SYNTHESIS OF β-D-GLUCOPYRANOSIDES OF 6-SUBSTITUTED 2-(INDOL-3-YL)BENZOTHIAZOLES

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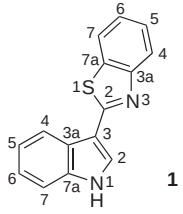
A linear synthesis of substituted 1-(β-D-glucopyranosyl)benzocamalexins starting from indoline and penta-*O*-acetyl-β-D-glucopyranose was elaborated. Jacobson cyclization of corresponding 4-substituted peracetylated β-D-glucopyranosylindole-3-carbothioanilides employing potassium ferricyanide under basic conditions was a key synthetic step.

Keywords: Indoles; Jacobson reaction; Phytoalexins; Benzocamalexin; Glycosides; Glycosidations; Benzothiazoles; Thioamides; Nucleosides.

Aryl benzothiazoles are interesting synthetic targets. An early study of 2-arylbenzothiazoles described their antimicrobial activity against *Mycobacterium tuberculosis*[1]. More recent studies revealed in these heterocycles a broad spectrum of antitumor activities. Polyhydroxylated 2-phenylbenzothiazoles and 2-(4-aminophenyl)benzothiazole, designed as a potential tyrosine kinase inhibitors, exhibited cytotoxicity against a range of human cancer cell lines[2a]. Subsequent extensive SAR studies of this simple pharmacophore[2b–2g] resulted in development of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole as an L-lysinamide water-soluble prodrug which was scheduled to enter Phase 1 clinical evaluation[2h,2i]. Some arylbenzothiazoles were synthesized as bioisosteres of active 2-arylbenzoxazoles and tested as inhibitors of lysophosphatic acid acyltransferase-β, the protein playing an important role in signaling pathways involved in tumor cell survival[3]. Moody et al.[4] performed quite a wide range of studies devoted to

indolylthiazoles and the highest antiproliferative effect achieved against SKBr3 breast cancer cells with 2-(benzothiazol-2-yl)-1-methylindole.

2-Indol-3-ylbenzothiazole, benzocamalexin (**1**), attracted our interest due to its structural analogy with the naturally occurring phytoalexin camalexin[5a] **2** which exhibited antifungal activity against *Alternaria brassicae Cladosporium* sp. or *Alternaria brassicicola*[5b,5c] and significant cytotoxic activity against human breast cancer cell line SKBr3 [4]. In addition, antiproliferative activity of 1-β-D-ribofuranosyl- and 1-α-D-mannopyranosylbenzocamalexin was recently described by our group[6]. These outcomes prompted us to study a method for the introduction of substituents on the benzothiazole moiety of 1-glycosylbenzocamalexins.



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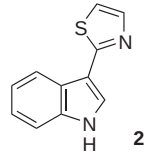

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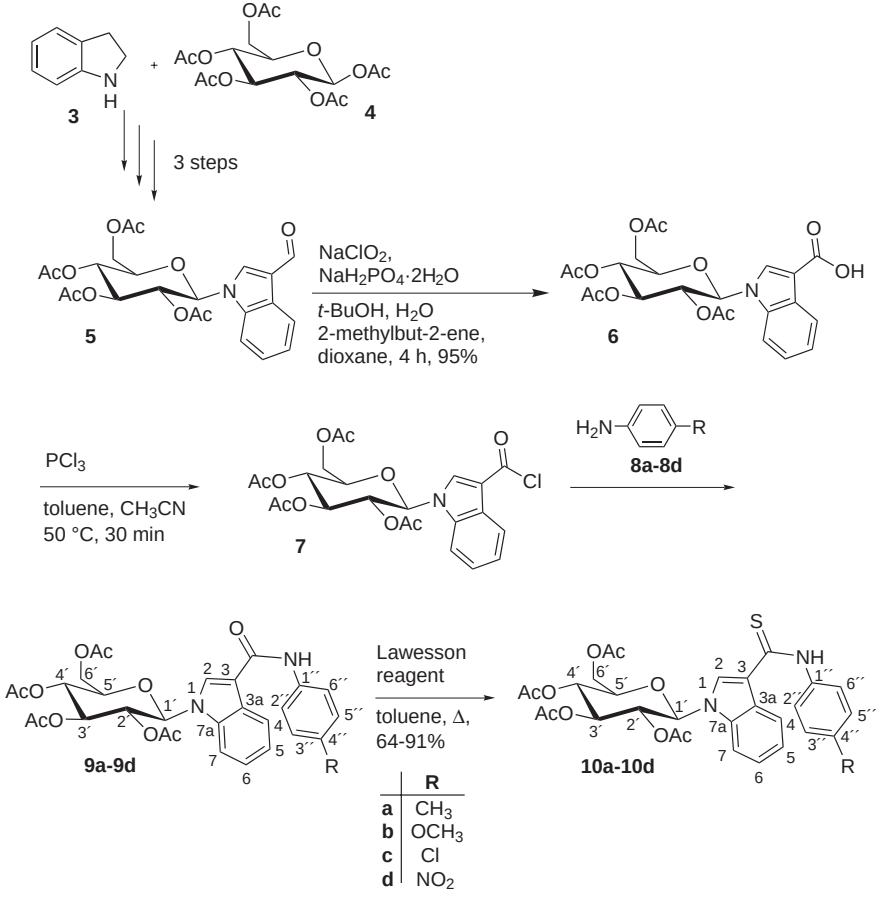
Syntheses of benzothiazole ring via the reactions of aldehydes and ketones with 2-aminobenzene-1-thiol is well known and 2-(indol-3-yl)-benzothiazole and its 1-substituted derivatives were synthesized in reactions of indole-3-carbaldehyde[7] and 1-glycosylindole-3-carbaldehyde[6]. Unfortunately using of substituted 2-aminobenzene-1-thiols does not seem to be advantageous for the synthesis of 2-(indol-3-yl)benzothiazoles bearing substituents on benzothiazole moiety. The main reason is the poor commercial and synthetic availability of substituted 2-aminobenzene-1-thiols. Only a few syntheses of such derivatives have been reported to date[8]. In addition, this method is often not appropriate for many substituted 2-arylbenzothiazoles due to the difficulties encountered in the synthesis caused by the readily oxidisable 2-aminobenzene-1-thiols bearing substituent groups[2g]. On the other hand, introduction of substituents into benzocamalexin was performed via the cyclization of 4-substituted indole-3-carbothioanilides under Hugeshoff conditions[9]. Therefore we decided to investigate applicability of this approach to the synthesis of *N*-glycosides of substituted benzocamalexins using D-glucose as a model saccharide.

