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SYNTHESIS OF ACID STABLE FLUORINATED ACYCLONUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENTS.

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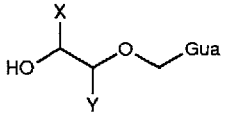
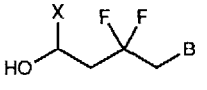
Abstract:
The synthesis of new α-di- and trifluoromethyl and α–difluoromethylene purine and pyrimidine derivatives are described.

The discovery of the potent and selective antiherpes agents 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir)[2] **1** and its hydroxymethyl analogs 9-[(1,3-dihydroxy-2-propoxy)methyl)]guanine (ganciclovir)[3] **2a** and 9-[(2,3-dihydroxy-1-propoxy)methyl)]guanine[4] **2b** has led to an extensive search for novel nucleosides with improved properties.

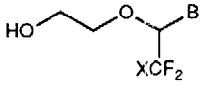
The incorporation of fluorine atoms into organic molecules has often been associated with profound changes in the biological profiles of the fluorinated analogs compared to their hydrocarbon counterparts. Such changes are the consequence of the extreme electronegativity of the fluorine atom as well as its ability to replace a hydrogen atom without notable steric consequences In addition, the fluorine atom is able to form hydrogen bonds and has been substituted for hydroxyl groups to permit fluorodeoxy analogs of nucleosides to be recognized by enzymes, which have the corresponding hydroxyl analogs as substrate.[5] For instance, 3'-deoxy-3'-fluorothymidine, after phosphorylation by kinases, is a very potent chain terminator of DNA polymerase.[6]



1 X=H Y=H
2a X=CH_2OH Y=H
2b X=H Y=CH_2OH



3 X=H B=Gua
4 X=H B=Cyt
5 X=CH_2OH B=Gua

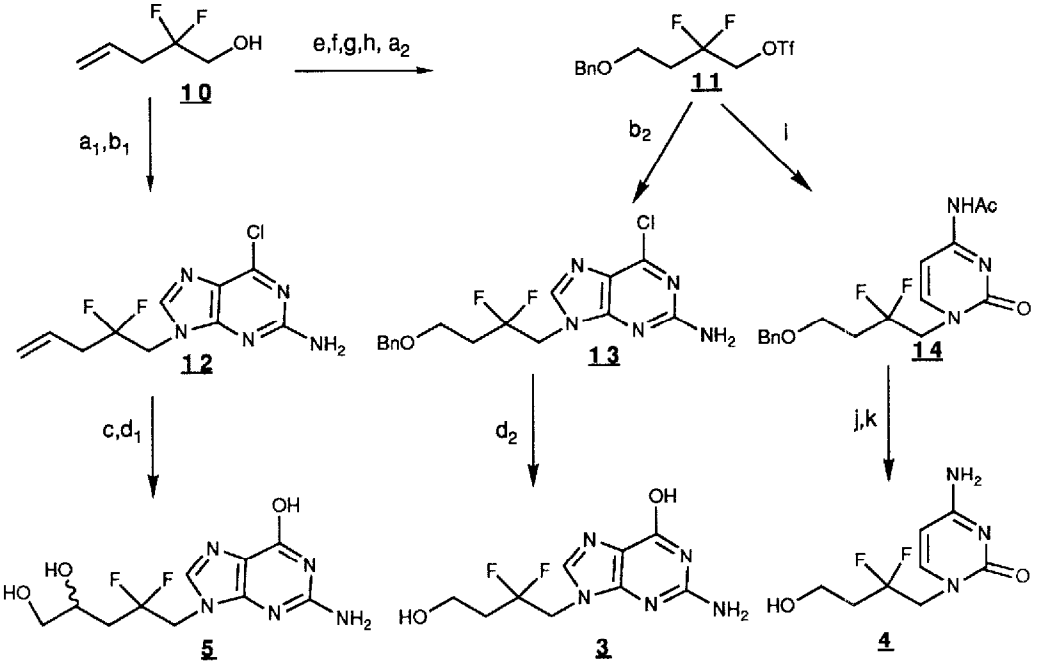


6 X=H B=Gua
7 X=F B=Gua
8 X=H B=Cyt
9 X=F B=Cyt

More recently a number of 2'-fluoro or carbofluoronucleosides[7] have been described but only two examples of the corresponding acyclo derivatives have been found in the literature[8] Since the activity of nucleoside analogs is highly dependent on the selectivity of various kinases for the formation of the active nucleotide species, we found it interesting to investigate the antiviral potency of fluoroacyclic nucleosides, in which a fluoromethylene group replaces an oxygen atom in either a hemiacetal function or a carbinol function in α–position of the purine or pyrimidine base. In all cases the strongly electron withdrawing and inductive effects of the fluorine atoms could stabilize the bond with the nucleic base, which is known to be very labile.[9]

