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cis- and *trans*-1-[3-(Hydroxymethyl)-1,4-dioxepan-5-yl]pyrimidines: a new nucleoside prototype with a seven-membered moiety

María A. Trujillo, José A. Gómez, Joaquín Campos, Antonio Espinosa and Miguel A. Gallo*

Departamento de Química Orgánica, Facultad de Farmacia, c/ Campus de Cartuja s/n, 18071 Granada, Spain

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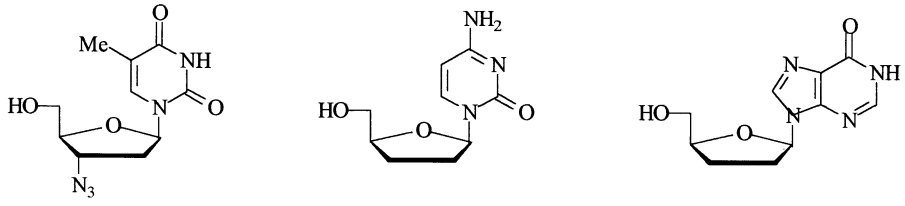
Abstract—We synthesized nucleoside analogues with a seven-membered moiety as the carbohydrate fragment mimicking the upper part of biologically active natural and synthetic nucleosides, starting from 3-iodomethyl-5-methoxy-1,4-dioxepane. The reaction sequence involved the substitution of the iodine atom by the acetoxy group, condensation with the nucleobases and subsequent saponification. The *cis/trans* mixtures of the target compounds were separated by reversed-phase preparative HPLC. The relative configurations of each of the hydrogen atoms of the *cis* and *trans* newly synthesized compounds were determined by spin decoupling, 2D NOESY and COSY experiments. None of this series showed activity in antiviral tests in cell cultures.

1. Introduction

The pathologies related to viral and/or neoplastic affections are one of the primary causes of death in the world. Natural nucleosides have been the primary models for the design of important antitumoural and/or antiviral antimetabolites.[1,2] The differences between the therapeutic nucleosides and the natural ones are in either the heterocyclic base or in the carbohydrate fragment. The broad majority of therapeutic nucleosides contain a glycosidic moiety. Although nucleoside and nucleotide analogues such as 3′-azido-3′-deoxythymidine (AZT, **1**), 2′,3′-dideoxycytidine (ddC, **2**), and 2′,3′-dideoxyinosine (ddI, **3**) (Fig. 1) have shown remarkable activity as inhibitors of the human immunodeficiency virus (HIV), their long-term usefulness is somewhat limited by their toxicities which include bone marrow toxicity, peripheral neuropathy, pancreatitis and hepatotoxicity.[3,4] The development of resistant strains on prolonged clinical use of these compounds and their cross resistance to related nucleosides are major concerns in the development of new nucleoside antiviral agents. For this reason, the synthesis of new and distinctly different nucleosides is of considerable significance in this area. Additionally, if the new nucleosides are structurally unlike the currently used antiviral agents, the probability of cross resistance to AZT or other nucleoside resistant strains should be expected to diminish. However, the nucleoside structural modification cannot be so great that either the new nucleoside is not recognized by cellular kinases, or that its triphosphate, if cellularly produced, does not bind competitively to HIV reverse transcriptase.

On the basis of these data, we decided to prepare some new nucleoside analogues in which the 'sugar moiety', different



1 **2** **3**

Figure 1.

Keywords: 1-[3-(hydroxymethyl)-1,4-dioxepan-5-yl]pyrimidines; reversed-phase high-performance liquid chromatography, RP-HPLC; 1,4-chelation; external ion pair.

* Corresponding author. Tel.: +34-958-249976; fax: +34-958-243845; e-mail: magallo@ugr.es

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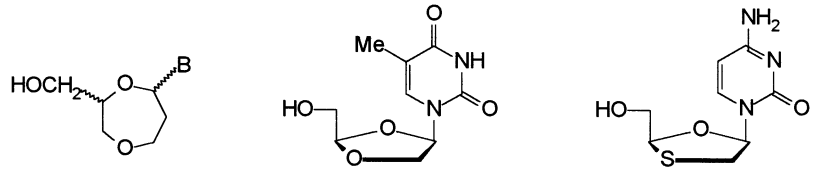


4a B = 5-fluorouracil
4b B = 5-bromouracil
4c B = 5-(trifluoromethyl)uracil
4d B = thymine
4e B = cytosine

5 **6**

Figure 2.

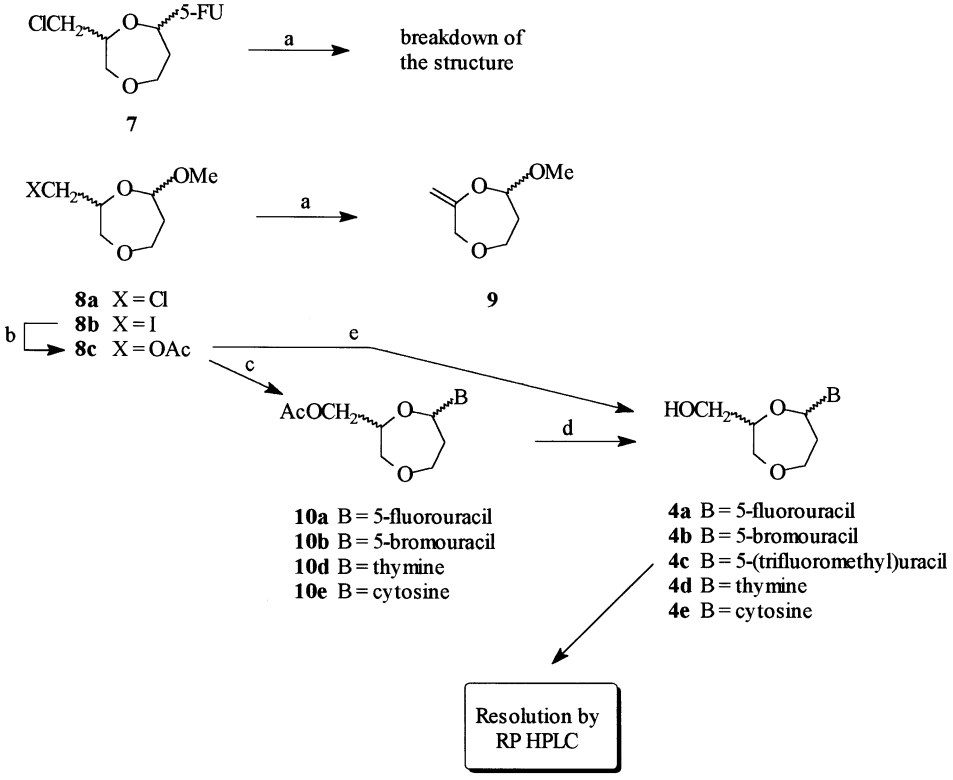
from those already utilized, are linked to pyrimidine bases (5-fluorouracil, 5-bromouracil, 5-trifluoromethyluracil, thymine and cytosine) present in pharmacologically active nucleosides.

We therefore synthesized the new 1,4-dioxepane nucleoside analogues of type **4** which, on the 1,4-dioxepane ring, present the hemiaminal oxygen adjacent to the hydroxymethyl group, which is also *cis* or *trans* to the basic nucleus; in the former case, this relationship is the same present in natural furanoside nucleosides and also in several synthetic ones: dideoxynucleoside prototypes containing two heteroatoms within the carbohydrate framework have led to several promising anti-HIV agents, such as dioxolane-T,[5] **5** and BCH-189[6] **6** (Fig. 2). The dioxolane series is exemplified by oxygen atoms at the apex and 3′-position, as in **5**.

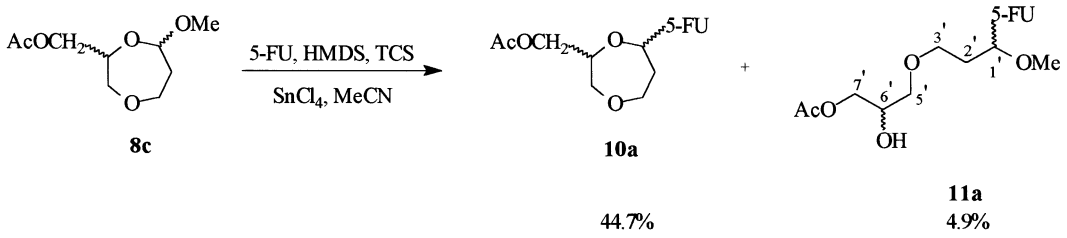
Compound **4d** (Fig. 2) can be considered as a ring-expanded analogue of dioxolane-T, **5** (Fig. 2) where two methylene groups are inserted into the 1,3-dioxolane ring, each one on both sides of the ethereal oxygen atom (*O*-3′).

