Journal of Medicinal Chemistry

ARTICLE

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Discovery of *N*-(1-Ethylpropyl)-[3-methoxy-5-(2-methoxy-4-trifluoromethoxyphenyl)-6-methyl-pyrazin-2-yl]amine 59 (NGD 98−2): An Orally Active Corticotropin Releasing Factor-1 (CRF-1) Receptor Antagonist

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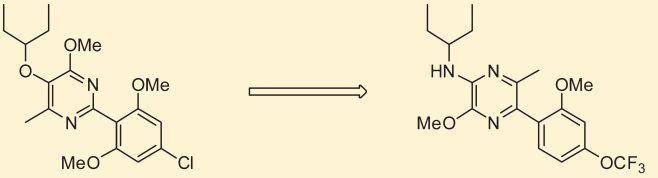
Supporting Information

ABSTRACT: The design, synthesis, and structure−activity relationships of a novel series of pyrazines, acting as corticotropin releasing factor-1 (CRF-1) receptor antagonists, are described. Synthetic methodologies were developed to prepare a number of substituted pyrazine cores utilizing regioselective halogenation and chemoselective derivatization. Noteworthy, an efficient 5-step synthesis was developed for the lead compound **59** (NGD 98−2), which required no chromatography. Compound **59** was characterized as an orally bioavailable, brain penetrant, and highly selective CRF-1 receptor antagonist. Occupancy of rat brain CRF-1 receptors was quantified using *ex vivo* receptor occupancy assays, using both brain tissue homogenates as well as brain slices receptor autoradiography. Behaviorally, oral administration of **59** significantly antagonized CRF-induced locomotor activity at doses as low as 10 mg/kg and dose-dependently reduced the restraint stress-induced ACTH increases.



14 hCRF-1 K*i* = 9 nM
Rat F = 6%

59 hCRF-1 K*i* = 1.0 nM
Rat F = 45%

INTRODUCTION

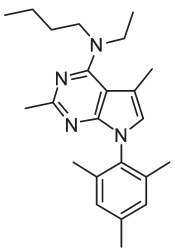
Corticotropin releasing factor (CRF), a 41 amino acid peptide originally isolated by Vale in 1981 from ovine brain extract, is the prime regulator of the hypothalamic-pituitary-adrenal (HPA) stress response.[1] CRF exerts its biological functions through activation of its receptors, CRF-1 and CRF-2, both of which belong to the class B subfamily of G-protein coupled receptors.[2] While the pharmacological benefits of blocking the CRF-2 receptor remain uncertain, evidence from preclinical animal models[3] and early clinical studies[4] suggests that antagonism of the CRF-1 receptor has the potential to produce therapeutically useful anxiolytic and antidepressant effects. The first small molecule CRF-1 receptor antagonists disclosed in the late 1990s, and subsequently well characterized, include **1** (CP-154,5264),[5] **2** (NBI-27914),[6] and **3** (SSR125543A)[7] (Chart 1). These early analogues were very potent *in vitro* and demonstrated efficacy in animal models. However, they are highly lipophilic (cLogP> 7) and poorly water-soluble. Clinical development of compounds of this nature, especially as CNS drugs, has been hindered by issues including unattractive pharmacokinetics, extensive tissue accumulation, and undesirably long elimination half-lives.

In the ensuing years, efforts have focused on reducing the lipophilicity of these molecules[8] to values considered more suitable for a CNS drug (cLogP values between 2 and 5).[9] Successful approaches to lowering lipophilicity have included the replacement of the hydrophobic top-chain with a more polar group (e.g., **4**[10] and **5**[11]) or substitution of the lipophilic pendant phenyl ring by a heterocycle (e.g., the pyridines **6**[12] and **7**[13] and the thiazole **8**[14]).

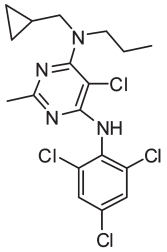
A number of CRF-1 receptor antagonists have been reported to have entered clinical trials for depression and anxiety related disorders.[15] Notably, **7** (R121919) demonstrated efficacy in treating patients with depression in a small open-label phase IIa clinical trial, although further development was halted due to hepatotoxicity issues.[16] In a placebo-controlled clinical study, designed specifically to evaluate whether subchronic treatment with **9** (NBI-34041, Chart 2)[17] would decrease the stress hormone response following a psychological stressor, there was improved resistance to psychological stress by reducing stress hormone secretion.[18] This provided additional clinical support to the CRF-1 receptor antagonism hypothesis. However, in a double-blind, placebo-controlled clinical trial for the treatment of major depressive disorder, **10** (CP-316311)[19] was not efficacious.[20] Likewise, **6** (BMS-562086) also was not efficacious in generalized anxiety disorder.[12b] While the clinical results to date generally have been disappointing, a complete evaluation requires consideration of a number of factors, including the

Received: March 28, 2011
Published: May 27, 2011

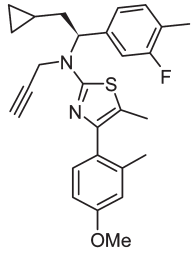
Chart 1. Examples of CRF-1 Receptor Antagonists



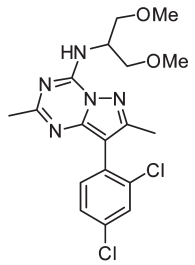
1 hCRF-1 K*i* = 3 nM
cLogP = 7.9
(topology I)



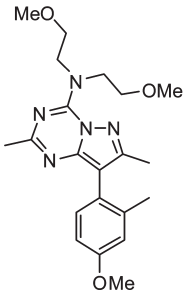
2 hCRF-1 K*i* = 2 nM
cLogP = 8.8
(topology I)



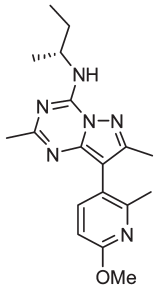
3 hCRF-1 K*i* = 2 nM
cLogP = 7.7
(topology II)



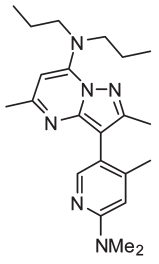
4 hCRF-1 K*i* = 2 nM
cLogP = 3.6
(topology I)



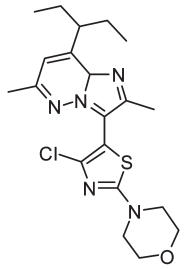
5 rCRF-1 IC_{50} = 4.2 nM
cLogP = 2.9
(topology I)



6 rCRF-1 IC_{50} = 6.1 nM
cLogP = 3.5
(topology I)



7 hCRF-1 K*i* = 3 nM
cLogP = 5.0
(topology I)



8 hCRF-1 K*i* = 0.2 nM
cLogP = 4.9
(topology I)

potential need to target clinical subpopulations with demonstrated CRF-1 receptor hyperactivation in stress response pathways.[15a,b] A number of additional compounds,[21] including **11** (CP-376395),[21a] **5** (BMS-561388),[11] and GSK 561679,[21b] have been reported to enter clinical trials. The results of these trials and additional clinical studies, in particular, those with structurally diverse CRF-1 receptor antagonists, may further define the role of CRF in various human illnesses.

Structural features common to most CRF-1 receptor antagonists include a core central heterocycle that contains a critical hydrogen bond acceptor; an out-of-plane pendant aromatic ring; and a top side-chain filling a largely hydrophobic area of the receptor. These have previously been classified into two topologies based on distinct structural features.[8c] In the first topology, which contains the majority of compounds to have reached advanced preclinical development or clinical stage, the hydrogen bond acceptor and the pendant aryl substituent are separated by two atoms (e.g., **1**), while in the second topology, a single intervening atom is present (e.g., **3**).

Given the relatively limited patentable chemical space within topology I, we set out to examine the possibility of identifying and characterizing novel CRF-1 receptor antagonists from the relatively under-explored topology II template. We have previously reported that repositioning of the pendant aryl group, the hydrogen bond acceptor, and the 2-methyl group of the quinoline **12**[22] (topology I) led to the identification of the novel isoquinoline **13**, which formally belongs to the topology II template class (Chart 3).[23] In an effort to increase hydrophilicity and improve general pharmacokinetic properties, the bicyclic isoquinoline was replaced with a less lipophilic, monocyclic pyrimidine core. Identified compounds with good *in vitro* potencies (e.g., **14**) were optimized.[24] However, despite lower lipophilicity and increased solubility relative to isoquinoline **13**, very poor oral exposures in rat rendered this series of compounds unsuitable for further evaluation. The low oral exposures were attributed, in part, to metabolic liabilities (based on their poor *in vitro* microsomal stability), which proved difficult to overcome within the pyrimidine series. To circumvent this issue, we investigated other monocyclic heterocycles as replacements of the pyrimidine core. In this paper, we describe the synthesis and evaluation of a series of pyrazine analogues (generic structure **15**) as CRF-1 receptor antagonists. A related series of pyrazine analogues from the topology II class of CRF-1 receptor antagonists were also recently described.[25] The most potent analogue was **16** with a top-chain derived from *cis*-1-amino-2-indanol and the ether linked 4-methylpyridine.

CHEMISTRY

The general syntheses of the substituted 3,6-diethyl pyrazines described in this study are outlined in Scheme 1. Buchwald coupling of the known 2-chloro-3,6-diethylpyrazine **17**[26] with 1-ethylpropylamine produced amine **18a**. Bromination of **18a** with *N*-bromosuccinimide (NBS) yielded the 5-bromopyrazine **18b**. The introduction of different aryl groups at the 5-position in the final step was accomplished by Suzuki coupling of **18b** with substituted aryl boronic acids and afforded good yields of the aryl-pyrazines **19a**−**m**. Alternatively, the top-chain could be introduced in the final step. To this end, the aryl ring was first introduced by Suzuki coupling of **17** and 2,4-dichlorophenylboronic acid, which gave **20** in good yield. Direct chlorination of **20** was not possible, but formation of the *N*-oxide and treatment with phosphorus oxychloride gave a moderate yield of **21**. The 2-chloropyrazine **21** proved to be an excellent intermediate for

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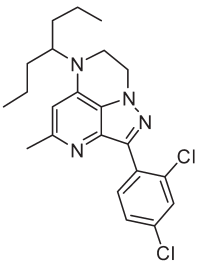
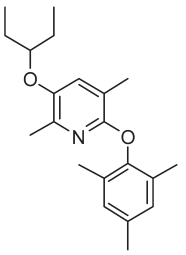
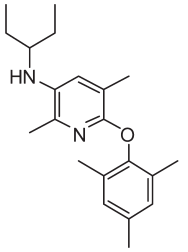
Chart 2. Additional CRF-1 Receptor Antagonists Reported to Have Reached Clinical Trials



9 hCRF-1 K*i* = 4.0 nM
cLogP = 8.2
(topology I)

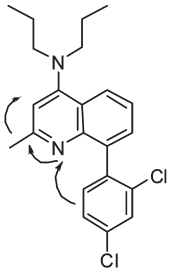


10 rCRF-1 IC_{50} = 6.8 nM
cLogP = 7.6
(topology I)



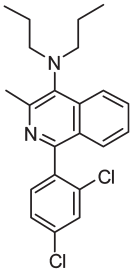
11 rCRF-1 IC_{50} = 5.1 nM
cLogP = 7.6
(topology I)

Chart 3. Evolution of Topology II CRF-1 Receptor Antagonists

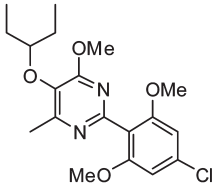


12 hCRF-1 K*i* = 0.9 nM
cLogP = 8.4
(topology I)

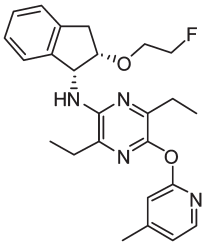
3 group shift



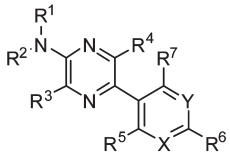
13 hCRF-1 K*i* = 103 nM
cLogP = 8.4
(topology II)



14 hCRF-1 K*i* = 9 nM
cLogP = 5.0
Rat F = 6%
(topology II)



16 hCRF-1 K*i* = 11 nM
cLogP = 5.2
(topology I)



15 (topology II)

the introduction of a variety of top-chains with different linking atoms in the final step. For example, (i) Buchwald amination gave the *N*-substituted analogues **22a**−**g**; (ii) reaction with the alkoxide of 3-pentanol gave the ether **23**; (iii) addition of the anion of butan-2-thiol gave the *S*-linked analogue **24**; and (iv) Suzuki coupling with the borane derived from the hydroboration of 3-methylenepentane with 9-borabicyclo[3.3.1]nonane (9-BBN) gave the *C*-linked analogue **25**.