The strategy for the synthesis of these compounds is based on the substitution of a leaving group in the fluorinated synthon by the various nucleic bases rather than the build up of the heterocycle from a primary amine. This is in fact the critical step, since nucleophilic substitution is disfavored in α–position of a fluoromethylene group, due to the electron withdrawing effect of the fluorine, and the effect is enhanced by the number of fluorine atoms bonded to this carbon atom. The advantage of such an approach is the direct access to the final products from a common precursor in a few steps. The general procedure for the synthesis of compounds **3, 4 and 5** is outlined in scheme 1

Scheme 1

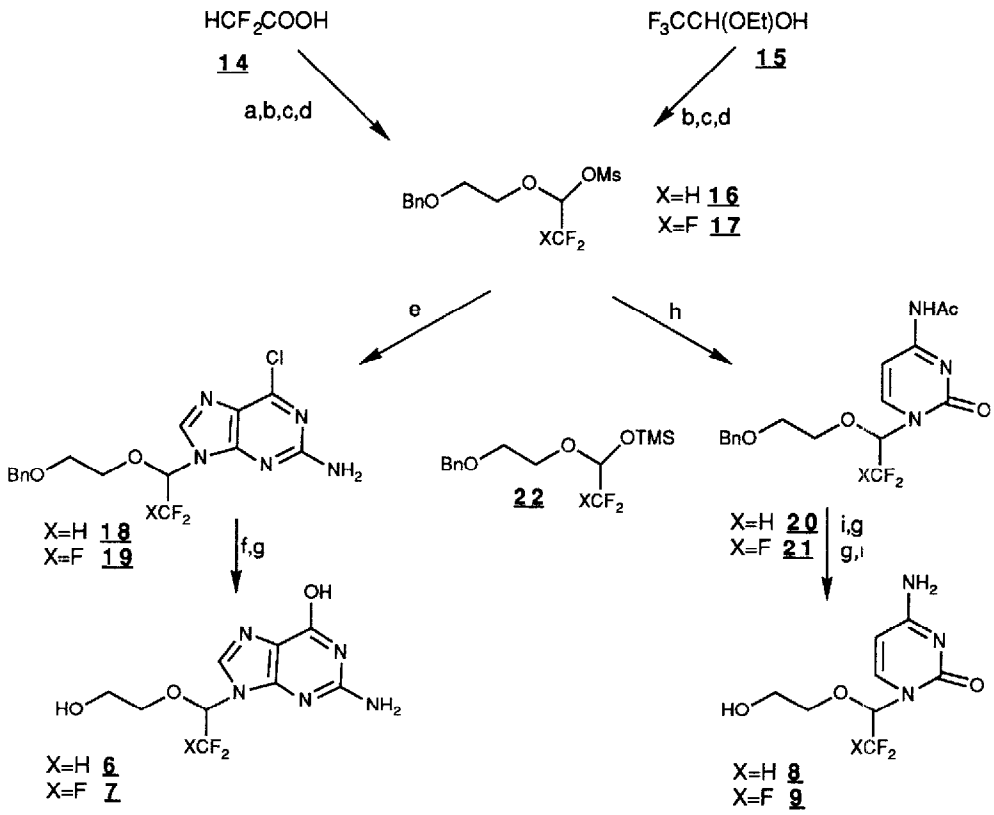


a Tf_2O, CH_2Cl_2, pyridine (a_1 83% , a_2 : 97%), b: 2-amino-6-chloropurine, K_2CO_3, DMF (b_1 : 75% ; b_2 63%)
c: NMNO, OsO_4, H_2O, acetone (66%); d HCl 2N (d_1 96% ; d_2 : 63%), e: DHP, APTS, CH_2Cl_2 (94%)
f. O_3, $CH_2Cl_2/NaBH_4$, EtOH (71%); g: BnBr, t-BuOK, THF (98%); h APTS, MeOH (73%),
i N^4-acetylcytosine, K_2CO_3, DMF (20%), j: NH_3, MeOH; k· $Pd(OH)_2$, cyclohexene, EtOH (j-k : 81%)

The readily accessible 2,2-difluoro-4-hexen-1-ol (**10**)[10] was transformed into the corresponding triflate and allowed to react with 2-amino-6-chloropurine to produce **12**. Oxidation of the double bond by a catalytic amount of osmium tetroxide in the presence of N-methylmorpholine N-oxide[11] followed by acidic hydrolysis of the chloroguanine afforded **5** in 39 % overall yield from **10**.[14]

