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Synthesis of novel HEPT analogues as potential anti-HIV-1 agents.

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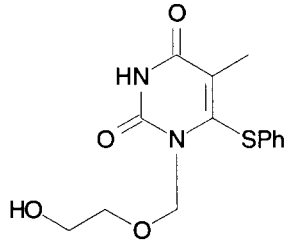
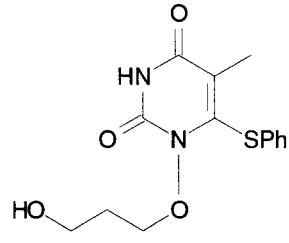
HEPT (1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine) has recently been found to be an inhibitor of HIV-1 reverse transcriptase (RT). Although HEPT contains structural elements common to nucleosides, its mode of action parallels that of a nonnucleoside RT inhibitor. Extensive structure activity relationship studies have provided several potent compounds, some of which are active in the micromolar range.

In our search for therapeutically useful antiviral agents, we have investigated a series of HEPT analogues in which the oxygen and the acetal carbon has been transposed, i.e. giving **1**. The synthesis and antiviral activity of this class of compounds will be presented.



HEPT



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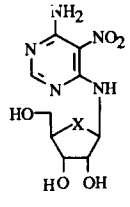
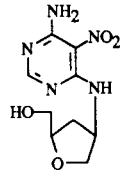
Synthesis and anti-HIV activity of isonucleosides and acyclic nucleotides related to clitocine. P. Franchetti, L. Cappellacci, G. Abu Sheikha, M. Grifantini, L. Messini, *A. G. Loi, *A. De Montis, *M. G. Spiga and *P. La Colla. *Dipartimento di Scienze Chimiche, Università di Camerino, 62032 Camerino, and *Dipartimento di Biologia Sperimentale, Università di Cagliari, 09124 Cagliari, Italy.*

Clitocine, [6-amino-5-nitro-(β-D-ribofuranosylamino)pyrimidine] (**1**), a natural nucleoside isolated by the mushroom *Clitocybe inversa*, has shown strong insecticidal activity and potent cytostatic effects against several leukemia cell lines. It was found to be a substrate and inhibitor of adenosine kinase. The carbocyclic clitocine analogue **2** was also found to be readily phosphorylated by adenosine kinase and significantly active both *in vitro* and *in vivo* against influenza A virus (Singapore). The observation that, from the structural point of view, clitocine shows a biogenetic relationship with adenosine, prompted us to prepare analogues of the anti-HIV agents 2',3'-dideoxy-3'-oxoadenosine (isoddA) and 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) (compounds **3** and **4**), in which the adenine moiety is replaced from 4,6-diamino-5-nitropyrimidine, the clitocine aglycon. Synthesis, antiviral activity and structure-activity relationships of the title compounds will be reported.



1 X = O

2 X = CH_2



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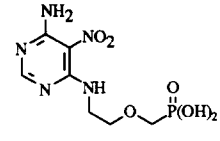

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