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Nucleosides, Nucleotides and Nucleic Acids

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Synthesis, Conformation and Biological Properties of Selenonucleosides

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SYNTHESIS, CONFORMATION AND BIOLOGICAL PROPERTIES OF SELENONUCLEOSIDES

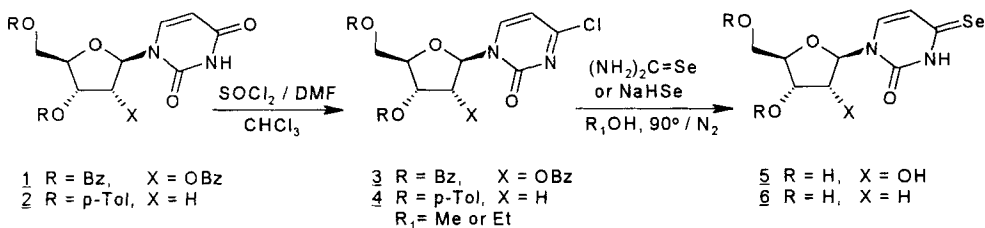
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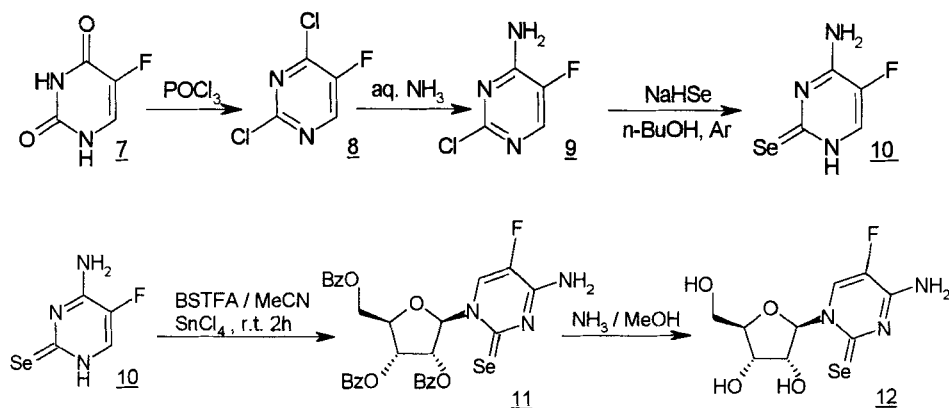
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ABSTRACT. Synthesis, conformation and antitumour properties of novel 2- and 4-selenopyrimidine nucleosides are described.

Biological activities of selenopyrimidine nucleosides have been little studied¹. We have recently shown that 2- and 4- thiouracil nucleosides exhibit significant antileukemic activity *in vitro*, correlated with inhibition of thymidylate synthase (TS) by their 5'-monophosphates². This prompted us to extend the foregoing to the corresponding seleno analogues, isosters of the thionucleosides with further decreased pK_a values for dissociation of the N(3)-H. 4-Selenouracil nucleosides **5**, **6** were prepared by rapid heating (90°C, 30') in a sealed tube of appropriately blocked 4-chloro-2-oxypyrimidine nucleosides **3**, **4** with selenourea or NaHSe in anhydrous alcohols.



2-Se-5-F-cytosine (**10**) was prepared by selenation of 2-Cl-5-F-cytosine (**9**) with NaHSe in refluxing *n*-butanol. Compound **10** was converted to its TMS derivative with BSTFA and



condensed with ABR in the presence of Friedel-Crafts catalyst (SnCl₄) in MeCN to give, after workup and deblocking, 2-seleno-5-fluorocytidine (**12**) in moderate yield (23%).

¹H NMR spectroscopy showed that the sugar conformation in D₂O of the 4-selenonucleosides **5** and **6** was predominantly *S* (60-70%), with an exocyclic rotamer population of 50% +*sc* (*gauche-gauche*), hence similar to their 4-thio counterparts, notwithstanding that the former are fully ionized at physiological pH, while 2-selenonucleoside **12** exerted 80% of *N*- and 90% of +*sc* conformation.

Both ribo- and 2'-deoxyribo- nucleosides exhibited marked cytotoxicity against mouse leukemic cells L 5178Y, with CC₅₀ values in the range 10⁻⁶ - 10⁻⁵ M, 2-seleno-5-fluorocytidine being the most potent cytotoxic agent with CC₅₀ ~ 10⁻⁶ M.

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