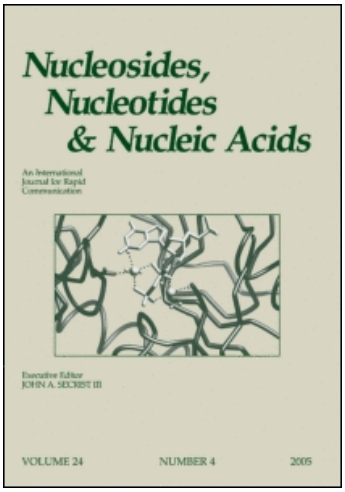


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# Synthesis and Biological Activities of Phosphonylalkylpurine Derivatives

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# SYNTHESIS AND BIOLOGICAL ACTIVITIES OF PHOSPHONYLALKYLPURINE DERIVATIVES

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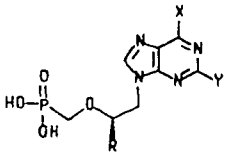
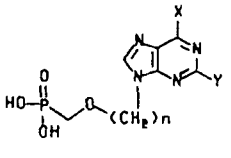
ABSTRACT: Syntheses and biological activities of 2-phosphonylmethoxyethyl (PME) purine analogs are described.



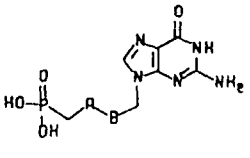
Recently, (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA, 1), 2-phosphonylmethoxyethylpurines (guanine, PMEG, 2; adenine, PMEA, 3) and their derivatives have been described as potent and broad spectrum antiviral agents.[1] These phosphonate derivatives contain a chemically and biologically stable phosphonylmethyl ether functionality as an isopolar functionality of a phosphate.[2] With the aim of studying the structure activity relationships, we have prepared various phosphonylalkyl adenine and guanine derivatives. First, because of the resemblance of PME purine analogs to acyclovir monophosphate, it appeared of interest to prepare longer alkyl chain derivatives (4-6) as potential mono-, di- and triphosphate analogs of acyclovir (ACV).[3] Furthermore, in order to define structural requirements for activity of PME purine analogs, isosteric isomers of PMEG were also prepared. Those include the 2'-oxo (7), the carba (8) and the thia (9) analogs.



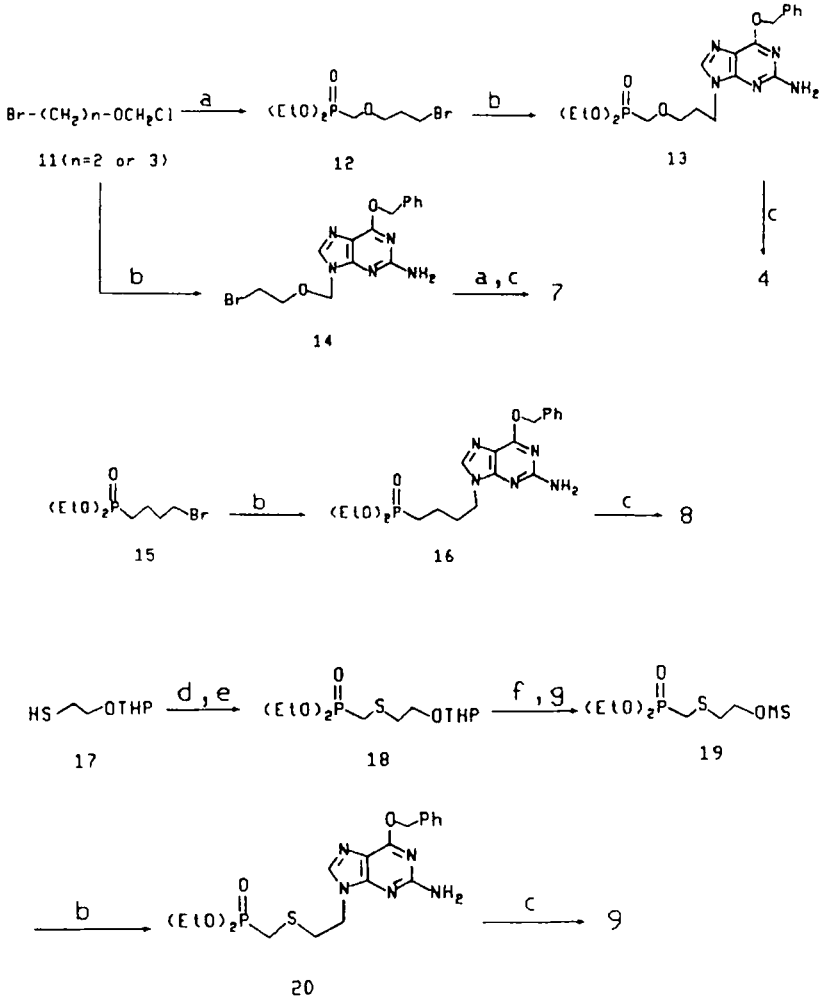
1 X=$NH_2$, Y=H, R=$CH_2OH$
2 X=OH, Y=$NH_2$, R=H
3 X=$NH_2$, Y=R=H



