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O- and *N*-glycosides of pyrazolo[3,4-*c*]isoquinoline. Synthesis and structural investigation by NMR

Presented by Corresponding Member of the NAS of Ukraine Yu.V. Rassukana

The synthetic potential of polyfunctional derivatives of the condensed system of pyrazolo[3,4-c] isoquinoline has been investigated. For the first time, a series of derivatives with a glucosamine fragment has been obtained and their spectral properties have been described.

Keywords: *pyrazolo[3,4-c]isoquinolines, glycosylation, correlation spectroscopy, N,O-glucosides, oxazoline.*

Introduction. Isoquinolines condensed with azoles and other heterocycles on the "*c*" margin have recently become popular in medicinal chemistry. Based on the modified Pictet—Spengler reaction, we have developed a convenient method for the preparation of pyrazolo[3,4-*c*]isoquinolines **I** [1, 2] (scheme 1), which have become hit-leaders in the search for new inhibitors

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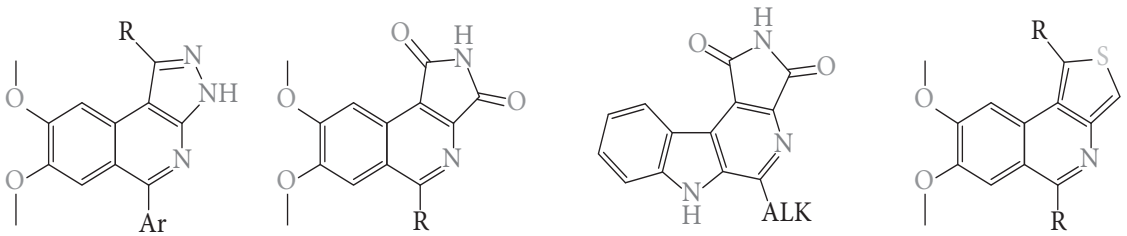
of anaplastic lymphoma kinase [3—5]. They also increase the effectiveness of chemotherapy drugs and antibiotics, contribute to detoxication of cells and tissues, and regulate multidrug transport systems across the blood brain barrier [6]. The distinctive feature of pyrazolo[3,4-*c*] isoquinolines is their low toxicity. Pyrrolo[3,4-*c*]isoquinoline-2,5-diones **II** [7, 8] are inhibitors of glycogen synthase kinase 3 (GSK 3) and activators of Wnt signaling pathway [9], which is important for cell proliferation, differentiation, and apoptosis. Pyrrolo[3,4-*c*]-β-carboline-1,3-diones **III** have been studied as a new class of inhibitors of tyrosine kinases [10, 11]. Therefore, the probability of new medicinal substances with a condensed isoquinoline structure is very high, and the development of alternative methods for the synthesis and functionalization of azolo- and other condensed isoquinolines appears to be relevant, especially for medicinal chemistry.

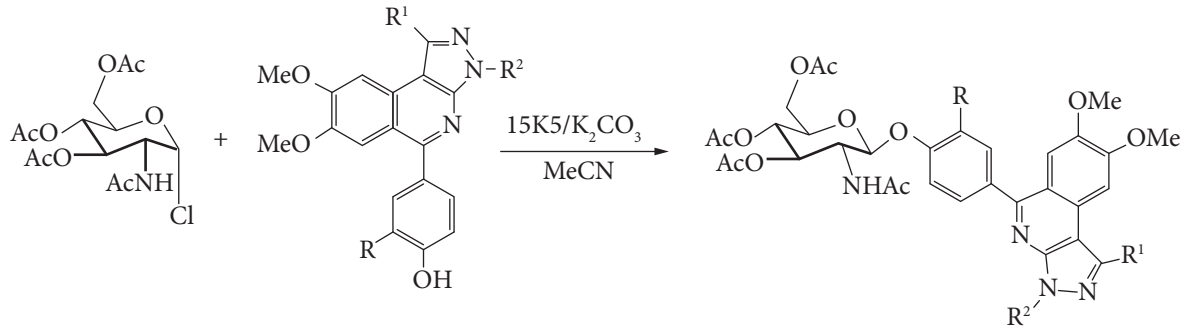


Scheme 1. Biologically active condensed isoquinoline derivatives

However, there is still a long way to go from the substance with a specific activity to the drug. For heterocyclic systems **I—IV** a serious limitation is their low solubility, and, accordingly, bioavailability. Glycosylation is one of the perspective ways of modifying the molecule properties, including the solubility improvement. This is well illustrated by the example of existing anticancer and antiviral drugs, such as zidovudine, emtricitabine, cytarabine, and azacitidine. Thus, the synthesis of new glycosides containing a pyrazolo[3,4-*c*]isoquinoline as aglycone moiety and NMR studies of their structure were the aim of this work.

