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The novel structural modification of pyridoxal *via* its cyclization into 2-acyl- and 2-heteroarylfuro[2,3-*c*]pyridines

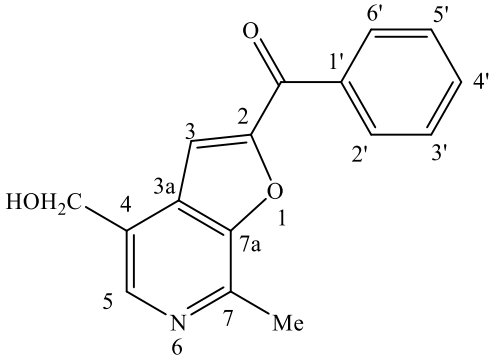
Anatolii S. Morkovnik, Alexander A. Zubenko, Ludmila N. Divaeva, Viktor G. Kartsev, Gennadii S. Borodkin and Alexander I. Klimenko

1. General Information

The starting compounds were provided by InterBioscreen Ltd. (Russia) and used without further purification. The solvents were purified according to standard procedures. NMR spectra of newly synthesized compounds were recorded at 20ºC on Bruker Avance 600 spectrometer (600 MHz) in DMSO-d_6. Chemical shifts of ^{1}H and ^{13}C nuclei were measured relative to the residual signals of deuterosolvent (δ = 2.49 ppm for protons and 39.5 ppm for carbons). Coupling constants (*J*) are given in Hertz (Hz). Melting points were determined by using Fisher-Johns Melting Point Apparatus (Fisher Scientific) and were uncorrected. Elemental analysis was performed by the classical method of microanalysis. The reaction and purity of the obtained compounds were monitored by TLC (plates with Al_2O_3 III activity grade, eluent $CHCl_3$, evaporation of iodine vapor in a moist chamber).

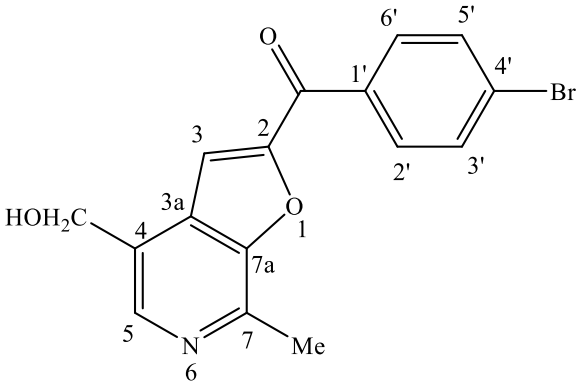
2. Synthesis and characterization of 2-acyl- and 2-heteroarylfuro[2,3-*c*]pyridines 4a-g

(4-Hydroxymethyl-7-methylfuro[2,3-c]pyridine-2-yl)(phenyl)methanone (**4a**).



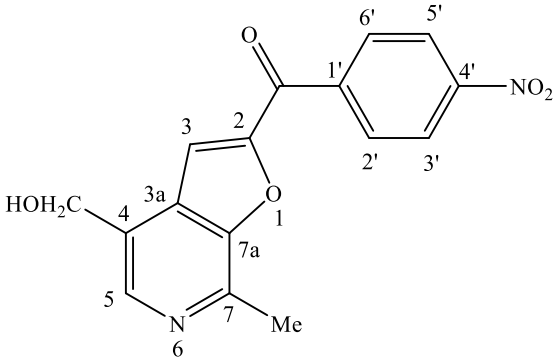
A mixture of pyridoxal hydrochloride **(1** · **HCl) (**1.02 g; 0.05 mol) and 2-bromo-1-phenylethan-1-one (**3a**) (1.0 g; 0.05 mol) with saturated aqueous solution of K_2CO_3 (15 ml) and acetonitrile (15 ml) was stirred vigorously for 2 hours at 50-60 °C. The mixture was then cooled, poured into water (100 ml), the precipitate formed is filtered off and washed with water (15 ml). The yield was 0.76 g (57%). Light beige crystals, mp 146-148 ºC (EtOAc). ^{1}H NMR (DMSO-d_6) δ, ppm: 2.71 (s, 3H, Me), 4.79 (s, 2H, CH_2), 5.44 (br. s, 1H, OH), 7.63 (t, 2H, H-3',5', *J* 7.4), 7.75 (t, 1H, H-4', *J* 7.4), 7.87 (s, 1H, H-3), 8.03 (d, 2H, H-2',6', *J* 7.1), 8.30 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6, 150 MHz,) δ, ppm: 18.34 (Me), 58.94 (CH_2), 114.57 (C3), 128.79 [C(3',5')], 129.27 [C(2',6')], 130.14 (C3a), 130.77 (C4), 133.43 (C4'), 136.28 (C1'), 140.00 (C5), 142.51 (C7), 150.28 (C7a), 152.32 (C2), 183.73 (CO). Found (%): C, 71.66; H, 4.62; N, 5.00. Calc. for $C_{16}H_{13}NO_3$ (%): C, 71.90; H, 4.90; N, 5.24.

