Synthesis and SAR of 2-Aryloxy-4-alkoxy-pyridines as Potent Orally Active Corticotropin-Releasing Factor 1 Receptor Antagonists

Yuhpyng L. Chen,*[,†] John Braselton,[‡] James Forman,[†] Randall J. Gallaschun,[†] Robert Mansbach,[‡] Anne W. Schmidt,[‡] Thomas F. Seeger,[‡] Jeff S. Sprouse,[‡] F. David Tingley, III,[‡] Elizabeth Winston,[‡] and David W. Schulz[‡]

Medicinal Chemistry and Neuroscience Departments, PGRD, Pfizer Inc., Groton, Connecticut 06340

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A series of 2-aryloxy-4-alkoxy-pyridines (**1**) was identified as novel, selective, and orally active antagonists of the corticotropin-releasing factor 1 (CRF_1) receptor. Among these, compound **2** (CP-316311) is a potent and selective CRF_1 receptor antagonist with an IC_{50} value of 6.8 nM in receptor binding and demonstrates oral efficacy in central nervous system (CNS) in vivo models. The regiochemistry of compounds in this series was determined by an X-ray structural analysis. A method to control regioselectivity via pyridine-*N*-oxides was developed. The synthesis of compounds in series **1** (Figure 1) and [^{3}H]-**2** as well as the structure−activity relationship (SAR) are discussed. The in vitro, ex vivo, and in vivo properties of representative compounds are described herein. Compound **2** was advanced to phase II depression trials to test the hypothesis that CRF_1 antagonists could be used clinically as antidepressant drugs.

Introduction

Corticotropin-releasing factor (CRF), a 41 amino acid peptide neurotransmitter, coordinates the body's response to stress through the release of adrenocorticotropic hormone (ACTH). CRF has been shown to mediate stress-induced changes in the autonomic system and to cause numerous neuroendocrine changes and behavioral effects.[1] Clinical data indicate that patients with depression and post-traumatic stress disorder show significantly elevated concentrations of CRF in cerebrospinal fluid when compared to normal controls.[2] In addition, patients with depression, anxiety, anorexia nervosa, and post-traumatic stress disorder showed a blunted ACTH response to intraveneous CRF, indicating that their CRF receptors may be down-regulated possibly due to chronic hypersecretion of CRF.[3] Receptor subtypes include CRF_1 and CRF_2 receptors that are widely distributed throughout the central nervous system (CNS) and peripheral tissues.[4] A selective CRF_1 receptor antagonist may represent a novel class of compounds for the treatment of anxiety, depression, and stress-related diseases. Published preclinical data support the hypothesis that a small molecule CRF_1 receptor antagonist such as CP-154526 (**3a**) or CP-156181 (antalarmin, **3b**) blocks neuroendocrine effects (e.g., increased ACTH induced by i.v. CRF), autonomic responses (e.g., hypertensive effects), or increased heart rate or behavioral changes induced by i.c.v. CRF or stress stimuli.[5,6] In a continuation of our structure−activity relationship (SAR) efforts around **3a**, structural modifications in the pyrrolo-pyrimidine core template and peripheral side chains led to various novel chemotypes, in which the pyridine series represents one of the most attractive series because of its low molecular weight coupled with excellent preclinical efficacy and safety. SAR efforts led to the discovery of a clinical candidate **2** that was advanced to phase II to test the ability of a CRF_1 receptor antagonist to treat depressed patients. Herein we would like to report the regioselective synthesis and the SAR of compounds in series **1**. The ex vivo and in vivo results of representative compounds are presented.

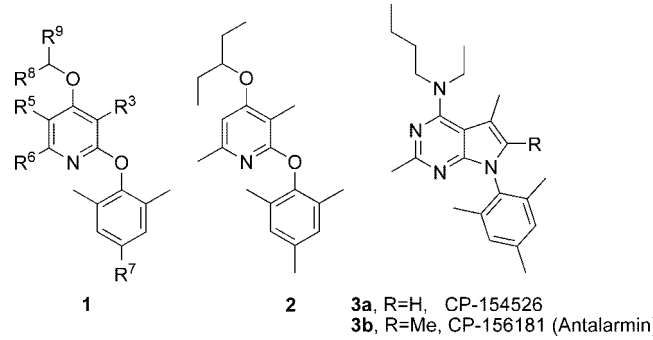

Figure 1. CRF_1 antagonists.

2,4-Dichloro-3,6-dimethyl-pyridine (**4**) was prepared by the method analogous to a literature report[7] as shown in Scheme 1. Direct coupling of 2,4-dichloro-3,6-dimethyl-pyridine with sodium 2,4,6-trimethylphenoxide provided a 3:1 mixture of regioisomers **5** and **6** as white crystals, in which the minor component **6** was found to be the desired isomer. The regiochemistry of **5** was determined by X-ray structural analysis. Reaction of each isomer **5** and **6** with 3-pentanoxide in DMSO at 120 °C provided compounds **7** and **2**, respectively. Compound **2**, derived from the minor isomer **6**, was found to be more potent than the major isomer **7**, with IC_{50} values for the CRF_1 receptor of 6.8 and 3400 nM, respectively. Reversing the order of addition by adding 3-pentoxide first in an attempt to address the regioselectivity issue surprisingly switched the selectivity from preferably attacking at the C_4 position as seen in the case of trimethylphenoxide to the C_2 position in the pyridine ring, thus again providing the undesired regioisomer **8** as a major component as shown in Scheme 1.

A regioselective method was needed in order to rapidly generate SAR and to efficiently scale up key compounds to support toxicology studies. We thought that if we could increase the reactivity at C_2 of the pyridine ring through the formation of the pyridine-*N*-oxide, **8**, we might be able to control the regioselectivity in the coupling step to provide the desired isomer. Indeed such an approach successfully delivered the bulk

* To whom correspondence should be addressed. Phone: (860) 444-2438. Fax: (860) 444-2438. E-mail: yuhpyng888@yahoo.com.
† Medicinal Chemistry Department.
‡ Neuroscience Department.

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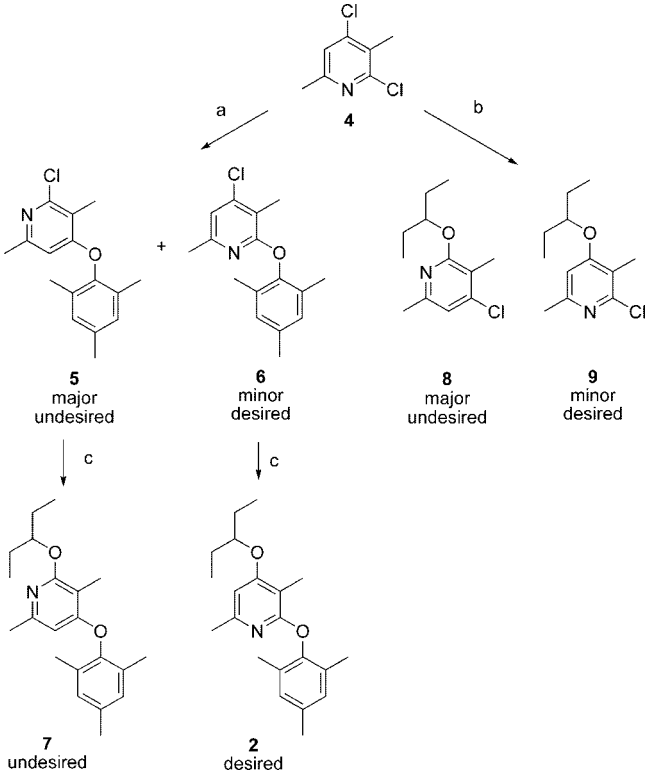
Scheme 1[a]