The aim of our research is to develop a convenient method for the synthesis of pyrazolo[3,4-*c*]isoquinoline *O*- and *N*-glycosides in order to improve the antitumor properties of this heterocyclic system.

Results and discussion. The structure of pyrazolo[3,4-*c*]isoquinolines **2—5** (scheme 2) has two reactive sites which may react with 2-acetamido-2-deoxy-alpha-*D*-glucopyranosyl chloride 3,4,6-triacetate, the phenolic hydroxyl group at position 5 of the substituent, and the unsubstituted nitrogen atom N(3) of the pyrazole moiety of the molecule. Glucosaminides **6—9** were obtained by the interaction of pyrazolo[3,4-*c*]isoquinolines **2—5** with α-*D*-glucosaminyl chloride **1** under phase transfer catalysis reaction [12, 13]. Glucosaminides **6—9** were obtained in yields of 49—66 %. It was found that the reaction of pyrazolo[3,4-*c*]isoquinoline **5** with 2-acetamido-2-deoxy-alpha-*D*-glucopyranosyl chloride 3,4,6-triacetate yielded only one of the two possible regioisomers **9**. The nitrogen atom of the pyrazole ring did not interact with 2-acetamido-2-deoxy-alpha-*D*-glucopyranosyl chloride 3,4,6-triacetate under the conditions used in the reaction.

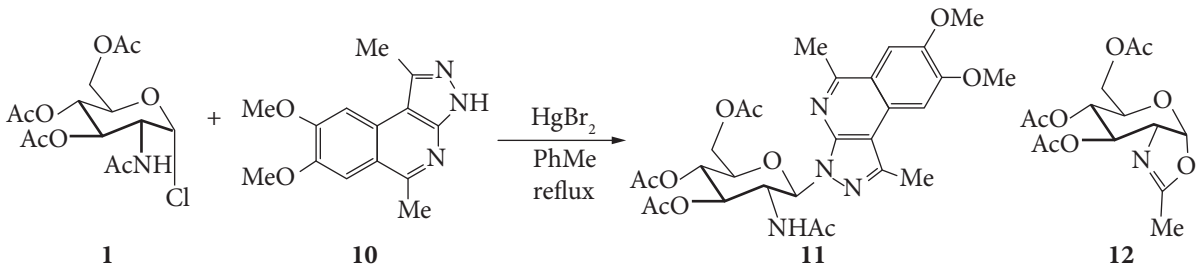


1 **2—5** **6—9**

2, **6**: R = H, R^1 = Me, R^2 = Ph **4**,**8**: R = H, R^1 = Et, R^2 = Ph
3, **7**: R = OMe, R^1 = Et, R^2 = Ph **5**, **9**: R = H, R^1 = Me, R^2 = H

Scheme 2. Synthesis of *O*-glycosides of pyrazolo[3,4-*c*]isoquinoline

Attempt to synthesize *N*-glycoside from compound **10** under phase transfer catalysis (PTC) was unsuccessful. Therefore, the method described in the article [14] was used. We obtained glucosaminide **11** by heating 2-acetamido-2-deoxy-alpha-*D*-glucopyranosyl chloride 3,4,6-triacetate **1** with pyrazolo[3,4-*c*]isoquinoline **10** in the presence of excess mercury (II) bromide in toluene. Low yield of the desired product (18 %) caused stringent conditions of synthesis, which have led to partial thermal degradation of carbohydrates in the reaction mixture and the formation of the oxazoline **12** (scheme 3).



1 **10** **11** **12**

Scheme 3. Synthesis of 3-*N*-glycoside of pyrazolo[3,4-*c*]isoquinoline

To determine the structure of the obtained compounds, a combination of 1D and 2D ^{1}H NMR spectroscopy was used. The ^{1}H NMR spectrum of 4-(1-ethyl-7,8-dimethoxy-3-phenyl-3*H*-pyrazolo[3,4-*c*]isoquinolin-5-yl)phenyl 3,4,6-tri-*O*-acetyl-2-(acetylamino)-2-deoxy-hexapyranoside **8** does not contradict the proposed structure but due to overlapping signals a number of them cannot be identified by the 1D spectrum. However, normalization of the integral intensities of the signals belonging to different parts of the molecule shows that the ratio between them is integral and corresponds to the expected structure (Fig. 1).

