Adenosine Kinase Inhibitors. 2. Synthesis, Enzyme Inhibition, and Antiseizure Activity of Diaryltubercidin Analogues

Bheemarao G. Ugarkar,* Angelo J. Castellino, Jay M. DaRe, Joseph J. Kopcho, James B. Wiesner, Juergen M. Schanzer, and Mark D. Erion

Metabasis Therapeutics Inc., 9390 Towne Centre Drive, San Diego, California 92121

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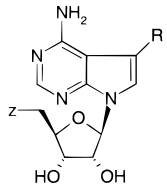
In the preceding article (Ugarkar et al. *J. Med. Chem.* **2000**, *43*) we reported that analogues of tubercidin are potent adenosine kinase (AK) inhibitors with antiseizure activity in the rat maximum electroshock (MES) model. Despite the discovery of several highly potent AK inhibitors (AKIs), e.g., 5′-amino-5′-deoxy- 5-iodotubercidin **(1c)** (IC_{50} = 0.0006 μM), no compounds were identified that exhibited a safety, efficacy, and side effect profile suitable for further development. In this article, we demonstrate that substitution of the tubercidin molecule with aromatic rings at the N4- and the C5-positions not only retains AKI potency but also improves in vivo activity. Synthesis of such compounds entailed transformation of 4-arylamino-5-iodotubercidin analogues to their corresponding 5-aryl derivatives via the Suzuki reaction. Alternatively, 4-*N*-arylamino-5-arylpyrrolo[2,3-*d*]pyrimidine bases were constructed and then glycosylated with appropriately protected α-ribofuranosyl chlorides using a phase-transfer catalyst. Several compounds exhibited potent activity in the rat MES seizure assay with ED_{50}s ≤ 2.0 mg/kg, ip, and showed relatively mild side effects.

Introduction

In our continuing effort to develop adenosine regulating agents (ARAs) as an alternative to adenosine or its receptor agonists, we have pursued inhibition of the cytosolic enzyme adenosine kinase (AK).[1] Inhibition of AK was hypothesized to increase intracellular adenosine levels which, following transport out of the cell, would stimulate nearby adenosine receptors and induce a protective pharmacological response. We have demonstrated that adenosine kinase inhibitors (AKIs) exhibit anticonvulsive effects against MES-induced seizures in rats. Moreover, the effects are reversed by the nonspecific adenosine receptor antagonist theophylline, suggesting that the pharmacological effect is mediated by an adenosine receptor.[1] Based on the potent AKI activities reported for 5-iodotubercidin (**1a**, IC_{50} = 0.026 μM) and 5′-deoxy-5-iodotubercidin (**1b**, IC_{50} = 0.009 μM) (Chart 1) a number of tubercidin analogues were prepared to study the SAR of AK inhibition.[1] Our results revealed that a halogen (I or Br) at the C5-position and an NH_2, Cl, or SCH_3 at the C4-position of tubercidin yield molecules that potently inhibit AK (IC_{50} ≤ 0.1 μM). The enzyme was found to accommodate both hydrophobic and hydrophilic substituents at the C5′-position, with the 5′-amino-linked tubercidin analogues exhibiting the highest potencies (**1c**, IC_{50} = 0.0006 μM; **1d,** IC_{50} = 0.0002 μM). The above compounds, however, were not considered ideal development candidates for various reasons. For example, **1a** is suspected to be a cytotoxic agent due to its 5′-phosphorylation by intracellular kinases,[2] whereas **1b** is reported to produce side effects such as sedation, hypothermia, and muscle flaccidity[3] at doses similar to those required for inhibition of MES seizure in rats.[1] Furthermore, compounds **1c**,**d**, though very potent in the enzyme inhibition assay, exhibited weak activity in the rat MES seizure assay.[1] The weak in vivo potency of these compounds was believed to be due to their poor brain penetration or poor cell penetration. Consequently, we sought to make structural changes that included large hydrophobic substituents on the C4-NH_2 and at the C5-position of the tubercidin molecule in order to enhance the AK specificity and selectivity, as well as enhance their brain/cell penetration.

Chart 1



1a R = I; Z = OH

1b R = I; Z = H

1c R = I; Z = NH_2

1d R = Br; Z = NH_2

In this report, we disclose the discovery that tubercidin analogues with an aromatic amine at the C4-position and an aromatic ring at the C5-position exhibit potent AK inhibition and potent antiseizure activities. Several of these compounds were found to exhibit reduced side effects when compared with adenosine receptor agonists. The synthesis, AK inhibition, antiseizure activity, and side effects of these potent AKIs are described in detail.

Chemistry

Two separate strategies were employed for the synthesis of AKIs shown in Table 1. The first strategy used 2′,3′-*O*-isopropylidene-protected 4-chloro-5-iodopyrrolo-[2,3-*d*]pyrimidine nucleosides[1] as the key starting ma-

* To whom correspondence should be addressed. Phone: 858-622-5535. Fax: 858-622-5526. E-mail: ugarkar@mbasis.com.

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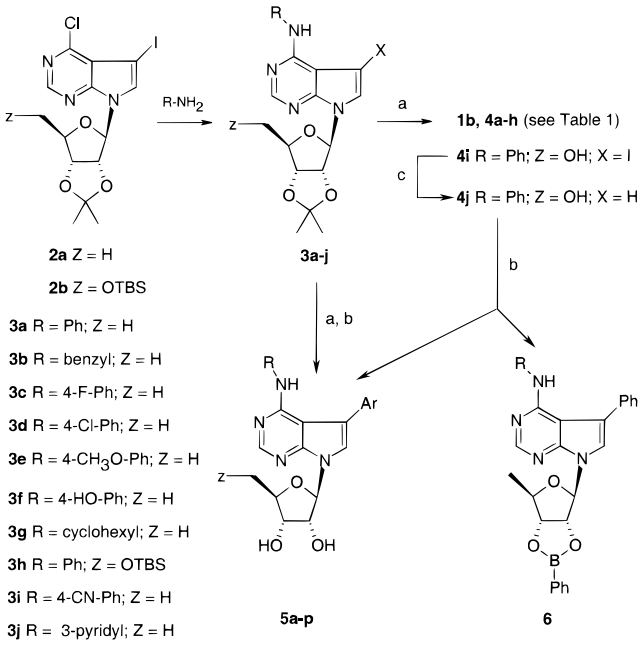
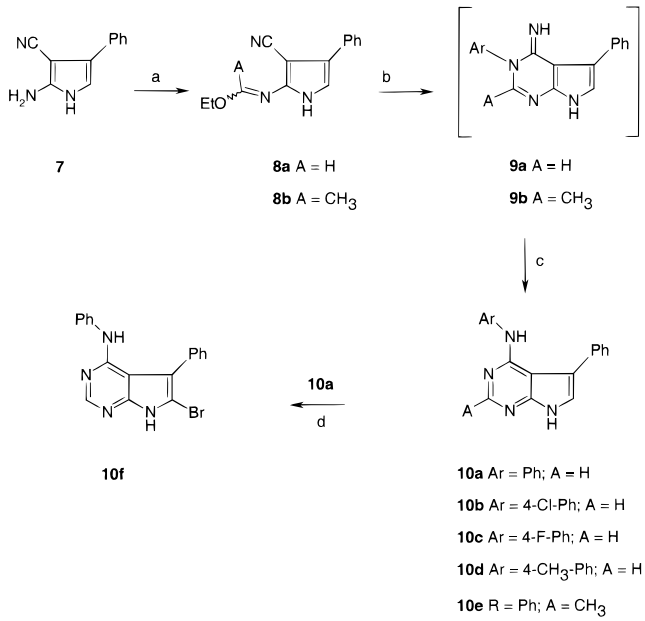
Scheme 1[a]



[a] (a) 70% TFA; (b) $ArB(OH)_2/Pd(Ph_3P)_4$; (c) $H_2/Pd-C$.

Scheme 2[a]



[a] (a) $HC(OEt)_3$ or $H_3CC(OEt)_3$/*p*-TSA; (b) DMF/$ArNH_2$; (c) H_2O, reflux; (d) NBS/DMF.

terials, which were condensed with a number of anilines and amines. Then the C5-aromatic ring was introduced via the Suzuki reaction[4] to generate the target molecules after acid catalyzed removal of the protecting group. The second strategy entailed construction of a fully substituted pyrrolopyrimidine base followed by glycosylation and deprotection.

Condensation of 2′,3′-*O*-isopropylidene-protected nucleosides **2a**[1] and **2b**[1] with amines, including various anilines, benzylamine, and cyclohexylamine, provided the corresponding 4-*N*-substituted-amino-5-iodopyrrolopyrimidine nucleoside intermediates **3a**−**j**, as shown in Scheme 1. These intermediates were subjected to acid-catalyzed deprotection to furnish **1a** and **4a**−**i** in 60−70% overall yields.

The key step in synthesizing the desired molecules **5a**−**p** was the arylation of 5-iodo nucleoside intermediates **1b** and **4a**−**i** via the Suzuki reaction.[4] For example, reaction of **1b**[5] with phenylboronic acid in the presence of $Pd(PPh_3)_4$ gave **5a** in 65% yield. In general, unprotected nucleosides gave lower yields of the desired products presumably due to partial formation of 2′,3′-*O*-cyclic borates (e.g., **6)**, whereas isopropylidene-protected nucleosides **3g**,**j** gave >85% yield of the Suzuki products.

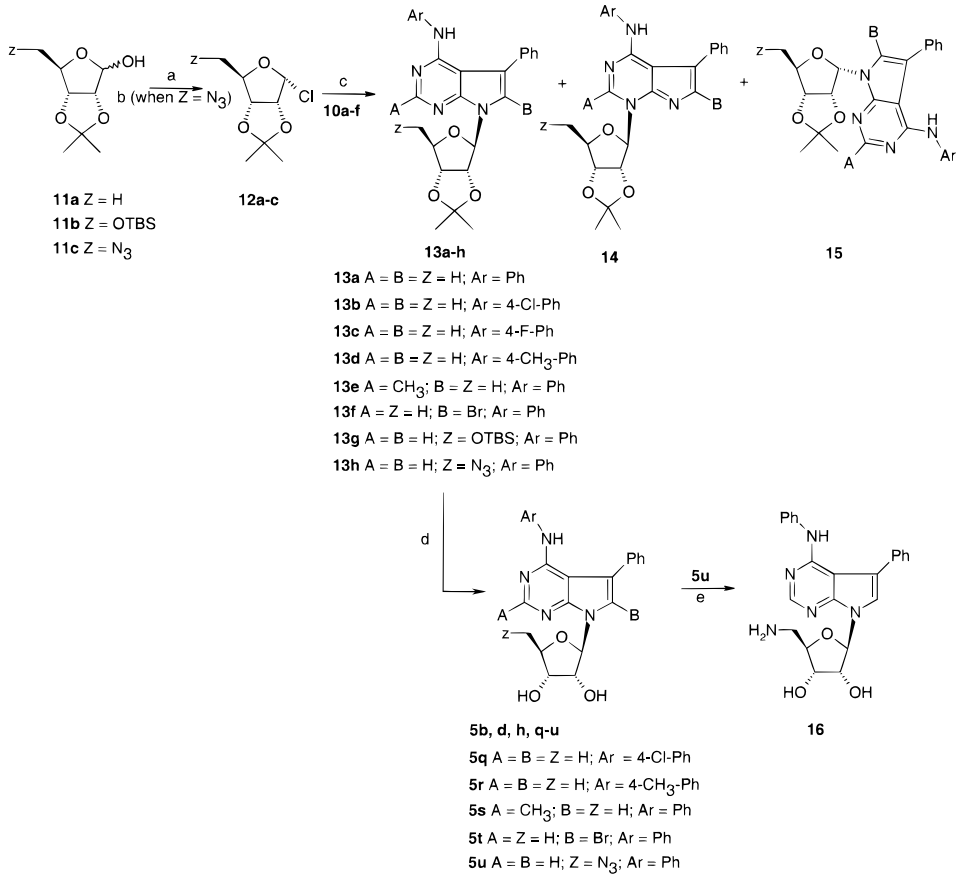
Attempts to condense **2a** with *p*-cyanoaniline and heteroarylamines, such as 2-, 3-, and 4-aminopyridines, 2-aminothiazole, 2-aminoimidazole, and 4-amino-1,2,4-triazole, resulted in either no reaction or decomposition of the starting material. This was attributed to poor nucleophilicity of the amines. Therefore, when a strong base such as *t*-BuOK was used for activating the amine function, **2a** readily condensed with *p*-cyanoaniline giving the desired intermediate **3i** in 82% yield. Unfortunately, under the similar conditions only one heteroarylamine, 3-aminopyridine, reacted to give the desired intermediate **3j** in 79% yield.

