Novel Inhibitors of the Nuclear Factor of Activated T Cells (NFAT)-Mediated Transcription of β-Galactosidase: Potential Immunosupressive and Antiinflammatory Agents

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The preparation of a series of quinazoline-2,4-diones, **1–3**, and pyrrolo[3,4-*d*]pyrimidine-2,4-diones, **4–8** is described. A small number of quinazolinedione analogs were identified from random screening to possess low micromolar (1.3–4.4 μM) potency in the nuclear factor of activated T cells-1-regulated β-galactosidase expression assay. An expanded analog search resulted in identifying pyrrolopyrimidinedione **4b** which is 5–10-fold (0.26 μM) more potent than the quinazolinediones. Replacement of the benzyl group with naphthyl led to greater potency and conformationally restricted analogs **4u–w**. The naphthyl and acenaphthyl analogs are 10–100 times more potent inhibitors of β-galactosidase expression than **4b**. Binding affinity data for displacement of radiolabeled **4s** from Jurkat cell membranes reflected an excellent correlation with the IC_{50} value for inhibition of β-galactosidase activity. These products, whose structure–activity relationships are discussed, are of interest as potential agents for preventing interleukin-2 gene transcription.

Introduction

T cells are essential components of the immune response. They are activated upon contact with foreign substances, or antigens, present on invading microorganisms.[1] In autoimmune disease, however, T cells are activated against particular tissues, such as the joint in rheumatoid arthritis.[2–4] Similarly, T cells which recognize a newly transplanted tissue as foreign play a leading role in graft rejection.[5–7]

One of the earliest events that occurs after T cells recognize foreign antigen is the induction of the interleukin-2 (IL-2) gene.[8] IL-2 is an essential autocrine growth factor for T cells,[9] and its appearance marks a commitment of the T cell to the activation pathway.[8] These activated cells go on to release a variety of biologically active molecules whose cumulative downstream effects initiate and perpetuate an immune/inflammatory response.[10] IL-2 itself also directly activates B cells, natural killer cells, cytolytic T cells, and lymphokine-activated killer cells.[11]

The impact IL-2 has on the development of the immune response makes it an attractive molecule for pharmacological intervention. Clinicians have met with some success using IL-2 receptor antibodies or IL-2 toxin conjugates in the treatment of immune disorders.[11] Clinical studies with cyclosporin A (CSA), and later with FK-506, indicate that preventing IL-2 gene transcription is also therapeutically beneficial in cases of graft rejection and autoimmune disease.[5–7]

The region 300 base pairs upstream of the IL-2 structural gene contains multiple DNA sequences important in the regulation of IL-2 gene transcription.[8,12–14] The region 257–286 base pairs upstream of the IL-2 structural gene binds to a protein, nuclear factor of activated T cells-1 (NFAT-1), prior to IL-2 gene transcription. Numerous studies clearly demonstrate the essential nature of this protein/DNA interaction.[8,15–18] In addition, NFAT-1 is expressed in relatively few cells besides T cells and is markedly upregulated upon stimulation of the T cell receptor.[19] This makes it a highly restricted target for activated T cells.

We have sought to identify compounds which inhibit transcription regulated by the DNA region bound by the NFAT-1 protein. Toward that end, we developed an assay using a T cell line, J.NFATZ.1, which contains a stable gene construct consisting of the NFAT-1 binding site linked to the reporter gene for lac-z.[20] When the cell is activated, the NFAT-1 protein binds the DNA at its recognition site and induces the transcription of β-galactosidase (β-gal), the product of the lac-z gene. Using this assay, we identified a series of compounds which inhibit β-gal expression in this cell line. This paper describes the structure-activity relationships (SAR) around these compounds. Furthermore, we show how this SAR correlates with binding activity in the Jurkat cells, the parent cell from which J.NFATZ.1 was derived. Studies describing the effects of these compounds on NFAT-1-regulated IL-2 transcription and synthesis are described elsewhere.[21]

Chemistry

Methods for the preparation of quinazolinediones[22] and pyrrolopyrimidinediones[23] were adapted for the synthesis of the novel target series **1–8**. Scheme 1 outlines the synthesis of the 7-substituted analogs. Alkylation of 4-nitroanthranilic ester **9** by reductive amination of isobutyric acid followed by ester–amide

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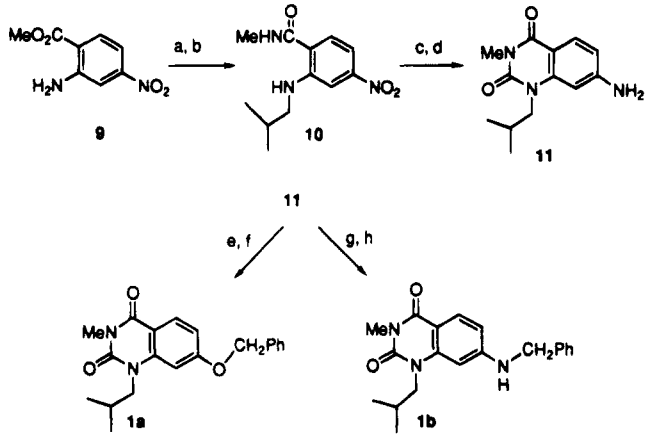
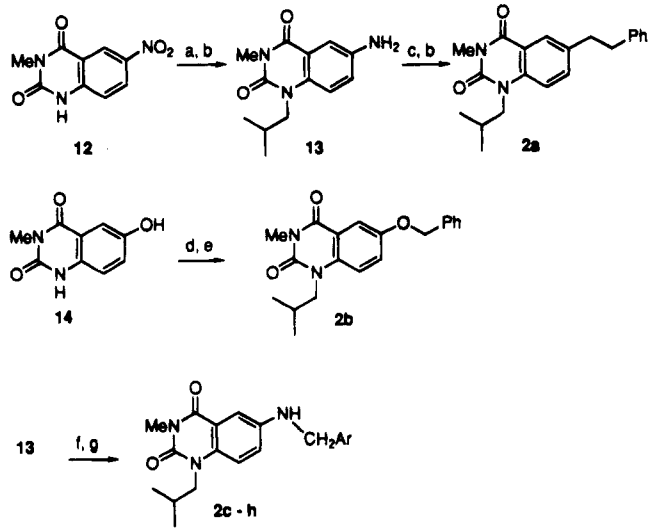
Scheme 1[a]



[a] Reagents: (a) *iso*-butyric acid, $NaBH_4$; (b) $MeNH_2$, H_2O; (c) PhOCOCl, NaH; (d) Pd/C; (e) $NaNO_2$, H_2O; (f) BnBr, KOH; (g) PhCHO; (h) $NaBH_4$.

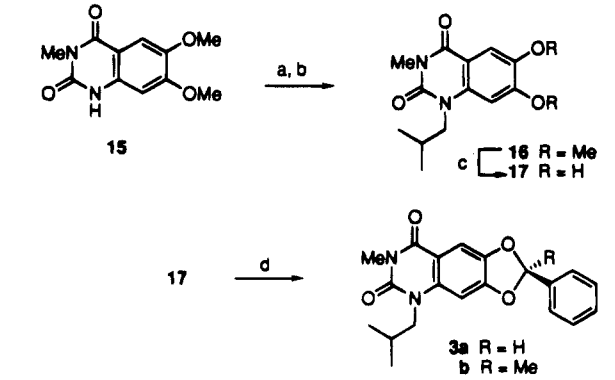
Scheme 2[a]



[a] Reagents: (a) methallyl bromide, K_2CO_3; (b) H_2, Pd/C; (c) *t*-BuONO, styrene, $Pd(dba)_2$; (d) BnBr, K_2CO_3; (e) *i*-BuI, KOH; (f) ArCHO; (g) BH_3.

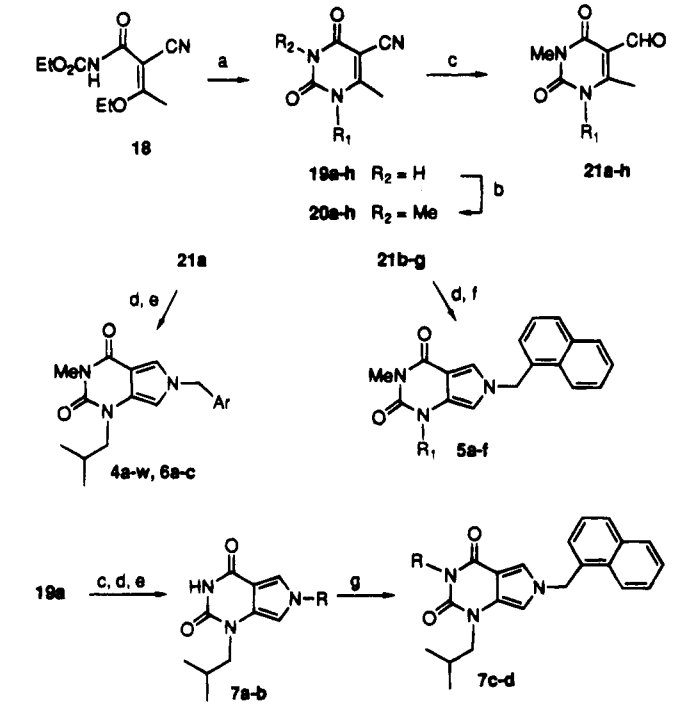
exchange with methylamine gave **10**. Reaction of this amino amide with phenyl chloroformate followed by reduction gave the aniline **11**. Diazotization of **11** followed by hydrolysis gave a phenol which was alkylated with benzyl bromide to give target **1a**. Compound **11** was also reductively alkylated with benzaldehyde to give target **1b**. The targets **2a–h** could all be assembled from the advanced intermediate **13** as shown in Scheme 2. Melting 5-nitroanthranilic acid with 1,1′-dimethylurea (1,1′-DMU) gave quinazolinedione **12**. This material was alkylated with methallyl bromide. Reduction of the olefin and nitro group with H_2 and Pd/C gave the aniline **13**. The diazo species, generated from **13** and *t*-BuONO, was coupled with styrene in a Heck type arylation.[24] The stilbene intermediate was hydrogenated to phenethyl target **2a**. Phenol **14** was first O-benzylated and subsequently N-alkylated to give **2b**. Reductive alkylation of **13** with variously substituted benzaldehydes led to targets **2c–h**. The 1,1′-DMU melt chemistry was used to prepare the known quinazolinedione **15**.[25] The two step alkylation/reduction sequence was used to introduce the isobutyl side chain (**16**; Scheme 3). Aryl ether dealkylation was accomplished with BBr_3 to give catechol **17**. The methylenedioxy targets **3a,b** were prepared by the acid-catalyzed condensation of catechol **17** and benzaldehyde dimethylacetal or acetophenone dimethylketal, respectively.

Scheme 3[a]



[a] Reagents: (a) methallyl bromide; (b) H_2, Pd/C; (c)BBr_3; (d) $PhCR(OMe)_2$, *p*-TSA, 150 °C.

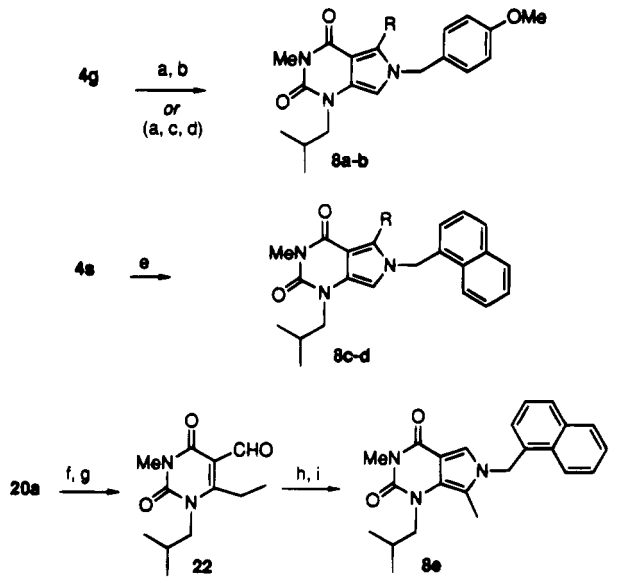
Scheme 4[a]



[a] Reagents: (a) R_1NH_2, EtOH; (b) $(Me)_2SO_2$, NaOH; (c) Ra Ni, HCO_2H; (d) Br_2, $CHCl_3$; (e) RNH_2, EtOH; (f) 1-naphthylmethylamine, EtOH; (g) RI, DMF, K_2CO_3.

The pyrrolopyrimidine-2,4-dione targets were assembled in five synthetic steps starting from *N*-carbethoxybutenamide **18** (Scheme 4). While the substituent on N-1 of the pyrimidine ring is introduced in the first step, the substituents at N-3 and N-6 can be introduced in the last two steps. This allows for the convenient preparation of a variety of analogs from the late intermediate **21a**. Alternatively, alkylation at N-3 can be performed at the beginning of the synthetic process without consequence on overall yield. Thus, the substituent at N-1 of the pyrimidinedione ring system was installed in the first step of synthesis through the condensation of the appropriate primary amine with **18**. The resulting intermediates **19a–h** were methylated to provide pyrimidinediones **20a–h**. The nitrile was then reduced to an aldehyde with freshly prepared RaNi. The

Scheme 5[a]



[a] Reagents: (a) *n*-BuLi; (b) MeSSMe; (c) DMF; (d) (i) morpholine, (ii) $NaBH_4$; (e) LDA, $TolSO_2SR$; (f) *t*-BuOK, MeI; (g) Ra Ni, HCO_2H; (h) Pyr·HBr·Br_2; (i) 1-naphthylmethylamine, $HaHCO_3$.

