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CARBOCYCLIC THYMIDINE ANALOGUES FOR USE AS POTENTIAL THERAPEUTIC AGENTS

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□ *The discovery of azidothymidine's (AZT) activity against human immunodeficiency virus (HIV) provided strong rationale for the design of additional thymidine analogues. One drawback of many nucleoside analogues is the toxicity that often arises due to phosphorylation by cellular kinases. In order to overcome this problem, a number of truncated nucleosides lacking the 4′-hydroxymethyl group have been synthesized. In that regard, the synthesis and preliminary biological results for two truncated carbocyclic thymidine analogues are presented herein.*

Keywords Carbocyclic; nucleosides; pyrimidine; SAHase; neplanocin; aristeromycin

INTRODUCTION

Despite the significant biological activity exhibited by a variety of novel unnatural nucleosides, the pursuit of new analogues continues in an effort to decrease toxicity and improve efficacy in various biological systems.[1] As a result, manipulation of the nucleoside scaffold both in the heterocyclic base and the sugar moiety has resulted in a number of potent antiviral and anticancer drugs.[1–4] In that regard, a number of uridine and 5-substituted 2′-deoxyuridine nucleoside analogues (shown in Figure 1) such as 5-(E)-(bromovinyl)-2′-deoxyuridine (BVDU,[5–7] **A**), 5-trifluoromethyl-2′-deoxyuridine (F3TDR, **B**), 5-iodo-2′-deoxyuridine (IUDR, **C**)[8] and 5-bromo-2′-deoxyuridine (**D**), and 5-fluoro-2′-deoxyuridine (**E**) have exhibited antiviral and/or anticancer activity.[7,9–11]

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In honor of and in celebration of Morris J. Robins' 70th birthday.
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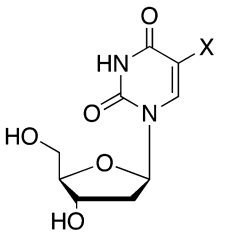
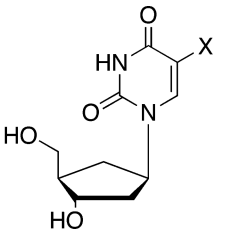
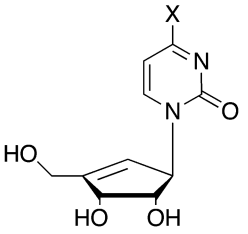


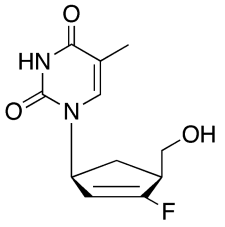
A; X=CH=CHBr, BVDU
B; X=I, IUDR
C; X=CF_3, trifluorothymidine
D; X=Br, 5-bromo-2'-deoxyuridine
E; X=F, 5-fluoro-2'-deoxyuridine



F; X=CH_3, carbocyclic thymidine
G; X=I, carbocyclic 5-iodo-2'-deoxyuridine
H; X=Br, carbocyclic 5-bromo-2'-deoxyuridine
I; X=NH_2, carbocyclic 5-amino-2'-deoxyuridine



J; X=OH, cyclopentenyl uridine (CPUC)
K; X=NH_2, cyclopentenyl cytosine (CPEC)



L; Carbocyclic-L-fluorothymidine

FIGURE 1 Biologically significant pyrimidine nucleosides.

One particular structural modification that has proven fruitful is found in the carbocyclic nucleosides.[12–16] Carbocyclic nucleosides possess a methylene group in place of the furanose oxygen in the sugar moiety of the nucleoside. This structural change imparts significant stability to the glycosidic bond, as well as increasing the overall lipophilicity of the nucleoside.[17,18] A number of carbocyclic nucleosides have been synthesized and many have been found to possess potent biological activity, including the naturally occurring Neplanocin (NpcA) and Aristeromycin (Ari). [9,17,19–21] To date most have been purine analogues, however due to the significant biological activity found among 2′-deoxy and 5-substituted 2′-deoxy pyrimidines the synthesis of the analogous carbocyclic nucleosides was also of interest and indeed, several have proven to be active.[9,10,18,22,23]

In that regard, the carbocyclic analogue of thymidine (**F**) (Figure 1) exhibited activity against leukemia L1210 cell lines, as well as HSV-1 with a MIC_{50} of 0.8 μg/mL.[9,22,23] Furthermore, carbocyclic analogues of 5-substituted uridine (**G-J**) were found to be highly active *in vitro* against the herpes simplex virus, both type 1 and 2.[9,17,20,22,23] The 5-iodo uridine analogue (**G**) proved to be the most active against HSV-1 with a MIC_{50} in the range of 0.1–0.5 μg/mL.[9,22,23] Other examples of biologically

