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Synthesis, Structure−Activity Relationships, and In Vivo Evaluation of N^3-Phenylpyrazinones as Novel Corticotropin-Releasing Factor-1 (CRF_1) Receptor Antagonists

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Evidence suggests that corticotropin-releasing factor-1 (CRF_1) receptor antagonists may offer therapeutic potential for the treatment of diseases associated with elevated levels of CRF such as anxiety and depression. A pyrazinone-based chemotype of CRF_1 receptor antagonists was discovered. Structure−activity relationship studies led to the identification of numerous potent analogues including **12p**, a highly potent and selective CRF_1 receptor antagonist with an IC_{50} value of 0.26 nM. The pharmacokinetic properties of **12p** were assessed in rats and Cynomolgus monkeys. Compound **12p** was efficacious in the defensive withdrawal test (an animal model of anxiety) in rats. The synthesis, structure−activity relationships and in vivo properties of compounds within the pyrazinone chemotype are described.

Introduction

Corticotropin-releasing factor-1 (CRF_1[a]) receptor antagonists are of considerable interest as a potential novel treatment of stress-related disorders such as anxiety and depression.[1−6] Corticotropin-releasing factor (CRF), a 41 amino acid neuropeptide first isolated by Vale and co-workers,[7] functions as the primary regulator of the hypothalamic−pituitary−adrenal (HPA) axis, coordinating endocrine, behavioral, and autonomic responses to stress.[8,9] CRF mediates its action through binding to two extensively characterized, class B subtype, G-protein coupled receptors, CRF_1 and CRF_2, which are widely distributed throughout the central and peripheral nervous systems.[10] Furthermore, three splice variants of CRF_2 subtype receptors have been identified (α, *β*, and *γ*).[11,12] CRF, upon synthesis and release from the paraventricular region of the hypothalamus, binds to receptors in the anterior pituitary, promoting the subsequent release of adrenocorticotropic hormone (ACTH), *β*-endorphin, and other proopiomelanocortin (POMC)-derived peptides. Increased levels of ACTH, in turn, induce the production and secretion of cortisol from the adrenal cortex, resulting in a variety of metabolic changes that facilitate the body's response to a stressor. It should be noted that CRF may not originate exclusively from paraventricular neurons controlling ACTH secretion as these neurons represent only one element of an extensive system of CRF neurons and projections throughout the brain.[13]

CRF_1 receptors have been more extensively characterized than the CRF_2 receptor subtypes. CRF_1 receptors are expressed primarily in the central nervous system, whereas CRF_2 receptors are found primarily in the periphery. Numerous studies have provided evidence that hypersecretion of CRF is associated with various affective disorders including depression and anxiety.[1−5,14] Patients suffering with depression have been found to have elevated levels of CRF in cerebrospinal fluid.[15,16] Successful treatment of depression resulted in normalization of CRF levels.[10,17,18] In addition, experiments with CRF_1 receptor knockout mice have implicated the involvement of CRF_1 receptors in the stress response mediated by the HPA axis.[19] In the presence of increasing levels of CRF, an increase in ACTH secretion was not observed in the pituitary cells of mice lacking the CRF_1 receptor. Experiments showed that intracerebroventricular administration of CRF to rats promoted behavioral effects similar to those observed in anxiety and depression.[8,10,20] In contrast, administration of the peptide-based CRF antagonists α-helical $CRF_{(9-41)}$ and astressin successfully blocked the effects of CRF.[21]

A number of small molecule CRF_1 receptor antagonists, including compounds **1** (CP-154526),[22−25] **2** (DMP696),[26−29] **3** (DMP904),[27,30] and **4** (R121919, also known as NBI-30775),[31−34] have been extensively studied in numerous preclinical behavioral models and were shown to be efficacious in rat models for anxiety and/or depression (Figure 1). These results suggest that CRF_1 receptor antagonists may offer therapeutic potential for the treatment of diseases resulting from elevated levels of CRF such as anxiety and depression. The clinical efficacy results of a small number of CRF_1 receptor antagonists have slowly begun to appear in the literature. The first clinical study published was a small, open-label clinical trial with **4** wherein it was found that depressed patients showed reductions in depression symptoms, as rated by both patients and clinicians.[35] Compound **5** (NBI-34041)[36] was subsequently tested in a placebo-controlled proof-of-concept study designed to evaluate whether subchronic treatment with this

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[a] Abbreviations: CRF, corticotropin-releasing factor; HPA, hypothalamic−pituitary−adrenal; ACTH, adrenocorticotropic hormone; POMC, proopiomelanocortin; SAR, structure−activity relationships; cAMP, cyclic adenosine monophosphate; GSH, glutathione.

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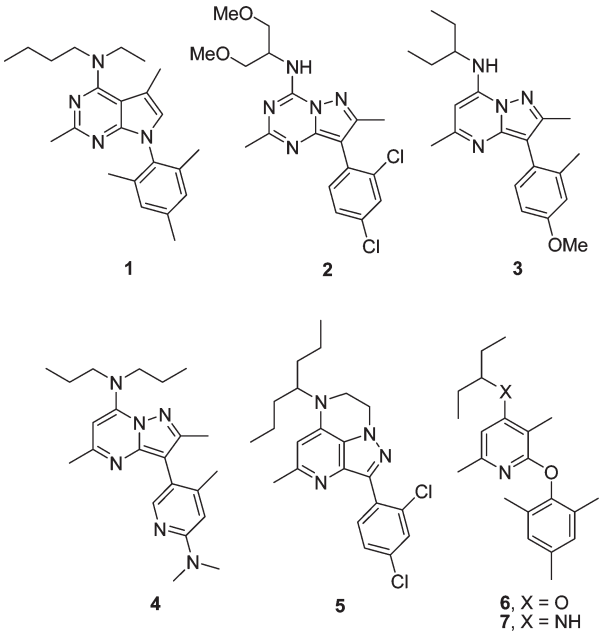


Figure 1. CRF_1 receptor antagonists.

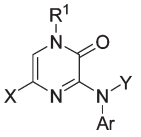


Figure 2. Substituted pyrazinone ring system.

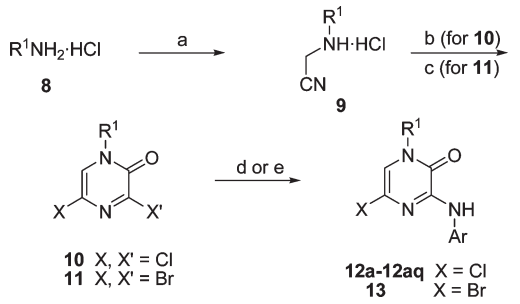
investigational drug would decrease the stress hormone response following a psychological stressor.[37] Briefly, the results of this study indicated that **5** may improve resistance to psychological stress by reducing stress hormone secretion. In a double-blind, placebo-controlled clinical trial to evaluate **6** (CP-316311)[38] for the treatment of major depressive disorder, it was found that the group treated with **6** was not significantly different in the primary efficacy end point from the placebo-treated group, indicating a lack of efficacy.[39] Several additional CRF_1 antagonists, including **7** (CP-376395),[40] are reported to have entered clinical trials but the results have not yet been disclosed.[1] Although the outcome of clinical trials reported to date have been mixed, the prospect that CRF_1 receptor antagonists may offer therapeutic potential for the treatment of diseases resulting from elevated levels of CRF continues to drive efforts to discover and develop viable, structurally diverse CRF_1 receptor antagonists.

In our search for structurally diverse CRF_1 receptor antagonists, we investigated the structure−activity relationships (SAR) of a series of N^3-phenylpyrazinones (Figure 2), a chemotype that was first disclosed in a patent publication.[41] The pyrazinone ring system was an attractive scaffold based on its structural relationship to the well-established pharmacophore model of known CRF_1 receptor antagonists.[6] The synthesis and SAR of these pyrazinone-based compounds is described below.

Results and Discussion

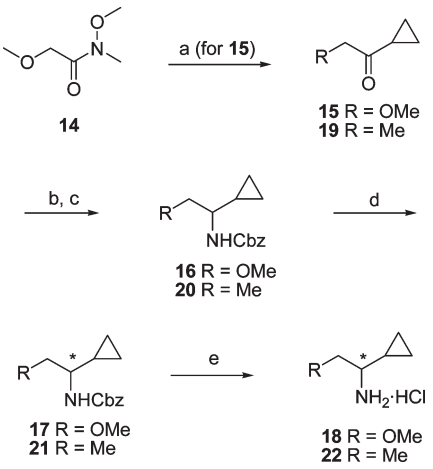
Chemistry. The general synthetic scheme employed to prepare 1-alkyl-3-anilino-5-halopyrazin-2-ones is shown in Scheme 1. Treatment of alkylamine hydrochlorides **8** with chloroacetonitrile in the presence of potassium iodide and potassium carbonate in acetonitrile afforded cyanomethylamines **9** in high

Scheme 1[a]



[a] Reagents and conditions: (a) chloroacetonitrile, KI, K_2CO_3, CH_3CN, 50 °C (84−96%); (b) $(COCl)_2$, toluene, 55 °C (43−76%) or $(COCl)_2$, dioxane/CH_2Cl_2, 55 °C (69−74%); (c) $(COBr)_2$, CH_2Cl_2, 45 °C (64%); (d) base, $ArNH_2$, THF or DMF; (e) $ArNH_2$, $Pd(OAc)_2$, BINAP, K_2CO_3, toluene.

Scheme 2[a]

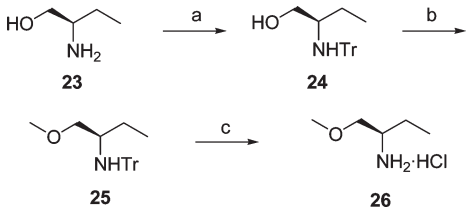


[a] Reagents and conditions: (a) cyclopropylmagnesium bromide, THF (81%); (b) $NaBH(OAc)_3$, $NH_4O_2CCF_3$, THF; (c) benzyl chloroformate, Na_2CO_3, CH_2Cl_2/H_2O, (41−78%, 2 steps); (d) Enantiomers of **16** were separated on a Chiralpak AD column and enantiomers of **20** were separated on a Chiralpak AS column; (e) H_2, Pd/C, 4 N HCl in dioxane, EtOH (95−100%).

yield. The cyanomethylamine intermediate was then heated in the presence of oxalyl chloride in toluene at 55 °C to form dichloropyrazinone intermediates **10**.[42] For analogues with an ether moiety in the R^1 group, improved yields were obtained by heating the reaction mixture at 55 °C in a mixture of dioxane and dichloromethane. Preparation of dibromopyrazinone intermediate **11** was carried out in an analogous fashion whereby cyanomethylamine **9** was treated with oxalyl bromide.[43] Coupling of the dichloro- and dibromopyrazinones **10** and **11**, respectively, with a variety of aryl amines in the presence of a base then furnished the desired products **12** and **13**, respectively.

The various alkylamines from which R^1 was comprised were either purchased, synthesized according to literature references, or synthesized as illustrated in Schemes 2−3.[44] The synthesis of **18** began with addition of cyclopropylmagnesium bromide to (*N*-methyl-*N*-methoxy)methoxyacetamide[45] (**14**) (Scheme 2) to afford cyclopropylmethoxymethyl ketone **15** in 81% yield. The ketone was transformed to **16** via a two-step, one-pot procedure whereby **15** was treated with sodium triacetoxyborohydride in the presence of ammonium trifluoroacejtate. Upon completion of the reaction, the solvent was removed under reduced pressure and the remaining material

Scheme 3[a]



[a] Reagents and conditions: (a) Ph_3CCl, Et_3N, CH_2Cl_2 (82%); (b) NaH, MeI, THF (100%); (c) 2 N HCl in ether, CH_2Cl_2/MeOH (85%).

was taken up in CH_2Cl_2/H_2O with sodium carbonate and was treated with benzyl chloroformate to afford **16** (78% yield, two steps). Separation of **16** into its enantiomers was achieved by chromatography on chiral support to provide **17** in > 99% ee.[46] Removal of the Cbz group by hydrogenation then afforded **18** in quantitative yield.

The synthesis of **22** was completed in three steps as depicted in Scheme 2. Cyclopropylethyl ketone **19**[47] was transformed to **20** as described for the preparation of **16** (41% yield over two steps). Separation of **20** into its enantiomers was achieved by chromatography on chiral support resulting in material with > 99% ee.[48] Removal of the Cbz group by hydrogenation then afforded **22** in high yield.

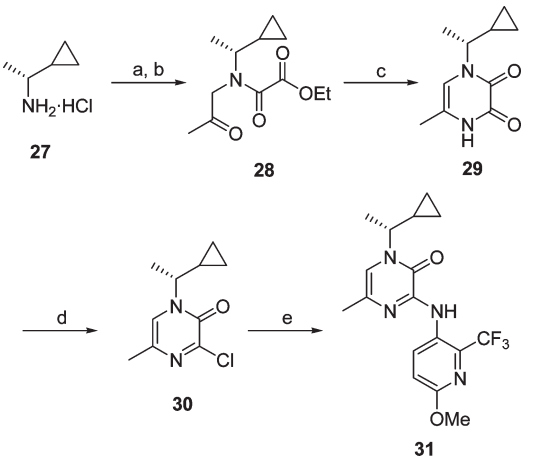
The synthesis of **26** was carried out as illustrated in Scheme 3. Protection of the amine of commercially available aminoalcohol **23** with a triphenylmethyl group proceeded in good yield. Subsequent alkylation with methyl iodide followed by deprotection with HCl in ether afforded the desired product (**26**).

Methyl pyrazinone analogues (X=Me) were prepared by two different methods. In the first method, a four-step procedure was employed to synthesize 3-chloro-5-methylpyrazinone intermediate **30** (Scheme 4). Treatment of **27** with chloroacetone in the presence of potassium carbonate followed by subsequent treatment with ethylchlorooxoacetate afforded **28**. Cyclization was carried out by heating **28** in acetic acid in the presence of ammonium acetate to furnish **29**. Compound **29** was heated at reflux in thionyl chloride with a catalytic amount of DMF to give methylpyrazinone **30** in good yield. Compound **30** was then coupled with an arylamine as described previously to afford **31**.

Alternatively, methylpyrazinone analogue **31** was prepared from the corresponding bromopyrazinone **13** by palladium-catalyzed coupling with methylboronic acid as shown in Scheme 5. Bromopyrazinone **13** also served as an intermediate for other variations at the 5-position of the pyrazinone. Preparation of the *des*-halo analogue was effected by subjecting **13** to Pd/C under hydrogen, resulting in debromination to furnish **32**. Synthesis of the cyanopyrazinone was completed by coupling bromopyrazinone **13** with zinc cyanide in the presence of a palladium catalyst[49] to furnish the desired cyanopyrazinone product (**33**) in good yield. Alkynylpyrazinone **34** was prepared in two steps from **13** via palladium-catalyzed coupling with (trimethyl)silylacetylene followed by basic hydrolysis of the TMS group. Subsequent hydrogenation of the alkyne afforded ethylpyrazinone **35**. Allylpyrazinone **36** was prepared via palladium-catalyzed coupling of **13** with allyltributyltin.

Biology. Compounds were tested in a CRF_1 receptor binding titration assay using rat frontal cortex homogenate in which inhibition of specific binding of [^{125}I]Tyr-ovine-CRF by our test compounds was measured to determine their receptor binding affinity. Selected compounds were

Scheme 4[a]



[a] Reagents and conditions: (a) chloroacetone, K_2CO_3, KI, MeCN (77%); (b) ethyl chlorooxoacetate, pyridine, CH_2Cl_2 (44%); (c) NH_4OAc, HOAc (58%); (d) DMF, $SOCl_2$ (78%); (e) NaHMDS, 3-amino-6-methoxy-2-trifluoromethylpyridine, THF (14%).

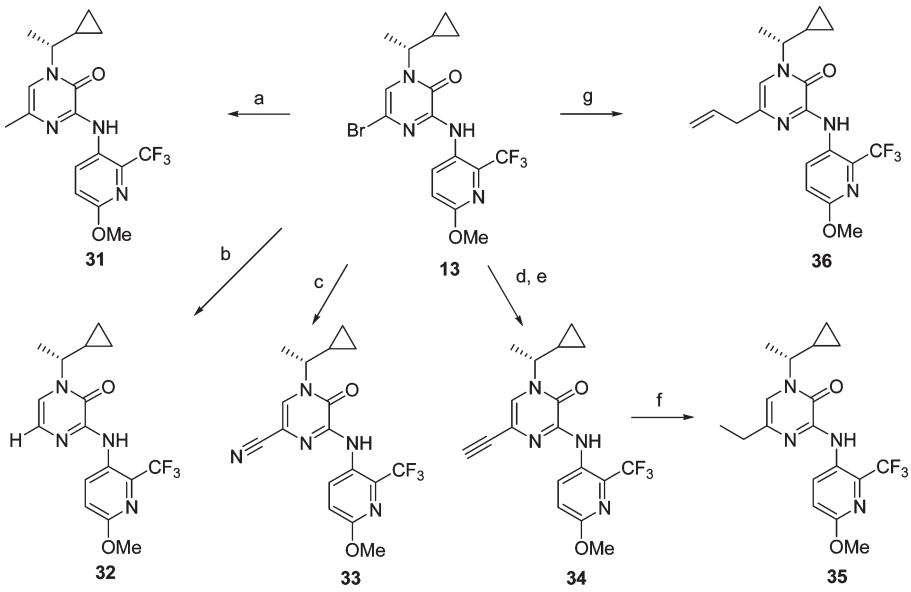
screened for binding affinity at CRF_2 and for their functional activity in Y79 cells to assess antagonist properties. The CRF_2 receptor binding titration assay employed porcine choroid plexus homogenate and [^{125}I]-sauvagine binding inhibition to determine binding affinities. Compounds with appropriate potency were evaluated in pharmacokinetic studies and in the defensive withdrawal model of anxiety in rats.[29,50] In conjunction with the behavioral studies, compounds were examined in an ex vivo binding assay to determine CRF_1 receptor occupancy. In vivo plasma levels after oral dosing were also measured.

