



## Structure–Activity Studies on 4-Substituted-2-anilinopyrimidine Corticotropin Releasing Factor (CRF) Antagonists

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**Abstract**—Structure–activity studies around the 4-position of 2-anilinopyrimidine corticotropin releasing factor (CRF) antagonists suggest that there is a large lipophilic cavity in the rat CRF receptor, which can accommodate a wide variety of substituents at this position in contrast to the steric constraints observed for other positions on the 2-anilinopyrimidine core. The chemical syntheses and biological activities of 2-anilinopyrimidine CRF antagonists with carbon-linked substituents at the 4-position are reported. Significant improvements in rat pharmacokinetic parameters were achieved relative to those for the lead structure. While the lead compound **1** (rCRF  $K_i$  = 44 nM) afforded no detectable rat plasma levels after intraperitoneal (ip) or oral (po) dosing, compounds **3-3** (rCRF  $K_i$  = 16 nM) and **3-4** (rCRF  $K_i$  = 59 nM) gave high rat plasma levels at 30 mg/kg (ip, po) ( $C_{max}$  = 1389 nM and 8581 nM (ip) respectively;  $C_{max}$  = 113 nM and 988 nM (po), respectively). Furthermore **3-3** and **3-4** had superior bioavailabilities at these doses (59 and 46% (ip), respectively; 2 and 10% (po), respectively). © 1999 DuPont Pharmaceuticals Company.

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### Introduction

Corticotropin releasing factor (or hormone, CRF or CRH) coordinates endocrine, autonomic, behavioral and immune responses to stress<sup>1–3</sup> due to its predominant role in regulation of the hypothalamus-pituitary-adrenal (HPA) axis.<sup>1</sup> CRF receptors have become medicinal chemistry targets since disruption in the HPA axis has been associated with various disease states. Over-secretion of CRF in the central nervous system has been proposed to mediate depression and anxiety-related disorders. Elevated plasma levels of adrenocorticotropin (ACTH) and cortisol, two products of the HPA axis which are downstream from CRF, have been

noted in a large segment of the depressed patient population.<sup>1,4</sup> Similarly, levels of CRF in the cerebrospinal fluid (CSF) of depressed patients have been reported to be higher than those levels in control subjects.<sup>5</sup> CRH secreting cells are increased fourfold in the hypothalamus of depressed people, based on postmortem data.<sup>6</sup> Chronic antidepressant therapy or chronic electroconvulsant shock treatment have been reported to reduce CSF levels of CRF and plasma levels of ACTH and cortisol to normal values.<sup>7,8</sup> Arguments for a role of CRF in anxiety disorders are also based on observations of the effects of stress on the HPA axis. Neonatal stress in rodents and primates leads to long term activation of the HPA axis.<sup>9–13</sup> Intracerebroventricular (icv) injection of CRF in rats arouses behavioral and physiological events, which may be termed ‘stress-like’.<sup>14–16</sup> These processes may be hindered by the peptide antagonist  $\alpha$ -helical CRF (9–41). Chronic restraint of rodents or primates causes long term potentiation of the HPA axis. Transgenic mice, which overexpress CRF, have high ACTH and corticosterone levels in plasma and behave in a ‘stressed’ manner.<sup>17,18</sup> Therefore, CRF antagonists may be useful for the treatment of depression or anxiety.

Key words: Corticotropin releasing factor; receptor; antagonists; substituent effects.

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Previously compound **1** has been reported to be a potent and selective antagonist of rat CRF receptors in vitro (rCRF  $K_i$  = 44 nM).<sup>19,20</sup> Administration of this compound by several routes of administration (dose = 12 mg/kg (iv), 30 mg/kg (ip, po)) generated no detectable plasma levels in the rat. As part of an exploration of the SAR of the 4-position of **1** and related 2-anilinopyrimidine CRF antagonists, analogues with carbon-linked substituents at the 4-position of the pyrimidine ring were prepared in an attempt to improve rat pharmacokinetic parameters. The biological evaluation of the resulting analogues revealed that nitrogen-linked groups are not necessary for high binding affinity and support the proposition that there is a large cavity in CRF receptors which can accommodate diverse functional groups, provided certain lipophilicity and  $pK_a$  constraints are observed.

## Results and Discussion

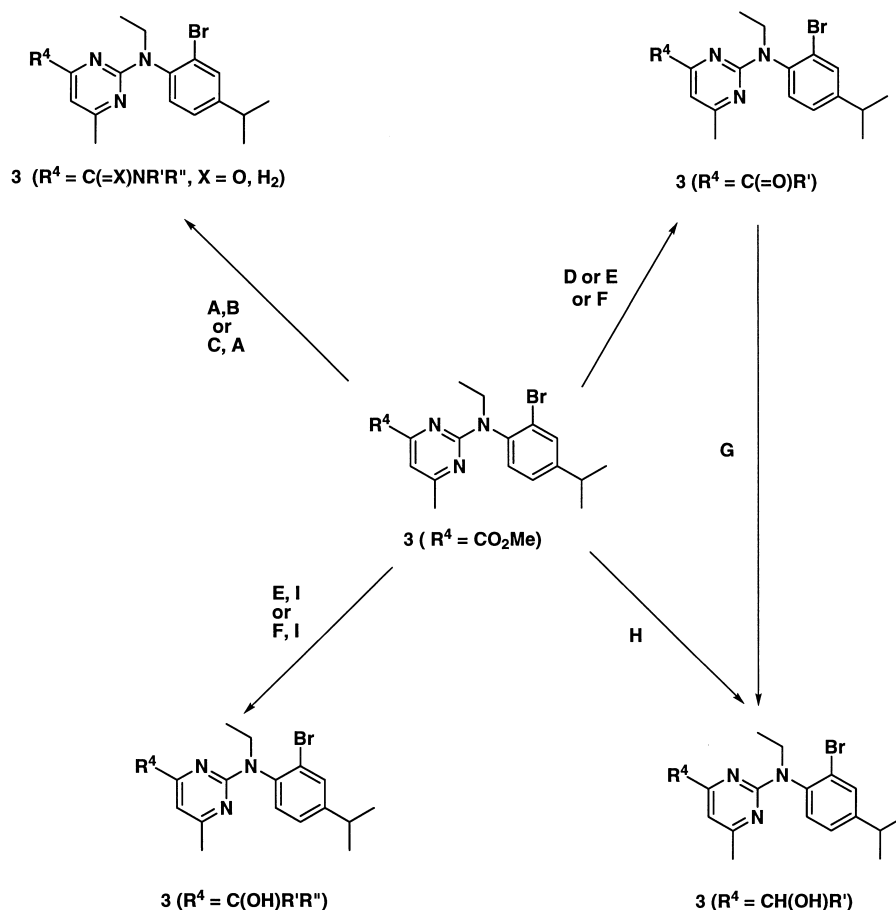
### Chemistry

Ester **2** (where  $R^4 = \text{CO}_2\text{Me}$ ) was a versatile intermediate for the preparation of compounds **3** with a wide variety of carbon-linked substituents at the 4-position of

