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Hetero-expanded Purine Nucleosides. Design, Synthesis and Preliminary Biological Activity

Katherine L. Seley-Radtke[1,*], **Zhibo Zhang**[1], **Orrette R. Wauchope**[1], **Sarah C. Zimmermann**[1], **Alexander Ivanov**[2], and **Brent Korba**[3]

[1]University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, MD, 21250, USA

[2]Engelhardt Institute of Molecular Biology RAS, Moscow, Russia

[3]Georgetown University Medical Center, 3900 Reservoir Road, Medical-Dental Building SW319, Washington, DC 20057, USA

Abstract

Several thieno-expanded purine nucleoside analogues were synthesized for use as tools in ongoing investigations into nucleic acid structure and function in our laboratories. The inclusion of the thiophene ring system in the nucleoside endows the purine scaffold with advantages not previously available in other reported expanded purines. The synthesis and preliminary biological studies are reported herein.

INTRODUCTION

A number of research groups[1-5], including ours[6-9], have designed and synthesized a number of varients of structurally unique unnatural nucleosides to study various aspects of nucleic acid structure and function. Each new foray into the expansion of the genetic alphabet allows for further investigation of just how absolute the requirements for base-pairing and stacking, helix stability and recognition by enzyme systems such as polymerases or other nucleoside-metabolizing enzymes involved in critical biological processes, really are.

A number of design strategies have focused on size or shape complementarities, or matching hydrogen-bonding interactions, pairing up complementary donor-acceptor patterns between unnatural bases. Recently, use of benzene-expanded purines such as Nelson Leonard's *lin*-benzoadenosine[10] has been explored, an approach we began to pursue some time ago beginning with the synthesis of a series of thieno-expanded tricyclic purines.[7] In contrast to Leonard's, and Kool's[11-15] more recent extension of Leonard's work, and Matteucci's linear systems[16-18], use of a heteroaromatic spacer ring provides a number of advantages over the benzene spacers, including offering forth a less dramatic expansion of the helix due to the curvature of the nonlinear base pairing, while still retaining the hydrogen bonding elements involved in recognition and pairing.

In terms of stacking, high-level molecular dynamics calculations have indicated that inclusion of the heteroaromatic spacer ring will significantly increase the overall aromaticity and polarizability for these modified bases[19-21], which in turn, should result in dramatic increases in stacking effects.

*Corresponding author. kseley@umbc.edu.

Parallel to those studies, the tricyclic ribose nucleosides were converted to their triphosphate analogues to explore requirements for polymerase recognition, since studies have shown that the presence of a heteratom increases the potential for incorporation by many polymerases.[22,23] In that regard, preliminary results are discussed.

RESULTS AND DISCUSSION

The synthesis of the ribose tricyclic guanosine and adenosine have been reported.[9,7] To obtain the 2′-deoxy from the ribose derivatives, a Barton deoxygenation was employed using standard conditions.[24-26] Subsequent conversion of the tricyclics to the triphosphates[27] gave the desired nucleotides in reasonable yields.

The triphosphates of the ribose analogues were initially evaluated as substrates/inhibitors with the two most commonly studied RNA-dependent RNA polymerases (RdRp), T7 and SP6. The tricyclic ribose GTP proved to be a good substrate but not a terminator for T7, and a poor substrate, but a moderate kinetic terminator of SP6 as shown in Table 1 on the next page. In addition, the tricyclic ribose GTP inhibited HCV1B NS5B RdRp (data not shown). Studies are currently underway with the 2′-deoxy analogues with various biologically significant DNA polymerases.

CONCLUSION

The Rd-RNA polymerases readily recognized the unnatural triphosphates and surprisingly, exhibited remarkable differences in recognition, thus providing impetus to examine more selective polymerases. Investigations with DNA polymerases are currently underway with the 2-deoxy analogues and those studies are currently underway and the results will be reported as they become available.