The CRF_1 receptor binding affinities for pyrazinone-based analogues are shown in Tables 1−6. Four points of diversity were examined, designated as R^1, X, Y, and Ar in Figure 2. The R^1 substituent SAR is summarized in Table 1 wherein the phenyl group was either a 2,4,6-trimethylphenyl or a 2,5-dimethyl-4-methoxyphenyl group. On the basis of SAR studies in earlier chemotypes, we focused on branched substituents at R^1.

It was found that improved CRF_1 receptor binding affinity was achieved when the branching point was on the carbon atom bonded directly to the pyrazinone ring; compounds with a carbon atom between the pyrazinone nitrogen and branching point were much less potent (e.g., compare **12c** vs **12d** and **12k** vs **12l**). Incorporation of a cyclopropyl group within R^1 resulted in an improvement in potency over the corresponding straight-chain alkyl analogues (compare **12f** vs **12d** and **12n** vs **12l**). A single methoxy group within R^1 was also well-tolerated. A decrease in potency of approximately 30-fold was observed when the methoxy group in compounds **12b** and **12p** was replaced with a hydroxy group (compounds **12j** and **12t**).

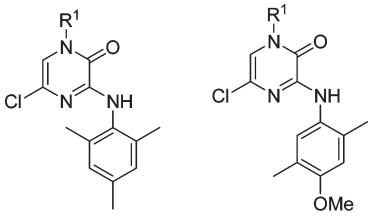
In a limited investigation of the effect of stereogenicity within the R^1 substituent, we found little difference in activity between enantiomers (Table 2). For example, the binding affinities of a pair of enantiomers with a cyclopropyl and methoxymethyl group within R^1 were equivalent (compare **12p** vs **12u**), perhaps due to the cyclopropyl and methoxymethyl groups being fairly similar in size to each other. In some cases, a differential in potency of 2−3 fold was observed (e.g., **12v**/**12w**, **12x**/**12y**, and **12r**/**12z**), but even this was considered a modest difference. Compounds **12p** and

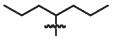
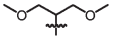
Scheme 5[a]



[a] Reagents and conditions: (a) $MeB(OH)_2$, $Pd(Pt\text{-}Bu_3)_2$, K_2CO_3, dioxane (23%); (b) H_2, 10% Pd/C, EtOH (98%); (c) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, H_2O, DMF (71%); (d) (trimethyl)silylacetylene, $Pd(PPh_3)_4$, Et_3N, DMF, 120 °C, microwave (16%); (e) 10 N NaOH, MeOH (49%); (f) H_2, 10% Pd/C, MeOH (29%); (g) allyltributyltin, $Pd(PPh_3)_4$, toluene, 120 °C, microwave (51%).

Table 1. CRF_1 Receptor Binding Affinity SAR for R^1 Substitution

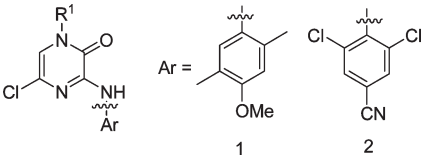


Cmpd	R^1	IC_{50} (nM)[a]	Cmpd	IC_{50} (nM)[a]
12c		39 ± 10	**12k**	76 ± 27
12d		2.9 ± 0.3	**12l**	0.80 ± 0.21
12e		2.4 ± 1.9	**12m**	0.62 ± 0.11
12f		0.63 ± 0.14	**12n**	0.27 ± 0.04
12a		1.7 ± 0.2	**12o**	0.42 ± 0.10
12b		1.3 ± 0.3	**12p**	0.26 ± 0.09
12g		1.4 ± 0.5	**12q**	0.59 ± 0.25
12h		12 ± 3	**12r**	1.7 ± 0.4
12i		16 ± 1	**12s**	2.1 ± 0.2
12j		35 ± 5	**12t**	10 ± 1

[a] All values are the average of at least $n = 3 \pm$ standard deviation. The IC_{50} of *o*-CRF = 2.9 ± 1.0 nM and the IC_{50} of **2** = 1.2 ± 0.2 nM in this assay.

12u were also tested in the CRF_2 receptor binding assay.[51] It was found that both compounds were inactive in this assay (CRF_2 IC_{50} > 10 μM for each compound), indicating that these compounds are selective CRF_1 receptor antagonists.

Table 2. Comparison of CRF_1 Receptor Binding Affinity for Enantiomers

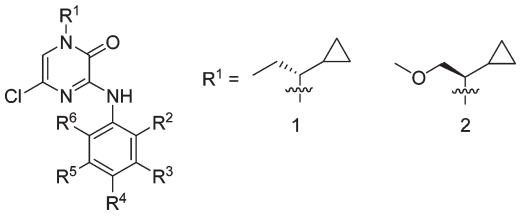


Cmpd	R^1	Aryl	IC_{50} (nM)[a]
12p		1	0.26 ± 0.09
12u		1	0.29 ± 0.10
12v		2	1.2 ± 0.2
12w		2	2.8 ± 0.9
12x		2	2.4 ± 1.1
12y		2	6.3 ± 0.4[b]
12r		1	1.7 ± 0.4
12z		1	5.8 ± 1.8

[a] All values are the average of at least $n = 3 \pm$ standard deviation unless indicated otherwise. [b] Value determined by two measurements.

SAR results of phenyl group substituent modifications are shown in Table 3. A comparison of compounds **12aa** thru **12ac** shows that a 2,4,6-substitution pattern gave optimal CRF_1 receptor binding affinity compared to compounds with a 2,6-substitution pattern or only a 4-substituent. Nearly a 20-fold decrease in potency occurred upon removal of the 4-chloro group (compare **12aa** vs **12ab**),

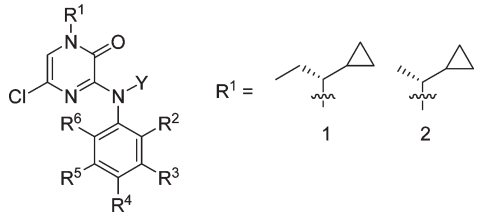
Table 3. Effect of Phenyl Group Substituents on CRF_1 Receptor Binding Affinity



compd	R^1	R^2	R^3	R^4	R^5	R^6	IC_{50} (nM)[a]
12aa	1	Cl	H	Cl	H	Me	0.53 ± 0.18
12ab	1	Cl	H	H	H	Me	9.3 ± 1.3
12ac	1	H	H	Cl	H	H	180 ± 50
12ad	1	Me	H	Me	H	H	6.6 ± 1.4
12f	1	Me	H	Me	H	Me	0.63 ± 0.14
12ae	1	Me	H	Me	Me	H	2.4 ± 0.5
12af	1	Me	H	OMe	H	Me	0.52 ± 0.04
12n	1	Me	H	OMe	Me	H	0.27 ± 0.04
12p	2	Me	H	OMe	Me	H	0.26 ± 0.04
12ag	2	Me	H	OEt	Me	H	1.5 ± 0.6
12ah	2	Me	H	OBn	Me	H	910 ± 160
12ai	2	Me	H	OH	Me	H	280 ± 70

[a] All values are the average of at least $n = 3 \pm$ standard deviation.

Table 4. Effect of Aniline Alkylation on CRF_1 Receptor Binding Affinity

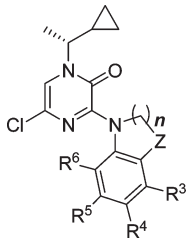


compd	R^1	R^2	R^3	R^4	R^5	R^6	Y	IC_{50} (nM)[a]
12ae	1	Me	H	Me	Me	H	H	2.4 ± 0.5
12aj	1	Me	H	Me	Me	H	Et	1.5 ± 0.3
12f	1	Me	H	Me	H	Me	H	0.63 ± 0.14
12ak	1	Me	H	Me	H	Me	Et	4.6 ± 1.4
12al	2	Cl	H	OMe	H	Cl	H	1.1 ± 0.1
12am	2	Cl	H	OMe	H	Cl	Et	34 ± 7

[a] All values are the average of at least $n = 3 \pm$ standard deviation.

and when both ortho substituents in **12aa** were removed, a decrease in potency greater than 300-fold was observed (**12ac**). On the basis of these results, we concluded that an ortho substituent was required to achieve good binding affinity to the CRF_1 receptor. This observation has been reported in the literature for other chemotypes as well. A compound with a 2,4-dimethylphenyl group (**12ad**) was approximately 10-fold less potent than the corresponding 2,4,6-trimethylphenyl analogue (**12f**). In contrast to the 2,4-dimethyl substituted analogue (**12ad**), analogues with a 2,4,5-substitution pattern were similar in potency to comparable 2,4,6-substituted analogues (compare **12ae** vs **12f** and **12n** vs **12af**[52]). Variation of the 4-methoxy group on the 2,4,5-substituted phenyl group was examined with compounds **12p**, **12ag**, and **12ah**. The results suggested limited steric tolerance at R^4, with potency decreasing as the substituent at R^4 increased in size.[53] In addition, polar groups at R^4 were not well tolerated, as illustrated by compound **12ai**.

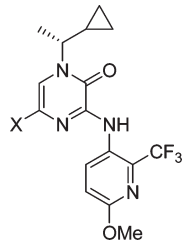
Table 5. Effect of Tieback Modifications of the Phenyl Group on CRF_1 Receptor Binding Affinity



compd	Z	*n*	R^3	R^4	R^5	R^6	IC_{50} (nM)[a]
12an	CH_2	1	H	OMe	H	Cl	0.62 ± 0.23
12ao	CH_2	1	H	OMe	H	Br	0.94 ± 0.20
12ap	O	2	H	OMe	H	Br	19 ± 3

[a] All values are the average of at least $n = 3 \pm$ standard deviation.

Table 6. CRF_1 Receptor Binding Affinity SAR for Substitution at X



compd	X	IC_{50} (nM)[a]
32	H	150 ± 70
12aq	Cl	1.8 ± 0.4
13	Br	1.2 ± 0.3
31	Me	3.8 ± 2.1
33	C≡N	6.7 ± 1.0
34	C≡CH	5.6 ± 2.4
35	Et	180 ± 20
36	allyl	1200 ± 400

[a] All values are the average of at least $n = 3 \pm$ standard deviation.

A group of compounds was prepared to determine the effect of alkylation of the aniline nitrogen (Table 4). In the 2,4,5-substituted aryl series, alkylation was well-tolerated (compare **12ae** vs **12aj**) whereas in the 2,4,6-substituted aryl series, alkylation led to an 8−30-fold decrease in potency (compare **12f** vs **12ak** and **12al** vs **12am**). Analogues were also prepared to determine the effect of tying back the ethyl substituent at Y to form a bicyclic ring system (Table 5).[54] The two indoline derivatives,[55] **12an** and **12ao**, were similar in potency to **12al** and much more potent than the corresponding *N*-ethyl analogue **12am**. When the indoline was replaced with a 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine ring system[56] (**12ap**), a 20-fold decrease in binding affinity was observed.

The SAR of substituents at X was explored with a series of compounds containing the 1-(*R*)-cyclopropylethyl group at R^1 (Table 6). Compound **32**[57] with a hydrogen at X was approximately 100-fold less potent than the corresponding chloro analogue **12aq**. Replacement of the chloro group with a nitrile or an alkyne resulted in a 3- to 4-fold decrease in potency. The limited steric tolerance at this position was evident by the 100- and 700-fold decrease in potencies when the chloro group was replaced by an ethyl or allyl group, respectively. Thus, the SAR results indicate the need for a small lipophilic group at X.

Table 7. Discrete Pharmacokinetic Properties of **12p** in Rats and Cynomolgus Monkeys

PK parameters	**12p** in rats	**12p** in monkeys
iv dose (2 mg/kg)[a]		
Cl (mL/min/kg)	170	21
V_{ss} (L/kg)	97	7.7
$t_{1/2}$ (h)	18	9.3
po dose (10 mg/kg)[b]		
AUC (nM·h)	360	410
C_{max} (nM)	52	32
F%	14	2

[a] Vehicle: PEG/ethanol, 90:10 (v/v); $n = 2$ animals. [b] Vehicle: 1% Tween 80 in 0.5% methylcellulose; $n = 3$ animals.

Compound **12p** was chosen for further evaluation due to its excellent potency ($IC_{50} = 0.26$ nM). The measured logD of **12p** was 4.35 at pH = 7.4.[58] It was determined by equilibrium dialysis that **12p** was 2.1% unbound in plasma. In a cell-based functional assay, the antagonist properties of **12p** were assessed by measuring inhibition of CRF-stimulated cyclic adenosine monophosphate (cAMP) production in human Y-79 retinoblastoma cells. **12p** produced a concentration-dependent inhibition of CRF (1nM)-induced cAMP production with an IC_{50} value of 1.9 ± 0.6 nM and completely suppressed CRF-stimulated cAMP production at higher concentrations, indicating that this compound behaves as an antagonist. No agonist properties were detected at concentrations up to 10 μM. In addition, **12p** was not active in a CRF_2 receptor binding assay (vide supra), indicating that this compound is a selective CRF_1 receptor antagonist.

Shown in Table 7 is the pharmacokinetic profile of **12p** after iv (2 mg/kg) and oral dosing (10 mg/kg) in male Sprague–Dawley rats and Cynomolgus monkeys. The results indicate that in rats **12p** was a high clearance compound with a clearance higher than hepatic blood flow (55 mL/min/kg). The long half-life of this compound is likely due to its large volume of distribution, which in turn can be ascribed to its lipophilic nature. **12p** had modest oral bioavailability in rats (F% = 14). **12p** was a moderate clearance compound in monkeys (47% of hepatic blood flow), and had a much lower volume of distribution compared to that in rats. However, **12p** had only 2% oral bioavailability in monkeys.

Compound **12p** was tested in rats in the defensive withdrawal test to determine behavioral efficacy and efficacious plasma concentrations.[29,50] This experiment was carried out by measuring the time required for a rat to emerge from a darkened chamber placed within an open, illuminated field. A compound was considered to be efficacious if the latency time period to emerge from the chamber was significantly reduced relative to that of vehicle-treated animals. It was found in previous studies with **2** that the in vitro IC_{50} was similar to the plasma-free concentration of **2** corresponding to 50% CRF_1 receptor occupancy (in vivo IC_{50}).[28] In turn, CRF_1 receptor occupancy greater than 50% was associated with anxiolytic efficacy in the defensive withdrawal test. Figure 3 and Table 8 summarize the results of the behavioral studies for **12p** following oral dosing at 1, 3, and 10 mg/kg. CRF_1 receptor occupancy in the parietal cortex was determined by ex vivo autoradiography.[28] Figure 3 shows exit latencies for each dose at 60 min after oral administration of **12p** or the positive control compound **2** (dosed at 10 mg/kg). The results showed that **12p** was effective at reducing exit latency at 3 and 10 mg/kg ($n = 8$). The lowest

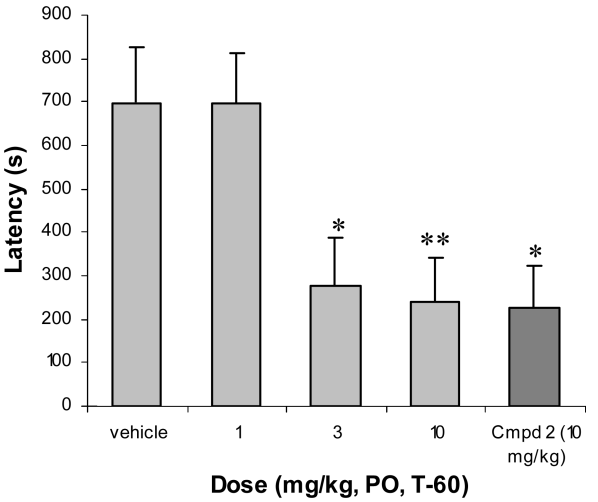


Figure 3. Anxiolytic-like effects of **12p** in the defensive withdrawal test in rats at 1, 3, and 10 mg/kg with **2** as a positive control, * $p < 0.05$ vs vehicle, ** $p < 0.01$ vs vehicle.

Table 8. Mean Total and Plasma Free Concentrations and CRF_1 Receptor Occupancies in the Defensive Withdrawal Test in Rats Following Oral Doses of Compound **12p**

oral dose (mg/kg)	mean total plasma conc (nM)[a,b]	mean plasma free conc (nM)[a,c]	CRF_1 receptor occupancy (%)[a,d,e]	% decrease in exit latency[b]
1	4.9 ± 4.5	0.10 ± 0.09	37 ± 8	< 5
3	14 ± 9	0.29 ± 0.20	72 ± 10	60[f]
10	76 ± 36	1.6 ± 0.8	94 ± 8	65[g]

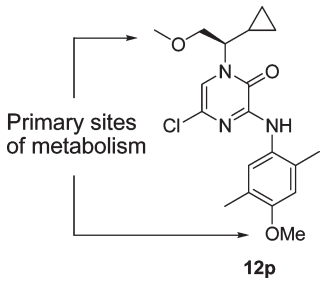
[a] ±SEM. [b] $n = 8$. [c] Based on an unbound fraction of 2.1% in plasma determined by equilibrium dialysis. [d] $n = 4$. [e] Receptor occupancy of **2** at 10 mg/kg = 92 ± 5. [f] $p < 0.05$ vs vehicle. [g] $p < 0.01$ vs vehicle.

effective dose of 3 mg/kg decreased exit latency by 60% relative to vehicle treated controls. **12p** decreased exit latency by 65% at the higher dose of 10 mg/kg. **12p** occupied 72% and 94% of CRF_1 receptors ($n = 4$) at doses of 3 and 10 mg/kg, respectively. The mean plasma free concentrations were similar to, or greater than, the in vitro IC_{50} (0.26 nM) at doses of 3 and 10 mg/kg (Table 8).