*(4-Hydroxymethyl-7-methylfuro[2,3-c]pyridine-2-yl)(4-bromophenyl)methanone (**4b**).*



A mixture of **1**·HCl, (1.02 g; 0.05 mol) 2-bromo-1-(4-bromophenyl)ethan-1-one, **3b** (1.39 g; 0.05 mol), with saturated aqueous solution of K_2CO_3 (15 ml) and DMF (15 ml) was stirred vigorously for 2 hours at 25-30 °C. The reaction was then carried out as in the case of compound **4a.** The yield of **4b** was 1.40 g (81 %). Light brown crystals, mp 183-185 ºC (MeCN). ^{1}H NMR (DMSO-d_6) δ: 2.71 (s, 3H, Me), 4.79 (s, 2H, CH_2), 5.43 (br. s, 1H, OH), 7.83(d, 2H, H-3',5', *J* 8.64), 7.89 (s, 1H, H-3), 7.96 (d, 2H, H-2',6', *J* 8.64), 8.30 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6, 150 MHz) δ, ppm: 18.32, 58.90, 114.73, 127.52, 130.13, 130.69, 131.24, 131.85, 135.24, 140.03, 142.52, 150.28, 152.09, 185.27. Found (%): C, 55.19; H, 3.14; Br, 22.72, N, 4.26. Calc. for $C_{16}H_{12}BrNO_3$ (%): C, 55.51; H, 3.49; Br, 23.08, N, 4.05.

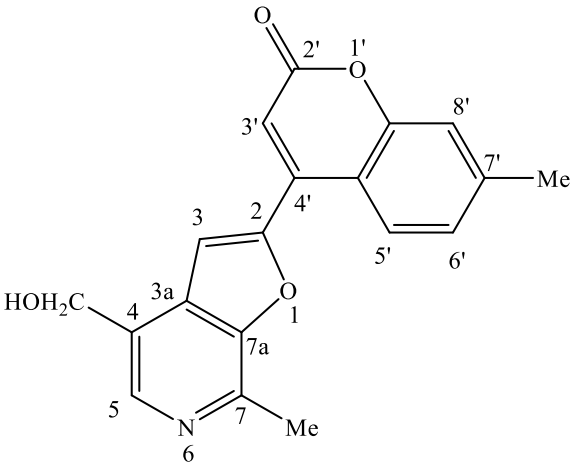
*(4-Hydroxymethyl-7-methylfuro[2,3-c]pyridine-2-yl)(4-nitrophenyl)methanone (**4c**).*



A mixture of hydrochloride **1**·HCl (1.02 g; 0.05 mol)**,** 2-bromo-1-(4-nitrophenyl)ethan-1-one, **3c** (1.22 g; 0.05 mol) and finely powdered K_2CO_3 (2.1 g ; 0.015 mol) in DMF (15 ml) was stirred vigorously for 2 hours at 25-30 °C. The reaction was then carried out as in the case of compound **4a.** The yield was 1.17 g (75%). Light beige crystals, mp 203-205 ºC (EtOH). ^{1}H NMR (DMSO-d_6) δ, ppm: 2.71 (s, 3H, Me), 4.78 (d, 2H, CH_2, *J* 4.5), 5.44 (t, 1H, OH, *J* 5.7), 7.63 (s, 1H, H-3), 8.23-8.24 (m, 2H, H-2',6'), 8.31 (s, 1H, H-5), 8.41-8.42 (m, 2H, H-3',5').^{13}C NMR (DMSO-d_6, 150 MHz) δ, ppm: 18.32, 58.89, 115.56, 123.74, 130.23, 130.64, 130.65, 140.10, 141.30, 142.65, 149.85, 150.38, 151.83, 182.59. Found (%): C, 61.28; H, 3.52; N, 8.56. Calc. for $C_{16}H_{12}N_2O_5$ (%): C, 61.54; H, 3.87; N, 8.97.

