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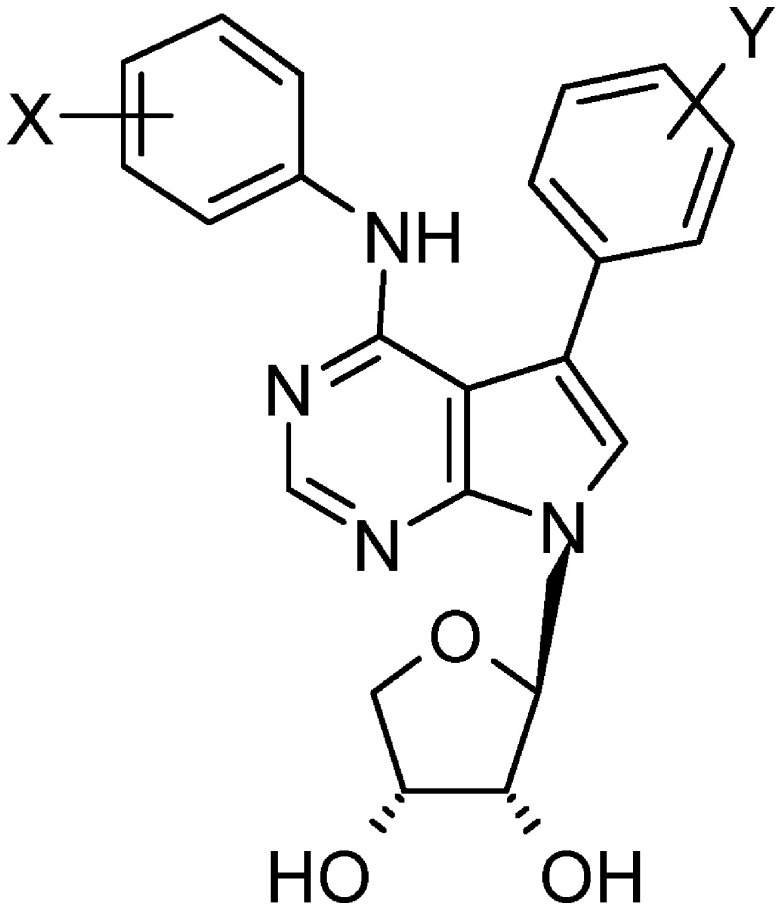

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Adenosine Kinase Inhibitors. 5. Synthesis, Enzyme Inhibition, and Analgesic Activity of Diaryl-*erythro*-furanosyltubercidin Analogues

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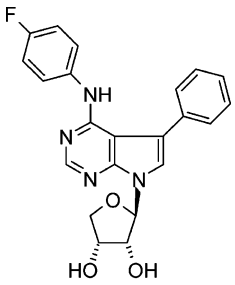
Adenosine is an endogenous neuromodulator that when produced in the central and the peripheral nervous systems has anticonvulsant, anti-inflammatory, and analgesic properties. However, efforts to use adenosine receptor agonists are plagued by dose-limiting cardiovascular side effects. As an alternative, we explored the use of adenosine kinase inhibitors (AKIs) as potential antiseizure agents and demonstrated an adenosine receptor mediated therapeutic effect in the absence of overt cardiovascular side effects. These activities were associated with elevation of extracellular adenosine concentrations due to inhibition of AK in a site and event specific manner. Several tubercidin based AKIs, including the *ribo*- and *lyxo*-furanosyltubercidin analogues as well as the newly discovered *erythro*-furanosyltubercidin analogues, designed to prevent 5′-O-phosphorylation and associated toxicities, were tested for their analgesic activity in the rat formalin paw model. Described herein are the synthesis, enzyme inhibition structure−activity relationships (SARs) of *erythro*-furanosyltubercidin analogues, and SARs of analgesic activity of various classes of AKIs. Also reported is the characterization of a lead AKI, **19d** (GP3966), an orally bioavailable compound ($F\% = 60\%$ in dog) which exhibits broad-spectrum analgesic activities ($ED_{50} \leq 4$ mg/kg, per os) that are reversible with an adenosine receptor antagonist (theophylline).

Introduction

Adenosine kinase (AK)[1] is a key intracellular enzyme that regulates the gradient between the intra- and extracellular concentrations of adenosine via the phosphorylation of adenosine to adenosine monophosphate. Inhibition of AK increases the extracellular concentration of adenosine, which stimulates local cell surface adenosine receptors resulting in protective pharmacological effects in a relatively event specific manner.[2] Previous reports from our laboratories described the potential of AK as a therapeutic target and AK inhibitors (AKIs) as therapeutics for the treatment of inflammation,[3] epilepsy,[4] and stroke.[5] Adenosine also plays a critical role in modulating nociception in the brain and in the spinal cord.[6] Its protective effects were demonstrated using both adenosine receptor agonists[7] and AKIs.[8] Recently, a non-nucleoside class of AKIs with potent anti-inflammatory and analgesic activity was reported, establishing AK as a potential therapeutic target for the treatment of pain.[9] An advantage of AKIs in harnessing the benefits of adenosine lies in their ability to produce pharmacological effects in what appears to be a site and event specific manner without causing overt cardiovascular side effects[4b,c] such as hypotension and tachycardia. These effects are the hallmarks of adenosine receptor agonists that have limited their development as therapeutic agents.[6b,7,10] The drug discovery program described herein was designed to identify potent AKIs and to evaluate their analgesic properties in animal models of nociception.

Chart 1



19d (GP3966)

The newly discovered series of *erythro*-furanosyltubercidin analogues and the previously reported series of *ribo*- and *lyxo*-furanosyltubercidin analogues[3a,4a,4b] were selected for these studies. *erythro*-Furanosyltubercidin analogues were discovered as part of our structure−activity relationship (SAR) studies to design nucleosides that do not undergo 5′-O-phosphorylation and, consequently, do not exhibit toxicities associated with their incorporation into the nucleotide pools.[2] Described herein are the syntheses, SAR of AK inhibition, and oral analgesic properties of both C4′-disubstituted and C4′-unsubstituted β-D-*erythro*-furanosyltubercidin analogues. Also described are the results of advanced pharmacological, pharmacokinetic, and side effect studies on a lead AKI, **19d** (GP3966, Chart 1).

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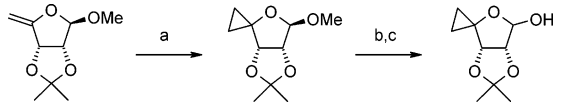
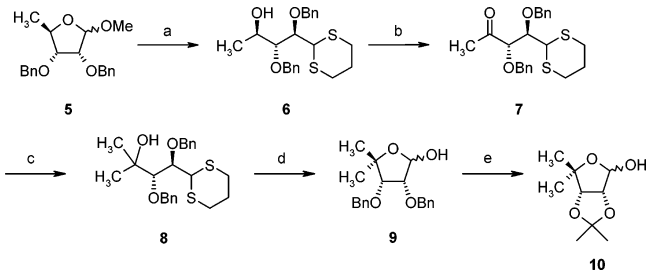
Scheme 1



Reagents: (a) Zn/Cu, CH_2I_2, Et_2O (47%); (b) H_2SO_4, H_2O; (c) 2,2-dimethoxypropane, *p*-TsOH·H_2O, DMF (50% for 2 steps).

Scheme 2



Reagents: (a) Propanedithiol, BF_3·Et_2O, CH_2Cl_2 (92%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (80%); (c) MeLi, THF, −78 °C (98%); (d) $CaCO_3$, MeI (88%); (e) (i) $Pd(OH)_2$/C, H_2, EtOAc; (ii) 2,2-dimethoxypropane, *p*-TsOH·H_2O, DMF (34% for 2 steps).

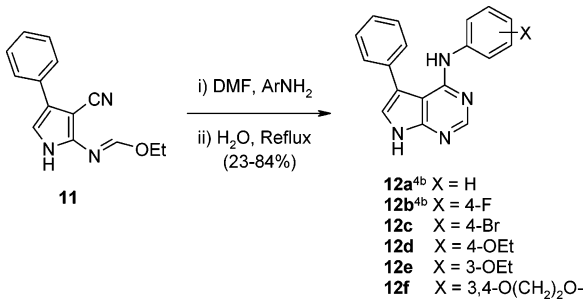
Chemistry

The new diaryltubercidin analogues used in this study were prepared by methodologies described previously.[3a,4b] For example, **22a**−**e** were prepared by first coupling 2,3-*O*-isopropylidene-α-D-*erythro*-furanosyl chloride with 4-chloro-5-iodopyrrolo[2,3-*d*]pyrimidine (**15**)[11] and derivatizing the resulting intermediate to introduce a phenylamino group at C4 and a phenyl group at C5, as described previously (Scheme 4). Alternatively, other AKIs, such as **19a**−**h**, were prepared via direct glycosylation of 5-aryl-4-*N*-arylaminopyrrolo[2,3-*d*]pyrimidine bases **12a**−**f** with the appropriate chloro sugar intermediates **14a**−**c**, followed by the removal of the protecting group.

The sugar precursors and bases required for the current work were synthesized as follows. 2,3-*O*-Isopropylidene-4-spirocyclopropyl-D-*erythro*-furanose (**4**) was prepared by first subjecting 5-deoxy-2,3-*O*-isopropylidene-*β*-D-*erythro*-pent-4-enofuranoside (**2**)[12] to the Simmons−Smith cyclopropanation reaction[13] to give the spirocyclopropyl derivative **3**, followed by manipulation of the protecting groups as shown in Scheme 1. The sugar precursor **10,** on the other hand, was synthesized in five steps as depicted in Scheme 2. Perbenzylated methyl *ribo*-furanoside **5**[14] was first treated with 1,3-propanedithiol and boron trifluoride etherate to produce dithiane **6**, which was subjected to a Swern oxidation to give ketone **7**. Conversion to tertiary alcohol **8** was accomplished by methyl lithium addition. Finally, the dithiane[15] and the benzyl protecting groups were removed and the 2,3-*O*-isopropylidene group was introduced using standard reaction conditions to give the desired C4-methyl furanose **10** in an overall 22% yield. The new diarylpyrrolopyrimidine heterocycles **12c**−**f** were synthesized by condensing various anilines with 3-cyano-2-ethoxymethyleneimino-4-phenylpyrrole (**11**, Scheme 3), as described previously.[4b,16]

Sugars **4** and **10** were activated to their corresponding α-furanosyl chlorides **14a** and **b**, respectively, via the previously described hexamethylphosphorus triamide (HMPT)/carbon tetrachloride procedure (Scheme 4).[4a,17]

Scheme 3



However, under similar reaction conditions, 2,3-*O*-isopropylidene-D-*erythro*-furanose (**13**)[18] gave an intractable mixture of products. After evaluating several chlorinating procedures, Vilsmeyer's reagent was shown to cleanly react with **13** to give predominantly the desired 2,3-*O*-isopropylidene-α-D-*erythro*-furanosyl chloride **14c**, as determined by ^{1}H NMR spectroscopy.[19] The activated chloro sugar intermediates **14a**−**c** were used as crude solutions in the tris[2-(2-methoxyethoxy)ethyl]-amine (TDA-1) mediated glycosylation of pyrrolopyrimidine bases[3a,4b] **12a**−**f** to give compounds **18a**−**h** in 10−64% yield**,** which were deprotected with either 70% TFA or 0.4 N HCl/MeOH to produce the desired final compounds **19a**−**h** in 60−91% yield.

