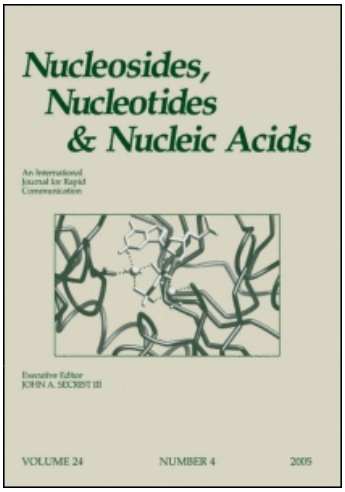

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

l-Nucleosides Containing Modified Nucleobases

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To cite this Article Seela, Frank , Lin, W. , Kazimierczuk, Z. , Rosemeyer, H. , Glaçon, V. , Peng, X. , He, Y. , Ming, X. , Andrzejewska, M. , Gorska, A. , Zhang, X. , Eickmeier, H. and La Colla, P.(2005) 'l-Nucleosides Containing Modified Nucleobases', Nucleosides, Nucleotides and Nucleic Acids, 24: 5, 859 — 863
To link to this Article: DOI: 10.1081/NCN-200059206
URL: http://dx.doi.org/10.1081/NCN-200059206

Nucleosides, Nucleotides, and Nucleic Acids, 24 (5–7):859–863, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200059206

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L-NUCLEOSIDES CONTAINING MODIFIED NUCLEOBASES

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▫ *The synthesis of base modified L-nucleosides is described with pyrrolo[2,3-d]pyrimidines, pyrazolo[3,4-d]pyrimidines, benzimidazoles, and imidazo[1,2-a]-s-triazines as nucleobases. The conformation of the nucleosides is studied and the antiviral activity is evaluated.*

Keywords L-Nucleosides, Glycosylation, 7-Deazapurine, 8-Aza-7-Deazapurine, Benzimidazole, Imidazo[1,2-a]-s-Triazine, X-Ray Analysis, Conformation, Antiviral Activity

INTRODUCTION

L-Nucleosides are recognized by virus-encoded enzymes, which can cause minimal host toxicity but good antiviral activity. The L-nucleoside of dT was already described in 1964[1] and related ribonucleosides in 1969.[2] L-Nucleosides show antiviral activity against HIV, HBV, or other viruses. Some of them are active against *Plasmodium falciparum*,[3] 3TC was the first L-nucleoside approved for the therapy against HIV and HBV.[3,4] L-Nucleosides can be phosphorylated to their active triphosphates by deoxycytidine kinases and other phosphorylating enzymes. This manuscript reports on the synthesis, conformation and antiviral activity of the β-L-nucleosides **1–8** (Scheme 1).

We gratefully acknowledge financial support by the European Community (Grant No.: QLRT-2001-00506, "Flavitherapeutics").

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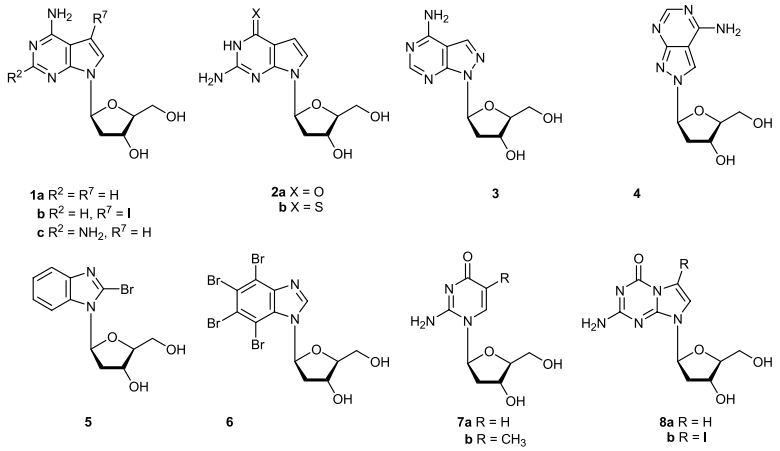
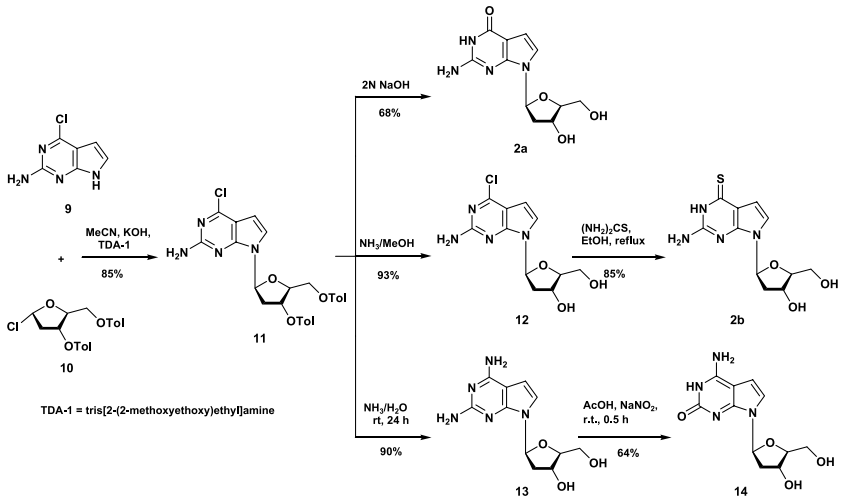


