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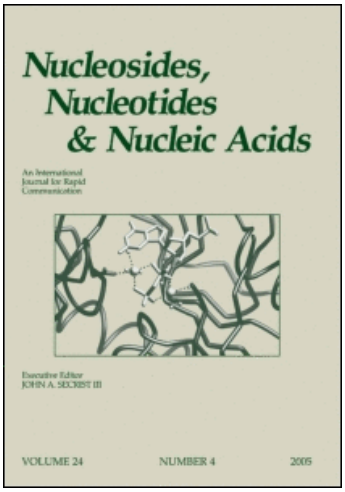

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
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5-Fluoro-1-(3,4-dideoxy-3-fluoro-6-0-trityl-beta-D-glycero-hex-3-eno-pyranos-2-ulosyl (Uracil): Anticancer Agent

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To cite this Article Ollapally, Abraham P. , Bennouna-dorange, Ismet and Whitaker Jr., Thomas L.(1999) '5-Fluoro-1-(3,4-dideoxy-3-fluoro-6-0-trityl-beta-D-glycero-hex-3-eno-pyranos-2-ulosyl (Uracil): Anticancer Agent', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 703 — 705
To link to this Article: DOI: 10.1080/15257779908041547
URL: http://dx.doi.org/10.1080/15257779908041547

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NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 703–705 (1999)

5-FLUORO-1-(3,4-DIDEOXY-3-FLUORO-6-0-TRITYL-BETA-D-GLYCERO-HEX-3-ENO-PYRANOS-2-ULOSYL (URACIL): ANTICANCER AGENT

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ABSTRACT: 1,2:5,6-Di-0-isopropylidene glucofuranose on mild oxidation, reduction, fluorination and deisopropylidenation followed by acetylation gave peracetylated 3-deoxy-3-fluoro-alpha-D-glucopyranose. This was coupled with silylated 5 fluorouracil. The nucleoside was deacetylated and after several subsequent protection and deprotection and final oxidation afforded the title compound.

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As an extension of our studies on ketounsaturated hexose nucleosides with 5-fluoro uracil which showed biological activity, we decided to use a fluorinated hexose to study any variation in biological activity. To this end, we first prepared the peracetylated 3-deoxy-3-fluoro-α-D-flucopyranose[1,2] **1**. This was coupled with silylated 5-fluorouracil **2**, in presence of TMS triflate to yield the protected nucleoside[3] **3**.

Deacetylation of **3** in methanolic ammonia gave **4** in quantitative yield. **4** was reacted with trimethylorthoformate in dry THF to protect 4',6' hydroxyls to give **5**. The protected methoxy methylene nucleoside was treated with t-butyldimethylsilyl chloride in DMF in presence of imidazole to give the completely protected nucleoside **6**. The 4',6'-methoxy methylidene protective group was cleaved in glacial acetic acid in acetone with trace of water to afford **7** which was dried well and treated with triphenyl methyl chloride in pyridine, giving the 6'-0-trityl nucleoside **8**. Acetylation of **8** under standard method gave an excellent yield of 4'-0-acetyl nucleoside **9**. On treating **9** with IM solution of tetra n-butyl ammonium fluoride in THF gave 93% yield of **10**.

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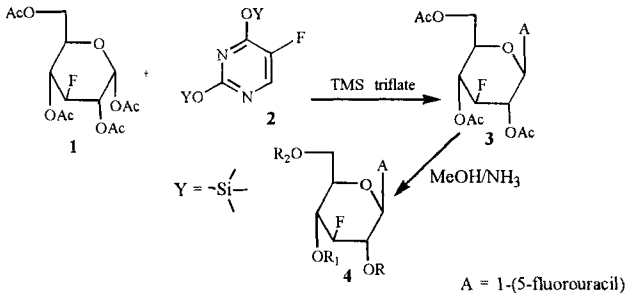
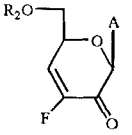
Scheme



4. R = R_1 = R_2 = H
5. R = H, R_1R_2 = Methoxymethylidene
6. R = TBDMS, R_1R_2 = Methoxymethylidene
7. R = TBDMS, R_1 = R_2 = H
8. R = TBDMS, R_1 = H, R_2 = Trityl.
9. R = TBDMS, R_1 = Ac, R_2 = Trityl.
10. R = H, R_1 = Ac, R_2 = Trityl.
11. R_2 = Trityl.



