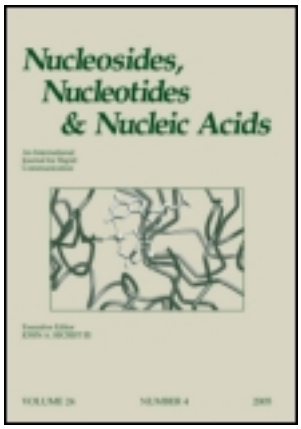

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Synthesis and Antiviral Properties of Arabino and Ribonucleosides of 1,3-Dideazaadenine, 4-Nitro-1, 3-dideazapurine and Diketopiperazine

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ABSTRACT

Different arabinosides and ribosides, viz. **Ara-DDA** or 9(1-β-D-arabinofuranosyl) 1,3-dideazaadenine (**6**), **Ara-NDDP** or 9(1-β-D-arabinofuranosyl) 4-nitro-1,3-dideaza-purine (**7**), **Ara-DKP** or 1(1-β-D-arabinofuranosyl) diketopiperazine (**8**), **Ribo-DDA** or 9(1-β-D-ribofuranosyl) 1,3-dideazaadenine (**9**) and **Ribo-NDDP** or 9(1-β-D-ribofuranosyl) 4-nitro-1,3-dideazapurine (**10**) have been synthesized as probable antiviral agents. The arabinosides have been synthesized using the catalyst TDA-1 that causes stereospecific formation of β-nucleosides while a one-pot synthesis procedure was adopted for the synthesis of the ribonucleosides where β-anomers were obtained in higher yields. All the five nucleoside analogs have been screened for antiviral property against HIV-1 (III_B), HSV-1 and 2, parainfluenza-3, reovirus-1 and many others. It was observed that arabinosides had greater inhibitory action than ribosides.

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The compound **7** or Ara-NDDP has shown maximum inhibition of HIV-1 replication than the rest of the molecules with an IC_{50} of 79.4 μg/mL.

Key Words: Antivirals; Arabinosides; Ribosides; Dideazapurines; Diketopiperazine.

INTRODUCTION

Nucleoside analogs act as antitumor and antiviral agents[1–14] via inhibition of the enzymes, viz. DNA and RNA polymerases, thymidylate synthetase, adenosine deaminase, adenosine kinase, SAH hydrolase etc. of nucleoside, nucleotide or nucleic acid metabolism of the tumor cells or pathogens.

Arabinosides are known to act as good selective antiviral agents[15] and are probably the most extensively investigated inhibitors of DNA polymerase.[16,17] Though it has been difficult to assign a mechanism for their action, these inhibitors may be said to be rather poor substrates for DNA polymerases, often leading to chain termination during replication. The best-known inhibitor belonging to the arabinoside series is Ara-A or Vidarabin.[16–19] It is an important antiviral and antitumor agent but its activity is restricted by its deamination caused by the enzyme adenosine deaminase.[2–5] So, we can see that there is a need for developing adenosine deaminase resistant analogs of Ara-A and in the same pursuance the compounds **6** and **9** have been synthesized. The compounds **7**, **8**, and **10** have been synthesized as broad-spectrum probable antiviral agents. The compound **8** is expected to have antileukemic activity and cause inhibition of the enzymes thymidylate synthetase and cytidine deaminase as well. The results are to be reported elsewhere along with studies on other structurally similar compounds.

CHEMISTRY

The nucleosides of the purine analog- benzimidazole or 1,3-dideazapurine, with substitutions at 2 and/or 5, 6 positions, have exhibited good antiviral properties[20–26] and efforts are on to increase their potency.[7,27] The nucleoside analog 9-(1-β-D-deoxyribofuranosyl) 1,3-dideazaadenine has been indicated to be resistant to adenosine deaminase.[28] The molecule 9-(1-β-D-ribofuranosyl) 3-deazaadenine[29–32] has been found to exhibit a wide range of antiviral properties and is supposed to be adenosine deaminase resistant. The compounds (**6**) and (**9**) can be considered as analogs of Ara-A or 3-deazaadenosine or 9-(1-β-D-deoxyribofuranosyl) 1,3-dideazaadenine and this analogy, as we expected, might result in a molecule that has good antiviral property, particularly against HSV-1 like Ara-A, and is at the same time adenosine deaminase resistant also. However, these molecules could not show good antiviral property against HSV-1. The study on adenosine deaminase resistant properties of these molecules is in progress.

