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The Synthesis and Cytotoxic Activity of *D*-Ribofuranosides and 2-Deoxy-*D*-Ribofuranosides of Substituted Bis(indolyl)furan, Bis(indolyl)pyrrole, and Indolo[2,3-*a*]carbazole Derivatives

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Abstract—1-(2,3,5-Tri-*O*-acetyl)-β-*D*-ribofuranosyl indole, the key compound in the synthesis of glycosides with the bis(indole) aglycone, was obtained for the first time by the indoline–indole method. There were synthesized 3-(1-methylindol-3-yl)-4-(1-glycosylindol-3-yl)furan(or pyrrole)-2,5-diones containing the residue of β-*D*-ribofuranose or 2-deoxy-β-*D*-ribofuranose and analogous glycosides of indolo[2,3-*a*]furano(or pyrrolo)[3,4-*c*]carbazol-5,7-diones, which are structurally relative to the antitumor antibiotic rebeccamycin. Their cytotoxicities toward a number of human tumor cell lines were studied *in vitro*, and the carbazole *N*-glycosides were shown to be more active than the bis(indole) glycosides. At the same time, the ribofuranosides were found to be less active than the corresponding ribopyranosides synthesized previously.

Key words: *bis(indolyl)furan, bis(indolyl)pyrrole, 2-deoxy-D-ribofuranosides, indolocarbazole, N-glycosides, D-ribofuranosides*

INTRODUCTION

We had previously reported the synthesis of *N*-glycopyranosides of bis(indole) derivatives and substituted indolo[2,3-*a*]carbazoles, analogues of the natural antitumor antibiotic rebeccamycin [1–3].[2] The study of biological properties of the synthesized glycosides showed that the nature of glycoside residue markedly affects their cytotoxic and antitumor activities *in vitro* [4] and also their activity toward protein kinase C [5]. The compounds that contained the β-*D*-ribopyranosyl or α-*L*-arabinopyranosyl residues turned out to be most cytotoxic. This fact prompted us to study also the dependence of the biological properties of the glycosides on the size of their carbohydrate rings. To this end, we have synthesized *D*-ribofuranosides and 2-deoxy-*D*-ribofuranosides of substituted bis(indoles) and indolocarbazoles.

Microbiological methods or chemical glycosylation by the Mitsunobu reaction or the method of mercuric, silver, and other salts are usually used for introducing a glycoside residue into the indolocarbazole molecule [6–11]. However, these methods are rather laborious, because they require the selective introduction of protective groups and their subsequent removal owing to three possible glycosylation sites in the indolocarbazole molecule. Therefore, as previously, we chose the indoline–indole method for the synthesis of the starting indolyl *N*-glycoside; this provides the necessary configuration of glycoside bond and does not require the preliminary protection of the aglycone [12].

First, we were to synthesize the ribose derivative in the fixed furanose form for the subsequent glycosylation. The interaction of *D*-ribose with TBDMS chloride led in 83% yield to 5-*O*-TBDMS-*D*-ribofuranose (**I**), which was initially targeted for the glycosylation. However, the treatment of (**I**) with indoline and subsequent acetylation resulted in a complex mixture of products, from which we failed to isolate *O*-protected β-*D*-ribofuranosyl indoline. Therefore, (**I**) was acetylated by a standard procedure. The glycosylation of indoline with the resulting 1,2,3-tri-*O*-acetyl-5-*O*-TBDMS-*D*-ribofuranose (**II**) and subsequent dehydration with manganese dioxide in benzene resulted in the protected *N*-glycoside (**III**). However, the low total yield of this compound (<1% from *D*-ribose) hindered its use as the starting compound in the chosen synthetic scheme.

RESULTS AND DISCUSSION

We attempted to obtain 2',3',5'-tri-*O*-acetyl derivative (**IV**), even though it had previously been considered unavailable [12, p. 19]. 1-(2,3,5-Tri-*O*-acetyl)-β-*D*-ribofuranosyl indoline was obtained in 53% yield after a prolonged (~27 h) reflux of 1,2,3,5-tetra-*O*-

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[2] Abbreviations: DDQ, dichlorodicyanobenzoquinone; HR MS, high resolution mass spectrometry; TBDMS, *tert*-butyldimethylsilyl; and Tol, *p*-toluyl (*p*-$CH_3C_6H_4CO$).

