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Synthesis and Antiviral Effects of 2-Heteroaryl Substituted Adenosine and 8-Heteroaryl Substituted Guanosine Derivatives

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Abstract—2-(2"- and 3"-Thienyl)adenosine and the corresponding furyl derivatives were prepared through Pd(0)-catalyzed coupling of 2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-2-iodoadenosine with the appropriate tributyltin derivatives followed by deprotection. Preparation of the 8-(2"- and 3"-thienyl)guanosines and 8-(2"- and 3"-furyl)guanosines followed a similar route. Antiviral properties of these compounds and the related 2,6-diaminopurine ribofuranosides were of no pharmacological interest.

Introduction

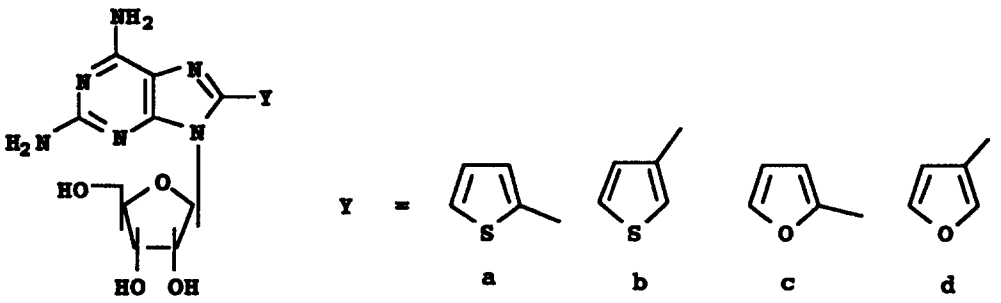
We have previously found that 5-heteroaryl-substituted 2'-deoxyuridines show interesting antiviral properties. The triphosphates of some of them are potent inhibitors of HIV reverse transcriptase (RT).[1-2] However, in a cell-culture assay the corresponding unphosphorylated nucleoside analogs were not active against HIV[2,3] and the analogs with 3',5'-di-*p*-toluoyl protecting groups were inhibitory but with poor selectivity.[3] The 5-heteroaryl-substituted 2'-deoxyuridines also have antiherpes activities.[1,4] In a recent paper it was found that oligonucleotides containing 5-heteroaryl-substituted 2'-deoxyuridines gave enhanced thermal stability to complementary RNA relative to thymidine.[5]

Various purine nucleosides with modified sugars have shown good antiviral properties and 2',3'-dideoxyinosine has been approved for the treatment of acquired immunodeficiency syndrome (AIDS).[6] 9-(2-Hydroxy-ethoxymethyl)guanine (ACV),[7] 2',3'-dideoxy-2'-fluoro-purine nucleosides[8-10] and also 3'-fluoro-substituted purine nucleosides have been prepared as potent antiviral agents (for review see Ref. 11). 2-Substituted 2'-deoxyadenosine compounds have anti-metabolic properties. The 2-chloro analog is a potent antileukemic agent[12] and other 2-halo-adenine nucleosides have also been investigated.[13]

However, when we started our present work no systematic structure–activity study of purine nucleosides, having heterocyclic rings in the 2-, 6- and/or 8-positions, had been carried out. Recently, however, two compounds, 8-(2"-thienyl)- and 8-phenyl-adenosine, have been prepared and designed as possible drugs for treatment against sleeping sickness.[14] During recent years, an increased interest in the study of antiviral activity of modified purine nucleosides, substituted in the purine ring, has arisen.