the pyrimidine ring (Scheme 1). Nucleophilic displacement with various amines afforded amides **3** where  $R^4 = \text{CONR}'\text{R}''$  in virtually quantitative yields in the presence of sodium hydride or Hunig's base ( $i\text{Pr}_2\text{NEt}$ ). Reduction with borane led to (substituted amino)-methyl analogues **3** where  $R^4 = \text{CH}_2\text{NR}'\text{R}''$ . Ester **2** was preferably transformed to ketones **3** where  $R^4 = \text{C}(=\text{O})\text{R}'$  by the following sequence of reactions: saponification and subsequent treatment of the resulting acids with organolithium reagents. The addition of  $\text{CeCl}_3$  was often necessary to stop the additions at the ketone stage.<sup>21</sup> Reduction of ketones **3** where  $R^4 = \text{C}(=\text{O})\text{R}'$ , with  $\text{NaBH}_4$  gave the cognate alcohols **3** ( $R^4 = \text{CH}(\text{OH})\text{R}'$ ). Alternatively, the ketones **3** where  $R^4 = \text{C}(=\text{O})\text{R}'$  were converted to tertiary alcohols where  $R^4 = \text{C}(\text{OH})\text{R}'\text{R}''$  by subsequent reaction with organolithium reagents in 30–70% yields.

### Pharmacology

We employed a rat receptor binding assay, in which the displacements of  $^{125}\text{I}$ -0-tyr-o-CRF by our test compounds from rat frontal cortex homogenates were measured. Subsequent studies have shown the rat  $\text{CRF}_1$  subtype to be expressed in high density in the rat cortex



**Scheme 1.** (A)  $\text{HNR}'\text{R}''$ , NaH, THF or DMF (35–90% yields); (B)  $\text{BH}_3$ -THF (60–80% yields); (C) (i)  $\text{LiBH}_4$ , THF, (ii)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C, (30–70% yields); (D)  $\text{R}'\text{MgBr}$ , THF, –78 °C (30–80% yields); (E) (i) 1 N NaOH, EtOH, (ii)  $\text{R}'\text{Li}$ ,  $\text{CeCl}_3$ , THF, –78 °C (30–70% yields); (F)  $\text{R}'\text{Li}$ , THF, –78 °C (30–70% yields); (G)  $\text{NaBH}_4$ , EtOH (60–80% yields); (H) 1 equiv  $\text{R}'\text{Li}$ , THF, –78 °C (30–70% yields); (I)  $\text{R}'\text{Li}$ , THF, –78 °C (30–70% yields).

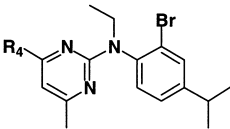
in contrast to the rCRF<sub>2</sub> counterpart.<sup>1</sup> Antagonist potency for some high affinity compounds was assessed in an adenylate cyclase inhibition assay using rat frontal cortex homogenates. None of the compounds described in this study inhibited basal or isoproterenol-stimulated adenylate cyclase activity. Compounds with high affinity (rCRF  $K_i \leq 50$  nM) were then evaluated in rat pharmacokinetic studies.

The introduction of carbon-linked substituents at the 4-position of the pyrimidine ring in the 2-(2-bromo-4-isopropylanilino)pyrimidines provided several moderate to high affinity CRF ligands (Table 1). Only very simple amides had moderate binding affinity (i.e. **3-2** (rCRH  $K_i = 74$  nM) or **3-3** (rCRH  $K_i = 16$  nM)). Certain 4-(substituted aminomethyl) analogues, which were derived from the corresponding amides, had moderately good affinity provided the side chains were not too basic (e.g. **3-4** and **3-5** (rCRF  $K_i = 59$  and 64 nM, respectively)). Dibasic aminomethyl side chains could also be introduced only if the basicity of the second nitrogen was attenuated by appropriate substitution (compare **3-7** with **3-8** (rCRF  $K_i > 1000$  versus 50 nM). The acid **3-1** and the tetrazole **3-9** were inactive (rCRF  $K_i > 1000$  nM). These results indicate that  $pK_a$  changes can alter binding affinity significantly. Some 4-substituted carbonyl pyrimidines had good binding affinity; compounds **3-10**, **3-11**, **3-12** and **3-14** had rCRF  $K_i$  values equal to 36, 39, 49, and 36 nM, respectively. Some 4-hydroxyalkyl derivatives also had significant binding affinities; analogues **3-17**, **3-18**, **3-19** and **3-21** had rCRH  $K_i$  values equal to 22, 12, 63, and 11 nM, respectively.

The above data suggest that the region of space which accommodates the 4-substituent on the pyrimidine ring is quite promiscuous. One possible explanation is that substituents at the 4-position lie outside the receptor cavity and are exposed to solvent. However, there are some examples of specificity (compare **3-7** with **3-8** (rCRF  $K_i > 1000$  versus 50 nM) and **3-4** with **3-7** (rCRF  $K_i = 59$  nM versus  $> 1000$  nM)). Lipophilic substituents, which may be weakly basic or hydrogen bonding, tend to be favored; very basic or acidic moieties are not well tolerated. Size alone does not control binding affinity. While most bulky amides are inactive,<sup>19</sup> some bulky tertiary alcohols (e.g. **3-21** and **3-20**, rCRF  $K_i = 11$  and 15 nM, respectively) or bulky ketones (e.g. **3-14**, rCRF  $K_i = 36$  nM) have good binding affinity. The data argue for the existence of a large lipophilic cavity, which can accommodate various substituents at this position in space, provided they are not strongly basic or acidic groups. However, the diversity of the shapes of the substituents, which enhance binding affinity, obscures the complementary topology of this cavity. Another possible confounding factor may be the presence of two receptor subtypes, although CRF<sub>1</sub> receptors predominate greatly over CRF<sub>2</sub> sites (vide supra).