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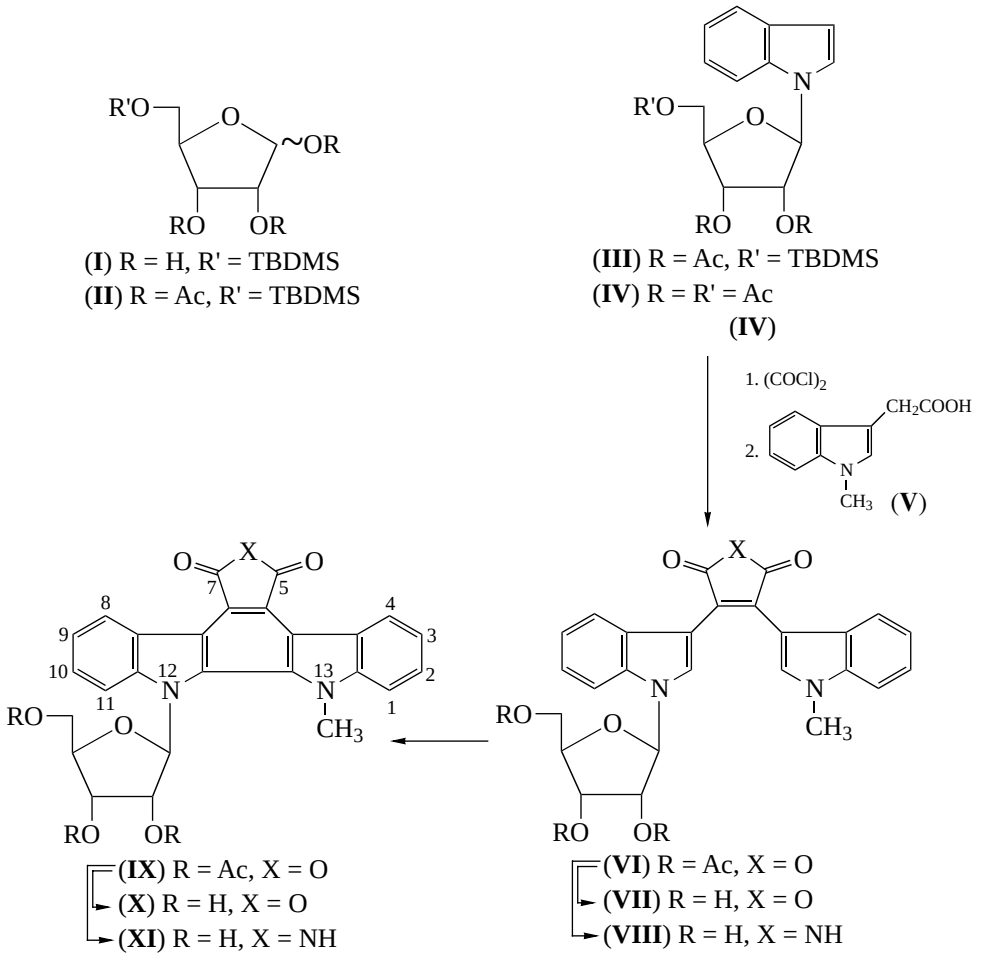
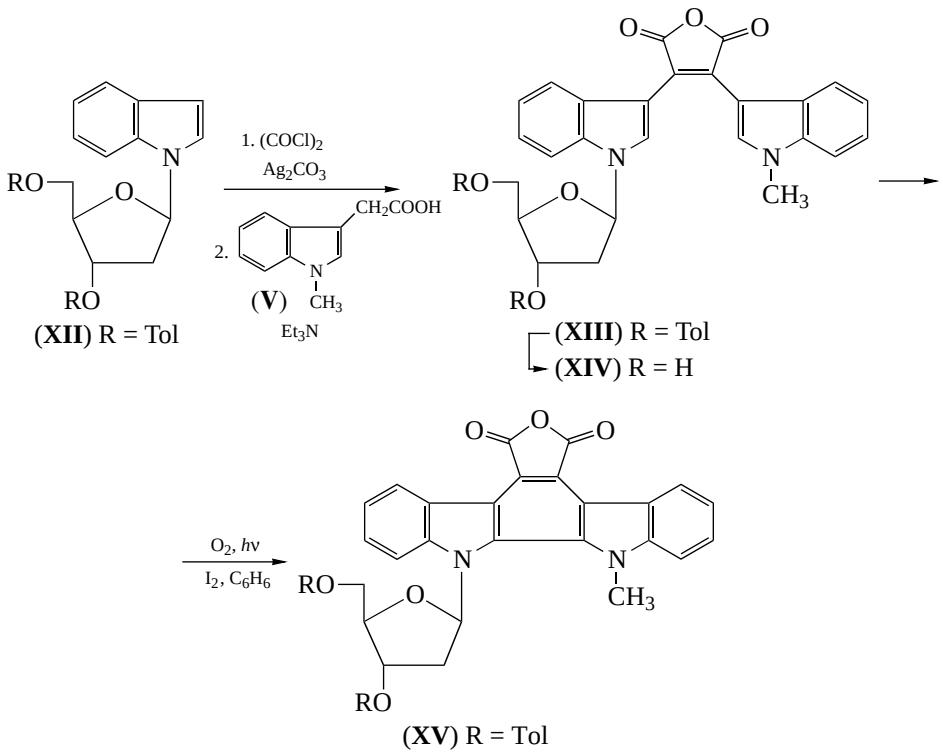


Scheme 1.

acetyl-β-*D*-ribofuranose and indoline in ethanol. The subsequent dehydration of this compound with DDQ in toluene led to the target indole derivative (**IV**) in 76% yield (Scheme 1).