Direct C-8-lithiation with lithium diisopropylamide of sugar protected adenosine, inosine and guanosine has been used for the preparation of a number of 8-substituted derivatives.[15-17] Purine nucleosides alkylated in the 2- and 8-positions have been prepared by the palladium-catalyzed coupling of 2- and 8-bromo-adenosine and 8-bromoguanosine derivatives with trialkylaluminum derivatives.[18] Alternatively, tetra-alkyltin derivatives have been used in a Pd-catalyzed coupling of 2-, 6- and 8-halogenated purine nucleosides in order to prepare the corresponding alkyl derivatives.[19,20] Vinylation and allylation in the 8-position has also been achieved by Pd(0)-catalyzed coupling between 8-iodo-derivatives of *t*-butyl-dimethylsilyl protected adenosine, 2'-deoxyadenosine and 2',3'-dideoxyadenosine and vinyltributyltin or allyltributyltin.[21] 2-Alkynyladenosines were prepared in 1985 by Pd-catalyzed cross-coupling of 2-iodoadenosine and terminal acetylenes.[22] The coupling of protected 2-iodoadenosine with tributylstannyl acetone was utilized for the synthesis of 2-acetonyladenosine.[23] In a recent paper, the synthesis of 8-alkynyl-2'-deoxyadenosine analogs through Pd-catalyzed cross-coupling of 8-bromo-2'-deoxyadenosine with terminal alkynes in the presence of copper(I) iodide in *N,N*-dimethylformamide was described. These compounds were converted by catalytic hydrogenation to the corresponding 8-alkenyl- and 8-alkyl derivatives, and the antiviral activities were studied.[24] Purine derivatives, such as 6-alkoxypurine 2',3'-dideoxynucleosides have recently been found to inhibit the cytopathic effect of the HIV virus.[25]

In this paper, we describe the synthesis and the antiviral properties of 2-thienyl- and furyl-substituted adenosines, and of 8-thienyl- and furyl-substituted guanosines. Antiviral properties of the related 2,6-diaminopurine ribofuranosides **1a–d** are also reported. Their synthetic route is described elsewhere.[26]

