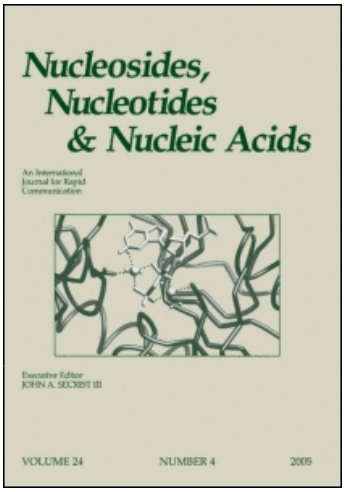


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Modified Nucleoside 5'-Triphosphonates as a New Type of Antiviral Agents

E. A. Shirokova[a]; A. V. Shipitsin[a]; L. S. Victorova[a]; N. B. Dyatkina[a]; L. E. Goryunova[b]; R. Sh. Beabealashvilli[b]; C. J. Hamilton[c]; S. M. Roberts[d]; A. A. Krayevsky[a]
[a] Engelhardt Institute of Molecular Biology, RAS, Moscow, Russia [b] Institute of Experimental Cardiology, National Cardiology Research Center, Moscow, Russia [c] University of Exeter, Exeter, UK [d] Department of Chemistry, Liverpool University, Liverpool, UK

To cite this Article Shirokova, E. A. , Shipitsin, A. V. , Victorova, L. S. , Dyatkina, N. B. , Goryunova, L. E. , Beabealashvilli, R. Sh. , Hamilton, C. J. , Roberts, S. M. and Krayevsky, A. A.(1999) 'Modified Nucleoside 5'-Triphosphonates as a New Type of Antiviral Agents', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 1027 — 1028
To link to this Article: DOI: 10.1080/15257779908041639
URL: http://dx.doi.org/10.1080/15257779908041639

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 1027–1028 (1999)

MODIFIED NUCLEOSIDE 5'-TRIPHOSPHONATES AS A NEW TYPE OF ANTIVIRAL AGENTS

E. A. Shirokova*, A. V. Shipitsin, L. S. Victorova, N. B. Dyatkina, L. E. Goryunova+, R. Sh. Beabealashvilli+, C. J. Hamilton#, S. M. Roberts##*, A. A. Krayevsky

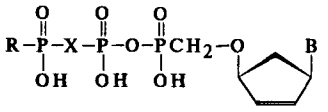
Engelhardt Institute of Molecular Biology, RAS, 32 Vavilov Str., Moscow, 117984, Russia; +Institute of Experimental Cardiology, National Cardiology Research Center, 15A Cherepkovskaya Str., Moscow, 121522, Russia; #Chemistry Building, University of Exeter, Stocker Rd, Exeter, EX4 4QD, UK; ##Department of Chemistry, Liverpool University, PO box 147, Liverpool, L69 7ZD, UK

The design of dNTP analogs with increased stability *in vivo* could produce a new group of highly effective inhibitors of HIV reproduction. The advantages of such compounds would be as follows: (i) Independence on the phosphorylation process catalyzed by intracellular enzymes, and direct inhibition of proviral DNA synthesis. (ii) The lack of the cell cycle effect on their activity. (iii) The ability to inhibit reverse transcription of the virus circulating in blood plasma. It is also desirable that such dNTP/rNTP analogs possess selective substrate properties towards viral enzymes and be hydrophobic enough to penetrate into the cell or be able to be bound by membrane proteins which would facilitate their transportation into cells. We present the biological evaluation of carbocyclic analogs of L-d_4NTP of **I-III** types in cell-free systems with HIV and avian myeloblastosis reverse transcriptases, DNA polymerases α and β, terminal deoxynucleotidyl transferase, as well as in Rat1 cell culture infected by artificial retrovirus containing Mu-MLV RT. The stability of **I-III** in human serum is also reported.

Syntheses of **Ia-IIa** are reported in (1), **Ib-IIb** in (2), **IIc** and **IIIc,d** in (3); synthesis of **Ic** and **IIIa,b** will be published elsewhere.

All the compounds were evaluated as terminating substrates for AMV and HIV-1 reverse transcriptases, human placenta DNA polymerases α and β and calf thymus TDT. Triphosphonates **Ib**, **Ic**, **IIb** and **IIc** selectively inhibit DNA synthesis catalyzed by AMV

RT and template independent TDT and do not affect the process catalyzed by DNA polymerases α and β. Unlike **Ic** and **IIc**, the activity of **Ib** and **IIb** towards HIV RT is sharply lowered.



B = Ade **Ia** X=O, R=OH
Ib $X=CBr_2$, R=OH
Ic $X=CF_2$, R=OH

B = Gua **IIa** X=O, R=OH
IIb $X=CBr_2$, R=OH
IIc $X=CF_2$, R=OH

B = Ade **IIIa** X=O, R=Ph
IIIb $X=CH_2$, R=Me
B = Gua **IIIc** $X=CF_2$, R=Me
IIId $X=CF_2$, R=Ph

The study of the stability of triphosphonates **Ib**, **Ic**, **IIb** and **IIc** in human blood serum testifies that the phosphate bond between Pα and Pβ is much more stable towards enzymatic hydrolysis than that of natural triphosphates. The half-life of **Ic**, **IIb** and **IIc** was shown to be 70-100 times higher than that for the corresponding natural dNTP, whereas for **Ib** this value was 200. Surprisingly, the half-life of **IIIc** and **IIId** bearing an additional modification at the γ-phosphate residue was about 10 h.

Inhibition of pSG1 virus replication in Rat1 cells by the compounds under study is clearly evident. Triphosphonate **Ib** is about 60 times more effective then the corresponding monophosphonate. Compound **IIc** exhibits the efficiency similar to the monophosphonate with the adenine base while guanine monophosphonate shows no activity up to the concentration of 100 mM. The 50% inhibition of virus reproduction by **Ib** in this system is 40 times lower (and **IIc** - 4000 times lower) than that of AZT but 7 times higher than that of d_4T.

Triphosphonates **IIIa-IIId** proved to be poor substrates of RTs and, moreover, were inactive in the tests on inhibition of pSG1 virus replication.

These compounds are examples of a new generation of dNTP analogs modified at the triphosphate residue and glycone that inhibit replication of retroviruses in cell cultures and show high stability in human blood serum.

ACKNOWLEDGEMENTS. The work was supported by the Russian Foundation for Basis Research, projects 96-04-48277 and 96-04-48278; program Russian National Priorities in Medicine, AIDS, projects sp1 and sp2; The National Institute of Health (Career Development Award Grant).

1. Dyatkina, N.B., Theil, F., Janta-Lipinski, M. Tetrahedron **1995,** *51*, 761-772.
2. Dyatkina, N., Shirokova, E., Theil, F., Roberts, S.M. and Krayevsky, A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2639-2642.
3. Hamilton, C.J. Roberts, S.M., Shipitsin, A.V. *J. Chem. Soc. Perkin Trans I*, . **1998,** 1087-1088.