The synthesis of 1-(β-D-glucopyranosyl)indole-3-carbothioamides as a key scaffold for the Hugeshoff reaction started from 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)indole-3-carbaldehyde[6,10f] (**5**; Scheme 1) prepared from

indoline (**3**) and peracetylated β-D-glucose (**4**) applying the indoline–indole protocol[10]. Aldehyde **5** was efficiently oxidized at room temperature with $NaClO_2$[11] in a mixture of *tert*-butyl alcohol, dioxane and water in the presence of 2-methylbut-2-ene and $NaH_2PO_4 \cdot 2H_2O$. Thus carboxylic acid **6** was prepared in an excellent of 95% yield (Scheme 1).

The reaction of **6** with PCl_3 in a mixture of toluene and acetonitrile at 50 °C gave chloride **7** (Scheme 1). The reaction mixture was concentrated under reduced pressure to 1/6 of the initial volume and unstable crude product **7** was used without further purification in the subsequent reaction.



SCHEME 1

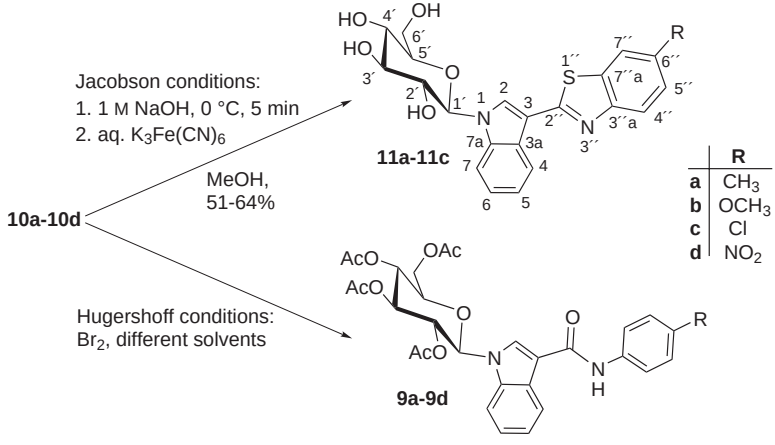
The incorporation of different substituents into the aglycon moiety was performed through the reactions of crude chloride **7** with 4-substituted anilines **8a**–**8d** in toluene (Scheme 1). The acylation of 4-methyl- **8a** and 4-methoxyaniline **8b** possessing electron-donating substituents proceeded readily and afforded anilides **9a** and **9b** in 99 and 85% yield during 24 h (Scheme 1). In **8c**, the electron-withdrawing chlorine slightly decreased nucleophilicity of nitrogen and reaction with chloride **7** required prolonged reaction time (48 h) at room temperature affording product **9c** in a very good 88% yield. The least reactive 4-nitroaniline **8d** afforded no product at room temperature even after stirring for 5 days. It was found: that the reaction can be successfully performed at the reflux temperature in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP), affording compound **9d** in 75% yield within 2 h (Scheme 1). Conversion of anilides **9a**–**9c** to thioanilides **10a**–**10c** (Scheme 1) proceeded readily with the Lawesson reagent in boiling toluene[12] during 0.5 h and gave very good yields of compounds **10a** (91%), **10b** (94%) and **10c** (83%). Less reactive **9d** required 24-h heating and afforded thioanilide **10d** in 64% yield.

The most common method for preparation of benzothiazoles is the Hugershoff reaction of arylthioureas[13]. Using the recently described conditions[9], we tried to achieve the Hugershoff ring closure by the reaction of 1-glucosylthioanilides **10a**–**10d** with Br_2 in $CHCl_3$ (Table I, entry 1). TLC monitoring of the reactions revealed the consumption of the starting material and formation of an unstable product along with anilides **9a**–**9d** in 15 min. Attempts to work up the reaction by washing with saturated solution of $NaHCO_3$ led only to isolation of anilides **9a**–**9d**. Simple evaporation of the solvent under reduced pressure gave a mixture of thioanilides and

TABLE I
Attempts at cyclization of *N*-(4-substituted phenyl)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-indole-3-carbothioamides **10a**–**10d**

Reagent (equiv.)	Solvent
Br_2 (1.1–3)	$CHCl_3$[13], dioxane, CH_3COOH[14]
$SOCl_2$[15] (5)	$CHCl_3$
N-Bromosuccinimide (2)	$CHCl_3$
Br_2 + tetrabutylammonium bromide[16] (1.2 + 1.2)	$CHCl_3$
Pyridiniumtribromide (2)	$CHCl_3$
m-Chloroperoxybenzoic acid[17] (2)	CH_2Cl_2

anilides in the ratio ca. 1:1. Using of strictly anhydrous conditions under nitrogen atmosphere afforded the same result. On the basis of these observations it seems plausible that a highly unstable intermediate, arising in the reaction mixture, quickly hydrolyzed in contact with air moisture or aqueous work up. Several modifications of reaction conditions (Table I, entries 2–6) gave the same result: fast consumption of the starting material and isolation of amides **9a**–**9d** as main products (Scheme 2). Since the ring closure of indole-3-carbothioamides substituted on indole nitrogen proceeded smoothly[9], the failure of the Hugershoff cyclization with thioamides **10a**–**10d** can be attributed to electronic and/or steric effects of the saccharide moiety. Study of this problem will be the subject of our future investigation.



