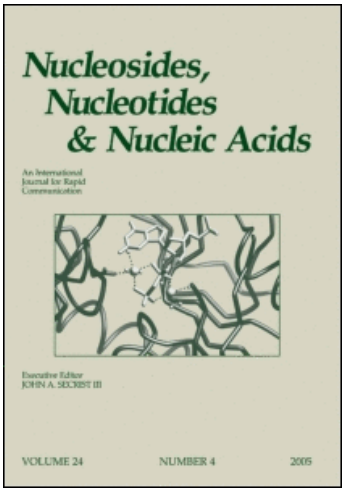

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Piyush Kumar[a]; Kazue Ohkura[b]; Jan Balzarini[c]; Erik De Clercq[c]; Koh-ichi Seki[d]; Leonard I. Wiebe[a]
[a] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada [b] Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Hokkaido, Japan [c] Rega Institute of Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium [d] Central Institute of Isotope Science, Hokkaido University, Sapporo, Japan

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Synthesis and Antiviral Activity of Novel Fluorinated 2′,3′-Dideoxynucleosides†

Piyush Kumar,[1] Kazue Ohkura,[2] Jan Balzarini,[3] Erik De Clercq,[3] Koh-ichi Seki,[4] and Leonard I. Wiebe[1,*]

[1]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada
[2]Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobestsu, Hokkaido, Japan
[3]Rega Institute of Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium
[4]Central Institute of Isotope Science, Hokkaido University, Kita-ku, Sapporo, Japan

ABSTRACT

A series of 5-(trifluoroethoxymethyl)-2′,3′-dideoxyuridines and 5-[*bis*(trifluoroethoxy)-methyl]-2′,3′-dideoxyuridines have been prepared and screened for antiviral activity. The conformations of these compounds are discussed on the bases of NOE studies and the MO calculations. Modelling and NOE studies suggest both *syn*- and *anti* conformations for these 5-(2,2,2-trifluoroethoxymethyl)- and 5-[bis(2,2,2-trifluoroethoxy)-methyl]- derivatives. The NOE parameters are also suggested to be more attributable to the nature of the fluorine atom than to structural or conformational changes. Compounds **17**, **26** and **30** showed some activity in anti-HIV-1 and anti-HIV-2 assays, but the compounds were devoid of activity against HSV

†In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

*Correspondence: Leonard I. Wiebe, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada, T6G 2N8; E-mail: leonard.wiebe@ualberta.ca.

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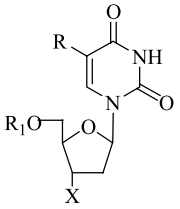
and human rhinovirus. The compounds tested exhibited low cytotoxicity and were inactive against a bank of cancer cells in vitro.

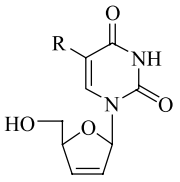
Key Words: Fluorinated 2′,3′-dideoxynucleosides; Syntheses; NOE; Antiviral nucleosides.

INTRODUCTION

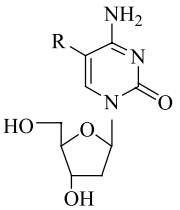
Viral diseases have long been intractable to chemotherapy because of the intimate association of viruses with normal cellular biochemistry. However, chemical modification of physiological nucleosides can impart therapeutic activity against viruses. The antiviral potential of appropriately modified nucleosides depends on their selective interaction with both host- and virus-encoded enzymes in infected cells. Particularly for the herpesvirus family, many important structure-activity relationships for antiviral activity have been elucidated over the past several decades. It is known, for example, that many derivatives of 2′,3′-dideoxyribopyrimidine nucleosides having a C-5 substituent no longer than a four carbon chain and starting with a carbon atom have antiviral properties.[1–3] These properties extend to C-5 ether substituents, 5-methoxymethyl-2′-deoxyuridine (MMdU) and its 2′-deoxycytidine analogs,[4] which are active against various strains of herpes simplex virus type 1 (HSV-1).[5] Incorporation of fluorine and fluoro-alkyl substituents at C-5 similarly establishes



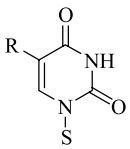
1; X = OH; R = -$CH_2OCH_2CF_3$; R_1 = H
1a; X = OH; R = -$CH_2OCH_2CF_3$; R_1 = TBDPS
2; X = OH ; R = -$CH(OCH_2CF_3)_2$; R_1 = H
2a; X = OH; R = -$CH(OCH_2CF_3)_2$; R_1 = TBDPS
3; X = Cl; R = -$CH_2OCH_2CF_3$



4; R = -$CH_2OCH_2CF_3$
5: R = -$CH(OCH_2CF_3)_2$



6; R = -$CH_2OCH_2CF_3$



7; R = -OCH_2CF_3; S = 1-β-D-ribose
8; R = -OCH_2CF_3; S = 1-β-D-arabinose

Figure 1. C-5-Elaborated 2′,3′-dideoxynucleosides.

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antiviral activity. Of the fluoropyrimidine nucleosides, 5-fluoro-2′-deoxyuridine (FUdR) was developed for the treatment of cancer, whereas 5-trifluoromethyl-2′-deoxyuridine (trifluridine; TFT), has clinical efficacy in the treatment of herpetic eye infection.[6] 5-(2-Fluoroethyl)-2′-deoxyuridine (FEDU) inhibits HSV-1 replication.[7,8] Introduction of fluorine into the sugar moiety creates antiviral selectivity, especially in the C-2′-arabino configuration, as in the case of 2′-fluoroarabinothymidine, which is a selective inhibitor of HSV-1 and HSV-2.[9] Several dideoxy- and didehydrodideoxynucleosides are useful in the chemotherapy of human immunodeficiency virus (HIV) infections.[10,11] 3′-Azido-3′-deoxythymidine (zidovudine, AZT)[12,13] and stavudine (3′-deoxy-2′,3′-didehydrothymidine, D4T)[14,15] are active as inhibitors of reverse transcriptase, and 5-chloro-3′-fluoro-2′,3′-dideoxyuridine (FddClUrd) has a selectivity index similar to that of AZT.[16] Finally, ring-opening of the sugar moiety imparts selective antiviral activity among a range of nucleosides including 1-(2-hydroxyethoxymethyl)-6-(phenylthio)thymine (HEPT),[17] which also demonstrates selective inhibition of HIV-1. Several excellent reviews of antiviral nucleosides have been published.[18,19]

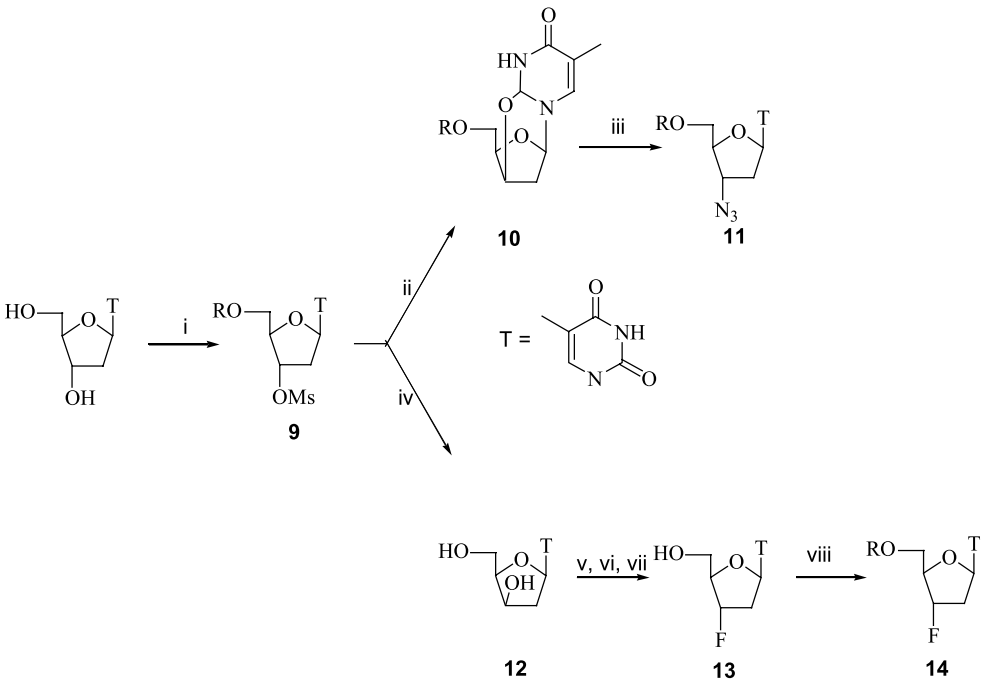
The syntheses of several novel pyrimidine nucleosides that feature selected chemical modifications described above are now reported. Specifically, a series of 5-(trifluoroethoxymethyl)-2′,3′-dideoxyuridines and 5-[bis(trifluoroethoxy)methyl]-2′,3′-dideoxyuridines (Figure 1) have been prepared and screened for antiviral activity. Antiviral activities of previously reported but un-tested pyrimidine nucleosides are also presented.[20,21]

RESULTS AND DISCUSSION

Chemistry

The synthesis of compounds **1–8** (Figure 1) has been described in previous communications.[20,21] 3′-Substituted-5′-O-protected-3′-deoxythymidines, the synthons for the corresponding 5-(2,2,2-trifluoroethoxymethyl)- and 5-[bis(2,2,2-trifluoroethoxy) methyl]- derivatives now reported, were prepared by sequential bromination and then trifluoroethoxylation at C-5 methyl of thymidine. The C-5 halomethyluracils are very labile in protic solvents or moisture and undergo nucleophilic displacement of the halogen via a 1,4-conjugate addition–elimination mechanism.[22–24] However, appropriately protected 5-α-bromomethyl pyrimidine nucleosides resist solvolysis and yet undergo facile nucleophilic substitution in the presence of strong nucleophiles such as trifluoroethoxide-copper complex, to afford the corresponding 5-trifluoroethoxymethyl derivatives (Scheme 1).