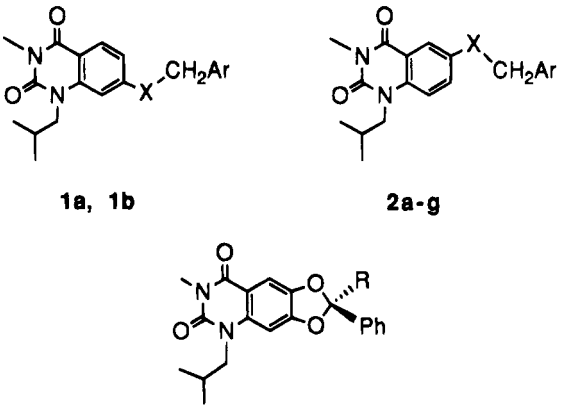
5-formyl intermediates were exposed to a chloroform solution of bromine to afford a bromomethyl compound which was treated directly with an excess of amine. This resulted in formation of the pyrrole ring in series **4**–**7**. In general, 2 equiv of the amine base was used or triethylamine was substituted for the extra equivalent of base to act as an acid scavenger. The 5-substituted pyrrolopyrimidine targets **8** were prepared by alkylation of the pyrrole ring (Scheme 5). The pyrrole anion was generated with *n*-BuLi or LDA and captured with a disulfide or thiosulfinate to give **8a**,**c**,**d**. Acylation of the pyrrole with DMF and subsequent reductive amination with morpholine gave **8b**. The 7-substituted analog was prepared by methylation/reduction of **20a** to give **22**. Bromination and ring closure gave target **8e**.

Results and Discussion

Random screening of our chemical files disclosed the activity of the 7-(benzyloxy)quinazolinedione **1a** (Table 1) in the NFAT-1-regulated β-galactosidase expression assay. A search for other quinazolinediones resulted in the identification of a small number of analogs. Moving the benzylic-X group to position 6 (**2a**–**c**) had little affect on activity, whereas replacement of the O with N (**1b**) led to a decrease in activity. Since the 6-benzylamino compounds were readily available, additional analogs, **2d**–**h**, were prepared. With the exception of **2d**, all the analogs were less active than **1a**. The data shown for **2c**–**h** argue for a steric effect at position 4 since substituents larger than fluorine result in a decrease in activity regardless of the electronic nature of the substituent.

In an effort to determine if the benzylic group exhibited a conformational preference in the active compounds, NOE measurements were made on **1a**,**b** and **2b**,**c**. The benzylic hydrogens were irradiated and enhancements of the ortho hydrogens on the quinazoline ring noted. The data are shown in Table 2. While weak enhancements are observed, there is no indication in any compound of clear conformational preference. A more rigorous probe of the conformational requirement

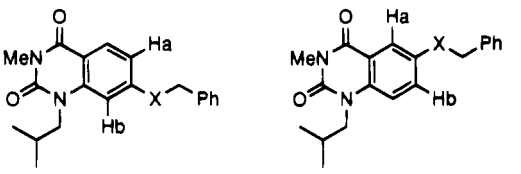
Table 1. Inhibition of NFAT-1-Regulated β-Gal Activity by Quinazolinediones



compd	X	Ar	β-gal[a]
1a	O	Ph	2.05
1b	NH	Ph	40% at 10 μM
2a	CH_2	Ph	4.03
2b	O	Ph	2.50
2c	NH	Ph	4.47
2d	NH	2-F-Ph	1.32
2e	NH	4-MeO-Ph	15% at 10 μM
2f	NH	4-CO_2Me-Ph	35% at 10 μM
2g	NH	4-CO_2H-Ph	30% at 10 μM
2h	NH	4-*t*-Bu-Ph	34% at 10 μM
3a		R = H	2.25
3b		R = Me	4.48

[a] Mean of two determinations, μM.

Table 2. NOE Data and β-Galactosidase Activity

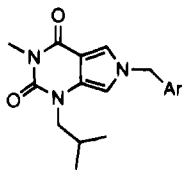


compd	X	NOE *a*/*b*	IC_{50} β-gal
1a	O	7/5	2.05
1b	N	4/4	40% at 10 μM
2a	O	10/2	2.50
2b	N	14/6	4.47

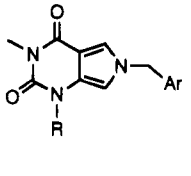
of the benzylic ring was made using **3a**,**b**. In these compounds the phenyl substituent is confined to the region between the dioxolane oxygen atoms but may interconvert between axial and equatorial conformers. It was hoped that the presence or absence of a geminal methyl group would influence the axial/equatorial equilibrium so as to further define the conformational requirement of the phenyl ring. However, molecular mechanics calculations indicated only a small difference in energy between the two compounds for this interconversion (0.6–1.3 kcal/mol for **3a** vs 0.9–2.1 kcal/mol for **3b**). The difference in biological activity is also small (Table 1), and thus no meaningful conclusion regarding active conformation can be drawn.

An expanded analog search and further biological testing resulted in **4b** (Table 3), a pyrrolopyrimidinedione which is 5–10-fold more potent than the quinazolinediones. However, synthesis and testing of additional analogs, **4a**,**c**–**p**, resulted in little additional information regarding SAR. In order to compare the structures

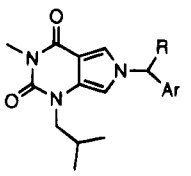
Table 3. Inhibition of NFAT-1-Regulated β-Gal Activity and of [^3H_3C]-**4r** Binding to Jurkat Cell Membranes



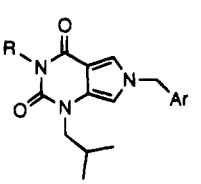
4a-w



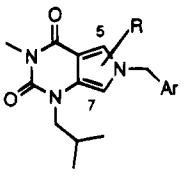
5b-h



6a-c



7a-d



8a-e

compd	R	Ar	β-gal[a]	binding, K_i[a]
4a		Ph	870	
4b		*o*-Cl-Ph	260	122
4c		*o*-F-Ph	630	
4d		*p*-Cl-Ph	435	
4e		*o*-MeO-Ph	275	170
4f		*m*-MeO-Ph	275	
4g		*p*-MeO-Ph	240	
4h		*p*-MeS-Ph	260	
4i		*p*-*n*-BuO-Ph	190	158
4j		*p*-OH	640	
4k		*p*-Me-Ph	320	
4l		*p*-CF_3-Ph	1300	
4m		2,3-di-Cl-Ph	1200	
4n		2,3-di-MeO-Ph	224	
4o		2,4-di-MeO-Ph	310	88
4p		3,4-di-MeO-Ph	378	
4q		3-I,4-MeO-Ph	166	
4r		3-I,4-HO-Ph	89	
4s		1-naphthyl	26	23.0
4t		2-naphthyl	75	29.4
4u		acenaphthyl	8.0	
4v		1-indanyl	186	
4w		2-indanyl	312	4.8
5a	Et	1-naphthyl	440	
5b	*i*-Pr	1-naphthyl	21.5	15.3
5c	CH_2-c-C_3H_5	1-naphthyl	140	
5d	*i*-pentyl	1-naphthyl	815	
5e	CH_2-c-C_6H_{11}	1-naphthyl	1210	
5f	*2*-propanol	1-naphthyl	3950	697
5g	*s*-Bu	acenaphthyl	5.4	
5g(i)	*s*-Bu	acenaphthyl	2.6	
5g(ii)	*s*-Bu	acenaphthyl	6.7	
5g(iii)	*s*-Bu	acenaphthyl	17.0	
5g(iv)	*s*-Bu	acenaphthyl	48.0	
6a	Ph	Ph	1460	
6b	*S*-(−)-Me	Ph	1300	301
6c	*R*-(+)-Me	Ph	1200	562
7a	H	1-naphthyl	3000	
7b	H	acenaphthyl	660	454
7c	Et	1-naphthyl	90	
7d	$MeNHCO(CH_2)_3$	1-naphthyl	na	
8a	5-SMe	*p*-MeO-Ph	360	305
8b	5-CH_2-morpholino	*p*-MeO-Ph	800	315
8c	5-SMe	1-naphthyl	89	
8d	5-$S(CH_2)_3OH$	1-naphthyl	6.0	1.1
8e	7-Me	1-naphthyl	150	

[a] Mean of two determinations, nM.

of the quinazoline and pyrrolopyrimidine series, a conformational search of the benzyl group in **1a** and **4a** was carried out and the pyrimidinedione moieties were overlaid. In none of the conformations for the two series did the phenyl rings completely overlap; in many conformations the phenyl ring in one series was closely adjacent to that in the other (Figure 1). This suggested that a naphthyl in place of the phenyl in **4a** might be tolerated. Indeed, the resulting 1-naphthyl analog **4s** is 10-fold more potent than **4b**. The corresponding 2-naphthyl **4t** is also active but is about 3-fold less potent than **4s**. There are two degrees of rotational freedom about the single bonds attaching the naphthalene to the pyrrole nitrogen of **4s**. One of these was eliminated by replacing the 1-naphthylmethyl group with the acenaphthyl group to give **4u**, resulting in a 3-fold enhancement in potency over **4s**. That both benzene rings of **4u** are required for high potency is demonstrated by eliminating one or the other by preparation of indanes **4v**,**w**; these compounds are considerably less potent than **4u**.

The SAR for position 1 was investigated using **4s** and **5a**−**f** wherein the N-3 and N-6 substituents were held constant at methyl and 1-naphthylmethyl, respectively. Decreasing the size of the 1-substituent to ethyl (**5a**) reduces potency about 17-fold relative to **4s**. The isopropyl derivative **5b** is equivalent to isobutyl, whereas the isopentyl **5d** and the cyclohexylmethyl **5e** are much less potent. The cyclopropylmethyl **5c** is about 5-fold less potent than **4s**, and the 2-propanol **5f** is about 180-fold less potent than **5b**. Thus, in general, potency increases with bulk up to a point and then decreases,

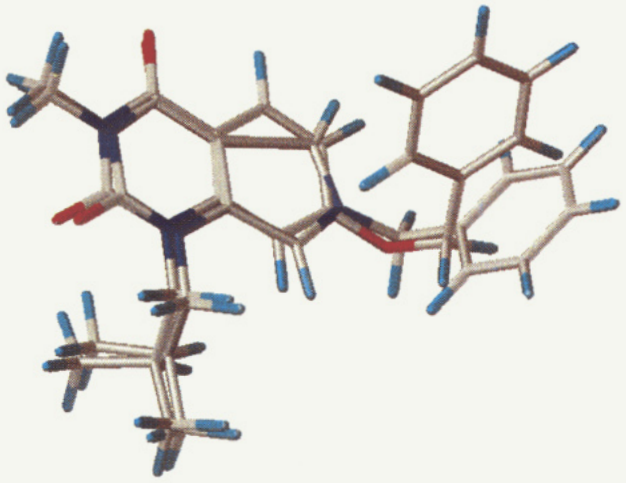


Figure 1.

and it appears that hydrophilic substituents are not tolerated. Taken together, the data on this set of compounds suggest that the region around N-1 binds to a site consisting of a size-restricted hydrophobic pocket.

Compounds **4u**,**v** are racemic about the same carbon atom, but attempts to resolve **4u** were not successful. Therefore, in order to determine enantioselectivity at this position, **6b**,**c** were prepared from the readily available α-methylbenzyl amines. These compounds are less potent than **4a**, presumably because they lack the second benzene ring required for maximum potency, and enantioselectivity is not observed. A second chiral atom was introduced in the N-1 side chain by changing the isobutyl group of **4u** to a *sec*-butyl group to give **5g**. The initial sample, a mixture of racemic diastereomers (four compounds) is equivalent in potency to **4u**. Resolution of the mixture gave the pure enantiomers **5g**(**i**−**iv**). A weak enantioselectivity (18-fold) is observed between the most potent, **5g**(**i**), and the least potent, **5g**(**iv**). This is perhaps not surprising since the chiral atoms are associated with hydrophobic groups whose binding mode may not be as strongly directional as other modes such as hydrogen or ion/dipole binding.

In order to localize the binding site to determine the mechanism of action of this series, a radiolabeled ligand was required for binding studies. Initially, iodinated ligands were considered and **4q**,**r** were prepared. However, these compounds were considered insufficiently potent to be useful for the development of a binding assay. Tritium was next considered and chemistry developed to allow preparation of [3-^3H_3C]-**4s** via alkylation of **7a**. Highly specific binding is observed in the membrane fraction of Jurkat cells. Binding affinity data were generated for 15 selected compounds of Table 3. There is a highly significant correlation ($r^2 = 0.934$) between the IC_{50} values for inhibition of β-galactosidase activity and those for inhibition of labeled **4s** binding to Jurkat cell membranes. Neither the identity of this binding site nor its functional relationship to inhibition of NFAT-1-regulated β-galactosidase activity are known at this time.

In preparation for eventual isolation and purification of the membrane binding site, a number of positions around the pyrrolopyrimidine ring were investigated as potential attachment sites for affinity ligands. Position 3 was eliminated when **7d** was found inactive in the β-galactosidase assay. Position 7 is a possibility (**8e**), but the chemistry to elaborate an attachment function will be arduous. Finally, position 5 is the most likely to produce usable affinity ligands as **8a**−**d** all exhibit activity. Of particular interest is **8d**, since it is among the most potent in the β-galactosidase assay and the most potent ligand in the binding assay. The chemistry at position 5 is reasonably straightforward, and the OH group of **8d** can be elaborated in a variety of ways for attachment to an affinity substrate.

In summary, a series of pyrrolopyrimidinediones were found through screening to inhibit NFAT-1-regulated β-galactosidase activity. Structure−activity relationships were developed and activity was optimized using a combination of classical and computational approaches. Using a tritiated ligand, a binding site with high pharmacological correlation to β-galactosidase activity has been localized to Jurkat cell membranes, and preliminary work toward development of affinity ligands was completed. The functional significance of the binding site in relation to NFAT-1 regulated β−galactosidase activity is the subject of further investigation.

