# Design of 2,5-Dimethyl-3-(6-dimethyl-4-methylpyridin-3-yl)-7-dipropylamino-pyrazolo[1,5-*a*]pyrimidine (NBI 30775/R121919) and Structure−Activity Relationships of a Series of Potent and Orally Active Corticotropin-Releasing Factor Receptor Antagonists

Chen Chen,* Keith M. Wilcoxen, Charles Q. Huang, Yun-Feng Xie, James R. McCarthy, Thomas R. Webb, Yun-Fei Zhu, John Saunders, Xin-Jun Liu, Ta-Kung Chen, Haig Bozigian, and Dimitri E. Grigoriadis

*Neurocrine Biosciences, Inc., 10555 Sciences Center Drive, San Diego, California 92121*

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We have previously shown that 3-phenylpyrazolo[1,5-*a*]pyrimidines exemplified by **8** were potent antagonists of the human corticotropin-releasing factor-1 receptor. A series of 3-pyridylpyrazolo-[1,5-*a*]pyrimidines **15**, **25**−**30**, **34**, and **35** containing a weakly basic pyridine ring at the 3-position of the bicyclic nucleus was designed to reduce lipophilicity from the initial leads such as **7**. Here, we showed that these 3-pyridyl compounds exhibited potent antagonists at the human $CRF_1$ receptor. Moreover, the hydrophilic and weakly basic pyridine moiety increased the water solubility of some analogues. Compound **26h** exhibited good binding affinity at the human $CRF_1$ receptor with a $K_i$ value of 3.5 nM. As a functional antagonist, it dose-dependently inhibited CRF-stimulated cAMP production in cells expressing the $CRF_1$ receptor ($IC_{50}$ = 50 nM), and CRF-stimulated ACTH release from cultured rat pituitary cells ($IC_{50}$ = 20 nM). **26h** had a log *P* value of 4.9 and water solubility of greater than 10 mg/mL. Pharmacokinetic studies in rats showed that **26h** was orally bioavailable and able to penetrate into the brain. **26h** has been demonstrated in vivo efficacy in animal behavioral models that measure anxiolytic activity. These results suggest that analogues from this series were potent $CRF_1$ receptor antagonists with proper physicochemical properties and good pharmacokinetic profiles. **26h** was developed into a clinical compound and exhibited efficacy in patients with major depression.

## Introduction

Corticotropin-releasing factor (CRF, also known as corticotropin-releasing hormone), a neuropeptide isolated from mammalian brain,[1] is the prime regulator of the hypothalamus−pituitary−adrenocortical (HPA) axis.[2] It has broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological, and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain.[3] CRF has been implicated as the mediator for the integrated physiological response to stress,[4] and it mediates its actions through high affinity binding to its receptors, $CRF_1$-R and $CRF_2$-R, both of which are members of the class B G-protein-coupled receptor superfamily.[5] Inhibition of $CRF_1$ receptor has been shown to reduce ACTH level in plasma of stressed animals.[6] Antagonists of the $CRF_1$ receptor are expected to have utility in treatment of stress-related diseases such as anxiety/depression and diseases involving the HPA axis.[7]

Since the first small molecule $CRF_1$ receptor antagonist CP-154,526 was reported in 1996,[8] many compounds from different chemical classes have appeared in the literature.[9] Potent $CRF_1$ antagonists such as **1** (CP-154,526), **2** (Antalarmin),[10] **3** (NBI 27914),[11] **4** (DMP904),[12] **5** (CRA1000),[13] and **6** (SRA125543A)[14] (Figure 1) have been widely studied in different animal models for CRF related behavior. Although these compounds possess excellent in vitro activities as $CRF_1$ antagonists, and several of them have exhibited in vivo efficacy in anxiety models when dosed orally, most of the compounds reported earlier suffer from high lipophilicity and poor water solubility.[15] Therefore, it is very difficult to develop these compounds into pharmaceutical agents for clinical usage. For example, **1** has a very long half-life (51 h) associated with high volume distribution (105 L/kg) in rats.[16] Recent efforts on discovery of more hydrophilic $CRF_1$ antagonists have resulted in compounds such as **8**−**10** with proper lipophilicity.[17] In our efforts to identify potent $CRF_1$ antagonists with drug-like properties, we synthesized 3-phenylpyrazolo-[1,5-*a*]pyrimidines such as **8** (NBI 30545)[17a] by incorporation of polar alkoxy groups into the highly lipophilic molecules such as **7**.[18] By using ACD/LogP software,[19] we calculated log *P* values of some small molecule $CRF_1$ antagonists to assess the relative lipophilicities of these compounds. For example, the *C* log *P* values of **1** and **3** were 8.43 and 9.71. However, **8** had a *C* log *P* of 3.18, a desirable value for CNS agents,[20] which was much lower than that of **7** (*C* log *P* = 5.86). As an alternative, replacement of the 3-phenyl group of the 3-phenylpyrazolo[1,5-*a*]pyrimidine with a hydrophilic and weakly basic pyridine moiety should reduce the lipophilicity of this series of compounds. In addition, alternation of substituents at the pyridine ring will also change the basicity and hydrophilicity of the target molecules. In this paper we report the design, synthesis, and structure−activity relationships of a series of 3-pyridylpyrazolo[1,5-*a*]pyrimidines as potent $CRF_1$ receptor antago-

* Corresponding author. Phone: 1-858-658-7634. Fax: 1-858-658-7619. E-mail: cchen@neurocrine.com.

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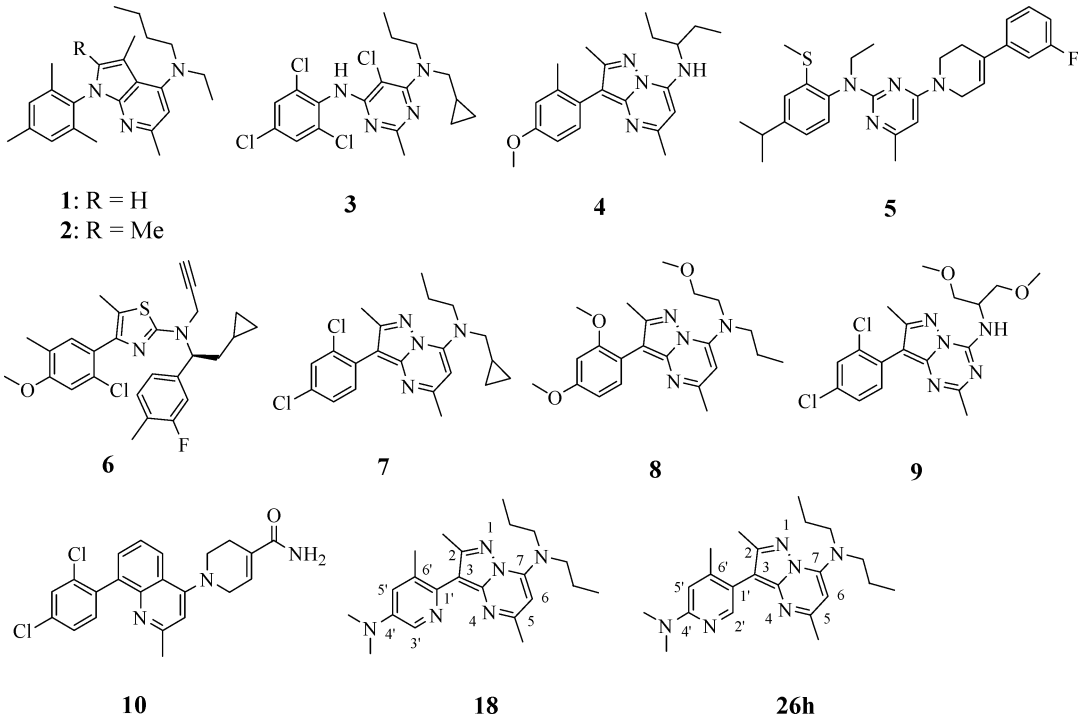
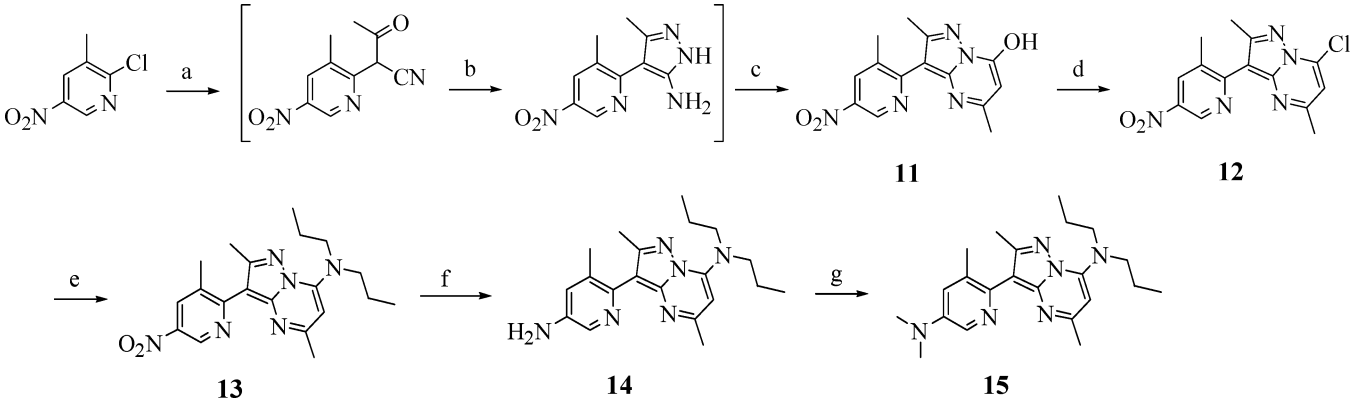



**Figure 1.** Some small molecule $CRF_1$ receptor antagonists.

**Scheme 1.** Synthesis of 3-(Pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine **15**[a]




[a] Reagents and conditions: (a) MeC(ONa)=CHCN/DMSO; (b) (i) $NH_2NH_2HBr/H_2O$/EtOH/reflux; (c) ethyl acetoacetate/dioxane/reflux; (d) $POCl_3$/reflux; (e) $Pr_2NH$/acetonitrile/reflux; (f) $H_2$/Pd−C/EtOH; (g) $CH_2O/NaBCNH_3$/AcOH.

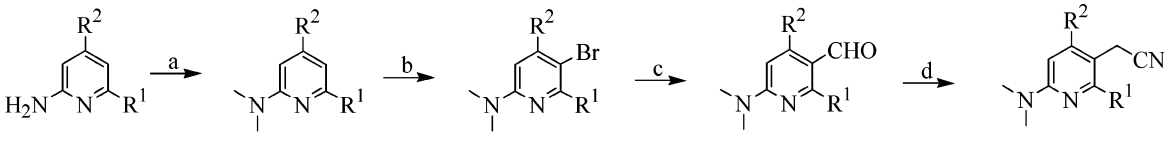
nists.[21] In particular, the discovery, in vitro activities, and pharmacokinetic properties of **26h** (NBI 30775/R121919), which has exhibited anxiolytic effects in vivo[22] and clinical efficacy in patients with major depression,[23] will be discussed.