As previously reported for other *N*-glycosides, the synthesized per-*O*-acetylated ribofuranoside (**IV**) was converted into the derivative of bis(indolyl)furan-2,5-dione (**VI**) in 44% yield by the treatment with oxalyl chloride in dichloromethane and subsequent interaction of the resulting intermediate with (1-methylindol-3-yl)acetic acid (**V**) [1]. The removal of acetyl groups from (**VI**) by sodium methylate in methanol gave (**VII**) in 68% yield. Heating of the mixture of furan derivative (**VI**) with ammonia solution in DMF at 140°C resulted in transformation of the furan to pyrrole cycle and the deprotection of carbohydrate residue to give (**VIII**) in 75% yield. Like other similar compounds, (**VI**) was photochemically oxidized by the atmospheric oxygen in benzene in the presence of catalytic amount of iodine to transform its bis(indole) into the carbazole structure [3]. Acetyl derivative (**IX**) was obtained in 52% yield. The deacetylation of (**IX**) with heated potassium carbonate in anhydrous methanol resulted in 82% yield of riboside (**X**). To transform its furan ring into the pyrrole one, per-*O*-acetylated derivative of (**IX**) was treated with ammonia, which, as in the case of bis(indoles), led to (**XI**) isolated in 73% yield.

O-Protected 1-(2-deoxy-β-*D*-ribofuranosyl)indole (**XII**), which was synthesized from indole and 2-deoxy-2,5-di-*O*-*p*-toluyl-α-*D*-ribofuranosyl chloride by the reported procedure [13] in 54% yield, was used as the starting compound in the synthesis of 2-deoxyribofuranoside derivatives of indolocarbazoles. The treatment of (**XII**) with oxalyl chloride in anhydrous dichloromethane at 0°C for 2.5 h and the subsequent reaction with (1-methylindol-3-yl)acetic acid (**V**) was accompanied by anomerization; it gave a hardly separable mixture of 3-(1-methylindol-3-yl)-4-[1-(2-deoxy-3,5-di-*O*-*p*-toluyl-*D*-ribofuranosyl)indol-3-yl]furan-2,5-dione (**XIII**) and its α-anomer in a ratio of 1 : 1 (according to ^{1}H NMR) (cf. [12], p. 90). Silver carbonate was added to the reaction mixture to bind hydrogen chloride that is generated in the reaction and catalyzes the anomerization. Furthermore, the time of treatment with oxalyl chloride was decreased to 40 min. This allowed the isolation of (**XIII**) in 53% yield. The minor admixture of



Scheme 2.

the corresponding α-anomer generated in the reaction mixture was easily separated by preparative TLC. We deacetylated (**XIII**) by 0.1 N sodium methylate in methanol for 20 min at room temperature and obtained bis(indole) glycoside (**XIV**) in 91% yield. The photochemical oxidation of (**XIII**) in benzene in the presence of a catalytic amount of iodine at air bubbling and irradiation with a Hg lamp for 3 h led to (**XV**) in 42% yield (Scheme 2). All the attempts to transform the furandione to the pyrroldione ring in (**XV**) or to deacetylate it resulted in the complete degradation of the carbohydrate residue (^{1}H NMR data).

The carbohydrate residue in the resulting (**III**), (**IV**), and (**VI**)–(**XI**) is in the furanose form and has the β-configuration of the glycoside bond. The size of the carbohydrate ring is confirmed by ^{1}H NMR spectroscopy (Table 1). A downfield shift of the signal of the anomeric proton ($\Delta\delta \sim 0.3$ ppm) and a simultaneous upfield shift of the protons at C3' ($\Delta\delta \sim 0.1$–0.4 ppm) were observed in the spectra of (**IV**) and (**VI**)–(**XI**) in comparison with the corresponding ribopyranosyl derivatives (cf. [1, 3]). A significant upfield shift of the proton signal at C4' ($\Delta\delta \sim 0.9$ ppm) due to the absence of acetyl group at C4' was observed for acetyl derivatives (**IV**) and (**VII**). In the case of ribofuranosyl derivatives (**IV**) and (**VI**)–(**XI**), the spin–spin coupling constant of the anomeric proton is in the range 5.0–6.9 Hz, whereas their values are 8.5–10.0 Hz for their β-ribopyranose analogues [1, 3]. The ^{1}H NMR data do not allow the unambiguous conclusion about the stereochemistry of glycoside bond in the synthesized ribofuranosides. However, it had been previously shown by the method of circular dichroism that, irrespective of the aglycone nature, the indoline–indole method results in the *N*-riboside with the β-configuration of the glycoside bond as the main (or even the only) reaction product [12].

The ^{1}H NMR spectra of acylated deoxyribosides (**XIII**) and (**XV**) manifest the signals of anomeric protons as the doublets of doublets with the $J_{1'2'}$ coupling constants equal to 6.5 and 8.5 and 5.9 and 9.4 Hz, respectively. This is characteristic of the presence of bulky substituents at C3' and C5' of the deoxyribose residue. At the same time, the signal of anomeric proton in (**XIV**) with the free hydroxyl groups in the carbohydrate residue is a pseudotriplet with the coupling constant of 6.6 Hz, which is characteristic of β-anomers of pyrimidine and purine nucleosides. The resonances from the protons at C2' in the spectra of each of compounds (**XIII**), (**XIV**), and (**XV**) practically coincide and form multiplets at 2.68–2.80, 2.48–2.34, and 2.94–3.06 ppm, respectively. This is also characteristic of the β-anomers of deoxyribofuranosides [14].

