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SYNTHESIS OF N-ACETYLGLUCOSAMINIDES WITH COUMARIN AND CHROMONE AGLYCONES

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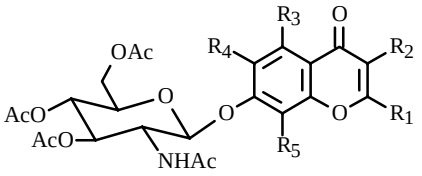
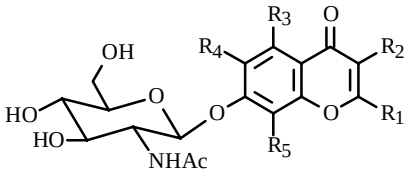
β-O-Glycosides of N-acetylglucosamine with substituted 7-hydroxychromones and 7-hydroxycoumarins as the aglycones are synthesized. The phenyl hydroxyls are O-glycosylated in a solid—liquid system with crown-ether catalysts. The structures of the chromone and coumarin N-acetylglucosaminides and their per-O-acetates are proved by PMR spectroscopy.

Key words: glycoside synthesis, 7-hydroxychromone glycosides, 7-hydroxycoumarin glycosides, N-acetylglucosamine glycosides, crown ether.

Natural and synthetic derivatives of 7-hydroxycoumarin and 7-hydroxychromone exhibit a wide spectrum of biological activity. The corresponding O-glycosides of neutral sugars are widely distributed in the plant kingdom and also have a variety of physiological activities [1]. In particular, rutin and its analogs act as vitamins [2] and possess antispasmodic [3], anti-inflammatory, and anti-allergic activity [4]. Anti-oxidants, cardiostimulants, hypoglycemics, hepatoprotectants [5], and antibiotics, for example, novobiocin [6] are represented among this class of compounds.

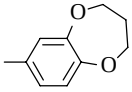


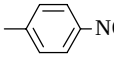
2a - e

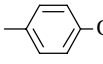


3a - e

2a, 3a: R_1 = Me, R_2 =  , $R_3 = R_4 = R_5 = H$

2b, 3b: R_1 = Me, R_2 =  , $R_3 = R_4 = R_5 = H$

2c, 3c: R_1 = Me, R_2 =  , $R_3 = R_4 = R_5 = H$

2d, 3d: R_1 = Me, R_2 =  , $R_3 = R_4 = R_5 = H$

2e, 3e: R_1 = H, R_2 =  , $R_3 = R_5 = H$, R_4 = Et

1) V. I. Vernadskii Tavricheskii National University, 95007, Ukraine, Simferopol′, ul. Yaltinskaya, 4, fax (0652) 23 23 10, e-mail: vladimir@tnu.crimea.ua; 2) Taras Shevchenko Kiev National University, 01033, Ukraine, Kiev, ul. Vladimirskaya, 60, fax (044) 23 51 273, e-mail: alexish@i.com.ua; 3) Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences, Ukraine, 02094, Ukraine, Kiev, ul. Murmanskaya, 1. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 125-128, March-April, 2002. Original article submitted April 5, 2002.