[a] Reagents and conditions: (a) 2,4,6,-trimethylphenol, KO*t*-Bu, DMSO; (b) 3-pentanol, NaH or KO*t*-Bu, THF; (c) 3-pentanol, NaH or KO*t*-Bu, DMSO or 1-methyl-2-pyrrolidinone.

of **2** for pharmacology and toxicology studies.[8,9] Pyridine-*N*-oxide **10a** was prepared by reaction of **4** with m-CPBA in chloroform at room temperature in 77% yield as white crystals. Coupling of pyridine-*N*-oxide **10a** with 2,4,6-trimethylphenol and sodium hydride in refluxing THF for 2 h provided the desired regioisomer **11a** exclusively in 89% yield as cubic crystals. Reduction of **11a** with 1 equiv of PCl_3 in refluxing methylene chloride for 1 h yielded the desired product **6** as white crystals in 95% yield as shown in Scheme 2. Analogues in this series were prepared for SAR by the method analogous to that described in the synthesis of compound **2** as illustrated in Scheme 3. [^{2}H]-**2** was synthesized as a mixture of deuterium addition products at positions C_1, C_2, and C_3 by reduction of the precursor **13** with deuterium in the presence of 10% Pd/C in ethyl acetate at atmospheric pressure. Compound **13** was prepared as a mixture of cis/trans isomers by reacting **6** with pent-1-en-3-ol and NaH in DMSO, where the olefin isomerization occurred under basic conditions as shown in Scheme 3. The developed reduction method was used for preparing [^{3}H]-**2** to give a 45 Ci/mmol specific activity of the radiolabeled material, which was used for drug metabolism studies.

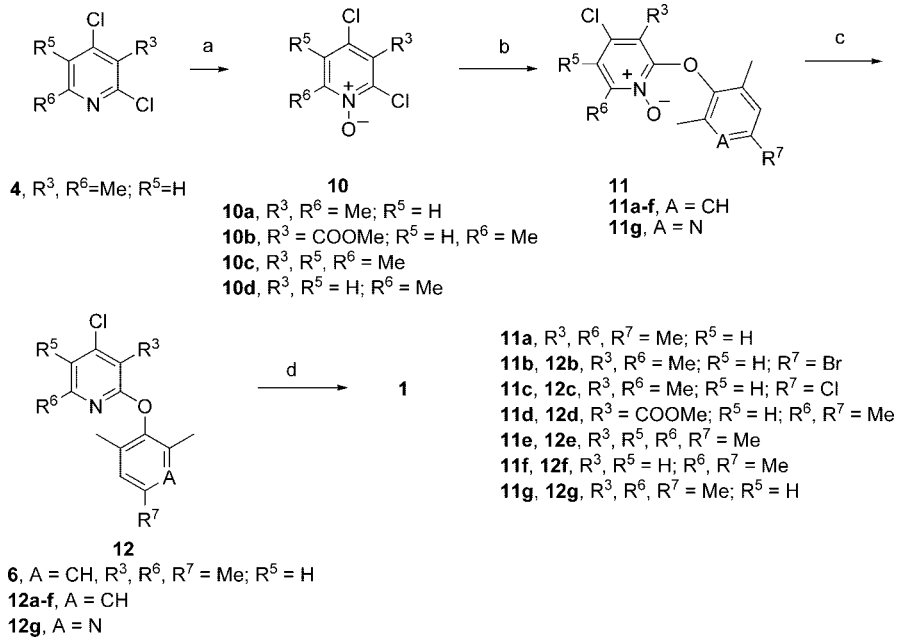
Compounds in series **1** were tested in a rat cortex binding assay by using ^{125}I-ovine-CRF (^{125}I-oCRF) as shown in Tables 1−3. Low nanomolar compounds were selected for ex vivo evaluations. Because compounds in the blood can gain access to the pituitary gland without crossing the blood−brain barrier, the decrease in binding in the brain or pituitary gland gives an estimate of the relative brain/plasma ratio of systemically administered compounds via either the oral (p.o.) or subcutaneous (s.c.) route. Several compounds exhibit excellent ex vivo activity in the cortex and pituitary ^{125}I-oCRF displacement assay at 3.2 mg/kg, indicating compounds penetrate the CNS well via either p.o. or s.c. administration.

The area around substituents at C_5 and C_6 in the pyridine series **1** was found to have a narrow SAR; for example, changing R^5 from H to Et resulted in a change in IC_{50} values from 6.8 nM to >10,000 nM, respectively, whereas the area at R^3 seems to tolerate a variety of groups, including Me, Et, Br, nitro, and amino, as shown in Table 1. The optimized substituents at R^3, R^5, and R^6 are Me, H, and Me (compound **2**), respectively, which also offers good metabolic stability, brain penetrability, and oral activity, as shown in the ex vivo data. Table 2 describes the SAR in the *p*-aryloxy group, in which R^7 seems to tolerate various groups and R^7 as Me and $CONH_2$ provided excellent ex vivo inhibition in cortex after p.o. administration. Although the methoxy group in **35** seems to increase polarity and demonstrates excellent ex vivo inhibition in cortex after oral dosing, it shows poor metabolic stability perhaps due to demethylation. Table 3 describes the limited SAR on the top alkoxide side chain, in which the branched alkoxide is required for potency based on our SAR in series **3a**.[10] In order to add basicity and polarity, the 2,4,6-trimethyl-phenoxy group of **2** was replaced with a 3-(2,4,6-trimethyl-pyridoxy) to give compound **14**, which showed a pK_a increase from ~3.5 to 4.97 and improved kinetic water solubility from <1 μg/mL to 10 μg/mL.[11] Compound **14** had an IC_{50} value of 10 nM and demonstrated excellent ex vivo cortex displacement (70% inhibition at 3.2 mg/kg, s.c.) but is relatively more labile than **2** in human microsomes.