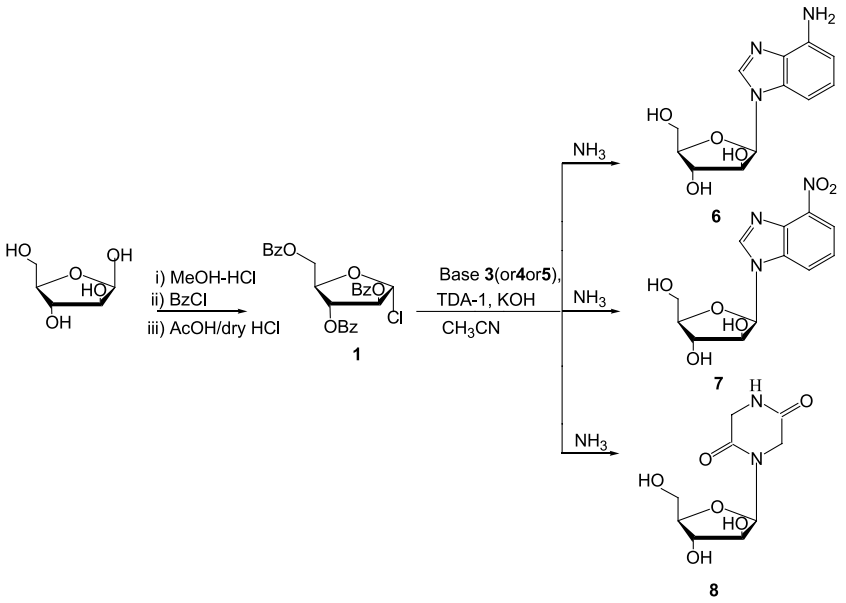
The nucleosides of uracil mimetics have also exhibited antiviral properties.[33–36] The compound (**8**) too can be considered as a structural mimetic of uracil and Ara-U. Another reason for choosing diketopiperazine nucleus for development as nucleoside analog was that piperazine derivatives have been shown as antagonists of HIV-1.[37]

The nucleoside analogs Ara-NDDP (**7**) and Ribo-NDDP (**10**) have been synthesized for screening their broad-spectrum antimicrobial properties as well.

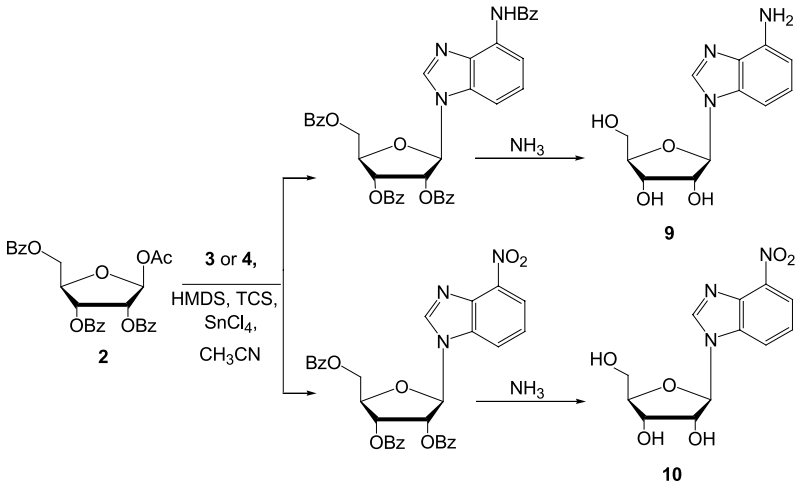
For the synthesis of arabinosides **6**, **7** and **8**, D(–)arabinose was first converted into 2,3,5-tri-*O*-benzoyl-α-D-arabinosyl chloride (**1**) which was then coupled with N-benzoyl-1,3-dideazaadenine (**3**), 4-nitro-1,3-dideazapurine (**4**) and bis (trimethylsilyl) diketopiperazine (**5**), respectively, at room temperature in the presence of the catalyst TDA-1. This catalyst has been proved to produce β-anomers selectively.[38] Ribonucleosides **9** and **10** were synthesized by coupling N-benzoyl-1,3-dideazaadenine (**3**) and 4-nitro-1,3-dideazapurine (**4**), respectively with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (ABR) (**2**) at room temperature, in a one-pot synthesis using HMDS, TCS and $SnCl_4$.[39,40] The nucleosides **6**, **7**, **8**, **9** and **10** were obtained after deprotection with 25% ammonia solution and purified by silica gel column chromatography. Their yields were 40%, 70%, 50%, 40% and 60%, respectively. The synthetic routes used for the preparation of these compounds are outlined in Schemes 1 and 2.