0009-3130/02/3802-0149$27.00

TABLE 1. PMR Spectra of **2a**-**j***

Compound	Atom												
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6A}$; $J_{5,6B}$)	H-6 (J_{gem})	NAc, OAc	NH ($J_{NH,2}$)	R_1	R_2	R_3	R_4	R_5
2a	5.58d (8.5)	4.09ddd (10)	5.26dd (9.5)	4.96dd (9.5)	4.27ddd (2.5; 5.5)	4.19dd, 4.23dd (12)	1.81s, 1.97s, 2.03s, 2.06s	8.12d (8)	2.27s	7.30m, 7.43m	7.99d	7.09dd	7.29d
2b	5.56d (8.5)	4.09ddd (10)	5.26dd (9.5)	4.96dd (9.5)	4.26ddd (2.5; 5.5)	4.17dd, 4.22dd (12)	1.80s, 1.97s 2.03s, 2.05s	8.11d (8.5)	2.28s	2.14m, 4.18t, 6.90s, 7.01d, 7.08d	7.97d	6.86dd	7.27d
2c	5.58d (8.5)	4.09ddd (10)	5.24dd (9.5)	4.96dd (9.5)	4.30ddd (2.5; 5)	4.11dd, 4.20dd(12)	1.80s, 1.97s, 2.02s, 2.05s	8.17d (9)	2.30s	7.63d, 8.30d	8.00d	7.10dd	7.34d
2d	5.57d (8.5)	4.08dd (10)	5.24dd (9.5)	4.95dd (9.5)	4.30ddd (2; 5)	4.11dd, 4.20dd (12.5)	1.79s, 1.96s, 2.02s, 2.05s	8.16d (9.5)	2.27s	7.33d, 7.50d	7.98d	7.08dd	7.31d
2e	5.03d (8.5)	4.39ddd (10)	5.24dd (9.5)	5.10dd (9.5)	3.68ddd (2.5; 5)	4.18dd 4.22dd (12)	2.05s, 2.06s, 2.07s, 2.09s	6.24d (8)	7.07s	2.52s, 8.96s	7.82s	1.15t, 2.56q	6.82s
2f	5.58d (8.5)	4.07ddd (10)	5.24dd (9.5)	4.95dd (9.5)	4.30ddd (2; 5)	4.10dd 4.20dd (12)	1.79s, 1.96s, 2.02s, 2.05s	8.17d (8.5)	2.37s	7.02dd, 7.11dd	7.95d	7.09dd	7.36d
2g	5.47d (8.5)	4.18ddd (10)	5.24dd (9.5)	4.98dd (9.5)	4.35ddd (2; 5)	4.14dd 4.23dd (12)	1.79s, 1.98s, 2.02s, 2.05s	8.17d (9)	8.66s	1.17d, 2.84m 6.89d, 7.15d	7.84s	1.10t, 2.59m	7.40s
2h	5.24 (8.5)	4.32ddd (10)	5.36dd (9.5)	5.17dd (9.5)	3.85ddd (2.5; 5.5)	4.15dd 4.24dd (12)	2.01s, 2.04c (6H), 2.06s	6.07d (8.5)	6.16s	7.29 - 7.48m	7.19d	6.84d	2.28s
2i	5.36d (8.5)	4.20ddd (10)	5.37dd (9.5)	5.13dd (9.5)	3.95ddd (2.5; 5)	4.16dd 4.29dd (12)	1.96s, 2.05s, 2.07s, 2.09s	6.14d (8.5)	1.79m, 2.47m, 2.66m		7.36d	6.86dd	6.86d
2j	5.56d (8)	4.08ddd (10)	5.25dd (9.5)	4.97dd (9.5)	4.31ddd (2; 5)	4.11dd 4.22dd (12.5)	1.80s, 1.98s, 2.03s, 2.04s	8.15d (9)	2.47s, 8.96s	7.44d	7.98d	7.08dd	7.25d

*Working frequency 400 MHz; for **2a**, -**b**, -**e**, -**h**, and -**i**, 300 MHz. Solvent DMSO-d_6; for **2e**, -**h**, and -**i**, $CDCl_3$.

Adding carbohydrates to the coumarin or chromone structures substantially changes the hydrophilic—lipophilic balance. Therefore, transport in biological systems is affected. We determined the influence of the carbohydrate component on the biological activity of modified 7-hydroxycoumarins and chromones by synthesizing the corresponding N-acetylglucosaminides. The glycosylation of 7-hydroxycoumarin and -chromone derivatives by glycosyl donors based on only neutral sugars has been described [7].

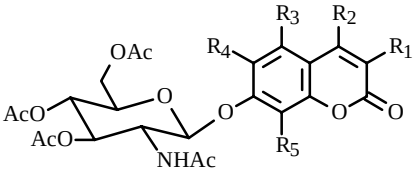
We developed a method for preparing arylglycosides of N-acetylglucosamine under phase-transfer catalysis conditions in a solid—liquid system [8] and used it to glycosylate hydroxyl derivatives of coumarin and chromone. The reaction between equivalent amounts of phenolic compounds, anhydrous K_2CO_3, and glycosyl donor, α-glucosaminyl chloride peracetate (**1**), was carried out at room temperature in acetonitrile in the presence of 15-crown-5 (20 mol %). The reaction was usually complete in 24 h. Glycosides **2a-j** were isolated by crystallization in 63-84% yields. Signals for protons of the aglycone and carbohydrate were unambiguously identified in the PMR spectra (Table 1). In particular, the presence in the spectra of doublets for the anomeric protons at 5.03-5.58 ppm and spin—spin coupling constants 8-8.5 Hz is consistent with formation of a 1,2-*trans*-glycoside bond.

De-acetylation of the peracetates (**2a-j**) by a modified Zemplen method produced the desired N-acetylglucosaminides (**3a-j**). The chromone and coumarin algycones were not opened under the synthetic conditions. This was confirmed by PMR spectroscopy (Table 2).

