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Synthesis of Novel 5-Fluorouracil Derivatives with 1,4-Oxaheteroepane Moieties.

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

Departamento de Química Orgánica, Facultad de Farmacia, Campus de Cartuja s/n, 18071 Granada (Spain).
Fax: +34-958-243845; E-mail: aespinos@goliat.ugr.es

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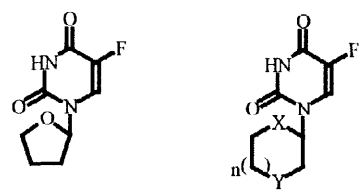
Abstract: A series of new ring-expanded isosteres (1,4-oxaheteroepanes) of Ftorafur [1-(2-tetrahydrofuranyl)-5-fluorouracil] has been synthesized. The branching of C-3 of the seven-membered cycloacetal and the electronegativity of the Y group on the 3-YCH_2 moities (Y being H, I and Cl), respectively, seem to direct their regiochemical and stereochemical outcome. The more electronegative the group Y is (and favouring accordingly the formation of an external ion pair), the more diastereoselectivity that is reached. The *in vitro* cytotoxicity versus HT-29 has been tested, showing that *cis*-**3g** was the only moderately active compound.

INTRODUCTION

Prodrugs have been described as the chemical modification of a biologically active compound to form a new compound, which upon either *in vivo* enzymatic or non-enzymatic attack will liberate the parent drug.[1-3] Novel prodrug derivatives of 5-fluorouracil (5-FU) possessing a broader spectrum of antitumour activity and fewer side effects than 5-FU have been sought diligently in a number of laboratories. Therefore, new prodrugs should be distinctly dissimilar in structure to the current families of analogues. A derivative which has received great attention is 1-(2-tetrahydrofuranyl)-5-fluorouracil (**1**, Ftorafur).[4] In addition to several clinical studies,[5] the human pharmacology of this compound has been extensively investigated,[6] and several improved methods of chemical synthesis have been developed.[7] Few derivatives have been synthesized in which the group attached to *N*-1 of 5-FU contains a six-membered ring such as the 1,4-dioxan-2-yl **2a**,[8,9] 1,4-dithian-2-yl **2b**,[8] 1,4-oxathian-2-yl **2c**,[8,9] and 1,4-oxathian-3-yl **2d**[8] fragments. Examples of 1-(1,4-diheteroepanyl)-5-fluorouracils have been few in literature with 1-(1,4-dioxepan-2-yl)-5-fluorouracil **2e** being the only analogue reported[9] as a by-product of the Lewis acid-catalyzed condensation of 1,1-diethoxy-2-(3-trimethylsilyloxypropoxy)ethane with 5-fluoro-2,4-bis(trimethylsilyloxy)-pyrimidine, but no biological data was provided.



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2a n = 1; X = Y = O
2b n = 1; X = Y = S
2c n = 1; X = O; Y = S
2d n = 1; X = S; Y = O
2e n = 2; X = Y = O

To fulfill the need for analogues in this unexplored area, we have embarked on a programme to synthesize a wide range of 5-FU derivatives linked to saturated annelated heptatomic moieties through *N*-1. This has been made possible due to the relatively ready access to the key 5- or 7-methoxy-1,4-oxaheteroepane starting materials.[10] Compounds **3a-c** bear a close structural resemblance to Ftorafur **1** and they can actually be considered as ring-expanded isosteres of the latter. In this paper we also propose a new approach to control the stereochemistry in the preparation of 5-FU derivatives during the coupling of a seven-membered cycloacetal to 5-FU. At this stage of our research we have worked with racemic mixtures or with diastereomeric mixtures of *cis* and *trans* isomers.

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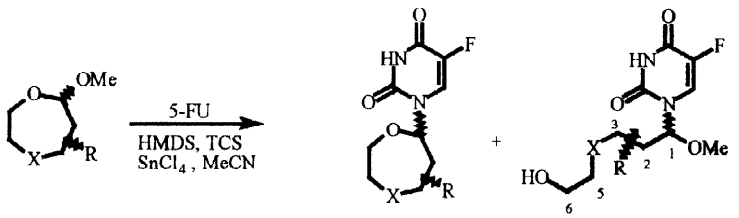
Cytotoxic activity against HT-29 colon carcinoma was also determined to test the behaviour of the products on cellular systems.

SYNTHESIS OF *N*-1-(1,4-OXAHETEROEPANYL) DERIVATIVES OF 5-FLUOROURACIL

The Table lists reaction times and yields obtained for the seven-membered cyclic 5-FU derivatives **3** and the acyclic analogues **4**.



5 3 4

Table. Seven-membered Cyclic[11] and Acyclic 5-FU Derivatives.

Entry	Comp. No.	X	R	**5** (*c/t*)	Reaction time (h)	**3** (*c/t*)	Yield[a] (%) **3**	Yield[a] (%) **4**
1	**a**	O	H	-	0.75	-	-	31[12]
2	**a**	O	H	-	23.5	-	8	22
3	**b**	S	H	-	24	-	17	29
4	**c**	NTs	H	-	24	-	20	50
5	**d**	O	6-Me	1/3.3	7.5	1/1.9	15	34[b]
6	**e**	O	7-Me	4/1	7.5	1/1	23	16[c]
7	**f**	O	3-Me	1/6.1	24	1/1	19[d]	-
8	**g**	O	3-CH_2Cl	1/5.3	1	-	-	-
9	**g**	O	3-CH_2Cl	1/5.3	18	5.5/1	39[e]	-
10	**h**	O	3-CH_2I	1/3.4	24	4.4/1	27[f]	-

[a] All the yields reported refer to pure cyclic analogues **3** and to acyclic ones **4** after chromatographic purification. [b]2-Me. [c]3-Me. Both racemic diastereoisomers were separated by flash chromatography (1'*R**,3'*R**: 7%; 1'*R**,3'*S**: 9%). [d]In addition to **3f**, 1,3-bis(3-methyl-1,4-dioxepan-5-yl)-5-fluorouracil **8** (8%) was obtained. [e]Both isomers were separated by flash chromatography (33% of *cis*-**3g** and 6% of *trans*-**3g**). [f]Both isomers were separated by flash chromatography (22% of *cis*-**3h** and 5% of *trans*-**3h**).

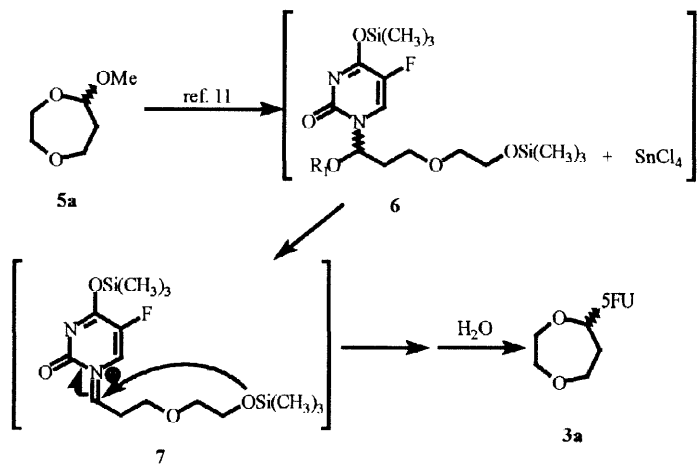
The formation of acyclonucleoside-like compounds **4**[12] and other analogues in which their 3-hydroxyethoxypropyl moiety was modified[13] has been recently explained by us. **5** are very reactive difunctionalized molecules that can rearrange to 1,3-dioxolane rings,[14] can be opened to give acyclonucleosides,[12] and, under further elimination (of the ethylene glycol moiety), can give hemiaminals of acrolein.[12] All this could be the reason for the unexpectedly low yields of the title reaction. Starting from the methoxy-1,4-oxaheteroepanes **5**, and when reaction

time is kept short (*i.e.*, 1 h or less), the acyclic *O,N*-acetals **4** are the only products obtained [*eg.*, from 5-methoxy-1,4-dioxepane **5a** the reaction yields **4a** in 31% yield, when the reaction time is 0.75 h (Table, entry 1)].[12] When reaction time is extended from 0.75 to *ca.* 24 h , **3a-e** are obtained in addition to **4a-e** (Table, entries 2-6).

DISCUSSION

According to the experimental details, it seems logical to assume that cyclic analogues **3a-e** may arise from the corresponding acyclic ones **4a-e** by an intramolecular cyclization.[15] This is supported by the two following facts: a) the same process carried out under equal molar conditions but with increased reaction time (0.75 h → 23.5 h, Table, entries 1 and 2) gives rise to the cyclic compound **3a** and the acyclic one **4a**; and b) the sum of the yields of **3a** and **4a** (Table, entry 2), is the same as that of **4a** when the reaction time is 0.75 h[12] (Table, entry 1). This could be rationalized through the intermediates **6** and **7** (Scheme 1). The straightforward cyclization step is favoured by means of the *gauche effect*[16] that leads the trimethylsilyloxy fragment to come close to the electrophilic carbon of the iminium ion **7**.

We have previously reported that the conformational analysis carried out in an isopropoxy analogue of **4a** showed that the $N_{1'}(sp^2)$-C_1-C_2-C_3 moiety tended to fold in a *gauche* conformation.[12] Hager and Liotta[17] have rationalized the selectivity observed in the cyclization process to yield exclusively the β-anomer of AZT from a non-carbohydrate precursor by using such a *gauche effect*. We conclude that a substantial amount of, or maybe all, the cyclic derivatives **3a-e** are formed *via* the corresponding acyclic analogues **4a-e**.



Scheme 1

Since the lipophilicity of a molecule is increased by the introduction of a sulfur-containing group or tosylation of the amino function, compounds **3b,c** and **4b,c** (Table, entries 3 and 4) were also synthesized.

At this point it was necessary to raise several aspects of the synthesis and stereochemical outcome of the seven-membered *O,N*-acetal analogues **3**: (a) compounds of type **3** have to be obtained in a one pot/step reaction without the necessity of carrying out chromatographic separations from the acyclic analogues of type **4**;[18] and (b) the level of diastereoselectivity in the synthesis of such cyclic *O,N*-acetal analogues has to be improved. The introduction of a methyl group in the cyclic analogues **3** on positions 7-, 6- and 3- was next investigated. After aqueous workup and chromatographic separation, a first moving spot was isolated and identified as the *cis/trans* mixture of **3d** and **3e**. No stereocontrol was achieved when the reaction was carried out on **5e** because the *cis/trans* ratio of **3e** was 1:1,

based on the hemiaminal hydrogen signals in the ^{1}H NMR spectra. The minor fraction was the acyclic *O,N*-acetal **4e** which showed two sets of signals in both ^{1}H NMR and ^{13}C NMR spectra, revealing it to be a mixture of diastereomers. Rigorous analysis of the minor fraction by TLC revealed two close moving spots which were separated by gradient elution ($CHCl_3$/MeOH: 100/2 → 100/4) and identified as (1'*R**,3'*R**)-**4e** (7%) and (1'*R**,3'*S**)-**4e** (9%) based on comparison of their ^{1}H NMR and ^{13}C NMR shifts to similar compounds.[12] On passing from **3e** to **3d** only a very modest selectivity was attained (**3d** *cis/trans* ≈ 1/1.9, favouring the *trans* isomer instead of the *cis* one. Again, no stereocontrol was achieved when the reaction was carried out on **5f** (*cis*-**3f**/*trans*-**3f** was 1/1). It seems that the branching at C-3 of **5** and a long reaction time (*ca.*, 24 h) are the necessary conditions sufficient for obtaining the 5-FU 1,4-dioxepane derivatives **3**,[18] as the *only* products, when tin (IV) chloride is used as Lewis acid.