We have tried to increase the yield of the compound **7** further by coupling the base **4** with 2,3,5-tri-*O*-benzoyl-α-D-arabinosyl bromide,[41,42] since bromide is supposed to be a better leaving group than chloride. The catalyst and the reaction conditions were exactly the same as before but the coupling did not take place. Another set of reaction was carried out using a mixture of DCM and CH_3CN as solvents and 4 Å molecular sieves[6] in the absence of TDA-1. The reaction mixture was stirred at room temperature for about 72 h. However, the yield of the protected nucleoside was not very significant to proceed further.

Another thing that the authors wish to point out is that a survey of the available literature has shown that there are only a few reports on arabinosides synthesis by



Scheme 1. Synthesis of arabinosides.



Scheme 2. Synthesis of ribosides.

direct coupling of the sugar arabinose with natural/non-natural bases. In most cases, arabinosides have been synthesized by post-coupling modification of ribosides, which leads to increased number of synthetic steps. The authors, therefore, have tried to synthesize arabinosides by direct coupling of appropriately protected and activated D-arabinose with base analogs and have thereby been able to produce these nucleosides in considerably shorter time with significant yields in some cases like that of **Ara-NDDP** or compound **7**.

The compounds 1,3-dideazaadenine **(3a)**, 4-nitro-1,3-dideazapurine (**4**) and di-ketopiperazine **(5a)** were prepared using standard procedures.[43,44] The compound **3a** was N-benzoylated with 1.5 equivalents of benzoyl chloride following the usual benzoylation procedure to get **3**. The compound **5a** was silylated with HMDS and TCS to get **5**.

Prior to coupling of silylated base **5** with halogenose (**1**), HMDS and TCS were completely removed at pump. This was done after taking lead from the work of Kotick et al.[45] where it has been pointed out that trimethylsilyl chloride might cause anomerization of the halogenose during the coupling reaction, presumably by chloride exchange. Since the method we have used for nucleoside synthesis involves TDA-1, a phase transfer catalyst, which causes specific formation of β-anomers as major products, removal of HMDS and TCS seemed necessary. On the basis of the observations of Kotick et al., if the coupling reaction proceeds by nucleophilic attack of the silylated base on the glycosyl halide, with a single Walden inversion (SN2 mechanism), then the reaction of a pure α halogenose should lead to the formation of a β nucleoside. In the coupling procedure we have followed, TDA-1 is already causing stereospecific formation of β-anomers. The presence of HMDS and TCS may lead to a double Walden inversion and as a result an undesired major product, i.e., α nucleoside will be obtained. Hence removal of HMDS and TCS completely from the reaction mixture was an essential requirement prior to the coupling step.

Table 1. Anti-viral screening results of compounds **6–10**.

