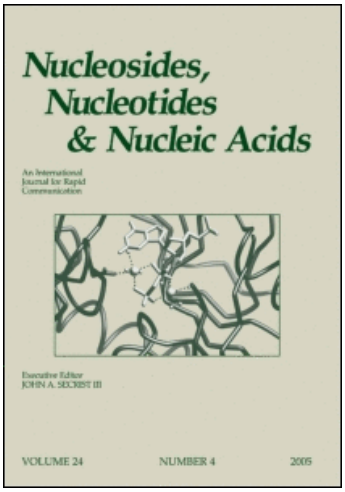

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

9-[2-(Phosphonomethoxy)alkoxy]purines, A New Series of Antiviral Acyclonucleotides

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To cite this Article Duckworth, D. M. , Harnden, M. R. , Perkins, R. M. and Planterose, D. N.(1991) '9-[2-(Phosphonomethoxy)alkoxy]purines, A New Series of Antiviral Acyclonucleotides', Nucleosides, Nucleotides and Nucleic Acids, 10: 1, 427 — 430
To link to this Article: DOI: 10.1080/07328319108046495
URL: http://dx.doi.org/10.1080/07328319108046495

NUCLEOSIDES & NUCLEOTIDES, 10(1-3), 427-430 (1991)

9-[2-(PHOSPHONOMETHOXY)ALKOXY]PURINES, A NEW SERIES OF ANTIVIRAL ACYCLONUCLEOTIDES.

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Abstract. **The synthesis and antiviral activities of a series of 9-[2-(phosphonomethoxy)alkoxy]purines are described. These compounds are the first reported acyclonucleotides in which a phosphonic acid bearing moiety is attached to N-9 of a purine via an N-O bond. Some of them show potent activity against herpesviruses and others are potent and selective inhibitors of the replication of visna virus, a lentivirus.**

We have recently reported the synthesis of a novel series of 9-alkoxypurine acyclonucleosides[1,2]. These compounds have potent and selective anti-herpesvirus activity[3]. In an unrelated series of acyclonucleosides, it has been shown that introduction of a phosphonomethoxy moiety into the acyclic substituent can lead to compounds with potent, broad spectrum antiviral activity and in particular, activity against retroviruses, eg. human immunodeficiency virus (HIV)[4]. In this report, we describe the synthesis and properties of a series of (phosphonomethoxy)alkoxypurines (**1-10**), some of which are potent and selective antiviral agents[5].

Two synthetic routes were employed. The first of these (**Scheme A**) involves reaction of an alkoxyamine with a 4,6-dichloro-5-formamidopyrimidine and subsequent formation of the imidazole ring. The second (**Scheme B**) involves coupling of an alcohol with a 9-hydroxypurine intermediate under Mitsunobu conditions.