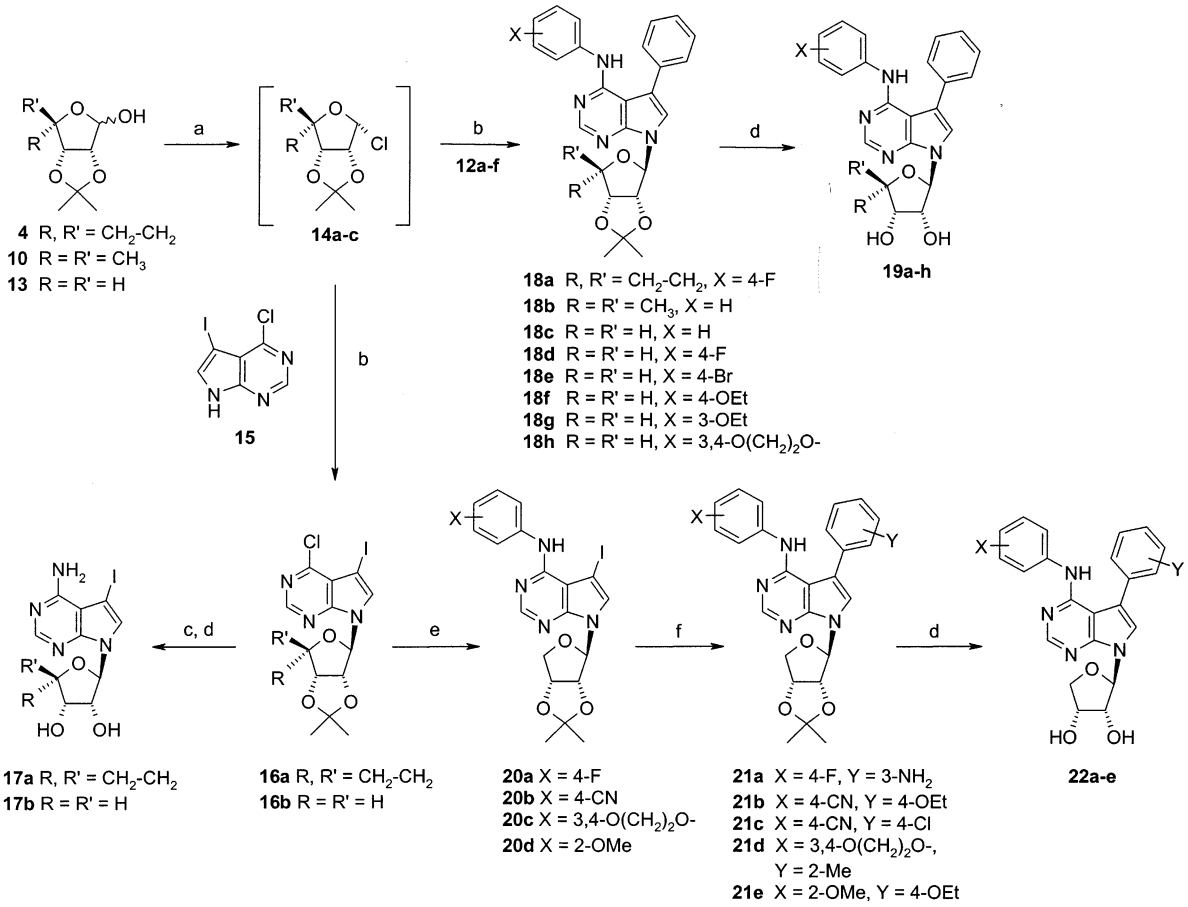
5-Iodotubercidin analogues **17a** and **b** were synthesized by coupling chloro sugars **14a** and **b** with the pyrrolopyrimidine base **15** to give **16a** and **b**. Amination of **16a** and **b** with methanolic ammonia followed by deprotection provided the desired compounds in 20% overall yields. Intermediate **16b** also provided easy access to **22a**−**e** in 35−50% overall yields via the three step sequence of condensing **16b** with anilines, followed by Suzuki arylation at the C5-position and, finally, deprotection.[3a,4b]

The structural assignments of the glycosidation products were made by ^{1}H NMR spectroscopy and are based on our previously reported findings for the TDA-1 mediated glycosidation of diarylpyrrolopyrimidines with *ribo*- and *lyxo*-furanosyl sugars.[3a,4b] For example, the ^{1}H NMR spectrum of C4′-disubstituted compound **18b** shows the anomeric proton as a doublet at 6.59 ppm with a coupling constant of 4.5 Hz, which is similar to the cases of other 2′,3′-*O*-isopropylidene-protected *β*-*ribo*-nucleosides of pyrrolo[2,3-*d*]pyrimidines.[4b] On the other hand, the ^{1}H NMR spectrum of *erythro*-furanosyl compound **18c** shows an apparent singlet at 6.3 ppm which, upon deprotection, becomes a doublet with a rather large coupling constant (J = 6.7 Hz), which is characteristic of *β*-*erythro*-furanosides of pyrrolopyrimidines.

Results and Discussion

The compounds listed in Table 1 were evaluated as inhibitors of recombinant human AK, and IC_{50} values were determined as described previously.[3a,20] Comparison of the IC_{50} values for the *ribo*- and *lyxo*-5-iodotubercidin analogues **1a**−**d** reveals that the active site of AK favors the C4′-substituent in the *ribo* configuration. Furthermore, a relative difference in IC_{50} values between **1a**[21] (IC_{50} = 27 nM) and **1b**[22] (IC_{50} = 9 nM) indicates that the 5′-hydroxyl does not contribute to the binding energy. However, when the slightly larger, but compact, hydrophobic cyclopropyl group was introduced

Scheme 4



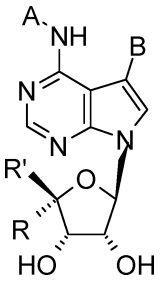
Reagents: (a) For **4** and **10** HMPT, CCl_4, toluene; for **13** $(COCl)_2$, DMF, acetonitrile; (b) KOH, TDA-1, toluene; (c) NH_3, MeOH; (d) for **17a** and **b**, **19a**, **b**, and **e**, and **22a**−**e** 70% aq TFA; for **19c**, **d**, **f**, **g**, and **h** 0.4 N HCl, MeOH; (e) $XPhNH_2$, *t*-BuOK, THF, (82−93%); (f) $YPhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, diglyme, H_2O (76−94%).

at the C4′-position, the resulting compound **17a** (IC_{50} = 600 nM) exhibited a weaker AKI activity, suggesting that the cyclopropyl group is too bulky to fit properly within the binding pocket and/or the spirocycle distorts the binding conformation of the nucleoside. This hypothesis is further supported by the potent AKI activity observed for β-D-*erythro*-furanosyltubercidin analogues which have no substituents at the C4′-position. For example, compound **17b** (IC_{50} = 6 nM) was found to be as potent as 5′-deoxy-5-iodotubercidin **1b** (IC_{50} = 9 nM), indicating that the C4′-methyl of compound **1b** or the C4′-hydroxymethyl of compound **1a** does not contribute to the binding energy of the AKIs to the active site of the enzyme. Therefore, the apparent differences in IC_{50}'s between various 5-iodotubercidin analogues (**1a**−**d** and **17a** and **b)** can be attributed to steric interferences between the inhibitor and the enzyme. Such steric interferences created by the C4′-substituents, however, appear to have minimal effects on diaryltubercidin analogues, as the AKI potencies of the C4′-spirocyclopropyl- (**19a**, IC_{50} = 0.3 nM) and the *erythro*-furanosyldiaryltubercidin **(19c**, IC_{50} = 4 nM) analogues are comparable to those of *ribo*- or *lyxo*-furanosyldiaryltubercidin analogues **1e**−**h**. These results are in line with our previous hypothesis that a large portion of the binding energy of diaryl-AKIs is provided by aromatic hydrophobic interactions with the active site,[3a,4b] although an anomaly to this trend was found with compound **19b** (IC_{50} = 4 μM), which has two methyl groups at the C4′-position, and may be attributed to a different and less favorable binding conformation.

Drawn by the simplicity of the *erythro*-furanosyl sugar, a number of diaryl-β-D-*erythro*-furanosyltubercidin analogues **19d**−**h** and **22a**−**e** with electron donating and electron withdrawing groups were prepared to broaden the in vitro SAR as well as to improve the pharmacological properties of the molecule. However, the enzyme inhibition data indicate that the substitution pattern and the electronic effects of the substituents on either of the phenyl rings, much in line with our previous observations,[3a,4b] had no significant impact on the AKI potency.

AKIs from the current study with IC_{50} < 50 nM, as well as a few selected compounds from the previously reported *ribo*- and *lyxo*-furanosyltubercidin series, were evaluated in vivo for analgesic activity in the rat formalin paw test[23] (Table 2). The formalin paw test was chosen for this purpose because it models a state of persistent pain in which transmission of pain signaling is facilitated by physiological mechanisms within the nervous system (such facilitated pain states are a feature of inflammatory and other hyperalgesic conditions, as well as neuropathic pain syndromes). Animals were dosed orally at 20 mg/kg, using polyethylene glycol 400 (PEG) as the vehicle, 2 h prior to formalin challenge, and the analgesic activity was measured as a percent inhibition of the licking and biting response. Comparison of the data in Table 2 indicates that the in vivo

Table 1. AK Inhibitor SAR



compd	R′	R	A	B	IC_{50}[a] (nM)
1a[b]	CH_2OH	H	H	I	26
1b[c]	CH_3	H	H	I	9
1c[d]	H	CH_2OH	H	I	68
1d[d]	H	CH_3	H	I	400
1e[e]	CH_2OH	H	Ph	Ph	0.8
1f[e]	CH_3	H	Ph	Ph	0.5
1g[f]	H	CH_2OH	Ph	Ph	0.47
1h[f]	H	CH_3	Ph	Ph	0.8
17a	CH_2-CH_2		H	I	600
17b	H	H	H	I	6
19a	CH_2-CH_2		4-F-Ph	Ph	0.3
19b	CH_3	CH_3	Ph	Ph	4000
19c	H	H	Ph	Ph	4
19d	H	H	4-F-Ph	Ph	6
19e	H	H	4-Br-Ph	Ph	5
19f	H	H	4-OEt-Ph	Ph	3
19g	H	H	3-OEt-Ph	Ph	2
19h	H	H	3,4-(OCH_2CH_2O)-Ph	Ph	4
22a	H	H	4-F-Ph	3-NH_2-Ph	10
22b	H	H	4-CN-Ph	4-OEt-Ph	2
22c	H	H	4-CN-Ph	4-Cl-Ph	7
22d	H	H	3,4-(OCH_2CH_2O)-Ph	2-Me-Ph	1
22e	H	H	2-OMe-Ph	4-OEt-Ph	5.3

[a] Enzyme inhibition assays were performed on human recombinant AK enzyme. IC_{50} values are results of a single experiment. [b] See ref 20. [c] See ref 21. [d] See ref 3a. [e] See ref 4b. [f] See ref 3a.

potency of AKIs is independent of the nature and pattern of the substituents on the phenyl rings or of the nature of the sugar moiety. A lack of a direct correlation between in vitro and in vivo potencies is attributed to potential differences in the pharmacokinetic properties of the compounds.

