilic property is often correlated with increased biological activity, and increased capability of penetration through the skin [18]. We have recently demonstrated that the introduction of a sugar part into the molecule of diclofenac (NSAID) by a glycosyl bond, with acetyl protecting rests, causes an increase of lipophilic property [19].

We have employed the HyperChem program 5.1P (Hypercube Inc.) to construct models of salicylic acid (**4a**), aspirin (**4b**), diclofenac (**4c**), indomethacin (**4d**) and their derivatives with 2-bromosugars having β-D-*gluco* (**5a**–**d**) and α-D-*manno* (**6**) configuration with acetyl rests in the sugar ring. Program ChemPlus 2.0 was used for the calculation of SAR data: surface area (GRID), volume of molecule, log *P*, polarizability, refractivity and dipole moment [20]. These data for compounds **5a**–**d**, **6** and parents drugs are presented in Table 1.

The analysis of the obtained data shows that the introduction of 2-bromosugar rest into a molecule of NSAID caused an increase of log P value, in comparison with this value for the parent drugs. The values of log *P* for derivatives of indomethacin with the configuration of β-D-*gluco* (**5d**) and α-D-*manno* of 2-bromosugars (**6**) are different, the compound **5d** shows higher value, and thus its lipophilic properties are better. The unexpectedly high value of dipole moment for the derivative **6**, as compared with the analogue **5d**, is connected with a different shape of the molecule, because **5d** has α-configuration and **6** is β-glucosyl derivative models of the **5d** and **6** molecules are shown in Fig. 1.

Table 1
Comparison of SAR properties of compounds **5a**–**d**, **6** and their parent drugs (ChemPlus ver. 2.0 calculations)

SAR properties of	**5a**	SAL [a]	**5b**	ASP [a]	**5c**	DIC [a]	**5d**	IND [a]	**6**
Surface area (GRID) of molecule (Å^2)	637.47	284.2	667.26	347.1	811.31	453.40	859.67	562.52	784.05
Volume of molecule (Å^3)	1133.8	422.3	1210.9	535.9	1470.4	754.94	1606.67	956.36	1545.72
Log *P* of molecule	1.595	1.461	1.378	1.244	4.099	3.965	3.806	3.255	3.033
Polarizability of molecule (Å^3)	40.31	13.63	44.06	17.38	56.37	29.69	61.54	36.70	63.29
Refractivity of molecule (Å^3)	100.43	34.51	109.97	43.95	141.38	75.461	156.46	96.36	161.23
Dipole moment (*D*)	2.60	2.20	4.68	4.13	4.84	0.92	3.87	2.71	7.39

[a] SAL, salicylic acid; ASP, acetylsalicylic acid; DIC, diclofenac; IND, indomethacin.