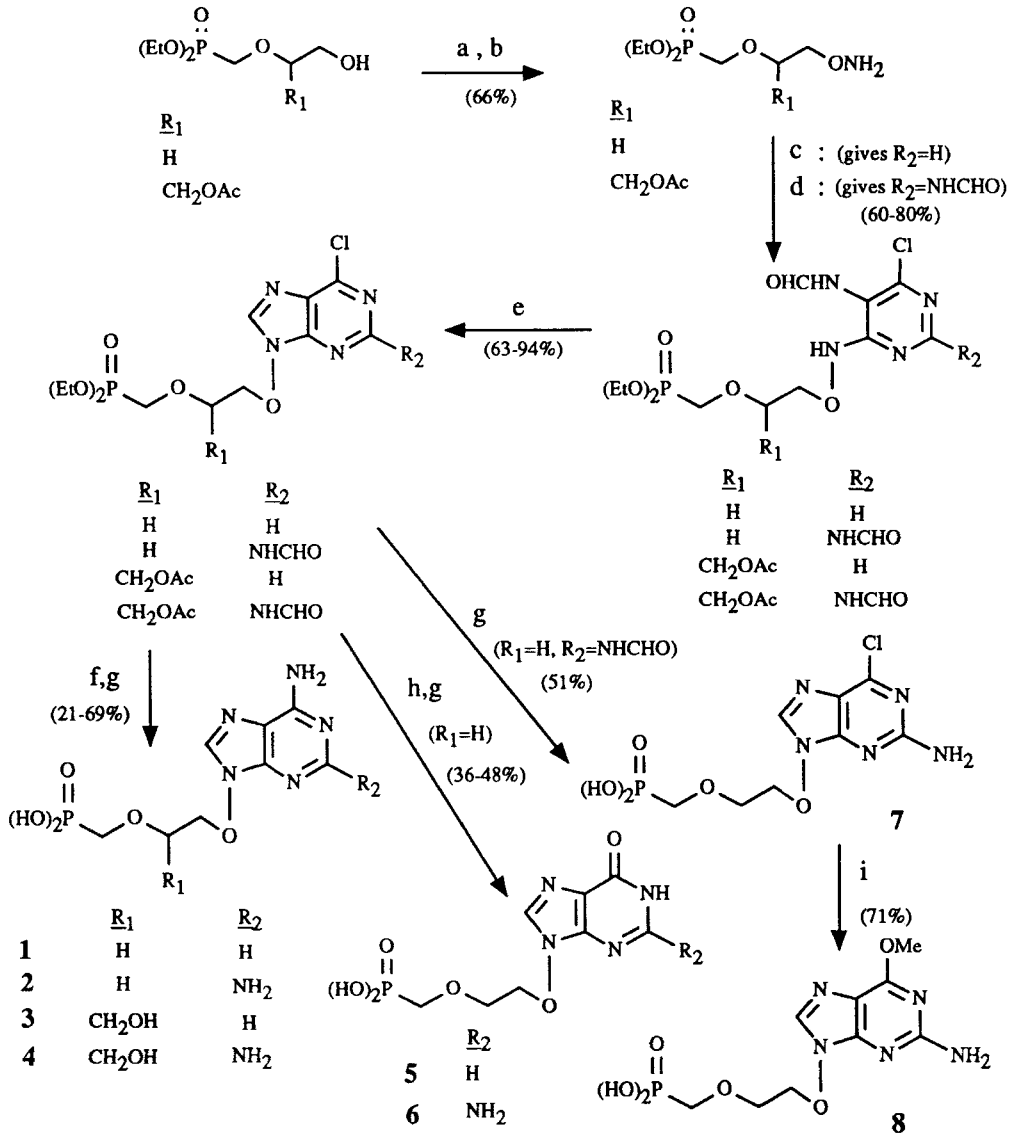
The following structure-antiviral activity relationships were observed for this new series of acyclonucleotides in cell culture. For inhibition of herpesviruses (HSV-1, HSV-2, VZV and CMV) in human fibroblast (MRC-5) cells the most potent compounds are the 2-amino-9-[2-(phosphonomethoxy)ethoxy]purines, **2**, **6**, **7** and **8**. Chain branching in the 9-substituent reduces the potency (cf. **4** with **2**; and **9** with **6**). The adenine and hypoxanthine derivatives, **1**, **3** and **5**, have no significant activity. These (phosphonomethoxy)alkoxypurines are not toxic for the MRC-5 cell monolayers used in the antiviral tests but at concentrations similar to those inhibiting herpesvirus replication they inhibit DNA synthesis in uninfected cells (as measured by incorporation of ^{3}H-thymidine). It is therefore unlikely that their activity is attributable to inhibition of a herpesvirus specific process.