The second strategy employed for the preparation of the target compounds involved glycosylation of preformed 4-arylamino-5-arylpyrrolo[2,3-*d*]pyrimidine bases followed by deprotection using 70% TFA. The heterocycles **10a**−**e** were synthesized by a procedure reported by Taylor et al.,[6] for the synthesis of 4-amino-5-phenylpyrrolo[2,3-*d*]pyrimidine. For example, 2-amino-3-cyano-4-phenylpyrrole (**7**)[7] was converted to 3-cyano-2-ethoxymethylenimino-4-phenylpyrrole (**8a**),[6] which was further condensed with aniline in boiling DMF to give a mixture of partially aromatized intermediate **9a** and the desired product **10a** (Scheme 2). Complete conversion of **9a** to **10a** was accomplished by diluting the reaction mixture with water and refluxing for an additional 4−8 h. This procedure of making pyrrolopyrimidine bases was found also to be useful in the synthesis of C2-methyl-substituted heterocycle **10e** by replacing triethyl orthoformate with triethyl orthoacetate in the first step. It should be noted here that the efforts to isolate pure **9a** or **9b** for characterization were unsuccessful due to their slow but spontaneous rearrangement to form the fully aromatized products during purification by chromatography or crystallization.

This method of synthesizing pyrrolo[2,3-*d*]pyrimidines was found to be effective for anilines with halogens and electron-donating substituents. In contrast, anilines with electron-withdrawing groups such as CN, COOEt, and NO_2, as well as heteroarylamines failed to react with **8a**.

Glycosylation of the heterocycles was accomplished using appropriately protected α-ribofuranosyl chloride as shown in Scheme 3. Sodium salt-mediated glycosylation[8] of **10a** with 5-deoxy-2,3-*O*-isopropylidene-α-D-ribofuranosyl chloride (**12a**)[1] resulted in a poor yield of the desired N7-glycosylated product **13a** (30−35%) along with two major byproducts, which are tentatively assigned as the N1-*β*-nucleoside **14** and the N7-α-nucleoside **15**. Similarly, glycosylation using 50% NaOH/methylene chloride and the phase-transfer catalyst tris[2-(methoxyethoxy)ethyl]amine[9] (TDA-1) gave **13a** (30−35%) along with **14** (12−20%) and **15** (10−15%).

Scheme 3[a]



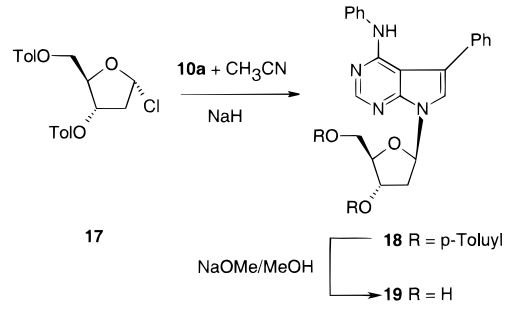
[a] (a) HMPT/CCl_4/toluene, −10 °C; (b) HMPT/CCl_4/THF, −76 °C; (c) KOH/toluene/TDA-1; (d) 70% TFA; (e) H_2, Pd/C.

During optimization of this procedure other phase-transfer catalysts, such as benzyltrimethylammonium bromide and benzyltributylammonium bromide, and solvents, such as acetonitrile, 1,2-dichloroethane, 1,4-dioxane, and THF, were examined. These experiments gave less desirable product mixtures. However, a much improved product profile resulted when the reaction was carried out in toluene using 2 equiv of powdered KOH, 1 equiv of TDA-1, and 2 full equiv of **12a**. Under these conditions **13a** was obtained in 45−50% yield. Moreover, the formation of the N1-nucleoside was minimized, and the α-nucleoside byproduct was eliminated. The higher yield of the desired nucleoside using a phase-transfer catalyst is attributed to better dissolution of the anion of the heterocycle which facilitates efficient condensation the reaction.

The moderate yield (≤50%) of **13a** even with 2 full equiv of the sugar was attributed to the short half-life of the chloro sugar **12a** ($t_{1/2} \leq 3$ h in THF) which may be even shorter in the strongly basic reaction conditions. Therefore, attempts were directed toward finding a suitable solvent and conditions that would improve the formation and stability of the α-chloro sugars. Since toluene was found to be the solvent of choice for the TDA-1-mediated glycosylation, chlorination of **11a** was attempted in toluene under a variety of reaction conditions. Careful investigation revealed that the chlorination proceeded well in toluene at a warmer temperature (−10 °C) vs THF (−78 °C). Furthermore, washing the chlorination mixture with ice-cold brine and drying over $MgSO_4$ increased the half-life of **12a** to >48 h at ≤4 °C. The α/β ratio of chloro sugars was established to be ≥95/5 based on the ^{1}H NMR signal integration of the anomeric proton of the respective isomers. When a solution of **12a** prepared in toluene was employed for the glycosylation of **10a**, the yield of **13a** increased to 65%. The yield of **14** decreased to 8% and that of **15** was negligible.

The structural assignments of the glycosylation products were made by ^{1}H NMR and UV spectroscopies. The anomeric proton of **13a** is a doublet at 6.3 ppm with a coupling constant of 2.9 Hz which is characteristic of other 2′,3′-*O*-isopropylidene-protected β-nucleosides of pyrrolo[2,3-*d*]pyrimidine bases.[1] Acid-catalyzed deprotection of **13a** gave a product which was identical by TLC, melting point, and ^{1}H NMR to **5b** prepared via the Suzuki reaction. The structure of N1-glycosylated product **14**, however, was established based on earlier studies[10] which reported that the UV spectra of N1-glycosylated pyrrolopyrimidine nucleosides have an absorption maximum at a higher wavelength compared to their N7-isomer. This trend was observed with compounds **13a** and **14** which showed λ_{max} values at 297 and 304 nm, respectively. Thus, the major product was assigned the N7-glycosyl structure **13a** and the minor product, the N1-glycosyl structure **14**. Although the ^{1}H NMR spectra of the two isomers are very similar, the chemical shifts for C2-H signals of **13a** (8.40 ppm) and **14** (8.66 ppm) are slightly different. Also, when subjected to trifluoroacetic acid-catalyzed deprotection **13a** gave **5b**, whereas **14** underwent deglycosylation giving **10a** as the only isolable product. Several attempts to

Scheme 4



successfully deprotect **14** under mild acidic conditions failed. Such acid instability of N1-glycosylated pyrrolopyrimidine nucleosides is well-known.[11] The α-nucleoside **15** obtained in the sodium salt glycosylation method was assigned by ^{1}H NMR spectrum based on the downfield chemical shift and the large coupling constant for the anomeric proton signal (6.7 ppm, $J \geq 7$ Hz).

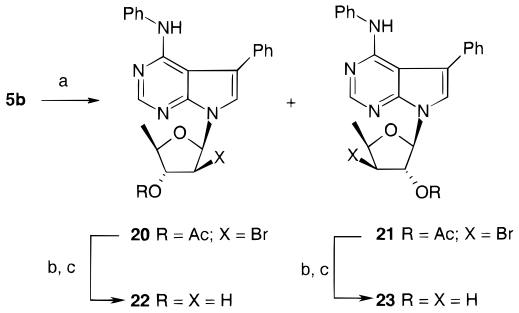
The potent AKI activity exhibited by 5′-amino-5′-deoxy nucleosides **1c**,**d** prompted the synthesis of the 5′-amino nucleoside **16**. Since earlier efforts had failed to convert the 5′-OH of **1a** to the corresponding 5′-amino derivative **1c** via a 5′-*O*-tosylate or Mitsunobu reaction, the 5-azido-α-chloro sugar **12c** was coupled to **10a** to give **13h**. Deprotection followed by hydrogenation of **13h** gave the desired product **16** in an overall 80% yield. It is important to note that, unlike **12a**,**b**, **12c** could not be generated in toluene due to the insolubility of the starting material **11c** in toluene at the reaction temperature (−10 °C). Instead, it was prepared in THF by the original procedure.[1]

With a view to evaluating the role of various OH groups of the ribofuranosyl moiety on AKI activity, 2′-deoxy nucleoside **19**, 2′,5′-dideoxy nucleoside **22**, and 3′,5′-dideoxy nucleoside **23** were prepared. Synthesis of compound **19** was accomplished as shown in Scheme 4. Glycosylation of **10a** with 2-deoxy-3,5-di-*O*-toluoyl-α-D-pentofuranosyl chloride (**17**)[12] using the sodium salt procedure[8] gave **18** which was deprotected using sodium methoxide in methanol to furnish **19** in an overall 51% yield. Interestingly, in this glycosylation experiment the formation of both N7-α- and N1-glycosylated byproducts was negligible.

The structural assignments of **18** were made using ^{1}H NMR spectroscopy. The signal for the anomeric proton of **18** appears at 6.60 ppm as a doublet of doublets (J_1 = 6.01 Hz and J_2 = 8.25 Hz) which is consistent with the data reported for similar compounds.[9,13] Similarly, the signal for the anomeric proton of the deprotected nucleoside **19** also appears as a sharp doublet of doublets at 6.64 ppm which is characteristic of 2′-deoxy nucleosides.[13] The UV spectrum of **19** shows the characteristic λ_{max} at 298 nm (ϵ 18900) at pH 7,[13] thus confirming regiochemistry of the glycosylation.

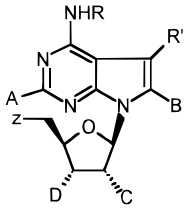
The synthesis of the dideoxy nucleosides **22** and **23** was accomplished by reacting **5b** with acetoxyisobutyryl bromide[14] in moist acetonitrile to give **20** (19%) and **21** (63%) which were separated by flash chromatography (Scheme 5). The compounds were characterized by comparing the chemical shifts and splitting patterns for the anomeric protons with those reported for the known 2′-*O*-acetyl-3′-*β*-bromoadenosine and 3′-*O*-acetyl-2′-*β*-bromoadenosine derivatives.[14,15] Hydrogenation and subsequent deprotection of **20** and **21** gave **22** and **23**,

Scheme 5[a]



[a] (a) Acetoxyisobutyryl bromide; (b) Pd(OH)$_2$/C, 10%, EtOAc, H$_2$; (c) MeOH/NaOMe.

Table 1. AK Inhibitor SAR



compd	R	R′	A	B	C	D	Z	AK IC_{50}[a] (μM)
4a	Ph	I	H	H	OH	OH	H	0.1
4b	Ph-CH_2	I	H	H	OH	OH	H	0.8
4c[16]	4-F-Ph	I	H	H	OH	OH	H	0.55
4e	4-MeO-Ph	I	H	H	OH	OH	H	0.775
4f	4-HO-Ph	I	H	H	OH	OH	H	0.2
4g	cyclohexyl	I	H	H	OH	OH	H	10
4h	4-CN-Ph	I	H	H	OH	OH	H	1.2
4i	Ph	I	H	H	OH	OH	OH	0.12
4j	Ph	H	H	H	OH	OH	OH	1.25
5a	H	Ph	H	H	OH	OH	H	0.32
5b	Ph	Ph	H	H	OH	OH	H	0.0005
5c	Ph-CH_2	Ph	H	H	OH	OH	H	0.03
5d[16]	4-F-Ph	Ph	H	H	OH	OH	H	0.0015
5e	4-MeO-Ph	Ph	H	H	OH	OH	H	0.006
5f	4-HO-Ph	Ph	H	H	OH	OH	H	0.001
5g	cyclohexyl	Ph	H	H	OH	OH	H	0.25
5h	Ph	Ph	H	H	OH	OH	OH	0.0008
5i	4-F-Ph	4-F-Ph	H	H	OH	OH	H	0.026
5j	Ph	4-Cl-Ph	H	H	OH	OH	H	0.0012
5k	4-Cl-Ph	4-Cl-Ph	H	H	OH	OH	H	0.0027
5l	4-CN-Ph	Ph	H	H	OH	OH	H	0.014
5m	4-CN-Ph	4-MeO-Ph	H	H	OH	OH	H	0.001
5n	Ph	2-furanyl	H	H	OH	OH	H	0.0036
5o	4-MeO-Ph	2-furanyl	H	H	OH	OH	H	0.009
5p	3-pyridyl	Ph	H	H	OH	OH	H	0.025
5q	4-Cl-Ph	Ph	H	H	OH	OH	H	0.0023
5r	4-Me-Ph	Ph	H	H	OH	OH	H	0.0015
5s	Ph	Ph	Me	H	OH	OH	H	0.047
5t	Ph	Ph	H	Br	OH	OH	H	0.001
5u	Ph	Ph	H	H	OH	OH	N_3	0.0015
16	Ph	Ph	H	H	OH	OH	NH_2	0.0063
19	Ph	Ph	H	H	H	OH	OH	0.3
22	Ph	Ph	H	H	H	OH	H	0.100
23	Ph	Ph	H	H	OH	H	H	0.044

[a] Enzyme inhibition assays were performed on human recombinant AK enzyme. IC_{50} values are results of a single experiment.

respectively. These products exhibited characteristically different NMR signal patterns which enabled definitive structural assignments. For example, the anomeric proton of **22** appears as a doublet of doublets at 6.63 ppm (J_1 = 5.5 Hz and J_2 = 5.8 Hz) confirming that it is a 2′-deoxy nucleoside, whereas the anomeric proton of **23** appears as a sharp doublet at 6.0 ppm (J = 2.2 Hz) which is characteristic of a *β*-nucleoside with a C2′-OH.