TLC analysis of the crude coupling product between **3f** and 5-FU indicated the presence of a small amount of a less polar material which was N^1,N^3-di-substituted **8**, but there was no evidence of any isomeric N^3-substituted derivative.

No NH group can be seen from the ^{1}H NMR spectrum ($CDCl_3$). After the doublet at δ 7.50 (J = 5.6 Hz) due to H-6 of 5-FU, three sets of signals can be seen centred at δ 6.52, 6.49 and 6.05: a) the two triplet-like signals (J = 3.7 Hz) at δ 6.52 and 6.49 correspond to hemiaminal protons in which the influence of a F atom is not detected. This fact and their presence at such abnormal lowfield (due to the proximity of a strong electron-withdrawing group like the imide moiety of the 5-FU fragment) led us to propose the linking between the 3-methyl-1,4-dioxepan-5-yl fragment and the 5-FU through N^3; b) two double doublet of doublets, centred at δ 6.05 (with one of their coupling constants being ≈ 1.4 Hz, and, hence, showing the proximity of the F atom) clearly showed the linking between the 1,4-dioxepane fragment and 5-FU through N^1. Finally, four doublets close to δ 1.10 indicated the presence of four different methyl groups corresponding to two diastereomers.

In order to acquire information other than empirical formula determination from a high resolution liquid secondary ion mass spectrum (HR LSIMS, calculated for $C_{16}H_{23}O_6N_2FNa$ 381.1437, found 381.1438), it is most important that some insight be gained into the fragmentation patterns (Figure).

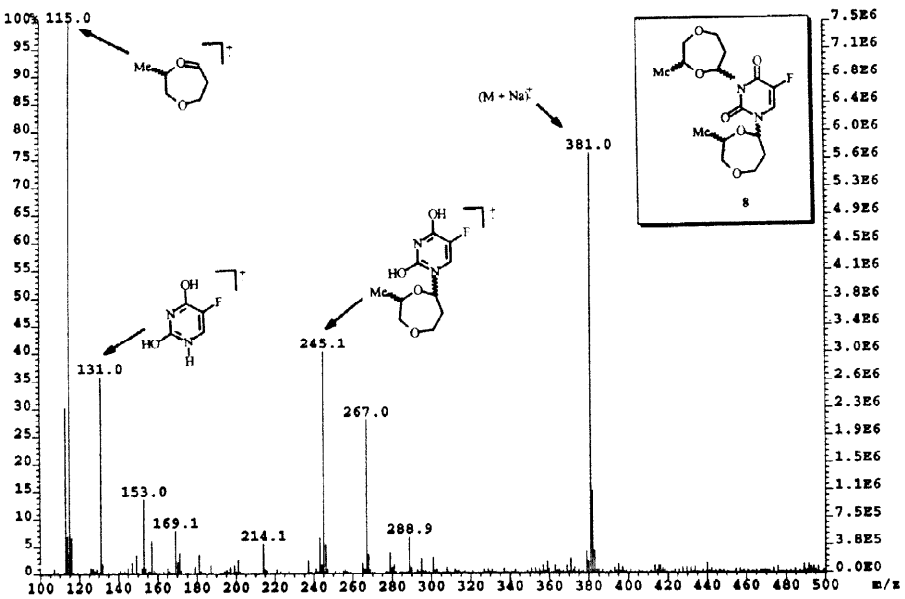


Figure. LSIMS of **8**.

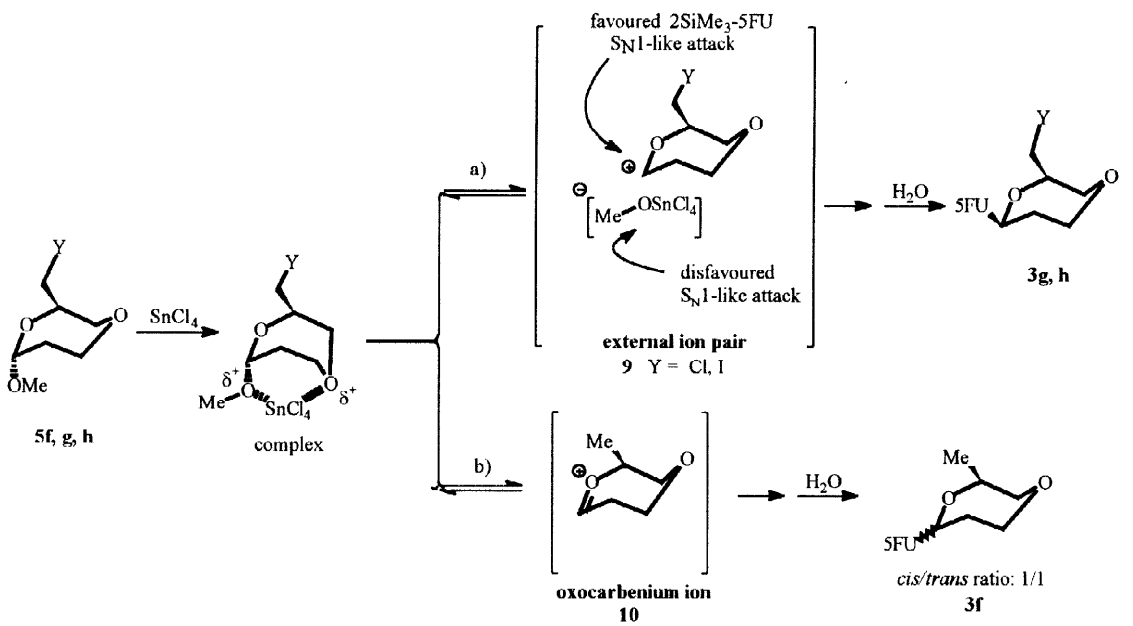
The *m/z* 381 is consistent with the N^1,N^3-disubstituted **8** ion [(M + Na)$^+$]. As expected, a major fragment ion at *m/z* 245 can be assigned for the ion resulting from splitting off one 3-methyl-1,4-dioxepan-5-yl radical from the

molecular ion. The parent peak at *m/z* 115 is compatible with the 3-methyl-1,4-dioxepan-5-yl ion and the peak at *m/z* 131 can be assigned to $(5\text{-FU} + H)^+$.

The possibility of isolating the N^1,N^3-disubstituted-5-FU derivative is surprising because after workup and chromatography N^1,N^3-disubstituted 2-tetrahydrofuranyl derivatives of 5-FU undergo a facile cleavage to the corresponding N^1-substituted derivative.[7]

Most 5-FU derivatives, including Ftorafur, are simply prodrugs of 5-FU and their stereochemistry is relevant only as far as it concerns the liberation of the active metabolite itself inside the cell. Nevertheless, from a chemical point of view it was necessary to improve the level of diastereoselectivity of the seven-membered cyclic *O,N*-acetals. The 5-FU acyclonucleoside formation exhibits a remarkable Lewis acid dependency and implies the active participation of tin(IV) chloride in the reaction transition state.[12] When the reaction time was short (*i.e.*, 1 h) no transformation was observed (Table, entry 8), but when the reaction time was extended to 18 h (Table, entry 9), **3g** was the *only* product formed in the reaction and with a selectivity of 5.5/1 (*cis/trans* ratio), starting from a 1/5.3 *cis/trans* mixture of **5g**.[19] One more positive example [*i.e.*, R = CH_2I, **3h** (Table, entry 10)] was tried but with lower diastereoselectivity [(4.4/1 (*cis/trans* ratio)].

Thus, it is obvious that the mechanism of the formation of **3g** and **3h** should follow a different pathway from that of the intramolecular cyclization. When the acetal compound has another coordinating functionality X (see Table), certain Lewis acids can form a chelated complex. In the reaction of such a complex, Lewis acids play two roles: one is as activator for the acetal group, and the other, is steric hindrance in the substrate. The latter could produce a diastereoselective nucleophilic attack on the cyclic system by the doubly silylated 5-FU molecule. For this purpose, effective chelation is essential. For the chelating role of Lewis acids, $SnCl_4$ is one of the most utilized. The complex must be set out between the ether O, the sterically less hindered exocyclic acetal oxygen atom and the tin (IV) chloride for the seven-membered cycle to remain just as it is. The *external ion pair*[20] proposal is helpful in accounting for the results cited above, which can be rationalized as shown in Scheme 2 (pathway a).



Scheme 2

If the second step in the substitution takes place from the ion pair (which results from the leaving of the methoxy group) instead of from the free ion, the departing group will still be sufficiently closely associated with the

carbocation **9** to affect the attack of the doubly silylated 5-FU through the two sides.

The $SnCl_4OMe^{\ominus}$ encumbers the bottom face sufficiently to direct approach of pyrimidine base from the top (through the side where the YCH_2 group is, because in **5g** and **5h** the *trans* isomer always predominates) meaning that formation of *cis*-**3g** and -**3h** occurs. In short, nucleophilic attack takes place from the back-side of the departing methoxy group.

In the formation of **3f** the endocyclic acetal oxygen atom feeds one of its lone pairs of electrons into the carbenium ion, giving an oxocarbenium (Scheme 2, pathway b), in which the positive charge is more delocalized and, hence, the existence of the corresponding ion pair is less probable, making the attack from either face of the oxocarbenium ion **10** with equal facility to afford an 1/1 *cis/trans* ratio. The use of trimethylsilyl trifluoromethanesulfonate (TMSOTf), whose role is solely to generate an oxonium ion, results in lower diastereoselectivity (*c/t*: 3/1) instead of tin(IV) chloride when used on **5g**. The diastereoselectivity of the nucleophilic attack on C-5 of **5g** is shown to be related to the bulkiness of the counterion ($CF_3COO^{\ominus} < SnCl_4OMe^{\ominus}$) involved in the *external ion pair*. The effect of the substituent at position 3 on the 1,4-oxaheteroepane ring seems to determine the whole regiospecificity and diastereoselectivity.[21] We have identified a stereochemical continuum arising from the intermediacy of two distinct species (external ion pair or oxocarbenium ion) each with its own stereochemical profile. The existence of the *external ion pair*[20] is more likely as long as the electronegativity of the substituent Y increases, as is demonstrated by the diastereoselectivity found in **3f**, **3g** and **3h**.