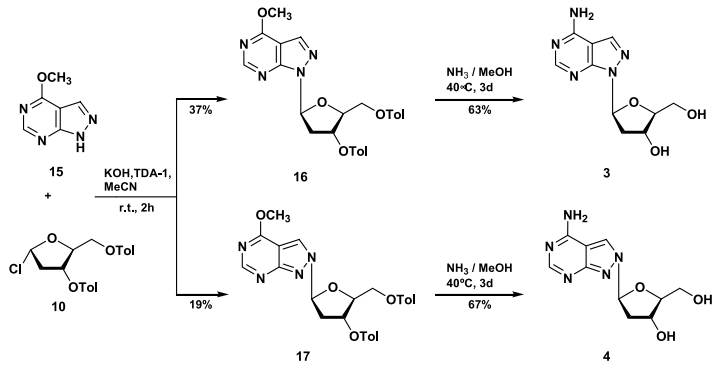
SCHEME 1

RESULTS AND DISCUSSION

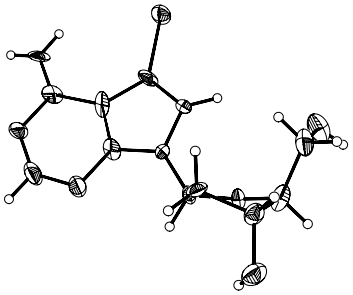
The synthesis of the nucleosides **1–8** was performed using the stereoselective nucleobase anion glycosylation.[5] The glycosylation of 2-amino-4-chloropyrrolo[2,3-d]pyrimidine **9** with 3,5-di-toluoyl-2-deoxy-α-L-ribofuranosyl chloride **10** gave **11** as outlined in Scheme 2. Compound **11** was converted into the 7-deazapurine β-L-nucleosides **2a,b** and **12–14**. Analogously, the β-L analogues of tubercidin (**1a–c**) were prepared. The same protocol was used for the synthesis of the pyrazolo[3,4-d]pyrimidine L-nucleosides **3** and **4** (Scheme 3). Although the glycosylation reaction is stereoselective, regioisomers are formed (**16** and **17**).



SCHEME 2



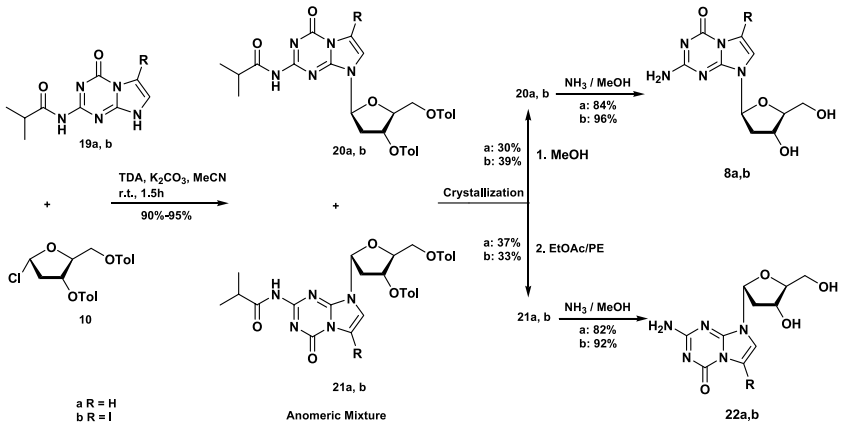
SCHEME 3



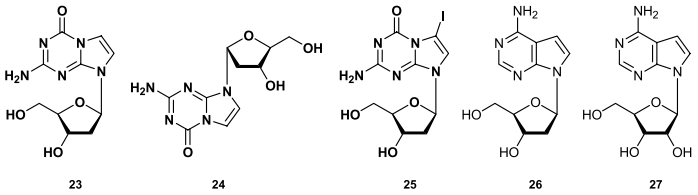
Conformation in the Solid State:
P = 197° τ_m = 32.7° χ = 147.1°
S-Conformation ^{3}E: 3‘-exo