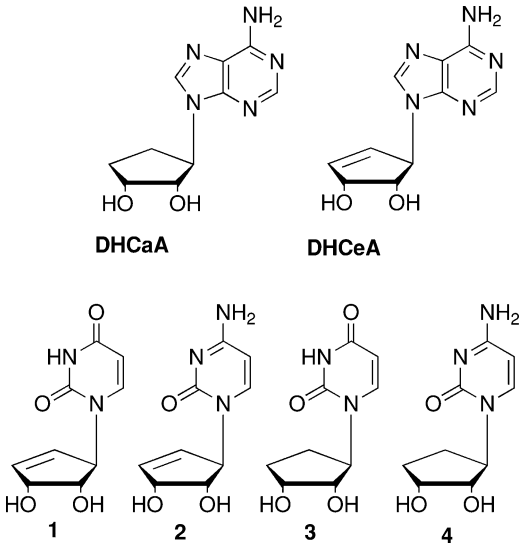


FIGURE 2 Truncated purine carbocyclic nucleosides.

active carbocyclic pyrimidine analogues include cyclopentenyl cytosine (CPE-C, **K**, Figure 1),[22,23] for which potent anti-West Nile activity was observed.[24,25] Additionally, Chu et al. reported that L-fluorothymidine **(L**, Figure 1**)** exhibited moderate activity against HIV.[24] The encouraging activity exhibited by the pyrimidine nucleoside analogues and in particular, thymidine analogues, provide an impetus to synthesize and explore the therapeutic activities of these analogues.

Despite their potent activity, one of the drawbacks of some carbocyclic nucleosides has been their susceptibility to phosphorylation by cellular kinases, resulting in significant cytotoxicity for the triphosphate analogues.[26] In response to this, strategic removal of the 4′-hydroxymethyl group of aristeromycin (Ari) and neplanocin (NpcA) resulted in the development of new analogues (1′R,2′S,3′R)-9-(2′,3′-dihydroxycyclopentan-1′-yl)adenine (DHCaA) and (1′R,2′S,3′R)-9-(2′,3′-dihydroxycyclopent-4′-enyl)adenine (DHCeA) (Figure 1).[27] Interestingly, both DHCaA and DHCeA retained potent antiviral activity but exhibited reduced cytotoxicity since neither DHCaA nor DHCeA serve as substrates for adenosine kinase or adenosine deaminase, both major causes of cytotoxicity associated with Ari and NpcA.[28]

Related to this, we recently reported the synthesis of several carbocyclic uridine and cytidine nucleoside analogues possessing the truncated scaffold (Figure 2).[30] The cytidine analogue **2** exhibited interesting activity against S-adenosylhomocysteine hydrolase (SAHase) and SAH nucleosidase. This finding was interesting because **2** is a pyrimidine analogue and these are adenosine-metabolizing enzymes.

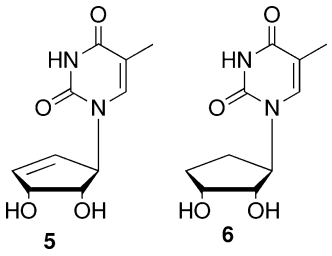


FIGURE 3 Proposed truncated thymidine carbocyclic targets.

As a logical extension to our previous studies of truncated pyrimidine nucleosides, synthesis of thymidine analogues **5** and **6** (Figure 3) was considered and the results are reported herein.