Experimental Section

General Methods. All solvents were HPLC grade and used as received with the exception of THF which was freshly distilled from sodium benzophenone ketyl. Melting points were determined using a Thomas Hoover apparatus and are uncorrected. Infrared spectra were run as 1% KBr pellets on a Nicolet 20-SX spectrometer or obtained from Oneida Research Services, Inc., Oneida, NY. Optical rotations were measured using a Rudolph Auto-Pol III spectrophotometer. Mass spectra were recorded as follows: electron impact spectra were obtained on a Hewlett Packard 5971 GC/MS spectrometer at 70 eV, desorption chemical ionization spectra were obtained on a Nermag R-10−10C spectrometer; fast atom bombardment spectra were obtained on a Kratos Profile HV-2 spectrometer; and high-resolution spectra were obtained by M-Scan, Inc., West Chester, PA. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Unity 300 or General Electric QE 300 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Where analyses are indicated by symbols of the elements, analytical results for those elements are ±0.4% of the theoretical values. [^{3}H]-**4s** (84 Ci/mmol) was synthesized by Amersham, Inc. by direct conversion of the *N*-desmethyl analog of **7a** using ^3H_3CI.

Assay for NFAT-1-Regulated β-Galactosidase Activity. A. Cell Culture. The cell line J.NFATZ.1[20] was obtained from Dr. Gerald Crabtree of the Howard Hughes Institute at Stanford University, Stanford, CA. The cells were maintained in RPMI 1640 media, supplemented with 10% fetal bovine serum, 0.5 mg/mL gentamicin, and 2 mM glutamine (growth media). Cells were discarded after the 25th passage.

B. Assay. Cells were spun and washed once in growth media; 80 μL containing 1.25×10^5 cells were aliquoted per well of a flat-bottomed 96-well tissue culture plate. To obtain a maximal readout, 10 μL of DMSO was added to the wells to give a final concentration of 0.1% DMSO. To obtain maximum suppression of β-galactosidase synthesis, 10 μL of cyclosporin A (CSA; obtained by prescription) was added to the wells to give a final concentration of 300 ng/mL. Other wells contained 10 μL of compounds at a final concentration of 0.1% DMSO. All wells received 10 μL of a mixture containing PMA at a final concentration of 2 ng/mL and ionomycin at a final concentration of 25 μM diluted in growth media. Cells were then incubated for 5 h at 37 °C. At the end of the incubation the plates were spun at 1000 rpm for 5 min. They were then inverted, flicked gently, and blotted dry; 25 μL of lysis buffer

(10 mM Tris HCl, pH 7.5, 0.5 mM $MgCl_2$, and 0.1% Triton X-100), was then added to each well, and the plates were vortexed lightly. Then 75 μL of assay buffer (50 mM KH_2PO_4, pH 7.8, containing 1 mM $MgCl_2$) was added to each well. A 1 mg/mL stock of 4-methylumbelliferyl β-D-galactoside was prepared in 90% dimethylformamide and 10% Triton X-100. This was further diluted to 100 μg/mL in assay buffer, and 10 μL was added to each well, to give a final concentration of 10 μg/mL. Plates were incubated at 37 °C for 1 h and read on an ICN/Flow Fluoroskan II instrument, using an excitation wavelength of 544 nM and an emission wavelength of 590 nM.

Binding Assay. A. Preparation of Jurkat Cell Membranes. Jurkat cells were grown in 3 L of defined medium and harvested by centrifugation at 1000*g*, 15 min. The cell pellets (2×10^9 cells) were resuspended in PBS, combined, and centrifuged as above. The final washed cell pellet was resuspended in 10 volumes (v/v, 80 mL) of assay buffer containing 50 mM Hepes, pH 7.8, 50 mM KCl, 10% glycerol, 0.1 mM EDTA, 1 mM DTT, leupeptin, and pepstatin A (5 μg/mL). The cells were lysed by dounce homogenization and 20 strokes with a tight fitting pestle followed by 3×10 s bursts with a Cole-Plamer ultrasonic homogenizer (setting = 70). The lysed cells were centrifuged at 1200 rpm for 10 min, and the supernatant was retained. The cytosolic extract was centrifuged at 40 000 rpm in a Ti 50.2 rotor for 30 min, and the supernatant was decanted. The membrane pellets were rinsed with assay buffer and then resuspended, combined, and homogenized in 80 mL of the same buffer. Ten milliliter aliquots were frozen at −70 °C until needed. The protein concentration of a typical membrane preparation, determined by the method of Bradford using BSA as a protein standard, was 2.83 mg/mL.

B. [^{3}H]-4s Binding Assay. Jurkat cell membranes (25 μg/tube) were incubated with [^{3}H]-**4s** (1−3 nM) in the absence or presence of increasing concentrations of test compound. Unlabeled **4s** (10 μM) was used to define nonspecific binding. All test compounds were diluted in 50 mM Hepes (pH 7.5) containing 0.1 mM EDTA and 10% DMSO. The final concentration of DMSO in the assay was 1%; this did not have any effect on specific [^{3}H]-**4s** binding. BSA (0.1% final assay concentration) was included in the assay to decrease nonspecific binding. The reagents in the binding assay were incubated at room temperature for 60 min. The assay was terminated by filtration through S&S no. 25 glass fiber filters on a Brandel cell harvester. The filters were washed with room temperature assay buffer (50 mM HEPES, 0.1% EDTA) and then counted in 5 mL of Ready Protein liquid scintillation cocktail.

Analysis of Data. Unless otherwise stated, analysis of [^{3}H]-**1r** binding data to determine values for K_D, K_i, and B_{max} was performed using LIGAND (Munson and Rodbard, 1980), a nonlinear least squares regression program on an IBM-PC computer. The IC_{50} values for inhibition of β-D-galactosidase expression in J.NFATZ.1 cells by the compounds were calculated using the four-parameter logistic equation ALLFIT on NLIN in RS1.[26]

***N*-Methyl-2-[(2-methylpropyl)amino]-4-nitrobenzamide (10).** The aniline **9** (65 g, 0.30 mol) was dissolved in *iso*-butyric acid (700 mL) and cooled to 0 °C. $NaBH_4$ (20 g, 0.50 mol) was added to the mechanically stirred solution over 6 h. The reaction mixture was allowed to stir at room temperature for 14 h. An additional portion of $NaBH_4$ (28 g, 0.75 mol) was added over 6 h. After complete addition of borohydride, the reaction mixture was stirred for 20 h. The reaction mixture was poured onto ice and neutralized with 35% NaOH. The aqueous mixture was extracted with *i*-Pr_2O ($3 \times$ 700 mL). The combined organics were washed with 2 N KOH, dried over $MgSO_4$, and evaporated to give 81 g of alkylated aniline. This material was dissolved in EtOH (50 mL) and treated with 40% $MeNH_2$ (800 mL) at 55 °C for 6 h followed by 14 h at room temperature. The reaction mixture was cooled in an ice bath to precipitate the product which was isolated by filtration. This gave 59 g (78%) of amide **10**: ^{1}H-NMR (DMSO-d_6) δ 8.15 (brs, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.35 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 6.80 (brs, 1H), 2.98 (t, J = 6.0 Hz, 2H), 2.75 (m, 3H), 1.87 (sept, J = 6 Hz, 1H), 0.95 (d, J = 7.2 Hz, 6H).

7-Amino-3-methyl-1-(2-methylpropyl)quinazoline-2,4-dione (11). A solution of NaH (22 g at 60%, 54 mol) in DMF (700 mL) was cooled to 0 °C. The amide **10** (59 g, 0.24 mol) was added over 45 min. Phenyl chloroformate (36 mL, 0.28 mol) was then added over 40 min, keeping the mixture cold. The reaction mixture was then warmed to room temperature with stirring for 2 h. Excess NaH was quenched by slow addition of H_2O. The mixture was then poured onto 2 L of ice water. The solid was filtered off and recrystallized from EtOH to give 49 g of nitroquinazolinedione. The nitro group was reduced with 10% Pd/C in HOAc on a Parr shaker at 50 psi. The catalyst was removed by filtration through Celite. The mother liquor was concentrated and the residue recrystallized from Tol/EtOH to give 30 g (51%/two steps) of amine **11**: ^{1}H-NMR ($CDCl_3$) δ 8.01 (d, J = 8.6 Hz, 1H), 6.52 (d, J = 8.6 Hz, 1H), 6.31 (s, 1H), 4.50 (brs, 2H), 3.93 (d, J = 7.1 Hz, 2H), 3.45 (s, 3H), 2.19 (sept, J = 7.6 Hz, 1H), 0.99 (d, J = 6.5 Hz, 6H). Anal. ($C_{13}H_{17}N_3O_2$) C, H, N.

3-Methyl-1-(2-methylpropyl)-7-(phenylmethoxy)-quinazoline-2,4-dione (1a). The aniline **11** (12 g, 48 mmol) was dissolved in H_2SO_4/H_2O (70 mL/400 mL) and cooled to 0 °C. $NaNO_2$ (4.2 g, 61 mmol) in H_2O (100 mL) was added dropwise over 40 min. The mixture was then warmed to room temperature and heated on a steam bath for 1 h until evolution of gas ceased. Upon cooling a solid formed which was isolated by filtration. This gave 8.9 g of phenol (36 mmol) after recrystallization and drying. The phenol and KOH (2.5 g, 44 mmol) were dissolved in DMF (90 mL) and stirred for 30 min. Benzyl bromide (4.8 mL, 40 mmol) in DMF (40 mL) was added dropwise and stirring continued for 3 h. The reaction mixture was concentrated to dryness. The off-white solid was slurried in H_2O, filtered, and rinsed with H_2O. Recystallization for EtOH gave 8.3 g (51%/two steps) of **1a**. mp 124−126 °C; ^{1}H-NMR (DMSO-d_6) δ 7.57 (d, J = 2.6 Hz, 1H), 7.48−7.32 (m, 7H), 5.18 (s, 2H), 3.93 (d, J = 7.6 Hz, 2H), 3.30 (s, 3H), 2.08 (sept, J = 6.7 Hz, 1H), 0.88 (d, J = 6.7 Hz, 6H). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

3-Methyl-1-(2-methylpropyl)-7-[(phenylmethyl)amino]-quinazoline-2,4-dione (1b). The aniline **11** (1.0 g, 4.0 mmol) and benzaldehyde (5.0 mL, 49 mmol) were stirred at room temperature for 14 h. The benzaldehyde was removed via vacuum distillation to leave a clear yellow oil. This oil was dissolved in EtOH (20 mL). $NaBH_4$ (600 mg, 16 mmol) was added over 10 min, the reaction mixture was allowed to stir at room temperature for 20 h, 20% NaOH (10 mL) was added, and the resultant precipitate was isolated by filtration. Recrystallization from toluene gave 900 mg (67%) of aniline **1c**: mp 167−169 °C; ^{1}H-NMR ($CDCl_3$) δ 8.01 (d, J = 8.7 Hz, 1H), 7.26−7.37 (m, 5H), 6.55 (d, J = 8.9 Hz, 1H), 6.14 (s, 1H), 4.45 (s, 2H), 3.80 (d, J = 7.4 Hz, 2H), 3.43 (s, 3H), 1.92 (sept, J = 7.2 Hz, 1H), 0.86 (d, J = 6.7 Hz, 6H). Anal. ($C_{20}H_{23}N_3O_2$) C, H, N.

6-Amino-3-methyl-1-(2-methylpropyl)quinazoline-2,4-dione (13). The quinazolinedione[27] **12** (7.9 g, 36 mmol), K_2CO_3 (4.9 g, 36 mmol), and methallyl bromide (3.6 mL, 36 mmol) were stirred in DMF (50 mL) at room temperature for 14 h. The solvent was removed, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated. This gave 6.6 g (67%) of alkylated material. The olefin was reduced using 10% Pd/C in EtOH/EtOAc on a Parr apparatus at 60 psi for 7 h. The catalyst was removed by filtration through Celite. Concentration of the reaction mixture gave 4.7 g (52%/two steps) of aniline **13**: mp 233−247 °C dec; ^{1}H-NMR ($CDCl_3$) δ 7.95 (d, J = 2.5 Hz, 1H), 7.65 (dd, J = 2.3 and 9.0 Hz, 1H), 7.57 (d, J = 9.1 Hz, 1H), 3.94 (d, J = 7.5 Hz, 2H), 3.30 (s, 3H), 2.08 (sept, J = 7.0 Hz, 1H), 0.90 (d, J = 6.6 Hz, 6H). Anal. ($C_{13}H_{17}N_3O_2$·HCl) C, H, N.

3-Methyl-1-(2-methylpropyl)-6-(2-phenylethyl)quinazoline-2,4-dione (2a). The aniline **13** (840 mg, 3.4 mmol) was dissolved in a 1:1 mixture of $ClCH_2CO_2H$:HOAc (12 mL). Styrene (780 μL, 6.8 mmol) and $Pd(dba)_2$ (100 mg, 0.17 mmol) were added, and the reaction mixture was immersed in a 60 °C bath. *tert*-Butyl nitrite (440 μL, 3.7 mmol) was added

dropwise over 2–3 min, and heating was continued for 40 min. Upon cooling, the entire reaction mixture was transferred to a Parr bottle with EtOH (20 mL); 10% Pd/C (100 mg) was added, and the solution was shaken under 60 psi of H_2 for 1.5 h. The catalyst was removed by filtration, and the EtOH was removed on a rotary evaporator. The residue was taken up in H_2O (100 mL) and extracted with 1:1 Hex:Et_2O (3 × 40). The combined organics were washed with NH_4OH and brine and dried over Na_2SO_4. Concentration followed by chromatography on silica gel eluting with 9:1 Hex/EtOAc gave 600 mg (52%) of **2a**: mp 71–72 °C; ^{1}H-NMR ($CDCl_3$) δ 8.08 (d, J = 2.1 Hz, 1H), 7.39 (dd, J = 2.1 and 8.7 Hz, 1H), 7.28 (dd, J = 6.0 and 6.8 Hz, 2H), 7.19 (t, J = 7.1 Hz, 1H), 7.17 (dd, J = 5.5 and 6.5 Hz, 2H), 7.07 (d, J = 8.6 Hz, 1H), 3.98 (d, J = 7.0 Hz, 2H), 3.49 (s, 3H), 2.94–2.99 (m, 4H), 2.19 (sept, J = 6.8 Hz, 1H), 0.99 (d, J = 6.6 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 162.0, 151.3, 141.0, 138.2, 136.3, 135.2, 128.4, 128.3, 128.1, 126.0, 115.4, 113.9, 50.3, 37.5, 36.7, 28.4, 26.9, 19.9; IR (1% KBr) 2953, 1698, 1651, 1620 cm^{-1}; MS (CI, CH_4) m/e 336 (M^+), 245 (M − 91). Anal. ($C_{21}H_{24}N_2O_2$) C, H, N.