2. Results and discussion

The substitution of the chloro atom from a *cis/trans* mixture of **7**[7] did not produce the expected nucleoside **4a** but instead led to a breakdown of the structure (Scheme 1). Some time ago, we reported the obtention of 2-(2-hydroxyethyl)-1,3-dioxolane and the *cis/trans* mixture of 2-(2-hydroxyethyl)-4-methyl-1,3-dioxolane by heating the corresponding chlorinated substrates, 2-(2-chloroethyl)-1,3-dioxolane and the *cis/trans* mixture of 2-(2-chloroethyl)-4-methyl-1,3-dioxolane, with Na_2CO_3-NaOH in a sealed tube at 160°C.[8] Nevetheless, 5-FU is stable in solutions which are not strongly basic (pH less than 9).[9] When subjected to strongly



Scheme 1. Several attempts and preparation of title compounds **4**. *Reagents and conditions*: (a) NaOH, $Na_2CO_3 \cdot 10H_2O$, 100°C; (b) KOAc, 18-crown-6, starting from **8a**; DMF, reflux; (c) Nucleobase, HMDS, TCS, $SnCl_4$; MeCN; (d) NaOH, H_2O, 21 h; (e) starting from **8c** and using 5-(trifluoromethyl)uracil as the pyrimidine base, under the conditions specified in (c).



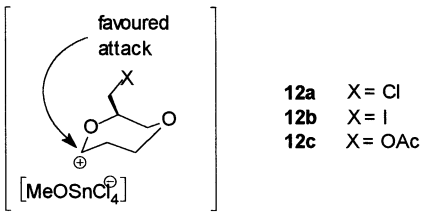
8c **10a** **11a**

44.7% 4.9%

Scheme 2.

basic conditions, 5-FU is hydrolysed to urea, fluoride, and an aldehyde. This hydrolysis is enhanced by increased pH and temperature.[9] In spite of decreasing the reaction temperature to 100°C (compared with that of the process in which the 1,3-dioxolane acetals were involved, i.e., 160°C), the reaction did not produce the expected results and led to the breakdown of the starting material **7**. After this unsuccessful reaction, the interchange of the chloro atom was tried on the *cis/trans* mixture of the cycloacetal **8a**;[7] however, the product **9** obtained had an exocyclic double bond as a consequence of the elimination process (Scheme 1).

The following set of reactions led to the target molecules **4**: cycloacetal **8c** was obtained by treatment of **8b**[7] (*cis/trans* mixture: 1/3.3) with potassium acetate and 18-crown-6 in *N,N*-dimethylformamide (DMF) at the reflux temperature of the mixture. Although we were able to isolate *trans*-**8c** after three consecutive flash-40[10] chromatographies, the next step was carried out with the unseparated mixture of isomers. Condensation between the *cis/trans* mixture (1/1.7) of the cycloacetal **8c** and the 5-substituted uracils and cytosine, in 1,1,1,3,3,3-hexamethyldisilazane (HMDS), trimethylchlorosilane (TCS), tin (IV) chloride in dry acetonitrile yielded the corresponding 1-[3-(acetoxymethyl)-1,4-dioxepan-5-yl]pyrimidine nucleobases **10a,b,d,e** in a one-step/one-pot reaction, a procedure previously reported by us for the synthesis of several types of 5-FU derivatives.[7,11–15] The protected nucleosides **10a,b,d,e** were deblocked by treatment with aqueous sodium hydroxide at room temperature and purified by flash chromatography to give the *cis/trans* mixtures of the target compounds **4a,b,d,e**. When the condensation reaction was carried out between the cycloacetal **8c** and 5-(trifluoromethyl)uracil, using the same experimental conditions, the results proved to be different: the nucleoside **4c** was directly obtained as a consequence of the hydrolysis of the acetate moiety after workup and flash chromatography. Finally, the resolution of the *cis/trans*-**4a-e** mixtures was brought about by reversed-phase high-performance liquid chromatography (RP-HPLC) (Scheme 1).



12a X= Cl
12b X= I
12c X= OAc

Figure 3.

Interestingly besides **10a** (44.7%), nucleoside analogue **11a** was obtained in 4.9% yield having an acyclic chain with the methoxy group intact (Scheme 2). This minor fraction showed two sets of signals in both ^{1}H NMR and ^{13}C NMR spectra, revealing it to be a mixture of diastereomers identified as (1′*R**,6′*R**)- and (1′*R**,6′*S**)-**11a**. Compound **10a** is a potential prodrug of **4a** and, hence, we accomplished the resolution of its *cis/trans* mixture for the biological evaluation of each isomer.

Alkoxy-1,4-dioxepanes exhibit two distinct types of reactivity in the reaction with 5-FU, giving rise to two kinds of compounds: (a) *seco*-nucleosides[12–14] (or acyclic nucleosides) having as the 'sugar' moiety a linear side chain, and (b) *O,N*-acetal analogues with a 1,4-dioxa seven-membered fragment.[7] In both cases, the reactions proceed through chelation by tin (IV) chloride forming an octahedral complex upon the strarting cycloacetal. In the former, the complexation takes place between the Lewis acid and the two endocyclic oxygen atoms of the 1,4-dioxepane moiety. The clue to modulate the reactivity to route (b) lies in the branching at C-3 of 5-methoxy-1,4-dioxepane and a long reaction time (ca. 24 h).[7] Moreover, the more electronegative the group X is in 3-(halomethyl)-5-methoxy-1,4-dioxepanes, the greater diastereoselectivity is reached.[7] The seven-membered acetal reacts with $SnCl_4$ in anhydrous medium predominantly by loss of the methoxy group with in situ formation of the corresponding 1,4-dioxepan-5-ylium ions **12**. When X=Cl, the reaction exhibited a moderatively high *cis* selectivity which was explained by considering an external ion pair intermediate (Fig. 3), where the attack of the doubly silylated 5-FU molecule occurred from the opposite face to the departing methoxy group.

In the case of **12c** (X=CH_3COO) the level of diastereoselectivity (i.e., *cis/trans*-**10a**) is 5.5/1, which is the same value when reaction starts from **8a** (X=Cl)[7] and higher than the diastereoselectivity starting from **8b** (X=I)[7] when the nucleophile is 5-fluoro-2,4-bis(trimethylsilyloxy)pyrimidine generated in situ. Our proposed external ion pair[7] seems to be correct, because the diastereoselectivity increases linearly with the electronegativity (Pauling units) of atom or group X. The concept of electronegativity evolved largely from the desire to understand reaction mechanisms in terms of the inductive effects of different functional groups.[16] Pauling electronegativity of the acetate group is 2.56[17] while those of Cl and I atoms are 3.0[18] and 2.5,[18] respectively. Further, the external ion pair is in agreement with the observed stereochemical course of the attack of the nucleophile. It is noteworthy that when a condensation reaction with 5-FU is carried out with pure *trans*-**8c**, *cis/trans*-**10a** mixture is obtained with the same ratio of

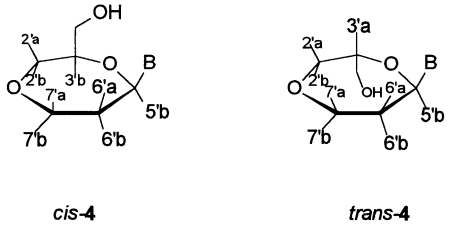
isomers reached by starting with the 1/1.7 *cis/trans* mixture of **8c**. Upon coordination of $SnCl_4$, the leaving of the methoxy group must take place giving a planar carbenium ion, which on steric grounds caused by $SnCl_4OMe^-$ explains the stereochemical outcome. This result definitively rejects an invertive S_N2-type substitution (because in this hypothetical case the product should have been, exclusively, *cis*-**10a** starting from *trans*-**8c**) on an intermediate Lewis acid complex in which the breaking bond is attached to the sterically most accessible acetalic oxygen (OMe). Poorer diastereoselectivities were obtained with the other nucleophiles (5-bromouracil, 5-trifluoromethyluracil, thymine and cytosine).

On the other hand, formation of the diastereomeric mixture of (1′*R**,6′*R**)-**11a** and (1′*R**,6′*S**)-**11a** could be interpreted by means of the previous complexation of $SnCl_4$ with the endocyclic ethereal oxygen and the exocyclic acetalic one of **8c**. The highly electronegative effect performed by the acetoxymethyl group slightly decreases the basicity of the endocyclic acetalic oxygen as opposed to that of the exocyclic one and, hence, these two points compete as chelation centres, even though the former continues prevailing.

3. Structure assignments

A very attractive issue is the unambiguous relative configurational assignment of each hydrogen atom of *cis*- and *trans*-**4a**. To this end, spin decoupling, NOE difference, 2D NOESY and ^{1}H-^{1}H COSY experiences have been carried out. Although 2D NOESY is the bidimensional equivalent to the NOE difference experience, the latter was first used throughout our research to quickly establish which were the ^{1}H NMR bases for the differentiation between the *cis* and *trans* isomers of **4**. We assume that 5-FU is directed towards the upper face of the plane established by the 1,4-dioxepane system; all the hydrogen atoms with the same orientation will be characterized by the subscript 'a' and all the hydrogens with the opposite orientation will be designed with the subscript 'b'. The numbering and subscripts of hydrogen atoms in each isomers are depicted in Fig. 4.