Results

The compounds were evaluated as inhibitors of the recombinant human AK (Table 1). The IC_{50} values were

determined as described previously.[1] The results reflect the importance of aromatic rings at the C4- and C5-positions and also of the 2′- and 3′- OH groups of the sugar component. Substituting the iodo group at the C5-position of **1b** with a phenyl ring resulted in a weaker AKI (**5a**, $IC_{50} = 0.32\ \mu M$).[1] Also a moderate loss of AKI activity was observed when the C4-NH_2 of **1b** was replaced with C_6H_5NH (**4a**, $IC_{50} = 0.1\ \mu M$). Remarkably, inhibitory potency was enhanced when the above two substitutions were both present (**5b**, $IC_{50} = 0.0005\ \mu M$). As reported earlier, **5b** undergoes oxidative metabolism in vivo to form the corresponding *p*-OH compound **5f** which is eliminated as the glucoronate.[16] This in vivo hydroxylation of the aromatic ring was avoided by substituting the *p*-position with F. Accordingly, we prepared **5b** analogues with CN, CH_3, and OCH_3 in the para-position of the aniline ring and F or Cl in the para-position of both the phenyl rings. These compounds, however, were relatively less potent than **5b** in the enzyme inhibition assay.

A moderate loss in AKI activity was observed when the C4-aniline of **5b** was replaced with 3-pyridylamine (**5p**, $IC_{50} = 0.025\ \mu M$), whereas a much smaller loss occurred when the C5-phenyl ring of **5b** or **5e** was replaced with a furan ring (**5n**, $IC_{50} = 0.0036\ \mu M$; **5o**, $IC_{50} = 0.009\ \mu M$). Moderate loss in potency was also observed when aniline in **5b** was replaced with benzylamine (**5c**, $IC_{50} = 0.03\ \mu M$), but a much greater loss in potency resulted for the corresponding C4-*N*-cyclohexylamino analogue **5g** ($IC_{50} = 0.25\ \mu M$).

5-Halogen-substituted tubercidin analogues **1a**,**b**, with OH and H in their respective C5′-positions, showed similar AKI potencies (**1a**, $IC_{50} = 0.026\ \mu M$; **1b**, $IC_{50} = 0.009\ \mu M$), whereas the C5′-NH_2 analogues **1c**,**d** showed a considerable increase in their ability to inhibit AK ($IC_{50} < 0.001\ \mu M$). However, such enhancement in AKI potency was not observed with diaryl AKIs when the C5′-OH of **5h** was replaced with C5′-NH_2 group to give **16** ($IC_{50} = 0.0063\ \mu M$).

In contrast to the C5′-OH, both the C2′- and C3′-OH groups are important for potent AKI activity as evidenced by the significant loss in the inhibitory potency of the 2′-deoxy compounds **19** ($IC_{50} = 0.3\ \mu M$) and **22** ($IC_{50} = 0.1\ \mu M$) and the 3′-deoxy compound **23** ($IC_{50} = 0.044\ \mu M$). The presence of a methyl group at the C2-position of adenosine is reported to have a deleterious effect on AK substrate efficiency, whereas a Br at the 8-position was well-tolerated.[17] The corresponding nucleosides **5s,t** followed these trends with IC_{50}s 0.047 and 0.001 μM, respectively.

Antiseizure Activity. Compounds with $IC_{50} < 0.05\ \mu M$ were screened for anticonvulsant activity in the rat MES seizure model. Ten AKIs showed potent activity (Table 2). Compound **5b** and several of its para-substituted analogues (compounds **5d**,**e**,**f**,**i**,**j**,**l**,**m**,**o**,**q**) inhibited MES seizures with ED_{50}s in the range of 0.7−7.1 mg/kg. Some of these compounds were shown also to exhibit potent activity with oral administration in rats.[16,18] Compounds **5h**,**t**,**u** and **16** which inhibited the enzyme with $\leq 0.01\ \mu M$ were found to be weak in the MES seizure model; information on the metabolism or pharmacokinetic characteristics is not currently available but will be needed to explain their in vivo potencies.

Table 2. Antiseizure Activity in Rat MES Seizure Model

compd	% inhib 5 mg/kg, ip[a]	ED_{50} (mg/kg, ip)[b]	compd	% inhib 5 mg/kg, ip[a]	ED_{50} (mg/kg, ip)[b]
5b	82	1.1	**5l**	87	1.1
5d	73	1.9	**5m**	100	0.7
5e	93	1.0	**5o**	50	5.0
5f	35	5.8	**5q**	62	7.1
5h	37	>5[a]	**5r**	50	≥5[a]
5i	100	1.1	**5t**	0	>5[a]
5j	83	1.7	**5u**	50	≥5[a]
5k	0	>5[a]	**16**	0	>5[a]

[a] Screened at 1 h after administration of 5 mg/kg, ip ($N = 8$). [b] $N = 8$/dose.

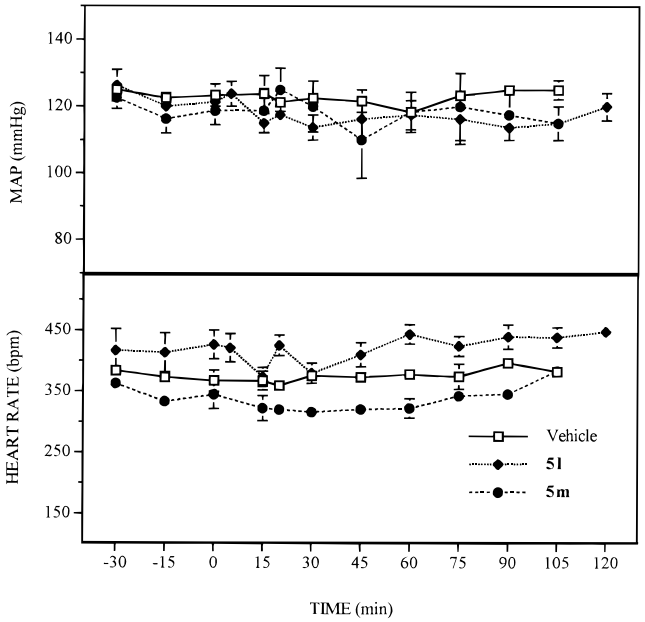


Figure 1. Effect of AKIs (**5l**,**m**) on mean arterial blood pressure (MAP) and heart rate at 10 mg/kg, ip. Data are means ± SEM ($n = 4$).

General behavioral effects observed following administration of the AKIs were qualitatively similar to those previously noted with other AKIs.[1] These include decreased locomotor activity, hypothermia, and muscular flaccidity. These side effects in rats were generally mild at or below the anticonvulsant ED_{50}s and are less pronounced than those observed with equi-effective doses of adenosine receptor agonists.[18] Also, in contrast to adenosine receptor agonists, AKIs (**5l**,**m**) did not cause a decrease in blood pressure or heart rate at doses 10-fold higher than the ED_{50} for inhibition of MES seizures (Figure 1).

Discussion

The present study evaluated the SAR of tubercidin analogues with large hydrophobic substituents at the C4- and C5-positions. The results suggest the possible existence of one or more hydrophobic binding pockets in the enzyme active site. The potent AKI activity exhibited by **1a**−**d** may therefore be attributed to a hydrophobic interaction between the halogen atom (I or Br) and a hydrophobic pocket. Replacement of the C5-halogen atom, however, with a methyl[1] or a phenyl group failed to retain the AKI activity. Whereas, attaching two phenyl rings to a tubercidin molecule resulted in highly potent AKIs (e.g., **5b**, $IC_{50} = 0.0005\ \mu M$). Replacement of the phenyl group on the C4-amino

with cyclohexyl or benzyl led to a significant loss in potency. These results suggest that the aryl group forms a distinct interaction with the AK binding site. Currently, we are evaluating the interactions of various AKIs with the active site using 3D X-ray crystal structure of the human AK−adenosine complex which was recently solved at high resolution.[19]

The potency of non-aryl AKIs is highly dependent on the substituent at the C5′-position. In contrast, the potency of diaryl AKIs is not affected by the nature of the substituent at the C5′-position suggesting that the aryl groups provide a significant proportion of the binding energy. Binding through aromatic hydrophobic interactions may change the orientation of these AKIs relative to that of the natural substrate adenosine or non-aryl AKIs. Under these circumstances the 5′-position of diaryl AKIs may be placed in a position that fails to interact significantly with the active site. Alternatively, it is conceivable that non-aryl- and aryl-substituted AKIs bind to different sites. For example, the non-diaryl AKIs **1a**−**d** could bind to the active site of the enzyme, whereas the diaryl AKIs could bind to the ATP site or to yet another site which may affect the protein conformation and/or the conformation of the active site.

The decreased inhibitory potency of the 2′-deoxy compounds **19** and **22** and the 3′-deoxy compound **23** suggest that hydrogen-bonding interactions by C2′- and C3′-OH groups are important for enzyme inhibition. The poor AKI activity of **19** (IC_{50} = 0.3 μM) also indicates that the presence of a C5′-OH group does not compensate for the lack of C2′-OH, reiterating the relatively insignificant role of the C5′-OH or C5′-NH_2 groups of diaryl AKIs in binding to the enzyme. These observations parallel the previous observation made with adenosine which is a better substrate than its 2′-deoxy and 3′-deoxy derivatives.[17]

Although **5b** showed potent anticonvulsant effect (ED_{50} = 1.1 mg/kg) when administered ip, it was less potent orally (5.5 mg/kg, po), due to poor oral bioavailability (<20%).[16] In addition, pharmacokinetic studies indicated that **5b** had a relatively short half-life (∼1.1 h) in dogs and high hepatic clearance in rats, dogs, and monkeys.[16] The short half-life of **5b** was determined to be due to its rapid metabolism to the corresponding *p*-hydroxy compound **5f** which was cleared as the glucoronate. Consequently, the *p*-fluoro-substituted compound **5d** was shown to have a longer half-life in dogs ($t_{1/2}$ = 4.2 h).[16] Other para-substituted AKIs showed potent anticonvulsant activity (e.g., **5e,i,l**−**m**) and are expected to have longer half-lives due to increased stability toward oxidative metabolism. Some of the potent inhibitors such as **5f**,**h**,**k**,**t**,**u** and **16** exhibited significantly reduced anticonvulsant potency; it could be speculated that this may be due to alteration in the pharmacokinetic characteristics responsible for distribution to the site of action or metabolism resulting in a less potent AKIs or both.