Reported approaches to the synthesis of AZT and FLT include a variety of protecting groups[25–27] depending on the demands of subsequent chemical reaction. We now report the synthesis of 5-(2,2,2-trifluoroethoxymethyl)- and 5-[bis(2,2,2-trifluoroethoxy)-methyl]- derivatives from 3′-substituted-5′-O-protected-3′-deoxythymidines (**11**, **14**). 5′-O-*tert*-Butyldiphenylsilyl protection of thymidine was selected to withstand the acidic conditions generated during bromination, and resist the strongly alkaline conditions of nucleophilic substitution by the trifluoroethoxy group.[28] Thus, thymidine was converted to **9** (86%), and hydrolysis of **9** with ethanolic sodium afforded the anhydrothymidine **10** (80%), which, in turn formed the 5′-O-TBDPS-3′-azido-3′-deoxythymidine **11** (46%) upon treatment with NaN_3. Insertion of the azide group was confirmed by ^1H NMR and by IR (absorbance at 2125 cm^{-1}). FLT **13** was



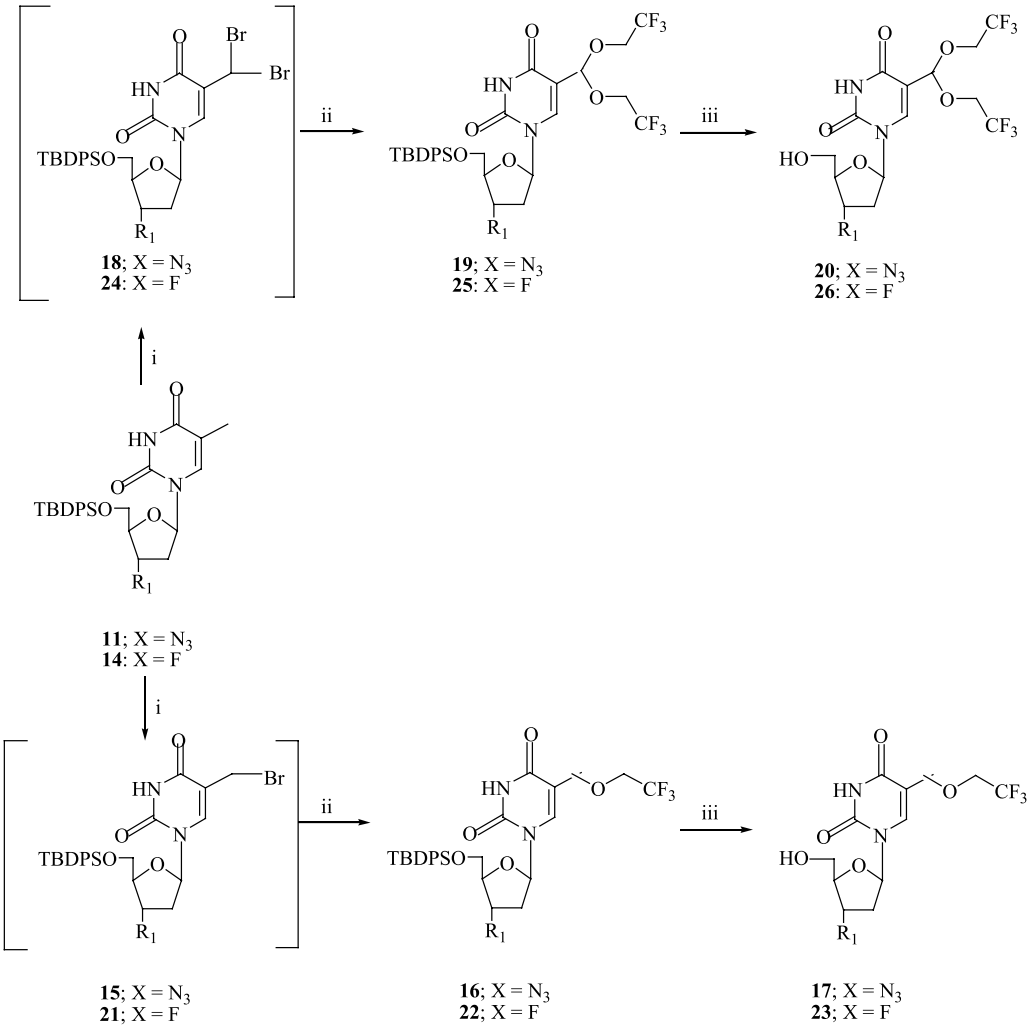
Where, i = TBDPS-Cl/Pyridine/CH_3SO_2Cl; ii = 1N.NaOH/EtOH; iii = LiN_3/DMF; iv =10N NaOH/EtOH/Reflux; v = Trityl Chloride/Pyridine/DMAP/50°C; vi = DAST/CH_2Cl_2; vii = 80% AcOH; viii = TBDPS-Cl/Pyridine and R = TBDPS

Scheme 1. Preparation of the synthons 5′-O-*tert*-butyl-AZT (**11**) and -FLT (**14**).

prepared by basic hydrolysis of **9** to afford threothymidine **12** (70%), which, after C-5′ triphenylmethyl protection, was fluorinated with diethylaminosulfurtrifluoride (DAST) and sequential acidic deprotection to afford FLT **13** (65%) (Scheme 1). The incorporation of fluorine at 3′- was confirmed by ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectroscopy of **14**. 5′-O-TBDPS-3′-azido-3′-deoxythymidine (**11**) and 5′-O-TBDPS-3′-fluoro-3′-deoxythymidine (**14**) were the key precursors for preparing substituted 5-fluoroalkoxy products.

For C-5 methyl bromination, a solution of bromine and **11** was irradiated under a 75 W UV lamp to afford **15** or **18**, depending on the amount of bromine used (Scheme 2). These brominated intermediates are unstable, and were therefore used immediately. Upon reaction with potassium trifluoroethoxide alone, most of the bromomethylthymidine was hydrolyzed to the corresponding 5-hydroxymethyl-3′azido-5′-O-TBDPS-3′-deoxythymidine, but reaction of 2,2,2-trifluoroethoxide-copper complex[a] with **15** gave **16**, and reaction with **18** afforded the *bis*-substituted **19**, both in moderate yields. Introduction of

[a]In the absence of cuprous iodide, most of the bromomethylthymidine was hydrolyzed to the corresponding 5-hydroxymethyl-3′azido-5′-O-TBDPS-thymidine.

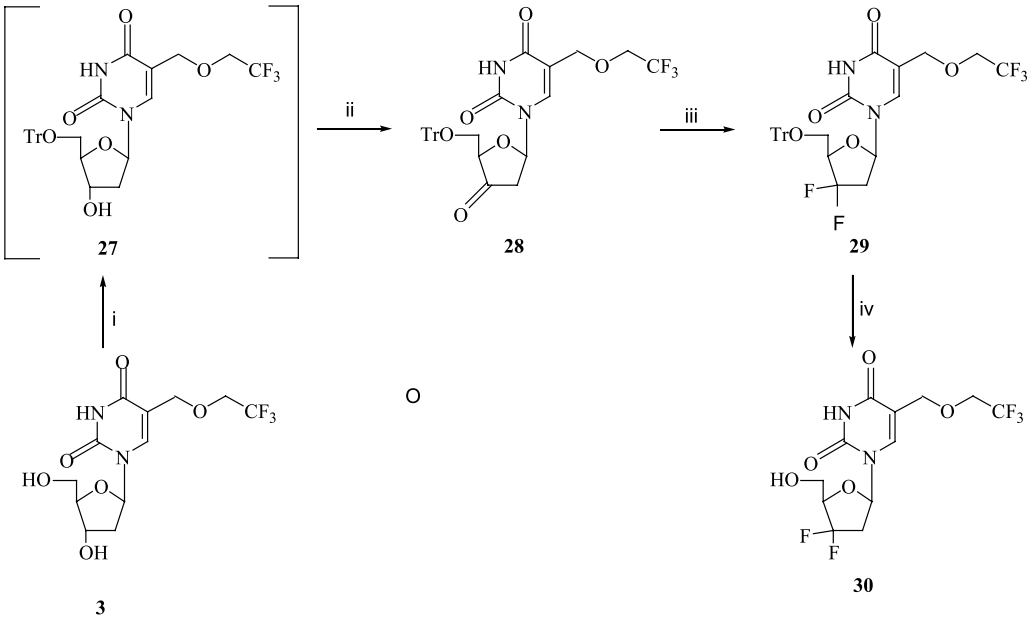


Where, i = Br_2/UV/CCl_4; ii = CF_3CH_2ONa/Cu-bronze; iii = NH_4F/MeOH

Scheme 2. Synthesis of 5-(2,2,2-trifluoroethoxymethyl)- and 5-[*bis*-(2,2,2-trifluoroethoxy)-methyl]- dideoxynucleosides **17**, **20**, **23**, and **26**.

trifluoroethoxymethyl moieties at C-5 of **16** and **19** was confirmed by ^{19}F NMR. Fluorine–carbon couplings (quartets) were observed in ^{13}C NMR spectra, at the expected chemical shifts. Desilylation of **16** and **19**, gave **17** (71%) and **20** (57%), respectively (Scheme 2). Removal of the silyl protecting groups was confirmed by the characteristic downfield shifts of the fluorine signals of **17** and **20** in their ^{19}F NMR spectra.

The synthesis (Scheme 2) of **22** and **25** started from **14** and followed similar reaction pathways as described for the synthesis of **16** and **19**. A characteristic CH_2CF_3 proton quartet in **22** reflected the coupling of these methylenic protons with fluorine



Scheme 3. Synthesis of the *gem*-difluorodideoxynucleoside **30**.

atoms at CF_3. In the case of **25**, similar observations confirmed formation of the 5-[*bis*-(2,2,2-trifluoroethoxy)methyl]- group.

The *gem*-difluoro nucleoside **30** was prepared from **1**[29] via the 3′-keto dideoxynucleoside **28** (Scheme 3). The ^{19}F NMR spectrum of **30** exhibited signals at δ 51.43 and δ 65.44, corresponding to two fluorine atoms with strong geminal fluorine coupling (Jgem = 238.8 Hz) at C-3′. In addition, a triplet at δ127.75 ppm in the ^{13}C NMR spectrum of **30** was ascribed to the coupling of C-3′ with geminal fluorine atoms at this position.

In addition, protection of the 5′-OH group and trifluoroethoxylation at C-5 methyl also had significant electronic impact on various substituents of these molecules. For example, desilylation of **22**, **25**, **16** and **19** induced not only the expected upfield shifts of the C-5′-protons in the respective deblocked compounds **23**, **26**, **17** and **20**, and deshielded H-6, C-6, and the methylene protons and fluorine in CH_2CF_3. The impact of silylation on fluorine chemical shifts of the trifluoroethoxy group at C-5 (compare **1** to **1a**, **2** to **2a**, **22** to **23** and **25** to **26**) and the fluorine present at C-3′ is also evident, with CF_3 fluorines appearing at higher chemical shift after desilylation. The effect of desilylation on C-3′ fluorines was inconsistent, shifting 3′-fluorine downfield in **23** and upfield in **26**. These results (Table 1) indicate that these 5-(2,2,2-trifluoroethoxymethyl)- and 5-[*bis*-(2,2,2-trifluoroethoxy)methyl]- derivatives may adopt the *anti*-conformation.

The contribution of the *anti*-conformation to the stereochemistry of these molecules (**1**, **2**, **22**, **25** and **26**, Figure 2) were further demonstrated by NOE experiments. As seen in Table 2, significant NOE correlation between H-5′ (or *tert*-butyl

Table 1. Perturbation of ^{1}H, ^{13}C and ^{19}F-NMR chemical shifts for H-6, C-6 and the 5-(2,2,2-trifluoroethoxymethyl)- substituents, by the 3′-substituent (-OH, -F or N_3).

