Synthesis and study of 9-deazaguanosine derivatives as potential inhibitors of RNA virus replication

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ABSTRACT

9-Deazaguanosine and the \( \alpha \) and \( \beta \) anomers of its 2'-C-methyl counterpart, have been synthesized and evaluated against a broad range of RNA viruses, including hepatitis C virus.

INTRODUCTION

RNA viruses are the agents of numerous wide-spread and often severe diseases. Among these viruses, we can cite dengue fever virus (50 million cases annually)\textsuperscript{1} and hepatitis C virus (HCV, more than 170 million infections worldwide)\textsuperscript{2}. Currently, no specific antiviral drugs are available for the prevention or the treatment of infections caused by the majority of RNA viruses. Perhaps the only exception is represented by HCV, current therapy for chronic hepatitis C consisting of pegylated interferon-\( \alpha \) and the nucleoside analogue ribavirin.\textsuperscript{3} However, such standard therapy is poorly tolerated and has limited efficacy, with no more than 45% and 52% response rates among patients infected with the most prevalent HCV genotypes 1 and 4,\textsuperscript{4} Therefore, there is an urgent need for more efficient and better tolerated anti-HCV agents, as well as for specific and selective treatments against a higher number of RNA virus infection. The unique RNA-dependant RNA polymerase (RDRP) is essential for replication of RNA viruses, and recent progress have been made in the development of inhibitors of the HCV RDRP.\textsuperscript{5} In this regard, we had investigated sugar-modified ribonucleoside analogues and discovered that compounds possessing a \( \beta \)-methyl substituent at the 2'-position of the D-ribose moiety are potent and broad-spectrum anti-RNA virus agents.\textsuperscript{6} Here, we focused on the synthesis and biological studies of guanine C-nucleoside derivatives, and particularly on 9-deazaguanosine 1 and its 2'-C-methyl counterpart 2.

RESULTS AND DISCUSSION

Syntheses of 9-deazaguanosine derivatives—For the synthesis of the already known 9-deazaguanosine 1,\textsuperscript{7} we chose to follow a similar procedure than the one described in 1999 by Gibson et al. for the synthesis of 2'-deoxy-9-deazaguanosine.\textsuperscript{8} First, \( N' \)-benzylated-9-deazaguanine 8 was prepared in 6 steps starting from commercially available 2-amino-6-methyl-(3H)-oxopyrimidine as depicted in scheme 1.

Scheme 1

Then, the protected guanine derivative 9 was condensed with 1-O-acetyl-2,3,5-tri-O-benzoyl-\( \beta \)-D-ribofuranose, and after deprotection steps, the desired 9-deazaguanosine 1 has been isolated with 20% overall yield (Scheme 2).

Scheme 2

A similar strategy was tried for the synthesis of 2'-C-methyl-9-deazaguanosine 2,\textsuperscript{7} but no nucleoside was detected during the condensation step. Another approach based on the introduction of the 2'-C-methyl branching on
nucleoside 1, also failed. We finally applied a longer and
time consuming strategy similar to the ones described by
Lim et al.⁷ and Butora et al.⁸ in their preparation of 9-
deazaguanosine derivatives. Thus, hydroxyl groups of 2-C-
methyl-γ-D-ribonolactone were protected and the base built
step by step to afford a α/β anomic mixture of 15a and
15b, which were separated by silica gel column
chromatography. The β-anomer 15b was converted into the
intermediate 16, which was cyclised to give 17.
Surprisingly, some isomerisation and cycle extension
occurred during the final deprotection step of 17, leading to
2'-C-methyl-9-deazaguanosine 2, its α-anomer 18 and the
pyranosyl compound 19, which were isolated in 19%, 10%
and 12% yield, respectively (Scheme 3).

**Scheme 3**

Antiviral Evaluations—9-Deazaguanosine 1 and its 2'-
C-methyl counterpart 2, as well as derivatives 18 and 19
were evaluated in cell-based assays against viruses
representative of two genera of the ssRNA⁺ Flaviviridae,
that is, Flavivirus (Yellow Fever, Dengue and West Nile
viruses) and Hepacivirus (HCV), following methods
described in the reference 6b. Unfortunately, all the
compounds showed neither antiviral activity nor
cytotoxicity at the highest concentration tested (generally
75 µM).

**CONCLUSION**

9-Deazaguanosine 1 and its 2'-C-methyl counterpart 2 were
synthesised and evaluated against a broad range of ssRNA⁺
viruses (including HCV). Both compounds were found
inactive and non cytotoxic in all antiviral assays.
Several factors could be responsible for the inactivity of 9-
deazaguanine C-nucleoside derivatives. Their inability to
enter cells or to serve as substrates for intracellular
enzymes catalysing phosphorylation, as well as a lack of
inhibition of viral polymerases by their triphosphate forms,
would all account for their antiviral inactivity. Further
research would be needed to support these hypotheses,
and work on this topic is currently in progress in our
laboratories.

**ACKNOWLEDGEMENT**

This work is part of the Ph.D. of Marie Hamann, who is
particularly grateful to Idenix Pharmaceuticals and to the
French Association Nationale de la Recherche Technique
(ANRT) for a doctoral “CIFRE” fellowship.

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is a patent [Butora, G., MacCoss, M., Bhat, B., Eldrup,
A. B. (2005) (Merck & Co., Inc.; Isis Pharmaceuticals Inc.)
WO 2005/123087], where this compound was cited but not exemplified.

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