

SYNTHESIS OF THE NOVEL BICYCLIC OXEPINOPYRIMIDINE AND FLUORINATED PYRROLIDINOPYRIMIDINES

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Abstract – The new 5,6-disubstituted pyrimidine nucleoside analogues (**5-8**) were synthesized by addition of the C-6 lithiated pyrimidine derivative to oxirane as key reaction step. The bicyclic tetrahydrooxepinopyrimidine (**9**) and fluorinated pyrrolidinopyrimidines (**12** and **15**) were obtained by intramolecular linkage of acyclic chain to the CH₂-5 and N-1 of the pyrimidine ring. The structure of compound (**9**) containing pyrimidine and tetrahydrooxepine skeleton was determined unequivocally by its X-Ray crystal structure analysis.

INTRODUCTION

Uracil derivatives substituted either at C-5 or C-6 position and their nucleosides have considerable importance in the field of chemotherapy. Among the important 6-substituted uracil, 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine (HEPT)¹ and its derivatives have emerged as new anti-HIV-1 agents. Another group of 6-substituted uracils, *viz.* 3,4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs)² behave as non-nucleoside reverse transcriptase inhibitors (NNRTIs). The synthesis and biological activity of variously 6-substituted uracils and their derivatives have also been reported.³ Our

previous studies have shown that C-6 alkylated pyrimidine nucleoside analogues have good binding affinities to herpes simplex virus type 1 thymidine kinase (HSV-1 TK) and no cytotoxic effect.⁴ Furthermore, radiolabelled pyrimidine nucleosides were evaluated as tracers for non-invasive positron emission tomography (PET) imaging of HSV-1 TK gene expression.⁵ Labelled thymidine is preferred radiopharmaceutical for indicating cellular proliferation, because its specific incorporation into DNA is linked to the S phase of the cell cycle.⁶ Additionally, the tissue distribution of 5-[¹⁸F]fluorouracil showed that this compound indeed accumulates in different animal⁷ and human tumors.⁸ Excellent biological activities exhibited by both 5- and 6-substituted uracil derivatives provided the impetus to explore chemistry and biological activities of 5,6-disubstituted uracils.⁹

In this connection and related to our studies on acyclic pyrimidine nucleoside analogues,^{4, 10} our interest was enhanced on C-6 alkylated pyrimidine derivatives and fluorinated pyrrolidinopyrimidine derivatives. In this paper we report the synthesis of new 5,6-disubstituted pyrimidines (**5-8**) and bicyclic pyrimidine derivatives (**9**, **12** and **15**) formed by linkage of acyclic chain to the CH₂-5 and N-1 (Figure 1).

