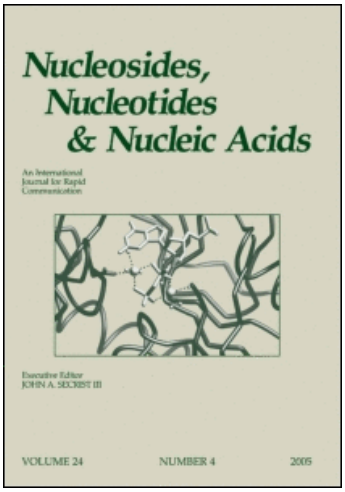

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Phosphoramidate Protides of 2′,3′-Dideoxy-3′-fluoroadenosine and Related Nucleosides with Potent Activity Against HIV and HBV

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ABSTRACT

Syntheses of phosphoramidate protides of several 2′,3′-dideoxy-3′-fluoroadenosine derivatives by treatment of the nucleoside with phosphorochloridates in the presence of pyridine and t-BuMgCl is described. Several of these protides showed significantly improved antiviral potency over the parent nucleoside against HIV and HBV. Especially marked was the improvement in potency of phosphoramidate protides of 2′,3′-dideoxy-3′-fluoroadenosine against both HIV and HBV.

Key Words: Phosphoramidate; 2′,3′-Dideoxy-3′-fluoroadenosine; HIV; HBV.

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INTRODUCTION

2′,3′-Dideoxyribofuranosides have received considerable attention as this class of nucleosides includes several compounds with good anti-HIV activity (e.g., ddI, ddA and analogs).[1] However, rapid deamination of ddA by adenosine deaminase results in the formation of ddI. DdI is not converted to triphosphate, instead its monophosphate (ddI-MP) enters the adenosine anabolic pathway, where it is converted by adenylosuccinate synthetase and adenylosuccinate lyase to ddA monophosphate (ddA-MP). This conversion of ddI-MP to ddA-MP is the rate limiting step for formation of ddA triphosphate. Due to this complicated metabolic activation of ddA to its triphosphate,[2] ddA has received significant attention as a candidate for prodrug strategies that deliver monophosphate intracellularly[3] avoiding deamination by adenosine deaminase. These prodrug strategies, which include phosphoramidate derivatives,[4] cycloSal derivatives[5] and bis(MeSATE) phosphotriester derivatives[6] have been shown to significantly improve the potency of ddA against HIV and HBV. We became interested in investigating how such prodrug strategies would affect the activity of β-D-2′,3′-dideoxy-3′-fluoroadenosine.[7] 2′,3′-Dideoxy-3′-fluoroadenosine is deaminated by adenosine deaminase at a rate similar to that of 2′,3′-dideoxyadenosine, but is more hydrolytically stable at the glycosidic bond than 2′,3′-dideoxyadenosine. 2′,3′-Dideoxy-3′-fluoroadenosine and related analogs have shown interesting activity against HIV and HBV[8] suggesting that these analogs could be desirable candidates for prodrug delivery.

Herein we describe the synthesis of phosphoramidate prodrugs of 2′,3′-dideoxy-3′-fluoroadenosine and some related nucleosides along with their HIV and HBV activity.

RESULTS AND DISCUSSION

Several different prodrug strategies have been designed to deliver monophosphates intracellularly. We decided to use the phosphoramidates as this approach is well validated and the nucleoside can be converted to the phosphoramidate prodrug in one chemical step. We chose to synthesize the phenyl-(methoxy-L-alaninyl) phosphoramidate and the phenyl-(methoxy-dimethylglycinyl) phosphoramidate protides as these have been reported to give good improvement in activity against HIV and HBV over parent nucleosides.[9] 9-(2′,3′-Dideoxy-3′-fluoro-β-D-ribofuranosyl) adenine,[7] phenyl-(methoxy-L-alaninyl)phosphorochloridate[9] and phenyl-(methoxy-dimethylglycinyl)phosphorochloridate[9] were synthesized as described in the literature. Treatment of the nucleoside with the phosphorochloridate reagent in pyridine in the presence of t-BuMgCl (as outlined in Sch. 1) gave good yields of protides **4** and **5**.