Visna virus replication in sheep choroid plexus (SCP) cells is inhibited by all of these (phosphonomethoxy)alkoxypurines and several of them show extremely high potency and selectivity against this lentivirus. The 2-amino-6-substituted purines (**2**, **4**, **6**, **7**, **8**, **9** and **10**) are more active than the adenine and hypoxanthine derivatives (**1**, **3** and **5**). In contrast to the structure-activity relationship observed against herpesviruses, chain branching in the 9-substituent results in increased potency and selectivity (cf. **3** with **1**; **4** with **2**; and **9** with **6**). Cyclisation of **9** to the cyclic phosphonate **10** slightly reduces the anti-visna virus activity but **10** retains good selectivity. Thus, the concentrations of

compounds **3**, **4**, **9** and **10** that inhibit visna virus replication are 74-7000 times lower than those required for inhibition of ^{3}H-thymidine incorporation into SCP cell DNA.

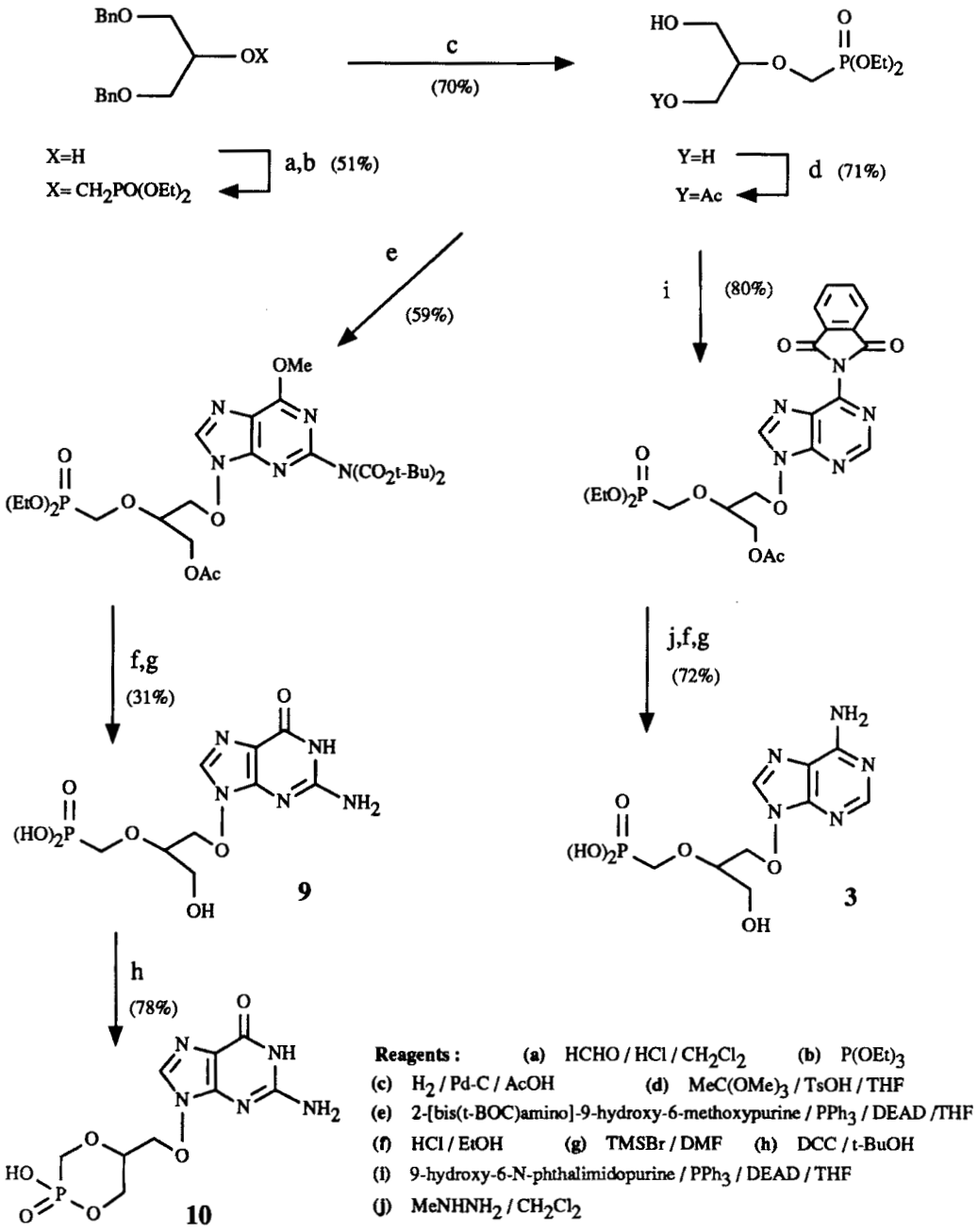
The activities of these highly selective anti-retrovirus agents against HIV are now being investigated.