Virus/cells	IC_{50} (μg/ml)				
	6	**7**	**8**	**9**	**10**
HIV-1(III_B)/MT-4 cells	>125	= 79.4	>125	>125	>125
Vesicular stomatitis virus/HeLa cells	>40	>80	>80	>40	>40
Coxsackie virus B4/HeLa cells	>40	>80	>80	>40	>40
Respiratiory syncytial virus/HeLa cells	>40	>80	>80	>40	>120
Parainfluenza-3 virus/Vero cells	>40	>400	>400	>200	>200
Reovirus-1/Vero cells	>40	>400	>400	>200	>200
Sindbis virus/Vero cells	>40	>400	>400	>200	>200
Coxsackie virus B4/Vero cells	>40	>400	>400	>200	>200
Punta Toro virus/Vero cells	>40	>400	>400	>200	>200
Herpes simplex virus-1 (KOS)/HEL cells	>200	>400	>400	>200	>200
Herpes simplex virus-2/HEL cells	>200	>400	>400	>200	>200
Vaccinia virus/HEL cells	>200	>400	>400	>200	>200
Vesicular stomatitis virus/HEL cells	>200	>400	>400	>200	>200
Herpes simplex virus-1 TK^-KOS ACV^r/HEL cells	>200	>400	>400	>200	>200

BIOLOGY

All the five nucleoside analogs **6–10** have been evaluated for their antiviral and enzyme inhibition properties. The anti-HIV-1 screening was done in MT-4 cells using the MTT method.[46] Similarly, these molecules were screened for their antiviral properties against a number of viruses using different cell cultures : compound **6** has shown good inhibitory action against vesicular stomatitis virus, coxsackie virus, respiratory syncytial virus, parainfluenza-3 and reovirus-1; compound **7** against HIV-1, vesicular stomatitis virus, coxsackie virus and respiratory syncytial virus; compound **8** against vesicular stomatitis virus, coxsackie virus and respiratory syncytial virus; compound **9** against vesicular stomatitis virus, coxsackie virus and respiratory syncytial virus and compound **10** against vesicular stomatitis virus and coxsackie virus.

However, these molecules have shown little inhibitory effect in the case of other viruses.

The results have been shown in Table 1 in the form of IC_{50} values for these compounds.

The evaluation of all the five nucleoside analogs against HIV-2 is also in progress.

EXPERIMENTAL SECTION

Silica gel G for TLC and silica gel (60–120 mesh) for column chromatography were obtained from E-Merck India Ltd. Hexamethyldisilazane (HMDS), chlorotrimethylsilane (TCS), tris [2-(methoxyethoxy)ethyl]amine (TDA-1), arabinose and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (ABR) (**2**) were purchased from Aldrich Chemical Co. USA. UV measurement was carried out on Hitachi 220S

spectrophotometer. ^{1}H NMR was recorded using DRX 300 instrument with DMSO as solvent. All solvents were dried and distilled prior to use.

2,3,5-Tri-*O*-benzoyl-α-D-arabinosyl chloride (1). The compound **1** was synthesized starting from D-arabinose (10 g) which was first converted into methyl-α-D-arabinofuranoside-tri-*O*-benzoate (15 g). The latter was then dissolved in glacial acetic acid (75 mL) and to this was added glacial acetic acid saturated with dry HCl gas (75 mL) to get a clear solution. The mixture was stirred at room temperature for 30 minutes. After passing additional amounts of dry HCl gas through it for another 20 minutes, CH_2Cl_2 (300 mL) was added to the reaction mixture. Finally, the whole mixture was poured into ice-cold water (1000 mL). Dichloromethane fraction, separated immediately, was washed quickly with saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, filtered and its volume reduced at pump to get crystalline **1**. Yield 9.5g (63%); m.p. 65°C.