To the best of our knowledge, this is a new approach to the control of the regiochemical and stereochemical outcome of seven-membered cyclic *O,N*-acetals.[22]

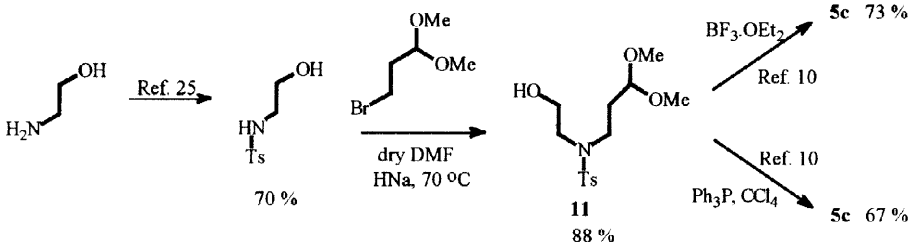
STRUCTURAL CHARACTERISTICS OF *cis/trans*-1-{(3-HALOMETHYL)-1,4-DIOXEPAN-5-YL}-5-FLUOROURACILS

cis And *trans* isomers of **3g** were separated by flash chromatography on silica gel. The assignment of the *cis-trans* stereochemistry of **3h** was based on NOE experiments. When H-5 of *cis*-**3h** [δ ($CDCl_3$) 6.06] was irradiated, enhancement of the H-3 peak of **3h** [δ ($CDCl_3$) 3.90] was observed, while no enhancement of the H-3 peak of *trans*-**3h** [δ (DMSO-d_6) 4.33] was observed on irradiating the H-5 peak of *trans*-**3h** [δ (DMSO-d_6) 6.02]. The stereochemistry of **3g** was assigned based on the comparison of the ^{1}H-NMR patterns of **3h**. Additionally, the chemical shifts of the hemiaminal proton (H-5) of *cis*-**3g** appeared upfield [δ ($CDCl_3$) 6.06] relative to that of the hemiaminal one of *trans*-**3g** [δ ($CDCl_3$) 6.14]. Furthermore, the H-3 of *cis*-**3g** appeared upfield [δ ($CDCl_3$) 4.03] from that observed for its *trans* isomer [δ ($CDCl_3$) 4.39] because of the deshielding effect by the 5-FU moiety.[23] The signal for H-5 is a doublet of doublets, coupled to H-6. The coupling constants between H-5 and H-6 (J = 3.5 and 9.4 Hz) were different in *cis*-**3g**, whereas those in *trans*-**3g** showed far more different values (J = 2.6 and 10.8 Hz).

SYNTHESIS OF INTERMEDIATES

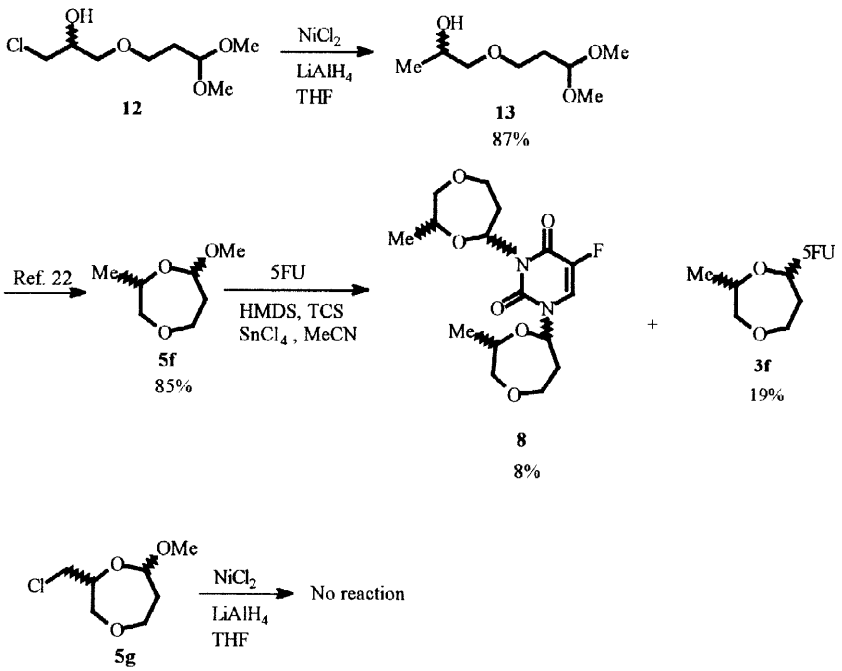
The cycloacetals **5a**,[24] and **5b**[12] have been previously reported by us. Compound **5c** was prepared via Scheme 3. Reaction of 2-aminoethanol and *p*-toluenesulfonyl chloride in refluxing toluene afforded the N-*p*-toluenesulfonyl-2-aminoethanol[25] (70%) whose anion, generated with sodium hydride in dimethylformamide, was alkylated with 3-bromopropanal dimethyl acetal to give **11** (88%). Finally, the desired (*RS*)-7-methoxy-4-*p*-toluenesulfonyl-1,4-oxazepane **5c** was obtained under either an acid-catalyzed intramolecular cyclization (73%) or by the neutral condi-

tions mediated by the triphenylphosphine/carbon tetrachloride system (67%) on the latter hydroxyacetal in both cases.[10]



Scheme 3

The requisite acetals **5d,e,f** were previously reported by us,[23] but **5f** was prepared via the alternative route shown in Scheme 4: reduction of the chloroacetal **12**[13] according to the method of Ashby and Lin[26] yielded the acetal (*RS*)-**13** (87%) and subsequent cyclization produced **5f**. Finally, its coupling reaction with 5-FU gave **3f** and **8**.



Scheme 4

It is worth emphasizing that the same reduction carried out on the cyclic acetal **5g** failed and the starting material was recovered unchanged. **5f** was obtained from (*RS*)-**12**[13] by a $BF_3.OEt_2$-mediated cyclization (49%), under conditions previously reported by us.[10] **5h** was obtained by the coupling of the following two reactions: namely, substitution of the chlorine atom of **12** with NaI in acetone (91%) and, subsequent cyclization (56%) as carried out to obtain **5g**. In this case the reaction of interchange of chlorine for iodine on the cyclic acetal **5g** failed.

IN VITRO CYTOTOXICITY VERSUS HT-29

Because **1** lacks a 5'-hydroxy group, it cannot be directly phosphorylated by pyrimidine kinases, and so the conversion to nucleotides that is necessary for cytotoxicity must be effected *via* alternative pahways. There is now good evidence that the activity of **1** against tumour cells in culture depends on its cleavage to 5-FU by uridine

phosphorylase, an enzyme which is not ubiquitously present as is thymidine phosphorylase but is distributed unequally among various tissues and organs.[27] Based on the approach of Owen *et al.*[28] we thought that the presence of a chlorine atom at the methylene group on position 3 could make the hemiaminal linkage of the prodrug more labile making it possible to provide a more rapid source of 5-FU at locations rich in uridine phosphorylase, if **3g-h** were good substrates for the enzyme.

The cytotoxic activity was assessed with the crystal violet method.[29] *cis*-**3g** exhibited moderate cytotoxicity against HT-29 cells in culture (IC_{50} = 30 μM). It is 6.5-fold less active than 5-FU (4.5 μM, with the same protocol), the rest of the series showing IC_{50} values greater than 100 μM. Probably compounds **3** are relatively poor substrates for the enzyme.

CONCLUSION

The chemistry demonstrated above offers access to *O,N*-acetal analogues with a 1,4-oxahetero seven-membered fragment. Furthermore, the level of diastereoselectivity in the preparation of **3g**, although modest, suggests a potentially general approach for controlling the stereochemisty of this unexplored class of reactions involving the preparation of 5-FU seven-membered derivatives. This approach should also be applicable for the preparation of several analogues of **3g** and **3h**.The present method is rapid and economical, and is clearly adaptable to the synthesis of other seven-membered pyrimidine nucleoside analogues for biological evaluation of their antitumour and/or antiviral properties.

EXPERIMENTAL

For general procedures, see ref. 12. Analytical samples all gave single TLC spots. The presence of H_2O as indicated by elemental analysis was verified by ^1H NMR. Chemical shifts (δ) quoted in the case of multiplets were measured from the approximate centre. Monodimensional NOE difference experiments on *cis*- and *trans*-**3h** were performed by irradiation for 4 s in series of 8 scans with alternating on-resonance and off-resonance. The irradiating power was set to achieve selectivity. DEPT experiments were carried out for the identification of the CH_3, CH_2, CH and C carbons. The following parameters were used for such experiments: PW (135°), 9.0 μs; recycle time 1 s; $1/2J(CH)$ = 4 ms; 65,536 data points acquired and transformed from 1,024 scans; spectral width, 15 kHz; and line broadening, 1.3 Hz.

Final Products

Reaction between Methoxy-1,4-oxaheteroepane 5 and 5-Fluorouracil. General Procedure: To a suspension of methoxy-1,4-oxaheteroepane **5** (1 mmol), 5-fluorouracil (1 mmol), which contains trimethylchlorosilane (TCS, 0.8 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 0.8 mmol) in dry acetonitrile (10 ml/mmol of **5**) was added a solution of anhydrous tin(IV) chloride (1.25 mmol) in dry acetonitrile (0.4 ml/mmol of the Lewis acid) dropwise with stirring under argon at rt. After 0.75-24 h of stirring the reaction was quenched by the addition of a concentrated aqueous solution of Na_2CO_3. The solvent was removed with a rotary evaporator. The sticky residue was dissolved in MeOH, and silica gel was added. The solvent was removed with a rotary evaporator, and the residue was applied to the top of a flash chromatography column packed with $CHCl_3$/MeOH (100/2). Elution with mixtures of $CHCl_3$/MeOH by gradient elution (100/2 → 100/4) and concentration with a rotary evaporator gave

the target molecules. The numbering system of 1,4-oxaheteroepane rings is shown in ref. 11.

(*RS*)-1-(1,4-Dioxepan-5-yl)-5-fluorouracil 3a and (*RS*)-1-{[3-(2-hydroxyethoxy)-1-methoxy]propyl}-5-fluorouracil 4a:[12] Reaction of 5-methoxy-1,4-dioxepane **5a** (1.44 g, 10.9 mmol) with 5-fluorouracil (1.55 g, 11.99 mmol) for 23.5 h according to the general procedure yielded **3a** (0.200 g, 8%) as a colourless thick oil. R_f (100/4, $CHCl_3$/MeOH): 0.25. ^{13}C NMR (100.03, $CDCl_3$) δ 156.83 (d, *J* = 26.46, C-4'), 148.53 (C-2'), 140.71 (d, *J* = 237.97, C-5'), 124.10 (d, *J* = 33.71, C-6'), 84.68 (C-5), 72.31, 70.47, 66.64 (C-2, C-3, C-7), 36.88 (C-6). ^1H NMR (400.13, $CDCl_3$) δ 9.42 (s, 1H, N*H*), 7.52 (d, *J* = 6, 1H, H-6'), 5.96 (dd, *J* = 9.6 and 3.6, 1H, H-5), 4.04 (m, 2H, H-3), 3.94 (ddd, *J* = 12.8, 7 and 4.8, 1H, H-7), 3.81 (m, 4H, H-2, H-3, H-7), 2.34 (dddd, *J* = 14.8, 6.5, 4.3 and 4.3, 1H, H-6), 2.13 (dddd, J = 14.6, 9.4, 7, 4.8, 1H, H-6). IR (cm^{-1}, neat): 3494 (w, NH), 3080 (m, aromatics), 2956 (s) and 2869 (s, aliphatic C-H groups), 1712 (s, C=O), 1665 (s, aromatic ring multiple bond), 1264 (s) and 1141 (s, C-O-C). HR LSIMS calcd. for $C_9H_{12}O_4N_2F$ (M^+ + 1) 231.0781, found: 231.0782. Anal. for $C_9H_{11}O_4N_2F{\cdot}H_2O$: Calc.: C, 43.55; H, 5.28; N, 11.28. Found: C, 43.82; H, 4.97; N, 11.20.