In both *cis*- and *trans*-**4a** (500.13 MHz, $CDCl_3$), H-3′ was well resolved and easily distinguished by a large difference in chemical shift. It is well known that protons *syn* to the base are more deshielded than those which were *anti*.[19] The H-3′ of *cis*-**4a** appeared at a considerably higher field (δ, 3.88 ppm, H-3′b) than that of *trans*-**4a** (δ, 4.32 ppm, H-3′a). Assignments of the *cis* and *trans* configurations of derivative **4a** were based on ^{1}H NOE difference spectroscopy upon irradiation of H-5′ in *cis*-**4a** leads to enhancement of H-3′, suggesting a *syn* orientation, while no enhancement was observed in *trans*-**4a**, indicating the *anti* configuration. These characteristic ^{1}H NMR features, which were also found in compounds **4b–d**, were used to assign their *cis* and *trans* configurations. The resonance lines for H-5′ in *cis*-**4a** (δ, 6.00 ppm) and *trans*-**4a** (δ, 6.11 ppm) are observed as ddd (double doublet of doublet) with the coupling constants 4.6, 8.4 and 1.5 Hz for the former and 3.1, 10.9 and 1.5 Hz for the latter. The J=1.5 Hz is due to the long-range coupling with the fluoro atom.[14] Noteworthy are the signals for H-6 in appearing as sharp doublets in each case with J=6.6 and J=6.5 Hz in *cis*- and *trans*-**4a**, respectively, due to the coupling with the fluoro atom, which, along with the elemental analyses shows unambiguously that the the 5-FU moiety is linked through *N*-1 and not through *N*-1 and *N*-3 to the 1,4-dioxepane cycle.[14,20]



cis-**4** *trans*-**4**

Figure 4.

In order to assign H-2′ of *cis*-**4a**, ^{1}H homonuclear decoupling was applied. Selective irradiation at the centre of the dd (doublet of doublet) at δ 3.59 ppm (J=8.9, 12.7 Hz), which integrates by one hydrogen, simplified both the ddd at δ 3.88 ppm (H-3′b, J=3.2, 5.1 and 13.7 Hz) and the dd at 3.95 ppm (J=3.2 and 12.7 ppm); accordingly the signal at δ 3.59 ppm could be assigned to H-2′a and H-2′b or vice versa. Indirectly, by means of the integrals, the ddd at δ 3.79 ppm (J=6.2, 6.2 and 12.6 Hz) and at δ 3.94 ppm (J=5.9, 5.9 and 12.6 Hz) could be assigned to H-7á and H-7′b or vice versa.

The relative configuration of the several types of hydrogen atoms (including the previous ambiguities) was determined by nuclear Overhauser and exchange spectroscopy (NOESY). In one case a diagnostic cross peak due to dipolar coupling was found between H-3′b and the ddd at δ 3.95 ppm, consistent with a *syn* relationship between them and hence, this signal is assigned to H-2′b (*cis*-**4a**), while the diagnostic cross peak with the dd at δ 3.79 ppm, allowed us to assign this resonance to H-7′b. Proton correlated spectroscopy (COSY) confirms the previous conclusions.

The protons of the hydroxymethyl moiety are equivalent in *cis*-**4** because they resonate as d (doublets) with J=5.0 Hz, whilst those of *trans*-**4** are distinguishable and, hence, diastereotopic resonating as dd (doublet of doublets) with an average coupling constant with H-3′a of 4.7 Hz and a geminal one of nearly 12 Hz.

The assignment of all the resonance signals of *trans*-**4a** was carried out by using the same techniques used for *cis*-**4a**, and analysis of the spectra of the rest of the series (*cis*- and *trans*-**4b–e**) was then easily derived. ^{1}H NMR spectra of *cis*-**4** and *trans*-**4** are shown in Tables 1 and 2, respectively. The ^{13}C signals of the title compounds were fully assigned, using the concerted application of one- and two-dimensional NMR techniques, including DEPT experiments and 2D-Heteronuclear ^{1}H-^{13}C (HETCOR) spectroscopy. ^{13}C NMR spectra of *cis*-**4** and *trans*-**4** are shown in Tables 3 and 4, respectively.

4. Antiviral activities

All compounds were inactive against the replication of

Table 1. ^{1}H NMR (CD_3OD) data of *cis*-1-[3-hydroxymethyl)-1,4-dioxepan-5-yl]pyrimidines

	Compound				
Hydrogens	**4a**	**4b**	**4c**	**4d**	**4e**
H-6 (Ar)	7.94 (d, $J_{H,F}$=6.6)	8.10 (s)	8.19 (d, $J_{H,F}$=0.9)	7.62 (d, $J_{6,CH3}$=1.2)	7.80 (d, $J_{6,5Cyt}$=7.4)
H-2′a[a]	3.59 (dd, $J_{2'a,3'b}$=8.9 $J_{2'a,2'b}$=12.7)	3.96 (dd, $J_{2'a,3'b}$=4.5 $J_{2'a,2'b}$=12.6)	3.96 (dd, $J_{2'a,3'b}$=3.2 $J_{2'a,2'b}$=12.5)	3.96 (dd, $J_{2'a,3'b}$=3.1 $J_{2'a,2'b}$=12.7)	3.96 (dd, $J_{2'a,3'b}$=3.1 $J_{2'a,2'b}$=12.6)
H-2′b	3.95 (dd, $J_{2'b,3'b}$=3.2 $J_{2'b,2'a}$=12.7)	3.61 (dd, $J_{2'b,3'b}$=8.8 $J_{2'b,2'a}$=12.6)	3.61 (dd, $J_{2'b,3'b}$=8.7 $J_{2'b,2'a}$=12.5)	3.60 (dd, $J_{2'b,3'b}$=8.9 $J_{2'b,2'a}$=12.7)	3.64 (dd, $J_{2'b,3'b}$=8.5 $J_{2'b,2'a}$=12.6)
H-3′b	3.88 (ddd, $J_{3'b,2'a}$=3.2 $J_{3'b,CH2OH}$=5.1 $J_{3'b,2'b}$=13.7)	3.88 (ddt, $J_{3'b,2'a}$=4.5 $J_{3'b,CH2OH}$=5.1 $J_{3'b,2'b}$=8.8)	3.88 (ddd, $J_{3'b,2'a}$=3.2 $J_{3'b,CH2OH}$=4.9 $J_{3'b,2'b}$=8.7)	3.87 (ddt, $J_{3'b,2'a}$=3.1 $J_{3'b,CH2OH}$=5.1 $J_{3'b,2'b}$=8.9)	3.90 (ddd, $J_{3'b,2'a}$=3.1 $J_{3'b,CH2OH}$=5.1 $J_{3'b,2'b}$=8.5)
H-5′b	6.00 (ddd, $J_{5'b,F}$=1.5 $J_{5'b,6'b}$=4.6 $J_{5'b,6'a}$=8.4)	6.02 (dd, $J_{5'b,6'b}$=4.4 $J_{5'b,6'a}$=8.5)	6.03 (dd, $J_{5'b,6'b}$=3.8 $J_{5'b,6'a}$=9.1)	6.02 (dd, $J_{5'b,6'b}$=4.5 $J_{5'b,6'a}$=8.7)	6.06 (dd, $J_{5'b,6'b}$=3.5 $J_{5'b,6'a}$=8.9)
H-6′a	2.25 (m)	2.24 (m)	2.26 (m)	2.24 (m)	2.27 (m)
H-6′b	2.25 (m)	2.24 (m)	2.26 (m)	2.24 (m)	2.13 (m)
H-7′a	3.94 (ddd, $J_{7'a,6'a}$=5.9 $J_{7'a,6'b}$=5.9 $J_{7'a,7'b}$=12.6)	3.95 (ddd, $J_{7'a,6'a}$=1.5 $J_{7'a,6'b}$=4.6 $J_{7'a,7'b}$=12.5)	4.00 (ddd, $J_{7'a,6'a}$=3.0 $J_{7'a,6'b}$=3.0 $J_{7'a,7'b}$=12.5)	3.96 (ddd, $J_{7'a,6'a}$=1.9 $J_{7'a,6'b}$=3.1 $J_{7'a,7'b}$=12.6)	3.95 (ddd, $J_{7'a,6'a}$=1.2 $J_{7'a,6'b}$=6.9 $J_{7'a,7'b}$=12.5)
H-7′b	3.79 (ddd, $J_{7'b,6'a}$=6.2 $J_{7'b,6'b}$=6.2 $J_{7'b,7'a}$=12.6)	3.79 (ddd, $J_{7'b,6'a}$=6.2 $J_{7'b,6'b}$=6.2 $J_{7'b,7'a}$=12.5)	3.79 (ddd, $J_{7'b,6'a}$=6.5 $J_{7'a,6'b}$=6.0 $J_{7'b,7'a}$=12.5)	3.81 (ddd, $J_{7'b,6'a}$=6.3 $J_{7'a,6'b}$=6.3 $J_{7'a,7'b}$=12.6)	3.80 (ddd, $J_{7'b,6'a}$=6.5 $J_{7'a,6'b}$=5.6 $J_{7'a,7'b}$=12.5)
CH_2OH	3.5 (d, $J_{CH2OH,3'b}$=5.0)	3.5 (d, $J_{CH2OH,3'b}$=5.0)	3.5 (d, $J_{CH2OH,3'b}$=4.9)	3.5 (d, $J_{CH2OH,3'b}$=5.1)	3.5 (dd, $J_{CH2OH,3'b}$=5.1 $J_{CH2OH,OH}$=1.9)
Others				CH_3 Thym 1.89 (d, $J_{CH3,6}$=1.2)	H-5 Cyt 5.90 (d, $J_{5,6}$=7.4)

[a] It is assumed that 5-FU is directed towards the upper face of the plane established by the 1,4-dioxepane system; all the hydrogen atoms with the same orientation are characterized by the subscript "a" and all the hydrogens with the opposite orientation are designed with the subscript "b".