9-(1-β-D-Arabinofuranosyl) 1,3-dideazaadenine (6). For the synthesis of Ara-DDA, **3** (3.8 mmol), dried overnight over P_2O_5 in a vacuum desiccator, was first dissolved in dry actetonitrile (100 mL) and then to it were added TDA-1 (0.3 mmol) and powdered KOH (9.5 mmol) and the mixture was stirred at room temperature for 30 minutes. Subsequently, **1** (4 mmol) was added and the reaction mixture was again stirred for 2 h at room temperature. The solid separated was filtered out and the filtrate was evaporated at the pump to get crystals of impure protected nucleoside. The latter was deprotected by dissolving it in minimum amount of acetonitrile and heating the resulting solution with ammonia (25%) for 5 h at 60°C. After deprotection, TLC indicated the presence of two isomers, which were actually the *N-7* and *N-9* regioisomers of the nucleoside. The yield of *N-9* isomer or the title compound (**6**) was higher than that of the *N-7* isomer. The nucleoside also gave positive ninhydrin test indicating the presence of a free primary amino group that is actually present at position 4 in the 1,3-dideazaadenine molecule (the aglycone). The nucleoside was purified by silica gel column chromatography. Compound **6** eluted between 9–11% CH_3OH in CH_2Cl_2. R_f = 0.2 (DCM/MeOH, 9.2:0.8). UV (MeOH) λmax 220, 263, 315 nm. ^{1}H NMR (DMSO- D_6) δ 3.37–3.42 (m, 1H, H2′); 3.54–3.57 (m, 2H, H5′); 3.64–3.67 (m, 1H, H4′); 4.12–4.14 (m, 1H, H3′); 4.6 (s, 2H, NH_2); 5.3–5.5 (d, 1H, H1′); 7.52–7.69 (m, 4H, aro). MS (EI) m/z 265 (M^+). Anal. Calcd for $C_{12}H_{15}N_3$: C, 54.33; H, 5.66; N, 15.84. Found: C, 54.28; H, 5.64; N, 15.80.

9-(1-β-D-Arabinofuranosyl) 4-nitro-1,3-dideazapurine (7). The nucleoside **7** was synthesized following the same procedure and molar ratios as that for **6**. TLC indicated the formation of **7** as the only regioisomer. After the coupling reaction the solid separated was filtered, the filtrate was evaporated at pump and the residue was recrystallized with ethanol to get crystals of pure protected nucleoside. The protected nucleoside was stirred with methanolic ammonia (25%) for 5 h at room temperature and after deprotection, the reaction mixture was partitioned between water and ether and **7** was obtained in the water fraction. The latter was evaporated at pump and recrystallized from ether-ethanol. R_f = 0.78 (DCM /MeOH, 8:2). UV (MeOH) λmax 240, 274, 316 nm. ^{1}H NMR (DMSO- D_6) δ 3.36–3.41 (m, 1H, H2′); 3.53–3.56 (m, 2H, H5′); 3.63–3.67 (m, 1H, H4′); 4.12–4.14 (m, 1H, H3′); 4.59 (s, 2H, NH_2); 5.4–5.5

(d, 1H, H1′); 7.42–7.87 (m, 4H, aro). MS (EI) m/z 295 (M^+). Anal. Calcd for $C_{12}H_{13}N_3$: C, 48.81; H, 4.41; N, 14.24. Found: C, 48.72; H, 4.38; N, 14.20.

1-(1-β-D-Arabinofuranosyl) diketopiperazine (8). Ara-DKP was synthesized by coupling **5** (3.8 mmol) with **1** (4 mmol) following the same procedure used for the synthesis of **6** and **7**. After deprotection of the nucleoside with methanolic ammonia (25%), TLC showed the presence of two isomers, 1 and 2 with R_f = 0.7 and 0.4 (DCM/MeOH, 9.6:0.4), respectively. The title compound (isomer 2) was purified by silica gel column chromatography using 4% CH_3OH in CH_2Cl_2. The pure nucleoside could not be crystallized from ether-ethanol and had the appearance of brown colored jelly. UV (MeOH) λmax 268 nm. ^{1}H NMR (DMSO-D_6) δ 3.19–3.26 (m, 1H, H2′); 3.30–3.32 (m, 2H, H5′); 3.77–4.00 (m, 1H, H4′); 4.26–4.48 (m, 1H, H3′); 5.36–5.45 (d, 1H, H1′); 7.4–7.97 (m, 5H, aro). MS (EI) m/z 246 (M^+). Anal. Calcd for $C_9H_{14}N_2$: C, 44.26; H, 5.74; N, 11.48. Found: C, 44.15; H, 5.68; N, 11.4

