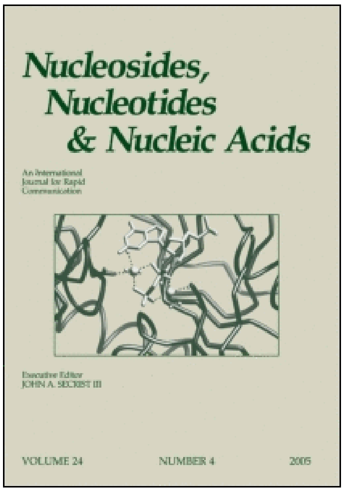

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Thionucleotides as Inhibitors of Ribonucleotide Reductase

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Thionucleotides as Inhibitors of Ribonucleotide Reductase

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ABSTRACT

Ribonucleosides and xylonucleosides bearing a disulfide function on the sugar ring were synthesized. Ribonucleosides belonging to the cytidine series were found to efficiently reduce dNTP pools in the human lymphoblastoïd CEM/SS cell line.

Key Words: Ribonucleotide reductase; Thionucleosides; Disulfides.

Ribonucleotide reductase (RNR) is an essential enzyme that catalyzes the de novo synthesis of 2′-deoxyribonucleotides. As RNR is absolutely required for DNA synthesis, this enzyme is considered to be one of the important target for anticancer and antiviral drugs. In previous studies, we have demonstrated that 2′-deoxy-2′-mercaptouridine 5′-diphosphate strongly inactivates recombinant *E. coli*

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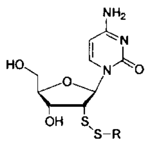
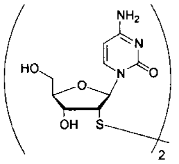
RNR.[1] As an extension of this work, our purposes were:

(1) To synthesize methyl or propyl disulfides of pyrimidine ribonucleosides and xylonucleosides as stable precursors for mercaptonucleosides.
(2) To evaluate their effect on cellular RNR indirectly, by measuring dNTP pools in the CEM/SS and CEM/dCK$^-$ human cell lines after 24 h of treatment.
(3) To establish a structure/activity relationship for these nucleoside analogues.



1: R = CH_3
2: R = $(CH_2)_2CH_3$



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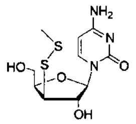

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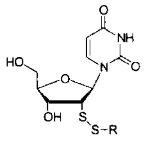
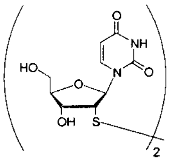


5 : R = CH_3
6 : R = $(CH_2)_2CH_3$



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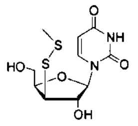

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The preparation of the disulfides **2**, **3**, **6** and **7** has been previously reported.[2] The methyl disulfides **1**, **4**, **5**, **8** were synthesized in good yields by treatment of the corresponding 2-(trimethylsilyl) ethyl sulfides with dimethyl(methylthio) sulfonium tetrafluoroborate in the presence of an excess of dimethyl disulfide at room temperature in THF.[3]

The mixed cytidine disulfides **1** and **2** were found to be the most efficient in lowering dNTP levels in CEM/SS ($IC_{50} = 50\,\mu M$). Proliferation was also inhibited by 30% at 200 μM of **1** or **2**. The symmetric cytidine disulfide **3** was less active. Since the nucleosidic function can be easily released under mild reduction conditions (DTT, room temperature), inhibition of RNR probably occurs after intracellular reduction of the corresponding disulfides. The observed similar activities for the mixed disulfides **1** and **2** support this assumption. The inhibitory potential of nucleosides **1**–**3** was abolished in CEM/dCK$^-$ cells, suggesting that deoxycytidine kinase was responsible for the phosphorylation of these cytidine derivatives. The uridine derivatives **5**–**7** and the xylonucleosides **4** and **8** did not change dNTP pools in CEM/SS cells. Since 2′-deoxy-2′-mercaptouridine 5′-disphosphate inactivates purified *E. coli* RNR, we assume that uridine derivatives are not efficiently phosphorylated in cells. In conclusion, nucleoside disulfides, especially mixed disulfides, can be considered as interesting prodrugs for bioactive mercaptonucleotides.

REFERENCES

1. Covès, J.; Le Hir de Fallois, L.; Le Pape, L.; Décout, J.-L.; Fontecave, M. Inactivation of Escherichia coli ribonucleotide reductase by 2′-deoxy-2′-mercaptouridine 5′-diphosphate. Electron paramagnetic resonance evidence for a transient protein perthiyl radical. Biochemistry **1996**, *35*, 8595–8602.

2. Le Hir de Fallois, L.; Décout, J.-L.; Fontecave, M. Synthesis of 2′-thio-uridine and -cytidine derivatives as potential inhibitors of ribonucleotide reductase: thionitrites, disulfides and 2′-thiouridine 5′-diphosphate. J. Chem. Soc. Perkin Trans. **1997**, *1*, 2587–2595.
3. Chambert, S.; Gautier-Luneau, I.; Fontecave, M.; Décout, J.-L. 2-(trimethylsilyl)ethanethiol in nucleoside chemistry. A short route for preparing thionucleosides and their methyl disulfides. J. Org. Chem. **2000**, *65*, 249–253.

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