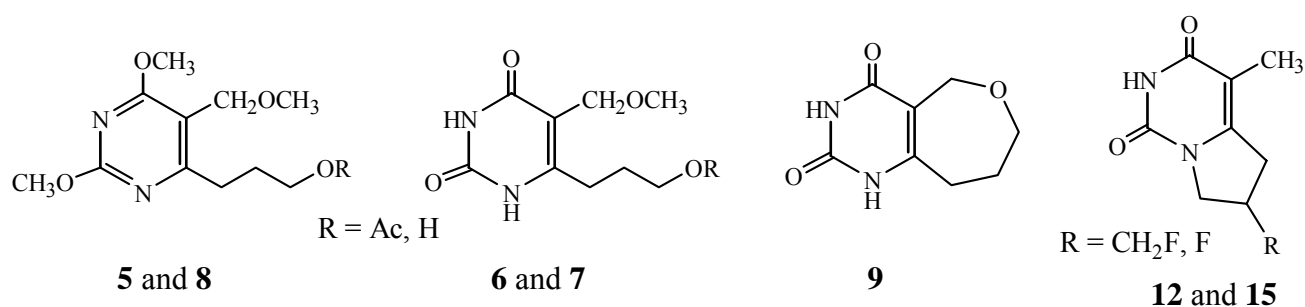
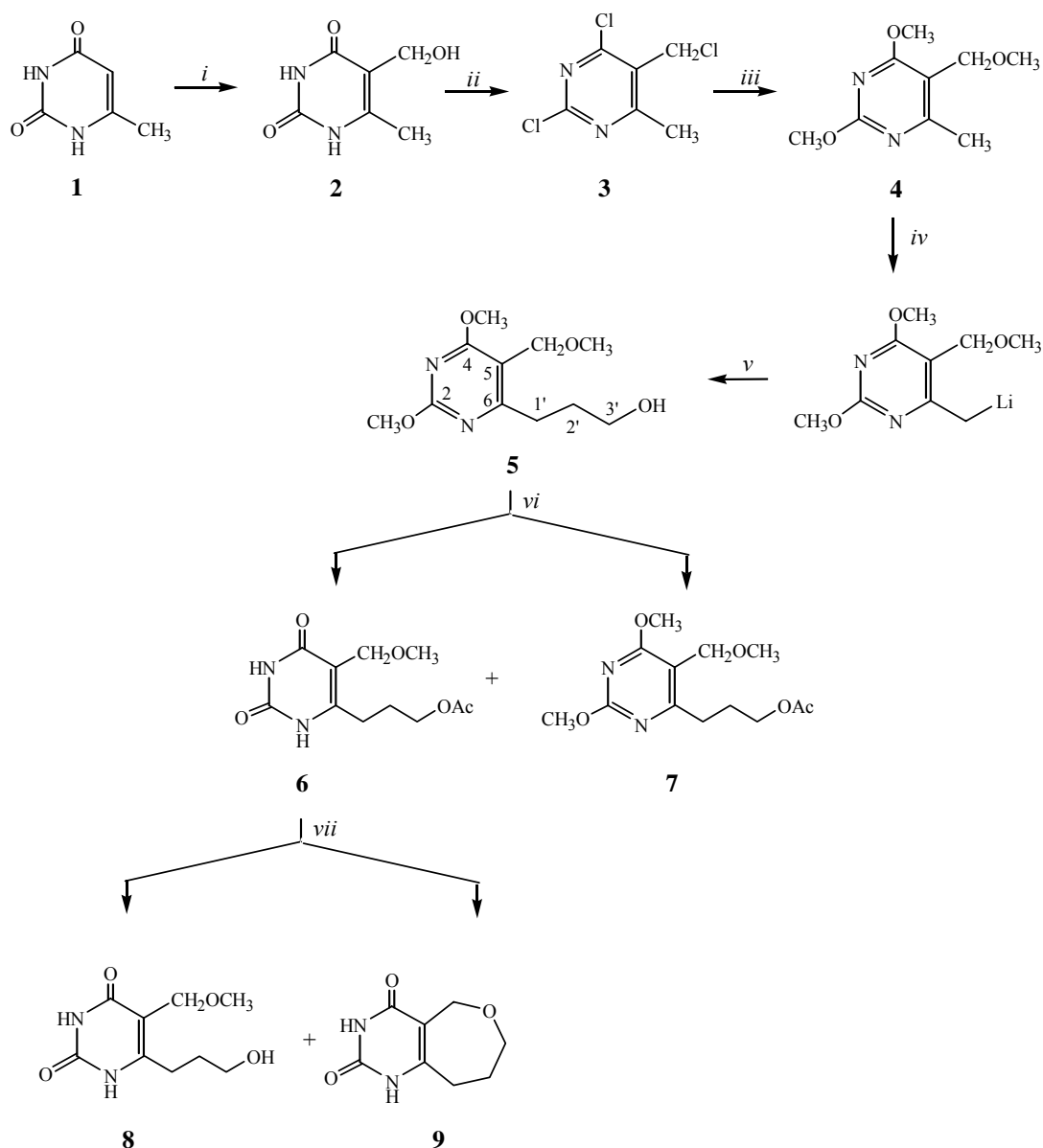


Figure 1. The novel 5,6-dialkylated pyrimidines (**5-8**) and bicyclic tetrahydrooxepinopyrimidine (**9**) and fluorinated pyrrolidinopyrimidines (**12** and **15**).

RESULTS AND DISCUSSION

CHEMISTRY

Introduction of hydroxymethyl side chain at C-5 of the pyrimidine ring was performed by addition of formaldehyde to 6-methyluracil (Scheme 1) according to the procedure analogous to that for the preparation of 5-hydroxymethyluracil.¹¹ 5-Hydroxymethyl-6-methyluracil (**2**) has been shown to decompose when subjected to hydrolysis forming 6-methyluracil and formaldehyde.¹² On the contrary to this, we found that the synthesis of **2** proceeded successfully and in good yield. Chlorination of **2** with phosphoryl chloride and subsequent methoxylation of **3** with sodium methoxide in methanol gave 2,4-dimethoxy-5-methoxymethyl-6-methylpyrimidine (**4**, Scheme 1). Alkylation at C-6 position of the pyrimidine moiety was performed *via* an addition reaction of the lithiated pyrimidine derivative of **4** to oxirane as electrophile.