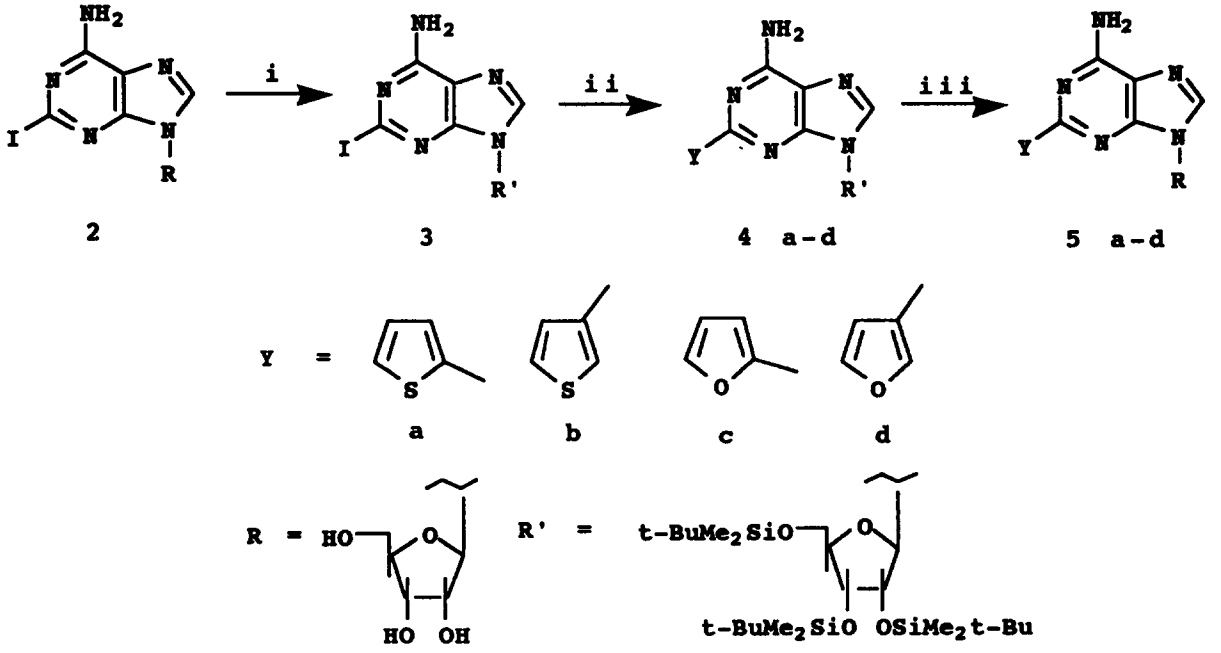


1 a-d

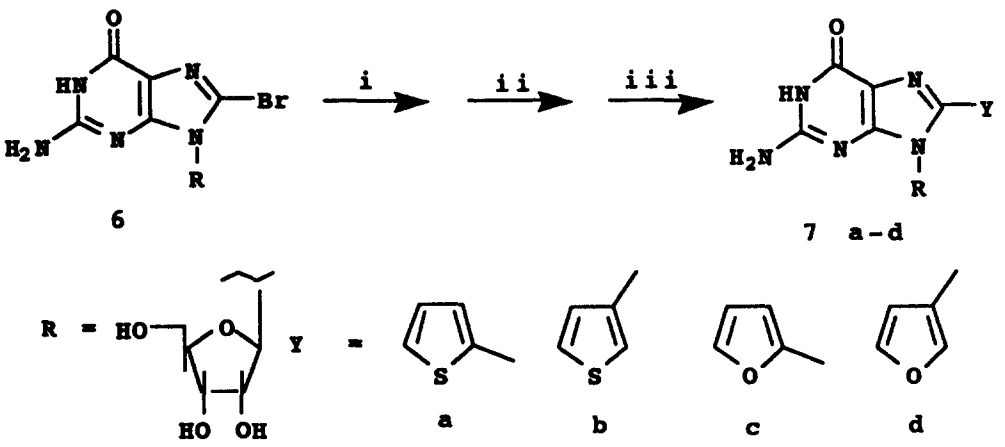
Chemistry

2-(2"-and 3"-Thienyl)adenosine (**5a**, **b**) and the corresponding furyl derivatives (**5c**, **d**) were prepared through Pd(0)-catalyzed coupling of 2',3',5'-tri-*O*-(*t*-butyldimethylsilyl)-2-iodoadenosine (**3**) with the appropriate tributyltin derivatives followed by deprotection. Compound **2** was prepared from guanosine by acetylation followed by chlorination to 9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-2-amino-6-chloropurine according to Robins and Uznanski.[27] This compound was then iodinated in the 2-position by heating with pentyl nitrite and diiodomethane to 9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-2-iodo-6-chloropurine,[28] which was treated with ethanolic ammonia at 0 °C yielding 2-iodoadenosine (**2**).[29] The hydroxyl groups of **2** were protected through reaction with *t*-butyldimethylsilyl chloride to give **3**.[30] The Pd(0)-catalyzed coupling of **3** with five equivalents of 2- or 3-tributylstannylthiophene or 2- or 3-tributylstannylfuran was carried out using $PdCl_2(PPh_3)_2$ in refluxing tetrahydrofuran[31,32] and the reaction times were about 50 h. This strategy gave the *t*-butyldimethylsilyl protected compounds **4a–d** in 82–95% yields. Deprotection of the nucleosides was carried out by treatment with 0.1 M methanolic hydrogen chloride according to Olgivie *et al.*[30] yielding **5a–d** in 62–72% yield. The 2"-thienyl derivative **5a** has previously been prepared by reaction of 2-cyanothiophene with the riboside of 5-amino-4-cyanoimidazole (AICN-riboside) in methanolic ammonia;[33,34] however, no yield was given.

Preparation of the 8-(2"- and 3"-thienyl)guanosines and 8-(2"- and 3"-furyl)guanosines (**7a–d**) also started from guanosine, which was brominated to 8-bromoguanosine (**6**).[35] As described for the adenosine derivatives, the sugar was protected with *t*-butyldimethylsilyl groups. The Pd(0)-catalyzed coupling with 2- or 3-tributylstannylthiophene or 2- or 3-tributylstannylfuran could be carried out successfully. However, upon attempted deprotection with 0.1 M methanolic hydrogen chloride, the glycosidic bond was cleaved. According to Ratsep *et al.*[36] the presence of strong electron-withdrawing groups in the 8-position makes the glycosidic



i. *t*-$BuMe_2SiCl$, Imidazole, DMF
ii. $YSn(Bu)_3$, $PdCl_2(PPh_3)_2$, THF, Δ
iii. 0.1 M HCl/MeOH



i. HMDS, pyridine, $(NH_4)SO_4$, Δ
ii. $YSn(Bu)_3$, $PdCl_2(PPh_3)_2$, THF, Δ
iii. K_2CO_3, MeOH

bond very acid labile. Although thienyl and furyl groups can be both electron-withdrawing or electron-donating, we hardly expected such a strong effect on the glycosidic bond. Finally, we used a modification of the method described by Mamos *et al.*[19] consisting of *in situ* protection of **5** by refluxing with hexamethyl-disilazane, followed by Pd(0)-catalyzed coupling of the crude product with 2- or 3-tributylstannylthiophene or 2- or 3-tributylstannylfuran.[32]

Compounds **7a–d** were obtained in 52–58% yield after deprotection with potassium carbonate in methanol at room temperature. Further purification of **7a–d** was achieved by HPLC chromatography on a reversed-phase column using acetonitrile:water (20:80) as eluent.