With a view to identifying a lead AKI for development, compounds with good efficacy in the formalin paw screening assay were tested at several doses for ED_{50} determination (Table 2, Figure 1). On the basis of the dose response curves in Figure 1, AKI **19d** was selected as the lead compound. Although structurally very similar to GP3269,[4d] compound **19d** showed a number of advantages, primarily the relative absence of emesis in cynomolgus and rhesus monkeys at doses as high as 100 mg/kg, per os (po).[24] Encouraged by these results, **19d** was tested in a number of animal models of pain and inflammation to evaluate its potential as a development candidate. The studies and the results are summarized in Table 3. The low ED_{50} value obtained in the formalin paw animal model indicates that **19d** exhibits potent analgesic activity in a state of persistent pain. In this regard, the analgesic activity of **19d** is similar to that of the standard opioid analgesic, morphine. This observation with **19d** is extended by the low ED_{50} values obtained in an inflammatory state induced by carrageenan in the rat hyperalgesia models. In this inflammatory state, hyperalgesia to both mechanical and thermal stimulus modalities was inhibited with a high degree of efficacy, in a fashion that mimics the effect of

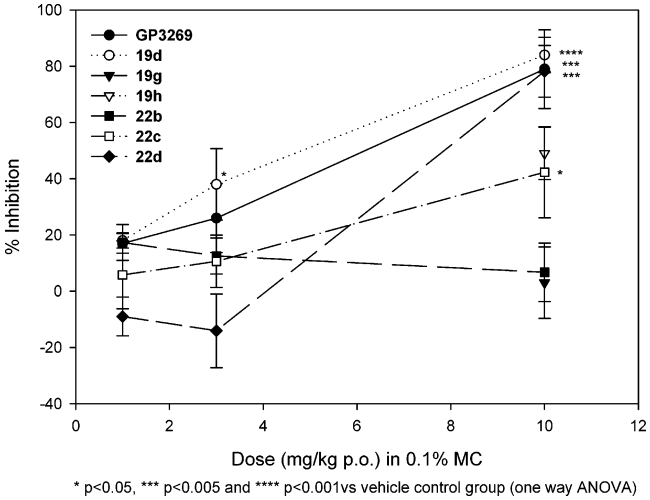


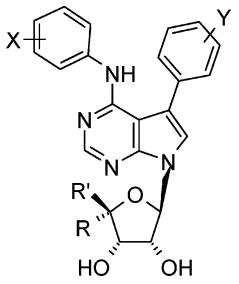
Figure 1. Dose response curves of AKIs on formalin-induced licking/biting behavior in rats (6 rats/group).

anti-inflammatory drugs such as indomethacin. This efficacy was observed when **19d** was administered either before (prophylactically) or after (therapeutically) induction of the inflammation. Thus, following therapeutic administration (a greater challenge of analgesic efficacy), the response of the inflamed paw to the thermal stimulus was completely (99%) reduced to the control (noninflamed) response level. Additionally, the analgesic activity of **19d** was shown on a broader spectrum, albeit with lower potency, in the hot plate test, a model of acute nociceptive pain. Such an analgesic effect on nociceptive pain is supported by an efficacy of 151% following prophylactic administration in the thermal hyperalgesia model, as a level of efficacy exceeding 100% in this model likely represents attenuation of acute nociception in conjunction with the reduction of inflammatory hyperalgesia. Thus, the activity of **19d** appears to combine features of both opioids and non-steroidal anti-inflammatory drugs (NSAIDs), with some differential potency exhibited against acute nociceptive pain. Although a mild sedative side effect was observed in the rat rotarod test, the therapeutic index (TI) for analgesic activity in the formalin paw assay was >3.

Earlier experiments with GP3269 in human clinical trials indicated that central nervous system (CNS) active AKIs could produce headaches, nausea, and vomiting in some patients. To assess whether **19d** would have a suitable therapeutic index in this regard, the compound was administered to marmoset monkeys. In the bradykinin-induced pain assay, **19d** reduced the licking response with an ED_{50} of 3.8 mg/kg, po, mimicking the effect of morphine (morphine ED_{50} 0.33 mg/kg, subcutaneously (sc)). Emesis was observed in only $^1/_6$ of the animals that received **19d** at a dose of 30 mg/kg, po, thus demonstrating a TI exceeding 7.9. In a previous study using the same assays, GP3269 had shown no separation between its analgesic activity and its emetic side effects (unpublished observations).

The pharmacokinetics of **19d** in the rat and dog are summarized in Table 4. Although plasma half-lives of **19d** are similar, the systemic exposure of the compound as measured by plasma AUC is considerably higher in the dog than it is in the rat due to higher clearance of **19d** in the rodent. Compound **19d** is orally bioavailable

Table 2. Analgesic Activity in Formalin Paw Assay



compd	R′	R	X	Y	% inh L/B at 20 mg/kg, po[a]	ED_{50} mg/kg, po[b]
1e	CH_2OH	H	H	H	41	
1f	CH_3	H	H	H	75	
GP3269[c]	CH_3	H	4-F	H	59	6.4
GP790 (**1g**)[d]	H	CH_2OH	H	H	90 @ 5 mg/kg	
19c	H	H	H	H	78	
19d	H	H	4-F	H	76	3.6
19e	H	H	4-Br	H	33	
19f	H	H	4-OEt	H	41	
19g	H	H	3-OEt	H	76	>10
19h	H	H	3,4-(OCH_2CH_2O)	H	80	10
22a	H	H	4-F	3-NH_2	31	
22b	H	H	4-CN	4-OEt	84	>10
22c	H	H	4-CN	4-Cl	75	>10
22d	H	H	3,4-(OCH_2CH_2O)	2-Me	99	6.9
22e	H	H	2-OMe	4-OEt	16	

[a] Inhibition of the licking and biting behavior in response to formalin injection, PEG vehicle, $n = 6$ rats. [b] 0.1% methylcellulose (MC) vehicle, $n = 6$ rats. [c] See ref 4d. [d] See ref 3a.

Table 3. Summary of Pharmacological Activities of Compound **19d**

AK	$IC_{50} = 6.3$ nM
rat formalin paw pain assay	$ED_{50} = 3.6$ mg/kg, po
rat hot plate test (50 °C)	$ED_{50} = 16$ mg/kg, po
carrageenan-induced mechanical hyperalgesia	$ED_{50} = 2.4$ mg/kg, po
carrageenan-induced thermal hyperalgesia	
prophylactic (20 mg/kg, po)	151% inhibition
therapeutic (20 mg/kg, po)	99% inhibition
marmoset monkey bradykinin-induced licking	$ED_{50} = 3.8$ mg/kg, po
oral rat rotorod assay	
2 h	$ED_{50} = 21.7$ mg/kg
5 h	$ED_{50} = 11.9$ mg/kg
oral marmoset monkey **19d**-induced emesis	$^1/_6$ @ 30 mg/kg

in both species, but a comparison of the T_{max} following oral administration indicates a delay in the rate of absorption of the compound in the rat. As **19d** is a hydrophobic compound, the volume of distribution is high for both species with the value for the rat considerably greater than that observed in the dog. **19d** was found to be stable in human liver microsome incubation studies ($T_{1/2} = 6.4$ h), suggesting that it is not prone to oxidative, first-pass metabolism. However, it forms two glucuronide conjugates of undetermined structures. Protein binding of **19d** was found to be >99% in human and dog plasma, which may be attributed to its poor solubility (<0.05 μg/mL) in physiological medium (pH 7.4).

The postulated mechanism for the analgesic activity of **19d** entails an increase in the local concentration of adenosine in the spinal cord through inhibition of AK-mediated metabolism of adenosine. Increased concentration of extracellular adenosine results in greater and/or prolonged activation of adenosine receptors. To further probe this hypothesis, mechanistic studies were conducted on **19d** using a nonselective adenosine receptor antagonist, theophylline. Administration of theophylline to animals pretreated with **19d** significantly suppressed its analgesic activity in the rat formalin paw model in a dose dependent manner (Figure 2). Furthermore, administration of theophylline alone to naive animals led to an increase in licking/biting behavior, confirming the involvement of adenosine receptors in the pain response. Similarly, the previously observed side effects such as sedation (suppression of spontaneous locomotor activity in the monkey and in the rat rotarod

Table 4. Pharmacokinetic Parameters for **19d** in Rats and Dogs ($n = 3$)

		dog				rat			
		po[a]		iv[b]		po[a]		iv[b]	
		mean ±	S.D.	mean ±	S.D.	mean ±	S.D.	mean ±	S.D.
C_{max}	ng/mL	628.0	142.9	585.4[c]	84.4	134.9	61.3	523.4[c]	129.5
T_{max}	h	1.6	1.0			3.5	0.5		
AUC_{0-24h}	ng h/mL	5342.1	735.7	2965.9	684.3	1440.6[d]	517.5	785[d]	81
$T_{1/2}$	h	4.0	0.4	3.9	0.8	3.0	0.2	3.2	0.7
Vd	L/kg	2.2	0.2	2.0	0.1	6.2	0.6	6.9	2.4
CL	L/(h kg)	0.4	0.0	0.4	0.1	1.5	0.0	1.3	0.1
F	%	60.0	16.1			61.2	22.9		

[a] 3 mg/kg suspension in 0.1% aqueous MC. [b] 1 mg/kg in 75% PEG−25% saline. [c] C_0. [d] AUC_{0-8h}.

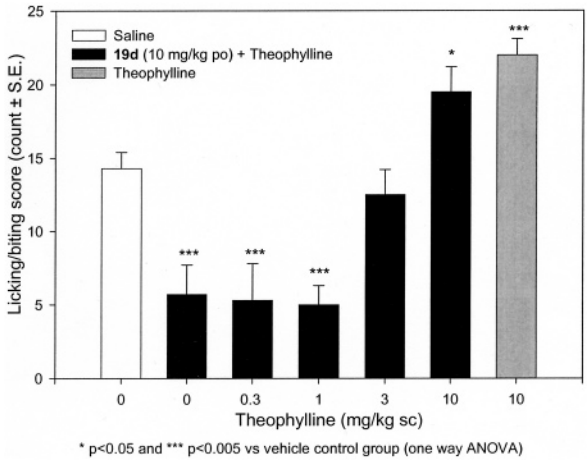


Figure 2. Antagonism of the analgesic activity of **19d** with theophylline on formalin-induced licking/biting behavior in the rat. Data are means ± SEM from an *n* of 6; 0.1% MC is the vehicle.

test), nausea, and emesis in the monkey test at high doses of **19d** were also antagonized by theophylline (data not shown).