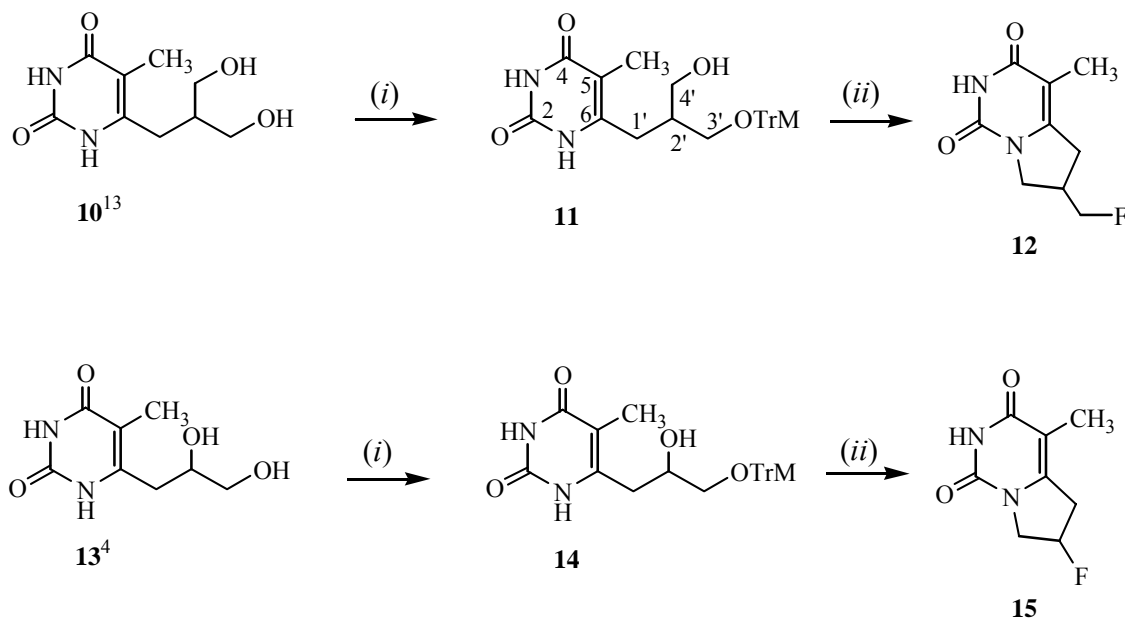


Scheme 1. Reagents and conditions: (i) paraformaldehyde, KOH, 50 °C; (ii) POCl₃, reflux; (iii) NaOCH₃, CH₃OH, rt; (iv) *n*-C₄H₉Li, THF; (v) oxirane, -50 °C, NH₄Cl; (vi) AcCl, H₂O; (vii) conc. HCl, 60 °C.

Ring opening reaction afforded pyrimidine containing 3-hydroxypropyl side-chain at C-6. Compound (**5**) was then treated with acetyl chloride, containing several drops of water. Hydrolysis of 2- and 4- methoxy groups of **5** gave acetylated pyrimidine-2,4-dione (**6**) and acetylated 2,4-dimethoxypyrimidine (**7**) derivatives. Hydrolysis of **6** in concentrated hydrochloric acid afforded deacetylated pyrimidine-2,4-dione derivative (**8**) and bicyclic tetrahydrooxepinopyrimidine (**9**) as predominant product (Scheme 1). When a reaction of **5** with acetyl chloride and water was performed during 7 days a mixture of all compounds (**6-9**) was obtained. By monitoring of hydrolysis by TLC, we found that acetylation of hydroxy group occurred first, following demethoxylation together with deacetylation and finally cyclization. Depending

on reaction time, ratio of thus obtained products (**6-9**) varied. Thus, bicyclic product (**9**) was obtained as major product with prolonged time.

Conformationally constrained carbon-bridged pyrimidine acyclic nucleosides containing fluoromethyl (**12**) or fluoro group (**15**) attached to the pyrrolidine moiety were also obtained (Scheme 2).



Scheme 2. Reagents and conditions: (i) 4-methoxytrityl chloride, DMAP, TEA, DMF, 50 °C; (ii) DAST, CH₂Cl₂, rt.

A primary hydroxy group in 6-[3-hydroxy-2-(hydroxymethyl)propyl]thymine (**10**)¹³ and 6-(2,3-dihydroxypropyl)thymine (**13**)⁴ was protected with 4-methoxytrityl chloride using the method which has been previously applied for the preparation of tritylated ganciclovir.¹⁴ The **11** and **14** were then subjected to fluorination using DAST (Scheme 2).

These reactions proceeded by ring closure and formation of the bicyclic products (**12**) and (**15**). This reaction most likely occurs through an initial proton abstraction from N-1 by fluoride and subsequent nucleophilic attack at the methylene position by the N-1 of the pyrimidine ring.

¹H AND ¹³C NMR SPECTRA

The structures of the new compounds were deduced by analysis of their ¹H and ¹³C NMR spectra (see EXPERIMENTAL). Assignment of ¹H and ¹³C NMR spectra was performed on the basis of chemical shifts, signal intensities, magnitude and multiplicity of H-H coupling constants. The ¹H NMR spectroscopic data of **2-9**, **11**, **12**, **14** and **15** are displayed in Table 1. The chemical shifts and H-H coupling constants are consistent with the proposed structures. The chemical shift assignments agree with the corresponding ones of the related compounds.^{3,4}

Table 1. ¹H NMR chemical shifts (δ/ppm)^a and coupling constants (J/Hz)^b of compounds (**2-9**, **11**, **12**, **14** and **15**, *c.f.* Schemes 1 and 2).

