SYNTHESIS OF SOME NEW ACYCLIC PYRIMIDINE NUCLEOSIDES
SINTEZA E DISA NUKLEOZIDEVE TË REJA ACIKLIKE TË PIRIMIDINËS

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ABSTRACT
A new acyclic nucleosides substituted at 5-position of the uracil ring have been synthesized. We synthesized 5-(bromomethyl)-1-(2,3-O-acetyl-2,3-dihydroxypropyl)uracil (2) and with the nucleophilic displacement with sodium cyanide we prepared the corresponding 5-(cyanomethyl)-1-(2,3-O-acetyl-2,3-dihydroxypropyl)uracil. (3) From this compound we synthesized other new 5-substituted acyclic nucleosides. Hydrogenation of (3) in anhydrous acetic acid over Pd/C catalyst gave the 5-acetaminoethyl-substituted derivative (4), the methanolysis afforded 5-(methoxycarbonyl) methyl derivative (5) and acidic hydrolysis gave the 5-(amidomethyl)-1-(2,3-O-acetyl-2,3-dihydroxypropyl)uracil(6). All compounds were characterized by 1H and 13C NMR, IR and by elementary analysis.

PERMBLEDHJE
Janë sintetizua disa aciklo nukleozide te reja të zëvendësuarë në pozicion -5. Është sintetizua 5-(bromometil)-1-(2,3-O-acetil-2,3-dihidroksipropil)uracil (2) dhe me çvendosjen nukleofile me cianur natriumi kemi përgaditë 5-(cianometil)-1-(2,3-O-acetil-2,3-dihidroksipropil)uracil-in përkatës (3). Nga ky komponim janë sintetizua nukleozidet tjera aciklike të zëvendësuarë në pozicion-5. Hidrogjenimi katalitik i komponimit (3) mbi Pd/C në acid acetik anhider ka dhënë 5-acetaminoetil-derivatin e zëvendësuar (4), metanoliza jep 5-(metoksikarbonil) metil derivat (5) dhe hidroliza acide jep 5-(amidometil)-1-(2,3-O-acetil-2,3-dihidroksipropil)uracil(6). Te gjitha komponimet jane karakterizua me 1H dhe 13C NMR, IR dhe me analizën elementare.

Key Words: acyclic nucleosides, 5-substituted nucleosides, pyrimidine nucleosides

INTRODUCTION
A respectable number of pyrimidine nucleosides analogues as derivative of natural pyrimidine exhibits biological activity. Consequently, modified nucleosides are studied for their potential activity as enzyme inhibitors resulting in antiviral and antitumor activity. In particular, uracil derivatives substituted at C-5 position or modified at the furanose ring present strong biological activity such as the well known (E)-5-(2-bromovinyl)-dUrd (BVDU)$. 5-Fluorouracil (FU) cream is in the clinical use for the treatment of the‘actinic keratosis’$. On the other hand, 5-FU pyrimidine acyclonucleosides was analyzed to find fewer side effects and the safe limits expansion$^5$ and a characteristic biochemical modulator 5-cloro-2,4-dihydroxypryridine was found as a potent inhibitor of degradation of 5-FU in vivo$^6$ which is active for the treatment of gastric, colorectal, head, neck and other solid tumors$. Compound 5-bromo deoxyuridine derivative shows a broad spectrum of antiviruses activity towards herpes simplex virus type-1 and type-2 (HSV-1, HSV-2), varicella zoster virus (VZV), and human cytomegalovirus (HCMV)$^8$. Recently 5-substituted pyrimidine nucleosides have drawn attention and were valued for their antiviral activity against poxviruses$^9$. A series of acyclic nucleoside analogues of 5'-O-tritylthymidine (such as 5-jodouracil, 5-ethyluracil, 5-methylcytosine, 3-N-methylthymine,) were synthesized and valued as potential human mitochondrial thymidine kinase (TK-2) inhibitors$^{10}$ and some compounds showed a marked specificity. The esterified acetic acid chain was isolated from yeast t-RNA and was identified as 2-tio-5-uridineacetic acid methyl ester$^{11}$. 5-Methoxymethyl -2'-deoxyuridine (MMUdR) was found to have potent antiviral activity against herpes simplex virus type-1, and was not toxic to host cells with antiviral concentrations and greater$^{12}$ than 100, and N4-Butanoyl-5-methoxymethyl-2'-
deoxycytidine is a potent inhibitor of HSV-1 replication\textsuperscript{13}. Synthesis of 5-substituted acyclic pyrimidine analogue represents a significant synthetic challenge for the discovery of a potential drug. With respect to found biological activity it appeared of interest to synthesize the present acyclic pyrimidine nucleosides specifically substituted in 5-position at pyrimidine base.