The mass spectra of the synthesized compounds (Table 2) exhibit peaks of molecular $[M]^+$ and aglycone ions, which confirm their structure. Degradation of the molecules of *O*-acyl derivatives (**IV**), (**VI**), (**IX**), and (**XIII**) occurs with the formation of the carbohydrate residue ion. In all, the mass spectra of *D*-ribofuranosides and 2-deoxy-*D*-ribofuranosides of substituted

Table 1. ^{1}H NMR spectra of the synthesized compounds*

Compound, solvent	Aglycone	Chemical shifts, δ, ppm (*J*, Hz)					
		carbohydrate residue					
		H1′	H2′	H3′	H4′	H5′	other protons
(I) $(CD_3)_2CO$	–	5.10dd (≈1.0, 5.7)	3.75m, 3.69m		4.16m	3.79m [2H]	4.89d (5.7) [1'-OH]; 4.08d(5.0); 3.94d(5.2) [2'-OH, 3'-OH]; 0.91s [$3CH_3$]; 0.09c [$2CH_3$]
(II) $CDCl_3$		6.15d (1.9)	5.36dd (1.9, 5.0)	5.40dd (5.0, 5.3)	4.20 ddd (5.3, 4.0, 4.0)	3.76dd; 3.74dd (≈11)	0.91s [$3CH_3$]; 0.07s, 0.06s [2 CH_3; 2.10s, 2.08s, 2.06s [3Ac]
(III) $CDCl_3$	7.60d (7.9)*; 7.54d (8.2); 7.42d [H2, (3.4)]; 7.21t; 7.12t; 6.56d [H3]	6.18d (5.3)	5.58dd (5.3, 5.7)	5.51dd (5.7, 2.6)	4.22ddd (2.6, 2.3, 2.3)	3.91dd [2 H] (≈11)	0.97s [$3CH_3$]; 0.15s [$2CH_3$]; 2.15s, 1.98s [2Ac]
(IV) $CDCl_3$	7.61d; 7.49d; 7.28d [H3, (3.3)]; 7.23dt; 7.15dt; 6.60d [H2]	6.18d (6.3)	5.59dd (6.3, 6.3)	5.46dd (6.3, 3.7)	4.41–4.33m [3H]		2.16s [2Ac]; 2.03s [Ac]
(VI) $CDCl_3$	7.84s; 7.80s; 7.49d; 7.31d; 7.2–7.1m [3H]; 6.90t; 6.81d; 6.79d; 3.87s [CH_3]	6.18d (6.4)	5.46dd (6.4, 6.4)	5.31dd (6.4, 3.8)	4.37ddd (3.8, 3.8, 3.0)	4.20dd (3.8.12.7), 4.11dd(3.0)	2.15s; 2.07s; 2.05s [3Ac]
(VII) $(CD_3)_2CO$	8.14s; 7.90s; 7.43d; 7.34d; 7.11t [2 H]; 6.88d; 6.79t [2H]; 6.75d; 3.93s [CH_3]	6.05d (5.1)	4.37dd (5.1, 5.1)	4.2dd (5.1, 5.1)	4.08ddd (5.1, 3.8, 3.8)	3.77dd(3.8,12.6) 3.69dd (3.8)	
(VIII) $(CD_3)_2CO$	9.68‾c [NH]; 7.99s; 7.77s; 7.56d; 7.36d; 7.05t [2H]; 7.01d; 6.88d; 6.71t; 6.77t; 3.90s [CH_3]	6.01d (5.0)	4.36dd (5.0, 4.8)	4.19dd (4.8, 5.1)	4.06ddd (5.1, 3.9, 3.9)	3.78dd (3.9.12.6), 3.69dd(3.9)	
(IX) $CDCl_3$	9.09d; 9.04d; 7.92d; 7.70d; 7.62d; 7.56t; 7.50t; 7.45t; 4.28 s [CH_3]	6.43d (6.6)	5.44dd (6.6, 6.6)	5.40dd (6.6, 6.6)	4.44ddd (6.6,≈3; 3)	4.61m [2 H]	2.32s; 2.07s; 1.55s [3Ac]
(X) $(CD_3)_2CO$	9.08d; 9.06d; 8.36d; 7.84d; 7.40t; 7.61t; 7.51t [2 H]; 4.38s [CH_3]	6.42d (6.9)	4.55m	4.36m	4.25m	4.15–4.00m [2H]	
(XI) $(CD_3)_2CO$	9.91s [NH]; 9.21d; 9.17d; 8.22d; 7.71d; 7.63d; 7.50t; 7.40t; 7.38t; 4.30s [CH_3]	6.36d (6.7)	4.45dd (6.7, 6.7)	4.30dd (6.7, ≈3.5)	4.20ddd (≈3.5, 2.8, 3.2)	4.09dd (2.8.12.0) 4.01dd (3.2)	
(XII) $CDCl_3$	7.59dd; 7.50d; 7.27d [H3, (3.5)]; 7.00–7.18m [2H]; 6.52d [H2, (3.5)]	6.46dd (5.6, 9.0)	2.85ddd (9.0, 6.8,14.3), 2.63ddd (5.6, 2.4)	5.70ddd (6.8, 2.4, 2.4)	4.54m	4.65m [2H]	7.97d*; 7.93d; 7.25d; 7.22d [2H each, 2Tol]; 2.44s; 2.41s [$2CH_3$]
(XIII) $CDCl_3$	7.73s; 7.62d; 7.50d, 7.28d [2H]; 7.13m [2H]; 6.93t; 6.85m; 6.75m; 3.81 [CH_3]	6.46dd (6.5, 8.5)	2.68–2.80m [2H]	5.59ddd (5.7, 2.6, 2.6)	4.51m	4.34m [2H]	7.96d*; 7.85d; 7.29d, 7.21d [2H each, 2 Tol]; 2.45s; 2.41s [$2CH_3$]
(XIV) CD_3OD	7.93s; 7.84s; 7.53d; 7.39d; 7.11m [2H]; 7.02d; 6.84–6.66m [3H]; 3.86s [CH_3]	6.43pt (6.6)	2.34–2.48m [2H]	4.34m	3.95m	3.65–3.45m [2H]	
(XV) $CDCl_3$	9.02m [2H]; 7.94d; 7.62d; 7.70–7.35m [4H]; 4.30s [CH_3]	6.85dd (5.7, 9.2)	2.94–3.06m [2H]	5.75m	4.59ddd (≈4, 2.7, 3.5)	5.02dd (2.7, 12.3) 4.83dd (3.5)	8.10d*, 7.90d, 7.34d, 7.21d [2H each, 2 Tol]; 2,51s, 2.40s [$2CH_3$]