Conclusions

The current AKIs were designed to prevent phosphorylation of the 5′-hydroxyl of tubercidin analogues by removing the CH_2OH from the C4′-position. Our results demonstrate that neither the hydroxymethylene group nor a hydrophobic group at the C4′-position plays a significant role in the binding of tubercidin-based AKIs to the active site and that a significant portion of the binding energy of diaryltubercidin AKIs is contributed by aromatic hydrophobic interactions in the active site. On the basis of the ED_{50} values of several AKIs in the formalin paw assay, **19d** was chosen for further evaluation. Profiling in advanced animal models of pain and inflammation indicated that **19d** is a potent and broad-spectrum analgesic for the treatment of acute pain/hyperalgesia. Reversal of the analgesic activity, as well as the mild side effects, with an adenosine receptor antagonist suggests that the pharmacological effects of **19d** are adenosine receptor mediated and are consistent with the elevation of endogenous adenosine levels due to the inhibition of AK. Studies in marmoset monkeys suggest that additional safety and efficacy studies are warranted to further evaluate the potential of **19d** as a development candidate for the treatment of pain.

Experimental Section

General Information. Glassware for moisture sensitive reactions was flame dried and cooled to room temperature in a desiccator, and all reactions were carried out under an atmosphere of nitrogen. Anhydrous solvents were purchased from Aldrich. Thin-layer chromatography was performed on EM Science silica gel 60 F_{254} plates that were visualized with a UV lamp (254 nm) or cerium stain. Column chromatography was performed on 230−400 mesh EM Science silica gel 60. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR were obtained on a Varian Gemini-200 operating at 200 and 50 MHz, respectively, or a Varian Mercury-300 operating at 300 and 75 MHz, respectively. ^1H and ^{13}C NMR spectra were recorded in δ units using the solvent's chemical shift as the reference line. C, H, and N microanalyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ, or NuMega Resonance Labs, Inc., San Diego, CA. All protocols involving animal experimentation were reviewed and approved by the Metabasis Therapeutics IACUC (Institution Animal Care and Use Committee) and the Nagoya Laboratories of Pfizer Global Research and Development IACUC and follow the guidelines established by the NRC "Guide for the Care and Use of Laboratory Animals".

Methyl 2,3-*O*-Isopropylidene-4-*C*-spirocyclopropyl-D-*erythro*-pentofuranoside (3). A solution of **2**[12] (4.0 g, 21.5 mmol) and diiodomethane (8.7 mL, 107.5 mmol) in dry ether (20 mL) was added dropwise over 4 h to a refluxing suspension of freshly made zinc−copper couple in dry ether. The reaction mixture was refluxed overnight, cooled, diluted with ether, and washed with saturated aqueous NH_4Cl. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 90/10 to 80/20) to provide **3** (1.92 g, 47%): ^1H NMR ($CDCl_3$) δ 4.95 (s, 1H), 4.69 (d, J = 6.3 Hz, 1H), 4.41 (d, J = 6.3 Hz, 1H), 3.33 (s, 3H), 1.54 (s, 3H), 1.36 (s, 3H), 1.10−0.60 (m, 4H).

2,3-*O*-Isopropylidene-4-*C*-spirocyclopropyl-D-*erythro*-pentofuranose (4). A mixture of **3** (2.57 g, 12.8 mmol), 1 N HCl (20 mL), and THF (20 mL) was refluxed for 1 h. The cooled reaction mixture was neutralized with DOWEX 1 × 8−200 ion-exchange resin (OH^- form), filtered, and rinsed with MeOH. The combined filtrates were concentrated under reduced pressure and azeotroped twice with DMF. The residue was dissolved in DMF (10 mL). *p*-TsOH·H_2O (catalytic) and 2,2-dimethoxypropane (4.6 mL, 32 mmol) were added. After stirring for 4 h at room temperature, the reaction mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$ and then brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/ether 70/30 to 40/60) to provide lactol **4** (1.2 g, 50%): ^1H NMR ($CDCl_3$) δ 5.43 (d, J = 2.0 Hz, 1H), 4.75 (d, J = 6.3 Hz, 1H), 4.48 (d, J = 6.3 Hz, 1H), 2.52 (br s, 1H, exchangeable with D_2O), 1.55 (s, 3H), 1.38 (s, 3H), 1.10−0.70 (m, 4H).

1,2-Dibenzyloxy-1-([1,3]dithian-2-yl)-D-*ribo*-butane (6). BF_3·Et_2O (3.67 mL, 29.8 mmol) was added to a solution of **5**[13] (7.0 g, 21.3 mmol) and 1,3-propanedithiol (3.2 mL, 31.95 mmol) in dry CH_2Cl_2 (40 mL) at −48 °C. The reaction mixture was stirred for 30 min at −48 °C and warmed to room temperature in the course of 1 h. After stirring at room temperature for 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$, diluted with EtOAc, and washed with saturated aqueous $NaHCO_3$ and then brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate 80/20 to 60/40) to provide dithiane **6** (7.9 g, 92%) as an oil: ^1H NMR ($CDCl_3$) δ 7.50−7.20 (m, 10H), 5.00 (d, J = 11.1 Hz, 1H), 4.75 (s, 2H), 4.68 (d, J = 11.1 Hz, 1H), 4.53 (d, J = 4.6 Hz, 1H), 4.15−3.95 (m, 1H), 3.8−3.6 (m, 2H), 2.90−2.70 (m, 4H), 2.45 (d, J = 5.0 Hz, 1H), 2.20−1.80 (m, 2H), 1.22 (d, J = 6 Hz, 3H).

(3*S*,4*R*)-3,4-Dibenzyloxy-4-([1,3]dithian-2-yl)-butan-2-one (7). A solution of DMSO (6.93 mL, 97.5 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise over 5 min to a solution of oxalyl chloride (5.1 mL, 58.5 mmol) in dry CH_2Cl_2 (50 mL) at −78 °C. After stirring for 5 min at −78 °C, a solution of alcohol **6** (7.9 g, 19.5 mmol) in dry CH_2Cl_2 (25 mL) was added slowly over 5 min at −78 °C. After stirring at −78 °C for 15 min, a solution of Et_3N (27.2 mL, 195 mmol) in dry CH_2Cl_2 (50 mL) was added slowly over 10 min at −78 °C. The reaction mixture was allowed to warm to −40 °C over 30 min, quenched with saturated aqueous NH_4Cl, and warmed to room temperature. The layers were separated, and the aqueous layer was back extracted twice with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate 90/10 to 80/20) to provide ketone **7** (6.32 g, 80%) as an oil: ^1H NMR ($CDCl_3$) δ 7.40−7.20 (m, 10H), 4.82 (d, J = 11.1 Hz, 1H), 4.65 (s, 2H), 4.65 (d, J = 11.1 Hz, 1H), 4.25−4.10 (m, 3H), 2.90−2.40 (m, 4H), 2.15 (s, 3H), 2.10−1.90 (m, 2H).

(3*S*,4*R*)-3,4-Dibenzyloxy-4-([1,3]dithian-2-yl)-2-methylbutan-2-ol (8). A solution of ketone **7** (2.0 g, 5 mmol) in dry THF (25 mL) was added dropwise over 5 min to a solution of MeLi (20 mmol) in dry THF (20 mL) at −78 °C. After stirring for 20 min at −78 °C, the reaction mixture was quenched slowly with a solution of AcOH (2 mL) in THF, warmed to room temperature, diluted with EtOAc, and washed with saturated aqueous $NaHCO_3$ and then brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate 85/15 to 75/25) to provide **8** (2.04 g, 98%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.50−7.20 (m, 10H), 5.21 (d, J = 11.0 Hz, 1H), 4.81 (s, 2H), 4.57 (d, J = 1.8 Hz, 1H), 3.85 (dd, J = 7.2, 1.8 Hz, 1H), 3.55 (d, J = 7.2 Hz, 1H), 3.48 (s, 1H), 2.90−2.55 (m, 4H), 2.20−1.80 (m, 2H), 1.29 (s, 3H), 1.21 (s, 3H).

2,3-Di-*O*-benzyl-5-deoxy-4-*C*-methyl-D-*ribo*-furanose (9). A heterogeneous mixture of $CaCO_3$ (4.9 g, 48.7 mmol), MeI (1.5 mL, 24.35 mmol), and dithiane **8** (2.04 g, 4.9 mmol) in acetonitrile/THF/H_2O (2/2/9, 50 mL) was refluxed overnight. More MeI (1.5 mL, 24.35 mmol) was added, and refluxing was continued for 24 h. The mixture was cooled, diluted with EtOAc, washed with saturated aqueous NH_4Cl, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate 75/25 to 60/40) to provide lactol **9** (1.4 g, 88%) as a 1/1 mixture of anomers: ^{1}H NMR ($CDCl_3$) δ 7.50−7.25 (m, 10H), 5.42 (d, J = 1.9 Hz, 0.5H), 5.30 (dd, J = 11.1, 3.3 Hz, 0.5H), 4.95−4.52 (m, 4H), 4.28 (d, J = 11.1 Hz, 0.5H), 4.13 (t, J = 5.0 Hz, 0.5H), 4.00−3.90 (m, 1H), 3.75 (d, J = 5.0 Hz, 0.5H), 2.60 (br s, 0.5H), 1.45 (s, 0.5H), 1.42 (s, 0.5H), 1.40 (s, 0.5H), 1.22 (s, 0.5H).

5-Deoxy-2,3-*O*-isopropylidene-4-*C*-methyl-D-*ribo*-furanose (10). $Pd(OH)_2$ (20%/carbon, 500 mg) was added to a solution of furanose **9** (2.62 g, 8 mmol) in EtOAc (50 mL), and the degassed reaction mixture was stirred under 1 atm of H_2 at room temperature. After 3 h, the catalyst was removed by filtration through Celite and rinsed with boiling MeOH. The combined filtrates were concentrated under reduced pressure and azeotroped twice with DMF. The oily residue was taken-up into DMF (10 mL) to which *p*-TsOH·H_2O (cat.) and 2,2-dimethoxypropane (4.6 mL, 40 mmol) were added. After stirring at room temperature for 16 h, the reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate 80/20 to 70/30) to provide lactol **10** (507 mg, 34%): ^{1}H NMR ($CDCl_3$) δ 5.38 (d, J = 2.5 Hz, 1H), 4.74 (d, J = 7.6 Hz, 1H), 4.44 (d, J = 7.6 Hz, 1H), 2.63 (bd, J = 2.5 Hz, 1H), 1.48 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H).