Compd	CH ₃ -6	CH ₃ -5	OCH ₃ -2 OCH ₃ -4	CH ₂ -1'	CH ₂ -2'	CH ₂ -3'	OH	NH-1 NH-3	CH ₂ -5	CH ₂ OCH ₃
2	2.11 (s, 3H)	-	-	-	-	-	4.51 (t, 1H) J=4.83	10.72 (s, 1H) 10.91 (s, 1H)	4.14 (s, 2H)	-
3	2.62 (s, 3H)	-	-	-	-	-	-	-	4.87 (s, 2H)	-
4	2.50 (s, 3H)	-	4.01 (s, 3H) 4.04 (s, 3H)	-	-	-	-	-	4.46 (s, 2H)	3.38 (s, 3H)
5	-	-	3.89 (s, 3H) 3.87 (s, 3H)	2.69 (t, 2H) J=7.59	1.78 (m, 2H)	3.43 (t, 2H) J=6.06	4.48 (t, 2H) J=4.99	-	4.33 (s, 2H)	3.23 (s, 3H)
6^b	-	-	-	2.47 (t, 2H) J=7.82	1.86 (m, 2H)	4.02 (t, 2H) J=6.32	-	10.86 (s, 1H) 11.02 (s, 1H)	4.09 (s, 2H)	3.19 (s, 3H)
7^c	-	-	3.90 (s, 3H) 3.88 (s, 3H)	2.73 (t, 2H) J=7.48	1.96 (m, 2H)	4.04 (t, 2H) J=6.49	-	-	4.33 (s, 2H)	3.24 (s, 3H)
8	-	-	-	2.43 (t, 2H) J=7.52	1.67 (m, 2H)	3.39 (t, 2H) J=6.11	4.47 (s, 1H)	10.92 (s, 1H) 10.94 (s, 1H)	4.08 (s, 2H)	3.27 (s, 3H)
9	-	-	-	2.70 (t, 2H) J=4.80	1.72 (m, 2H)	3.79 (t, 2H) J=4.81	-	10.94 (s, 1H) 10.87 (s, 1H)	4.36 (s, 2H)	-
11^d	-	1.61 (s, 3H)	-	2.34 (d, 2H) J=7.4	2.07 (m, 1H)	3.0 (2H, m)	4.59 (s, 1H)	10.89 (s, 1H) 10.47 (s, 1H)	-	-
12^e	-	1.71 (s, 3H)	-	2.93 (2H) (m, 2H)	2.86 (m, 1H)	3.77 (2H) (m, 2H)	-	11.07 (s, 1H)	-	-
14^f	-	1.68 (s, 3H)	-	2.91 (m, 2H)	3.97 (m, 1H)	3.46 (m, 2H)	5.11 (d, 1H) J=5.4	10.90 (s, 1H) 10.45 (s, 1H)	-	-
15	-	1.75 (s, 3H)	-	3.23 (m, 2H)	5.51 (m, 1H)	4.03 (m, 2H)	-	11.20 (s, 1H)	-	-

^a DMSO-*d*₆ solutions. Multiplicity of couplings and number of protons are given in parentheses.

^b Chemical shift for CH₃CO: 2.0 (s, 3H). ^c Chemical shift for CH₃CO: 1.99 (s, 3H). ^d Chemical shifts for CH₂-4': 3.43 (m, 2H); C₆H₅: 7.35-6.86 (m, 14H); OCH₃: 3.74 (s, 3H). ^e Chemical shifts for CH₂-4': 4.47 (m, 2H). ^f Chemical shifts for C₆H₅: 7.43-6.88 (m, 14H); OCH₃: 3.74 (s, 3H).

X- RAY CRYSTAL STRUCTURE STUDY

The structure of the bicyclic compound (**9**) was determined by X-Ray crystal structure analysis. The molecular structure with the atom numbering is displayed in Figure 2.

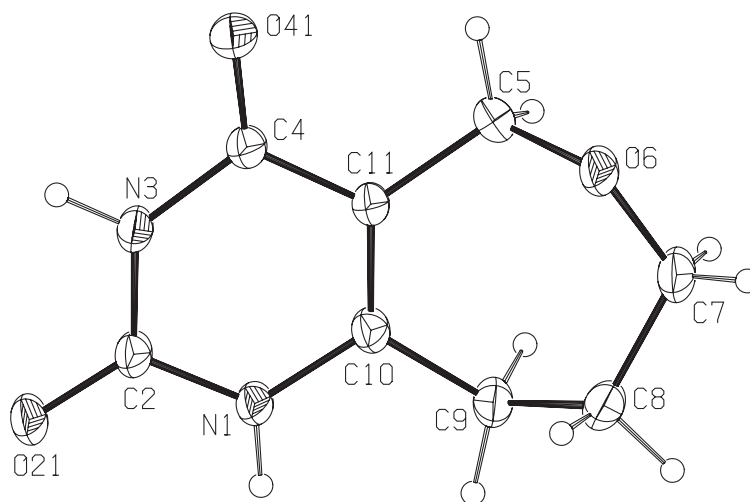


Figure 2. The molecular structure and labelling of **9**. Displacement ellipsoids are drawn at the 30 % probability level.