Two rCRF antagonists, **3-3** and **3-4** were profiled further. Both compounds antagonized CRF-stimulated adenylate cyclase activity in rat cortical homogenates (Table 2). Compound **3-3** was evaluated at 30 mg/kg (iv, ip, po) in rats. Intraperitoneal administration afforded higher plasma levels (mean  $C_{max} = 8581$  versus 988 nM) and higher bioavailability (46 versus 10%) than did oral

Table 1. Rat CRF receptor binding affinity and chemical data<sup>a</sup>



Example	R4	rCRF $K_i$ (nM)	Synthesis reactions	Formula	mp (°C)
<b>1</b>	Me	44 ± 24 (3)	—	—	—
<b>2</b>	CO <sub>2</sub> -Me	> 1000	a	C <sub>18</sub> H <sub>22</sub> BrN <sub>3</sub> O <sub>2</sub>	88–89
<b>3-1</b>	CO <sub>2</sub> H	> 1000	a	C <sub>17</sub> H <sub>20</sub> BrN <sub>3</sub> O <sub>2</sub>	40–41
<b>3-2</b>	CONHMe	74 ± 8 (2)	A	C <sub>18</sub> H <sub>23</sub> BrN <sub>4</sub> O	oil
<b>3-3</b>	CONMe <sub>2</sub>	16 ± 6 (2)	A	C <sub>19</sub> H <sub>25</sub> BrN <sub>4</sub> O	80–82
<b>3-4</b>	CH <sub>2</sub> -morpholinyl	59 ± 36 (3)	A,B	C <sub>21</sub> H <sub>29</sub> BrN <sub>4</sub> O	oil
<b>3-5</b>	CH <sub>2</sub> -imidazolyl	16 ± 6 (2)	C,A	C <sub>20</sub> H <sub>24</sub> BrN <sub>5</sub>	oil
<b>3-6</b>	CH <sub>2</sub> -piperidinyl	> 1000	A,B	C <sub>22</sub> H <sub>31</sub> BrN <sub>4</sub>	oil
<b>3-7</b>	CH <sub>2</sub> -(N-Me-piperazinyl)	> 1000	A,B	C <sub>22</sub> H <sub>32</sub> BrN <sub>5</sub> -2C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	176–177
<b>3-8</b>	CH <sub>2</sub> -N-(2-pyrazinyl)piperazinyl	50 ± 6 (2)	A,B	C <sub>25</sub> H <sub>37</sub> BrN <sub>7</sub>	amorphous
<b>3-9</b>	CH(Me)-5-tetrazolyl	> 1000	a	C <sub>19</sub> H <sub>24</sub> BrN <sub>7</sub>	127–129
<b>3-10</b>	COCH <sub>3</sub>	36 ± 6 (2)	D	C <sub>18</sub> H <sub>22</sub> BrN <sub>3</sub> O	oil
<b>3-11</b>	COPh	39 ± 6 (2)	H	C <sub>23</sub> H <sub>24</sub> BrN <sub>3</sub> O	56–58
<b>3-12</b>	CO-2-imidazolyl	49 ± 6 (2)	F	C <sub>20</sub> H <sub>22</sub> BrN <sub>5</sub> O	75–76
<b>3-13</b>	CO(2-furyl)	86 ± 6 (2)	F	C <sub>21</sub> H <sub>22</sub> BrN <sub>3</sub> O <sub>2</sub>	136–138
<b>3-14</b>	CO-2-pyridyl	36 ± 23 (3)	F	C <sub>22</sub> H <sub>23</sub> BrN <sub>4</sub> O	oil
<b>3-15</b>	CO-3-indolyl	> 1000	E	C <sub>25</sub> H <sub>25</sub> BrN <sub>4</sub> O	105–107
<b>3-16</b>	CO-4-pyrazolyl	> 1000	F	C <sub>20</sub> H <sub>22</sub> BrN <sub>5</sub> O	171–173
<b>3-17</b>	CH(OH)Me	22 ± 6 (2)	E,G	C <sub>18</sub> H <sub>24</sub> BrN <sub>3</sub> O	oil
<b>3-18</b>	CH(OH)-2-furyl	12 ± 6 (2)	H,I	C <sub>21</sub> H <sub>24</sub> BrN <sub>3</sub> O <sub>2</sub>	oil
<b>3-19</b>	C(OH)Me <sub>2</sub>	63 ± 6 (2)	E	C <sub>19</sub> H <sub>26</sub> BrN <sub>3</sub> O	oil
<b>3-20</b>	C(OH)(C <sub>6</sub> H <sub>4</sub> -OMe-p) <sub>2</sub>	15 ± 6 (3)	F	C <sub>31</sub> H <sub>34</sub> BrN <sub>3</sub> O <sub>3</sub>	63–65
<b>3-21</b>	C(OH)(2-furyl) <sub>2</sub>	11 ± 5 (3)	F	C <sub>25</sub> H <sub>26</sub> BrN <sub>3</sub> O <sub>3</sub>	97–99

<sup>a</sup> See Experimental. Standard deviations are reported. Parenthetical values are the number of determinations.

**Table 2.** Inhibition of o-CRF-stimulated adenylate cyclase activity

Example	Mean adenylate cyclase IC <sub>50</sub> (nM)	<i>n</i>
α-helical CRF (9–41)	108.8 ± 31.6	3
<b>3-3</b>	256.8 ± 11.5	2
<b>3-4</b>	121.4 ± 23.4	2

administration. The clearance was high (1.93 L/h/kg). Compound **3-4** was also studied at 30 mg/kg (iv, ip, po)) in rats. Intraperitoneal administration generated higher plasma levels (mean  $C_{\max}$  = 1389 versus 113 nM) and higher bioavailability (59 versus 2%) than did oral administration. The clearance was unusually high for **3-19** (7.93 L/h/kg). The HPLC log*P* values were 4.71 and 5.09 for **3-3** and **3-4** versus >6.4 for **1**. Reduction in lipophilicity relative to **1** improved intraperitoneal, and to a lesser extent, oral plasma levels in the rat in these two cases (Table 3).

### Conclusion

The structure–activity relationships at the 4-position of 2-anilino-pyrimidine CRF antagonists have been explored further with carbon-linked substituents. The biological data support the existence of a large lipophilic cavity at the CRF receptor, which can accommodate a diverse range of substituents, provided certain limits on basicity are observed. The topology of this lipophilic cavity might be better defined by studies with more rigid substituents. Nonetheless, compounds **3-3** and **3-4** have greatly improved rat pharmacokinetic profile relative to that of the lead compound **1**. Further manipulations of substitution at the 4-position of the pyrimidine ring may lead to further improvements in rat pharmacokinetics without reductions in rCRF binding affinity.