	^{1}H NMR		^{19}F NMR	^{13}C NMR		
Compound	*H*-6	CH_2CF_3	CF_3	*C*-6	CH_2CF_3	CF_3
1	8.16	4.00	89.44	141.38	68.63	125.75
1a	7.74	3.75	87.65	138.66	68.37	123.91
2	8.24	4.09	89.56	139.15	64.36	125.36
2a	7.68	3.92	87.29	139.12	64.12	123.47
16	7.6	3.70	87.64	138.48	68.49	*
17	8.08	3.96	89.52	142.27	69.14	126.22
19	7.25	3.82	87.32	138.98	64.18	133.92
20	8.22	4.07	89.70	140.36	68.20	125.22
14	7.60			134.48		
22	7.73	3.77	87.24	138.55	68.39	123.85
23	8.11	4.00	89.34	138.55	68.62	123.85
25	7.83	4.22	87.32	138.68	64.11	123.42
26	8.28	4.08	89.45	141.36	64.32	125.38

*embedded.

or phenyl protons) and H-6 was observed for **1**, **2**, and **25**, supporting the importance of the *anti*-conformation, wherein H-6 stands towards the C-5′ substituents. Compound **22** and **26** showed weak NOE at H-6 upon irradiation at H-5′, while no NOE was observed at H-5′ when H-6 was irradiated. These findings may suggest that contribution of the *syn*-conformation increased for compounds **22** and **26**, while the *anti*-conformation is still involved as an important conformation though the contribution is reduced. NOE correlation between 6-H and 3′-H which was observed for **1**, and **2**, disappeared for compounds substituted by a fluorine atom at C-3′ (**22**, **25** and **26**), suggesting that the fluorine atom is aligned in such a way that these proton interactions are reduced or the introduced fluorine atom served to diminish the NOE interaction between 6-H and 3′-H, Similarly NOE correlation between 3′-H and 4′-H observed for compounds **1** and **2** disappeared for the compounds **22**, **25**, and **26**.

In order to investigate changes occurring upon introducing fluorine at C-3′, conformational analysis (MM2 method) was applied to the structures of **2** and **26.** Structures were optimized by the PM3 method using MOPAC (Cache ver. 94, release 3.7, CaChe Scientific Inc.). As shown in Figure 3, no remarkable changes were found either in the structure or in the energy curves of the conformational analysis. Similar energy curves are seen for **2** and **26** with the lowest points at the dihedral angles of 64° and 60°, corresponding to the *anti*-conformation. The energy curves for **2** and **26** show three local minimum points at − 110°/ − 116° (corresponding to *syn*-conformation), 0°/0° (staggered conformation), and 170°/170° (staggered conformation) (**2/26**) suggesting that both conformations can be involved as the rotational isomers.

No significant differences were observed from the computational analysis to explain the changes in the NOE due to the introduction of the C-3′ fluorine atom, suggesting that the above findings are more attributable to the nature of the fluorine atom than the structural or conformational changes.

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Figure 2. Structures of nucleosides selected for NOE studies.

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Table 2. NOE correlations for compounds **1**, **2**, **22**, **25** and **26**.

	NOE observed (%)				
Irradiated at	**1**	**2**	**22**	**25**	**26**
5-CH or 5-(CH_2)	6(6.6) OCH_2(5.7)	6(1.9) OCH_2(12.4)	6(2.6) OCH_2(2.5) 5′(1.2), t-Bu(1.0)	6(2.4) OCH_2(15.4)	6(7.3) OCH_2(15.8)
OCH_2CF_3	5-CH_2(1.3) 6(0.4)	5-CH (5.5) 6(1.3)	5-CH_2(1.6) t-Bu(0.6)	5-CH (5.3) 6(0.7); t-Bu(0.4)	5-CH (5.0) 6(1.2)
6-H	OCH_2(1.6)1′(1.5) 2′(6.9) 3′(2.3) 4′(1.8) 5′H2(1.8)	OCH_2(3.7) 1′(4.6) 2′(4.6) 3′(1.5) 5-CH(2.3) 5′H2(1.2)	OCH_2(1.0) 1′(1.5), 2′(2.5), 5-CH_2(2.0) Ph(3.3), t-Bu(1.5)	OCH_2(3.6) 1′(8.2), 2′(1.3), 5-CH (2.5) 5′H2(1.9)	OCH_2(5.5) 1′(6.3) 2′(5.0) 5-CH(3.0)
3′-H	2′(9.1) 4′(4.3) 5′H2(1.8) 6(1.8)	2′(6.9) 4′(3.4) 5′H2(2.4) 6(1.8) 1′(0.3)	2′(5.7), Ph(5.0)	2′(7.9) Ph(1.3) 5′H2(2.7) t-Bu(1.7)	2′(11.2) 5′H2(4.2)
5′-$H_{2(a\ \&/or\ b)}$	6(1.3) 3′(2.4) 4′(10.1)	6(4.9) 3′(6.2) 4′(17.6)	5’-Ha (□□3.88): 5′-Hb(6.3), 4′(8.9) Ph(4.0) t-Bu(2.3) 5’-Hb (□□3.94): 5′-Ha(2.8) 4′(4.0) Ph(5.3) 6(1.3) 5CH_2(3.3)	6(2.5) 3′(1.6) 4′(5.9) Ph(5.4)	5′-Hb(24.0), 6 (1.4) 5′-Ha (25.0) 4′(6.5) 3′(1.0) 6(0.8)

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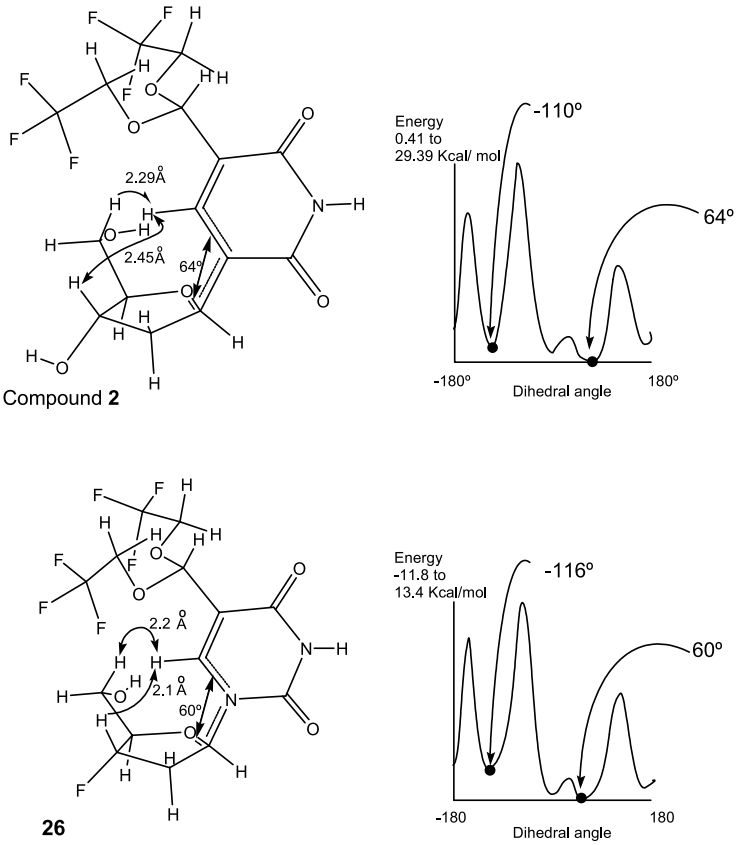

Figure 3. Optimized structures for **2** and **26**. Conformational analysis was made by rotating the pyrimidine moiety on the axis of N-1 and C-1′.

It was also observed that C-4′ and C-5′ protons showed significant electronic deshielding in the 3′-fluorine in compounds **23** and **26**, while substitution by an azido function at the same position made little difference in the chemical shifts of these protons. The effect on carbon chemical shifts by replacing the 3′-OH group in compounds **1** and **2** with fluorine or azido groups is anticipated within the sugar moiety, but these effects are surprisingly extended to the carbon atoms of pyrimidine base at C-6 and its C-5 substituent. It is apparent from the data in Table 1 that both C-6 and CF_3 carbons have shifted upfield in 3′-fluoro-5-trifluoroethoxymethyl analogue **23**, whereas they appeared at higher chemical shifts in the corresponding 3′-fluoro-5-[bis(trifluoroethoxy)methyl]- and 3′azido analogues (compare **1** with **17**, and **23** and **2** with **20** and **26,** respectively).

Antiviral Activity

Compounds **17**, **26** and **30** showed significant potency in the HIV-1 and HIV-2 assays (Table 3). Activity of **1**, **2**, **7** and **8** against rhinovirus type 1A and rhinovirus type 39 in

Table 3. Anti-HIV-1 and -HIV-2 activity of the compounds **1**, **2**, **6**, **17**, **26** and **30** in human T-lymphocyte (CEM cells).

	EC_{50} (μg/mL)*	
Compound	HIV-I	HIV-2
1	> 100	100
2	>100	>100
6	>100	>100
17	1.50 ± 0.87	3.1 ± 1.6
26	15.0 ± 7.1	35.0 ± 7.1
30	53.3 ± 41.6	≥100

*50% Effective concentration or concentration required to protect CEM cells against the cytopathogenicity of HIV by 50%; the AZT EC_{50} is 10 nM (2.5 ng/mL) in this system.

W138 cells was minimal, with IC_{50} and CC_{50} concentrations of > 50 μg/mL in each case. In this assay, the positive reference compound WIN (2,6-dimethyl-1-(3-[3-methyl-5-isoxazolyl]-propanyl)-4-[4-methyl-2h-tetrazol-2-yl]-phenol) was active against rhinovirus 1A (25 μg/mL) and rhinovirus 39 (5 μg/mL), with a CC_{50} of > 25 μg/mL. Similar low potencies (IC_{50} and CC_{50} were > 50 μg/mL) were observed against TK^+ VZV (YS and OKA strains), TK^-VZV (07/1 and YS/R strains) and CMV (AD-169 and Davis strains) in human embryonic cells (HEL). VZV was similarly insensitive to **1**, **2**, **6**, **17**, **26** and **30**, in comparison to positive controls ACV (IC_{50}: 0.9, 0.96, 6 and 8 μg/mL, respectively; MCC_{50} > 50 and CC_{50} > 200 μg/mL) and BVDU (IC_{50}: 0.0047, 0.0043, > 50 and > 50 μg/mL, respectively; MCC_{50} > 50 and CC_{50}> 200 μg/mL). CMV-active compounds ganciclovir and cidofovir had IC_{50} values of 2 and 3 μg/mL and 0.35 and 0.85 μg/mL for the respective strains, respectively (Table 3). In the CMV assay, ganciclovir and cidofovir had MCC_{50} and CC_{50} > 50, with cidofovir being slightly more toxic to the host (HEL) cells in the CC_{50} (35 μg/mL) determination.

Cytotoxicity

Growth of L1210/0, FM3A/0 and CEM/0 cells was inhibited by **1** IC_{50}: 7.2, 53 and 8.3 μg/mL. Inhibitory concentrations of **2** were 35.5, > 100 and 35.5 μg/mL for these cell lines. These compounds (**1**, **2**, **6**, **17**, **26** and **30**) were not toxic to Molt4/C8 cells in this study. All compounds were rated inactive in the NCI in vitro antitumor screen (data not shown).

CONCLUSION

A series of 5-(trifluoroethoxymethyl)-2′,3′-dideoxyuridines and 5-[bis(trifluoro-ethoxy)methyl]-2′,3′-dideoxyuridines were prepared. The structural assignments for **1**, **2**, **22**, **25**, and **26** are based on NOE experiments and MO calculations. Compounds **1**, **2**, and **25** are suggested to adopt *anti*-conformation more favourably in solution, while

compound **22** and **26** may take the *syn*-conformation more preferably than the *anti*-conformation. As anticipated on the basis of the bulky C-5 substituents, these compounds were devoid of anti-HSV activity. This structural feature reduced, but did not totally eliminate anti-HIV activity. The compounds were not active against a bank of cancer cell lines in vitro.