Eluted second was **5a** as an amorphous white powder (0.610 g, 22%).[12]

(*RS*)-1-(1,4-Oxathiepan-7-yl)-5-fluorouracil 3b and (*RS*)-1-{[3-(2-hydroxyethylthio)-1-methoxy]-propyl}-5-fluorouracil 5b: Reaction of 7-methoxy-1,4-oxathiepane **5b** (0.900 g, 6.07 mmol) with 5-fluorouracil (0.870 g, 6.67 mmol) for 24 h according to the general procedure yielded **3b** (0.260 g, 17%) as a colourless thick oil. R_f (100/2, $CHCl_3$/MeOH): 0.30. ^{13}C NMR (100.03, $CDCl_3$) δ 156.87 (d, *J* = 26.36, C-4'), 148.55 (d, *J* = 237.96, C-2'), 140.76 (d, *J* = 33.60, C-5'), 124.27 (d, *J* = 33.60, C-6'), 85.89 (C-7), 73.16 (C-2), 36.62 and 36.46 (C-3 and C-5). ^1H NMR (400.13, $CDCl_3$) δ 9.38 (s, 1H, N*H*), 7.51 (d, *J* = 5.9, 1H, H-6'), 6.13 (dd, *J* = 10.0 and 2.7, 1H, H-7), 4.24 (ddd, J = 12.0, 4.4 and 4.4, 1H, H-2), 3.88 (ddd, *J* = 12.3, 9.1 and 3.4, 1H, H-2), 2.81 (m, 4H, H-3, H-5), 2.33 (m, 1H, H-6), 2.05 (m, 1H, H-6). IR (cm^{-1}, neat): HR LSIMS calcd. for $C_9H_{12}O_3SN_2F$ (M^+ + 1) 247.0553, found: 247.0554. Anal. for $C_9H_{11}O_3SN_2F{\cdot}H_2O$: Calc.: C, 40.90; H, 4.96; N, 10.60; S, 12.13. Found: C, 40.93; H, 4.86; N, 10.79; S, 12.30.

Eluted second was **5b** as a yellowish thick oil (0.490 g, 29%). R_f (CH_2Cl_2/MeOH, 100/5): 0.22. ^{13}C NMR (100.03, $CDCl_3$) δ 157.05 (d, *J* = 26.41, C-4'), 149.99 (C-2'), 141.37 (d, *J* = 238.27, C-5'), 122.73 (d, *J* = 32.81, C-6'), 86.48 (C-1), 60.82 (C-6), 57.13 (O*Me*), 35.13, 34.78 (C-3, C-5), 26.88 (C-2). ^1H NMR (400.13, $CDCl_3$) δ 10.01 (s, 1H, N*H*), 7.37 (d, *J* = 5.6, 1H, H-6'), 5.75 (dt, *J* = 5.2, 1.7, 1H, H-1), 3.74 (t, *J* = 5.9, 2H, H-2), 3.36 (s, 3H, O*Me*), 2.68 (m, 5H, H-3, H-5, O*H*), 1.98 (m, 2H, H-2). IR (cm^{-1}, neat): 3452 (s, OH), 3172 (s, NH), 3042 (m, aromatics), 2978 (s, aliphatic C-H groups), 1711 (s, C=O), 1696 (s, aromatic ring multiple bond), 1240 (s) and 1180 (s, C-O-C). MS (CI): *m/z* (%) 288 (3, M^+ - 18), 246 (1), 177 (3), 159 (3), 117 (100), 89 (23). HR LSIMS calcd. for $C_{10}H_{15}O_4SN_2F$ (M^+ + 1) 279.0815, found: 279.0816. Anal. for $C_{10}H_{15}O_4SN_2F$: Calc.: C, 43.16; H, 5.43, N, 10.07. Found: C, 42.99; H, 5.20; N, 10.21.

(*RS*)-1-[4-Toluenesulfonyl-(1,4-oxazepan-7-yl)]-5-fluorouracil 3c and (*RS*)-1-{[N-2-hydroxyethyl)toluenesulfonamido-1-methoxy]propyl}-5-fluorouracil 4c: Reaction of 7-methoxy-4-toluenesulfonyl-1,4-oxazepane **5c** (0.509 g, 1.75 mmol) with 5-fluorouracil (0.25 g, 1.92 mmol) for 24 h according to the general procedure yielded **3c** (0.130 g, 20%) as an amorphous white solid. Mp 94-96 °C. R_f (100/4, $CHCl_3$/MeOH): 0.27. ^{13}C NMR (75.78, $CDCl_3$) δ 148.17 (C-4'), 144.02 (C-2'), 135.75 (C-5'), 130.07 ($C\text{-}2_{Tos}$ and $C\text{-}6_{Tos}$), 127.15 ($C\text{-}3_{Tos}$ and $C\text{-}5_{Tos}$), 123.96 (d, *J* = 33.86, C-6'), 84.96 (C-7), 69.49 (C-2), 50.93 (C-3), 44.96 (C-

5), 35.09 (C-6), 21.61 (*Me*). ^{1}H NMR (300.13, $CDCl_3$) δ 8.95 (s, 1H, N*H*), 7.67 (d, *J* = 8.5, 2H, H-2_{Tos} and H-6_{Tos}), 7.36 (d, *J* = 6, 1H, H-6'), 7.35 (d, *J* = 8.5, 2H, H-3_{Tos} and H-5_{Tos}), 5.81 (ddd, *J* = 9.8, 3.7 and 1.4, 1H, H-7), 4.11 (ddd, *J* = 12.9, 3.9 and 3.9, 1H, H-2), 3.81 (ddd, *J* = 12.7, 9.3 and 3.3, 1H, H-2), 3.54 (ddd, *J* = 14.1, 3.6 and 3.6, 1H, H-3), 3.39 (m, 3H, H-3 and H-5), 2.43 (s, 3H, *Me*), 2.30 (m, 1H, H-6), 1.97 (dddd, *J* = 14.5, 9.7, 7 and 4.9, 1H, H-6). IR (cm^{-1}, KBr): 3208 (w, NH), 3079 (m) and 3031 (m, aromatics), 2964 (m), 2930 (m) and 2889 (s, aliphatic C-H groups), 1711 (s, C=O), 1667 (s, aromatic ring multiple bond), 1259 (s) and 1162 (s, C-O-C). HR LSIMS calcd. for $C_{16}H_{19}O_5SN_3F$ (M^+ + 1) 384.1029, found: 384.1026. Anal. for $C_{16}H_{18}O_5SN_3F{\cdot}H_2O$: Calc.: C, 47.88; H, 5.02; N, 10.47; S, 7.99. Found: C, 47.92; H, 4.86; N, 10.31; S, 7.85.

Eluted second was **4c** as a colourless thick oil (0.370 g, 50%). R_f (100/4, $CHCl_3$/MeOH): 0.16. ^{13}C NMR (75.78, DMSO-d_6) δ 157.04 (d, *J* = 25.84, C-4'), 149.59 (C-2'), 143.07 (C-$\frac{1}{Tos}$), 140.54 (d, *J* = 231.24, C-5'), 129.74 (C-2_{Tos} and C-6_{Tos}), 126.81 (C-3_{Tos} and C-5_{Tos}), 124.02 (d, *J* = 33.25, C-6'), 83.83 (C-1), 59.62 (C-6), 55.73 (O*Me*), 50.18, 44.65 (C-3, C-5), 33.09 (C-2), 20.85 (*Me*). ^{1}H NMR (300.13, DMSO-d_6) δ 11.82 (d, *J* = 5.0, 1H, N*H*), 7.90 (d, *J* = 6.8, 1H, H-6'), 7.66 (d, *J* = 8.2, 2H, H-2_{Tos} and H-6_{Tos}), 7.40 (d, *J* = 8.2, 2H, H-3_{Tos} and H-5_{Tos}), 5.52 (ddd, *J* = 7.6, 5.4 and 1.5, 1H, H-1), 3.45 (t, *J* = 6.4, 2H, H-6), 3.20 (s, 3H, O*Me*), 3.12 (m, 4H, H-3 and H-5), 2.38 (s, 3H, *Me*), 2.02 (m, 1H, H-2), 1.91 (m, 1H, H-2). Anal. for $C_{17}H_{22}O_6SN_3F$: Calc.: C, 49.15; H, 5.34; N, 10.11; S, 7.72. Found: C, 49.35; H, 5.09; N, 10.23; S, 7.45.

***cis/trans*-1-(6-Methyl-1,4-dioxepan-5-yl)-5-fluorouracil 3d and 1-[3-(2-hydroxyethoxy)-2-methyl-1-methoxypropyl-5-fluorouracil 4d (mixture of diastereomers):** Reaction of 5-methoxy-6-methyl-1,4-dioxepane **5d**[23] (0.200 g, 1.37 mmol) as a 1/3.3 *cis/trans* mixture (obtained by the $BF_3.OEt_2$ cyclization on the corresponding hydroxyacetal, retention time, glc: 4.61 and 4.94 min; programme: isotherm 75 °C/2 min, ramp 25 °C/min, isotherm 200 °C/2 min) with 5-fluorouracil (0.195 g, 1.5 mmol) for 7.5 h according to the general procedure yielded **3d** (0.050 g, 15%) as a colourless thick oil. R_f ($CHCl_3$/MeOH, 100/4): 0.34. ^{1}H NMR reveals to be a *cis/trans* mixture (1/1.9 ratio). *cis*-**3d**: ^{13}C NMR (75.78, $CDCl_3$) δ (selected data) 89.30 (C-5), 74.89, 73.32, 71.82 (C-2, C-3, C-7), 41.36 (C-6), 14.68 (*Me*). ^{1}H NMR (300.13, $CDCl_3$) δ 9.80 (s, 1H, N*H*), 7.43 (d, *J* = 5.9, 1H, H-6'), 5.68 (dd, *J* = 9.5, 1.6, 1H, H-5), 3.7 (m, 6H, H-2, H-3, H-7), 2.26 (m, 1H, H-6), 0.93 (d, *J* = 7.0, 3H, *Me*). *trans*-**3d**: ^{13}C NMR (75.78, $CDCl_3$) δ (selected data) 87.67 (C-5), 74.13, 72.05, 70.93 (C-2, C-3, C-7), 38.03 (C-6), 10.81 (*Me*). ^{1}H NMR (300.13, $CDCl_3$) δ 9.80 (s, 1H, N*H*), 7.58 (d, *J* = 6.3, 1H, H-6'), 5.85 (dd, *J* = 3.8, 1.3, 1H, H-5), 3.7 (m, 6H, H-2, H-3, H-7), 2.66 (m, 1H, H-6), 0.79 (d, *J* = 7.1, 3H, *Me*). IR *cis/trans* mixture (cm^{-1}, KBr): 3459 (w, NH), 3199 (m, aromatics), 2965 (s, aliphatic C-H groups), 1723 (s, C=O), 1696 (s, aromatic ring multiple bond), 1249 (s) and 1146 (s, C-O-C). MS (CI) *cis/trans* mixture : *m/z* (%) 245 (3, M^+ + 1), 131 (18), 115 (51), 85 (75), 71 (16), 57 (16), 49 (100), 43 (94). HR LSIMS *cis/trans* mixture calcd. for $C_{10}H_{14}O_4N_2F$ (M^+ + 1) 245.0938, found: 245.0928. Anal. for $C_{10}H_{13}O_4N_2F$ *cis/trans* mixture: Calc.: C, 49.16; H, 5.37 N, 11.47. Found: C, 49.26; H, 5.20; N, 11.63.