Of the diaryl AKIs tested, the two compounds with the most potent anticonvulsant activity, **5l**,**m**, showed little or no effect on blood pressure or heart rate at doses well above those required for inhibition of MES seizures. These results parallel the previous finding[18] that another active diaryl AKI, compound **5b**, was devoid of hypotensive or bradycardic effects in rats. This hemodynamic neutrality contrasts markedly with the severe effects of adenosine receptor agonists, which exert profound effects on blood pressure and heart rate. For example, the adenosine receptor agonist cyclopentyladenosine reduced blood pressure and heart rate to one-third of its baseline levels at a dose equalling the ED_{50} for inhibition of MES seizures,[18] and other adenosine receptor agonists have been shown to have similar hemodynamic effects.[20,21] The improved side effect profile of diaryl AKIs compared with the agonists is a significant finding and may be attributed to a relatively site- and event-specific increase of adenosine levels within brain tissue undergoing epileptiform activity.[18] It is also notable that certain of these compounds exemplified by **5b** result in less overt toxicity, seen as much higher LD_{50} in rats compared with the non-aryl AKI **1a**.[18] Thus, the discovery of these new AKIs provides an opportunity for clinical development of selected compounds that offer this novel therapeutic approach.

Conclusion

The previous manuscript showed that a combination of groups such as a Br or I at the C5-position and a NH_2, Cl, and SCH_3 at the C4-position was important for potent AK inhibition, whereas the results in this report suggest that two aryl rings, one on the C4-amine function and another at the C5-position of tubercidin, enable potent AKI activity in vitro and in vivo. In contrast to the first series, an NH_2 group at the C5′-position did not increase the inhibitory potency of diaryl AKIs. The results also emphasize that the C2′-OH and C3′-OH are essential for potent AKI activity. Finally, diaryltubercidin-based AKIs are potent anticonvulsant agents which exhibit relatively mild side effects compared to adenosine receptor agonists at equi-effective doses and therefore represent a potential strategy to harness the neuroprotective properties of adenosine receptor activation.

Experimental Section

^{1}H and ^{13}C NMR spectra were obtained using a Varian Gemini-200 spectrophotometer at 200 MHz. NOE experiments were conducted on a Bruker AM-500 spectrophotometer at 500 MHz by NuMega Resonance Labs, Inc., San Diego, CA. The chemical shifts are expressed in δ units with respect to tetramethylsilane (δ 0.00) as an internal standard.The ultra violet absorption spectra were recorded on Perkin-Elmer UV/VIS spectrometer, Lambda 2, and the λ_{max} are cm^{-1} units. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography was performed on silica gel, GHLF 250-μm plates. Silica gel, 230−400 mesh (E. Merck), was used for the column chromatography. Elemental analyses were determined by Robertson Microlit Laboratories, Madison, NJ.

4-*N*-Phenylamino-5-iodo-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3a). A mixture of **2a**[1] (2.5 g, 5.73 mmol), aniline (1.4 g, 15 mmol) and sodium acetate (2.5 g, 18 mmol) taken in ethanol (25 mL) and heated to reflux for 24 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with 0.5 N HCl solution (25 mL). The organic layer was dried ($MgSO_4$), evaporated and the residue was purified by chromatography on a silica gel column (20% ethyl acetate in hexanes) to give **3a** as a colorless glassy solid (2.2 g, 78.5%): ^{1}H NMR (DMSO-d_6) δ 1.25 (d, 3H), 1.35 and 1.55 (2s, 6H), 4.17 (m, 1H), 4.7 (m, 1H), 5.35 (m, 1H),

6.2 (d, $J = 3.7$ Hz, 1H), 7.4 (m, 5H), 7.85 (s, 1H), 8.27 (s, 1H, exchangeable with D_2O), 8.38 (s, 1H).

4-*N*-Benzylamino-5-iodo-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3b). Condensation of benzylamine with **2a** by the procedure described for **3a** gave **3b** as a glassy solid in 83% yield: ^{1}H NMR (DMSO-d_6) δ 1.23 (d, 3H), 1.36 and 1.6 (2s, 6H), 4.2 (m, 1H), 4.65 (m, 1H), 4.8 (d, 2H), 5.32 (m, 1H), 6.18 (d, $J = 3.5$ Hz, 1H, 1′-CH), 7.22 (m, 7H), 8.2 (s, 1H).

4-*N*-(4-Fluorophenyl)amino-5-iodo-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3c). Condensation of 4-fluoroaniline with **2a** by the procedure described for **3a** gave **3c** as a glassy solid in 77% yield: ^{1}H NMR (DMSO-d_6) δ 1.25 (d, 3H), 1.32 and 1.53 (2s, 6H), 4.2 (m, 1H), 4.7 (m, 1H), 5.3 (m, 1H), 6.2 (d, $J = 3.3$ Hz, 1H, 1′-CH), 7.5 (m, 4H), 7.85 (s, 1H), 8.27 (s, 1H, exchangeable with D_2O), 8.39 (s, 1H).

4-*N*-(4-Chlorophenyl)amino-5-iodo-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3d). Condensation of 4-chloroaniline with **2a** by the procedure described for **3a** gave **3d** as a glassy solid in 65% yield: ^{1}H NMR (DMSO-d_6) δ 1.24 (d, 3H), 1.33 and 1.56 (2s, 6H), 4.3 (m, 1H), 4.7 (m, 1H), 5.4 (m, 1H), 6.2 (d, $J = 3.5$ Hz, 1H, 1′-CH), 7.5 (m, 4H), 7.8 (s, 1H), 8.2 (s, 1H, exchangeable with D_2O), 8.4 (s, 1H).

4-*N*-(4-Methoxyphenyl)amino-5-iodo-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3e). Condensation of 4-methoxyaniline with **2a** by the procedure described for **3a** gave **3e** as a glassy solid in 65% yield: ^{1}H NMR (DMSO-d_6) δ 1.26 (d, 3H), 1.32 and 1.53 (2s, 6H), 3.77 (s, 3H), 4.18 (m, 1H), 4.75 (m, 1H), 5.3 (m, 1H), 6.19 (d, $J = 3.06$ Hz, 1H, 1′-CH), 6.97 (d, 2H), 7.6 (d, 2H), 7.81 (s, 1H), 8.1 (s, 1H, exchangeable with D_2O), 8.31 (s, 1H).

4-*N*-(4-Hydroxyphenyl)amino-5-iodo-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3f). Condensation of 4-aminophenol with **2a**[1] by the procedure described for **3a** gave **3f** as a glassy solid in 62% yield: ^{1}H NMR ($CDCl_3$) δ 1.3 (d, 3H), 1.31 and 1.6 (2s, 6H), 4.17 (m, 1H), 4.7 (m, 1H), 5.31 (m, 1H), 6.2 (d, $J = 3.3$ Hz, 1H, 1′-CH), 6.8 (d, 2H), 7.5 (d, 2H), 7.8 (s, 1H), 8.0 (s, 1H, exchangeable with D_2O), 8.3 (s, 1H), 9.3 (s, 1H, exchangeable with D_2O).

4-*N*-Cyclohexylamino-5-iodo-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3g). Condensation of cyclohexylamine with **2a**[1] by the procedure described for **3a** gave **3g** as a glassy solid in 88% yield: ^{1}H NMR (DMSO-d_6) δ 1.65 (m, 19H), 4.17 (m, 2H), 4.7 (m, 1H), 5.35 (m, 1H), 6.15 (d, $J = 3.5$ Hz, 1H, 1′-CH), 6.22 (d, 1H, exchangeable with D_2O), 7.7 (s, 1H), 8.22 (s, 1H).

4-Phenylamino-5-iodo-7-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3h). Condensation of aniline with **2b** by the procedure described for **3a** gave **3h** as a glassy solid in 68% yield: ^{1}H NMR ($CDCl_3$) δ 0.55 (m, 15H), 1.4 and 1.66 (2s, 6H), 3.85 (m, 2H), 4.35 (m, 1H), 5.0 (m, 1H), 5.2 (m, 1H), 6.33 (d, $J = 3.1$ Hz, 1H, 1′-CH),7.4 (m, 5H), 7.85 (s, 1H), 8.27 (s, 1H, exchangeable with D_2O), 8.38 (s, 1H).

4-*N*-(Cyanophenyl)amino-5-iodo-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3i). To a solution of 4-cyanoaniline (450 mg, 4 mmol) in dry DMF (15 mL) was added a 1 M solution of *t*-BuOK in *tert*-butyl alcohol (4 mL) over a period of 10 min. The resulting dark red solution was cooled in an ice bath, treated with **2a** (800 mg, 1.8 mmol) in portions, and stirred at room temperature for 1 h. The reaction mixture was concentrated under high vacuum and the residue was partitioned between brine and ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by chromatography on a silica gel column (5% methanol in methylene chloride) to furnish a solid which was crystallized from ethanol to give **3i** (760 mg, 82%): mp 110−112 °C; ^{1}H NMR (DMSO-d_6) δ 1.28 (d, 3H), 1.3 and 1.55 (2s, 6H), 4.2 (m, 1H, 4′-CH), 4.71 (m, 1H), 5.3 (m, 1H), 6.21 (d, $J = 3.2$ Hz, 1H, 1′-CH), 7.8 (d, 2H), 7.9 (d, 2H), 7.91 (s, 1H), 8.45 (s, 1H), 8.75 (br s, 1H, exchangeable with D_2O).

4-*N*-(3-Pyridyl)amino-5-iodo-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3j). Condensation of 3-aminopyridine with **2a**[1] by the procedure described for **3i** gave **3j** as a glassy solid in 82% yield: ^{1}H NMR (DMSO-d_6) δ, 1.28 (d, 3H), 1.32 and 1.58 (2s, 6H), 4.17 (m, 1H), 4.75 (m, 1H), 5.28 (m, 1H), 6.21 (d, $J = 3.5$ Hz, 1H, 1′-CH), 7.35−8.9 (m, 6H).

4-*N*-Phenylamino-5-iodo-7-(5-deoxy-*β*-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (4a). A solution of **3a** (500 mg, 1 mmol) in 70% TFA (10 mL) was stirred at room temperature for 45 min and concentrated under high vacuum. The residue was coevaporated with water (2 × 10 mL) and ethanol (10 mL), and the resulting semisolid was stirred with aqueous $NaHCO_3$ for 10 min. The solid was collected by filtration, washed with water, dried and crystallized from boiling ethanol to give **4a** as needles (358 mg, 78%): mp 230−233 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (d, 3H), 3.8−4.0 and 4.45 (m, 3H), 5.18 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.14 (d, $J = 5.4$ Hz, 1H, 1′-CH), 7.47 (m, 6H), 8.28 (s, 1H, exchangeable with D_2O), 8.4 (s, 1H). Anal. ($C_{17}H_{17}IN_4O_3$) C, H, N.

4-*N*-Benzylamino-5-iodo-7-(5-deoxy-*β*-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (4b). Compound **3b** was subjected to deprotection by the procedure described for **4a** to give **4b** as a crystalline solid in 63% yield: mp 198−199 °C; ^{1}H NMR (DMSO-d_6) δ 1.28 (d, 3H), 3.9 (m, 1H), 4.4 (m, 2H), 4.8 (d, 2H), 5.1 (d, 1H, exchangeable with D_2O) 5.33 (d, 1H, exchangeable with D_2O), 6.0 (d, $J = 5.5$ Hz, 1H, 1′-CH), 6.8−7.4 (m, 6H), 7.65 (s, 1H), 8.18 (s, 1H). Anal. ($C_{18}H_{19}IN_4O_3$) C, H, N.

4-*N*-(4-Fluorophenyl)amino-5-iodo-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (4c). Compound **3c** was subjected to deprotection by the procedure described for **4a** to give **4c** as a crystalline solid in 69% yield: mp 190−192 °C; ^{1}H NMR (DMSO-d_6) δ 1.29 (d, 3H), 3.86 (m, 1H), 4.42 (m, 2H), 5.2 and 5.43 (2d, 2H, exchangeable with D_2O), 6.15 (d, $J = 5.6$ Hz, 1H, 1′-CH), 7.35−7.9 (m, 5H), 8.35 (s, 1H, exchangeable with D_2O), 8.38 (s, 1H). Anal. ($C_{17}H_{16}FIN_4O_3$) C, H, N.

4-*N*-(4-Chlorophenyl)amino-5-iodo-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (4d). Compound **3d** was subjected to deprotection by the procedure described for **4a** to give **4d** as a crystalline solid in 75% yield: mp 201−202 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (d, 3H), 3.9 (m, 1H), 4.42 (m, 2H), 5.15 and 5.4 (2d, 2H, exchangeable with D_2O), 6.1 (d, $J = 5.8$ Hz, 1H, 1′-CH), 7.4−7.9 (m, 5H), 8.32 (s, 1H, exchangeable with D_2O), 8.4 (s, 1H). Anal. ($C_{17}H_{16}ClIN_4O_3 \cdot 0.33H_2O$) C, H, N.