EXPERIMENTAL SECTION

Abbreviations. AZT, 3′azido-3′-deoxythymidine; D4T, didehydrodeoxythymidine; (FddClUrd), 5-chloro-3′-fluoro-2′,3′-dideoxyuridine; (FEDU), 5-(2-fluoroethyl)-2′-deoxyuridine; (HEPT), 1-(2-hydroxyethoxymethyl)-6-(phenylthio)thymine; (MMdU), 5-methoxymethyl-2′-deoxyuridine; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; CMV, cytomegalovirus; VZV, varicella zoster virus; AIDS, acquired-immune deficiency syndrome; HeLa (human epithelial carcinoma cells); HIV-1, human immunodeficiency virus type 1; HIV-2. Human immunodeficiency virus type-2; s, singlet; d, doublet; dd, doublet of doublet; dddd, doublet of doublet of doublet of doublet, q, quartet, t, triplet; m, multiplet; br, broad; tlc, thin layer chromatography; TBDPS, *tert*-butyldiphenylsilyl; THF, tetrahydrofuran; DME, 1,2-dimethoxyethane; DAST, diethylaminosulfurtrifluoride; DMAP, N,N-dimethylaminopyridine; CCl_4, carbon tetrachloride; DMF, dimethylformamide; EtOH, ethanol.

Cytotoxicity and Antiviral Activity Assays. The methodology used to assess the activity against varicella-zoster virus in human embryonic lung (HEL) cells, cytomegalovirus in human embryonic lung (HEL) cells, proliferation of murine leukemia cells (L1210/0), murine mammary carcinoma cells (FM3A) and human T-lymphocyte cells (Molt4/C8, CEM/0), HIV-1 and HIV-2 proliferation has been described by De Clercq.[30]

In vitro KB cell cytotoxicity assay. Test compounds (0.05, 0.1, 0.5, 1.0, 5, and 10 μg/mL) were added to wells of a 96-well plates. Each well was seeded with KB cells (ATCC-CCL17; 10^4 cells in 100 μL). The plates were incubated for 3 days at 37°C in a CO_2 incubator. The toxicity was determined using the neutral red dye uptake assay: neutral red solution (25 μL) was added to each well, followed by incubation at 37°C for 2.5 h. The cells were then washed with PBS. Washing buffer (50 μL) was added to each well, followed by a two-hour incubation, when the plates were optically read at 540 nm on a spectrophotometer. The concentration of compound required to reduce cell viability by 50% was determined to be the TD_{50}.

In vitro Human Rhinovirus (HRV-1A, HRV-39) Antiviral Assay. Test compounds (50 μL; 0.2, 1.0, 5, 10, 25 and 50 μg/mL) were added to wells of a 96 well plate. Each well was seeded with W138 cells (ATCC-CCL75; 10^4 cells in 100 μL) and 50 μL of rhinovirus type 1A (nasopharyngeal washing/ATCC-VR1110) or rhinovirus type 39 (nasal washing/ATCC-VR340) was added to the appropriate plate. The plates were incubated at 37°C in a CO_2 incubator. The cytopathic effect caused by the virus was scored and the concentration of compound required to reduce this effect by 50% was determined.

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Chemistry. The reagents used in the chemical reactions were of reagent grade, purchased from Aldrich Chemical Co. Anhydrous solvents were dried over appropriate drying agents and freshly distilled at the time of use. The progress of reactions was monitored by tlc on Whatman MK6F silica gel micro slides (250 μm thickness) and the products were purified by silica gel (Merck 7734; particle size 100–200 mesh) column chromatography using the eluent of choice. Melting points were determined on a Büchi capillary apparatus and are uncorrected. The compounds were characterized by their elemental analyses for C, H and N. In some cases, exact ionization high resolution mass spectral analyses (HRMS-EI) were obtained in lieu of elemental analyses. Nuclear magnetic resonance spectra (^{1}H, ^{13}C and ^{19}F NMR) were recorded on a Bruker AM 300 spectrometer. Chemical shifts are reported in δ ppm downfield from tetramethylsilane (^{1}H) and hexafluorobenzene (^{19}F) that were used as internal standards. ^{1}H NMR assignments were confirmed by double irradiation experiments. ^{13}C NMR resonances were assigned using the J modulation spin echo technique (Jmod) where methyl and methine carbon resonances appear as positive peaks, and methylene and quaternary carbons appear as negative peaks.

5′-O-*tert*-Butyldiphenylsilyl-3′-O-methanesulfonylthymidine (9). *tert*-Butylchloro diphenylsilane (5.76 mL, 21.79 mmol) was added to a solution of thymidine (5 g, 20.7 mmol) in anhydrous pyridine (20 mL) and the mixture was stirred overnight at 25°C under an atmosphere of argon. Tlc at this point showed complete disappearance of thymidine. The contents were cooled to 0°C and methanesulfonyl chloride (2.45 mL, 21.79 mmol) was added drop-wise. Stirring was continued for 2 h and then the mixture was allowed to warm up to 25°C. After stirring the reaction for an additional 30 min., the contents were poured into crushed ice/water and then the solvent was evaporated in vacuo. The viscous mass so obtained was taken in chloroform (100 mL) and washed with water (20 mL × 2). The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated on a rotary evaporator to obtain impure product. Silica gel column purification, eluting with a linear gradient beginning with toluene and ending with 10% ethyl acetate, afforded pure 9 (9.65 g, 86%) as a foam: mp 76°C; Rf 0.41 ($CHCl_3$:MeOH, 9:1); **^{1}H NMR** ($CDCl_3$)- δ 1.13 (s, 9H, *t*-butyl), 1.62 (s, 3H, CH_3), 2.34 (d, $J_{1',2''}$ = 8.6 Hz, of d, $J_{3',2''}$ = 6.3 Hz, of d, Jgem = 13.7 Hz), 2.64 (d, $J_{1',2''}$ = 5.1 Hz, of d, Jgem = 13.7 Hz, 1H, H-2′), 3.07 (s, 3H, SO_2CH_3), 3.96 and 4.02 (two d, $J_{4',5''}$ = 2.3 Hz, of d, Jgem = 11.4 Hz, 2H, H-5′ and H-5″), 4.37 (d, $J_{5',4'} = J_{5'',4'}$ = 2.3 Hz, 1H, H-4′), 5.41 (d, $J_{2'',3'}$ = 6.3 Hz, 1H, H-3′), 6.43 (d, $J_{2',1'}$ = 5.1 Hz of d, $J_{2'',1'}$ = 8.6 Hz, 1H, H-1′), 7.38–7.54 (m, 7H, 1H of H-6 and 6H aromatic), 7.62–7.72 (m, 4H, aromatic) and 9.24 (s, br, 1H, NH) ppm; **^{13}C NMR** ($CDCl_3$)- δ11.97 (SO_2CH_3), 19.34 (*tert*-C of butyl), 26.98 (5-CH_3), 38.44 (C-2′), 38.66 (CH_3's of *tert*-butyl group), 63.47 (C-5′), 79.42 (C-3′), 84.21 (C-4′), 84.72 (C-1′), 111.69 (C-5), 128.05–132.59 (aromatic carbons), 134.66 (C-6), 135.22 and 135.49 (remaining aromatic carbons), 150.23 (C-2) and 163.39 (C-4); anal. for $SiC_{27}H_{34}N_2O_7$ calc. C 58.05, H 6.13, N 5.01; found C 58.62, H 5.97 and N 4.89.

2,3′-Anhydro-5′-O-*tert*-butyldiphenylsilyl-3′-deoxythymidine (10). An aqueous solution of 1N NaOH (0.4 g, 10 mmol) was added to a refluxing solution of **9** (5.58 g, 10 mmol) in absolute EtOH (35 mL) drop-wise. Stirring was continued at this temperature for 2 h. At that time, the tlc showed complete conversion of starting

material to the product. The content was cooled to 25°C and neutralized with acetic acid to pH 7.0. The solution was evaporated to dryness and the residue purified on a silica gel column by elution first with chloroform and ending with 3% methanol to yield 4.33 g (80%) of pure **10** as a semisolid: **^{1}H NMR** ($CDCl_3$)- δ 1.06 (s, 9H of *tert*-butyl group), 1.90 (s, 3H, 5-CH_3), 2.41 (d, $J_{3',2}$ = 3.0 Hz of d, $J_{1',2''}$ = 4.0 Hz of d, Jgem = 13.0 Hz, 1H, H-2″), 2.72 (d, Jgem = 13.0 Hz, 1H, H-2′), 3.78 (d, $J_{4',5''}$ = 7.0 Hz of d, Jgem = 15 Hz, 1H, H-5″), 3.84 (d, $J_{4',5'}$ = 7.0 Hz of d, Jgem = 15 Hz, 1H, H-5′), 4.31 (d, $J_{5',4'}$ = 7.0 Hz of d, $J_{3',4'}$ = 2.0 Hz, 1H, H-4′), 5.20 (br, 1H, H-3′), 5.48 (d, $J_{2'',1'}$ = 4.0 Hz, 1H, H-1′), 6.9 (s, 1H, H-6), and 6 7.30–7.70 (m, 10H of two phenyl groups) ppm; anal. calc. for $SiC_{26}H_{31}N_2O_4$ (463.66), C 67.38, H 6.69, N 6.04; found, C 67.28, H 6.51, N 5.89.

3′-Azido-5′-O-*tert*-butyldiphenylsilyl-3′-deoxythymidine (11). A mixture of sodium azide (1.95 g, 30 mmol) and 2,3′-anhydro-5′-O-*tert*-butyldiphenylsilyl thymidine 10 (2.77 g, 6.0 mmol) in anhydrous DMF (10 mL) was heated at 110°C under stirring for 24 h. The progress of the reaction was monitored by tlc. After the reaction was complete, the solvent was evaporated in vacuo, and the crude mass extracted with chloroform/cold water (20 mL × 2). The chloroform phase was dried over anhydrous magnesium sulfate, filtered and evaporated to collect a solid that was purified on a silica gel column, eluting with toluene and finally with 20% ethyl acetate, to give 1.4 g (46%) of pure **11**: mp 55°C (softened); **^{1}H NMR** ($CDCl_3$)- δ 1.14 (s, 9H, *tert*-butyl group), 1.66 (s, 3H, CH_3), 2.33 (d, $_{1',2''}$ = 6.2 Hz of d, $J_{3',2''}$ = 6.2 Hz of d, Jgem = 13.8 Hz, 1H, H-2″), 2.48 (d, $J_{1',2'}$ = 6.2 Hz of d, $J_{3',2'}$ = 3.75 Hz of d, Jgem = 13.8 Hz, 1H, H-2′), 3.85 (d, $J_{4',5''}$ = 3.8 Hz of d, Jgem = 12.5Hz, 1H, H-5″), 3.99 (d, $J_{3',4'}$ = 7.5 Hz of d, $J_{5',4'}$ = 3.8 Hz, 1H, H-4′), 4.04 (d, $J_{4',5'}$ = 3.8 Hz of d, Jgem = 12.5 Hz, 1H, H-5′), 4.34 (quintet, $J_{4',3'}$ = 7.5 Hz, $J_{2',3'}$ = 3.8 Hz, $J_{2'',3'}$ = 6.2 Hz, 1H, H-3′), 6.28 (t, $J_{2',1'}$ = 6.2 Hz, H-1′), 7.56–7.36 (m, 7H, 6H of phenyls and 1H of H-6), 7.76–7.64 (m, 4H of two phenyls) and 9.24 (s, br, D_2O exchangeable, 1H, NH) ppm; anal. calc. for $SiC_{26}H_{31}N_5O_4$ (505.646); C, 61.76; H, 6.17; N, 13.85; found; C, 62.86; H, 6.36; N, 12.85.