For analogues that keep the 6-ethyl group constant, the synthesis of compounds with different groups at the 3-position is described in Scheme 2. Commercially available 2,6-dichloropyrazine **26** proved to be an excellent starting material in this regard. Thermal reaction of **26** with 1-ethylpropylamine gave only the monosubstituted pyrazine **27** in 84% yield. Optimal conditions to introduce the 6-ethyl group proved to be a Kumada,[27] $NiCl_2$(dppp)-catalyzed Grignard reaction, which gave minimal reduction of the starting material and produced the desired 6-ethylpyrazine **28** in 87% yield. Treatment of **28** with NBS gave predominantly bromination at the 5-position, and the 5-bromopyrazine **29** was isolated in 70% yield following chromatography. The aryl ring was introduced by Suzuki coupling of **29** and 2,4-dichlorophenylboronic acid, which gave **30** in 96% yield. With the 2-, 5-, and 6-substituents in place, a number of groups could be introduced at the 3-position. Halogenation at the 3-position gave the corresponding 3-fluoro **31**, 3-chloro **32**, 3-iodo **33**, and 3-bromo **34** analogues. The 3-bromopyrazine **34** was used to introduce either an ether substituent at the 3-position (e.g., **35** and **36**) or an alky group (e.g., **37** and **38**). In a similar manner, the 3,6-dimethylpyrazine analogue **39** was prepared from commercially available 2-chloro-3,6-dimethylpyrazine.

The synthesis of the 3-ethyl-6-methylpyrazine core is shown in Scheme 3. Bromination of the 2-aminopyrazine **27** afforded

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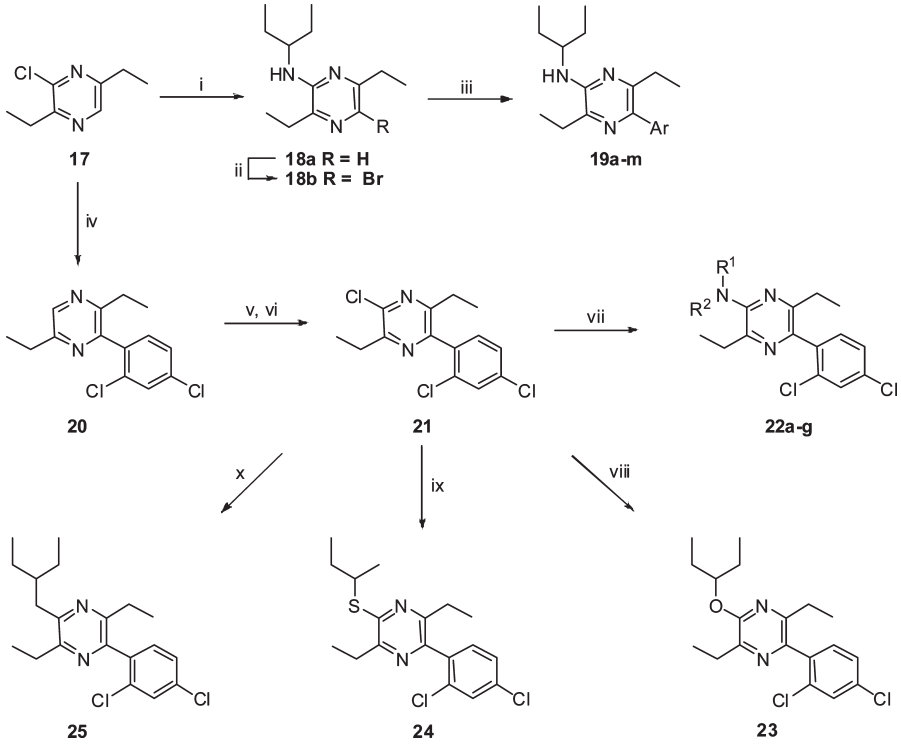
Scheme 1. General Synthesis of Substituted 3,6-Diethyl Pyrazines[a]



[a] Reaction conditions: (i) 1-ethylpropylamine, $Pd_2(dba)_3$, BINAP, Na^{t}OBu, PhMe, 80 °C (71%); (ii) NBS, $CHCl_3$, 0 °C to room temperature (83%); (iii) $ArB(OH)_2$, 2 M K_2CO_3, $Pd(PPh_3)_4$, PhMe, 85 °C (83%); (iv) 2,4-dichlorophenylboronic acid, 2 M K_2CO_3, $Pd(PPh_3)_4$, PhMe, 90 °C (98%); (v) MCPBA, CH_2Cl_2, 0 °C; (vi) $OPCl_3$, 90 °C (50% over two steps); (vii) HNR^1R^2, $Pd_2(dba)_3$, P^{t}Bu$_3$, K^{t}OBu, PhMe, 80 °C (57−79%); (viii) 3-pentanol, NaH, NMP, 70 °C (77%); (ix) butan-2-thiol, NaH, THF, reflux (51%); (x) 3-methylenepentane, 9-BBN, THF, reflux, then $Pd(PPh_3)_4$, NaOH, H_2O, 50 °C (37%).

5-bromopyrazine **40** in 77% yield. Suzuki coupling of **40** was selective for the 5-bromo position and gave the pyrazine **41** in 94% isolated yield. A second bromination gave the 3-bromo-6-chloropyrazine **42**. Suzuki coupling of **42** with ethylboronic acid gave a 49% isolated yield of the desired product **43**. LCMS and TLC (thin layer chromatography) analyses of the crude reaction mixture also indicated the presence of unreacted starting material **42** and the debrominated product **41**. Again, optimal conditions to introduce the 6-alkyl group proved to be a Kumada coupling reaction, which minimized formation of reduction side-product and produced the desired 6-methylpyrazine **44** in 58% isolated yield.

The 6-chloropyrazine **41** also proved to be a useful intermediate in the synthesis of the 3,6-dimethoxypyrazine **46**, 3-methyl-6-methoxypyrazine **47**, and the isomeric 3-methoxy-6-methylpyrazine **48** (Scheme 4). Treatment of **41** with sodium methoxide installed the 6-methoxy group, and subsequent bromination with NBS gave 3-bromopyrazine **45**. Introduction of a second methoxy group was possible (sodium methoxide in NMP at 80 °C for three days) and gave the target **46** in 65% yield. A Kumada reaction of **45** with methyl magnesium bromide gave a 47% yield of the 3-methyl-6-methoxypyrazine **47**. The 3-methoxy-6-methylpyrazine **48** was obtained by reversing the order of reactions from the 6-chloropyrazine **41** (Kumada nickel-catalyzed Grignard reaction, NBS bromination, and reaction with sodium methoxide).

A route to 3-ethyl-6-methoxy substituted analogues, that allowed the introduction of the 5-aryl group in the final step, was developed (Scheme 5). Reaction of the 6-chloropyrazine **27** with sodium methoxide gave **49**, and bromination with NBS produced a mixture of the two momobromides **50** and **51b** accompanied by the dibromide **51a**, which were separated by flash chromatography. Nickel-catalyzed reaction of **50** with ethyl magnesium bromide gave a mixture of the 3-ethylpyrazine **52** and the reduction product **49**, which were separated by chromatography in 64% and 29% isolated yields, respectively. Bromination of **52** gave **53** and Suzuki coupling gave the final target **54**.

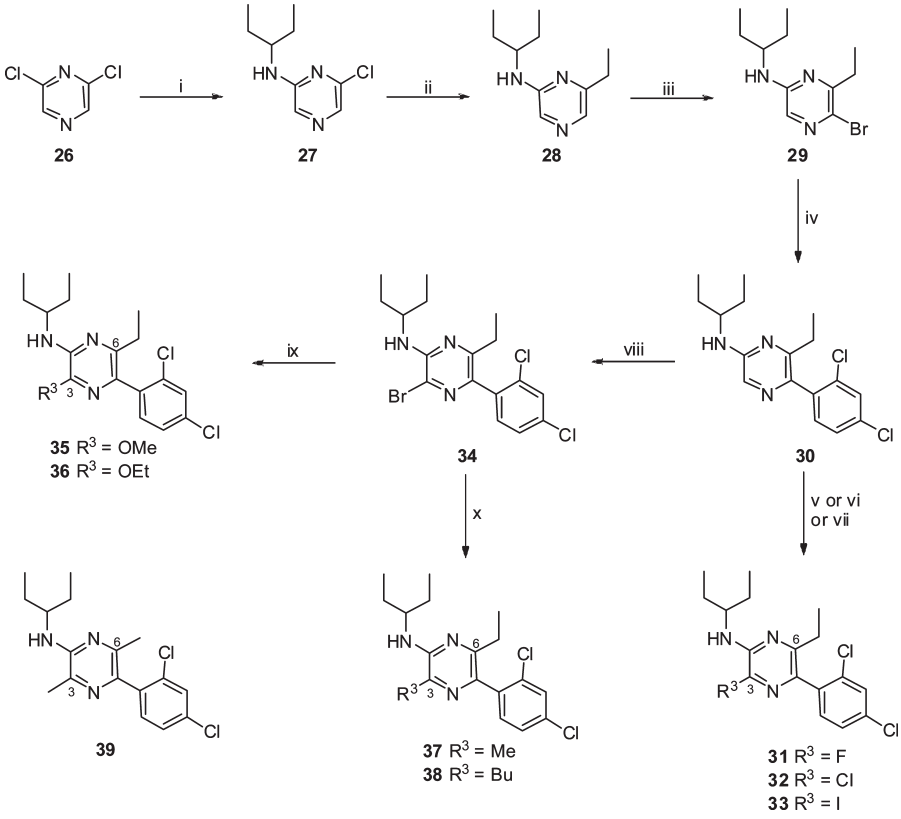
Compounds **55**−**65** described in the study were prepared using chemistry analogous to that outlined in the above schemes.