* All the aromatic protons exhibit usual values of coupling constants (*J*) in the ^{1}H NMR spectra.

Table 2. Mass spectra of the synthesized compounds

Compound	*m*/*z* (*I*, %)		
	$[M]^+$	aglycone fragments	carbohydrate fragments
(III)	447 (45.12)	117 (89.71), 118 (17.5), 89 (63.75)	331 (23.91), 330 (64.39), 288 (75.10), 271 (26.28), 270 (100.00), 229 (63.84)
(IV)	375 (33.43)	117 (34.51)	259 (49.52), 157 (15.69), 139 (100)
(VI)	600 (59.05)	342 (36.12), 343 (8.28), 270 (15.48)	259 (32.15), 139 (100), 97 (47.61)
(VII)	474 (43.28)	342 (100), 343 (24.88), 270 (52.60), 269 (23.84), 255 (13.06)	
(VIII)	473 (38.80)	341 (100), 342 (24.00), 324 (10.11), 297 (8.52), 270 (11.89), 269 (17.87), 255 (7.69)	
(IX)	598 (8.62)	339 (6.73), 340 (6.39), 268 (11.89), 267 (11.92)	259 (60.94), 199 (1.91), 157 (15.94), 139 (100), 97 (39.66), 43 (71.74)
(X)	472	340 (100.00), 341 (23.04), 268 (83.24), 267 (16.59)	
(XI)	471	339 (100), 340 (23.56), 324 (21.60) 268 (22.26), 267 (11.85)	
(XIII)	694 (41.1)	343 (14.01), 342 (60.70), 297 (3.48), 270 (18.02), 255 (2.84)	353 (2.98), 119 (58.79), 81 (100)
(XIV)	458 (32.08)	343 (24.24), 342 (100), 341 (3.77), 297 (5.38), 270 (52.47), 255 (9.60), 227 (6.63)	
(XV)	692 (2.95)	341 (23.02), 340 (100), 268 (83.30), 253 (16.19)	119 (15.91), 81 (6.51)

Table 3. Antiproliferative activity of β-*D*-ribofuranosides and 2-deoxy-β-*D*-ribofuranosides (**VII**), (**VIII**), (**XI**), and (**XIV**) (the concentration inhibiting the tumor growth by 50%, GI_{50}, M, is given)

Cell line	**(VII)**	**(VIII)**	**(XI)**	**(XIV)**
Leukemia				
SR	–	2.47×10^{-6}	3.49×10^{-7}	$>1.00 \times 10^{-4}$
CCRF-CEM	4.90×10^{-5}	1.67×10^{-5}	1.71×10^{-7}	3.76×10^{-5}
ä-562	$>1.00 \times 10^{-4}$	3.54×10^{-6}	2.22×10^{-7}	–
Breast Cancer				
MDA-MB-435	$>1.00 \times 10^{-4}$	3.09×10^{-6}	7.20×10^{-7}	$>1.00 \times 10^{-4}$
MDA-N	6.51×10^{-5}	2.51×10^{-6}	7.29×10^{-7}	4.44×10^{-5}
Ovarian Cancer				
OVCAR-3	5.10×10^{-5}	–	5.23×10^{-7}	6.61×10^{-5}
IGROV1	2.99×10^{-5}	1.45×10^{-5}	2.45×10^{-7}	1.78×10^{-5}
Non–small Cell Lung Cancer				
NCI-H522	3.90×10^{-5}	6.04×10^{-6}	4.26×10^{-7}	5.03×10^{-5}

bis(indole) and indolocarbazoles are close to those of the analogous *D*-ribopyranosides synthesized previously [1, 3].

The study of the cytotoxic activity of *N*-glycosides synthesized was performed in the National Institute of Cancer (United States) using the panel of 60 lines of human tumor cells of various geneses. The data listed in Table 3 attest that the derivatives of indolocarbazoles are the most active as in the case of other compounds of this series. At the same time, ribofuranosides are somewhat less cytotoxic than the corresponding ribopyranosides synthesized previously [1–5].

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on a Bruker WH-360 (Germany) spectrometer using tetramethylsilane as an internal standard. The method of double resonance was used for assigning the signals in the spectra and for refinement of the spin–spin coupling constants.