4-*N*-(4-Methoxyphenyl)amino-5-iodo-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (4e). Compound **3e** was subjected to deprotection by the procedure described for **4a** to give **4e** as microplates in 70% yield: mp 190−192 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (d, 3H), 3.8 (s, 3H), 3.95 (m, 1H), 4.42 (m, 2H), 5.15 (d, 1H, exchangeable with D_2O), 5.38 (d, 1H, exchangeable with D_2O), 6.1 (d, $J = 5.7$ Hz, 1H, 1′-CH), 7.0 and 7.65 (2d, 4H), 7.8 (s, 1H), 8.1 (s, 1H, exchangeable with D_2O), 8.3 (s, 1H). Anal. ($C_{18}H_{19}IN_4O_4$) C, H, N.

4-*N*-(4-Hydroxyphenyl)amino-5-iodo-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (4f). Compound **3f** was subjected to deprotection by the procedure described for **4a** to give **4f** as a crystalline solid in 73% yield: mp 233−235 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (d, 3H), 3.9 (m, 1H), 4.45 (m, 2H), 5.15 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.08 (d, $J = 5.5$ Hz, 1H, 1′-CH), 6.8 (d, 2H), 7.5 (d, 2H), 7.78 (s, 1H, 6-CH), 8.0 (s, 1H, exchangeable with D_2O), 8.29 (s, 1H), 9.3 (s, 1H, exchangeable with D_2O). Anal. ($C_{17}H_{17}IN_4O_4$) C, H, N.

4-*N*-Cyclohexylamino-5-iodo-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (4g). Compound **3g** was subjected to deprotection by the procedure described for **4a** to give **4g** as crystalline solid in 68% yield: mp 161−164 °C; ^{1}H NMR (DMSO-d_6) δ 1.65 (m, 13H), 3.65 (m, 4H), 5.1 (1d, 1H, exchangeable with D_2O), 5.35 (1d, 1H, exchangeable with D_2O),

6.0 (d, $J = 5.5$ Hz, 1H, 1′-CH), 6.2 (d, 1H, exchangeable with D_2O), 7.62 (s, 1H), 8.2 (s, 1H). Anal. ($C_{17}H_{23}IN_4O_3 \cdot 0.5H_2O$) C, H, N.

4-*N*-(Cyanoyphenyl)amino-5-iodo-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (4h). Compound **3i** was subjected to deprotection by the procedure described for **4a** to give **4h** as a crystalline solid in 65% yield: mp 259−261 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (d, 3H), 3.95 (m, 2H), 4.50 (m, 1H), 5.18 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.11 (d, $J = 5.8$ Hz, 1H, 1′-CH), 6.8 (d, 2H), 7.8−8.0 (m, 5H), 8.5 (s, 1H), 8.75 (s, 1H, exchangeable with D_2O).

4-*N*-Phenylamino-5-iodo-7-*β*-D-ribofuranosylpyrrolo-[2,3-*d*]pyrimidine (4i). Compound **3h** was subjected to deprotection by the procedure described for **4a** to give **4i** as needles in 62% yield: mp 224−225 °C; ^{1}H NMR (DMSO-d_6) δ 3.62 (m, 2H), 3.95 (m, 3H), 5.1−5.5 (m, 3H, exchangeable with D_2O), 6.12 (d, $J = 5.8$ H, 1H, 1′-CH), 7.05−7.9 (m, 6H), 8.28 (br s, 1H, exchangeable with D_2O), 8.39 (s, 1H). Anal. ($C_{17}H_{17}IN_4O_4$) C, H, N.

4-*N*-Phenylamino-7-*β*-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine (4j). Compound **4i** (460 mg, 1 mmol) was dissolved in methanol (50 mL) and purged with argon. To the solution was added 10% Pd/C (50 mg) and subjected to hydrogenation under 20 psi of H_2 for 12 h. The reaction mixture was filtered through a Celite pad and the filtrate was evaporated to dryness. The residue was crystallized from ethanol to obtain **4j** as microcrystals (250 mg, 75%): mp 145−146 °C; ^{1}H NMR (DMSO-d_6) δ 3.68 (m, 2H), 4.0 (m, 3H), 5.1−5.5 (m, 3H, exchangeable with D_2O), 6.2 (d, $J = 5.6$ H, 1H, 1′-CH), 6.95−7.9 (m, 7H), 7.9 (br s, 1H, exchangeable with D_2O), 8.39 (s, 1H). Anal. ($C_{17}H_{18}N_4O_4$) C, H, N.

4-Amino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo-[2,3-*d*]pyrimidine (5a). To a solution of 4-amino-5-iodo-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine[1] (**1b**; 376 mg, 1 mmol), and tetrakis(triphenylphosphine)palladium (115 mg, 0.1 mmol) in diglyme (25 mL) were added a saturated solution of Na_2CO_3 (4 mL) and a solution of phenylboronic acid (488 mg, 4 mmol) in ethanol (7 mL). The resulting heterogeneous mixture was heated at 100 °C for 4 h. The reaction mixture was cooled, filtered through a Celite pad and the Celite pad was washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was purified by chromatography on a silica gel column (10% methanol in methylene chloride) to give **5a** as solid microplates (255 mg, 78%): mp 106−109 °C; ^{1}H NMR (DMSO-d_6) δ 1.29 (d, 3H), 3.95 (m, 2H), 4.5 (m, 1H), 5.1 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.15 (d, $J = 6.2$ Hz, 1H, 1′-CH), 5.8−6.3 (br s, 2H, exchangeable with D_2O), 7.55 (m, 6H), 8.18 (s, 1H). Anal. ($C_{17}H_{18}N_4O_3 \cdot H_2O$) C, H, N.

4-*N*-Phenylamino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5b). Compound **4a** was reacted with phenylboronic acid by the procedure described for **5a** to give **5b** as a crystalline solid in 70% yield: 207−208 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (d, 3H), 3.93 (m, 2H), 5.03 (m, 1H), 5.1 (d, 1H, exchangeable with D_2O), 5.45 (d, 1H, exchangeable with D_2O), 6.18 (d, $J = 6.9$ Hz, 1H, 1′-CH), 6.95−7.7 (m, 6H), 8.42 (s, 1H). Anal. ($C_{23}H_{22}N_4O_3$) C, H, N.

4-*N*-Benzylamino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5c). Compound **4b** was reacted with phenylboronic acid by the procedure described for **5a** to give **5c** as crystalline solid in 63% yield: mp 139−141 °C; ^{1}H NMR (DMSO-d_6) δ 1.25 (d, 3H), 3.93 (m, 2H), 4.5 (m, 1H), 4.71 (d, 2H), 5.1 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.07 (d, $J = 6.7$ Hz, 1H, 1′-CH), 5.95 (t, 1H, exchangeable with D_2O), 6.12 (d, 1H, $J = 6.3$ Hz, 1′-CH), 7.2−7.6 (m, 11H), 8.22 (s, 1H). Anal. ($C_{24}H_{24}N_4O_3$) C, H, N.

4-*N*-(4-Methoxyphenyl)amino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5e). Compound **4e** was reacted with phenylboronic acid by the procedure described for **5a** to give **5e** as needles in 59% yield:162−165 °C; ^{1}H NMR (DMSO-d_6) δ 1.31 (d, 3H), 3.72 (s, 3H), 3.95 (m, 1H), 4.49 (m, 2H), 5.12 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.17(d, $J = 5.6$ Hz, 1H, 1′-CH), 7.42 (m, 10H), 8.41 (s, 1H). Anal. ($C_{24}H_{24}N_4O_4$) C, H, N.

4-*N*-(4-Hydroxyphenyl)amino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5f). Compound **3f** was reacted with phenylboronic acid by the procedure described for **5a** to give 4-*N*-(4-hydroxyphenyl)amino-5-phenyl-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine as a glassy solid: ^{1}H NMR (DMSO-d_6) δ 1.3 (d, 3H), 1.32 and 1.57 (2s, 6H), 4.19 (m, 1H), 4.75 (m, 1H), 5.38 (m, 1H), 6.28 (d, $J = 3.1$ Hz, 1H, 1′-CH), 7.2 (m, 11H), 8.35 (s, 2-CH), 9.21 (s, 1H, exchangeable with D_2O). This intermediate was subjected to TFA catalyzed deprotection as described for **4a** to give **5f** as a crystalline solid in an overall 55% from **2a**: 188−189 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (d, 3H), 4.25 (m, 3H), 5.1 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.18 (d, $J = 6.0$ Hz, 1H, 1′-CH), 7.2 (m, 11H), 8.31 (s, 1H), 9.2 (s, 1H, exchangeable with D_2O). Anal. ($C_{23}H_{22}N_4O_4$) C, H, N.

4-*N*-Cyclohexylamino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5g). Compound **3g** was reacted with phenylboronic acid by the procedure described for **5a** to give 4-*N*-cyclohexylamino-5-phenyl-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine as a glassy solid in 85% yield: ^{1}H NMR (DMSO-d_6) δ 1.27 (d, 3H), 1.31 and 1.6 (2s, 6H), 1.51 (m, 10H), 4.12 (m, 2H), 4.75 (m, 1H), 5.15 (d, 1H, exchangeable with D_2O), 5.35 (m, 1H), 6.23 (d, $J = 3.4$ Hz, 1H, 1′-CH), 7.55 (m, 6H), 8.28 (s, 1H). This intermediate was subjected to TFA catalyzed deprotection by the procedure described for **4a** to give **5g** as needles in 68% yield: mp 156−158 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (d, 3H), 1.55 (m, 10H), 4.23 (m, 4H), 5.23 (m, 3H, exchangeable with D_2O), 6.1 (d, $J = 6.5$ Hz, 1H, 1′-CH), 7.5 (m, 6H), 8.22 (s, 1H). Anal. ($C_{23}H_{28}N_4O_3 \cdot 0.5H_2O$) C, H, N.

4-*N*-Phenylamino-5-phenyl-7-*β*-D-ribofuranosylpyrrolo-[2,3-*d*]pyrimidine (5h). Compound **4h** was reacted with phenylboronic acid by the procedure described for **5a** to give **5h** as microplates in 58% yield: mp 228−229 °C; ^{1}H NMR (DMSO-d_6) δ 3.58 (m, 2H), 4.25 (m, 3H), 5.25 (m, 3H, exchangeable with D_2O), 6.19 (d, $J = 6.2$ Hz, 1H, 1′-CH), 7.35 (m, 11H), 7.7 (s, 1H), 8.4 (s, 1H). Anal. ($C_{23}H_{22}N_4O_4$) C, H, N.

4-*N*-(4-Fluorophenyl)amino-5-(4-fluorophenyl)-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5i). Compound **4c** was reacted with 4-fluorophenylboronic acid by the procedure described for **5a** to give **5i** as a crystalline solid in 62% yield: mp 204−205 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (d, 3H), 3.9 (m, 2H), 4.5 (m, 1H), 5.15 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.2 (d, $J = 5.7$ Hz, 1H, 1′-CH), 7.15 (t, 2H), 7.35 (t, 2H), 7.65 (m, 6H), 8.4 (s, 1H). Anal. ($C_{23}H_{20}F_2N_4O_3$) C, H, N.

4-*N*-Phenylamino-5-(4-chlorophenyl)-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5j). Compound **4a** was reacted with 4-chlorophenylboronic acid by the procedure described for **5a** to give **5j** as a crystalline solid in 58% yield: mp 235−236 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (d, 3H), 4.22 (m, 3H), 5.17 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.17 (d, $J = 5.6$ Hz, 1H, 1′-CH), 7.35 (m, 11H), 8.3 (s, 1H). Anal. ($C_{23}H_{21}ClN_4O_3$) C, H, N.

4-*N*-(4-Chlorophenyl)amino-5-(4-chlorophenyl)-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5k). Compound **4d** was reacted with 4-chlorophenylboronic acid by the procedure described for **5a** to give **5k** as needles in 50% yield: mp 199−201 °C; ^{1}H NMR (DMSO-d_6) δ 1.31 (d, 3H), 4.22 (m, 3H), 5.15 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.18 (d, $J = 5.9$ Hz, 1H, 1′-CH), 7.55 (m, 9H), 8.0 (br s, 1H, exchangeable with D_2O), 8.4 (s, 1H). Anal. ($C_{23}H_{20}Cl_2N_4O_3$) C, H, N.