RESULTS AND DISCUSSION

The compounds described in this study are listed in Tables 1, 2, 3, and 4. The affinity of these compounds for the CRF-1 receptor was determined by using a modified version of the assay described by Grigoriadis and De Souza[28] and by examining their competition with ^{125}I-sauvagine at membrane preparations of CRF-1 receptors endogenously expressed in IMR-32 human neuroblastoma cells. The effects of changes to the top-chain are summarized in Table 1. The 2,4-dichlorophenyl and the 3,6-diethylpyrazine core were kept unchanged to allow comparison among compounds in the table. Small, secondary amines were investigated first, with both the isopentyl amine **19a** and the dicyclopropyl analogue **22a** having excellent affinity at the CRF-1 receptor (hK_i = 4.1 and 3.7 nM, respectively). However, the lipophilicity of both compounds was high (cLogP > 7). Introduction of methoxy ether substituents into the top-chain of a

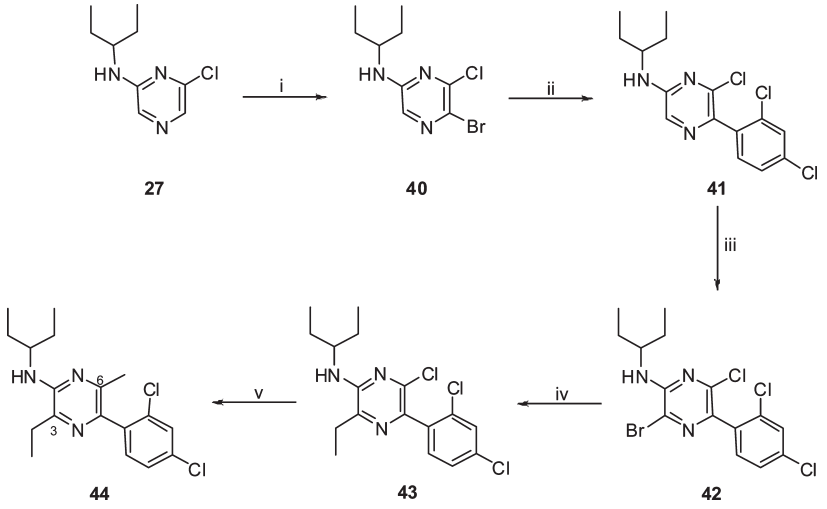
dx.doi.org/10.1021/jm200365y |J. Med. Chem. 2011, 54, 4187–4206

Scheme 2. Representative Synthesis of 3-Substituted-6-Alkyl Pyrazines[a]



[a] Reaction conditions: (i) 1-ethylpropylamine, PrOH, Et_3N, 98 °C (84%); (ii) EtMgBr, THF, $NiCl_2$(dppp), 10−15 °C (87%); (iii) NBS, $CHCl_3$, 0 °C (70%); (iv) 2,4-dichlorophenylboronic acid, 1 M Na_2CO_3, $Pd(PPh_3)_4$, DME, 90 °C (96%); (v) SelectFluor, $CHCl_3$, 0 °C (63%); (vi) NCS, $CHCl_3$, 0 °C (74%); (vii) NIS, $CHCl_3$, 0 °C (70%); (viii) NBS, $CHCl_3$, 0 °C (93%); (ix) $NaOR^3$, R^3OH, NMP, 75 °C (49−85%); (x) R^3 MgBr, THF, $NiCl_2$(dppp), room temperature (65−76%).

Scheme 3. Representative Synthesis of 3-Ethyl-6-Methyl Pyrazines[a]

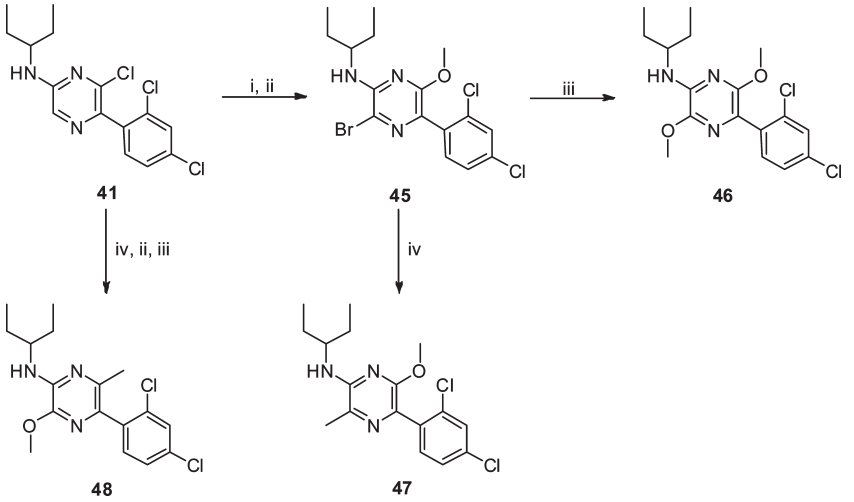


[a] Reaction conditions: (i) NBS, $CHCl_3$, 0 °C (77%); (ii) 2,4-dichlorophenylboronic acid, 1 M Na_2CO_3, $Pd(PPh_3)_4$, DME, 90 °C (94%); (iii) NBS, $CHCl_3$, 0 °C (86%); (iv) $EtB(OH)_2$, 1 M Na_2CO_3, $Pd(PPh_3)_4$, DME, 90 °C (49%); (v) MeMgBr, THF, $NiCl_2$(dppp), 10−15 °C (58%).

topology I template (e.g., pyrazolotriazine **4**) reduced lipophilicity, while maintaining CRF-1 receptor affinity. Unfortunately, in the pyrazine series (e.g., **22b**), this modification resulted in a considerable loss in affinity (hK_i = 224 nM). Furthermore, incorporation of a basic amine into the top-chain (e.g., **22c**) was not tolerated. It is also interesting to note that the isopentyl amine top-chain only gave moderately active compounds in the topology I pyrazine series previously described by Corbett

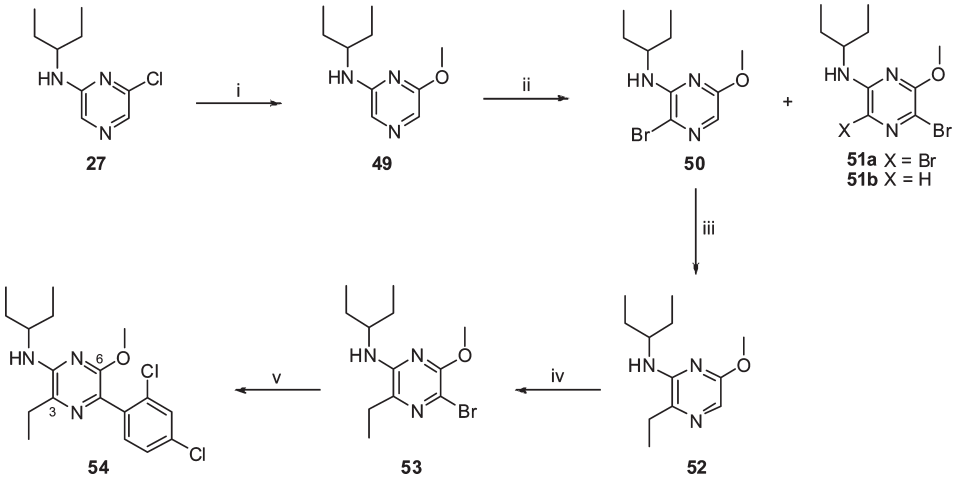
dx.doi.org/10.1021/jm200365y |J. Med. Chem. 2011, 54, 4187–4206

Scheme 4. Synthesis of Various Methoxypyrazines[a]



[a] Reaction conditions: (i) NaOMe, MeOH, NMP, 75 °C; (ii) NBS, $CHCl_3$, 0 °C (73% over two steps); (iii) NaOMe, MeOH, NMP, 75 °C (65%); (iv) MeMgBr, THF, $NiCl_2$(dppp), 10−15 °C (47%).

Scheme 5. Representative Synthesis of 3-Alkyl-6-Substituted Pyrazines[a]



[a] Reaction conditions: (i) NaOMe, MeOH, NMP, 50 °C (92%); (ii) NBS, $CHCl_3$, 0 °C (29%); (iii) EtMgBr, THF, $NiCl_2$(dppp), 0 °C (64%); (iv) NBS, $CHCl_3$, 0 °C (98%); (v) 2,4-dichlorophenylboronic acid, 2 M K_2CO_3, $Pd(PPh_3)_4$, DME, 75 °C (99%).

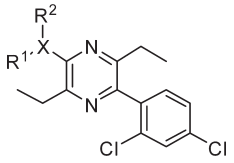
(hK_i > 100nM); in that series, top-chains derived from *cis*-1-amino-2-indanol were preferred (e.g., **16**, K_i = 11 nM).[25] Unfortunately, the analogous *cis*-1-amino-2-indanol derived analogues were not made in the present study and so could not be compared. In terms of stability, the quinoline[22] and pyrimidine[23] templates were plagued by short microsomal half-lives and poor oral exposures in rat. Despite its high lipophilicity, isopentyl amine **19a** had an encouraging stability in human microsomes ($T_{1/2}$ = 17 min) and modest stability in rat microsomes ($T_{1/2}$ = 4.2 min). In an *in vivo* rat PK study on **19a**, its short microsomal half-life did not translate to either a short half-life or high clearance (Table 5). Compound **19a** had low clearance (16 mL/min/kg), compared to 65 mL/min/kg for rat hepatic blood flow, and a moderate volume of distribution of 6.5 L/kg and a $T_{1/2}$ of 4.9 h. In addition, **19a** had an oral bioavailability of 83% and high brain penetration (brain to plasma ratio of 2.5). In the pyrazine series, in general, microsomal stability was better than in the corresponding quinoline or pyrimidine series, particularly in human microsomes. Turnover in rat microsomes for the series was much higher than in human microsomes, although, *in vivo*, the compounds tested generally had lower clearance and longer half-lives than might have been predicted from microsomal data.

In the pyrimidine template, tertiary alkyl amine top-chains were the preferred substituent in terms of CRF-1 receptor activity. However, the pyrazine series was also different in this regard, too. For example, the tertiary amines **22d** and **22e** were 4−5-fold less active than the isopentyl amine **19a**. Not surprisingly, addition of ethers (**22f**) or alkyl amine (**22g**) to the top-side chain did not improve the affinity. Changing the linking atom (X) from nitrogen to oxygen (**23**) or carbon (**25**) brought about a 10-fold loss in affinity relative to **19a**, while the sulfur analogue (**24**, *sec*-butyl top-chain) was considerably less active.

The 3-pentyl amine top-chain and 3,6-diethylpyrazine core were kept constant as the 2-aryl group was modified (Table 2).

dx.doi.org/10.1021/jm200365y |*J. Med. Chem.* 2011, 54, 4187–4206

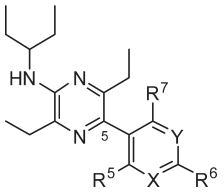
Table 1. Effects of the Top-Chain and Linking Atom (X) on CRF-1 Receptor Binding



					microsomal $T_{1/2}$ (min)		
no	X	R^1	R^2	cLogP	*h*	*r*	hCRF-1 K_i (nM)[a]
19a	N	H	$CH(Et)_2$	7.4	17	4.2	4.1 ± 1.4
22a	N	H	$CH(^cPr)_2$	7.3	11	2.5	3.7 ± 1.2
22b	N	H	$CH_2(CH_2OMe)_2$	5.3	9	2.5	224 ± 56
22c	N	H	$CH(Me)CH_2NMe_2$	6.1	7	<1	489 ± 202
22d	N	$CH_2{}^cPr$	$CH_2{}^cPr$	7.6	8	<1	26 ± 9
22e	N	^{n}Pr	$CH_2{}^cPr$	7.7	12	4.2	19.2 ± 4
22f	N	CH_2CH_2OMe	CH_2CH_2OMe	5.7	2	<1	128 ± 37
22g	N	^{n}Pr	$CH_2CH_2NMe_2$	6.9	5	<1	1538 ± 582
23	O	-	$CH(Et)_2$	7.6	10	2.5	46 ± 27
24	S	-	$CH(CH_3)CH_2CH_3$	7.8	17	4.1	401 ± 126
25	CH	H	$CH(Et)_2$	7.7	13	2.5	68 ± 14

[a] Unless otherwise stated, all values are the mean ± SEM of at least three separate experiments.