Finally, oxidation[4] of **10** with pyridinium dichromate in presence of molecular sieves 3Å in dry CH_2Cl_2 gave the fluoroketo unsaturated nucleoside **11**, the target compound.

Experimental

Melting points (uncorrected) were recorded using Mel-Temp apparatus. ^1H NMR spectra were recorded on a Brucker/IBM-5Y2000 spectrometer at 270 MHz with Me_4Si as internal standard, ^{19}F NMR spectra were done with trifluoroacetic acid as an external standard. TLC was performed on a precoated silica gel plastic sheets $60F_{254}$ (0.2 mm) EM Reagents. Compound visualization was effected with a uv lamp (254 nM) and confirmed by spraying a 5%, H_2SO_4/EtOH followed by heating.

5-Fluoro-1-(3-deoxy-3-fluoro-2,4,6-tri-0-acetyl-β-D-glucopyranosyl) uracil **3**.

A mixture of 5-fluorouracil **2** (9.94 mmol) and saccharin 50 mg was dried with few mL of dry THF and evaporated. To this was added HMDS (11.92 mmol) and unhydr. CH_3CN 20 mL, then refluxed for 3 h. The solvent was distilled to get an oily residue. A solution of **1** (8.20 mmol) in anhyd. acetonitride (30 mL) was added to the mixture after cooling the flask to 3-4°C, followed by TMS triflate 9.44 mmol in anhyd. CH_3CN (3 mL). The reaction mixture was heated at 85°C for 1 h. Cooled and then stirred overnight. Later, cooled in an ice bath, 50 mL of H_20 was added and neutralized with aq. $NaHC0_3$ (10%), then extracted with CH_2Cl_2 (2x100 mL). The organic layer was washed with water (1x80 mL) and dried over anhydrous sodium sulphate, evaporated to dryness, finally purified by column

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chromatography (silica gel) using CH_2Cl_2:MeOH (9:1) as eluent. Yield 92%, mp: 93-94°C. Anal. Calcd. for $C_{16}H_{16}N_2O_9F_2$: C, 45.75; H, 4.28; N, 6.66. Found: C, 45.91; H, 4.09; N, 6.39. Also confirmed by NMR. Compounds **4** to **10** were confirmed by ^1H NMR.

5-fluoro-1-(3,4-dideoxy-3-fluoro-6-0-trityl-β-D-glycero-hex-3-eno-pyranos-2-ulosyl) uracil **11**. 3.0g (5.2 mmol) of **10** and 10 mmol of PDC were dried with THF. 9.0g of molecular sieves 3Å, freshly activated at 375°C was cooled and added to the flask followed by 100mL of dry CH_2Cl_2 and 5 drops of glacial acetic acid. After 5 h. stirring at rt, the mixture was filtered over a bed of silica gel and washed with 0.8L of dry CH_2Cl_2. Concentrated and purified by column chromatography without applying any pressure to yield 1.22 g of **11**. 46% sirup. ^{1}HNMR (CH_3Cl_3): δ8.65 (m,1H, H-3), 7.22-7.50 (m 15H, $3C_6H_5$), 6.75 (m, 1H, H-4'), 6.66 (s, 1H, H-1'), 4.12 (qd, 1H, J=13.7 Hz, J=7.25 Hz, H-5'), 3.55 (dd, 1H, J=8.0 Hz, J=5.4 Hz, H-6a'), 3.35 (dd, 1H, J=8.1 Hz, J=5.4 Hz H-6b'). ^{19}F NMR (DMSD-d_6): -90.40 - 116.35. Biological activity: showed moderate activity against Leukemias and colon cancer *in vitro*.

Acknowledgment

Financial support from N.I.H. (MBRS) is gratefully acknowledged.

REFERENCES

1. Stevens, J.D. *Methods in Carbohydr. Chem.*, VI, *123-128*, Acad. Press, New York, **1966**.

2. Tenson, T.J.; Welch, J.M., **1978**, *J. Org. Chem., 43*, 1090-92.

3. Sharma, A.P.; Ollapally, A.P.; Jones, W.; Lemon, T. *Nucleosides and Nucleotides*, **1992**, 11, *1009-1038*.

4. Herscovici, J.; Antonakis, K. *J. Chem. Soc.*, Chem. Commun. **1980**, *561-563*.

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