Table 2. ^{1}H NMR (CD_3OD) data of *trans*-1-[3-hydroxymethyl)-1,4-dioxepan-5-yl]pyrimidines

	Compound				
Hydrogens	**4a**	**4b**	**4c**	**4d**	**4e**
H-6 (Ar)	7.95 (d, $J_{H,F}$=6.5)	8.19 (s)	8.39 (d, $J_{H,F}$=0.9)	7.67 (d, $J_{6,CH3}$=1.2)	7.85 (d, $J_{6,5Cyt}$=7.5)
H-2′a[a]	3.94 (dd, $J_{2'a,3'a}$=1.8 $J_{2'a,2'b}$=13.3)	3.95 (dd, $J_{2'a,3'a}$=1.8 $J_{2'a,2'b}$=13.3)	3.93 (dd, $J_{2'a,3'a}$=1.6 $J_{2'a,2'b}$=13.3)	3.96 (dd, $J_{2'a,3'a}$=1.7 $J_{2'a,2'b}$=13.3)	3.97 (dd, $J_{2'a,3'a}$=2.0 $J_{2'a,2'b}$=13.4)
H-2′b	3.50 (dd, $J_{2'b,3'a}$=8.5 $J_{2'b,2'a}$=13.3)	3.50 (dd, $J_{2'b,3'a}$=8.4 $J_{2'b,2'a}$=13.3)	3.49 (dd, $J_{2'b,3'a}$=8.5 $J_{2'b,2'a}$=13.3)	3.51 (dd, $J_{2'b,3'a}$=8.4 $J_{2'b,2'a}$=13.3)	3.55 (dd, $J_{2'b,3'a}$=8.4 $J_{2'b,2'a}$=13.4)
H-3′a	4.32 (dddd, $J_{3'a,2'a}$=1.8 $J_{6'a,CH2'OH}$=5.1 $J_{6'a,CH2OH}$=6.3 $J_{3'a,2'b}$=8.5)	4.36 (dddd, $J_{3'a,2'a}$=1.8 $J_{3'a,CH2'OH}$=4.7 $J_{3'a,CH2OH}$=6.4 $J_{3'a,2'b}$=8.4)	4.43 (dddd, $J_{3'a,2'a}$=1.6 $J_{3'a,CH2'OH}$=4.6 $J_{3'a,CH2OH}$=6.7 $J_{3'a,2'b}$=8.5)	4.33 (ddd, $J_{3'a,2'a}$=1.7 $J_{3'a,CH2'OH}$=4.8 $J_{3'a,CH2OH}$=6.7 $J_{3'a,2'b}$=8.5	4.30 (dddd, $J_{3'a,2'a}$=2.0 $J_{3'a,CH2'OH}$=4.8 $J_{3'a,CH2OH}$=6.1 $J_{3'a,2'b}$=8.4
H-5′b	6.11 (ddd, $J_{5'b,F}$=1.5 $J_{5'b,6'b}$=3.1 $J_{5'b,6'a}$=10.9)	6.09 (dd, $J_{5'b,6'b}$=3.0 $J_{5'b,6'a}$=10.9)	6.07 (dd, $J_{5'b,6'b}$=3.2 $J_{5'b,6'a}$=10.9)	6.02 (dd, $J_{5'b,6'b}$=4.5 $J_{5'b,6'a}$=8.7)	6.16 (dd, $J_{5'b,6'b}$=2.8 $J_{5'b,6'a}$=10.9)
H-6′a	2.49 (dddd, $J_{6'a,7'a}$=3.2 $J_{6'a,7'b}$=10.8 $J_{6'a,5'b}$=10.9 $J_{6'a,6'b}$=15.0)	2.53 (dddd, $J_{6'a,7'a}$=3.2 $J_{6'a,7'b}$=10.9 $J_{6'a,5'b}$=10.9 $J_{6'a,6'b}$=15.0)	2.52 (dddd, $J_{6'a,7'a}$=2.8 $J_{6'a,7'b}$=10.8 $J_{6'a,5'b}$=10.9 $J_{6'a,6'b}$=15.1)	2.58 (dddd, $J_{6'a,7'a}$=3.2 $J_{6'a,7'b}$=10.9 $J_{6'a,5'b}$=11.0 $J_{6'a,6'b}$=15.0)	2.58 (dddd, $J_{6'a,7'a}$=3.3 $J_{6'a,7'b}$=10.9 $J_{6'a,5'b}$=10.9 $J_{6'a,6'b}$=14.9)
H-6′b	2.13 (dddd, $J_{6'b,7'b}$=1.2 $J_{6'b,5'b}$=3.1 $J_{6'b,7'a}$=3.7 $J_{6'a,6'b}$=15.0)	2.16 (dddd, $J_{6'b,7'b}$=1.6 $J_{6'b,5'b}$=3.0 $J_{6'b,7'a}$=3.5 $J_{6'a,6'b}$=15.0)	2.17 (dddd, $J_{6'b,7'b}$=1.6 $J_{6'b,5'b}$=3.2 $J_{6'b,7'a}$=3.8 $J_{6'a,6'b}$=15.1)	2.08 (dddd, $J_{6'b,7'b}$=1.6 $J_{6'b,5'b}$=3.0 $J_{6'b,7'a}$=4.2 $J_{6'a,6'b}$=15.0)	2.15 (dddd, $J_{6'b,7'b}$=1.7 $J_{6'b,5'b}$=2.8 $J_{6'b,7'a}$=4.3 $J_{6'a,6'b}$=14.9)
H-7′a	4.04 (ddd, $J_{7'a,6'a}$=3.2 $J_{7'a,6'b}$=3.7 $J_{7'a,7'b}$=12.6)	4.04 (ddd, $J_{7'a,6'a}$=3.2 $J_{7'a,6'b}$=3.5 $J_{7'a,7'b}$=12.6)	4.05 (ddd, $J_{7'a,6'a}$=2.8 $J_{7'a,6'b}$=3.8 $J_{7'a,7'b}$=12.6)	4.06 (ddd, $J_{7'a,6'a}$=3.2 $J_{7'a,6'b}$=4.2 $J_{7'a,7'b}$=12.5)	4.05 (ddd, $J_{7'a,6'a}$=3.3 $J_{7'a,6'b}$=4.3 $J_{7'a,7'b}$=12.6)
H-7′b	3.66 (ddd, $J_{7'b,6'b}$=1.2 $J_{7'b,6'a}$=10.8 $J_{7'b,7'a}$=12.6)	3.66 (ddd, $J_{7'b,6'b}$=1.6 $J_{7'b,6'a}$=10.9 $J_{7'b,7'a}$=12.6)	3.67 (ddd, $J_{7'b,6'b}$=1.6 $J_{7'b,6'a}$=10.8 $J_{7'b,7'a}$=12.6)	3.67 (ddd, $J_{7'b,6'b}$=1.6 $J_{7'b,6'a}$=10.9 $J_{7'b,7'a}$=12.5)	3.68 (ddd, $J_{7'b,6'b}$=1.7 $J_{7'b,6'a}$=10.9 $J_{7'b,7'a}$=12.6)
CH_2OH	3.5 (dd, $J_{CH2OH,3'a}$=6.3 J_{gem}=11.7)	3.5 (d, $J_{CH2OH,3'a}$=6.4 J_{gem}=11.1)	3.5 (d, $J_{CH2OH,3'a}$=6.7 J_{gem}=11.7)	3.5 (d, $J_{CH2OH,3'a}$=6.3 J_{gem}=11.7)	3.5 (dd, $J_{CH2OH,3'a}$=6.1 J_{gem}=11.8)
$CH_2'OH$	3.5 (dd, $J_{CH2'OH,3'a}$=4.6 J_{gem}=11.7)	3.5 (dd, $J_{CH2'OH,3'a}$=4.7 J_{gem}=11.1)	3.5 (dd, $J_{CH2'OH,3'a}$=4.6 J_{gem}=11.7)	3.5 (dd, $J_{CH2'OH,3'a}$=4.8 J_{gem}=11.7)	3.5 (dd, $J_{CH2'OH,3'a}$=4.8 J_{gem}=11.8)
Others				CH_3 Thym 1.89 (d, $J_{CH3,6}$=1.2)	H-5 Cyt 5.90 (d, $J_{5,6}$=7.5)

[a] It is assumed that 5-FU is directed towards the upper face of the plane established by the 1,4-dioxepane system; all the hydrogen atoms with the same orientation are characterized by the subscript "a" and all the hydrogens with the opposite orientation are designed with the subscript "b".

