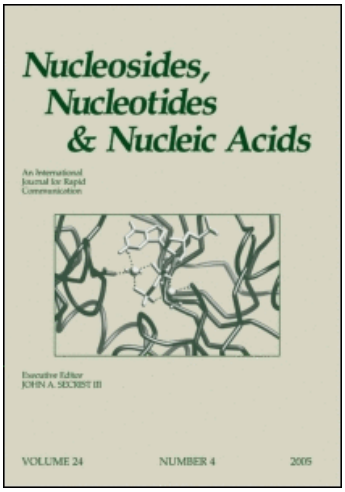

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The Synthesis and Preliminary Biological Evaluations of Selected Analogues of the Potent Broad-Spectrum Antiviral Agent Ganciclovir 1',3'-Cyclic Monophosphate[1] (2'-Nor-cGMP)

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THE SYNTHESIS AND PRELIMINARY BIOLOGICAL EVALUATIONS OF SELECTED ANALOGUES OF THE POTENT BROAD-SPECTRUM ANTIVIRAL AGENT GANCICLOVIR 1',3'-CYCLIC MONOPHOSPHATE[1] (2'-nor-cGMP).

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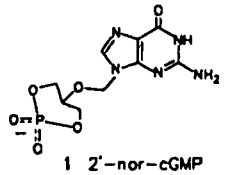
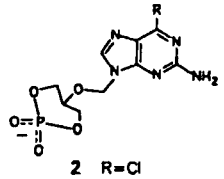
Abstract: The syntheses and antiviral activity of a series of analogues of the potent antiherpetic 2'-nor-cGMP are described. These derivatives contain systematic changes in either the heterocycle, the acyclic moiety, or the phosphate ring.

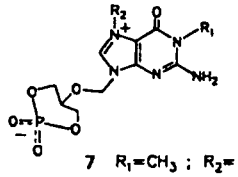
2'-Nor-cGMP (1) is a potent broad spectrum antiviral agent[3-8] whose activity is independent of the viral thymidine kinase (HSV-TK)[3-6,9-11]. In order to evaluate the structure-activity relationship for this class of derivatives a series of analogues (2-21) have been prepared and examined as antiherpetic agents. Several synthetic schemes were utilized, depending on the derivatives being prepared. Thus, 2-4,7,10,11,17, 20 and 21



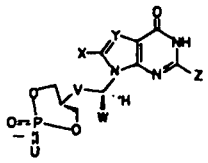
1 2'-nor-cGMP

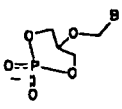


2 R=Cl
3 R=H
4 R=NH_2
5 R=$N(CH_3)_2$
6 R=OCH_2Ph



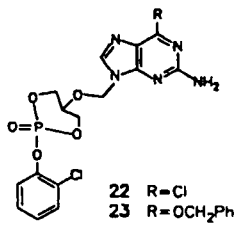
7 R_1=CH_3 ; R_2= —
8 R_1=H ; R_2=CH_3
9 R_1=CH_3 ; R_2=CH_3





18 B=thymine
19 B=uracil
20 B=adenine
21 B=cytosine

10 U=O; V=O; W=H; X=H; Y=CH; Z=NH_2
11 U=O; V=O; W=H; X=H; Y=N; Z=H
12 U=S; V=O; W=H; X=H; Y=N; Z=NH_2
13 U=O; V=O; W=H; X=Br; Y=N; Z=NH_2
14 U=O; V=CH_2; W=H; X=H; Y=N; Z=NH_2
15 U=O; V=O; W=CH_2OH; X=H; Y=N; Z=NH_2
16 U=O; V=O; W=H; X=H; Y=N; Z=$NHCO(CH_2)_2CH_3$
17 U=O; V=O; W=H; X=H; Y=N; Z=$NH-(pC_6H_4)-(CH_2)_3CH_3$



22 R=Cl
23 R=OCH_2Ph

were synthesized from the appropriately substituted acyclonucleoside by direct reaction with phosphoryl tris-triazole[4] or $POCl_3$[3-5,12] under high dilution conditions; **5** was prepared from **22** by nucleophilic displacement at C6 with $NH(CH_3)_2$ followed by deblocking of the phosphotriester; **6** was prepared from **23** by similar deblocking methods[4]; **8** and **9** were prepared from **1** and **7** respectively by regioselective methylation of the purine ring using $(CH_3)_2SO_4$ at controlled pH[13]; **12** was prepared from N^2-acetyl-O^6-triisopropylbenzenesulfonyl-ganciclovir[4] by reaction with $PSCl_3$ in CH_3CN under dilute conditions, followed by deblocking; **13** was prepared from **1** by direct bromination using standard conditions[14]; **14**, **18** and **19** were prepared by alkylation of the appropriate heterocycle with a preformed side-chain containing a cyclic phosphotriester followed by deblocking and conversion to cyclic phosphodiester[4]; **15** was prepared from the corresponding acyclic derivative by intramolecular cyclization with DCC in aqueous pyridine[15]; and **16** was prepared from **1** by direct N-acylation using $[CH_3(CH_2)_2CO]_2O$ in pyridine[4].

Evaluation of the antiherpetic activity in cell culture of compounds **1-21** showed **1,2** and **14** to be the most active derivatives. In addition, compounds **1,7,10**, and **12-14** were incubated with mouse liver extract and the rate of phosphate ring-opening (to give the appropriate acyclonucleoside monophosphate) was monitored. The order of stability was shown to be **12 > 14 > 1 > 7 > 10 > 13**.

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