3-Methyl-1-(2-methylpropyl)-6-(phenylmethoxy)-quinazoline-2,4-dione (2b). Benzyl bromide (630 μL, 5.3 mmol), phenol[28] **14** (1.0 g, 5.3 mmol), and K_2CO_3 (730 mg, 5.3 mmol) were stirred at room temperature in DMF (30 mL) for 14 h. The reaction mixture was diluted with H_2O (120 mL), and the precipitate was isolated by filtration. The solid was dried in vacuo. This residue was taken up in DMF (30 mL) and treated with isobuty liodide (350 μL, 3 mmol) and KOH (130 mg, 2.3 mmol) at room temperature for 14 h. The DMF was removed in vacuo and the residue partitioned between EtOAc and H_2O. The aqueous layer was separated and extracted with EtOAc. The combined organics were dried over Na_2SO_4 and evaporated. Purification on silica gel eluting with 4:1 Hex/EtOAc gave **2b**: mp 117–119 °C; ^{1}H-NMR ($CDCl_3$) δ 7.78 (d, J = 3.1 Hz, 1H), 7.30–7.47 (m, 6H), 7.13 (d, J = 9.6 Hz, 1H), 5.14 (s, 2H), 3.98 (d, J = 7.6 Hz, 2H), 3.50 (s, 3H), 2.18 (sept, J = 6.5 Hz, 1H), 1.00 (d, J = 6.7 Hz, 6H). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

General Procedure for Preparation of 6-[(Arylalkyl)-amino]-2,4-quinazolinediones 2c,d,f,h. In a Dean–Stark apparatus, the aniline **13** (1 equiv), aldehyde (1.2 eq), and p-TSA (catalytic) were heated to reflux in toluene (0.5–1.0 M) for 10–14 h. The toluene was removed using a rotary evaporator. The residue was taken up in THF (0.5–1.0 M) and cooled to 0 °C. Borane (2 eq) in THF was added dropwise with stirring. The reaction mixture was kept cold for 3–4 h at which time the excess borane was quenched by adding H_2O dropwise. The reaction mixture was diluted with H_2O and extracted with EtOAc (3×). The combined organics were washed with brine, dried over Na_2SO_4, and evaporated. Purification was carried out using silica gel and eluting compounds with EtOAc/Hex.

3-Methyl-1-(2-methylpropyl)-6-[(phenylmethyl)amino]-quinazoline-2,4-dione (2c): mp 148–150 °C; ^{1}H-NMR ($CDCl_3$) δ 7.53 (s, 1H), 7.27–7.40 (m, 5H), 7.04 (s, 2H), 4.39 (s, 2H), 3.94 (d, J = 7.6 Hz, 2H), 3.48 (s, 3H), 2.18 (sept, J = 7.0 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H). Anal. ($C_{20}H_{23}N_3O_2$) C, H, N.

6-[[(2-Fluorophenyl)methyl]amino]-3-methyl-1-(2-methylpropyl)quinazoline-2,4-dione (2d): ^{1}H-NMR (DMSO-d_6) δ 7.38–7.30 (m, 1H), 7.27–7.07 (m, 6H), 6.50 (brs, 1H), 4.34 (d, J = 4.9 Hz, 2H), 3.87 (d, J = 7.4 Hz, 2H), 3.33 (s, 3H), 2.22–1.98 (m, 1H), 0.87 (d, J = 6.7 Hz, 6H). Anal. ($C_{20}H_{22}N_3O_2F$) C, H, N, F.

6-[[[4-(Methoxycarbonyl)phenyl]methyl]amino]-3-methyl-1-(2-methylpropyl)quinazoline-2,4-dione (2f): ^{1}H-NMR (DMSO-d_6) δ 7.91 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.8 Hz, 1H), 7.09–7.04 (m, 1H), 7.05 (t, J = 6.1 Hz, 1H), 4.40 (d, J = 5.6 Hz, 2H), 3.88–3.79 (m, 5H), 3.25 (s, 3H), 2.04 (sept, J = 6.7 Hz, 1H), 0.86 (d, J = 6.6 Hz, 6H). Anal. ($C_{22}H_{25}N_3O_4$) C, H, N.

6-[[[4-(1,1-Dimethylethyl)phenyl]methyl]amino]-3-methyl-1-(2-methylpropyl)quinazoline-2,4-dione (2h): ^{1}H-NMR (DMSO-d_6) δ 7.35–7.23 (m, 5H), 7.14–7.06 (m, 2H), 6.49 (brs, 1H), 4.24 (d, J = 4.9 Hz, 2H), 3.87 (d, J = 7.4 Hz, 2H), 3.33 (s, 3H), 2.22–1.98 (m, 1H), 1.25 (s, 9H), 0.87 (d, J = 6.7 Hz, 6H). Anal. ($C_{24}H_{31}N_3O_2$) C, H, N.

6-[[(4-Methoxyphenyl)methyl]amino]-3-methyl-1-(2-methylpropyl)quinazoline-2,4-dione (2e). In a Dean-Stark apparatus, the aniline **14** (900 mg, 3.6 mmol), 4-methoxybenzaldehyde (530 μL, 4.4 mmol), and TSA (100 mg) were heated to reflux in toluene (8 mL) for 14 h. The reaction mixture was partitioned with EtOAc and saturated $NaHCO_3$. The aqueous layer was separated and extracted with EtOAc (3×). The combined organics were washed with brine, dried over Na_2SO_4, and evaporated. The residue (500 mg) was hydrogenated on a Parr apparatus in 1:1 EtOAc/EtOH (60 mL) using 10% Pd/C and 50 psi of hydrogen. After 1 h the reaction mixture was filtered through Celite, rinsing the pad with EtOAc. The solvent was evaporated, and the residue was passed through silica gel eluting with 3:2 Hex/EtOAc. The product **2e** precipitated from the appropriate fraction to yield 275 mg (20%/two steps) of yellow-green crystals. mp 178–180 °C; ^{1}H-NMR (DMSO-d_6) δ 7.21–7.29 (m, 3H), 7.05–7.13 (m, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.21 (s, 2H), 3.86 (d, J = 6.7 Hz, 2H), 3.71 (s, 3H), 3.26 (s, 3H), 2.04 (sept, J = 6.7 Hz, 1H), 0.87 (d, J = 6.7 Hz, 6H). Anal. ($C_{21}H_{25}N_3O_3$) C, H, N.

6-[[(4-Carboxyphenyl)methyl]amino]-3-methyl-1-(2-methylpropyl)quinazoline-2,4-dione (2g). The ester **2f** (770 mg, 1.9 mmol) and LiOH·H_2O (820 mg, 19 mmol) were dissolved in THF, adding H_2O to obtain a homogeneous mixture. After 1 h the reaction mixture was made acidic and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give the acid **2g**: mp 160–162 °C; ^{1}H-NMR (DMSO-d_6) δ 7.89 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 7.7 Hz, 2H), 7.25 (d, J = 8.3 Hz, 1H), 7.09 (m, 2H) 4.39 (s, 2H), 3.86 (d, J = 8.1 Hz, 2H), 3.25 (s, 3H), 2.04 (sept, J = 6.6 Hz, 1H), 0.87 (d, J = 6.6 Hz, 6H). Anal. ($C_{21}H_{23}N_3O_4 \cdot H_2O$) C, H, N.

6,7-Dimethoxy-3-methyl-1-(2-methylpropyl)quinazoline-2,4-dione (16). Quinazolinedione[25] **15** (4.4 g, 18.6 mmol), KOH (2.8 g, 28 mmol), and methallyl bromide (5.0 mL, 51 mmol) were stirred at room temperature in DMF (70 mL) for 14 h. The reaction mixture was diluted with H_2O (200 mL) and extracted with Et_2O (3 × 70 mL). The combined organics were washed with brine, dried over Na_2SO_4, and evaporated. This gave 3.6 g (69%) of alkylated material: mp 152–153 °C; ^{1}H-NMR ($CDCl_3$) δ 7.60 (s, 1H), 6.61 (s, 1H), 4.99 (t, J = 1.35 Hz, 1H), 4.81 (t, J = 0.81 Hz, 1H), 4.72 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.49 (s, 3H), 1.79 (s, 3H); IR (1% KBr) 2937, 1695, 1647, 1618 cm^{-1}; MS (CI, CH_4) m/e 290 (M^+). Anal. ($C_{15}H_{18}N_2O_4$) C, H, N.

The olefin (2.4 g, 8.3 mmol) was hydrogenated by stirring with 10% Pd/C (200 mg) in 1:1 THF/ EtOAc (60 mL) under a balloon pressure of H_2 for 14 h. The catalyst was removed by filtering through Celite. The solution was concentrated to give 2.2 g (91%) of reduced material **16**: mp 162–163 °C; ^{1}H-NMR ($CDCl_3$) δ 7.61 (s, 1H), 6.59 (s, 1H), 3.97 (s, 3H), 3.97 (d, J = 7.4 Hz, 2H), 3.94 (s, 3H), 3.47 (s, 3H), 2.21 (sept, J = 6.7 Hz, 1H), 1.01 (d, J = 6.7 Hz, 6H); IR (1% KBr) 2960, 1699, 1648, 1621 cm^{-1}; MS (CI, CH_4) m/e 292 (M^+). Anal. ($C_{15}H_{20}N_2O_4$) C, H, N.

6,7-Dihydroxy-3-methyl-1-(2-methylpropyl)quinazoline-2,4-dione (17). A slurry of the bis-ether **16** (3.37 g, 11 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C. A solution of BBr_3 (50 mL, 1= M in CH_2Cl_2) was added dropwise over 15 min. After stirring cold for 3 h, the solution was warmed to room temperature and stirring continued for 1 h. The reaction was quenched by adding MeOH (50 mL). Water (50 mL) was added with stirring. The solid that formed was removed by filtration and recrystallized from hot acetone to give 2.33 g (77%) of catechol **17**: mp 239–241 °C; ^{1}H-NMR (DMSO-d_6) δ 10.19 (s, 1H), 9.43 (s, 1H), 7.34 (s, 1H), 6.72 (s, 1H), 3.82 (d, J = 7.4 Hz, 2H), 3.24 (s, 3H), 2.06 (sept, J = 6.7 Hz, 1H), 0.88 (d, J = 6.7 Hz, 6H); IR (1% KBr) 3280–3400, 2956, 1675, 1617, 1496 cm^{-1}; MS (CI, CH_4) m/e 264 (M^+). Anal. ($C_{13}H_{16}N_2O_4$) C, H, N.

7-Methyl-5-(2-methylpropyl)-2-phenyl-1,3-dioxolo[4,5-*g*]quinazoline-6,8-dione (3a). Catechol **17** (2.0 g, 7.6 mmol) and benzaldehyde dimethylacetal (4.5 g, 30 mmol) were heated to 150 °C in 1,2-dichlorobenzene with a small amount of p-TSA (50 mg). The liberated MeOH was allowed to distill out of the reaction flask. After 45 min the flask was cooled to 100 °C,

and the bulk of the dichlorobenzene was removed under vacuum. The residue was applied directly to a pad of silica gel and eluted with 5% MeOH/$CHCl_3$. This gave 2.0 g (75%) of acetal **3a**: mp 88–90 °C; ^{1}H-NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.54–7.57 (m, 2H), 7.46–7.50 (m, 3H), 7.09 (s, 1H), 6.67 (s, 1H), 3.95 (d, J = 7.45 Hz, 2H), 3.47 (s, 3H), 2.18 (sept, J = 6.9 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); IR (1% KBr) 3080, 2957, 1694, 1650, 1488 cm^{-1}; MS (CI, CH_4) m/e 353 (MH^+). Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

2,7-Dimethyl-5-(2-methylpropyl)-2-phenyl-1,3-dioxolo-[4,5-*g*]quinazoline-6,8-dione (3b). Catechol **17** (2.0 g, 7.6 mmol) and acetophenone dimethylacetal (4.5 g, 27 mmol) were heated to 180 °C in 1,2-dichlorobenzene with a small amount of TSA (50 mg). The liberated MeOH was distilled out of the reaction flask. After 2 h the flask was cooled to 100 °C, and the bulk of the dichlorobenzene was removed under vacuum. The residue was diluted with Hex (40 mL) to precipitate unreacted starting material which was removed by filtration. The mother liquor was applied to a pad of silica gel and eluted with Hex followed by 5% MeOH/$CHCl_3$. This gave 2.6 g (93%) of ketal **3b**: mp 118–120 °C; ^{1}H-NMR ($CDCl_3$) δ 7.59 (s, 1H), 7.58 (d, J = 6.3 Hz, 2H), 7.38–7.41 (m, 3H), 6.61 (s, 1H), 3.95 (dd, J = 7.5 and 14.4 Hz, 1H), 3.89 (dd, J = 7.5 and 14.2 Hz, 1H), 3.45 (s, 3H), 2.16 (sept, J = 6.9 Hz, 1H), 2.03 (s, 3H), 0.98 (d, J = 7.0 Hz, 6H); IR (1% KBr) 3080, 2957, 1694, 1650, 1492 cm^{-1}; MS (CI, CH_4) m/e 367 (MH^+). Anal. ($C_{21}H_{22}N_2O_4$) C, H, N.