In the compound (**9**), a pyrimidine ring is fused with a seven-membered oxepine ring *via* common carbon atoms C10 and C11. The pyrimidine ring is planar, because the largest observed deviation of the ring atoms from the mean plane of the ring is 0.018(2) Å for the C2 atom. The carbonyl oxygen atoms O21 and O41 lie almost in the ring plane; the dihedral angles between the O21-C2 and O41-C4 bond lines and the mean plane of the pyrimidine ring amount to 2.2(1) and 1.2(1)°. The oxepine ring adopts a chair conformation. The C10, C11 and C7 atoms deviate from the mean plane of the atoms C5/C8/C9/O6 by +0.979(1), +1.013(1) Å and -0.692(3) Å, respectively.

Both N-H donor atoms participate in the hydrogen-bonding, so generating two N-H...O hydrogen bonds (Figure 3). Thus, two N1...O21ⁱ intermolecular hydrogen bonds connect the neighbouring molecules of **9** into a centrosymmetric R₂²(8) dimer [symmetry code: (i) -x, -y+1, -z+2]. The N1...O21 distance and N1-H...O21 angle amount to 2.792(2) Å and 176(2)°, respectively. Furthermore, the N3 atom acts as a donor to O6ⁱⁱ atom of the oxepine ring [symmetry code: (ii) -x+1, +y+1/2, -z+3/2], so producing infinite C(6) chain motif along *b* axis [N3...O6 = 2.869(2) Å; N3-H...O6 = 165(2)°]. The combination of these two motifs generates (1 0 2) sheets (Figure 3). The action of these two hydrogen bonds are reinforced by that of a C8...O41ⁱⁱⁱ hydrogen bond [symmetry code: (iii) x, -y+1/2, +z+1/2], which forms infinite C(7) chains [C8...O41 = 3.502(3) Å; C8-H...O41 = 150(2)°]. This third motif is perpendicular to the first two hydrogen-bonding motifs and links (1 0 2) sheets into a three-dimensional network (Figure 4).

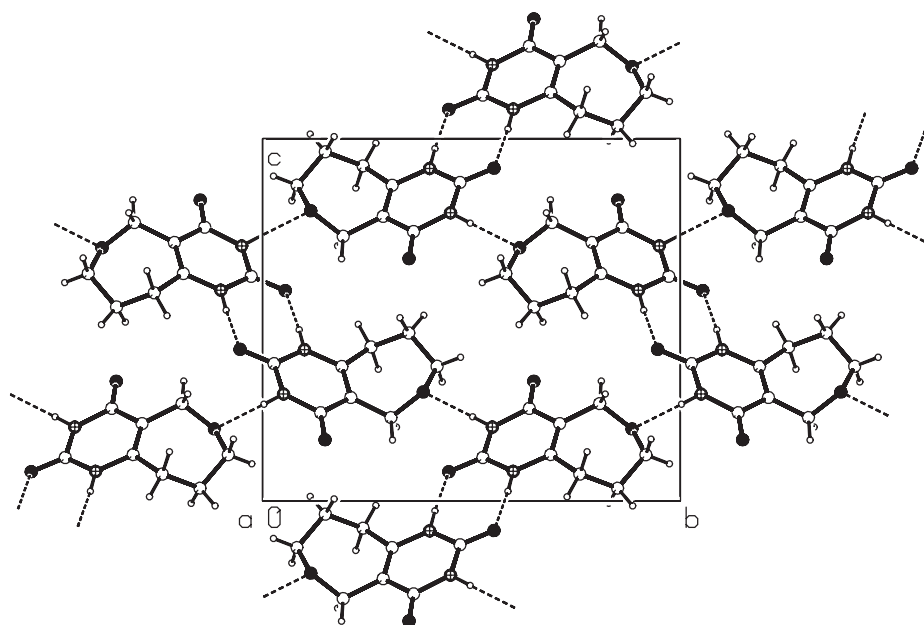


Figure 3. Crystal packing diagram of **9** along *a* axis, showing N-H...O hydrogen bonds that generate (1 0 2) sheets. Hydrogen bonds are indicated by dashed lines.

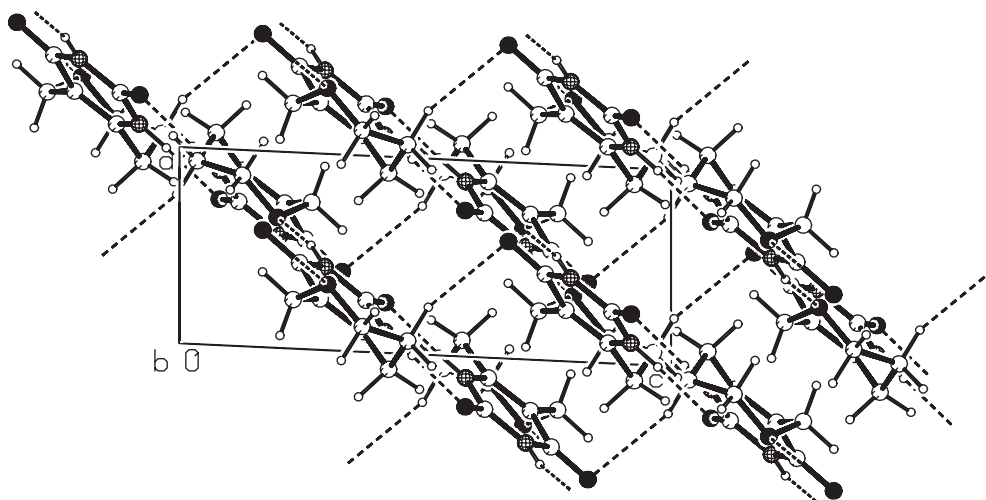


Figure 4. Crystal packing diagram of **9** along *b* axis, showing C8...O41 hydrogen bond which links (1 0 2) sheets into a three-dimensional network. Hydrogen bonds are indicated by dashed lines.

