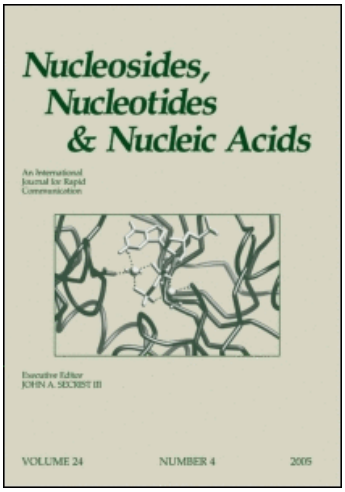

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF 5-HALOVINYL-6-AZA-2'-DEOXYURIDINES

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Abstract: (E)-5-(2-bromovinyl)-6-aza-2'-deoxyuridine and some related analogues have been synthesized and evaluated for antiherpes activity.

During the 1960's 5-substituted 6-aza-2'-deoxyuridines received attention as potential antiviral and antitumour agents[1,2]. However, the nature of the 5-substitution was limited to halogen, methyl, hydroxymethyl and trifluoromethyl. The advent of (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU; 1) as a potent and selective antiherpes agent[3] has led us to evaluate further 5-substituted 6-aza-2'-deoxyuridines as potential therapeutic agents. We now describe the synthesis and antiherpes activity of the novel (E)-5-(2-bromovinyl)-6-aza-2'-deoxyuridine (6-aza-BVDU; 2) and some closely related derivatives (3) - (6).

Our first synthesis of 6-aza-BVDU required (E)-5-(2-bromovinyl)-6-azauracil (8). Oxidation of 5-hydroxymethyl-6-azauracil to the carboxaldehyde (7) was accomplished using benzeneseleninic anhydride[4] [82%; THF, reflux]. Condensation of (7) with malonic acid [piperidine cat./ pyridine], followed by treatment with N-bromosuccinimide (NBS) [aq. KOAc, 60^0] gave (8) in 30% overall yield from (7) [^{1}H NMR[$(CD_3)_2SO$] δ 6.98 (d,J14Hz,HC=CHBr) and 7.7 (d,J14Hz, HC=CHBr].

The trimethylsilyl derivative of (8) was condensed with 2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl chloride [stannic chloride (1.1eq.), 1,2-dichloroethane, 25^0] to afford an anomeric mixture of blocked 2'-deoxyribonucleosides (9) [34%; $\beta:\alpha$=2:3]. Deprotection [NaOMe/methanol] followed by chromatographic separation of the anomers provided 6-aza-BVDU (2) [32%; ^{1}H NMR [$(CD_3)_2SO$] δ 6.38 (dd,J7,5Hz,1'-H),

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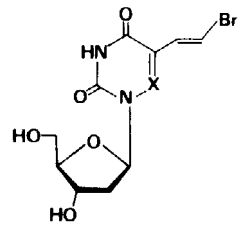
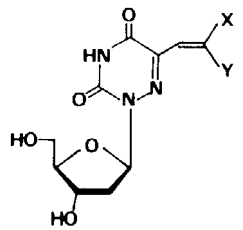
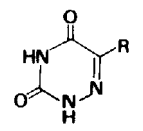


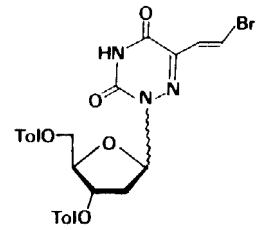
(1) X = CH (BVDU)
(2) X = N (6-aza-BVDU)



(3) X = Br, Y = F
(4) X = Cl, Y = H
(5) X = SMe, Y = H
(6) X = Y = Br



(7) R = CHO
(8) R = CH=CHBr (E)

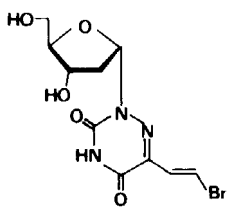


(9)

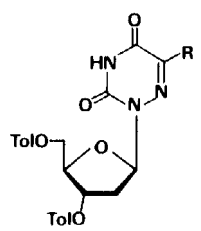
7.00 (d,J14Hz, CH=CHBr), and 7.69 (d,J14Hz,CH=CHBr)] and its α-anomer (10) [40%; ^{1}H NMR [$(CD_3)_2SO$] δ 6.27 (t,J6Hz,1'-H), 7.06 (d,J14Hz, CH=CHBr), and 7.72 (d,J14Hz,CH=CHBr)].

The somewhat tedious separation of (2) and (10) directed us to adopt an alternative approach. This utilized the known 5-hydroxymethyl-2'-deoxy-6-azauridine (11)[2], obtainable as its pure β-anomer. Oxidation of (11) with diphenyldiselenide-t-butylhydroperoxide[5] [benzene, reflux] afforded in 80% yield the carboxaldehyde (12), a versatile intermediate for our synthesis of 5-vinyl-6-aza-2'-deoxyuridines. Treatment of (12) with carbomethoxymethylenetriphenylphosphorane [CH_3CN, reflux] effected smooth (85%) conversion to the α,β-unsaturated ester (13). Hydrolysis of the ester with concomitant deblocking of the sugar residue [82%; KOH, methanol] afforded (14). Subsequent brominative decarboxylation of (14) [36%; NBS, aq. KOAc, 60°] gave anomerically pure 6-aza-BVDU (2). The β-configuration of (2) was confirmed by the n.O.e. difference method[6].

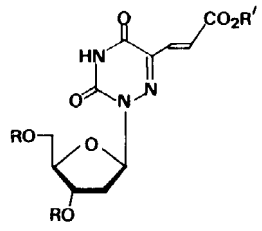
The corresponding fluoro-substituted system (3) was obtained via a similar strategy. Wadsworth-Emmons reaction of (12) [78%; $(EtO)_2P(=O)$-



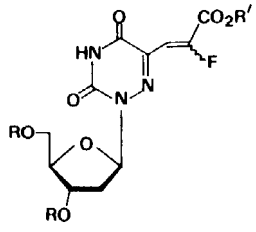
(10)



(11) R = CH_2OH
(12) R = CHO



(13) R = Tol, R' = Me
(14) R = R' = H



(15) R = Tol, R' = Et
(16) R = R' = H

$CHFCO_2Et$, NaH, THF, 20^0] afforded the fluoroacrylates (15) as a mixture of E:Z isomers (1:1), hydrolysis of which [86%; KOH, aq. methanol] gave the acids (16). Treatment of the latter compounds with NBS [aq. KOAc, 100^0] provided a 20% yield of (3) after chromatography. Wittig reaction of (12) with chloromethylenetriphenylphosphorane in THF gave a 1:1 mixture of E:Z isomers (81%) which were deprotected [51%, K_2CO_3, MeOH] and separated to provide the chlorovinyl analogue (4). Similar schemes employing methylthiomethylene- and dibromomethylenetriphenylphosphoranes afforded (5) (9%) and (6) (55%), respectively, from (12).

In the plaque reduction assay (2) showed modest activity vs. HSV-1 (IC_{50}=8μg/ml), about 1000 fold less potent than BVDU, and weak activity vs. HSV-2 (IC_{50}=190μg/ml). The α-anomer (10) was inactive against these viruses. The chlorovinyl analogue (4) showed a similar profile of activity: IC_{50}=20μg/ml vs. HSV-1, IC_{50}=215μg/ml vs. HSV-2.

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