The synthesis of the fluorinated carbon chain backbone of compounds **3** and **4** was achieved by a straightforward reaction sequence of **10** to the triflate **11** in 46 % yield Substitution of the triflate **11** by 2-amino-6-chloropurine followed by acid hydrolysis afforded the guanine derivative **3** in 18 % overall yield from **10**. The substitution of **11** by N^4-acetylcytosine was much less efficient and only 20 % of the desired product **14** was obtained besides 2 % of the N^4-alkylated side product. Deprotection of the amine by treatment with NH3/MeOH followed by transfer hydrogenation afforded the cytosine derivative **4** in 7,5 % overall yield from **10**. [14]

Scheme 2



a: $LiAlH_4$, Et_2O (44%), b H_3PO_4; c: $BnOCH_2CH_2OH$,THF; d: MsCl, Et_3N (14-16 · 69% 15-17 : 76%)
c: 2-amino-6-chloropurine, BSA, TMSOTf, CH_2Cl_2 (X=H . 31% , X=F 8%)
f · HCOOH 50% (X=H . 98% ; X=F 87%)
g. $Pd(OH)_2$, cyclohexene, EtOH (X=H 18-6 . 39% ; X=F 19-7 87%)
h : N^4-acetylcytosine, BSA, $(CH_2Cl)_2$ (X=H · 42% ; X=F · 29%) ı . NH_3, MeOH (X=H 20-8 68 % ; X=F 21-9 · 27%)

The syntheses of the di- and trifluoromethyl acyclonucleosides **6** to **9** are based on the substitution of the mesylates of the corresponding hemiacetal **16** or **17**, respectively by 2-amino-6-chloropurine, or N^4-acetylcytosine (scheme 2). These alkylating agents were obtained by condensing ethyleneglycol monobenzylether with di- or trifluoroacetaldehyde, generated in situ,[12,13] followed by treatment with mesylanhydride. (The triflate derivatives were found to be too unstable.) The substitution of the mesylates **16** or **17** was achieved with silylated 2-amino-6-chloropurine, or N^4-acetylcytosine in the presence of trimethylsilyloxytriflate as a catalyst (TMSOTf). Unfortunately, in both cases a significant amount of the trimethylsilylacetal **22** (20-30 %) was formed,probably by silylation of the oxonium intermediate by the catalyst TMSOTf. In the case of the purine analogs, a mixture of N^7 and N^9 alkylated products was obtained in a ratio of nearly 1·1. Nevertheless the various products were easily separated by flash chromatography on silica gel. Acid hydrolysis to give the guanine derivative, followed by phase transfer hydrogenolysis, afforded the α–di- and α–trifluoromethylanalogs of acyclovir **6** and **7** in respectively 35 % and 5 % overall yields.[14]

In the case of the pyrimidine derivatives, the substitution was achieved in reasonnable yield and the di- and trifluoromethyl cytosine analogs of acyclovir **8** and **9** were obtained in 12 % and 6 % overall yield, respectively, after aminolysis and phase transfer hydrogenolysis.[14]

The antiviral activity of these new types of fluorinated acyclonucleosides was evaluated using MRC-5 cells infected with human cytomegalovirus or echovirus 6, Vero cells infected with herpes simplex virus 1 or 2, or parainfluenzavirus 2; MDCK cells infected by influenzavirus A or B; and in HeLa cells infected with rhinovirus 2 or coxsachievirus A21. The synthesised compounds were found to be less active than the reference drug acyclovir in these tests. Details of their antiviral activities will be published elsewhere.

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14 All new compounds were fully characterized by CHN analysis, IR and NMR spectra. Mp and ^{19}F NMR (338,8 MHz, ref= C_6F_6 unless otherwise specified) of the final products are the following :

3 : mp= 282°C, ^{19}F NMR (DMSO) δ ppm 62 (tt,^3J=16Hz)

4 : mp=99°C, ^{19}F NMR ($CDCl_3$ + CD_3OD) δ ppm 61 (tt, ^3J=12 8 Hz, ^3J=16.6 Hz)

5 : mp=280°C dec.,^{19}F NMR (DMSO) δ ppm 66 8 and 66.1 (2m, F_A) 61.1 and 60 4 (2m,F_B) J_{AB}=243 Hz

6 : mp= 225 °C dec., ^{19}F NMR (CD_3OD, ref=CF_3COOH) δ ppm -54 (ddd,F_A) ^2J=54 Hz,^3J=6 3Hz, J_{AB}=293 Hz, -58 1 (ddd, F_B) ^2J=55 Hz,^3J=10 6Hz

7 mp= 260°C, ^{19}F NMR (DMSO) δ ppm 83 8 (d, ^3J=5 Hz)

8 : mp=129°C, ^{19}F NMR ($CDCl_3$ + CD_3OD) δ ppm 31 75 (ddd,F_A) 32 9 (ddd, F_B) J_{AB}=292 Hz, ^3J=54 Hz, ^3J=9 7 Hz)

9 : mp=158°C,^{19}F NMR ($CDCl_3$ + CD_3OD) δ ppm 81.9 (d, ^3J=4 8 Hz)

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