Table 2. Effects of the 5-Aryl Substituent on CRF-1 Receptor Binding



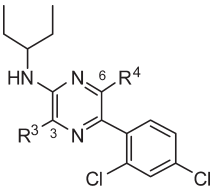
							microsomal $T_{1/2}$ (min)		
no	R^5	R^6	R^7	X	Y	ClogP	*h*	*r*	hCRF-1 K_i (nM)[a]
19a	Cl	Cl	H	CH	CH	7.4	17	4.2	4.1 ± 1.4
19b	OMe	OMe	H	CH	CH	5.8	8	2.5	7.3 ± 1.9
19c	OMe	OCF_3	H	CH	CH	6.9	13	2.5	7.2 ± 3.4
19d	OMe	OEt	H	CH	CH	6.3	nt	nt	7.8 ± 4.3
19e	OMe	OiPr	H	CH	CH	6.6	11	<1	4.2 ± 1.7
19f	OMe	Me	H	CH	CH	6.2	11	<1	23.7 ± 3.8
19g	OMe	CF_3	H	CH	CH	7.3	11	nt	5.6 ± 0.9
19h	OH	OMe	H	CH	CH	5.6	18	5.9	1181 ± 476
19i	OCF_3	OMe	H	CH	CH	6.9	16	4.1	4.1 ± 0.8
19j	CF_3	OMe	H	CH	CH	7.3	12	4.3	4.4 ± 2.1
19k	H	Me	NMe_2	N	CH	6.1	7	<1	7.6 ± 2.4
19l	OMe	OMe	H	N	CH	5.6	9	2.5	11.6 ± 3.8
19m	OMe	OMe	H	N	N	5.3	7	<1	17.2 ± 6.7

[a] Unless otherwise stated, all values are the mean ± SEM of at least three separate experiments; nt = not tested.

For optimal CRF-1 receptor binding, previous studies[29] suggested that the aryl ring lies out of the plane of the core heterocycle, and that an *ortho*-substituent is generally required to enforce this conformation. Our earlier results with topology II templates were in accord with this model, and, for these reasons, analogues were focused on the 2,4-disubstitution pattern. The 2,4-dimethoxyphenyl analogue **19b** had similar affinity to the 2,4-dichloro analogue **19a**, but it was less stable in human microsomes. The five analogues **19c**−**19g** retained the 2-OMe group as the 4-position was varied. The 4-OCF_3 **19c**, 4-OEt **19d**, and 4-O^{i}Pr **19e** had very similar affinities and stability in human microsomes. The 4-Me analogue **19f** was approximately 3-fold

dx.doi.org/10.1021/jm200365y |*J. Med. Chem.* 2011, 54, 4187–4206

Table 3. Effects of Variations to the R^3 and R^4 Groups on CRF-1 Receptor Binding



				microsomal $T_{1/2}$ (min)		
no	R^3	R^4	ClogP	*h*	*r*	hCRF-1 K_i (nM)[a]
19a	Et	Et	7.4	17	4.2	4.1 ± 1.4
30	H	Et	6.4	28	nt	545 ± 78
31	F	Et	6.6	73	21	167 ± 26
32	Cl	Et	7.2	10	<1	71 ± 12
33	I	Et	7.3	nt	nt	12 ± 2.1
35	OMe	Et	7.4	35	nt	5.9 ± 0.6
36	OEt	Et	7.9	120	74	151 ± 27
38	^{n}Bu	Et	8.5	22	4.2	3657 ± 437
37	Me	Et	6.9	27	11	54 ± 7.6
44	Et	Me	6.9	18	4.2	8.6 ± 1.4
39	Me	Me	6.4	29	3.2	27 ± 4.0
48	OMe	Me	6.8	nt	nt	4.3 ± 0.8
46	OMe	OMe	6.6	16	2.5	8.4 ± 1.1
47	Me	OMe	6.6	56	17	14.4 ± 3.0
54	Et	OMe	7.1	42	11	8.0 ± 2.2

[a] Unless otherwise stated, all values are the mean ± SEM of at least three separate experiments; nt = not tested.

less active than the 4-OMe analogue **19b**, but switching from Me to CF_3 (**19g**) improved the receptor affinity. Demethylation of the *ortho* methoxy group of **19b** gave the 2-phenol **19h** and a dramatic loss in affinity (hK_i = 1181 nM). This loss in affinity can be attributed to an intramolecular H-bond interaction between the 2-OH and the pyrazine nitrogen, enforcing a more planar orientation between the core and the aryl ring. Other changes to the 2-position (e.g., **19i** ($R^5 = OCF_3$) and **19j** ($R^5 = CF_3$)) resulted in compounds of similar affinity to **19b**. Our SAR findings at the 2-position are in contrast to the *O*- and *N*-aryl linked pyrazine series described by Corbett; in that series, 2-substitution on the aryl ring was not well tolerated. In the *O*- and *N*-aryl linked pyrazine series, compounds presumably adopted an alternative binding mode and ether-linked 4-methylpyridines were preferred (e.g., **16**, K_i = 11 nM).[25] Previous approaches to lowering the lipophilicity of CRF-1 receptor antagonists have included replacement of the aryl ring by a more polar heterocycle (e.g., **7**, Figure 1). Indeed, the dimethylaminopyridine **19k**, the dimethoxy pyridine **19l**, and the pyrimidine **19m** had similar activity, lipophilicity, and microsomal stability as **19b**.

Variations to the 3- and 6-pyrazine substituents were next examined, and the data are summarized in Table 3. In examples 30 to 38, the R^4 group was kept constant (R^4 = Et) and the R^3 group was varied. Deletion of the R^3 substituent (**30**, R = H) resulted in a dramatic loss in affinity compared to the diethyl analogue **19a**. Introduction of a halogen substituent improved affinity as the size of the substituent increased from fluoro **31**, to chloro **32**, to iodo **33**, although affinities under 10 nM were not achieved. The 3-methoxy analogue **35** had comparable activity to the parent **19a**. However, increasing the size to ethoxy **36** resulted in a substantial loss in activity. Increasing the size of the substituent to butyl **38** resulted in an almost complete loss in activity, and contracting the 3-ethyl group to 3-methyl **37** led to a 10-fold loss in activity. Reversing the R^3 and R^4 substituents, however, (R^3 = Et, R^4 = Me, **44**) produced a significant boost in affinity (compare **44** with **37**), although the size of the R^3 group could not be reduced further without a loss in affinity (R^3 = Me, **39**). The analogue **48** (R^3 = OMe) had both excellent affinity and microsomal stability. In the final three examples, R^4 = OMe was kept constant as the R^3 group was varied. The R^3 = OMe and Et analogues **46** and **54** had similar activity (hK_i = 8.4 and 8.0 nM) although **54** was more stable in microsomes. Modifications to the R^3 and R^4 groups also brought about some interesting changes in lipophilicity. Surprisingly, the change in R^3 from Et to OMe had no effect on ClogP (compare **19a** to **35**), whereas the change in R^4 from Et to OMe resulted in the expected reduction of ClogP from 7.4 to 7.1 (compare **19a** to **54**). Presumably, in compound **35**, an internal hydrogen bond between the NH and 3-OMe masks the change in polarity. The same unexpected effect was observed between the methyl analogues **48** (ClogP = 6.8) and **47** (ClogP = 6.6).

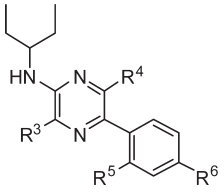
The 3-methoxy-6-ethyl-, 3-methoxy-6-methyl-, and 3-ethyl-6-methoxy-pyrazine cores (analogues **35**, **48**, and **54**) were identified as having a good balance between CRF-1 receptor affinity and lipophilicity, and a number of compounds with different 5-aryl groups were prepared with these cores (Table 4). Compounds from all three different cores were identified with excellent affinity at the human CRF-1 receptor and low turnover in human microsomes (**55**−**65**). The most potent compound was the 3-methoxy-6-methyl-pyrazine **59** (hK_i = 1.0 nM), which was also stable in both human and rat microsomes.

Compound **59** was selected for further evaluation. An improved synthesis, capable of generating multigram quantities, was developed as outlined in Scheme 6. The Kumada reaction proved to be the method of choice for the introduction of the methyl group, and an 87% yield of **66** resulted from the reaction of **27** and methylmagnesium bromide. Bromination of **66** with 2 equiv of bromine gave the corresponding dibromide, which was used without purification in the next step. Treatment of the dibromide with sodium methoxide was selective and gave the 3-methoxy-5-bromopyrazine **67** in an excellent 85% yield. Finally, Suzuki coupling of **67** with 2-methoxy-4-trifluoromethoxyphenylboronic acid gave an 89% yield of **59**. The 5-step sequence, from commercially available 2,6-dichloropyrazine **26**, could be performed conveniently on a 500 g scale, required no chromatography, and resulted in an overall yield of 46% of compound **59**.

The functional activity of **59** was assessed in whole IMR-32 cells. In this system, the CRF peptide dose-dependently stimulated the production of 3′-5′-cyclic adenosine monophosphate (cAMP) (EC_{50} = 0.5 ± 0.1 nM). Under the same conditions, compound **59** had no effect on cAMP production at concentrations as high as 10 μM. Compound **59**, however, dose-dependently antagonized the cAMP production stimulated by a 3.0 nM concentration of CRF with an IC_{50} of 93 ± 23 nM. These data confirm that compound **59** is a functional antagonist at the CRF-1 receptor. Related analogues tested from the series (data not shown) were also confirmed to be functional antagonists at the CRF-1 receptor.

The 3,6-diethylpyrazine **19a** had an encouraging pharmacokinetic profile in rat. Compound **59** also demonstrated encouraging oral and high brain exposure (Table 5). Following oral

Table 4. Examples of Compounds with 3-Methoxy-6-ethyl-, 3-Methoxy-6-methyl- and 3-Ethyl-6-methoxy-pyrazine Cores



						microsomal $T_{1/2}$ (min)		
no	R^3	R^4	R^5	R^6	ClogP	*h*	*r*	hCRF-1 K_i (nM)[a]
19a	Et	Et	Cl	Cl	7.4	17	4.2	4.1 ± 1.4
55	OMe	Et	Et	OMe	5.7	120	120	1.9 ± 0.2
56	OMe	Et	OMe	CF_3	5.5	73	23	4.4 ± 0.9
57	OMe	Et	CF_3	OMe	7.3	120	120	2.2 ± 0.3
58	OMe	Et	Cl	$OCHF_2$	7.2	120	47	1.4 ± 0.2
59	OMe	Me	OMe	OCF_3	6.3	120	120	1.0 ± 0.4
60	OMe	Me	OMe	CF_3	6.2	120	120	1.3 ± 1.0
61	OMe	Me	Cl	$OCHF_2$	6.7	120	48	4.6 ± 0.9
62	OMe	Me	Cl	OEt	6.7	120	47	5.9 ± 0.7
63	Et	OMe	OMe	OCF_3	5.4	52	36	6.1 ± 1.1
64	Et	OMe	Cl	OMe	6.5	120	nt	1.1 ± 0.3
65	Et	OMe	Cl	$OCHF_2$	6.9	120	17	2.5 ± 0.8

[a] Unless otherwise stated, all values are the mean ± SEM of at least three separate experiments; nt = not tested.

Table 5. Rat Pharmacokinetic Data for 19a and 59[a]

no	iv/po dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0-24\ h}$ (ng.h/mL)	T_{max} (h)	$T_{1/2}$ (h)	CL (mL/min/kg)	V_{ss} (L/kg)	*F* (%)	B/P
19a	3/5	627	4309	1.3	4.9	16	6.5	83	2.5
59	1/10	456	4499	4	8.4	12	7.8	45	5.4

[a] Compounds were dosed in 2% Vitamin E TPGS (tocopheryl polyethylene glycol 1000 succinate).

