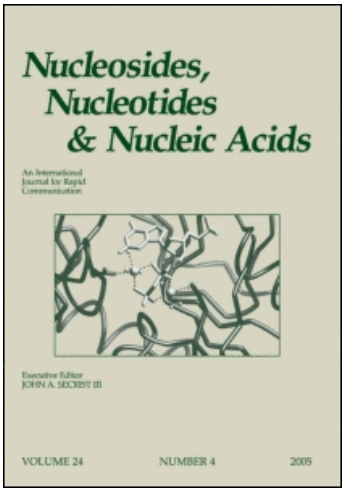

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SYNTHESIS OF ISOXAZOLIDINO ANALOGUES OF 2',3'-DIDEOXYNUCLEOSIDES

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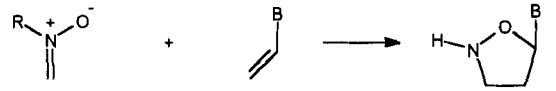
ABSTRACT : The complete set of the 4'-*aza* analogues of 2',3'-dideoxynucleosides was synthesized by cycloaddition of *N*-tetrahydropiranyl or *N*-trityl methylene nitrones on suitably protected vinyl nucleobases. The convertible nucleoside approach was used in the preparation of cytosine and 5-methyl cytosine analogues.

The cycloaddition approach to 4'-*aza*-2',3'-dideoxy-erythrofuranosyl nucleosides requires the use of methylene nitrones *N*-protected with acid labile groups and of *N*-vinylnucleobases suitably protected at the exocyclic amino function.

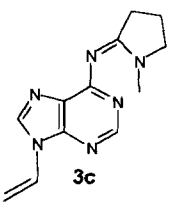


1, 2 **3a-f** **4a-**

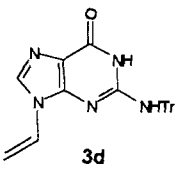
a = Thymine
b = Cytosine
c = Adenine
d = Guanine
e = Uracil
f = 5-methylcytosine

1) R = Tetrahydropiranyl (THP)
2) R = Trityl (Tr)

The same synthetic protocol used for **4a**, which has shown encouraging anti-HIV activity [1], was applied in the formation of **4b-f**. Model studies [2, 3] on the accessibility of **4c** by the proposed method have shown that the major drawbacks are represented by (i) the selection of



3c



3d

appropriate protecting groups [4] (ii) the facile access to the dipolarophile (**3a-f**) and (iii) the final deprotection step.

Good yields of **4c** and **4d** were obtained when **3c** and **3d** react with the nitrone **1** and **2**, respectively. The cyclic amidino protecting group of *N*-9-vinyladenine can be left on the final isoxazolidino nucleoside to serve as a device for transferring the potential drug across cellular membrane [5]. Unprotected **3d** was obtained with satisfactory yields by means of a new procedure, the trityl group enhances the lipophilicity of the molecule.

The cytosine derivative **4b** is available either by the cycloaddition of nitrone **1** to **3b**, protected at the exocyclic amino group as for **3c**, or by the convertible nucleoside approach [6] starting from **4e**, which was prepared similarly to **4a**. The latter can be easily transformed by the same procedure into **4f.** All new compounds have been characterised by ^{1}H NMR using dimethylsulfoxide as solvent and by fast atom bombardment mass spectrometry.

4'-aza-2',3'-dideoxycytidine (AdC, 4b): δ 8.37 (d, 6-CH; 1H), 7.52 (d, 5-CH; 1H), 7.13 (s_{broad}, 4-NH_2; 2H), 7.00 (dd, 4'-NH; 1H), 6.28 [dd, $^3J_{cis}$(H1',H2') = 7.4 Hz and $^3J_{trans}$(H1',H2') = 5.8 Hz, 1'-CH; 1H)], 3.23 -3.29 (m, 3'-CH_2; 1H), 2.95-3.00 (m, 3'-CH_2; 1H), 2.39-2.44 (m, 2'-CH_2; 1H) and 2.28-2.34 (m, 2'-CH_2; 1H). FAB MS (Gly, +): *m/z* 205 ([M+Na]$^+$, 53.2%), 183 ([M+H]$^+$, 78.4), 140 (31.8), 138 (37.5), 111 ([Cyt+H]$^+$, 45.0) and 72 (100).