### Experimental

#### Chemistry

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on Varian VXR or

**Table 3.** Rat pharmacokinetic data<sup>a</sup>

Example	Dose (mg/kg, route)	CL (L/h/kg)	<i>t</i> <sub>1/2</sub> (h)	<i>C</i> <sub>max</sub> (nM)	<i>T</i> <sub>max</sub> (h)	%F
<b>3-3</b>	12 (iv)	1.93	9.8	—	—	—
	30 (ip)	—	—	8581	0.3	46
	30 (po)	—	—	988	0.6	10
<b>3-4</b>	12 (iv)	1.93	1.8	—	—	—
	30 (ip)	—	—	1389	0.25	59
	30 (po)	—	—	113	1.38	2

<sup>a</sup> *N* = 4. Mean values are given throughout. 5% Methocel–water was the vehicle for oral and ip administrations; a mixed solvent system was employed for iv studies (*N,N*-dimethylacetamide/ethanol/propylene glycol/PEG400/0.1 N NaOH, 1/1/3/3/2). HPLC detection was used for all studies.

Unity 300 FT-NMR instruments (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethylsilane standard in deuteriochloroform or deuterodimethylsulfoxide as specified below. Coupling constants (*J*) were recorded in Hertz (Hz). Mass spectra (MS) were recorded on a Finnegan MAT 8230 spectrometer or a Hewlett–Packard 5988A model spectrometer (both using chemi-ionization (CI) with NH<sub>3</sub> as the carrier gas). Gas chromatography–mass spectroscopy (GC–MS) were occasionally obtained using the former instrument. Chemi-ionization high resolution mass spectra (CI–HRMS) were obtained on a VG 7-VSE instrument with NH<sub>3</sub> as the carrier gas. Combustion analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Melting points were measured on a Buchi Model 510 melting point apparatus or a Thomas Hoover capillary apparatus and are uncorrected. Boiling points are uncorrected.

Reagents were purchased from commercial sources and, when necessary, purified prior to use according to the general procedures outlined by D. Perrin and W.L.F. Armarego.<sup>22</sup> Chromatography was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight. All reactions were performed under a nitrogen atmosphere using magnetic stirring. Reactions requiring anhydrous conditions were performed in glassware, which had been flame-dried or oven-dried with purging under a nitrogen atmosphere. Reactions using aqueous media were run under the ambient atmosphere. Anhydrous magnesium sulfate (MgSO<sub>4</sub>) was used routinely to dry the combined organic layers from extractions. Solvent was routinely removed in vacuo, using a rotary evaporator, followed by evacuation with vacuum pump.

Commonly used abbreviations are: EtOAc (ethyl acetate), MeOH (methanol), EtOH (ethanol), DMF (*N,N*-dimethylformamide), HOAc (acetic acid), THF (tetrahydrofuran), and TLC (thin-layer chromatography).

***N*-(2-Bromo-4-isopropylphenyl)-*N*-ethyl-4-carbomethoxy-6-methylpyrimidin-2-amine (**2**).** A mixture of 4-carbomethoxy-2-chloro-6-methylpyrimidine<sup>23</sup> (22.8 g, 122 mmol), 2-bromo-4-isopropylaniline (26.2 g, 122 mmol) in dioxane (200 mL) was stirred at reflux temperature for 24 h. After the reaction mixture was cooled to ambient temperature, solvent was removed in vacuo and the residue was taken up in EtOAc (500 mL). Two washings with a saturated NaHCO<sub>3</sub> solution, one washing with water, drying, filtration, and removal of solvent in vacuo were performed. Column chromatography (EtOAc/hexanes, 1/9) gave, after removal of solvent in vacuo, *N*-(2-bromo-4-isopropylphenyl)-4-carbomethoxy-6-methyl-pyrimidin-2-amine, a pale-yellow solid (23.5 g, 53% yield); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.43 (d, 1H, *J* = 8 Hz), 7.64 (br s, 1H), 7.43 (d, 1H, *J* = 1 Hz), 7.31 (s, 1H), 7.22 (dd, 1H, *J* = 8, 1 Hz), 4.00 (s, 3H), 2.92–2.88 (m, 1H), 2.73 (s, 3H), 1.25 (d, 6H, *J* = 8 Hz).

Sodium hydride (60% in oil, 2.71 g, 67.7 mmol) was washed with hexanes and decanted twice. Anhydrous

DMF (50 mL) was added. A solution of *N*-(2-bromo-4-isopropylphenyl)-4-carbomethoxy-6-methylpyrimidin-2-amine (22.4 g, 61.5 mmol) in DMF (100 mL) was added and the resulting mixture was stirred for 30 min. Iodoethane (11.5 g, 73.8 mmol) was added and stirring was continued for 5 h. The reaction was quenched with water (850 mL) and extracted three times with chloroform (200 mL). The combined organic layers were washed with water (200 mL) twice, then dried. Filtration and removal of solvent in vacuo provided a brown oil. Column chromatography (EtOAc/hexanes, 1/7) gave the title compound, a pale-yellow solid (13.3 g, 55% yield): mp 85–86°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.3–7.1 (m, 2H), 7.1 (s, 1H), 4.30–4.15 (m, 1H), 4.05–3.70 (m, 4H), 2.9 (quintet, 1H, *J* = 7 Hz), 2.5–2.2 (m, 3H), 1.4–1.2 (m, 9H). Anal. calcd for C<sub>18</sub>H<sub>22</sub>BrN<sub>3</sub>O<sub>2</sub>: C, 55.11, H, 5.65, N, 10.71, Br, 20.37; found: C, 54.88, H, 5.64, N, 10.62, Br, 20.67.

**2-(*N*-(2-Bromo-4-isopropylphenyl)-*N*-ethyl)amino-6-methylpyrimidine-4-carboxylic acid, morpholine amide (Step A).** Sodium hydride (60% in oil, 240 mg, 6 mmol) was washed with hexanes and decanted twice. Anhydrous THF (5 mL) was added. A solution of morpholine (0.52 g, 6 mmol) in THF (5 mL) was added with stirring. The reaction mixture was heated to reflux temperature and stirred at that temperature for 45 min. A solution of **2** (2 g, 5.1 mmol) in THF (10 mL) was added and the resulting mixture was stirred for 17 h at reflux temperature. After being cooled to room temperature, water (50 mL) was added carefully and the resulting mix was extracted twice with EtOAc. The combined organic layers were dried and filtered. Column chromatography (ether) gave the title product (900 mg, 39% yield): mp 145°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.50 (d, 1H, *J* = 1 Hz), 7.20 (dd, 1H, *J* = 7, 1 Hz), 7.10 (d, 1H, *J* = 7 Hz), 6.80 (br s, 1H), 4.30–4.15 (m, 1H), 3.90–3.32 (m, 11H), 3.10–3.00 (m, 1H), 2.90 (septet, 1H, *J* = 7 Hz), 1.30 (d, 6H, *J* = 7 Hz), 1.25 (t, 3H, *J* = 7 Hz). Anal. calcd for C<sub>21</sub>H<sub>27</sub>BrN<sub>4</sub>O<sub>2</sub>: C, 56.38, H, 6.08, N, 12.52, Br, 17.86; found: C, 56.07, H, 6.05, N, 12.29, Br, 18.08.