Liver toxicity had been a key issue in our early CRF program, but compounds in this series proved to be safe and no liver toxicity was seen in five day rat toxicology studies.[10] Compounds in series **1** have high affinity for the CRF_1 receptor subtype and low affinity for the CRF_2 receptor (>1 μM). The representative compound **2** fully antagonized CRF-stimulated adenylate cyclase activity in rat cortex and at human CRF_1 receptors endogenously expressed in IMR32 cells with apparent K_i values of 7.6 and 8.5 nM, respectively. Compound **2** is highly selective for the CRF_1 receptor and has affinities of greater than 1 μM for more than 40 other receptors, channels, enzymes, and uptake proteins. Ex vivo binding studies in rats demonstrate that oral administration of **2** (3.2 mg/kg) inhibits ^{125}I-oCRF binding by >80%. Oral activity has been obtained in rats by using models that reflect antagonism of CRF-mediated responses in the periphery and the brain. Compound **2** significantly attenuates activation of the hypothalamic−pituitary−adrenal (HPA) axis, as measured by increased plasma ACTH levels in response to exogenous CRF administration with an MED value of 10 mg/kg, p.o. ($p < 0.05$ versus CRF alone, One Way ANOVA, Dunnett's post hoc test, $N = 12$) and a calculated ID_{50} value (p.o.) of 35 mg/kg (4 μg/kg oCRF, i.v.) with a confidence interval of 26.7−45.4 mg/kg. Systemically administered compound **2** blocks the effects of both the exogenous and endogenous CRF in the CNS. For example, it demonstrated activity in several behavioral models, including reversal of i.c.v. CRF-induced excitation of locus coeruleus neurons (60% inhibition at 0.3 mg/kg, i.v.), reversal of startle potentiation induced by i.c.v. CRF (100% at 32 mg/kg, p.o.), and activity in the defensive withdrawal model of anxiety at 10 mg/kg, i.p. administration.[10]

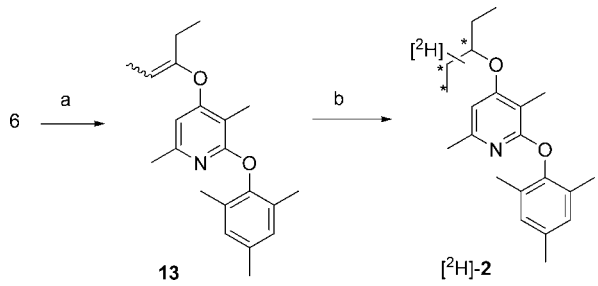
In summary, a regioselective synthesis was developed for rapid SAR assessment of series **1**. Compounds in the pyridine series **1** are potent and highly selective antagonists of the CRF_1 receptor subtype. A representative compound, **2**, fully antagonizes CRF-stimulated adenylate cyclase activity and significantly attenuates activation of the HPA axis as measured by blocking plasma ACTH elevation induced by i.v. oCRF. Systemically

Scheme 2[a]



[a] Reagents and conditions: (a) *m*-CPBA, $CHCl_3$, or CH_2Cl_2; (b) 2,4,6,-trimethylphenol, NaH, THF; (c) 2 M PCl_3 in CH_2Cl_2, 95%; (d) 3-pentanol, NaH, or KO*t*-Bu, DMSO or NMP.

Scheme 3[a]



[a] Reagents and conditions: (a) 3 equiv of CH_2=CHCH(OH)(Et), 1.2 equiv of NaH in DMSO, 130 °C; (b) deuterium, 10% Pd/C in EtOAc, 1 atm, quantitative yield.

administered **2** blocks the effects induced by the exogeneous or endogeneous CRF in the brain in rat models. It demonstrates oral efficacy in the i.c.v. CRF-induced and fear potentiated startle models after oral administration. **2** was selected for clinical investigation in a placebo-controlled study in depressed patients.[10]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. High field ^{1}H NMR spectra were recorded on a Varian XL-300, XL-400, Bruker AM 250, or Bruker AM 300 instrument. Elemental analyses were carried out by Schwarzkopf Microanalytical, Woodside, NY.

2,4-Dichloro-3,6-dimethyl-pyridine 1-Oxide (10a).[8] A mixture of 2,4-dichloro-3,6-dimethyl-pyridine (790 mg, 4.49 mmol) and 50% *m*-chloro-perbenzoic acid (1.544 g, 4.49 mmol) in 10 mL of chloroform was stirred at room temperature for 20 h. The reaction was quenched with water, washed with saturated sodium thiosulfate, saturated sodium carbonate, and brine, and extracted with chloroform. The organic layer was dried and concentrated to give 0.954 g of crude material. The material was purified through silica gel and recrystallized from THF to give 0.662 g (77%) of the desired product as white crystals, mp 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 7.22 (s, 1H), 2.51 (s, 3H), 2.47 (s, 3H) ppm; Anal. ($C_7H_7Cl_2NO$) C, H, N.

Compounds **10b–d** were prepared by the method analogous to that described in preparation of **10a**, starting with an appropriate 2,4-dichloro-pyridine and an oxidizing agent.

2,4-Dichloro-6-methyl-1-oxy-nicotinic Acid Methyl Ester (10b). White crystals, mp 90–91.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (s, 1H), 3.98 (s, 3H), 2.54 (s, 3H) ppm; Anal. ($C_8H_7NO_3Cl_2$) C, H, N.

2,4-Dichloro-3,5,6-trimethyl-pyridine 1-Oxide (10c). White crystals, mp 146–148 °C; ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 2.49 (s, 3H), 2.38 (s, 3H) ppm; Anal. ($C_8H_9NOCl_2$) C, H, N.

2,4-Dichloro-6-methyl-pyridine 1-Oxide (10d). White crystals, mp 100–102 °C; ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 1H), 7.22 (d, 1H), 2.55 (s, 3H) ppm; Anal. ($C_6H_5NOCl_2$) C, H, N.

4-Chloro-2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine 1-Oxide (11a). A solution of 2,4,6-trimethylphenol (31.166 g, 0.229 mmol) in dry THF (700 mL) was treated with 60% sodium hydride in oil (9.16 g, 0.229 mmol) at room temperature. After all of the H_2 was evolved, 2,4-dichloro-3,6-dimethyl-pyridine 1-oxide (44.000 g, 0.229 mmol) was added, and the resulting mixture was heated at reflux for 2 h. The reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to give a solid. The solid was recrystallized from petroleum ether to give 59.41 g (89%) of the title compound as white crystals, mp 106–107 °C; ^{1}H NMR ($CDCl_3$) δ 7.04 (s, 1H), 6.78 (s, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H), 2.06 (s, 6H) ppm; Anal. ($C_{16}H_{18}NO_2Cl$) C, H, N.

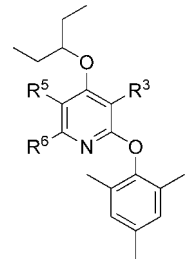
Compounds **11b–g** were prepared by the method analogous to that described in the preparation of **11a**, starting with an appropriate 2,4-dichloro-pyridine 1-oxide and an appropriate phenol in the presence of a base (KO*t*-Bu, NaH, or KH) at a temperature between room temperature and reflux in dry THF.

2-(4-Bromo-2,6-dimethyl-phenoxy)-4-chloro-3,6-dimethyl-pyridine 1-Oxide (11b). White crystals, mp 137–139 °C; ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 2H), 7.08 (s, 1H), 2.42 (s, 6H), 2.09 (s, 6H) ppm; Anal. ($C_{15}H_{15}BrClNO_2$) C, H, N.