## Chemistry

The 3-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine **15** was synthesized as showed in Scheme 1. Thus, reaction of 2-chloro-3-methyl-5-nitropyridine with acetoacetonitrile sodium salt, obtained from 2-methylisoxazole and sodium ethoxide,[24] afforded 2-(3-methyl-5-nitropyridin-2-yl)acetoacetonitrile in 61% yield,[25] which was cyclized with hydrazine hydrobromide in a mixture of ethanol−water (10:1) at reflux to give 3-amino-4-(3-methyl-5-nitropyridin-2-yl)-5-methylpyrazole in 41% yield. This compound was subjected to a second cyclization with ethyl acetoacetate in refluxing dioxane to provide the 3-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidone **11** as a white solid (26%). Conversion of the pyrimidone **11** to the corresponding 7-chloropyrazolo[1,5-*a*]pyrimidine **12** was accomplished with $POCl_3$ in refluxing acetonitrile (91% yield). Compound **13** was synthesized by reaction of **12** with dipropylamine in refluxing acetonitrile in 69% yield. This nitro compound **13** was reduced under palladium-catalyzed hydrogenation conditions to give the corresponding analine **14** in 80% yield, which was further modified to **15** by using a standard reductive alkylation protocol with formaldehyde.[26]

The 3-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidines **25**−**30** were prepared by the procedures outlined in Schemes 3−5 and illustrated below. Commercially available 2-aminopyridines **16a**−**d** were converted to the corresponding dimethylaminopyridines **17a**−**d** using a standard reductive alkylation protocol with formaldehyde and sodium cyanoborohydride.[26] The pyridines **17a**−**d** were brominated in dichloromethane to give the corresponding 2-dimethylamino-5-bromopyridines **18a**−**d** as the major products.[27] The regioisomeric structures were assigned on the basis of the coupling constants of $^1H$

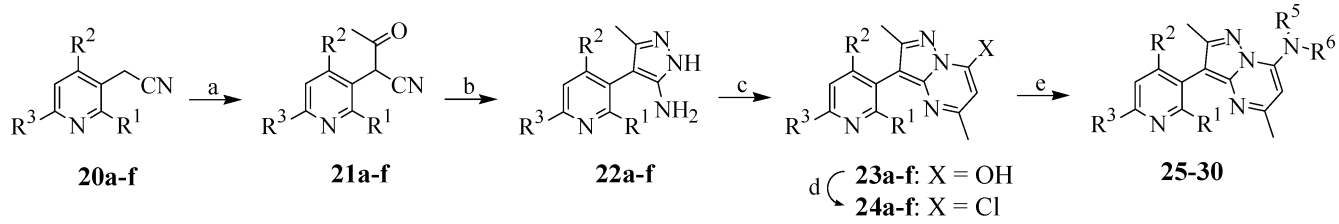
**Scheme 2.** Synthesis of 6-Dimethylaminopyridin-3-ylacetonitriles **20a**−**d**[a]




**a**: $R^1 = R^2 = H$; **b**: $R^1 = H$, $R^2 = Me$; **c**: $R^1 = Me$, $R^2 = H$; **d**: $R^1 = R^2 = Me$

[a] Reagents and conditions: (a) 37% aqueous $CH_2O/NaCNBH_3/AcOH$; (b) $Br_2$/aqueous $Na_2CO_3/CH_2Cl_2$/room temperature; (c) Mg/THF, then DMF/0 °C to room temperature; (d) TosMIC/t-BuOK/DME/−50 °C, then MeOH/reflux.

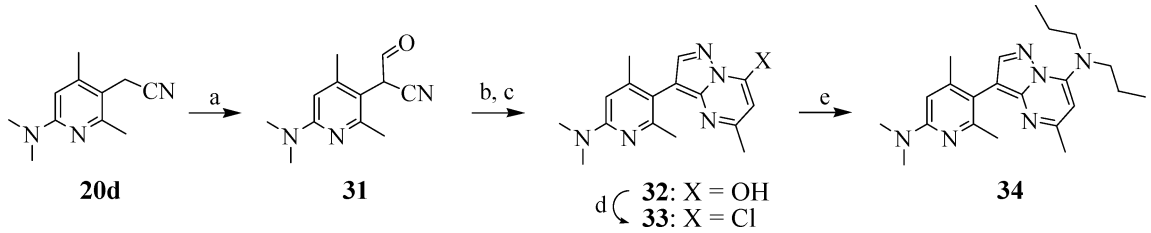
**Scheme 3.** Synthesis of 3-(Pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidines **25**−**30**[a]




**a**: $R^1 = R^2 = H$, $R^3 = Me_2N$; **b**: $R^1 = H$, $R^2 = Me$, $R^3 = Me_2N$; **c**: $R^1 = Me$, $R^2 = H$, $R^3 = Me_2N$;
**d**: $R^1 = R^2 = Me$, $R^3 = Me_2N$; **e**: $R^1 = R^2 = H$, $R^3 = Me$; **f**: $R^1 = H$, $R^2 = R^3 = Me$.

[a] Reagents and conditions: (a) NaH/THF/EtOAc/room temperature; (b) $NH_2NH_2HBr/EtOH-H_2O$/reflux; (c) ethyl acetoacetate/dioxane/reflux; (d) $POCl_3$/ACN/reflux; (e) $R^5R^6NH$/ACN/reflux.

**Scheme 4.** Synthesis of 2-Desmethyl-3-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine **34**[a]




[a] Reagents and conditions: (a) NaH/CHOOEt/THF; (b) $NH_2NH_2 \cdot HBr$/EtOH/reflux; (c) $MeCOCH_2COOEt$/dioxane/reflux; (d) $POCl_3$/reflux; (e) $Pr_2NH$/ACN/reflux.

NMR spectra. The bromopyridines **18a**−**d** were reacted with butyllithium at −78 °C and the anions were quenched with dry DMF[28] to give the 3-pyridylcarboxaldehydes **19a**−**d**, which were converted to the acetonitriles **20a**−**d** using the TosMIC protocol (Scheme 2).[29]

The pyridylacetonitriles **20e**,**f** were synthesized from substituted nicotinic esters.[30] Thus, 6-methylnicotinic acids were reduced using lithium aluminum hydride in THF to give the corresponding alcohols, which were converted to the chloromethylpyridines with thionyl chloride. Reaction of chloromethylpyridines with NaCN in DMF afforded **20e**,**f**.

Acetylation of the acetonitriles **20a**−**f** was accomplished in THF in the presence of sodium hydride and ethyl acetate to give the corresponding acetoacetonitriles **21a**−**f** (Scheme 3), which were cyclized to the aminopyrazoles **22a**−**f** with hydrazine hydrobromide in aqueous ethanol. For this cyclization reaction, the hydrazine salt gave better yields of the desired products than free hydrazine.[31] The aminopyrazoles **22a**−**f** were then subjected to a second cyclization with ethyl acetoacetate in refluxing dioxane, and the corresponding pyrazolo[1,5-*a*]pyrimidones **23a**−**f** precipitated out from the reaction solution. Conversion of **23a**−**f** to the 7-chloropyrazolo[1,5-*a*]pyrimidines **24a**−**f** was accomplished in refluxing acetonitrile with phosphorus oxychloride. Finally, substitution of **24** with an alkylamine in acetonitrile at reflux provided the desired compounds **25**−**30**.

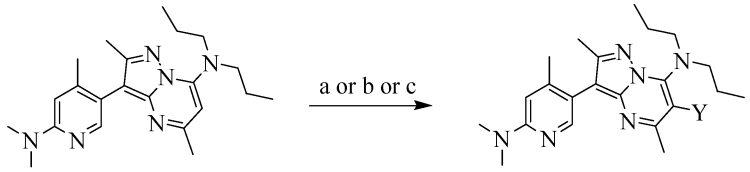
The 2-desmethyl analogue (**34**) of **28** was synthesized from the acetonitrile **20d** following a procedure described in Scheme 4. Formylation of **20d** with ethyl formate in the presence of sodium hydride in THF gave **31**, which was cyclized with hydrazine hydrobromide, followed by a second cyclization with ethyl acetoacetate to afford the 2-desmethylpyrazolo[1,5-*a*]pyrimidone **32**. **34** was obtained from the chloro intermediate **33** using dipropylamine.

Halogenation of compound **26h** with *N*-fluorobenzenesulfonimide, *N*-chlorosuccinimide, or *N*-bromosuccinimide in chloroform at room temperature gave the corresponding 6-halopyrazolo[1,5-*a*]pyrimidines **35a**−**c**, respectively (Scheme 5).

## Results and Discussion

The synthesized compounds were tested for their binding affinities at the cloned human $CRF_1$ receptor expressed in CHO cells using [$^{125}$I]o-CRF as the radiolabeled ligand, and the $K_i$ values were determined from dose−response curves using concentrations ranging from 1 nM to 10 $\mu$M as described.[32,38] The binding affinities of 3-pyridin-2-yl compounds are depicted in Table 1. The structure−activity relationships of substi-

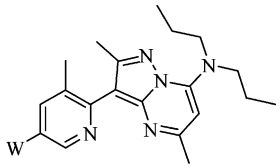
**Scheme 5.** Synthesis of 6-Halo-3-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidines **35a**−**c**[a]




**26h** **35a**: Y = F; **35b**: Y = Cl; **35c**: Y = Br

[a] Reagents and conditions: (a) NBFS/$CHCl_3$/room temperature 2 days; (b) NCS/$CHCl_3$/room temperature 2 h; (c) NBS/$CHCl_3$/room temperature, overnight.

**Table 1.** SAR of 7-Dipropylamino-3-(2-pyridyl)pyrazolopyrimidines **13**−**15**

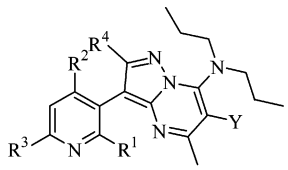


**13-15**

| compound | W | $K_i$ (nM)[a] |
|---|---|---|
| **7** | | 1.6 |
| **8** | | 3.4 |
| **13** | $NO_2$ | 9.1 |
| **14** | $NH_2$ | 85 |
| **15** | $NMe_2$ | 10 |

[a] Receptor binding was conducted as described previously. Data are average of two or more independent determinations. Typical standard errors were ≤30%.