**2-(*N*-(2-Bromo-4-isopropylphenyl)-*N*-ethyl-6-methyl-4-(morpholinylmethyl)pyrimidin-2-amine (3-4) (Step B).** A solution of borane in THF (1 M, 3.6 mL, 3.6 mmol) was added dropwise via syringe to a stirred solution of the above intermediate (800 mg, 1.79 mmol) in anhydrous THF (3 mL). The reaction mixture was heated to reflux temperature and stirred for 19 h. After being cooled to ambient temperature, the reaction was quenched by addition of glacial HOAc (1 mL) and subsequent heating at reflux temperature for 30 min. The reaction mixture was cooled to room temperature. Solvent was removed in vacuo. The residue was treated with a 1 N NaOH solution (10 mL) (pH 12) and the resulting aqueous mix was extracted three times with EtOAc (20 mL). The combined organic layers were washed twice with water (10 mL), dried and filtered. Solvent was removed in vacuo to give an oil. Column chromatography (EtOAc) gave the title product (*R<sub>f</sub>* 0.3). Removal of solvent in vacuo afforded a pale-yellow oil (300 mg, 39% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.50 (d, 1H, *J* = 1 Hz), 7.2 (dd, 1H, *J* = 7, 1 Hz), 7.10 (d, 1H, *J* = 7), 6.50 (s,

1H), 4.30–4.10 (m, 1H), 3.80–3.60 (m, 8H), 3.50–3.30 (m, 2H), 2.9 (septet, 1H, *J* = 8 Hz), 2.55–2.45 (m, 3H), 1.30 (d, 6H, *J* = 8 Hz), 1.20 (t, 3H, *J* = 7 Hz); CI-HRMS *m/z* calcd: 433.1603, Found: 433.1586 (M<sup>+</sup> + H).

**2-(*N*-(2-Bromo-4-isopropylphenyl)-*N*-ethyl-6-methyl-4-(imidazol-1-yl)methyl)pyrimidin-2-amine (3-5) (Steps C, A).** A solution of **2** (4 g, 10.2 mmol) in dry THF (20 mL) was cooled to 0°C with stirring. A solution of lithium borohydride in THF (2 M, 10 mL, 20 mmol) was added dropwise. The mixture was gradually warmed to room temperature over 19 h and then it was poured onto water (50 mL). The aqueous mix was extracted three times with EtOAc (20 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give 2-(*N*-(2-bromo-4-isopropylphenyl)-*N*-ethyl-6-methyl-4-(hydroxymethyl)pyrimidin-2-amine, a clear, colorless oil (3.64 g): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.55 (d, 1H, *J* = 1 Hz), 7.20 (dd, 1H, *J* = 7, 1 Hz), 7.15 (d, 1H, *J* = 7 Hz), 6.30 (s, 1H), 4.60–4.30 (m, 2H), 4.30–4.10 (m, 1H), 3.85–3.50 (br s, 2H), 3.00–2.85 (m, 1H), 2.50–2.20 (br s, 3H), 1.27 (d, 6H, *J* = 7 Hz), 1.22 (t, 3H, *J* = 7 Hz); CI-MS *m/z* 366, 364 (M<sup>+</sup> + H).

A solution of 2-(*N*-(2-bromo-4-isopropylphenyl)-*N*-ethyl-6-methyl-4-(hydroxymethyl)pyrimidin-2-amine (1.57 g, 4.3 mmol) and triethylamine (2.5 mL, 17 mmol) in dichloromethane (15 mL) was cooled to 0–5°C with stirring. Methanesulfonyl chloride (0.54 g, 4.73 mmol) was added dropwise. Stirring at 0–5°C was continued for 1.5 h. The reaction mixture was transferred to a separatory funnel, washed once with an ice-cold 1 N HCl solution (17 mL), washed twice with a saturated NaHCO<sub>3</sub> solution and once with brine. Drying, filtration and removal of solvent in vacuo afforded 2-(*N*-(2-bromo-4-isopropylphenyl)-*N*-ethyl-6-methyl-4-(methanesulfonyloxy-methyl)pyrimidin-2-amine, a clear colorless oil (1.6 g): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.50 (d, 1H, *J* = 1 Hz), 7.25–7.10 (m, 2H), 6.50 (s, 1H), 5.05–4.90 (br s, 2H), 4.30–4.10 (m, 1H), 3.80–3.60 (m, 1H), 3.00–2.85 (m, 1H), 2.70 (br s, 3H), 2.35 (br s, 3H), 1.30 (d, 6H, *J* = 8 Hz), 1.20 (t, 3H, *J* = 8 Hz); CI-MS *m/z* 444, 442 (M<sup>+</sup> + H).

Sodium hydride (60% in oil, 0.1 g, 2.4 mmol) was washed with hexanes and decanted twice. Dry THF (10 mL) was added, followed by imidazole (146 mg, 2.14 mmol). The reaction mix was heated to reflux temperature, stirred for 2 h, then cooled to ambient temperature. A solution of 2-(*N*-(2-bromo-4-isopropylphenyl)-*N*-ethyl-6-methyl-4-(methanesulfonyloxy-methyl)pyrimidin-2-amine (900 mg, 2 mmol) in dry THF (10 mL) was added. The reaction mixture was stirred at room temperature for 68 h, then it was poured onto water (50 mL). Three extractions with EtOAc (20 mL), drying the combined organic layers, filtration, and removal of solvent in vacuo gave a brown oil. Column chromatography (EtOAc) gave two fractions after removal of solvent in vacuo: (1) 2-(*N*-(2-bromo-4-isopropylphenyl)-*N*-ethyl-6-methyl-4-(methanesulfonyloxy-methyl)pyrimidin-2-amine (*R<sub>f</sub>* 0.7, 130 mg) and (2) the title product, a yellow oil (500 mg, 59% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.60–7.40 (m, 2H), 7.20 (dd, 1H, *J* = 7, 1 Hz), 7.15 (d, 1H, *J* = 8 Hz), 7.05 (s, 1H), 7.00–6.80 (m, 1H), 6.05 (s,

1H), 5.05–4.75 (br s, 2H), 4.25–4.10 (m, 1H), 3.80–3.60 (m, 1H), 3.00–2.85 (m, 1H), 2.40–2.10 (br s, 3H), 1.30 (d, 6H,  $J=8$  Hz), 1.20 (t, 3H,  $J=8$  Hz); CI-HRMS  $m/z$  calcd for  $C_{20}H_{24}BrN_5$ : 413.1293; found: 413.1275 ( $M^+ + H$ ).