Activity of derivatives **4** and **5** against HIV and HBV is shown in Tables 1 and 2, respectively. The L-alaninylphosphoramidate protide of D-2′,3′-dideoxy-3′-fluoroadenosine (**4**) is about 280 fold more potent than the parent nucleoside (**1**) against HIV and about 7800 fold more potent than **1** against HBV. The dimethylglycinylphosphoramidate protide (**5**) showed 20 fold improvement in activity against HIV and 20,000 fold improvement for HBV. Thus, while both protides gave similar

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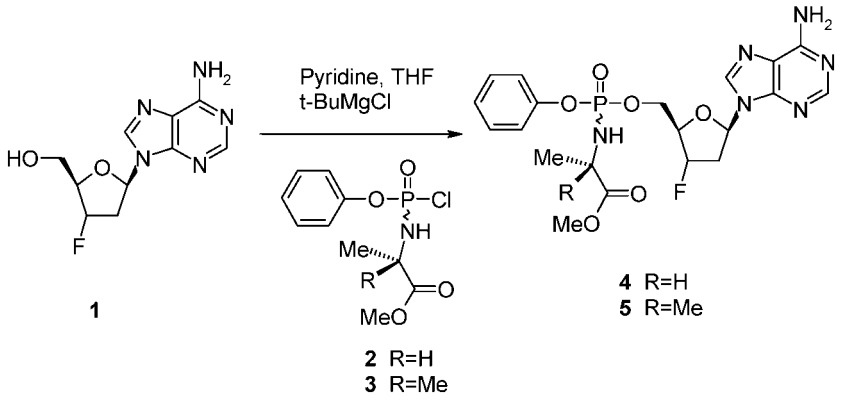

Scheme 1. Synthesis of phosphoramidate protides.

Table 1. Anti-HIV-1 (3B) activity and cytotoxicity in MT-4 lymphocytes[13] of 2′,3′-dideoxy-3′-fluororibofuranosyl derivatives and their corresponding phosphoramidates.

Compound number[a]	IC_{50} (μM)[b]	CC_{50} (μM)[b]	Selectivity index[b]
1 (nucleoside)	34	>200	>6
4 (protide of **1**)	0.12	1.9	16
5 (protide of **1**)	1.7	57	33
6 (nucleoside)	>200	>200	–
7 (protide of **6**)	4	20	5
8 (nucleoside)	>100	>100	–
9 (protide of **8**)	52	120	2.3
10 (nucleoside)	>200	>200	–
11 (protide of **10**)	>80	200	–
DdA[c]	5.3	>250	>47
Protide of ddA[d]	0.01	6.5	650

[a]All protides were tested as 1:1 mixtures of diastereomers at phosphorus.
[b]IC_{50} is 50% inhibitory concentration, CC_{50} is 50% cytotoxix concentration, selectivity index is CC_{50}/IC_{50}.
[c]From Ref.[4].
[d]L-alaninylphosphoramidate protide of ddA from Ref.[4].

improvement in activity over the parent nucleoside for HBV the alaninylphosphoramidate showed about 10 fold better enhancement in activity than the dimethylglycinylphosphoramidate against HIV. These improvements in potency of **4** over the nucleoside **1** compare favorably to the reported[4] improvement in activity for the L-alaninylphosphoramidate protide of ddA over ddA (Table 1 and 2).

Based on this impressive improvement in activity of **1** upon protide delivery we became interested in investigating if the L-alaninylphosphoramidate protide would also improve activity of 2′,3′-dideoxy-3′-fluororibofuranosyl derivatives that were

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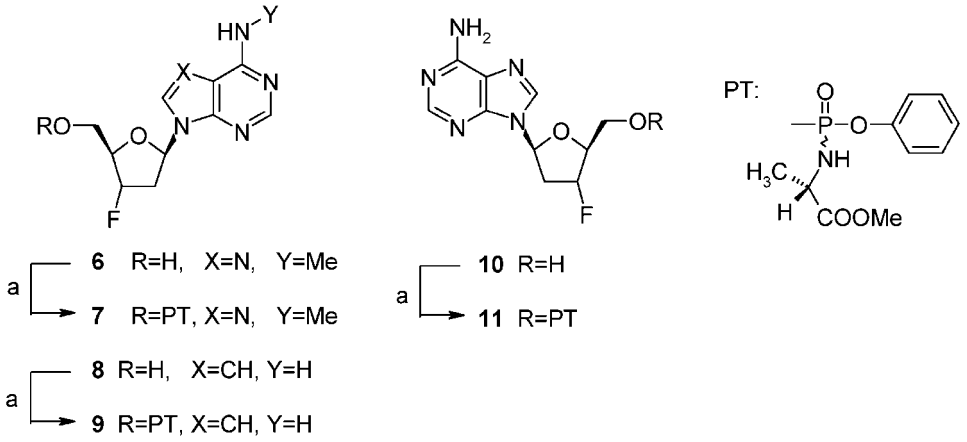
Table 2. Anti-HBV activity and cytotoxicity in HepG2-2.2.15 cells[15] of 2′,3′-dideoxy-3′-fluororibofurnosyl derivatives and the corresponding phosphoramidates.

