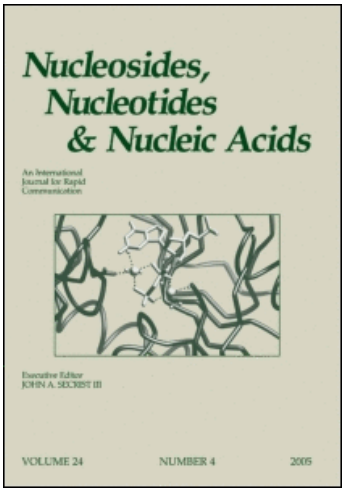

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A. Van Aerschot[ab]; G. Schepers[a]; R. Busson[a]; J. Neyts[a]; E. De Clercq[a]; P. Herdewijn[a]
[a] Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium [b] Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, 3000, Leuven, Belgium

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Synthesis and Antiviral Evaluation of Ribavirin Congeners Containing a Hexitol Moiety

A. Van Aerschot,* G. Schepers, R. Busson, J. Neyts, E. De Clercq, and P. Herdewijn

Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium

ABSTRACT

Several ribavirin congeners containing a hexitol moiety were prepared via ring opening of two different epoxides with the methylcarboxylate ester of triazole and further elaboration. Unfortunately, none of the newly synthesized compounds displayed appreciable antiviral activity.

Key Words: Antiviral; Ribavirin; Anhydroexitol; Nucleosides; HCV.

Inhibitors of IMP dehydrogenase as a key enzyme in the de novo biosynthesis of purine mononucleotides reduce the intracellular pool levels of GTP and dGTP. Therapeutic strategies towards viral infections can be based upon such approaches because of the increased need for DNA and RNA building blocks in virus-infected cells. Ribavirin is a well-known inhibitor of this enzyme,[1] and has since long been approved for clinical use for the treatment of respiratory syncytial virus (RSV) infections and, more importantly, for the treatment of hepatitis C virus (HCV) infections,

*Correspondence: A. Van Aerschot, Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, 3000 Leuven, Belgium; E-mail: arthur.vanaerschot@rega.kuleuven.ac.be.

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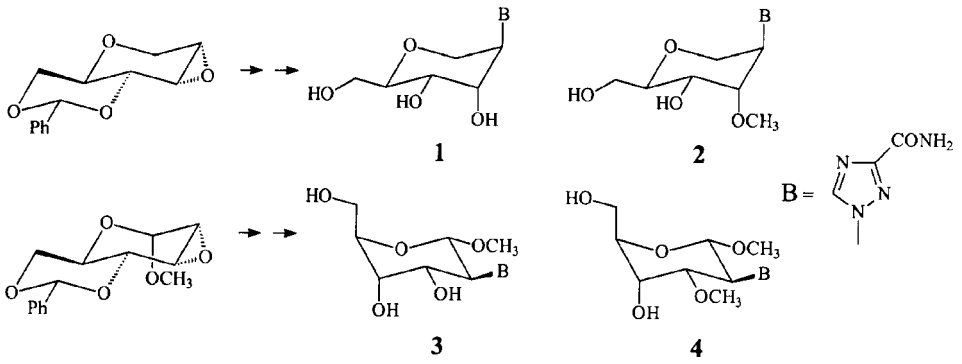
the latter in combination with interferon-α.[2] Ribavirin is also a selective inhibitor of the replication of flaviviruses, although it may be insufficiently potent to cause any beneficial effect against flavivirus infections in vivo.

Some of the 1,5-anhydrohexitol nucleoside analogues have been documented before for their antiviral properties,[3,4] and the hexitol moiety has been described to be endowed with a constrained ribonucleoside-like conformation. Combination of the 6-membered moiety with the triazole carboxamide, therefore, was a logic extension to the series.

The base was introduced as the carboxylate ester on two different epoxides, both obtained from glucose via well-known synthetic procedures.[5–7] The site of alkylation proved difficult to ascertain, but a ghmbc spectrum (indicative for ^{2}J and ^{3}J couplings) for the products obtained in both ring opening reactions, displayed a C5 – H2′ connectivity confining the alkyl group to either N1 or N4. As no further connectivity could be found for H2′ with C3, the hexitol had to reside on N1.

Optional further alkylation with methyl iodide afforded the 3′-*O*-methylated analogues. Treatment of all analogues with ammonia in methanol gave the triazolyl carboxamide derivatives, which were deprotected with trifluoroacetic acid to yield the target compounds. While the small $J_{1',2'}$ for the 1,5-anhydrohexitol derivatives are indicative for the predominant axial orientation of the base moiety ($^{4}C_{1}$), the larger $J_{1',2'}$ of 6.8 Hz for the 1′-*O*-methyl-glycoside containing derivatives, along with a large $J_{2',3'}$ of 10.3 Hz proves the equatorial orientation of the base along with equatorially oriented methoxyl substituents, yielding a $^{1}C_{4}$ conformation. The steric hindrance between both methoxyl substituents precludes their axial orientation, and therefore imposes the equatorial position on the base moiety, in contrast with other hexitol nucleoside analogues.

All congeners with a triazolyl carboxamide moiety were evaluated for their inhibitory properties against a wide variety of viruses including BVDV (bovine viral diarrhea virus) and yellow fever virus (YFV). In contrast to ribavirin, none of its derivatives displayed any appreciable antiviral activity; nor was any cytotoxic effect noted in any cell line. Only a marginal activity was found for the 3′-*O*-methylated analogue **2** against BVDV [50% effective concentration (EC_{50}): 64 μg/mL].



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