CONCLUSIONS

The 5,6-disubstituted (**5-8**) pyrimidine nucleoside analogues were prepared by hydroxymethylation at C-5 position and subsequent addition of the lithiated pyrimidine at C-6 with oxirane as electrophile. Ring closure of C-5 and C-6 side chains in **6** by acid hydrolysis gave bicyclic compound (**9**) containing tetrahydrooxepine and pyrimidine rings. The exact stereostructure of this compound was determined by

X-Ray structural analysis. Fluorinated pyrrolidinopyrimidine derivatives (**12** and **15**) were formed by N-1 linkage to the acyclic moiety at C-6 position.

EXPERIMENTAL

General. Melting points (uncorrected) were determined with Kofler micro hot-stage (Reichert, Wien). Precoated Merck silica gel 60F-254 plates were used for thin layer chromatography (TLC) and the spots were detected under UV light (254 nm). Column chromatography was performed using silica gel (0.063-0.2 mm) Kemika; glass column was slurry-packed under gravity. The EIMS spectra were recorded with an EXTREL FT MS 2001 instrument with ionising energy 70 eV. Elemental analyses were performed in the Central Analytic Service, Ruđer Bošković Institute, Zagreb. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer, operating at 75.46 MHz for the ^{13}C resonance. The samples were dissolved in DMSO- d_6 and measured in 5 mm NMR tubes. The ^1H and ^{13}C NMR chemical shift values (δ) are expressed in ppm referred to TMS and coupling constants (J) in Hz.

5-Hydroxymethyl-6-methylpyrimidine-2,4-dione (**2**)

A solution of 6-methyluracil (20 g; 0.159 mol), paraformaldehyde (5.95 g; 0.198 mol) and KOH (277.8 mL, 0.42 M) was stirred for 73 h at 50 °C. After dilution with water, reaction mixture was stirred with freshly washed DOWEX (H^+ form, strongly acidic, 100-200 mesh) (60 g) and filtrated to remove resin and a little insoluble product. The filtrate was concentrated by evaporation on small volume, refrigerated and filtered. Recrystallization from acetone and water (2:1) gave white crystals of **2** (18.92 g; 76.4 %; mp > 308 °C). ^{13}C NMR δ 164.26 (C-2), 151.52 (C-4), 109.37 (C-5), 151.01 (C-6), 53.31 (CH_2 -5), 15.94 (CH_3 -6); MS (70 eV) m/z: 156 [M^+].

2,4-Dichloro-5-chloromethyl-6-methylpyrimidine (**3**)

The mixture of 5-hydroxymethyl-6-methylpyrimidine-2,4-dione (**2**) (10 g; 64.045 mmol) and POCl_3 (100 mL; 1.092 mol) was heated under reflux for 1 h. Excess of POCl_3 was then removed under reduced pressure and the residue was added to ice. Cold mixture was filtrated to give yellow crystals of **3** (8.14 g, 60.1 %; mp 38 °C). ^{13}C NMR δ 181.82 (C-2), 170.99 (C-4), 137.02 (C-5), 167.27 (C-6), 49.00 (CH_2 -5), 31.55 (CH_3 -6); MS (70 eV) m/z: 212 [M^+].

2,4-Dimethoxy-5-methoxymethyl-6-methylpyrimidine (**4**)

To a solution of sodium (1.49 g; 64.944 mmol) in methanol (36.6 mL) was added compound (**3**) (4.358 g; 20.607 mmol). The reaction mixture was refluxed for 3 h. The solvent was evaporated and water was added to dissolve NaCl. The oily layer was extracted with dichloromethane, dried over sodium sulfate and

concentrated under reduced pressure. The residue was kept in refrigerator and then applied to column chromatography (CH₂Cl₂:MeOH = 40:1) to give **4** (2.52 g; 61.74 %; mp 40 °C). ¹³C NMR δ 169.36 (C-2), 168.95 (C-4), 108.42 (C-5), 163.55 (C-6), 63.69 (CH₂-5), 57.39, 54.24 (OCH₃-2, OCH₃-4), 53.91 (OCH₃-5), 21.0 (CH₃-6); MS (70 eV) m/z: 198 [M⁺].