**Table 2.** Binding Affinity of CRF Antagonists **25**−**30**, **34**, and **35**



**25-30, 34, 35**

| compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Y | $K_i$ (nM)[a] |
|---|---|---|---|---|---|---|
| **25** | H | H | $Me_2N$ | Me | H | 4.2 |
| **26h** | H | Me | $Me_2N$ | Me | H | 3.5 |
| **27** | Me | H | $Me_2N$ | Me | H | 2.2 |
| **28** | Me | Me | $Me_2N$ | Me | H | 5.2 |
| **34** | Me | Me | $Me_2N$ | H | H | 20 |
| **29** | H | H | Me | Me | H | 21 |
| **30** | H | Me | Me | Me | H | 7.3 |
| **35a** | H | Me | $Me_2N$ | Me | F | 5.6 |
| **35b** | H | Me | $Me_2N$ | Me | Cl | 39 |
| **35c** | H | Me | $Me_2N$ | Me | Br | 240 |

[a] Receptor binding was conducted as described previously. Data are average of two or more independent determinations. Typical standard errors were ≤30%.

tutions at the 3-pyridyl moiety and the 6-position of pyrazolopyrimidine core are summarized in Table 2. The results from variation of 7-alkylamino groups are tabulated in Table 3. Selected compounds were also measured for their abilities to inhibit CRF-stimulated cAMP production in the same cell line as that used in the binding studies above, however, utilizing a live whole cell preparation to assess their functional antagonism (Table 4). **26** was further determined in a functional assay based on its ability to inhibit CRF-stimulated ACTH release in cultured rat pituitary cells.[33]

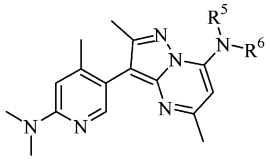
The 3-phenylpyrazolo[1,5-*a*]pyrimidines exemplified by **7** have been discovered as potent $CRF_1$ antagonists by several groups.[12,18,34] Although many compounds from this series were identified to possess excellent in vitro $CRF_1$ receptor binding affinities, like many other compounds reported earlier, most of them suffer from high lipophilicity and poor water solubility (for **7**, $K_i$ = 1.3 nM, *C* log *P* = 5.86; the hydrochloride or mesylate salt of **7** was largely insoluble in water). By incorporation of polar alkoxy groups into these molecules we successfully identified potent $CRF_1$ receptor antagonists such as **8** ($K_i$ = 3.4 nM, *C* log *P* = 3.18, measured log *P* = 2.78 at pH of 7.4) with proper lipophilicity and adequate water solubility (>10 mg/mL, mesylate salt).[17a] Alternatively, we designed a series of 3-pyridylpyrazolo-[1,5-*a*]pyrimidines **15**, **25**−**30**, and **34** by utilizing a hydrophilic and weakly basic pyridine[35] to replace the highly lipophilic phenyl group.

The 2-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine **15** possessed a $K_i$ value of 10 nM and a *C* log *P* of 4.76, while the 5-nitro- **13** and the 5-aminopyridin-2-yl analogue **14** had $K_i$ values of 9.1 and 85 nM, respectively. Apparently, one advantage of **15** over **7** was its lower lipophilicity. This initial success prompted us to study a series of 3-(pyridine-3-yl)pyrazolo[1,5-*a*]pyrimidines since 2-aminopyridine ($pK_a$ = 6.8) is slightly more basic than 3-aminopyridine ($pK_a$ = 6.2).

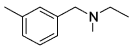
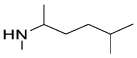
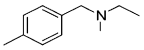
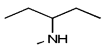
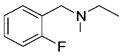
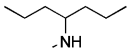
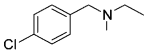
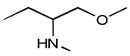
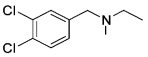
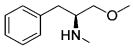
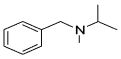
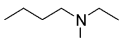
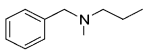
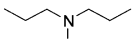
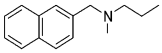
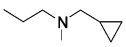
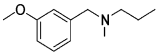
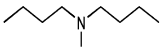
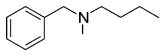
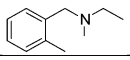
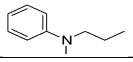
Compound **25**, which had a 6-dimethylaminopyridin-3-yl group at the 3-position of the pyrazolo[1,5-*a*]-pyrimidine core and possessed a *C* log *P* value of 4.36, had a $K_i$ value of 4.2 nM in the competitive binding assay. We then studied the effect of methyl substitution at the "ortho" position of the pyridine ring, on which a substituent may change the orthogonal relationship between the 3-aromatic ring and the bicyclic core.[11,36] Thus, introduction of a methyl group at the 6′-position of **25** resulted in compound **26h**, which had a $K_i$ value of 3.5 nM. This result is somewhat unexpected since this methylation could cause some changes at the dihedral angle between the two aromatic rings. A methyl group at the 2′-position improved the binding slightly (**27**, $K_i$ = 2.2 nM). Incorporating two methyl groups at both 2′- and 6′-positions also had little effect on the receptor binding (**28**, $K_i$ = 5.2 nM). On the contrary, the 6′-methyl group increased the binding affinity of the 4′-methylpyridin-1′-yl compound **29** ($K_i$ = 21 nM) about 3-fold (**30**, $K_i$ = 7.3 nM). However, deletion of the methyl group at the 2-position of pyrazolo[1,5-*a*]pyrimidine **28** resulted in a 4-fold decrease in binding affinity (**34**, $K_i$ = 20 nM).

Next we examined the structure−activity relationships of the 7-substitution of 3-(pyridin-3-yl)-pyrazolo-[1,5-*a*]pyrimidines **26**. A small lipophilic side chain, such as dipropylamino (**26h**), *N*-ethyl-*N*-butylamino (**26g**), *N*-propyl-*N*-cyclopropanemethylamino (**26i**), or *N*-benzyl-*N*-ethylamino (**26k**, **26l**, **26m**, **26n**, **26o**, **26p**),

**Table 3.** SAR of 7-Alkylamino- or 7-Dialkylaminopyrazolopyrimidines **26a**−**v**



**26a-v**

| Compound | $R^5NR^6$ | $K_i$ (nM)[a] | Compound | $R^5NR^6$ | $K_i$ (nM)[a] |
|---|---|---|---|---|---|
| **26a** |  | 17 | **26l** |  | 2.4 |
| **26b** |  | 13 | **26m** |  | 2.3 |
| **26c** |  | 9.4 | **26n** |  | 3.4 |
| **26d** |  | 4.8 | **26o** |  | 1.3 |
| **26e** |  | 260 | **26p** |  | 2.5 |
| **26f** |  | 6.5 | **26q** |  | 11 |
| **26g** |  | 2.6 | **26r** |  | 5.2 |
| **26h** |  | 3.5 | **26s** |  | 15 |
| **26i** |  | 2.6 | **26t** |  | 24 |
| **26j** |  | 4.2 | **26u** |  | 2.9 |
| **26k** |  | 2.4 | **26v** |  | 8.8 |

[a] Receptor binding was conducted as described previously. Data are average of two or more independent determinations. Typical standard errors were ≤30%.

**Table 4.** Inhibition of CRF-Stimulated cAMP Production for Selected Compounds

| compound | $K_i$ (nM)[a] | $IC_{50}$ (nM)[a] |
|---|---|---|
| **7** | 1.6 | 29 |
| **8** | 3.4 | 76 |
| **13** | 9.1 | 180[b] |
| **15** | 10 | 160 |
| **25** | 4.2 | 110 |
| **26h** | 3.5 | 50 |
| **27** | 2.2 | 190 |
| **28** | 5.2 | 40 |
| **30** | 7.3 | 300[b] |
| **35a** | 5.6 | 50 |

[a] Receptor binding and function antagonism were conducted as described previously. Data are average of two or more independent determinations. Typical standard errors were ≤30%. [b] Single determination.

resulted in compounds with good binding affinity ($K_i$ value < 5 nM). Derivatives from some primary amines also exhibited good binding (i.e. 4-heptylamino analogue **26d**).

The 6-halogenated analogues of **26h** displayed very interesting results. While the fluorinated analogue of **26h** had a binding affinity (**35a**, $K_i$ = 5.6 nM) very similar to that of the parent, the chloro (**35b**, $K_i$ = 39 nM) and the bromo analogue **35c** ($K_i$ = 240 nM) exhibited reduced binding affinities. The proton NMR spectra of these four compounds were almost identical except a singlet at 2.45−2.72 ppm (**35a**, 2.76; **35b**, 2.72; **35c**, 2.62; **26h**, 2.46 ppm), which was assigned to the 5-methyl group of the pyrazolo[1,5-*a*]pyrimidine. Since the fluorine, which possesses the strongest electron negativity among these halogens, was similar in size to a hydrogen atom, and the $K_i$ value of **35a** was similar to that of **26h**, the large change in chemical shift was most likely caused by strong electronic negativity of the fluorine. Thus, these results suggest that the 6-position of this core is limited to substitution of bulky group, due to a requirement of the receptor binding pocket.

Selected compounds such as **15**, **25**, **26h**, **27**, **28**, and **35a** were tested in the CRF-stimulated cAMP release assay to assess their functional antagonism. Compounds **26h**, **28**, and **35a** inhibited the accumulation of cAMP concentration with an $IC_{50}$ values of 50, 40, and 50 nM, respectively, and these numbers were comparable to those of **8** ($IC_{50}$ = 76 nM) and **7** ($IC_{50}$ = 29 nM). Compounds **25** and **27** were slightly less potent in this assay ($IC_{50}$ values of 110 and 190, respectively). These results demonstrated that compounds from this class were functional $CRF_1$ antagonists.

Compound **26h** was weakly basic with a p$K_a$ value of 6.9. It possessed moderate lipophilicity with a log *P* value of 4.9, which closely matched with the calculated value (*C* log *P* = 4.76) using ACD/LogP software. Its hydrochloride salt was readily soluble in water (>10 mg/mL, pH ∼4). This compound had little affinity to the $CRF_2$ receptor expressed in CHO cells at 10 $\mu$M concentration.[37] **26h** showed no significant binding at 10 $\mu$M to over 60 different receptors, ion channels, and transporters including benzodiazepin and dopaminergic and VIP receptors.

## Inhibition of CRF-Stimulated ACTH Release

**26h** was further evaluated in a functional assay based on its ability to inhibit CRF-stimulated ACTH release

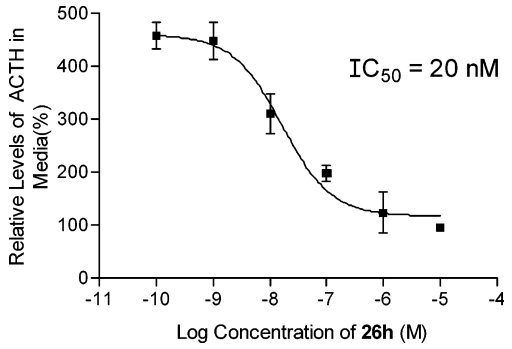



**Figure 2.** Inhibition of CRF stimulated ACTH release from rat pituitary cells by **26h**.

from cultured rat pituitary cells.[33] The result showed that **26h** was a highly potent inhibitor with an $IC_{50}$ value of 20 nM (Figure 2).