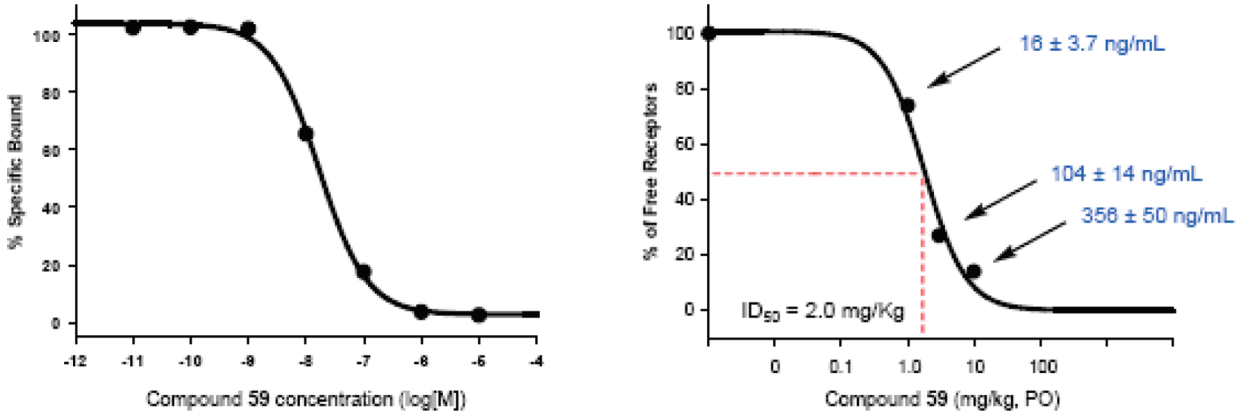


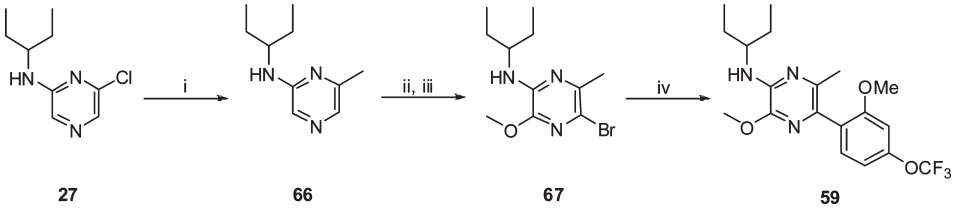
Figure 1. Rat cortical homogenate CRF-1 receptor binding. Left panel: compound **59** dose-dependently displaces the binding of [^{125}I]-sauvagine from rat CRF-1 receptor (rat cortical membrane homogenate) with a K_i = 9.8 ± 1.7 nM.

administration, **59** also had higher brain penetration (brain to plasma ratio greater than 5) but lower oral exposure (compounds **19a** and **59** had similar $AUC_{0-24\ h}$, but **59** was at twice the dose). In a subsequent assessment, plasma protein binding compound **59** was determined to be 99.2% bound to human plasma protein.

In order to quantitatively evaluate the rat cortical CRF-1 receptor occupancy of compounds following oral dosing, *ex vivo* binding methods were utilized. Prior to the *ex vivo* determinations, a control study using [^{125}I]-sauvagine, in which multiple concentrations of test compound were directly added to

dx.doi.org/10.1021/jm200365y |*J. Med. Chem.* 2011, 54, 4187–4206

Scheme 6. Optimized Synthesis of 59[a]



[a] Reaction conditions: (i) MeMgCl, THF, $NiCl_2$(dppp), room temperature (87%); (ii) Br_2, HOAc (84%); (iii) NaOMe, MeOH, 65 °C (85%); (iv) 2-methoxy-4-trifluoromethoxyphenylboronic acid, 2 M K_2CO_3, $Pd(PPh_3)_4$, PhMe, 85 °C (89%).

Table 6. *Ex Vivo* Data for 59 and 7

no	hCRF-1 K_i (nM)	rat cortex K_i (nM)	*ex vivo* ID_{50} (mg/kg)	*ex vivo* IC_{50} (ng/mL)
59	1.0 ± 0.4	9.8 ± 1.7	2.0	71
7	8.7 ± 1.6	3.8 ± 1.1	7.2	74

rat cortical membranes, was performed. In the case of **59**, this exogenous addition experiment generated a K_i = 9.8 ± 1.7 nM (Figure 1, left-hand panel). Quantitative determination of the CRF-1 receptor occupancy of **59**, following oral administration (1, 3, and 10 mg/kg), was determined by assessing the amount of specific [^{125}I]-sauvagine bound and comparing that to the amount specifically bound in the vehicle-treated rats (theoretical 100% occupancy). Dose−response studies were used to determine the dose of **59** required for 50% receptor occupancy (*ex vivo* ID_{50}) at a time point of 3 h; the time empirically determined from earlier *ex vivo* receptor binding studies, with **59**, to be the time of maximum receptor occupancy. The *ex vivo* ID_{50} of **59** was determined to be 2.0 ± 0.2 mg/kg (Figure 1, right-hand panel). In satellite cohorts, plasma samples were taken 3 h after dosing to determine compound levels at each of the three doses (1.0, 3.0, and 10.0 mg/kg); this allowed the plasma concentration that was associated with 50% occupancy of brain CRF-1 receptors (*ex vivo* IC_{50}) to be calculated. From these data, the *ex vivo* IC_{50} of **59** was determined to be 71 ng/mL.

Compound **7**, which had demonstrated efficacy in a small open-label phase IIa clinical trial,[16] was also characterized in the *ex vivo* receptor occupancy assay. The profiles of **59** and **7** are compared in Table 6. In IMR-32 human neuroblastoma cells, **59** was approximately 9-fold more active than **7**; in rat cortex, however, the rank order of affinities was reversed, and **7** was 2−3-fold more active than **59**. Despite the lower affinity in rat cortex, a dose of 2 mg/kg of **59** was required to achieve 50% receptor occupancy at 3 h, whereas a dose of 7.2 mg/kg of **7** was required for the same receptor occupancy. The lower required dose of **59** presumably reflects a higher brain exposure relative to **7**. The plasma concentrations associated with 50% occupancy of brain CRF-1 receptors for **7** and **59** were similar, 74 and 71 ng/mL, respectively.

Ex vivo receptor autoradiographic analysis of CRF receptors in the rodent brain was performed. One micromolar oCRF is not selective for the CRF-1 over the CRF-2 receptor subtype (Figure 2 top-left), while [^{125}I]sauvagine labels both the CRF-1 and the CRF-2 receptor subtypes (Figure 2 top-right). The [^{125}I]sauvagine was dose-dependently displaced with increasing doses of **59** (middle and bottom panels) with the pattern of labeling indicating selectivity for CRF-1 over CRF-2 receptors.

Due to aqueous solubility limitations, the pyrazine **59** was tested at a concentration of 4 μM in a selectivity panel of 69 receptors, ion channels, and 6 enzymes (see Supporting Information for full list) and did not show inhibition greater than 16% in any assay. In addition, no significant hERG (human ether-à-go-go related gene) activity was recorded in a whole cell (Cos7) electrophysiological assay (17% inhibition @ 3 μM). On the basis of the high affinity and functional antagonism, excellent oral, and high brain exposure, occupancy of brain CRF-1 receptors, as quantified by *ex vivo* receptor binding autoradiography and selectivity profile, the pyrazine **59** was further evaluated in several *in vivo* pharmacology models.

ICV administration of CRF causes a robust increase in locomotor activity relative to vehicle (Figure 3). The large increase in movement time elicited by 0.3 μg CRF (compare TPGS vs TPGS/CRF) was significantly reduced by a 3 h pretreatment with compound **59** at both 10 and 30 mg/kg PO.

To rule out potential sedative effects of **59** as an explanation for the reduction of CRF-induced locomotor activity, the effects of **59** on spontaneous locomotor activity and rearing in rats that were not habituated to the testing environment were measured. Compound **59** had no effect on horizontal (movement time) or vertical activity at any of the doses (3, 10, and 30 mg/kg) tested.

In a second rodent model, a 10 min period of restraint causes a marked elevation in plasma ACTH levels (compare veh/no stress vs veh/stress, Figure 4). This effect was dose-dependently antagonized by pretreatment with **59**, and a significant attenuation of plasma ACTH levels was demonstrated at the 10 mg/kg dose.

The CRF-1 receptor antagonist **7** (1−30 mg/kg, po, 1 h pretreatment) was run as a positive control in the mechanistic *in vivo* paradigms to demonstrate their sensitivity for detecting CRF-1 receptor antagonism. As expected from published literature,[30] **7** produced dose-dependent reductions of icv CRF-enhanced locomotor activity and restraint stress-induced stimulation of ACTH release (minimal effective doses of 3 mg/kg and 10 mg/kg, respectively). Compound **7** produced no effect on spontaneous locomotor activity at the minimal effective doses in these two assays, though a slight reduction was found at the highest dose of 30 mg/kg. Taken together, these results with **7** are consistent with the conclusion that the effects of **59** in the two mechanistic assays are attributable to CRF-1 receptor antagonism.

In mass balance studies in rat with [^{14}C]-**59**, poor mass recoveries were observed and extensive accumulation of

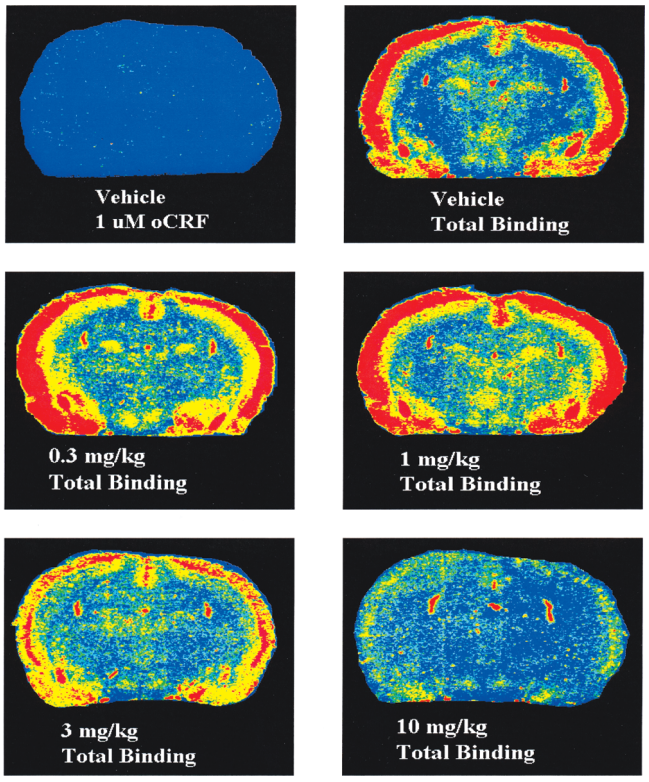


Figure 2. CRF-1 receptor occupancy, following oral dosing of **59** to rats at 0.3, 1.0, 3.0, and 10 mg/kg, measured using [^{125}I]sauvagine autoradiography.

