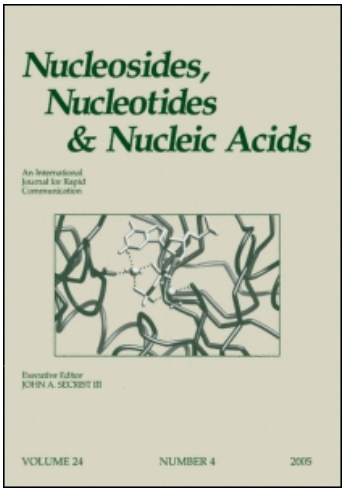

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SYNTHESIS OF (*E*)-5-(2-IODOVINYL)-3'-*O*-(1-METHYL-1,4-DIHYDROPYRIDYL-3 -CARBONYL)-2'-FLUORO-2'-DEOXYURIDINE (IVFRUCDS) FOR BRAIN TARGETTED DELIVERY OF IVFRU, AN ANTIVIRAL NUCLEOSIDE

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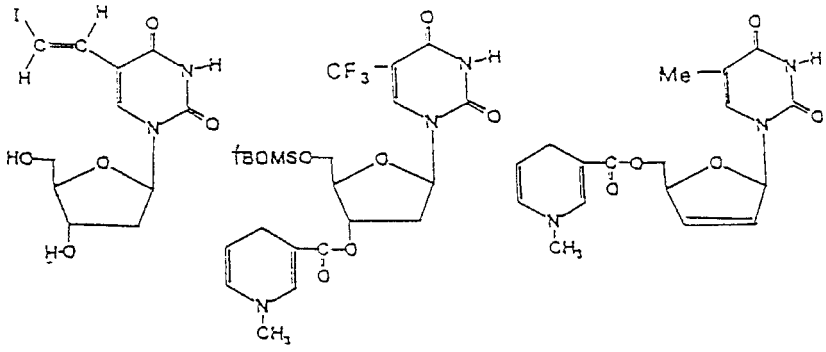
ABSTRACT: (*E*)-5-(2-Iodovinyl)-2'-fluoro-3'-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2'-deoxyuridine **(11)** was synthesized for future evaluation as a lipophilic, brain-selective, pyrimidine phosphorylase-resistant, antiviral agent for the treatment of Herpes simplex encephalitis (HSE). Treatment of (*E*)-5-(2-iodovinyl)-2'-fluoro-2'-deoxyuridine **(6)** with TBDMSCl in the presence of imidazole in DMF yielded the protected 5'-*O*-*t*-butyldimethylsilyl derivative **(7)**. Subsequent reaction with nicotinoyl chloride hydrochloride in pyridine afforded (*E*)-5-(2-iodovinyl)-2'-fluoro-3'-*O*-(3-pyridylcarbonyl)-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyuridine **(8)**. Deprotection of the silyl ether moiety of **8** with n-$Bu_4N^+F^-$ and quaternization of the resulting 3'-*O*-(3-pyridylcarbonyl) derivative **9** using iodomethane afforded the corresponding 1-methylpyridinium salt **10**. The latter was reduced with sodium dithionite to yield (*E*)-5-(2-iodovinyl)-2'-fluoro-3'-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2'-deoxyuridine **(11)**.

INTRODUCTION

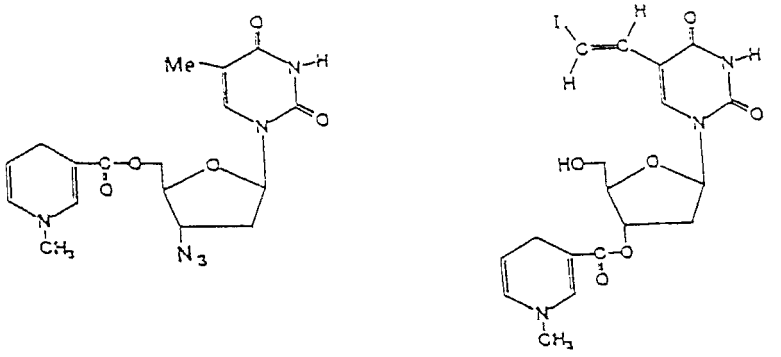
Herpes simplex virus type 1 (HSV-1) is one of the most common causes of fatal encephalitis in humans.[1] (*E*)-5-(2-Iodovinyl)-2'-deoxyuridine (**1**, IVDU) is an effective antiviral agent which is known to be active against Herpes simplex virus type 1 (HSV-1).[2] The effectiveness of IVDU in the treatment of HSV encephalitis (HSE) is limited, since it undergoes rapid cleavage of the glycosidic bond by pyrimidine phosphorylase[3] and it is unable to cross the blood brain barrier (BBB) in therapeutic concentrations.[4] Therefore, IVDU requires modification to increase its *in vivo* stability and lipophilicity in order to enhance brain uptake.