Eluted second was **4d** as a thick oil (0.130 g, 34%) as a mixture of diastereomers. R_f ($CHCl_3$/MeOH, 100/4): 0.18. ^{13}C NMR (75.78, $CDCl_3$) δ 157.08 (d, *J* = 26.56, C-4' of one diastereomer), 156.97 (d, *J* = 26.64, C-4' of the other one), 150.58 (C-2' of one diastereomer), 150.30 (C-2' of the other one), 141.22 (d, *J* = 238.48, C-5' of one diastereomer), 141.22 (d, *J* = 238.48, C-5' of the other one), 123.48 (d, *J* = 32.90, C-6' of one diastereomer), 123.55 (d, *J* = 33.05, C-6' of the other one), 89.31 (C-1 of one diastereomer), 88.60 (C-1 of the other one), 72.77, 72.11, (C-3, C-5 of one diastereomer), 72.65, 71.68, (C-3, C-5 of the other one), 61.61 (C-6 of one diasteomer), 61.41 (C-6 of the other one), 57.08 (O*Me*), 57.19 (O*Me*), 38.66 (C-2), 38.95 (C-2), 13.1 (*Me*), 12.35 (*Me*). ^{1}H NMR of one diastereomer (300.13, $CDCl_3$) δ 10.05 (s, 1H, N*H*), 7.32 (d, *J* = 5.8, 1H, H-6'), 5.52 (dd, *J* = 8.2, 1.9,

1H, H-1), 3.50 (m, 6H, H-3, H-5, H-6), 3.34 (s, 3H, O*Me*), 2.07 (m, 1H, H-2), 1.06 (d, J = 6.9, 3H, *Me*). ^{1}H NMR of the other one (300.13, $CDCl_3$) δ 9.80 (s, 1H, N*H*), 7.35 (d, J = 5.9, 1H, H-6'), 5.58 (dd, J = 7.2, 1.9, 1H, H-1), 3.50 (m, 6H, H-3, H-5, H-6), 3.34 (s, 3H, O*Me*), 2.07 (m, 1H, H-2), 0.94 (d, J = 7.1, 3H, *Me*). IR *cis/trans* mixture (cm^{-1}, neat): 3438 (w, NH), 3076(s, aromatics), 2930 (s, aliphatic C-H groups), 1709 (s, C=O), 1668 (s, aromatic ring multiple bond), 1244 (s) and 1123 (s, C-O-C). MS (CI) mixture of diastereomers : *m/z* (%) 277 (16, M^+ + 1), 130 (14), 115 (100), 85 (53), 71 (18), 45 (57). Anal. for $C_{11}H_{17}O_5N_2F{\cdot}2/3H_2O$: Calc.: C, 45.83; H, 6.18; N, 9.72. Found: C, 45.95; H, 6.12; N, 9.41.

***cis/trans*-1-(7-Methyl-1,4-dioxepan-5-yl)-5-fluorouracil 3e, (1'*R**,3'*R**) and (1'*R**,3'*R**) 1-{[3-(2-hydroxyethoxy)-1-methoxy]butyl}-5-fluorouracil 4e:** Reaction of 5-methoxy-7-methyl-1,4-dioxepane **5e**[23] (0.370 g, 2.53 mmol) as a 4/1 *cis/trans* mixture (obtained by the $BF_3.Et_2O$ cyclization on the corresponding hydroxyacetal, retention time, glc: 6.72 and 8.37 min; programme: isotherm 75 °C/10 min, ramp 25 °C/min, isotherm 200 °C/2 min) with 5-fluorouracil (0.363 g, 2.79 mmol) for 7.5 h according to the general procedure yielded **3e** (0.140 g, 23%) as an amorphous white solid. Mp 103-105°C. R_f ($CHCl_3$/MeOH, 100/4): 0.36.[1] H NMR reveals to be a *cis/trans* mixture (1/1 ratio). *cis*-**3e**: ^{13}C NMR (75.78, $CDCl_3$) δ 156.9 (d, J = 26.56, C-4'), 148.65 (C-2'), 140.71 (d, J = 238.11, C-5'), 124.22 (d, J = 33.81, C-6'), 83.99 (C-5), 74.12 (C-7), 72.55, 68.69 (C-2, C-3), 44.13 (C-6), 22.63 (*Me*). ^{1}H NMR (300.13, $CDCl_3$) δ 9.40 (s, 1H, N*H*), 7.53 (d, J = 6.0, 1H, H-6'), 5.97 (ddd, J = 8.1, 3.1, 1.5, 1H, H-5), 3.88 (m, 5H, H-2, H-3, H-7), 2.09 (m, 2H, H-6), 1.27 (d, J = 6.4, 3H, *Me*). *trans*-**3e**: ^{13}C NMR (75.78, $CDCl_3$) δ 156.8 (d, J = 26.79, C-4'), 148.43 (C-2'), 140.71 (d, J = 238.11, C-5'), 124.05 (d, J = 33.73, C-6'), 83.56 (C-5), 72.62 (C-7), 72.43, 68.29 (C-2, C-3), 43.80 (C-6), 22.15 (*Me*). ^{1}H NMR (300.13, $CDCl_3$) δ 9.35 (s, 1H, N*H*), 7.49 (d, J = 6.0, 1H, H-6'), 5.95 (ddd, J = 5.0, 3.3, 1.6, 1H, H-5), 3.88 (m, 5H, H-2, H-3, H-7), 2.09 (m, 2H, H-6), 1.26 (d, J = 6.3, 3H, *Me*). IR *cis/trans* mixture (cm^{-1}, KBr): 3188 (w, NH), 3078 (m, aromatics), 2933 (s, aliphatic C-H groups), 1711 (s, C=O), 1666 (s, aromatic ring multiple bond), 1257 (s) and 1152 (s, C-O-C). MS (CI) *cis/trans* mixture : *m/z* (%) 245 (23, M^+ + 1), 171 (10), 131 (28), 115 (100). Anal. for $C_{10}H_{13}O_4N_2F{\cdot}0.6H_2O$ *cis/trans* mixture: Calc.: C, 47.10; H, 5.61; N, 10.98. Found: C, 46.97; H, 5.61; N, 10.74.

Eluted second was (1'*R**,3'*R**)-**4e** as an amorphous white solid (0.050 g, 7%). R_f($CHCl_3$/MeOH, 100/5): 0.22. Mp 148-150 °C. ^{13}C NMR (75.78, acetone-d_6) δ 157.35 (d, J = 26.56, C-4'), 151.13 (C-2'), 142.23 (d, J = 233.96, C-5'), 124.33 (d, J = 33.43, C-6'), 85.13 (C-1), 71.84, (C-3), 70.76 (C-5), 62.17 (C-6), 56.28 (O*Me*), 41.79 (C-2), 19.48 (*Me*). ^{1}H NMR (300.13, acetone-d_6) δ 10.50 (s, 1H, N*H*), 7.71 (d, J = 6.6, 1H, H-6'), 5.82 (dc, J = 7.7, 5.6, 2.0, 1H, H-1), 3.43 (m, 5H, H-3, H-5, H-6), 3.30 (s, 3H, O*Me*), 2.82 (s, O*H*, D_2O exchangeable), 1.98 (dc, J = 11.5, 7.7, 3.8, 1H, H-2), 1.98 (dc, J = 11.5, 5.6, 1.7, 1H, H-2), 1.14 (d, J = 6.1, 3H, *Me*). IR (cm^{-1}, KBr): 3481 (w, NH), 3076 (s, aromatics), 2932 (s, aliphatic C-H groups), 1708 (s, C=O), 1670 (s, aromatic ring multiple bond), 1241 (s) and 1141 (s, C-O-C). MS (CI): *m/z* (%) 277 (100, M^+ + 1), 245 (33), 130 (16), 115 (69), 85 (17), 71 (14), 45 (84). Anal. for $C_{11}H_{17}O_5N_2F$: Calc.: C, 47.82; H, 6.20; N, 10.14. Found: C, 47.83; H, 6.49; N, 9.82.

Eluted third was (1'*R**,3'*S**)-**4e** as an amorphous white solid (0.061 g, 9%). R_f($CHCl_3$/MeOH, 100/5): 0.14. Mp 129-131 °C. ^{13}C NMR (75.78, acetone-d_6) δ 157.35 (d, J = 26.56, C-4'), 150.59 (C-2'), 142.23 (d, J = 233.96, C-5'), 124.47 (d, J = 33.36, C-6'), 85.49 (C-1), 72.58, (C-3), 70.93 (C-5), 61.16 (C-6), 56.50 (O*Me*), 42.66 (C-2), 19.99 (*Me*). ^{1}H NMR (300.13, acetone-d_6) δ 10.46 (s, 1H, N*H*), 7.67 (d, J = 6.6, 1H, H-6'), 5.78 (dc, J = 7.7, 5.1 2.0, 1H, H-1), 3.52 (m, 5H, H-3, H-5, H-6), 3.33 (s, 3H, O*Me*), 2.82 (s, O*H*, D_2O exchangeable), 1.91 (dc, J = 14.2, 7.7, 3.9, 1H, H-2), 1.82 (dc, J = 14.2, 9.0, 5.1, 1H, H-2), 1.14 (d, J = 6.1, 3H, *Me*). IR (cm^{-1}, KBr): 3486 (w, NH), 3077 (s, aromatics), 2930 (s, aliphatic C-H groups), 1709 (s, C=O), 1243 (s) and 1141 (s, C-O-C). MS

(CI): *m/z* (%) 277 (6, M^++1), 159 (21), 131 (34), 115 (100), 89 (48), 73 (21). Anal. for $C_{11}H_{17}O_5N_2F{\cdot}0.4H_2O$: Calc.: C, 46.61; H, 6.33; N, 9.88. Found: C, 46.74; H, 5.95; N, 9.50.

1,3-Bis(3-methyl-1,4-dioxepan-5-yl)-5-fluorouracil 8 (mixture of diastereomers) and *cis/trans*-(*RS*)-1-(3-methyl-1,4-dioxepane-5-yl)-5-fluorouracil 3f : Reaction of 5-methoxy-3-methyl-1,4-dioxepane **5f**[23] (0.910 g, 6.23 mmol) as a 1/6.1 *cis/trans* mixture as can be deduced from its ^{1}H NMR spectrum (obtained by the Ph_3P/CCl_4 cyclization on the corresponding hydroxyacetal, retention time, glc: 4.52 min; programme: isotherm 75 °C/2 min, ramp 25 °C/min, isotherm 200 °C/2 min) with 5-fluorouracil (0.890 g, 6.85 mmol) for 24 h according to the general procedure yielded **8** (0.180 g, 8%) as an amorphous white solid. Mp 71-76 °C. R*f* ($CHCl_3$/MeOH, 100/5): 0.51. ^{13}C NMR (75.78, $CDCl_3$) mixture of diasteomers (selected data): δ 148.38 (C-2'), 140.22 (d, *J* = 237.76, C-5'), 122.43 (d, *J* = 34.21, C-6'), 83.70 (C-5), 78.63, 77.66, 67.97, 67.09 (C-2, C-7), 77.58, 75.03, (C-3), 36.95, 34.09 (C-6), 17.78, 17.06, 16.97 (*Me*). ^{1}H NMR (400.13, $CDCl_3$) mixture of diastereomers (selected data): δ 7.50 (d, *J* = 5.6, 2H, H-6'), 6.51 (dt, *J* = 11.8, 3.7, 2H, H-5), 6.05 (ddd, *J* = 3.8, 1.4, 2H, H-5), 5.02 (q, *J* = 7.0, 2H, H-3), 4.07 (m, 4H), 3.95 (m, 4H), 3.79 (d, *J* = 12.9, 2H), 3.71 (ddd, *J* = 13.2, 7.7, 6.0, 2H), 3.63 (dd, *J* = 12.3, 10.8, 2H), 3.31 (m, 4H), 2.39 (m, 2H, H-6), 2.00 (m, 2H, H-6), 1.89 (dt, *J* = 15.1, 4.8, 4.8, 0.0, 2H, H-6), 1.66 (s, 2H, H-6), 1.10 (four d, 12H, *Me*). LSIMS mixture of diastereomers: *m/z* (%) 381 [80, $(M + Na)^+$], 245 (40), 169 (10), 115 (100). HR LSIMS mixture of diastereomers calcd. for $C_{16}H_{23}O_6N_2FNa$ $(M + Na)^+$ 381.1437, found: 381.1438.