Compound number[a]	IC_{50} (μM)[b]	CC_{50} (μM)[b]	Selectivity index[b]
1 (nucleoside)	140	>200	–
4 (protide of **1**)	0.018	7	390
5 (protide of **1**)	0.007	3.2	457
6 (nucleoside)	>200	>200	–
7 (protide of **6**)	0.5	58	116
8 (nucleoside)	117	>200	>2.5
9 (protide of **8**)	10	149	15
10 (nucleoside)	186	187	1
11 (protide of **10**)	24	>200	>8
DdA[c]	>10	–	–
Protide of ddA[d]	0.1–0.01	–	–

[a]All protides were tested as 1:1 mixtures of diastereomers at phosphorus.
[b]IC_{50} is 50% inhibitory concentration, CC_{50} is 50% cytotoxic concentration, selectivity index is CC_{50}/IC_{50}.
[c]From Ref.[4].
[d]L-alaninylphosphoramidate protide of ddA from Ref.[4].



Scheme 2. Additional phosphoramidate protides. a) PT-Cl, pyridine/THF, t-BuMgCl, where PT-Cl is methyl N-[chloro(phenoxy)phosphoryl]-L-alaninate.

heterocycle modified (Sch. 2), such as 6-methylamino-9-(2′,3′-dideoxy-3′-fluoro-β-D-ribofuranosyl)purine (**6**)[10] and 7-(2′,3′-dideoxy-3′-fluoro-β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine-4-amine (2′,3′-dideoxy-3′-fluorotubercidine, **8**).[11] The 6-methylamino derivative has been reported to have activity against HIV and the triphosphate of 2′,3′-dideoxy-3′-fluorotubericidin has been reported to effectively inhibit HIV reverse transcriptase (to a similar extent as ddATP).[11]

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For the 6-methylamine derivative **6**, protide delivery improved activity against HIV >25 fold and against HBV > 400 fold. For both viruses activity of **7** is not as great as seen for **4**. Phosphoramidate delivery of **6** would be expected to eliminate deamination by adenosine deaminase, the further modification of the monosphospate to the 2′,3′-dideoxy-3′-fluoroadenosine triphosphate may be carried out by a similar pathway as reported for abacavir.[12]

While neither 2′,3′-dideoxy-3′-fluorotubericidin **8** nor its protide **9** showed significant activity against HIV, the protide improved the activity of **8** against HBV about 12 fold. Again this increase in activity does not compare with the improvement in activity seen for protides of **1**. This could indicate that the 6-amine can be modified to some extent (alkylated) due to alternative metabolic pathways (see Ref.[12]) that form 2′,3′-dideoxy-3′-fluoroadenosine triphosphates from 6-alkylamino protide derivatives such as **7**, while major heterocycle modifications (as for **8**) appear to give protide derivatives such as **9**, that are not efficiently converted to the triphosphate stage.

Finally, because of the significant antiviral activity shown by several L-nucleosides we were interested in investigating if protide delivery could be used to improve the activity of 9-(2′,3′-dideoxy-3′-fluoro-β-L-ribofuranosyl)adenine.[14] The L-2′,3′-dideoxy-3′-fluoroadenosine (**10**) did not show activity against HIV in MT-4 lymphocytes, which is consistent with previously published results.[11] Its phosphoramidate (**11**) also showed no activity against HIV. The protide **11** showed better activity against HBV than **10** (8 fold), but again improvement in activity was much less than that seen for the corresponding D-analogs (280 fold).

In conclusion protides of D-2′,3′-dideoxy-3′-fluoroadenosine significantly improved activity against HIV (about 2 orders of magnitude) and against HBV (about 4 orders of magnitude). This was not the case for heterocycle modified D-2′,3′-dideoxy-3′-fluororibofurnosyl derivatives nor for the corresponding L-2′,3′-dideoxy-3′-fluoroadenosine. We continue to investigate improvement in activity of nucleosides by protide delivery.