Bodor *et.al.*[5] have demonstrated that drugs can be selectively delivered to the brain using a dihydropyridine ⇆ pyridinium salt redox chemical delivery system (CDS). This approach involves the coupling of a lipophilic 1-methyl-1,4-dihydropyridyl promoiety to a drug entity via a biologically - cleavable ester link. The resulting prodrug would be expected to localize selectively in the brain by diffusion through the BBB, due to its high lipophilicity. The promoiety can also be oxidized to a polar pyridinium salt in the brain via a process analogous to the NAD -→NADH redox system. The resulting polar pyridinium salt is unable to egress out of the brain due to the lipoidal nature of the BBB, resulting in an elevated and sustained concentration of the prodrug in the brain. The entrapped salt can undergo slow hydrolysis to release the non-toxic trigonelline and the active drug.

This type of dihydropyridine ⇆ pyridinium salt redox CDS is potentially useful for the selective delivery of antiviral agents such as 5-trifluoromethyl-2'-deoxyuridine (CDS-**2**)[6], 2',3'-didehydro-2',3'-dideoxy thymidine (CDS-**3**)[7] and 3'-azido-3'-deoxythymidine (CDS-**4**)[8] to the brain. In an earlier study we reported the synthesis of (*E*)-5-(2-iodovinyl)-3'-*O*-(1-



1 CDS-2 CDS-3



CDS-4 CDS-5

methyl-1,4-dihydropyridyl-3-carbonyl)-2'-deoxyuridine (IVDU-CDS-**5**)[9] which was as active as IVDU *in vitro* against HSV-1 and VZV and more (40 times) potent than IVDU against HSV-2[10]. However, CDS-**5** was inactive an *in vivo* study[10] in HSV-1 encephalitic mice, most likely due to its rapid catabolism to the corresponding pyrimidine base, 5-(2-iodovinyl)-uracil, by the action of pyrimidine phosphorylase.[3] Stabilization of IVDU (**1**) against *in vivo* phosphorolysis has been achieved by incorporating a fluorine atom at the C-2' position of the furanosyl moiety (IVFRU, **6**) without decreasing its anti HSV-1 activity.[11] It was therefore expected that the CDS-coupled (*E*)-5-(2-iodovinyl)-2'-fluoro-2'-deoxyuridine (IVFRU-CDS, **11**) could be an

