

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

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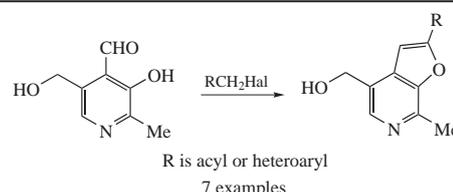
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A simple method for pyridoxal structural modification *via* furan ring closure was developed resulting in 2-acyl- and 2-heteroaryl-furo[2,3-*c*]pyridines. The reaction products can be proposed as pyridoxal mimetics to inhibit pyridoxal 5'-phosphate-dependent enzymes.



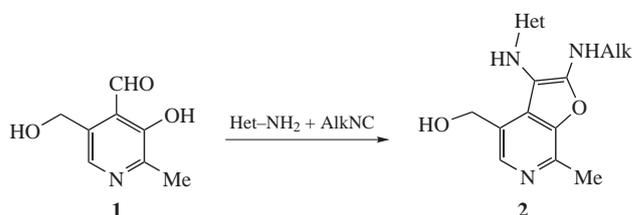
Small-molecular natural xenobiotics and endobiotics as well as their derivatives obtained *via* structural modification or *via* total synthesis play an important role for the development of new pharmaceuticals.^{1,2} Almost half (49%) of all antitumor substances ever discovered are either original natural compounds or structural derivatives similar to them.¹

Vitamins as representatives of endobiotics have their derivatives possessing remarkable biological activity sometimes different from the activity of the parent compounds. As an example, *N*-nicotinamide riboside derived from vitamin PP (nicotinic acid) is able to correct age-related deficiency of NAD⁺ coenzyme and thus to decrease mitochondriopathy caused by NAD⁺ deficiency and finally to improve lifespan in mammals.³ MitoQ, 10-(4,5-dimethoxy-2-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)decyltriphenylphosphonium methanesulfonate, a derivative of vitamin Q (ubiquinone), where the ubiquinone moiety is included in the Skulachev-type cation, is an effective mitochondria-directed antioxidant⁴ with strong spasmolytic effect important for the treatment of cardiovascular diseases.^{5,6} Another example is α -tocopherol succinate that is derived from vitamin E and represents an anti-cancer agent with the ability to induce selective apoptosis of cancer cells through their mitochondrial destabilization.^{7–9}

Vitamin B₆ (pyridoxal, **1**), which is the subject of this work, has an important O-phosphorylated derivative pyridoxal 5'-phosphate (PLP) that functions as enzyme cofactor.^{10,11} Pyridoxal derivatives and mimetics are known as cardioprotectors,¹² anti-malarials blocking the malarial plasmodium PLP-dependent enzymes¹³ and as selective activators of toll-like receptors of type 8 (TLR8)¹⁴ triggering antiviral protection activation. Pyridoxal derivatives are also described as prospective adjuvants for antiviral vaccines.¹⁵

As follows from the known data on the chemistry of pyridoxal and its derivatives, the syntheses of various pyridoxal-based metal complexes and bicyclic structures, especially with an additional annelated hetero ring, have been most actively developed. Compounds of the latter type have been prepared by the heterocyclization route, where the formyl group of pyridoxal is involved

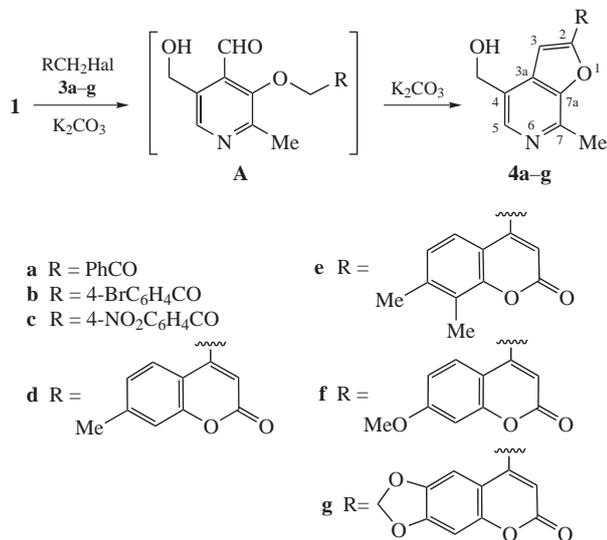
in combination with its hydroxymethyl or hydroxyl group.^{12,16} Thus, **1** reacts¹⁴ with heteroarylamines and isocyanides *via* furan ring closure to form compounds **2** as novel representatives of furo[2,3-*c*]pyridine class of pyridoxal derivatives (Scheme 1). It should be highlighted that the above mentioned TLR8 activators have been actually discovered from compounds of that class.



Scheme 1

In the present work, the possibility and efficiency of more convenient transformation of pyridoxal **1** into its furo[2,3-*c*]pyridine derivatives **4** (Scheme 2) has been demonstrated. The reaction occurs *via* base-catalyzed cyclization of the starting compound **1** with methylene-active alkylating agents, such as acylmethyl halides and halomethylheteroarenes **3** (see Scheme 2). The mechanism of this process presumably includes the formation of O-substituted intermediates **A** and their subsequent furanic cyclization. Potassium carbonate was chosen as a catalyst due to its soft base character and inability to destruct the aldehyde group. However, this choice led to the narrowing of the appropriate halomethylheteroarenes to the group of compounds with a fairly electronegative heteroaryl substituent as an activator of methylene moiety. According to the results of quantum-chemical calculations,¹⁷ 4-halomethylcoumarins corresponded completely to this requirement. Therefore, we used 4-halomethylcoumarins **3d–g** in order to verify the possibility of reactions involving halomethylheteroarenes (see Scheme 2).