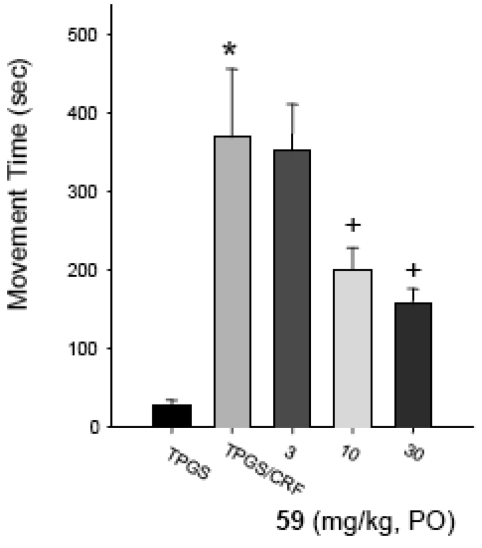


Figure 3. Antagonism of 0.3 μg ICV CRF-elicited increase in locomotor activity by **59**. Dosed in 2% vitamin E TPGS. * = significantly different from TPGS; + = significantly different from TPGS/CRF.

radioactivity in adipose tissues was determined. Subsequent metabolite identification in rat also indicated a high number of metabolites that included oxidations of the isopentyl group, dealkylation of the isopentyl group, and demethylation of either or both methoxy groups. On the basis of the long terminal half-life, accumulation in adipose tissues, and potential to form a large

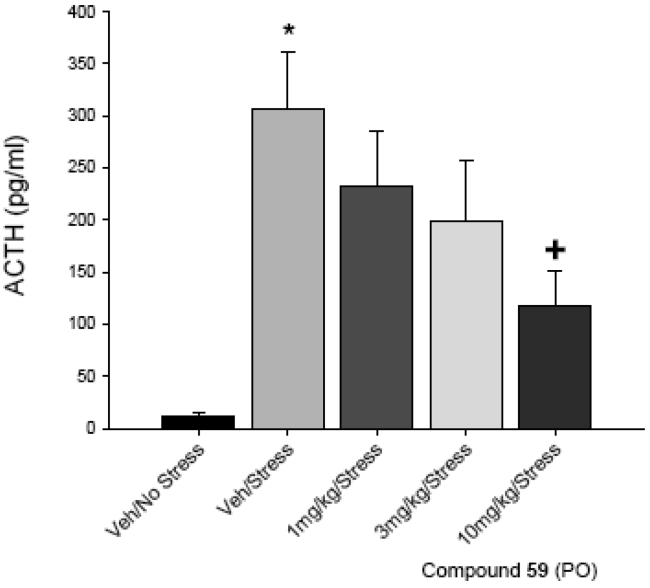


Figure 4. Antagonism of stress-induced ACTH release by compound **59**. Dosed in 2% vitamin E TPGS. * = significantly different from Vehicle/No Stress; + = significantly different from Veh/Stress.

number of metabolites, further preclinical development of **59** was terminated.

CONCLUSION

The design, synthesis, and structure—activity relationships of a novel series of pyrazines as corticotropin releasing factor (CRF-1) receptor antagonists were described. The pyrazine core proved superior to the earlier quinoline and pyrimidine templates; in particular, in terms of increased metabolic stability and oral and brain exposure. New methods were developed to synthesize a number of substituted pyrazine cores utilizing regioselective halogenation and chemoselective derivatization. Compound **59** was extensively profiled and displayed a high affinity for both the human and rat CRF-1 receptor (K_i = 1.0 and 9.8 nM, respectively), and it also was a functional antagonist vs CRF-mediated cAMP accumulation (IC_{50} = 93 nM) in human neuroblastoma cells. Oral administration to rats resulted in good systemic and high brain exposure. Occupancy of brain CRF-1 receptors was quantified using *ex vivo* receptor binding in brain membranes and brain slice receptor autoradiography. Fifty percent brain receptor occupancy was achieved at oral doses of 2.0 mg/kg in both paradigms, with the pattern of labeling indicating selectivity for CRF-1 over CRF-2 receptors. The *in vivo* pharmacological characteristics were evaluated in tests of acute functional activity following ICV CRF application and in behavioral/biochemical models of stress. Following ICV administration of CRF to male rats, a wide variety of well-characterized behavioral, biochemical, and autonomic events occurred. Oral administration of compound **59** significantly antagonized CRF-induced alterations of locomotor activity with effective doses as low as 10 mg/kg. Rats undergoing a 10 min session of physical restraint demonstrated marked increases in hypothalamic pituitary adrenal axis activation, as evidenced by increased plasma ACTH levels. Compound **59**, administered orally, significantly reduced the elevated levels of ACTH. The long terminal half-life and potential to accumulation in adipose tissues raised a potential

dx.doi.org/10.1021/jm200365y |*J. Med. Chem.* 2011, 54, 4187–4206

safety issue for chronic dosing in human, and further development of **59** was halted. Our efforts to overcome these issues with other novel topology II compounds, in particular, those directed toward increased hydrophilicity and a lower propensity to partition in adipose tissue will be reported in due course.

EXPERIMENTAL SECTION

General. Melting points were determined using a capillary melting apparatus and were uncorrected. ^{1}H NMR spectra were recorded in deuteriochloroform (unless otherwise noted) with tetramethylsilane as the internal standard at 400 MHz. Coupling constants (J values) are quoted to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded in deuteriochloroform (unless otherwise noted) at 100 MHz. Mass spectra were recorded on a VG 70SE magnetic sector mass spectrometer. For selected compounds, elemental analyses were obtained on the appropriate salt and were within 0.4% of theoretical C, H, and N. Analytical HPLC, used to determine the purity of all biologically tested compounds, was conducted using two different methods; all tested compounds had purity >95% by both methods. Method 1: Analyses were performed using a 2790 HT-Alliance HPLC system (Waters Corporation, Milford, MA), a Waters 996 Diode Array Detector interfaced to a Waters Quattro Micro Mass Spectrometer. Data acquired using *MassLynx 4.0* software. HPLC Conditions: column: 4.6 × 150 mm, Waters XBridge C18, 5 μm; column temperature: 30 °C; UV: 254 nm; scan rate: 10 points/s; flow rate: 1.0 mL/min; injection volume: 20 μL; mobile phase A: water with 0.1% formic acid; mobile phase B: methanol; gradient: 10% B (0−1 min), 10−100% B (1−12 min), 100% B (12−19 min), 10% B (19.1 min); run time: 22 min. MS Conditions: Electrospray in positive ion mode, cone voltage 35 V, scan range 100−750 amu. Method 2: Analyses were performed using an Acquity Ultra Performance Liquid Chromatography (UPLC) system (Waters Corporation, Milford, MA) and a Waters Acquity PDA Detector interfaced to a Waters ZQ Mass Spectrometer. Data was acquired using *MassLynx 4.1* software. HPLC Conditions: column: 2.0 × 50 mm, Phenomenex Luna C18(2), 2.5 μm; column temperature: 30 °C; UV: 254 nm; scan rate: 10 points/s; flow rate: 0.6 mL/min; injection volume: 5 μL; mobile phase A: 95% water, 5% acetonitrile with 0.1% ammonium hydroxide; mobile phase B: 5% water, 95% acetonitrile with 0.1% ammonium hydroxide; gradient: 5% B (0−2 min), 5−100% B (2−7 min), 100% B (7−9.5 min), 5% B (9.51 min); run time: 10 min. MS Conditions: electrospray in positive ion mode; cone voltage 35 V; and scan range 100−750 amu. Organic solutions were dried using anhydrous magnesium sulfate and concentrated by rotary evaporation. Analytical thin layer chromatography (TLC) was carried out on Camlab Polygram SIL G/UV$_{254}$ plates. Unless otherwise stated, preparative column chromatography was carried out on 60H silica gel (Merck 9385). Compositions of solvent mixtures are quoted as ratios of volume. Known compounds gave spectral and analytical data consistent with literature values.

***N*-(1-Ethyl)propyl-3,6-diethylpyrazine-2-amine (18a).** To a mixture of 2-chloro-3,6-diethylpyrazine (**17**) (14.5 g, 85 mmol), BINAP (3.11 g, 5 mmol), and tris(dibenzylideneacetone)dipalladium(0) (1.5 g, 1.7 mmol) in toluene (350 mL) under nitrogen was added 1-ethylpropylamine (15 mL) followed by sodium *tert*-butoxide in THF (1M, 127 mL, 127 mmol). The mixture was heated at 80 °C for 2.5 h, cooled to room temperature, diluted with aqueous ammonium chloride (250 mL), and extracted with 1:1 hexane/ether (2 × 250 mL). The combined extracts were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (elution with hexane/ethyl acetate 10:1 to 4:1 gradient) to give the title compound **18a** (13.3 g, 71%). MS 222 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 6H), 1.24 (t, 3H), 1.29 (t, 3H), 1.50 (m, 2H), 1.64 (m, 2H), 2.59 (m, 4H), 4.06 (m, 2H), 7.56 (s, 1H).

5-Bromo-[*N*-(1-ethyl)propyl]-3,6-diethylpyrazine-2-amine (18b). A solution of *N*-(1-ethyl)propyl-3,6-diethylpyrazine-2-amine (**18a**) (13.29 g, 60 mmol) in chloroform (200 mL) was cooled to 0 °C and NBS (0.72 g, 4.1 mmol) was added in portions. The mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was concentrated, triturated with hexane, filtered, and washed with hexane. The combined filtrates were concentrated and purified by flash chromatography (elution with hexane/ethyl acetate 19:1) to give the title compound **18b** (15.0 g, 83%). MS 301 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 6H), 1.23 (t, 3H), 1.27 (t, 3H), 1.49 (m, 2H), 1.63 (m, 2H), 2.55 (q, 2H) 2.74 (q, 2H), 4.06 (brs, 2H).

3,6-Diethyl-*N*-(1-ethylpropyl)-5-(2,4-dichlorophenyl)pyrazin-2-amine (19a). To a solution of 5-bromo-[*N*-(1-ethyl)propyl]-3,6-diethylpyrazine-2-amine (**18b**) (300 mg, 1.0 mmol) and tetrakis-(triphenylphosphine)palladium(0) (46 mg, 0.04 mmol) in toluene (8 mL) at room temperature under a nitrogen atmosphere was added 2,4-dichlorobenzeneboronic acid (229 mg, 1.2 mmol) and aqueous potassium carbonate (2.0 M, 1.5 mL). The mixture was heated at 85 °C for 1.5 h, diluted with 0.1 N sodium hydroxide (10 mL), and extracted with 1:1 hexane−ether (2 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (elution with hexane/ethyl acetate 3:1) to give the title compound **19a** (304 mg, 83%). MS 366 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H), 1.14 (t, 3H), 1.28 (t, 3H), 1.57 (m, 2H), 1.67 (m, 2H), 2.43 (m, 2H), 2.64 (q, 2H), 4.12 (m, 2H), 7.25 (d, 1H), 7.30 (dd, 1H), 7.46 (d, 1H). HPLC (method 1): 96.2% purity. HPLC (method 2): 97.3% purity. To a solution of **19a** (183 mg, 0.5 mmol) in ethyl acetate (4 mL) at room temperature was added dropwise 1 M hydrochloric acid in ether (0.6 mL, 0.6 mmol). After stirring at room temperature for 1 h, the resulting white solid was collected by filtration, washed with ether (5 mL), and dried in a vacuum oven (145 mg). Mp 136−137 °C. Anal. Calcd for $C_{19}H_{26}Cl_3N_3$: C, 56.66; H, 6.51; N, 10.43. Found: C, 57.01; H, 6.68; N, 10.44.

Following the method described for the synthesis of **19a**, the following compounds were prepared from 5-bromo-[*N*-(1-ethyl)propyl]-3,6-diethylpyrazine-2-amine (**18b**) and the appropriate boronic acid:

*3,6-Diethyl-N-(1-ethylpropyl)-5-(2,4-dimethoxyphenyl)pyrazin-2-amine (**19b**).* MS 358 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.15 (t, 3H), 1.25 (t, 3H), 1.6 (m, 4H), 2.45 (q, 2H), 2.65 (q, 2H), 3.75 (s, 3H), 3.85 (s, 3H), 4.1 (br, 2H), 6.5 (s, 1H), 6.55 (d, 1H), 7.2 (d, 1H). HPLC (method 1): 95.2% purity. HPLC (method 2): 96.3% purity. The HCl salt of **19b** had MP 127−128 °C. Anal. Calcd for $C_{21}H_{32}ClN_3O_2$: C, 64.02; H, 8.19; N, 10.67. Found: C, 64.31; H, 8.33; N, 10.29.