Because of the high clearance of **12p** in rats, a metabolite ID study was conducted in human and rat liver microsomes. LC/MS analysis of metabolites formed in microsomal incubations suggested that the three major metabolites were *O*-demethylation of the upper methoxy group, *O*-demethylation of the lower methoxy group, and *O*-demethylation of both. Oxidation of the pyrazinone ring was only a minor metabolite. In a trapping experiment performed to detect the potential for reactive metabolite formation, **12p** was incubated with NADPH fortified human and rat liver microsomes for 30 min at a concentration of 10 μM in the presence of glutathione (GSH) to trap potential reactive intermediates. The resulting GSH adducts formed via pyrazinone oxidation accounted for < 1% of drug related materials. The results of this study provided us with a starting point from which to further optimize this class of compounds.

Conclusion

In conclusion, efforts to identify structurally diverse CRF_1 receptor antagonists led to the discovery of pyrazinone-based compounds. Highly potent analogues with subnanomolar



12p

Figure 4. Summary of the metabolite ID study with compound **12p**.

binding affinity have been identified. In particular, **12p** was a high affinity CRF_1 receptor antagonist ($IC_{50} = 0.26$ nM) and a potent inhibiter of CRF-stimulated cAMP production in human Y-79 retinoblastoma cells ($IC_{50} = 1.9$ nM). Compound **12p** was a high clearance compound in rats and a moderate clearance compound in monkeys; nevertheless, **12p** showed efficacy in the defensive withdrawal model of anxiety at a minimally efficacious dose of 3 mg/kg. A metabolite ID study with **12p** indicated that the major metabolites were the result of *O*-demethylation. Further optimization of the pharmacokinetic properties of pyrazinone-based CRF_1 receptor antagonists will be reported.

Experimental Section

Chemistry. All procedures were carried out under a nitrogen atmosphere unless otherwise indicated using anhydrous solvents purchased from commercial sources without further purification. Reactions requiring anhydrous conditions were performed in glassware, which was flame-dried or oven-dried and placed under a nitrogen atmosphere. Column chromatography was performed on silica gel using the solvent systems indicated. Solvent systems are reported as v/v percent ratios. All reactions were monitored by TLC using EM Science, 0.25 mm, precoated silica gel plates or by LC/MS. Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise indicated. Melting points were obtained on a Laboratory Devices, Inc. Mel Temp 3.0 melting point apparatus and are uncorrected. Proton NMR spectra were recorded on either a Varian (Palo Alto, CA) Inova 300, 400, or 500 MHz or Bruker 400 or 500 MHz NMR spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane. Atmosphere pressure chemical ionization (APCI) low-resolution mass spectra were obtained on a Finnigan Navigator LC/MS single-quadrupole mass spectrometer. Electrospray ionization (ESI) high-resolution mass spectra were obtained on a Finnigan MAT95S or Thermo Scientific MAT900 mass spectrometer. All final products had a purity of ≥95%. The purity of final products was determined by either combustion analysis or HPLC. Combustion analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. HPLC purity was measured using two methods for each compound. Method A: Phenominex analytical C18 column (4.6 mm × 50 mm, 5 μm); mobile phase: A = H_2O with 0.1% TFA, B = acetonitrile with 0.1% TFA, 0−1 min, 20% B; 1−7 min, 20% B→ 95% B; 7−8 min, 95% B; flow rate = 3 mL/min; $\lambda = 254$ nm; run time = 8 min. Method B: Phenominex analytical Synergi polar RP(phenoxy) column (4.6 mm × 50 mm, 4 μm); mobile phase: A = 90% H_2O/10% methanol with 0.1% TFA, B = 90% methanol/10% H_2O with 0.1% TFA, 0−4 min, 40% B → 100% B; 4−6 min, 100% B; flow rate = 4 mL/min; $\lambda = 254$ nm; run time = 6 min.

General Procedure for Alkylaminonitrile Formation (9). (*R*)-2-(1-Cyclopropylethylamino)acetonitrile Hydrochloride (9a). To a suspension of (*R*)-1-cyclopropylethylamine (8.53 g, 70.5 mmol) in anhydrous acetonitrile (165 mL) at room temperature was added potassium carbonate (29.10 g, 77.6 mmol), potassium iodide (12.78 g, 77.6 mmol), and chloroacetonitrile (4.5 mL, 70.5 mmol). The reaction mixture was heated at 50 °C for 16 h with vigorous stirring. The resulting mixture was then cooled to room temperature and was filtered through a pad of celite with acetonitrile rinsing. The filtrate was concentrated, and the product was purified by column chromatography on silica gel (3% methanol in dichloromethane) to give a brown oil (8.1 g). The oil was dissolved in diethyl ether (140 mL) and then converted to the hydrochloride salt by the addition of 2 M HCl in diethyl ether (60 mL). The mixture was cooled to 0 °C, and the solid was collected on a Buchner funnel with ether rinsings and was dried under vacuum to give (*R*)-2-(1-cyclopropylethylamino)acetonitrile hydrochloride (**9a**) (9.54 g, 85% yield) as pale-yellow solid: mp 115−116.1 °C; $[\alpha]^{25}_D$ +25.0 (*c* 0.779, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s br, 2H), 4.14 (s, 2H), 2.41−2.36 (m, 1H), 1.25 (d, $J = 6.8$ Hz, 3H), 0.91−0.82 (m, 1H), 0.62−0.55 (m, 1H), 0.55−0.41 (m, 2H), 0.24−0.18 (m, 1H). LRMS (ESI) *m*/*e* 125.0 [$(M+H)^+$, calcd for $C_7H_{13}N_2$ 125.1].

All alkylaminonitrile intermediates of structure **9** (corresponding to the R^1 groups in compounds **12a**−**12i**, **12u**, **12w**, **12y**, and **12z**) were prepared by the above procedure using appropriate starting materials. In some cases, the hydrochloride salt did not precipitate from the solution. In these cases, the mixture was concentrated and then reconcentrated from hexanes (2×) and dried under vacuum to give a viscous oil. The oil was placed in the freezer overnight to give the corresponding hydrochloride salt as a solid.

General Procedures for Dichloropyrazinone Formation (10). Method A: (*R*)-3,5-Dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (10a). Oxalyl chloride (12.7 mL, 147.0 mmol) was added via syringe to a suspension of (*R*)-2-(1-cyclopropylethylamino)acetonitrile hydrochloride (**9a**) (4.71 g, 29.4 mmol) in toluene (130 mL) at 0 °C. After the addition was complete, the cooling bath was removed and the reaction mixture was heated at 55 °C for 16 h. The mixture was then cooled to room temperature and concentrated. The residue was transferred directly onto a silica gel column in a fume hood (caution: column chromatography of the crude product should be performed in a fume hood because some gas evolution occurred as residual oxalyl chloride decomposed) and was eluted (20% ethyl acetate in hexanes) to give (*R*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**10a**) (5.08 g, 74% yield) as a colorless solid: mp 104.5−105.5 °C; $[\alpha]^{25}_D$ −27.5 (*c* 0.454, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 4.26−4.20 (m, 1H), 1.46 (d, $J = 6.9$ Hz, 3H), 1.13−1.05 (m, 1H), 0.85−0.77 (m, 1H), 0.66−0.59 (m, 1H), 0.57−0.50 (m, 1H), 0.39−0.33 (m, 1H). LRMS (APCI) *m*/*e* 233.0 [$(M + H)^+$, calcd for $C_9H_{11}N_2OCl_2$ 233.0].

Method B: (*R*)-3,5-Dichloro-1-(1-cyclopropyl-2-methoxyethyl) pyrazin-2(1*H*)-one (10b). To a solution of (*R*)-2-(1-cyclopropyl-2-methoxyethylamino)acetonitrile hydrochloride (**9b**) (6.00 g, 31.7 mmol) in dioxane (75 mL) was added CH_2Cl_2 (50 mL). The mixture was cooled to 0 °C, and oxalyl chloride (13.6 mL, 159 mmol) was added slowly via syringe. After the addition was complete, the cooling bath was removed and the reaction mixture was heated at 55 °C for 16 h. The mixture was cooled to room temperature and concentrated. The residue was transferred directly onto a silica gel column in a fume hood (caution: column chromatography of the crude product should be performed in a fume hood because some gas evolution occurred as residual oxalyl chloride decomposed) and was eluted (20% → 25% ethyl acetate in hexanes) to give (*R*)-3,5-dichloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1*H*)-one (**10b**) (6.10 g, 74% yield) as a colorless solid: mp 108.5−109.5 °C; $[\alpha]^{25}_D$ +90.9 (*c* 0.481, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 4.13−4.08 (m, 1H), 3.73 (dd, $J_{AB} = 10.3$, $J_{AX} = 4.4$ Hz, 1H), 3.63 (dd, $J_{BA} = 10.3$, $J_{BX} = 3.0$ Hz, 1H), 3.33 (s, 3H), 1.43−1.35 (m, 1H), 0.84−0.77 (m, 1H), 0.67−0.60 (m, 1H), 0.55−0.49 (m, 1H), 0.33−0.27 (m, 1H). LRMS (APCI) *m*/*e* 263.2 [$(M + H)^+$, calcd for $C_{10}H_{13}N_2O_2Cl_2$ 263.0].

Remaining dichloropyrazinone intermediates of structure **10** (**10c**−**10i** and **10k**−**10m** with R^1 groups corresponding to those in compounds **12c**−**12i**, **12w**, **12y**, and **12z**) were prepared by method A using appropriate starting materials. The dichloropyrazinone intermediate **10j** (with an R^1 group corresponding to that in compound **12u**) was prepared by method B. Experimental procedures for the preparation of these dichloropyrazinone intermediates are included in the Supporting Information.

(*R*)-3,5-Dibromo-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (11). To a suspension of (*R*)-2-(1-cyclopropylethylamino)acetonitrile hydrochloride (**9a**) (2.50 g, 15.56 mmol) in CH_2Cl_2 (25 mL) at −78 °C was added oxalyl bromide (23.3 mL, 44.7 mmol, 2 M in CH_2Cl_2) via syringe. The reaction mixture was allowed to warm to room temperature and was then heated at 45 °C for 18 h. The mixture was cooled to room temperature and concentrated. The residue was transferred directly onto a silica gel column in a fume hood (caution: column chromatography of the crude product should be performed in a fume hood because some gas evolution occurred as residual oxalyl bromide decomposed) and was eluted (20% ethyl acetate in hexanes) to afford (*R*)-3,5-dibromo-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**11**) (3.18 g, 64% yield) as a colorless solid: mp 130.5−131.5 °C; $[\alpha]^{25}_D$ −26.9 (*c* 0.617, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 4.21−4.16 (m, 1H), 1.43 (d, J = 6.7 Hz, 3H), 1.10−1.05 (m, 1H), 0.82−0.76 (m, 1H), 0.62−0.57 (m, 1H), 0.52−0.47 (m, 1H), 0.36−0.32 (m, 1H). LRMS (APCI) *m*/*e* 321.1 $[(M + H)^+$, calcd for $C_9H_{11}N_2OBr_2$ 320.9].

General Procedures for Coupling of the Dichloropyrazinones with Anilines (12). Method A: (*R*)-5-Chloro-1-(1-cyclopropylethyl)-3-(2,4,6-trimethylphenylamino)pyrazin-2(1*H*)-one (12a). To a mixture of (*R*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**10a**) (200 mg, 0.858 mmol) and 2,4,6-trimethylaniline (0.120 mL, 0.858 mmol) in THF (4 mL) at 0 °C was added NaHMDS (1.802 mL, 1.802 mmol, 1 M in THF) slowly while maintaining the temperature of the reaction mixture below 10 °C. The reaction was stirred at 0 °C for 2 h. The mixture was transferred to a separatory funnel containing saturated aq $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with ethyl acetate (3× 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (20 → 30% ethyl acetate in hexanes) to afford **12a** (230 mg, 81% yield) as a yellow solid: $[\alpha]^{25}_D$ −19.1 (*c* 0.254, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 6.94 (s, 2H), 6.80 (s, 1H), 4.32−4.26 (m, 1H), 2.31 (s, 3H), 2.22 (s, 6H), 1.46 (d, J = 6.6 Hz, 3H), 1.18−1.14 (m, 1H), 0.83−0.75 (m, 1H), 0.65−0.57 (m, 1H), 0.56−0.45 (m, 1H), 0.45−0.38 (m, 1H). HRMS (ESI) *m*/*e* 332.1543 $[(M + H)^+$, calcd for $C_{18}H_{23}N_3OCl$ 332.1530]. HPLC method A: t_R = 5.80 min, > 99%; method B: t_R = 3.47 min, 98.9%.

Method B: (*R*)-3,5-Dichloro-4-[6-chloro-4-(1-cyclopropylpropyl)-3-*oxo*-3,4-dihydropyrazin-2-ylamino]benzonitrile (12v). To a solution of 4-amino-3,5-dichlorobenzonitrile (93 mg, 0.500 mmol) in DMF (1 mL) at 0 °C was added NaH (30 mg, 0.75 mmol, 60% in mineral oil). After stirring for 20 min, (*R*)-3,5-dichloro-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (**10f**) (123 mg, 0.500 mmol) dissolved in DMF (1 mL) was then added via cannula. The reaction mixture was warmed to room temperature and was then heated at 55 °C for 16 h. The reaction mixture was cooled to room temperature and was transferred to a separatory funnel containing ether (25 mL). The organic layer was washed with water (4 × 5 mL), brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on silica gel (5% → 10% ethyl acetate in hexanes) to afford **12v** (92 mg, 46% yield) as a colorless solid: mp 237−237.5 °C; $[\alpha]^{25}_D$ −14.3 (*c* 0.279, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.72 (s, 2H), 6.92 (s, 1H), 4.12−4.03 (m, 1H), 1.97−1.82 (m, 2H), 1.15−1.04 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H), 0.87−0.80 (m, 1H), 0.60−0.53 (m, 2H), 0.38−0.31 (m, 1H). HRMS (ESI) *m*/*e* 397.0406 $[(M+H)^+$, calcd for $C_{17}H_{16}N_4OCl_3$ 397.0390]. HPLC method A: t_R = 5.60 min, > 99%, method B: t_R = 3.73 min, > 99%. (Improved yields could be obtained using 2.2 eq. of NaH.)

Method C: (*R*)-5-Chloro-1-(1-cyclopropylpropyl)-3-(2,4,5-trimethylphenylamino)pyrazin-2(1*H*)-one (12ae). To a solution of (*R*)-3,5-dichloro-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (**10f**) (150 mg, 0.610 mmol), prepared according to the procedure described for **10a** using appropriate starting materials, 2,4,5-trimethylaniline (83 mg, 0.610 mmol) and K_2CO_3 (590 mg, 4.30 mmol) in toluene (2 mL) in an oven-dried round-bottom flask under N_2 was added $Pd(OAc)_2$ (7 mg, 0.031 mmol) and BINAP (20 mg, 0.031 mmol). The reaction mixture was heated at reflux for 5 h. The reaction mixture was cooled to room temperature and was transferred to a separatory funnel containing saturated aq $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to give **12ae** (150 mg, 71% yield) as an orange solid: $[\alpha]^{25}_D$ −11.9 (*c* 0.371, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.06 (s, 1H), 6.95 (s, 1H), 6.74 (s, 1H), 4.05−3.99 (m, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H), 1.96−1.74 (m, 2H), 1.09−1.00 (m, 1H), 0.92 (t, J = 7.5 Hz, 3H), 0.78−0.73 (m, 1H), 0.58−0.45 (m, 2H), 0.32−0.25 (m, 1H). HRMS (ESI) *m*/*e* 346.1677 $[(M + H)^+$, calcd for $C_{19}H_{25}N_3OCl$ 346.1686]. Anal. ($C_{19}H_{24}N_3OCl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropyl-2-methoxyethyl)-3-(2,4,6-trimethylphenylamino)pyrazin-2(1*H*)-one (12b). Compound **12b** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1*H*)-one (**10b**) (50 mg, 0.190 mmol) and 2,4,6-trimethylaniline (26 mg, 0.190 mmol). The product was purified by column chromatography to afford **12b** (45 mg, 65% yield) as a colorless solid: $[\alpha]^{25}_D$ +37.3 (*c* 0.364, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 6.90 (s, 2H), 6.86 (s, 1H), 4.21−4.16 (m, 1H), 3.73 (dd, J_{AB} = 10.3, J_{AX} = 5.8 Hz, 1H), 3.68 (dd, J_{BA} = 10.3, J_{BX} = 3.5 Hz, 1H), 3.35 (s, 3H), 2.27 (s, 3H), 2.19 (s, 6H), 1.32−1.24 (m, 1H), 0.79−0.73 (m, 1H), 0.64−0.57 (m, 1H), 0.53−0.47 (m, 1H), 0.39−0.34 (m, 1H). HRMS (ESI) *m*/*e* 362.1637 $[(M + H)^+$, calcd for $C_{19}H_{25}N_3O_2Cl$ 362.1635]. Anal. ($C_{19}H_{24}N_3O_2Cl$) C, H, N.

5-Chloro-1-(2-ethylbutyl)-3-(2,4,6-trimethylphenylamino)pyrazin-2(1*H*)-one (12c). Compound **12c** was prepared according to the procedure described for the synthesis of **12a** (method A) using 3,5-dichloro-1-(2-ethylbutyl)pyrazin-2(1*H*)-one (**10c**) (100 mg, 0.400 mmol) and 2,4,6-trimethylaniline (54 mg, 0.400 mmol). The product was purified by column chromatography to afford **12c** (52 mg, 37% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.90 (s, 2H), 6.51 (s, 1H), 3.77 (d, J = 7.6 Hz, 2H), 2.27 (s, 3H), 2.17 (s, 6H), 1.82−1.77 (m, 1H), 1.41−1.34 (m, 4H), 0.93 (t, J = 7.3 Hz, 6H). HRMS (ESI) *m*/*e* 348.1845 $[(M+H)^+$, calcd for $C_{19}H_{27}N_3OCl$ 348.1843]. HPLC method A: t_R = 6.56 min, > 99%; method B: t_R = 3.85 min, 96.4%.