Mass spectra, including the high resolution mass spectra, were registered on a Finnigan MAT 8430 (Germany) mass spectrometer with the SS-300 system of data processing (the accelerating voltage was 3 kV, the energy of ionizing ions was 70 eV, the temperature of ion source was 250°C; the system of the direct inlet of substance in the ionization area functioning at 170–250°C was used.

UV spectra were taken on a Specord UV–VIS (Germany) spectrophotometer in ethanol at an optical length of 1 cm; the values of λ_{max}, nm (ε, M^{-1} cm^{-1}), are given.

IR spectra were recorded on a Perkin-Elmer 283 (United States) instrument in KBr pellets; the values of characteristic oscillations (cm^{-1}) are given.

Analytical TLC was performed on Silufol UV_{254} precoated plates. Preparative TLC was carried out on Silica gel $60_{PF254+366}$ (Germany) and Silica gel LSL_{254} 5–40 μm (Chemapol, Czechia) precoated glass plates with a layer thickness of 2.5 mm. The spots were visualized on the plates by UV irradiation with a MinUVIS (Desaga, Germany) lamp at wavelength of 254 or 366 nm. Column chromatography was performed on Sephadex LH-20 (Sigma, United States) at the elution with acetone.

1,2,3,5-Tetra-*O*-acetyl-β-*D*-ribofuranose (Sigma, United States) was used for the synthesis of 1-(2,3,5-tri-*O*-acetyl-β-*D*-ribofuranosyl)indole (**IV**).

Photochemical oxidation was performed using a Hg lamp with a rated input of 250 W.

Antiproliferative activity of the synthesized compounds was studied in the National Institute of Cancer (United States) on a series of human cell lines according to the method [15].

5-*O*-TBDMS-*D*-ribofuranose (I). A mixture of *D*-ribose (1.58 g, 10.5 mmol) and TBDMS chloride (1.90 g, 12.6 mmol) in anhydrous pyridine (15 ml) was stirred for 18 h at room temperature. Then a saturated $NaHCO_3$ solution was added, and the product was extracted with chloroform (3 × 10 ml). The combined extracts were filtered and evaporated in a vacuum to give 2.33 g (83%) of (**I**) as almost colorless oil.

5-*O*-TBDMS-1,2,3-tri-*O*-acetyl-*D*-ribofuranose (II). Acetic anhydride (1.53 ml) was added to a stirred solution of 5-*O*-TBDMS-*D*-ribofuranose (**I**) (0.76 g, 2.88 mmol) in anhydrous pyridine (7 ml) cooled to 0°C. After 1 h, the cooling was removed, the reaction mixture was kept at room temperature for 18 h, and then poured in ice. The resulting suspension was filtered, and the resulting residue was purified by preparative TLC in 20 : 1 benzene–acetone system. The substance was detected by sulfuric acid. The zone with R_f 0.63 was eluted to give 0.18 g (16%) of (**II**) as colorless glassy substance.

1-(5-*O*-TBDMS-2,3-di-*O*-acetyl-β-*D*-ribofuranosyl)indole (III). A solution of 5-*O*-TBDMS-1,2,3-tri-*O*-acetyl-*D*-ribofuranose (**II**) (0.26 g, 0.67 mmol) and a freshly distilled indoline (0. 15 g, 2.03 mmol) in ethanol (2.5 ml) was refluxed for 5.5 h and evaporated. The residue was chromatographed on plates in a 40 : 1 benzene–acetone system. The zone with R_f 0.22 was eluted to give 0.07 g (21%) of 1-(5-*O*-TBDMS-2,3-di-*O*-acetyl-β-*D*-ribofuranosyl)indoline. The resulting compound (0.31 g, 0.69 mmol) and MnO_2 (1.55 g) in benzene (50 ml) were refluxed under vigorous stirring in an apparatus supplied with a Dean–Stark trap for 7 h [16]. The reaction mixture was cooled and filtered, the solvent was removed in a vacuum, and the residue was isolated by a preparative TLC in a 40 : 1 benzene–acetone system. The zone with R_f 0.69 was eluted to give 0.095 g (31%) of (**III**) as a colorless oil; UV: 265 (7800), 277 (6000), and 288 (3800); IR: 1755 (CO); HR MS, *m*/*z*: $[M]^+$ found 447.2121, calculated for $C_{23}H_{33}NO_6Si$ 447.2077.

1-(2,3,5-Tri-*O*-acetyl-β-*D*-ribofuranosyl)indole (IV). A solution of 1,2,3,5-tetra-*O*-acetyl-β-*D*-ribofuranose (3.1 g, 9.78 mmol) and indoline (1.40 g, 19.56 mmol) in absolute ethanol (35 ml) was refluxed for 26.5 h under a TLC-monitoring in a 20 : 1 benzene–acetone and evaporated in a vacuum. The residue was chromatographed on plates using the same developing system (double development) to yield 2.04 g (55%) of 1-(2,3,5-tri-*O*-acetyl-β-*D*-ribofuranosyl)indoline. A solution of DDQ (0.30 g, 1.31 mmol) in anhydrous toluene (3 ml) was added dropwise at room temperature to a solution of the resulting compound (0.45 g, 1.19 mmol) in anhydrous toluene (12 ml). After 18 h, the reaction mixture was evaporated in a vacuum, and the residue was purified by preparative TLC in a 30 : 1 chloroform–acetone to give 0.34 g (76%) of (**IV**); UV: 262 (6000), 277 (4300), and 287 (3000); IR: 1755 (CO); HR MS, *m*/*z*: $[M]^+$ found 375.1398, calculated for $C_{19}H_{21}NO_7$ 375.1318.