General Procedure for Preparation of 1-Alkyl-5-cyano-6-methylpyrimidine-2,4-diones 19a–h. A mixture of amine (1.1 eq) and *N*-(ethoxycarbonyl)-2-cyano-3-ethoxy-2-butenecarboxamide (**18**) (1.0 eq) was refluxed for 4 h in ethanol (0.5 M). The solution was cooled to room temperature, and after 16 h the crystalline product was recovered by filtration on a glass-fritted funnel. The crystals were rinsed with Et_2O to afford the pyrimidinediones **19**.

5-Cyano-6-methyl-1-(2-methylpropyl)pyrimidine-2,4-dione (19a): mp 203–205 °C; ^{1}H-NMR ($CDCl_3$) δ 8.86 (s, 1H), 3.77 (d, J = 7.6 Hz, 2H), 2.62 (s, 3H), 2.10 (sept, J = 6.9 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H). Anal. ($C_{10}H_{13}N_3O_2$) C, H, N.

5-Cyano-1-ethyl-6-methylpyrimidine-2,4-dione (19b): ^{1}H-NMR (DMSO-d_6) δ 3.87 (q, J = 7.5 Hz, 2H), 2.54 (s, 3H), 1.27 (t, J = 7.5 Hz, 3H); MS (FAB, NBA) m/e 180 (MH^+). Anal. ($C_8H_9N_3O_2$) C, H, N.

5-Cyano-6-methyl-1-(1-methylethyl)pyrimidine-2,4-dione (19c): ^{1}H-NMR (DMSO-d_6) δ 4.44 (m, 1H), 2.50 (s, 3H), 1.42 (d, J = 6.4 Hz, 6H); IR (1% KBr) 3233, 3082, 2228, 1729, 1700, 1584 cm^{-1}; MS (CI, CH_4) m/e 194 (MH^+). Anal. ($C_9H_{11}N_3O_2$) C, H, N.

5-Cyano-1-(cyclopropylmethyl)-6-methylpyrimidine-2,4-dione (19d): ^{1}H-NMR (DMSO-d_6) δ 3.79 (d, J = 7.0 Hz, 2H), 2.59 (s, 3H), 1.21–1.03 (m, 1H), 0.55–0.42 (m, 2H), 0.42–0.32 (m, 2H); IR (1% KBr) 3174, 3118, 3015, 2833, 2224, 1727, 1678, 1577, 1488, 1426 cm^{-1}; MS (CI, CH_4) m/e 206 (MH^+); HRMS (LSIMS) $C_{10}H_{11}N_3O_2$ (MH^+) requires 206.09295, found 206.09240, Δ = −2.69 ppm.

5-Cyano-6-methyl-1-(3-methylbutyl)pyrimidine-2,4-dione (19e): ^{1}H-NMR (DMSO-d_6) δ 11.89 (brs, 1H), 3.89–3.72 (m, 2H), 2.51 (s, 3H), 1.69–1.51 (m, 1H), 1.51–1.37 (m, 2H), 0.90 (d, J = 7.0 Hz, 6H); IR (1% KBr) 3030, 2959, 2932, 2842, 2225, 1722, 1688, 1670, 1587, 1489, 1428, 1397, 1363 cm^{-1}; MS (CI, CH_4) m/e 222 (MH^+). Anal. ($C_{11}H_{15}N_3O_2$) C, H, N.

5-Cyano-1-(cyclohexylmethyl)-6-methylpyrimidine-2,4-dione (19f): ^{1}H-NMR (DMSO-d_6) δ 11.09 (s, 1H), 3.70 (d, J = 8.1 Hz, 2H), 2.51 (s, 3H), 1.79–1.50 (m, 6H), 1.25–1.05 (m, 3H), 1.05–0.82 (m, 2H); IR (1% KBr) 3020, 2929, 2921, 2852, 2224, 1730, 1689, 1584, 1494 cm^{-1}; MS (CI, CH_4) m/e 247 (MH^+). Anal. ($C_{13}H_{17}N_3O_2$) C, H, N.

5-Cyano-1-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-propyl]-6-methylpyrimidine-2,4-dione (19g): ^{1}H-NMR (DMSO-d_6) δ 5.09 (brs, 1H), 4.12–4.01 (m, 1H), 3.90 (dd, J = 2.0 and 12.0 Hz, 1H), 3.78–3.64 (m, 1H), 2.55 (s, 3H), 1.09 (d, J = 6.3 Hz, 3H), 0.79 (s, 9H), 0.00 (s, 3H), −0.19 (s, 3H); MS (CI, CH_4) m/e 324 (MH^+). Anal. ($C_{15}H_{25}N_3O_3Si$) C, H, N.

5-Cyano-6-methyl-1-(1-methylpropyl)pyrimidine-2,4-dione (19h): ^{1}H-NMR ($CDCl_3$) δ 8.44 (brs, 1H), 4.11 (m, 1H), 2.61 (s, 3H), 2.20 (m, 2H), 1.56 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); MS (FAB, NBA) m/e 208 (MH^+). Anal. ($C_{10}H_{13}N_3O_3$) H, N; C: calcd, 57.94; found, 57.24.

General Procedure for Preparation of 1-Alkyl-5-cyano-3,6-dimethylpyrimidine-2,4-diones 20a–h. Imide **19** (1 eq), NaOH (1.2 eq), and dimethyl sulfate (1.2 eq) were dissolved in H_2O (0.5 M). The solution was stirred for 18 h. The reaction mixture was cooled in ice and filtered. The solid was taken up in $CHCl_3$, which was dried over Na_2SO_4 and evaporated. Recrystallization from Et_2O/Hex gave the methylated pyrimidinediones **20**.

5-Cyano-3,6-dimethyl-1-(2-methylpropyl)pyrimidine-2,4-dione (20a): mp 112–113 °C; ^{1}H-NMR ($CDCl_3$) δ 3.79 (d, J = 7.7 Hz, 2H), 3.37 (s, 3H), 2.66 (s, 3H), 2.12 (sept, J = 6.7 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H). Anal. ($C_{11}H_{15}N_3O_2$) C, H, N.

5-Cyano-3,6-dimethyl-1-ethylpyrimidine-2,4-dione (20b): ^{1}H-NMR (DMSO-d_6) δ 3.93 (q, J = 7.5 Hz, 2H), 3.17 (s, 3H), 2.55 (s, 3H), 1.19 (t, J = 7.5 Hz, 3H); MS (FAB, nba) m/e 194 (MH^+). Anal. ($C_9H_{11}N_3O_2$) H, N; C: calcd, 55.93; found, 55.47.

5-Cyano-3,6-dimethyl-1-(1-methylethyl)pyrimidine-2,4-dione (20c): ^{1}H-NMR (DMSO-d_6) δ 4.50 (m, 1H), 3.12 (s, 3H), 2.52 (s, 3H), 1.42 (d, J = 6.4 Hz, 6H); IR (1% KBr) 3007, 2974, 2942, 2226, 1718, 1661, 1588 cm^{-1}; MS (FAB, nba) m/e 207 (MH^+). Anal. ($C_{10}H_{13}N_3O_2$) C, H, N.

5-Cyano-1-(cyclopropylmethyl)-3,6-dimethylpyrimidine-2,4-dione (20d): ^{1}H-NMR (DMSO-d_6) δ 3.85 (d, J = 6.9 Hz, 2H), 3.19 (s, 3H), 2.60 (s, 3H), 1.21–1.05 (m, 1H), 0.55–0.42 (m, 2H), 0.42–0.30 (m, 2H); IR (1% KBr) 3019, 2953, 2225, 1720, 1662, 1591, 1484, 1430, 1373 cm^{-1}; MS (CI, CH_4) m/e 220 (MH^+). Anal. ($C_{11}H_{13}N_3O_2$) C, H, N.

5-Cyano-3,6-dimethyl-1-(3-methylbutyl)pyrimidine-2,4-dione (20e): ^{1}H-NMR (DMSO-d_6) δ 3.92–3.80 (m, 2H), 3.17 (s, 3H), 2.57 (s, 3H), 1.71–1.55 (m, 1H), 1.54–1.40 (m, 2H), 0.92 (d, J = 7.0 Hz, 6H); IR (1% KBr) 2955, 2870, 2225, 1718, 1673, 1658, 1593, 1484, 1368 cm^{-1}; MS (FAB, nba) m/e 336 (MH^+). Anal. ($C_{12}H_{17}N_3O_2$) C, H, N.

5-Cyano-1-(cyclohexylmethyl)-3,6-dimethylpyrimidine-2,4-dione (20f): ^{1}H-NMR (DMSO-d_6) δ 3.75 (d, J = 8.1 Hz, 2H), 3.17 (s, 3H), 2.51 (s, 3H), 1.79–1.51 (m, 6H), 1.25–1.05 (m, 3H), 1.05–0.85 (m, 2H); IR (1% KBr) 2929, 2855, 2220, 1728, 1671, 1593 cm^{-1}; MS (FAB, nba) m/e 262 (MH^+). Anal. ($C_{14}H_{19}N_3O_2$) C, N; H: calcd, 7.33; found, 6.89.

5-Cyano-3,6-dimethyl-1-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]pyrimidine-2,4-dione (20g). Prior to N-3-alkylation, the side chain hydroxyl was protected as the TBDMS ether. This was accomplished using TBDMSCl and imidazole in DMF. In this case N-3-alkylation was carried out using anhydrous conditions, K_2CO_3, MeI, and DMF: ^{1}H-NMR (DMSO-d_6) δ 4.15–4.00 (m, 1H), 3.99–3.90 (m, 1H), 3.85–3.72 (m, 1H), 3.19 (s, 3H), 2.59 (s, 3H), 1.15 (d, J = 6.4 Hz, 3H), 0.79 (s, 9H), 0.00 (s, 3H), −0.21 (s, 3H); MS (EI) m/e 280 (MH − *i*-Bu). Anal. ($C_{16}H_{27}N_3O_3Si$) C, H, N.

5-Cyano-3,6-dimethyl-1-(1-methylpropyl)pyrimidine-2,4-dione (20h): ^{1}H-NMR ($CDCl_3$) δ 4.10 (m, 1H), 3.33 (s, 3H), 2.59 (s, 3H), 2.18 (m, 1H), 1.91 (m, 1H), 1.55 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C-NMR (DMSO-d_6) δ 163.0, 159.4, 149.4, 115.6, 88.6, 58.6, 27.9, 26.2, 20.42, 17.7, 11.06; IR (1% KBr) 2973, 2221, 1723, 1672, 1585 1448 cm^{-1}; MS (FAB, nba) 222 (MH^+). Anal. ($C_{11}H_{15}N_3O_2$) C, H, N.

General Procedure for Preparation of 1-Alkyl-3,6-Dimethyl-5-formyl-pyrimidine-2,4-diones 21a–h. The nitrile **20** (1 eq) was dissolved in 75% HCO_2H (0.3 M) and warmed to 95 °C. An equivalent weight of Ra Ni was added all at once; heating was continued for 15 min. The reaction mixture was filtered through Celite and concentrated. The residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (2×). The combined organics were washed with $NaHCO_3$, dried over Na_2SO_4, and evaporated. This gave the aldehydes **21**.

3,6-Dimethyl-5-formyl-1-(2-methylpropyl)pyrimidine-2,4-dione (21a): ^{1}H-NMR ($CDCl_3$) δ 10.05 (s, 1H), 3.79 (d, J = 7.7 Hz, 1H), 3.37 (s, 3H), 2.66 (s, 3H), 2.12 (sept, J = 6.7 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H).

3,6-Dimethyl-1-ethyl-5-formylpyrimidine-2,4-dione (21b): ^{1}H-NMR (DMSO-d_6) δ 10.05 (s, 1H), 3.99 (q, J = 7.5 Hz, 2H), 3.21 (s, 3H), 2.73 (s, 3H), 1.19 (t, J = 7.5 Hz, 3H).

3,6-Dimethyl-5-formyl-1-(1-methylethyl)pyrimidine-2,4-dione (21c): ^{1}H-NMR (DMSO-d_6) δ 10.05 (s, 1H), 4.61 (m, 1H), 3.17 (s, 3H), 2.72 (s, 3H), 1.42 (d, J = 6.4 Hz, 6H); MS (CI, CH_4) m/e 211 (MH^+). Anal. ($C_{10}H_{14}N_2O_3$) C, H, N.

3,6-Dimethyl-5-formyl-1-(cyclopropylmethyl)pyrimidine-2,4-dione (21d): ^{1}H-NMR (DMSO-d_6) δ 10.01 (s, 1H), 3.91 (d, J = 7.0 Hz, 1H), 3.21 (s, 3H), 2.77 (s, 3H), 1.21–1.05 (m, 1H), 0.55–0.42 (m, 2H), 0.42–0.35 (m, 2H); MS (CI, CH_4) m/e 223 (MH^+). Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

3,6-Dimethyl-5-formyl-1-(3-methylbutyl)pyrimidine-2,4-dione (21e): ^{1}H-NMR (DMSO-d_6) δ 10.09 (s, 1H), 3.98–3.83 (m, 2H), 3.20 (s, 3H), 2.72 (s, 3H), 1.71–1.55 (m, 1H), 1.54–1.40 (m, 2H), 0.92 (d, J = 7.0 Hz, 6H); MS (CI, CH_4) m/e 239 (MH^+). Anal. ($C_{12}H_{18}N_2O_3$) C, H, N.

3,6-Dimethyl-5-formyl-1-(cyclohexylmethyl)pyrimidine-2,4-dione (21f): ^{1}H-NMR (DMSO-d_6) δ 10.09 (s, 1H), 3.81 (d, J = 8.1 Hz, 2H), 3.20 (s, 3H), 2.51 (s, 3H), 1.78–1.51 (m, 6H), 1.25–1.05 (m, 3H), 1.05–0.85 (m, 2H); MS (CI, CH_4) m/e 265 (MH^+). Anal. ($C_{14}H_{20}N_2O_3$) C, H, N.

3,6-Dimethyl-5-formyl-1-[2-(hydroxyformyl)propyl]-pyrimidine-2,4-dione (21g): ^{1}H-NMR (DMSO-d_6) δ 10.05 (s, 1H), 8.10 (s, 1H), 5.18 (m, 1H), 4.20 (dd, J = 9 and 16 Hz, 1H), 4.06 (dd, J = 4 and 16 Hz, 1H), 3.19 (s, 3H), 2.73 (s, 3H), 1.24 (d, J = 6.9 Hz, 3H).