Inhibition of Viral Replication in Cell Culture Assays

Compounds **1a–d**, **2**, **4a–d**, **5a–d** and **7a–d** were tested in cell culture assays for their inhibition of multiplication of human immunodeficiency virus 1 (HIV-1), herpes simplex virus-1 (HSV-1), human cytomegalovirus (HCMV) and influenza virus A. In addition, the effect on the growth of uninfected cells was determined. The activities of the compounds were studied at 1, 10 and 100 μg mL^{-1} concentrations.

All compounds were inactive against HSV-1. Two compounds, **1b** and **1d** had weak activities against influenza A, showing 50% inhibition at the highest concentration, 100 μg mL^{-1}. In the HIV-1 assay, only compound **2** showed some activity and was retested at lower concentrations (0.1, 0.01 and 0.001 mg mL^{-1}). The 50% inhibitory concentration, ED_{50}, was found to be 0.5 μg mL^{-1}. However, at 100 μg mL^{-1} the compound completely inhibited cellular proliferation. Compounds **5a**, **1b** and **1d** exhibited some activity against HCMV, both in an ELISA and cytopathogenic (CPE) assay. In the ELISA assay, the ED_{50}s were 12, 14 and 20 μg mL^{-1}, respectively. In the CPE assay, **5a** showed a > 75% inhibition at 100 μg mL^{-1}. However, in the virus free assay, cellular proliferation was also inhibited (95%) at 100 μg mL^{-1} by this compound. For compounds **1b** and **1d**, no definite antiviral cytopathogenic effect could be seen at 100 μg mL^{-1}, due to interfering cellular toxicity.

In the cell growth assay, all compounds had some inhibitory activity at the highest concentration, 100 μg mL^{-1}. Compounds **4a**, **4b**, **4c**, **5a**, **1a**, **1b** and **1d** showed about 95% inhibition each, while compounds **2**, **4d**, **5b**, **5c**, **5d** and **1c** about 50% inhibition and compounds **7a–d** about 30% inhibition.

Experimental

Chemistry

The ^1H NMR spectra were recorded on a Varian XL-300 spectrometer. The mass spectra were recorded on a JEOL JMS-SX 102 spectrometer. Melting points are uncorrected. Flash column chromatography was carried out using Merck silica gel 60. Tetrahydrofuran (THF) was dried by refluxing and distillation over sodium wire. *N,N*-Dimethylformamide (DMF) was dried over 4 Å molecular sieves. Pyridine was distilled and stored over 4 Å molecular sieves. All other solvents were distilled prior to use.

*Preparation of 9-[2',3',5'-tri-*O*-(t-butyldimethylsilyl)-β-D-ribofuranosyl]-6-amino-2-iodopurine (3).* To a mixture of 0.96 g (6.4 mmol) of *t*-butyldimethylsilylchloride and 0.89 g (13 mmol) of imidazole in 4.0 mL of anhydrous DMF, 0.50 g (1.3 mmol) of 9-(β-D-ribofuranosyl)-6-amino-2-iodopurine (**2**) was added. The resulting solution was stirred for 28 h at room temperature. When no starting material remained (checked by thin-layer chromatography (TLC), toluene:ethylacetate 4:1), the mixture was poured into an ethyl acetate/water solution. The organic layer was separated, dried, and evaporated

to dryness. The residue was chromatographed using toluene:ethyl acetate (4:1) as eluent, to give 0.65 g (68%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) showed the same δ values as those given in the literature.[37]

General procedure for preparation of 2-(2"-heteroaryl)-9-[2',3',5'-tri-O-(t-butyldimethylsilyl)-β-D-ribofuranosyl]-adenine. A mixture of **3**, $PdCl_2(PPh_3)_2$ and tributylstannylheteroaryl[32] in anhydrous THF was heated with stirring under nitrogen at 90 °C. The reaction was followed by TLC using dichloromethane:methanol (9:1) as eluent. When the starting material was consumed, the reaction mixture was allowed to reach room temperature and was evaporated to dryness. The residue was column chromatographed using toluene:ethyl acetate (4:1) as eluent. Further purification was achieved by HPLC using a nucleosil column (500 × 10 mm) and toluene:methanol (7:3) as eluent to give the desired compound.