SCHEME 2

The unexpected failure of cyclization of 1-glucosylindole-3-carbothioamides **10a**–**10d** made us apply another method to obtain desired 1-glucosylbenzocamalexins. Synthesis of benzothiazole ring is also possible using the Jacobson oxidative cyclization[2b,2g,18] of arylthioanilides unsubstituted in *ortho*-position[18e]. Ring closure proceeded in the presence of potassium ferricyanide in basic medium, usually in aqueous 1 M NaOH. The solubility of tetraacetylated 1-glucosylthioanilides **10a**–**10b** in aqueous medium was very poor, therefore they were dissolved in methanol and 1 M aqueous solution of NaOH was added. Immediate deacetylation of the saccharide moiety was observed by TLC (fast disappearance of the starting material) and occurrence of a new spot on the start line (in cyclohexane–ethyl acetate 3:1). Deacetylated products were not isolated and subsequent

addition of 15% aqueous solution of $K_3[Fe(CN)_6]$ resulted in the formation of target compounds **11a**–**11c** (Scheme 2). The best result was achieved with 6 equivalents of NaOH and 3 equivalents of $K_3[Fe(CN)_6]$. The reaction time was influenced by substituents on the anilide moiety of **10a**–**10d**. Electron-donating CH_3 and CH_3O groups facilitated electrophilic substitution. Reaction proceeded at room temperature and after 2–2.5 h gave cyclic product **11a** (64%) or **11b** (61%). Slightly-electron withdrawing chlorine atom caused prolongation of reaction time and the reaction with $K_3[Fe(CN)_6]$ gave **11c** in 51% yield after 4.5 h. In all cases unidentified decomposition products were present in the reaction mixture. In **10d**, the strong electron-withdrawing nitrogroup deactivates the benzene ring of thioanilide making electrophilic substitution difficult. No progress was observed performing the reaction under conditions used with **10a**–**10c**. Heating at 60 °C, stronger basic condition (8 equivalents of NaOH) and higher excess of $K_3[Fe(CN)_6]$ (5 equivalents) resulted after 18 h in complete decomposition of starting compound without formation of compound **11d**.

As a primary in vitro screening for growth inhibition and cytotoxicity, compounds **11a**–**11c** were submitted to the National Cancer Institute, Bethesda, U.S.A.) for testing. Their cytotoxic potency on three human cell lines NCI-H460 lung cancer, MCF7 breast cancer and SF-268 glioma was evaluated. A compound is considered active when it reduces the growth of any of the cell lines to 32% or less and it is passed on for evaluation in the full panel of sixty cell lines. Compound **11b** was active in this test. The panel of sixty human tumor cell lines is organized into subpanels representing leukemia, melanoma and cancers of lung, colon, kidney, ovary, breast, prostate and central nervous system. The test compounds were dissolved in DMSO and evaluated using five concentrations at ten-fold dilutions, the highest being 10^{-4} mol l^{-1} and the others 10^{-5}–10^{-8} mol l^{-1}. Compound **11b** did not show a level of activity sufficient to enter the subsequent in vivo step.

The synthesis of three novel derivatives of 1-glucosylbenzocamalexin was performed by applying the indoline–indole method and Jacobson cyclization. Introduction of substituents into the benzothiazole moiety allowed evaluating their influence on the anticancer effect. In terms of mean GI_{50} values across the cell panel, **11b** showed the best activity against ovarian cancer cell line IGROV1 (13.4 μmol l^{-1}). This enhancement of antiproliferative activity is undoubtedly attributed to the presence of methoxy group in its structure compared to recently synthesized inactive unsubstituted 1-glucosylbenzocamalexin[6].

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini 2000 NMR spectrometer operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. Chemical shifts (δ-scale) are reported in ppm, downfield from tetramethylsilane used as an internal standard; coupling constants (*J*) in Hz. Microanalyses were performed with a Perkin–Elmer, Model 2400 analyzer. The EI mass spectra were recorded on a Finigan SSQ 700 spectrometer at ionization energy 70 eV, whereas MALDI-TOF mass spectra were measured on a MALDI IV (Shimadzu, Kratos Analytical) instrument. For MALDI measurements the analyzed samples were dissolved in an acetonitrile–water mixture (1:1). The matrix, 2,5-dihydroxybenzoic acid, was dissolved in the same mixture. Solutions of a sample and the matrix were mixed in the ratio 1:10. After drying on target, the samples were bombarded with a 3-ns dose (100 doses) of a nitrogen laser (λ = 337 nm). Ion acceleration voltage was 5 kV. The reaction course was monitored by thin layer chromatography, using plates Macherey–Nagel Alugram®Sil G/UV254. The preparative column chromatography (flash chromatography) was performed on Kieselgel Merck Type 9385, 230–400 mesh.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)indole-3-carboxylic Acid (**6**)

Aldehyde **5** (6.50 g, 13.67 mmol) was dissolved in *tert*-butyl alkohol (146 ml) and 2-methybut-2-ene (146 ml). The solution was cooled to 0 °C and sodium chlorite (24.6 g, 271.6 mmol) was added followed by a solution of $NaH_2PO_4 \cdot 2H_2O$ (31.9 g, 204.6 mmol) in 146 ml of water. Finally dioxane (169 ml) was added and the reaction mixture was stirred at room temperature for 4 h. After addition of water (130 ml), the reaction mixture was extracted with $CHCl_3$ (2 × 150 ml) and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure and the crude product was recrystallized from a mixture of ethyl acetate–hexane. Yield 6.37 g (95%) of white crystals, m.p. 224–226 °C (ethyl acetate–hexane). For $C_{23}H_{25}NO_{11}$ (491.4) calculated: 56.21% C, 5.13% H, 2.85% N; found: 56.56% C, 5.38% H, 2.69% N. ^{1}H NMR ($CDCl_3$): 1.71 s, 3 H (CH_3); 2.05 s, 3 H (CH_3); 2.11 s, 3 H (CH_3); 2.12 s, 3 H (CH_3); 4.04 m, 1 H (H-5′); 4.21 d, 1 H, *J*(6′a,6′b) = 12.3 (H-6′b); 4.34 dd, *J*(6′a,6′b) = 12.6, *J*(6′a,5′) = 4.8 (H-6′a); 5.34 m, 1 H (H-4′); 5.51 m, 2 H (H-3′, H-2′); 5.68 d, *J* = 8.63 (H-1′); 7.35 m, 2 H; 7.49 m, 1 H; 8.25 m, 1 H and 8.09 s, 1 H (H-arom.). ^{13}C NMR ($CDCl_3$): 20.06, 20.61, 20.75 (CH_3CO); 61.77 (C-6′); 67.94 (C-4′); 70.77 (C-2′); 73.02 (C-3′); 75.12 (C-5′); 83.76 (C-1′); 109.19, 110.42, 122.27, 123.09, 123.72, 126.93, 132.54, 136.32 (C arom.); 168.57, 169.40, 169.60, 170.21, 170.65 (C=O). MS MALDI-TOF, *m/z* (%): 530 $[M + K]^+$ (36); 514 $[M + Na]^+$ (76); 492 $[M + H]^+$ (30).