Table 3. ^{13}C NMR (CD_3OD) data of *cis*-1-[3-hydroxymethyl)-1,4-dioxepan-5-yl]pyrimidines

	Compound							
	4a		**4b**	**4c**		**4d**	**4e**	
carbons	δ (ppm)	J (Hz)	δ (ppm)	δ (ppm)	J (Hz)	δ (ppm)	δ (ppm)	J (Hz)
C_2=O	150.43		152.52	150.72		151.99	158.10	
C_4=O	159.34		161.57	161.00		166.42	167.62	
C_5 Ar	141.91	232.57	141.79	143.15	6.0	138.21	142.73	6.2
C_6 Ar	126.57	34.31	97.88	106.04	22.00	111.58	96.05	6.2
CF_3				123.81	267.38			
$C_{2'}$	74.59		74.59	74.52		74.64	73.73	
$C_{3'}$	82.40		82.42	82.66		82.25	79.54	
$C_{5'}$	84.70		84.98	85.25		84.27	85.21	
$C_{6'}$	37.57		37.93	37.87		37.73	37.76	
$C_{7'}$	68.08		68.12	68.01		68.18	69.15	
CH_2OH	62.69		62.70	62.64		62.74	62.87	
CH_3 Thym						12.37		

Table 4. ^{13}C NMR (CD_3OD) data of *trans*-1-[3-hydroxymethyl)-1,4-dioxepan-5-yl]pyrimidines

	Compound						
	4a		**4b**	**4c**		**4d**	**4e**
carbons	δ (ppm)	J (Hz)	δ (ppm)	δ (ppm)	J (Hz)	δ (ppm)	δ (ppm)
C_2=O	150.69		152.62	152.06		152.25	154.69
C_4=O	159.60		165.47	162.27		166.47	165.52
C_5 Ar	141.84	235.05	141.97	143.65	5.8	138.49	141.31
C_6 Ar	126.75	33.75	97.68	105.25	32.51	111.41	93.82
CF_3				124.05	267.38		
$C_{2'}$	73.70		73.67	73.64		73.76	74.48
$C_{3'}$	79.86		79.84	80.36		79.65	81.88
$C_{5'}$	85.19		85.63	86.80		84.55	85.29
$C_{6'}$	37.16		37.41	37.31		37.34	38.43
$C_{7'}$	68.76		68.86	68.63		68.97	68.09
CH_2OH	62.63		62.64	62.49		62.69	62.91
CH_3 Thym						12.28	

HIV-1 (III_B) and HIV-2 (ROD) at subtoxic concentrations in MT-4 cells. This inactivity most probably results from the poor intracellular phosphorylation of these compounds. These [3-(hydroxymethyl)-1,4-dioxepan-5-yl]pyrimidine nucleosides are apparently not recognized as substrates by cellular or viral kinases, and hence no antiviral activity is found.

5. Conclusion

The synthesis and separation of the novel *cis*- and *trans*-[3-(hydroxymethyl)-1,4-dioxepan-5-yl]pyrimidine nucleosides was carried out. The relative configurations of each hydrogen atom of the seven-membered ring in relation to the pyrimidine base, and the corresponding chemical shifts were determined. Further structural modification and biological evaluation of this novel class of nucleoside analogues are in progress.

6. Experimental

General methods were the same as those previously described.[14,15] Concentrations were performed under diminished pressure (1–2 kPa) at a bath temperature not exceeding 40°C. Anhydrous solvents were obtained as follows: methanol was refluxed on magnesium methoxide (I_2, Mg, MeOH) overnight and then distilled; water was removed from DMF by distillation with benzene followed by distillation in vacuo; dichloromethane was stored on calcium hydride, refluxed and distilled; diethyl ether was refluxed overnight on sodium and distilled. All reactions were carried out in dry glassware and protected from atmospheric moisture. NMR spectra were recorded on a 500.13 MHz ^1H and 125.03 MHz ^{13}C NMR Brucker AMX-500, a 400.13 MHz ^1H and 100.03 MHz ^{13}C NMR Brucker ARX-400, and a 300.13 MHz ^1H and 75.78 MHz ^{13}C NMR Bruker AMX-300 spectrometers and chemical shifts are reported relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at δ 7.24 and 77.1 ppm). Analytical high-performance liquid chromatography (HPLC) was performed on a Waters HPLC 600 apparatus with an UV detector Waters 486 set at 254 nm and a Waters Symmetry® C18 3,9×150 mm column. Solvent mixtures of A=H_2O and B=CH_3CN were used. The flow rate was 1 mL/min. For preparative HPLC, a Prep Nova-Pak® HR C18 6 μm 60 A column with a length of 100 mm and and internal diameter of 25 mm was used. The solvent mixtures were as above and the flow rate was 20 mL/min. The flash-40 chromatography equipment was supplied by Biotage UK Limited.[10]

6.1. *cis/trans* Mixture of 3-(acetoxymethyl)-5-methoxy-1,4-dioxepane 8c

In a two-necked round-bottomed flask fitted with a reflux condenser were placed 3-iodomethyl-5-methoxy-1,4-dioxepane **8b**[7] (1.46 g, 5 mmol), potassium acetate (0.98 g, 10 mmol), 18-crown-6 (0.15 g, 0.10 g/1g of acetal **8b**) and DMF (30 mL), and the mixture was refluxed and stirred for 6 h. After cooling, diethyl ether (100 mL) was added and the solution was washed with H_2O (4×30 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash chromatography (diethyl ether/hexane: 1/6) yielding **8c** (0.39 g, 35.5%) as a 1/1.7 *cis/trans* mixture. TLC R_f (diethyl ether/hexane 1/4): 0.28. Retention time (t_R), glc: 3.04 min; programme: isotherm 175°C/10 min). ^{1}H NMR (400.13, $CDCl_3$) *cis*-**8c**: δ 4.73 (dd, $J_{5b,6b}$=3.9, $J_{5b,6a}$=6,9 Hz, 1H, H-5b), 3.71 (ddd, $J_{7b,7a}$=12.4, $J_{7b,6a}$=4.5, $J_{7b,6b}$=10.0, 1H, H-7b), 4.12 (dd, $J_{2a,2b}$=12.2, $J_{2a,3a}$=6.3, 1H, H-2a), 3.46 (dd, $J_{2b,2a}$=12.2, $J_{2b,3a}$=9.8, 1H, H-2b), 3.42 (s, 3H, O*Me*), 2.05 (s, 3H, C*H*$_3$COO). ^{13}C NMR (100.03, $CDCl_3$) *cis*-**8c**: δ 170.72 (C=O), 104.46 (C-5), 76.79 (C-3), 74.03 (C-7), 67.13 (C-2), 63.75 (*C*H$_2$OAc), 55,79 (O*Me*), 37.46 (C-6), 20.82 (*C*H$_3$COO).

^{1}H NMR (400.13, $CDCl_3$) *trans*-**8c**: δ 4.74 (dd, $J_{5b,6b}$=7.2, $J_{5b,6a}$=6.0, 1H, H-5b), 4.21 (m, $J_{3a,2b}$=10.2, $J_{3a,CH2OAc}$=5.1, 1H, H-3a), 4.02 (dd, $J_{CH2'OAc,\ gem}$=11.5, $J_{CH2'OAc,3a}$=6.1, 1H, C*H*$'_2$OAc), 3.96 (dd, $J_{CH2OAc,gem}$=11.5, $J_{CH2OAc,3a}$=6.1, 1H, C*H*$_2$OAc), 3.80 (ddd, $J_{7b,7a}$=12.5, $J_{7b,6a}$=5.1, $J_{7b,6b}$=2.0, 1H, H-7b), 3.80 (dd, $J_{2a,2b}$=12.4, $J_{2a,3a}$=4.9, 1H, H-2a), 3.54 (dd, $J_{2b,2a}$=12.4, $J_{2b,3a}$=10.2, 1H, H-2b), 3.36 (m, 1H, H-7a), 3.37 (s, 3H, O*Me*), 2.18 (m, 1H, H-6a), 2.04 (s, 3H, C*H*$_3$COO), 2.00 (m, $J_{6b,6a}$=12.2, $J_{6b,5b}$=8.1, $J_{6b,7a}$=4.2, $J_{6b,7b}$=2.0, 1H, H-6b). ^{13}C NMR (100.03, $CDCl_3$) *trans*-**8c**: δ 170.72 (C=O), 101.26 (C-5), 72.09(C-7), 70.65 (C-3), 65.61 (C-2), 64.26 (*C*H$_2$OAc), 55.30 (O*Me*), 38.54 (C-6), 20.81 (*C*H$_3$).