3,6-Dimethyl-5-formyl-1-(1-methylpropyl)pyrimidine-2,4-dione (21h): ^{1}H-NMR ($CDCl_3$) δ 10.28 (s, 1H), 4.27 (m, 1H), 3.35 (s, 3H), 2.77 (s, 3H), 2.18 (m, 1H), 1.93 (m, 1H), 1.55 (d, J = 6.7 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); MS (CI, CH_4) m/e 225 (MH^+). Anal. ($C_{11}H_{16}N_2O_3$) C, H, N.

General Procedure for Preparation of Pyrrolopyrimidines 4a–w, 5b–h, 6a–c, and 7a,b. A solution of bromine (1.0 eq) in $CHCl_3$ (2.0 M) was added dropwise to a stirred solution of 21 (1 eq) in $CHCl_3$ (0.5 M) at 50 °C. After 1 h the solvent was removed in vacuo. The reaction mixture was partitioned with H_2O. The aqueous layer was extracted with $CHCl_3$ (2×). The combined organics were washed with $NaHCO_3$, dried over Na_2SO_4, and evaporated. This gave the 5-formyl 6-bromomethyl intermediates which were taken on to the pyrrolopyrimidines. The appropriate amine (1.4 eq), TEA (3 eq), and the bromoaldehyde (1.0 eq) were dissolved in EtOH (1 M) and allowed to stir at room temperature for 2–3 days. The reaction mixture was concentrated to dryness. The residue was partitioned between EtOAc and 1 N HCl. The organic layer was washed with 1 N HCl (3×), dried over Na_2SO_4, and evaporated. Purification on silica gel eluting with Hex/EtOAc gave pure samples of pyrrolopyrimidinediones 4.

3-Methyl-1-(2-methylpropyl)-6-(phenylmethyl)pyrrolo-[3,4-*d*]pyrimidine-2,4-dione (4a): ^{1}H-NMR ($CDCl_3$) δ 7.4 (m, 3H), 7.3 (s, 1H), 7.2 (m, 2H), 6.31 (s, 1H), 5.12 (s, 2H), 3.61 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 312 (MH^+). Anal. ($C_{18}H_{21}N_3O_2$) C, H, N.

6-[(2-Chlorophenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4b): ^{1}H-NMR ($CDCl_3$) δ 7.4 (m, 1H), 7.3 (m, 3H), 7.0 (m, 1H), 6.35 (s, 1H), 5.25 (s, 2H), 3.61 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 346 (MH^+). Anal. ($C_{18}H_{20}ClN_3O_2$) C, H; N: calcd, 12.15; found, 10.18.

6-[(2-Fluorophenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4c): ^{1}H-NMR ($CDCl_3$) δ 7.34 (m, 2H), 7.12 (m, 3H), 6.34 (d, J = 2.3 Hz, 1H), 5.15 (s, 2H), 3.61 (d, J = 7.5 Hz, 2H), 3.38 (s, 3H), 2.20 (sept, J = 7.0 Hz, 1H), 0.94 (d, J = 6.8 Hz, 6H). Anal. ($C_{18}H_{20}FN_3O_2$) C, H, N.

6-[(4-Chlorophenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4d): ^{1}H-NMR ($CDCl_3$) δ 7.35 (d, J = 6.8 Hz, 2H), 7.32 (s, 1H), 7.11 (d, J = 6.8 Hz, 2H), 6.30 (s, 1H), 5.10 (s, 2H), 3.62 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 346 (MH^+). Anal. ($C_{18}H_{20}ClN_3O_2$) C, H; N: calcd, 12.15; found, 10.36.

6-[(2-Methoxyphenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4e): ^{1}H-NMR ($CDCl_3$) δ 7.4 (m, 1H), 7.35 (s, 1H), 7.0 (m, 3H), 6.30 (s, 1H), 5.10 (s, 2H), 3.85 (s, 3H), 3.6 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 342 (MH^+). Anal. ($C_{19}H_{23}N_3O_3$) C, H, N.

6-[(3-Methoxyphenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4f): ^{1}H-NMR ($CDCl_3$) δ 7.3 (m, 2H), 6.8 (m, 1H), 6.65 (m, 2H), 6.30 (s, 1H), 5.10 (s, 2H), 3.8 (s, 3H), 3.61 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 342 (MH^+). Anal. ($C_{19}H_{23}N_3O_3$) C, H, N.

6-[(4-Methoxyphenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4g): ^{1}H-NMR ($CDCl_3$) δ 7.28 (s, 1H), 7.15 (d, J = 6.8 Hz, 2H), 6.83 (d, J = 6.8 Hz, 2H), 6.30 (s, 1H), 5.10 (s, 2H), 3.82 (s, 3H), 3.61 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 342 (MH^+). Anal. ($C_{19}H_{23}N_3O_3$) C, H, N.

3-Methyl-1-(2-methylpropyl)-6-[4-(methylthio)phenyl]-methyl]pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4h): ^{1}H-NMR ($CDCl_3$) δ 7.28 (d, J = 2.3 Hz, 1H), 7.24 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 6.27 (d, J = 2.4 Hz, 1H), 5.05 (s, 2H), 3.60 (d, J = 7.6 Hz, 2H), 3.39 (s, 3H), 2.48 (s, 3H), 2.19 (sept, J = 6.9 Hz, 1H), 0.94 (d, J = 6.8 Hz, 6H). Anal. ($C_{19}H_{23}N_3O_2S$) C, H, N.

6-[[4-(Butyloxy)phenyl]methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4i): ^{1}H-NMR ($CDCl_3$) δ 7.26 (d, J = 3.0 Hz, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.27 (d, J = 2.2 Hz, 1H), 5.02 (s, 2H), 3.95 (t, J = 6.4 Hz, 2H), 3.60 (d, J = 7.6 Hz, 2H), 3.38 (s, 3H), 2.19 (sept, J = 6.9 Hz, 1H), 1.77 (pent, J = 6.9 Hz, 2H), 1.48 (sextet, J = 7.6 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H), 0.94 (d, J = 6.8 Hz, 6H). Anal. ($C_{22}H_{29}N_3O_3$) C, H, N.

6-[(4-Hydroxyphenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4j). Boron tribromide (33 mL at 1 M, 33.0 mmol) was added dropwise to a stirred CH_2Cl_2 (150 mL) solution of **4g** at 0 °C. The temperature was not allowed to exceed 5 °C over a 30 min period. The ice bath was removed and stirring continued an additional 4 h. The reaction mixture was poured into chilled water and the aqueous layer made weakly basic with $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 70 mL). The organic extracts were combined, dried over Na_2CO_3, filtered, and evaporated. The off-white solid was recrystallized from EtOAc to afford 5.1 g of phenol **4j** (71%): ^{1}H-NMR ($CDCl_3$) δ 8.65 (s, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.26 (s, 1H), 7.25 (t, J = 7.2 Hz, 1H), 7.18 (t, J = 6.4 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.86 (t, J = 7.1 Hz, 1H), 5.10 (s, 2H), 3.60 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 328 (MH^+). Anal. ($C_{18}H_{21}N_3O_3$) C, H, N.

3-Methyl-6-[(4-methylphenyl)methyl]-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4k): ^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 1H), 7.20 (d, J = 6.8 Hz, 2H), 7.11 (d, J = 6.8 Hz, 2H), 6.30 (s, 1H), 5.10 (s, 2H), 3.61 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.41 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 326 (MH^+). Anal. ($C_{19}H_{23}N_3O_2$) C, H, N.

3-Methyl-1-(2-methylpropyl)-6-[[4-(trifluoromethyl)-phenyl]methyl]-pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4l): ^{1}H-NMR ($CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 8.2 Hz, 2H), 6.28 (d, J = 2.3 Hz, 1H), 5.18 (s, 2H), 3.61 (d, J = 7.5 Hz, 2H), 3.40 (s, 3H), 2.19 (sept, J 6.9 Hz, 1H), 0.94 (d, J = 6.8 Hz, 6H). Anal. ($C_{19}H_{20}F_3N_3O_2$) C, H, N.

6-[(2,3-Dichlorophenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4m): ^{1}H-NMR ($CDCl_3$) δ 7.48 (d, J = 8.1 Hz, 1H), 7.27 (s, 1H), 7.19 (t, J = 8.0 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.31 (s, 1H), 5.25 (s, 2H), 3.60 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); IR (1% KBr) 3117, 1701, 1655, 1607, 1417, 1291, 756 cm^{-1}; HRMS (LSIMS) $C_{18}H_{20}N_3Cl_2O_2$ (MH^+) requires 380.09326, found 380.0924; Δ = −2.26 ppm.

6-[(2,3-Dimethoxyphenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4n): ^{1}H-NMR ($CDCl_3$) δ 7.32 (s, 1H), 6.8 (m, 3H), 7.19 (t, J = 8.0 Hz, 1H), 6.30 (s, 1H), 5.03 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.6 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99

(d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 371 (M^+). Anal. ($C_{20}H_{25}N_3O_4$) C, H, N.

6-[(2,4-Dimethoxyphenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4o): ^{1}H-NMR ($CDCl_3$) δ 7.26 (d, J = 2.5 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.44 (m, 2H), 6.31 (d, J = 2.4 Hz, 1H), 5.01 (s, 2H), 3.81 (s, 6H), 3.61 (d, J = 7.4 Hz, 2H), 3.37 (s, 3H), 2.21 (sept, J = 6.8 Hz, 1H), 0.94 (d, J = 6.7 Hz, 6H). Anal. ($C_{20}H_{25}N_3O_4$) C, H, N.

6-[(3,4-Dimethoxyphenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4p): ^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 1H), 7.05 (s, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.3 (s, 1H), 5.03 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.6 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); HRMS (LSIMS) $C_{20}H_{26}N_3O_4$ (MH^+) requires 372.1923, found 372.1926, Δ = 0.84 ppm.

6-[(3-Iodo-4-methoxyphenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4q): ^{1}H-NMR ($CDCl_3$) δ 7.60 (s, 1H), 7.26 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.26 (s, 1H), 4.98 (s, 2H), 3.86 (s, 3H), 3.6 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 468 (MH^+). Anal. ($C_{19}H_{22}IN_3O_3$) C, H, N.

6-[(4-Hydroxy-3-iodophenyl)methyl]-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4r): ^{1}H-NMR ($CDCl_3$) δ 7.50 (s, 1H), 7.26 (s, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.45 (s, 1H), 6.27 (s, 1H), 4.98 (s, 2H), 3.6 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 454 (MH^+). Anal. ($C_{18}H_{20}IN_3O_3$) C, H, N.

3-Methyl-1-(2-methylpropyl)-6-(1-naphthylmethyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4s): ^{1}H-NMR ($CDCl_3$) δ 7.8 (m, 3H), 7.5 (m, 3H), 7.2 (m, 2H), 6.36 (s, 1H), 5.56 (s, 2H), 3.62 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 362 (MH^+). Anal. ($C_{22}H_{23}N_3O_2$) C, H, N.

3-Methyl-1-(2-methylpropyl)-6-(2-naphthylmethyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4t): ^{1}H-NMR ($CDCl_3$) δ 7.8 (m, 3H), 7.61 (s, 1H), 7.5 (m, 2H), 7.32 (s, 1H), 7.2 (m, 1H), 6.31 (s, 1H), 5.25 (s, 2H), 3.61 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 362 (MH^+). Anal. ($C_{22}H_{23}N_3O_2$) C, H, N.

6-(1-Acenaphthyl)-3-methyl-1-(2-methylpropyl)pyrrolo-[3,4-*d*]pyrimidine-2,4-dione (4u): ^{1}H-NMR ($CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 1H), 7.7 (d, J = 8.2 Hz, 1H), 7.55 (m, 2H), 7.37 (d, J = 7.1 Hz, 1H), 7.34 (d, J = 6.6 Hz, 1H), 7.2 (s, 1H), 6.25 (s, 1H), 6.1 (dd, J = 3.3 and 8.3 Hz, 1H), 4.1 (dd, J = 8.3 and 17.5 Hz, 1H), 3.6 (d, J = 7.5 Hz, 2H), 3.48 (dd, J = 3.3 and 17.5 Hz, 1H), 3.42 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 374 (MH^+). Anal. ($C_{23}H_{23}N_3O_2$) H, N; C: calcd, 73.97; found, 73.55.

6-(1-Indanyl)-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4v): ^{1}H-NMR ($CDCl_3$) δ 7.3 (m, 2H), 7.2 (m, 2H), 7.12 (d, J = 7.3 Hz, 1H), 6.28 (s, 1H), 5.60 (t, J = 7.7 Hz, 1H), 3.60 (d, J = 7.5 Hz, 2H), 3.37 (s, 3H), 3.11 (dd, J = 5.0 and 8.4 Hz, 1H), 3.02 (m, 1H), 2.75 (m, 1H), 2.12 (m, 2H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 338 (MH^+). Anal. ($C_{20}H_{23}N_3O_2 \cdot {}^1/_4H_2O$) C, H, N.

6-(2-Indanyl)-3-methyl-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (4w): ^{1}H-NMR ($CDCl_3$) δ 7.3 (m, 4H), 7.2 (m, 1H), 6.31 (s, 1H), 5.25 (pentet, J = 5.2 Hz, 1H), 3.61 (d, J = 7.5 Hz, 2H), 3.52 (dd, J = 5.2 and 16.1 Hz, 2H), 3.42 (s, 3H), 3.20 (dd, J = 5.2 and 16.1 Hz, 2H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 338 (MH^+). Anal. ($C_{20}H_{23}N_3O_2 \cdot {}^7/_4H_2O$) C, H, N.