5-Chloro-1-(1-ethylpropyl)-3-(2,4,6-trimethylphenylamino)pyrazin-2(1*H*)-one (12d). Compound **12d** was prepared according to the procedure described for the synthesis of **12a** (method A) using 3,5-dichloro-1-(pentan-3-yl)pyrazin-2(1*H*)-one (**10d**) (50 mg, 0.210 mmol) and 2,4,6-trimethylaniline (28 mg, 0.210 mmol). The product was purified by column chromatography to afford **12d** (40 mg, 67% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 6.91 (s, 2H), 6.46 (s, 1H), 4.79−4.75 (m, 1H), 2.27 (s, 3H), 2.18 (s, 6H), 1.82−1.73 (m, 2H), 1.68−1.57 (m, 2H), 0.88 (t, J = 7.3 Hz, 6H). HRMS (ESI) *m*/*e* 334.1678 $[(M+H)^+$, calcd for $C_{18}H_{25}N_3OCl$ 334.1686]. HPLC method A: t_R = 6.03 min, > 99%; method B: t_R = 3.51 min, > 99%.

5-Chloro-1-(1-propylbutyl)-3-(2,4,6-trimethylphenylamino)-pyrazin-2(1*H*)-one (12e). Compound **12e** was prepared according to the procedure described for the synthesis of **12a** (method A) using 3,5-dichloro-1-(heptan-4-yl)pyrazin-2(1*H*)-one (**10e**) (150 mg, 0.570 mmol) and 2,4,6-trimethylaniline (77 mg, 0.570 mmol). The product was purified by column chromatography to afford **12e**

(115 mg, 56% yield) as a colorless solid: mp 189.6−190.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 6.94 (s, 2H), 6.52 (s, 1H), 5.01−4.96 (m, 1H), 2.31 (s, 3H), 2.21 (s, 6H), 1.71−1.62 (m, 4H), 1.37−1.22 (m, 4H), 0.95 (t, J = 7.3 Hz, 6H). HRMS (ESI) m/e 362.2021 [$(M + H)^+$, calcd for $C_{20}H_{29}N_3OCl$ 362.1999]. Anal. ($C_{20}H_{28}N_3OCl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropylpropyl)-3-(2,4,6-trimethylphenylamino)pyrazin-2(1*H*)-one (12f). Compound **12f** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (**10f**) (120 mg, 0.486 mmol) and 2,4,6-trimethylaniline (66 mg, 0.486 mmol). The product was purified by column chromatography to afford **12f** (72 mg, 43% yield) as a colorless solid: mp 181−182 °C; $[\alpha]^{25}_D$ −12.1 (*c* 0.382, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 6.94 (s, 2H), 6.72 (s, 1H), 4.09−4.05 (m, 1H), 2.31 (s, 3H), 2.22 (s, 6H), 1.94−1.80 (m, 2H), 1.10−1.02 (m, 1H), 0.97 (t, J = 7.7 Hz, 3H), 0.82−0.79 (m, 1H), 0.58−0.52 (m, 2H), 0.40−0.35 (m, 1H). HRMS (ESI) m/e 346.1705 [$(M + H)^+$, calcd for $C_{19}H_{25}N_3OCl$ 346.1686]. Anal. ($C_{19}H_{24}N_3OCl$) C, H, N.

(*R*)-5-Chloro-1-[1-(methoxymethyl)propyl]-3-(2,4,6-trimethylphenylamino)pyrazin-2(1*H*)-one (12g). Compound **12g** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-methoxybutan-2-yl) pyrazin-2(1*H*)-one (**10g**) (50 mg, 0.200 mmol) and 2,4,6-trimethylaniline (27 mg, 0.200 mmol). The product was purified by column chromatography to afford **12g** (20 mg, 30% yield) as a colorless solid: $[\alpha]^{25}_D$ −38.7 (*c* 0.336, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.90 (s, 2H), 6.71 (s, 1H), 4.97−4.93 (m, 1H), 3.64 (dd, J_{AB} = 10.5, J_{AX} = 6.0 Hz, 1H), 3.56 (dd, J_{BA} = 10.5, J_{BX} = 3.5 Hz, 1H), 3.35 (s, 3H), 2.27 (s, 3H), 2.18 (s, 6H), 1.88−1.82 (m, 1H), 1.78−1.72 (m, 1H), 0.93 (t, J = 7.6 Hz, 3H). HRMS (ESI) m/e 350.1646 [$(M + H)^+$, calcd for $C_{18}H_{25}N_3O_2Cl$ 350.1635]. Anal. ($C_{18}H_{24}N_3O_2Cl$) C, H, N.

(*R*)-5-Chloro-1-(2-methoxy-1-methylethyl)-3-(2,4,6-trimethylphenylamino)pyrazin-2(1*H*)-one (12h). Compound **12h** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-methoxypropan-2-yl)pyrazin-2(1*H*)-one (**10h**) (140 mg, 0.625 mmol) and 2,4,6-trimethylaniline (85 mg, 0.625 mmol). The product was purified by column chromatography to afford **12h** (31 mg, 15% yield) as a light-brown oil: $[\alpha]^{25}_D$ + 36.2 (*c* 0.350, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 6.94 (s, 2H), 6.77 (s, 1H), 5.23−5.20 (m, 1H), 3.63−3.60 (m, 2H), 3.40 (s, 3H), 2.31 (s, 3H), 2.21 (s, 6H), 1.44 (d, J = 7.0 Hz, 3H). HRMS (ESI) m/e 336.0787 [$(M + H)^+$, calcd for $C_{17}H_{23}N_3O_2Cl$ 336.1479]. HPLC method A: t_R = 5.18 min, 99.3%; method B: t_R = 3.10 min, > 99%.

5-Chloro-1-[2-methoxy-1-(methoxymethyl)ethyl]-3-(2,4,6-trimethylphenylamino)pyrazin-2(1*H*)-one (12i). Compound **12i** was prepared according to the procedure described for the synthesis of **12a** (method A) using 3,5-dichloro-1-(1,3-dimethoxypropan-2-yl)pyrazin-2(1*H*)-one (**10i**) (267 mg, 1.00 mmol) and 2,4,6-trimethylaniline (168 mg, 1.20 mmol). The product was purified by column chromatography to afford **12i** (126 mg, 35% yield) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.93 (s, 2H), 6.89 (s, 1H), 5.24−5.20 (m, 1H), 3.78 (dd, J_{AB} = 10.5, J_{AX} = 6.2 Hz, 2H), 3.71 (dd, J_{BA} = 10.4, J_{BX} = 4.7 Hz, 2H), 3.40 (s, 6H), 2.31 (s, 3H), 2.22 (s, 6H). HRMS (ESI) m/e 366.1580 [$(M + H)^+$, calcd for $C_{18}H_{25}N_3O_3Cl$ 366.1584]. Anal. ($C_{18}H_{24}N_3O_3Cl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropyl-2-hydroxyethyl)-3-(2,4,6-trimethylphenylamino)pyrazin-2(1*H*)-one (12j). To a solution of **12b** (100 mg, 0.28 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added BBr_3 (0.56 mL, 0.56 mmol, 1 M in CH_2Cl_2) slowly via syringe. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was then transferred to a separatory funnel containing saturated aq $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (20% → 50% ethyl acetate in hexanes) to afford **12j** (80 mg, 83% yield) as a colorless solid: $[\alpha]^{25}_D$ + 41.7 (*c* 0.364, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.90 (s, 2H), 6.84 (s, 1H), 4.11−3.29 (m, 2H), 3.91 (dd, J_{AB} = 11.3, J_{AX} = 6.3 Hz, 1H), 2.27 (s, 3H), 2.18 (s, 6H), 2.12 (s br, 1H), 1.28−1.19 (m, 1H), 0.88−0.77 (m, 1H), 0.68−0.61 (m, 1H), 0.55−0.49 (m, 1H), 0.39−0.32 (m, 1H). HRMS (ESI) m/e 348.1474 [$(M + H)^+$, calcd for $C_{18}H_{23}N_3O_2Cl$ 348.1479]. Anal. ($C_{18}H_{22}N_3O_2Cl$) C, H, N; calcd N, 12.08; found N, 11.65.

5-Chloro-1-(2-ethylbutyl)-3-(4-methoxy-2,5-dimethylphenylamino)pyrazin-2(1*H*)-one (12k). Compound **12k** was prepared according to the procedure described for the synthesis of **12a** (method A) using 3,5-dichloro-1-(2-ethylbutyl)pyrazin-2(1*H*)-one (**10c**) (100 mg, 0.400 mmol) and 4-methoxy-2,5-dimethylaniline (75 mg, 0.400 mmol). The product was purified by column chromatography to afford **12k** (80 mg, 55% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.86 (s, 1H), 6.66 (s, 1H), 6.55 (s, 1H), 3.80 (s, 3H), 3.77 (d, J = 7.3 Hz, 2H), 2.29 (s, 3H), 2.21 (s, 3H), 1.82−1.77 (m, 1H), 1.42−1.33 (m, 4H), 0.92 (t, J = 7.3 Hz, 6H). HRMS (ESI) m/e 364.1808 [$(M + H)^+$, calcd for $C_{19}H_{27}N_3O_2Cl$ 364.1792]. Anal. ($C_{19}H_{26}N_3O_2Cl$) C, H, N.

5-Chloro-1-(1-ethylpropyl)-3-(4-methoxy-2,5-dimethylphenylamino)pyrazin-2(1*H*)-one (12l). Compound **12l** was prepared according to the procedure described for the synthesis of **12a** (method A) using 3,5-dichloro-1-(pentan-3-yl)pyrazin-2(1*H*)-one (**10d**) (100 mg, 0.426 mmol) and 4-methoxy-2,5-dimethylaniline (64 mg, 0.426 mmol). The product was purified by column chromatography to afford **12l** (75 mg, 50% yield) as a light-brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.88 (s, 1H), 6.66 (s, 1H), 6.50 (s, 1H), 4.78−4.71 (m, 1H), 3.80 (s, 3H), 2.30 (s, 3H), 2.21 (s, 3H), 1.83−1.73 (m, 2H), 1.68−1.57 (m, 2H), 0.86 (t, J = 7.3 Hz, 6H). HRMS (ESI) m/e 350.1620 [$(M + H)^+$, calcd for $C_{18}H_{25}N_3O_2Cl$ 350.1635]. Anal. ($C_{18}H_{24}N_3O_2Cl$) C, H, N.

5-Chloro-3-(4-methoxy-2,5-dimethylphenylamino)-1-(1-propylbutyl)pyrazin-2(1*H*)-one (12m). Compound **12m** was prepared according to the procedure described for the synthesis of **12a** (method A) using 3,5-dichloro-1-(heptan-4-yl)pyrazin-2(1*H*)-one (**10e**) (500 mg, 1.90 mmol) and 4-methoxy-2,5-dimethylaniline (290 mg, 1.90 mmol). The product was purified by column chromatography to afford **12m** (680 mg, 95% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.88 (s, 1H), 6.66 (s, 1H), 6.51 (s, 1H), 4.13−4.08 (m, 1H), 3.80 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H), 1.69−1.58 (m, 4H), 1.32−1.19 (m, 4H), 0.90 (t, J = 7.6 Hz, 6H). HRMS (ESI) m/e 378.1953 [$(M + H)^+$, calcd for $C_{20}H_{29}N_3O_2Cl$ 378.1948]. Anal. ($C_{20}H_{28}N_3O_2Cl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropylpropyl)-3-(4-methoxy-2,5-dimethylphenylamino)pyrazin-2(1*H*)-one (12n). Compound **12n** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (**10f**) (250 mg, 1.02 mmol) and 4-methoxy-2,5-dimethylaniline (154 mg, 1.02 mmol). The product was purified by column chromatography to afford **12n** (300 mg, 82% yield) as a colorless solid: mp 112.3 − 113.3 °C; $[\alpha]^{25}_D$ + 58.8 (*c* 0.353, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.90 (s, 1H), 6.79 (s, 1H), 6.65 (s, 1H), 4.03−4.01 (m, 1H), 3.80 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H), 1.94−1.76 (m, 2H), 1.08−1.01 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H), 0.79−0.73 (m, 1H), 0.54−0.45 (m, 2H), 0.31−0.26 (m, 1H). HRMS (ESI) m/e 362.1650 [$(M + H)^+$, calcd for $C_{19}H_{25}N_3O_2Cl$ 362.1635]. Anal. ($C_{19}H_{24}N_3O_2Cl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropylethyl)-3-(4-methoxy-2,5-dimethylphenylamino)pyrazin-2(1*H*)-one (12o). Compound **12o** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropylethyl)-pyrazin-2(1*H*)-one (**10a**) (150 mg, 0.640 mmol) and 4-methoxy-2,5-dimethylaniline (100 mg, 0.640 mmol) with DMF (3 mL) as the solvent. The product was purified by column chromatography to afford **12o** (150 mg, 68% yield) as a tan solid: $[\alpha]^{25}_D$ + 43.7 (*c* 0.205, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.84 (s, 1H),

6.80 (s, 1H), 6.67 (s, 1H), 4.26−4.20 (m, 1H), 3.81 (s, 3H), 2.30 (s, 3H), 2.21 (s, 3H), 1.43 (d, J = 6.8 Hz, 3H), 1.12−1.06 (m, 1H), 0.78−0.71 (m, 1H), 0.59−0.52 (m, 1H), 0.49−0.43 (m, 1H), 0.37−0.32 (m, 1H). HRMS (ESI) m/e 348.1469 $[(M + H)^+$, calcd for $C_{18}H_{23}N_3O_2Cl$ 348.1479]. Anal. ($C_{18}H_{22}N_3O_2Cl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropyl-2-methoxyethyl)-3-(4-methoxy-2,5-dimethylphenylamino)pyrazin-2(1*H*)-one (12p). Compound **12p** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1*H*)-one (**10b**) (1.50 g, 5.73 mmol) and 4-methoxy-2,5-dimethylaniline (865 mg, 5.73 mmol) with DMF (28 mL) as the solvent. The product was purified by column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **12p** (1.62 g, 75% yield). The product was subsequently recrystallized from hexanes/ethyl acetate to afford **12p** as a light-brown crystalline solid: mp 112.4 − 113.9 °C; $[\alpha]^{25}_D$ +58.8 (c 0.353, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.86 (s, 1H), 6.80 (s, 1H), 6.66 (s, 1H), 4.20−4.15 (m, 1H), 3.80 (s, 3H), 3.75 (dd, J_{AB} = 10.5, J_{AX} = 6.4 Hz, 1H), 3.67 (dd, J_{BA} = 10.5, J_{BX} = 3.6 Hz, 1H), 3.34 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H), 1.31−1.25 (m, 1H), 0.79−0.73 (m, 1H), 0.61−0.56 (m, 1H), 0.53−0.48 (m, 1H), 0.37−0.32 (m, 1H). HRMS (ESI) m/e 378.1602 $[(M + H)^+$, calcd for $C_{19}H_{25}N_3O_3Cl$ 378.1585]. Anal. ($C_{19}H_{24}N_3O_3Cl$) C, H, N.

(*R*)-5-Chloro-3-(4-methoxy-2,5-dimethylphenylamino)-1-[1-(methoxymethyl)propyl]pyrazin-2(1*H*)-one (12q). Compound **12q** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-methoxybutan-2-yl)pyrazin-2(1*H*)-one (**10g**) (70 mg, 0.280 mmol) and 4-methoxy-2,5-dimethylaniline (43 mg, 0.280 mmol) with DMF (2 mL) as the solvent. The product was purified by column chromatography to afford **12q** (20 mg, 20% yield) as a brown solid: $[\alpha]^{25}_D$ +39.4 (c 0.507, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.80 (s, 1H), 6.72 (s, 1H), 6.66 (s, 1H), 4.97−4.91 (m, 1H), 3.80 (s, 3H), 3.63 (dd, J_{AB} = 10.4, J_{AX} = 6.3 Hz, 1H), 3.55 (dd, J_{BA} = 10.4, J_{BX} = 3.6 Hz, 1H), 3.33 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H), 1.88−1.70 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). HRMS (ESI) m/e 366.1573 $[(M + H)^+$, calcd for $C_{18}H_{25}N_3O_3Cl$ 366.1585]. HPLC method A: t_R = 5.59 min, > 99%; method B: t_R = 3.58 min, 98.1%.

(*R*)-5-Chloro-3-(4-methoxy-2,5-dimethylphenylamino)-1-(2-methoxy-1-methylethyl)pyrazin-2(1*H*)-one (12r). Compound **12r** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-methoxypropan-2-yl)pyrazin-2(1*H*)-one (**10h**) (200 mg, 0.850 mmol) and 4-methoxy-2,5-dimethylaniline (130 mg, 0.850 mmol) with DMF (3 mL) as the solvent. The product was purified by column chromatography to afford **12r** (200 mg, 67% yield) as a light-brown solid. The product was subsequently recrystallized from hexanes/ethyl acetate to afford **12r** as a light-brown crystalline solid: mp 90.4−90.9 °C; $[\alpha]^{25}_D$ +47.5 (c 0.433, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.82 (s, 1H), 6.74 (s, 1H), 6.66 (s, 1H), 5.18−5.14 (m, 1H), 3.80 (s, 3H), 3.59 (dd, J_{AB} = 10.3, J_{AX} = 6.1 Hz, 1H), 3.55 (dd, J_{BA} = 10.4, J_{BX} = 4.1 Hz, 1H), 3.55 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H), 1.40 (d, J = 7.1 Hz, 3H). HRMS (ESI) m/e 352.1430 $[(M + H)^+$, calcd for $C_{17}H_{23}N_3O_3Cl$ 352.1428]. Anal. ($C_{17}H_{22}N_3O_3Cl$) C, H, N.