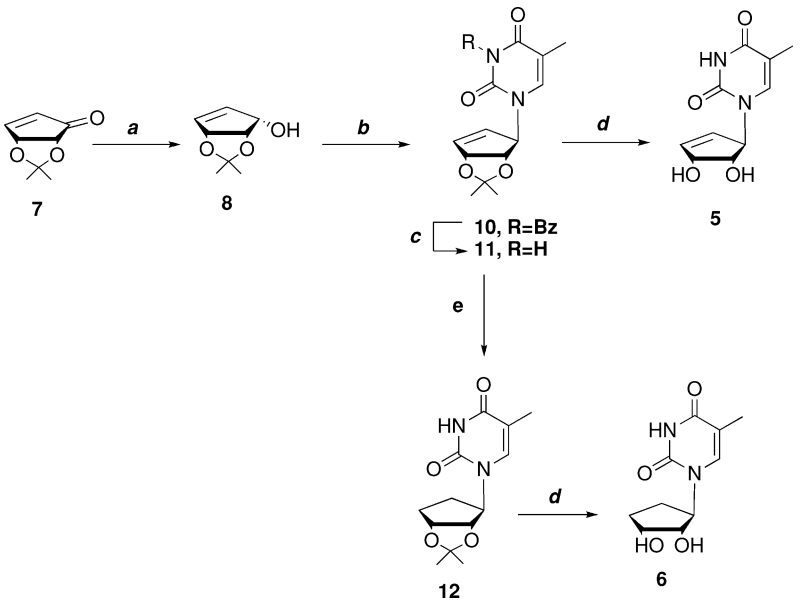
RESULTS AND DISCUSSION

Traditional Mitsunobu coupling of the thymine ring to an appropriate cyclopentyl intermediate was envisioned as a logical route to realize the targets **5** and **6**.[30–32] Synthesis began with the reduction of the known protected carbocyclic ketone **7**, a common building block in carbocyclic nucleoside research that is obtained from commercially available D-ribose in five steps.[33] Using literature methods,[34] the carbonyl group on intermediate **7** was stereospecifically reduced to the down alcohol **8** using Luche[35] conditions with cerium (III) chloride heptahydrate as shown in Scheme 1. Compound **8** was then coupled to N^3-Bz-thymine **9** using Mitsunobu conditions to afford **10** in 60% yield.[30–32]

Next, the benzoyl-protecting group on **10** was deblocked (Scheme 1) by treatment with a 1% NaOH solution in MeOH to afford intermediate **11** in 75% yield.[30,32] The isopropylidene group of analogue **11** was then removed using a mixture of TFA and H_2O (2:1) in THF to result in the first thymidine target **5**.[30]

In order to obtain the saturated target **6**, protected intermediate **11** was reduced using 10% Pd/C and H_2 at 25 psi to give **12** in 90% yield.[28,30] The isopropylidene group of **12** was then deprotected under standard conditions to quantitatively provide **6**.[28,36]

Carbocyclic thymidine analogues **5** and **6** were then screened against the National Cancer Institute's 60 cell lines, as well as subjected to broad screen testing against a number of viruses by Southern Research Institute. Unfortunately neither **5** nor **6** showed any meaningful activity. In addition, because of the unexpected inhibitory activity exhibited by our previous truncated pyrimidine analogues against SAHase, **5** and **6** were also assayed against this enzyme.[30] Not surprisingly however, since, as previously mentioned, SAHase is almost exclusively an adenosine-metabolizing enzyme, neither of



SCHEME 1 Synthesis of **5** and **6**. Reagents and conditions: a, $CeCl_3 \bullet 7H_2O$ $NaBH_4$, MeOH, 0°C; b, i) PPh_3, DIAD, CH_3CN, 0°C to rt, 24 h; c, NaOH, MeOH, 12 h; d, TFA:H_2O (2:1), 1 h, rt; e, 10% Pd/C, H_2, 25 psi, 25 min, rt.

these compounds proved to be an inhibitor. Current efforts are underway to investigate additional modifications, and the results of those studies will be reported as they become available.

EXPERIMENTAL

General Experimental Methods

All chemicals were obtained from commercial sources and used without further purification unless otherwise noted. Anhydrous DMF, MeOH, DMSO, and toluene were purchased from Fisher Scientific. Anhydrous THF, acetone, CH_2Cl_2, CH_3CN, and ether were obtained using a solvent purification system (mBraun Labmaster 130). NMR solvents were purchased from Cambridge Isotope Laboratories (Andover, MA, USA). All ^1H and ^{13}C NMR spectra were obtained on a JEOL ECX 400 MHz NMR, operated at 400 and 100 MHz respectively, and referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and b (broad). Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F254 precoated plates. Column chromatography was performed using silica gel (63–200 μm) from Dynamic Adsorbtions Inc. (Norcross, GA, USA), and

eluted with the indicated solvent system. Yields refer to chromatographically and spectroscopically ('H and 13C NMR) homogeneous materials. Mass spectra were recorded at the Johns Hopkins Mass Spectrometry Facility. Elemental analyses were recorded at Atlantic Microlabs, Inc. (Norcross, GA, USA). All chemicals were obtained from commercial sources and used without further purification unless otherwise noted.

Preparation of 1-(2′-3′-*O*-Isopropylidenedioxycylopent-1-yl)-thymine (11)

To **8**[35] (0.75 g, 4.8 mmol), N^3-benzoylthymine (2.2 g, 9.61 mmol) and PPh_3 (3.14 g, 12 mmol) in anhydrous CH_3CN (500 mL) at 0°C was added dropwise diisopropylazodicarboxylate (2.42 g, 12 mmol, 2.36 mL). After stirring at room temperature for 15 hours, the mixture was concentrated and purified by column chromatography eluting with EtOAc:hexane (3:1) to afford 1.71 g of **10** as a white solid (66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3 H, s); 1.38 (3 H, s); 1.84 (3 H, s); 4.68 (1 H, m); 5.31 (1 H, dd); 5.37 (1 H, dd); 5.79 (1 H, m); 6.21 (1 H, m); 7.22 (1 H, s); 7.51 (2 H, m); 7.72 (1 H, m); 7.92 (2 H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.1, 22.4, 24.7, 26.4, 60.2, 68.8, 83.3, 84.7, 110.1, 111.7, 129.2, 129.4, 130.3, 131.6, 135.2, 138.7, 149.9, 163.5, 169.3, 171.5.