It is impossible to identify doublets relating to para-substituted phenylene ring against the background of doublets of monosubstituted phenyl system without additional information in the area of aromatic protons (8.4—7.2 ppm multiplet system). Furthermore, the absence of a quartet of ethyl group in the aliphatic region in 1M spectrum should be noted. We used the technique of 2D COSY GP ("Bruker", USA) with PGF. The spectrum was obtained using default settings. A relatively broad lines of the least rapidly relaxing methyl groups allowed us to rely on the absence of an appreciable contribution of T1 noise (Fig. 2).

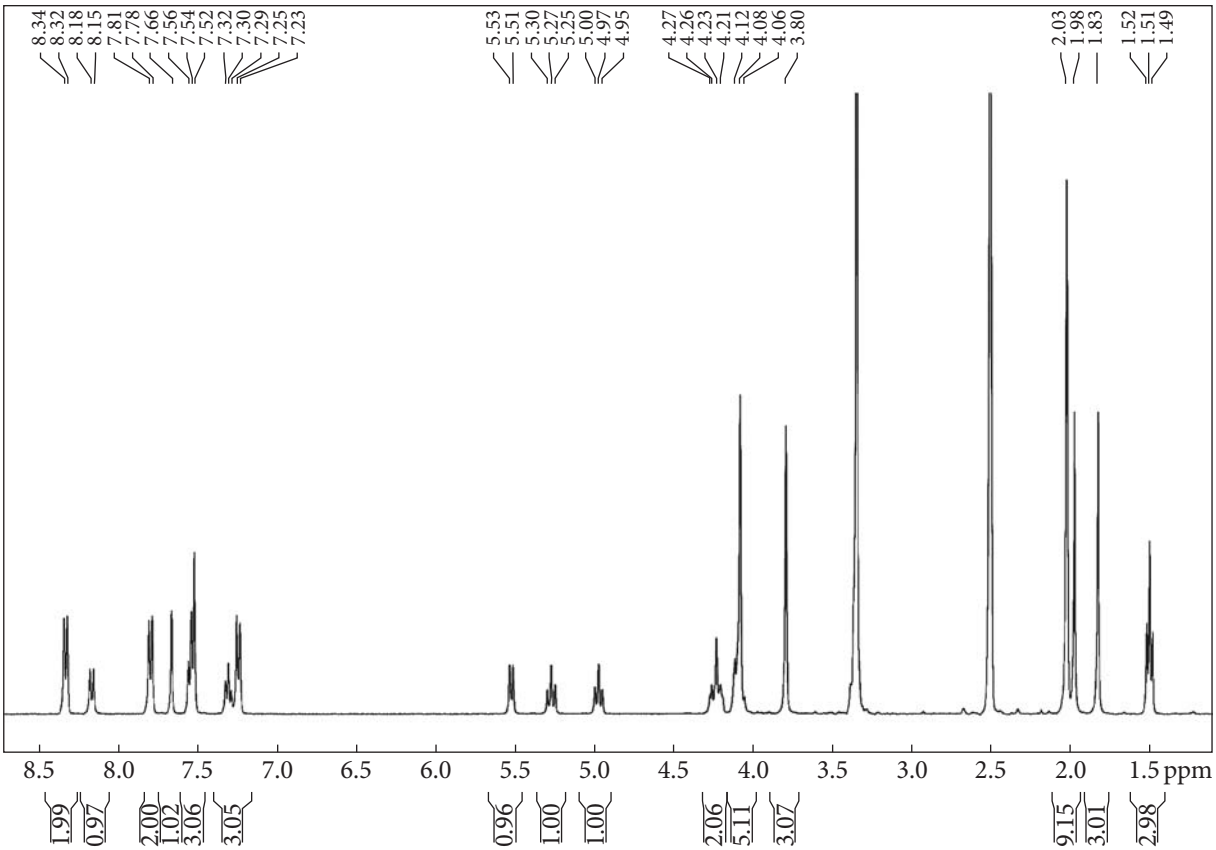


Fig. 1. [1]H NMR spectrum of 4-(1-ethyl-7,8-dimethoxy-3-phenyl-3*H*-pyrazolo[3,4-*c*]isoquinolin-5-yl)phenyl 3,4,6-tri-*O*-acetyl-2-(acetylamino)-2-deoxy-hexapyranoside **8**

Evident approach to the analysis of COSY spectra is the "unwinding" of the topological network of the spin system of simply connected site atom. The signal of a single NH group is a doublet at 8.16 ppm (1H, 7.0 Hz coupling constant) is one of the most advantageous starts in this molecule. This signal shows a cross-peak with multiplet at 4.15—4.00 ppm partially overlapping with the singlet of one methyl group and even with one proton of glycoside fragment.