Eluted second was **3f** (0.289, 19%) as a colourless thick oil. ^{1}H NMR reveals to be a *cis/trans* mixture (1/1.9 ratio). R$_f$ ($CHCl_3$/MeOH, 100/4): 0.34. ^{13}C NMR (100.03, $CDCl_3$) *cis/trans*-**3f**: δ (selected data) 148.72, 148.57 (C-2'), 157.01 (d, *J* = 26.16, C-4'), 140.72 (d, *J* = 238.47, C-5'), 124.00 (d, *J* = 25.16, C-6'), 124.34 (d, *J* = 24.65, C-6'), 83.30, 82.64 (C-5), 78.52, 76.25, 67.90, 66.99 (C-2, C-7), 77.54, 74.05 (C-3), 37.13, 36.96 (C-6), 17.15, 17.04 (*Me*). ^{1}H NMR (400.13, $CDCl_3$) *cis/trans*-**3f**: δ 9.68 (s, 1H, N*H*), 7.57 (d, *J* = 6.0, 1H, H-6'$_{cis}$), 7.47 (d, *J* = 6.0, 1H, H-6'$_{trans}$), 6.05 (ddd, *J* = 9.2, 1.5, 1H, H-5), 6.03 (ddd, *J* = 9.4, 4.0, 1.4 1H, H-5), 4.37 (ddc, *J* = 6.5, 6.5, 2.2, 1H, H-3$_{trans}$), 4.04 (m, 3H), 3.94 (dd, *J* = 12.7, 2.9, 1H), 3.88 (dd, *J* = 13.5, 2.3, 1H), 3.70 (m, 2H), 3.43 (dd, *J* = 13.5, 8.5, 1H), 3.34 (dd, *J* = 12.7, 9.5, 1H), 2.40 (m, 1H, H-6), 2.31 (m, 1H, H-6), 2.19 (m, 1H, H-6), 2.02 (m, 1H, H-6), 1.20 (d, *J* = 6.6, 3H, *Me*) 1.14 (d, *J* = 6.3, 3H, *Me*). HR LSIMS *cis/trans* mixture calcd. for $C_{10}H_{14}O_4N_2F$ $(M^+ + 1)$ 245.0938, found: 245.0937. Anal. for $C_{10}H_{13}O_4N_2F$ *cis/trans* mixture: Calc.: C, 49.16; H, 5.37 N, 11.47. Found: C, 49.26; H, 5.20; N, 11.63.

***cis/trans*-1-(3-Chloromethyl-1,4-dioxepan-5-yl)-5-fluorouracil 3g**: Reaction of 3-chloromethyl-5-methoxy-1,4-dioxepane **5g** (as a 1/5.3 *cis/trans* mixture) (0.233 g, 1.23 mmol) with 5-fluorouracil (0.220 g, 1.71 mmol) for 18 h according to the general procedure yielded *cis*-**3g** as a colourless thick oil (0.116 g, 33%). R$_f$ (100/4, $CHCl_3$/MeOH): 0.24. ^{13}C NMR (75.78 MHz, $CDCl_3$): δ 157.0 (d, *J* = 26.56, C-4'), 148.69 (C-2'), 140.80 (d, *J* = 238.26, C-5'), 124.02 (d, *J* = 33.96, C-6'), 83.17 (C-5), 79.33 (C-3), 73.98 and 67.4 (C-2 and C-7), 43.07 (CH_2Cl), 36.91 (C-6). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 9.85 (s, 1H, N*H*), 7.56 (d, *J* = 6.0, 1H, H-6'), 6.06 (ddt, *J* = 9.4, 3.5, 1.2, 1H, H-5), 4.03 (m, 3H, H-2, H-3), 3.79 (m, 1H, H-7), 3.67 (m, 1H, H-7), 3.52 (d, *J* = 5.8, 2H, CH_2Cl), 2.33 (m, 1H, H-6), 2.09 (m, 1H, H-6). IR (cm^{-1}, neat): 3196 (s, NH), 3080 (s, aromatics), 1712 (s, C=O), 1668 (s, aromatic ring multiple bond), 1271 (s), 1136 (s) and 1021 (s, C-O-C). MS (CI): *m/z* (%) 281 (M+2, 22), 279 (66), 171 (14), 169 (19), 151 (12), 149 (39), 131 (100). Anal. for $C_{10}H_{12}O_4N_2ClF{\cdot}H_2O$: Calcd.: C, 40.48; H, 4.42; N, 9.44. Found: C, 40.78; H, 4.02; N, 9.19.

Eluted second was *trans*-**3g** as an amorphous white powder (0.020 g, 6%). R$_f$ (100/5, $CHCl_3$/MeOH): 0.3.

Mp 212-214 °C. ^{13}C NMR (75.78 MHz, DMSO-d_6): δ 156.9 (d, J = 26.26, C-4'), 148.9 (C-2'), 138.27 (d, J = 238.26, C-5'), 125.95 (d, J = 33.81, C-6'), 82.36 (C-5), 76.07 (C-3), 72.16 and 66.86 (C-2 and C-7), 44.20 (CH_2Cl), 34.50 (C-6). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.15 (s, 1H, N*H*), 7.54 (d, J = 6.0, 1H, H-6'), 6.14 (ddd, J = 10.8, 2.6, 1.5, 1H, H-5), 4.39 (dddd, J = 8.2, 5.8, 2.4, 1H, H-3), 4.09 (ddd, J = 12.7, 3.8, 3.8, 1H, H-7), 4.04 (dd, J = 13.6, 2.4, 1H, H-2), 3.70 (ddd, J = 13.0, 10.8, 2.4, 1H, H-7), 3.63 (dd, J= 13.7, 8.2, 1H, H-2), 3.56 (dd, J = 5.8, 2H, CH_2Cl), 2.38 (dddd, J = 14.7, 10.8, 3.9, 1H, H-6), 2.12 (dddd, J = 14.7, 3.8, 2.6, 1H, H-6). IR (cm^{-1}, KBr): 3173 (s, NH), 3092 (s, aromatics), 2922 (s, aliphatic C-H groups), 1712 (s, C=O), 1697 (s, aromatic ring multiple bond), 1263 (s), 1168 (s) and 1087 (s, C-O-C). MS (CI): *m/z* (%) 281 (M^+ + 2, 34), 279 (100), 171 (14), 169 (18), 151 (13), 149 (37), 131 (99), 47 (94). Anal. for $C_{10}H_{12}O_4N_2ClF{\cdot}1/4H_2O$: Calcd.: C, 42.42; H, 4.45; N, 9.89. Found: C, 42.68; H, 4.15; N, 9.97.

***cis/trans*-1-(3-Iodomethyl-1,4-dioxepan-5-yl)-5-fluorouracil 3h:** Reaction of 3-iodomethyl-5-methoxy-1,4-dioxepane **5g** (as a 1/3.4 *cis/trans* mixture) (2 g, 7.35 mmol) with 5-fluorouracil (1.05 g, 8.08 mmol) for 24 h according to the general procedure yielded a mixture of *cis/trans*-**3h**, which was separated by flash chromatography. *cis*-**3h** was purified as a thick oil (0.592 g, 22%). R_f (100/5, $CHCl_3$/MeOH): 0.39. ^{13}C NMR (75.78 MHz, $CDCl_3$): δ 156.81 (d, J = 26.83, C-4'), 148.52 (C-2'), 140.81 (d, J = 238.57, C-5'), 124.15 (d, J = 33.93, C-6'), 83.25 (C-5), 79.48, 76.10 (C-2, C-3), 67.37 (C-7), 36.88 (C-6), 2.58 (CH_2I). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 9.12 (s, 1H, N*H*), 7.61 (d, J = 6.0, 1H, H-6'), 6.06 (ddd, J = 9.3, 3.6. 1.3, 1H, H-5), 4.10 (dd, J = 12.8, 3.1, 1H, H-2), 4.03 (dd, J = 12.3, 6.2, 6.0, 1H, H-7), 3.90 (ddd, J = 11.4, 5.7, 5.7, 1H, H-3), 3.78 (ddd, J = 12.8, 6.4, 6.0, 1H, H-7), 3.57 (dd, J = 12.8, 8.6, 1H, H-2), 3.19 (dd, J = 10.8, 5.3, 1H, CH_2I), 3.14 (dd, J = 10.8, 6.5, 1H, CH_2I), 2.39 (dddd, J = 13.8, 6.7, 6.7, 3.7, 1H, H-6), 2.10 (dddd, J = 9.3, 6.0, 6.0, 1H, H-6). MS (CI): *m/z* (%) 372 (M^+ +2, 5), 371 (M^+ + 1, 44), 241 (49), 131 (100), 113 (96), 57 (87). HR LSIMS *cis/trans* mixture calcd. for $C_{10}H_{13}O_4N_2FI$ (M^+ + 1) 370.9904, found: 370.9904. Anal. for $C_{10}H_{12}O_4N_2IF$: Calcd.: C, 32.45; H, 3.27; N, 7.57. Found: C, 32.97; H, 3.48; N, 7.44.

Eluted second was *trans*-**3h** as an amorphous white powder (0.136 g, 5%). Selected data: R_f (100/5, $CHCl_3$/MeOH): 0.38. Mp 70-71 °C. ^{13}C NMR (100.03 MHz, DMSO-d_6): δ 157.03 (d, J = 26.16, C-4'), 149.17 (C-2'), 139.89 (d, J = 230.49, C-5'), 126.37 (d, J = 33.20, C-6'), 82.14 (C-5), 75.82 (C-3), 73.68 (C-7), 66.82 (C-2), 34.24 (C-6), 6.32 (CH_2I). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 11.85 (d, J = 4.9, 1H, N*H*), 8.29 (d, J = 7.2, 1H, H-6'), 6.02 (dd, J = 11.4, 3.0, 1H, H-5), 4.33 (m, J = 8.0, 3.7, 1H, H-3), 3.90 (m, 2H, H- 7, H-2), 3.55 (dd, J = 11.4, indet., 2H, H-2), 3.31 (dd, J = 12.9, 8.2, 1H, H-7), 3.28 (dd, J = 10.5, 3.5, 1H, CH_2I), 3.11 (dd, J = 10.4, 8.3, 1H, CH_2I), 2.66 (m, 1H, H-6), 1.97 (dt, J = 14.9, 3.8, 1H, H-6). MS (CI): *m/z* (%) 241 (M^+ +1 - 5-FU, 6), 131 (100). HR LSIMS calcd. for $C_{10}H_{13}O_4N_2FI$ (M^+ + 1) 370.9904, found: 370.9905. Analysis for $C_{10}H_{12}O_4N_2IF$: Calcd.: C, 32.45; H, 3.27; N, 7.57. Found: C, 32.44; H, 3.32; N, 7.43.