4-Chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine 1-Oxide (11c). ^{1}H NMR ($CDCl_3$) δ 7.08 (s, 1H), 6.97 (s, 2H), 2.42 (s, 6H), 2.09 (s, 6H) ppm; Anal. ($C_{15}H_{15}Cl_2NO_2$) C, H, N.

4-Chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-1-oxy-nicotinic Acid Methyl Ester (11d). ^{1}H NMR ($CDCl_3$) δ 7.04 (s, 1H), 6.78 (s, 2H), 3.48 (s, 3H), 2.52 (s, 3H), 2.22 (s, 3H), 2.08 (s, 6H) ppm.

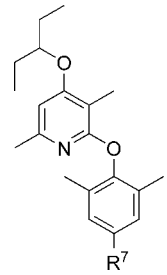
Table 1. In Vitro CRF_1 Inhibition (IC_{50})[a] and ex Vivo Data[b] Using a Radiolabeled CRF Displacement Assay in Rat Cortex and Pituitary for Compounds in the Pyridine Series



				in vitro,[a] rat cortex		ex vivo[b]		
compound no.	R^3	R^5	R^6	$pIC_{50} \pm$ SEM (M)	IC_{50} (nM)	3.2 mg/kg route	cortex (% inh ± SD)	pituitary (% inh ± SD)
2	Me	H	Me	8.17 ± 0.04	6.8	p.o.	75 ± 7	72 ± 11
15	Me	H	Et	7.06 ± 0.34	86		NT	NT
16	Et	H	Me	8.04 ± 0.18	9.1	s.c.	57 ± 8	66 ± 18
17	H	H	Me	6.83 ± 0.06	150		NT	NT
18	COOMe	H	Me	6.33 ± 0.08	470		NT	NT
19	NO_2	H	Me	7.82 ± 0.05	15	s.c.	59 ± 10	35 ± 9
20	NH_2	H	Me	7.91 ± 0.24	12*	s.c.	78 ± 16	51 ± 5
21	NMe_2	H	Me	7.60 ± 0.16	25		NT	NT
22	Br	H	Me	8.01 ± 0.14	9.8		NT	NT
23	COOH	H	Me	<5.00	>10,000		NT	NT
24	Me	Me	Me	6.74 ± 0.25	180		NT	NT
25	Me	Et	Me	<5.00	>10,000		NT	NT

[a] Values reported are the geometric mean of at least three experimental runs using rat cortex (*except compound **20**, $n = 2$). [b] Compounds were administered via oral (p.o.) or subcutaneous (s.c.) route at 3.2 mg/kg. ^{125}I-oCRF binding to brain and pituitary tissues in rats was measured by using an ex vivo autoradiographic assay or brain homogenate binding displacement assay. Percent inhibition values are mean ± SD. NT = not tested.

Table 2. SAR of the 2-Aryloxy Group in the Pyridine Series in Vitro[a] and ex Vivo Data[b]



		in vitro,[a] rat cortex		ex vivo[b]		
compound no.	R^7	$pIC_{50} \pm$ SEM (M)	IC_{50} (nM)	3.2 mg/kg route	cortex (% inhibition)	pituitary (% inhibition)
2	Me	8.17 ± 0.04	6.8	p.o.	75 ± 7	72 ± 11
26	H	6.96 ± 0.14	110		NT	NT
27	Et	7.97 ± 0.13	11	s.c.	55 ± 7	56 ± 16
28	*n*-Pr	8.01 ± 0.09	9.8	s.c.	42 ± 21	34 ± 19
29	F	7.50 ± 0.16	32		NT	NT
30	Cl	8.26 ± 0.24	5.5	p.o.	66 ± 8	76 ± 7
31	Br	8.58 ± 0.16	2.6	p.o.	47 ± 16	84 ± 1
32	I	7.91 ± 0.27	12	s.c.	27 ± 4	72 ± 11
33	$CONH_2$	7.74 ± 0.12	18	p.o.	33 ± 22	15 ± 12
34	OH	5.87 ± 0.29	1400		NT	NT
35	OMe	8.69 ± 0.10	2	p.o.	75 ± 4	55 ± 1
36	OEt	7.70 ± 0.11	20	p.o.	43 ± 15	33 ± 1
37	O*i*-Pr	6.96 ± 0.18	110		NT	NT
38	CHO	7.40 ± 0.15	40		NT	NT
39	CH_2OH	7.21 ± 0.10	61	p.o.	42 ± 25	−20 ± 4
40	CH_2OMe	8.50 ± 0.12	3.2	p.o.	57 ± 2	12 ± 1
41	$CMe_2(OH)$	7.40 ± 0.14	40		NT	NT

[a] Values reported are the geometric mean of at least three experimental runs using rat cortex. [b] Compounds were administered via oral (p.o.) or subcutaneous (s.c.) route at 3.2 mg/kg. ^{125}I-oCRF binding to brain and pituitary tissues in rats was measured using an ex vivo autoradiographic assay or brain homogenate binding displacement assay. Percent inhibition values are mean ± SD. NT = not tested.

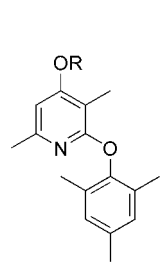
4-Chloro-2,3,5-trimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine 1-Oxide (11e). White crystals, mp 132–134 °C; ^{1}H NMR ($CDCl_3$) δ 6.75 (s, 2H), 2.47 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 2.04 (s, 6H) ppm; Anal. ($C_{17}H_{20}ClNO_2$) C, H, N.

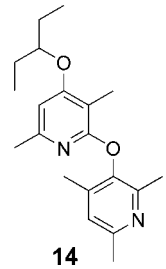
4-Chloro-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyridine 1-Oxide (11f). White crystals, mp 191–193 °C; ^{1}H NMR ($CDCl_3$) δ 6.96 (s, 1H), 6.95 (s, 2H), 2.62 (s, 3H), 2.32 (s, 3H), 2.13 (s, 6H) ppm; Anal. ($C_{15}H_{16}ClNO_2$) C, H, N.

4-Chloro-3,6-dimethyl-2-(2,4,6-trimethyl-3-pyridyl)-pyridine 1-Oxide (11g). White crystals, mp 113–114 °C; ^{1}H NMR ($CDCl_3$) δ 7.09 (s, 1H), 6.82 (s, 1H), 2.44 (s, 6H), 2.41 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H) ppm; Anal. ($C_{15}H_{17}ClN_2O_2$) C, H, N.