5-Chloro-3-(4-methoxy-2,5-dimethylphenylamino)-1-[2-methoxy-1-(methoxymethyl)ethyl]pyrazin-2(1*H*)-one (12s). Compound **12s** was prepared according to the procedure described for the synthesis of **12a** (method A) using 3,5-dichloro-1-(1,3-dimethoxypropan-2-yl)pyrazin-2(1*H*)-one (**10i**) (150 mg, 0.560 mmol) and 4-methoxy-2,5-dimethylaniline (86 mg, 0.560 mmol). The product was purified by column chromatography to afford **12s** (140 mg, 65% yield) as a light-brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.82 (s, 1H), 6.87 (s, 1H), 6.65 (s, 1H), 5.19−5.14 (m, 1H), 3.79 (s, 3H), 3.74 (dd, J_{AB} = 10.3, J_{AX} = 6.5 Hz, 1H), 3.66 (dd, J_{BA} = 10.4, J_{BX} = 4.5 Hz, 2H), 3.35 (s, 6H), 2.28 (s, 3H), 2.20 (s, 3H). HRMS (ESI) m/e 382.1524 $[(M + H)^+$, calcd for $C_{18}H_{25}N_3O_4Cl$ 382.1534]. Anal. ($C_{18}H_{24}N_3O_4Cl_3$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropyl-2-hydroxyethyl)-3-(4-methoxy-2,5-dimethylphenylamino)pyrazin-2(1*H*)-one (12t). Compound **12t** was prepared from **12p** (200 mg, 0.53 mmol) according to the procedure described for the synthesis of **12j**. The product was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **12t** (90 mg, 47% yield) as a pale-yellow solid: mp 181.6 − 182.1 °C; $[\alpha]^{25}_D$ + 38.4 (c 0.450, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.81 (s, 1H), 6.86 (s, 1H), 6.66 (s, 1H), 4.06−4.00 (m, 2H), 3.94 (dd, J_{AB} = 12.1, J_{AX} = 7.3 Hz, 1H), 3.80 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H), 1.72 (s br, 1H), 1.30−1.22 (m, 1H), 0.84−0.77 (m, 1H), 0.67−0.60 (m, 1H), 0.55−0.49 (m, 1H), 0.37−0.31 (m, 1H). HRMS (ESI) m/e 364.1416 $[(M + H)^+$, calcd for $C_{18}H_{23}N_3O_3Cl$ 364.1428]. Anal. ($C_{18}H_{22}N_3O_3Cl$) C, H, N.

(*S*)-5-Chloro-1-(1-cyclopropyl-2-methoxyethyl)-3-(4-methoxy-2,5-dimethylphenylamino)pyrazin-2(1*H*)-one (12u). Compound **12u** was prepared according to the procedure described for the synthesis of **12b** (method B) using (*S*)-3,5-dichloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1*H*)-one (**10j**) (150 mg, 0.570 mmol) and 4-methoxy-2,5-dimethylaniline (90 mg, 0.570 mmol) with DMF (2 mL) as the solvent. The product was purified by column chromatography to afford **12u** (160 mg, 56% yield) as a yellow crystalline solid: $[\alpha]^{25}_D$ −40.4 (c 0.436, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.87 (s, 1H), 6.88 (s, 1H), 6.66 (s, 1H), 4.20−4.15 (m, 1H), 3.80 (s, 3H), 3.75 (dd, J_{AB} = 10.2, J_{AX} = 6.1 Hz, 1H), 3.68 (dd, J_{BA} = 10.2, J_{BX} = 3.4 Hz, 1H), 3.34 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H), 1.32−1.25 (m, 1H), 0.79−0.73 (m, 1H), 0.63−0.56 (m, 1H), 0.53−0.47 (m, 1H), 0.37−0.32 (m, 1H). HRMS (ESI) m/e 378.1585 $[(M + H)^+$, calcd for $C_{19}H_{25}N_3O_3Cl$ 378.1584]. Anal. ($C_{19}H_{24}N_3O_3Cl$) C, H, N.

(*S*)-3,5-dichloro-4-[6-chloro-4-(1-cyclopropylpropyl)-3-*oxo*-3,4-dihydropyrazin-2-ylamino]benzonitrile (12w). Compound **12w** was prepared according to the procedure described for the synthesis of **12v** (method B) by using 4-amino-3,5-dichlorobenzonitrile (187 mg, 1 mmol) and (*S*)-3,5-dichloro-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (**10k**) (246 mg, 1 mmol). The product was purified by column chromatography to afford **12w** (161 mg, 41% yield) as a yellow solid. The product was subsequently recrystallized from hot acetonitrile to afford **12w** as a colorless crystalline solid: mp 236−237 °C; $[\alpha]^{25}_D$ + 15.8 (c 0.278, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s br, 1H), 7.72 (s, 2H), 6.92 (s, 1H), 4.12−4.03 (m, 1H), 1.97−1.82 (m, 2H), 1.12−1.07 (m, 1H), 0.98 (t, J = 7.3 Hz, 3H), 0.87−0.82 (m, 1H), 0.60−0.53 (m, 2H), 0.37−0.33 (m, 1H). HRMS (ESI) m/e 397.0372 $[(M + H)^+$, calcd for $C_{17}H_{16}N_4OCl_3$ 397.0390]. Anal. ($C_{17}H_{15}N_4OCl_3$) C, H, N.

(*R*)-3,5-dichloro-4-[6-chloro-4-(1-cyclopropylethyl)-3-*oxo*-3,4-dihydropyrazin-2-ylamino]benzonitrile (12x). Compound **12x** was prepared according to the procedure described for the synthesis of **12v** (method B) using 4-amino-3,5-dichlorobenzonitrile (187 mg, 1.00 mmol) and (*R*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**10a**) (233 mg, 1.00 mmol). The product was purified by column chromatography and was subsequently recrystallized from hexanes/CH_2Cl_2/THF to afford **12x** (159 mg, 42% yield) as an off-white crystalline solid: mp 243.5−244.5 °C; $[\alpha]^{25}_D$ − 29.5 (c 0.306, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.72 (s, 2H), 7.01 (s, 1H), 4.34−4.24 (m, 1H), 1.48 (d, J = 7.0 Hz, 3H), 1.17−1.08 (m, 1H), 0.85−0.76 (m, 1H), 0.66−0.55 (m, 1H), 0.54−0.47 (m, 1H), 0.44−0.37 (m, 1H). HRMS (ESI) m/e 383.0232 $[(M + H)^+$, calcd for $C_{16}H_{14}N_4OCl_3$ 383.0233]. Anal. ($C_{16}H_{13}N_4OCl_3$) C, H, N.

(*S*)-3,5-dichloro-4-(6-chloro-4-(1-cyclopropylethyl)-3-*oxo*-3,4-dihydropyrazin-2-ylamino)benzonitrile (12y). Compound **12y** was prepared according to the procedure described for the synthesis of **12v** (method B) using 4-amino-3,5-dichlorobenzonitrile (187 mg, 1.00 mmol) and (*S*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**10l**) (233 mg, 1.00 mmol). The product was purified by column chromatography and was subsequently recrys-

tallized from ethyl acetate to afford compound **12y** (159 mg, 42% yield) as an off-white crystalline solid: mp 248−249 °C; $[\alpha]^{25}_D$ + 28.5 (*c* 0.304, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.72 (s, 2H), 7.01 (s, 1H), 4.34−4.24 (m, 1H), 1.48 (d, J = 7.0 Hz, 3H), 1.17−1.08 (m, 1H), 0.85−0.76 (m, 1H), 0.66−0.59 (m, 1H), 0.57−0.47 (m, 1H), 0.44−0.38 (m, 1H). HRMS (ESI) *m*/*e* 383.0231 $[(M + H)^+$, calcd for $C_{16}H_{14}N_4OCl_3$ 383.0233]. Anal. ($C_{16}H_{13}N_4OCl_3$) C, H, N.

(*S*)-5-Chloro-3-(4-methoxy-2,5-dimethylphenylamino)-1-(2-methoxy-1-methylethyl)pyrazin-2(1*H*)-one (12z). Compound **12z** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*S*)-3,5-dichloro-1-(1-methoxypropan-2-yl)pyrazin-2(1*H*)-one (**10m**) (70 mg, 0.300 mmol) and 4-methoxy-2,5-dimethylaniline (45 mg, 0.300 mmol) with DMF (1.5 mL) as the solvent. The product was purified by column chromatography to afford compound **12z** (90 mg, 86% yield) as a brown solid: $[\alpha]^{25}_D$ −34.4 (*c* 0.450, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.82 (s, 1H), 6.74 (s, 1H), 6.66 (s, 1H), 5.18−5.14 (m, 1H), 3.80 (s, 3H), 3.60 (dd, J_{AB} = 10.5, J_{AX} = 6.1 Hz, 1H), 3.55 (dd, J_{BA} = 10.5, J_{BX} = 4.1 Hz, 1H), 3.35 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H), 1.40 (d, J = 7.1 Hz, 3H). HRMS (ESI) *m*/*e* 352.1430 $[(M + H)^+$, calcd for $C_{17}H_{23}N_3O_3Cl$ 352.1428]. HPLC method A: t_R=5.24 min, >99%; method B: t_R=3.40 min, 98.4%.

(*R*)-5-Chloro-1-(1-cyclopropylpropyl)-3-(2,4-dichloro-6-methylphenylamino)pyrazin-2(1*H*)-one (12aa). Compound **12aa** was prepared according to the procedure described for the synthesis of **12v** (method B) using 2,4-dichloro-6-methylaniline (88 mg, 0.500 mmol) and (*R*)-3,5-dichloro-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (**10f**) (123 mg, 0.500 mmol). The product was purified by column chromatography to afford **12aa** (73 mg, 38% yield) as a colorless solid: $[\alpha]^{25}_D$ −14.2 (*c* 0.193, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.21 (d, J = 1.9 Hz, 1H), 6.81 (s, 1H), 4.12−4.04 (m, 1H), 2.30 (s, 3H), 1.96−1.78 (m, 2H), 1.10−1.03 (m, 1H), 0.97 (t, J = 7.7 Hz, 3H), 0.85−0.79 (m, 1H), 0.59−0.52 (m, 2H), 0.38−0.32 (m, 1H). HRMS (ESI) *m*/*e* 386.0619 $[(M + H)^+$, calcd for $C_{17}H_{19}N_3OCl_3$ 386.0594]. Anal. ($C_{17}H_{18}N_3OCl_3$) C, H, N.

(*R*)-5-Chloro-3-(2-chloro-6-methylphenylamino)-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (12ab). Compound **12ab** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (**10f**) (40 mg, 0.160 mmol) and 2-chloro-6-methylaniline (23 mg, 0.160 mmol) with DMF (1 mL) as the solvent. The product was purified by column chromatography to afford **12ab** (40 mg, 71% yield) as a colorless solid: $[\alpha]^{25}_D$ −8.6 (*c* 0.442, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.29 (dd, J = 7.6, 1.6 Hz, 1H), 7.19−7.11 (m, 2H), 6.77 (s, 1H), 4.09−4.03 (m, 1H), 2.29 (s, 3H), 1.94−1.78 (m, 2H), 1.08−1.02 (m, 1H), 0.95 (t, J = 7.5 Hz, 3H), 0.79−0.76 (m, 1H), 0.55−0.50 (m, 2H), 0.36−0.31 (m, 1H). HRMS (ESI) *m*/*e* 352.0976 $[(M + H)^+$, calcd for $C_{17}H_{20}N_3OCl_2$ 352.0984]. Anal. ($C_{17}H_{19}N_3OCl_2$) C, H, N.

(*R*)-5-Chloro-3-(4-chlorophenylamino)-1-(1-cyclopropylpropyl)-pyrazin-2(1*H*)-one (12ac). Compound **12ac** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (**10f**) (40 mg, 0.160 mmol) and 4-chloroaniline (21 mg, 0.160 mmol) with DMF (1 mL) as the solvent. The product was purified by column chromatography to afford **12ac** (40 mg, 74% yield) as a light-brown solid: $[\alpha]^{25}_D$ −5.3 (*c* 0.483, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.72 (dd, J = 6.8, 2.0 Hz, 2H), 7.31 (dd, J = 6.8, 2.0 Hz, 2H), 6.80 (s, 1H), 4.06−4.00 (m, 1H), 1.95−1.88 (m, 1H), 1.83−1.75 (m, 1H), 1.08−1.02 (m, 1H), 0.91 (t, J = 7.6 Hz, 3H), 0.81−0.75 (m, 1H), 0.53−0.46 (m, 2H), 0.29−0.24 (m, 1H). HRMS (ESI) *m*/*e* 338.0820 $[(M + H)^+$, calcd for $C_{16}H_{18}N_3OCl_2$ 338.0827]. Anal. ($C_{16}H_{17}N_3OCl_2$) C, H, N; calcd N, 12.42; found: N, 11.84.

(*R*)-5-Chloro-1-(1-cyclopropylpropyl)-3-(2,4-dimethylphenylamino)-pyrazin-2(1*H*)-one (12ad). Compound **12ad** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (**10f**) (100 mg, 0.405 mmol) and 2,4-dimethylaniline (49 mg, 0.405 mmol). The product was purified by column chromatography to afford **12ad** (72 mg, 54% yield) as a colorless solid: $[\alpha]^{25}_D$ −7.9 (*c* 0.433, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.23 (d, J = 8.1 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.01 (s, 1H), 6.76 (s, 1H), 4.06−3.99 (m, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 1.95−1.77 (m, 2H), 1.08−1.02 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H), 0.80−0.74 (m, 1H), 0.54−0.46 (m, 2H), 0.32−0.27 (m, 1H). HRMS (ESI) *m*/*e* 332.1531 $[(M + H)^+$, calcd for $C_{18}H_{23}N_3OCl$ 332.1530]. Anal. ($C_{18}H_{22}N_3OCl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropylpropyl)-3-(4-methoxy-2,6-dimethylphenylamino)pyrazin-2(1*H*)-one (12af). Compound **12af** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropylpropyl)pyrazin-2(1*H*)-one (**10f**) (150 mg, 0.610 mmol) and 4-methoxy-2,6-dimethylaniline (92 mg, 0.610 mmol). The product was purified by column chromatography to afford **12af** (170 mg, 77% yield) as a colorless solid: $[\alpha]^{25}_D$ −11.5 (*c* 0.436, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 6.68 (s, 1H), 6.63 (s, 2H), 4.07−4.01 (m, 1H), 3.77 (s, 3H), 2.19 (s, 6H), 1.94−1.76 (m, 2H), 1.06−1.01 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H), 0.81−0.73 (m, 1H), 0.55−0.46 (m, 2H), 0.33−0.29 (m, 1H). HRMS (ESI) *m*/*e* 362.1645 $[(M + H)^+$, calcd for $C_{19}H_{25}N_3O_2Cl$ 362.1635]. Anal. ($C_{19}H_{24}N_3O_2Cl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropyl-2-methoxyethyl)-3-(4-ethoxy-2,5-dimethylphenylamino)pyrazin-2(1*H*)-one (12ag). Compound **12ag** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1*H*)-one (**10b**) (100 mg, 0.380 mmol) and 4-ethoxy-2,5-dimethylaniline (63 mg, 0.380 mmol). The product was purified by column chromatography to afford **12ag** (85 mg, 57% yield) as a light-brown solid: $[\alpha]^{25}_D$ + 49.4 (*c* 0.457, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.86 (s, 1H), 6.87 (s, 1H), 6.65 (s, 1H), 4.19−4.14 (m, 1H), 3.99 (q, J = 6.8 Hz, 2H), 3.74 (dd, J_{AB} = 10.5, J_{AX} = 6.3 Hz, 1H), 3.66 (dd, J_{BA} = 10.4, J_{BX} = 3.6 Hz, 1H), 3.33 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.32−1.23 (m, 1H), 0.79−0.72 (m, 1H), 0.62−0.55 (m, 1H), 0.52−0.46 (m, 1H), 0.36−0.30 (m, 1H). HRMS (ESI) *m*/*e* 392.1747 $[(M + H)^+$, calcd for $C_{20}H_{27}N_3O_3Cl$ 392.1741]. Anal. ($C_{20}H_{26}N_3O_3Cl$) C, H, N.

(*R*)-3-[4-(Benzyloxy)-2,5-dimethylphenylamino]-5-chloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1*H*)-one (12ah). Compound **12ah** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropyl-2-methoxyethyl)pyrazin-2(1*H*)-one (**10b**) (330 mg, 1.25 mmol) and 4-(benzyloxy)-2,5-dimethylphenylaniline (330 mg, 1.25 mmol). The product was purified by column chromatography to afford **12ah** (380 mg, 67% yield) as an amber-brown solid: $[\alpha]^{25}_D$ + 40.1 (*c* 0.464, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.28 (s, 1H), 7.76 (s, 1H), 7.51−7.49 (m, 2H), 7.40−7.36 (m, 2H), 7.32−7.29 (m, 1H), 7.13 (s, 1H), 6.92 (s, 1H), 5.11 (s, 2H), 4.23−4.17 (m, 1H), 3.90 (dd, J_{AB} = 10.6, J_{AX} = 7.8 Hz, 1H), 3.69 (dd, J_{BA} = 10.6, J_{BX} = 3.8 Hz, 1H), 3.28 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 1.44−1.37 (m, 1H), 0.73−0.68 (m, 1H), 0.56−0.49 (m, 2H), 0.33−0.28 (m, 1H). HRMS (ESI) *m*/*e* 454.1899 $[(M + H)^+$, calcd for $C_{25}H_{29}N_3O_3Cl$ 454.1897]. Anal. ($C_{25}H_{28}N_3O_3Cl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropyl-2-methoxyethyl)-3-(4-hydroxy-2,5-dimethylphenylamino)pyrazin-2(1*H*)-one (12ai). Compound **12ai** was prepared according to the procedure described for the synthesis of **12a** (method A) by using the appropriate dichloropyrazinone (**10**) (150 mg, 0.570 mmol) and 4-amino-2,5-dimethylphenol (78 mg, 0.570 mmol). The product was purified by column chromatography to afford **12ai** (64 mg, 32% yield) as a tan solid: mp 164.5−165.5 °C; $[\alpha]^{25}_D$ + 59.2 (*c* 0.412, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.69 (s, 1H), 6.88 (s, 1H), 6.56 (s, 1H), 5.19 (s, 1H), 4.19−4.14 (m, 1H), 3.74 (dd, J_{AB} = 10.4, J_{AX} = 6.3 Hz, 1H), 3.67 (dd, J_{BA} = 10.6, J_{BX} = 3.5 Hz, 1H), 3.34 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.31−1.24 (m, 1H), 0.80−0.73 (m, 1H), 0.62−0.56 (m, 1H), 0.52−0.46 (m, 1H), 0.37−0.30 (m, 1H).