2-(2"-Thienyl)-9-[2',3',5'-tri-O-(t-butyldimethylsilyl)-β-D-ribofuranosyl]adenine (4a). This compound was obtained from 250 mg (0.34 mmol) of **3**, 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$ and 634 mg (1.70 mmol) of 2-tributylstannylthiophene[32] in 2.5 mL of anhydrous THF. After 48 h, work up and purification by HPLC the yield was 193 mg (82%); mp 235–237 °C. ^{1}H NMR ($CDCl_3$): δ 8.14 (*s*, 1H, H8), 7.90 (*dd*, 1H, H3", J = 3.7, 1.2 Hz), 7.38 (*dd*, 1H, H5", J = 5.0, 1.2 Hz), 7.10 (*dd*, 1H, H4", J = 5.0, 3.7 Hz), 6.00 (*d*, 1H), 5.54 (*s*, NH_2), 4.81 (*t*, 1H, H2'), 4.36 (*t*, 1H, H3'), 4.10 (*m*, 1H, H5'), 3.84 (*d*, 1H, H4'), 0.97–0.82 (*m*, 27H, Si-*t*-Bu), 0.16–0.10 (*m*, 18H, $SiMe_3$). Peak matching for (M^+ + H), calcd for $C_{32}H_{58}O_4N_5Si_3S$: 692.3517; found: 692.3526.

2-(3"-Thienyl)-9-[2',3',5'-tri-O-(t-butyldimethylsilyl)-β-D-ribofuranosyl]adenine (4b). This compound was obtained from 250 mg (0.34 mmol) of **3**, 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$ and 634 mg (1.70 mmol) of 2-tributylstannylthiophene[32] in 2.5 mL of anhydrous THF. After 48 h, work up and purification by HPLC the yield was 209 mg (89%); mp 190–191 °C. ^{1}H NMR ($CDCl_3$): δ 8.18 (*s*, 1H, H8), 8.16 (*dd*, 1H, H2", J = 2.9, 1.1 Hz), 7.86 (*dd*, 1H, H4", J = 5.0, 1.1 Hz), 7.32 (*dd*, 1H, H5", J = 5.0, 2.9 Hz), 6.06 (*d*, 1H, H1'), 5.48 (*s*, NH_2), 4.73 (*t*, 1H, H2'), 4.35 (*t*, 1H, H3'), 4.13 (*m*, 1H, H5'), 3.85 (*d*, 1H, H4'), 0.97–0.82 (*m*, 27H, Si-*t*-Bu), 0.16–0.10 (*m*, 18H, $SiMe_3$). Peak matching for (M^+ + H), calcd for $C_{32}H_{58}O_4N_5Si_3S$: M_r 692.3517; found: 692.3526.

2-(2"-Furyl)-9-[2',3',5'-tri-O-(t-butyldimethylsilyl)-β-D-ribofuranosyl]adenine (4c). This compound was obtained from 250 mg (0.34 mmol) of **3**, 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$ and 606 mg (1.70 mmol) of 2-tributylstannylfuran[32] in 2.5 mL of anhydrous THF. After 72 h, work up and purification by HPLC the yield was 216 mg (94%); mp 252–255 °C. ^{1}H NMR ($CDCl_3$): δ 8.20 (*s*, 1H, H8), 7.57 (*dd*, 1H, H5", J = 1.8, 0.9 Hz), 7.18 (*dd*, 1H, H3", J = 3.4, 0.9 Hz), 6.52 (*dd*, 1H, H4", J = 3.4, 1.8 Hz), 6.03 (*d*, 1H, H1'), 5.65 (*s*, NH_2), 4.69 (*dd*, 1H, H2'), 4.35 (*dd*, 1H, H3'), 4.12 (*m*, 1H, H5'), 3.82 (*dd*, 1H, H4'), 0.98–0.82 (*m*, 27H, Si-*t*-Bu), 0.17–0.10 (*m*, 18H, $SiMe_3$). Peak matching for (M^+ + H), calcd for $C_{32}H_{58}O_5N_5Si_3$: 676.3746; found: 676.3746.

