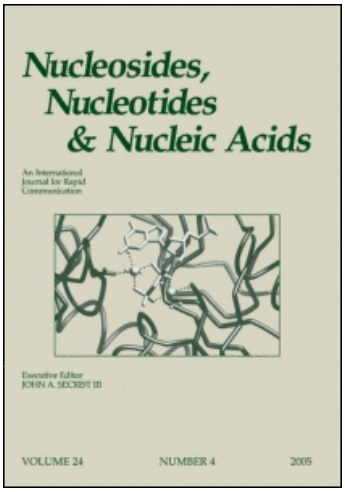

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Non-Glycosidic Derivatives of 5-Fluorouracil

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NON-GLYCOSIDIC DERIVATIVES OF 5-FLUOROURACIL

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Abstract: The synthesis and the chemical and biological properties of several non-glycosidic derivatives of 5-fluorouracil are described.

The reported cytostatic activity of Ftorafur (1-tetrahydrofuranyl--5-fluorouracil) 1 stimulated our interest in other non-glycosidic derivatives of 5-fluorouracil (5-FU)[2]. The unsaturated lactone-system 2[3] was found highly active in the P-388 leukemia test system (T/C = 196% at 60 mg/kg). The reduced compound 3a was found inactive.

Since it is well established, that inhibition of thymidylate synthetase by 5-fluorodeoxyuridinemonophosphate is the result of addition of a cysteinylthiolgroup to the 5,6-double bond, we studied the reaction of 2 with a variety of nucleophiles. With benzylthiol additionproduct 4 was isolated, while with harder nucleophiles like cyclic amines, attack on the carbonylgroup took place, leading to the production of 5-FU, via the elimination mechanism depicted in structure 5[4]. Production of 5FU from 1 is assumed to take place after in vivo oxydation at C_5, or C_2,. To test the first possibility, we carried out DIBAL-reductions of 3a at -70°C. Even under those conditions, we were unable to detect hydroxycompound 3b. In accordance with the proposed mechanism 5FU was the sole product.

Reaction of 2,4-bis-trimethylsilyloxy-5-fluoropyrimidine with epoxybutyrolactone/$SnCl_4$ produced 6.

Protected derivatives of 5FU were treated with lithium-diisopropylamide. Reaction of the resulting 6-lithioderivatives with acetaldehyde gave 7. The 6-vinylsubstituted 5FU-derivatives 8 were obtained via conversion into the iodo-derivatives followed by elimination of HI.

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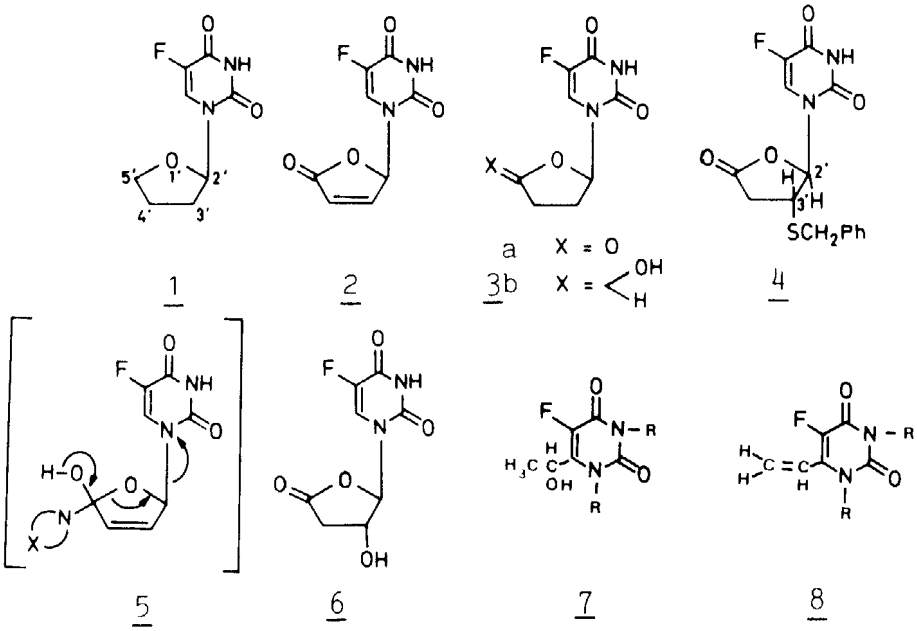

1 2 3b 4

5 6 7 8

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