9-(1-β-D-Ribofuranosyl) 1,3-dideazaadenine (9). Synthesis of Ribo-DDA was achieved by following the one pot synthesis method proposed by Vorbrüggen and Bennua.[39] N-benzoyl-1,3-dideazaadenine (5 mmol) and **2** (5 mmol) were dissolved in dry acetonitrile (75 mL) and stirred for a few minutes to get a clear solution. After this HMDS (4 mmol) and TCS (4 mmol) were added. Finally, the catalyst $SnCl_4$ (6 mmol) in dry acetonitrile (25 mL) was added to the reaction vessel. The reaction mixture was stirred overnight at room temperature, filtered and the filtrate dried completely under vacuum (40°–50°C). The residue was dissolved in CH_2Cl_2 (30 mL) and this organic fraction was washed consecutively with saturated solutions of $NaHCO_3$ (20 mL) and NaCl (20 mL), dried on Na_2SO_4, filtered and reduced at the pump. The residue was recrystallized from ethanol to get white crystals of one isomer of the resulting nucleoside while the mother liquor contained the second isomer. Both isomers were contaminated with unreacted ABR and were purified by silica gel column chromatography. The first isomer of the nucleoside eluted out between 2.5–4% CH_3OH in CH_2Cl_2. The second isomer of the nucleoside present in the mother liquor along with unreacted sugar was eluted with 2% CH_2Cl_2 in hexane. R_f = 0.65 and 0.39 (DCM/MeOH, 9.8:0.2) for isomers 1 and 2 respectively. Both the isomers were separately deprotected by first dissolving them in a very small volume of CH_2Cl_2-CH_3OH mixture and then stirring them with methanolic ammonia (25%) for 5 h at room temperature. Pure nucleoside **9** was obtained by partitioning the deprotection reaction mixture of isomer 1 between ether and water followed by drying of the water fraction at the pump; though the yield of pure nucleoside was not satisfactory. The formation of **9** was also confirmed by positive ninhydrin test for the amino group present in the aglycone at position 4. R_f = 0.3 (DCM/MeOH, 9.2:0.8). UV (MeOH) λmax 235, 240, 317 nm. ^{1}H NMR (DMSO-D_6) δ 1.85–2.5 (m, 1H, H 2′); 3.34–3.46 (m, 1H, H5′); 4.36–4.46 (m, 2H, H4′); 4.59 (s, 2H, NH_2); 4.67–4.81 (m, 1H, H3′); 5.66–5.68 (d, 1H, H1′); 7.79–8.01 (m, 4H, aro). MS (EI) m/z 265 (M^+). Anal. Calcd for $C_{12}H_{15}N_3$: C, 54.33; H, 5.66; N, 15.84. Found: C, 54.25; H, 5.60; N, 15.75.

9-(1-β-D-Ribofuranosyl) 4-nitro-1,3-dideazapurine (10). The nucleoside **10** was synthesized following the same procedure and molar ratios as that for **9**. TLC indicated

the formation of a single isomer which was separated from unreacted ABR by recrystallizing with ethanol. After deprotection with methanolic ammonia (25%), the reaction mixture was partitioned between water and ether whereby **10** was obtained in the water fraction. R_f = 0.25 (DCM/CH_3OH, 9.5:0.5). UV (MeOH) λmax 235, 292, 305 (sh) nm. ^1H NMR (DMSO-D_6) δ 1.85–2.5 (m, 1H, H 2′); 3.34–3.46 (m, 1H, H5′); 4.36–4.46 (m, 2H, H4′); 4.59 (s, 2H, NH_2); 4.67–4.81 (m, 1H, H3′); 5.66–5.68 (d, 1H, H1′); 7.79–8.01 (m, 4H, aro). MS (EI) m/z 295 (M^+). Anal. Calcd for $C_{12}H_{13}N_3$: C, 48.81; H, 4.41; N, 14.24. Found: C, 48.80; H, 4.35; N, 14.00.