**[2-[[2-Bromo-4-(1-methylethyl)phenyl]ethylamino]-6-methyl-4-pyrimidinyl]-indol-3-yl-methanone (3-15) (Step D).**

A solution of indole (0.3 g, 2.5 mmol) in dry ether (8 mL) was stirred at room temperature. A solution of methylmagnesium bromide in ether (3 M, 0.89 mL, 2.65 mmol) was added slowly such that the solution refluxed gently. Stirring was continued for 45 min. A solution of **2** (1 g, 2.5 mmol) in ether (10 mL) was added dropwise over 15 min. The resulting suspension was stirred at room temperature for 16 h. A saturated ammonium chloride solution (10 mL) was added. The resulting mixture was extracted three times with EtOAc (20 mL). The combined organic layers were washed twice with water (20 mL), dried, filtered, and concentrated in vacuo. Column chromatography (EtOAc/hexanes, 1/9) gave the title product, after removal of solvent in vacuo (650 mg, 50% yield): mp 105–107°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.50 (br d, 1H,  $J=4$  Hz), 7.95 (br s, 1H), 7.58 (s, 1H), 7.5–7.4 (m, 1H), 7.40–7.15 (m, 4H), 6.23 (br s, 1H), 4.4–4.2 (m, 1H), 3.85–3.70 (m, 1H), 3.00–2.85 (m, 1H), 2.55 (s, 3H), 2.4–2.2 (m, 1H), 1.23 (d, 9H,  $J=6$  Hz); CI-HRMS  $m/z$  calcd for  $C_{25}H_{25}BrN_4O$ : 477.1290; found: 477.1286 ( $M+H$ )<sup>+</sup>. Anal. calcd for  $C_{25}H_{25}BrN_4O$ : C, 63.01, H, 5.25, N, 11.76, Br, 16.80; found: C, 62.77, H, 5.22, N, 11.58, Br, 16.81.

**[2-[[2-Bromo-4-(1-methylethyl)phenyl]ethylamino]-6-methyl-4-pyrimidinyl]-1H-imidazol-2-yl-methanone (3-12) (Step F).**

A solution of imidazole (10.2 g, 150 mmol) and dimethylamine-hydrochloride (12.2 g, 150 mmol) in water was stirred at room temperature. A concentrated HCl solution was added dropwise until pH 5. Formalin (13.5 g, 150 mmol) was added and the reaction mixture was stirred at ambient temperature for 43 h. The aqueous mix was basified by addition of a 20% KOH solution, saturated with  $K_2CO_3$  and extracted three times with chloroform (200 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give a clear colorless oil. Vacuum distillation (bp 71–72°C, 2 Torr) afforded 1-(dimethylaminomethyl)imidazole,<sup>24</sup> a clear colorless liquid (15.6 g, 83% yield):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.5 (s, 1H), 7.1 (s, 1H), 6.95 (s, 1H), 4.65 (s, 2H), 2.3 (s, 6H); CI-MS  $m/z$  126 ( $M^+ + H$ ).

A solution of 1-(dimethylaminomethyl)imidazole (0.63 g, 5 mmol) in anhydrous ether (40 mL) was cooled to –78°C with stirring. A solution of *n*-butyl lithium in hexanes (2.4 M, 2.1 mL, 5 mmol) was added dropwise over 5 min. The resulting pale-yellow white suspension was stirred at –78°C for 1 h. A solution of **2** (1.47 g, 5 mmol) in dry ether (10 mL) was added dropwise and the reaction mixture was warmed gradually to room temperature over 24 h. A 1 N HCl solution was added until pH 1 (wet indicator paper) and the mix was stirred for 4 h. A 1 N NaOH solution was added until pH 12. Three extractions with EtOAc (50 mL), drying the combined organic layers, filtration, and removal of

solvent in vacuo provided a brown oil. Column chromatography ( $CHCl_3/MeOH$ , 9/1) gave the title compound ( $R_f$  0.64, 900 mg, 42% yield): mp 75–76°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  12.2–12.1 (m, 1H), 7.7 (d, 1H,  $J=1$  Hz), 7.45–7.35 (m, 2H), 7.3–7.2 (m, 2H), 6.55 (br s, 1H), 4.3 (sextet, 1H,  $J=7$  Hz), 3.8 (sextet, 1H,  $J=7$  Hz), 3.05 (septet, 1H,  $J=7$  Hz), 2.65 (s, 3H), 1.4 (d, 6H,  $J=7$  Hz), 1.3 (t, 3H,  $J=7$  Hz); CI-HRMS  $m/z$  calcd for  $C_{20}H_{23}BrN_5O$ : 428.1086, found: 428.1089 ( $M^+ + H$ ). Anal. calcd for  $C_{20}H_{23}BrN_5O$ : C, 56.08, H, 5.18, N, 16.35, 18.68; found: C, 56.20, H, 5.10, N, 15.88, Br, 18.73.

***N*-(2-Bromo-4-isopropylphenyl)-*N*-ethyl-4-carboxy-6-methylpyrimidin-2-amine (3-1).**

A mixture of *N*-(2-Bromo-4-isopropylphenyl)-*N*-ethyl-4-carbomethoxy-6-methylpyrimidin-2-amine **2** (10 g, 25 mmol), a 1 N NaOH solution (250 mL, 250 mmol) and ethanol (10 mL) was stirred at reflux temperature for 7 h. After being cooled to room temperature, the mix was concentrated twofold in vacuo, acidified with a concentrated HCl solution and extracted three times with chloroform (100 mL). The combined organic layers were dried, filtered and concentrated in vacuo to afford a yellow oil, which solidified on standing (mp 102–104°C;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  7.55 (d, 1H,  $J=1$  Hz), 7.25–7.20 (m, 2H), 7.15 (d, 1H,  $J=8$  Hz), 4.30–4.15 (m, 1H), 3.85–3.70 (m, 1H), 3.00–2.90 (m, 1H), 2.65–2.25 (br s, 3H), 1.30 (d, 6H,  $J=8$  Hz), 1.25 (t, 3H,  $J=8$  Hz); CI-HRMS  $m/z$  calcd for  $C_{17}H_{20}BrN_3O_2$ : 378.0817, found: 378.0809 ( $M^+ + H$ ).

