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SYNTHESIS OF 9-[2-(PHOSPHONOMETHOXY)ETHYLAMINO]ADENINE AND 9-[(PHOSPHONOMETHOXY)ACETAMIDO]ADENINE, ANALOGUES OF A POTENT ANTI-HIV ACYCLONUCLEOTIDE

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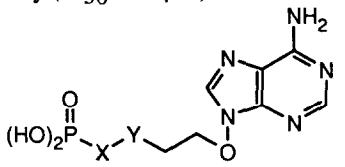
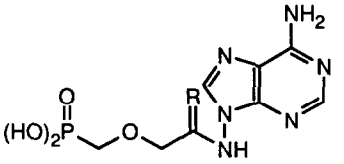
Abstract 9-[2-(Phosphonomethoxy)ethylamino]adenine (**5**) and 9-[(phosphonomethoxy)acetamido]adenine (**6**) were synthesised and tested for antiviral activity.

There has been considerable recent interest in the use of the phosphonomethoxy group as a stabilised phosphate mimic in the synthesis of nucleotide analogues as antiviral agents.[1-3] 9-[2-(Phosphonomethoxy)-ethoxy]adenine (BRL 47923) (**1**) was synthesised in these laboratories and found to be a potent and selective inhibitor of the replication of human immunodeficiency virus (HIV) with an IC_{50} of 0.3 μM.[4,5] Replacement of the methyleneoxy group with methylenethio (**2**) leads to a substantial reduction in activity.[6] Replacement of this function with a *cis* alkene (**3**) has a similar effect, but introduction of a *trans* alkene (**4**) gives a compound of moderate potency (IC_{50} = 10 μM).[7]



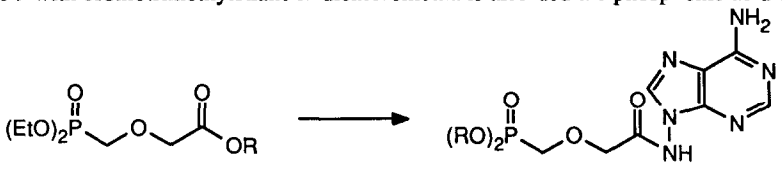
1 X = CH_2 Y = O
2 X = CH_2 Y = S
3 X,Y = *c* CH=CH
4 X,Y = *t* CH=CH



5 R = H_2
6 R = O

We have previously shown that in guanine acyclonucleosides, introduction of a nitrogen atom at the 1-position of the side chain results in compounds which retain anti-herpesvirus activity.[8] Here we describe the synthesis and antiviral activity of analogues of **1** where the adenine is linked to the side chain by an amino (**5**) or amido (**6**) nitrogen. Compound **6** is the first example of a nucleoside or nucleotide analogue with an amido nitrogen at the 1-position of the side chain.

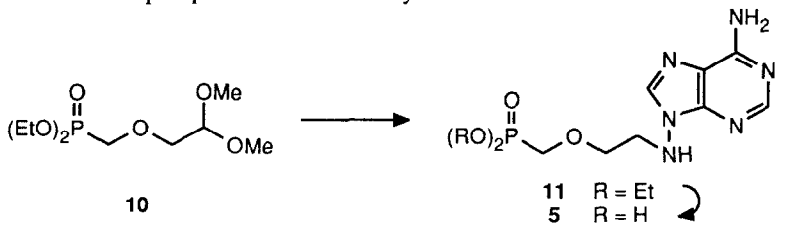
Compound **7** was prepared by treatment of methyl glycolate with formaldehyde and hydrogen chloride in the presence of zinc chloride, followed by heating with triethyl phosphite. Hydrolysis of **7** with 1.0 equiv. aqueous sodium hydroxide followed by neutralisation gave the acid **8** in 93% yield. Coupling of **8** to 9-aminoadenine[9] with dicyclohexylcarbodiimide in DMF afforded the amide **9** in 25% yield. Deprotection of the phosphonate **9** with bromotrimethylsilane in dichloromethane afforded the phosphonic acid **6** in 42% yield.



7 R = Me
8 R = H

9 R = Et
6 R = H

Reaction of the sodium salt of diethyl hydroxymethylphosphonate (generated *in situ* from diethyl phosphite, sodium hydride and paraformaldehyde)[10] with bromoacetaldehyde dimethyl acetal in dimethoxyethane at reflux gave **10** in 43% yield. Whilst the acetal **10** is a more stable intermediate than the aldehydes previously used for condensation with N-aminobases,[8,9] it also requires considerably more rigorous condensation conditions. Thus reaction of **10** with 9-aminoadenine in DMSO in the presence of 0.5 equivalent of trifluoroacetic acid at 120°C for 2 hr followed by treatment with ethanol and sodium borohydride at room temperature gave **11** in 21% yield. Deprotection of the phosphonate **11** with bromotrimethylsilane in dichloromethane afforded the phosphonic acid **5** in 90% yield.



10 **11** R = Et **5** R = H

For compounds **5**, **6**, **9** and **11**, the location of the side chains on the 9-amino rather than the 6-amino group was confirmed by UV and ^{1}H NMR spectroscopy.[9] In cyclic compounds related to **5**, the nitrogen attached to N-9 is very non-basic and does not undergo zwitterion formation with the phosphonic acid;[11] consistent with this, there was no change in the NMR shifts of the ethylene protons in going from **11** to **5**.

In assays in cell culture systems, the phosphonic acids **5** and **6** had no effect on the replication of HIV at 10 μM and no effect on the replication of herpes simplex virus types 1 and 2, varicella zoster virus, or cytomegalovirus at concentrations up to 300 μM.

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