The synthesis of 4-(hydroxymethyl)-7-methylfuro[2,3-c]pyridin-2-yl)-2*H*-chromen-2-ones **4d-g** was carried out with 4-chloromethyl-2*H*-chromen-2-ones **3d-g** as cyclizing reagents anologously to preparation of compound **4b** but at 50-60 °C**.**

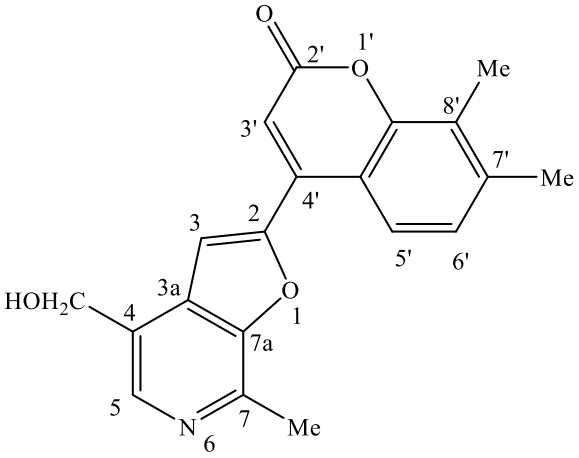
*4-(4-Hydroxymethyl-7-methylfuro[2,3-c]pyridin-2-yl)-7-methyl-2H-chromen-2-one (**4d**)*



The compound **4d** was synthesized from hydrochloride of **1** and 4-chloromethyl derivative **3d.** The yield was 68%. Light beige crystals, mp 250-253 ºC (DMF). ^{1}H NMR (DMSO-d_6) δ,

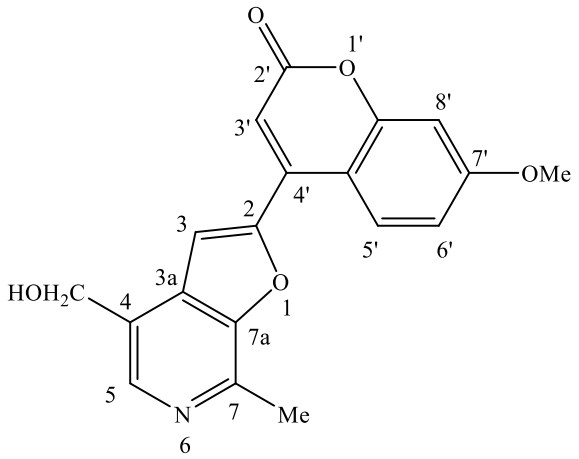
ppm: 2.43 (s, 3H, Me), 2.71 (s, 3H, Me), 4.80 (d, 2H, CH_2, *J* 5.7), 5.41 (t, 1H, OH, *J* 5.8), 6.91 (s, 1H, H-3'), 7.26-7.28 (m, 1H, H-6'), 7.31 (s, 1H, H-8'), 7.91 (s, 1H, H-3), 8.12 (d, 1H, H-5', *J* 8.2), 8.27 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6, 150 MHz) δ, ppm: 15.25, 20.95, 58.98, 109.21, 113.27, 113.76, 117.21, 125.93, 125.98, 128.97, 131.66, 140.12, 141.11, 141.45, 143.51, 149.98, 151.18, 153.75, 159.40. Found (%): C, 69.76; H, 4.45; N, 4.08. Calc. for $C_{19}H_{15}NO_4$ (%): C, 71.02; H, 4.71; N, 4.36.

*4-(4-Hydroxymethyl-7-methylfuro[2,3-c]pyridin-2-yl)-7,8-dimethyl-2H-chromen-2-one (**4e**)*