5-(2,2,2-Trifluoroethoxy)methyl-3′-azido-5′-O-*tert*-butyldiphenylsilyl-2′,3′-dideoxyuridine (16). Bromine (0.14 mL, 2.48 mmol) was dissolved in anhydrous carbon tetrachloride (10 mL) and added drop-wise to a stirred refluxing solution of **11** (1.0 g, 1.99 mmol) in CCl_4 (30 mL) under irradiation with a 75 W UV lamp.[31] Strict anhydrous reaction atmosphere was maintained by circulating argon through the reaction vessel. After the addition of bromine was complete and showed no **11**, argon was bubbled through the reaction mixture to remove residual bromine and HBr generated during the reaction. The solvent was evaporated under complete exclusion of moisture to give 5-(bromomethyl)-3′-azido-2′,3′-dideoxyuridine **15**. This bromo intermediate was used without further purification. It was re-dissolved in anhydrous 1,2-dimethoxyethane (DME) (15 mL) and added to a solution of trifluoroethoxide-copper complex[20,21] (2.5 mmol) in DME (15 mL). The mixture was stirred overnight at 25°C under argon, and then diluted with diethyl ether (150 mL). The organic layer was washed with ammonium hydroxide solution (28%, 15 mL × 2) followed by cold water until the pH of the mixture was neutral, then dried over anhydrous $MgSO_4$, filtered and the solvent evaporated in vacuo. Purification of this impure product on a

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silica gel column using toluene/ethyl acetate (20%) afforded 0.21 g (17%) of pure 16 as a foam: mp 76°C (softening); Rf 0.61 ($CHCl_3$:MeOH, 9.5:0.5); IR (neat)- 2110 cm^{-1} (N_3 stretch);**^{1}H NMR** ($CDCl_3$)- δ 1.04 (s, 9H of *tert*-butyl group), 2.21 (quintet, Jgem = 14.0 Hz, $J_{1',2''}$ = 6.75 Hz, $J_{3',2''}$ = 6.75 Hz, 1H, H-2″), 2.44 (d, Jgem = 14.0 Hz of d, $J_{1',2'}$ = 6.75 Hz of d, $J_{3',2'}$ = 3.9 Hz, 1H, H-2′), 3.70 (q, $J_{F,H}$ = 8.3 Hz, 2H of OCH_2CF_3), 3.78 (d, $J_{4',5'}$ = 3.9 Hz of d, Jgem = 12.4 Hz, 1H, H-5′), 3.90 (m, 2H, 1H, H-4′ and 1H, H-5′), 4.02 (d, Jgem = 11.3 Hz, 1H of $CH_2OCH_2CF_3$), 4.06 (d, Jgem = 11.3Hz, 1H of $CH_2OCH_2CF_3$), 4.20 (quintet, $J_{4',3'}$ = 3.9 Hz, $J_{2',3'}$ = 3.9 Hz, $J_{2'',3'}$ = 8.5 Hz, 1H, H-3), 6.12 (t, $J_{2',1'}$ = $J_{2'',1'}$ = 6.8 Hz, 1H, H-1′), 7.28–7.44 (m, 6H of phenyls), 7.53–7.64 (m, 5H, 4H of phenyls and 1H of H-6), and 9.25 (s, broad, D_2O exchangeable, 1H, NH) ppm; **^{19}FMR** ($CDCl_3$+ C_6F_6)- δ 87.64 (t, $J_{F,H}$ = 8.3 Hz) ppm; **^{13}C NMR** ($CDCl_3$)- δ 19.31 (*tert*-carbon of *tert*-butyl group), 26.98 (methyl carbons of *tert*-butyl group), 37.92 (C-2′), 60.59 (C-4′), 63.52 (C-5′), 66.55 ($CH_2OCH_2CF_3$), 68.49 (q, $J_{F,C}$ = 33.9 Hz, CH_2CF_3), 84.57 (C-3′), 85.09 (C-1′), 111.12 (C-5), CF_3 embedded in the basal line, 135.53–130.26 (phenyl carbons), 138.48 (C-6), 149.67 (C-2), and 162.10 (C-4) ppm; anal. calc. for $SiC_{28}H_{27}F_3N_5O_5$ (603.66); C, 55.70; H, 5.34; N, 11.60; found; C, 55.68; H, 5.46; N, 11.21.

5-(2,2,2-Trifluoroethoxy)methyl-3′-azido-2′,3′-dideoxyuridine (17). Tetrabutyl ammonium fluoride (0.19 mL, 0.19 mmol) solution was added to a solution of 16 (0.1 g, 0.18 mmol) in anhydrous THF under argon, and the reaction mixture was stirred overnight at 25°C. Evaporation of the solvent in vacuo, followed by the purification of impure material on a silica gel column by eluting with 5% methanol in chloroform gave 40 mg (71%) of pure **17** as a semisolid: Rf 0.48 ($CHCl_3$:MeOH, 9:1,v/v); IR (neat)- 2110 cm^{-1} (N_3 stretch); **^{1}H NMR** (CD_3OD)- δ 2.4 (t, $J_{3',2'}$ = $J_{1',2'}$ = 6.2 Hz, 2H, H-2′), 3.71 (d, $J_{4',5''}$ = 2.3 Hz of d, Jgem = 12.4 Hz, 1H, H-5″), 3.81 (d, $J_{4',5'}$ = 2.3 Hz of d, Jgem = 12.4 Hz IH, H-5′), 3.90 (d, $J_{5',4'}$ = 2.3 Hz of d, $J_{3',4'}$ = 7.9 Hz, 1H, H-4′), 3.96 (q, $J_{F,H}$ = 8.9 Hz, 2H, OCH_2CF_3), 4.34 (m, 3H, 2H of $CH_2OCH_2CF_3$ and 1H of H-3′), 6.12 (t, $J_{2',1'}$ = 6.2 Hz, 1H, H-1′) and 8.08 (s, 1H, H-6) ppm; **^{19}FMR** (CD_3OD + C_6F_6)- δ 89.52 (t, $J_{H,F}$ = 8.9 Hz) ppm; **^{13}C NMR** (CD_3OD)- δ 39.08 (C-2′), 61.99 (C-4′), 62.79 (C-5′), 68.34 ($CH_2OCH_2CF_3$), 69.14 (q, $J_{F,C}$ = 34.2 Hz, OCH_2CF_3), 86.87 (C-3′), 87.12 (C-1′), 112.01 (C-5), 126.22 (q, J_{F-C} = 278 Hz, CF_3), 142.27 (C-6), 152.51 (C-2) and 165.60 (C-4) ppm; LRMS- M^+ (relative abundance 0.8%); anal. calc. for $C_{12}H_{14}F_3N_5O_5$ (365.27); C:, 39.46; H, 3.86; N, 19.17; found; C, 39.44; H, 3.95; N, 17.56.

5-[bis(2,2,2-Trifluoroethoxy)methyl]-3′-azido-5′-O-*tert*-butyldiphenylsilyl-2′,3′-dideoxyuridine (19). Bromine (0.14 mL, 2.48 mmol) solution in carbon tetrachloride (10 mL) was added drop-wise to a refluxing solution of **11** (0.5g, 0.99 mmol) in anhydrous carbon tetrachloride (25 mL), under argon atmosphere. This reaction mixture was continuously irradiated through a 75 W UV lamp. When the reaction mixture showed no evidence of **11** on tlc, excess bromine and HBr were removed from the reaction mixture. The work up was done as described in the synthesis of **16**. The bromide intermediate **18**, so obtained, was dissolved in anhydrous DME (15 mL) and transferred to the flask containing 2,2,2-trifluoroethoxide-copper complex (2.5 mmol) in anhydrous ethylene glycol dimethyl ether (DME, 10 mL). The contents were stirred under argon overnight and then extracted sequentially with chloroform/ ammonium hydroxide (5:1; 60 mL × 2) followed

by cold water until the pH was neutral. The organic phase was dried over anhydrous magnesium sulfate, filtered and evaporated, in vacuo, to afford impure **19**. It was purified on a silica gel column using toluene:ethyl acetate (80:20, v/v) to give (0.4g, 57%) of a viscous product **19**: Rf 0.56 ($CHCl_3$:MeOH, 9.5:0.5, v/v); IR (neat)- 2110 cm^{-1}; **^{1}H NMR** ($CDCl_3$)- δ 1.06 (s, 9H, *tert*-butyl), 2.17 (d, $J_{1',2''}$ = 7.5 Hz of d, $J_{3',2''}$ = 7.0 Hz of d, Jgem = 14.5 Hz, 1H, H-2″), 2.44 (d, $J_{1',2'}$ = 6.5 Hz of d, $J_{3',2'}$ = 3.5 Hz of d, Jgem = 14.5 Hz, 1H, H-2′), 3.82 (two q, $J_{F,H}$ = 8.5 Hz, 4H for 2 × OCH_2CF_3), 3.88 (d, $J_{4',5'}$ = 3.5 Hz of d, Jgem = 11.0 Hz, 1H of H-5′), 4.0 (d, $J_{4',5''}$ = 3.5 Hz of d, Jgem = 11.0 Hz, 1H, H-5″), 4.0 (quintet, $J_{3',4'} = J_{5',4'} = J_{5'',4'}$ = 3.5 Hz, 1H, H-4′), 4.20 (d, $J_{2'',3'}$ = 7.0 Hz of d, $J_{4',3'}$ = 3.5 Hz, 1H, H-3′), 5.61 (s, 1H, 5-CH), 6.01 (d, $J_{2',1'}$ = 7.5 Hz of d, $J_{2'',1'}$ = 6.5 Hz, 1H, H-1′), 7.25 (s, 1H, H-6), 7.30–7.60 (m, 10H, phenyls) and 8.24 (s, br, 1H, NH, exchanges with deuterium) ppm; **^{19}F NMR** ($CDCl_3$)- δ 87.32 (t, $J_{H,F}$ = 8.0 Hz, for one CH_2CF_3 moiety) and 87.35 (t, $J_{H,F}$ = 8.5 Hz, for other CH_2CF_3 moiety); **^{13}C NMR** ($CDCl_3$)- δ 26.56 (CH_3s of *tert*-butyl group), 29.67 (tertiary carbon of *tert*-butyl), 39.53 (C-2′), 61.20 (C-4′), 63.52 (C-5′), 64.18 (two q, merged, two OCH_2CF_3s, $J_{F,C}$ = 34.0 Hz), 84.72 (5-CH), 86.05 (C-3′), 97.49 (C-1′), 110.16 (C-5), 127.71–135.51 (aromatic carbons), 133.92 (q, $J_{F,C}$ = 278.0 Hz, two CF_3), 138.98 (C-6), C-4 and C-2 were buried in the basal line due to dilution of the sample; EI for $SiC_{30}H_{33}F_6N_5O_6$ (701.60) found, M^+ (1.5%).