Bases **12c**−**f** were synthesized by condensation of the appropriate aniline with carbonitrile **11**[16] by the procedure described for the synthesis of **12a**.[4b]

4-*N*-(4-Bromophenyl)amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (12c). Brown solid, 84% yield: ^{1}H NMR (DMSO-d_6) δ 11.50 (br s, 1H, exchangeable with D_2O), 8.37 (s, 1H), 7.70−7.40 (m, 11H, 1H exchangeable with D_2O).

4-*N*-(4-Ethoxyphenyl)amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (12d). Brown solid, 50% yield: ^{1}H NMR (DMSO-d_6) δ 11.50 (br s, 1H, exchangeable with D_2O), 8.38 (s, 1H), 7.70−7.35 (m, 9H, 1H exchangeable with D_2O), 6.85 (d, J = 9 Hz, 2H), 3.98 (q, J = 7 Hz, 2H), 1.32 (t, J = 7 Hz, 3H).

4-*N*-(3-Ethoxyphenyl)amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (12e). Brown solid, 23% yield: ^{1}H NMR (DMSO-d_6) δ 11.30 (br s, 1H, exchangeable with D_2O), 8.38 (s, 1H), 7.70−7.30 (m, 7H, 1H exchangeable with D_2O), 7.17 (t, J = 8.4 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 6.56 (dd, J = 8.1, 2.1 Hz, 1H), 3.98 (q, J = 7.0 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H).

4-*N*-(3,4-Ethylenedioxyphenyl)amino-5-phenylpyrrolo-[2,3-*d*]pyrimidine (12f). Recrystallized from toluene as a gray powder, 58% yield: ^{1}H NMR (DMSO-d_6) δ 12.07 (br s, 1H, exchangeable with D_2O), 8.31 (s, 1H), 7.63−7.35 (m, 11H), 7.27 (d, J = 2.2 Hz, 1H), 7.20 (s, 1H, exchangeable with D_2O), 6.83 (dd, J = 8.4, 2.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 4.26−4.13 (m, 4H).

4-Chloro-5-iodo-7-(2′,3′-*O*-isopropylidene-4′-*C*-spirocyclopropyl-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (16a). Hexamethylphosphorus triamide (1.7 mL, 7.98 mmol) was added to a solution of CCl_4 (1.03 mL, 10.64 mmol) and furanose **4** (500 mg, 2.66 mmol) in dry toluene (25 mL) at −78 °C. The reaction mixture was warmed to 0 °C in the course of 1 h and stirred at 0 °C for 30 min. The orange solution was quenched with water, diluted with toluene, and washed with water and then brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to a volume of ca. 5 mL. The resulting chloro sugar solution was added to a mixture of **15**[11] (1.11 g, 3.99 mmol), finely powdered KOH (85%, 350 mg, 5.32 mmol), TDA-1 (1.7 mL, 5.32 mmol), and 4 Å molecular sieves in dry toluene (25 mL) which had been stirring at room temperature for 2 h. After stirring overnight at room temperature, the reaction mixture was filtered through Celite, and the filtering pad was rinsed with EtOAc. The filtrate was diluted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate 90/10 to 70/30) to provide nucleoside **16a** (402 mg, 34%): ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 7.40 (s, 1H), 6.28 (s, 1H), 5.52 (d, J = 6.3 Hz, 1H), 4.82 (d, J = 6.3 Hz, 1H), 1.62 (s, 3H), 1.42 (s, 3H), 1.17−0.97 (m, 2H), 0.80−0.50 (m, 2H).

4-Chloro-5-iodo-7-(2′,3′-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (16b). Oxalyl chloride (5.4 mL, 61.9 mmol) was added dropwise (keeping the temperature below 35 °C) to a solution of DMF (4.9 mL, 63.2 mmol) in toluene (60 mL) and acetonitrile (25 mL). The white slushy mixture was stirred at room temperature for 15 min and then cooled to −12 °C. A solution of **13**[18] (9.97 g, 62.2 mmol) in toluene (10 mL) was added to the reaction mixture, maintaining the temperature below −12 °C. After stirring at −12 °C for 20 min, the yellow solution was cooled to −16 °C and a solution of Et_3N (10.8 mL, 77.4 mmol) in toluene (11 mL) was added, maintaining the temperature below 0 °C. The yellow heterogeneous mixture was stirred for 15 min at 0 °C, and the salts were filtered off over a pad of Celite and rinsed with toluene (10 mL). The combined filtrates were added to a mixture of **15**[11] (8.7 g, 31.1 mmol), finely powdered KOH (85%, 4.11 g, 62.2 mmol), and TDA-1 (10 mL, 31.2 mmol) in dry toluene (40 mL) which had been stirring at room temperature for 1 h. After stirring for 4 h at room temperature, the reaction mixture was diluted with EtOAc, washed with water and then a solution of 0.5 N HCl, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate 70/30 to 50/50) to provide nucleoside **16b** (3.96 g, 30%): ^{1}H NMR (DMSO-d_6) δ 8.68 (s, 1H), 8.09 (s, 1H), 6.27 (s, 1H), 5.35 (d, J = 6.4 Hz, 1H), 5.23 (dd, J = 6.4, 2.5 Hz, 1H), 4.18−4.03 (m, 2H), 1.48 (s, 3H), 1.32 (s, 3H).

4-Amino-5-iodo-7-(4′-*C*-spirocyclopropyl-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (17a). Liquid ammonia (15 mL) was added to a solution of **16a** (200 mg) in MeOH (15 mL) at −78 °C in a bomb. The bomb was sealed and heated at 100 °C. After 24 h, the bomb was cooled to room temperature and vented. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in 70% aqueous TFA. After stirring at room temperature for 30 min, the reaction mixture was concentrated under reduced pressure, and the residue was azeotroped with H_2O and EtOH. The oily residue was neutralized with saturated aqueous $NaHCO_3$. The white precipitate was filtered and rinsed with water. Recrystallization from EtOH gave nucleoside **17a** (72.5 mg, 42%): mp 232 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.13 (s, 1H), 7.66 (s, 1H), 6.69 (br s, 2H, exchangeable with D_2O), 6.15 (d, J = 6.8 Hz, 1H), 5.43 (d, J = 6.9 Hz, 1H, exchangeable with D_2O), 5.17 (d, J = 4.72 Hz, 1H, exchangeable with D_2O), 4.85−4.73 (m, 1H), 3.86 (t, J = 4.7 Hz, 1H), 0.90−0.60 (m, 4H). Anal. ($C_{12}H_{13}IN_4O_3$·0.25C_2H_5OH) C, H, N.

4-Amino-5-iodo-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (17b). Compound **17b** was synthesized by the procedure described for **17a** (325 mg, 63%): mp 232 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.11 (s, 1H), 7.68 (s, 1H), 6.68 (br s, 2H, exchangeable with D_2O), 6.01 (d, J = 7 Hz, 1H), 5.33 (d, J = 6.9 Hz, 1H, exchangeable with D_2O), 5.12 (d, J = 4.72 Hz, 1H, exchangeable with D_2O), 4.60−4.50 (m, 1H), 4.29 (dd, J = 9.3, 3.7 Hz, 1H), 4.20−4.13 (m, 1H), 3.75 (dd, J = 9.3, 1.2 Hz, 1H). Anal. ($C_{10}H_{11}IN_4O_3$) C, H, N.

4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(2′,3′-*O*-isopropylidene-4′-*C*-spirocyclopropyl-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (18a). Protected nucleoside **18a** was synthesized from furanose **4** and pyrrolopyrimidine base **12b**[4b] by the procedure described for **16a** (294 mg, 26%): ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H), 7.70−7.40 (m, 7H), 7.10−6.90 (m, 3H), 6.88 (s, 1H), 6.49 (s, 1H), 5.62 (d, J = 5.0 Hz, 1H), 4.86 (d, J = 5.0 Hz, 1H), 1.65 (s, 3H), 1.45 (s, 3H), 1.20−0.95 (m, 2H), 0.83−0.58 (m, 2H).

4-*N*-Phenylamino-5-phenyl-7-(5′-deoxy-2′,3′-*O*-isopropylidene-4′-*C*-methyl-β-D-*ribo*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (18b). Protected nucleoside **18b** was synthesized from furanose **10** and pyrrolopyrimidine base **12a**[4b] by the procedure described for **16a** (223 mg, 34%): ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H), 7.70−7.20 (m, 10H), 7.10−6.90 (m, 1H), 6.59 (d, J = 4.5 Hz, 1H), 5.00 (dd, J = 5.8, 4.5 Hz, 1H), 4.52 (d, J = 5.8 Hz, 1H), 1.60 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H).

4-*N*-Phenylamino-5-phenyl-7-(2′,3′-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (18c). Protected nucleoside **18c** was synthesized from *erythro*-furanose **13** and pyrrolopyrimidine base **12a**[4b] by the procedure described for **16b** (1.98 g, 60%): ^{1}H NMR (DMSO-d_6) δ 8.41 (s, 1H), 7.67−7.38 (m, 9H), 7.30 (t, J = 7.6 Hz, 2H), 7.01 (t, J = 7.1 Hz, 1H), 6.30 (s, 1H), 5.40 (d, J = 6.4 Hz, 1H), 5.28 (dd, J = 6.4, 3.8 Hz, 1H), 4.20 (dd, J = 10.2, 3.8 Hz, 1H), 4.06 (d, J = 10.2 Hz, 1H), 1.48 (s, 3H), 1.35 (s, 3H).

4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(2′,3′-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (18d). Protected nucleoside **18d** was synthesized from *erythro*-furanose **13** and pyrrolopyrimidine base **12b**[4b] by the procedure described for **16b** (2.79 g, 63%): ^{1}H NMR ($CDCl_3$) δ 8.43 (s, 1H), 7.60−7.40 (m, 7H), 7.04 (s, 1H), 7.01 (t, J = 8.9 Hz, 2H), 6.89 (s, 1H), 6.08 (s, 1H), 5.61 (d, J = 6.4 Hz, 1H), 5.32 (dd, J = 6.4, 3.8 Hz, 1H), 4.36 (dd, J = 10.2, 3.8 Hz, 1H), 4.24 (d, J = 10.2 Hz, 1H), 1.61 (s, 3H), 1.43 (s, 3H).

4-*N*-(4-Bromophenyl)amino-5-phenyl-7-(2′,3′-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (18e). Protected nucleoside **18e** was synthesized from *erythro*-furanose **13** and pyrrolopyrimidine base **12c** by the procedure described for **16b** (247 mg, 10%): ^{1}H NMR (DMSO-d_6) δ 8.42 (s, 1H), 7.73 (s, 1H, exchangeable with D_2O), 7.65−7.35 (m, 10H), 6.30 (s, 1H), 5.39 (d, J = 6.4 Hz, 1H), 5.28 (dd, J = 6.4, 3.8 Hz, 1H), 4.18 (dd, J = 10.2, 3.8 Hz, 1H), 4.05 (d, J = 10.2 Hz, 1H), 1.50 (s, 3H), 1.34 (s, 3H).

