SYNTHESIS OF 7-DEAZAHYPOXANTHINE DERIVATIVES AND EVALUATION OF THEIR ACTIVITY AGAINST XANTHINE OXIDASE

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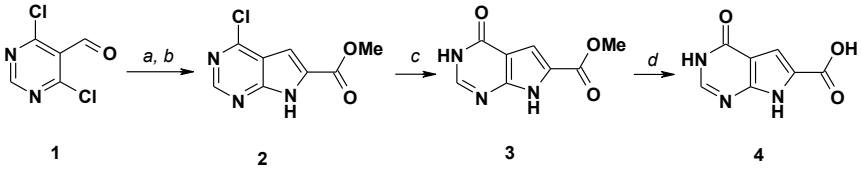
Xanthine oxidase is a key enzyme in purine metabolism catalysing the conversion of hypoxanthine and xanthine to uric acid with production of superoxide radical. The increased enzyme activity leads to hyperuricemia, gout, inflammatory and cardiovascular diseases. Allopurinol and febuxostat are xanthine oxidase inhibitors that are widely used in clinical practice, but they have adverse effects. Therefore the search for new xanthine oxidase inhibitors remains relevant. Among purine isosteres, 7-deazahypoxanthine was known to be a xanthine oxidase inhibitor.

Here we propose a method for the synthesis of previously undescribed 6-functionalized pyrrolo[2,3-*d*]pyrimidines **3**, **4**. Methyl 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate **2** was synthesized based on the available 4,6-dichloropyrimidine-5-carbaldehyde **1**. New 8-functionally substituted 7-deazahypoxanthine **3** was obtained from compound **2** in high yield. The hydrolysis of compound **3** gave 7-deazahypoxanthine-8-carboxylic acid **4**. The structures of the synthesized compounds were confirmed by elemental analysis, ^{1}H NMR, ^{13}C NMR and MS spectral data.



1 **2** **3** **4**

a) methyl glycinate, K_2CO_3, MeOH, rt; *b*) $SOCl_2$, reflux; *c*) AcOH/H_2O, reflux; *d*) NaOH, H_2O.

The new pyrrolo[2,3-*d*]pyrimidines **3** and **4** were evaluated for their ability to inhibit xanthine oxidase. It was found that the presence of an ester group in the structure of inhibitor **3** leads to 10-fold increased inhibitory activity against the enzyme as compared to compound **4**. Thus compound **3** inhibited enzyme activity with an IC_{50} value of 11 μM, while compound **4** was characterized by IC_{50} value of 103 μM. The obtained data can be useful for designing xanthine oxidase inhibitors with pyrrolo[2,3-*d*]pyrimidine scaffold.