4-*N*-(4-Cyanophenyl)amino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5l). Compound **4h** was reacted with phenylboronic acid by the procedure described for **5a** to give **5l** as a crystalline solid in 52% yield: mp 194−196 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (d, 3H), 4.55 (m, 1H), 4.95 (m, 2H), 5.2 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.2 (d, $J = 6.1$ Hz, 1H, 1′-CH),

7.4−7.9 (m, 9H), 8.3 (br s, 1H, exchangeable with D_2O), 8.51 (s, 1H). Anal. ($C_{24}H_{21}N_5O_3$) C, H, N.

4-*N*-(4-Cyanophenyl)amino-5-(4-methoxyphenyl)-7-(5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5m). Compound **4h** was reacted with 4-methoxyphenylboronic acid by the procedure described for **5a** to give **5m** as a crystalline solid in 50% yield: mp 207−210 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (d, 3H), 3.85 (s, 3H), 4.55 (m, 1H), 4.95 (m, 2H), 5.18 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.2 (d, J = 5.9 Hz, 1H, 1′-CH), 7.1−7.8 (m, 9H), 8.2 (br s, 1H, exchangeable with D_2O), 8.5 (s, 1H). Anal. ($C_{25}H_{23}N_5O_4$) C, H, N.

4-*N*-Phenylamino-5-(2-furanyl)-7-(5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5n). Compound **4a** was reacted with furan-2-boronic acid by the procedure described for **5a** to give **5n** as needles in 53% yield: mp 214−216 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (d, 3H), 3.95(m, 2H), 4.55 (m, 1H), 5.18 (d, 1H, exchangeable with D_2O), 5.42 (d, 1H, exchangeable with D_2O), 6.19 (d, J = 6.0 Hz, 1H, 1′-CH), 6.8 (dd, 1H), 7.46 (m, 5H), 8.0 (s, 1H), 8.05 (2d, 2H), 8.41 (s, 1H), 9.0 (s, 1H, exchangeable with D_2O). Anal. ($C_{21}H_{20}N_4O_4$) C, H, N.

4-*N*-(4-Methoxyphenyl)amino-5-(2-furanyl)-7-(5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5o). Compound **4e** was reacted with furan-2boronic acid by the procedure described for **5a** to give **5o** as a crystalline solid in 59% yield: mp 222−224 °C; ^{1}H NMR (DMSO-d_6) δ 1.34 (d, 3H), 3.79 (s, 3H), 3.97 (m, 1H), 4.47 (m, 2H), 5.18 (d, 1H, exchangeable with D_2O), 5.42 (d, 1H, exchangeable with D_2O), 6.15 (d, J = 5.7 Hz, 1H, 1′-CH), 6.7 (dd, 1H), 6.95 (d, 1H), 8.0 (d, 1H), 7.4 (m, 5H), 8.35 (s, 1H), 8.8 (s, 1H, exchangeable with D_2O). Anal. ($C_{22}H_{22}N_4O_5$) C, H, N.

4-*N*-(3-Pyridyl)amino-5-phenyl-7-(5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5p). Compound **3j** was reacted with phenylboronic acid by the procedure described for **5a** to give 4-*N*-(3-pyridyl)amino-5-phenyl-7-(2,3-*O*-isopropylidene-5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine intermediate as a glassy solid in 88% yield: ^{1}H NMR (DMSO-d_6) δ 1.3 (d, 3H), 1.35 and 1.58 (2s, 6H), 4.31 (m, 1H), 4.78 (m, 1H), 5.40 (m, 1H), 6.31 (d, J = 3.4 Hz, 1H, 1′-CH), 8.0 (m, 11H). This material was subjected to TFA catalyzed deprotection to give **5p** as crystalline microplates in 70% yield: mp 211−212 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (d, 3H), 3.95 (m, 1H), 4.52 (m, 2H), 5.12 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.2 (d, J = 5.9 Hz, 1H, 1′-CH), 7.25−8.7 (m, 11H). Anal. ($C_{22}H_{21}N_5O_5 \cdot 0.25H_2O$) C, H, N.

4-*N*-Phenylamino-5-phenylpyrrolo[2,3-*d*]pyrimidine (10a). A mixture of 2-amino-4-phenylpyrrole-3-carbonitrile (18.3 g, 0.1 mol),[7] triethyl orthoformate (50 mL, 0.3 mol) and *p*-toluenesulfonic acid (75 mg) in dry THF (100 mL) was heated to reflux for 30 min. The solvent was evaporated under reduced pressure and the residue kept under high vacuum to give 2-ethoxymethyleneimino-4-phenylpyrrole-3-carbonitrile (**8a**)[6] as a dark solid: ^{1}H NMR (DMSO-d_6) δ 1.25−1.4 (t, 3H), 4.3 (q, 2H), 7.37 (m, 6H), 8.38 (s, 1H), 11.8 (br d, 1H, exchangeable with D_2O). A mixture of this intermediate and aniline (15 g, 0.16 mol) was dissolved in dry DMF (100 mL) and refluxed for 45 min. To the reaction mixture water (150 mL) was added carefully through the condenser and refluxed for 8 h. Upon cooling, a solid formed in the reaction mixture which was collected by filtration, washed with water and dried in air. The crude material was decolorized and crystallized from ethyl acetate to give **10a** as needles (18.5 g, 65%): mp 240−243 °C; ^{1}H NMR (DMSO-d_6) δ 7.3 (m, 12H), 8.36 (s, 1H), 11.5 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ 100.10, 114.15, 118.44, 120.58, 121.23, 125.97, 127.67, 128.00, 133.86, 138.50, 149.96, 150.46, 152.49.

4-*N*-(4-Chlorophenyl)amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (10b). Condensation of 4-chloroaniline with **8a** by the procedure described for **10a** gave **10b** as off-white solid in 62% yield: mp 248−250 °C; ^{1}H NMR (DMSO-d_6) δ 7.0−7.75 (m, 11H), 8.38 (s, 1H), 11.5 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ 101.82, 117.05, 117.44, 117.80, 123.33, 123.45, 123.58, 128.55, 129.61, 129.89, 135.44, 137.68, 138.01, 151.14, 152.38, 156.06, 159.10, 162.35.

4-*N*-(4-Fluorophenyl)amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (10c). Condensation of 4-fluoroaniline with **8a** by the procedure described for **10a** gave **10c** as a light pink solid in 66% yield: mp 231−233 °C; ^{1}H NMR (DMSO-d_6) δ 7.0−7.7 (m, 11H), 8.35 (s, 1H), 12.1 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ 102.62, 116.55, 116.94, 117.00, 123.19, 123.29, 123.34, 128.48, 130.31, 130.50, 135.52, 137.51, 137.58, 152.545, 153.18, 155.16, 158.90, 161.65.

4-*N*-(4-Methylphenyl)amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (10d). Condensation of *p*-toluidine with **8a** by the procedure described for **10a** gave **10d** as an off-white solid in 68% yield: mp 180−182 °C; ^{1}H NMR (DMSO-d_6) δ 2.2 (s, 3H), 7.35 (m, 11H), 8.33 (s, 1H), 11.2 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ 24.82, 101.10, 113.10, 117.84, 120.73, 121.57, 126.08, 127.67, 128.15, 134.26, 138.60, 148.99, 150.55, 154.49.

2-Methyl-4-*N*-phenylamino-5-phenylpyrrolo[2,3-*d*]pyrimidine (10e). A mixture of 2-amino-4-phenylpyrrole-3-carbonitrile (9.15 g, 0.05 mol), triethyl orthoacetate (25 mL, 135 mmol) and *p*-toluenesulfonic acid (75 mg) in dry THF (100 mL) was heated to reflux for 30 min. Volatiles were removed under reduced pressure and the residue kept under high vacuum to give 2-ethoxymethylmethyleneimino-4-phenylpyrrole-3-carbonitrile (**8b**) as a dark solid: ^{1}H NMR (DMSO-d_6) δ 1.32 (t, 3H), 4.26 (q, 2H), 7.06 (d, 1H), 7.2−7.7 (m, 6H), 11.43 (br.d, 1H, exchangeable with D_2O). This intermediate was condensed with aniline (7.5 g, 0.16 mol) by the procedure described for **10a** to give **10e** as an off-white solid (6.5 g, 43%): mp >240 °C; ^{1}H NMR (DMSO-d_6) δ 2.54 (s, 3H), 6.9−7.7 (m, 11H), 11.89 (br.s, 1H, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ 24.52, 97.82, 113.98, 118.05, 119.73, 120.95, 125.88, 127.62, 127.67, 128.00, 134.06, 138.76, 151.43, 152.25, 158.47.

6-Bromo-4-*N*-phenylamino-5-phenylpyrrolo[2,3-*d*]pyrimidine (10f). To a stirred solution of **10a** (10.0 g, 35 mmol) in dry DMF (200 mL) was added *N*-bromosuccinimide (6.7 g, 41 mmol) in portions over 10 min. After 30 min the solid was collected by filtration and washed with DMF (10 mL). The combined filtrate and washings were evaporated under reduced pressure, and the residue stirred with water (50 mL) to give a second crop, which was collected by filtration and washed with water. The two crops were combined, stirred in hot ethanol (75 mL) for 10 min and cooled to room temperature. The resulting pale yellow solid was collected by filtration, washed with cold ethanol and dried under vacuum to give **10f** as an off-white solid (12.27 g, 96%): mp 245−249 °C; ^{1}H NMR (DMSO-d_6) δ 6.9−7.7 (m, 10H) 8.33 (s, 1H), 12.9 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ 102.58, 107.03, 113.93, 119.41, 122.64, 128.30, 128.88, 129.15, 120.37, 132.79, 139.16, 140.90, 151.38, 152.38.

5-Deoxy-2,3-*O*-isopropylidene-α-D-ribofuranosyl Chloride (12a). A 100-mL three-neck flask was charged with a solution of 5-deoxy-2,3-*O*-isopropylidene-D-ribofuranose (**11a**[1]; 5.3 g, 30.5 mmol), carbon tetrachloride (3.4 mL, 35.3 mmol) and toluene (60 mL). The contents were cooled to ca. −15 °C in a dry ice acetone bath. A 85% solution of hexamethylphosphorus triamide (6.6 mL, 34.7 mmol) was added dropwise maintaining the internal temperature between −10 and −5 °C over a period of 20 min. After stirring the reaction mixture for an additional 20 min at ca. −5 °C, the pale yellow solution was transferred to a 125 mL separatory funnel, washed with ice-cold brine (100 mL) and the organic layer was dried ($MgSO_4$). A small aliquot was pulled out and evaporated to make a sample for ^{1}H NMR spectrum: ^{1}H NMR ($CDCl_3$) δ 1.29 (d, 3H), 1.31 and 1.65 (2s, 6H), 4.37 (m, 1H), 4.80 (m, 2H) and 6.15 (d, J = 3.8 Hz, 1H, 1-CH). The presence of the β-chloro isomer was determined by the singlet at 6.1 ppm which is consistent with our earlier observation for the β-chloro sugar.[1] The approximate ratio of the α/β-chloro sugars was determined by comparison of signal integrations for the anomeric protons and found to be 95:5. This material was used immediately in the glycosylation experiment.

5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-α-D-ribofuranosyl Chloride (12b). Chlorination of 5-*O*-*tert*-

butyldimethylsilyl-2,3-*O*-isopropylidene-α-D-ribofuranose (**11b**) was carried out by the procedure described for **12a**. ^{1}H NMR of this material was identical to the one obtained by Wilcox's procedure.[18] The presence of *β*-chloro isomer was confirmed by the singlet at 6.15 ppm, which is consistent with our earlier observation.[1] The approximate ratio of the α/*β*-chloro sugars was determined by comparison of signal integrations for the anomeric protons and found to be 85:15. This mixture of chloro sugars was used immediately in the following glycosylation experiment.