Starting materials

3-[2-(Hydroxyethylthio)propanal dimethyl acetal: 2-[2-(2-Hydroxyethylthio)ethyl]-1,3-dioxolane[12] (10 g, 56 mmol) was dissolved in anhydrous MeOH (79 mL, 1.95 mol), which contained concentrated H_2SO_4 (0.20 mL) to give a final 1% concentration of the acid. The solution was kept for 14 h at rt, basified (NaOH/MeOH) and concentrated. The residue was dissolved in $CHCl_3$ (100 mL) and washed with H_2O (2 × 30 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated and the residue was distilled under diminished pressure (bp 94-97 °C/ 0.6 torr) yielding pure 3-[2-(hydroxyethylthio)propanal dimethyl acetal (6.94 g, 70%) as an oil. ^{1}H NMR

(300.13 MHz, $CDCl_3$): δ 4.47 (t, *J* = 5.5, 1H, H-1), 3.71 (dt, *J* = 6.0, 2H, H-6), 3.32 (s, 6H, O*Me*), 2.82 (t, *J* = 6.0, 1H, O*H*, D_2O exchangeable), 2.70 (t, *J* = 6, 2H, H-5), 2.57 (t, *J* = 7.5, 2H, H-3), 1.85 (dt, *J* = 7.5, 5.5, 2H, H-2). IR (cm^{-1}, neat): 3426 (f, OH stretching), 2933, 2835 (s, aliphatic C-H groups), 1442, 1385 (m, Me), 1285 (m), 1193 (m) and 1058 (s, C-O-C). LSIMS: *m/z* (%) 148 (M^+ + 1 - MeOH, 8), 117 (14), 103 (1), 89 (10), 75 (5), 60 (100). Anal. for $C_7H_{16}O_3S$: Calcd.: C, 46.64; H, 8.95; S, 17.79. Found: C, 46.78; H, 9.03; S, 17.48.

(*RS*)-7-Methoxy-1,4-oxathiepane 5b: It was obtained by intramolecular cyclization of 3-[2-(hydroxyethylthio)propanal dimethyl acetal mediated either under the neutral and mild conditions of the Ph_3P/CCl_4[10] system (52%), or under the acid-catalysis of $BF_3.OEt_2$ (41%).[10] Bp 32-34 °C (0.7 torr). Retention time, glc: 4.59 min, area 98.7%; a Perkin-Elmer fused silica glass capillary column; phase: bonded methyl 5% phenyl silicone; length: 10 m × 0.53 mm i.d.; film thickness 5.0 microns; programme: isotherm 75 °C/2 min, ramp 25° C/min, isotherm 170 °C/1 min. ^{13}C NMR (75.78, $CDCl_3$) δ 105.34 (C-7), 68.42 (C-2), 55.10 (O*Me*), 38.29 (C-3), 35.17 (C-5), 27.36 (C-6). ^1H NMR (300.13, $CDCl_3$) δ 4.65 (dd, *J* = 8.6, 4.7, 1H, H-7), 4.14 (ddd, *J* = 12.7, 6.1, 3.2, 2H, H-2), 3.67 (ddd, *J* = 12.7, 7.3, 3.2, 1H, H-2), 3.25 (s, 3H, O*Me*), 2.68 (ddd, *J* = 14.5, 9.4, 4, 1H, H-5), 2.60 (ddd, *J* = 14.3, 7.3, 3.2, 1H, H-5), 2.50 (ddd, *J* = 14.5, 6.3, 4.8, 1H, H-3), 2.64 (m, 1H, H-3), 2.23 (dddd, *J* = 14.7, 9.4, 4.8, 4.7, 1H, H-6), 1.97 (dddd, *J* = 14.7, 8.6, 6.3, 4.0, 1H, H-6). IR (cm^{-1}, neat): 2926 (s, aliphatic C-H groups), 1126 (s), 1076 (s), 1025 (s), 911 (m) and 893 (m, C-O-C). MS (CI): *m/z* (%) 148 (8, M^+), 117 (14), 103 (1), 89 (10), 75 (5), 60 (100). Anal. for $C_6H_{12}O_2S$: Calc.: C, 48.62; H, 8.16; S, 21.63. Found: C, 4849; H, 7.83; S, 21.82.

3-[2-(*p*-Toluenesulfonyloxy)ethoxy]propanal dimethyl acetal 11: N-*p*-Toluenesulfonyl-2-aminoethanol[25] (2.59 g, 11.2 mmol) dissolved in dry DMF (6 mL) was added to a suspension of NaH (80% dispersion in mineral oil, 0.361 g, 12 mmol) in dry DMF (5 mL) under continuous stirring for 1 h at rt and it was warmed at 70 °C. Then, a solution of 3-bromopropanal dimethyl acetal (2.2 g, 12 mmol) in dry DMF (20 mL) was added dropwise during aproximately 1 h and the reaction mixture was kept for 15 h and at 70 °C under stirring. After pouring out into icy water (100 mL) the solution was rotaevaporated off. Acetone was added, the solid filtered and the filtrate was rotaevaporated off to dryness. The residue was purified by flash chromatography using a gradient elution (diethyl ether/hexane/Pr^iOH, 50/50/0.5 → diethyl ether/hexane/Pr^iOH, 50/20/0.5 → diethyl ether) yielding **10** (2.35 g, 62%) as a thick oil. ^{13}C NMR (100.62, CD_3Cl) δ 143.64 (C-1_{Tos}), 135.58 (C-4_{Tos}), 129.81 (C-3_{Tos}, C-5_{Tos}), 127.35 (C-2_{Tos}, C-6_{Tos}), 102.81 (C-1), 61.49 (C-6), 53.35 (O*Me*), 52.07 (C-5), 46.32 (C-3), 32.24 (C-2), 21.56 (*Me*). ^1H NMR (400.13, $CDCl_3$) δ 7.68 (dt, *J* = 8.4, 1.9, 2H, H-2_{Tos}, H-6_{Tos}), 7.29 (d, *J* = 8.4, 2H, H-3_{Tos}, H-5_{Tos}), 4.46 (t, *J* = 5.4, 1H, H-1), 3.74 (t, *J* = 5.30, 2H, H-6), 3.32 (s, 6H, O*Me*), 3.19 (t, *J* = 7.4, 2H, H-3), 3.17 (t, *J* = 5.30, 2H, H-5), 2.55 (s, O*H*, D_2O exchangeable), 2.40 (s, 3H, *Me*), 1.91 (dt, *J* = 7.4, 5.4, 2H, H-2). Anal. for $C_{14}H_{23}O_5NS$: Calc.: C, 52.98; H, 7.30; N, 4.41; S, 10.10. Found: C, 52.73; H, 6.99; N, 4.51; S, 10.23.

(*RS*)-7-Methoxy-4-toluenesulfonyl-1,4-oxazepane 5c: It was obtained by intramolecular cyclization of **11** mediated either under the neutral and mild conditions of the Ph_3P/CCl_4[10] system (67%), or under the acid-catalysis of $BF_3.OEt_2$ (73%).[10] The microcrystalline white solid (*RS*)-**5c** obtained by the two methods has the same spectroscopical and analytical properties. Mp 115-117 °C. ^{13}C NMR (75.78, $CDCl_3$) δ 143.48 (C-1_{Tos}), 135.33 (C-4_{Tos}), 129.79 (C-3_{Tos}, C-5_{Tos}), 127.26 (C-2_{Tos}, C-6_{Tos}), 102.31 (C-7), 62.10 (C-2), 55.17 (O*Me*), 50.71 (C-3), 43.62 (C-5), 35.67 (C-6), 21.54 (*Me*). ^1H NMR (300.13, $CDCl_3$) δ 7.62 (dt, *J* = 8.1, 2H, H-2_{Tos}, H-6_{Tos}), 7.29 (d, *J* = 8.1, 2H, H-3_{Tos}, H-5_{Tos}), 4.60 (dd, *J* = 7.7, 5.3, 1H, H-7), 3.58 (m, 3H, H-2, H-3, H-5), 3.30 (s, 3H, O*Me*), 2.97

(m, 1H, H-3), 2.86 (ddd, J = 13.7, 9.0, 2.1, 1H, H-5), 2.41 (s, 3H, *Me*), 2.19 (dddd, J = 15.5, 8.1, 5.3, 2.1, 1H, H-6), 1.93 (dddd, J = 15.5, 9.0, 7.7, 2.1, 1H, H-6). IR (cm^{-1}, KBr): 3036 (s, aromatics), 2908 (s, aliphatic C-H groups), 1599 (s, aromatic ring multiple bond), 1339 and 1163 (s, SO_2N), 1138 and 1101 (s, C-O-C stretching). Anal. for $C_{13}H_{19}O_4NS$: Calc.: C, 54.72; H, 6.71; N, 4.91; S, 11.24. Found: C, 54.43; H, 4.65; N, 4.91; S, 11.48.

1-[3-(2-Hydroxypropoxy)propanal dimethyl acetal 13: $NiCl_2$ (0.14 g, 1.1 mmol) was transferred into a 250 mL Erlenmeyer flask which had been oven-dried, equipped with a magnetic stirrer and sealed with a rubber septum. THF (91 mL) was syringed into the flask and the temperature then adjusted by dry ice (*ca.* - 40 °C). (*RS*)-**11**[13] (2.31 g, 11 mmol) in THF was then added followed by the addition of $LiAlH_4$ (0.417 g, 11 mmol). During $LiAlH_4$ addition, gas evolution and a black solid were observed. After 10 min, the reaction was warmed to room temperature overnight and the reaction mixture quenched with a saturated solution of Na_2SO_4. After filtration and washing thoroughly with THF, the resulting solution was dried ($MgSO_4$), filtered, rotaevaporated off and purified by flash chromatography using a mixture of diethyl ether/hexane 1/1 yielding **13** as a colourless mobile liquid (1.68 g, 87%). Its spectroscopic and analytical properties are superposable with those of a previously reported sample.[24] R_f (diethyl ether/hexane, 1/1): 0.16. Retention time, glc: 1.45 min, area 98.5%; programme: isotherm 175 °C/10 min, ramp 25 °C/min, isotherm 200 °C/1 min).

