SYNTHESIS OF VARIOUS 5-(3-SUBSTITUTED PHENYL)-2'-DEOXYURIDINES'

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A series of 5-aryl-2'-deoxyuridines has been prepared and evaluated as antiviral agents. The following substituents have been used in position 3 of the phenyl ring: chloro, iodo, amino, azido, methylthio, and vinyl. None of the new compounds showed any significant activity when tested against human immunodeficiency virus 1 (HIV-1), herpes simplex virus 1 (HSV-1), or human cytomegalovirus (HCMV).

5-(3-Bromophenyl)-2'-deoxyuridine (BPDU) is structurally reminiscent of (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU). BVDU has potent activity against herpes simplex virus type 1 (HSV-1), for a review see [1]. We have previously reported that BPDU has some activity against HSV-1, and in contrast to BVDU also a weak activity against human cytomegalovirus (HCMV) [2].

5-(Heteroaryl)-substituted 2'-deoxyuridines have earlier been reported to possess potent anti-HSV-1 activities [3-6]. However, we have found that in contrast to BVDU, the anti-HSV-1 activity of this class of compounds is highly dependent on the cells and virus strains used in the assay and differ by a factor 500 or more [2]. HCMV infections often lead to severe diseases in immunocompromised individuals, such as acquired immunodeficiency syndrome (AIDS) patients and transplant recipients [7-11].

Dedicated to Professor Edmund Lukevits on the occasion of his 60th birthday.
The two drugs currently of choice for the treatment of HCMV, 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG, GCV ganciclovir) and phosphonoformic acid (PFA, foscarnet) [12-15], both result in serious side effects as well as the emergence of drug-resistant virus [15, 16].

In view of this we have studied, and earlier reported, antiviral activities of structural variations on the lead compound BPDU. A second meta-substituent on the 5-phenyl function does not alter the activity against HSV-1 and HCMV [17]. Bromo substituted 5-furyl- and 5-thienyl-2'-deoxyuridines also have about the same anti-HCMV activities and slightly differing anti-HSV-1 activities [2]. The ribofuranosyl, arabinofuranosyl, and 2'-deoxy-2'-fluoroarabinofuranosyl analogues of BPDU were slightly more active against HCMV but inactive against HSV-1 [18]. In continuing this structure-activity investigation we decided to prepare some 5-(3-substituted phenyl)-2'-deoxyuridines with 3-substituents that would be able to closely mimic the bromo group. The considerations in choosing the appropriate 3-substituents as well as the preparation of the corresponding uracils has been reported elsewhere [19]. In the present work these uracils have been coupled with 2-deoxy-3,5-di-O-p-toluoylribonosyl chloride. The α- and β-anomers were separated and the sugar moiety deprotected, giving the desired 5-(3-substituted phenyl)-2'-deoxyuridines.

5-(3-Chlorophenyl)-, 5-(3-iodophenyl)-, 5-(3-aminophenyl)-, 5-(3-azidophenyl)-, 5-(3-methylthiophenyl)-, and 5-(3-styryl)uracils 1-6 (Scheme 1) were prepared as previously described [18]. The coupling between 2,4-di-(trimethylsiloxy)pyrimidines and 2-deoxy-3,5-di-O-p-toluoyl-D-erythropentosyl chloride [20] usually results in a mixture of α- and β-anomers. By performing the reaction in anhydrous chloroform [21] with copper(I) iodide catalysis [22], the α/β-ratio can be lowered due to less anomerization of the chloro sugar and faster coupling. Since it has been shown that the unnatural α-anomers of certain nucleosides show biological activity [23-25], we were also interested in obtaining the α-anomers of the 5-(3-substituted phenyl)-2'-deoxyuridines presented in this paper.

![Scheme 1. Preparation of 5-(3-substituted phenyl)-2'-deoxyuridines.](image-url)