Cross-peak with the multiplet system (5H) at 4.15—4.00 ppm indicates the position of the proton in C_2 associated with it. Proton d 1H signal at 5.52 ppm is linked (cross-peak) to the same proton by a single structure splitting of which may correspond to the proton at C_1. Thus, the position of the proton signals at C_1 and C_2 is precisely determined, and it belongs to the NH group of acetylaminopyranoside residue. The integral intensity of the multiplet at 4.15—4.00 ppm, 5H, 3H of them occur at CH_3 group, 1H at C_2 proton. To classify the remaining proton, the additional analysis was performed. Triplet 1H at 5.27 ppm has a cross-peak with a signal referred above to the proton at C_2. Thus, this is a proton on C_3 position. The signal form is a triplet, which corresponds to the nearest environment of the two protons at C_2 and C_4. This triplet has a strong cross-peak with a triplet 1H at 4.97 ppm, corresponding to proton in C_4. The signal at 4.97 shows a cross-peak in the component of multiplet 2H at 4.3—4.2 ppm which demonstrates the relationship with the C_5. The two remaining non-equivalent protons of the anomeric atom C_6 are presented by multplets of 1H in the range of 4.30—4.2 and 4.15—4.00 ppm,

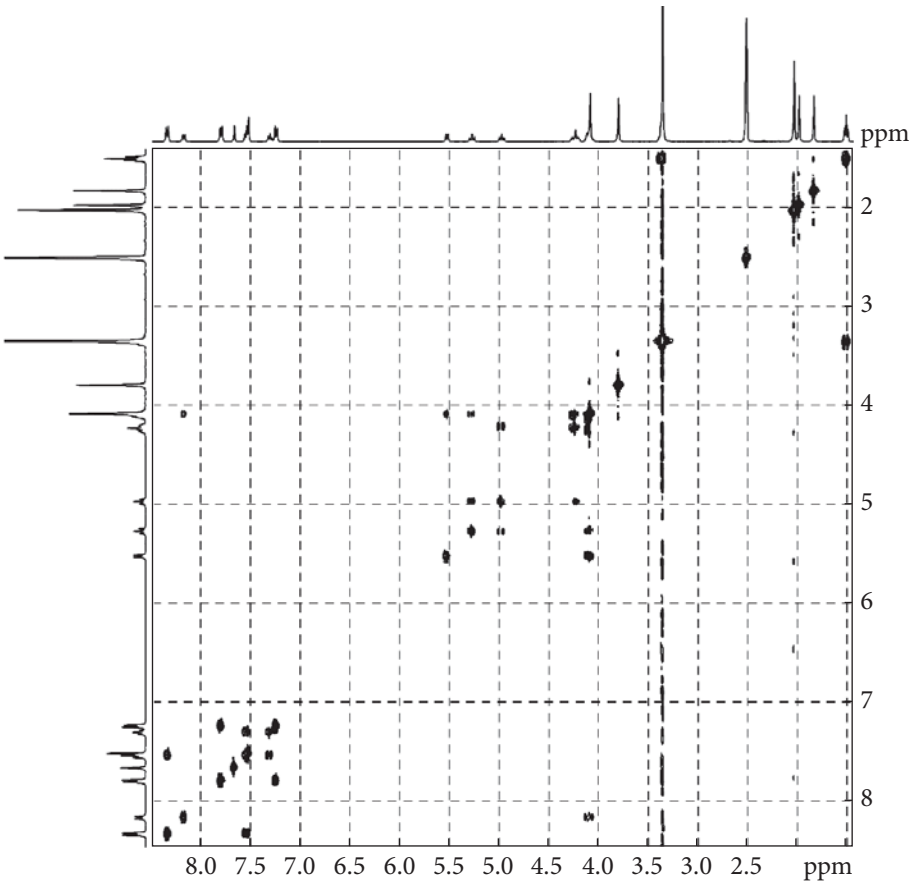


Fig. 2. 2M 1H COSY NMR spectrum of the glycoside **8**

which corresponds to the fine pattern of interactions in this area in COSY spectrum. Thus, previously unidentified 1H in this multiplet is a signal which belongs to one of the C_6 protons. 3H triplet at 1.51 ppm belongs to ethyl group in position 1, as well as its only neighbor, obviously, apparently a quartet located at the 3.45 ppm signal of water. Four 3H singlets at 4.21, 3.80, 1.98 and 1.83 are signals of the three methyl groups of the acetyl and one acetamino substituents in hexa-pyranoside cycle. Field of aromatic protons is attributable likewise. Thus, it is easy to distinguish the protons of para-substituted phenylene rings, two doublets for 2H at 7.24 and 7.80 ppm, demonstrating the cross-peak at COSY only among themselves. The system of lines (d, 2H, 8.33) — (t, 2H, 7.54) — (t, 1H, 7.30 ppm) is mono-substituted phenyl substituent at the 3-position. They are isolated by 1H singlet at 7.52 and 7.66 ppm, corresponding to protons in positions 6 and 9. The spectral pattern of the other compounds is as discussed above. The significant difference in the spectrum of glycoside 9 is a signal (N3) — H of pyrazole nucleus is 1H singlet at 13.29 ppm. Signal of NH of acetylamino group is located at 8.16 ppm (d, 1H) and has a coupling constant 8.9 Hz.