4-Chloro-3,6-dimethyl-2-(2,4,6-trimethyl-phenyoxy)-pyridine (6).[9] To a solution of 4-chloro-2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine 1-oxide (55.00 g, 185.5 mmol) in 130 mL of dry methylene chloride was added 2 M PCl_3 in methylene chloride

Table 3. In Vitro CRF_1 Inhibition (IC_{50})[a] and Ex Vivo Data[b] Using Radiolabeled CRF for Displacement Assays in Rat Cortex and Pituitary for Compounds with 4-Alkoxy SAR in the Pyridine Series





14

		in vitro,[a] rat cortex		ex vivo[b]		
compound no.	OR	$pIC_{50} \pm$ SEM (M)	IC_{50} (nM)	3.2 mg/kg administration route	cortex (% inhibition)	pituitary (% inhibition)
2	$OCH(Et)_2$	8.17 ± 0.04	6.8	p.o.	75 ± 7	72 ± 11
42	OCH(Et)(Me)	7.55 ± 0.13	28	s.c.	74 ± 5	42 ± 1
43	$OCH(Et)(CH_2OMe)$	7.96 ± 0.06	11	s.c.	75 ± 9	49 ± 14
13	$OC(=\text{-}CH_3)(Et)$	7.79 ± 0.09	16	s.c.	75 ± 21	55 ± 6
44	O-3-THF	6.99 ± 0.09	100		NT	NT
14		7.99 ± 0.27	10	s.c.	70 ± 6	6 ± 13

[a] Values reported are the geometric mean of at least three experimental runs using rat cortex. [b] Compounds were administered via oral (p.o.) or subcutaneous (s.c.) route at 3.2 mg/kg. ^{125}I-oCRF binding to brain and pituitary tissues in rats was measured using an ex vivo autoradiographic assay or brain homogenate binding displacement assay. Percent inhibition values are mean ± SD. NT = not tested.

(95 mL, 190 mmol) dropwise during a period of 1 h. After addition, the mixture was heated at reflux for 0.5 h, cooled, and concentrated to dryness. The residue was poured into ice–water and extracted with methylene chloride. The organic layer was washed with brine, neutralized with saturated sodium carbonate, dried, and concentrated to give 56.75 g of the crude material. The crude material was purified through a 150 g silica gel column by using chloroform as eluent to give 49.27 g (95%) of the desired product as white crystals, mp 57–62 °C; HRMS for $C_{16}H_{18}ClNO$: calc 275.1072, found 275.70172; IR (KBr) 2951, 2920, 1592, 1564 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87 (s, 2H), 6.77 (s, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 2.18 (s, 3H), 2.03 (s, 6H) ppm.

Compounds **12b–g** were prepared by the method analogous to that described in the preparation of **6**, starting with an appropriate 4-chloro-6-substituted-phenoxy/pyridoxy-pyridine 1-oxide and phosphorus trichloride.

2-(4-Bromo-2,6-dimethyl-phenoxy)-4-chloro-3,6-dimethyl-pyridine (12b). White crystals; ^1H NMR ($CDCl_3$) δ 7.22 (s, 2H), 6.81 (s, 1H), 2.40 (s, 3H), 2.20 (s, 3H), 2.05 (s, 6H) ppm; Anal. ($C_{15}H_{15}BrClNO$) C, H, N.

4-Chloro-2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine (12c). White crystals; ^1H NMR ($CDCl_3$) δ 7.07 (s, 2H), 6.81 (s, 1H), 2.41 (s, 3H), 2.20 (s, 3H), 2.06 (s, 6H) ppm; Anal. ($C_{15}H_{15}Cl_2NO$) C, H, N.

4-Chloro-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic Acid Methyl Ester (12d). Yellow crystals; mp 122–125 °C; ^1H NMR ($CDCl_3$) δ 6.84 (s, 2H), 6.82 (s, 1H), 3.94 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H), 2.04 (s, 6H) ppm; Anal. ($C_{17}H_{18}ClNO_3$) C, H, N.

4-Chloro-2,3,5-trimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine (12e). White crystals; mp 101–103 °C; ^1H NMR ($CDCl_3$) δ 6.85 (s, 2H), 2.39 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 2.01 (s, 6H) ppm; Anal. ($C_{17}H_{20}ClNO$) C, H, N.

4-Chloro-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyridine (12f). White crystals; mp 46–48 °C; ^1H NMR ($CDCl_3$) δ 6.92 (s, 2H), 6.83 (d, 1H), 6.30 (d, 1H), 2.44 (s, 3H), 2.31 (s, 3H), 2.09 (s, 6H) ppm; Anal. ($C_{15}H_{16}ClNO$) C, H, N.

4-Chloro-3,6-dimethyl-2-(2,4,6-trimethyl-3-pyridyl)-pyridine (12g). White crystals; mp 72–73 °C; ^1H NMR ($CDCl_3$) δ 6.89 (s, 1H), 6.81 (s, 1H), 2.50 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H), 2.04 (s, 3H) ppm; Anal. ($C_{15}H_{17}ClN_2O \cdot 0.25H_2O$) C, H, N.

4-(1-Ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (2). To a solution of 3-pentanol (56 mL, 0.5205 mol) in DMSO (760 mL) was added 60% sodium hydride in oil (7.64 g, 0.191 mol) portionwise. After stirring at room temperature for 30 min, a solution of 4-chloro-2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine (47.80 g, 0.174 mol) in 50 mL of dry THF was added, and the resulting mixture was heated at 130 °C for 3 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried, and concentrated to give 68.21 g of yellow solid. The solid was purified through silica gel column chromatography using 10% chloroform in hexane grading to chloroform as eluent to give 52.20 g (92%) of the title compound as white crystals, mp 72.5–74 °C; ^1H NMR ($CDCl_3$) δ 6.84 (s, 2H), 6.26 (s, 1H), 4.16 (m, 1H), 2.27 (s, 3H), 2.17 (s, 6H), 2.04 (s, 6H), 1.69 (m, 4H), 0.95 (t, 6H) ppm; Anal. ($C_{21}H_{29}NO_2$) C, H, N. The mesylate salt of 4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine was prepared by addition of 1 equiv of methanesulfonic acid in ethyl acetate. The white crystals formed from ethyl acetate, mp 117–119 °C; Anal. ($C_{22}H_{33}NO_5S$) C, H, N, S.

The following compounds were prepared by the method analogous to that described for compound **2**, starting from an appropriate 4-chloro-2-methyl-6-substituted-phenoxy-pyridine with an appropriate alcohol and base.

***cis/trans*-4-(1-Ethyl-propenyloxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (13).** ^1H NMR ($CDCl_3$) δ 6.85 (s, 2H), 6.30 (s, 0.3H), 6.21 (s, 0.7H), 5.10 (m, 0.7H), 4.95 (m, 0.3H), 2.27 (s, 3H), 2.24 (s, 2.1H), 2.19 (s, 0.9H), 2.14 (s, 3H), 2.05 (s, 6H), 1.65 (d, 0.9H), 1.50 (d, 2.1H), 1.08 (t, 1.8H), 1.05 (t, 3.2H) ppm.

6-Ethyl-4-(1-ethyl-propoxy)-3-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (15). ^1H NMR ($CDCl_3$) δ 6.87 (s, 2H), 6.28 (s, 1H), 4.20 (m, 1H), 2.46 (q, 2H), 2.30 (s, 3H), 2.20 (s, 3H), 2.07 (s, 6H), 1.72 (m, 4H), 1.05 (t, 3H), 0.99 (t, 6H) ppm; Anal. ($C_{22}H_{31}NO_2$) C, H, N.

3-Ethyl-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (16). ^1H NMR($CDCl_3$) δ 6.85 (s, 2H), 6.26 (s, 1H), 4.18 (m, 1H), 2.73 (q, 2H), 2.28 (s, 3H), 2.17 (s, 3H), 2.05 (s, 6H), (m, 4H), 1.18 (t, 3H), 0.96 (t, 6H) ppm.