A. Synthesis via pyrimidines



Reagents : (a) N-hydroxyphthalimide / PPh_3 / DEAD / THF (b) $MeNHNH_2$ / CH_2Cl_2
(c) 4,6-dichloro-5-formamidopyrimidine / NEt_3 /1,4-dioxane
(d) 4,6-dichloro-2,5-diformamidopyrimidine / i-Pr_2EtN / diglyme
(e) i. $(EtO)_2CHOAc$ ii. NH_3 / MeOH (f) NH_3 / EtOH (g) TMSBr / CH_2Cl_2 or DMF
(h) 80% HCO_2H / H_2O (i) NaOMe / MeOH

B. Synthesis via 9-hydroxypurines



Reagents : (a) HCHO / HCl / CH_2Cl_2 (b) $P(OEt)_3$
(c) H_2 / Pd-C / AcOH (d) $MeC(OMe)_3$ / TsOH / THF
(e) 2-[bis(t-BOC)amino]-9-hydroxy-6-methoxypurine / PPh_3 / DEAD /THF
(f) HCl / EtOH (g) TMSBr / DMF (h) DCC / t-BuOH
(i) 9-hydroxy-6-N-phthalimidopurine / PPh_3 / DEAD / THF
(j) $MeNHNH_2$ / CH_2Cl_2

ANTIVIRAL ACTIVITY

Compound	IC_{50} (uM) [a]						MIC [b] (uM)	Selectivity index for anti-visna virus activity [e]
	Herpesviruses [c]				MRC-5 cell ^{3}H-dT incorp.	SCP cell ^{3}H-dT incorp.	Visna [d] virus (K184)	
	HSV-1 (SC 16)	HSV-2 (MS)	VZV (Ellen)	CMV (AD169)				
1	>350	270	280	>350	173	173	8.0	22
2	49	9.5	3.9	8.2	6.9	24	1.0	24
3	>310	>310	210	>310	260	230	3.1	74
4	300	75	>300	>300	51	26	0.06	430
5	>340	>340	>340	>340	240	-	100	-
6	1.1	0.26	0.20	0.07	0.26	0.07	0.007	10
7	20	12	1.5	0.62	0.80	0.71	0.009	79
8	2.2	3.8	<0.09	0.16	0.09	0.09	0.003	30
9	24	33	60	20	10	21	0.003	7,000
10	32	49	26	14	50	7.1	0.009	790
acyclovir	3.9	4.3	21	93	355	-	-	-
zidovudine	-	-	-	-	-	>370	5.6	>66

a) Concentration of compound which inhibited by 50% the number of plaques (HSV-2, VZV and CMV) or cytopathic effect (HSV-1) in infected cells, or incorporation of ^{3}H-dT into uninfected cells. b) Minimum concentration of compound which completely inhibited the cytopathic effect in infected cells. c) Carried out in human fibroblast (MRC-5) cells. d) Carried out in sheep choroid plexus (SCP) cells. e) $\frac{IC_{50} \text{ SCP cell } ^3\text{H-dT incorporation.}}{\text{MIC visna virus}}$

Acknowledgements. We thank Dr. H.T. Serafinowska for her assistance in the preparation of compound **8**, Mr. M.R. Boyd and his colleagues for the anti-herpesvirus data, Mrs. K. Reynolds for her expert technical assistance in the anti-visna virus and ^{3}H-thymidine incorporation tests, and Dr. A.G. Brown for his interest and support for these studies.

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