**MATERIALS AND METHOD**

Melting points, uncorrected, were taken with a Kofler hot-stage apparatus. IR spectra were determined for potassium bromide pellets on a Perkin Elmer 297 spectrophotometer; \textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR spectra for solutions in DMSO-d\textsubscript{6}, unless otherwise stated, were recorded on a “JEOL FX90Q” spectrometer operating at 89.55 and 22.5 MHz, respectively with tetramethylsilane as internal standard (s, d, t and q refer to off-resonance decoupled spectra). The silica gel (Merck, HF\textsubscript{254} type 60) for TLC and preparative TLC was activated at 110 °C for 60 min. The products were developed in CH\textsubscript{3}Cl\textsubscript{2}/MeOH (9:1) and recovered from TLC chromatographic plates with acetone, unless otherwise stated. The products were rendered visible by UV illumination or iodine vapour.

5-[(Methoxycarbonyl)methyl]-1-(2,3-dihydroxypropyl)uracil (3) To a solution of 1 (1.088 g, 4.38 mmol) in 1,2-dichloroethane, NBS (880 mg, 496 mmol) was added. The mixture was stirred at 70 °C for 2 h under a N\textsubscript{2}-atmosphere and the solvent was evaporated to dryness under reduced pressure. The crude product was dissolved in CH\textsubscript{3}Cl\textsubscript{2} and filtered off and the filtrate evaporated to dryness under reduced pressure. The crude product was isolated in 53% yield; mp 219-220.5 °C from CH\textsubscript{3}Cl\textsubscript{2}. IR: ν: 3366, 3160, 3040, 2920, 2830, 1750, 1730, 1690(s), 1680, 1650, 1540, 1475, 1410, 1373, 1345, 1275, 1255, 1235, 1175, 1070, 1048, 1022, 958, 875 cm\textsuperscript{-1}. \textsuperscript{1}H NMR: δ = 1.77 (s, 3 H, OCH\textsubscript{3}), 1.98 (s, 3 H, Me), 2.02 (s, 3 H, Me), 2.29 (t, 2 H, J\textsubscript{H-7, J} = 6.7 Hz), 3.08-3.12 (2 H, m, H-8), 4.21-4.32 (4 H, m, H\textsubscript{2-1'}, H\textsubscript{2-3'}), 5.18-5.30 (1 H, m, H-2'), 7.38 (1 H, s, H-6), 7.64-7.78 (1 H, m, NHCO), 11.17 (1 H, s, 3-NH ). \textsuperscript{13}C NMR: δ = 170.09 (s, NHCOME), 169.75 (s, COOME), 169.07 (s, COMe), 163.88 (s, C-4), 109.85 (s, C-2), 142.07 (d, C-6), 69.86 (d, C-2'), 7.72 (1 H, s, 3-NH ) .

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5-(Amidomethyl)-1-(2,3-O-acetyl-2, 3-dihydroxypropyl) uracil (6) Compound 3 (120 mg, 0.38 mmol) was treated with conc. HCl (1 mL). The mixture was stirred at room temp. for 18 h and evaporated to dryness. The residue was dissolved in anhydrous pyridine (5 mL), cooled to 5 °C, and acetic anhydride (2 mL) was added. The suspension was then stirred at room temp. for 4 h and evaporated to dryness. Preparative TLC (3 developments in CH$_2$Cl$_2$/MeOH 95:5) gave the product (96 mg, 76%); mp 197-199 °C (from MeOH).