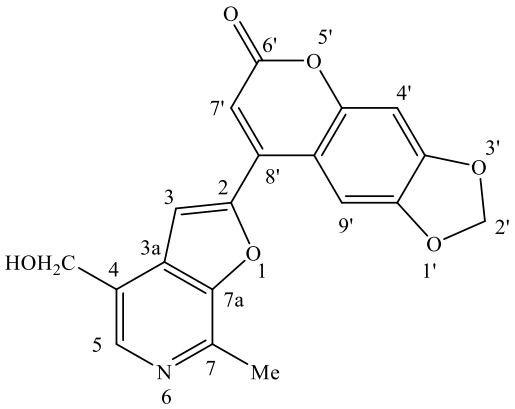
This compound was synthesized analogously with 4-chloromethyl-7,8-dimethyl-2*H*-chromen-2-one (**3e)**. The yield was 83%. Light beige crystals, mp 259-261 ºC (DMF). ^{1}H NMR (DMSO-d_6) δ, ppm: 2.23 (s, 3H, Me), 2.33 (s, 3H, Me), 2.66 (s, 3H, Me), 4.75 (d, 2H, CH_2, *J* 5.7), 5.39 (t, 1H, OH, *J* 5.7), 6.81 (s, 1H, H-3'), 7.19 (d, 1H, H-6', *J* 8.2), 7.80 (s, 1H, H-3), 7.89 (d, 1H, H-5', *J* 8.2), 8.23 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6, 150 MHz) δ, ppm: 11.23, 18.16, 19.76, 58.94, 109.10, 113.18, 113.24, 122.90, 124.17, 125.87, 128.86, 131.52, 140.00, 141.30, 141.33 (as shoulder on 141.30 peak), 141.88, 149.81, 151.15, 151.56, 159.31. Found (%): C, 71.26; H, 5.34; N, 4.00. Calc. for $C_{20}H_{17}NO_4$ (%): C, 71.63; H, 5.11; N, 4.18.

*4-(4-Hydroxymethyl-7-methylfuro[2,3-c]pyridin-2-yl)-7-methoxy-2H-chromen-2-one (**4f**)*



Compound **4f** was synthesized from hydrochloride **1** and 4-chloromethyl-7-methoxy-2*H*-chromen-2-one (**3f**). The yield is 66%. Light beige crystals, mp 246-248 °C (DMF). ^{1}H NMR (DMSO-d_6) δ, ppm: 2.70 (s, 3H, Me), 3.87 (s, 3H, OMe), 4.78 (d, 2H, CH_2, *J* 5.7), 5.39 (t, 1H, OH, *J* 5.7), 6.77 (s, 1H, H-3'), 7.00-7.03 (m, 2H, H-6', H-8'), 7.86 (s, 1H, H-3), 8.13 (d, 1H, H-5', *J* 8.9), 8.25 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6, 150 MHz) δ, ppm: 18.24, 55.96, 58.97, 101.37, 109.06, 111.33 (most likely, this signal with increased line width was the superposition of the singlets of two ^{13}C nuclei with almost equal chemical shifts), 112.72, 127.45, 128.92, 131.61, 140.09, 141.21, 141.42, 149.97, 151.41, 155.67, 159.56, 162.61. Found (%): C, 67.29; H, 4.12; N, 3.87. Calc. for $C_{19}H_{15}NO_5$ (%): C, 67.65; H, 4.48; N, 4.15.

8-(4-Hydroxymethyl-7-methylfuro[2,3-c]pyridin-2-yl)[1,3]dioxolo[4,5-g]chromen-6-one ***(4g)***



The compound was synthesized analogously from **1**·HCl and chloromethyl derivative **3g**. The yield was 80%. Light beige crystals, mp 274-276 °C (DMF). The structure of this compound was confirmed by its ^{1}H NMR spectrum which consisted of signals of hydroxymethyl group (one-proton triplet and two-proton doublet) and seven singlets of other types of protons. ^{1}H NMR (DMSO-d_6) δ, ppm: 2.68 (s, 3H, Me), 4.77 (d, 2H, CH_2, *J* 5.6), 5.38 (t, 1H, OH, *J* 5.7), 6.19 (s, 2H, CH_2), 6.77 (s, 1H, H-9'), 7.13 (s, 1H, H-4'), 7.59 (s, 1H, H-3), 7.86 (s, 1H, H-7'), 8.24 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6, 150 MHz) δ, ppm: 18.21, 58.92, 98.44, 102.83, 103.34, 109.00, 109.15, 111.40, 128.93, 131.56, 140.04, 141.34, 144.95, 149.91, 151.18, 151.24, 159.50. The spectrum evidently has pairwise superposed signals of two pairs of ^{13}C nuclei with practically equal chemical shifts. Found (%): C, 64.60; H, 4.00; N, 3.65. Calc. for $C_{19}H_{13}NO_6$ (%): C, 64.94; H, 3.73; N, 3.99.