The spectrum of *N*-glycoside **11** with glycoside moiety at the pyrazole nitrogen atom has noticeable differences. The signal at C_1 and up to 4.8 (+0.3 ppm) signal at C_5 of glycosidic residue have broadened significantly and shifted to a weak field, up to 6.49 ppm (+1.0 ppm). The proton signals at C_3 and C_4 are also shifted downfield retaining their characteristic symmetry which increased difference in chemical shifts of protons of the exocyclic CH_2 group up to 0.3 ppm (Fig. 3).

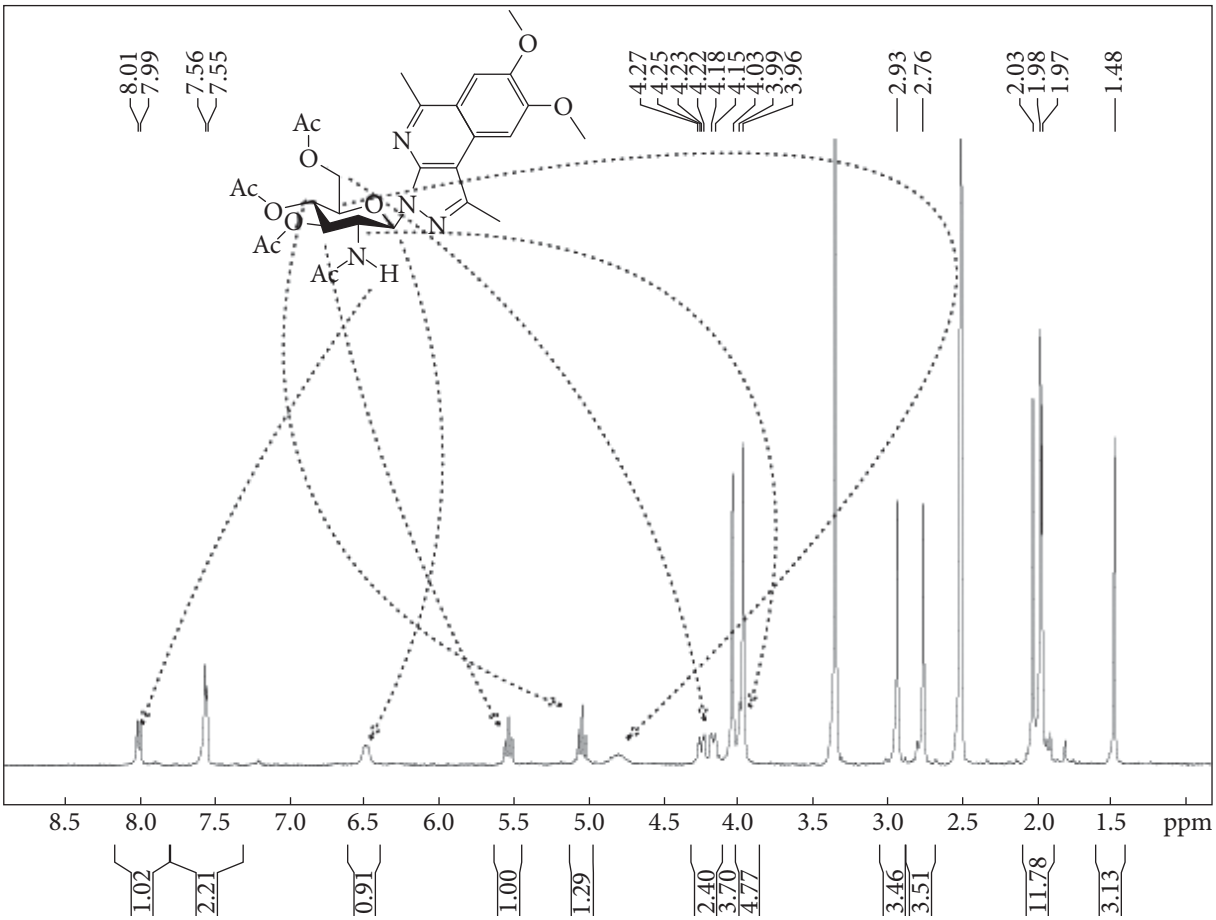


Fig. 3. ^{1}H NMR spectrum of 1,5-dimethyl-3-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyloxy)-7,8-dimetoxypirazolo[3,4-*c*]isoquinoline **11**