## Pharmacokinectics

A pharmacokinetic profile of **26h** was determined in male Sprague−Dawley rats following intravenous and oral administrations at 10 mg/kg. After an iv injection, the results indicated that **26h** had a high plasma clearance (CL = 112 mL/min kg) and a large volume of distribution ($V_d$ = 16.7 L/kg) in this species, which resulted in a terminal half-life of 1.7 h. After oral administration, the $C_{max}$ in plasma and brain occurred at 0.25 and 0.5 h post dosing, respectively. The mean maximal concentrations ($C_{max}$) in plasma and brain tissue via oral administration were 296 ng/mL and 290 ng/g, respectively. Oral bioavailability was estimated to be 34%, and, on the basis of the AUC (0−6 h) ratio, the brain tissue was exposed to approximately 67% of the plasma concentration of **26h** at this dosage.[38]

## Effects on Stress-Induced Anxiogenic-like Behavior in Mice

Ability to attenuate stress-induced anxiogenic-like behavior in mice has been used as an animal model to evaluate anxiolytic and antianxiety compounds, and activation of CRF secretion by stress has been extensively documented.[39] When mice are subjected to restraint stress and then placed in a novel environment, they tend to assume a frozen posture and spend little time to explore the surroundings.[40] Compound **26h**, given orally, dose-dependently reversed swim stress induced reduction of time spent in the open arms in the elevated plus-maze paradigm in mice. The time spent in the lighted area in the light/dark exploration paradigm was also significantly reduced among the **26h** (2.5 and 10 mg/kg, po) treated animals after they had been subjected to forced swim stress compared with the non-swim-stressed mice.[41]

## Conclusions

In the present study, we showed that pyrazolo[1,5-*a*]-pyrimidines bearing a 2- or 3-pyridyl group at the 3-position of the core structure were potent $CRF_1$ antagonists. The antagonistic activities of these compounds were demonstrated by their high affinities in binding to the $CRF_1$ receptor and inhibition of CRF-stimulated cAMP production. The presence of a weakly basic and hydrophilic pyridine group confers good physicochemical properties, in particular, adequate lipophilicity and water solubility of some analogues. A representative from this series, compound **26h**, possessed proper lipophilicity as a CNS agent, good in vitro biological activities, and a good pharmacokinetic profile. **26h** not only inhibited CRF-stimulated adrenocorticopin hormone (ACTH) release in vitro but also dose-dependently attenuated peak plasma ACTH in stressed rats in vivo.[42] Compound **26h** has demonstrated oral activity in several animal models in rodents.[22] These results suggest that orally active $CRF_1$ receptor antagonists have the potential to treat stress-related anxiety/depression in humans. Because of these desirable profiles, **26h** was evaluated in clinical trials and demonstrated efficacy in patients with major depression,[23a] although the clinical development of this compound has been discontinued due to reversible elevations of liver enzymes in two healthy subjects.[23b]

## Experimental Section

**General.** $^1$H NMR spectra were recorded on a Varian Spectrometer (Mercury 300 Hz) using TMS as the internal standard and $CDCl_3$ as solvent except where indicated. HPLC purification and purity analyses of final compounds were performed on a reversed phase HPLC−MS system (HP-4500 series with APCI mode for mass detection), and purity was determined to be at least 95% based on absorbance of two UV wavelengths (220 nm, 254 nm) and total ion current (TIC) monitoring the mass spectrometer. GC−MS was performed on a Hewlett-Packard 5890 series II system equipped with a 5972 series mass detector. The results from elemental analysis are indicated by atom symbols and within 0.4% of theoretical values.

**3-(3-Methyl-5-dimethylaminopyridin-2-yl)-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine Hydrochloride (15). 3-(3-Methyl-5-nitropyridin-2-yl)-2,5-dimethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (11).** To a solution of cyanoacetone sodium salt[43] (25.24 g, 240 mmol) in DMSO (160 mL) was added 2-chloro-3-methyl-5-nitropyridine[44] (27.6 g, 160 mmol) in DMSO (20 mL) at −10 °C under nitrogen atmosphere. The mixture was stirred at room temperature overnight and poured into saturated aqueous $NH_4Cl$. The solid was collected, washed with water, and dried in vacuo to give 2-cyano-2-(3-methyl-5-nitropyridin-2-yl)acetone (21.5 g, 61%), which was used for the next step without further purification: $^1$H NMR 2.51 (s, 3H), 2.77 (s, 3H), 8.22 (s, 1H), 8.78 (s, 1H); MS (EI) 218 ($MH^+$).

A mixture of the above compound (6.16 g, 30 mmol) and hydrazine hydrobromide (6.78 g, 60 mmol), acetic acid (30 mL) in ethanol (60 mL), dioxane (30 mL), and water (5 mL) was heated at reflux for 16 h. The reaction mixture was then concentrated in vacuo, and the residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was treated with ether to precipitate 3-amino-4-(3-methyl-5-nitropyridin-2-yl)-5-methyl-1*H*-pyrazole as a pale yellow solid, which was collected by filtration (2.9 g, 41% yield): $^1$H NMR 2.54 (s, 6H), 8.35 (s, 1H), 9.27 (s, 1H); MS (EI) 234 ($MH^+$).

A solution of the above compound (2.9 g, 12.4 mmol) and ethyl acetoacetate (3.2 g, 24.9 mmol) in dioxane (20 mL) was heated at reflux overnight. A white solid was formed, which was collected by filtration (0.98 g, 26% yield), to give the title compound **11**: $^1$H NMR (DMSO-$d_6$) 2.33 (s, 3H), 2.41 (s, 3H), 5.68 (s, 1H), 8.41 (d, $J$ = 2.7 Hz, 1H), 9.32 (d, $J$ = 2.7 Hz, 1H), 11.35 (brs, 1H); MS (EI) 300 ($MH^+$). Anal. ($C_{14}H_{13}N_5O_3$) C, H, N.

**3-(3-Methyl-5-nitropyridin-2-yl)-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (13).** A mixture of **11** (800 mg, 2.67 mmol) and phosphorus oxychloride (5 mL) was heated at reflux for 1 h. The reaction mixture was poured into

ice water and basified with sodium bicarbonate. The product was extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, filtered through a silica gel pad, and concentrated in vacuo to yield 7-chloro-3-(3-methyl-5-nitropyridin-2-yl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine **(12)** as a pale yellow oil (770 mg, 91% yield): GC−MS (100%, $t_R$ =13.7 min, *m/e* 317); $^1$H NMR 2.46 (s, 3H), 2.59 (s, 6H), 6.89 (s, 1H), 8.43 (d, $J$ = 2.1 Hz, 1H), 9.37 (d, $J$ = 2.1 Hz, 1H); MS (EI) 318 ($MH^+$).

A solution of **12** (518 mg, 1 mmol) and dipropylamine (2 mL) in acetonitrile (10 mL) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified on silica gel with ethyl acetate−hexanes (1:5) to yield the title compound **13** as a colorless oil (420, 69% yield): GC−MS (100%, $t_R$ = 19.6 min, *m/e* 382); $^1$H NMR 0.96 (t, $J$ = 7.1 Hz, 6H), 1.75 (m, 4H), 2.44 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 3.74 (m, 4H), 5.84 (s, 1H), 8.36 (s 1H), 9.32 (s, 1H); MS (EI) 383 ($MH^+$).

**3-(3-Methyl-5-dimethylaminopyridin-2-yl)-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine dihydrochloride (15).** A mixture of **13** (400 mg, 0.52 mmol) and Pd/C (10%, 80 mg) in ethanol (30 mL) was hydrogenated at 32 psi for 2 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to yield 3-(5-amino-3-methylpyridin-2-yl)-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (**14**) as an orange solid (320 mg, 80% yield): $^1$H NMR 0.92 (t, $J$ = 7.4 Hz, 6H), 1.70 (m, 4H), 2.19 (s, 3H), 2.39 (s, 3H), 2.42 (s, 3H), 3.62 (brs, 2H), 3.70 (m, 4H), 5.78 (s, 1H), 6.92 (d, $J$ = 2.1 Hz, 1H), 8.04 (d, $J$ = 2.1 Hz, 1H); MS (EI) 353 ($MH^+$).

Into a solution of **14** (31.2 mg, 0.09 mmol) and formaldehyde (37%, 1 mL) in acetonitrile (1 mL) was added sodium cyanoborohydride (17 mg, 0.267 mmol), followed by three drops of acetic acid. The mixture was stirred at room temperature for 2 h. The mixture was then partitioned between ethyl acetate and saturated $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified on silica gel with $CH_2Cl_2$−MeOH−$NH_4OH$ (150:10:1) to give the title compound (**15**): $^1$H NMR 0.93 (t, $J$ = 7.2 Hz, 6H), 1.70 (m, 4H), 2.24 (s, 3H), 2.39 (s, 3H), 2.42 (s, 3H), 2.99 (s, 6H), 3.71 (m, 4H), 5.79 (s, 1H), 6.95 (s, 1H), 8.12 (s, 1H); MS (EI) 381 ($MH^+$).

**15** (200 mg) was dissolved in ether (2 mL) and treated with excess 1 N HCl in ether. The yellow solid was collected by filtration (160 mg). Anal. ($C_{22}H_{32}N_6$·2HCl) C, H, N.

**3-(6-Dimethylamino-4-methylpyridin-3-yl)-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (26h). 2-Dimethylamino-4-methyl-5-(cyanomethyl)pyridine (20b).** To a mixture of 2-amino-4-picoline (**16b**, 33 g, 0.3 mol), $NaBH_3CN$ (57 g, 3 equiv), formaldehyde (37% aqueous solution, 240 mL) in acetonitrile (1 L) and water (200 mL) was added dropwise acetic acid (60 mL) at 0 °C in 2 h. The resultant solution was stirred at room temperature for 7 days and then concentrated in vacuo. The residue was basified with solid NaOH to pH 10, and the product extracted with hexanes (3 × 700 mL). The combined extract was washed with 1 N NaOH and brine, dried over $Na_2SO_4$, and evaporated in vacuo to give 2-dimethylamino-4-methylpyridine (**17b**)[45] as a colorless oil: $^1$H NMR 2.26 (s, 3H), 3.07 (s, 6H), 6.33 (s, 1H), 6.40 (d, $J$ = 8.1 Hz, 1H), 8.02 (d, $J$ = 8.1 Hz, 1H); MS (EI) 137 ($MH^+$).

A mixture of **17b** (32 g, 0.235 mol), $Na_2CO_3$ (30 g, 1.2 equiv) in dichloromethane (50 mL), and water (400 mL) was treated dropwise with a solution of bromine (13 mL, 1.05 equiv) in dichloromethane (50 mL) at 0 °C in 0.5 h. The resultant light brown suspension was stirred at 0 °C for another half hour. The product was extracted with hexanes (2 × 600 mL), and the combined extract was washed with brine, dried over $Na_2SO_4$, and evaporated in vacuo. The crude product was purified by chromatography on silica gel with 1:5 ethyl acetate/hexanes to give 5-bromo-2-dimethylamino-4-methylpyridine (**18b**) as a tan solid (78% yield): $^1$H NMR 2.30 (s, 3H), 3.04 (s, 6H), 6.38 (s, 1H), 8.14 (s, 1H); MS (EI) 216 ($MH^+$).