2-(3"-Furyl)-9-[2',3',5'-tri-O-(t-butyldimethylsilyl)-β-D-ribofuranosyl]adenine (4d). This compound was obtained from 250 mg (0.34 mmol) of **3**, 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$ and 606 mg (1.70 mmol) of 3-tributylstannylfuran[32] in 2.5 mL of anhydrous THF. After 72 h, work up and purification by HPLC the yield was 218 mg (95%); mp 214–215 °C. ^{1}H NMR ($CDCl_3$): δ 8.18 (*s*, 1H, H8), 8.11 (*dd*, 1H, H2", J = 1.5, 1.0 Hz), 7.44 (*dd*, 1H, H5", J = 1.8, 1.5 Hz), 7.01 (*dd*, 1H, H4", J = 1.8, 1.0 Hz), 6.03 (*d*, 1H, H1'), 5.48 (*s*, NH_2), 4.64 (*dd*, 1H, H2'), 4.34 (*dd*, 1H, H3'), 4.08 (*m*, 1H, H5'), 3.82 (*dd*, 1H, H4'), 0.98–0.80 (*m*, 27H, Si-*t*-Bu), 0.17–0.10 (*m*, 18H, $SiMe_3$). Peak matching for (M^+ + H), calcd for $C_{32}H_{58}O_5N_5Si_3$: M_r 676.3746; found: (M + 1) 676.3739.

General procedure for the deprotection of compounds 4a–d. Compounds **4a–d** were each dissolved in 0.1 M methanolic hydrochloric acid and stirred at room temperature for 24 h. The reaction was followed by TLC using dichloromethane:methanol (9:1) as eluent. The solvent was evaporated and the residue column chromatographed using a gradient of dichloromethane:methanol (9:1–7:3) as eluent. Further purification was achieved on HPLC using a nucleosil (500 × 10 mm) column and chloroform:methanol as eluent.

2-(2"-Thienyl)adenosine (5a). This compound was obtained from 120 mg (0.17 mmol) of **4a** and 30 mL of 0.1 M methanolic hydrochloric acid in a yield of 38 mg (63%); mp 244–246 °C (lit. 250 °C).[33] The proportions for the eluent were 92:8. ^{1}H NMR (DMSO-d_6): δ 8.34 (*s*, 1H, H8), 7.83 (*dd*, 1H, H3", J = 3.6, 1.3 Hz), 7.63 (*dd*, 1H, H5", J = 5.1, 1.3 Hz), 7.40 (*s*, NH_2), 7.15 (*dd*, 1H, H4", J = 5.1, 3.6 Hz), 5.91 (*d*, 1H, H1'), 4.72 (*dd*, 1H, H2'), 4.22 (*dd*, 1H, H3'), 3.96 (*dd*, 1H, H4'), 3.64 (*m*, 1H, H5'). Peak matching (M^+ + H), calcd for $C_{14}H_{16}O_4N_5S$: 350.0923; found: 350.0929.

2-(3"-Thienyl)adenosine (5b). This compound was obtained from 120 mg (0. 17 mmol) of **4b** and 30 mL of 0.1 M methanolic hydrochloric acid in a yield of 43 mg (72%); mp 185–188 °C. The proportions for the eluent were 92:8. ^{1}H NMR (DMSO-d_6): δ 8.35 (*s*, 1H, H8), 8.17 (*dd*, 1H, H2", J = 3.1, 1.2 Hz), 7.78 (*dd*, 1H, H4", J = 5.1, 1.2 Hz), 7.59 (*dd*, 1H, H5", J = 5.1, 3.1 Hz), 7.34 (*s*, NH_2), 5.93 (*d*, 1H, H1'), 4.74 (*t*, 1H, H2'), 4.22 (*dd*, 1H, H3'), 3.96 (*dd*, 1H, H4'), 3.61 (*m*, 1H, H5'). Peak matching for (M^+ + H), calcd for $C_{14}H_{16}O_4N_5S$: 350.0923; found: 350.0926.