IR (cm^{-1}, neat) *cis/trans*-**8c** mixture: 2959 (s, aliphatic C-H groups), 2869 (ether), 1747 (aliphatic ester), 1370 (OCH_3). EM LSIMS *m/z* (%): 227 $(M + 23)^+$. HR LSIMS calcd for $C_9H_{16}O_5Na$ $(M + Na)^+$ 227.0895, found: 227.0897. Anal. for $C_9H_{16}O_5$: Calcd: C, 52.93, H, 7.90. Found: C, 52.63, H, 7.93.

6.2. General procedure for the preparation of 1-[3-acetoxymethyl)-1,4-dioxepan-5-yl]pyrimidine nucleobases 10a,b,d,e

3-(Acetoxymethyl)-5-methoxy-1,4-dioxepane **8c** (4.89 mmol), the pyrimidine nucleobase (5.38 mmol) and anhydrous acetonitrile (15 mL) were added to a flask and the solution was stirred under argon. 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 4.89 mmol), trimethylchlorosilane (TCS, 4.89 mmol) were injected and the suspension was left with stirring under argon for 30 min. Then, $SnCl_4$ (5.87 mL dissolved in CH_2Cl_2) was injected and the resulting solution was left with stirring under argon for 24 h at rt. The reaction was neutralized by addition of a K_2CO_3 saturated solution. The salts formed were filtered and washed thoroughly with $CHCl_3$/MeOH: 100/5, the filtrate rotaevaporated off and the residue was purified by flash chromatography ($CHCl_3$/MeOH, 100/2.5) to give **10a,b,d,e**.

6.3. *cis* and *trans*-1-(3-Acetoxymethyl-1,4-dioxepan-5-yl)-5-fluorouracil 10a, (1′*R**,6′*R**)- and (1′*R**,6′*S**)- 1-[3-(3-acetoxy-2-hydroxypropoxy)-1-methoxypropyl]-5-fluorouracil 11a (mixture of diastereoisomers)

Reaction with 5-fluorouracil (0.7 g) according to the general procedure yielded *cis/trans*-**10a** mixture (0.66 g, 44.7%). Secondly, the open-chain product 11a (0.08, 4.9%) was eluted.

The *cis/trans*-**10a** mixture was separated by HPLC (H_2O/CH_3CN: 92/8). The retention times in analytical conditions and using the same proportions of eluant were, t_R (*cis*-**10a**): 21.29 min and t_R (*trans*-**10a**): 17.98 min. ^{1}H NMR (400.13, CD_3OD) *cis*-**10a**: δ 7.77 (d, $J_{H,F}$=6.4, 1H, H-6$_{5\text{-FU}}$), 6.10 (ddd, $J_{5'b,6'a}$=8.3, $J_{5'b,6'b}$=4.5, $J_{5'b,F}$=1.6, 1H, H-5′b), 4.15 (m, 2H, H-7′a, H-3′b), 4.00 (dd, $J_{2'a,2'b}$=12.8, $J_{2'a,3'b}$=6.4, 1H, H-2′a), 3.86 (ddd, $J_{7'b,7'a}$=12.5, $J_{7'b,6'b}$=6.2, $J_{7'b,6'a}$=6.2, 1H, H-7′b), 3.66 (dd, $J_{2'a,2'b}$=12.8, $J_{2'a,3'b}$=8.4, 1H, H-2′b), 3.60 (d, $J_{CH2OAc,3'b}$=5.0, 2H, C*H*$_2$OAc), 2,27 (m, 2H, H-6′a, H-6′b), 2.08 (s, 3H, C*H*$_3$). ^{13}C NMR (100.03, CD_3OD) *cis*-**9a**: δ 172.49 (*C*OOCH$_3$), 166.30 (C-4$_{5\text{-FU}}$), 155.90 (C-2$_{5\text{-FU}}$), 143.03 (d, $J_{5\text{-F}}$=236.77, C-5$_{5\text{-FU}}$), 124.85 (d, $J_{6,F}$=34.81, C-6$_{5\text{-FU}}$), 84.7 (C-5′), 79.13 (C-3′), 74.29 (C-2′), 68.44 (C-7′), 64.58 (*C*H$_2$OAc), 37.81 (C-6′), 20.62 (*C*H$_3$). HR LSIMS calcd for $C_{12}H_{15}O_6N_2FNa$ $(M+Na)^+$ 325.0812, found: 325.0811. Anal. for $C_{12}H_{15}O_6N_2F$: Calcd: C, 47.67; H, 5.00; N, 9.27. Found: C, 47.60; H, 5.10; N, 9.18.

^{1}H NMR (400.13, CD_3OD) *trans*-**10a**: δ 8.07 (d, $J_{H,F}$=6.6, 1H, H-6$_{5\text{-FU}}$), 6.16 (dd, $J_{5'b,6'a}$=11.2, 1H, H-5′b), 4.59 (m, 1H, H-3′a), 4.20 (m, J=11.5, 6.7, 1H, H-7′a), 4.11 (m, 2H, H-7′b, H-2′a), 4.01 (m, $J_{CH2OAc,gem}$=13.2, 1H, C*H*$_2$Ac), 3.74 (m, $J_{CH2'OAc,gem}$=13.2, 1H, C*H*$_2$′OAc), 3.60 (dd, $J_{2'b\text{-}2'a}$=13.1, $J_{2'b,3'a}$=8.1, 1H, H-2′b), 2.61 (m, 1H, H-6′a), 2.17 (m, 1H, H-6′b), 2′08 (s, 3H, C*H*$_3$). ^{13}C NMR (75.03, CD_3OD) *trans*-**10a**: δ 172.3 (*C*OOCH$_3$), 159.4 (C-4$_{5\text{-FU}}$), 150.6 (C-2$_{5\text{-FU}}$), 141.8 (d, $J_{5\text{-F}}$=233.1, C-5$_{5\text{-FU}}$), 126.7 (d, $J_{6\text{-F}}$=34.32, C-6$_{5\text{-FU}}$), 84.77 (C-5′), 76.71 (C-3′), 73.20 (C-2′), 68.8 (C-7′), 64.43 (*C*H$_2$OAc), 37.0 (C-6′), 20.57 (CH$_3$). EM (LSIMS) *m/z*325.1 $(M+Na)^+$. HR LSIMS calcd for $C_{12}H_{15}O_6N_2FNa$ $(M+Na)^+$ 325.0812, found: 325.0814. Anal. for $C_{12}H_{15}O_6N_2F$: Calcd: C, 47.67; H, 5.00; N, 9.27. Found: C, 47.50; H, 5.04; N, 9.15.

The numbering of **(1′*R**,6′*R**)** and **(1′*R**,6′*S**)-11a** are shown in Scheme 2: ^{1}H NMR (400.13, $CDCl_3$) of one diastereomer: δ 9.88 (s, 1H, N*H*), 7.33 (d, $J_{F,6}$=5.7, 1H, H-6), 5.86 (ddd, $J_{1',2'}$=7.6, $J_{1',2'}$=5.5, $J_{1',F}$=1.8,1H, H-1′), 4.16 (m, 1H, H-6′), 4.09 (dd, $J_{7',7'}$=12.9, $J_{7',6'}$=5.0, 1H, H-7′), 3.38 (ddd, $J_{3',3'}$=9.3, $J_{3',2'}$=9.3, $J_{3',2'}$=3.2, 2H, H-3); 3.34 (s, 3H, O*Me*); 2.29 (m, 2H, H-5′); 2.06 (s, 3H, C*H*$_3$CO). ^{1}H NMR of the other one (400.13, $CDCl_3$): δ 9.74 (s, 1H, N*H*), 7.32 (d, $J_{F,6}$=5.6, 1H, H-6), 5.76 (ddd, $J_{1',2'}$=6.9, $J_{1',2'}$=5.4, $J_{1',F}$=1.5, 1H, H-1′), 4.13 (m, 1H, H-6′), 4.06 (dd, $J_{5',5'}$=11.8, $J_{5',6'}$=5.0, 1H, H-5′), 3.34 (s, 3H, O*Me*); 3.38 (ddd, $J_{3',3'}$=9.3, $J_{3',2'}$=9.3, $J_{3',2'}$=3.2, 2H, H-3); 2.04 (s, 3H, C*H*$_3$CO). Anal. for $C_{13}H_{19}O_7N_2F$ (mixture

of diastereomers **11a**): Calcd: C, 46.69; H, 5.73; N, 8.38. Found: C, 47.00; H, 5.45; N, 8.20.

