Bioorganic & Medicinal Chemistry Letters, Vol.2, No.4, pp. 307-310, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

SYNTHESIS AND ANTI-HIV ACTIVITY OF 9-[(2R,5R)-2,5-DIHYDRO-5-(PHOSPHONOMETHOXY)-2-FURANYL]-2,6-DIAMINOPURINE

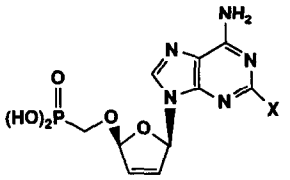
Choung Un Kim*, Bing Y. Luh, and John C. Martin[1]

Bristol-Myers Squibb Company, Pharmaceutical Resarch Institute, 5 Research Parkway, Wallingford, Connecticut 06492-7660

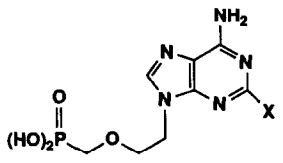
(*Received* 10 *January* 1992)

ABSTRACT: The synthesis of 9-[(2R,5R)-2,5-dihydro-5-(phosphonomethoxy)-2-furanyl]-2,6-diaminopurine (**2**) is described. This compound exhibited good inhibitory activity against HIV replication in MT-4 cells.

The discovery of human immunodeficiency virus (HIV) as the causive agent of acquired immunodeficiency syndrom (AIDS) has led to an intense effort to find compounds that selectively block the replication of HIV.[2] Recently, 9-(2-phosphonomethoxy)adenine (**3**: PMEA)[3] was reported as a new class of acyclic nucleoside phosphonate analogues with potent and selective activity against HIV. The structure-activity relationships (SAR) of the PMEA analogues showed 9-(2-phosphnomethoxyethyl)-2,6-diaminopurine (4 : PMEDAP) to be the most potent against HIV replication in MT-4 cells (IC_{50} = 1 μM) followed closely by PMEA (IC_{50} = 2 μM). As part of a program to study SAR of the PMEA class of compounds, we previously reported the preparation of the cyclic phosphonate **1** in which the phosphonomethoxy functionality was incorporated into the 2',3'-didehydro-2',3'-dideoxy nucleoside structure.[5] The new cyclic phosphonate **1** has exhibited potent



1 X = H
2 X = NH_2

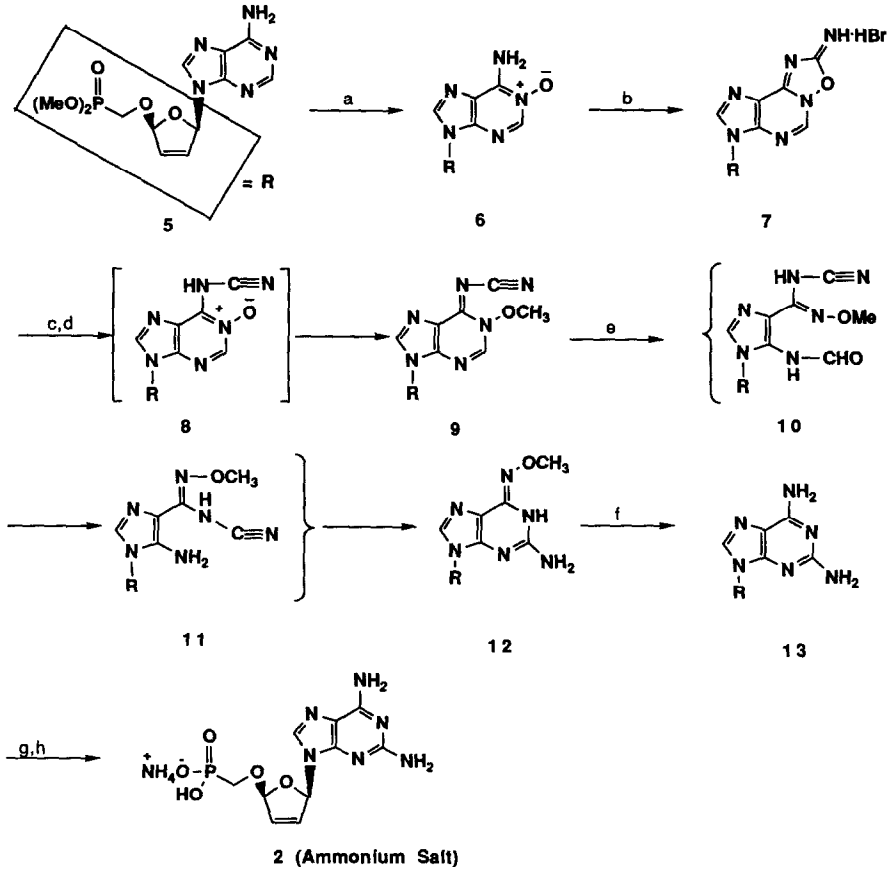


3 X = H (PMEA)
4 X = NH_2 (PMEDAP)

HIVactivity (IC_{50} = 4.3 μM) without sign of the cell toxicity up to 600 μM in MT-4 cells.[5] In view of the excellent HIV activity demonstrated for PMEDAP, we have undertaken the synthesis of the 2,6-diaminopurine analogue **2** for further studying SAR of this class of compounds.