2-(2"-Furyl)adenosine (5c). This compound was obtained from 207 mg (0.31 mmol) of **4c** and 100 mL of 0.1 M methanolic hydrochloric acid in a yield of 64 mg (62%); mp 137–139 °C (lit. 135–140 °C).[33] The pro-

portions for the eluent were 90:10. ^{1}H NMR (DMSO-d_6): δ 8.36 (*s*, 1H, H8), 7.81 (*dd*, 1H, H5", *J* = 1.8, 0.8 Hz), 7.43 (*s*, NH_2), 7.13 (*dd*, 1H, H3", *J* = 3.4, 0.8 Hz), 6.63 (*dd*, 1H, H4", *J* = 3.4, 1.8 Hz), 5.92 (*d*, 1H, H1'), 4.68 (*dd*, 1H, H2'), 4.19 (*dd*, 1H, H3'), 3.97 (*dd*, 1H, H4'), 3.20 (*m*, 1H, H5'). Peak matching for (M^+ + H), calcd for $C_{14}H_{16}O_5N_5$: 334.1151; found: 334.1155.

2-(3"-Furyl)adenosine (5d). This compound was obtained from 201 mg (0.30 mmol) of **4d** and 100 mL of 0.1 M methanolic hydrochloric acid in a yield of 67 mg (67%); mp 154–155 °C. The proportions for the eluent were 90:10. ^{1}H NMR (DMSO-d_6): δ 8.32 (*s*, 1H, H8), 8.21 (*dd*, 1H, H2", *J* = 1.6, 0.9 Hz), 7.74 (*dd*, 1H, H5", *J* = 1.8, 1.6 Hz), 7.32 (*s*, NH_2), 7.00 (*dd*, 1H, H4", *J* = 1.8, 0.9 Hz), 5.91 (*d*, 1H, H1'), 4.72 (*dd*, 1H, H2'), 4.20 (*t*, 1H, H3'), 3.98 (*dd*, 1H, H4'), 3.68 (*m*, 1H, H5'). Peak matching for (M^+ + H), calcd for $C_{14}H_{16}O_5N_5$: 334.1151; found: 334.1142.

General procedure for the preparation of 8-(heteroaryl)guanosine. A suspension of 8-bromoguanosine (**6**), 1,1,1,3,3,3-hexamethyldisilazan (HMDS) and pyridine in the presence of a catalytic amount of ammonium sulfate was refluxed overnight under an atmosphere of nitrogen. After cooling to room temperature, the volatiles were removed *in vacuo* to give the trimethylsilyl-protected nucleoside as a syrup, which was used in the next step without purification. The crude product was dissolved in anhydrous THF, $PdCl_2(PPh_3)_2$ and the tributylstannylheteroaryl were added, after which the suspension was heated at 90 °C under an atmosphere of nitrogen until no starting material remained (checked by RP C_{18}-TLC using acetone:water (1:1) as eluent). After cooling to room temperature, the solvent was removed *in vacuo* and the crude product was filtered through a silica gel 60 column using dichloromethane:methanol (9:1) as eluent. The trimethylsilyl groups were removed by treatment with potassium carbonate in methanol at room temperature for 1 h. The reaction mixture was evaporated to dryness and the crude product was purified directly by HPLC on a dynamax RP C_{18} column (500 × 10 mm) using acetonitrile:water as eluent.

8-(2"-Thienyl)guanosine (7a). This compound was obtained from 250 mg (0.69 mmol) of **6**, 25.0 mL of HMDS, 2.5 mL of pyridine, 25 mg (0.03 mmol) of $PdCl_2(PPh_3)_2$ and 1.29 g (3.45 mmol) of 2-tributylstannylthiophene.[32] After 25 h and HPLC purification (eluent 20:80) the yield was 146 mg (58%); mp 249 °C (dec). ^{1}H NMR (DMSO-d_6): δ 7.74 (*dd*, 1H, H5", *J* = 5.1, 1.0 Hz), 7.48 (*dd*, 1H, H3", *J* = 3.6, 1.0 Hz), 7.21 (*dd*, 1H, H4", J = 5.1, 3.6 Hz), 5.85 (*d*, 1H, H1'), 5.45 (*s*, NH_2), 5.09 (*t*, 1H, H2'), 4.12 (*dd*, 1H, H3'), 3.88 (*dd*, 1H, H4'), 3.58 (*m*, 1H, H5'). Peak matching for (M^+ + H), calcd for $C_{14}H_{16}O_5N_5S$: 366.0872; found: 366.0870.