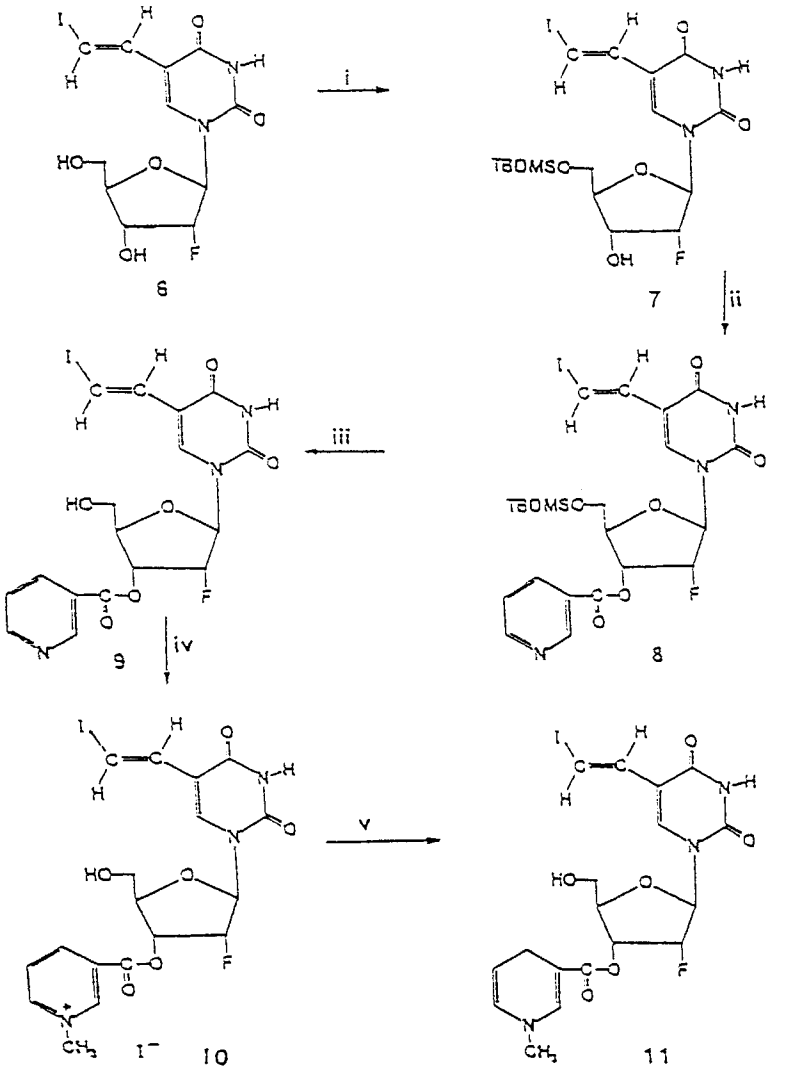
efficient prodrug to enhance the *in vivo* stability and selective delivery of IVFRU into virus-infected brain tissue.

We recently reported the synthesis of IVFRU-CDS **(11)** in 5% overall yield using a six step reaction sequence starting from 2'-fluoro-2'-deoxyuridine. The key step in this reaction involved the stereospecific iododemetallation and subsequent reduction of (*E*)-5-(2-trimethylsilylvinyl)-2'-fluoro-3'-*O*-(1-methylpyridinium-3-carbonyl)-2'-deoxyuridine iodide in one step.[12]

We now report an alternative synthesis of IVFRU-CDS **(11)**, starting from 2'-fluoro-2'-deoxyuridine in 7% overall yield.

CHEMISTRY

The regiospecific reaction of (*E*)-5-(2-iodovinyl)-2'-fluoro-2'-deoxyuridine **(6)** with *t*-butyldimethylsilyl chloride in the presence of imidazole afforded the 5'-*O*-*t*-butyldimethylsilyl (TBDMS) derivative **(7)** in 74% (Scheme 1). The TBDMS protecting group was selected since it can be readily removed to regenerate the C-5' hydroxyl group which is required for phosphorylation by viral kinases. Reaction of **7** with nicotinoyl chloride hydrochloride in the presence of pyridine yielded (*E*)-5-(2-iodovinyl)-2'-fluoro-3'-*O*-(3-pyridylcarbonyl)-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyuridine **(8)** in 77% yield. Deprotection of **8** using n-$Bu_4N^+F^-$ afforded (*E*)-5-(2-iodovinyl)-2'-fluoro-3'-*O*-(3-pyridylcarbonyl)-2'-deoxyuridine **(9)** in 90% yield. Quaternization of the nicotinoyl ester **9** using an excess of iodomethane in acetone at reflux gave the corresponding 1-methyl pyridinium iodide salt **10** in 90% yield. Finally, reduction of the pyridinium salt **10** using sodium dithionite under basic reaction conditions [6,9] using a two-phase solvent system (water:ethyl acetate; 1:1, v/v) gave (*E*)-5-(2-iodovinyl)-2'-fluoro-3'-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2'-deoxyuridine **(11)** in 62% yield.