1-Ethyl-3-methyl-6-(1-naphthylmethyl)pyrrolo[3,4-*d*]-pyrimidine-2,4-dione (5a): ^{1}H-NMR (DMSO-d_6) δ 8.17 (d, J = 8.3 Hz, 1H), 7.99–7.91 (m, 2H), 7.61–7.49 (m, 4H), 7.29 (d, J = 7.3 Hz, 1H), 6.92 (d, J = 1 Hz, 1H), 5.72 (s, 2H), 3.75 (q, J = 7.5 Hz, 2H), 3.33 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H); MS (CI, CH_4) m/e 334 (MH^+), 333 (M^+). Anal. ($C_{20}H_{19}N_3O_2$) C, H, N.

3-Methyl-1-(1-methylethyl)-6-(1-naphthylmethyl)-pyrrolo[3,4-*d*]pyrimidine-2,4-dione (5b): ^{1}H-NMR (DMSO-d_6) δ 8.17 (d, J = 8.5 Hz, 1H), 8.00–7.89 (m, 2H), 7.62–7.43 (m, 4H), 7.29 (d, J = 7.3 Hz, 1H), 7.02 (d, J = 1.0 Hz, 1H), 5.72 (s, 2H), 4.69 (m, 1H), 3.17 (s, 3H), 1.37 (d, J = 6.4 Hz, 6H); IR (1% KBr) 3127, 2967, 2941, 1695, 1645, 1599, 1536 cm^{-1}; MS (CI, CH_4) m/e 347 (M^+). Anal. ($C_{21}H_{21}N_3O_2$) C, H, N.

1-(Cyclopropylmethyl)-3-methyl-6-(1-naphthylmethyl)-pyrrolo[3,4-*d*]pyrimidine-2,4-dione (5c): ^{1}H-NMR (DMSO-d_6) δ 8.17 (d, J = 8.5 Hz, 1H), 8.00–7.86 (m, 2H), 7.62–7.44 (m, 4H), 7.27 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 1.0 Hz, 1H), 5.71 (s, 2H), 3.63 (d, J = 6.9 Hz, 2H), 3.19 (s, 3H), 1.32–1.09 (m, 1H), 0.48–0.27 (m, 4H); MS (CI, CH_4) m/e 360 (M^+). Anal. ($C_{22}H_{21}N_3O_2$) C, H, N.

3-Methyl-1-(3-methylbutyl)-6-(1-naphthylmethyl)-pyrrolo[3,4-*d*]pyrimidine-2,4-dione (5d): ^{1}H-NMR (DMSO-d_6) δ 8.22 (d, J = 8.6 Hz, 1H), 7.99–7.85 (m, 2H), 7.61–7.42 (m, 4H), 7.25 (d, J = 7.2 Hz, 1H), 6.87 (s, 1H), 5.73 (s, 2H), 3.77–3.65 (m, 2H), 3.19 (s, 3H), 1.61–1.39 (m, 3H), 0.87 (d, J = 7.0 Hz, 6H); IR (1% KBr) 3112, 2957, 1698, 1655, 1608, 1544, 1291 cm^{-1}; MS (CI, CH_4) m/e 375 (M^+). Anal. ($C_{23}H_{25}N_3O_2$) C, H, N.

1-(Cyclohexylmethyl)-3-methyl-6-(1-naphthylmethyl)-pyrrolo[3,4-*d*]pyrimidine-2,4-dione (5e): ^{1}H-NMR (DMSO-d_6) δ 8.15 (d, J = 8.4 Hz, 1H), 8.00–7.86 (m, 2H), 7.62–7.44 (m, 4H), 7.24 (d, J = 7.3 Hz, 1H), 6.91 (d, J = 1 Hz, 1H), 5.70 (s, 2H), 3.57 (d, J = 8.1 Hz, 2H), 3.17 (s, 3H), 1.85–1.45 (m, 6H), 1.20–0.81 (m, 5H); MS (CI, CH_4) m/e 401 (M^+). Anal. ($C_{25}H_{27}N_3O_2$) H, N; C: calcd, 74.79; found, 74.35.

1-(2-Hydroxypropyl)-3-methyl-6-(1-naphthylmethyl)-pyrrolo[3,4-*d*]pyrimidine-2,4-dione (5f): ^{1}H-NMR (DMSO-d_6) δ 8.16 (d, J = 9.3 Hz, 1H), 7.99–7.91 (m, 2H), 7.61–7.47 (m, 4H), 7.26 (d, J = 6.6 Hz, 1H), 6.87 (d, J = 2 Hz, 1H), 5.72 (s, 2H), 4.75 (brs, 1H), 3.99–3.96 (m, 2H) 3.61 (d, J = 6.4 Hz, 2H), 3.17 (s, 3H), 1.03 (d, J = 6.3 Hz, 2H); IR (1% KBr) 3398, 3118, 3059, 2972, 2934, 2891, 1700, 1641, 1606, 1543, 1419, 1372, 1288 cm^{-1}; MS (CI, CH_4) m/e 364 (MH^+). Anal. ($C_{21}H_{21}N_3O_3$) C, H, N.

(*R,*R**)- and (*R**,*S**)-(±)-6-(1-Acenaphthyl)-3-methyl-1-(1-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (5g).** For the mixture of diastereomers: ^{1}H-NMR ($CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.52–7.56 (m, 2H), 7.34 (d, J = 6.9 Hz, 1H), 7.31 (d, J = 7.1 Hz, 1H), 7.23 (d, J = 1.6 Hz, 1H), 6.34 (d, J = 1.6 Hz, 1H), 6.07 (dd, J = 3.3 and 8.3 Hz, 1H), 4.4–4.5 (m, 1H), 4.05 (dd, J = 8.3 and 17.5 Hz, 1H), 3.44 (dd, J = 3.3 and 17.5 Hz, 1H), 3.34 (s, 3H), 1.6–1.7 (m, 1H), 1.5–1.6 (m, 1H), 1.37 (d, J = 6.9 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H); Anal. ($C_{23}H_{23}N_3O_2 \cdot {}^1/_4H_2O$) C, H, N.

The diastereomeric mixture of enantiomers was separated into its four components using a CHIRALPAK AS column eluting with Hex/EtOH/DEA. The components gave a set of ^{1}H-NMR spectra which were all superimposible with a spectrum of the mixture. The compounds did exhibit different circular dichroism spectra and retention times eluting from a CHIRALPAK AS column. **(i):** t_R = 10.04 min; CD (230 nM) = (+); HRMS (LSIMS) $C_{23}H_{24}N_3O_2$ (MH^+) requires 374.1868, found 3374.1876, Δ = 2.11 ppm. **(ii):** t_R = 11.26 min; CD (230 nM) = (+); HRMS (LSIMS) $C_{23}H_{24}O_2$ (MH^+) requires 374.1868, found 3374.1869, Δ = 0.11 ppm. **(iii):** t_R = 18.71 min; CD (230 nM) = (−); HRMS (LSIMS) $C_{23}H_{24}N_3O_2$ (MH^+) requires 374.1868, found 3374.1876, Δ = 2.04 ppm. **(iv):** t_R = 26.65 min; CD (230 nM) = (−); HRMS (LSIMS) $C_{23}H_{24}N_3O_2$ (MH^+) requires 374.1868, found 3374.1862, Δ = −1.72 ppm.

6-(Diphenylmethyl)-1-(2-methylpropyl)pyrrolo[3,4-*d*]-pyrimidine-2,4-dione (6a): ^{1}H-NMR ($CDCl_3$) δ 7.3 (m, 6H), 7.24 (s, 1H), 7.0 (m, 4H), 6.46 (s, 1H), 6.29 (s, 1H), 3.6 (d, J = 7.5 Hz, 2H), 3.37 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 388 (MH^+). Anal. ($C_{24}H_{25}N_3O_2$) H, N; C: calcd, 73.49; found, 73.94.

(*S*)-(−)-1-(2-Methylpropyl)-6-(1-phenylethyl)pyrrolo-[3,4-*d*]pyrimidine-2,4-dione (6b): ^{1}H-NMR ($CDCl_3$) δ 7.3 (m, 5H), 7.1 (m, 1H), 6.29 (s, 1H), 5.32 (q, J = 6.9 Hz, 1H), 3.6 (m, J = 7.5 Hz, 2H), 3.37 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 1.88 (d, J = 7.2 Hz, 3H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 326 (MH^+); $[\alpha]^{Na}$ = +34.4° ($CHCl_3$, c = 1.0). Anal. ($C_{19}H_{23}N_3O_2$) C, H, N.

(*R*)-(+)-1-(2-Methylpropyl)-6-(1-phenylethyl)pyrrolo-[3,4-*d*]pyrimidine-2,4-dione (6c): ^{1}H-NMR ($CDCl_3$) δ 7.37

(m, 5H), 7.15 (m, 1H), 6.29 (s, 1H), 5.3 (q, J = 6.9 Hz, 1H), 3.6 (m, J = 7.5 Hz, 2H), 3.37 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 1.88 (d, J = 7.2 Hz, 3H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 326 (MH^+); $[\alpha]^{Na} = -34.4°$ ($CHCl_3$, c = 1.0). Anal. ($C_{19}H_{23}N_3O_2$) C, H, N.

1-(2-Methylpropyl)-6-(1-naphthylmethyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (7a): ^{1}H-NMR ($CDCl_3$) δ 7.8 (m, 3H), 7.5 (m, 3H), 7.2 (m, 2H), 6.36 (s, 1H), 5.56 (s, 2H), 3.61 (d, J = 7.5 Hz, 2H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 348 (MH^+). Anal. ($C_{21}H_{21}N_3O_2$) C, H, N.

6-(1-Acenaphthyl)-1-(2-methylpropyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (7b). ^{1}H-NMR ($CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.5 (m, 2H), 7.37 (d, J = 7.1 Hz, 1H), 7.34 (d, J = 6.6 Hz, 1H), 7.21 (s, 1H), 6.25 (s, 1H), 6.12 (dd, J = 3.3 and 8.3, 1H), 4.10 (dd, J = 8.3 and 17.5, 1H), 3.62 (d, J = 7.5 Hz, 2H), 3.48 (dd, J = 3.3 and 17.5, 1H), 2.12 (sept, J = 7.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 360 (MH^+); HRMS (LSIMS) $C_{22}H_{22}N_3O_2$ (MH^+) requires 360.1712, found 360.1710, Δ = −0.48 ppm. Anal. ($C_{22}H_{21}N_3O_2 \cdot {}^1/_4H_2O$) C, H, N.

3-Ethyl-1-(2-methylpropyl)-6-(1-naphthylmethyl)-pyrrolo[3,4-*d*]pyrimidine-2,4-dione (7c). To a DMF (10 mL) solution of amine **7a** (1.0 g, 2.88 mmol) was added K_2CO_3 (0.8 g, 5.76 mmol) and ethyl iodide (0.54 g, 3.45 mmol). The solution was stirred for 18 h followed by addition of Et_2O (60 mL). The solution was washed with 1 N NaOH (2 × 15 mL), H_2O (1 × 15 mL), and brine (1 × 15 mL). The organic layer was dried over K_2CO_3, filtered, and concentrated in vacuo to yield a glassy solid that was crystallized from Et_2O/Hex to give 0.63 g of **7c** as slender needles. ^{1}H-NMR ($CDCl_3$) δ 7.8 (m, 3H), 7.5 (m, 3H), 7.2 (m, 2H), 6.36 (s, 1H), 5.56 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.62 (d, J = 7.5 Hz, 2H), 2.12 (sept, J = 7.1 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.7 Hz, 6H); MS (CI, CH_4) m/e 375 (MH^+). Anal. ($C_{23}H_{25}N_3O_2$) C, H, N.

3-(*N*-methyl-4-butyramido)-1-(2-methylpropyl)-6-(1-naphthylmethyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (7d). To a DMF (10 mL) solution of amine **7a** (1.7 g, 4.88 mmol) were added K_2CO_3 (1.4 g, 10.1 mmol) and ethyl 4-bromobutyrate (1.4 g, 7.2 mmol). The solution was stirred for 18 h followed by addition of Et_2O (90 mL). The solution was washed with 1 N NaOH (2 × 15 mL), H_2O (1 × 15 mL), and brine (1 × 15 mL). The organic layer was dried over K_2CO_3, filtered, and concentrated in vacuo to yield an oily residue that was purified by silica gel chromatography [eluent: Hex (90%)/EtOAc (10%)] to give 0.7 g of the ethyl ester intermediate. The ester was treated with LiOH (0.11 g, 5.0 mmol), H_2O (3 mL), and dioxane (10 mL) at a gentle reflux for 20 h. The solution was acidified with 1 N HCl (15 mL) and extracted with EtOAc (3 × 20 mL). The organic layers were combined and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo to yield 0.5 g of the intermediate acid. The acid was combined with THF (15 mL) and TEA (0.17 mL, 1.2 mmol) and chilled to 0 °C. Isobutyl chloroformate (0.17 g, 1.2 mmol) was added dropwise followed by stirring for 90 min before addition of $MeNH_2$ (4 mL at 0.7 M, 3.0 mmol) followed by stirring for an additional 3 h. The solution was diluted with EtOAc (50 mL) and washed with 1 N NaOH (2 × 15 mL), H_2O (1 × 15 mL), and brine (1 × 15 mL). The organic layer was dried over K_2CO_3, filtered, and concentrated in vacuo to yield an oily residue that was purified by silica gel chromatography [eluent: $CHCl_3$ (95%)/MeOH (5%)] to give 0.33 g of the amide **7d** (26%/three steps): ^{1}H-NMR ($CDCl_3$) δ 7.9 (m, 2H), 7.8 (m, 1H), 7.5 (m, 2H), 7.52 (t, J = 7.1 Hz, 1H), 7.22 (m, 2H), 6.71 (brs, 1H), 6.39 (s, 1H), 5.56 (s, 2H), 4.00 (t, J = 6.6 Hz, 2H), 3.60 (d, J = 7.5 Hz, 2H), 2.80 (s, 3H), 2.20 (m, 3H), 1.95 (m, 2H), 0.99 (d, J = 6.7 Hz, 6H); MS (EI) m/e 447 (MH^+). Anal. ($C_{26}H_{30}N_4O_3$) C, H, N.