Into a suspension of magnesium (11.3 g, 2 equiv) in THF (20 mL) was added a quarter of the solution of **18b** (48.5 g from above) in THF (100 mL). The reaction was initiated with 5 drops of 1,2-dibromoethane with slight heating. The reaction became vigorous after initiation and 10 mL of THF was added. The rest of the bromo compound was added dropwise to maintain a gentle reflux. After addition the red mixture was stirred at room temperature for 0.5 h before DMF (27.5 mL, 1.5 equiv) was slowly injected at 0 °C. The resultant mixture was stirred at room temperature overnight and quenched with saturated aqueous $NH_4Cl$. The product was extracted with ether (2 × 500 mL), and the combined extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by chromatography on silica gel with 1:5 ethyl acetate/hexanes to give 2-dimethylamino-4-methyl-5-formylpyridine (**19b**) as a tan solid (77% yield). The analytic sample was obtained by crystallization from ether/hexanes: $^1$H NMR 2.57 (s, 3H), 3.11 (s, 6H), 6.28 (s, 1H), 8.43 (s, 1H), 9.87 (s, 1H); MS (EI) 165 ($MH^+$).

Into a suspension of KOBu-t (12.5 g) in DME (70 mL) at −50 °C was added dropwise a solution of TosMIC (15.6 g) in DME (70 mL). The brown solution was stirred at −50 °C for 10 min before a solution of **19b** (11 g, 68 mmol) in DME (70 mL) was added dropwise. The resultant mixture was stirred at −50 °C for 0.5 h and quenched with methanol (70 mL). This mixture was heated to reflux for 1 h, the solvent was evaporated, and the residue was partitioned in ethyl acetate−water. The organic layer was washed with brine, dried over $MgSO_4$, and filtrated through a silica gel pad with ethyl acetate. This workup gave 2-dimethylamino-4-methyl-5-(cyanomethyl)pyridine as a yellow solid (**20b**, 9.5 g, 80%): $^1$H NMR 2.31(s, 3H), 3.08 (s, 6H), 3.54 (s, 2H), 6.36 (s, 1H), 7.99 (s, 1H); MS (EI) 176 ($MH^+$). Anal. ($C_{10}H_{13}N_3$) C, H, N.

**3-(4-Methyl-6-dimethylaminopyridin-3-yl)-2,5-dimethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (23b).** Into a suspension of **20b** (40 g, 0.23 mol) and NaH (2.5 equiv) in THF (100 mL) was added about 5 mL of ethyl acetate. The mixture was stirred at room temperature until an exothermic reaction started and hydrogen evolved vigorously. Fifty milliliters of ethyl acetate was then added dropwise to maintain a gentle reflux. The mixture was stirred at room temperature for 2 h before it was quenched with water (100 mL). The organic phase was separated and the aqueous phase was washed several times with ethyl ether. The aqueous phase was then acidified with acetic acid and the product extracted with ethyl acetate (5 × 800 mL). The combined extract was washed with brine (50 mL) and dried over $MgSO_4$. Concentration in vacuo gave 1-cyano-1-(6-dimethylamino-4-methylpyridin-3-yl)acetone as a brown solid (**21b**, 40 g, 80% yield): $^1$H NMR (1:1 mixture of enol and ketone forms) 2.24 (s, 1.5 × 3H), 2.32 (s, 0.5 × 3H), 2.88 (s, 0.5 × 6H), 3.09 (s, 0.5 × 6H), 4.50 (brs, 0.5 × 1H), 4.62 (s, 0.5 × 1H), 6.13 (s, 0.5 × 1H), 6.35 (s, 0.5 × 1H), 7.60 (s, 0.5 × 1H), 8.05 (s, 0.5 × 1H); MS (EI) 218 ($MH^+$).

A mixture of **21b** (30 g, 0.14 mol) and hydrazine hydrobromide (62 g, 4 equiv) in ethanol (150 mL) and water (20 mL) was heated to reflux for 1 h. Ethanol was removed in vacuo, and the residue was diluted with water (50 mL). This aqueous phase was basified with solid $Na_2CO_3$, and the product was extracted with ethyl acetate. The extract was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 3-amino-4-(6-dimethylamino-4-methylpyridin-3-yl)-5-methylpyrazole **22b** as a brownish oil (30 g, 93% yield), which was crystallized from ether−hexanes: $^1$H NMR 2.07 (s, 3H), 2.14 (s, 3H), 3.10 (s, 6H), 4.10 (brs, 3H), 6.45 (s, 1H), 7.92 (s, 1H); MS (EI) 232 ($MH^+$).

A solution of **22b** (29.5 g, 128 mmol) and ethyl acetoacetate (2.5 equiv) in dioxane (100 mL) was heated to reflux for 20 h. The suspension was cooled, and ether (200 mL) was added. The solid was collected by vacuum filtration, and the title compound **23b** was obtained as a tan solid (23.5 g, 62% yield): $^1$H NMR 2.10 (s, 3H), 2.20 (s, 3H), 2.33 (s, 3H), 2.91 (s, 6H), 5.64 (s, 1H), 6.24 (s, 1H), 7.65 (s, 1H); MS (EI) 298 ($MH^+$). Anal. ($C_{16}H_{19}N_5O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine Hydrochloride (26h·HCl).** A suspension of **23b** (11 g, 37 mmol) and

$POCl_3$ (2 equiv) in acetonitrile (50 mL) was heated to reflux for 8 h. The reaction was quenched with ice and basified with $Na_2CO_3$. The product was extracted with ethyl acetate (2 × 200 mL). The extract was dried over $MgSO_4$, filtered through a silica gel pad, and concentrated in vacuo to give 2,5-dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-chloropyrazolo-[1,5-*a*]pyrimidine **24b** as a yellowish solid (11.5 g, 99% yield): $^1$H NMR 2.13 (s, 3H), 2.43 (s, 3H), 2.53 (s, 3H), 3.11 (s, 6H), 6.49 (s, 1H), 6.78 (s, 1H), 8.01 (s, 1H); MS (EI) 316 ($MH^+$).

A solution of **24b** (11.5 g, 36.5 mmol) and dipropylamine (4 equiv) in acetonitrile (50 mL) was heated to reflux for 3 h. The mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate and filtered through a short silica gel column with ethyl acetate, and the filtrate was concentrated in vacuo to give the title compound **26h** as a yellowish powder, which was recrystallized from ether−hexanes to give an off-white solid (10 g, 72% yield): $^1$H NMR 0.96 (t, $J$ = 7.1 Hz, 6H), 1.72 (m, 4H), 2.17 (s, 6H), 2.33 (s, 3H), 2.41 (s, 3H), 3.11 (s, 6H), 3.70 (m, 4H), 5.78 (s, 1H), 6.49 (s, 1H), 8.03 (s, 1H); MS (EI) 381 ($MH^+$). Anal. ($C_{22}H_{32}N_6$) C, H, N.

**Hydrochloride Salt Formation. 26h** (10 g, 26 mmol) was dissolved in dichloromethane (50 mL) and treated with HCl in ether (1 M solution, 26.5 mL) at room temperature. The solution was diluted with ether (about 200 mL) to precipitate 2,5-dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine hydrochloride as an off-white solid, which was collected by vacuum filtration (10 g, 96% yield).