4-*N*-Phenylamino-5-phenyl-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (13a). Glycosylation of 10a by the Sodium Salt Method. To an ice-cold solution of **10a** (2.86 g, 10 mmol) in dry acetonitrile (50 mL) was added NaH (80% dispersion in oil, 0.33 g, 11 mmol) in small portions, and stirred for 30 min. A solution of **12a** (prepared from 6.1 g of **11a**, 20 mmol) prepared by the original procedure[1] was cannulated into the reaction mixture and stirred overnight at room temperature. The reaction was concentrated under reduced pressure to give a residue, which was stirred with ethyl acetate (50 mL) and filtered. The filtrate was evaporated, and the crude product was purified by chromatography on silica gel (25% ethyl acetate in hexanes) to provide **13a** as a glassy product (1.5 g, 35%): ^{1}H NMR (DMSO-d_6) δ 1.28 (d, 3H), 1.3 and 1.6 (2s, 6H), 4.22 (m, 1H), 4.8 (m, 1H), 5.4 (m, 1H), 6.3 (d, J = 2.9 Hz, 1H, 1′-CH), 7.42 (m, 12H), 8.4 (s, 1H); UV (methanol) nm^{-1} λ_{max} 290 (ϵ 18300), λ_{min} 258 (ϵ 2300).

Further elution of the column provided **14** (850 mg, 20%) which was isolated as a yellow glassy solid: ^{1}H NMR (DMSO-d_6) δ 1.26 (d, 3H), 1.32 (s, 3H), 1.54 (s, 3H), 4.32 (m, 1H), 4.90 (m, 1H), 5.55 (m, 1H), 6.41 (s, 1H, J = 5.7 Hz 1′-CH), 7.4 (m, 12H), 8.66 (s, 1H); UV (methanol) nm^{-1} λ_{max} 304 (ϵ 17600), λ_{min} 275 (ϵ 2100).

Continued elution provided **15** (635, 15%) as a glassy solid: ^{1}H NMR (DMSO-d_6) δ 1.28 (d, 3H), 1.15 (s, 3H), 1.25 (s, 3H), 4.55 (m, 1H), 4.76 (m, 1H), 6.70 (d, J = 7.4 Hz, 1H), 7.42 (m, 12H), 8.4 (s, 1H); UV (methanol) nm^{-1} λ_{max} 292 (ϵ 18500), λ_{min} 256 (ϵ 1900).

4-*N*-Phenylamino-5-phenyl-7-(5-deoxy-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (13a). Glycosylation of 10a by Phase-Transfer Catalysis Method (TDA-1 Method). To a well-stirred mixture of **10a** (2.86 g, 10 mmol), powdered KOH (1.2 g, 20 mmol) and TDA-1 (3.3 mL, 10 mmol) in toluene (40 mL) was added the chloro sugar **12a** (prepared from **11a**, 3.5 g, 20 mmol). After stirring the reaction mixture at room temperature overnight, the dark solution was transferred to a separatory funnel and washed successively with water, 0.5 N HCl solution (10 mL) and again with water. The organic layer was separated and concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column (20% ethyl acetate in hexane) to provide **13a** as a glassy solid (2.9 g, 65%). Further elution provided **14** (320 mg, 6.7%).

4-*N*-Phenylamino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5b). Deprotection of **13a** by the procedure described for **4a** gave **5b** which was identical by TLC, melting point, and ^{1}H NMR to the one prepared from **4a** via Suzuki reaction.

4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5d). Glycosylation of **10c** with **12a** by the TDA-1 method gave **13c** in 66% yield as a glassy solid: ^{1}H NMR (DMSO-d_6) δ 1.28 (d, 3H), 1.3 and 1.6 (2s, 6H), 4.21 (m, 1H), 4.8 (m, 1H), 5.4 (m, 1H), 6.3 (d, J = 3.2 Hz, 1H), 7.43 (m, 11H), 8.4 (s, 1H). TFA-catalyzed deprotection of **13c** by the procedure described for **4a** followed by crystallization from boiling ethanol gave **5d** in 68% yield which was identical by TLC, melting point, and ^{1}H NMR to the one obtained from **4c** via Suzuki reaction.

4-*N*-Phenylamino-5-phenyl-7-*β*-D-ribofuranosylpyrrolo-[2,3-*d*]pyrimidine (5h). Glycosylation of **10a** with **12b** using the TDA-1 method gave **13g** in 62% yield as a foam: ^{1}H NMR ($CDCl_3$) δ 0.55 (m, 15H), 1.4 and 1.66 (2s, 6H), 3.85 (m, 2H), 4.35 (m, 1H), 5.0 (m, 1H), 5.2 (m, 1H), 6.43 (d, J = 3.1 Hz, 1H, 1′-CH), 7.25 (m, 12H), 8.52 (s, 1H). This intermediate was subjected to TFA-catalyzed deprotection followed by crystallization from boiling ethanol to give **5h** in 58% yield which was identical by TLC, melting point, and ^{1}H NMR to the one obtained from **4h** via Suzuki reaction.

4-*N*-(4-Chlorophenyl)amino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5q). Glycosylation of **10b** with **12a** by the TDA-1 method gave **13b** in 63% yield as a glassy solid: ^{1}H NMR ($CDCl_3$) δ 1.4 (d, 3H), 1.38 and 1.6 (2s, 6H), 4.28 (m, 1H), 4.65 (m, 1H), 5.3 (m, 1H), 6.25 (d, J = 3.4 Hz, 1H, 1′-CH), 6.9−7.55 (m, 12H), 8.5 (s, 1H). TFA-catalyzed deprotection of this intermediate gave a semisolid that was crystallized from boiling ethanol to furnish **5q** as a crystalline solid in 68% yield: mp 176−178 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (d, 3H), 4.25 (m, 3H), 5.17 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.2 (d, J = 5.7 Hz, 1H, 1′-CH), 7.25−7.8 (m, 10H), 8.41 (s, 1H). Anal. ($C_{23}H_{21}ClN_4O_3$) C, H, N.

4-*N*-(4-Methylphenyl)amino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5r). Glycosylation of **10d** with **12a** by the TDA-1 method gave **13d** in 68% yield as a glassy solid: ^{1}H NMR (DMSO-d_6) δ 1.3 (d, 3H), 1.33 and 1.56 (2s, 6H), 2.26 (s, 3H), 4.2 (m, 1H), 4.75 (m, 1H), 5.40 (m, 1H), 6.29 (d, J = 3.0 Hz, 1H, 1′-CH), 7.35 (m, 11H), 8.41 (s, 1H). This intermediate was subjected to TFA-catalyzed deprotection and the resulting crude product crystallized from ethanol to give **5r** as needles in 68% yield: mp 180−182 °C; ^{1}H NMR (DMSO-d_6) δ 1.31 (d, 3H), 2.29 (s, 3H), 3.91 (m, 1H), 4.55 (m, 2H), 5.15 (d, 1H, exchangeable with D_2O), 5.4 (d, 1H, exchangeable with D_2O), 6.17 (d, J = 5.8 Hz, 1H, 1′-CH), 7.35 (m, 11H), 8.4 (s, 1H). Anal. ($C_{24}H_{24}N_4O_3$) C, H, N.

2-Methyl-4-*N*-phenylamino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5s). Glycosylation of **10e** with **12a** by the TDA-1 method gave **13e** as a glassy solid in 58% yield: ^{1}H NMR ($CDCl_3$) δ 1.29 (d, 3H), 1.38 and 1.68 (2s, 6H), 2.56 (s, 3H,), 4.2 (m, 1H), 4.75 (m, 1H), 5.40 (m, 1H), 6.29 (d, J = 3.0 Hz, 1H, 1′-CH), 6.9−7.7 (m, 11H). This intermediate was subjected to deprotection by the procedure described for **4a** and the resulting crude product crystallized from ethanol to give **5s** as needles in 58% yield: 194−196 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (d, 3H), 2.57 (s, 3H), 3.94 (m, 2H), 4.53 (m, 1H), 5.15 (d, 1H, exchangeable with D_2O), 5.37 (d, 1H, exchangeable with D_2O), 6.19 (d, J = 5.4 Hz, 1H, 1′-CH), 7.25 (m, 12H). Anal. ($C_{24}H_{24}N_4O_3$) C, H, N.

6-Bromo-4-*N*-phenylamino-5-phenyl-7-(5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5t). The heterocycle **10f** was coupled to **12a** by the TDA-1 method gave **13f** in 62% yield as a glassy solid: ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 3H), 1.35 and 1.57 (2s, 6H), 4.20 (m, 1H), 4.91 (m, 1H), 5.71 (m, 1H), 6.3 (d, J = 2.5 Hz, 1H, 1′-CH), 7.35 (m, 12H), 8.48 (s, 1H). This intermediate was subjected to deprotection by the procedure described for **4a** to give **5t** as a crystalline solid in 72% yield: mp 168−169 °C; ^{1}H NMR (DMSO-d_6) δ 1.34 (d, 3H), 3.9 (m, 1H), 4.21 (m, 1H), 5.1−5.4 (m, 3H), 6.06 (d, J = 4.48 Hz, 1H, 1′-CH), 7.3 (m, 12H), 8.45 (s, 1H). Anal. ($C_{23}H_{21}BrN_4O_3$) C, H, N.

4-*N*-Phenylamino-5-phenyl-7-(5-azido-5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5u). Glycosylation of **10a** using 5-azido-5-deoxy-2,3-*O*-isopropylidene-α-D-ribofuranosyl chloride, **12c,**[1] by the TDA-1 method gave **13h** in 58% yield as a glassy solid: ^{1}H NMR (DMSO-d_6) δ 1.33 and 1.55 (2s, 6H), 3.67 (d, 2H), 4.27 (m, 1H), 5.00 (m, 1H), 5.40 (m, 1H), 6.29 (d, J = 2.8 Hz, 1H, 1′-CH), 7.05−7.9 (m, 11H), 8.31 (s, 1H, exchangeable with D_2O), 8.38 (s, 1H). This material was deprotected by the procedure described for **4a** to give **5u** as needles in 58% yield: mp 108−109 °C dec;^{1}H NMR (DMSO-d_6) δ 3.65 (m, 2H), 4.10 (m, 1H), 4.57 (m, 2H), 5.35 (d, 1H, exchangeable with D_2O), 5.6 (d, 1H, exchangeable with D_2O), 6.29 (d, J = 5.86 Hz, 1H, 1′-CH), 7.35 (m, 12H), 8.42 (s, 1H). Anal. ($C_{23}H_{21}N_7O_3$) C, H, N.

4-*N*-Phenylamino-5-phenyl-7-(5-amino-5-deoxy-*β*-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (16). A solution of **5u** (24 mg, 0.05 mmol) in ethanol (5 mL) was purged with N_2, treated with 10% Pd on C (25 mg) and hydrogenated under 1

atm of H_2. The catalyst was removed by filtration through a Celite pad and the pad was washed with ethanol. The combined filtrate and washings were filtered through a 0.45-μm membrane. The filtrate was evaporated to dryness and the residue dried under high vacuum at 60 °C to give **16** as an amorphous solid (18 mg, 80%): mp 150−153 °C; ^{1}H NMR (DMSO-d_6) δ 2.9−3.1 (m, 2H), 3.1−3.8 (br s, 2H, exchangeable with D_2O), 3.9−4.22 and 4.5−4.65 (3m, 3H), 5.1−5.6 (2 br s, 2H, exchangeable with D_2O), 6.2 (d, 1H, J = 6.1 Hz, 1′-CH), 6.95−7.7 (m, 12H), 8.42 (s, 1H). Anal. ($C_{23}H_{23}N_5O_3$·1.2H_2O) C, H, N.