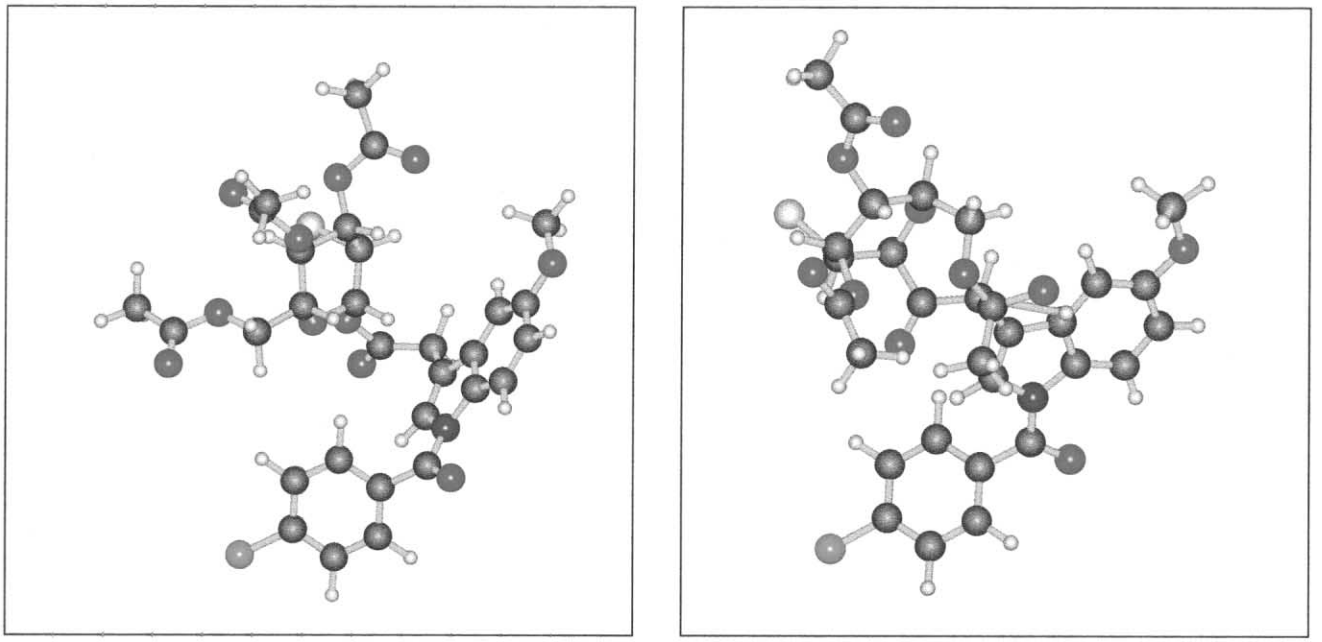


Fig. 1. Comparison of the shape of molecules **5d** and **6** (the chlorobenzoyl residues of indomethacin were placed in the plane of figure).

Table 2
Reaction conditions and physical data for glucosyl esters of 2-bromosugars of the NSAIDs, **5a**–**d** and **6**

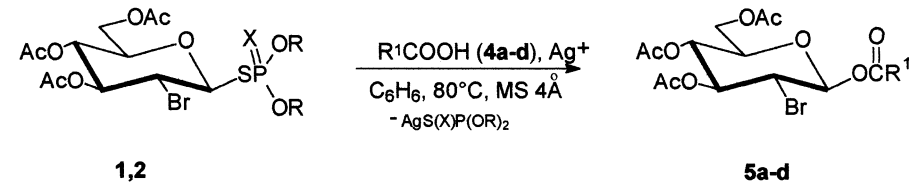
Entry	Glycosyl donor	Acceptor	Ester	Reaction time (h) [a]	$[\alpha]_{578}^{27}$ in $CHCl_3$(c)	M.p. (°C) [b]	Formula [c]
1	**1**	**4a**	**5a**	13	−1.9 (1.1)	153–154	$C_{19}H_{21}BrO_{10}$ (489.27)
2	**2**	**4b**	**5b**	12	+3.2 (1.0)	158–160	$C_{21}H_{23}BrO_{11}$ (531.31)
3	**2**	**4c**	**5c**	14	+3.8 (1.1)	179–181	$C_{26}H_{26}BrCl_2NO_9$ (647.30)
4	**1**	**4d**	**5d**	13	+1.2 (1.5)	191–192	$C_{31}H_{31}BrClNO_{11}$ (708.94)
5	**3**	**4d**	**6**	16	+66 (1.1)	142–144	$C_{31}H_{31}BrClNO_{11}$ (708.94)

[a] Reaction performed in boiling benzene.
[b] Crystallization from ethanol, repeated three times.
[c] All esters were analyzed for C, H, N and results agreed to ±0.4% of theoretical values.

Total correlation of the calculated SAR parameters with pharmacological activity of these derivatives will be possible to obtain after pharmacological results have been seen. This will enable the construction of further examples of glycosyl derivatives of therapeutic agents with acid function groups which will show better therapeutic properties.