5-[bis(2,2,2-Trifluoroethoxy)methyl]-3′-azido-2′,3′-dideoxyuridine (20). Tetrabutyl ammonium fluoride solution in THF (0.22 mL, 0.22 mmol) was added to a solution of **19** (95 mg, 0.135 mmol) in anhydrous tetrahydrofuran (5 mL) under nitrogen. The contents were stirred at 25°C overnight, and then the solvent was removed in vacuo. Chromatography of the crude residue on silica gel with 2% methanol in chloroform afforded **20** as a semisolid: yield, 20 mg (32%); Rf 0.53 ($CHCl_3$:MeOH, 9:1, v/v); IR (neat)- 2120 cm^{-1} (N_3 stretch); **^{1}H NMR** (CD_3OD)-δ 2.45 (t, $J_{3',2'} - J_{1',2''}$ = 6.2 Hz, 2H, H-2″), 3.73 (d, $J_{4',5''}$ = 3.4 Hz of d, Jgem = 11.3 Hz, 1H, H-5″), 3.80 (d, $J_{4',5'}$ = 3.4 Hz of d, Jgem = 11.3 Hz, 1H, H-5′), 3.98 (d, $J_{5',4'}$ = 3.4 Hz of d, $J_{3',4'}$ = 8.4 Hz, 1H, H-4′), 4.07 (two q, merged together, $J_{F,H}$ = 9.0 Hz, 4H of two OCH_2CF_3 groups), 4.32 (d, $J_{2'',3'}$ = 6.2 Hz of $_d$, $J_{4',3'}$ = 8.4 Hz, 1H, H-3′), 5.73 (s, 1H, $CH(OCH_2CF_3)_2$), 6.14 (t, $J_{2',1'} = J_{2'',1'}$ = 6.2 Hz, 1H, H-1′), and 8.22 (s, 1H, H-6) ppm; **^{19}F NMR** (CD_3OD + C_6F_6)-δ 89.70 (t, $J_{F,H}$ = 9.0 Hz, for one OCH_2CF_3 group) and 89.65 (t, $J_{F,H}$ = 8.6 Hz, for the other OCH_2CF_3 group) ppm; **^{13}C NMR** ($CDCl_3$)- δ30.72 (C-2′), 61.19 (C-4′), 62.12 (C-5′), 68.20 (two q, merged, two OCH_2CF_3, $J_{F,C}$ = 34.0 Hz), 86.53 (5-CH), 87.48 (C-3′), 98.20 (C-1′), 110.60 (C-5), 125.22 (q, $J_{F,C}$ = 272.0 Hz, two CF_3), 140.36 (C-6), 151.53 (C-2) and 163.51 (C-4) ppm; LRMS- M^+ (relative abundance 0.4%); HRMS-EI for $C_{14}H_{15}F_6N_5O_6$, calc. 463.0926 ; found, 463.0926, M^+ 1.21%.

Threothymidine (12). 5′-O-*tert*-Butyldiphenylsilyl-3′-O-methanesulphonyl thymidine 9 (4.45 g, 7.94 mmol) was dissolved in 98% EtOH (25 mL) and warmed to reflux. A 10N aqueous solution of sodium hydroxide (1.27 g, 31.8 mmol in 32 mL water) was added to this solution and the refluxing was continued for 4 h. A tlc examination at this time showed complete disappearance of 5′-O-tert-butyldiphenylsilyl-3′-O-methanesulphonylthymidine. The mixture was cooled down to 25°C and acidified with 1N HCl to pH 7.0, filtered, evaporated and purified on a silica gel column. The elution started with chloroform and ended with 5% methanol to afford 1.29 g of pure **12** (70%): mp

172–173°C (reported 170–171°C);[32] **^{1}H NMR** (D_2O)- δ 1.73 (s, 3H, 5-CH_3), 1.91 (d, $J_{1',2''}$ = 2.5 Hz of d, Jgem = 15.0 Hz, 1H, H-2″), 2.57 (d, Jgem = 15.0 Hz of d $J_{1',2'}$ = 8.5 Hz of d, $J_{3',2'}$ = 5.5 Hz, 1H, H-2′), 3.74 (d, $J_{4',5''}$ = 7.0 Hz of d, Jgem = 13.5 Hz, 1H, H-5″), 3.90 (d, $J_{4',5'}$ = 4.5 Hz of d, Jgem = 13.5 Hz, 1H, H-5′), 3.95 (d, $J_{5',4'}$ = 4.5 Hz of d, $J_{3',4'}$ = 3.2 Hz of d, $J_{5'',4'}$ = 7.0 Hz, 1H, H-4′), 4.33 (d, $J_{2',3'}$ = 5.5 Hz of d, $J_{4',3'}$ = 3.0 Hz, 1H, H-3′), 6.00 (d, $J_{2'',1'}$ = 2.5 Hz of d, $J_{2',1'}$ = 8.2 Hz, 1H, H-1′) and 7.73 (s, 1H, H-6) ppm.

3′-Fluoro-3′-deoxythymidine (13). Threothymidine (2.3 g, 9.5 mmol) was dissolved in anhydrous dimethylformamide (10 mL) and triphenylmethyl chloride (2.91 g, 10.45 mmol) was added to this solution under stirring at 25°C. This was followed by the addition of N,N-dimethylaminopyridine (DMAP, 58 mg, 0.48 mmol) and heating of the reaction mixture at 50°C for 4 h. Threothymidine was completely changed to its 5′-trityl analog at this time. The solvent was evaporated on a rotary evaporator and ice/water was poured into the resulting viscous mixture. A white solid precipitated (3.9 g, 85%) that was filtered and washed thoroughly with cold water, dried over P_2O_5, re-dissolved in anhydrous dichloromethane (150 mL) and then cooled to 0°C. Diethylaminosulfurtrifluoride (2.46 mL, 16.9 mmol) was added to this solution under stirring while the temperature was maintained at 0°C.[33] The mixture was allowed to warm to 25°C once the addition of DAST was over and stirred for further 4 h. The contents were poured into a saturated solution of sodium bicarbonate (200 mL), and the organic phase was washed with cold water and dried over anhydrous sodium sulfate. Evaporation of the solvent led to a brown semi-crystalline mass that was treated with 80% acetic acid at 25°C. Detritylation was complete after 3 h of acid treatment. The viscous mass, obtained after evaporation of acetic acid, was purified on the silica gel column using 5% methanol in chloroform as eluent to afford 1.28 g (65%) of pure **13**; mp 178–179°C. Spectroscopic data for this compound corresponded to literature data.[34]

3′-Fluoro-5′-O-*tert*-butyldiphenylsilyl-3′-deoxythymidine (14). 3′-Fluoro-3′-deoxythymidine **13** (0.4 g, 1.64 mmol) was dissolved in anhydrous pyridine (5 mL) and *tert*-butyldiphenylchlorosilane (0.59 g, 2.13 mmol) was added to it while stirring. The reaction was allowed to proceed overnight at 25°C and then quenched by adding ice/water to the reaction mixture. The solvent was removed in vacuo and the impure product was purified on a silica gel column. Elution with 20% ethyl acetate in toluene afforded 0.71 g (90%) of **14**: mp 72°C (softened); **^{1}H NMR** ($CDCl_3$)- δ 1.29 (s, 9H, *tert*-butyl group), 1.35 (s, 3H, CH_3), 2.18 (d, $_{1',2''}$ = 9.0 Hz of d, $J_{3',2''}$ = 5.0 Hz of d, Jgem = 14.5 Hz of d, $J_{F,H}$ = 39.0 Hz, 1H, H-2″), 2.64 (d, $J_{1',2'}$ = 5.5 Hz of d, Hz of d, Jgem = 14.5 Hz, $J_{F,H}$ = 20.9 Hz, 1H, H-2′), 3.87 (d, $J_{4',5''}$ = 2.0 Hz of d, Jgem = 11.5Hz, 1H, H-5″), 4.02 (d, $J_{4',5'}$ = 1.5 Hz of d, Jgem = 11.5 Hz, 1H, H-5′), 4.29 (d, $J_{5'',4'}$ = 2.0 Hz of d, $J_{5',4'}$ = 1.5 Hz of d, $J_{F,4'}$ = 28.0 Hz,1H, H-4′), 5.29 (d, $J_{2'',3'}$ = 5.0 Hz of d, $J_{F,3'}$ = 54.0 Hz, 1H, H-3′), 6.43 (d, $J_{2',1'}$ = 5.5 Hz of d, $J_{2'',1'}$ = 9.5 Hz, 1H, H-1′), 7.38–7.72 (m, 11H, 10H of phenyls and 1H of H-6) and 8.08 (s, br, D_2O exchangeable, 1H, NH) ppm; **^{19}F NMR** ($CDCl_3$)- δ -14.26 (d, $J_{3',F}$ = 53.7 of d, $J_{2'',F}$ = 39.3 Hz of d, $J_{2',F}$ = 20.9 Hz of d, $J_{4',F}$ = 28.1 Hz) ppm; **^{13}C NMR** ($CDCl_3$)- δ 11.99 (CH_3 at C-5), 19.39 (*tert*-carbon of t-butyl group), 27.60 (methyl carbons of *tert*-butyl group), 38.83 (d, $J_{F,C}$ = 21.3 Hz, C-2′), 63.92 (d, $J_{F,C}$ = 11.1 Hz, C-5′), 84.57 (C-1′), 84.98 (d, $J_{F,C}$ = 25 Hz, C-4′), 94.64 (d, $J_{F,C}$ = 177.8 Hz, C-3′), 111.41

(C-5), 134.84 (C-6), 135.50–128.07 (phenyl carbons), 147.60 (C-2) and 163.15 (C-4) ppm; anal. calc. for $SiC_{26}H_{31}FN_2O_4.1/4H_2O$ (487.116); C, 64.02; H, 6.52; N, 5.75; found; C,63.86; H, 6.65; N, 5.42.