*3,6-Diethyl-N-(1-ethylpropyl)-5-(2-methoxy-4-trifluoromethoxyphenyl)pyrazin-2-amine (**19c**).* MS 412 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H), 1.15 (t, 3H), 1.28 (t, 3H), 1.57 (m, 2H), 1.67 (m, 2H), 2.42 (m, 2H), 2.66 (q, 2H), 3.78 (s, 3H), 4.10 (br, 2H), 6.77 (s, 1H), 6.89 (d, 1H), 7.27 (d, 1H). HPLC (method 1): 96.0% purity. HPLC (method 2): 96.8% purity.

*3,6-Diethyl-N-(1-ethylpropyl)-5-(2-methoxy-4-ethoxyphenyl)pyrazin-2-amine (**19d**).* MS 372 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.14 (t, 3H), 1.28 (t, 3H), 1.43 (t, 3H), 1.55 (m, 2H), 1.67 (m, 2H), 2.46 (q, 2H), 2.65 (q, 2H), 3.74 (s, 3H), 4.07 (q, 2H), 4.10 (m, 2H), 6.51 (d, 1H), 6.54 (dd, 1H), 7.15 (d, 1H). HPLC (method 1): 98.9% purity. HPLC (method 2): 97.4% purity.

*3,6-Diethyl-N-(1-ethylpropyl)-5-[2-methoxy-4-(2-propoxy)phenyl]-pyrazin-2-amine (**19e**).* MS 386 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.14 (t, 3H), 1.28 (t, 3H), 1.33 (d, 6H), 1.55 (m, 2H), 1.67 (m, 2H), 2.46 (q, 2H), 2.65 (q, 2H), 3.74 (s, 3H), 4.02 (d, 1H), 4.08 (m, 1H), 4.59 (m, 1H), 6.51 (d, 1H), 6.54 (dd, 1H), 7.15 (d, 1H). HPLC (method 1): 99.0% purity. HPLC (method 2): 98.2% purity.

*3,6-Diethyl-N-(1-ethylpropyl)-5-(2-methoxy-4-methylphenyl)pyrazin-2-amine (**19f**).* MS 342 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.14 (t, 3H), 1.28 (t, 3H), 1.55 (m, 2H), 1.67 (m, 2H), 2.38 (s, 3H),

2.46 (m, 2H), 2.64 (q, 2H), 3.75 (s, 3H), 4.10 (m, 2H), 6.74 (s,1H), 6.82 (d, 1H), 7.14 (d, 1H). HPLC (method 1): 95.0% purity. HPLC (method 2): 96.3% purity.

*3,6-Diethyl-N-(1-ethylpropyl)-5-(2-methoxy-4-trifluoromethylphenyl)-pyrazin-2-amine (**19g**).* MS 396 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H), 1.15 (t, 3H), 1.28 (t, 3H), 1.57 (m, 2H), 1.67 (m, 2H), 2.42 (m, 2H), 2.63 (q, 2H), 3.82 (s, 3H), 4.10 (m, 2H), 7.14 (s, 1H), 7.28 (d, 1H), 7.38 (d, 1H). HPLC (method 1): 97.7% purity. HPLC (method 2): 96.3% purity.

*3,6-Diethyl-N-(1-ethylpropyl)-5-(2-hydroxy-4-methoxyphenyl)-pyrazin-2-amine (**19h**).* MS 344 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.30 (t, 3H), 1.37 (t, 3H), 1.55 (m, 2H), 1.67 (m, 2H), 2.64 (q, 2H), 2.86 (q, 2H), 3.82 (s, 3H), 4.15 (m, 2H), 6.48 (dd, 1H), 6.59 (d, 1H), 7.31 (d, 1H). HPLC (method 1): 95.4% purity. HPLC (method 2): 95.2% purity.

*3,6-Diethyl-N-(1-ethylpropyl)-5-(2-trifluoromethoxy-4-methoxy-phenyl)pyrazin-2-amine (**19i**).* MS 412 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H), 1.15 (t, 3H), 1.27 (t, 3H), 1.57 (m, 2H), 1.67 (m, 2H), 2.45 (q, 2H), 2.63 (q, 2H), 3.85 (s, 3H), 4.10 (br, 2H), 6.86 (brs, 1H), 6.89 (dd, 1H), 7.29 (d, 1H). HPLC (method 1): 97.7% purity. HPLC (method 2): 95.5% purity. The HCl salt of **19i** had Mp 154 °C. Anal. Calcd for $C_{21}H_{29}ClF_3N_3O_2$: C, 56.31; H, 6.53; N, 9.38. Found: C, 56.45; H, 6.80; N, 9.09.

*3,6-Diethyl-N-(1-ethylpropyl)-5-(2-trifluoromethyl-4-methoxyphenyl)-pyrazin-2-amine (**19j**).* MS 396 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H), 1.11 (t, 3H), 1.24 (t, 3H), 1.57 (m, 2H), 1.67 (m, 2H), 2.34 (q, 2H), 2.63 (q, 2H), 3.87 (s, 3H), 4.10 (m, 2H), 7.07 (dd, 1H), 7.24 (d, 1H), 7.25 (s, 1H). HPLC (method 1): 95.9% purity. HPLC (method 2): 96.2% purity.

*[N-(1-Ethyl)propyl]-5-[(2-dimethylamino-4-methyl)pyridin-5-yl]-3,6-diethylpyrazine-2-amine (**19k**).* MS 356 (M+1), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, 6H), 1.14 (t, 3H), 1.28 (t, 3H), 1.57 (m, 2H), 1.67 (m, 2H), 2.12 (s, 3H), 2.48 (m, 2H), 2.64 (q, 2H), 3.12 (s, 6H), 4.10 (m, 2H), 6.43 (s, 1H), 7.89 (s, 1H). HPLC (method 1): 98.9% purity. HPLC (method 2): 96.0% purity.

*3,6-Diethyl-N-(1-ethylpropyl)-5-(2,6-dimethoxypyridin-3-yl)-pyrazin-2-amine (**19l**).* MS 359 (M+1), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, 6H), 1.15 (t, 3H), 1.28 (t, 3H), 1.6 (m, 4H), 2.46 (q, 2H), 2.65 (q, 2H), 3.91 (s, 3H), 3.94 (s, 3H), 4.07 (m, 2H), 6.40 (d, 1H), 7.50 (d, 1H). HPLC (method 1): 96.0% purity. HPLC (method 2): 96.2% purity.

*5-(2,4-Dimethoxypyrimidin-5-yl)-3,6-diethyl-N-(1-ethylpropyl)-pyrazin-2-amine (**19m**).* MS 360 (M+1), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 6H), 1.16 (t, 3H), 1.28 (t, 3H), 1.55 (m, 2H), 1.78 (m, 2H), 2.42 (q, 2H), 2.62 (q, 2H), 3.94 (s, 3H), 4.01 (s, 3H), 4.12 (m, 2H), 8.2 (s, 1H). HPLC (method 1): 99.4% purity. HPLC (method 2): 98.3% purity.

3-(2,4-Dichlorophenyl)-2,5-diethylpyrazine (20). To a mixture of 2-chloro-3,6-diethylpyrazine (**17**) (5.1 g, 30 mmol) and tetrakis-(triphenylphosphine)palladium(0) (1.0 g, 0.86 mmol) in toluene (150 mL) at room temperature under a nitrogen atmosphere was added 2,4-dichlorobenzeneboronic acid (5.74 g, 30 mmol) and aqueous potassium carbonate (2.0 M, 15 mL). The mixture was heated at 85 °C for 4 h, then diluted with 0.1 N sodium hydroxide and extracted with 1:1 hexane/ether (2 × 100 mL). The combined extracts were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (elution with hexane/ether 3:1) to give the title compound **20** (8.2 g, 98%). MS 281 (M+1), ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H), 1.36 (t, 3H), 2.62 (brs, 2H), 2.84 (q, 2H), 7.25 (d, 1H), 7.38 (d, 1H), 7.50 (s, 1H), 8.42 (s, 1H).

2-Chloro-5-(2,4-dichlorophenyl)-3,6-diethylpyrazine (21). To a solution of 3-(2,4-dichlorophenyl)-2,5-diethylpyrazine (**20**) (2.8 g, 10 mmol) in dichloromethane (60 mL) at 0 °C was added 3-chloroperbenzoic acid (~77%, 3.44 g, ~15 mmol). The solution was allowed to return to room temperature and stirred overnight. Sodium hydroxide (1 M, 25 mL) was added, and the mixture extracted with further dichloromethane (2 × 50 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and evaporated. Phosphorus oxychloride (20 mL) was added to the residue, and the mixture heated at 90 °C for 4 h. The excess reagent was evaporated, the residue partitioned between ethyl acetate (50 mL) and saturated aqueous $NaHCO_3$ (20 mL), and the mixture extracted with further ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with hexane/ether 19:1) and gave the title compound **21** (1.6 g, 50%). MS 316 (M+1), ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3H), 1.32 (t, 3H), 2.60 (brs, 2H), 2.99 (q, 2H), 7.22 (d, 1H), 7.38 (d, 1H), 7.54 (s, 1H).

3,6-Diethyl-*N*-(dicyclopropylmethyl)-5-(2,4-dichlorophenyl)pyrazin-2-amine (22a). To a solution of 2-chloro-5-(2,4-dichlorophenyl)-3,6-diethylpyrazine (**21**) (296 mg, 0.94 mmol) and tris(dibenzylideneacetone)dipalladium(0) (11 mg) in toluene (10 mL) under nitrogen was added a 0.2 M solution of tri-*tert*-butylphosphine in toluene (0.1 mL). After 15 min at room temperature, dicyclopropylmethylamine (125 mg, 1.0 mmol), and potassium *tert*-butoxide (1.0 M in THF, 1.4 mL, 1.4 mmol) were added, and the reaction mixture heated at 80 °C for 4 h. The mixture was cooled to room temperature, diluted with ether, washed with aqueous ammonium chloride solution, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (elution with hexane/ethyl acetate 3:1) and give the title compound **22a** (288 mg, 76%). MS 391 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.5 (m, 8H), 1.03 (m, 2H), 1.1 (t, 3H), 1.3 (t, 3H), 2.4 (b, 2H), 2.66 (m, 2H), 3.5 (m, 1H), 4.25 (d, 1H), 7.25 (m, 2H), 7.46 (s, 1H). HPLC (method 1): 95.4% purity. HPLC (method 2): 96.0% purity.

Following the method described above, the following compounds were prepared from 2-chloro-5-(2,4-dichlorophenyl)-3,6-diethylpyrazine (**21**) and the appropriate amine:

*3,6-Diethyl-N-[2-methoxy-1-(methoxymethyl)ethyl]-5-(2,4-dichlorophenyl)pyrazin-2-amine (**22b**).* MS 399 (M+1), ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H), 1.29 (t, 3H), 2.43 (b, 2H), 2.66 (m, 2H), 3.42 (s, 6H), 3.56 (m, 2H), 3.68 (m, 2H), 4.55 (m, 1H), 4.86 (d, 1H), 7.3 (m, 2H), 7.48 (m, 1H). HPLC (method 1): 98.9% purity. HPLC (method 2): 97.7% purity.