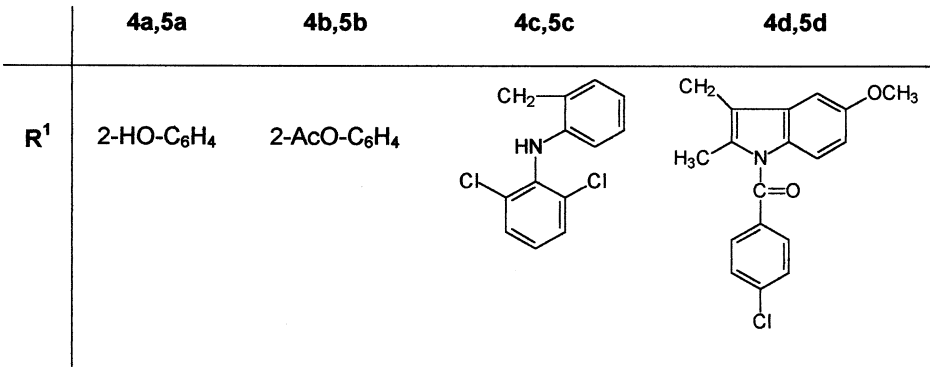
We have synthetized glycosyl derivatives of 2-bromo-2-deoxy-β-D-glucopyranose (**5a**–**d**) and α-D-mannopyranose (**6**) in the reaction of phosphorodithioates (**1**) [19] and thioates (**2** and **3**) of 2-bromosugars [20] with some NSAIDs (mentioned above), which have the structure of carboxylic acids (**4a**–**d**). The reaction in boiling benzene, for reaction conditions see Table 2, in the presence of silver carbonate as the activator of leaving groups, and molecular sieves (4 Å) led to derivatives of **5a**–**d** (Scheme 1) and **6** (Scheme 2) with quantitative yields. The α/β ratio was determined on crude post- reaction mixture by ^1H and ^{13}C NMR spectroscopy. The data indicated highly stereoselective course of the reaction of compounds **1** and **2** with **4a**–**d**. Glycosyl derivative of indomethacin (**6**) was afforded from the reaction of **4d** and **3** with similar stereoselectivity. Crystallization from ethanol gave pure esters of **5a**–**d** and **6** with satisfactory yields. Physical data are presented in Table 2, entries 1–5. The data from ^1H NMR, chemical shift in the region $\delta = 5.79$–6.03 ppm (as doublet) and the value of vicynal coupling constant $J_{1,2} = 9.1$ Hz for the anomeric proton of glycosyl derivatives **5a**–**d** indicated their β-D-*gluco* configuration. The signal of H-1 in down field $\delta = 6.23$ (as a doublet) and the value of coupling constant between H-1 and H-2, $J_{1,2} = 1.3$Hz, show that idomethacine glycosyl derivative of the **6** has α-D-*manno* configuration.

Synthetized glycosyl esters of 2-bromo-2-deoxy-D-hexopyranoses (**5a**–**d** and **6**) are stable for several months at ambient temperature and constitute new examples of derivatives for NSAIDs.

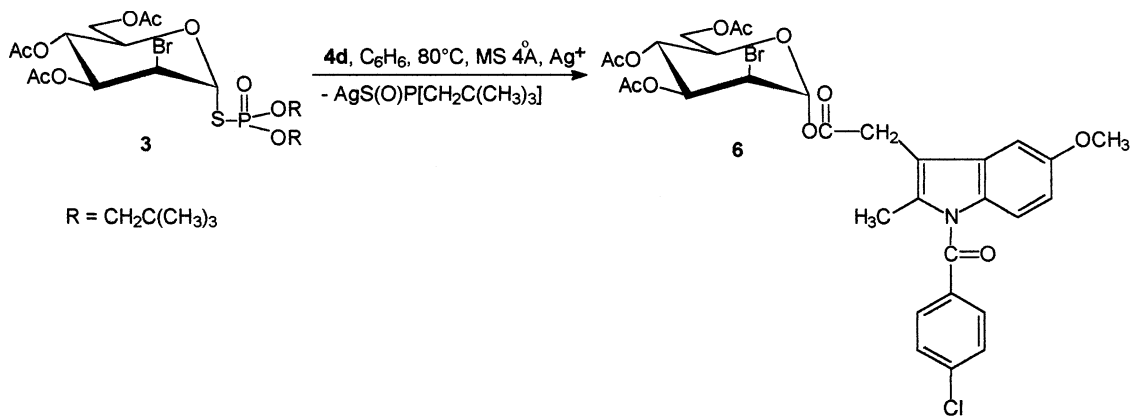


1,2 5a-d

1. X = S, 2. X = O R =



Scheme 1. Glycosylation of the NSAIDs **4a**–**d** by **1** and **2**.



Scheme 2. Glucosylation of indomethacin **4d** by **3**.

Acknowledgements

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