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2- and 3-Fluoro-3-deazaneplanocins, 2-fluoro-3-deazaaristeromycins, and 3-methyl-3-deazaneplanocin: Synthesis and antiviral properties

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ABSTRACT

The 3-deaza analogs of the naturally occurring adenine-based carbocyclic nucleosides aristeromycin and neplanocin possess biological properties that have not been optimized. In that direction, this paper reports the strategic placement of a fluorine atom at the C-2 and C-3 positions and a methyl at the C-3 site of the 3-deazaadenine ring of the aforementioned compounds. The synthesis and *S*-adenosylhomocysteine hydrolase inhibitory and antiviral properties of these targets are described. Some, but not all, compounds in this series showed significant activity toward herpes, arena, bunya, flavi, and orthomyxoviruses.

1. Introduction

The clinical success of entecavir (**1**)[1] and abacavir (**2**)[2] (Fig. 1) have given carbocyclic nucleosides a prominent place among antiviral drug therapeutics and, as a consequence, serve to invigorate the search for other carbocyclic antiviral leads.[1,3] While compounds **1** and **2** are guanine and diaminopurine based agents (as prodrugs of the active triphosphates),[4] finding carbocyclic nucleoside antivirals based on the adenine ring continues in our[5] and other[6] laboratories as a result of their inhibition of *S*-adenosylhomocysteine hydrolase.[7] Aristeromycin (**3**) and neplanocin A (**4** herein referred to as neplanocin) represent the parent structures in those studies.

Because of their structural similarity to adenosine, the naturally occurring **3** and **4** have been shown to possess biological characteristics,[8] including inhibition of *S*-adenosylhomocysteine hydrolase (SAHase)[7] and 5′-nucleotide formation[9] that have been designated as loci for their antiviral properties. The synthetic 3-deaza analogs of **3** and **4** (i.e., **5** and **6**) arose to expand on the structural features of **3** and **4** and have been found to possess similar antiviral profiles most often associated with their potent inhibition of SAHase (**6** > **5**),[10] which, in turn, affects AdoMet-dependent methylation reactions,[6] including those of viral origin.[6] Also, the class of 3-deazaadenine nucleosides has drawn attention since they are less susceptible to adenosine deaminase and adenosine kinase and, consequently, less toxic than their aza parents.[11]

Continuing our interest in the 3-deaza category,[12] we recently reported that 3-halo-3-deazaadenine carbocyclic nucleosides displayed promising activity[5d,e] that prompted us to further explore this structural characteristic with the synthesis and antiviral status of 2- and 3-fluoro-3-deazaneplanocins (**7** and **8**), 2-fluoro-3-deazaaristeromycins (**9**), and 3-methyl-3-deazaneplanocin (**10**) (Fig. 1).

Target **7a** was selected as the 3-deaza congener of the antiviral candidate 2-fluoroneplanocin[13] while **8a** offers the 3-fluorolog of the broad spectrum agent 3-bromo-3-deazaneplanocin.[5e] Compound **9a** places it (i) along side of 3-fluoro-3-deazaaristeromycin, which has favorable antiviral promise,[14] and (ii) as the 3-deaza analog of the anti-malarial prospect 2-fluoroaristeromycin.[15] The compound represented by **10** became part of this study to ascertain whether 3-alkyl-3-deazaneplanocins offer antiviral potential and to provide access to functionalized carbon units at the 3-deaza site for further agent discovery. The 5′-homo targets (**7b**, **8b**, and **9b**) have also been included as a consequence of the antiviral properties of 5′-homoneplanocin[16a] and 5′-homoaristeromycin.[16b] The 5′-nor derivative of **9a** (i.e., **9c**) follows from the significant antiviral properties of 5′-nor aristeromycin.[5d]

2. Results and discussion

2.1. Synthesis

The plan to the target compounds was designed to subject readily accessible cyclopentenols **11**[5e] or **12**[16a] (shown in Scheme 2)