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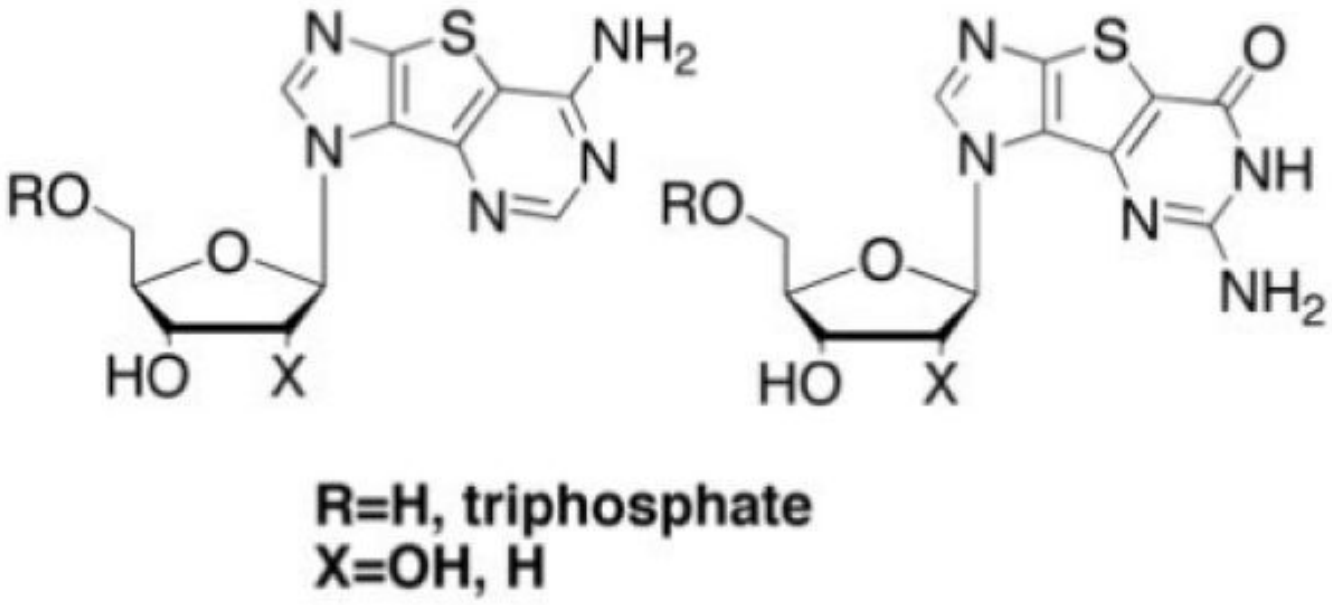
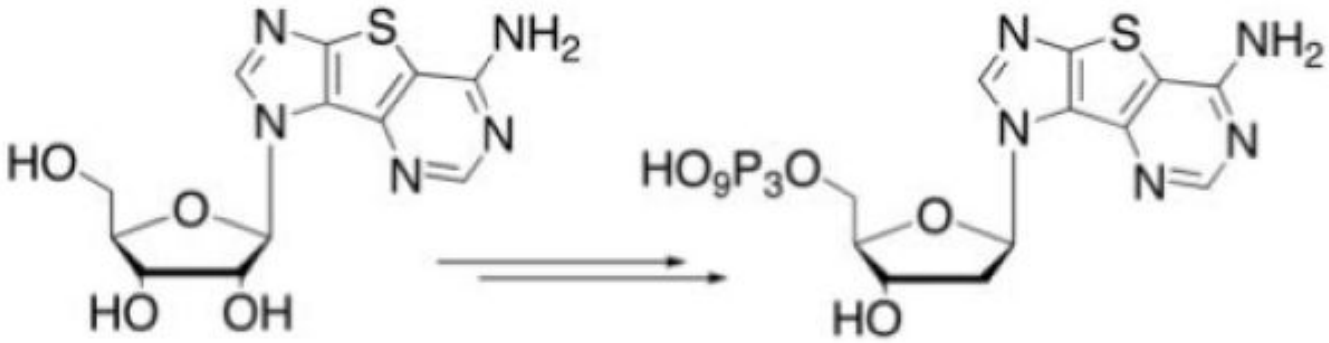


Fig 1.
Hetero-expanded purine analogues.



Scheme 1.
General synthesis overview.

Table 1

Polymerase assays

Nucleotide	T7 RNA Polymerase (K_m, μM)	SP6 RNA Polymerase (K_m, μM)
GTP	0.61	0.41
Tricyclic GTP	3.1	5.8
UTP after GTP	0.72	0.96
UTP after tri-GTP	0.79	4.98