In 1978, Ueda and co-workers reported a new method of converting the adenine ring of adenosine to the 2,6-diaminopurine moiety.[6] Therefore, we were intrigued with the possibility of the chemical transformation of the adenine analogue **1** to the 2,6-diaminopurine analogue **2**. Because of the labile acetal functionality present in the structure **1**, selection of mild reaction conditions was critical to the success of this ring transformation. As illustrated in Scheme I, oxidation of the adenine intermediate **5**[5] with m-chloroperbenzoic acid gave N-oxide **6** which was further converted to the cyanogen bromide adduct **7**. Treatment of **7** with TEA in DMF followed by an excess of methyl iodide produced the N_1-methoxy-N_6-cyano adenine intermediate **9** via N-oxide **8**. The ring opening of **9** was effected with the very mild basic conditions (0.05 N NaOH, room temperature) and further saponification of the resulting formamide **10** gave amine **11** which upon cyclization to the cyano functionality, led to the 2-aminopurine derivative **12**. The reductive cleavage of methoxyimine **12** with aluminum amalgam produced the 2,6-diaminopurine intermediate **13**. The final removal of the phosphonate ester in **13** was accomplished by exposing **13** to trimethylsilylbromide in DMF in the presence of 2,6-lutidine[7] followed by treatment with ammonium hydroxide. The phosphonate analogues described in this paper were evaluated for their inhibitory effect on the replication of HIV in MT-4 cells, and activity results were summarized in Table I. Although the 2,6-diaminopurine analogue **2** (ammonium salt) exhibited good inhibition of HIV-induced cytoparthogenicity, its activity was much weaker than that of compound 1. This result appears to indicate that SAR of cyclic phosphonates is different from that of acyclic phosphonates in which PMEDAP (**4**) is more potent than PMEA (**3**) against the replication of HIV. It also should be noted that both compounds **1** and **2** (ammonium salt) were much less cytotoxic compared to PMEA in MT-4 cells. Complete SAR of cyclic phosphonate analogues related to **1** will be the subject of future reports.

Scheme I



(a) MCPBA, CH_2Cl_2, 23°C, 3h, (92%); (b) CNBr, CH_3OH, 23°C, 2h (90%); (c) TEA, DMF, 23°C, 6h; (d) 10 equiv MeI (66%); (e) 0.05N NaOH, 23°C, 10h (75%); (f) Al/Hg, THF-H_2O (9:1), 70°C, 1h (48%); (g) TMSBr, 2,6-lutidine, DMF, 23°C, 18 h, (h) NH_4OH (56%).

TABLE I. **Antiretroviral and Anticellular Activities of Phosphonates in Tissue Culture**

Compound	IC_{50} (μM)[a]	TC_{50} (μM)[b]
1	4.3	>100
2 (Ammonium Salt)	82.5	>100
PMEA	6.5	40

[a]Concentration needed to inhibit HIV replication by 50a% in MT-4 cells.
[b]Concentration affecting viability of the uninfected cells by 50% when assayed in parallel with the antiviral assay in MT-4 cells.

Acknowledgement: The authors wish to thank Bristol-Myers Squibb Antiviral Biology Department for antiviral assays.

References and Notes

1. Present address: Gilead Sciences, 344 Lakeside Drive, Foster City, CA 94404.

2. (a) Mitsuya, H.; Weinhold, K.J.; Furman, P.A.; St. Clair, M.H.; Nusinoff-Lehrman, S.; Gallo, R.C.; Bolognesi, D.; Barry, D.W.; Broder, S. *Natl. Acad. Sci. U.S.A.* **1985**, 82, 7096. (b) *AIDS: Modern Concepts and Therapeutic Challenges;* Broder, S., Ed.; Marcel Dekker: New York, **1987**.

3. (a) DeClercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P.C. *Nature* **1986**, 323, 464. (b) Balzarini, J.; Naesens, L.; Slachmuylders, J.; Niphuis, H.; Rosenberg, I.; Holy, A.; Schellekens, H.; DeClercq, E. *AIDS* **1991**, 5, 21.

4. Paunels, R.; Balzarini, J.; Schols, D.; Baba, M.; Desmyter, J.; Rosenberg, I; Holy, A.; DeClercq, E. *Antimicrob. Agents Chemother.* **1988**, 32, 1025.

5. (a) Kim, C.U.; Luh, B.Y.; Martin, J.C. *J. Org. Chem.* **1991** 56, 2642. (b) Kim, C.U.; Luh, B.Y.; Misco, P.F.; Martin, J.C. *Nucleosides and Nucleotides* **1991**, 10, 371.

6. Ueda, T.; Mirua, K.; Kasai, T. *Chem. Pharm. Bull. (Tokyo)* **1978**, 26, 2122.

7. Without 2.6-lutidine, only decomposed products were isolated.

8. Spectral data for **14**: UVmax (H_2O) 256 nm (ε 8406), 280 nm (ε 9044); ^1H NMR (D_2O, 300 MHz, δ-ppm rel. to TMS) 3.34 (dd, J=8.9, 21.5 Hz, 1H), 3.52 (dd, J=10.5 , 21.5 Hz, 1H), 5.98 (s, 1H), 6.35 (d, J=6.0 Hz, 1H), 6.42 (d, J=6.0 Hz, 1H), 6.63 (s, 1H), 7.82 (s, 1H); ^{13}C NMR (D_2O), 68.05 (d, J=149 Hz), 88.01, 112.20 (d, J=10.6 Hz), 115.69, 131.47, 135.57, 140.63, 153.51, 156.67, 161.09.