HRMS (ESI) *m/e* 364.1414 [(M + H)$^+$, calcd for $C_{18}H_{23}N_3O_3Cl$ 364.1428]. Anal. ($C_{18}H_{22}N_3O_3Cl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropylpropyl)-3-[ethyl(2,4,5-trimethylphenyl)amino]pyrazin-2(1*H*)-one (12aj). To a solution of **12ae** (100 mg, 0.301 mmol) in DMF (2 mL) was added NaH (36 mg, 0.900 mmol, 60% in mineral oil). After stirring for 15 min at room temperature, ethyl iodide (104 mg, 0.660 mmol) was added and the reaction mixture was heated at 50 °C for 16 h. The mixture was cooled to room temperature, and the reaction was quenched by the addition of water. The mixture was transferred to a separatory funnel containing brine, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **12aj** (30 mg, 28% yield) as a pale-yellow oil: $[\alpha]^{25}_D$ +17.1 (*c* 0.257, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.74 (s, 2H), 3.91 (q, *J* = 8.1 Hz, 2H), 3.73−3.62 (m br, 1H), 2.18 (s, 3H), 2.15 (s, 3H), 2.06 (s, 3H), 1.79−1.62 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.95−0.87 (m, 1H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.71−0.64 (m, 1H), 0.45−0.33 (m, 2H), 0.18−0.13 (m, 1H). HRMS (ESI) *m/e* 374.2008 [(M + H)$^+$, calcd for $C_{21}H_{29}N_3OCl$ 374.1999]. HPLC method A: t_R = 7.34 min, 97.5%; method B: t_R = 4.22 min, 96.2%.

(*R*)-5-Chloro-1-(1-cyclopropylpropyl)-3-[ethyl(2,4,6-trimethylphenyl)amino]pyrazin-2(1*H*)-one (12ak). Compound **12ak** was prepared according to the procedure described for the synthesis of **12aj** by using **12f** (100 mg, 0.301 mmol). The residue was purified by column chromatography to afford **12ak** (35 mg, 32% yield) as a pale-yellow oil: $[\alpha]^{25}_D$ + 66.6 (*c* 0.186, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ NMR 6.81 (s, 2H), 6.66 (s, 1H), 3.95−3.88 (m, 1H), 3.74 (q, *J* = 6.9 Hz, 2H), 2.24 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.77−1.58 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.92−0.85 (m, 1H), 0.80 (t, *J* = 7.6 Hz, 3H), 0.66−0.61 (m, 1H), 0.40−0.30 (m, 2H), 0.15−0.11 (m, 1H). HRMS (ESI) *m/e* 374.2006 [(M + H)$^+$, calcd for $C_{21}H_{29}N_3OCl$ 374.1999]. Method A: t_R = 7.38 min, 94.8%; method B: t_R = 4.17 min, 95.6%.

(*R*)-5-Chloro-1-(1-cyclopropylethyl)-3-(2,6-dichloro-4-methoxyphenylamino)pyrazin-2(1*H*)-one (12al). Compound **12al** was prepared according to the procedure described for the synthesis of **12v** (method B) by using (*R*)-3,5-dichloro-1-(1-cyclopropylethyl)-pyrazin-2(1*H*)-one (**10a**) (233 mg, 1.00 mmol) and 2,4-dichloro-6-methoxyaniline (190 mg, 1.00 mmol). The product was purified by column chromatography to afford **12al** (170 mg, 44% yield) as a colorless solid: mp 161.5−162 °C; $[\alpha]^{25}_D$ −19.8 (*c* 0.270, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 6.97 (s, 2H), 6.89 (s, 1H), 4.32−4.27 (m, 1H), 3.83 (s, 3H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.17−1.05 (m, 1H), 0.81−0.75 (m, 1H), 0.64−0.58 (m, 1H), 0.53−0.45 (m, 1H), 0.43−0.39 (m, 1H). HRMS (ESI) *m/e* 388.0361 [(M + H)$^+$, calcd for $C_{16}H_{17}N_3O_2Cl_3$ 388.0386]. Anal. ($C_{16}H_{16}N_3O_2Cl_3$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropylethyl)-3-[(2,6-dichloro-4-methoxyphenyl)(ethyl)amino]pyrazin-2(1*H*)-one (12am). Compound **12am** was prepared according to the procedure described for the synthesis of **12aj** using **12al** (100 mg, 0.301 mmol). The residue was purified by column chromatography to give **12am** (110 mg, 69% yield) as an amber-brown oil: $[\alpha]^{25}_D$ + 23.1 (*c* 0.750, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.845 (d, *J* = 3.0 Hz, 2H), 6.84 (s, 1H), 4.09−4.03 (m, 1H), 3.88−3.77 (m, 2H), 3.76 (s, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.99−0.93 (m, 1H), 0.68−0.62 (m, 1H), 0.49−0.42 (m, 1H), 0.35−0.29 (m, 1H), 0.24−0.19 (m, 1H). HRMS (ESI) *m/e* 416.0698 [(M + H)$^+$, calcd for $C_{18}H_{21}N_3O_2Cl_3$ 416.0699]. HPLC method A: t_R = 6.91 min, 96.4%; method B: t_R = 4.16 min, 97.5%.

(*R*)-5-Chloro-3-(7-chloro-5-methoxyindolin-1-yl)-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (12an). To a solution of (*R*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**10a**) (150 mg, 0.640 mmol) and 7-chloro-5-methoxyindoline hydrochloride (140 mg, 0.640 mmol) in THF (6 mL) at 0 °C was added NaHMDS (2.00 mL, 2.00 mmol, 1 M in THF). The reaction mixture was stirred at 0 °C for 1.5 h. The mixture was transferred to a separatory funnel containing saturated aq $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (20% → 25% ethyl acetate in hexanes) followed by purification by reverse-phase HPLC (acetonitrile/water containing 0.1% TFA as mobile phase, C18 column) to afford **12an** (35 mg, 14% yield) as a yellow solid: $[\alpha]^{25}_D$ −11.4 (*c* 0.421, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.72 (s, 2H), 4.32 (t, *J* = 7.8 Hz, 2H), 4.25−4.21 (m, 1H), 3.75 (s, 3H), 3.07 (t, *J* = 7.8 Hz, 2H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.09−1.04 (m, 1H), 0.75−0.71 (m, 1H), 0.57−0.53 (m, 1H), 0.46−0.41 (m, 1H), 0.38−0.33 (m, 1H). HRMS (ESI) *m/e* 380.0934 [(M + H)$^+$, calcd for $C_{18}H_{20}N_3O_2Cl_2$ 380.0933]. HPLC method A: t_R = 5.50 min, > 99%; method B: t_R = 3.68 min, > 99%.

(*R*)-3-(7-Bromo-5-methoxyindolin-1-yl)-5-chloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (12ao). Compound **12ao** was prepared according to the procedure described for the synthesis of **12an** using (*R*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**10a**) (150 mg, 0.640 mmol) and 7-bromo-5-methoxyindoline hydrochloride (169 mg, 0.640 mmol). The residue was purified by column chromatography to afford **12ao** (30 mg, 11% yield) as a yellow solid: $[\alpha]^{25}_D$ −7.7 (*c* 0.286, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.90 (s, 1H), 6.76 (s, 1H), 4.33 (t, *J* = 7.8 Hz, 2H), 4.28−4.20 (m, 1H), 3.76 (s, 3H), 3.08 (t, *J* = 7.8 Hz, 2H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.10−1.04 (m, 1H), 0.77−0.70 (m, 1H), 0.58−0.52 (m, 1H), 0.48−0.42 (m, 1H), 0.38−0.32 (m, 1H). HRMS (ESI) *m/e* 424.0408 [(M + H)$^+$, calcd for $C_{18}H_{20}N_3O_2BrCl$ 424.0428]. HPLC method A: t_R = 5.54 min, > 99%; method B: t_R = 3.75 min, > 99%.

(*R*)-3-[5-Bromo-7-methoxy-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl]-5-chloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (12ap). Compound **12ap** was prepared according to the procedure described for the synthesis of **12an** using (*R*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**10a**) (200 mg, 0.860 mmol) and 5-bromo-7-methoxy-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine hydrochloride (240 mg, 0.860 mmol). The residue was purified by column chromatography to afford **12ap** (210 mg, 56% yield) as a brown solid: $[\alpha]^{25}_D$ −14.1 (*c* 0.693, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 7.52 (s, 1H), 6.74 (s, 1H), 6.51 (s, 1H), 4.28−3.94 (m, 5H), 3.76 (s, 3H), 1.41 (d, *J* = 7.0 Hz, 3H), 1.38−1.26 (m, 1H), 0.74−0.60 (m, 1H), 0.54−0.39 (m, 2H), 0.30−0.16 (m, 1H). HRMS (ESI) *m/e* 440.0374 [(M + H)$^+$, calcd for $C_{18}H_{20}N_3O_3BrCl$ 440.0377]. Anal. ($C_{18}H_{19}N_3O_3BrCl$) C, H, N.

(*R*)-5-Chloro-1-(1-cyclopropylethyl)-3-[6-methoxy-2-(trifluoromethyl)pyridin-3-ylamino]pyrazin-2(1*H*)-one (12aq). Compound **12aq** was prepared according to the procedure described for the synthesis of **12a** (method A) using (*R*)-3,5-dichloro-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**10a**) (150 mg, 0.640 mmol) and 6-methoxy-2-(trifluoromethyl)pyridin-3-amine (125 mg, 0.640 mmol). The product was purified by column chromatography to afford **12aq** (120 mg, 48% yield) as a pale-yellow solid: $[\alpha]^{25}_D$ −19.6 (*c* 0.433, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 9.0 Hz, 1H), 8.64 (s, 1H), 6.98 (d, *J* = 9.0 Hz, 1H), 6.92 (s, 1H), 4.27−4.19 (m, 1H), 3.95 (s, 3H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.12−1.05 (m, 1H), 0.79−0.73 (m, 1H), 0.60−0.53 (m, 1H), 0.50−0.44 (m, 1H), 0.38−0.33 (m, 1H). HRMS (ESI) *m/e* 389.0998 [(M + H)$^+$, calcd for $C_{16}H_{17}N_4O_2ClF_3$ 389.0992]. Anal. ($C_{16}H_{16}N_4O_2ClF_3$) C, H, N.

(*R*)-5-Bromo-1-(1-cyclopropylethyl)-3-[6-methoxy-2-(trifluoromethyl)pyridin-3-ylamino]pyrazin-2(1*H*)-one (13). To a solution of (*R*)-3,5-dibromo-1-(1-cyclopropylethyl)pyrazin-2(1*H*)-one (**11**) (150 mg, 0.470 mmol) and 6-methoxy-2-(trifluoromethyl)pyridin-3-amine (90 mg, 0.470 mmol) in THF (2 mL) at 0 °C was added NaHMDS (0.94 mL, 0.94 mmol, 1 M in THF). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 12 h. The mixture was transferred to a separatory funnel containing saturated aq $NaHCO_3$ solution (5 mL), and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to

afford **13** (120 mg, 59% yield) as a tan solid: $[\alpha]^{25}_D$ −15.6 (*c* 0.450, benzene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 9.3 Hz, 1H), 8.63 (s,1H), 7.00 (s, 1H), 6.98 (d, J = 9.0 Hz, 1H), 4.24−4.20 (m, 1H), 3.95 (s, 3H), 1.44 (d, J = 6.9 Hz, 3H), 1.11−1.05 (m, 1H), 0.78−0.72 (m, 1H), 0.58−0.53 (m, 1H), 0.48−0.43 (m, 1H), 0.38−0.33 (m, 1H). HRMS (ESI) *m*/*e* 433.0494 [$(M + H)^+$, calcd for $C_{16}H_{17}N_4O_2BrF_3$ 433.0487]. Anal. ($C_{16}H_{16}N_4O_2BrF_3$) C, H, N.

1-Cyclopropyl-2-methoxyethanone (15). Magnesium turnings (15.2 g, 632 mmol) were added to a 5 L round-bottom flask equipped with an addition funnel, after which the flask and funnel were flame-dried. A reflux condenser was then placed on the flask. Diethyl ether (100 mL) was added to the flask, followed by cyclopropyl bromide (5 mL, 7.55 g, 62.4 mmol) and several crystals of iodine. After the reaction was initiated, additional diethyl ether (400 mL) was added to the reaction mixture followed by cyclopropyl bromide (87.28 g, 721 mmol) slowly over 30 min with intermittent cooling of the reaction mixture with an ice−water bath. After the addition was complete and the magnesium had reacted, additional diethyl ether (700 mL) was added and the reaction mixture was cooled to 0 °C. The magnetic stirrer was replaced with a mechanical stirrer, and a solution of N^2-dimethoxy-*N*-methylacetamide (**14**) (42.07 g, 316 mmol) dissolved in diethyl ether (500 mL) was added slowly over 30 min via the addition funnel. A white solid formed during this time. After the addition was complete, the cooling bath was removed and the mixture was stirred at room temperature for 1 h. The mixture was then cooled to 0 °C and was quenched by the addition of 1 N HCl (700 mL, added slowly at first). After stirring for an additional 15 min, the mixture was transferred to a separatory funnel and the aqueous layer was extracted with ether (3 × 500 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ solution (400 mL), brine (400 mL), dried over $MgSO_4$, filtered, and concentrated with minimal vacuum (500 mbar). The product was purified by distillation under reduced pressure while cooling the collection flask in a dry ice/isopropyl alcohol bath to afford **15** (29.23 g, 81% yield) as a colorless oil: bp 35−38 °C, 5 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 2H), 3.43 (s, 3H), 2.11−2.07 (m, 1H), 1.10−1.06 (m, 2H), 0.94−0.89 (m, 2H). GC/MS (CI) *m*/*e* 115.1 [$(M + H)^+$, calcd for $C_6H_{11}O_2$ 115.1].

Benzyl 1-Cyclopropyl-2-methoxyethylcarbamate (16). Compound **15** (10.03 g, 87.98 mmol) in THF (1000 mL) was treated with ammonium trifluoroacetate (115.25 g, 880 mmol), and the mixture was cooled to 0 °C. Sodium triacetoxyborohydride (27.85 g, 133 mmol) was added, the cooling bath was removed, and the reaction mixture was gently heated at 40 °C with a warm water bath for 2 h. The mixture was cooled to room temperature and concentrated to give 1-cyclopropyl-2-methoxyethanamine, which was used directly in the next step.

Crude 1-cyclopropyl-2-methoxyethanamine from the previous step was dissolved in CH_2Cl_2/H_2O (300 mL/300 mL), and Na_2CO_3 (111.9 g, 1.06 mol) was added. The reaction mixture was placed in an ice bath and benzyl chloroformate (16.46 g, 96.78 mmol) was added via syringe. During the addition, the internal reaction mixture temperature was maintained at 15−20 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 2 h. The mixture was poured into a separatory funnel, diluted with H_2O, (300 mL), and extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to furnish **16** (17.17 g, 78% yield, 2 steps) as an oil, which crystallized upon standing: mp 190.5−192 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39−7.29 (m, 5H), 7.17 (d, J = 8.5 Hz, 1H), 5.00 (s, 2H), 3.36−3.34 (m, 2H), 3.23 (s, 3H), 3.19−3.14 (m, 1H), 0.85−0.79 (m, 1H), 0.43−0.37 (m, 1H), 0.35−0.22 (m, 2H), 0.20−0.16 (m, 1H). LRMS (ESI) *m*/*e* 250.3 [$(M + H)^+$, calcd for $C_{14}H_{20}NO_3$ 250.1].

(*R*)-Benzyl 1-Cyclopropyl-2-methoxyethylcarbamate (17). Racemic **16** was separated into its enantiomers by HPLC: Chiralpak AD column (10 cm × 50 cm); mobile phase = 94% heptane/6% ethanol; flow rate = 300 mL/min; λ = 210 nm; 1 g per injection, 30 min method, peak 1 (*S* enantiomer), peak 2 (*R* enantiomer). Each enantiomer had an optical purity >99% ee as determined by analytical HPLC: Chiralpak AD column (4.6 mm × 250 mm, 10 μm); mobile phase = 95% hexane/5% ethanol; flow rate = 0.8 mL/min; λ = 210 nm; t_R (*S* enantiomer) = 14.77 min, t_R (*R* enantiomer) = 17.05 min. The *R* enantiomer (**17**) was used in the next step. The characterization data for the *R* enantiomer is as follows: mp 59.6−60.8 °C; $[\alpha]^{25}_D$ +18.9 (*c* 0.596, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39−7.29 (m, 5H), 7.17 (d, J = 8.5 Hz, 1H), 5.00 (s, 2H), 3.36−3.34 (m, 2H), 3.23 (s, 3H), 3.19−3.14 (m, 1H), 0.85−0.79 (m, 1H), 0.43−0.37 (m, 1H), 0.35−0.22 (m, 2H), 0.20−0.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 136.9, 128.0, 127.38, 127.34, 74.0, 64.8, 57.8, 53.5, 12.6, 2.2, 1.5. LRMS (ES^+) *m*/*e* 272.3 [$(M + Na)^+$, calcd for $C_{14}H_{19}NO_3Na$ 272.1].