3-(1-Methylindol-3-yl)-4-[1-(2,3,5-tri-*O*-acetyl-β-*D*-ribofuranosyl)indol-3-yl]furan-2,5-dione (VI). Oxalyl chloride (0.233 ml, 2.50 mmol) in anhydrous dichloromethane (2 ml) was added dropwise to a solution of (**IV**) (0.625 g, 1.67 mmol) in anhydrous dichloromethane (13 ml) cooled to 0°C, and the mixture was kept overnight at room temperature. The solution was evaporated to dryness. The resulting foam-like residue was dried in a vacuum over P_2O_5, dissolved in anhydrous dichloroethane (12 ml), and a solution of (1-methylindol-3-yl)acetic acid (**V**) (0.417 g, 2.20 mmol) and triethylamine (0.51 g, 3.89 mmol) in dichloroethane (4 ml) was added dropwise. The reaction mixture was refluxed for 8 h, cooled, and evaporated to dryness. The residue was separated by preparative TLC in 30 : 1 chloroform–acetone (double development) to give 0.425 g (44%) of (**VI**) as amorphous red powder; UV: 284 (10 200), 370 (5900), and 460 (10 800); IR: 1816 and 1755 (CO). HR MS, *m*/*z*: $[M]^+$ found 600.1796, calculated for $C_{32}H_{28}N_2O_{10}$ 600.1743.

3-(1-Methtylindol-3-yl)-4-(1-β-*D*-ribofuranosylindol-3-yl)furan-2,5-dione (VII). A 1 M solution of sodium methylate in methanol (0.315 ml) was added to

a suspension of (**VI**) (0.150 g, 0.25 mmol), and the mixture was stirred for 30 min at room temperature. Then the solution was neutralized with KU-2 (H^+) cation exchange resin to pH 7 using a universal indicator. The resin was removed and washed with methanol, the solvent was removed in a vacuum, and the residue was purified by preparative TLC in 1 : 1 benzene–acetone and then on a Sephadex LH-20 column to give 0.081 g (68%) of (**VII**); UV: 227 (26 000), 285 (9400), 370 (5000), and 460 (8600); IR: 1816 and 1750 (CO). HR MS, *m*/*z*: $[M]^+$ found 474.1502, calculated for $C_{26}H_{22}N_2O_7$ 474.1427.

3-(1-Methylindol-3-yl)-4-(1-β-*D*-ribofuranosylindol-3-yl)-1*H*-pyrrol-2,5-dione (VIII). Concentrate ammonia (2 ml) was added to a solution of (**VI**) (0.100 g, 0.17 mmol) in DMF (2 ml), and the mixture was kept in an autoclave at 140°C for 4 h. The reaction mixture was cooled and evaporated to dryness. The residue was dissolved in acetone (2 ml) and chromatographed on a Sephadex LH-20 column to give 0.059 g (75%) of glycoside (**VIII**) as a red powder; UV: 227 (27000), 282 (8800), 370 (4000), and 453 (6000); IR: 3400, 1710 (NH), and 1754 (CO); HR MS, *m*/*z*: $[M]^+$ found 473.1585, calculated for $C_{26}H_{23}N_3O_6$ 473.1586.

13-Methyl-12-(2,3,5-tri-*O*-acetyl-β-*D*-ribofuranosyl)indolo[2,3-*a*]furano[3,4-*c*]carbazol-5,7-dione (IX). A mixture of (**VI**) (0.225 g, 0.37 mmol), toluene (200 ml), and iodine (a catalytic amount) was placed in a quartz flask, irradiated with the Hg lamp for 3 h when bubbling air, and evaporated to dryness. Methanol (50 ml) was added to the residue, and the mixture was cooled to 5°C. The precipitate was separated, washed with cooled methanol, and dried in a vacuum over P_2O_5 to give 0.117 g (52%) of (**IX**) as an yellow powder; UV: 237 (19200), 255 (9000), 289 (18600), 305 (28000), 313 (38300), and 400 (4100); IR: 1822 and 1752; HR MS, *m*/*z*: $[M]^+$ found 598.1635, calculated for $C_{32}H_{26}N_2O_{10}$ 598.1587.

13-Methyl-12-(β-*D*-ribofuranosyl)indolo[2,3-*a*]furano[3,4-*c*]carbazol-5,7-dione (X). Absolute methanol (3 ml) and dried by heating potash (0.80 g) were added to (**IX**) (0.085 g, 0.14 mmol), and the mixture was stirred for 20 min at room temperature (TLC monitoring in 1 : 1 benzene–acetone). Then the precipitate was removed, and the solution was neutralized with KU-2 (H^+) cation exchange resin to pH 7. The resin was removed and washed with methanol, and the filtrate was evaporated in a vacuum. The residue was chromatographed on a Sephadex LH-20 column to give 0.045 g (82%) of (**X**) as an yellow powder; UV: 238 (24600), 256 (11100), 277sh (10 400), 291sh (16500), 307sh (31200), 316 (46700), and 406 (4200); IR: 1816 and 1745; HR MS, *m*/*z*: $[M]^+$ found 472.1282, calculated for $C_{26}H_{20}N_2O_7$ 472.1270.