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-(1,2-dimethylpropylamino)pyrazolo[1,5-*a*]pyrimidine Ditrifluoroacetate (26a).** A solution of **24b** (32 mg, 0.1 mmol) and 1,2-dimethylpropylamine (4 equiv) in acetonitrile (0.5 mL) was heated to reflux for 3 h. The product was purified by LC−MS to give the product as a colorless oil, 42 mg: $^1$H NMR 1.07 (d, $J$ = 6.3 Hz, 3H), 1.09 (d, $J$ = 6.6 Hz, 3H), 1.40 (d, $J$ = 6.9 Hz, 3H), 2.02 (m, 1H), 2.24 (s, 3H), 2.33 (s, 3H), 2.62 (s, 3H), 3.32 (s, 6H), 3.69 (m, 1H), 5.94 (s, 1H), 6.73 (s, 1H), 6.99 (d, $J$ = 9.3 Hz, 1H), 8.17 (s, 1H); MS (EI) 367 ($MH^+$). Anal. ($C_{21}H_{30}N_6$·2TFA·2/3$H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-(5-methyl-2-hexylamino)pyrazolo[1,5-*a*]pyrimidine Ditrifluoroacetate (26b).** This was prepared in a manner similar to the procedure described for **26a** using 2-amino-5-methylhexane: colorless oil, 44 mg; $^1$H NMR 0.94 (d, $J$ = 6.3 Hz, 6H), 1.32 (m, 2H), 1.44 (d, $J$ = 6.6 Hz, 3H), 1.61 (m, 1H), 1.75 (m, 1H), 2.24 (s, 3H), 2.33 (s, 3H), 2.62 (s, 3H), 3.32 (s, 6H), 3.83 (m, 1H), 5.93 (s, 1H), 6.98 (brs, 1H), 8.16 (s, 1H); MS (EI) 395 ($MH^+$). Anal. ($C_{23}H_{34}N_6$·2.3TFA) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-(3-pentylamino)pyrazolo[1,5-*a*]pyrimidine Ditrifluoroacetate (26c).** This was prepared in a manner similar to the procedure described for **26a** using 3-aminopentane: colorless oil, 38 mg; $^1$H NMR 1.05 (t, $J$ = 7.2 Hz, 3H), 1.06 (t, $J$ = 7.5 Hz, 3H), 1.76 (m, 2H), 1.86 (m, 2H), 2.20 (s, 3H), 2.32 (s, 3H), 2.60 (s, 3H), 3.31 (s, 6H), 3.63 (m, 1H), 6.01 (s, 1H), 6.81 (s, 1H), 7.19 (d, $J$ = 9.6 Hz, 1H), 7.96 (s, 1H); MS (EI) 367 ($MH^+$). Anal. ($C_{21}H_{30}N_6$·3TFA·$^1/_4H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-(4-heptylamino)pyrazolo[1,5-*a*]pyrimidine Ditrifluoroacetate (26d).** This was prepared in a manner similar to the procedure described for **26a** using 4-heptylamine: colorless oil, 27 mg; $^1$H NMR 0.98 (t, $J$ = 6.9 Hz, 3H), 0.99 (t, $J$ = 7.5 Hz, 3H), 1.46 (m, 4H), 1.74 (m, 4H), 2.22 (s, 3H), 2.32 (s, 3H), 2.59 (s, 3H), 3.31 (s, 6H), 3.80 (m, 1H), 6.00 (s, 1H), 6.83 (s, 1H), 7.24 (d, $J$ = 9.6 Hz, 1H), 7.91 (s, 1H); MS (EI) 395 ($MH^+$). Anal. ($C_{23}H_{34}N_6$·3TFA) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-[1-(methoxymethyl)propylamino]pyrazolo[1,5-*a*]pyrimidine Ditrifluoroacetate (26e).** This was prepared in a manner similar to the procedure described for **26a** using 2-amino-1-methoxybutane: colorless oil, 34 mg; $^1$H NMR 0.94 (t, $J$ = 7.2 Hz, 3H), 1.85 (m, 2H), 2.20 (s, 3H), 2.31 (s, 3H), 2.56 (s, 3H), 3.30 (s, 6H), 3.35 (s, 3H), 3.54 (m, 2H), 3.88 (m, 1H), 6.12 (s, 1H), 6.81 (s, 1H), 7.56 (d, $J$ = 9.6 Hz, 1H), 7.90 (s, 1H); MS (EI) 383 ($MH^+$). Anal. ($C_{21}H_{30}N_6O$·3TFA·3$H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-[{(1*S*)-methoxymethyl}phenethylamino]pyrazolo-[1,5-*a*]pyrimidine Ditrifluoroacetate (26f).** This was prepared in a manner similar to the procedure described for **26a** using (*S*)-benzyl(methoxymethyl)methylamine: colorless oil, 48 mg; $^1$H NMR 2.21 (s, 3H), 2.33 (s, 3H), 2.49 (s, 3H), 3.08 (dd, $J$ = 7.5, 10.5 Hz, 1H), 3.13 (dd, $J$ = 6.6, 10.5 Hz, 1H), 3.32 (s, 6H), 3.47 (s, 3H), 3.61 (dd, $J$ = 4.8, 10.6 Hz, 1H), 3.64 (dd, $J$ = 3.3, 10.6 Hz, 1H), 4.06 (m, 1H), 5.64 (brs, 1H), 6.73 (s, 1H), 7.30 (m, 5H), 7.45 (d, $J$ = 8.7 Hz, 1H), 8.12 (s, 1H); MS (EI) 445 ($MH^+$). Anal. ($C_{26}H_{32}N_6O$ ·2.5TFA) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-(*N*-butyl-*N*-ethylamino)pyrazolo[1,5-*a*]pyrimidine Trifluoroacetate Ditrifluoroacetate (26g).** This was prepared in a manner similar to the procedure described for **26a** using *N*-ethyl-*N*-butylamine: colorless oil, 43 mg; $^1$H NMR 1.04 (t, $J$ = 6.9 Hz, 3H), 1.47 (t, $J$ = 7.8 Hz, 3H), 1.49 (m, 2H), 1.86 (m, 2H), 2.21 (s, 3H), 2.27 (s, 3H), 2.48 (s, 3H), 3.30 (s, 6H), 4.02 (brs, 4H), 5.81 (s, 3H), 6.83 (s, 1H), 7.89 (s, 1H); MS (EI) 381 ($MH^+$). Anal. ($C_{22}H_{32}N_6$ ·3TFA) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-(*N*-cyclopropanemethyl-*N*-propylamino)pyrazolo-[1,5-*a*]pyrimidine Ditrifluoroacetate (26i).** This was prepared in a manner similar to the procedure described for **26a** using *N*-cyclopropanemethyl-*N*-propylamine: colorless oil, 32 mg; $^1$H NMR 0.45 (m, 2H), 0.74 (m, 2H), 1.04 (t, $J$ = 6.9 Hz, 3H), 1.23 (m, 1H), 1.89 (m, 2H), 2.20 (s, 3H), 2.27 (s, 3H), 2.49 (s, 3H), 3.29 (s, 6H), 4.02 (brs, 4H), 5.94 (s, 1H), 6.85 (s, 1H), 7.85 (s, 1H); MS (EI) 393 ($MH^+$). Anal. ($C_{23}H_{32}N_6$ ·3TFA) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-dibutylaminopyrazolo[1,5-*a*]pyrimidine Ditrifluoroacetate (26j).** This was prepared in a manner similar to the procedure described for **26a** using dibutylamine: colorless oil, 43 mg; $^1$H NMR 1.03 (t, $J$ = 6.9 Hz, 6H), 1.47 (m, 4H), 1.84 (m, 4H), 2.20 (s, 3H), 2.26 (s, 3H), 2.47 (s, 3H), 3.29 (s, 6H), 4.02 (brs, 4H), 5.80 (s, 1H), 6.84 (s, 1H), 7.85 (s, 1H); MS (EI) 409 ($MH^+$). Anal. ($C_{24}H_{36}N_6$·3TFA·0.5$H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-[*N*-(2-methylbenzyl)-*N*-ethylamino]pyrazolo[1,5-*a*]-pyrimidine Ditrifluoroacetate (26k).** This was prepared in a manner similar to the procedure described for **26a** using *N*-ethyl-*N*-(2-methylbenzyl)amine: colorless oil, 48 mg; $^1$H NMR 1.50 (t, $J$ = 6.9 Hz, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 2.38 (s, 3H), 2.50 (s, 3H), 3.32 (s, 6H), 4.15 (m, 2H), 5.12 (brs, 1H), 5.14 (brs, 1H), 5.73 (s, 1H), 6.73 (s, 1H), 7.07 (d, $J$ = 6.9 Hz, 1H), 7.29 (m, 3H), 8.17 (s, 1H); MS (EI) 429 ($MH^+$). Anal. ($C_{26}H_{32}N_6$·2.7TFA) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-[*N*-(3-methylbenzyl)-*N*-ethylamino]pyrazolo[1,5-*a*]-pyrimidine Ditrifluoroacetate (26l).** This was prepared in a manner similar to the procedure described for **26a** using *N*-ethyl-*N*-(2-methylbenzyl)amine: colorless oil, 47 mg; $^1$H NMR 1.47 (t, $J$ = 6.9 Hz, 3H), 2.25 (s, 3H), 2.29 (s, 3H), 2.39 (s, 3H), 2.52 (s, 3H), 3.32 (s, 6H), 4.07 (m, 2H), 5.20 (m, 2H), 5.73 (s, 1H), 6.74 (s, 1H), 7.08 (d, $J$ = 7.5 Hz, 1H), 7.10 (s, 1H), 7.19 (d, $J$ = 7.8 Hz, 1H), 7.32 (t, $J$ = 7.5 Hz, 1H), 8.18 (s, 1H); MS (EI) 429 ($MH^+$). Anal. ($C_{26}H_{32}N_6$ ·2.3TFA·0.7$H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-[*N*-(4-methylbenzyl)-*N*-ethylamino]pyrazolo[1,5-*a*]-pyrimidine Ditrifluoroacetate (26m).** This was prepared in a manner similar to the procedure described for **26a** using *N*-ethyl-*N*-(4-methylbenzyl)amine: colorless oil, 50 mg; $^1$H NMR 1.46 (t, $J$ = 6.9 Hz, 3H), 2.24 (s, 3H), 2.29 (s, 3H), 2.38 (s, 3H), 2.51 (s, 3H), 3.32 (s, 6H), 4.05 (m, 2H), 5.18 (brs, 1H), 5.36 (brs, 1H), 5.82 (s, 1H), 6.74 (s, 1H), 7.18 (d, $J$ = 8.1 Hz, 2H), 7.23 (d, $J$ = 8.1 Hz, 2H), 8.17 (s, 1H); MS (EI) 429 ($MH^+$). Anal. ($C_{26}H_{32}N_6$ ·2.3TFA·0.7$H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-[*N*-(2-fluorobenzyl)-*N*-ethylamino]pyrazolo[1,5-*a*]-

**pyrimidine Ditrifluoroacetate (26n).** This was prepared in a manner similar to the procedure described for **26a** using *N*-ethyl-*N*-(2-fluorobenzyl)amine: colorless oil, 45 mg; $^1$H NMR 1.46 (t, $J$ = 6.9 Hz, 3H), 2.25 (s, 3H), 2.29 (s, 3H), 2.53 (s, 3H), 3.32 (s, 6H), 3.97 (q, $J$ = 6.3 Hz, 2H), 5.32 (brs, 1H), 5.52 (brs, 1H), 5.85 (s, 1H), 6.73 (s, 1H), 7.18 (m,2H), 7.33 (m, 2H), 8.18 (s, 1H); MS (EI) 433 ($MH^+$). Anal. ($C_{25}H_{29}FN_6$·2TFA·$2H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-[*N*-(4-chlorobenzyl)-*N*-ethylamino]pyrazolo[1,5-*a*]-pyrimidine Ditrifluoroacetate (26o).** This was prepared in a manner similar to the procedure described for **26a** using *N*-ethyl-*N*-(4-chlorobenzyl)amine: colorless oil, 51 mg; $^1$H NMR 1.43 (t, $J$ = 6.9 Hz, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 2.53 (s, 3H), 3.32 (s, 6H), 3.92 (m, 2H), 5.27 (brs, 1H), 5.42 (brs, 1H), 5.84 (s, 1H), 6.73 (s, 1H), 7.27 (d, $J$ = 9.0 Hz, 2H), 7.39 (d, $J$ = 9.0 Hz, 2H), 8.17 (s, 1H); MS (EI) 449 ($MH^+$). Anal. ($C_{25}H_{29}ClN_6$ ·2TFA·$2H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-[*N*-(3,4-dichlorobenzyl)-*N*-ethylamino]pyrazolo[1,5-*a*]pyrimidine Ditrifluoroacetate (26p).** This was prepared in a manner similar to the procedure described for **26a** using *N*-ethyl-*N*-(3,4-dichlorobenzyl)amine: colorless oil, 48 mg; $^1$H NMR 1.43 (t, $J$ = 6.9 Hz, 3H), 2.25 (s, 3H), 2.27 (s, 3H), 2.53 (s, 3H), 3.32 (s, 6H), 3.85 (m, 2H), 5.35 (brs, 1H), 5.40 (brs, 1H), 5.88 (s, 1H), 6.74 (s, 1H), 7.19 (dd, $J$ = 2.4, 8.4 Hz, 1H), 7.46 (d, $J$ = 2.4 Hz, 1H), 7.49 (d, $J$ = 8.4 Hz, 1H), 8.14 (s, 1H); MS (EI) 483 ($MH^+$). Anal. ($C_{25}H_{28}Cl_2N_6$·2TFA·$2H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-(*N*-benzyl-*N*-isopropylamino)pyrazolo[1,5-*a*]pyrimidine (26q).** This was prepared in a manner similar to the procedure described for **26h** using *N*-isopropyl-*N*-benzylamine: colorless oil, 18 mg; $^1$H NMR 1.38 (d, $J$ = 6.6 Hz, 6H), 2.14 (s, 3H), 2.31 (s, 3H), 2.36 (s, 3H), 3.10 (s, 6H), 4.66 (s, 2H), 5.41 (hept, $J$ = 7.2 Hz, 1H), 5.82 (s, 1H), 6.48 (s, 1H), 7.27 (m, 5H), 8.02 (s, 1H); MS (EI) *m/e* 429 ($MH^+$). Anal. ($C_{26}H_{32}N_6$·$^2/_3H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-(*N*-benzyl-*N*-propylamino)pyrazolo[1,5-*a*]pyrimidine Ditrifluoroacetate (26r).** This was prepared in a manner similar to the procedure described for **26a** using *N*-propyl-*N*-benzylamine: colorless oil, 29 mg; $^1$H NMR 1.03 (t, $J$ = 7.5 Hz, 3H), 1.92 (m, 2H), 2.22 (s, 3H), 2.27 (s, 3H), 2.45 (s, 3H), 3.30 (s, 6H), 4.00 (brs, 2H), 5.26 (m, 2H), 5.85 (s, 1H), 6.84 (s, 1H), 7.28 (m, 2H), 7.41 (m, 3H), 7.90 (s, 1H); MS (EI) 429 ($MH^+$). Anal. ($C_{26}H_{32}N_6$·3TFA·$0.5H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-[*N*-(2-naphthylmethyl)-*N*-propylamino]pyrazolo-[1,5-*a*]pyrimidine Ditrifluoroacetate (26s).** This was prepared in a manner similar to the procedure described for **26a** using *N*-propyl-*N*-(naphthylmethyl)amine: colorless oil, 22 mg; $^1$H NMR 1.01 (t, $J$ = 7.5 Hz, 3H), 1.93 (m, 2H), 2.26 (s, 3H), 2.30 (s, 3H), 2.50 (s, 3H), 3.33 (s, 6H), 3.95 (brs, 2H), 5.41 (brs, 1H), 5.52 (brs, 1H), 5.85 (s, 1H), 6.73 (s, 1H), 7.40 (dd, $J$ = 1.8, 8.1 Hz, 1H), 7.53 (m, 1H), 7.54 (d, $J$ = 9.3 Hz, 1H), 7.71 (s, 1H), 7.86 (m, 2H), 7.91 (d, $J$ = 8.7 Hz, 1H), 8.21 (s, 1H); MS (EI) 479 ($MH^+$). Anal. ($C_{30}H_{34}N_6$·2TFA·$0.5H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-[*N*-(3-methoxybenzyl)-*N*-propylamino]pyrazolo[1,5-*a*]pyrimidine Ditrifluoroacetate (26t).** This was prepared in a manner similar to the procedure described for **26a** using *N*-propyl-*N*-(3-methoxybenzyl)amine: colorless oil, 19 mg; $^1$H NMR 1.00 (t, $J$ = 6.9 Hz, 3H), 1.90 (m, 2H), 2.26 (s, 3H), 2.30 (s, 3H), 2.49 (s, 3H), 3.32 (s, 6H), 3.82 (s, 3H), 3.92 (brs, 2H), 5.19 (brs, 1H), 5.26 (brs, 1H), 5.80 (s, 1H), 6.73 (s, 1H), 6.83 (s, 1H), 6.89 (m, 2H), 7.33 (t, $J$ = 8.1 Hz, 1H), 8.18 (s, 1H); MS (EI) 459 ($MH^+$). Anal. ($C_{27}H_{34}N_6O$·2TFA·$0.5H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-(*N*-benzyl-*N*-butylamino)pyrazolo[1,5-*a*]pyrimidine (26u).** This was prepared in a manner similar to the procedure described for **26h** using *N*-butyl-*N*-benzylamine: colorless oil, 18 mg; $^1$H NMR 0.92 (t, $J$ = 7.5 Hz, 3H), 1.33 (m, 2H), 1.74 (m, 2H), 2.18 (s, 3H), 2.34 (s, 3H), 2.40 (s, 3H), 3.11 (s, 6H), 3.62 (t, $J$ = 6.9 Hz, 2H), 5.13 (s, 2H), 5.82 (s, 1H), 6.50 (s, 1H), 7.31 (m, 5H), 8.05 (s, 1H); MS (EI) 443 ($MH^+$). Anal. ($C_{27}H_{34}N_6$·$0.5H_2O$) C, H, N.