**[2-[[2-Bromo-4-(1-methylethyl)phenyl]ethylamino]-6-methyl-4-pyrimidinyl]-ethanone (3-10) and *N*-(2-bromo-4-isopropylphenyl)-*N*-ethyl-4-(1-hydroxy-1-methylethyl)-6-methylpyrimidin-2-amine (3-19) (Step E).**

Cerium (III) chloride (11.8 g, 43 mmol) was heated at 100°C under high vacuum for 3 h to remove residual moisture, after cooling to room temperature, a nitrogen atmosphere was introduced. Dry THF (150 mL) was added and the mix was stirred for 19 h to afford a solution. The solution was cooled to –78°C. A solution of **3-1** in dry THF (100 mL) was cooled in a separate flask to –78°C and a solution of methyl lithium in ether (1.6 M, 14 mL, 22.4 mmol) was added dropwise over 15 min. After 2 h, the above cold solution of cerium chloride in THF was transferred via cannula into the reaction mixture. Stirring at –78°C was continued for 4.5 h, then a solution of methyl lithium in ether (1.6 M, 13 mL, 20.8 mmol) was added dropwise again over 15 min. The reaction mixture was gradually warmed to ambient temperature over 16 h, then cooled to –78°C. A solution of methyl lithium in ether (1.6 M, 13 mL, 20.8 mmol) was added dropwise again over 15 min. The reaction mixture was stirred at –78°C for 6 h; then it was poured onto a 1 N HCl solution (150 mL, 150 mmol) and mixed. Three extractions with EtOAc (100 mL), drying the combined organic layers, filtration and removal of solvent in vacuo provided a brown oil. Column chromatography (EtOAc/hexanes, 1/4) gave two fractions after removal of solvent in vacuo: (1) the title product, an oil ( $R_f$  0.6, 3.4 g, 43% yield): NMR ( $CDCl_3$ )  $\delta$  7.55 (d, 1H,  $J=1$  Hz), 7.22 (dd, 1H,  $J=7, 1$  Hz), 7.18 (d, 1H,  $J=7$  Hz), 6.98 (s, 1H), 4.25–4.10 (m, 1H), 3.90–3.70 (m, 1H), 3.00–2.85 (m, 1H), 2.55–2.05 (m, 6H), 1.35–1.20 (m,

9H); CI-HRMS  $m/z$  calcd for  $C_{18}H_{22}BrN_3O$ : 375.1025, found: 375.1042 ( $M^+ + H$ ); (2) *N*-(2-bromo-4-isopropylphenyl)-*N*-ethyl-4-(1-hydroxy-1-methylethyl)-6-methylpyrimidin-2-amine (**3-19**), an oil ( $R_f$  0.3, 1 g, 3% yield):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.55 (d, 1H,  $J=1$  Hz), 7.15–7.10 (m, 1H), 7.18 (d, 1H,  $J=7$  Hz), 6.42 (s, 1H), 4.30–4.10 (m, 1H), 3.90–3.70 (m, 1H), 3.00–2.85 (m, 1H), 2.50–2.20 (br s, 3H), 1.37 (s, 6H), 1.30–1.20 (m, 9H); CI-HRMS  $m/z$  calcd for  $C_{19}H_{26}BrN_3O$ : 392.1337, found: 392.1332 ( $M + H$ ) $^+$ .

***N*-(2-Bromo-4-isopropylphenyl)-*N*-ethyl-4-(1-hydroxyethyl)-6-methylpyrimidin-2-amine (**3-17**) (Step G).**

Sodium borohydride (100 mg, 2.7 mmol) was added to a solution of **3-31** (500 mg, 1.3 mmol) in ethanol (10 mL). The reaction mixture was stirred at room temperature for 24 h, then it was poured onto water (30 mL). Three extractions with EtOAc (100 mL), drying the combined organic layers, filtration, and removal of solvent in vacuo provided a clear, colorless oil. Column chromatography (EtOAc/hexanes, 1/1) gave the title compound, a clear colorless oil ( $R_f$  0.6, 420 mg, 84% yield) after removal of solvent in vacuo:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.50 (d, 1H,  $J=1$  Hz), 7.25–7.10 (m, 2H), 6.35 (s, 1H), 4.65–4.40 (m, 1H), 4.35–4.05 (m, 2H), 3.85–3.65 (m, 1H), 3.00–2.85 (m, 1H), 2.50–2.05 (br s, 3H), 1.35 (s, 6H), 1.30–1.10 (m, 9H); CI-HRMS  $m/z$  calcd for  $C_{18}H_{24}BrN_3O$ : 378.1181, found: 378.1178 ( $M^+ + H$ ).

***N*-(2-Bromo-4-isopropylphenyl)-*N*-ethyl-4-(1-hydroxy-1,1-bis-(2-furyl)methyl)-6-methylpyrimidin-2-amine (**3-21**), (2-((*N*-(2-bromo-4-isopropylphenyl)-*N*-ethylamino)-6-methylpyrimidin-4-yl)-(2-furyl)methanone (**3-13**) and *N*-(2-bromo-4-isopropylphenyl)-*N*-ethyl-4-(1-(2-furyl)-1-hydroxymethyl)-6-methylpyrimidin-2-amine (**3-18**) (Steps E, F, H, and I).** A solution of furan (0.21 g, 3.12 mol) in ether (10 mL) was cooled to 0°C with stirring. A solution of *n*-butyl lithium in hexanes (2.4 M, 1.6 mL, 3.7 mmol) was added dropwise over 5 min. The reaction mixture was stirred at 0°C for 30 min. In a separate flask, a solution of **2** (1 g, 2.6 mmol) in anhydrous ether was cooled to –78°C with stirring. The furyl lithium solution was transferred dropwise via cannula. Stirring at –78°C was continued for 4 h. The reaction mixture was gradually warmed to room temperature over 16 h, then it was poured onto water (100 mL). Three extractions with EtOAc (50 mL), drying the combined organic layers, filtration and removal of solvent in vacuo provided an oil. Column chromatography (EtOAc/hexanes, 1/4) gave three fractions: (1) **3-21**, a tan solid ( $R_f$  0.4, 200 mg, 16% yield): mp 97–99°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.50 (d, 1H,  $J=1$  Hz), 7.40 (s, 2H), 7.20 (dd, 1H,  $J=7$ , 1 Hz), 7.18 (d, 1H,  $J=7$  Hz), 6.50 (s, 1H), 6.32 (s, 2H), 6.30–6.10 (m, 2.5H), 5.90–5.78 (m, 0.5H), 4.30–4.10 (m, 1H), 3.90–3.70 (m, 1H), 3.00–2.80 (m, 1H), 2.30 (br s, 3H), 1.35–1.15 (m, 9H); CI-HRMS  $m/z$  calcd for  $C_{25}H_{26}BrN_3O_3$ : 496.1236, found: 496.1232 ( $M^+ + H$ ); calcd for  $C_{22}H_{23}BrN_4O$ : C, 60.59, H, 5.25, N, 8.48, Br, 16.16; found: C, 60.93, H, 5.58, N, 8.11, Br, 15.80; (2) **3-13**, a tan solid ( $R_f$  0.3, 400 mg, 32% yield): mp 136–138°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.70–7.50 (m, 2H), 7.35–7.20 (m, 3H), 6.95 (s, 1H), 6.18 (s, 1H), 4.40–4.20