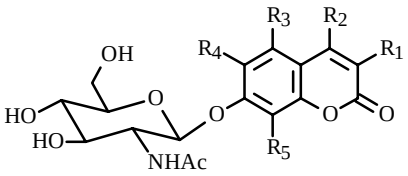
TABLE 2. PMR Spectra of **3a-j***

Compound	Atom								
	H-1($J_{1,2}$)	OH	NAc	NH ($_{JNH,2}$)	R_1	R_2	R_3	R_4	R_5
3a	5.20d (8)	4.69t, 5.17m	1.82s	7.88d (9)	2.27s	7.30m, 7.45m	7.96d	7.04dd	7.18d
3b	5.20d (8)	4.68t, 5.15d 5.18d	1.82s	7.87d (9)	2.28s	2.13m, 4.16t, 4.18t, 6.90d, 7.02m	7.95d	6.85dd	7.16d
3c	5.22d (8.5)	4.67t, 5.16d, 5.19d	1.82s	7.87d (9)	2.31s	7.62d, 8.30d	7.97d	7.06dd	7.20d
3d	5.21d (8.5)	4.67t, 5.14d, 5.18d	1.82s	7.86d (9)	2.27s	7.33d, 7.50d	7.96d	7.04dd	7.17d
3e	5.10d (8.5)	4.75t, 5.16d, 5.24d	1.82s	7.88d (9.5)	7.35s	2.44s, 9.21s	7.95s	1.13t, 2.62m	7.33s
3f	5.21d (9)	4.66t, 5.16d, 5.19d	1.82s	7.87d (9)	2.38s	7.01dd, 7.11dd	7.94d	7.05dd	7.22d
3g	5.08d (8)	4.72t, 5.16d, 5.23d	1.82s	7.87d (9.5)	8.64s	1.17d, 2.84m, 6.88d, 7.15d	7.81s	1.10t, 2.59m	7.30d
3h	4.94d (8)	4.63br t, 5.18m	1.83s	7.85d (9)	6.29s	7.53m, 7.57m	7.23d	7.12d	2.19s
3i	5.10d (9)	4.69t, 5.13d, 5.17d	1.81s	7.84d (8.5)	1.74m, 2.41m, 2.77m		7.63d	6.93dd	6.98
3j	5.19d (9)	4.68t, 5.16d, 5.19d	1.82s	7.87d (9)	2.46s, 8.95	7.42s	7.95d	7.03dd	7.12d

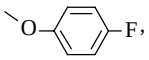
*Working frequency 400 MHz, solvent DMSO-d_6.

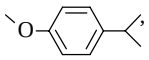


2f - j



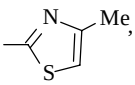
3f - j

2f, 3f: R_1 = Me, R_2 =  $R_3 = R_4 = R_5 = H$

2g, 3g: R_1 = H, R_2 =  $R_3 = R_5 = H$, R_4 = Et

2h, 3h: R_1 = H, R_2 =  $R_3 = R_4 = H$, R_5 = Me

2i, 3i: $R_1R_2 = -(CH_2)_4-$, $R_3 = R_4 = R_5 = H$

2j, 3j: R_1 =  $R_2 = R_3 = R_4 = R_5 = H$

We previously used glycosides (**2a** and **-b**) to prepare the corresponding glycoside derivatives of N-acetylmuramoyl-L-alanyl-D-isoglutamine [9].

EXPERIMENTAL

Melting points were determined on a PTP apparatus; optical rotation, at 20-22°C on a Polamat-A polarimeter. ^{1}H NMR spectra were obtained on Varian VXR-300 (300 MHz) and Varian Mercury 400 (400 MHz) spectrometers with TMS internal standard. Chemical shifts are given in ppm using the δ scale. TLC was performed on Sorbfil-AFV-UV plates (Sorbpolimer, Russia) with development by H_2SO_4 in ethanol (5%) with heating to 200-300°C and UV light (254 nm). Solvent systems used $CHCl_3$—propan-2-ol (15:1, 1; 3:1, 2).

The synthesis of substituted 7-hydroxycoumarins and 7-hydroxychromones has been published [10-13].