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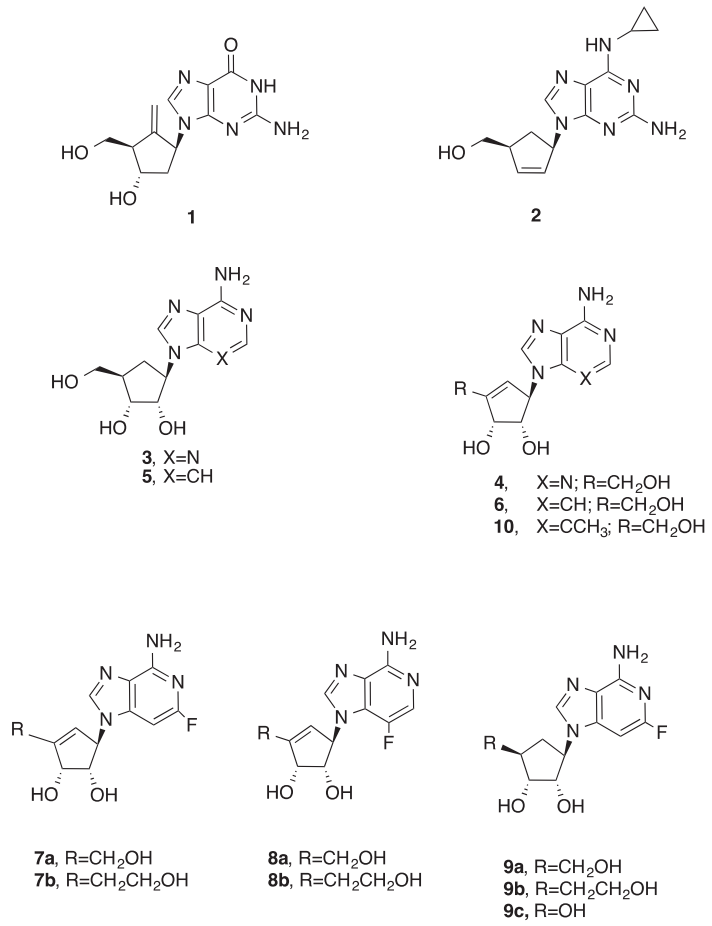


Figure 1. Relevant purine carbocyclic nucleosides.

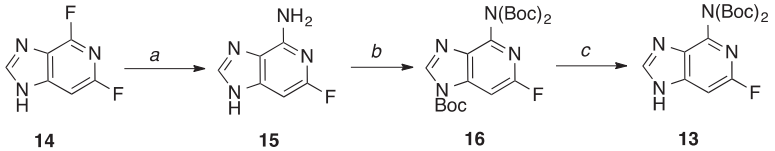
and cyclopentanols **25**,[5e] **26**,[14] and **27**[14] (shown in Scheme 3) to a Mitsunobu procedure[12a] with requisite 3-deazaadenines **13** (Scheme 1), **17**[14] and **18**[5e] (shown in Scheme 2). The preparation of **13** began with 4,6-difluoroimidazo[4,5-*c*]pridine (2,6-difluoro-3-deazaadenine, **14**)[17] with the awareness that the 6-fluoro (purine numbering) would be more susceptible to displacement by ammonia than a chloro at that position, which would require hydrazine and Raney nickel conditions as is common for 3-deazaadenine nucleosides.[12a] This conclusion was validated with the facile conversion of **14**–**15**. Realizing that the free amino on **15** would compete with the Mitsunobu coupling, it was transformed into the tri-Boc derivative **16** that was, in turn, converted to **13** with tetrabutylammonium fluoride.[5e] Besides NMR data, the structure of **13** was further confirmed by X-ray crystallography.

The five neplanocin analog targets (**7a**/**7b**, **8a**/**8b**, and **10**) were synthesized according to Scheme 2 employing **11**, **12** and **13**, **17**[14] and **18**,[5e] under Mitsunobu conditions[12a] to yield the coupling products **19**–**23**. That the coupling occurred on the purine N-9 position was confirmed by the X-ray crystal structures of **8a** and **8b**. Removal of the silyl protecting groups of **19**–**22** under acidic conditions gave targets **7a**, **7b**, **8a**, and **8b**. A palladium catalyzed cross-coupling reaction with trimethylaluminum converted **23** into **24**, which was followed by the same silyl deprotection as used previously to afford **10**.

In a similar approach, the three aristeromycin targets **9a**–**c** were synthesized according to Scheme 3. Subjecting **13** to Mitsunobu coupling conditions with **25**,[5e] **26**,[14] and **27**[14] smoothly gave products **28**–**30**. Target compounds **9a**–**c** were subsequently obtained after acidic removal of the silyl protecting groups.

2.2. Antiviral and enzyme assay results

Tables 1 and 2 summarizes the viruses toward which the compounds synthesized showed activity.[14,18] The 3-deaza-3-fluoroneplanocin series (**8a**, **8b**) (Table 1) exhibit broad antiviral activities against herpes (dsDNA), arena ((−)ssRNA), bunya ((−)ssRNA), flavi ((+)ssRNA), and orthomyxoviruses ((−)ssRNA). Target **8a** showed potent activities against tacaribe virus, human cytomegalovirus (HCMV), influenza A (H5N1), influenza B and moderate activity against Rift Valley fever and dengue virus. The 5′ homo analog



Scheme 1. Synthesis of **13**. Reagents and conditions: (a) NH_3/MeOH, 93%; (b) $(Boc)_2O$, DMAP, THF; (c) TBAF, THF, 53% from **15**.