4-*N*-Phenylamino-5-phenyl-7-(2-deoxy-β-D-erythropentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (19). Sodium hydride (300 mg, 7.0 mmoL, 60% dispersion in mineral oil) was rinsed with hexane under N_2 atmosphere. Dry acetonitrile (70 mL) was introduced into the flask and the flask was immersed in an ice bath. Powdered **10a** (1.75 g, 6.1 mmol) was added in three equal portions with constant stirring. After the addition was complete, the cooling bath was removed and stirring was continued until the evolution of H_2 gas ceased. A solution of 2-deoxy-3,5-di-*O*-toluoyl-α-D-erythropentofuranosyl chloride[12] (**17**; 2.37 g, 6.1 mmol) in acetonitrile (10 mL) was added over a 5 min period. TLC (silica gel, 2:1 hexanes−EtOAc) after 1.5 h indicated complete consumption of the chloro sugar. The reaction mixture was filtered to remove the unreacted **10a**.The filtrate was evaporated, and the crude product was purified by chromatography over silica gel (25% EtOAc in hexanes) to give pure 4-*N*-phenylamino-5-phenyl-7-(3,5-di-*O*-toluoyl-2-deoxy-β-D-erythropentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**18**) as a glassy solid (2.55 g, 65%): ^{1}H NMR (DMSO-d_6) δ 2.35 and 2.45 (2s, 6H), 2.77 and 3.13 (2m, 2H), 4.6 (m, 3H), 5.8 (m, 1H), 6.83 (dd, J_1 = 6.01 Hz and J_2 = 8.25 Hz, 1H, 1′-CH), 6.95−8.05 (m, 19H), 8.4 (s, 1H). This material was dissolved in methanol (70 mL) to which a freshly prepared solution of sodium methoxide (4 mL, 2 M solution in methanol) was added. The mixture was stirred at room temperature for 1 h before glacial acetic acid was added gradually to adjust the pH to ∼4. The off-white solid formed was collected by filtration, washed with small volumes of methanol (2 × 5 mL) and crystallized from boiling ethanol to give **19** as a crystalline solid (1.28 g, 79%): mp 89−96 °C; ^{1}H NMR (DMSO-d_6) δ 2.25 and 2.57 (2m, 2H), 3.55 (m, 3H), 4.37 (m, 1H), 5.01 (t, 1H, exchangeable with D_2O), 5.29 (d, 1H, exchangeable with D_2O), 6.65 (dd, J_1 = 7.1 Hz and J_2 = 9.35 Hz, 1H, 1′-CH), 6.95−7.7 (m, 12H), 8.38 (s, 1H). Anal. ($C_{23}H_{22}N_4O_3$) C, H, N.

4-*N*-Phenylamino-5-phenyl-7-(3-*O*-acetoxy-2-β-bromo-2,5-dideoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (20) and 4-*N*-Phenylamino-5-phenyl-7-(2-*O*-acetoxy-3-β-bromo-3,5-dideoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (21). To a suspension of **5b** (450 mg, 1.1 mmol) in acetonitrile (15 mL) was added 3 drops of water followed by acetoxyisobutyryl bromide (1 mL, 6.8 mmol) over a 5−10 min period. After stirring the reaction mixture for 40 min, a saturated solution of $NaHCO_3$ (10 mL) was added slowly and the mixture was partitioned with EtOAc (40 mL). The organic layer was dried ($MgSO_4$), evaporated under reduced pressure, and the residue was purified by chromatography over silica gel (25% EtOAc in hexanes) to give two products as glassy solids. The fast moving spot was characterized to be 4-*N*-phenylamino-5-phenyl-7-(3-*O*-acetoxy-2-β-bromo-2,5-dideoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**20**; 90 mg, 19%): ^{1}H NMR ($CDCl_3$) δ 1.68 (d, 3H), 2.20 (s, 3H), 4.12 (m, 1H), 4.72 (m, 1H), 5.37 (m, 1H), 6.62 (d, J = 4.2 Hz, 1H, 1′-CH), 6.9−7.7 (m, 12H, NH and aromatic), 8.48 (s, 1H). The slow moving spot was characterized to be 4-*N*-phenylamino-5-phenyl-7-(2-*O*-acetoxy-3-β-bromo-3,5-dideoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**21**; 290 mg, 63%): ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3H), 2.10 (s, 3H), 4.30 (m, 1H), 4.82 (d, 1H), 5.65 (d, 1H), 6.39 (d, J = 3.0 Hz, 1H, 1′-CH), 6.95−7.6 (m, 12H), 8.40 (s, 1H).

4-*N*-Phenylamino-5-phenyl-7-(2,5-dideoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (22). A degassed solution of **20** (90 mg, 0.17 mmol) in methanol (10 mL) was treated with $Pd(OH)_2$ on C (5%, 15 mg) and subjected to hydrogenation under 50 psi of H_2 on a Parr apparatus. After 72 h the catalyst was removed by filtration and washed with methanol. The combined filtrate and washings were evaporated and the residue was purified by chromatography over silica gel (25% ethyl acetate in hexanes) to give 4-N-phenylamino-5-phenyl-7-(3-*O*-acetoxy-2,5-dideoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine as a glassy solid (55 mg, 75%). This material was subjected to deprotection according to the procedure described for **18** to give **22** as off-white needles from aqueous ethanol (34 mg, 68%): mp 91−92 °C; ^{1}H NMR (DMSO-d_6) δ 1.25 (d, 3H), 2.25 and 2.7 (2m, 2H), 3.9 (m, 1H), 4.16 (m, 1H), 5.32 (d, 1H, exchangeable with D_2O), 6.63 (dd, J_1 = 5.5 Hz and J_2 = 5.8 Hz, 1H, 1′-CH), 6.95−7.7 (m, 12H), 8.49 (s, 1H). Anal. ($C_{23}H_{22}N_4O_2$·0.6H_2O) C, H, N.

4-*N*-Phenylamino-5-phenyl-7-(3,5-dideoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (23). By the procedure described for **22**, **21** was subjected to hydrogenation and the resulting intermediate 4-*N*-phenylamino-5-phenyl-7-(2-*O*-acetyl-3,5-dideoxy-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine was subjected to base-catalyzed deprotection to give **23** as needles from aqueous ethanol: yield 57%; mp 80−83 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (d, 3H), 2.03 (m, 2H), 4.36 (m, 1H), 4.53 (m, 1H), 5.60 (d, 1H, exchangeable with D_2O), 6.18 (d, 1H, J = 2.2 Hz, 1′-CH), 6.95−7.7 (m, 12H), 8.39 (s, 1H). Anal. ($C_{23}H_{22}N_4O_2$) C, H, N.

Enzyme Assay. AK activity was measured in a radiochemical assay similar to the procedure of Yamada et al.,[23] with minor modifications as described previously.[1] The results are shown in Table 1.

MES Seizure Assay. Rat MES seizure activity was determined by the procedure described previously,[1] and the results are shown in Table 2.

Hemodynamic Studies. The hemodynamic effects of **5l**,**m** were determined by the protocol described earlier.[18]

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References

(1) Ugarkar, B. G.; DaRe, J.; Kopcho, J.; Browne, C. E.; Schanzer, J.; Wiesner, J. B.; Erion, M. D. Adenosine Kinase Inhibitors. 1. Synthesis, Enzyme Inhibition, and Antiseizure Activity of 5-Iodotubercidin Analogues. *J. Med. Chem.* **2000**, *43*, 2883−2893.

(2) Davies, L. P.; Jamieson, D. D.; Baird-Lambert, J. A.; Kazlauskas, R. Halogenated Pyrrolopyrimidine Analogues of Adenosine From Marine Organisms: Pharmacological Activities and Potent Inhibition of Adenosine Kinase. *Biochem. Pharmacol.* **1984**, *33*, 347−355.

(3) Davies, L. P.; Baird-Lambert, J.; Marwood, J. F. Studies On Several Pyrrolo[2,3-*d*]pyrimidine Analogues of Adenosine Which Lack Significant Agonist Activity at A1 and A2 Receptors But Have Potent Pharmacological Activity In Vivo. *Biochem. Pharmacol.* **1986**, *35*, 3021−3029.

(4) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457−2483.

(5) Cook, A. F.; Holman, M. J. Synthesis of the Natural Product 5′-Deoxy-5-iodotubercidin and Related Halogenated Analogues. *Nucleosides Nucleotides* **1984**, *3*, 401−411.

(6) Taylor, E. C.; Hendess, R. W. Synthesis of Pyrrolo[2,3-*d*]-pyrimidines. The Aglycone of Toyocamycin. *J. Am. Chem. Soc.* **1965**, *87*, 1995−2003.

(7) Gewald, K. Reaktion von Malonsauredinitril mit a-Aminoketonen. *Z. Chem.* **1961**, *1*, 349.

(8) Ramasamy, K.; Imamura, N.; Robins, R. K.; Revankar, G. R. A Facile Synthesis of Tubercidin and Related 7-Deazapurine Nucleosides Via The Stereospecific Sodium Salt Glycosylation Procedure. *Tetrahedron Lett.* **1987**, *28*, 5107−5110.

(9) Seela, F.; Kretschmer, U. Synthesis and Properties of Conformationally Locked 1,3 Bisalkyl-7-deazaxanthine 2′-deoxy-D-ribofuranosides. *J. Heterocycl. Chem.* **1985**, *27*, 479−486.

(10) Anderson, J. D.; Bontems, R. J.; Geary, S.; Cottam, H. B.; Larson, S. B.; Matsumoto, S. S.; Smee, D. F.; Robins, R. K. Synthesis of Tubercidin, 6-Chlorotubercidin and Related Nucleosides. *Nucleosides Nucleotides* **1989**, *8*, 1201−1216.

(11) Murai, Y.; Shiroto, H.; Ishizaki, T.; Iimori, T.; Kodama, Y.; Ohtsuka, Y.; Oishi, T. A Synthesis and an X-ray Analysis of 2′-C, 3′-C and 5′-C-Methylsangivamycins. *Heterocycles* **1992**, *33*, 391−404.

(12) Hoffer, M. α-Thymidin. *Chem. Ber.* **1960**, *93*, 2777−2781
(13) Ramasamy, K.; Imamura, N.; Robins, R. K.; Revankar, G. R. A Facile and Improved Synthesis of Tubercidin and Certain Related Pyrrolo[2,3-*d*]pyrimidine Nucleosides By The Stereospecific Sodium Salt Glycosylation Procedure [1]. *J. Heterocycl. Chem.* **1988**, *25*, 1893−1898.
(14) Robins, M. J.; Hansske, F.; Low, N. H.; Park, J. I. A Mild Conversion of Vicinal Diols to Alkenes. Efficient Transformation of Ribonucleosides Into 2′-ene And 2′,3′- Dideoxynucleosides. *Tetrahedron Lett.* **1984**, *25*, 367−370.
(15) Robins, M. J.; McCarthy, J. R., Jr.; Jones, R. A.; Mengel, R. Nucleic Acid Related Compounds. 5. The Transformation of Formycin and Tubercidin into 2′- and 3′- Deoxynucleosides. *Can. J. Chem.* **1973**, *51*, 1313−1321.
(16) Erion, M. D.; Ugarkar, B. G.; DaRe, J.; Castellino, A. J.; Fujitaki, J. M.; Dixon, R.; Appleman, J. R.; Wiesner, J. B. Design, Synthesis and Anticonvulsant Activity of the Potent Adenosine Kinase Inhibitor GP3269. *Nucleosides Nucleotides* **1997**, *16*, 1013−1021.
(17) Miller, R. L.; Adamczyk, D. L.; Miller, W. H.; Koszalka, G. W.; Rideout, J. L.; Beacham, L. M. III; Chao, E. Y.; Haggerty, J. J.; Krenitsky, T. A.; Elion, G. B. Adenosine Kinase From Rabbit Liver. *J. Biol. Chem.* **1979**, *254*, 2346−2352.
(18) Wiesner, J. B.; Ugarkar, B. G.; Castellino, A. J.; Barankiewicz, J.; Dumas, D. P.; Gruber, H. E.; Foster, A. C.; Erion, M. D. Adenosine Kinase Inhibitors as a Novel Approach to Anticonvulsant Therapy. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 1669−1677.
(19) Mathews, I. I.; Erion, M. D.; Ealick, S. E. Structure of Human Adenosine Kinase at 1.5 Å Resolution. *Biochemistry* **1998**, *37*, 15607−15620.
(20) Phillis, J. W.; Wu, P. H. Roles of Adenosine and Adenosine Nucleotides in the Central Nervous System. In *Physiology and Pharmacology of Adenosine Derivatives*; Daly, J. W., Phillis, J. W., Kuroda, Y., Shimitzu, S., Ui, M., Eds.; Raven Press: New York, 1983; pp 219−236.
(21) Malhotra, J.; Gupta, Y. K. Effect of Adenosine Receptor Modulation on Pentylenetetrazole-induced Seizures in Rats. *Br. J. Pharmacol.* **1997**, *120*, 282−288.
(22) Wilcox, C. S.; Otoski, R. M. Stereoselective Preparations of Ribofuranosyl Chlorides and Ribofuranosyl Acetates. Solvent Effects and Stereoselectivity in the Reaction of Ribofuranosyl Acetates with Trimethylallylsilane. *Tetrahedron Lett.* **1986**, *27*, 1011−1014.
(23) Yamada, Y.; Goto, H.; Ogasawara, N. Adenosine Kinase from Human Liver. *Biochim. Biophys. Acta* **1981**, *660*, 36−43.

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