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)indole-3-carbonyl Chloride (**7**)

To stirred solution of carboxylic acid **6** (1.50 g, 3.05 mmol) in a mixture of toluene (18 ml) and acetonitrile (3 ml) was added PCl_3 (0.836 g, 0.53 ml, 6.10 mmol) at 50 °C. The reaction mixture was stirred at 50 °C until the whole amount of the acid was dissolved, and stirring continued for 20 min. The reaction mixture was cooled to room temperature, poured into another flask and residue of phosphoric acid was washed with 15 ml of toluene. Solvents were evaporated under reduced pressure to 1/6 of the initial volume. The obtained solution of crude chloride **7** was used for subsequent reaction.

N-(4-Substituted phenyl)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)indole-3-carboxamides **9a**–**9d**. General Procedure

Concentrated solution of crude chloride **7** (approx. 3.05 mmol) was diluted with 20 ml of dry toluene and 4-substituted aniline **8a**–**8d** (7.63 mmol) was added to the obtained solution. The reaction mixture was stirred at room temperature for 24 h (48 h required for **8c**), diluted with ethyl acetate and washed with aqueous 1 M HCl (2×), saturated aqueous solution of $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and the crude product was recrystallized from an ethyl acetate–hexane mixture.

*1-(2,3,4,6-Tetra-O-acetyl-*β*-D-glucopyranosyl)-N-p-tolylindole-3-carboxamide* (**9a**). Yield 99% of white crystals, m.p. 190–194 °C (ethyl acetate–hexane). For $C_{30}H_{32}N_2O_{10}$ (580.6) calculated: 62.06% C, 5.56% H, 4.83% N; found: 62.31% C, 5.27% H, 4.51% N. ^{1}H NMR ($CDCl_3$): 1.68 s, 3 H (CH_3); 2.03 s, 3 H (CH_3); 2.09 s, 6 H (2 × CH_3); 2.34 s, 3 H (Ph-C**H**$_3$); 4.01 ddd, 1 H, *J*(5′,6′b) = 2.0, *J*(5′,6′a) = 5.0, *J*(4′,5′) = 10.2 (H-5′); 4.15 dd, 1 H, *J*(6′a,6′b) = 12.6, *J*(5′,6′b) = 2.0 (H-6′b); 4.32 dd, 1 H, *J*(6′a,6′b) = 12.6, *J*(5′,6′a) = 5.0 (H-6′a); 5.26 t, 1 H, *J* = 10.2 (H-4′); 5.42–5.53 bm, 2 H (H-2′, H-3′); 5.66 d, 1 H, *J*(1′,2′) = 8.6 (H-1′); 7.17 d, 2 H, *J* = 8.4 (H-3″, H-5″); 7.29–7.37 bm, 2 H (H-6, H-5); 7.47–7.49 m, 1 H (H-7); 7.53 d, 2 H, *J* = 8.4 (H-2″, H-6″); 7.67 s, 1 H (NH); 7.87 s, 1 H (H-2); 8.12–8.14 m, 1 H (H-4). ^{13}C NMR ($CDCl_3$): 20.35, 20.81, 20.85, 20.98 (C**H**$_3$CO); 21.16 (Ph-C**H**$_3$); 62.02 (C-6′); 68.18 (C-4′); 70.45 (C-2′); 73.20 (C-3′); 75.22 (C-5′); 83.56 (C-1′); 110.49 (H-7); 114.33 (C-3); 120.36 (C-2″, C-6″); 121.42 (C-4); 122.83 (C-5); 123.79 (C-6); 126.33 (C-3a); 127.31 (C-2); 129.71 (C-3″, C-5″); 133.87 (C-4″); 135.74 (C-1″); 136.48 (C-7a); 162.63 (CONH); 168.86, 169.49, 170.21, 170.71 (CH$_3$**C**O). MS MALDI-TOF, *m/z* (%): 619 [M + K]$^+$ (15); 603 [M + Na]$^+$ (77); 581 [M + H]$^+$ (100).

*N-(4-Methoxyphenyl)-1-(2,3,4,6-tetra-O-acetyl-*β*-D-glucopyranosyl)indole-3-carboxamide* (**9b**). Yield 85% of white crystals, m.p. 202–204 °C (ethyl acetate–hexane). For $C_{30}H_{32}N_2O_{11}$ (596.6) calculated: 60.40% C, 5.41% H, 4.70% N; found: 60.23% C, 5.10% H, 4.37% N. ^{1}H NMR ($CDCl_3$): 1.68 s, 3 H (CH_3); 2.03 s, 3 H (CH_3); 2.09 s, 6 H (2 × CH_3); 3.82 s, 3 H (Ph-OC**H**$_3$); 4.02 ddd, 1 H, *J*(5′,6′b) = 2.2, *J*(5′,6′a) = 5.0, *J*(4′,5′) = 10.2 (H-5′); 4.13 dd, 1 H, *J*(6′a,6′b) = 12.5, *J*(5′,6′b) = 2.2 (H-6′b); 4.33 dd, 1 H, *J*(6′a,6′b) = 12.5, *J*(5′,6′a) = 5.0 (H-6′a); 5.26 t, 1 H, *J* = 10.2 (H-4′); 5.42–5.53 bm, 2 H (H-2′, H-3′); 5.65 d, 1 H, *J*(1′,2′) = 8.8 (H-1′); 6.91 d, 2 H, *J* = 9.1 (H-3″, H-5″); 7.26–7.37 bm, 2 H (H-6, H-5); 7.47–7.50 m, 1 H (H-7); 7.55 d, 2 H, *J* = 9.1 (H-2″, H-6″); 7.64 s, 1 H (NH); 7.86 s, 1 H (H-2); 8.12–8.15 m, 1 H (H-4). ^{13}C NMR ($CDCl_3$): 20.36, 20.82, 20.85, 20.98 (C**H**$_3$CO); 55.75 (Ph-OC**H**$_3$); 62.03 (C-6′); 68.17 (C-3′); 70.95 (C-2′); 73.20 (C-4′); 75.22 (C-5′); 83.52 (C-1′); 110.45 (H-7); 114.27 (C-3); 114.40 (C-3″, C-5″); 121.45 (C-4); 122.23 (C-2″, C-6″); 122.80 (C-5); 123.78 (C-6); 123.35 (C-3a); 127.21 (C-2); 131.38 (C-1″); 136.57 (C-7a); 156.48 (C-4″); 162.66 (CONH); 168.86, 169.51, 170.21, 170.71 (CH$_3$**C**O). MS MALDI-TOF, *m/z* (%): 635 [M + K]$^+$ (13); 619 [M + Na]$^+$ (89); 597 [M + H]$^+$ (100).