4-*N*-(4-Ethoxyphenyl)amino-5-phenyl-7-(2′,3′-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (18f). Protected nucleoside **18f** was synthesized from *erythro*-furanose **13** and pyrrolopyrimidine base **12d** by the procedure described for **16b** (690 mg, 64%): ^{1}H NMR (DMSO-d_6) δ 8.34 (s, 1H), 7.65−7.50 (m, 4H), 7.55 (s, 1H), 7.43 (t, J = 7.1 Hz, 1H), 7.41 (d, J = 9.0 Hz, 2H), 7.31 (s, 1H), 6.87 (d, J = 9.0 Hz, 2H), 6.29 (s, 1H), 5.39 (d, J = 6.4 Hz, 1H), 5.28 (dd, J = 6.4, 3.8 Hz, 1H), 4.20 (dd, J = 10.2, 3.8 Hz, 1H), 4.05 (d, J = 10.2 Hz, 1H), 3.98 (q, J = 7 Hz, 2H), 1.50 (s, 3H), 1.34 (s, 3H), 1.31 (t, J = 7 Hz, 3H).

4-*N*-(3-Ethoxyphenyl)amino-5-phenyl-7-(2′,3′-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (18g). Protected nucleoside **18g** was synthesized from *erythro*-furanose **13** and pyrrolopyrimidine base **12e** by the procedure described for **16b** (550 mg, 51%): ^{1}H NMR (DMSO-d_6) δ 8.42 (s, 1H), 7.65−7.40 (m, 7H, 1H exchangeable with D_2O), 7.55 (s, 1H), 7.32 (t, J = 1.8 Hz, 1H), 7.17 (t, J = 8.4 Hz, 1H), 6.92 (dd, J = 7.6, 1.8 Hz, 1H), 6.58 (dd, J = 7.6, 2.5 Hz, 1H), 6.31 (s, 1H), 5.39 (d, J = 6.4 Hz, 1H), 5.28 (dd, J = 6.4, 3.8 Hz, 1H), 4.19 (dd, J = 10.2, 3.8 Hz, 1H), 4.06 (d, J = 10.2 Hz, 1H), 3.98 (q, J = 7.0 Hz, 2H), 1.5 (s, 3H), 1.34 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H).

4-*N*-(3,4-Ethylenedioxyphenyl)amino-5-phenyl-7-(2′,3′-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (18h). Protected nucleoside **18h** was synthesized from *erythro*-furanose **13** and pyrrolopyrimidine base **12f** by the procedure described for **16b** (480 mg, 45%): ^{1}H NMR (DMSO-d_6) δ 8.36 (s, 1H), 7.65−7.35 (m, 6H), 7.31 (s, 1H), 7.24 (d, J = 1.4 Hz, 1H), 6.85−6.73 (m, 2H), 6.29 (s, 1H), 5.39 (d, J = 6.4 Hz, 1H), 5.28 (dd, J = 6.4, 3.8 Hz, 1H), 4.27−4.11 (m, 5H), 4.06 (d, J = 10.2 Hz, 1H), 1.50 (s, 3H), 1.34 (s, 3H).

4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(4′-*C*-spirocyclopropyl-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (19a). A solution of **18a** (289 mg) in 70% aqueous TFA (20 mL) was stirred at 0 °C for 1 h and at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and azeotroped twice with H_2O and twice with EtOH. The residue was neutralized with saturated aqueous $NaHCO_3$, and the precipitate was filtered and rinsed with water. Recrystallization from ethanol provided nucleoside **19a** (160 mg, 60%): mp 142 °C; ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.76 (s, 1H), 7.6−7.4 (m, 5H), 7.35−7.25 (m, 2H), 6.89 (t, J = 8.4 Hz, 2H), 6.84 (s, 1H), 6.39 (d, J = 6.2 Hz, 1H), 4.86 (dd, J = 6.2, 4.8 Hz, 1H), 4.14 (d, J = 4.8 Hz, 1H), 1.20−0.90 (m, 2H), 0.85−0.70 (m, 2H). Anal. ($C_{24}H_{21}FN_4O_3$) C, H, N.

4-*N*-Phenylamino-5-phenyl-7-(5′-deoxy-4′-*C*-methyl-β-D-*ribo*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (19b). Compound **18b** (220 mg) was deprotected by the procedure described for the synthesis of compound **19a**. Recrystallization from ethanol provided nucleoside **19b** (130 mg, 65%): mp 198−200 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 7.60−7.40 (m, 7H), 7.40−7.25 (m, 2H), 7.15−7.00 (m, 2H), 6.01 (d, J = 7.3 Hz, 1H), 4.94 (m, 1H), 3.99 (m, 1H), 3.35 (m, 2H), 1.52 (s, 3H), 1.33 (s, 3H). Anal. ($C_{24}H_{24}N_4O_3$) C, H, N.

4-*N*-Phenylamino-5-phenyl-7-(β-D-*erythro*-furanosyl)-pyrrolo[2,3-*d*]pyrimidine (19c). A solution **18c** (1.95 g) in MeOH (40 mL) and 0.4 N HCl was heated at 65 °C for 3 h. The cooled solution was neutralized with saturated aqueous $NaHCO_3$, and the heterogeneous mixture was stirred at room temperature for 2 h before collecting the precipitate by filtration and rinsing the solid with water. Recrystallization from EtOH provided nucleoside **19c** (1.37 g, 77%): mp 210.5−212 °C; ^{1}H NMR (DMSO-d_6) δ 8.43 (s, 1H), 7.77 (s, 1H), 7.70−7.40 (m, 8H, 1H exchangeable with D_2O) 7.32 (t, J = 8.3 Hz, 2H), 7.03 (t, J = 7.3 Hz, 1H), 6.19 (d, J = 6.7 Hz, 1H), 5.44 (d, J = 6.7 Hz, 1H, exchangeable with D_2O), 5.23 (d, J = 3.7 Hz, 1H, exchangeable with D_2O), 4.80−4.68 (m, 1H), 4.37 (dd, J = 9.2, 3.7 Hz, 1H), 4.27 (br s, 1H), 3.81 (dd, J = 9.2, 1.4 Hz). Anal. ($C_{22}H_{20}N_4O_3$) C, H, N.

4-*N*-(4-Fluorophenyl)amino-5-phenyl-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (19d). Compound **18d** (4.83 g) was deprotected by the procedure described for the synthesis of compound **19c**. Recrystallization from EtOH provided nucleoside **19d** (4.06 g, 91%): mp 194−195 °C; ^{1}H NMR (DMSO-d_6) δ 8.41 (s, 1H), 7.76 (s, 1H), 7.70−7.35 (m, 8H, 1H exchangeable with D_2O), 7.16 (t, J = 8.9 Hz, 2H), 6.20 (d, J = 6.6 Hz, 1H), 5.44 (d, J = 6.8 Hz, 1H, exchangeable with D_2O), 5.23 (d, J = 4.0 Hz, 1H, exchangeable with D_2O), 4.80−4.68 (m, 1H), 4.37 (dd, J = 9.2, 3.7 Hz, 1H), 4.32−4.22 (m, 1H), 3.81 (dd, J = 9.2, 1.4 Hz, 1H); ^{13}C NMR 158.0 (d, J = 238 Hz), 153.8, 151.5, 151.2, 135.9 (d, J = 2.3 Hz), 134.8, 129.1, 128.8, 127.3, 122.6, 122.1 (d, J = 7.6 Hz), 116.2, 115.3 (d, J = 22 Hz), 101.9, 87.1, 74.8, 73.3, 70.4; MS (EI) m/z 407 $(M + 1)^+$ and 405 $(M - 1)^-$. Anal. ($C_{22}H_{19}FN_4O_3$) C, H, N.

4-*N*-(4-Bromophenyl)amino-5-phenyl-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (19e). Compound **18e** (234 mg) was deprotected by the procedure described for the synthesis of compound **19a**. Recrystallization from EtOH provided nucleoside **19e** (158 mg, 73%): mp 208−209 °C; ^{1}H NMR (DMSO-d_6) δ 8.41 (s, 1H), 7.76 (s, 1H), 7.73 (s, 1H, exchangeable with D_2O), 7.65−7.35 (m, 9H), 6.17 (d, J = 6.8 Hz, 1H), 5.40 (d, J = 6.8 Hz, 1H, exchangeable with D_2O), 5.23 (br s, 1H, exchangeable with D_2O), 4.75−4.65 (m, 1H), 4.34

(dd, J = 9.4, 3.9 Hz, 1H), 4.28−4.19 (m, 1H), 3.77 (dd, J = 9.4, 1.4 Hz, 1H). Anal. ($C_{22}H_{19}BrN_4O_3$) C, H, N.

4-*N*-(4-Ethoxyphenyl)amino-5-phenyl-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (19f). Compound **19f** (620 mg) was deprotected by the procedure described for the synthesis of compound **19c**. Recrystallization from EtOH provided nucleoside **19f** (370 mg, 65%): mp 164−165 °C; ^{1}H NMR (DMSO-d_6) δ 8.33 (s, 1H), 7.77 (s, 1H), 7.65−7.48 (m, 4H), 7.48−7.36 (m, 1H), 7.42 (d, J = 8.9 Hz, 2H), 7.30 (s, 1H, exchangeable with D_2O), 6.87 (d, J = 8.9 Hz, 2H), 6.16 (d, J = 6.8 Hz, 1H), 5.40 (d, J = 6.7 Hz, 1H, exchangeable with D_2O), 5.19 (d, J = 3.7 Hz, 1H, exchangeable with D_2O), 4.77−4.64 (m, 1H), 4.33 (dd, J = 9.2, 3.7 Hz, 1H), 4.30−4.20 (m, 1H), 3.98 (q, J = 7 Hz, 2H), 3.80 (dd, J = 9.2, 1.4 Hz, 1H), 1.31 (t, J = 7 Hz, 3H). Anal. ($C_{24}H_{24}N_4O_4 \cdot 0.5H_2O$) C, H, N.

4-*N*-(3-Ethoxyphenyl)amino-5-phenyl-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (19g). Compound **18g** (490 mg) was deprotected by the procedure described for the synthesis of compound **19c**. Recrystallization from ethanol provided nucleoside **19g** (365 mg, 84%): mp 183−184 °C; ^{1}H NMR (DMSO-d_6) δ 8.42 (s, 1H), 7.75 (s, 1H), 7.65−7.48 (m, 6H, 1H exchangeable with D_2O), 7.35 (t, J = 1.8 Hz, 1H), 7.17 (t, J = 8.2 Hz, 1H), 6.93 (dd, J = 7.9, 1.8 Hz, 1H), 6.57 (dd, J = 7.9, 2.5 Hz, 1H), 6.17 (d, J = 6.7 Hz, 1H), 5.40 (d, J = 6.7 Hz, 1H, exchangeable with D_2O), 5.19 (d, J = 4 Hz, 1H, exchangeable with D_2O), 4.77−4.64 (m, 1H), 4.35 (dd, J = 9.2, 3.7 Hz, 1H), 4.30−4.20 (m, 1H), 3.98 (q, J = 7 Hz, 2H), 3.78 (dd, J = 9.2, 1.4 Hz, 1H), 1.31 (t, J = 7 Hz, 3H). Anal. ($C_{24}H_{24}N_4O_4$) C, H, N.