Conformation in Solution:
P_N = 18° P_S = 159° τ_m = 38°
72% S ^{2}E: 2‘-endo
28% N ^{3}E: 3‘-endo

FIGURE 1 Perspective views of the molecule **1b** according to the X-ray structure.



SCHEME 4



SCHEME 5

For the determination of conformational parameters the β-L-nucleoside **1b** was selected. The solid state structure was obtained from single crystal X-ray analyses (Figure 1). The conformation around the glycosylic bond of compound **1b** was found to be anti and the sugar pucker is S. The conformation was also determined in solution on the basis of $^1H,^1H$ coupling constants using the program PSEUROT.

Next, the imidazo[1,2-a]-s- triazine L-nucleosides were prepared. The glycosylation of the nucleobases **19a,b** gave anomeric mixtures (**20a,b** and **21a,b**), which are difficult to separate by chromatographical methods. We found an effective separation by fractional crystallization in two different solvents, MeOH for the β-L anomers **20a,b** and ethyl acetate/petrol ether (80°) for the α-L compounds **21a,b**. Deprotection in methanolic ammonia furnished **8a,b** or **22a,b**[6] (Scheme 4).

Next, the antiviral activity of the L-nucleosides was determined. The iodinated 2′-deoxy-L-tubercidin **1b** is rather toxic, while the non-iodinated compound **1a** does not shows such properties. Also, the benzimidazole β-L-nucleoside **6** is a toxic compound; the other L-nucleosides do not developed significant antiviral activity or toxicity. For comparison antiviral activity data of D-nucleosides are shown. Note, that the β-D imidazo[1,2-]-s-triazine nucleoside **23** shows low but selective activity against BVDV (Scheme 5) (Table 1).

TABLE 1 Antiviral Activity of Selected Nucleosides

	HBV	HBV RI	HIV-1		BVDV		YFV		DENV-2	
Comp	CC_{50}	EC_{50}	CC_{50}	EC_{50}	CC_{50}	EC_{50}	CC_{50}	EC_{50}	CC_{50}	EC_{50}
1a	>100	>10	>100	>100	>100	100/100	>100	>100	>100	>100
1b	4	>4	16/18	16/18	36/46	36/46	14/12	14/12	20/12	20/12
1c	ND	ND	>100	>100	>100	>100	>100	>100	ND	ND
2a	ND	ND	>100	>100	ND	ND	ND	ND	ND	ND
3	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
6	7.8	>8	7.6	7.6	5	5	6	6	6.5	6.5
7b	ND	ND	>100	>100	75	75	>100	>100	>100	>100
8a	>100	>10	ND	ND	>100	>100	>100	>100	>100	>100
					>100	95	>100	>100		
23	100	10	>100	>100	>100	**21/27**	>100	>100	>100	>100
24	>100	>10	ND	ND	>100	>100	>100	>100	>100	>100
25	ND	ND	ND	ND	>100	95	>100	>100	ND	ND
26	>100	0.5	>100	>100	>100	>100	>100	>100	>100	>100
27	0.3	>0.3	0.06	>0.06	0.9	0.9	0.8	0.8	1	1

REFERENCES

1. Šmejkal, J.; Šorm, F. Collect. Czechoslov. Chem. Commun. **1964**, *29*, 2809–2813.
2. Holy, A.; Šorm, F. Collect. Czechoslov. Chem. Commun. **1969**, *34*, 3383–3401.
3. Wang, P.; Hong, J.H.; Cooperwood, J.S.; Chu, C.K. Antivir. Res. **1998**, *40*(1–2), 19–44.
4. Graciet, J.-C.G.; Schinazi, R.F. Adv. Antiv. Drug Des. **1999**, *3*, 1–68.
5. Winkeler, H.-D.; Seela, F. J. Org. Chem. **1983**, *48*, 3119–3122.
6. Lin, W.; Zhang, X.; Seela, F. Helv. Chim. Acta **2004**, *87, in press.*