EXPERIMENTAL

Chemistry

Nuclear magnetic resonance (NMR) spectra were obtained at 300 MHz on Varian Unity Plus NMR spectrophotometer. The chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. Elemental analysis were performed by Atlantic Microlab Inc. Flash column chromatography was performed using Merck Silica gel 60 (230–400 mesh), and the stated solvent system under pressure. Mass spectra were obtained on Micromass Platform mass spectrometers from Micromass Ltd. Altrincham, UK, using Electrospray Ionization.

9-(2′,3′-Dideoxy-3′-fluoro-β-D-ribofuranosyl)adenine-5′-[phenyl-(methoxy-L-alaninyl)]phosphoramidate (4). To a solution of **1** (100 mg, 0.39 mmol) in pyridine (4 mL) was added t-BuMgCl (0.5 mL of 1M solution in tetrahydrofuran, 0.5 mmol) and then **2** (221 mg, 0.8 mmol in 5 mL tetrahydrofuran). The resulting mixture was stirred at

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room temperature for 12 h. Dichloromethane was added to the reaction mixture and the organic phase washed with water and brine. The organic phase was dried over magnesium sulfate. Filtration and concentration followed by purification by flash chromatography (5% methanol in dichloromethane) gave **4** (126 mg, 65%) as a white foam (1:1 mixture of phosphorus diastereomers). ^{1}H-NMR ($CDCl_3$): δ 8.36 (2 s, 1H), 8.05 (2 s, 1H), 7.37–7.18 (m, 5H), 6.50 (m, 1H), 5.95 (broad s, 2H), 5.50 (m, 1H), 4.6–4.3 (m, 3H), 4.05 (m, 2H), 3.72 (2 s, 3H), 2.70 (m, 1H), 1.37 (2 d, 3H); ^{31}P-NMR ($CDCl_3$): δ 4.02 and 3.61 (1:1); MS m/z 495 (M + H). Anal. Calcd for $C_{20}H_{24}N_6O_6FPxH_2O$: C 46.88, H 5.11, N 16.40; Found, C 46.88, H 4.93, N 16.40.

9-(2′,3′-Dideoxy-3′-fluoro-β-D-ribofuranosyl)adenine-5′-[phenyl-(methoxy-dimethyl-glycinyl)]phosphoramidate (5). To a solution of **1** (100 mg, 0.39 mmol) in pyridine (4 mL) was added t-BuMgCl (0.5 mL of 1M solution in tetrahydrofuran, 0.5 mmol) and then **3** (219 mg, 0.8 mmol in 4 mL tetrahydrofuran), in a similar manner as described for the preparation of **4** above, to give **5** (130 mg, 66%) as a white foam (1:1 mixture of phosphorus diastereomers). ^{1}H-NMR ($CDCl_3$): δ 8.33 (s, 1H), 8.05 (2 s, 1H), 7.357–7.15 (m, 5H), 6.48 (m, 1H), 6.33 (broad s, 2H), 5.50 and 5.32 (2 dd, 1H), 4.6–4.3 (m, 3H), 3.72 (2 s, 3H), 2.8–2.6 (m, 3H), 1.55 (2 s, 6H); ^{31}P-NMR ($CDCl_3$): δ 2.67 and 2.39 (1:1); MS m/z 509 (M + H). Anal. Calcd for $C_{21}H_{26}N_6O_6FP$: C 49.61, H 5.15, N 16.53; Found, C 49.86, H 5.05, N 16.89.

6-Methylamino-9-(2′,3′-dideoxy-3′-fluoro-β-D-ribofuranosyl)purine-5′-[phenyl-(methoxy-L-alaninyl)]phosphoramidate (7). A solution of **6** (80 mg, 0.29 mmol) was treated with **2** (221 mg, 0.5 mmol in tetrahydrofuran) in a similar manner as described above to give, after flash chromatography (20% methanol in dichloromethane), 75 mg (51%) of **7** as a white foam (1:1 mixture of phosphorus diastereomers). ^{1}H-NMR ($CDCl_3$): δ 8.40 (s, 1H), 7.98 (2 s, 1H), 7.36–7.17 (m, 5H), 6.48 (m, 1H), 6.25 (broad s, 1H), 5.52 and 5.34 (2 dd, 1H), 4.56 and 4.47 (2 m, 1H), 4.45–4.0 (m, 3H), 3.71 (2 s, 3H), 3.22 (broad s, 3H), 2.8–2.5 (m, 3H), 1.35 (2 d, 3H); ^{31}P-NMR ($CDCl_3$): δ 4.07 and 3.69 (1:1); MS m/z 510 (M + H). Anal. Calcd for $C_{21}H_{26}N_6O_6FPx$ 0.5 CH_2Cl_2: C 46.87, H 4.94, N 15.25; Found, C 46.83, H 4.89, N 15.37.