General Glycosylation Method. A solution of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosylchloride (**1**, 1.7 g, 4.65 mmole) [11] in acetonitrile (30 mL) was treated with 2-methyl-7-hydroxyisoflavone (1.17 g, 4.65 mmole), finely ground anhydrous K_2CO_3 (640 mg, 4.65 mmole), and 15-crown-5 (185 μL, 0.93 mmole). The reaction mixture was stirred at room temperature until the glycosyl donor completely disappeared (TLC monitoring using system 1). The solvent was evaporated. The solid was dissolved in $CHCl_3$ (100 mL) and washed with KOH (1 N, 2×20 mL) and water (3×30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated. Crystallization of the solid from isopropanol produced:

2-methyl-7-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)isoflavone (2a), yield 66%, mp 194-196°C, $[\alpha]_{546}$ +2° (*c* 1.0, methylenechloride);

2-methyl-3′,4′-trimethylenedioxy-7-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)isoflavone (2b), yield 76%, mp 233-235°C (dec.), $[\alpha]_{546}$ +10° (*c* 1.0, methylenechloride);

2-methyl-4′-nitro-7-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)isoflavone (2c), yield 65%, mp 249-250°C, $[\alpha]_{546}$ -8° (*c* 1.0, methylenechloride);

2-methyl-4′-chloro-7-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)isoflavone (2d), yield 84%, mp 241-242°C, $[\alpha]_{546}$ -19° (*c* 1.0, methylenechloride);

3-(4-methylthiazolyl-2)-6-ethyl-7-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)chromone (2e), yield 63%, mp 257-258°C, $[\alpha]_{546}$ -27° (*c* 1.0, methylenechloride);

2-methyl-3-(4′-fluorophenoxy)-7-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)chromone (2f), yield 73%, mp 229-230°C, $[\alpha]_{546}$ -17° (*c* 1.0, methylenechloride);

3-(4′-isopropylphenoxy)-6-ethyl-7-(2-acetamido-3,4,6-tri-O-acetyl-2-dexoy-β-D-glucopyranosyloxy)chromone (2g), yield 72%, mp 209-210°C, $[\alpha]_{546}$ -29° (*c* 0.95, $CHCl_3$);

4-phenyl-8-methyl-7-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)coumarin (2h), yield 80%, mp 221-222°C, $[\alpha]_{546}$ -62° (*c* 1.0, methylenechloride);

7-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)-3,4-tetramethylenecoumarin (2i), yield 67%, mp 206-209°C, $[\alpha]_{546}$ -31° (*c* 1.0, methylenechloride);

3-(4-methylthiazolyl-2)-7-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)coumarin (2j), yield 70%, mp 250-251°C, $[\alpha]_{546}$ -11° (*c* 0.75, $CHCl_3$—isopropan-2-ol, 3:1).

General Deacetylation Method. A solution or suspension of acetate (**2a**, 1.7 g, 2.9 mmole) in a mixture (50 mL) of dry methanol and dichloromethane (1:1) was treated with NaOMe (0.1 N, 0.5 mL) in methanol. The precipitate that formed after 12 h (TLC monitoring using system 2) was filtered off and washed with cold methanol. The mother liquor was neutralized using KU-2 cation exchanger (H^+). The resin was filtered off. The filtrate was evaporated and treated with ether to produce an additional portion of crystals. This method produced:

2-methyl-7-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)isoflavone (3a), yield 86%, mp 163-165°C, $[\alpha]_{546}$ -10° (*c* 1.0, DMF);

2-methyl-3′,4′-trimethylenedioxy-7-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)isoflavone (3b), yield 90%, mp 148-150°C, $[\alpha]_{546}$ -15° (*c* 1.0, DMF);

2-methyl-4′-nitro-7-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)isoflavone (3c), yield 89%, mp 232-234°C, $[\alpha]_{546}$ -13° (*c* 1.0, DMF);

2-methyl-4′-chloro-7-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)isoflavone (3d), yield 86%, mp 243-244°C, $[\alpha]_{546}$ -8° (*c* 1.0, DMF);

3-(4-methylthiazolyl-2)-6-ethyl-7-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)chromone (3e), yield 95%, mp 201°C (dec.), $[\alpha]_{546}$ -42° (*c* 1.0, DMF);

2-methyl-3-(4′-fluorophenoxy)-7-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)chromone (3f), yield 82%, mp 271-272°C, $[\alpha]_{546}$ -21° (*c* 1.0, DMF);

3-(4′-isopropylphenoxy)-6-ethyl-7-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)chromone (3g), yield 87%, mp 221-222°C, $[\alpha]_{546}$ -48° (*c* 1.0, DMF);

4-phenyl-7-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)-8-methylcoumarin (3h), yield 97%, mp 203-204°C, $[\alpha]_{546}$ -63° (*c* 1.0, DMF);

7-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)-3,4-tetramethylenecoumarin (3i), yield 92%, mp 195-196.5°C, $[\alpha]_{546}$ -10° (*c* 1.0, DMF);

3-(4-methylthiazolyl-2)-7-(2-acetamido-2-deoxy-β-D-glucopyranosyloxy)coumarin (3j), yield 94%, mp 187-188°C, $[\alpha]_{546}$ -8° (*c* 1.0, DMF).

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