13-Methyl-12-(β-*D*-ribofuranosyl)indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazol-5,7-dione (XI). Concentrate ammonia (2 ml) was added to a solution of (**VII**) (0.090 g, 0.15 mmol) in DMF (2 ml), and the mixture was kept in an autoclave at 140°C for 4 h. After cooling, the reaction mixture was evaporated to dryness, and water was added to the residue. The resulting precipitate was separated, dried in air, and chromatographed on a Sephadex LH-20 column to give 0.052 g (73%) of carbazole (**XI**) as an yellow powder; UV: 238 (29 200), 255 (14100), 280 (15 400), 288 (19 800), 306 (27 300), 316 (44300), and 400 (3300); IR: 3400, 1755, and 1710; HR MS, *m*/*z*: $[M]^+$ found 471.1429, calculated for $C_{19}H_{21}N_3O_6$ 471.1430.

1-(2-Deoxy-3,5-di-*O*-*p*-toluyl-β-*D*-ribofuranosyl)indole (XII) [13]. A mixture of indole (0.35 g, 2.99 mmol) and sodium hydride (0.15 g of 80% suspension in oil, 5 mmol) in anhydrous acetonitrile (30 ml) was stirred under nitrogen at room temperature for 30 min. Then 2-deoxy-3,5-di-*O*-*p*-toluyl-α-*D*-ribofuranosyl chloride (1.41 g, 3.63 mmol) [17] was added in portions, and the reaction mixture was kept at the same temperature for 24 h. The precipitate was separated, acetonitrile was removed in a vacuum, and the residue was purified by preparative TLC in 20 : 1 benzene–ethyl acetate. Yield of (**XII**) 0.75 g (54%).

3-(1-Methylindol-3-yl)-4-[1-(2-deoxy-3,4-di-*O*-*p*-toluyl-β-*D*-ribofuranosyl)indol-3-yl]furan-2,5-dione (XIII). A solution of oxalyl chloride (0.12 g, 0.91 mmol) in anhydrous dichloromethane (2 ml) was added to a cooled to 0°C and stirred solution of (**XII**) (0.1 g, 0.21 mmol) in anhydrous dichloromethane(2 ml) containing a suspension of silver carbonate (0.15 g, 0.36 mmol). The reaction mixture was stirred for 40 min at 0°C and filtered from the precipitate of silver salts. The filtrate was evaporated to dryness, and (1-methylindol-3-yl)acetic acid (**V**) (0.05 g, 0.26 mmol) and triethylamine (0.1 ml, 0.72 mmol) were added to the residue dissolved in dichloroethane (3 ml) at 0°C. The reaction mixture was refluxed for 4 h, evaporated in a vacuum, and the residue was separated by preparative TLC in 4 : 1 CCl_4–acetone (double development) to isolate 0.08 g (53%) of (**XIII**); UV: 237 (40000), 277 (11000), 370 (5300), and 462 (8300); IR: 1820 and 1750; HR MS, *m*/*z*: $[M]^+$ found 694.2250, calculated for $C_{42}H_{34}N_2O_8$ 694.2315.

3-(1-Methylindol-3-yl)-4-[1-(2-deoxy-β-*D*-ribofuranosyl)indol-3-yl]furan-2,5-dione (XIV). A 0.1 N solution of sodium methylate in methanol (1 ml) was added to a solution of (**XIII**) (0.05 g, 0.7 mmol) in methanol (2 ml). The reaction mixture was stirred for 20 min at room temperature and then neutralized with Dowex 50 (H^+) cation exchange resin to pH 7 using an universal indicator. The resin was filtered off, and the filtrate was evaporated in a vacuum. Product (**XIV**) was isolated by preparative TLC in 20 : 1 ethyl acetate–methanol; yield 0.03 g (91%); UV: 227 (16700), 278 (10800), 375 (5500), 530 (2800), and 610 (4800); IR: 1820 and 1750; HR MS, *m*/*z*: $[M]^+$ found 458.1503, calculated for $C_{26}H_{22}N_2O_6$ 458.1477.

13-Methyl-12-(2-deoxy-3,5-di-*O*-*p*-toluyl-β-*D*-ribofuranosyl)indolo[2,3-*a*]furano[3,4-*c*]carbazol-5,7-dione (XV). A solution of (**XIII**) (0.19 g, 0.37 mmol) and a catalytic amount of iodine in benzene (190 ml) was placed in a quartz tube and irradiated with the Hg lamp for 3 h at air bubbling (TLC monitoring in 10 : 1 CCl_4–acetone). The benzene solution was washed with a saturated sodium thiosulfate (2×50 ml) and water (2×50 ml) and evaporated in a vacuum, and the residue was purified by preparative TLC in the same developing system (double development) to give 0.08 g (42%) of (**XV**); UV: 238 (31 000), 315 ((32 500), and 400 (4170); IR: 1830 and 1760; HR MS, *m*/*z*: $[M]^+$ found 692.2092, calculated for $C_{42}H_{32}N_2O_8$ 692.2158.

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