Reagents: i, TBDMSCl, imidazole, DMF, 25 °C; ii, nicotinoyl chloride.HCl, pyridine, 25 °C; iii, n-$Bu_4N^+F^-$, THF, 25 °C; iv, MeI, acetone, reflux; v, $Na_2S_2O_4$, $NaHCO_3$, H_2O:EtOAc (1:1, v/v), 25 °C.

SCHEME 1

Compound **11** was obtained in 7% overall yield starting from 2'-fluoro-2'-deoxyuridine .

EXPERIMENTAL

Melting points were determined with a Buchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H NMR) were determined for solutions in $CDCl_3$ or DMSO-d_6 with TMS as internal standard, on a Bruker AM-300 spectrometer. Silica gel column chromatography was carried out using Merck 7734 silica gel (60-200 μ particle size). Aluminum oxide chromatography was performed using Camag 507-C neutral aluminum oxide. IVFRU **(6)** was prepared by the literature method.[11]

(*E*)-5-(2-Iodovinyl)-2'-fluoro-5-'*O*-*t*-butyldimethylsilyl-2'-deoxyuridine (7) .

Imidazole (0.06 g, 0.88 mmol) and TBDMSCl (0.045 g, 0.3 mmol) were added to a solution of **6** (0.10 g, 0.25 mmol) in DMF (5 ml) and the reaction was allowed to proceed for 24 h with stirring. An additional aliquot of TBDMSCl (0.09 g, 0.6 mmol) was added to the reaction mixture and the reaction was allowed to proceed with stirring for 24 hours. Removal of the solvent *in vacuo* and purification of the product by elution from a silica gel column using chloroform:methanol (95:5, v/v) as eluent gave **7** (0.095 g, 74%); mp 155-60 ^{0}C (decomp.) ^{1}H NMR ($CDCl_3$) δ: 0.14 and 0.16 (2s, 6H, Me_2Si), 0.95 (s, 9H, Me_3C), 3.88 (d, J_{gem} = 12.0 Hz, 1H, H-5'), 4.03-4.14 (m, 2H, H-4' and H-5"), 4.32 (ddd, $J_{3',F}$ = 18.0 Hz, $J_{3',4'}$ = 6.0 Hz, $J_{2',3'}$ = 4.5 Hz,1H, H-3'), 4.98 (dt, $J_{2',F}$ = 51 Hz, $J_{2',3'}$ = 4.0 Hz, $J_{1',2'}$ = 2.0 Hz, 1H, H-2'), 6.06 (dd, $J_{1',F}$ = 15 Hz, $J_{1',2'}$ = 2.0 Hz, 1H, H-1'), 6.96 (d, J_{trans} = 16 Hz, 1H, C<u>H</u>=CHI), 7.38 (d, J_{trans} = 16 Hz, 1H, CH=C<u>H</u>I), 7.70 (s,1H, H-6), 7.98 (s,1H, NH, exchanges with deuterium

oxide). Anal. calcd. for $C_{17}H_{26}FIN_2O_5Si$: C, 39.84; H, 5.11 N, 5.46. Found: C, 39.78; H, 5.29; N, 5.50.

(*E*)-5-(2-Iodovinyl)-2'-fluoro-3'-*O*-(3-pyridylcarbonyl)-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyuridine (8).

