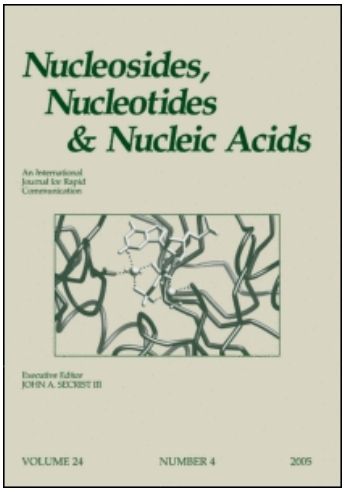

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5-(Thien-2-yl)-2'-deoxyuridine: A New and Potent Inhibitor of Herpes Simplex Virus Type 1 Replication

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5-(THIEN-2-YL)-2'-DEOXYURIDINE: A NEW AND POTENT INHIBITOR OF HERPES SIMPLEX VIRUS TYPE 1 REPLICATION

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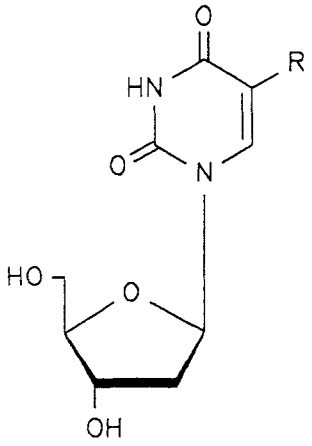
Abstract. 5-(Thien-2-yl)-2'-deoxyuridine, synthesized by coupling of 5-iodo-2'-deoxyuridine with 2-trimethylstannylthiophene in the presence of a Pd catalyst, shows potent anti-HSV-1 activity *in vitro*.

Various 5-substituted 2'-deoxyuridines are able to inhibit the replication of HSV-1 (herpes simplex virus type 1) at non toxic concentrations. Some of these compounds [IdUrd (**1a**) and EtdUrd (**1b**)] are commercially available for the topical treatment of HSV-1 infections (i.e. herpetic keratitis). The most potent among the 5-substituted 2'-deoxyuridines are those with a 5-halogenovinyl substituent. (E)-5-(2-Bromovinyl)-2'-deoxyuridine [BVDU (**1c**)] was selected for clinical trials for the topical treatment of herpetic keratitis, for herpes eye infections and for the oral treatment of systemic HSV-1 and VZV (varicella-zoster virus) infections. The selectivity of these nucleoside analogues can be accounted for, at least in part, by their preferential phosphorylation by the virus-encoded thymidine kinase. The 5'-triphosphates of the 5-substituted 2'-deoxyuridines inhibit the viral DNA polymerase to a significantly greater extent than the cellular DNA polymerases.

In attempts to find other selective anti-HSV agents, we introduced different 5-membered heteroaromatic rings in the 5-position of 2'-deoxyuridine. For the synthesis of these compounds, we investigated the Palladium catalysed coupling reactions between IdUrd and activated heteroaromatics. Variable results were obtained using $[ZnCl]^+$ salts of different heteroaromatics. Also the work-up procedure was rather complicated because of the large amount of $ZnCl_2$ that had to be used.

Therefore we tried the coupling reactions of IdUrd with organotin derivatives of heterocycles. The trimethyltin derivates of the heterocycles were prepared by adding 1.1 equivalents of trimethylstannyl chloride to the lithium salts of the heterocycles. The organotin derivatives of furan, thiophene and N-methyl-pyrrole react readily and in good yields with IdUrd to give 5-(furan-2-yl)-2'-deoxyuridine, 5-(thien-2-yl)-2'-deoxyuridine and 5-(N-methylpyrrol-2-yl)-2'-deoxyuridine, respectively. No protection of the alcoholic functions is needed during these reactions.

5-(Thien-2-yl)-2'-deoxyuridine (**1d**) inhibits the replication of HSV-1 at a concentration of 0.1 μM. No toxicity was found at the highest concentration tested (200 μM), which means that the selectivity index of this compound is greater than 2000.



1a: R= I

b: R= CH_2-CH_3

c: R= CH=CHBr(E)

d: R= thien-2-yl