**2,5-Dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-(*N*-phenyl-*N*-propylamino)pyrazolo[1,5-*a*]pyrimidine Ditrifluoroacetate (26v).** This was prepared in a manner similar to the procedure described for **26a** using *N*-propyl-*N*-phenylamine: colorless oil, 45 mg; $^1$H NMR 1.00 (t, $J$ = 6.9 Hz, 3H), 1.89 (m, 2H), 2.26 (s, 3H), 2.32 (s, 3H), 2.38 (s, 3H), 3.32 (s, 6H), 4.47 (brs, 1H), 4.64 (brs, 1H), 5.37 (s, 1H), 6.73 (s, 1H), 7.32 (dm, $J$ = 7.8 Hz, 2H), 7.51 (t, $J$ = 7.8 Hz, 1H), 7.60 (t, $J$ = 7.2 Hz, 2H); MS (EI) 415 ($MH^+$). Anal. ($C_{25}H_{30}N_6$·2TFA·$0.75H_2O$) C, H, N.

**3-(6-Dimethylaminopyridin-3-yl)-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (25).** 3-(6-Dimethylaminopyridin-3-yl)-2,5-dimethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (**23a**) was prepared, in a manner similar to the procedure described for **23b** using 2-aminopyridine, as a tan solid: $^1$H NMR 2.18 (s, 3H), 2.38 (s, 3H), 3.02 (s, 6H), 5.39 (s, 1H), 6.70 (d, $J$ = 8.8 Hz, 1H), 7.88 (dd, $J$ = 2.1, 8.8 Hz, 1H), 8.40 (s, 1H); MS (EI) 284 ($MH^+$). Anal. ($C_{15}H_{17}N_5O$) C, H, N.

A suspension of **23a** (2 g) and $POCl_3$ (2 equiv) in acetonitrile (20 mL) was heated to reflux for 1 h. The reaction was quenched with ice and basified with $Na_2CO_3$. The product was extracted with ethyl acetate (2 × 100 mL). The extract was dried over $MgSO_4$, filtered through a silica gel pad, and concentrated in vacuo to give 2,5-dimethyl-3-(6-dimethylaminopyridin-3-yl)-7-chloropyrazolo[1,5-*a*]pyrimidine **24a** as a yellowish solid: $^1$H NMR 2.54 (s, 3H), 2.61 (s, 3H), 3.11 (s, 6H), 6.63 (d, $J$ = 8.8 Hz, 1H), 6.75 (s, 1H), 7.80 (d, $J$ = 8.8 Hz, 1H), 8.46 (s, 1H); MS (EI) 302 ($MH^+$).

A solution of **24a** obtained above and dipropylamine (3 mL) in acetonitrile (20 mL) was heated to reflux for 2 h. The mixture was concentrated in vacuo, and the residue was dissolved in ethyl acetate and filtered through a short silica gel column with ethyl acetate. The filtrate was concentrated in vacuo to give 2,5-dimethyl-3-(6-dimethylaminopyridin-3-yl)-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine **25** as a yellowish solid, which was crystallized from ether−hexanes (1.6 g): $^1$H NMR 0.94 (t, $J$ = 7.3 Hz, 6H), 1.72 (m, 4H), 2.45 (s, 3H), 2.54 (s, 3H), 3.12 (s, 6H), 3.70 (m, 4H), 5.79 (s, 1H), 6.64 (d, $J$ = 8.8 Hz, 1H), 7.90 (dd, $J$ = 2.4, 8.8 Hz, 1H), 8.48 (d, $J$ = 2.4 Hz, 1H); MS (EI) 367 ($MH^+$). Anal. ($C_{21}H_{30}N_6$), C, H, N.

**3-(2-Methyl-6-dimethylaminopyridin-3-yl)-2,5-methyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (27).** 3-(2-Methyl-6-dimethylaminopyridin-3-yl)-2,5-methyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (**23c**), prepared in a manner similar to the procedure described for **23b** using 2-amino-5-bromo-6-methyl-pyridine, was converted to 3-(2-methyl-6-dimethylaminopyridin-3-yl)-2,5-methyl-7-chloropyrazolo[1,5-*a*]pyrimidine **24c** as a yellowish solid: $^1$H NMR 2.30 (s, 3H), 2.40 (s, 3H), 2.52 (s, 3H), 3.14 (s, 6H), 6.47 (d, $J$ = 8.0 Hz, 1H), 6.78 (s, 1H), 7.34 (d, $J$ = 8.0 Hz, 1H); MS (EI) 316 ($MH^+$).

A solution of **24c** (32 mg, 0.1 mmol) and dipropylamine (4 equiv) in acetonitrile (0.5 mL) was heated to reflux for 3 h. The mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate and filtered through a short silica gel column with ethyl acetate, and the filtrate was concentrated in vacuo to give the title compound as a yellowish solid, which was crystallized from ether−hexanes: $^1$H NMR 0.92 (t, $J$ = 7.0 Hz, 6H), 1.70 (m, 4H), 2.28 (s, 6H), 2.41 (s, 3H), 3.09 (s, 6H), 3.68 (m, 4H), 5.77 (s, 1H), 6.40 (d, $J$ = 8.0 Hz, 1H), 7.32 (d, $J$ = 8.0 Hz, 1H); MS (EI) 381 ($MH^+$). Anal. ($C_{22}H_{32}N_6$) C, H, N.

**3-(2,4-Dimethyl-6-dimethylaminopyridin-3-yl)-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (28).** 3-(2,4-Dimethyl-6-dimethylaminopyridin-3-yl)-2,5-dimethyl-7-chloropyrazolo[1,5-*a*]pyrimidine (**24d**) was prepared, in a manner similar to the procedure described for **24b** using 2-amino-5-bromo-4,6-dimethylpyridine, as a yellow solid: $^1$H NMR 2.00 (s, 3H), 2.28 (s, 3H), 2.33 (s, 3H), 2.49 (s, 3H), 3.24 (s, 6H), 6.52 (s, 1H), 6.80 (s, 1H); MS (EI) 330 ($MH^+$).

A solution of **24d** (33 mg, 0.1 mmol) in dipropylamine (excess) was heated to reflux for 3 h. The mixture was concentrated in vacuo and the residue dissolved in ethyl

acetate. This solution was filtered through a short silica gel column with ethyl acetate, and the filtrate was concentrated in vacuo to give the title compound as a colorless oil: $^1$H NMR 0.96 (t, $J$ = 7.6 Hz, 6H), 1.74 (m, 4H), 1.92 (s, 3H), 2.19 (s, 3H), 2.23 (s, 3H), 2.40 (s, 3H), 3.12 (s, 6H), 3.70 (m, 4H), 5.70 (s, 1H), 6.38 (s, 1H); MS (EI) 395 ($MH^+$). Anal. ($C_{23}H_{34}N_6$) C, H, N.

**3-(6-Methylpyridin-3-yl)-2,5-methyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (29). 3-(6-Methylpyridin-3-yl)-2,5-methyl-7-chloropyrazolo[1,5-a]pyrimidine (24e).** A solution of methyl 6-methylnicotinate (30.2 g, 0.2 mol) in dry THF (40 mL) was added dropwise into a suspension of $LiAlH_4$ (10.5 g) in THF (100 mL) at room temperature. The addition caused a gentle reflux. The gray suspension was then stirred at room temperature for 1 h. The reaction was quenched carefully with a limited amount of water, and the mixture was diluted with ethyl acetate (300 mL). More water was added carefully to generate a white suspension, and the yellow solution was decanted and washed several time with ethyl acetate. The combined solution was concentrated in vacuo to give 5-(hydroxylmethyl)-2-methylpyridine as a yellow oil (22.5 g): MS (EI) 124 ($MH^+$).

To a stirred solution of 3-(hydroxymethyl)-2-methylpyridine (5.0 g) in dichloromethane (200 mL) was added thionyl chloride (50 mL). The mixture was stirred at room temperature for 4 h and then concentrated in vacuo. The residue was partitioned between saturated $NaHCO_3$ (150 mL) and $CH_2Cl_2$ (150 mL). The organic layer was removed, and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 100 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give 5-(chloromethyl)-2-methylpyridine[46] as a yellowish oil, which was used for the next step without further purification: MS (EI) 142 ($MH^+$).