A number of signals of glycoside residues, which demonstrated high intramolecular mobility in previous compounds, were significantly elongated in this case due to exchange between the sterically caused conformers. This effect most strongly impacts protons in C_1 and C_5 nuclei of carbohydrate residue that logically linked to the influence of heterocyclic fragment. Relaxation time of signals series is so short that in the 2D COSY spectra they do not demonstrate cross-peaks expected for their molecular structure (spin system has time to cool during the incremental pause of pulse sequence).

Features of distribution of magnetic anisotropy zone in the pyrazoloisoquinoline nucleus have not yet been studied. Our early results [2, 14] show that the fragments are located in a plane orthogonal to the pyrazole cycle, typical downfield shift. However, for aromatic substituents in the 3-position of the heterocyclic system such significant inhibition of intramolecular movements was not observed. Comparing stability of the signals position in Fig. 4 shows the aliphatic region of the spectra of all received glycosides.

Experimental. ^{1}H spectra were recorded with a Bruker AVANCE 400 MHz spectrometer at 400.16 MHz in solutions DMSO-d_6. Chemical shifts (δ) in ppm are reported by using TMS as an

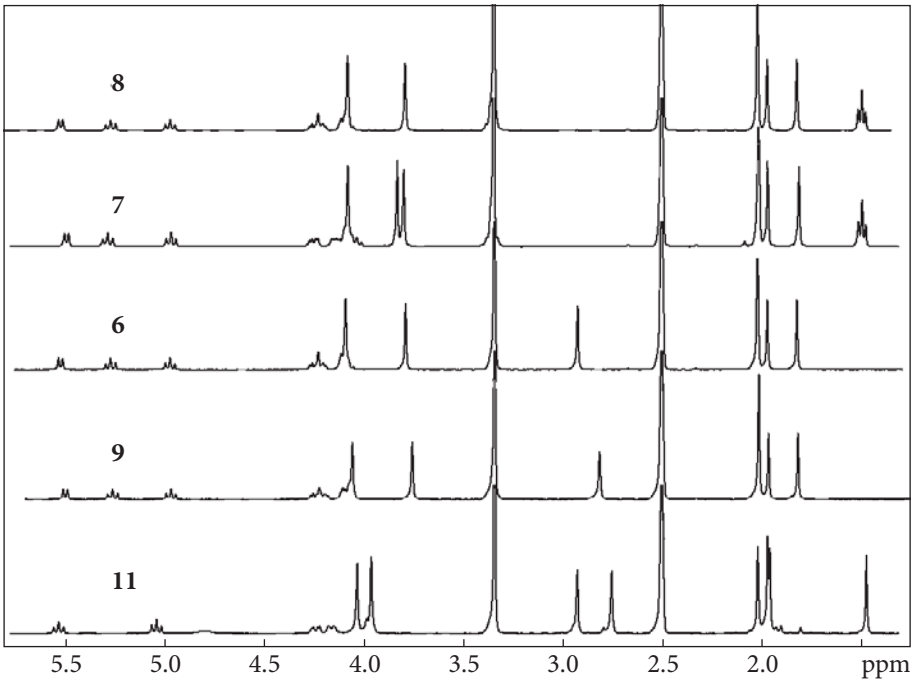


Fig. 4. Comparison of aliphatic areas ^{1}H NMR spectra of compounds **6, 7, 8, 9, 11** reviewed in the article

internal standard. The coupling constants (*J*) are given in Hz. Melting points were measured on a PTP capillary melting point apparatus. Optical rotations were measured at 20—22°C on a Polamat-A polarimeter. Column chromatography was carried out using Kieselgel silica gel 60, 0.063—0.2 mm ("Merck", Germany). TLC was carried out on silica gel plates ("Merck"). Visualisation was achieved by UV (254) or 5 % solution of H_2S0_4 in butanole-1 staining. Starting compounds 2—5 and 10 was obtained in according to [2] and [15].