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REFERENCES

1. Robins, R.K.; Revankar, G.R. Design of nucleoside analogs as potential antiviral agents. In *Antiviral Drug Development, A Multidisciplinary Approach*; Clercq, E.D., Walker, R.T., Eds.; Series A: Life Sicences, Plenum Press: New York, 1988; Vol. 143, 11.
2. Elion, G.B. Science **1989**, *244*, 41.
3. Elion, G.B.; Hitchings, G.H. Adv. Chemother. **1965**, *2*, 91.
4. Legraverend, M.; Aubertin, A.M.; Oberg, G.; Huel, C.; Bisagni, E. Synthesis and anti-HIV evaluation of 7-deaza analogues of carbovir. Nucleosides & Nucleotides **1994**, *13* (4), 915–923.
5. Elion, G.B. Adv. Enzyme Regul. **1985**, *24*, 323.
6. Gudmundsson, K.S.; Freeman, G.A.; Drach, J.C.; Townsend, L.B. J. Med. Chem. **2000**, *43* (12), 2473.
7. Zackny, V.L.; Gershburg, E.; Davis, M.G.; Biron, K.K.; Pagano, J.S., Jr. J. Virol. **1999**, *73* (9), 7271.
8. Underwood, M.R.; Harvey, R.J.; Stanat, S.C.; Hemphill, M.L.; Miller, T.; Drach, J.C.; Townsend, L.B.; Biron, K.K. J. Virol. **1998**, *72* (1), 717.
9. Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Nitta, I.; Baba, M.; Shigeta, S.; Walker, R.T.; Clercq, E.D.; Miyasaka, T. J. Med. Chem. **1992**, *35*, 4713.
10. Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Inouye, N.; Baba, M.; Shigeta, S.; Walker, R.T.; Clercq, E.D.; Miyasaka, T. J. Med. Chem. **1995**, *38*, 2860.
11. Genini, D.; Adachi, S.; Chao, Q.; Rose, D.W.; Carrera, C.J.; Cottam, H.B.; Carson, D.A.; Leoni, L.M. Blood **2000**, *96* (10), 3537.
12. Singh, R.K.; Ohuchi, S.; Wada, T.; Hata, T. Chem. Lett. **1992**, 1505.
13. Singh, R.K.; Ohuchi, S.; Wada, T.; Hata, T. Nucleosides Nucleotides **1998**, *17*, 123.
14. Lee, W.W.; Benitez, A.; Goodman, L.; Baker, B.R. J. Am. Chem. Soc. **1960**, *82*, 2648.
15. Chien, L.T.; Shabel, F.M.; Alford, C.A., Jr. Arabinosyl nucleosides and nucleotides.