*N-(4-Chlorophenyl)1-(2,3,4,6-tetra-O-acetyl-*β*-D-glucopyranosyl)indole-3-carboxamide* (**9c**). Yield 88% of white crystals, m.p. 201–202 °C (ethyl acetate–hexane). For $C_{29}H_{29}ClN_2O_{10}$ (601.0) calculated: 57.96% C, 4.86% H, 4.66% N; found: 58.14% C, 4.75% H, 4.95% N. ^{1}H NMR ($CDCl_3$): 1.67 s, 3 H (CH_3); 2.03 s, 3 H (CH_3); 2.08 s, 3 H (CH_3); 2.09 s, 3 H (CH_3); 4.02 ddd, 1 H, *J*(5′,6′b) = 2.2, *J*(5′,6′a) = 5.2, *J*(4′,5′) = 9.9 (H-5′); 4.14 dd, 1 H, *J*(6′a,6′b) = 12.5, *J*(5′,6′b) = 2.2 (H-6′b); 4.33 dd, 1 H, *J*(6′a,6′b) = 12.5, *J*(5′,6′a) = 5.2 (H-6′a); 5.24 t, 1 H, *J* = 9.9 (H-4′); 5.43–5.51 bm, 2 H (H-2′, H-3′); 5.67 d, 1 H, *J*(1′,2′) = 9.1 (H-1′); 7.30–7.38 bm, 4 H (H-3″, H-5″, H-6, H-5); 7.46–7.49 m, 1 H (H-7); 7.60 d, 2 H, *J* = 8.8 (H-2″, H-6″); 7.76 s, 1 H (NH);

7.88 s, 1 H (H-2); 8.12–8.15 m, 1 H (H-4). ^{13}C NMR ($CDCl_3$): 20.33, 20.81, 20.84, 20.98 (CH_3CO); 62.03 (C-6′); 68.17 (C-4′); 71.03 (C-2′); 73.12 (C-3′); 75.28 (C-5′); 83.41 (C-1′); 110.44 (H-7); 113.96 (C-3); 121.46 (C-2″, C-6″, C-4); 122.98 (C-5); 123.94 (C-6); 126.26 (C-3a); 127.34 (C-2); 129.12 (C-4″); 129.19 (C-3″, C-5″); 136.60 (C-7a); 136.95(C-1″); 162.68 (CONH); 168.88, 169.50, 170.17, 170.70 (CH_3CO). MS MALDI-TOF, *m/z* (%): 639 $[M + K]^+$ (10); 623 $[M + Na]^+$ (100); 601 $[M + H]^+$ (48).

*N-(4-Nitrophenyl)1-(2,3,4,6-tetra-O-acetyl-*β*-D-glucopyranosyl)indole-3-carboxamide* (**9d**). Concentrated solution of crude chloride **7** (ca. 3.05 mmol) was diluted with 40 ml of dry toluene, 4-nitroaniline (1.053 g, 7.63 mmol) and DMAP (37 mg, 0.305 mmol) were added to the solution. The reaction mixture was refluxed for 2 h, cooled to room temperature, diluted with ethyl acetate and washed with aqueous 6 M HCl (2×), saturated aqueous solution of $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4, filtered through Celite® and concentrated under reduced pressure. The crude product was recrystallized from a mixture of solvents ethyl acetate–hexane. Yield 1.40 g (75%) of pale orange crystals, m.p. 120–124 °C (ethyl acetate–hexane). For $C_{29}H_{29}N_3O_{12}$ (611.6) calculated: 56.96% C, 4.78% H, 6.87% N; found: 57.11% C, 4.81% H, 6.59% N. ^{1}H NMR ($CDCl_3$): 1.66 s, 3 H (CH_3); 2.02 s, 3 H (CH_3); 2.07 s, 3 H (CH_3); 2.09 s, 3 H (CH_3); 4.02 ddd, 1 H, *J*(5′,6′b) = 2.2, *J*(5′,6′a) = 5.2, *J*(4′,5′) = 10.2 (H-5′); 4.12 dd, 1 H, *J*(6′a,6′b) = 12.4, *J*(5′,6′b) = 2.2 (H-6′b); 4.33 dd, 1 H, *J*(6′a,6′b) = 12.4, *J*(5′,6′a) = 5.2 (H-6′a); 5.16 t, 1 H, *J* = 10.2 (H-4′); 5.39–5.49 bm, 2 H (H-2′, H-3′); 5.69 d, 1 H, *J*(1′,2′) = 8.8 (H-1′); 7.32–7.40 bm, 2 H (H-6, H-5); 7.45–7.49 m, 1 H (H-7); 7.82 d, 2 H, *J* = 9.1 (H-2″, H-6″); 7.96 s, 1 H (H-2); 8.15–8.18 m, 1 H (H-4); 8.22 d, 2 H, *J* = 9.1 (H-3″, H-5″); 8.25 bs, 1 H (NH). ^{13}C NMR ($CDCl_3$): 20.31, 20.78, 20.84, 20.98 (CH_3CO); 62.08 (C-6′); 68.19 (C-4′); 71.13 (C-2′); 73.98 (C-3′); 75.36 (C-5′); 83.20 (C-1′); 110.37 (C-7); 113.40 (C-3); 119.33 (C-2″, C-6″); 121.55 (C-4); 123.29 (C-5); 124.20 (C-6); 125.30 (C-3″, C-5″); 126.23 (C-3a); 127.59 (C-2); 136.64 (C-7a); 143.36 (C-4″); 144.46(C-1″); 162.82 (CONH); 168.93, 169.52, 170.12, 170.75 (CH_3CO). MS MALDI-TOF, *m/z* (%): 651 $[M + K]^+$ (6); 635 $[M + Na]^+$ (46); 612 $[M + H]^+$ (33).