Nicotinoyl chloride hydrochloride (0.028 g, 0.16 mmol) was added to a solution of **7** (0.08 g, 0.16 mmol) in pyridine (5 ml) and the mixture was stirred for 24 h at 25 ^{o}C . Removal of the solvent *in vacuo* and purification of the product by elution from a silica gel column using chloroform: methanol (95:5, v/v) as eluent yielded **8** (0.075 g, 77%) as a syrup. ^{1}H NMR ($CDCl_3$) δ: 0.12 (s, 6H, Me_2Si), 0.93 (s, 9H, Me_3C), 3.92 (d, J_{gem} = 12 Hz,1H, H-5'), 4.10 (d, J_{gem} = 12 Hz,1H, H-5"), 4.45 (d, $J_{3',4'}$ = 5.5 Hz, 1H, H-4'), 5.30 (dt, $J_{2',F}$ = 51 Hz, $J_{2',3'}$ = 4.5 Hz, $J_{1',2'}$ = 2.5 Hz, 1H, H-2'), 5.44 (ddd, $J_{3',F}$ = 13.0 Hz, $J_{3',4'}$ = 5.5 Hz, $J_{2',3'}$ = 4.5 Hz, 1H, H-3'), 6.22 (dd, $J_{1',F}$ = 15 Hz, $J_{1',2'}$ = 2.5 Hz, 1H, H-1'), 7.0 (d, J_{trans} = 15 Hz, 1H, C<u>H</u>=CHI), 7.44 (m, J_{trans} = 15 Hz, 2H, CH=C<u>H</u>I and pyridyl H-5), 7.64 (s,1H, H-6), 8.32 (d, $J_{4,5}$ = 8.2 Hz, 1H, pyridyl H-4), 8.83 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-6), 9.24 (s,1H, pyridyl H-2), 10.03, (s,1H, NH, exchanges with deuterium oxide). Anal. calcd. for $C_{23}H_{29}FI\ N_3O_6$ Si: C, 44.73; H, 4.72; N, 6.80. Found: C, 45.06; H, 4.84; N, 6.84.

(*E*)-5-(2-Iodovinyl)-2'-fluoro-3'-*O*-(3-pyridylcarbonyl)-2'-deoxyuridine (9).

A solution of n-$Bu_4N^+F^-$ (0.1 ml of 1 M) in THF was added to a solution of **8** (0.07 g, 0.01 mmol) in THF (5 ml) and the reaction was allowed to proceed with stirring for 2 h at 25 ^{o}C . Removal of the solvent *in vacuo* and elution of the product from a silica gel column using chloroform:methanol (95:5, v/v) as eluent afforded **9** (0.05 g, 90%) as a syrup. ^{1}H NMR (DMSO-d_6) δ : 3.72 (m, J_{gem} = 12.5 Hz,1H, H-5'), 3.82 (m, J_{gem} = 12.5 Hz,1H, H-5"), 4.38 (m, $J_{3',4'}$ = 6.6 Hz, 1H, H-4'), 5.40 (d,

$J_{OH\ 5'}$ = 4.5 Hz,1H, OH, exchanges with deuterium oxide), 5.50 (m, $J_{3',F}$ = 13.0 Hz, $J_{3',4'}$ = 6.6 Hz, $J_{2',3'}$ = 4.5 Hz, 1H, H-3'), 5.60 (m, $J_{2',F}$ = 52.0 Hz, $J_{2',3'}$ = 4.5 Hz, $J_{1',2'}$ = 2.0 Hz, 1H, H-2'), 6.04 (dd, $J_{1',F}$ = 20.0 Hz, $J_{1',2'}$ = 2.0 Hz, 1H, H-1'), 7.08 (d, J_{trans} = 15.0 Hz, 1H, C<u>H</u>=CHI), 7.22 (d, J_{trans} = 15.0 Hz, 1H, CH=C<u>H</u>I), 7.62 (dd, $J_{4,5}$ = 8.0 Hz of d , $J_{5,6}$ = 5.0 Hz, 1H pyridyl H-5), 8.12 (s,1H, H-6), 8.35 (d, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 1.2 Hz, 1H, pyridyl H-4), 8.85 (d, $J_{5,6}$ = 5.0 Hz, $J_{4,6}$ = 1.2 Hz, 1H, pyridyl H-6), 9.14 (d, $J_{2,4}$ = 1.2 Hz,1H, pyridyl H-2), 11.70, (s,1H, NH, exchanges with deuterium oxide). Anal. calcd. for $C_{17}H_{15}FI\ N_3O_6$: C, 40.57; H, 3.0; N, 8.35. Found: C, 40.38; H, 3.22; N, 8.41.

(*E*)-5-(2-Iodovinyl)-2'-fluoro-3'-*O*-(1-methylpyridinium-3-carbonyl)-2'-deoxyuridine Iodide (10).