4 X=OH, Y=$NH_2$(n=3)
5 X=OH, Y=$NH_2$(n=4-7)
6 X=$NH_2$, Y=H(n=3-7)



7 A=$CH_2$, B=O
8 A=B=$CH_2$
9 A=S, B=$CH_2$




REAGENTS; (a)$(EtO)_2P(O)Na$; (b)2-amino-6-benzyloxypurine/NaH;

(c)TMSBr/DMF; (d)n-BuLi; (e)$(EtO)_2P(O)CH_2OTs$;

(f)5% HCl; (g)$CH_3SO_2Cl$/TEA.

SCHEME 1

The syntheses of analogs 4-9 are outlined in Scheme I. The synthesis of 4 is described as a typical example of the straight chain alkyl derivatives. The chloromethyl ether 11 (n=3), readily prepared from 3-bromopropanol and paraformaldehyde-HCl was condensed with sodium diethyl phosphite to give the bromide 12 (75%). Coupling of 12 with 2-amino-6-benzyloxypurine sodium salt (DMF, 60°, 3h) gave a mixture of 13 and the N-7 isomer (2:1) in 65% combined yield. Chromatographically purified 13 was treated with TMSBr in DMF to give 4 (70%). By simply reversing the addition sequence of sodium diethyl phosphite and the purine base on 11 (n=2), the 2'-oxo isomer 7 was also obtained from 11 (32% overall yield). Similarly, 4-bromobutyl diethylphosphonate (15), prepared by condensation of sodium diethyl phosphite with excess 1,4-dibromobutane was converted into 16 (40%) which then was converted to the carba analog 8 (75%) by action of TMSBr in DMF. For the synthesis of the thia analog 9, the lithio derivative of 17 was reacted with diethyl phosphonomethyl-p-toluenesulfonate[4] to give 18 (45%). Removal of the protecting group followed by mesylation provided 19 (90%). Condensation of 19 with 2-amino-6-benzyloxypurine sodium salt generated 20 and its N-7 isomer (3:1) in 62% yield. Chromatographically purified 20 was treated with TMSBr in DMF to give the thia analog 9 (65%)

The phosphonylalkyl purine analogs 4-9 prepared in this study were tested against herpes viruses (HSV-1, HSV-2, HCMV and VZV) and a retrovirus MuLV (moloney-murine leukemia virus). The antiviral activity of purine acyclic nucleosides (e.g. ACV) has been demonstrated to result from the initial phosphorylation to the monophosphate form by the herpes thymidine kinase. The monophosphate of ACV is then converted further to the triphosphate by cellular enzymes and this triphosphate acts as a selective inhibitor of and/or substrate for the viral DNA polymerase.[3] It is also reported that cellular kinases converted HPMPA to the diphosphate which inhibits selectively HSV-1 DNA synthesis over cellular DNA synthesis.[5]

Despite apparent structural resemblance of 4 to ACV monophosphate, the activity profile of 4 is quite different from ACV as shown in Table. Contrary to ACV, compound 4 showed no activity against HSV-1 and HSV-2 but exhibited a substantial activity against other herpes viruses (HCMV and VZV) and MuLV. Of the other compounds in the straight chain

TABLE I. Antiviral Activity of Phosphonylalkylpurine Derivatives

| | $ID_{50}$ μg/mL | | | | |
|---|---|---|---|---|---|
| Compound | HSV-1 | HSV-2 | HCMV | VZV | M-MuLV |
| 2 (PMEG) | 0.08 | 0.69 | 0.04 | 0.017 | 0.0009 |
| 3 (PMEA) | 21.0 | 9.4 | >5.0 | 5.3 | 0.05 |
| 4 | >100 | >100 | 6.0 | 4.6 | 0.04 |
| 5-9 | >100 | >100 | N.T.[a] | N.T. | >32[b] |
| ACV | 0.5 | 2.4 | 38.4 | 6.5 | >100 |

Cell Lines: Vero (HSV-1, HSV-2); MRS-5 (HCMV, VZV); Sc-1/XC (MuLV)
a) Not Tested
b) Following compounds showed some MuLV activity (μg/mL) 6 (n=3) 20.6; 7, 10.1; 9, 16.37.



phosphonates (5 and 6), no antiviral activity was observed. Also, none of PMEG isosteric isomers (7, 8 and 9) showed significant inhibitory activity against HSV-1 and HSV-2. Since the molecular structures of 7, 8 and 9 are so similar to PMEG, their total lack of activity is striking. It is possible that the inactivity of these phosphonates is due to the inability of cellular or virally induced kinases to catalyze their conversion to the mono- and diphosphate forms. Alternatively, the respective diphosphates, if formed, may not be inhibitors of viral DNA synthesis.

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