N-(4-Substituted phenyl)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)indole-3-carbothioamides **10a**–**10d**. General Procedure

The corresponding amide **9a**–**9d** (3.01 mmol) was dissolved in dry toluene (30 ml) and the Lawesson reagent (0.61 g, 1.51 mmol) was added to the solution. The reaction mixture was refluxed for 30 min (**9a**–**9c**) or 24 h (**9d**), cooled to room temperature and toluene was evaporated under reduced pressure. The obtained residue was subjected to column chromatography (cyclohexane–ethyl acetate 2:1).

*1-(2,3,4,6-Tetra-O-acetyl-*β*-D-glucopyranosyl)-N-p-tolylindole-3-carbothioamide* (**10a**). Yield 1.63 g (91%) of yellow crystals, m.p. 103–104 °C (ethyl acetate–hexane). For $C_{30}H_{32}N_2O_9S$ (596.7) calculated: 60.39% C, 5.41% H, 4.70% N; found: 60.45% C, 5.32% H, 4.99% N. ^{1}H NMR ($CDCl_3$): 1.74 s, 3 H (CH_3); 2.03 s, 3 H (CH_3); 2.08 s, 3 H (CH_3); 2.09 s, 3 H (CH_3); 2.38 s, 3 H (Ph-C**H**$_3$); 4.02 ddd, 1 H, *J*(5′,6′b) = 2.2, *J*(5′,6′a) = 4.9, *J*(4′,5′) = 9.9 (H-5′); 4.18 dd, 1 H, *J*(6′a,6′b) = 12.6, *J*(5,6′b) = 2.2 (H-6′b); 4.32 dd, 1 H, *J*(6′a,6′b) = 12.6, *J*(5′,6′a) = 4.9 (H-6′a); 5.9 t, 1 H, *J* = 9.9 (H-4′); 5.42 t, 1 H, *J* = 9.3 (H-3′); 5.53 t, 1 H, *J* = 9.3 (H-2′); 5.63 d, 1 H, *J*(1′,2′) = 8.8 (H-1′); 7.23 d, 2 H, *J* = 8.4 (H-3″, H-5″); 7.27–7.36 bm, 2 H (H-6, H-5); 7.51–7.53 m, 1 H (H-7); 7.59 d, 2 H, *J* = 8.0 (H-2″, H6″); 8.03 s, 1 H (H-2); 8.7 bd, 1 H, *J* = 8.0 (H-4); 8.97 s, 1 H (NH). ^{13}C NMR ($CDCl_3$): 20.41, 20.79, 20.81, 20.96 (CH_3CO); 21.39 (Ph-CH_3); 61.99 (C-6′); 68.15 (C-4′); 70.86 (C-2′); 73.17 (C-3′); 75.29 (C-5′); 84.14 (C-1′);

111.26 (H-7); 120.79 (C-4); 122.18 (C-3); 123.07 (C-5); 123.87 (C-6); 124.30 (C-2″, C-6″); 124.81 (C-3a); 129.78 (C-3″, C-5″, C-2); 136.53 (C-4″); 136.69 (C-7a); 136.79 (C-1″); 168.91, 169.52, 170.27, 170.75 (CH_3CO); 191.33 (CSNH). MS MALTI-TOF, *m/z* (%): 635 $[M + K]^+$ (16); 619 $[M + Na]^+$ (44); 597 $[M + H]^+$ (65); 563 $[M - H_2S]^+$ (100).

*N-(4-Methoxyphenyl)-1-(2,3,4,6-tetra-O-acetyl-*β*-D-glucopyranosyl)indole-3-carbothioamide* (**10b**). Yield 94% of yellow crystals, m.p. 95–98 °C (ethyl acetate–hexane). For $C_{30}H_{32}N_2O_{10}S$ (612.7) calculated: 58.81% C, 5.26% H, 4.57% N; found: 58.68% C, 5.41% H, 4.62% N. ^{1}H NMR ($CDCl_3$): 1.73 s, 3 H (CH_3); 2.03 s, 3 H (CH_3); 2.08 s, 3 H (CH_3); 2.09 s, 3 H (CH_3); 3.84 s, 3 H (Ph-OC**H**$_3$); 4.02 ddd, 1 H, *J*(5′,6′b) = 2.2, *J*(5′,6′a) = 5.0, *J*(4′,5′) =10.2 (H-5′); 4.17 dd, 1 H, *J*(6′a,6′b) = 12.4, *J*(5′,6′b) = 2.2 (H-6′b); 4.32 dd, 1 H, *J*(6′a,6′b) = 12.4, *J*(5′,6′a) = 5.0 (H-6′a); 5.28 t, 1 H, *J* = 10.2 (H-4′); 5.46 t, 1 H, *J* = 9.2 (H-3′); 5.51 t, 1 H, *J* = 9.2 (H-2′); 5.64 d, 1 H, *J*(1′,2′) = 8.8 (H-1′); 6.96 d, 2 H, *J* = 9.1 (H-3″, H-5″); 7.27–7.36 bm, 2 H (H-6, H-5); 7.50–7.54 m, 1 H (H-7); 7.60 d, 2 H, *J* = 9.1 (H-2″, H-6″); 8.03 s, 1 H (H-2); 8.08 bd, 1 H, *J* = 6.31 (H-4); 8.95 bs, 1 H (NH). ^{13}C NMR ($CDCl_3$): 20.42, 20.79, 20.82, 20.96 (CH_3CO); 55.72 (Ph-OCH_3); 62.00 (C-6′); 68.16 (C-4′); 70.87 (C-2′); 73.18 (C-3′); 75.26 (C-5′); 84.11 (C-1′); 111.45 (H-7′); 114.37 (C-3, C-3″, C-5″); 120.80 (C-4); 123.03 (C-5); 123.85 (C-6); 126.85 (C-3a); 126.12 (C-2″, C-6″); 129.68 (C-2); 132.03 (C-1″); 136.68 (C-7a); 158.24 (C-4″); 168.88, 169.50, 170.23, 170.72 (CH_3CO); 191.40 (CSNH). MS MALDI-TOF, *m/z* (%): 652 $[M + K]^+$ (74); 636 $[M + Na]^+$ (76); 613 $[M + H]^+$ (80); 579 $[M - H_2S]^+$ (100).