5-(2,2,2-Trifluoroethoxymethyl)-3′-fluoro-5′-O-*tert*-butyldiphenylsilyl-2′,3′-dideoxyuridine (22). A solution of **14** (0.53 g, 1.08 mmol) in anhydrous CCl_4 (25 mL) was irradiated with a 75 W UV lamp and bromine (0.082 mL, 1.6 mmol) was added to it slowly under reflux. This precursor completely changed to its 5-bromomethyl derivative **21** in 1 h. After the removal of excess bromine, HBr and the solvent, as described earlier, this intermediate product was re-dissolved in anhydrous DME (25 mL) and added to trifluoroethoxide-copper complex (3.24 mmol). The reaction was allowed to stir for 16 h at 25°C under argon. Work-up of the reaction was performed as described for the synthesis of **16**. Purification of the impure product on a silica gel column with toluene:ethyl acetate (80:20, v/v) gave 380 mg (60%) of pure **22**: mp 55°C (softened); Rf 0.13 (toluene:ethyl acetate; 80:20, v/v); **^{1}HNMR** ($CDCl_3$)- δ 1.08 (s, 9H, *t*-butyl group), 2.18 (d, $J_{1',2''}$ = 8.5 Hz of d, $J_{3',2''}$ = 5.0 Hz of d, Jgem = 14.0 Hz of d, $J_{F,H}$ = 39.0 Hz, 1H, H-2″), 2.77 (d, $J_{1',2'}$ = 5.2 Hz of d, Jgem = 14.0 Hz of d, $J_{F,H}$ = 20.0 Hz, 1H, H-2′), 3.77 (q, $J_{F,H}$ = 8.5 Hz, 2H, CH_2CF_3), 3.87 (d, $J_{4',5''}$ = 3.0 Hz of d, Jgem = 11.5Hz, 1H, H-5″), 3.95 (d, $J_{4',5'}$ = 3.0 Hz of d, Jgem = 11.5 Hz, 1H, H-5′), 4.06 (d, Jgem = 12.0 Hz, 1H, CH_2OCH_2), 4.13 (d, Jgem = 12.0 Hz, 1H, CH_2OCH_2), 4.31 (dd, $J_{5'',4'}$ = $J_{5',4'}$ = 3.0 Hz of d, $J_{F,4'}$ = 26.5 Hz,1H, H-4′), 5.26 (d, $J_{2'',3'}$ = 5.0 Hz, $J_{F,3'}$ = 53.5 Hz, 1H, H-3′), 6.38 (d, $J_{2',1'}$ = 5.2 Hz of d, $J_{2'',1'}$ = 8.5 Hz, 1H, H-1′), 7.30–7.70 (m, 10H, phenyls), 7.73 (s, 1H, H-6) and 9.78 (s, broad, D_2O exchangeable, 1H, NH) ppm; **^{19}F NMR** ($CDCl_3$)- δ 87.24 (t, $J_{H,F}$ = 8.9 Hz, CH_2CF_3), − 13.68 (d, $J_{3',F}$ = 53.7 of d, $J_{2'',F}$ = 39.3 Hz of d, $J_{2',F}$ = 20.3 Hz of d, $J_{4',F}$ = 27.0 Hz, 3′-F) ppm; **^{13}C NMR** ($CDCl_3$)- δ 26.92 (methyl carbons of t-butyl group), 29.64 (*tert*-carbon of *tert*-butyl group), 39.02 (d, $J_{F,C}$ = 20.7 Hz, C-2′), 63.67 (d, $J_{F,C}$ = 10.2 Hz, C-5′), 66.51 (CH_2OCH_2), 68.39 (q, $J_{F,C}$ = 34.3 Hz, CH_2CF_3), 85.20 (d, $J_{F,C}$ = 24.8 Hz, C-4′), 85.24 (C-1′), 93.93 (d, $J_{F,C}$ = 178.4 Hz, C-3′), 111.24 (C-5), 123.85 (q, $J_{F,C}$ = 280.1 Hz, CF_3), 128.01–135.50 (phenyl carbons), 138.55 (C-6), 150.09 (C-2), and 162.73 (C-4) ppm; anal. calc. for $SiC_{28}H_{32}F_4N_2O_5.1/2H_2O$ (589.696); C, 57.03; H, 5.64; N, 4.75; found; C, 57.02; H, 5.64; N, 5.27.

5-(2,2,2-Trifluoroethoxymethyl)-3′-fluoro-2′,3′-dideoxyuridine (23). Compound **22** (300 mg, 0.50 mmol) was desilylated by treating it with ammonium fluoride (188 mg, 5.0 mmol, 10 equivalents) in refluxing ethanol (25 mL). The reaction was complete in 45 min. The contents were cooled and the solvent was removed. The mixture was purified on a silica gel column using $CHCl_3$:MeOH (95:5, v/v) as elution solvent to afford 130 mg (73%) of **23** as a semisolid: Rf 0.52 ($CHCl_3$: MeOH, 9:1, v/v); **^{1}H NMR** (CD_3OD)- δ 2.29 (d, $J_{1',2''}$ = 9.5 Hz of d, $J_{3',2''}$ = 5.5 Hz of d, Jgem = 14.0 Hz of d, $J_{F,H}$ = 39.0 Hz, 1H, H-2″), 2.57 (d, $J_{1',2'}$ = 5.5 Hz of d, Jgem = 14.0 Hz of d, $J_{F,H}$ = 21.5 Hz, 1H, H-2′), 3.86 (d, $J_{4',5''}$ = 3.0 Hz of d, Jgem = 11.0Hz, 1H, H-5″), 3.91 (d, $J_{4',5'}$ = 3.0 Hz of d, Jgem = 11.0 Hz, 1H, H-5′), 4.00 (q, $J_{F,H}$ = 8.5 Hz, 2H, CH_2CF_3), 4.27 (dd, $J_{5',4'}$ = $J_{5',4'}$ = 3.0 Hz of d, $J_{F,4'}$ = 26.5 Hz,1H, H-4′), 4.38 (s, 2H, CH_2OCH_2), 5.27 (d, $J_{2'',3'}$ = 5.5 Hz, $J_{F,3'}$ = 53.0 Hz, 1H, H-3′), 6.32 (d, $J_{2',1'}$ = 9.5 Hz of d, $J_{2'',1'}$ = 5.5 Hz, 1H, H-1′) and 8.11 (s, 1H, H-6) ppm; **^{19}F NMR** ($CDCl_3$)- δ 89.34 (t, $J_{H,F}$ = 8.6 Hz, CH_2CF_3), − 11.36 (d, $J_{3',F}$ = 53.6 of d, $J_{2'',F}$ = 38.9 Hz of d, $J_{2',F}$ = 21.7 Hz of d, $J_{4',F}$ = 27.3 Hz, 3′-F) ppm; **^{13}C NMR** ($CDCl_3$)- δ 39.43 (d, $J_{F,C}$ = 20.9 Hz, C-2′),

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62.65 (d, $J_{F,C}$ = 11.0 Hz, C-5′), 67.80 (CH_2OCH_2), 68.62 (q, $J_{F,C}$ = 34.0 Hz, CH_2CF_3), 86.80 (C-1′), 87.16 (d, $J_{F,C}$ = 23.8 Hz, C-4′), 93.93 (d, $J_{F,C}$ = 178.4 Hz, C-3′), 111.24 (C-5), 123.85 (q, $J_{F,C}$ = 280.1 Hz, CF_3), 128.01–135.50 (phenyl carbons), 138.55 (C-6), 150.09 (C-2), and 162.73 (C-4) ppm; HRMS-EI for $C_{12}H_{14}F_4N_2O_5$ calc. 342.0840; found; 342.0840; M^+ present (1.76%).

5-[bis(2,2,2-Trifluoroethoxy)methyl]-3′-fluoro-5′-O-*tert*-butyldiphenylsilyl-2′,3′-dideoxyuridine (25). This product was prepared by reacting **14** (400 mg, 0.82 mmol) with excess bromine (0.16 mL, 3.2 mmol) under UV irradiation using a similar procedure as described above for synthesis of **22**. Treatment of the 5-dibromomethyl intermediate **24** with trifluoroethoxide-copper complex (6.4 mmol) led to the formation of **25**. This impure product was purified on a silica gel column using toluene:ethyl acetate (80:20, v/v) as elution solvent to give 290 mg (52%) of pure **25**: Rf 0.23 (toluene:ethyl acetate, 80:20, v/v); mp 54°C (softened); **^{1}H NMR** ($CDCl_3$)- δ 1.04 (s, 9H, *tert*-butyl group), 2.20 (d, $J_{1',2''}$ = 10.0 Hz of d, $J_{3',2''}$ = 5.0 Hz of d, Jgem = 14.5 Hz of d, $J_{F,H}$ = 39.0 Hz, 1H, H-2″), 2.71 (d, $J_{1',2'}$ = 5.2 Hz of d, Jgem = 14.5 Hz of d, $J_{F,H}$ = 20.5 Hz, 1H, H-2′), 3.86 (m, 2H, H-5′ and H-5″), 4.22 (q, $J_{F,H}$ = 8.5 Hz, 4H, two CH_2CF_3), 4.33 (dd, $J_{5'',4'}$ = $J_{5',4'}$ = 5.0 Hz of d, $J_{3',4'}$ = 4.5 Hz of d $J_{F,4'}$ = 27.0 Hz,1H, H-4′), 5.13 (d, $J_{2'',3'}$ = 5.0 Hz, $J_{F,3'}$ = 54.0 Hz, 1H, H-3′), 5.66 (s, 1H, $CH(OCH_2CF_3)_2$), 6.10 (d, $J_{2',1'}$ = 5.2 Hz of d, $J_{2'',1'}$ = 10.0 Hz, 1H, H-1′), 7.35–7.76 (m, 10H, phenyls), 7.83 (s, 1H, H-6) and 9.64 (s, broad, D_2O exchangeable, 1H, NH) ppm; **^{19}F NMR** ($CDCl_3$)- δ 87.32 (t, $J_{H,F}$ = 10.9 Hz, CH_2CF_3), − 14.46 (d, $J_{3',F}$ = 54.0 of d, $J_{2'',F}$ = 39.9 Hz of d, $J_{2',F}$ = 21.1 Hz of d, $J_{4',F}$ = 25,8 Hz, 3′-F) ppm; **^{13}C NMR** ($CDCl_3$)- δ 26.77 (methyl carbons of *tert*-butyl group), 29.61 (*tert*-carbon of *tert*-butyl), 38.39 (d, $J_{F,C}$ = 20.7 Hz, C-2′), 63.10 (d, $J_{F,C}$ = 9.9 Hz, C-5′), 64.11 (two q, merged $J_{F,C}$ = 34.4 Hz, CH_2CF_3), 85.25 (d, $J_{F,C}$ = 24.6 Hz, C-4′), 86.07 (C-1′), 93.61 (d, $J_{F,C}$ = 178.4 Hz, C-3′), 97.52 (CH), 110.19 (C-5), 123.42 (q, $J_{F,C}$ = 278.3 Hz, CF_3), 128.73–135.42 (phenyl carbons), 138.68 (C-6), 149.49 (C-2), and 161.42 (C-4) ppm; anal. calc. for $SiC_{30}H_{34}F_7N_2O_6$ (679.66); C, 53.09; H, 4.90; N, 4.13; found; C, 53.27; H, 5.16; N, 4.22.