(m, 1H), 3.85–3.70 (m, 1H), 3.05–2.90 (m, 1H), 2.50 (br s, 3H), 1.40–1.20 (m, 9H); CI-HRMS  $m/z$  calcd for  $C_{21}H_{22}BrN_3O_2$ : 428.0974, found: 428.0968 ( $M^+ + H$ ). Anal. calcd for  $C_{21}H_{22}BrN_3O_2$ : C, 59.02, H, 5.15, N, 9.83, Br, 18.73; C, 58.85, H, 5.16, N, 9.73, Br, 18.50; (3) **3-18**, an orange oil ( $R_f$  0.2, 130 mg, 12% yield):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.52 (d, 1H,  $J=1$  Hz), 7.38 (s, 1H), 7.22 (dd, 1H,  $J=7$ , 1 Hz), 7.19 (d, 1H,  $J=7$  Hz), 6.35 (s, 1H), 6.32–6.15 (m, 2H), 5.50–5.40 (m, 1H), 4.35–4.10 (m, 1H), 3.90–3.65 (m, 1H), 3.00–2.85 (m, 1H), 2.30 (br s, 3H), 1.30 (d, 6H,  $J=7$  Hz), 1.20 (t, 3H,  $J=7$  Hz); CI-HRMS  $m/z$  calcd for  $C_{21}H_{24}BrN_3O_2$ : 430.1130, found: 430.1117 ( $M^+ + H$ ).

## Biology

**Rat CRF receptor binding assay.** This assay was performed essentially as described in the literature<sup>25,26</sup> with minor modifications. Mean  $K_i$  values from at least two determinations each are reported, unless otherwise noted (>1000 nM). Data from saturation curves were analyzed using the non-linear least-squares curve-fitting program LIGAND.<sup>27</sup>

## Inhibition of CRF-stimulated adenylate cyclase activity.

Inhibition of CRF-stimulated adenylate cyclase activity was generally studied as described by G. Battaglia et al.,<sup>28</sup> with minor modifications.

**Pharmacokinetic studies.** Pharmacokinetic parameters were determined in rats ( $n=4$ ) at the doses and vehicles specified in the text. At 15 min (iv only), 30 min, 1, 2, 4, 8 and 16 h after dosing, rats were sacrificed at the specified times and trunk blood samples were collected into tubes containing EDTA. Plasma was separated by centrifugation and stored frozen until analysis. Compounds were extracted from plasma by simple liquid–liquid extraction. The high pressure liquid chromatography consisted of a Perkin–Elmer series 200 solvent delivery system (Norwalk, CT), a Perkin–Elmer ISS 200 auto-injector and a Waters Symmetry octyl mini-bore column (2.1×50 mm). Concentrations were determined from UV absorption data relative to appropriate internal standards.

## Appendix

### Combustion analyses

Ex. No.	Formula		%C	%H	%N	%Other
<b>3-7</b>	$C_{22}H_{32}BrN_5$ - $2C_4H_4O_4$	Theory	53.10	5.94	10.32	Br: 11.78
		Found	53.24	6.00	10.27	Br: 11.52
<b>3-11</b>	$C_{23}H_{24}BrN_5O$	Theory	67.55	5.82	8.15	Br: 15.53
		Found	67.48	6.00	7.91	Br: 15.61
<b>3-12</b>	$C_{20}H_{22}BrN_5O$	Theory	56.08	5.18	16.35	Br: 18.68
		Found	56.20	5.10	15.88	Br: 18.73
<b>3-13</b>	$C_{21}H_{22}BrN_3O_2$	Theory	59.02	5.15	9.83	Br: 18.73
		Found	58.85	5.16	9.73	Br: 18.50
<b>3-15</b>	$C_{25}H_{25}BrN_4O$	Theory	63.01	5.25	11.76	Br: 16.80
		Found	62.77	5.22	11.58	Br: 16.81
<b>3-16</b>	$C_{20}H_{22}BrN_5O$	Theory	56.19	5.15	16.39	Br: 18.73
		Found	55.92	5.23	16.08	Br: 18.57
<b>3-21</b>	$C_{25}H_{26}BrN_3O_3$	Theory	60.59	5.25	8.48	Br: 16.16
		Found	60.93	5.58	8.11	Br: 15.80

### Chemi-ionization high-resolution mass spectral data

(All data for  $M^+ + H$ , unless otherwise indicated.)

2	$C_{18}H_{22}BrN_3O_2$	Theory	392.0974
		Found	392.0960
3-1	$C_{17}H_{20}BrN_3O_2$	Theory	378.0817
		Found	378.0809
3-2	$C_{18}H_{23}BrN_4O$	Theory	391.1133
		Found	391.1127
3-3	$C_{19}H_{25}BrN_4O$	Theory	404.1290
		Found	404.1294
3-4	$C_{21}H_{29}BrN_4O$	Theory	433.1603 ( $M + H - Br$ )
			433.1586
3-5	$C_{20}H_{24}BrN_5$	Theory	413.1293
		Found	413.1275
3-6	$C_{22}H_{31}BrN_4$	Theory	431.1810
		Found	431.1792
3-8	$C_{25}H_{32}BrN_7$	Theory	510.1981
		Found	510.1989
3-9	$C_{19}H_{24}BrN_7$	Theory	430.1355
		Found	430.1346

### Chemi-ionization high-resolution mass spectral data

(All data for  $M + + H$ , unless otherwise indicated.)

3-10	$C_{18}H_{22}BrN_3O$	Theory	375.1025
		Found	375.1042
3-14	$C_{22}H_{23}BrN_4O$	Theory	439.1133
		Found	439.1118
3-17	$C_{18}H_{24}BrN_3O$	Theory	378.1181
		Found	378.1178
3-18	$C_{21}H_{24}BrN_3O_2$	Theory	430.1130
		Found	430.1117
3-19	$C_{19}H_{26}BrN_3O$	Theory	392.1337
		Found	392.1332
3-20	$C_{31}H_{34}BrN_3O_3$	Theory	576.1862
		Found	576.1851

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