General procedures for synthesis of compound 6—9. A mixture of appropriate isoquinoline **2—5** (1.4 mmol), α-chloride **1** (1.4 mmol), anhydrous potassium carbonate (6.3 mmol) and 15-crown-5 (0.28 mmol) in dry acetonitrile was maintained at 20—22 °C temperature to full conversion of glycosyl-donor (TLC control). The solid phase was filtered off, washed with dry acetonitrile (2 × 5 ml), and the solvent was evaporated in vacuo. The residue was purified by column chromatography [silica gel, $CHCl_3$/iPrOH (100 : 1) → $CHCl_3$/iPrOH (30 : 1), to give target products **6—9**.

1-Methyl-3-phenyl-5-[4-(2-acetamido-3,4,6-tris-O-acetyl-2-desoxy-α-D-glycopyranosyloxy) phenyl]-7,8-dimethoxypyrazolo[3,4-c]isoquinoline (**6**). Yield 66 %; m.p. 274 °C, $[\alpha]_{546} = -25^{o}$ (*c* = 1,0; chloroform). ^{1}H NMR: d, 2H, 8.32 ppm, *J* = 8.3 Hz; d, 1H, 8.16 ppm, *J* = 8.9 Hz; d, 2H, 7.79 ppm, *J* = 8.50 Hz; s, 1H, 7.72 ppm, dd, 2H, 7.53 ppm, *J* = 8.3 Hz, *J* = 7.4 Hz; s, 1H, 7.51 ppm; t, 1H, 7.30 ppm, *J* = 7.4 Hz; d, 2H, 7.24 ppm, *J* = 8.50 Hz; d, 1H, 5.52 ppm, *J* = 8.3 Hz; dd, 1H, 5.27 ppm, *J* = 9.7 Hz, *J* = 9.8 Hz; dd, 1H, 4.97 ppm, *J* = 9.3 Hz, *J* = 9.5 Hz; m, 2H, 4.30—4.15 ppm; m, 5H, 4.15—4.05 ppm; s, 3H, 3.79 ppm; s, 3H, 2.93 ppm; s, 3H, 1.98 ppm; s, 3H, 1.83 ppm.

1-Ethyl-3-phenyl-5-[4-(2-acetamido-3,4,6-tris-O-acetyl-2-desoxy-α-D-glycopyranosyloxy-3-methoxy)phenyl]-7,8-dimethoxypyrazolo[3,4-c] isoquinoline (**7**). Yield 49 %; m.p. 230 °C, $[\alpha]_{546}$ = −0,03° (*c* = 1,0; chloroform). ^{1}H NMR: d, 2H, 8.35 ppm, *J* = 8.0 Hz; d, 1H, 8.14 ppm, *J* = 9.1 Hz; s, 1H, 7.66 ppm; s, 1H, 7.57 ppm, dd, 2H, 7.54 ppm, *J* = 8.0 Hz, *J* = 7.3 Hz; ws, 1H, 7.44 ppm; wd, 1H, 7.37 ppm, *J* = 7.4 Hz; d, 1H, 7.34 ppm, *J* = 7.4 Hz; t, 1H, 7.30 ppm, *J* = 7.3 Hz; d, 1H, 5.49 ppm, *J* = 8.5 Hz; dd, 1H, 5.28 ppm, *J* = 9.5 Hz, *J* = 10.0 Hz; dd, 1H, 4.97 ppm, *J* = 9.5 Hz, *J* = 9.5 Hz; m, 1H, 4.3—4.2 ppm; m, 6H, 4.15—4.00 ppm; s, 3H, 3.83 ppm; s, 3H, 3.80 ppm; s, 3H, 1.98 ppm; s, 3H, 1.82 ppm; t, 3H, 1.50 ppm, *J* = 7.4 Hz.

1-Ethyl-3-phenyl-5-[4-(2-acetamido-3,4,6-tris-O-acetyl-2-desoxy-α-D-glycopyranosyloxy) phenyl]-7,8-dimethoxypyrazolo[3,4-c]isoquinoline (**8**). Yield 60 %; m.p. 269 °C, $[\alpha]_{546}$ = −0,04° (*c* = 1,0; chloroform). ^{1}H NMR: d, 2H, 8.33 ppm, *J* = 8.3 Hz; d, 1H, 8.17 ppm, *J* = 9.0 Hz; d, 2H, 7.80 ppm, *J* = 8.2; s, 1H, 7.66 ppm, dd, 2H, 7.54 ppm, *J* = 8.33 Hz, *J* = 7.4 Hz; s, 1H, 7.52 ppm; t, 1H, 7.30 ppm, *J* = 7.4 Hz; d, 2H, 7.24 ppm, *J* = 8.2 Hz; d, 1H, 5.52 ppm, *J* = 8.5 Hz; dd, 1H, 5.27 ppm, *J* = 9.7 Hz, *J* = 10 Hz; dd, 1H, 4.97 ppm, *J* = 9.5 Hz, *J* = 9.7 Hz; m, 2H, 4.3—4.28 ppm; m, 5H, 4.15—4.05 ppm; s, 3H, 3.80 ppm; s, 3H, 1.98 ppm; s, 3H, 1.83 ppm; t, 3H, 1.51 ppm, *J* = 7.4 Hz.