In the case of haloketones **3a–c**, the cyclization was carried out in aqueous acetonitrile (50–60 °C) or either aqueous or anhydrous DMF (25–30 °C), while aqueous DMF (50–60 °C) was



Scheme 2

found optimal for 4-halomethylcoumarins **3d–g**. The reaction proceeded within 2–3 h in all cases and led to the previously unknown 2-acyl- (**4a–c**) or 2-(coumarin-4-yl)-4-hydroxymethyl-7-methylfuro[2,3-*c*]pyridines (**4d–g**). General procedure for the cyclization is exemplified by furo[2,3-*c*]pyridine **4a**.[†] The yields of ketones **4a–c** and coumarinyl derivatives **4d–g** were 54–81 and 66–83%, respectively. The reported transformation is novel for both pyridoxal and 3-hydroxy-4-acyl(formyl)pyridines in general.

Compounds **4** can be proposed as pyridoxal mimetics to inhibit the PLP-dependent enzymes since they, on the one hand, retain the significant structural similarity with pyridoxal and, on the other hand, hardly replace the PLP cofactor in their O-phosphorylated form due to the absence of aldehyde group.

The reported furanic cyclization is similar by its mechanism to the closure of azepine ring previously discovered by us in the study of pyridine–azepine recyclizations of condensed 2,3-dihydropyridines as their quaternary salts, wherein the reagents of type **3** were also involved.^{18,19}

The structure of obtained furo[2,3-*c*]pyridines were confirmed by elemental analysis data and 1- and 2-D NMR spectroscopy (see Online Supplementary Materials). ¹H and ¹³C NMR data for these compounds can be illustrated by the example of 2-benzoyl derivative **4a**. The ¹H NMR spectrum (DMSO-*d*₆, 600 MHz) of this ketone contained the proton signals from H-3 and H-5 of bicyclic system (singlets at 7.87 and 8.30 ppm, respectively), the benzoyl group [a two-proton, somewhat distorted doublet at 8.03 ppm (H-2', H-6') as well as triplets at 7.63 (2H, H-3', H-5', *J* 7.8 Hz) and 7.75 ppm (1H, H-4', *J* 7.4 Hz)], the hydroxymethyl group (two-proton and single-proton singlets at 4.79 and 5.43 ppm,

[†] *Synthesis of (4-hydroxymethyl-7-methylfuro[2,3-*c*]pyridin-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 K₂CO₃ (15 ml) and acetonitrile (15 ml) was stirred vigorously at 50–60 °C for 2 h. The mixture was then cooled, poured into water (100 ml), the precipitate formed was filtered off and washed with water (15 ml). The yield was 0.76 g (57%). Light beige crystals, mp 146–148 °C (EtOAc). ¹H NMR (DMSO-*d*₆) δ: 2.71 (s, 3H, Me), 4.79 (s, 2H, CH₂), 5.44 (br. s, 1H, OH), 7.63 (t, 2H, H-3', H-5', *J* 7.4 Hz), 7.75 (t, 1H, H-4', *J* 7.4 Hz), 7.87 (s, 1H, H-3), 8.03(d, 2H, H-2', H-6', *J* 7.1 Hz), 8.30 (s, 1H, H-5). ¹³C NMR (DMSO-*d*₆, 150 MHz) δ: 18.34 (Me), 58.94 (CH₂), 114.57 (C³), 128.79 (C^{3'}, C^{5'}), 129.27 (C^{2'}, C^{6'}), 130.14 (C^{3a}), 130.77 (C⁴), 133.43 (C^{4'}), 136.28 (C^{1'}), 140.00 (C⁵), 142.51 (C⁷), 150.28 (C^{7a}), 152.32 (C²), 183.73 (CO).

Compounds **4b–g** were prepared analogously. For their characteristics, see Online Supplementary Materials.

respectively), and the methyl group (singlet at 2.71 ppm). The ¹³C NMR spectrum of **4a** contained the expected set of 14 signals which were assigned by methods of two-dimensional NMR spectroscopy [¹H–¹³C HSQC and HMBC (¹H–¹³C and ¹H–¹⁵N)] (see Online Supplementary Materials). The most downfield shifted signals in the ¹³C NMR were those from the C^{7a}, C², and carbon atom in the CO group with chemical shifts of 150.28, 152.32 and 183.73 ppm, respectively. ¹H–¹⁵N HMBC spectrum confirmed the presence of only one nitrogen atom in compound **4a** with the value of chemical shift (314.5 ppm, ¹⁵NH₃ as standard) typical of pyridine moiety. Only two cross-peaks were observed in the spectrum: ¹⁵N/H-5 (*J*_{N–H} 10.8 Hz) and ¹⁵N/Me.

Therefore, the convenient method has been developed for the structural modification of pyridoxal, which allows one to efficiently replace its formyl and hydroxyl groups by the furan ring bearing the acyl or heteroaryl group at the α-position.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.040.

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