NaOH (10 mL, 1% in MeOH) was added to **10** (1.7 g, 4.7 mmol) and the mixture allowed to stir at room temperature for 12 hours, then neutralized with 1M HCl. The mixture was evaporated and the resulting residue dissolved in EtOAc (50 mL), washed with H_2O (25 mL), dried (anhydrous $MgSO_4$), and the solvent evaporated under vacuum. The residue was purified by column chromatography eluting with EtOAc:hexane (4:1) to afford 0.95 g of **11** as a white solid (79%). ^{1}H NMR (400 MHz, CD_3OD) δ 1.29 (3 H, s); 1.37 (3 H, s); 1.82 (3 H, s); 4.61 (1 H, d); 5.38 (1 H, m); 5.41 (1 H, m); 5.79 (1 H, m); 6.21 (1 H, m); 7.11 (1 H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.6, 26.4, 60.23, 68.24, 83.47, 84.7, 110.1, 111.6, 129.4, 138.2, 151.4, 165.1, 171.5. HRMS: Calcd for $C_{13}H_{16}N_2O_4$ (M+H)+, 265.1111; Found, 265.1429.

Preparation of 1(2′,3′-Dihydroxycyclopent-2-enyl)-thymine (5)

To a mixture of trifluoroacetic acid and H_2O (2:1, 50 mL) was added **11** (0.21 g, 0.75 mmol) and the mixture stirred for 2 hours. The solvent was removed under vacuum and the residue purified by column chromatography eluting with EtOAc:MeOH, (10:1) to afford 0.13 g of **5** as a white solid (78%). ^{1}H NMR (400 MHz, CD_3OD) δ 1.85 (3H, s); 4.11(1H, m); 4.04 (1H, t); 4.57(1H, m); 6.17 (1H, m); 7.19 (1H, m). ^{13}C NMR (75 MHz, CD_3OD) 10.9, 66.3, 72.9, 76.4, 110.4, 132.8, 136.3, 137.9, 151.9, 165.2. Anal. Calcd for

$C_{10}H_{12}N_2O_4$ (0.10 H_2O): C, 53.30, H, 5.40, N, 12.10. Found: C, 53.32, H, 5.50, N, 12.04.

Preparation of 1-(2′,3′-*O*-Isopropylidinedioxycylopent-l-yl- thimine (12)

To a solution of **11** (0.500 g, 1.89 mmol) in MeOH (10 mL) Pd/C (10%, 0.040 g) was added and the mixture subjected to hydrogenation conditions at a pressure of 0.17 MPa for 20 minutes. The mixture was filtered and the filtrate concentrated under vacuum to afford 0.498 g of **12** as a white solid (quantitative). ^{1}H NMR (400 MHz, CD_3OD) δ 1.26 (3 H, s); 1.37 (3 H, s); 1.81 (3 H, s); 1.88–1.98 (2 H, m); 4.63 (1 H, d); 5.35 (1 H, m); 5.41 (1 H, m); 5.79 (1 H, m); 6.21 (1 H, m); 7.11 (1 H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.6, 26.4, 60.3, 68.3, 83.5, 84.7, 110.1, 111.6, 129.1, 138.2, 151.3, 165.1, 171.5. HRMS: Calcd for $C_{13}H_{18}N_2O_4$ (M+H)+, 267.1267; Found, 267.1340.

Preparation of 1-(2′,3′-Dihydroxycyclopentyl-thimine (6)

Compound **12** (0.200 g, 0.75 mmol) was dissolved in a mixture of trifluoroacetic acid and water (2:1, 50 mL) and stirred for 2 hours. The solvent was removed under vacuum and the residue purified by column chromatography eluting with EtOAc: MeOH (10:1) to afford 0.16 g of **6** as a white solid (quantitative).^{1}H NMR (400 MHz, DMSO) δ 1.42–1.52 (2 H, m); 1.72–1.78 (3 H, m); 1.89–1.97 (2 H, m); 3.81–3.87 (1 H, m); 3.96–4.18 (1 H, m); 4.52–4.54 (1 H, d); 4.56–4.62 (1 H, m); 4.78–4.82 (1 H, d); 7.53–7.56 (1 H, d); 11.2 (1 H, s). ^{13}C NMR (75 MHz, DMSO) 15.5, 19.9, 26.2, 59.8, 77.2, 85.9, 110.9, 137.5, 150.9, 163.8. Anal. Calcd. for $C_{10}H_{14}N_2O_4$ (0.10 H_2O); C, 52.62, H, 6.22, N, 11.70. Found: C, 52.65, H, 6.34, N, 11.83.

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