4-(1-Ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyridine (17). ^1H NMR ($CDCl_3$) δ 6.90 (s, 2H), 6.34 (d, $J = 2$ Hz, 1H), 5.70 (d, $J = 2$ Hz, 1H), 4.05 (m, 1H), 2.40 (s, 3H), 2.30 (s, 3H), 2.11 (s, 6H), 1.62 (m, 4H), 0.89 (t, 6H) ppm; Anal. ($C_{20}H_{27}NO_2$) C, H, N.

4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic Acid Methyl Ester (18). Clear oil; ^1H NMR ($CDCl_3$) δ 6.84 (s, 2H), 6.39 (s, 1H), 5.04 (m, 1H), 3.85 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H), 2.05 (s, 6H), 1.5–1.7 (m, 4H), 0.95 (s, 6H) ppm; Exact mass ($C_{22}H_{29}NO_4$) calc 371.21, found 371.2097.

Mesylate Salt of 4-(1-Ethyl-propoxy)-2,3,5-trimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine (24). White crystals, mp 58–60 °C; ^1H NMR ($CDCl_3$) δ 6.90 (s, 2H), 4.20 (m, 1H), 2.70 (s, 3H), 2.61

(s, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 2.08 (s, 6H), 1.5–1.8 (m, 4H), 0.96 (t, 6H) ppm; Exact mass ($C_{22}H_{31}NO_2$) calc 341.2355, found 342.2440.

4-(1-Ethyl-propoxy)-3,6-dimethyl-5-ethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (25). Clear oil; Anal. ($C_{23}H_{33}NO_2$) C, H, N.

2-(2,6-Dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine (26). ^{1}H NMR ($CDCl_3$) δ 7.06 (m, 3H), 6.30 (s, 1H), 4.20 (m, 1H), 2.21 (s, 6H), 2.11 (s, 6H), 1.73 (m, 4H), 0.99 (t, 6H) ppm; APCI ($C_{21}H_{28}N_2O_3$) M + 1 = 357.3.

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine (30). ^{1}H NMR ($CDCl_3$) δ 7.05 (s, 2H), 6.31 (s, 1H), 4.20 (m, 1H), 2.20 (s, 6H), 2.08 (s, 6H), 1.73 (m, 4H), 0.99 (t, 6H) ppm; Anal. ($C_{20}H_{26}NO_2Cl$) C, H, N.

2-(4-Bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine (31). ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 2H), 6.30 (s, 1H), 4.22 (m, 1H), 2.20 (s, 6H), 2.05 (s, 6H), 1.73 (m, 4H), 1.00 (t, 6H) ppm; Anal. ($C_{20}H_{26}BrNO_2$) C, H, N.

4-*s*-Butoxy-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (42). ^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.31 (s, 1H), 4.35 (m, 1H), 2.30 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 2.07 (s, 6H), 1.7–1.9 (m, 2H), 1.34 (d, 3H), 1.01 (t, 3H) ppm; Anal. ($C_{20}H_{27}NO_2$) C, H, N.

4-(1-Methoxymethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (43). ^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.38 (s, 1H), 4.42 (m, 1H), 3.5–3.7 (m, 2H), 3.42 (s, 3H), 2.31 (s, 3H), 2.21 (s, 6H), 2.07 (s, 6H), 1.7–1.85 (m, 2H), 1.02 (t, 3H) ppm; Anal. ($C_{21}H_{29}NO_3$) C, H, N.

3,6-Dimethyl-4-(tetrahydro-furan-3-yloxy)-2-(2,4,6-trimethyl-phenoxy)-pyridine (44). ^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.25 (s, 1H), 4.99 (m, 1H), 3.9–4.1 (m, 4H), 2.31 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 2.1–2.3 (m, 2H), 2.07 (s, 6H) ppm; Anal. ($C_{20}H_{25}NO_3$) C, H, N.

4-(1-Ethyl-propoxy)-3,6-dimethyl-2-[3-(2,4,6-trimethyl-pyridinoxy)]-pyridine (14). To a solution of 3-pentanol (0.11 mL) in dry THF was added sodium hydride (60% in oil, 20 mg). After stirring for 5 min, a solution of 4-chloro-2,5-dimethyl-6-[3-(2,4,6-trimethyl-pyridinoxy)]-pyridine (92 mg, 0.33 mmol) in THF was added. DMSO was added, and the resulting mixture was heated at 130 °C in an oil bath overnight. The reaction was quenched with water and brine and extracted 3 times with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), and concentrated to dryness. After silica gel column chromatography purification, 47 mg (43%) of the desired product was obtained as a clear oil; ^{1}H NMR ($CDCl_3$) δ 6.88 (s, 1H), 6.37 (s, 1H), 4.21 (m, 1H), 2.5 (s, 3H), 2.29 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 2.07 (s, 3H), 1.70 (m, 4H), 0.98 (t, 6H) ppm. The oil was converted to the corresponding HCl salt to give a white solid (63 mg).

4-(1-Ethyl-propoxy)-6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridine (19). To a mixture of 2-chloro-4-(1-ethyl-propoxy)-6-methyl-3-nitro-pyridine (500 mg, 1.93 mmol) and 2,4,6-trimethylphenol (289 mg, 2.13 mmol) in dry THF was added KO*t*-Bu. The resulting mixture was stirred at room temperature overnight. The reaction was quenched with water and brine and extracted 3 times with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), and concentrated to dryness. After silica gel column chromatography purification, the title compound was obtained as a light yellow crystal, mp 106–109 °C; ^{1}H NMR ($CDCl_3$) δ 6.87 (s, 2H), 6.43 (s, 1H), 4.30 (m, 1H), 2.29 (s, 3H), 2.28 (s, 3H), 2.09 (s, 6H), 1.74 (m, 4H), 0.97 (t, 6H) ppm; Anal. ($C_{20}H_{26}N_2O_4$) C, H, N.

4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ylamine (20). A mixture of 4-(1-ethyl-propoxy)-6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridine (150 mg, 0.418 mmol) and 10% Pd/C (23 mg) in ethanol was hydrogenated at 50 psi for 15 h. An additional 10% Pd/C was added, and the resulting mixture was hydrogenated for an additional 24 h. The mixture was filtered through Celite, and the filtrate was concentrated to dryness to give 200 mg of crude material. The crude material was purified by silica gel column chromatography using 1:1 ethyl acetate/hexane as eluent to give 61 mg of the desired product with 94% purity by GC/MS. A portion of the free base (10 mg) was converted to the corresponding HCl salt to give a white solid, mp 96–98 °C; ^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.03 (s, 1H), 4.20 (m, 1H), 3.72 (brs, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 2.10 (s, 6H), 1.74 (m, 4H), 1.00 (t, 6H) ppm.