Iodomethane (0.18 g, 1.27 mmol) was added to a solution of the nicotinoate ester **9** (0.04 g, 0.08 mmol) in acetone (5 ml) and the resulting solution was heated at reflux for 24 h. After cooling to 25 ^0C , the yellow solid was filtered and washed with acetone to afford **10** (0.046 g, 90%). ^1H NMR (DMSO-d_6) δ: 3.72 (m, J_{gem} = 12.5 Hz,1H, H-5'), 3.85 (m, J_{gem} = 12.5 Hz,1H, H-5"), 4.40-4.50 (m, 4H, N-Me and H-4'), 5.44 (d, $J_{OH,\ 5'}$ = 4.5 Hz,1H, OH, exchanges with deuterium oxide), 5.54 (m, $J_{3',F}$ = 13.0 Hz, $J_{3',4'}$ = 6.6 Hz, 1H, H-3'), 5.65 (m, 1H, H-2'), 6.10 (dd, $J_{1',F}$ = 16.0 Hz, $J_{1',2'}$ = 2.0 Hz, 1H, H-1'), 7.10 (d, J_{trans} = 15.0 Hz, 1H, C<u>H</u>=CHI), 7.22 (d, J_{trans} = 15.0 Hz, 1H, CH=C<u>H</u>I), 8.24 (d, $J_{5,6}$ = 5.0 Hz, 1H pyridyl H-5), 8.30 (s, 1H, H-6), 9.04 (d, $J_{4,5}$ = 8.0 Hz, 1H, pyridyl H-4), 9.20 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-6), 9.62 (s, 1H, pyridyl H-2), 11.70, (s,1H, NH, exchanges with deuterium oxide). Anal. calcd. for $C_{18}H_{18}FI_2\ N_3O_6$: C, 33.50; H, 2.81; N, 6.51. Found: C, 33.10; H, 2.98; N, 6.60.

(*E*)-5-(2-Iodovinyl)-2'-fluoro-3'-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2'-deoxyuridine (11).

Sodium dithionite (0.03 g, 0.17 mmol) and sodium bicarbonate (0.013 g, 0.15 mmol) were added to a solution of the 1-methylpyridinium salt **10** (0.026 g, 0.04 mmol) in degassed water (1 ml) and ethyl acetate (2 ml) under a nitrogen atmosphere with stirring. The reaction was allowed to proceed with stirring at 25 ^{0}C for 3 h. The two fractions were separated and the ethyl acetate fraction was washed with water prior to drying (sodium sulfate). Removal of the solvent *in vacuo* and elution of the product from a neutral aluminum oxide column using chloroform:methanol (88:12, v/v) as eluent afforded **11** (0.013 g, 62%) as yellow solid; mp 132-135 ^{0}C . ^{1}H NMR ($CDCl_3$) δ: 2.92 (s, 3H, N-Me), 3.02 (br s , 2H, dihydropyridyl H-4), 3.76 and 4.02 (2d, J_{gem} = 12.5 Hz,1H each, H-5'), 4.20 (m, 1H, H-4'), 4.78 (dt, $J_{5,6}$ = 8.0 Hz, $J_{4,5}$ = 4.0 Hz, 1H, dihydropyridyl H-5) , 5.10 (m, $J_{2',F}$ = 51.0 Hz,1H, H-2'), 5.24 (m, 1H, H-3'), 5.60 (d, $J_{5,6}$ = 8.0 Hz, 1H, dihydropyridyl H-6), 5.97 (d, $J_{1',F}$ = 16.0 Hz, 1H, H-1'), 6.96 (d, J_{trans} = 15.0 Hz, 1H, C<u>H</u>=CHI), 7.0 (s, 1H, dihydropyridyl H-2), 7.30 (d, J_{trans} = 15.0 Hz, 1H, CH=C<u>H</u>I), 8.04 (s,1H, H-6). Anal. calcd. for $C_{18}H_{19}FIN_3O_6$ .1/2 H_2O: C, 40.92; H, 3.81; N, 7.95. Found: C, 41.02; H, 3.57; N, 7.63.

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