*N-(4-Chlorophenyl)-1-(2,3,4,6-tetra-O-acetyl-*β*-D-glucopyranosyl)indole-3-carbothioamide* (**10c**). Yield 83% of yellow crystals, m.p. 165–170 °C (ethyl acetate–hexane). For $C_{29}H_{29}ClN_2O_9S$ (617.1) calculated: 56.45% C, 4.74% H, 4.54% N; found: 56.71% C, 4.56% H, 4.78% N. ^{1}H NMR ($CDCl_3$): 1.73 s, 3 H (CH_3); 2.03 s, 3 H (CH_3); 2.08 s, 3 H (CH_3); 2.09 s, 3 H (CH_3); 4.03 ddd, 1 H, *J*(5′,6′b) = 2.0, *J*(5′,6′a) = 5.0, *J*(4′,5′) = 10.0 (H-5′); 4.17 dd, 1 H, *J*(6′a,6′b) = 12.7, *J*(5′,6′b) = 2.0 (H-6′b); 4.32 dd, 1 H, *J*(6′a,6′b) = 12.6, *J*(5′,6′a) = 5.2 (H-6′a); 5.28 t, 1 H, *J* = 10.0 (H-4′); 5.42–5.56 m, 2 H (H-3′, H-2′); 5.65 d, 1 H, *J*(1′,2′) = 9.0 (H-1′); 7.31–7.40 bm, 4 H (H-3″, H-5″, H-5, H-6); 7.50–7.55 m, 1 H (H-7); 7.69 d, 2 H, *J* = 8.8 (H-2″, H-6″); 8.03 s, 1 H (H-2); 8.06–8.10 m, 1 H (H-4); 9.03 bs, 1 H (NH). ^{13}C NMR ($CDCl_3$): 20.13, 20.54, 20.69 (CH_3CO); 61.72 (C-6′); 67.93 (C-4′); 70.72(C-2′); 72.89 (C-3′); 75.04 (C-5′); 83.77 (C-1′); 110.95, 120.66, 121.93, 122.97, 123.80, 124.58, 125.23, 129.04, 129.33, 131.61, 136.56, 137.40 (C arom.); 168.74, 169.35, 170.04, 170.55 (CH_3CO); 191.31 (CSNH). MS MALDI-TOF, *m/z* (%): 655 $[M + K]^+$ (12); 639 $[M + Na]^+$ (89); 617 $[M + H]^+$ (77); 583 $[M - H_2S]^+$ (100).

*N-(4-Nitrophenyl)-1-(2,3,4,6-tetra-O-acetyl-*β*-D-glucopyranosyl)indole-3-carbothioamide* (**10d**). Yield 64% of orange crystals, m.p. 118–121 °C (ethyl acetate–hexane). For $C_{29}H_{29}N_3O_{11}S$ (627.6) calculated: 55.50% C, 4.66% H, 6.70% N; found: 55.89% C, 4.53% H, 6.49% N. ^{1}H NMR ($CDCl_3$): 1.72 s, 3 H (CH_3); 2.03 s, 3 H (CH_3); 2.08 s, 3 H (CH_3); 2.09 s, 3 H (CH_3); 4.05 ddd, 1 H, *J*(5′,6′b) = 1.8, *J*(5′,6′a) = 4.9, *J*(4′,5′) = 10.2 (H-5′); 4.18 dd, 1 H, *J*(6′a,6′b) = 12.1, *J*(5′,6′b) = 1.7 (H-6′b); 4.34 dd, 1 H, *J*(6′a,6′b) = 12.1, *J*(5′,6′a) = 4.9 (H-6′a); 5.28 t, 1 H, *J* = 10.2 (H-4′); 5.33–5.55 m, 2 H (H-3′, H-2′); 5.66 d, 1 H, *J*(1′,2′) = 9.2 (H-1′); 7.33–7.40 bm, 2 H (H-6, H-5); 7.45–7.54 m, 1 H (H-7); 8.01–8.10 bm, 4 H; 8.24–8.23, bd, 2 H, *J* = 8.8 (H-4); 9.24 bs, 1 H (NH). ^{13}C NMR ($CDCl_3$): 20.12, 20.50, 20.53, 20.69 (CH_3CO); 61.73 (C-6′); 67.91 (C-4′); 70.82 (C-2′); 72.78 (C-3′); 75.14 (C-5′); 83.60 (C-1′); 110.91, 120.71, 122.38, 122.49, 123.26, 124.06, 124.52, 124.72, 129.28, 136.64, 144.52, 144.60 (C arom.); 168.84, 169.33, 169.99, 170.52 (CH_3CO); 191.55 (CSNH). MS MALDI-TOF, *m/z* (%): 665 $[M + K]^+$ (3); 650 $[M + Na]^+$ (32); 628 $[M + H]^+$ (41); 594 $[M - H_2S]^+$ (100).