[4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-dimethyl-amine (21). To a solution of 4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-ylamine in dry THF was added lithium bis(trimethylsilyl)amide at –78 °C. After stirring at –78 °C for 10 min, an excess of methyl iodide was added. The title compound was isolated after quenching with water and extracting with ethyl acetate. The crude material was purified by silica gel column chromatography using $CHCl_3$ as eluent to give 31 mg (70%) of the desired product as a tan foam; ^{1}H NMR ($CDCl_3$) δ 6.86 (s, 2H), 6.31 (s, 1H), 4.25 (m, 1H), 2.89 (s, 6H), 2.29 (s, 3H), 2.17 (s, 3H), 2.08 (s, 6H), 1.76 (m, 4H), 1.00 (t, 6H) ppm.

3-Bromo-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (22). A mixture of 3-amino-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine with $NaNO_2$, 48% HBr, CuBr, and water was stirred at 0 °C, heated at reflux for 10 min, and then cooled to room temperature. The resulting mixture was adjusted to pH 7.0 and extracted with ethyl acetate. The organic layer was separated, dried, and concentrated to give the title compound as a golden oil. The oil was purified by silica gel column chromatography using $CHCl_3$ as eluent to give a white solid, mp 85–87 °C; ^{1}H NMR ($CDCl_3$) δ 6.86 (s, 2H), 6.3 (s, 1H), 4.28 (m, 1H), 2.28 (s, 3H), 2.18 (s, 3H), 2.02 (s, 6H), 1.7 (m, 4H), 1.0 (t, 6H) ppm; Anal. ($C_{20}H_{26}BrNO_2$) C, H, N.

4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic Acid (23). To a −78 °C solution of 3-bromo-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (50 mg, 0.127 mmol) in 1 mL of dry THF was added 0.061 mL of 2.5 M *n*-BuLi in hexanes at −78 °C. The resulting mixture was stirred at −78 °C for 5 min. An excess of dry ice was added, and the resulting mixture was gradually warmed to room temperature. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate to give 50 mg of a light yellow oil that crystallized upon standing. The material was purified by silica gel column chromatography using $CHCl_3$ as eluent to give 41 mg of the desired product that was then dissolved in Et_2O and extracted with 1 N NaOH. The aqueous layer was acidified with 1 N HCl to pH 4 and extracted with Et_2O. The organic layer was separated, dried, and concentrated to give 31 mg of white crystals, mp 145–147 °C; Anal. ($C_{21}H_{27}NO_4$) C, H, N.

2-(4-Ethyl-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine (27). To a solution of 2.5 N *n*-BuLi in hexane (0.47 mL, 1.18 mmol) in 5 mL of dry THF was added a solution of 2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine (465 mg, 1.18 mmol) in 5 mL of dry THF at −78 °C. After stirring at that temperature for 5 min, an excess of ethyl iodide (0.4 mL) was added, and the resulting mixture was stirred at −78 °C for 30 min and then at 0 °C for 15 min. The reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried and concentrated to give a brown oil. The oil was purified by silica gel column chromatography using chloroform as eluent to give 260 mg of the title compound as a white solid; ^{1}H NMR ($CDCl_3$) δ 6.90 (s, 2H), 6.38 (s, 1H), 4.20 (m, 1H), 2.61 (q, 2H), 2.24 (s, 3H), 2.21 (s, 3H), 2.10 (s, 6H), 1.70 (m, 4H), 1.30 (t, 3H), 0.98 (t, 6H) ppm; Anal. ($C_{22}H_{31}NO_2$) C, H, N.

The following compounds were prepared by the method analogous to that described for compound **27**, starting from *n*-BuLi and 2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine, followed by quenching with an appropriate electrophile.

2-(2,6-Dimethyl-4-propyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine (28). ^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.30 (s, 1H), 4.20 (m, 1H), 2.54 (dd, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.09 (s, 6H), 1.6–1.8 (m, 6H), 0.9–1.1 (m, 9H) ppm; Anal. ($C_{23}H_{33}NO_2$) C, H, N.

4-(1-Ethyl-propoxy)-2-(4-fluoro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine (29). Colorless oil; Anal. ($C_{20}H_{26}FNO_2$) C, H, N.

4-(1-Ethyl-propoxy)-2-(4-iodo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine (32). ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 2H), 6.30 (s, 1H), 4.19 (m, 1H), 2.20 (s, 3H), 2.18 (s, 3H), 2.05 (s, 6H), 1.72 (m, 4H), 0.98 (t, 6H) ppm; Anal. ($C_{20}H_{26}INO_2$) C, H, N.

4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzaldehyde (38). ^{1}H NMR ($CDCl_3$) δ 9.94 (s, 1H), 7.61 (s, 2H), 6.32 (s, 1H), 4.20 (m, 1H), 2.21 (s, 3H), 2.16 (s, 9H), 1.70 (m, 4H), 0.98 (t, 6H) ppm; Anal. ($C_{21}H_{27}NO_3$) C, H, N.

2-{4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl}-propan-2-ol (41). ^{1}H NMR ($CDCl_3$) δ 7.15 (s, 2H), 6.25 (s, 1H), 4.20 (m, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 2.10 (s, 6H), 1.85 (brs, 1H), 1.70 (m, 4H), 1.60 (s, 6H), 0.95 (t, 6H) ppm; Anal. ($C_{23}H_{33}NO_3$) C, H, N.

4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzamide (33). To a solution of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzoic acid in anhydrous methylene chloride was added $SOCl_2$, and the mixture was stirred at room temperature for 1 h. The mixture was concentrated to dryness to provide the corresponding acyl chloride. The acyl chloride was quenched with an excess of NH_3 and stirred at room temperature to provide the desired product; ^{1}H NMR ($CDCl_3$) δ 7.51 (s, 2H), 6.32 (s, 1H), 6.2 (brs, 1H), 5.7 (brs, 1H), 4.20 (m, 1H), 2.22 (s, 3H), 2.19 (s, 3H), 2.12 (s, 6H), 1.72 (m, 4H), 0.97 (t, 6H) ppm.

4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenol (34). ^{1}H NMR ($CDCl_3$) δ 7.85 (brs, 1H), 6.36 (s, 1H), 6.24 (s, 2H), 4.24 (m, 1H), 2.39 (s, 3H), 2.20 (s, 3H), 2.02 (s, 6H), 1.74 (m, 4H), 1.00 (t, 6H) ppm.

4-(1-Ethyl-propoxy)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine (35). To a solution of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenol (40 mg, 0.12 mmol) in 3 mL of dry THF was added 10 mg of 60% sodium hydride in oil at room temperature. After stirring for 5 min, 0.3 mL of methyl iodide was added, and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow solid. The solid was purified by silica gel column chromatography using hexane to 1:1 chloroform/hexane as eluent to yield 20 mg of the title compound as a yellow solid; ^{1}H NMR ($CDCl_3$) δ 6.66 (s, 2H), 6.28 (s, 1H), 4.20 (m, 1H), 3.79 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 2.08 (s, 6H), 1.71 (m, 4H), 0.97 (t, 6H) ppm.