A mixture of 5-(chloromethyl)-2-methylpyridine (from above) and NaCN (50 mmol) in DMSO (30 mL) was heated at 100 °C for 1 h, cooled, and partitioned between ethyl acetate (100 mL) and water (50 mL). The aqueous layer was extracted twice with ethyl acetate (50 mL), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by chromatography on silica gel with 1:1 ethyl acetate−hexanes to give 5-(cyanomethyl)-2-methylpyridine as a colorless oil (1.8 g): MS (EI) 133 ($MH^+$).

To a suspension of 5-(cyanomethyl)-2-methylpyridine (1.8 g) and sodium hydride (1.4 g, 60% in mineral oil) in dry THF (10 mL) was added ethyl acetate (5 mL). This mixture was stirred at room temperature; after about 5 min an exothermic reaction started, and a brown suspension formed after 1 h. The mixture was concentrated in vacuo and coevaporated with THF twice. The residue was dissolved in ethanol−water−acetic acid (10:1:5 mL), mixed with hydrazine hydrobromide (3.1 g, 2 equiv), and refluxed for 1 h. Another portion of hydrazine hydrobromide (1.6 g) was added, and the reflux was continued for one more hour. Ethyl acetoacetate (7.1 g, 4 equiv) was added, and the mixture was refluxed overnight. The reaction mixture was cooled, and the resultant solid was collected by vacuum filtration to give 3-(6-methylpyridin-3-yl)-2,5-dimethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (8 g, mixed with NaBr).

A mixture of 3-(6-methylpyridin-3-yl)-2,5-dimethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (from above) and $POCl_3$ (16 mL) was refluxed for 1 h. The reaction mixture was poured into ice−water and neutralized with $Na_2CO_3$. The product was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated in vacuo to give the title compound **24e** as a yellow solid: MS (EI) 273 ($MH^+$).

**3-(6-Methylpyridin-3-yl)-2,5-methyl-7-dipropylaminopyrazolo[1,5-a]pyrimidine (29).** A solution of **24e** (50 mg) and dipropylamine (1.5 mL) was heated at 100°C in a sealed reacti-vial for 3 h. Chromatography on silica gel with 1:3 ethyl acetate−hexanes gave the desired product as a colorless oil, 35 mg: $^1$H NMR 0.96 (t, $J$ = 7.2 Hz, 6H), 1.75 (m, 4H), 2.22 (s, 3H), 2.32 (s, 3H), 2.40 (s, 3H), 2.55 (s, 3H), 3.72 (m, 4H), 5.80 (s, 1H), 7.12 (s, 1H), 8.35 (s, 1H); MS (EI) 338 ($MH^+$).

**3-(4,6-Dimethylpyridin-3-yl)-2,5-methyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (30).** 3-(4,6-Dimethylpyridin-3-yl)-2,5-methyl-7-chloropyrazolo[1,5-*a*]pyrimidine (**24f**) was prepared in a manner similar to the procedure described for **24e** using methyl 2,4-dimethylnicotinate:[24] $^1$H NMR 2.14 (s, 3H), 2.37 (s, 3H), 2.47 (s, 3H), 2.53 (s, 3H), 6.78 (s, 1H), 7.11 (s, 1H), 8.28 (s, 1H); MS (EI) *m/e* 287 ($MH^+$);

A solution of **24f** (50 mg) and dipropylamine (1.5 mL) was heated at 100 °C in a sealed reacti-vial for 3 h. Chromatography on silica gel with 1:3 ethyl acetate−hexanes gave the desired product as a colorless oil, 43 mg: $^1$H NMR 0.96 (t, $J$ = 7.2 Hz, 6H), 1.75 (m, 4H), 2.22 (s, 3H), 2.32 (s, 3H), 2.40 (s, 3H), 2.55 (s, 3H), 3.72 (m, 4H), 5.80 (s, 1H), 7.12 (s, 1H), 8.35 (s, 1H); MS (EI) 352 ($MH^+$). Anal. ($C_{23}H_{29}N_5$) C, H, N.

**3-(2,4-Dimethyl-6-dimethylaminopyridin-3-yl)-5-methyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (34). 3-(2,4-Dimethyl-6-dimethylaminopyridin-3-yl)-5-methyl-7-hydroxpyrazolo[1,5-*a*]pyrimidine (32).** A solution of 2,4-dimethyl-3-cyanomethyl-6-dimethylaminopyridine (10 g, 50 mmol) in THF (10 mL) was added slowly into a suspension of NaH (5 g, 125 mmol) in THF (15 mL) with vigorous stirring. Ethyl formate (3.8 g, 54 mmol) was added dropwise, and the resulting mixture was stirred at room temperature for 1 h, before being quenched with water. The product was extracted with ethyl acetate, dried over $MgSO_4$, filtered, and concentrated to give the crude 1-cyano-1-(6-dimethylamino-2,4-dimethylpyridin-3-yl)acetaldehyde **31**: MS (EI) 218 ($MH^+$).

The above compound was dissolved in an ethanol/water (9:1) mixture and treated with hydrazine hydrobromide (10 g). The mixture was heated at reflux for 1 h and then concentrated in vacuo. The residue was partitioned in ethyl acetate/aqueous $NaHCO_3$, and the organic layer was separated, dried, and concentrated in vacuo to give the crude 3-amino-4-(6-dimethylamino-2,4-dimethylpyridin-3-yl)pyrazole, which was used without further purification: MS (EI) 230 ($MH^+$).

The above compound was dissolved in dioxane (100 mL) and treated with ethyl acetoacetate (2 equiv). This mixture was heated at reflux overnight, cooled, and diluted with ether. The white precipitate was collected by filtration to give 3-(2,4-dimethyl-6-dimethylaminopyridin-3-yl)-5-methyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine **32** as a white solid: $^1$H NMR (DMSO-$d_6$): 1.98 (s, 3H), 2.11 (s, 3H), 2.25 (s, 3H), 3.25 (s, 6H), 5.60 (s, 1H), 6.50 (brs, 1H), 7.76 (s, 1H); MS (EI) 298 ($MH^+$). Anal. ($C_{16}H_{20}N_5O$) C, H, N.

**3-(2,4-Dimethyl-6-dimethylaminopyridin-3-yl)-5-methyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (34).** A mixture of **32** (0.5 g) and $POCl_3$ (5 mL) in acetonitrile (5 mL) was heated at reflux for 1 h, cooled, and poured into ice−water/EtOAc. This mixture was basified with solid sodium bicarbonate to pH ∼ 10. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate twice. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to give 3-(2,4-dimethyl-6-dimethylaminopyridin-3-yl)-5-methyl-7-chloropyrazolo[1,5-*a*]pyrimidine **33** (520 mg) as a yellow solid: $^1$H NMR 2.01 (s, 3H), 2.20 (s, 3H), 2.51 (s, 3H), 3.05 (s, 6H), 6.29 (s, 1H), 6.82 (s, 1H), 8.03 (s, 1H); MS (EI) 316 ($MH^+$).

A solution of **33** (30 mg, 0.1 mmol) in dipropylamine (excess) was heated to reflux for 3 h. The mixture was concentrated in vacuo, and the residue was dissolved in ethyl acetate. The mixture was filtered through a short silica gel column with ethyl acetate, and the filtrate was concentrated in vacuo to give the title compound as a colorless oil: $^1$H NMR 0.96 (t, $J$ = 7.6 Hz, 6H), 1.76 (m, 4H), 2.00 (s, 3H), 2.30 (s, 3H), 2.40 (s, 3H), 3.12 (s, 6H), 3.72 (m, 4H), 5.78 (s, 1H), 6.35 (s, 1H), 7.93 (brs, 1H); MS (EI) 381 ($MH^+$).

**3-(4-Methyl-6-dimethylaminopyridin-3-yl)-2,5-dimethyl-6-fluoro-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (35a).** A solution of **26h** (40 mg) and $(PhSO_2)_2NF$ (1.2 equiv) in chloroform (2 mL) was stirred at room temperature for 2 days. Chromatography on silica gel with 1:5 ethyl acetate/hexanes gave the product as a white solid: $^1$H NMR 0.87 (t, $J$ = 7.1 Hz, 6H), 1.56 (m, 4H), 2.16 (s, 3H), 2.35 (s, 3H), 2.76 (s,

3H), 3.11 (s, 6H), 3.57 (m, 4H), 6.49 (s, 1H), 8.02 (s, 1H); MS (EI) 399 ($MH^+$). Anal. ($C_{22}H_{31}FN_6$) C, H, N.

**3-(4-Methyl-6-dimethylaminopyridin-3-yl)-2,5-dimethyl-6-chloro-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (35b).** A solution of **26h** (40 mg) and NCS (1.2 equiv) in chloroform (2 mL) was stirred at room temperature for 2 h. Chromatography on silica gel with 1:5 ethyl acetate/hexanes gave the product as a white solid: $^1$H NMR 0.88 (t, $J$ = 7.1 Hz, 6H), 1.56 (m, 4H), 2.15 (s, 3H), 2.35 (s, 3H), 2.72 (s, 3H), 3.11 (s, 6H), 3.57 (m, 4H), 6.49 (s, 1H), 8.02 (s, 1H); MS (EI) 415 ($MH^+$).

**3-(4-Methyl-6-dimethylaminopyridin-3-yl)-2,5-dimethyl-6-bromo-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (35c).** A solution of **26h** (40 mg) and NBS (1.2 equiv) in chloroform (2 mL) was stirred at room temperature overnight. Chromatography on silica gel with 1:5 ethyl acetate/hexanes gave the product as a white solid: $^1$H NMR 0.90 (t, $J$ = 7.1 Hz, 6H), 1.56 (m, 4H), 2.13 (s, 3H), 2.35 (s, 3H), 2.62 (s, 3H), 3.11 (s, 6H), 3.57 (m, 4H), 6.49 (s, 1H), 8.02 (s, 1H); MS (EI) 460 ($MH^+$).

**Biological Evaluation.** $K_i$ values reported are the average of several independent measurements depending on compound potency, typically at least three measurements for compounds with $K_i$ values less than 50 nM. Experimental details for the $CRF_1$ receptor binding assay, inhibition of CRF stimulated cAMP inhibitory assay, and inhibition of CRF stimulated ACTH release assay in rat anterior pituitary cells have been previously reported.[42]

**Rat Pharmacokinetics.** Compound was dosed as hydrochloride salts in aqueous solution. The pharmacokinetic profile of **26h** was determined in male Sprague−Dawley rats ($N$ = 3/time points at a dose of 10 mg/kg). The dosing solution was prepared in purified water and filtered through a 0.2 $\mu$m Nylon filter before administration (2 mL/kg) via the tail vain (iv) or oral gavage (po).

**Supporting Information Available:** Elemental analyses for compounds **11**, **15**, **20b**, **23a**,**b**, **25**, **26a**−**v**, **27**−**28**, **30**, **32**, and **35a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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