6-(3-Hydroxypropyl)-2,4-dimethoxy-5-methoxymethylpyrimidine (5)

Lithium diisopropylamide (LDA) (4.34 mL; 8.42 mmol) in hexane was added dropwise to a solution of **4** (1.015 g; 5.12 mmol) in anhydrous tetrahydrofuran (14.21 mL) at -70 °C under argon atmosphere. The temperature was warmed to -55 °C and the solution was stirred for 30 min. Oxirane in excess (1.5 mL; 30.645 mmol) was added dropwise to the solution, temperature was raised to -10 °C and the stirring was continued for 3 h. The reaction mixture was neutralized by the addition of saturated ammonium chloride solution and the temperature was raised to rt. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane and water. Organic layer was dried over sodium sulfate and the solvent was removed by evaporation. The crude product was purified by column chromatography (CH₂Cl₂:MeOH = 20:1) providing oily compound (**5**) (0.773 g; 67.92 %). ¹³C NMR δ 172.27 (C-2), 169.58 (C-4), 108.29 (C-5), 163.70 (C-6), 63.40 (CH₂-5), 54.23, 53.96 (OCH₃-2, OCH₃-4), 31.51 (C-1'), 30.15 (C-2'), 60.38 (C-3'), 57.43 (OCH₃-5); MS (70 eV) m/z: 242 [M⁺]; Anal. Calcd for C₁₁H₁₈N₂O₄: C, 54.53; H, 7.49; N, 11.56. Found: C, 54.69; H, 7.47; N, 11.59.

6-(3-Acetoxypropyl)-5-methoxymethylpyrimidine-2,4-dione (6) and 6-(3-acetoxypropyl)-2,4-dimethoxy-5-methoxymethylpyrimidine (7)

A solution of **5** (560 mg, 2.31 mmol) in acetyl chloride (8 mL) was refluxed for 5.5 h. Water (1 mL) was added and the mixture was stirred at rt overnight. The solution was evaporated under reduced pressure. The residue was applied to column chromatography (CH₂Cl₂:MeOH = 15:1) to give white crystals of **6** (137.9 mg, 23.30%, mp 140-142 °C) and oily compound (**7**) (81 mg, 0.12%).

6: ¹³C NMR δ 170.28 (CO), 164.26 (C-2), 155.54 (C-4), 106.01 (C-5), 150.94 (C-6), 63.39 (CH₂-5), 27.20 (C-1'), 26.45 (C-2'), 57.14 (C-3'), 63.05 (OCH₃-5), 20.69 (CH₃CO); MS (70 eV) m/z: 256 [M⁺]; Anal. Calcd for C₁₁H₁₆N₂O₃: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.42; H, 6.30; N, 10.95.

7: ¹³C NMR δ 170.81 (CO), 171.65 (C-2), 170.01 (C-4), 108.85 (C-5), 164.12 (C-6), 63.74 (CH₂-5), 30.08 (C-1'), 27.30 (C-2'), 63.82 (C-3'), 57.87 (OCH₃-5), 54.70, 54.46 (OCH₃-2, OCH₃-4), 21.12 (CH₃CO); MS (70 eV) m/z: 284 [M⁺]; Anal. Calcd for C₁₃H₂₀N₂O₅: C, 54.92; H, 7.09; N, 9.85. Found: C, 54.83; H, 7.10; N, 9.88.

6-(3-Hydroxypropyl)-5-methoxymethylpyrimidine-2,4-dione (8) and 5,7,8,9-tetrahydrooxepino[4,3-d]pyrimidine-2,4-dione (9)

A solution of **6** (294 mg, 1.148 mmol) in concentrated hydrochloric acid (1.38 mL) was heated at 65 °C for 3 h. The solution was evaporated under reduced pressure. The residue was applied to column chromatography (CH₂Cl₂:MeOH = 5:1) to give **8** (9 mg, 4 %, mp 110-112 °C) and **9** (42 mg, 20 %, mp 243-245 °C).

8: ¹³C NMR δ 164.34 (C-2), 156.41 (C-4), 105.75 (C-5), 151.0 (C-6), 63.43 (CH₂-5), 31.38 (C-1'), 26.52 (C-2'), 57.15 (C-3'), 60.03 (OCH₃-5); MS (70 eV) m/z: 214 [M⁺]; Anal. Calcd for C₉H₁₄N₂O₄: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.61; H, 6.58; N, 13.11.

9: ¹³C NMR δ 163.36 (C-2), 156.16 (C-4), 109.02 (C-5), 150.65 (C-6), 63.01 (CH₂-5), 30.30 (C-1'), 26.56 (C-2'), 72.58 (C-3'); MS (70 eV) m/z: 182 [M⁺].

6-[2-Hydroxymethyl-3-(4-methoxytrityloxy)propyl]thymine (11)

6-[3-Hydroxy-2-(hydroxymethyl)propyl]thymine (**10**)¹³ (13.23 mg, 0.062 mmol), 4-methoxytrityl chloride (46.3 mg, 0.15 mmol), DMAP (0.76 mg, cat. amount, 0.007 mmol) and triethylamine (0.05 mL) were dissolved in dimethylformamide (1 mL). The reaction mixture was heated at 50 °C for 2 h, then diluted with ethyl acetate and washed with water. The combined organic phase was dried (MgSO₄), evaporated and purified by column chromatography (CH₂Cl₂:MeOH = 20:1) to yield **11** (16.6 mg, 55 %, mp 180-183 °C); MS (70 eV) m/z: 487 [M⁺].

