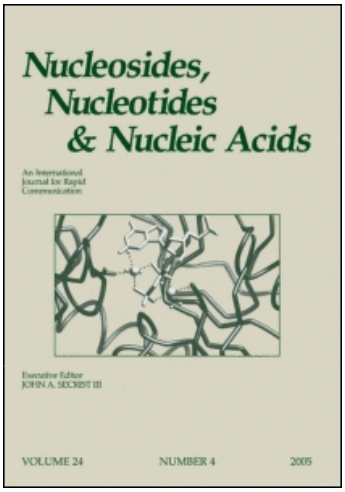


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

d4TMP Delivery from 7-Substituted *cyclo*Sal-d4TMPs

C. Meier[ab]; J. T. Renze[a]; J. Balzarini[c]; E. De Clercq[c]
[a] Institute of Organic Chemistry, University of Hamburg, Hamburg, Germany [b] Universität Hamburg, Institut für Organische Chemie, Hamburg, Germany [c] Rega Institute for Medical Research, Katholieke Universiteit, Leuven, Belgium

Online publication date: 09 August 2003

To cite this Article Meier, C. , Renze, J. T. , Balzarini, J. and De Clercq, E.(2003) 'd4TMP Delivery from 7-Substituted *cyclo*Sal-d4TMPs', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 825 — 827
To link to this Article: DOI: 10.1081/NCN-120022663
URL: http://dx.doi.org/10.1081/NCN-120022663

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 825–827, 2003

d4TMP Delivery from 7-Substituted *cyclo*Sal-d4TMPs

C. Meier,[1,*] J. T. Renze,[1] J. Balzarini,[2] and E. De Clercq[2]

[1]Institute of Organic Chemistry, University of Hamburg, Hamburg, Germany
[2]Rega Institute for Medical Research, Katholieke Universiteit, Leuven, Belgium

ABSTRACT

Benzyl-substituted *cyclo*Sal-d4T monophosphates were prepared and evaluated for their ability to release d4TMP selectively. In contrast to previously reported derivatives, two of the new compounds release d4TMP as the sole product while two others gave the expected benzyl phosphate diesters. However, these diesters were surprisingly stable against degradation to release d4TMP.

Key Words: Pronucleotides; Nucleotide delivery; *cyclo*Sal.

INTRODUCTION

The *cyclo*Saligenyl-(*cyclo*Sal) pronucleotide concept has been developed for the intracellular delivery of antivirally active nucleotides via a pH-driven selective chemical hydrolysis. Using a number of nucleoside analogues, the *cyclo*Sal-triesters released the corresponding nucleotides and improved the biological potency

*Correspondence: C. Meier, Universität Hamburg, Institut für Organische Chemie, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany; Fax: +49 404 2838 2495; E-mail: chris.meier@chemie.uni-hamburg.de.

DOI: 10.1081/NCN-120022663
1525-7770 (Print); 1532-2335 (Online)

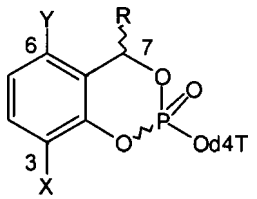
MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

considerably.[1,2] Recently, *cyclo*Sal-triesters bearing methyl-substitution or functionalized alkyl groups in the benzyl (7) position have been prepared. However, particularly the methyl derivative showed an entirely different hydrolysis mechanism as compared to the 7-unsubstituted triesters. A phenyl instead of a benzyl phosphate diester was the major product.[3] Here we present compounds that deliver d4TMP although they are modified by a 7-methyl substitution.

RESULTS

The modification of the 7-position led to the introduction of a secondary, benzylic carbon atom instead of the primary one in the original *cyclo*Sal-triesters. Obviously, a spontaneous or assisted S_N1-type heterolytic bond cleavage was then the favoured hydrolysis process that led to the formation of a phenyl phosphate diester. In the case of 7-methyl-*cyclo*Sal-d4TMP **1**, 83% of this diester was observed in addition to 17% d4TMP; 3,7-Dimethyl-*cyclo*Sal-d4TMP **2** gave 95% of the phenyl diester. The S_N1-type reaction led to the formation of a carbocation intermediate. So, our aim was to prevent the cation formation by destabilising the positively charged benzyl position. This can be done by introduction of electron withdrawing atoms in the 7-alkyl moiety or in the aromatic ring at the 6-position. Therefore, we prepared the 7-CH_2Cl- (**3**), 7-$CHCl_2$- (**4**), 7-CCl_3- (**5**) and the 6-Cl,7-methyl-*cyclo*Sal-d4TMP triester **6**. For comparison 6-Cl-*cyclo*Sal-d4TMP **7** and the prototype **8** were included. Interestingly, hydrolysis studies in phosphate buffer (12.5 mM, pH 7.3) revealed that triesters **3** and **6** released d4TMP exclusively, and thus the concurrent S_N1-type bond cleavage was entirely prevented. Triesters **4** and **5** also generated very high amounts of the benzyl diesters but proved to be chemically surprisingly stable under the reaction conditions. The small amounts of the phenyl diesters observed

Table 1. Hydrolysis half-lives and product distribution of triesters **1**–**8**.



Triester	R	X	Y	$t_{1/2}$ (h), pH 7.3	Benzyl diester	d4TMP	Phenyl diester
1	CH_3	H	H	0.31	–	17	83
2	CH_3	CH_3	H	0.30	–	5	95
3	CH_2Cl	H	H	5.2	–	100	–
4	$CHCl_2$	H	H	2.0	98	–	2
5	CCl_3	H	H	1.4	94	–	6
6	CH_3	H	Cl	3.6	–	100	–
7	H	H	Cl	2.0	–	100	–
8	H	H	H	8.1	–	99	1

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

were most probably a result of the high steric effect of the two or three chlorine atoms attached to methyl group in **4**, **5**. Although highly selective d4TMP release was observed for three compounds, the hydrolytical stability of the studied triesters was still insufficient to give satisfactory antiviral activity data. The hydrolysis data are summarized in Table 1.

REFERENCES

1. Meier, C. *cyclo*Sal-pronuceotides—design of chemical trojan horses. Mini Reviews Med. Chem. **2002**, *2*, 219–234.
2. Balzarini, J.; Aquaro, S.; Knispel, T.; Rampazzo, C.; Bianchi, V.; Perno, C.-F.; De Clercq, E. *cyclo*Saligenyl-2′,3′-didehydro-2′,3′-dideoxythymidine monophosphate: Efficient intracellular delivery of d4TMP. Mol. Pharmacol. **2000**, *58*, 928–935.
3. Renze, J.; Plath, M.; Ducho, C.; Balzarini, J.; De Clercq, E.; Meier, C. Benzyl-functionalized *cyclo*Sal-d4T monophosphates. Nucl. Nucl. & Nucleic Acids **2001**, *20*, 931–934.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016