4-(1-Ethyl-propoxy)-2-(4-isopropoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine (37). To a solution of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenol (58 mg, 0.18 mmol) in 3 mL of dry THF was added triphenylphosphine (70 mg, 0.264 mmol) and isopropanol (60 mg, 0.22 mmol). The resulting mixture was stirred at room temperature for 5 min; diethyl azodicarboxylate (46 mg, 0.26 mmol) was added. The mixture was stirred at room temperature overnight. An additional 20 mg of diethyl azodicarboxylate was added, and the mixture was stirred for an additional 4 h. The reaction was quenched with water and extracted with methylene chloride. The organic layer was dried and concentrated to give an oil. The oil residue was purified by silica gel column chromatography using 1:1 hexane/chloroform to 1:2 hexane/chloroform as eluent to give 38 mg (58%) of the title compound as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.60 (s, 2H), 6.28 (s, 1H), 4.50 (m, 1H), 4.18 (m, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 2.07 (s, 6H), 1.71 (m, 4H), 1.34 (d, 6H), 0.98 (t, 6H) ppm; Anal. ($C_{23}H_{33}NO_3$) C, H, N.

{4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl}-methanol (39). A mixture of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzaldehyde (114 mg, 0.41 mmol) and sodium borohydride (63 mg, 1.6 mmol) in 3 mL of methanol was stirred at room temperature for 2 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow oil. The oil was purified through silica gel using chloroform as eluent to give 70 mg of the title compound as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.04 (s, 2H), 6.32 (s, 1H), 4.55 (s, 2H), 4.21 (m, 1H), 2.30 (brs, 1H), 2.22 (s, 3H), 2.21 (s, 3H), 2.12 (s, 6H), 1.73 (m, 4H), 0.91 (t, 6H) ppm; Anal. ($C_{21}H_{29}NO_3$) C, H, N.

The following compounds were prepared by the method analogous to that described for compound **35**, starting with an appropriate pyridine-3,5-dimethylphenol or pyridine-3,5-dimethyl-phenyl methanol with a base, followed by quenching with an appropriate alkyl halide.

2-(4-Ethoxy-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine (36). ^{1}H NMR ($CDCl_3$) δ 6.60 (s, 2H), 6.28 (s, 1H), 4.19 (m, 1H), 3.99 (q, 2H), 2.19 (s, 3H), 2.18 (s, 3H), 2.07 (s, 6H), 1.74 (m, 4H), 1.40 (t, 3H), 0.97 (t, 6H) ppm.

4-(1-Ethyl-propoxy)-2-(4-methoxymethyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine (40). mp 58–60 °C; ^{1}H NMR ($CDCl_3$) δ 7.05 (s, 2H), 6.30 (s, 1H), 4.41 (s, 2H), 4.19 (m, 1H), 3.42 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 2.11 (s, 6H), 1.72 (m, 4H), 0.98 (s, 6H) ppm; Anal. ($C_{22}H_{31}NO_3$) C, H, N.

Biological Evaluation. Experimental details for the CRF receptor binding assays, in vitro adenylate cyclase functional assay, effect on elevations in plasma ACTH levels, CRF-induced increases in locus coeruleus firing in the rat, acoustic startle response induced by i.c.v. CRF, and fear-potentiated startle induced by electric foot shock have been reported previously.[5b]

Ex Vivo Receptor Binding Assay with ^{125}I-oCRF. ^{125}I-oCRF binding to brain and pituitary tissues in rats was measured at 1 h after dosing compounds at 3.2 mg/kg, p.o., by using either an ex vivo brain homogenate or autoradiographic binding techniques as described below.

A. Homogenate ex Vivo Binding Assay. Male Sprague–Dawley rats (weight of 200–300 g) were treated with a compound or vehicle at the doses indicated. After a specified treatment period, they were sacrificed via decapitation, and the brains and pituitary glands were rapidly removed and frozen immediately on dry ice. The tissues were suspended at 25 mg wet weight/mL in buffer (20 mM PIPES pH 7.0, 10 mM $MgCl_2$, 2 mM EGTA, 0.015% bacitracin, and 100 U/mL aprotinin). 100 μL aliquots of tissue homogenate were added to assay samples containing 40 pM ^{125}I-oCRF, yielding a final volume of 200 μL. Nonspecific binding was determined using 1 μM rat/human CRF. After a 2 h incubation at room temperature, assay samples were centrifuged for 10 min at 1000*g*. The supernatant was discarded. Samples were rinsed with 100 μL of ice-cold assay buffer and recentrifuged. Pellets were filtered onto betaplate filtermats A by using a Skatron cell harvester (setting 222). Radioactivity was quantified using a betaplate scintillation counter (Wallac).

B. Autoradiographic ex Vivo Binding Assay. Male Sprague–Dawley rats ($N = 4$, weight of 200–300 g) were sacrificed, and the brains and pituitary glands were rapidly removed. The pituitary was apposed to the underside of the brain close to its original location, and the brain was frozen in isopentane maintained at −30 °C. The brains were sectioned (16 μm) at the level containing the pituitary, mounted onto microscope slides, and dried at 5 °C under vacuum. After storage at −70 °C for no more than one week, midbrain sections were thawed and incubated in 20 mM PIPES buffer (pH 7.0), containing 10 mM $MgCl_2$, 2 mM EGTA, 0.05% bovine serum albumin, 0.01% bacitracin, and 60 pM ^{125}I-oCRF, for one hour at room temperature. Successive serial sections were incubated in the above mixture plus no inclusion (total binding) or 1 μM cold rat/human CRF (nonspecific binding). All sections were then washed for 2 × 5 min in ice cold wash buffer (50 mM Tris-HCl, 5 mM $MgCl_2$, 2 mM EGTA, pH 7.4), dipped briefly in distilled water, and dried in a stream of compressed air. The resulting slides were placed in standard X-ray cassettes and apposed to tritium-sensitive LKB Ultrofilm for a period of 7–10 days before developing.

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Supporting Information Available: Tables of elemental analysis data for compounds **2**, **15**, **17**, **19**, **22**, **23**, **25**–**32**, **34**, and **37**–**44** and intermediates **10a**–**d**, **11a**–**c**, **11e**–**g**, and **12b**–**g**, as well as X-ray data for **5** and atomic coordinates, bond lengths and angles, and displacement parameters for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Because the pyridine-*N*-oxide intermediates may show exothermic decomposition, it is recommended to test the differential scanning calorimeter (DSC) prior to scale-up synthesis. Pyridine-*N*-oxide intermediates **10** and **11** are not recommended for large scale preparation, and caution is required to ensure safety in the laboratory. In general, acceptable decomposition energy depends in part on the conditions of the chemistry, for example dilution and operating temperature, and so forth. In general, a 100 °C difference between process temperature and decomposition is considered to be acceptable.

(9) An alternative method for regioselective synthesis of compound **6** was developed for kilogram bulk preparation by the Process Department and will be described in a separate paper.

(10) The detailed information will be described in a separate publication.

(11) Kinetic water solubility data was obtained from an in-house high throughput assay. Compound **2** has water solubility of 0.2 and 3 μg/mL at pH 7.0 and pH 2.0, respectively. pK_a was determined by a UV method and after extrapolation to 0% organic solvent.

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