4'-aza-2',3'-dideoxyadenosine (AdA, 4c) δ 8.58 (s, 8-CH; 1H), 7.62 (s, 2-CH; 1H), 7.41 (s_{broad}, 6-NH_2; 2H), 7.11 (dd, 4'-NH; 1H), 6.38 [dd, $^3J_{cis}$(H1',H2') = 7.7 Hz and $^3J_{trans}$(H1',H2') = 5.5 Hz, 1'-CH; 1H)], 3.15-3.21 (m, 3'-CH_2; 1H), 2.95-3.00 (m, 3'-CH_2; 1H), 2.52-2.57 (m, 2'-CH_2; 1H) and 2.21-2.25 (m, 2'-CH_2; 1H). FAB MS (Gly, +): *m/z* 229 ([M+Na]$^+$, 42.0%), 165 (28.5), 163 (39.3), 136 ([Ade+H]$^+$, 100) and 72 (88.0). FAB MS (NBA, +): m/z 229 ([M+Na]$^+$, 37.5%), 207 ([M+H]$^+$, 61.7), 165 (32.0), 163 (38.4) and 72 (100).

4'-aza-2',3'-dideoxyguanosine (AdG, 4d): δ 11.05 (s, 1-NH; 1H), 9.79 (s_{broad}, 2-NH_2; 2H), 7.84 (s, 8-CH; 1H) 6.84 (dd, 4'-NH; 1H) 6.18 [dd, $^3J_{cis}$(H1',H2') = 7.32 Hz and $^3J_{trans}$(H1',H2') = 3.66 Hz, 1'-CH; 1H)] 3.46-3.51 (m, 3'-CH_2; 1H) 2.96-3.01 (m, 3'-CH_2; 1H), 2.67-2.71 (m, 2'-CH_2; 1H), 2.54- 2.59 (m, 2'-CH_2; 1H). FAB MS (Gly, +): *m/z* 245 ([M+Na]$^+$, 20.0%), 223 ([M+H]$^+$, 6.0), 152 ([G+H]$^+$, 18.0) and 72 (100).

4'-aza-2',3'-dideoxyuridine (AdU, 4e): δ 9.32 (s, 3-NH; 1H), 7.68 (d, 6-CH; 1H), 7.07 (t, 4'-NH; 1H), 6.34 [dd, $^3J_{cis}$(H1',H2') = 7.0 Hz and $^3J_{trans}$(H1',H2') = 5.3 Hz, 1'-CH; 1H)], 5.63 (d, 5-CH; 1H), 3.26-3.30 (m, 3'-CH_2; 1H), 3.01-3.06 (m, 3'-CH_2; 1H), 2.53-2.58 (m, 2'-CH_2; 1H) and 2.26-2.31 (m, 2'-CH_2; 1H). FAB MS (Gly, +): *m/z* 206 ($[M+Na]^+$, 39.0%), 184 ($[M+H]^+$, 68.1), 151(37.0), 141 (44.1), 139 (45.0), 112 ($[Ura+H]^+$, 19.1) and 72 (100).

4'-aza-5-methyl-2',3'-dideoxycytidine (5-MeAdC, 4f): δ 7.85 (dd, 4'-NH; 1H), 7.21 (s_{broad}, 4-NH_2; 2H), 6.33 [dd, $^3J_{cis}$(H1',H2') = 7.9 Hz and $^3J_{trans}$(H1',H2') = 6.1 Hz, 1'-CH; 1H)], 6.00 (s, 6-CH; 1H), 3.32-3.36 (m, 3'-CH_2; 1H), 3.07 (s, 5-CH_3; 3H), 2.89-2.94 (m, 3'-CH_2; 1H), 2.36-2.41 (m, 2'-CH_2; 1H) and 2.23-2.28 (m, 2'-CH_2; 1H). FAB MS (Gly, +): *m/z* 219 ($[M+Na]^+$, 48.2%), 197 ($[M+H]^+$, 65.4), 155 (37.5), 153 (43.9), 126 ([5-MeCyt+H]$^+$, 44.8) and 72 (100).

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