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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

Sugar and Base-Modified 2',3'-Dideoxynucleosides as Potential Anti-Aids Drugs

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To cite this Article Van Aerschot, Arthur , Balzarini, Jan , Pauwels, Rudi , Wigerinck, Piet , De Clercq, Erik and Herdewijn, Piet(1989) 'Sugar and Base-Modified 2',3'-Dideoxynucleosides as Potential Anti-Aids Drugs', *Nucleosides, Nucleotides and Nucleic Acids*, 8: 5, 1125 – 1126

To link to this Article: DOI: 10.1080/07328318908054306

URL: <http://dx.doi.org/10.1080/07328318908054306>

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SUGAR- AND BASE-MODIFIED 2',3'-DIDEOXYNUCLEOSIDES
AS POTENTIAL ANTI-AIDS DRUGS

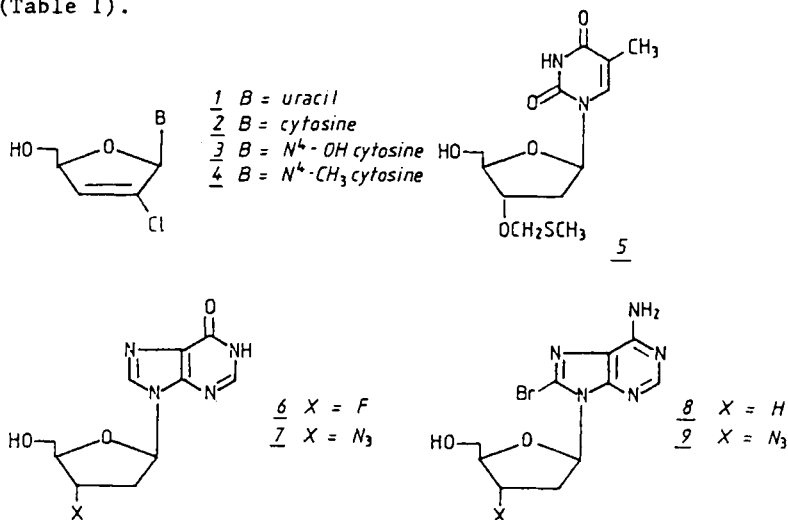
Arthur Van Aerschot^{*}, Jan Balzarini, Rudi Pauwels, Piet Wigerinck,
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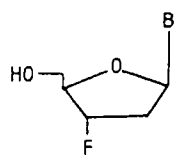
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Several 2',3'-dideoxynucleosides have proven to be effective against HIV-1 in cell culture. The 2',3'-unsaturated analogues dideoxycytidine (D4C) and dideoxythymidine (D4T) are among the most potent and selective inhibitors of HIV-1 replication *in vitro*. However, 2',3'-didehydro-2',3'-dideoxynucleosides are relatively unstable. A chlorine substituent at the 2'-position increases the stability, and, therefore, some 2'-chloro-2',3'-didehydro-2',3'-dideoxynucleosides were synthesized and evaluated for anti-HIV-1 activity.

Likewise, 3'-fluoro-2',3'-dideoxyuridine and -thymidine are known to be potent and selective anti-HIV-1 agents, and some modifications were introduced in the base with the aim to obtain compounds with increased selectivity. Finally, 3'-azido- and 3'-fluoro-2',3'-dideoxyinosine, 2',3'-dideoxy-8-bromo-adenosine and 3'-azido-2',3'-dideoxy-8-bromo-adenosine were synthesized, and their anti-HIV-1 activity was determined.

Of all these new 2',3'-dideoxynucleoside analogues, compound 10 (3'-fluoro-2',3'-dideoxy-5-chlorouridine, FddClUrd) offers the greatest promise as a potential anti-AIDS drug, as it achieved a selectivity index > 1000 (Table 1).





10 B = 5-chlorouracil
11 B = 5-bromouracil
12 B = 5-iodouracil

13 B = 5-methylcytosine
14 B = 0⁶-methyluracil

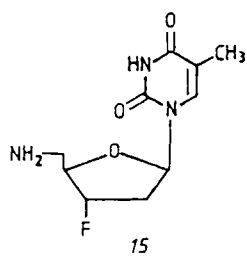
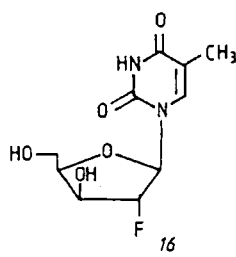
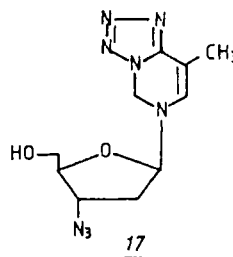
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TABLE 1. ANTI-HIV-1 ACTIVITY IN MT-4 CELLS

Compound	ED ₅₀ (μM)	CD ₅₀ (μM)	S.I.
<u>1</u>	> 500	> 500	—
<u>2</u>	> 500	> 500	—
<u>3</u>	> 500	> 500	—
<u>4</u>	> 500	> 500	—
<u>5</u>	> 500	> 500	—
<u>6</u>	222	818	3.7
<u>7</u>	> 8	15	< 2
<u>8</u>	484 ± 171	> 500	—
<u>9</u>	> 500	409 ± 53	—
<u>10</u>	0.38 ± 0.06	535 ± 41	1408
<u>11</u>	0.41 ± 0.16	24 ± 18	59
<u>12</u>	0.16 ± 0.11	2.2 ± 2.0	13.6
<u>13</u>	1.7 ± 0.8	7.7 ± 5.6	4.5
<u>14</u>	46 ± 14	348 ± 190	7.6
<u>15</u>	> 500	> 500	—
<u>16</u>	> 500	> 500	—
<u>17</u>	8.5 ± 0.3	39.0 ± 1.4	4.6
ddAdo	6.4	890	139
AzddAdo	5	10	2
FddThd	0.001	0.197	197
FddUrd	0.04	16	400

ED₅₀ : 50 % effective dose; CD₅₀ : 50 % cytotoxic dose; S.I. : selectivity index (ratio of CD₅₀ to ED₅₀).