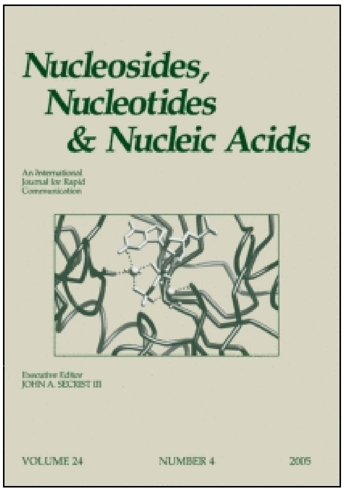

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D. Dukhan[a]; F. Leroy[a]; J. Peyronnet[a]; E. Bosc[a]; D. Chaves[a]; M. Durka[a]; R. Storer[b]; P. La Colla[c]; F. Seela[d]; G. Gosselin[a]
[a] Laboratoire Coopératif Idenix—CNRS, Université Montpellier II, Montpellier Cedex 5, France [b] Laboratoire de Chimie Médicinale Idenix, Parc Euromedecine, Montpellier, France [c] Universita di Cagliari, Monserrato, Italy [d] Universität Osnabrück, Osnabrück, Germany

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SYNTHESIS OF 5-AZA-7-DEAZAGUANINE NUCLEOSIDE DERIVATIVES AS POTENTIAL ANTI-FLAVIVIRUS AGENTS

D. Dukhan, F. Leroy, J. Peyronnet, E. Bosc, D. Chaves, and M. Durka ▫ *Laboratoire Coopératif Idenix—CNRS, Université Montpellier II, Montpellier Cedex 5, France*

R. Storer ▫ *Laboratoire de Chimie Médicinale Idenix, Parc Euromedecine, Montpellier, France*

P. La Colla ▫ *Universita di Cagliari, Monserrato, Italy*

F. Seela ▫ *Universität Osnabrück, Osnabrück, Germany*

G. Gosselin ▫ *Laboratoire Coopératif Idenix—CNRS, Université Montpellier II, Montpellier Cedex 5, France*

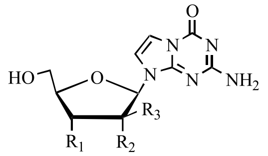
▫ *Coupling suitable sugars (D- or L-ribofuranose, 2′ or 3′-deoxysugar, branched sugars) with 2-aminoimidazo[1,2-a]-s-triazin-4-one was carried out using the different reaction conditions: 1) condensation in the presence of sodium hydride; or 2) condensation using Vorbrüggen's methods. The 5-aza-7-deazaguanine nucleoside analogues obtained were evaluated in cell culture experiments for the inhibition of the replication of a number of RNA viruses, including BVDV, YFV, and WNV.*

Keywords Flaviviruses, 5-Aza-7-Deazaguanine Nucleoside Analogues

INTRODUCTION

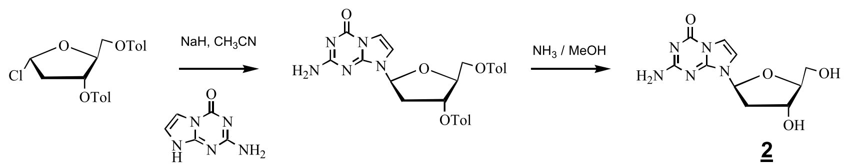
As a part of our continued effort to identify inhibitors of the replication of RNA viruses such as Flaviviruses, we decided to extend our current investigations to nucleoside analogues belonging to the 2-aminoimidazo[1,2-a]-1,3,5-triazine-4-one series. This ring system, which may be regarded as 5-aza-7-deazaguanine, is of particular interest since it retains both N_1 and N_3 of guanine with only C_5 and N_7 interchanged. The present work describes the coupling of suitable sugars (D- or L-ribofuranose, 2′- or 3′-deoxysugar, 2-*C*-methyl branched

Address correspondence to G. Gosselin, Laboratoire Coopératif Idenix–CNRS, Université Montpellier II, Place Eugène Bataillon, Case Courrier 008, 34095 Montpellier Cedex 5, France; Fax: +33-4-6754-9610; E-mail: gosselin@univ-montp2.fr



R_1 = OH, R_2 = R_3 = H **1** and L-enantiomer **2**
R_1 = R_3 = H, R_2 = OH **3**
R_1 = R_2 = OH, R_3 = H **4** and L-enantiomer **5**
R_1 = R_2 = OH, R_3 = CH_3 **6**

FIGURE 1 Structures of the target 5-aza-7-deazaguanine nucleoside analogues **1–6**.