4-*N*-(3,4-Ethylenedioxyphenyl)amino-5-phenyl-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (19h). Compound **18h** (460 mg) was deprotected by the procedure described for the synthesis of compound **19c**. Recrystallization from EtOH provided nucleoside **19h** (331 mg, 78%): mp 196−197 °C; ^{1}H NMR (DMSO-d_6) δ 8.35 (s, 1H), 7.70 (s, 1H), 7.65−7.36 (m, 5H), 7.30 (s, 1H, exchangeable with D_2O), 7.24 (d, J = 2.1 Hz, 1H), 6.82 (dd, J = 8.3, 2.1 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.15 (d, J = 6.7 Hz, 1H), 5.39 (d, J = 6.7 Hz, 1H, exchangeable with D_2O), 5.19 (d, J = 4 Hz, 1H, exchangeable with D_2O), 4.75−4.62 (m, 1H), 4.33 (dd, J = 9.2, 3.7 Hz, 1H), 4.28−4.14 (m, 5H), 3.77 (d, J = 9.2 Hz, 1H). Anal. ($C_{24}H_{22}N_4O_5$) C, H, N.

4-*N*-(4-Fluorophenyl)amino-5-iodo-7-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]-pyrimidine (20a). A solution of *t*-BuOK (18.3 mL, 1 M in THF, 18.3 mmol) was added to a solution of **16b** (5.14 g, 12.2 mmol) and 4-fluoroaniline (1.62 g, 14.6 mmol) in THF (24 mL) at −20 °C. After stirring at −20 °C for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting solution was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography (CH_2Cl_2/hexane 3/1) to provide nucleoside **20a** (5.44 g, 90%): ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1H), 7.85 (s, 1H), 7.75−7.60 (m, 2H), 7.15 (s, 1H), 7.10 (t, J = 8.9 Hz, 2H), 5.99 (s, 1H), 5.50 (d, J = 6.1 Hz, 1H), 5.24 (dd, J = 6.1, 3.8 Hz, 1H), 4.35−4.15 (m, 2H), 1.58 (s, 3H), 1.41 (s, 3H).

4-*N*-(4-Cyanophenyl)amino-5-iodo-7-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]-pyrimidine (20b). Coupling of 4-cyanoaniline (1.79 g, 15.19 mmol) with **16b** (5.07 g, 12.03 mmol) by the procedure described for the synthesis of **20a** provided nucleoside **20b** (4.99 g, 82%): ^{1}H NMR (DMSO-d_6) δ 8.87 (s, 1H, exchangeable with D_2O), 8.73 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.8 (d, J = 8.8 Hz, 2H), 7.79 (s, 1H), 6.22 (s, 1H), 5.32 (d, J = 5.9 Hz, 1H), 5.23 (dd, J = 5.9, 2.9 Hz, 1H), 4.13 (dd, J = 10.3, 2.9 Hz, 1H), 4.04 (d, J = 10.3 Hz, 1H), 1.47 (s, 3H), 1.32 (s, 3H).

4-*N*-(3,4-Ethylenedioxyphenyl)amino-5-iodo-7-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]-pyrimidine (20c). Coupling of 3,4-ethylenedioxyaniline (2.2 mL, 18.3 mmol) with **16b** (5.1 g, 12.3 mmol) by the procedure described for the synthesis of **20a** provided nucleoside **20c** (5.93 g, 90%): ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1H), 7.84 (s, 1H), 7.38 (d, J = 2.6 Hz, 1H), 7.12 (s, 1H), 7.03 (dd, J = 8.8, 2.6 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 5.96 (s, 1H), 5.78 (d, J = 5.8 Hz, 1H), 5.23 (dd, J = 5.8, 3.0 Hz, 1H), 4.35−4.17 (m, 6H), 1.57 (s, 3H), 1.40 (s, 3H).

4-*N*-(2-Methoxyphenyl)amino-5-iodo-7-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (20d). Coupling of 2-methoxyaniline (1.8 mL, 15.96 mmol) with **16b** (4.95 g, 11.73 mmol) by the procedure described for the synthesis of **20a** provided nucleoside **20d** (5.56 g, 93%): ^{1}H NMR (DMSO-d_6) δ 8.86 (s, 1H, exchangeable with D_2O), 8.8−8.7 (m, 1H), 8.41 (s, 1H), 7.71 (s, 1H), 7.15−6.90 (m, 3H), 6.19 (s, 1H), 5.30 (d, J = 6.1 Hz, 1H), 5.22 (dd, J = 6.1, 3.8 Hz, 1H), 4.10 (dd, J = 10.7, 3.8 Hz, 1H), 4.03 (d, J = 10.7 Hz, 1H), 4.03 (d, J = 10.7 Hz, 1H), 3.96 (s, 3H), 1.46 (s, 3H), 1.31 (s, 3H).

4-*N*-(4-Fluorophenyl)amino-5-(3-aminophenyl)-7-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]-pyrimidine (21a). A heterogeneous mixture of **20a** (1.0 g, 2.01 mmol), 3-aminophenylboronic acid (375 mg, 2.41 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) in EtOH (5 mL), ethylene glycol dimethyl ether (25 mL), and saturated aqueous Na_2CO_3 (5 mL) was heated at reflux for 7 h. The cooled reaction mixture was diluted with EtOAc and washed with H_2O and brine, dried (Na_2SO_4), and concentrated to dryness. The solid residue was purified by flash chromatography to provide protected nucleoside **21a** (876 mg, 94%): ^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1H), 7.60−7.45 (m, 2H), 7.31 (t, J = 6.9 Hz, 1H), 7.18 (s, 1H), 7.10−6.93 (m, 3H), 6.88 (d, J = 7.6 Hz, 1H), 6.84−6.70 (m, 2H), 6.07 (s, 1H), 5.58 (d, J = 6.4 Hz, 1H), 5.31 (dd, J = 6.4, 3.8 Hz, 1H), 4.35 (dd, J = 10.2, 3.8 Hz, 1H), 4.22 (d, J = 10.2 Hz, 1H), 3.75 (br s, 2H), 1.60 (s, 3H), 1.45 (s, 3H).

4-*N*-(4-Cyanophenyl)amino-5-(4-ethoxyphenyl)-7-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]-pyrimidine (21b). Suzuki coupling of **20b** (553 mg, 1.06 mmol) with 4-ethoxyphenylboronic acid (888 mg, 5.35 mmol) by the procedure described for the synthesis of **21a** provided protected nucleoside **21b** which was carried into the deprotection step without purification: ^{1}H NMR (DMSO-d_6) δ 8.49 (s, 1H), 8.15 (s, 1H, exchangeable with D_2O), 7.80−7.75 (m, 5H), 7.48 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.30 (s, 1H), 5.38 (d, J = 5.9 Hz, 1H), 5.27 (dd, J = 5.9, 3.7 Hz, 1H), 4.18 (dd, J = 10.2, 3.7 Hz, 1H), 4.08 (q, J = 7 Hz, 2H), 4.05 (d, J = 10.2 Hz, 1H), 1.49 (s, 3H), 1.36 (t, J = 7 Hz, 3H), 1.33 (s, 3H).

4-*N*-(4-Cyanophenyl)amino-5-(4-chlorophenyl)-7-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]-pyrimidine (21c). Suzuki coupling of **20b** (528 mg) with 4-chlorophenylboronic acid by the procedure described for the synthesis of **21a** provided protected nucleoside **21c** (404 mg, 79%): ^{1}H NMR (DMSO-d_6) δ 8.54 (s, 1H, exchangeable with D_2O), 8.51 (s, 1H), 7.8−7.65 (m, 5H), 7.60−7.4 (m, 4H), 6.32 (s, 1H), 5.39 (d, J = 5.9 Hz, 1H), 5.28 (dd, J = 5.9, 3.7 Hz, 1H), 4.19 (dd, J = 10.2, 3.7 Hz, 1H), 4.05 (d, J = 10.2 Hz, 1H), 1.49 (s, 3H), 1.39 (t, J = 7 Hz, 3H), 1.34 (s, 3H).

4-*N*-(3,4-Ethylenedioxyphenyl)amino-5-(2-methylphenyl)-7-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)-pyrrolo[2,3-*d*]pyrimidine (21d). Suzuki coupling of **20c** (525 mg) with 2-methylphenylboronic acid by the procedure described for the synthesis of **21a** provided protected nucleoside **21d** (446 mg, 91%): ^{1}H NMR (DMSO-d_6) δ 8.36 (s, 1H), 7.50−7.25 (m, 7H), 7.10 (d, J = 2.2 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.57 (dd, J = 8.4, 2.2 Hz, 1H), 6.27 (s, 1H), 5.38 (d, J = 5.9 Hz, 1H), 5.31−5.22 (m, 1H), 4.25−3.92 (m, 6H), 2.21 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H).

4-*N*-(2-Methoxyphenyl)amino-5-(4-ethoxyphenyl)-7-(2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (21e). Suzuki coupling of **20d** (521 mg, 1.03 mmol) with 4-ethoxyphenylboronic acid (856 mg, 5.16 mmol) by the procedure described for the synthesis of **21a** provided protected nucleoside **21e** (392 mg, 76%): ^{1}H NMR (DMSO-d_6) δ 8.82−8.75 (m, 1H), 8.44 (s, 1H), 7.68 (s, 1H, exchangeable with D_2O), 7.45 (d, J = 8.4 Hz, 2H), 7.44 (s, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.00−6.98 (m, 3H), 6.28 (s, 1H), 5.38 (d, J = 5.9 Hz, 1H), 5.27 (dd, J = 5.9, 3.7 Hz, 1H), 4.20 (dd, J = 10.2, 3.7

Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 4.05 (d, J = 10.2 Hz, 1H), 3.56 (s, 3H), 1.49 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H), 1.33 (s, 3H).

4-*N*-(4-Fluorophenyl)amino-5-(3-aminophenyl)-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (22a). Compound **21a** (870 mg) was deprotected by the procedure described for the synthesis of compound **17a**. Recrystallization from ethanol provided nucleoside **22a** (495 mg, 62%): mp 148−150 °C; ^{1}H NMR (DMSO-d_6) δ 8.38 (s, 1H), 7.65−7.50 (m, 4H, 1H exchangeable with D_2O), 7.30−7.10 (m, 3H), 6.83−6.6 (m, 3H), 6.16 (d, J = 6.8 Hz, 1H), 5.50−5.30 (m, 3H, exchangeable with D_2O), 5.20 (d, J = 4 Hz, 1H, exchangeable with D_2O), 4.78−4.65 (m, 1H), 4.35 (dd, J = 9.2, 3.7 Hz, 1H), 4.28−4.20 (m, 1H), 3.79 (d, J = 9.2 Hz, 1H). Anal. ($C_{22}H_{20}FN_5O_3 \cdot 0.6H_2O$) C, H, N.