***cis/trans*-3-Chloromethyl-5-methoxy-1,4-dioxepane 5g:** (*RS*)-**12**[13] (1.30 g, 4.70 mmol) was dissolved in dry ether (15 mL), and a few drops of $Et_2O.BF_3$ were added. The mixture was kept at rt for 6 days and washed with an aqueous solution of K_2CO_3 (10%), and the organic layer was dried, filtered and concentrated. The residue was purified by flash chromatography with diethyl ether/hexane (1/3), yielding 0.415 g (49%) of **5g** (as a 1/5.3 *cis/trans* mixture from its ^1H NMR spectrum) as a colourless oil. R_f (diethyl ether/hexane, 1/3): 0.27. Retention time, glc: 1.84 min, area 99.2%; programme: isotherm 175 °C/5 min, ramp 25 °C/min, isotherm 200 °C/4 min). ^{13}C NMR *trans*-**5g** (75.78, $CDCl_3$) δ 101.47 (C-5), 72.73 (C-2), 72.49 (C-3), 65.61 (C-7), 55.72 (O*Me*), 44.11 (*C*H_2Cl), 38.52 (C-6). ^1H NMR *trans*-**5g** (300.13, $CDCl_3$) δ 4.75 (dt, J = 8.2, 6.2, 1H, H-5), 4.20 (ddt, J = 8.9, 5.7, 1.2, 1H, H-3), 3.90 (dd, J = 12.3, 1.2, 1H, H-2), 3.80 (ddd, J = 12.5, 5.7, 1.9, 1H, H-7), 3.53 (ddd, J = 12.5, 10.2, 1.1, 1H, H-7), 3.43 (d, J = 6.1, 2H, C*H*$_2$Cl), 3.39 (s, 3H, O*Me*), 3.37 (dd, J = 12.3, 8.9, 1H, H-2), 2.18 (dddd, J = 16.0, 6.2, 5.7, 1.1, 1H, H-6), 2.00 (dddd, J = 16.0, 9.0, 10.2, 8.2, 1.9,1H, H-6). IR (cm^{-1}, neat): 2959 (s, aliphatic C-H groups), 1130 and 1091 (s, C-O-C stretching). LSIMS: *m/z* (%) 180 (1, M^+), 148 (12), 117 (15), 103 (15), 87 (36), 72 (100). HRMS (CI) calcd. for $C_7H_{14}O_3Cl$ (M^+ + 1) 181.0631, found: 181.0619. Anal. for $C_7H_{13}O_3Cl$: Calc.: C, 46.55; H, 7.25. Found: C, 46.81; H, 4.49.

(*RS*)-3-(3-Iodo-2-hydroxypropoxy)propanal dimethyl acetal: (*RS*)-**12**[13] (2.00 g, 9.40 mmol) and dry NaI (14 g, 9.40 mmol) were dissolved in butanone (20 mL) previously dried (K_2CO_3). The solution was refluxed overnight under argon. After cooling, filtration and concentration of the solvent *in vacuo*, (*RS*)-3-(3-Iodo-2-hydroxypropoxy)propanal dimethyl acetal was purified by flash chromatography (diethyl ether/hexane 2/1) as a colourless liquid (2.61 g, 91%). Retention time, glc: 6.85 min, area 96.5%; programme: isotherm 175 °C/10 min, ramp 25 °C/min, isotherm 200 °C/1 min). R_f ($CHCl_3$/MeOH, 10/0.1): 0.32; R_f (diethyl ether/hexane, 1/1): 0.16. ^{13}C NMR (75.78, $CDCl_3$) δ 102.25 (C-1), 73.36 (C-5), 69.87 (C-6), 67.53 (C-3), 53.14 (O*Me*), 32.80 (C-2), 9.07 (C-7). ^1H NMR (300.13, $CDCl_3$) δ 4.51 (t, J = 5.7, 1H, H-1), 3.73 (sx, J = 5.4, 1H, H-6), 3.32 (s, 6H, *Me*), 2.78 (d, J = 5.5, 1H, O*H*, D_2O exchangeable), 3.55 (t, J = 6.3, 2H, H-3), 3.51 (d, J = 5.1, 2H, H-5), 3.30 (dd, J = 11.1, 5.6, 1H,

H-7), 3.23 (dd, J = 10.1, 5.8, 1H, H-7), 1.87 (q, J = 6.1, 2H, H-2). LSIMS: *m/z* (%) 273 (M^+ + 1 - MeOH, 6), 242 (3), 241 (48), 113 (33), 75 (95), 71 (100). HR LSIMS calcd. for $C_8H_{16}O_4I$ (M^+ - 1) 303.0093, found: 303.0100. Anal. for $C_8H_{17}O_4I$: Calc.: C, 31.59; H, 5.63. Found: C, 31.81; H, 5.49.

***cis/trans*-3-Iodomethyl-5-methoxy-1,4-dioxepane 5h:** The procedure was identical to the one used to obtain **5g**: from (*RS*)-3-(3-iodo-2-hydroxypropoxy)propanal dimethyl acetal (2.12 g, 7.79 mmol), **5h** (*cis/trans* mixture) 1.05 g (56%) was obtained as a yellowish thick oil. R_f (diethyl ether/hexane, 1/3): 0.21. Retention time, glc: 3.21 min, area 97.5%; programme: isotherm 175 °C/10 min, ramp 25 °C/min, isotherm 200 °C/1 min). ^{1}H NMR reveals to be a mixture a *cis/trans* mixture (1/3.4). ^{13}C NMR *trans*-**5h** (100.13, $CDCl_3$) δ 101.56 (C-5), 74.62, 65.56 (C-2, C-7), 72.09 (C-3), 56.33 (O*Me*), 38.54 (C-6), 4.20 (CH_2I). ^{1}H NMR *trans*-**5h** (400.13, $CDCl_3$) δ 4.76 (dd, J = 8.3, 6.0, 1H, H-5), 4.06 (ddd, J = 8.6, 5.8, 0.0, 1H, H-3), 3.96 (d, J = 12.5, 0.0, 1H, H-2), 3.81 (ddd, J = 12.6, 5.7, 1.5, 1H, H-7), 3.55 (dd, J = 12.3, 10.6, 0.0, 1H, H-7), 3.46 (s, 3H, O*Me*), 3.38 (dd, J = 12.3, 8.6, 1H, H-2), 3.10 (dd, J = 10.7, 5.7, 1H, CH_2I), 3.07 (dd, J = 10.6, 5.7, 1H, CH_2I), 2.21 (dddd, J = 15.8, 5.8, 5.8, 0.0, 1H, H-6), 2.02 (dddd, J = 16.0, 10.3, 8.4, 1.8, 1H, H-6). ^{13}C NMR *cis*-**5h** (100.13, $CDCl_3$) δ 104.52 (C-5), 78.42 (C-3), 76.23, 67.23 (C-2, C-7), 56.99 (O*Me*), 37.77 (C-6), 3.31 (CH_2I). ^{1}H NMR *cis*-**5h** (400.13, $CDCl_3$) δ 4.74 (dd, J = 6.9, 4.2, 1H, H-5), 3.99 (dd, J = 12.4, 2.6, 1H, H-2), 3.88 (ddd, J = 12.4, 5.9, 3.7, 1H, H-7), 3.78 (dd, J = indet., 2.6, 1H, H-2), 3.69 (ddd, J = 12.4, 10.1, 4.5, 1H, H-7), 3.54 (s, 3H, O*Me*), 3.39 (m, 1H, H-3), 3.14 (m, 2H, CH_2I), 2.28 (dddd, J = 14.6, 10.2, 5.8, 4.4, 1H, H-6), 1.96 (m, 1H, H-6). IR (cm^{-1}, neat) *cis/trans* mixture: 2956 (s, aliphatic C-H groups), 1151 and 1070 (s, C-O-C stretching). MS (CI): *m/z* (%) 273 (M^+ + 1, 1), 241 (52), 113 (82), 71 (100). HR LSIMS *cis/trans* mixture calcd. for $C_7H_{14}O_3I$ $(M + 1)^+$ 272.9988, found: 272.9988. Anal. for $C_7H_{13}O_3I$: Calc.: C, 30.90; H, 4.82. Found: C, 31.39; H, 4.65.

BIOLOGICAL EVALUATION

In vitro cytotoxicity versus HT-29: HT-29 cells were grown in Dulbecco's Modified Eagle's medium (DMEM) supplemented with 10% new-born calf serum (NCS) under standard conditions of temperature (37 °C), humidity (95°C), and carbon dioxide (5%). The cells were seeded on 24-well plates and incubated for 24 h in DMEM supplemented with 10% NCS. Then the cells were washed with TD buffer (137 mM NaCl, 5 mM KCl, 20 mM Tris, pH 7.4) and incubated in DMEM containing the indicated amounts of serum and different concentrations of 5-FU derivatives. Three days later, the wells were aspirated, fresh medium added, and the cells maintained for three additional days. Quantification of the cells remaining in each well was carried out using the crystal violet method (See ref. 29), with some modifications. Briefly, the cells were washed with TD buffer and fixed with 1% pentanedial for 15 min. After having been washed again with TD, cell nuclei were stained with 0.1% crystal violet for at least 30 min, and washed three times with distilled water. Adsorbed dye was resuspended in 10% acetic acid and absorbance at 595 nm was determined in a spectrometer. The values for IC_{50} are the mean of three determinations carried out at different times.

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11. The systematic numbering of the 1,4-oxaheteroepane moiety is as follows:

X being S or NTs

In both cases Z can be the MeO- or the 5-FU moieties

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18. Reactions starting from the *iso*propoxy analogues of **5d** (*trans*-5-isopropoxy-6-methyl-1,4-dioxepane), **5e** (*cis*-5-isopropoxy-7-methyl-1,4-dioxepane), the cyclopentoxy analogue of **5a** [(*RS*)-5-

cyclopentoxy-1,4-dioxepane] and 5-FU were carried out under standard conditions (See Experimental Section). In spite of increasing the reaction time up to 16 h, the isopropoxy analogues of **4d**, (*RS*)-1-{[3-(2-hydroxyethoxy)-2-methyl-1-isopropoxy]propyl}-5-fluorouracil [64% as the mixture of the racemic diastereomers (1/1)], of **4e**, (1'*R**,3'*R**) and (1'*R**,3'*R**) 1-{[3-(2-hydroxyethoxy)-1-isopropoxy]butyl}-5-fluorouracil [56% as the mixture of the racemic diastereomers (1/1) which were separated by flash chromatography], and the cyclopentoxy analogue of **4a**, (*RS*)-1-{[3-(2-hydroxyethoxy)-1-cyclopentoxy]-propyl}-5-fluorouracil (41%) were the *only* products obtained (data not shown). In these cases the chelation has to take place between the $SnCl_4$, the ether oxygen atom and the *endocyclic* acetal oxygen, probably due to the steric hindrance caused by the isopropoxy group.

19. When the reaction was carried out on the *cis/trans* mixture of 5-isopropoxy-3-chloromethyl)-1,4-dioxepane even for 24 h, the starting material was recovered unchanged.
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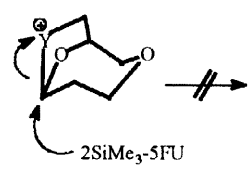
21. It is not plausible to accept the stabilization of the proximal incipient carbenium ion, which results from the leaving of the methoxy group to form a five-membered ring by the neighbouring-group participation of the chlorine or iodo atoms of **5g** and **5h**, for the following two reasons: a) *trans*-**5g** and *trans*-**5h** should be the major compounds but experimentally the *cis* products predominate, and b) neighbouring-group participation is well documented in carbohydrate chemistry, and is *usually* Lewis- acid independent; for this, see: Wilson, L. J.; Hager, M. W.; El-Kattan, Y. A.; Liotta, D. C. *Synthesis*, **1995**, 1465-1479.



Y = Cl, I

22. We now know the experimental conditions needed to direct the 5-FU nucleophilic-mediated tin (IV) chloride attack to the seven-membered methyl *O,O*-acetals **5** towards either the cyclic *O,N*-acetals type **3** or the acyclic ones type **4** (see ref. 12).
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