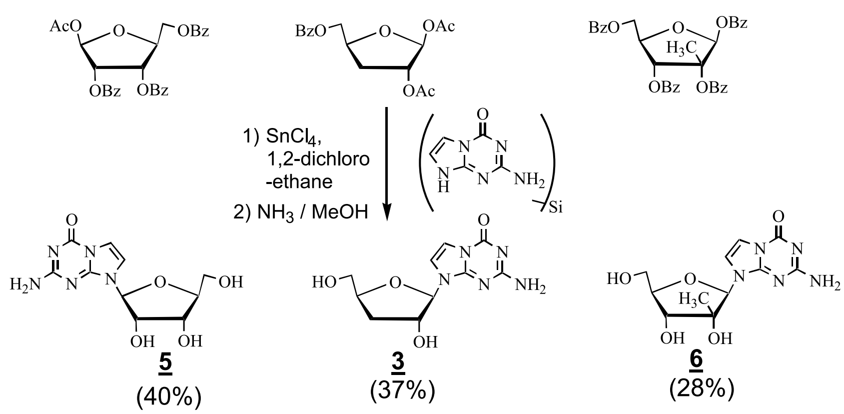


SCHEME 1 Synthesis of 2-amino-8-(β-L-2-deoxy-ribofuranosyl)-imidazo[1,2-a]-s-triazin-4-one **2**.

sugar) with 2-aminoimidazo[1,2-a]-s-triazin-4-one. The nucleoside analogues obtained **1–6** (Figure 1) were evaluated in cell culture experiments for inhibition of the replication of a number of RNA viruses, including yellow fever virus (YFV), bovine viral diarrhea virus (BVDV), dengue virus (DENV-2), and West Nile virus (WNV) (Figure 1).

CHEMISTRY

2-Amino-8-(β-L-2-deoxy-ribofuranosyl)-imidazo[1,2-a]-s-triazin-4-one **2** was synthesized following a similar procedure as that reported in the D series,[1,2] using salt sodium methodology and starting from 3,5-di-O-toluoyl-L-ribofuranosyl chloride (Scheme 1).



SCHEME 2 Synthesis of 2-amino-8-(β-L-ribofuranosyl)-imidazo[1,2-a]-s-triazin-4-one **5**, 2-amino-8-(β-D-3-deoxy-ribofuranosyl)-imidazo[1,2-a]-s-triazin-4-one **3**, and, 2-amino-8-(2-*C*-methyl-β-D-ribofuranosyl)-imidazo[1,2-a]-s-triazin-4-one **6**.

TABLE 1 Antiviral Evaluation of Compounds **1–6**

	Yellow fever		BVDV		DENV-2		West Nile		MT-4
Compounds	EC_{50} μM[a]	CC_{50} μM[b]	EC_{50} μM[a]	CC_{50} μM[b]	EC_{50} μM[c]	CC_{50} μM[d]	EC_{50} μM[e]	CC_{50} μM[d]	CC_{50} μM[f]
1	>100	>100	**21**	>100	>100	>100	>100	>100	>100
2	>100	>100	>100	>100	>100	>100	>100	>100	>100
3	>100	>100	>100	>100	>100	>100	>100	>100	>100
4	≥100	>100	**31**	>100	>100	>100	>100	>100	>100
5	>100	>100	>100	>100	>100	>100	>100	>100	>100
6	>100	>100	>100	>100	>100	>100	>100	>100	>100

Condensation of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose with silylated 5-aza-7-deazaguanine was performed following the same procedure as that reported in the D series,[3,4] in the presence of tin tetrachloride ($SnCl_4$) in 1,2-dichloroethane at room temperature, to give the corresponding 2-amino-8-(2,3,5-tri-*O*-benzoyl-β-L-ribofuranosyl)-imidazo[1,2-a]-s-triazin-4-one nucleoside in a 40% yield. Treatment of this protected sugar derivative with saturated methanolic ammonia afforded quantitatively 5-aza-7-deaza-L-guanosine **5**.

Using similar procedures, nucleoside analogues **3** and **6** were prepared in satisfactory yields starting from 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-D-erythropentofuranose and from 1,2,3,5-tetra-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranose, respectively (Scheme 2).

BIOLOGICAL EVALUATION

The 5-aza-7-dazaguanine nucleoside derivatives **1–6** were evaluated for their in vitro inhibitory effect on the replication of several RNA viruses (Table 1). Modest but selective activity against BVDV was found for the β-D-ribo- (**1**) and 2′-deoxy-β-D-ribo- (**4**) ribofuranosyl derivatives, without cytotoxicity up to 100 μM.

CONCLUSION

A series of 5-aza-7-deazaguanine nucleoside analogues **1–6** have been prepared. Among them, the β-D-ribo- (**1**) and 2′-deoxy-β-D-ribo- (**4**) ribofuranosyl derivatives exhibited modest and selective activity against BVDV, without concomitant cytotoxicity. Further study is currently in progress to explore the mode of action of compounds **1** and **4**.

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