6.4. *cis/trans* Mixture of 1-(3-acetoxymethyl-1,4-dioxepan-5-yl)-5-bromouracil 10b

Reaction with 5-bromouracil (1.21 g) according to the general procedure yielded the *cis/trans*-**10b** mixture (0.80 g, 45%). ^{1}H NMR (300.13, $CDCl_3$) *cis*-**10b**: δ 9.05 (s, 1H, NH), 7.79 (s, 1H, H-$6_{5\text{-BrU}}$), 6.02 (dd, $J_{5'b,6'a}$=9.4, $J_{5'b,6'b}$=3.5, 1H, H-5′b), 3.79 (ddd, $J_{7'b,7'a}$=12.6, $J_{7'b,6'b}$=6.3, $J_{7'b,6'a}$=6.3, 1H, H-7′b), 2.30 (m, 3H, H-6′), 2.07 (s, 3H, CH_3). ^{13}C NMR (75.03, $CDCl_3$) *cis*-**10b**: δ 172.46 (*C*OOCH$_3$), 151.16 (C-$2_{5\text{-BrU}}$), 141.74 (C-$5_{5\text{-BrU}}$), 97.82 (C-$6_{5\text{-BrU}}$), 84.87 (C-5′), 79.57 (C-3′), 74.20 (C-2′), 68.33 (C-7′), 64.43 (*C*H$_2$OOC), 37.48 (C-6′), 20.63 (*C*H$_3$).

^{1}H NMR (300.13, $CDCl_3$) *trans*-**10b**: δ 7.84 (s, 1H, H-$6_{5\text{-BrU.}}$), 6.12 (dd, $J_{5'b,6'a}$=10.6, $J_{5'a,6'b}$=3.2, 1H, H-5′b), 4.49 (m, 1H, H-3′a), 3.68 (m,1H, H-7′b), 2.30 (m, 3H, H-6′), 2.11 (s, 3H, CH_3). ^{13}C NMR (75.03, $CDCl_3$) *trans*-**10b**: δ 172.46 (*C*OOCH$_3$), 142.24 (C-$5_{5\text{-BrU}}$), 97.40 (C-$6_{5\text{-BrU}}$), 85.39 (C-5′), 76.93 (C-3′), 73.24 (C-2′), 68.81 (C-7′), 64.43 (*C*H$_2$OOC), 37.13 (C-6′), 20.74 (*C*H$_3$). EM (LSIMS) *cis/trans*-**10b** *m/z*362 (M)$^+$.

HR LSIMS *cis/trans*-**10b** calcd for $C_{12}H_{15}O_6N_2BrNa$ (M + Na)$^+$ 385.0011, found 385.0015. Anal. for $C_{12}H_{15}O_6N_2Br$ *cis/trans* mixture: Calcd: C, 39.78; H, 4.18; N, 7.74. Found: C, 39.30; H, 4.13; N, 7.54.

6.5. *cis/trans* Mixture of 1-(3-acetoxymethyl-1,4-dioxepan-5-yl)thymine 10d

Reaction with cytosine (0.70 g) according to the general procedure yielded the *cis/trans*-**10d** mixture (0.31 g, 20.9%). ^{1}H NMR (400.13, $CDCl_3$) *cis*-**10d**: δ 9.14 (s, 1H, H-6_{Thym}), 6.04 (dd, $J_{5'b,6'a}$=9.5, $J_{5'b,6'b}$=3.6, 1H, H-5′b), 3.79 (ddd, $J_{7'b,7'a}$=12.5, $J_{7'b,6'b}$=6.2, $J_{7'b,6'a}$=6.2, 1H, H-7′b), 2.27 (m, 1H, H-6′a), 2.04 (s, 3H, CH_3), 1.93 (s, 3H, CH_{3Thym}). ^{13}C NMR (100.03, $CDCl_3$) *cis*-**10d**: δ 170.67 (*C*OOCH$_3$), 163.74 (C-$4_{Thym.}$), 142.99 (C-$2_{Thym.}$), 135.44 (C-$5_{Thym.}$), 111.28 (C-$6_{Thym.}$), 82.96 (C-5′), 78.25 (C-3′), 73.77 (C-2′), 67.74 (C-7′), 63.26 (*C*H$_2$OOC), 37.74 (C-6′), 21.17 (*C*H$_3$), 12.99 (*C*H$_{3Thym.}$).

^{1}H NMR (400.13, $CDCl_3$) *trans*-**10d**: δ 9.15 (s, 1H, H-$6_{Thym.}$), 6.15 (dd, $J_{5'b,6'a}$=10.9, $J_{5'a,6'b}$=2.8, 1H, H-5′b), 4.43 (m, $J_{3'a,2'a}$=2.1, 1H, H-3′a), 3.66 (m, 1H, H-7′b), 2.39 (dddd, $J_{6'a,6'b}$=14.8, $J_{6'a,7'b}$=11.0, $J_{6'a,5'b}$=11.0, $J_{6'a,7'a}$=3.3, 1H, H-6′a), 2.05 (s, 3H, CH_3), 1.94 (s, 3H, C$H_{3Thym.}$). ^{13}C (100.03. $CDCl_3$) *trans*-**10d**: δ 170.67 (*C*OOCH$_3$), 163.74 (C-$4_{Thym.}$), 150.07 (C-$2_{Thym.}$), 135.51 (C-$5_{Thym.}$), 111.17 (C-$6_{Thym.}$), 83.17 (C-5′), 75.74 (C-3′), 72.72 (C-2′), 68.55 (C-7′), 63.26 (*C*H$_2$OOC), 37.47 (C-6′), 21.11 (*C*H$_3$), 12.99 (*C*H$_{3Thym}$).

Anal. for $C_{12}H_{18}O_6N_2$ (*cis/trans*-**10d** mixture): Calcd: C, 50.33; H, 6.34; N, 9.79. Found: C, 50.21; H, 6.15; N, 9.83.

6.6. *cis/trans* Mixture of 1-(3-acetoxymethyl-1,4-dioxepan-5-yl)cytosine 10e

Reaction with cytosine (0.60 g) according to the general procedure yielded the *cis/trans*-**10e** mixture (0.19 g, 14.7%). ^{1}H NMR (300.13, CD_3OD) *cis*-**10e**: δ 7.73 (d, $J_{6,5}$=7.5, 1H, H-6_{Cyt}), 6.07 (dd, $J_{5'b,6'a}$=9.1, $J_{5'b,6'b}$=3.7, 1H, H-5′b), 3.81 (ddd, $J_{7'b,7'a}$=12.4, $J_{7'b,6'b}$=6.2, $J_{7'b,6'a}$=6.2, 1H, H-7′b), 2.12 (m, 2H, H-6′a, H-6′b), 2.02 (s, 3H, CH_3). ^{13}C NMR (75.03, CD_3OD) *cis*-**10e**: δ 172.47 (*C*OOCH$_3$), 167.58 (C-$4_{Cyt.}$), 157.82 (C-$2_{Cyt.}$), 142.48 (C-$5_{Cyt.}$), 96.20 (C-$6_{Cyt.}$), 85.10 (C-5′), 79.14 (C-3′), 74.15 (C-2′), 68.37 (C-7′), 64.59 (*C*H$_2$OAc), 38.20 (C-6′), 20,59 (*C*H$_3$).

^{1}H NMR (300.13, CD_3OD) *trans*-**10e**: δ 7.77 (d, $J_{6,5}$=7.5, 1H, H-$6_{Cyt.}$), 6.17 (dd, $J_{5'b,6'a}$=10.8, $J_{5'a,6'b}$=3.0, 1H, H-5′b), 4.50 (dddd, $J_{3'a,2'b}$=10.9, $J_{3'a,CH2'OOC}$=6.5, $J_{3'a,CH2OOC}$=4.5, $J_{3'a,2'a}$=2.1, 1H, H-3′a), 3.96 (dd, $J_{2'a,2'b}$=13.2, $J_{2'a,3'a}$=2.4, 1H, H-2′a), 4.04 (dd, $J_{CH2OOC\ gem.}$=11.7, $J_{CH2OOC,3'a}$=4.5, 1H, CH_2OOC), 3.56 (dd, $J_{2'b,2'a}$=13.3, $J_{2'b,3'a}$=8.7, 1H, H-2′b), 2.41 (dddd, $J_{6'a,6'b}$=14.8, $J_{6'a,7'b}$=10.9, $J_{6'a,5'b}$= 10.9, $J_{6'a,7'a}$=3.3, 1H, H-6′a), 2.26 (m, 1H, H-6′b), 2.01 (s, 3H, CH_3). ^{13}C NMR (75.03, CD_3OD) *trans*-**10e**: δ 172.33 (*C*OOCH$_3$), 167.58 (C-$4_{Cyt.}$), 157.82 (C-$2_{Cyt.}$), 142.78 (C-$5_{Cyt.}$), 96.00 (C-$6_{Cyt.}$), 84.83 (C-5′), 76.46 (C-3′), 73.29 (C-2′), 69.18 (C-7′), 64.40 (*C*H$_2$OAc), 37.77 (C-6′), 20.59 (*C*H$_3$).

cis/trans-**10e** Mixture: HR LSIMS calcd for $C_{12}H_{18}O_5N_3Na$ (M + 1 + Na)$^+$ 307.1144, found: 307.1140. Anal. for $C_{12}H_{17}O_5N_3{\cdot}0.4H_2O$: Calcd: C, 49.60; H, 6.18; N, 14.47. Found: C, 49.74; H, 6.17; N, 14.14.