6-[(4-Methoxyphenyl)methyl]-3-methyl-1-(2-methylpropyl)-5-(methylthio)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (8a). The pyrrole **4g** (0.68 g, 2 mmol) was dissolved in THF (5 mL) and cooled to −65 °C. n-BuLi (0.88 mL at 2.5 M, 2.2 mmol) was added rapidly; stirring was continued for 10 min. Methyl disulfide was added, and the solution was kept at −65 °C for 30 min and then allowed to warm to room temperature with stirring for 1 h. The reaction mixture was partitioned with H_2O. The aqueous layer was extracted with Et_2O. The combined organics were dried over Na_2SO_4 and evaporated to give 1 g of oil which was purified on silica gel eluting with MBTE/Hex. This gave 600 mg (77%) of sulfide **8a**: mp 99−101 °C; ^{1}H-NMR ($CDCl_3$) δ 7.06 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.37 (s, 1H), 5.29 (s, 2H), 3.79 (s, 3H), 3.60 (d, J = 7.5 Hz, 2H), 3.41 (s, 3H), 2.43 (s, 3H), 2.18 (sept, J = 6.7 Hz, 1H), 0.93 (d, J = 6.6 Hz, 6H). Anal. ($C_{20}H_{25}N_3O_3S$) C, H, N.

6-[(4-Methoxyphenyl)methyl]-3-methyl-1-(2-methylpropyl)-5-[(4-morpholinyl)methyl]pyrrolo[3,4-*d*]pyrimidine-2,4-dione (8b). The pyrrole **4g** (50 g, 147 mmol) was dissolved in THF (500 mL) and cooled to −78 °C. n-BuLi (68 mL at 2.5 M, 170 mmol) was added dropwise over 15 min with additional stirring for 15 min. DMF (116 mL, 1.5 mol) in THF (100 mL) was added, keeping the temperature below −60 °C. The reaction mixture was kept cold for 45 min and then warmed to room temperature with stirring for 14 h. The mixture was poured into ice H_2O and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. This gave an oily residue which crystallized as yellow granules from EtOH to give 29 g (57%) of formylated pyrrole. The formylated pyrrole (6 g, 16 mmol) and morpholine (8.5 mL, 97 mmol) were dissolved in 0.5 N HCl/MeOH (90 mL). Sodium cyanoborohydride (710 mg, 11.4 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. The mixture was acidified to pH < 2 and the solvent removed on a rotary evaporator. The residue was slurried with H_2O and filtered. The mother liquor was washed with Et_2O and then made basic with 35% NaOH. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was recrystallized from Et_2O/EtOH containing HCl. This gave 4.0 g (52%) of **8b** as the hydrochloride: mp 200 °C dec; ^{1}H-NMR ($CDCl_3$) δ 7.05 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 1H), 6.54 (s, 1H), 5.85 (s, 2H), 4.3 (m, 4H), 3.94 (d, J = 12.5 Hz, 2H), 3.78 (s, 3H), 3.65 (d, J = 7.6 Hz, 2H), 3.39 (s, 3H), 3.2 (m, 4H), 2.20 (sept, J = 6.9 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H). Anal. ($C_{24}H_{32}N_4O_4 \cdot HCl \cdot {}^1/_4H_2O$) C, H, N.

3-Methyl-1-(2-methylpropyl)-6-(1-naphthylmethyl)-5-(methylthio)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (8c). LDA was prepared by adding n-BuLi (6.61 mL at 1.6 M, 10.57 mmol) to a solution of diisopropylamine (1.55 g, 11.4 mmol) in anhydrous THF (40 mL) at −78 °C. This solution was then added dropwise over 30 min to a solution of pyrrole **4s** (3.05 g, 8.45 mmol) and methyl p-toluenethiosulfate[29] (3.41 g, 16.9 mmol) in anhydrous THF (60 mL) under nitrogen at −78 °C. After 30 min at −78 °C, the reaction mixture was warmed to room temperature. The reaction mixture was diluted with ethyl acetate and then washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was filtered through silica gel eluting with 4:1 Hex/EtOAc to yield (*S*)-methylpyrrole **8c** (690 mg, 20%). Approximately 75% of the starting pyrrole was recovered. **8c**: ^{1}H-NMR ($CDCl_3$) δ 7.9 (m, 2H), 7.81 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.6 Hz, 2 H), 7.38 (t, J = 7.0 Hz, 1H), 6.78 (d, J = 6.7 Hz, 1H), 6.34 (s, 1H), 5.82 (s, 2H), 3.54 (d, J = 7.4 Hz, 2H), 3.42 (s, 3H), 2.49 (s, 3H), 2.12 (sept, J = 7.1 Hz, 1H), 0.87 (d, J = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$) 159.40, 151.68, 133.54, 132.33, 130 33, 129.85, 128.93, 128.69, 126.78, 126.17, 125.90, 125.38, 124.33, 122.21, 107.52, 104.55, 52.62, 48.64, 27.74, 26.72, 20.11,19.86; IR (1% KBr) 3853, 2958, 2924, 1700, 1660, 1699, 1517, 1415, 1283, 773 cm^{-1}. Anal. ($C_{23}H_{25}N_3O_2S$) C, H, N

5-[(3-Hydroxypropyl)thio]-3-methyl-1-(2-methylpropyl)-6-(1-naphthylmethyl)pyrrolo[3,4-*d*]pyrimidine-2,4-dione (8d). A solution of LDA in THF (6 mL) was prepared from n-BuLi (2.5 mL at 2.4 M, 6.0 mmol) and diisopropylamine (840 μL, 6.0 mmol) at −78 °C. A solution of the pyrrole **4s** (2 g, 5.5 mmol) and toluenethiosulfate[29] (4 g, 11 mmol) in THF (20 mL) was cooled to −78 °C. The LDA was added dropwise to the mixture of pyrrole and (silyloxy)propanethiosulfinate. After 30 min at −78 °C, the reaction mixture was warmed to room temperature. The reaction mixture was diluted with EtOAc (40 mL) and then washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was filtered

through silica gel eluting with 4:1 Hex/EtOAc. This gave 1.5 g (48% based on recovered starting material) of (propylsilyl)-oxy-alkylated pyrrole: ^{1}H-NMR ($CDCl_3$) δ 7.90–7.95 (m, 2H), 7.83 (d, J = 8.3 Hz, 1H), 7.54–7.58 (m, 2H), 7.39 (dd, J = 7.1 and 8.2 Hz, 1H), 6.79 (dd, J = 1.1 and 7.1 Hz, 1H), 6.36 (s, 1H), 5.85 (s, 2H), 3.82 (t, J = 7.8 Hz, 2H), 3.60 (t, J = 5.8 Hz, 2H), 3.42 (s, 3H), 3.07 (t, J = 7.1 Hz, 2H), 1.82 (pent, J = 6.4 Hz, 2H), 0.85 (s, 9H), 0.003 (s, 6H); IR (thin film) 2927, 1594, 1471, 1329 cm^{-1}; MS (CI, CH_4) m/e 360 (M^+). Anal. ($C_{31}H_{43}N_3O_3SSi$) H, N; C: calcd, 65.80; found, 65.23.

The silyl-protected alcohol (1.1 g, 2 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. A solution of n-Bu_4NF (3 mL at 1 M, 3 mmol) was added dropwise. After 1 h at 0 °C, the solution was allowed to warm to room temperature. The reaction mixture was diluted with Et_2O, washed with H_2O and brine, dried over Na_2SO_4, and concentrated. Recrystallization of the residue from $CHCl_3/Et_2O$ gave 500 mg (55%) of alcohol **8d**: ^{1}H-NMR ($CDCl_3$) δ 7.90–7.95 (m, 2H), 7.83 (d, J = 8.3 Hz, 1H), 7.54–7.58 (m, 2H), 7.39 (dd, J = 7.1 and 8.2 Hz, 1H), 6.79 (dd, J = 1.1 and 7.1 Hz, 1H), 6.36 (s, 1H), 5.85 (s, 2H), 3.82 (t, J = 7.8 Hz, 2H), 3.55 (d, J = 7.5 Hz, 2H), 3.42 (s, 3H), 3.10 (t, J = 6.6 Hz, 2H), 2.13 (sept, J = 6.9 Hz, 1H), 1.78 (pent, J = 6.3 Hz, 2H), 0.88 (d, J = 6.7 Hz, 6H); IR (1% KBr) 3466, 3140, 2927, 1699, 1660, 1594, 1518, 1284 cm^{-1}; MS (CI, CH_4) m/e 451 (M^+). Anal. ($C_{25}H_{29}N_3O_3S\cdot 1/2H_2O$) C, H, N.

6-Ethyl-5-formyl-3-methyl-1-(2-methylpropyl)pyrimidine-2,4-dione (22). The 6-methylpyrimidinedione **20a** (8 g, 36 mmol), t-BuOK (4.5 g, 40 mmol), and MeI (2.5 mL, 40 mmol) were dissolved in DMF (50 mL) and stirred for 2.5 h at room temperature. The reaction mixture was then poured into H_2O (250 mL). The precipitate was removed by filtration and dried in vacuo. This gave 7.3 g (86%) of the 5-cyano 6-ethyl derivative: ^{1}H-NMR ($CDCl_3$) δ 3.74 (d, J = 7.5 Hz, 2H), 3.31 (s, 3H), 2.84 (q, J = 7.6 Hz, 2H) 2.06 (sept, J = 7.2 Hz, 1H), 1.32 (t, J = 7.4 Hz, 3H), 0.93 (d, J = 6.70 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 166.1, 159.0, 150.6, 113.8, 88.6, 52.4, 28.5, 28.4, 25.8, 19.7, 12.7; MS (CI, CH_4) m/e 235 (M^+). Anal. ($C_{12}H_{17}N_3O_2$) C, H, N.

The 5-cyano 6-ethyl derivative (1 g, 4.25 mmol) was dissolved in HCO_2H (8 mL). A slurry of Ra Ni (1.4 g, wet) in HCO_2H was prepared and allowed to stand for 2–3 min as H_2 evolved. The two mixtures were combined and immersed in a 95 °C bath for 20 min. The catalyst was removed by filtration through Whatman 50 paper. The mother liquor was diluted with EtOAc. This organic layer was washed with $NaHCO_3$ (3 × 20 mL) and brine, dried over Na_2SO_4, and concentrated. This gave 800 mg (79%) of aldehyde **22**: ^{1}H-NMR ($CDCl_3$) δ 10.24 (s, 1H), 3.81 (d, J = 7.5 Hz, 2H), 3.35 (s, 3H), 3.16 (q, 6.5 Hz, 2H), 2.06 (sept, J = 7.0 Hz, 1H), 1.19 (t, J = 7.4 Hz, 3H), 0.94 (d, J = 6.7 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 189.4, 165.6, 162.9, 151.2, 106.6, 50.6, 28.7, 28.0, 21.8, 19.8, 12.7; MS (CI, CH_4) m/e 235 (M^+). Anal. ($C_{12}H_{18}N_2O_3$) C, H, N.

3,7-Dimethyl-1-(2-methylpropyl)-6-(1-naphthylmethyl)-pyrrolo[3,4-*d*]pyrimidine-2,4-dione (8e). The aldehyde **22** (100 mg, 0.4 mmol) was dissolved in 2:5 EtOAc/$CHCl_3$ (7 mL) and cooled to 0 °C. Pyridinium bromide perbromide (130 mg, 0.4 mmol) was added, and the reaction mixture was allowed to stir cold for 30 min before warming to room temperature with stirring overnight. The solution was diluted with CH_2Cl_2, washed with 1 N HCl and brine, dried over Na_2SO_4, and concentrated. Chromatography on silica gel eluting with 9:1 Hex/EtOAc gave 75 mg (60%) of the 5-(1-bromoethyl) derivative: ^{1}H-NMR ($CDCl_3$) δ 10.23 (s, 1H), 6.90 (brs, 1H), 4.13 (dd, J = 7.8 and 14 Hz, 1H), 3.98 (dd, J = 7.8 and 14 Hz, 1H), 3.37 (s, 3H), 2.35 (sept, J = 7.0 Hz, 1H), 1.98 (d, J = 7.4 Hz, 3H), 0.92 (d, J = 6.7 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 190.2, 162.5, 160.4, 150.9, 107.2, 52.9, 35.1, 28.2, 27.6, 23.5, 19.8, 19.7; IR (1% KBr) 2950, 1730, 1650, 1450 cm^{-1}. Anal. ($C_{12}H_{17}Br_1N_2O_3$) C, H, N, Br.

The bromoaldehyde (530 mg, 1.66 mmol), 1-naphthylmethylamine (270 μL, 1.8 mmol), and $NaHCO_3$ (154 mg, 1.8 mmol) were stirred in EtOH (15 mL) for 14 h. The mixture was diluted with $CHCl_3$, washed with 1 N HCl and brine, dried over Na_2SO_4, and concentrated. The residue was crystallized from EtOAc to 200 mg (32%) of pyrrolopyrimidine **8e**. ^{1}H-NMR ($CDCl_3$) δ 7.9 (m, 1H), 7.84–7.89 (m, 2H), 7.56–7.59 (m, 2H), 7.41 (t, J = 7.4 Hz, 1H), 7.24 (s, 1H), 6.75 (d, J = 7.1 Hz, 1H), 5.54 (s, 2H), 3.94 (d, J = 7.4 Hz, 2H), 3.40 (s, 3H), 2.35 (s, 3H), 2.10 (sept, J = 7.0 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 160.2, 152.6, 133.6, 131.2, 130.3, 129.1, 128.9, 126.9, 125.6, 124.6, 124.0, 122.0, 119.9, 109.6, 106.0, 50.6, 49.6, 28.0, 27.9, 19.6, 11.1; IR (1% KBr) 2950, 1650, 1450 cm^{-1}. Anal. ($C_{23}H_{25}N_3O_2\cdot 1/4H_2O$) C, H, N.

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