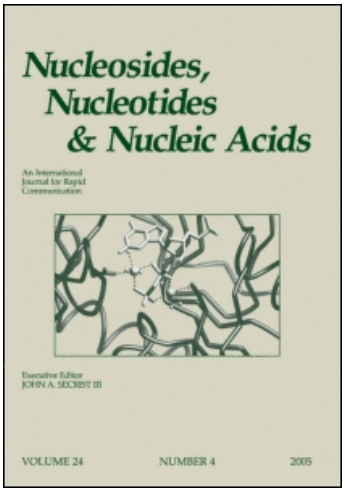

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Synthesis, Conformation and Biological Properties of Selenonucleosides

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SYNTHESIS, CONFORMATION AND BIOLOGICAL PROPERTIES OF SELENONUCLEOSIDES

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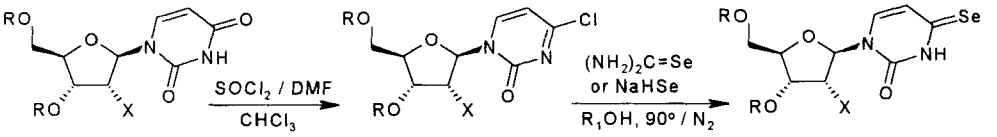
ABSTRACT. Synthesis, conformation and antitumour properties of novel 2- and 4-selenopyrimidine nucleosides are described.

Biological activities of selenopyrimidine nucleosides have been little studied [1]. 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'-monophosphates[2]. 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-oxopyrimidine nucleosides **3, 4** with selenourea or NaHSe in anhydrous alcohols.

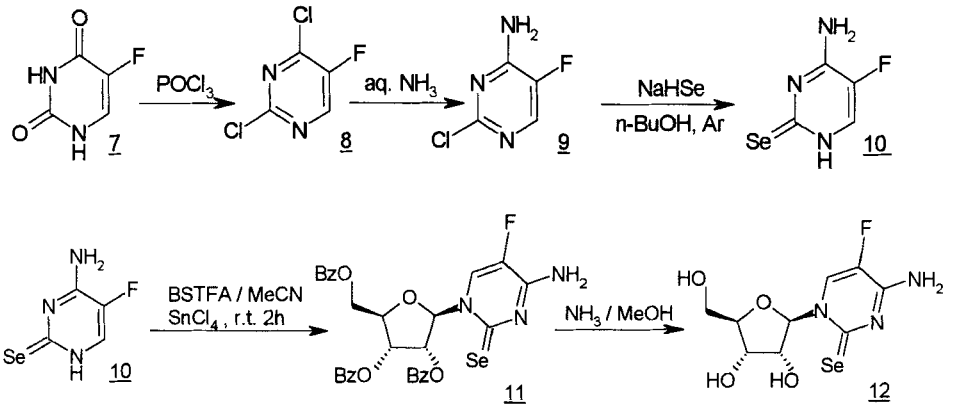


1 R = Bz, X = OBz
2 R = p-Tol, X = H

3 R = Bz, X = OBz
4 R = p-Tol, X = H
R_1 = Me or Et

5 R = H, X = OH
6 R = H, X = H

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 ($SnCl_4$) 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 D_2O 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 CC_{50} values in the range 10^{-6} - 10^{-5} M, 2-seleno-5-fluorocytidine beeing the most potent cytotoxic agent with $CC_{50} \sim 10^{-6}$ M.

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