(*R*)-1-Cyclopropyl-2-methoxyethanamine Hydrochloride (18). To a solution of **17** (4.24 g, 17.0 mmol) in ethanol (80 mL) and chloroform (3 mL) in a Parr bottle was added 4 N HCl in dioxane (5 mL) and 10% Pd/C (476 mg, wet, Degussa type). The reaction mixture was placed on the Parr shaker under an H_2 atm at 45 psi for 16 h. The mixture was filtered through a pad of celite, and the filtrate was concentrated. The residue was reconcentrated from hexanes (2×) to give **18** (2.65 g, 100% yield) as a colorless solid: mp 190−191.1 °C; $\alpha]^{25}_D$ −19.5 (*c* 0.482, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s br, 3H), 3.68 (d, J = 5.6 Hz, 2H), 3.39 (s, 3H), 2.64−2.60 (m, 1H), 1.20−1.13 (m, 1H), 0.71−0.58 (m, 3H), 0.32−0.28 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.1, 59.2, 57.5, 10.7, 4.2, 4.1. LRMS (ESI) *m*/*e* 231.2 [$(2M + H)^+$, calcd for $C_{12}H_{27}N_2O_2$ 231.2].

Benzyl 1-Cyclopropylpropylcarbamate (20). To a solution of **19** (39.6 g, 0.403 mmol) in THF (600 mL) in a three-necked round-bottom flask equipped with a mechanical stirrer was added ammonium trifluoroacetate (315 g, 2.42 mol). The mixture was cooled to 0 °C, and sodium triacetoxyborohydride (128 g, 0.604 mol) was added. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to give 1-cyclopropylpropan-1-amine, which was used directly in the next step.

To a solution of crude 1-cyclopropylpropan-1-amine from the previous step in CH_2Cl_2 (500 mL) and water (200 mL) in a round-bottom flask equipped with a mechanical stirrer was added Na_2CO_3 (256 g, 2.42 mol). The reaction mixture was cooled to 0 °C, and benzyl chloroformate (75.6 g, 0.443 mol) was added via syringe. The reaction mixture was allowed to warm up to room temperature and was stirred at room temperature overnight. The mixture was poured into a separatory funnel, diluted with ethyl acetate (400 mL), and the organic layer was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on silica gel (0% → 30% ethyl acetate in hexanes) to furnish **20** (38.64 g, 41% yield, 2 steps) as a pale-yellow solid: mp 77.7−78.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 5H), 5.08 (s, 2H), 4.64 (s br, 1H), 2.96−2.92 (m, 1H), 1.67−1.51 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H), 0.78−0.72 (m, 1H), 0.53−0.47 (m, 1H), 0.43−0.36 (m, 1H), 0.35−0.30 (m, 1H), 0.24−0.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 136.8, 128.5, 128.0, 66.5, 57.1, 28.6, 16.0, 10.3, 3.7, 2.4. LRMS (ESI) *m*/*e* 234.3 [$(M + H)^+$, calcd for $C_{14}H_{20}NO_2$ 234.1].

(*R*)-1-Cyclopropylpropylcarbamate (21). Racemic **20** was separated into its enantiomers by super critical fluid chromatography (SFC): Chiralpak AS column (3 cm × 25 cm); mobile phase = 10% isopropyl alcohol in CO_2; flow rate = 120 mL/min @ 15 °C and 100 bar; λ = 220 nm; 150 mg per injection per 4.2 min, Peak 1 (*S* enantiomer), peak 2 (*R* enantiomer). Each enantiomer had an optical purity >99% ee as determined by analytical SFC: Chiralcel OD-H column (4.6 mm × 250 mm, 5 μm); mobile phase = 5% heptane/isopropyl alcohol (1:1) in CO_2; flow rate = 2 mL/min @ 35 °C and 150 bar; λ = 210 nm; t_R (*R* enantiomer) = 6.95 min, t_R (*S* enantiomer) = 7.87 min. The *R* enantiomer (**21**) was used in

the next step. The characterization data for the *R* enantiomer is as follows: $[\alpha]^{25}_D$ +2.6 (*c* 0.393, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 5H), 5.08 (s, 2H), 4.65 (s br, 1H), 2.96−2.92 (m, 1H), 1.67−1.51 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H), 0.78−0.72 (m, 1H), 0.53−0.47 (m, 1H), 0.43−0.36 (m, 1H), 0.35−0.30 (m, 1H), 0.24−0.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 136.8, 128.5, 128.0, 66.5, 57.1, 28.6, 16.0, 10.3, 3.7, 2.4. LRMS (ESI) *m*/*e* 234.3 $[(M + H)^+$, calcd for $C_{14}H_{20}NO_2$ 234.1].

(*R*)-1-Cyclopropylpropan-1-amine Hydrochloride (22). To a solution of **21** (39.0 g, 167.2 mmol) in ethanol (250 mL) in a Parr bottle was added 4 N HCl in dioxane (46.3 mL) and 10% Pd/C (1.2 g). The reaction mixture was placed on the Parr shaker under an H_2 atm at 40 psi for 2 h. The mixture was filtered through a pad of celite with methanol rinsing, and the filtrate was concentrated. The residue was reconcentrated from hexanes (2×) to give **22** (21.5 g, 95% yield) as a colorless solid: mp 254.5−255.2 °C; $[\alpha]^{25}_D$ −13.5 (*c* 0.443, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s br, 3H), 2.36−2.33 (m, 1H), 1.97−1.85 (m, 2H), 1.10 (t, J = 7.3 Hz, 3H), 1.11−1.03 (m, 1H), 0.69−0.56 (m, 3H), 0.35−0.30 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.6, 27.0, 13.7, 10.3, 4.8, 3.4. GC/MS (CI) *m*/*e* 100 $[(M + H)^+$, calcd for $C_6H_{14}N$ 100].

(*R*)-2-(Tritylamino)butan-1-ol (24). Triethylamine (80 mL, 0.57 mol) was added dropwise at 0 °C to a solution of triphenylmethyl chloride (156 g, 560 mmol) in methylene chloride (400 mL). (*R*)-(−)-2-Amino-1-butanol (**23**) (50 g, 0.56 mol) in methylene chloride (100 mL) was then added dropwise at 0 °C. The mixture was stirred at 0 °C under nitrogen for 4 h and then slowly warmed to room temperature overnight. The mixture was diluted with ether (1 L) and then washed with water and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10% → 35% ethyl acetate in hexanes) to afford **24** (152 g, 82% yield) as a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.53 (m, 6H), 7.31−7.19 (m, 9H), 3.21 (dd, J = 10.0, 2.0 Hz, 1H), 3.05 (dd, J = 10.0, 4.0 Hz, 1H), 2.55−2.48 (m, 1H), 2.10−1.95 (m, 1H), 1.95−1.75 (m, 1H), 1.30−1.18 (m, 1H), 1.02−0.86 (m, 1H), 0.63 (t, J = 7.4 Hz, 3H).

(*R*)-1-Methoxy-*N*-tritylbutan-2-amine (25). To a suspension of sodium hydride (20.2 g, 505 mmol, 60% in mineral oil) in THF (1 L) was added **24** (152 g, 459 mmol) in THF (200 mL) dropwise at 0 °C. The mixture was stirred at 0 °C under nitrogen for 1 h. Iodomethane (31.8 mL, 510 mmol) was added dropwise at 0 °C. The mixture was slowly warmed to room temperature and stirred under nitrogen overnight. The mixture was cooled to 0 °C and quenched carefully with water. The mixture was transferred to a separatory funnel and was extracted with ethyl acetate (3×), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide **25** (158 g, quantitative yield) as a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.56 (m, 6H), 7.28−7.14 (m, 9H), 3.06 (s, 3H), 2.91 (dd, J = 10.0, 4.0 Hz, 1H), 2.50−2.35 (m, 2H), 2.15 (br s, 1H), 1.40−1.25 (m, 2H), 0.70 (t, J = 7.4 Hz, 3H).

(*R*)-1-Methoxybutan-2-amine hydrochloride (26). To a solution of **25** (158 g, 459 mmol) in methylene chloride (500 mL) and methanol (500 mL) was added HCl (700 mL, 700 mmol, 1.0 M in ether) at 0 °C over a period of 10 min. The mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The solvents were removed in vacuo, and the residue was washed with ether and hexanes (1:9) to provide crude product (56 g) as a light-yellow solid, which was purified by recrystallization from ethyl acetate to give **26** (54.8 g, 85% yield) as a white solid: mp 134−136 °C; $[\alpha]^{25}_D$ −24.3° (*c* 1.03, H_2O); $[\alpha]^{25}_D$ −16.6° (*c* 1.03, CH_3OH). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (br s, 3H), 3.46 (ddd, J = 16.0, 8.0, 4.0 Hz, 2H), 3.30 (s, 3H), 3.21−3.07 (m, 1H), 1.70−1.48 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H). LRMS (APCI) *m*/*e* 104.0 $[(M + H)^+$, calcd for $C_5H_{14}NO$ 104.1].

(*R*)-Ethyl 2-[(1-Cyclopropylethyl)(2-oxopropyl)amino]-2-oxoacetate (28). To a suspension of (*R*)-1-cyclopropylethanamine hydrochloride (**27**) (5.00 g, 41.1 mmol) and potassium carbonate (17.1 g, 124 mmol) in acetonitrile (200 mL) at 0 °C was added chloroacetone (3.3 mL, 41.1 mmol) via syringe followed by potassium iodide (7.55 g, 345.5 mmol). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 4 h. The mixture was filtered through a pad of celite, and the filtrate was concentrated. The product was purified by column chromatography on silica gel (10% → 15% MeOH in CH_2Cl_2) to give (*R*)-1-(1-cyclopropylethylamino)propan-2-one (4.46 g, 77% yield), which was used immediately in the next step. The product readily decomposes if stored at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (s, 1H), 3.60 (s, 2H), 2.12 (s, 3H), 1.83−1.76 (m, 1H), 1.14 (d, J = 6.5 Hz, 3H), 0.72−0.64 (m, 1H), 0.55−0.48 (m, 1H), 0.44−0.39 (m, 1H), 0.23−0.17 (m, 1H), 0.06−0.00 (m, 1 H).

To a solution of (*R*)-1-(1-cyclopropylethylamino)propan-2-one (4.46 g, 31.6 mmol) in CH_2Cl_2 (300 mL) at −78 °C was added pyridine (9.0 mL, 111 mmol) followed by ethyl chlorooxoacetate (4.5 mL, 40.40 mmol). The reaction mixture was stirred at −78 °C for 5 min and then warmed to room temperature and stirred at room temperature for 30 min. The reaction mixture was transferred to a separatory funnel and diluted with saturated aq $NaHCO_3$ solution, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on silica gel (45% → 55% ethyl acetate in hexanes) to furnish **28** (3.32 g, 44% yield) as a brown oil: $[\alpha]^{25}_D$ −26.8 (*c* 0.900, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35−4.26 (m, 2H), 4.09 (d, J = 2.6 Hz, 2H), 3.07−3.03 (m, 1H), 2.21 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.24 (d, J = 6.6 Hz, 3H), 0.89−0.81 (m, 1H), 0.65−0.60 (m, 1H), 0.52−0.45 (m, 1H), 0.41−0.31 (m, 1H), 0.28−0.23 (m, 1H). LRMS (APCI) *m*/*e* 242.3 $[(M + H)^+$, calcd for $C_{12}H_{20}NO_4$ 242.1].

(*R*)-1-(1-Cyclopropylethyl)-5-methylpyrazine-2,3(1*H*,4*H*)-dione (29). A solution of **28** (3.24 g, 13.43 mmol) in acetic acid (185 mL) was treated with ammonium acetate (10.36 g, 134 mmol) and the reaction mixture was heated at 100 °C for 2.5 h. The mixture was cooled to room temperature and concentrated. The residue was transferred to a separatory funnel containing saturated aq $NaHCO_3$ solution (500 mL, some bubbling occurred). The aqueous layer was extracted with ethyl acetate (7 × 250 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography on silica gel (5% → 10% MeOH in CH_2Cl_2) to afford **29** (1.51 g, 58% yield) as a light-brown solid: mp 196−197 °C; $[\alpha]^{25}_D$ +18.0 (*c* 0.338, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 6.15 (s, 1H), 4.22−4.15 (m, 1H), 2.13 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.03−0.97 (m, 1H), 0.71−0.64 (m, 1H), 0.52−0.39 (m, 2H), 0.36−0.30 (m, 1H). LRMS (APCI) *m*/*e* 195.5 $[(M + H)^+$, calcd for $C_{10}H_{15}N_2O_2$ 195.1].

(*R*)-3-Chloro-1-(1-cyclopropylethyl)-5-methylpyrazin-2(1*H*)-one (30). A solution of **29** (1.50 g, 7.72 mmol) and DMF (120 μL, 1.55 mmol) in thionyl chloride (75 mL) was heated at 75 °C for 1 h. The mixture was cooled to room temperature and was concentrated then reconcentrated from hexanes. The product was purified by column chromatography on silica gel (15% → 30% ethyl acetate in hexanes) to afford **30** (1.28 g, 78% yield) as a pale-yellow solid: mp 78.5−80 °C; $[\alpha]^{25}_D$ +4.7 (*c* 0.469, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 1H), 4.47−4.21 (m, 1H), 2.28 (s, 3H), 1.41 (d, J = 6.8 Hz, 3H), 1.09−1.05 (m, 1H), 0.79−0.72 (m, 1H), 0.57−0.50 (m, 2H), 0.49−0.31 (m, 1H). LRMS (APCI) *m*/*e* 213.3 $[(M + H)^+$, calcd for $C_{10}H_{14}N_2OCl$ 213.1].

(*R*)-1-(1-Cyclopropylethyl)-3-[6-methoxy-2-(trifluoromethyl)pyridin-3-ylamino]-5-methylpyrazin-2(1*H*)-one (31). Method A (from 30). To a solution of **30** (114 mg, 0.536 mmol) and 6-methoxy-2-(trifluoromethyl)pyridin-3-amine (103 mg, 0.536 mmol) in THF (4 mL) at 0 °C was added NaHMDS (1.1 mL, 1.12 mmol) dropwise via syringe. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 8 h. The mixture was transferred to a separatory funnel containing saturated aq

$NaHCO_3$ solution (15 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified via column chromatography on silica gel (10% → 30% ethyl acetate in hexanes) to afford **31** (27 mg, 14% yield) as a pale-yellow solid. See method B for **31** (below) for characterization data.

(*R*)-1-(1-Cyclopropylethyl)-3-[6-methoxy-2-(trifluoromethyl) pyridin-3-ylamino]-5-methylpyrazin-2(1*H*)-one (31). Method B (from 13). Bromopyrazinone **13** (50 mg, 0.120 mmol), potassium carbonate (50 mg, 0.360 mmol), methylboronic acid (8 mg, 0.132 mmol), and $Pd(P\text{-}t\text{-}Bu_3)_2$ (13 mg, 0.024 mmol) were combined in dioxane (1 mL) in a sealed vial. Nitrogen was bubbled through the mixture for several minutes, and the reaction mixture was heated at 120 °C for 24 h. The mixture was cooled to room temperature and transferred to a separatory funnel containing saturated aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **31** (10 mg, 23% yield) as a colorless solid: $[\alpha]^{25}_D$ −4.0 (*c* 0.329, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, J = 9.0 Hz, 1H), 8.61 (s, 1H), 6.94 (d, J = 9.0 Hz, 1H), 6.65 (s, 1H), 4.25−4.21 (m, 1H), 3.94 (s, 3H), 2.18 (s, 3H), 1.42 (d, J = 6.8 Hz, 3H), 1.12−1.07 (m, 1H), 0.75−0.69 (m, 1H), 0.53−0.41 (m, 2H), 0.37−0.32 (m, 1H). HRMS (ESI) *m*/*e* 369.1540 [(M + H)$^+$, calcd for $C_{17}H_{20}N_4O_2F_3$ 369.1539]. HPLC method A: t_R = 5.76 min, >99%; method B: t_R = 3.35 min, 97.5%.

(*R*)-1-(1-Cyclopropylethyl)-3-[6-methoxy-2-(trifluoromethyl)-pyridin-3-ylamino]pyrazin-2(1*H*)-one (32). Bromopyrazinone **13** (30 mg, 0.069 mmol) was dissolved in EtOH (2 mL) in a test tube placed inside a Parr bottle and was treated with 10% Pd/C (30 mg, wet, Degussa type). The mixture was placed on a Parr shaker under a hydrogen atmosphere at 50 psi for 1 h. The mixture was filtered through celite with methanol rinsing, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (10% → 20% ethyl acetate in hexanes) to afford **32** (24 mg, 98% yield) as a pale-yellow solid: $[\alpha]^{25}_D$ +27.7 (*c* 0.294, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 8.8 Hz, 1H), 8.41 (s, 1H), 6.85 (d, J = 4.7 Hz, 1H), 6.84 (d, J = 10.0 Hz, 1H), 6.79 (d, J = 4.9 Hz, 1H), 4.18−4.11 (m, 1H), 3.83 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H), 1.05−0.98 (m, 1H), 0.67−0.60 (m, 1H), 0.46−0.41 (m, 1H), 0.40−0.32 (m, 1H), 0.27−0.20 (m, 1H). HRMS (ESI) *m*/*e* 355.1379 [(M + H)$^+$, calcd for $C_{16}H_{18}N_4O_2F_3$ 355.1382]. HPLC method A: t_R = 5.61 min, 95.3%; method B: t_R = 3.08 min, 98.0%.