1-Methyl-3H-5-[4-(2-acetamido-3,4,6-tris-O-acetyl-2-desoxy-α-D-glycopyranosyloxy) phenyl]]-7,8-dimethoxypyrazolo[3,4-c]isoquinoline (**9**). Yield 42 %; m.p. 248 °C, $[\alpha]_{546}$ = −0,04° (*c* = 1,0; chloroform). ^{1}H NMR: s, 1H, 13.29 ppm; d, 1H, 8.16 ppm, *J* = 9.2 Hz; d, 2H, 7.71 ppm, *J* = 8.40 Hz; s, 1H, 7.67 ppm; s, 1H, 7.46 ppm; d, 2H, 7.21 ppm, *J* = 8.40 Hz; d, 1H, 5.50 ppm, *J* = 8.5 Hz; dd, 1H, 5.26 ppm, *J* = 9.8 Hz, *J* = 10.8 Hz; dd, 1H, 4.97 ppm, *J* = 9.5 Hz, *J* = 9.4 Hz; m, 2H, 4.30—4.15 ppm; m, 5H, 4.15—4.00 ppm; s, 3H, 3.76 ppm; s, 3H, 2.82 ppm; s, 3H, 1.97 ppm; s, 3H, 1.83 ppm.

1,5-Dimethyl-3-(2-acetamido-3,4,6-tris-O-acetyl-2-desoxy-α-D-glycopyranosyloxy)-7,8-dimethoxypyrazolo[3,4-c]isoquinoline (**11**). To a solution of isoquinoline **10** (1.2 mmol) and α-chloride **1** (1.2 mmol) in 10 ml of anhydrous toluene was added mercury(II)bromide (1.31 mmol). The reaction mixture was heated to reflux to full conversion of glycosyl-donor (TLC control). The solid phase was filtered off, washed by toluene (2 × 5 ml) solvent was evaporated in vacuo. The residue was purified by column chromatography [silica gel, $CHCl_3$/iPrOH (100 : 1) → $CHCl_3$/iPrOH (30 : 1), to give target product **11**. Yield 18 %; m.p. 273—275 °C, $[\alpha]_{546}$ = −25° (*c* = 1,0; chloroform). ^{1}H NMR: d, 1H, 8.00 ppm, *J* = 8.5 Hz; s, 1H, 7.56 ppm; s, 1H, 7.55 ppm; wd, 1H, 6.50 ppm, *J* = 8.5 Hz; dd, 1H, 5.53 ppm, *J* = 9.6 Hz, *J* = 9.6 Hz; dd, 1H, 5.04 ppm, *J* = 9.6 Hz, *J* = 9.8 Hz; wm, 1H, 4.7—4.9 ppm; m, 2H, 4.3—4.1 ppm, s, 3H, 4.18 ppm; m, 1H, 3.9—4.0 ppm; s, 3H, 3.96 ppm; s, 3H, 2.93 ppm; s, 3H, 2.76 ppm; s, 3H, 2.03 ppm; s, 3H, 1.98 ppm; s, 3H, 1.97 ppm; s, 3H, 1.48 ppm.

Conclusions. To sum it up, we describe the methods for obtaining *N*- and *O*-glycosides with the pyrazolo[3,4-*c*]isoquinoline as aglycone moiety. *O*-glycosides are obtained with good yield by phase transfer catalysis. Mercury (II) bromide is used for glycosylation of nitrogen atom at pyrazole ring. NMR study of the structure has shown high stability of the glycoside residue proton signals. Studies of the biological activity of the compounds is underway and will be presented in due course.

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O- ТА *N*-ГЛІКОЗИДИ ПІРАЗОЛО[3,4-*c*]ІЗОХІНОЛІНУ.
СИНТЕЗ ТА ЯМР-ДОСЛІДЖЕННЯ СТРУКТУРИ

Досліджено синтетичний потенціал поліфункціональних похідних конденсованої системи піразоло[3,4-*c*] ізохіноліну. Вперше отримано серію похідних з фрагментом глюкозаміну і досліджено їх спектральні характеристики.

Ключові слова: *піразоло[3,4-c]ізохіноліни, глікозилювання, кореляційна спектроскопія, N,O-глікозиди, оксазолін.*