In *Selective Inhibitiors of Viral Functions*; Carter, W.A., Ed.; CRC Press: Cleveland, OH, 1977; 227.
16. North, T.W.; Cohen, S.S. Pharmacol. Ther. **1979**, *4*, 81.
17. Muller, W.E.G.; Zahn, R.K.; Bittlingmaier, K.I.; Falke, D. Ann. N. Y. Acad Sci. **1977**, *284*, 34.
18. Vilde, G.L.; Bricaire, F.; Huchon, A.; Brun-Vezinet, F. J. Med. Virol. **1983**, *12*, 149.
19. Muler, W.E.G.; Zahn, R.K.; Berger, R.; Falke, D. Virology **1977**, *76*, 787.
20. Zou, R.; Kawashima, E.; Freeman, G.A.; Koszalka, G.W.; Drach, J.C.; Townsend, L.B. Nucleosides Nucleotides Nucl. Acids **2000**, *19* (1–2), 125.
21. Gudmundsson, K.S.; Tidwell, J.; Lippa, N.; Koszalka, G.W.; van Draanen, N.; Ptak, R.G.; Drach, J.C.; Townsend, L.B. J. Med. Chem. **2000**, *43* (12), 2464.
22. Townsend, L.B.; Gudmundsson, K.S.; Daluge, S.M.; Chen, J.J.; Zhu, Z.; Koszalka, G.W.; Boyd, L.; Chamberlain, S.D.; Freeman, G.A.; Biron, K.K.; Drach, J.C. Nucleosides Nucleotides **1999**, *18* (4–5), 509.
23. Chen, J.J.; Wei, Y.; Drach, J.C.; Townsend, L.B. J. Med. Chem. **2000**, *43* (12), 2449.
24. Zhu, Z.; Lippa, B.; Drach, J.C.; Townsend, L.B. J. Med. Chem. **2000**, *43* (12), 2430.
25. Krosky, P.M.; Ptak, R.G.; Underwood, M.R.; Biron, K.K.; Townsend, L.B.; Drach, J.C. Antivir. Chem. Chemother. **2000**, *11* (5), 349.
26. Krosky, P.M.; Borysko, K.Z.; Nassiri, M.R.; Devivar, R.V.; Ptak, R.G.; Davis, M.G.; Biron, K.K.; Townsend, L.B.; Drach, J.C. Antimicrob. Agents Chemother. **2002**, *46* (2), 478.
27. Cristalli, G.; Franchetti, P.; Grifantini, M.; Sauro, V.; Lupidi, G.; Riva, F.; Bordoni, T.; Geroni, C.; Verini, M.A. J. Med. Chem. **1988**, *31*, 390.
28. Seela, F.; Bourgeois, W. Synthesis **1989**, *12*, 912.
29. Rousseau, R.J.; Townsend, L.B.; Robins, R.K. Biochemistry **1966**, *5*, 756.
30. Bodner, J.P.; Cantoni, G.L.; Chiang, R.K. Biochem. Biophys. Res. Commun. **1981**, *98*, 476.
31. Bader, J.P.; Brown, N.R.; Chiang, R.K.; Cantoni, G.L. Virology **1978**, *89*, 494.
32. Pugh, C.S.G.; Borchardt, R.T.; Stone, H.O. Biochemistry **1977**, *16*, 3928.
33. Depelley, J.; Granet, R.; Krausz, P.; Piekarski, S. Nucleosides Nucleotides **1994**, *13* (4), 1007.
34. Reefschager, J.; Herrman, G.; Barwolff, D.; Schwarz, B.; Cech, D.; Langen, P. Antivir. Res. **1983**, *3*, 175.
35. Camiener, G.W. Studies of the enzymatic deamination of aracytidine V. Inhibition in vitro and in vivo by tetrahydrouridine and other reduced pyrimidine nucleosides. Biochem. Pharmacol. **1968**, *9*, 1981–1991.
36. Prusoff, W. Biochim. Biophys. Acta **1959**, *32*, 295.
37. McCombie, S.W.; Tagat, R.J.; Vice, S.F.; Lin, S.; Steensma, R.; Palani, A.; Neustadt, B.R.; Baroudy, B.M.; Stizki, J.M.; Endres, M.; Cox, K.; Dan, N.; Chou, C.C. Bioorg. Med. Chem. Lett. **2003**, *13* (3), 567.
38. Seela, F.; Bourgeois, W.; Rosemeyer, H.; Wenzel, T. Helv. Chim. Acta **1996**, *79*, 488.
39. Vorbrüggen, H.; Bennua, B. Chem. Ber. **1981**, *114*, 1279.
40. Singh, R.K.; Takaku, H. Nucleosides Nucleotides **1999**, *18*, 1403.
41. Wright, R.S.; Khorana, H.G. J. Am. Chem. Soc. **1958**, *80*, 1994.
42. Ness, R.K.; Fletcher, H.G., Jr. J. Am. Chem. Soc. **1958**, *80*, 2007.

43. Woolley, D.W. J. Biol. Chem. **1944**, *152*, 225.
44. Vogel, A.I. Some heterocyclic compounds. In *Practical Organic Chemistry*, 4th Ed.; Longmans, Green & Co. Ltd.: London, 1976; 909.
45. Kotick, M.P.; Szantay, C.; Bardos, T.J. J. Org. Chem. **1969**, *34* (12), 3806.
46. Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; Clercq, E.D. J. Virol. Meth. **1988**, *20* (4), 309.

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