(*R*)-4-(1-Cyclopropylethyl)-6-[6-methoxy-2-(trifluoromethyl)pyridin-3-ylamino]-5-*oxo*-4,5-dihydropyrazine-2-carbonitrile (33). To a solution of bromopyrazinone **13** (40 mg, 0.092 mmol) in DMF (5 mL) and water (0.075 mL) was added zinc cyanide (11 mg, 0.092 mmol). Nitrogen gas was bubbled through the suspension for 1 min. $Pd_2(dba)_3$ (4.2 mg, 0.005 mmol) and 1,1-bis(diphenylphosphino)ferrocene (dppf) (6.1 mg, 0.011 mmol) were added and the reaction mixture was heated under N_2 at 120 °C for 5 h. The mixture was then cooled to room temperature and transferred to a separatory funnel containing saturated aq NH_4Cl solution (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (30% → 40% ethyl acetate in hexanes) to afford a yellow film. The product was taken up in acetonitrile/water and was frozen and placed on the lyophilizer to afford **33** (25 mg, 71% yield) as a yellow solid: $[\alpha]^{25}_D$ −33.5 (*c* 0.442, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 9.0 Hz, 1H), 8.60 (s, 1H), 7.47 (s, 1H), 6.99 (d, J = 9.1 Hz, 1H), 4.25−4.21 (m, 1H), 3.96 (s, 3H), 1.46 (d, J = 6.8 Hz, 3H), 1.13−1.06 (m, 1H), 0.85−0.78 (m, 1H), 0.64−0.57 (m, 1H), 0.54−0.48 (m, 1H), 0.37−0.32 (m, 1H). HRMS (ESI) *m*/*e* 380.1329 [(M + H)$^+$, calcd for $C_{17}H_{17}N_5O_2F_3$ 380.1334]. Anal. ($C_{17}H_{16}N_5O_2F_3$) C, H, N.

(*R*)-1-(1-Cyclopropylethyl)-5-ethynyl-3-[6-methoxy-2-(trifluoromethyl)pyridin-3-ylamino]pyrazin-2(1*H*)-one (34). Bromopyrazinone **13** (300 mg, 0.69 mmol), Et_3N (190 μL, 1.38 mmol), (trimethylsilyl) acetylene (136 mg, 1.38 mmol), and $Pd(PPh_3)_4$ (160 mg, 0.14 mmol) were combined in DMF (2 mL), and the reaction mixture was heated at 120 °C in a microwave for 2 h. The mixture was cooled to room temperature and was transferred to a separatory funnel containing brine. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford (*R*)-1-(1-cyclopropylethyl)-3-(6-methoxy-2-(trifluoromethyl)pyridin-3-ylamino)-5-((trimethylsilyl)ethynyl)pyrazin-2(1*H*)-one as a yellow solid: $[\alpha]^{25}_D$ −29.1 (*c* 0.350, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 9.1 Hz, 1H), 8.55 (s, 1H), 7.15 (s 1H), 6.97 (d, J = 9.0 Hz, 1H), 4.23−4.17 (m, 1H), 3.93 (s, 3H), 1.44 (d, J = 6.8 Hz, 3H), 1.15−1.09 (m, 1H), 0.78−0.72 (m, 1H), 0.59−0.52 (m, 1H), 0.48−0.42 (m, 1H), 0.39−0.31 (m, 1H), 0.24 (s, 9H). ^{19}F NMR (375 MHz, $CDCl_3$) δ −64.8.

A solution of (*R*)-1-(1-cyclopropylethyl)-3-[6-methoxy-2-(trifluoromethyl)pyridin-3-ylamino]-5-[(trimethylsilyl)ethynyl]pyrazin-2(1*H*)-one (50 mg, 0.118 mmol) from above, 10 N NaOH (1 mL), and MeOH (6 mL) was stirred at room temperature for 1 h. The mixture was transferred to a separatory funnel containing brine. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) and was then taken up in acetonitrile/water and was frozen and placed on the lyophilizer to afford **34** (20 mg, 49% yield) as a tan solid: $[\alpha]^{25}_D$ −29.1 (*c* 0.350, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 9.0 Hz, 1H), 8.56 (s, 1H), 7.19 (s, 1H), 6.96 (d, J = 9.1 Hz, 1H), 4.24−4.19 (m, 1H), 3.93 (s, 1H), 3.03 (s, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.13−1.07 (m, 1H), 0.79−0.72 (m, 1H), 0.59−0.52 (m, 1H), 0.49−0.43 (m, 1H), 0.37−0.32 (m, 1H). HRMS (ESI) *m*/*e* 379.1363 [(M + H)$^+$, calcd for $C_{18}H_{18}N_4O_2F_3$ 379.1382]. Anal. ($C_{18}H_{17}N_4O_2F_3$) C, H, N.

(*R*)-1-(1-Cyclopropylethyl)-5-ethyl-3-[6-methoxy-2-(trifluoromethyl)pyridin-3-ylamino]pyrazin-2(1*H*)-one (35). Compound **34** (200 mg, 0.53 mmol) was dissolved in MeOH (5 mL) and was treated with 10% Pd/C (50 mg, wet, Degussa type). The mixture was stirred under hydrogen (1 atm) for 6 h. The mixture was filtered through celite with methanol rinsing, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford **35** (59 mg, 29% yield) as a pale-yellow amorphous solid: $[\alpha]^{25}_D$ −3.9 (*c* 0.207, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, J = 9.0 Hz, 1H), 8.62 (s, 1H), 6.93 (d, J = 9.1 Hz, 1H), 6.65 (s, 1H), 4.27−4.14 (m, 1H), 3.93 (s, 3H), 2.46 (q, J = 7.3 Hz, 2H), 1.41 (d, J = 6.8 Hz, 3H), 1.21 (t, J = 7.6 Hz, 3H), 1.14−1.06 (m, 1H), 0.75−0.68 (m, 1H), 0.54−0.40 (m, 2H), 0.37−0.31 (m, 1H). HRMS (ESI) *m*/*e* 383.1679 [(M + H)$^+$, calcd for $C_{18}H_{22}N_4O_2F_3$ 383.1695]. HPLC method A: t_R = 6.37 min, >99%; method B: t_R = 3.72 min, >99%.

(*R*)-5-Allyl-1-(1-cyclopropylethyl)-3-[6-methoxy-2-(trifluoromethyl)pyridin-3-ylamino]pyrazin-2(1*H*)-one (36). Bromopyrazinone **13** (150 mg, 0.35 mmol), allyltributyltin (172 mg, 0.52 mmol), and $Pd(PPh_3)_4$ (81 mg, 0.07 mmol) were combined in toluene (1 mL), and the reaction mixture was heated at 120 °C in a microwave for 2 h. The mixture was cooled to room temperature and was transferred to a separatory funnel containing brine. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **36** (70 mg, 51% yield) as a colorless solid: $[\alpha]^{25}_D$ −5.8 (*c* 0.257, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 9.1 Hz, 1H), 8.62 (s, 1H), 6.92 (d, J = 9.0 Hz, 1H), 6.66 (s, 1H), 6.03−5.93 (m, 1H), 5.18−5.12 (m, 2H), 4.26−4.19 (m, 1H), 3.93 (s, 3H), 3.21 (d, J = 6.8 Hz, 2H), 1.41 (d, J = 6.8 Hz, 3H), 1.14−1.05 (m, 1H), 0.75−0.68 (m, 1H), 0.54−0.40 (m, 2H), 0.36−0.30 (m, 1H). HRMS (ESI) *m*/*e* 395.1695 [(M + H)$^+$, calcd for

$C_{19}H_{22}N_4O_2F_3$ 395.1695]. HPLC method A: t_R = 6.61 min, >99%; method B: t_R = 3.82 min, >99%.

Biology. Binding Assays. Frozen rat frontal cortex (source of CRF_1 receptor) or frozen porcine choroid plexus (source of CRF_2 receptor) were thawed rapidly in assay buffer containing 50 mM Hepes (pH 7.0 at 23 °C), 10 mM $MgCl_2$, 2 mM EGTA, 1 μg/mL aprotinin, 1 μg/mL leupeptin, 1 μg/mL pepstatin A, 0.005% Triton X-100, 10U/mL bacitracin, and 0.1% ovalbumin and homogenized. The suspension was centrifuged at 32000*g* for 30 min. The resulting supernatant was discarded and the pellet resuspended by homogenization in assay buffer and centrifuged again. The supernatant was discarded and the pellet resuspended by homogenization in assay buffer and frozen at −70 °C. On the day of the experiment, aliquots of the homogenate were thawed quickly and homogenate (25 μg/well rat frontal cortex or 10 μg/well porcine choroid plexus) added to ligand (150 pM ^{125}I-ovine-CRF for CRF_1 binding or 100 pM ^{125}I-sauvagine for CRF_2 binding) and drugs in a total volume of 100 μL assay buffer. The assay mixture was incubated for 2 h at 21 °C. Bound and free radioligand were then separated by rapid filtration, using glass fiber filters (Whatman GF/B, pretreated with 0.3% PEI) on a Brandel cell harvester. Filters were then washed multiple times with ice cold wash buffer (PBS w/o Ca^{2+} and Mg^{2+}, 0.01% Triton X-100 (pH 7.0 at 23 °C)). Nonspecific binding was defined using 1 μM **3** in the CRF_1 binding assay and 1 μM α-helical CRF (9−41) in the CRF_2 binding assay. Filters were then counted in a Wallac Wizard γ counter. IC_{50} values were determined in a five-point (five drug concentrations) or ten-point (ten drug concentrations) competition assay using nonlinear regression by Microsoft Excel-fit.

Materials. Rat frontal cortex and porcine choroid plexus were obtained from Analytical Biological Services, Inc. (Wilmington, DE). ^{125}I-ovine-CRF (2200 Ci/mmol) and ^{125}I-sauvagine (2200 Ci/mmol) were obtained from PerkinElmer Life Sciences, Inc. (Boston, MA).

Functional Assay (Y-79 Cells). Human Y-79 retinoblastoma cells were suspended in assay buffer (Hank's Balanced Salt Solution containing 2 mM $CaCl_2$, 5 mM $MgCl_2$, 20 mM HEPES, 1 mM IBMX) and plated at 20000 cells/well in a 96-well black plate. CRF antagonists (typically 0.01 to 10,000 nM) were then added to wells as needed and allowed to equilibrate with the cells for 30 min at 37 °C. CRF (1 nM; CRF EC_{50} = 1.11 ± 0.14 nM, n = 6), dissolved in assay buffer + 0.1% BSA, was then added to the wells (30 min at 37 °C) to stimulate the production of cAMP. The reaction was terminated by the addition of a lysis solution containing homogeneous time-resolved florescence (HTRF) cAMP XL665 conjugate followed by HTRF anti-cAMP cryptate conjugate (CIS bio International). Plates were subsequently incubated at room temperature for 1 h prior to reading the time-resolved fluorescence signal. The amount of cAMP produced was estimated from a standard curve prepared using known concentrations of cAMP. The percentage inhibition of CRF-induced cAMP production was determined for each compound (triplicate determinations). The effect of CRF antagonists on basal cAMP production (i.e., in the absence of CRF) was also determined.

Protein Binding Studies. Unbound fraction of test compounds in rats was determined in vitro by equilibrium dialysis using the Dianorm dialysis system. Rat plasma was spiked with the test compound and equilibrated against isotonic phosphate buffer for 3 h at 37 °C. Following the incubation period, plasma and buffer samples were analyzed for compound concentrations using LC/MS/MS. Unbound fraction was calculated based on the ratio between buffer concentration and the plasma concentration.

Rat Pharmacokinetic Studies. Pharmacokinetic parameters were estimated in Sprague−Dawley rats following intravenous (2 mg/kg; n = 3) and oral (10 mg/kg; n = 3) dosing. Intravenous doses were prepared in a vehicle consisting of PEG:ethanol, 90:10 (v/v) at a volume of 1 mL/kg. The oral doses were prepared in a vehicle consisting of 1% Tween 80 in 0.5% methylcellulose suspension at a volume of 3 mL/kg. Blood samples were collected via a jugular vein catheter at 0, 0.17, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h postdose for the intravenous experiment and at 0, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h postdose for the oral experiment. Plasma was separated by centrifugation and stored frozen at −20 °C until analysis. Concentrations were determined by LC/MS/MS.

Cynomolgus Monkey Pharmacokinetic Studies. Pharmacokinetic properties were estimated in Cynomolgus monkeys (n = 3) following a 2 mg/kg intravenous dose. Intravenous doses were prepared in a vehicle consisting of PEG:ethanol, 90:10 (v/v) at a volume of 1 mL/kg. Blood samples were collected via a jugular vein at 0, 0.08, 0.17, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, and 24 h postdose. Plasma was separated by centrifugation and stored frozen at −20 °C until analysis. Plasma concentrations were determined by LC/MS/MS. Pharmacokinetic properties were estimated in Cynomolgus monkeys (n = 3) following a 10 mg/kg oral dose. Oral doses were prepared as a suspension in a vehicle consisting of 1% Tween in 0.5% methylcellulose at a volume 3 mL/kg. Blood samples were collected via a femoral vein at 0, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, and 24 h postdose. Plasma was separated by centrifugation and stored frozen at −20 °C until analysis. Plasma concentrations were determined by LC/MS/MS.

LC/MS/MS Conditions. Sample preparation was conducted as follows. Aliquots (typically, 50 μL) of the biological matrix from in vivo study and standard/QC samples were treated with acetonitrile (200 μL) containing an appropriate internal standard, followed by vortex mixing for 2 min. The supernatant was then separated from the precipitated proteins after a 20 min centrifugation at 3000 rpm, and 200 μL was transferred to a 96-well plate. The supernatant was evaporated under nitrogen using a TurboVap, with the plate heater set at 37 °C, and then reconstituted using 75 μL of 0.1% formic acid.

An aliquot (5 μL) was injected onto a Synergi Fusion-RP column (2 mm × 50 mm, 4 μm) (Phenomenex, Torrance, CA) at room temperature for LC/MS/MS-based analysis (mobile phase = 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B); flow rate = 0.4 mL/min). A combination of isocratic and linear gradients were used for peak separation. The HPLC was interfaced to a Micromass Quattro Ultima LC/MS/MS tandem mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray interface operating in the positive ionization mode. Detection of each analyte was achieved through selected reaction monitoring.

Behavioral Studies: Subjects. Male Sprague−Dawley rats weighing 180−300 g were purchased from Charles River Laboratories (Wilmington, MA.). The rats were housed individually in suspended wire cages in a colony room maintained at constant temperature (21 ± 2 °C) and humidity (50 ± 10%). The room was illuminated 12 h per day (lights on at 0600 h). The rats had ad libitum access to food and water throughout the study. Behavioral studies were conducted between 0600 and 1300 h. Animals were maintained in accordance with the guidelines of the Committee on Animals of the Bristol-Myers Squibb Company, the "Guide for Care and Use of Laboratory Animals" (Institute of Animal Laboratory Resources, 1996), and the guidelines published in the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Research protocols were approved by the Bristol-Myers Squibb Company Institutional Animal Care and Use Committee.

Defensive Withdrawal. The defensive withdrawal procedure was used as previously described.[29] Briefly, the testing apparatus consisted of an opaque plexiglass open field (106 cm length × 92 cm width × 50 cm height) containing a cylindrical galvanized chamber (14 cm length, 10 cm diameter) that was positioned lengthwise against one wall, with the open end 40 cm from the corner. The open field was illuminated by a 60 W incandescent bulb, and illumination was titrated by a powerstat transformer to a 23 lx reading at the entrance to the cylinder. Rats were habituated to handling by gently stroking their dorsal surface for approximately one minute the day before testing. To initiate testing, each rat was placed within the cylinder that was then secured to the floor. Behavior was assessed for 15 min by a trained observer (unaware of

treatment assignment). The latency to exit the chamber, defined by the placement of all four paws into the open field was recorded (in seconds). The plexiglass chamber and the cylinder were cleaned with 1.0% glacial acetic acid between animals to prevent olfactory cues from influencing the behavior of subsequently tested animals. All compounds were prepared in 0.25% methylcellulose suspension and beadmilled overnight. They were administered po, 1 h before testing in a volume of 2 mL/kg body weight. Data were analyzed using an analysis of variance, followed by individual mean comparisons using Fisher's least significant difference test. The significance level was set at $p < 0.05$.

Estimation of In Vivo CRF_1 Receptor Occupancy: Ex Vivo Binding Autoradiography Method. CRF_1 receptor occupancy studies were undertaken using the brain from rats tested in the situational anxiety model. In brief, following oral dosing of the test compound and evaluation in the situational anxiety behavioral test, the rats were sacrificed and the brains and pituitaries were collected, frozen, and sectioned in a Cryostat (20 μM) and the slide-mounted sections were stored at −80 °C. For the ex vivo ligand binding studies,[28] the sections from drug- and vehicle-treated rats were brought to 22−24 °C, air-dried for 20 min, and preincubated for 1 min in an assay solution containing 50 mM HEPES (pH 7.2), 10 mM $MgCl_2$, 2 mM EGTA, 100 KIU/mL aprotinin, 0.1 M bacitracin, and 0.1% ovalbumin. The sections were then incubated for 20 min at 22−24 °C in the same assay solution also containing 0.15−0.20 nM [^{125}I-Tyr^o] sauvagine. For CRF_1 occupancy studies, nonspecific binding was defined in adjacent brain sections from vehicle-treated rats by including 1 μM of **2** in the assay solution. After incubation, the sections were rinsed in cold phosphate buffer saline for 40 s and subsequently dried under a stream of cold air. The slides of sections were then placed in cassettes against iodine-sensitive storage phosphor-imaging screens (PerkinElmer Life Sciences) for 12−16 h, and the screens were then scanned with a Cyclone storage phosphor-imaging system (PerkinElmer Life Sciences). Captured storage phosphor images were analyzed with OptiQuant Acquisition and Analysis software (PerkinElmer Life Sciences). CRF_1 receptor occupancy was calculated as 100% minus % (total [^{125}I-Tyr^o]sauvagine binding in drug-treated minus nonspecific [^{125}I-Tyr^o]sauvagine binding in vehicle-treated)/(total [^{125}I-Tyr^o]sauvagine binding in vehicle-treated minus nonspecific [^{125}I-Tyr^o]sauvagine binding in vehicle-treated).

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Supporting Information Available: Tables of elemental analysis data, high-resolution mass spectral data with HPLC purity data for compounds lacking elemental analysis data, and experimental procedures for the preparation of the dichloropyrazinone intermediates **10c−10m** (corresponding to those used for compounds **12c−12i, 12u**, **12w**, and **12y−12z**). This material is available free of charge via the Internet at http://pubs.acs.org.

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