IR: ν = 3442, 3041, 2804, 2362, 2341, 2043, 1739, 1672, 1471, 1407, 1433, 1371, 1342, 1245, 1172, 1084, 1047, 1020, 972, 953, 907, 880, 810, 786, 762, 604, 567, 467 cm$^{-1}$.

$^1$H NMR: δ = 11.33 (s, 1 H, 3-NH), 7.48 (s, 1 H, H-6), 7.28 (s, 1 H, CONH$_2$), 6.87 (s, 1 H, CONH$_2$), 5.21-5.23 (m, 1 H, H-2'), 1.99 (s, 3 H, Me), 2.03 (s, 3 H, Me), 3.04 (d, 1 H, H$_a$-7, $J_{a,b}$ = 16 Hz), 2.94 (d, 1 H, H$_b$-7, $J_{b,a}$ = 16 Hz), 4.24 (dd, 1 H, H$_a$-3', $J_{a,2'}$ = 3.2 Hz, $J_{a,b}$ = 12.4 Hz), 4.10 (dd, 1 H, H$_b$-3', $J_{b,2'}$ = 5.6 Hz, $J_{b,a}$ = 12.4 Hz), 4.03 (dd, 1 H, H$_a$-1', $J_{a,2'}$ = 3.2 Hz, $J_{a,b}$ = 14 Hz), 3.75 (dd, 1 H, H$_b$-1', $J_{b,2'}$ = 8.8 Hz; $J_{b,a}$ = 14 Hz), $^{13}$C NMR: δ = 20.57 (q, Me), 32.53 (t, C-7), 47.92(t, C-1'), 68.72 (d, C-2'), 107.99 (s, C-5), 143.80 (s, C-6), 150.92 (s, C-2), 163.79 (s, C-4), 169.96 (s, COMe), 170.14 (s, COMe), 171.42 (s, CONH$_2$). Anal. C$_{18}$H$_{18}$N$_2$O$_7$ (327.29), calcd. C, 47.71; H, 5.23; N, 12.84; found: C, 47.77; H, 5.30; N, 12.73%.
RESULTS AND DISCUSSIONS

In the course of preparing aliphatic C-5 substituted uracil derivatives we starting from thymine. With a coupling reaction of silylated base with allyl bromide we prepared the 1-allylthymine and cis-hydroxylation of this compound using KMnO₄ as oxidant afforded 1-(2,3-dihydroxypropyl) thymine. The reaction with acetic anhydride in pyridine gave protected derivative 1-(2,3-diacilloxypropyl)thymine (1). In order to convert the compound 1 into the 5-(bromomethyl)-1-(2,3-dihydroxypropyl)uracil (2), we applied selective bromanilation of 1, (Scheme 1), with N-bromosuccinimide (NBS) using a reflecting photo-lamp under nitrogen atmosphere. Synthesis of 5-cyanomethyl-derivative 3 was realized in situ, without purifying the compound 2. The nucleophilic displacement with sodium cyanide yielded the corresponding 5-(cyanomethyl)-1-(2,3-O-acetyl-2,3-dihydroxypropyl)uracil (3) in 55%. The IR-spectrum of 3 produced an expected band at 2250 cm⁻¹ for CN, and the ¹³C and ¹H NMR spectra gave rise to resonances at 103.62 (s) and 3.48 ppm (s, 2 H), respectively, indicating the presence of the cyanomethyl group. Catalytic hydrogenation of cyanomethyl derivative 3 in anhydrous acetic acid over 10% Pd/C catalyst gave the 5-(Acetaminoethyl)-1-(2,3-O-acetyl-2,3-dihydroxypropyl)uracil (4) in 55%. The ¹³C and ¹H NMR spectra of compounds originating from NH-

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