4-*N*-(4-Cyanophenyl)amino-5-(4-ethoxyphenyl)-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (22b). Compound **21b** was deprotected by the procedure described for the synthesis of compound **17a**. Recrystallization from ether/MeOH provided nucleoside **22b** (143 mg, 29% for 2 steps): mp 188−190 °C; ^{1}H NMR (DMSO-d_6) δ 8.48 (s, 1H), 8.15 (s, 1H, exchangeable with D_2O), 7.80−7.65 (m, 5H), 7.30 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.18 (d, J = 6.6 Hz, 1H), 5.40 (d, J = 6.6 Hz, 1H, exchangeable with D_2O), 5.20 (d, J = 4 Hz, 1H, exchangeable with D_2O), 4.75−4.65 (m, 1H), 4.34 (dd, J = 9.2, 3.7 Hz, 1H), 4.28−4.20 (m, 1H), 4.08 (q, J = 7 Hz, 2H), 3.78 (dd, J = 9.2, 1.5 Hz, 1H), 1.36 (t, J = 7 Hz, 3H). Anal. ($C_{25}H_{23}FN_5O_4 \cdot H_2O$) C, H, N.

4-*N*-(4-Cyanophenyl)amino-5-(4-chlorophenyl)-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (22c). Compound **21c** was deprotected by the procedure described for the synthesis of compound **17a**. Recrystallization from MeOH/ether provided nucleoside **22c** (245 mg, 66%): mp 225−227 °C; ^{1}H NMR (DMSO-d_6) δ 8.54 (s, 1H, exchangeable with D_2O), 8.49 (s, 1H), 7.89 (s, 1H), 7.8−7.62 (m, 4H), 7.60−7.42 (m, 4H), 6.19 (d, J = 6.6 Hz, 1H), 5.40 (d, J = 6.6 Hz, 1H, exchangeable with D_2O), 5.20 (d, J = 4 Hz, 1H, exchangeable with D_2O), 4.75−4.65 (m, 1H), 4.35 (dd, J = 9.2, 3.7 Hz, 1H), 4.29−4.19 (m, 1H), 3.78 (dd, J = 9.2, 1.5 Hz, 1H). Anal. ($C_{23}H_{18}ClN_5O_3 \cdot 0.25H_2O$) C, H, N.

4-*N*-(3,4-Ethylenedioxyphenyl)amino-5-(2-methylphenyl)-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (22d). Compound **21d** was deprotected by the procedure described for the synthesis of compound **17a**. Recrystallization from pentane/CH_2Cl_2 provided nucleoside **22d** (258 mg, 63%): mp 140−144 °C; ^{1}H NMR (DMSO-d_6) δ 8.35 (s, 1H), 7.58 (s, 1H), 7.50−7.28 (m, 5H), 7.11 (d, J = 2.6 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 6.57 (dd, J = 8.8, 2.6 Hz, 1H), 6.12 (d, J = 6.6 Hz, 1H), 5.39 (d, J = 6.6 Hz, 1H, exchangeable with D_2O), 5.17 (d, J = 4.0 Hz, 1H, exchangeable with D_2O), 4.75−4.65 (m, 1H), 4.35 (dd, J = 9.2, 4.0 Hz, 1H), 4.27−4.10 (m, 5H), 3.78 (dd, J = 9.2, 1.5 Hz, 1H), 2.22 (s, 3H). Anal. ($C_{25}H_{24}N_4O_5 \cdot 0.25H_2O$) C, H, N.

4-*N*-(2-Methoxyphenyl)amino-5-(4-ethoxyphenyl)-7-(β-D-*erythro*-furanosyl)pyrrolo[2,3-*d*]pyrimidine (22e). Compound **21e** was deprotected by the procedure described for the synthesis of compound **17a**. Recrystallization from MeOH provided nucleoside **22e** (136 mg, 38%): mp 132−134 °C; ^{1}H NMR (DMSO-d_6) δ 8.85−8.75 (m, 1H), 8.43 (s, 1H), 7.67 (s, 1H, exchangeable with D_2O), 7.58 (s, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 7.00−6.85 (m, 3H), 6.15 (d, J = 6.6 Hz, 1H), 5.36 (d, J = 7.0 Hz, 1H, exchangeable with D_2O), 5.15 (d, J = 3.7 Hz, 1H, exchangeable with D_2O), 4.75−4.60 (m, 1H), 4.32 (dd, J = 8.4, 3.8 Hz, 1H), 4.28−4.18 (m, 1H), 4.13 (q, J = 7.0 Hz, 2H), 3.77 (dd, J = 8.4, 0.9 Hz, 1H), 3.56 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H). Anal. ($C_{25}H_{26}N_4O_5 \cdot 0.5H_2O$) C, H, N.

Water Solubility Determination. Into two vials, each containing 1 mg of test compound, was added 1 mL of DMSO and 1 mL of 100 mM MOPS pH 7.4 buffer, respectively. The vials were sonicated at room temperature for 15 min, allowed to sit for 10 min, and then filtered through 0.45 μm filters. The DMSO solution was diluted 10-fold with DMSO. A 50 μL sample of each solution was injected into a high-performance liquid chromatograph (UV detector set at 280 nm). Water solubility was calculated according to the following equation: solubility = ((peak area$_{buffer}$)/(peak area$_{DMSO}$ × 10))(1000 μg/mL).

Human Recombinant Adenosine Kinase IC_{50} Determination. The assay was performed as previously described.[4a]

Rat Formalin Paw Pain Assay.[23] Fasted male Sprague-Dawley (SD) rats (4 weeks, 100−120 g body weight) were used for each test. The test compound was suspended in 0.1% methylcellulose (MC) and administered orally (20 mg/kg for screening and 1, 3, and 10 mg/kg for ED_{50} determination; 0.5 mL/100 g rat) 15 min before the formalin challenge. A 0.1% MC solution in water was used as the vehicle. Animals were habituated to the observation chamber, and then 50 μL of a 2% formalin solution was injected subcutaneously into the plantar surface of the right hind paw. They were monitored for pain related behaviors at 0−5 min (1st phase) and 15−30 min (2nd phase) after the challenge. Licking and/or biting behavior was scored for 5 s every 30 s as follows: 0 = no licking and/or biting and 1 = licking and/or biting behaviors observed. Inhibition values are reported for the 2nd phase.

Hot Plate Assay. Fasted male SD rats (150−200 g) were orally gavaged with vehicle or various doses of test compound. Prior to gavage and at intervals from 0.5 to 4 h after gavage, each animal was placed on a 50 °C hot plate (Ugo Basile) for a maximum of 60 s. Latency to licking of the hind paw was recorded, and analgesic activity was expressed as maximal possible effect ([test latency − baseline latency]/[60 − baseline latency] × 100). The ED_{50} was calculated for the analgesic effect measured at 3 h after administration.

Rat Carrageenan-Induced Mechanical Hyperalgesia Test.[25] Fasted male SD rats (100−120 g body weight) were used for each test. The test compound was suspended in 0.1% MC (1, 3, and 10 mg/kg) and administered orally (0.5 mL/100 g rat) 1 h before intraplantar carrageenan injection (1%, 100 μL/paw). Analgesic effects were measured at 3, 4, and 5 h after carrageenan injection using a Randall-Selitto analgesimeter purchased from Ugo Basile.

Rat Carrageenan-Induced Thermal Hyperalgesia Assay. Fasted male SD rats (160−180 g) were injected sc with lambda carrageenan (2 mg in 100 μL in the plantar surface of the right hind paw), inducing a state of thermal hyperalgesia that was measured by the method of Hargreaves.[26] The vehicle (PEG400/0.2% Tween/5% propylene glycol) or the test compound (20 mg/kg) was administered by oral gavage either 0.5 h prior to (prophylactic administration) or 2 h after (therapeutic administration) carrageenan injection. Withdrawal reaction to the heat source was measured in both the inflamed paw and the noninflamed (control) paw at 3.5−4.5 h after carrageenan injection.

Bradykinin-Induced Licking Assay on Marmoset Monkeys.[27] Six individually housed male marmoset monkeys (*Callithrix jacchus*) weighing 250−340 g were each treated with the test compound at doses of 0.3, 3, 10, and 30 mg/kg, po, or with the vehicle, 0.1% MC (0.5 mL/100 g body weight, po), for the control. The appearance and behavior of the monkeys were monitored and videotaped individually for 75 min following the test compound administration. Sixty minutes after the administration, 100 μL of a 1 mM bradykinin solution in physiological saline was i.pl. injected into the foot pad of the animals. The licking, scratching, and biting in response to the bradykinin administration was recorded on videotape for 15 min, and the results were analyzed to give the pain score. The scores are as follows: 0 = moving the injected leg normally; 1 = keeping the injected foot close to the body; 2 = scratching of the injected area of the leg; and 3 = intensively and repetitively scratching or licking the injected area of the leg. Every 15 s a score was made over a period of 15 min as an index of pain behavior. The animals were subjected to the experiments with an interval of 2 weeks between experiments, and bradykinin was injected into the right and left foot pads, alternately.

Rat Rotorod Assay. The test compound was orally administered at 10−300 mg/kg doses in 0.1% MC to fasted male SD rats (90−110 g body weight). CNS side effects, sedation, and

ataxia were determined by rotarod treadmill (Natsume Seisakusho) rotated at 5 rpm. Rats were trained to walk on the rod for 150 s. The walking time was measured at 0, 0.5, 1, 2, and 5 h after administration with a cutoff time at 150 s.

Emesis Assay on Marmoset Monkeys. Sixteen individually housed male marmoset monkeys (*Callithrix jacchus*) weighing 270−360 g were each treated with the test compound at doses of 10, 30, and 50 mg/kg, po, or with the vehicle, 0.1% MC (0.5 mL/100 g body weight, po), for the control. Time to emesis was recorded over a period of 4 h.

Pharmacokinetics in Rat and Dog for 19d. A suspension of 3 mg/kg in 0.1% MC for the po leg and a solution of 1 mg/kg in 75% PEG 400/25% saline for the intraveneous (iv) leg were administered to rats and dogs. Plasma samples were taken at 0.25, 0.5, 1, 2, 4, 8, and 24 h, and concentrations were determined by high-performance liquid chromatography (HPLC).

Stability in Human Liver Microsomes for 19d. The test compound was incubated at a concentration of 1 μM with human liver microsomes (1.5 mg/mL). Samples were removed and evaluated by HPLC for the percent remaining of the test compound at 0, 0.5, 1, 2, and 4 h after initiation of the incubation.

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Supporting Information Available: Microanalysis data for all final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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