8-(3"-Thienyl)guanosine (7b). This compound was obtained from 250 mg (0.69 mmol) of **6**, 25.0 mL of HMDS, 2.5 mL of pyridine, 25 mg (0.03 mmol) of $PdCl_2(PPh_3)_2$ and 1.29 g (3.45 mmol) of 3-tributylstannylthiophene.[32] After 25 h and HPLC purification (eluent 23:77) the yield was 131 mg (52%); mp 270 °C (dec). ^{1}H NMR (DMSO-d_6): δ 7.89 (*dd*, 1H, H2", *J* = 2.9, 1.2 Hz), 7.72 (*dd*, 1H, H5", *J* = 5.0, 2.9 Hz), 7.44 (*dd*, 1H, H4", *J* = 5.0, 1.2 Hz), 6.66 (*s*, NH_2), 5.76 (*d*, 1H, H1'), 5.00 (*t*, 1H, H2'), 4.10 (*dd*, 1H, H3'), 3.88 (*dd*, 1H, H4'), 3.67 (*m*, 1H, H5'). Peak matching for (M^+ + H), calcd for $C_{14}H_{16}O_5N_5S$: 366.0872; found: 366.0867.

8-(2"-Furyl)guanosine (7c). This compound was obtained from 250 mg (0.69 mmol) of **6**, 25.0 mL of HMDS, 2.5 mL of pyridine, 25 mg (0.03 mmol) of $PdCl_2(PPh_3)_2$ and 1.23 mg (3.45 mmol) of 2-tributylstannylfuran.[32] After 40 h and HPLC purification (eluent 20:80) the yield was 128 mg (53%); mp 255 °C (dec). ^{1}H NMR (DMSO-d_6): δ 7.89 (*dd*, 1H, H5", *J* = 1.7, 0.8 Hz), 6.92 (*dd*, 1H, H3", *J* = 3.4, 0.8 Hz), 6.68 (*dd*, 1H, H4", *J* = 3.4, 1.7 Hz), 6.68 (*s*, NH_2), 5.94 (*d*, 1H, H1'), 5.02 (*t*, 1H, H2'), 4.13 (*dd*, 1H, H3'), 3.89 (*dd*, 1H, H4'), 3.67 (*m*, 1H, H5'). Peak matching for (M^+ + H), calcd for $C_{14}H_{16}O_6N_5$: 350.1100; found: 350.1110.

8-(3"-Furyl)guanosine (7d). This compound was obtained from 250 mg (0.69 mmol) of **6**, 25.0 mL of HMDS, 2.5 mL of pyridine, 25 mg (0.03 mmol) of $PdCl_2(PPh_3)_2$ and 1.23 mg (3.45 mmol) of 3-tributylstannylfuran.[32] After 40 h and HPLC purification (eluent 22:78) the yield was 140 mg (58%); mp 268 °C (dec). ^{1}H NMR (DMSO-d_6): δ 8.13 (*dd*, 1H, H2", *J* = 1.5, 0.9 Hz), 7.86 (*dd*, 1H, H5", *J* = 1.8, 1.5 Hz), 6.85 (*dd*, 1H, H4", *J* = 1.8, 0.9 Hz), 6.39 (*s*, NH_2), 5.71 (*d*, 1H, H1'), 4.98 (*dd*, 1H, H2'), 4.11 (*dd*, 1H, H3'), 3.86 (*dd*, 1H, H4'), 3.69 (*m*, 1H, H5'). Peak matching for (M^+ + 1), calcd for $C_{14}H_{16}O_6N_5$: 350.1100; found: 350.1096.

Biochemistry

Inhibition of HIV-1, HSV-1 and influenza A multiplication were performed as XXT assays in MT4 cells (human T cell line), vero cells and MDCK cells (with Victoria 3/75 strain), respectively. Effect on cell growth was determined as an XTT assay on non-confluent HEL cells without presence of any virus. In the CMV assay, reduction in cytopathic effect caused by the virus was determined in MRC-5 cells (human embryonic cells). These assays were performed as previously described.[38] The CMV ELISA assay was an *in situ* determination of viral antigens in HEL cells and performed essentially as previously described.[39]

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