5-[bis(2,2,2-Trifluoroethoxy)methyl]-3′-fluoro-2′,3′-dideoxyuridine (26). The silylated precursor **25** (250 mg, 0.37 mmol) was dissolved in methanol and ammonium fluoride (136 mg, 3.7 mmol) was added under reflux. The reaction was allowed to proceed for 45 min and then worked up as described in the synthesis of **23**. Purification of the reaction mixture, after evaporation of methanol, on a silica gel column using 5% methanol in chloroform afforded 100 mg (62%) of pure **26**: mp 55°C (softened); Rf 0.57 ($CHCl_3$:MeOH, 9:1, v/v); **^{1}H NMR** ($CDCl_3$)- δ 2.31 (d, $J_{1',2''}$ = 10.0 Hz of d, $J_{2'',3'}$ = 4.5 Hz of d, Jgem = 14.0 Hz of d, $J_{F,H}$ = 39.5 Hz, 1H, H-2″), 2.63 (d, $J_{1',2'}$ = 5.2 Hz of d, Jgem = 14.0 Hz of d, $J_{F,H}$ = 20.5 Hz, 1H, H-2′), 3.73 (d, $J_{4',5'}$ = 3.0 Hz of d, Jgem = 11.5 Hz of d $J_{F,5'}$ = 1.5 Hz, 1H, H-5′), 3.80 (d, $J_{4',5'}$ = 3.0 Hz of d, Jgem = 11.5 Hz, 1H, H-5″), 4.08 (two q, merged, $J_{F,H}$ = 9.0 Hz, 4H, two CH_2CF_3), 4.32 (d, $J_{F,4'}$ = 26.0 Hz of t, $J_{5'',4'}$ = $J_{5',4'}$ = 3.0 Hz,1H, H-4′), 5.26 (d, $J_{2'',3'}$ = 4.5 Hz, $J_{F,3'}$ = 53.0 Hz, 1H, H-3′), 5.74 (s, 1H, $CH(OCH_2CF_3)_2$), 6.28 (d, $J_{2',1'}$ = 5.2 Hz of d, $J_{2'',1'}$ = 10.0 Hz, 1H, H-1′) and 8.28 (s, 1H, H-6) ppm; **^{19}F NMR** ($CDCl_3$)- δ 89.45 (two t, merged $J_{H,F}$ = 9.6 Hz, CH_2CF_3), − 11.31 (d, $J_{3',F}$ = 53.0 of d, $J_{2'',F}$ = 39.5 Hz of d, $J_{2',F}$ = 21.0 Hz of d, $J_{4',F}$ = 25,8 Hz, 3′-F) ppm; **^{13}C NMR** ($CDCl_3$)- δ 39.81 (d, $J_{F,C}$ = 20.9 Hz, C-2′), 62.64 (d, $J_{F,C}$ = 11.0 Hz, C-5′), 64.32 (two q, merged $J_{F,C}$ = 34.4 Hz and

$J_{F,C}$ = 35.7, two CH_2CF_3), 87.43 (C-1′), 87.52 (d, $J_{F,C}$ = 22.6 Hz, C-4′), 96.68 (d, $J_{F,C}$ = 178.4 Hz, C-3′), 98.52 (CH), 110.62 (C-5), 125.38 (q, $J_{F,C}$ = 277.4 Hz, CF_3), 141.36 (C-6), 151.27 (C-2), and 163.70 (C-4) ppm; HRMS-EI for $C_{14}H_{15}F_7N_2O_6$ calc. 440.0823; found; 440.0821; M^+ present (0.51%).

5-(2,2,2-Trifluoroethoxymethyl)-5′-O-trityl-3′-keto-2′,3′-dideoxyuridine (28). Compound **1** (0.4 g; 1.18 mmol) was dissolved in anhydrous pyridine (20 mL) and triphenylmethylchloride (0.334 mg, 1.2 mmol) was added to it under an atmosphere of argon. N,N-Dimethylamino pyridine (15 mg) was also added to this mixture and the reaction was allowed to stir at 25°C. Pyridine was evaporated in vacuo and the viscous mass was triturated with ice/water. This resulted in the precipitation of corresponding 5′-trityl product **27** as a white solid that was filtered, washed with water, dried and then oxidized without any further purification. A solution of **27** (0.33 g, 0.57 mmol) in dichloromethane (20 mL) was pulverized and pre-dried molecular sieves (812 mg) were added. Pyridinium dichromate (812 mg) was then added slowly and the mixture was stirred vigorously. The oxidation was complete in 3 h (tlc). The solvent was evaporated and the product was extracted with ethyl acetate/water (30:10 mL × 2). The organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was removed to get a foamy material which was purified on a silica gel column. The elution started with toluene and ended with 20% ethyl acetate to give 0.25 g, 37%) of pure **28**: mp 202°C (dec.); Rf 0.54 (toluene:ethyl acetate, 8:2, v/v); **^{1}H NMR** (CD_3OD) δ 2.76 (d, $J_{1',2''}$ = 8.0 Hz of d, Jgem = 18.5 Hz 1H, H-2″), 3.12 (d, $J_{1',2'}$ = 6.8 Hz of d, Jgem = 18.5 Hz, 1H, H-2′), 3.38 (d, $J_{4',5''}$ = 2.5 Hz of d, Jgem = 11.0Hz, 1H, H-5″), 3.48 (d, Jgem = 11.5 Hz, 1H, CH_2OCH_2), 3.58 (q, $J_{F,H}$ = 8.5 Hz, 2H, CH_2CF_3), 3.68 (d, $J_{4',5'}$ = 2.5 Hz of d, Jgem = 11.0 Hz, 1H, H-5′), 3.89 (d, Jgem = 11.5 Hz, 1H, CH_2OCH_2), 4.19 (t, $J_{5'',4'}$ = $J_{5',4'}$ = 2.5 Hz,1H, H-4′), 6.52 (d, $J_{2',1'}$ = 6.8 Hz of d, $J_{2'',1'}$ = 8.5 Hz, 1H, H-1′), 7.14–7.54 (m, 15H, phenyls), 7.92 (s, 1H, H-6) and 8.04 (s, br, 1H, NH) ppm; **^{19}F NMR** ($CDCl_3$)- δ 86.58 (t, $J_{H,F}$ = 8.6 Hz, CH_2CF_3) ppm; **^{13}C NMR** ($CDCl_3$)- δ 42.04 (C-2′), 63.01 (C-5′), 66.07 (CH_2OCH_2), 68.43 (q, $J_{F,C}$ = 35.0 Hz, CH_2CF_3), 81.53 (C-1′ and C-4′), 87.66 (tertiary-C of trityl), 111.20 (C-5), 123.65 (q, $J_{F,C}$ = 286.8 Hz, CF_3), 127.23–128.55 (phenyl), 139.05 (C-6), 149.95 (C-2), 162.40 (C-4) and 208.79 (C-3′) ppm; anal. for $C_{31}H_{27}F_3N_2O_6.3/4\ H_2O$ (609.81) calc. C 61.05, H 4.46, N 4.61; found C 60.91, H 4.61 and N 4.30%.

5-(2,2,2-Trifluoroethoxymethyl)-5′-O-trityl-3′,3′-difluoro-2′,3′-dideoxyuridine (29). A solution of **28** (0.20 g, 0.33 mmol) in anhydrous dichloromethane (20 mL) was cooled to 0°C. DAST (0.11 g, 0. 70 mmol) was slowly added under an argon atmosphere. The contents were stirred at low temperature for 30 min and then allowed to warm to 25°C. Stirring was continued for an additional 4 h. The reaction was quenched by saturated solution of sodium bicarbonate (25 mL) and the product was extracted in dichloromethane. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The viscous mass was purified on a silica gel column. The elution started with toluene and ended with 20% ethyl acetate to give 0.11 g, 52%) of pure **29**: mp 55°C (softened); Rf 0.16 (toluene:ethyl acetate, 8:2, v/v); **^{1}H NMR** (CD_3OD)- δ 2.56 (d, $J_{1',2''}$ = 8.0 Hz of d, Jgem = 18.5 Hz 1H, H-2″), 2.96 (d, $J_{1',2'}$ = 6.8 Hz of d, Jgem = 18.5 Hz, 1H, H-2′), 3.46 (m, 2H, H-5′ and H-5″), 3.67 (q, $J_{F,H}$ = 8.5 Hz, 2H, CH_2CF_3), 3.78 (d, Jgem = 12.5 Hz, 1H, CH_2OCH_2), 4.00 (d,

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Jgem = 12.5 Hz, 1H, CH_2OCH_2), 4.20 (m, 1H, H-4′), 6.35 (d, $J_{2',1'}$ = 6.8 Hz of d, $J_{2'',1'}$ = 8.5 Hz, 1H, H-1′), 7.14–7.54 (m, 15H, phenyls), 7.70 (s, 1H, H-6) and 8.25 (s, br, 1H, NH) ppm; **^{19}F NMR** ($CDCl_3$)- δ δ 49.86 (m, J gem = 238.0 Hz, 3-F″), 63.59 (d, Jgem = 238.0 Hz of d, $J_{2',F'}$ = 15.0 Hz of d, $J_{4',F'}$ = 34.0 Hz, 3-F′), 86.61(t, $J_{H,F}$ = 8.6 Hz, CH_2CF_3) ppm.

5-(2,2,2-Trifluoroethoxymethyl)-3′,3′-difluoro-2′,3′-dideoxyuridine (30). Acetic acid (80%, 3 mL) was added to **29** (0.10 g, 0.16 mmol) and the contents were stirred at 25°C for 4 h. The solvent was evaporated in vacuo and the viscous mass was purified on a silica gel column. Elution with 5% methanol in chloroform gave 50 mg (87%) of pure **30**: mp 55°C (softened); **^{1}H NMR** (CD_3OD)- δ 2.65 (d, $J_{1',2''}$ = 7.0 Hz of d, Jgem = 14.0 Hz of d, $J_{3F',2''}$ = 14 Hz of d $J_{3F'',2''}$ = 7.5 Hz, 1H, H-2″), 2.88 (d, $J_{1',2'}$ = 7.0 Hz of d, Jgem = 14.0 Hz of d, $J_{3F'',2'}$ = 15.0 Hz of d, $J_{3F',2'}$ = 7.0 Hz, 1H, H-2′), 3.85 (m, br, 2H, H-5′ and H-5″), 4.01 (q, $J_{F,H}$ = 8.5 Hz, 2H, CH_2CF_3), 4.18 (d, $J_{5',4'}$ = 3.8 Hz of d, $J_{5'',4'}$ = 3.6 Hz of d, $J_{3F',4'}$ = 14.5 Hz of d, $J_{3F'',4'}$ = 7.8 Hz, 1H, H-4′), 4.40 (s, 2H, CH_2OCH_2), 6.30 (t, $J_{2',1'}$ = $J_{2'',1'}$ = 7.0 Hz, 1H, H-1′) and 8.10 (s, 1H, H-6) ppm; **^{19}F NMR** (CD_3OD)- δ 51.43 (m, J gem = 238.7 Hz, 3-F″), 65.44 (d, Jgem = 238.8 Hz of d, $J_{2',F'}$ = 15.2 Hz of d, $J_{4',F'}$ = 33.4 Hz, 3-F′) and 89.31 (t, $J_{H,F}$ = 8.8 Hz, CH_2CF_3) ppm; **^{13}C NMR** (CD_3OD)- δ 40.97 (t, $J_{F,2'}$ = 23.8 Hz, C-2′), 60.19 (C-5′), 67.74 (CH_2OCH_2), 68.65 (q, $J_{F,C}$ = 34.0 Hz, CH_2CF_3), 83.26 (C-1′), 83.32 (t, $J_{F,C}$ = 25.1 Hz, C-4′), 112.17 (C-5), 127.51 (q, $J_{F,C}$ = 278.3 Hz, CF_3), 127.75 (t, $J_{F,C}$ = 247.9 Hz, C-3′), 140.75 (C-6), 151.90 (C-2), 164.80 (C-4) ppm; HRMS-EI for $C_{12}H_{13}F_5N_2O_5$ calc. 360.0759; found 360.0752, M^+ 3.02%.

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