3,7-Dideazaneplanocin: Synthesis and antiviral analysis

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Abstract
Objective: To synthesize 3,7-dideazaneplanocin and evaluate its antiviral potential.
Methods: The target 3,7-dideazaneplanocin has been prepared in five steps from a readily available cyclopentenol. A thorough in vitro antiviral analysis was conducted versus both DNA and RNA viruses.
Results: A rational synthesis of 3,7-dideazaneplanocin was conceived and successfully pursued in such a way that it can be adapted to various analogs of 3,7-dideazaneplanocin. Using standard antiviral assays, no activity for 3,7-dideazaneplanocin was found.
Conclusion: Two structural features are necessary for adenine-based carbocyclic nucleosides (like neplanocin) for potential antiviral properties: (i) inhibition of S-adenosylhomocysteine hydrolase and/or (ii) C-5' activation via the mono-nucleotide. These two requisite adenine structural features to fit these criteria are not present in in the target 3,7-dideazaneplanocin: (i) an N-7 is necessary for inhibition of the hydrolase and the N-3 is claimed to be essential for phosphorylation at C-5'. Thus, it is not surprising that 3,7-dideazaneplanocin lacked antiviral properties.

Keywords
Carbocyclic nucleosides, neplanocin, 3,7-dideazaadenine nucleosides, antiviral activity

Introduction
Since the synthesis of aristeromycin [1] and its subsequent discovery in nature,[2] carbocyclic nucleosides have received considerable attention as a source of therapeutic agents.[3] Those efforts have led to the clinically useful antivirals entecavir [2] and abacavir [3] (Figure 1).[5]

Neplanocin A [4], also a naturally occurring adenine-based carbocyclic nucleoside,[6,7] has served as a cornerstone framework due to the presence of the cyclopentenyl unit that offers unique conformationally and chemically attractive features for expanding the carbocyclic nucleoside antiviral toolbox. While numerous variations of this center have been productive in the antiviral drug pursuit, modification of the purine ring has been rewarding. In that direction, results from 3-deazaneplanocin [5] and 7-deazaneplanocin [6] has been encouraging as anti-Ebola,[10] anti-orthopox, [11] and anti-HBV and -HCV candidates.[12] Several years ago we sought to combine these two leads with the synthesis and antiviral analysis of 3,7-dideazaneplanocin [7]. The results from this investigation are presented here.

Results and discussion

Synthesis

The synthesis of target [7] began by, first, converting the requisite trityl protected cyclopentenol [8] into mesylate [9]. This product was, in turn, reacted with 4-chloro-1H-pyrrolo[3,2-c]pyridine[14,a,15] in the presence of sodium hydride to provide [10], which was converted directly to the hydrazine derivative [11]. Raney nickel promoted reduction of [11] to [12] followed by acid catalyzed deketalization resulted in the desired [7] (Scheme 1).

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Antiviral results

Compound [7] was evaluated versus a number of viruses and found to be inactive.

Conclusion

Two structural features are necessary for adenine-based carbocyclic nucleosides to demonstrate potential antiviral properties: (i) inhibition of S-adenosylhomocysteine hydrolase and/or (ii) C-5 activation via the mono-nucleotide. These two requisite adenine structural features that fit these criteria are not present in [7]: (i) an N-7 is necessary for inhibition of the hydrolase and (ii) the N-3 is claimed to be essential for phosphorylation at C-5'. These observations may account for the lack of antiviral activity for [7].

Figure 1. Aristeromycin, neplanocin A and related synthetic analogs.

Scheme 1. Synthesis of [7]. a, MsCl, Et3N, CH2Cl2; b, 4-chloro-1H-pyrrolo[3,2-c]-pyridine, NaH, DMF; c, hydrazine monohydrate, 2-methoxyethanol; d, Raney Ni, H2O, 30% (from 8); e, 0.5 N HCl, MeOH, 92%.
Experimental section

Chemistry

The combustion analyses were performed at Atlantic Microlab, Norcross, GA. 1H and 13C NMR spectra were recorded on either a Bruker AV 600 spectrometer (600 MHz for proton and 150 MHz for carbon) or a Bruker AV 400 spectrometer (400 MHz for proton and 100 MHz for carbon), referenced to internal tetramethylsilane at 0.0 ppm. The reactions were monitored by thin-layer chromatography using 0.25 mm Whatman silica gel 60-F254 precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on either Whatman silica, 230–400 mesh, and 60 Å using elution with the indicated solvent system.

1-((3a,4R,6aR)-2,2-dimethyl-6-((trityloxy)methyl)-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-4-yl)-1H-pyrrolo[3,2-c]pyridin-4-amine [12]. To a solution of 4-chloro-1H-pyrrolo[3,2-c]pyridin-4-amine [12]) in anhydrous CH2Cl2 (20 ml) was added MsCl (0.2 ml, 1.42 mmol) and triethylamine (0.46 ml, 2.82 mmol) as a sticky yellow oil. This solution was stirred at reflux for 3 h. The hot solution was filtered through a pad of Celite that was repeatedly washed with EtOAc (1:5) to give a black residue. Water (20 ml) was added and the aqueous phase extracted with EtOAc (20 ml). The combined organic layers were dried (anhyd. Na2SO4), filtered, and evaporated under reduced pressure. The residue was then dissolved in MeOH and neutralized with IRA-67 resin (Al (56540) for which we are grateful. These assays are presented in Chen et al.15

Antiviral assays

These assays are presented in Chen et al.15

Acknowledgments

We are also indebted to the National Institute of Allergy and Infectious Diseases in vitro assay team for the viral data presented herein. The assistance of Dr Erik De Clercq of the Rega Institute is also recognized.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by funds from the NIH (AI 56540) for which we are grateful.

Notes

a. Using modification of a reported procedure.
b. Recently commercially available (Sigma-Aldrich, 28 June 2017).

c. There was no activity for [7] (host cell) for toward (EC50 values in μM): cowpox (HFF, >300), vaccinia (HFF and E6SM, >380), rhinovirus (HeLa Ohio-1, >100), adenovirus (A-549, >100), respiratory syncytial virus (HeLa and MA-104, >300), influenza A (H3N2) (MDCK, >100), PIV (MA-104, >100), SARS corona (Vero 76, >100), dengue (Vero, >52), West Nile (Vero, >100), hepatitis C (Huh-5-2, >52), HSV 1 and 2 (E6SM, >60), Tacaribe (BS-C-1, >100), HCMV AD 169 and Davis (HEL, >100), VZV TK and TK- (HEL >60), HIV-1 and HIV-2 (CEM, >50), parainfluenza virus 3 (Vero, >200), reovirus-1 (Vero, >200), Sindbis virus (Vero, >200), Coxsackie virus B4 (Vero, >200), Punto Toro virus (Vero, >200), vesicular stomatitis virus (E6SM, >200), HBV (HepG2 2.2.15, >10), yellow fever (Vero, >100), and measles (CV-1, >100).

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