6.7. *cis* and *trans*-1-(3-Hydroxymethyl-1,4-dioxepan-5-yl)-5-trifluoromethyluracil 4c

Reaction with 5-trifluoromethyluracil (1 g) according to the general procedure yielded *cis/trans*-**4c** mixture (0.27 g, 20.3%). The *cis/trans*-**4c** mixture was separated by HPLC (H_2O/CH_3CN: 94/6). The retention times in analytical conditions and using the same proportions of eluant were, t_R (*cis*-**4c**): 30.16 min and t_R (*trans*-**4c**): 19.83 min. The ^{1}H and ^{13}C NMR data of the *cis*- and *trans*-**4c** are shown in Tables 1–4.

cis-**4c**: HR LSIMS calcd for $C_{11}H_{13}N_2O_5F_3Na$ (M+Na)$^+$ 333.0674, found 333.0675. Anal. for $C_{11}H_{13}O_5N_2F_3$: Calcd: C, 42.57; H, 4.23; N, 9.03. Found: C, 42.75; H, 4.19; N, 8.97.

trans-**4c**: HR LSIMS calcd for $C_{11}H_{13}N_2O_5F_3Na$ (M+Na)$^+$ 333.0674, found 333.0676. Anal. for $C_{11}H_{13}O_5N_2F_3$: Calcd: C, 42.57; H, 4.23; N, 9.03. Found: C, 42.71; H, 4.30; N, 9.08.

6.8. General procedure for the saponification of the 1-(acetoxymethyl-1,4-dioxepan-5-yl)pyrimidine nucleobase *cis/trans* mixture 10a,b,d,e

6.8.1. Obtention of *cis*- and *trans*-1-(hydroxymethyl-1,4-dioxepan-1-yl)nucleobase 4a,b,d,e. *cis/trans*-**10a,b,d,e** mixture (0.88 mmol) was dissolved in the minimum amount

of MeOH (2 mL), NaOH (0.09 g) dissolved in H_2O (4 mL) was added and allowed to stir at rt overnight. This solution was cooled in an ice-water bath to 5°C and was neutralized with 35% HCl. The solvent was removed under reduced pressure, CH_2Cl_2/MeOH 7:3 was added, filtered and concentrated again giving a residue which was purified by flash chromatography, eluting with CH_2Cl_2/MeOH (100/4) to give the title compounds **4a,b,d,e**. The ^1H and ^{13}C NMR data of the *cis*- and *trans*-**4a,b,d,e** are shown in Tables 1–4.

6.8.2. *cis* and *trans*-1-(3-Hydroxymethyl-1,4-dioxepan-5-yl)-5-fluorouracil 4a. Reaction with **10a** (0.27 g) according to the general procedure yielded *cis/trans*-**4a** mixture (0.20 g, 85.3%). The *cis/trans*-**4a** mixture was separated by HPLC (H_2O/CH_3CN: 90/10). The retention times in analytical conditions and using the same proportions of eluant were, t_R (*cis*-**4a**): 15.87 min and t_R (*trans*-**4a**): 11.43 min.

cis-**4a**: HR LSIMS calcd for $C_{10}H_{13}O_5N_2FNa$ $(M+Na)^+$ 283.0706, found: 283.0706. Anal. for $C_{10}H_{13}O_5N_2F$: Calcd: C, 46.14; H, 5.04; N, 10.77. Found: C, 45.97; H, 5.22; N, 10.75.

trans-**4a**: HR LSIMS calcd for $C_{10}H_{13}O_5N_2FNa$ $(M+Na)^+$ 283.0706, found: 283.0704. Anal. for $C_{10}H_{13}O_5N_2F$: Calcd: C, 46.14; H, 5.04; N, 10.77. Found: C, 46.00; H, 4.99; N, 10.65.

6.8.3. *cis* and *trans*-1-(3-Hydroxymethyl-1,4-dioxepan-5-yl)-5-bromouracil 4b. Reaction with **10b** (0.40 g) according to the general procedure yielded *cis/trans*-**4b** mixture (0.19 g, 53.7%). The *cis/trans*-**4b** mixture was separated by HPLC (H_2O/CH_3CN: 95/5). The retention times in analytical conditions and using the same proportions of eluant were, t_R (*cis*-**4b**): 15.33 min and t_R (*trans*-**4b**): 10.81 min.

cis-**4b**: HR LSIMS calcd for $C_{10}H_{13}O_5N_2BrNa$ $(M+Na)^+$ 342.9906, found: 342.9905. Anal. for $C_{10}H_{13}O_5N_2Br$: Calcd: C, 37.50; H, 4.09; N, 8.75. Found: C, 37.15; H, 4.08; N, 8.58.

trans-**4b**: HR LSIMS calcd for $C_{10}H_{13}O_5N_2BrNa$ $(M+Na)^+$ 342.9906, found: 342.9903. Anal. for $C_{10}H_{13}O_5N_2Br$: Calcd: C, 37.50; H, 4.09; N, 8.75. Found: C, 37.45; H, 4.08; N, 8.61.

6.8.4. *cis* and *trans*-1-(3-Hydroxymethyl-1,4-dioxepan-5-yl)thymine 4d. Reaction with **10d** (0.27 g) according to the general procedure yielded *cis/trans*-**4d** mixture (0.16 g, 60%). The *cis/trans*-**4d** mixture was separated by HPLC (H_2O/CH_3CN: 96/4). The retention times in analytical conditions and using the same proportions of eluant were, t_R (*cis*-**4d**): 27.88 min and t_R (*trans*-**4d**): 23.46 min.

cis-**4d**: HR LSIMS calcd for $C_{11}H_{16}O_5N_2Na$ $(M+Na)^+$ 279.0957, found 279.0955. Anal. for $C_{11}H_{16}O_5N_2$: Calcd: C, 51.54; H, 6.30; N, 10.94. Found: C, 51.22; H, 6.01; N, 11.02.

trans-**4d**: HR LSIMS calcd for $C_{11}H_{16}O_5N_2Na$ $(M+Na)^+$ 279.0957, found 279.0957. Anal. for $C_{11}H_{16}O_5N_2$: Calcd: C, 51.54; H, 6.30; N, 10.94. Found: C, 51.32; H, 6.31; N, 11.10.

6.8.5. *cis* And *trans*-1-(3-hydroxymethyl-1,4-dioxepan-5-yl)cytosine 4e. Reaction with **10e** (0.15 g) according to the general procedure yielded *cis/trans*-**4e** mixture (0.12 g, 85%). The *cis/trans*-**4a** mixture was separated by HPLC (H_2O/CH_3CN: 98/2). The retention times in analytical conditions and using the same proportions of eluant were t_R (*cis*-**4e**): 6.83 min and t_R (*trans*-**4e**): 4.71 min.

cis-**4e**: HR LSIMS calcd for $C_{10}H_{15}N_3O_4Na$ $(M+Na)^+$ 264.0960, found 264.0962. Anal. for $C_{10}H_{15}O_4N_3$: Calcd: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.85; H, 6.02; N, 17.30.

trans-**4e**: HR LSIMS calcd for $C_{10}H_{15}N_3O_4Na$ $(M+Na)^+$ 264.0960, found 264.0959. Anal. for $C_{10}H_{15}O_4N_3$: Calcd: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.80; H, 6.20; N, 17.61.

6.8.6. (*RS*)-7-Methoxy-2-methylene-1,4-dioxepane 9. *cis/trans* Mixture of **8a**[7] (0.85 g), water (51 mL), $Na_2CO_3 \cdot 10H_2O$ (0.40 g) and 27% aqueous NaOH (1.04 mL) was heated at 100°C in a sealed tube for 16 h. The cooled product was taken up in $CHCl_3$ (4×30 mL), dried ($MgSO_4$), filtered and concentrated. Flash chromatography (diethyl ether/hexane: 1/3) of the residue gave **9** (0.11 g, 15.5%). TLC R_f (diethyl ether/hexane 1/3): 0.31. ^1H NMR (300.13, $CDCl_3$): δ 5.00 (dd, J=4.5, J=2.4, 1H, H-7); 4.28 [d, J=11.3, 1H, C*H*(*Z*)=C]; 4.21 (d, J=0.9, 2H, H-3); 4.19 [d, J=11.3, 1H, C*H*(*E*)=C]; 3.86 (m, J=3.8 and indeterm., 1H, H-5); 3.46 (s, 3H, C*H*$_3$); 3.76 (m, 1H, H-5′); 2.04 (m, 2H, H-6). HR LSIMS calcd for $C_7H_{12}O_3$ $(M)^+$ 144.0786, found: 144.0783.

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