6-Fluoromethyl-4-methylpyrrolido[1,2-c]pyrimidine-1,3-dione (12)

Dimethylaminosulfur trifluoride (DAST) (6 μL, 0.046 mmol) was added into solution of compound (**11**) (16.6 mg, 0.034 mmol) in dichloromethane (1.5 mL) under argon atmosphere. The reaction mixture was then stirred at rt for 1.5 h and the solvent was removed under reduced pressure and the residue was chromatographed (CH₂Cl₂:MeOH = 20:1) to give **12** (3.5 mg, 53 %, 160-163 °C); MS (70 eV) m/z: 198 [M⁺]; Anal. Calcd for C₉H₁₁N₂O₂F: C, 54.54; H, 5.59; N, 14.13. Found: C, 54.67; H, 5.58; N, 14.18.

6-[2-Hydroxy-3-(4-methoxytrityloxy)propyl]thymine (14)

Compound (**13**)⁴ (160 mg, 0.8 mmol), 4-methoxytrityl chloride (494 mg, 1.6 mmol), DMAP (12 mg, cat. amount), triethylamine (0.72 mL) were treated according to the procedure that is analogous to that for the preparation of **11**. Purification of crude product by column chromatography (CH₂Cl₂:MeOH = 12:1) gave **14** (160 mg, 43 %, 195-198 °C); MS (70 eV) m/z: 472 [M⁺].

6-Fluoro-4-methylpyrrolido[1,2-c]pyrimidine-1,3-dione (15)

Compound (**14**) (80 mg, 0.169 mmol) was dissolved in dry dichloromethane (7 mL). DAST (31.2 μ L, 0.236 mmol) was then added with stirring at rt under argon atmosphere. After 1 h the reaction mixture was poured into saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layer was concentrated and purified by column chromatography (CH_2Cl_2 :MeOH = 15:1) to afford **15** (13.6 mg, 44 %, 170-172 $^\circ\text{C}$); MS (70 eV) m/z : 184 [M^+]; Anal. Calcd for $\text{C}_8\text{H}_9\text{N}_2\text{O}_2\text{F}$: C, 52.17; H, 4.93; N, 15.21. Found: C, 52.03; H, 4.94; N, 15.24.

X-Ray crystal structure determination

Single crystal of the compound (**9**) suitable for X-Ray single crystal analysis was obtained at room temperature by partial evaporation from ethanol solution (96 %). Crystal data, data collection and refinement are summarized in Table 2.

Table 2. Crystal data and summary of data collection and refinement for **9**.

Formula	$\text{C}_8\text{H}_{10}\text{N}_2\text{O}_3$
Formula weight	182.18
Temperature [K]	295(2)
Crystal size [mm]	0.30x0.40x0.58
Crystal colour	colourless
Crystal system	monoclinic
Space group	$P 2_1/c$
a [\AA]	4.869(1)
b [\AA]	14.013(2)
c [\AA]	12.115(2)
β [$^\circ$]	92.68(2)
V [\AA^3]	825.6(3)
Z	4
$D_{\text{calc.}}$ [gcm^{-3}]	1.466
μ [mm^{-1}]	0.114
$F(000)$	384
scan-mode	ω and ϕ
θ range for data collection [$^\circ$]	4.45 to 28.99
Index ranges	$-6 \leq h \leq 6$ $-19 \leq k \leq 19$ $-16 \leq l \leq 16$
Collected / Independent reflections	25930 / 2182
Reflections [$I \geq 2\sigma(I)$] / R_{int}	1792 / 0.0773
Data / restraints / parameters	2182 / 0 / 158
Weighting parameters a, b^a	0.1095; 0.0544
Goodness-of-fit on F^2	1.172
R [$I \geq 2\sigma(I)$] / R [all data]	0.0581 / 0.0692

$wR [I \geq 2\sigma(I)] / R_w$ [all data]	0.1710 / 0.1825
Max. / min. electron density [$\text{e}\text{\AA}^{-3}$]	0.345 / -0.222
<hr/>	
$a_w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = (F_o^2 + 2F_c^2)/3$	

The intensities were collected at 295(2) K on a Oxford Diffraction Xcalibur2 diffractometer with graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The data collection and reduction were carried out with the CrysAlis programs.¹⁵ The intensities were corrected for Lorentz and polarization effects. The crystal structure was solved by direct methods. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares calculations based on F^2 . All hydrogen atoms were found in a difference Fourier map and their coordinates and isotropic thermal parameters have been refined freely. Programmes used for structure solution, refinement and analysis include SHELXS97,¹⁶ SHELXL97¹⁷ and PARST96.¹⁸ The molecular and crystal structure drawings were prepared by PLATON program.¹⁹

Supplementary Material

CCDC 244691 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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