6-Substituted 2-(1-(β-D-Glucopyranosyl)indol-3-yl)benzothiazoles **11a**–**11c**. General Procedure

Thioamide **10a**–**10c** (0.754 mmol) was dissolved in methanol (27 ml), the solution was cooled to 0 °C and aqueous 1 M NaOH (4.52 ml, 4.52 mmol) was added. After 5 min, consumption of the starting material was detected (TLC). A 15% aqueous solution of $K_3Fe(CN)_6$ (4 ml, 2.26 mmol) was added to the reaction mixture, and the yellow slurry was stirred at room temperature for 2.5 h. The reaction mixture was diluted with THF (30 ml) and inorganic salts were filtered off. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (dichloromethane–methanol–NH_4OH 100:10:1).

6-Methyl-2-(1-(β-D-glucopyranosyl)indol-3-yl)benzothiazole (**11a**). Yield 64% of pale yellow solid, m.p. 192–194 °C. For $C_{22}H_{22}N_2O_5S$ (426.5) calculated: 61.96% C, 5.20% H, 6.57% N; found: 62.14% C, 5.36% H, 6.38% N. ^{1}H NMR (DMSO-d_6): 2.46 s, 3 H (Ph-C**H**$_3$); 3.39 t, 1 H, *J* = 8.7; 3.47–3.57 bm, 3 H; 3.75 d, 1 H, *J* = 10.2 and 3.88 t, 1 H, *J* = 8.7 (H saccharide, H-2′–H-6′); 4.59 bs, 1 H (CD_3COOD exchangeable, OH); 5.18 bs, 1 H (CD_3COOD exchangeable, OH); 5.24 bs, 1 H (CD_3COOD exchangeable, OH); 5.38 bs, 1 H (CD_3COOD exchangeable, OH); 5.58 d, 1 H, *J* = 8.4 (H-1′); 7.25–7.43 bm, 3 H; 7.73 m, 1 H; 7.85–7.89 m, 2 H; 8.33 s, 1 H and 8.43 m, 1 H (H arom.). ^{13}C NMR ($CDCl_3$): 20.90 (Ph-**C**H$_3$); 60.78 (C-6′); 69.54, 71.72, 77.18, 79.54 (C-2′–C-5′); 85.02 (C-1′); 110.64, 111.81, 120.89, 121.26, 121.37, 121.65, 122.88, 124.81, 127.45, 129.09, 133.15, 133.96, 136.78, 151.65, 161.19 (C arom.). MS MALDI-TOF, *m/z* (%): 465 $[M + K]^+$ (3); 449 $[M + Na]^+$ (24); 427 $[M + H]^+$ (100).

6-Methoxy-2-(1-(β-D-glucopyranosyl)indol-3-yl)benzothiazole (**11b**). Yield 61% of pale yellow solid, m.p. 195–197 °C. For $C_{22}H_{22}N_2O_6S$ (442.5) calculated: 59.72% C, 5.01% H, 6.33% N; found: 60.05% C, 5.21% H, 6.55% N. ^{1}H NMR (DMSO-d_6): 3.41 t, 1 H, *J* = 9.3; 3.46–3.62 bm, 3 H; 3.74 d, 1 H, *J* = 9.6 and 3.72–3.90 m, 1 H (H saccharide, H-2′–H-6′); 3.86 s, 3 H (OCH_3); 4.57 bs, 1 H (CD_3COOD exchangeable, OH); 5.16 d, 1 H, *J* = 4.2 (CD_3COOD exchangeable, OH); 5.22 bs, 1 H (CD_3COOD exchangeable, OH); 5.36 d, 1 H, *J* = 5.4 (CD_3COOD exchangeable, OH); 5.57 d, 1 H, *J* = 9.3 (H-1′); 7.07 dd, 1 H, *J* = 2.6, 8.9; 7.27–7.34 bm, 2 H; 7.67 d, 1 H, *J* = 2.7; 7.72 m, 1 H; 7.88 d, 1 H, *J* = 8.7; 8.29 s, 1 H and 8.41 m, 1 H (H arom.). ^{13}C NMR ($CDCl_3$): 55.60 (OCH_3); 60.77 (C-6′); 69.57, 71.66, 77.19, 79.53 (C-2′–C-5′); 84.97 (C-1′); 104.74, 110.69, 114.96, 120.91, 121.56, 122.16, 122.84, 124.80, 125.06, 128.70, 134.41, 136.75, 147.92, 156.74, 159.84 (C arom.). MS MALTI-TOF, *m/z* (%): 481 $[M + K]^+$ (4); 465 $[M + Na]^+$ (5); 443 $[M + H]^+$ (100).

6-Chloro-2-(1-(β-D-glucopyranosyl)indol-3-yl)benzothiazole (**11c**). Yield 51% of pale yellow solid, m.p. 205–208 °C. For $C_{21}H_{19}ClN_2O_5S$ (446.9) calculated: 56.44% C, 4.29% H, 6.27% N; found: 56.54% C, 4.51% H, 6.44% N. ^{1}H NMR (DMSO-d_6): 3.35 t, 1 H, *J* = 9.0; 3.46–3.62 bm, 3 H; 3.74 d, 1 H, *J* = 8.4 and 3.88 t, 1 H, *J* = 9.0 (H saccharide, H-2′–H-6′); 4.58 bs, 1 H (CD_3COOD exchangeable, OH); 5.17 bs, 1 H (CD_3COOD exchangeable, OH); 5.32 bs, 2 H (CD_3COOD exchangeable, 2 × OH); 5.53 d, 1 H, *J* = 9.3 (H-1′); 7.30–7.35 m, 2 H; 7.51 dd, 1 H, *J* = 2.1, 8.7; 7.68–7.71 m, 1 H; 7.98 d, 1 H, *J* = 9.0; 8.02–8.05 m, 1 H; 8.18 s, 1 H and 8.21 d, 1 H, *J* = 1.8 (H arom.). ^{13}C NMR ($CDCl_3$): 60.74 (C-6); 69.48, 71.78, 77.04, 79.55 (C-2′–C-5′); 85.21 (C-1′); 106.33, 110.25, 112.06, 120.45, 121.83, 122.51, 123.03, 126.07, 133.06, 136.32, 152.39, 163.28, 164.34 (C arom.). MS MALDI-TOF, *m/z* (%): 485 $[M + K]^+$ (3); 469 $[M + Na]^+$ (12); 447 $[M + H]^+$ (100).

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