7-(2′,3′-Dideoxy-3′-fluoro-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine-4-amine-5′-[phenyl-(methoxy-L-alaninyl)]phosphoramidate (9). To a solution of **8** (100 mg, 0.4 mmol) in pyridine (4 mL) was added t-BuMgCl (0.6 mL of 1M solution in tetrahydrofuran, 0.6 mmol) and then **2** (221 mg, 0.8 mmol in tetrahydrofuran) in a similar manner as described above to give after flash chromatography (20% methanol in dichloromethane) 117 mg (60%) of **9** as a white foam (1:1 mixture of phosphorus diastereomers). ^{1}H-NMR ($CDCl_3$): δ 8.31 (s, 1H), 7.1–7.4 (m, 5H), 6.72 (m, 1H), 6.43 (2 d, 1H), 5.59 (broad s, 2H), 5.4 (2 m, 1H), 4.6–4.0 (m, 5H), 3.71 (2 s, 3H), 2.6 (m, 2H), 1.36 (2 d, 3H); ^{31}P-NMR ($CDCl_3$): δ 3.99 and 3.59 (1:1); MS m/z 494 (M + H). Anal. Calcd for $C_{21}H_{25}N_5O_6FPx0.5$ H_2O: C 50.20, H 5.22, N 13.94; Found, C 50.12, H 5.19, N 13.68.

9-(2′,3′-Dideoxy-3′-fluoro-β-L-ribofuranosyl)adenine-5′-[phenyl-(methoxy-L-alaninyl)]phosphoramidate (11). A solution of **10** (75 mg, 0.3 mmol) was treated as

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described above for **4** to give 100 mg (68%) of **11** as a white foam (1:1 mixture of phosphorus diastereomers). Anal. Calcd for $C_{20}H_{24}N_6O_6FPx0.75\ H_2O$: C 47.29, H 5.06, N 16.55; Found, C 47.64, H 4.94, N 16.40. All other spectral data identical to **4.**

ANTIVIRAL ASSAYS

HBV. Antiviral potency and growth inhibition potential of compounds was determined using the assay developed by Jansen et al.[a] Briefly, HepG2-2.2.15 cells constitutively producing HBV[16] were seeded into 96 well microtiter plates at a density of 5×10^3 per well and growth medium containing drug was replaced every other day for 9 days. Supernatants were then collected and analyzed for HBV content. Samples were tested in conjunction with both positive (.448 fg/ul plasmid DNA) and negative (RPMI medium supplemented with 2 mM L-glutamine and 10% fetal calf serum) controls. Data was normalized to non-drug treated cells, and expressed as a percent of control for analysis. Evaluation of toxicity (i.e., growth inhibition) was made by fixing monolayers with 70% ethanol, and staining with bisbenzimide H33342 for 1 hour at 37°C. Fluorescence values of drug treated cells were compared to non-drug treated cells and expressed as a percentage of control. HBV detection (and hence efficacy determination) was performed by "capturing" virus from supernatants on anti-HBsAg coated plates, washing, denaturing to release HBV DNA, performing PCR with biotinylated primers, streptavidin capture of biotinylated PCR products with concomitant probe hybridization, addition of substrate, and reading optical densities of the colorimetric reaction. Dilutions of a standardized HBV-containing supernatant were included on every plate, and HBV DNA concentrations of test wells were calculated from this HBV standard curve.

HIV. Anti-HIV-1 (3B) activity and cytotoxicity in MT-4 lymphocytes was determined as previously described by Averett et al.[b]

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[a]Compounds were tested for anti-HBV activity according to the method described by Jansen et al.[15]

[b]Compounds were assayed for HIV activity in MT-4 cells according to the method described by Averett.[13]

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