*N^2-[3,6-Diethyl-5(−2,4-dichlorophenyl)pyrazin-2-yl]-N^1,N^1-dimethylpropane-1,2-diamine (**22c**).* MS 382 (M+1), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, 3H), 1.28 (t, 3H), 1.35 (d, 3H), 2.25 (m, 2H), 2.29 (s, 6H), 2.5 (m, 2H), 2.68 (m, 2H), 4.06 (m, 1H), 5.15 (b, 1H), 7.28 (m, 2H), 7.47 (s, 1H). HPLC (method 1): 96.4% purity. HPLC (method 2): 95.5% purity.

*N,N-Bis(cyclopropylmethyl)-5-(2,4-dichlorophenyl)-3,6-diethylpyrazin-2-amine (**22d**).* MS 404 (M+1), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.5 (m, 8H), 1.03 (m, 2H), 1.1 (t, 3H), 1.3 (t, 3H), 2.4 (b, 2H), 2.66 (m, 2H), 3.5 (m, 1H), 4.25 (d, 1H), 7.25 (m, 2H), 7.46 (s, 1H). HPLC (method 1): 99.7% purity. HPLC (method 2): 96.8% purity.

*3,6-Diethyl-N-propyl-N-(cyclopropylmethyl)-5-(2,4-dichlorophenyl)-pyrazin-2-amine (**22e**).* MS 393 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.12 (m, 2H), 0.48 (m, 2H), 0.91 (t, 3H), 1.05 (m, 1H), 1.15 (m, 3H), 1.3 (m, 3H), 1.6 (m, 2H), 2.5 (b, 2H), 2.83 (m, 2H), 3.16 (m, 2H), 3.34 (m, 2H), 7.34 (s, 2H), 7.49 (s, 1H). HPLC (method 1): 96.4% purity. HPLC (method 2): 99.1% purity.

*3,6-Diethyl-N,N-(2-methoxyethyl)-5-(2,4-dichlorophenyl)pyrazin-2-amine (**22f**).* MS 413 (M+1), ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H), 1.24 (t, 3H), 2.5 (b, 2H), 2.84 (q, 2H), 3.33 (s, 6H), 3.6 (m, 8H), 7.31 (m, 2H), 7.49 (s, 1H). HPLC (method 1): 99.0% purity. HPLC (method 2): 96.9% purity.

*3,6-Diethyl-N-propyl-N-(2-dimethylaminoethyl)-5-(2,4-dichlorophenyl)pyrazin-2-amine (**22g**).* MS 410 (M+1), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H), 1.05 (t, 3H), 1.25 (t, 3H), 1.4 (m, 2H), 1.6 (m,

2H), 2.30 (s, 6H), 2.52 (m, 2H), 2.80 (m, 2H), 3.26 (m, 2H), 3.5 (b, 2H), 7.32 (m, 2H), 7.50 (s, 1H). HPLC (method 1): 97.4% purity. HPLC (method 2): 96.3% purity.

3,6-Diethyl-2-(1-ethylpropoxy)-5-(2,4-dichlorophenyl)-pyrazine (23). To a suspension of sodium hydride (60% in mineral oil, 40 mg, 1.0 mmol) in DMF (0.5 mL) under a nitrogen atmosphere was added 3-pentanol (88 mg, 1.0 mmol), and the mixture was stirred at room temperature for 15 min. To the resulting solution was added a solution of 2-chloro-5-(2,4-dichlorophenyl)-3,6-diethylpyrazine (**21**) (63 mg, 0.2 mmol) in *N*-methylpyrrolidinone (1 mL). The mixture was heated at 70 °C for 2 h, cooled, diluted with aqueous ammonium chloride solution (10 mL), and extracted with ether (3 × 10 mL). The combined organics were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (elution with hexane/ether 19:1) and give the title compound **23** (57 mg, 77%). MS 367 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 6H), 1.16 (t, 3H), 1.24 (t, 3H), 1.75 (m, 4H), 2.5 (br, 2H), 2.82 (m, 2H), 5.13 (m, 1H), 7.26 (d, 1H), 7.32 (d, 1H), 7.49 (s, 1H). HPLC (method 1): 95.2% purity. HPLC (method 2): 96.1% purity.

2-*sec*-Butylsulfanyl-5-(2,4-dichloro-phenyl)-3,6-diethyl-pyrazine (24). Sodium hydride (60% in mineral oil, 60 mg, 1.5 mmol) was added to a solution of butane-2-thiol (170 μL, 1.5 mmol) in THF (5 mL). After 10 min, 2-chloro-5-(2,4-dichlorophenyl)-3,6-diethylpyrazine (**21**) (104 mg, 0.33 mmol) in THF (1 mL) was added dropwise, and the mixture heated at reflux for 16 h. The mixture was diluted with aqueous ammonium chloride solution (10 mL) and extracted ether (3 × 10 mL). The combined organics were dried (Na_2SO_4) and evaporated. The residue was purified by preparative thin layer chromatography (elution with hexane) and furnished the title compound **24** (62 mg, 51%). MS 369 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H,), 1.12 (t, 3H), 1.20 (t, 3H), 1.36 (t, 3H), 1.6−1.8 (m, 4H), 2.58 (br, 2H), 2.72 (q, 2H), 3.92 (sext, 1H), 7.18 (d, 1H), 7.19 (d, 1H), 7.26 (dd, 1H). HPLC (method 1): 96.2% purity. HPLC (method 2): 97.1% purity.

2-(2,4-Dichlorophenyl)-3,6-diethyl-5-(2-ethylbutyl)-pyrazine (25). To a solution of 3-methylenepentane (252 mg, 3.0 mmol) in THF (20 mL) was added a solution of 9-BBN in THF (0.5 M, 6.0 mL, 3.0 mmol). The mixture was heated at reflux, under a nitrogen atmosphere for 12 h, and cooled. To the solution was added 2-chloro-5-(2,4-dichlorophenyl)-3,6-diethylpyrazine (**21**) (316 mg, 1.0 mmol), tetrakis(triphenylphosphine) palladium(0) (115 mg, 0.1 mmol) and sodium hydroxide (1.0 M, 3.0 mL, 3.0 mmol). The mixture was heated at 50 °C for 24 h and cooled. Hydrogen peroxide (30%, 1.0 mL) was added, the solution stirred for 1 h, and the reaction mixture extracted with ether (3 × 25 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (elution with hexane/diethyl ether 10:1) and gave the title compound **25** (135 mg, 37%). MS 365 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 6H), 1.18 (t, 3H), 1.24 (t, 3H), 1.42 (m, 4H), 1.82 (m, 1H), 2.59 (brs, 2H), 2.82 (m, 4H), 7.26 (d, 1H), 7.38 (d, 1H), 7.56 (s, 1H). HPLC (method 1): 97.2% purity. HPLC (method 2): 99.1% purity.

***N*-(1-Ethyl)propyl-6-chloropyrazine-2-amine (27).** A solution of 2,6-dichloropyrazine (**26**) (690 g, 4.63 mol), 1-ethylpropylamine (810 mL), and triethylamine (970 mL) in propanol (2 L) was heated at 98 °C for 12 h. The mixture was concentrated, diluted with water (1 L), and extracted with toluene (2 × 2 L). The combined extracts were dried (Na_2SO_4) and evaporated to give the title compound **27** (780 g, 84%). MS 200 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6H), 1.46 (m, 2H), 1.63 (m, 2H), 3.65 (m, 1H), 4.48 (brs, 1H), 7.74 (s, 1H), 7.76 (s, 1H).

***N*-(1-Ethyl)propyl-6-ethylpyrazine-2-amine (28).** A solution of *N*-(1-ethyl)propyl-6-chloropyrazine-2-amine (**27**) (6.25 g, 31.4 mmol) and $NiCl_2$(dppp) (170 mg, 0.31 mmol) in THF (50 mL) was cooled to 10−15 °C and ethyl magnesium bromide (3 M, 24 mL, 72 mmol) was added at a rate so as to maintain the internal temperature at 10−15 °C. After the addition, the mixture was stirred for a further 6 h, cooled to 0 °C in an ice bath, and quenched by the dropwise addition of methanol (2 mL) and then aqueous acetic acid (10% solution v/v, 38 mL). The mixture was stirred until homogeneous and extracted with toluene (3 × 100 mL). The combined extracts were washed with water (100 mL), aqueous sodium hydroxide (0.2 M, 100 mL), and brine (100 mL). The combined extracts were dried (Na_2SO_4), evaporated, and distilled (125−130 °C @ 1 mmHg) to afford the title compound **28** (5.3 g, 87%). MS 194 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 6H), 1.25 (t, 3H), 1.52 (m, 2H), 1.62 (m, 2H), 2.60 (q, 2H), 3.62 (m, 1H), 4.31 (brs, 1H), 7.66 (s, 1H), 7.68 (s, 1H).

5-Bromo-*N*-(1-ethyl)propyl-6-ethylpyrazine-2-amine (29). To a solution of *N*-(1-ethyl)propyl-6-ethylpyrazine-2-amine **28** (31.9 g, 0.165 mol) in chloroform (450 mL) at 0 °C was added NBS in portions (29.3 g, 0.165 mol). The reaction mixture was stirred at room temperature for 1 h and evaporated. The residue was redissolved in ethyl acetate (500 mL) and washed with saturated aqueous $NaHCO_3$ (500 mL)and brine (500 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with hexane/diethyl ether 10:1 then 5:1) and gave the title compound **29** (31.3 g, 70%). MS 273 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 6H), 1.23 (t, 3H), 1.49 (m, 2H), 1.63 (m, 2H), 2.77 (q, 2H), 3.61 (m, 1H), 4.38 (brs, 1H), 7.42.

5-(2,4-Dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl]pyrazine-2-amine (30). To a solution of 5-bromo-*N*-(1-ethyl)propyl-6-ethylpyrazine-2-amine (**29**) (3.61 g, 13.24 mmol) and tetrakis(triphenylphosphine)palladium(0) (760 mg, 0.66 mmol) in DME (80 mL) at room temperature under a nitrogen atmosphere was added 2,4-dichlorobenzeneboronic acid (2.86 g, 15 mmol) and an aqueous solution of sodium carbonate (1.0 M, 30 mL). The mixture was heated at 90 °C for 12 h, diluted with 0.1 N sodium hydroxide (100 mL), and extracted with hexane/ether (1:1, 2 × 150 mL). The combined extracts were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (elution with hexane/ethyl acetate 9:1) to give the title compound **30** (4.29 g, 96%). MS 338 (M+1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.13 (t, 3H), 1.56 (m, 2H), 1.65 (m, 2H), 2.45 (m, 2H), 3.72 (m, 1H), 4.45 (d, 1H), 7.25 (d, 1H), 7.30 (dd, 1H), 7.48 (d, 1H), 7.74 (s, 1H). HPLC (method 1): 95.2% purity. HPLC (method 2): 96.8% purity.

3-Fluoro-6-ethyl-*N*-(1-ethylpropyl)-5-(2,4-dichlorophenyl)-pyrazin-2-amine (31). To a solution of 5-(2,4-dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl]pyrazine-2-amine (**30**) (338 mg, 1 mmol) in chloroform (5 mL) at 0 °C was added in portions SelectFluor (708 mg, 2 mmol). The reaction mixture was stirred at room temperature for 4 h and evaporated. The residue was dissolved in dichloromethane (20 mL), washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with hexane/ether 9:1) and gave the title compound **31** (224 mg, 63%). MS 356 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H), 1.13 (t, 3H), 1.66 (m, 4H), 2.42 (m, 2H), 4.05 (m, 1H), 4.60 (d, 1H), 7.24 (d, 1H), 7.30 (dd, 1H), 7.48 (d, 1H). HPLC (method 1): 96.0% purity. HPLC (method 2): 95.8% purity.

3-Chloro-6-ethyl-*N*-(1-ethylpropyl)-5-(2,4-dichlorophenyl)-pyrazin-2-amine (32). To a solution of 5-(2,4-dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl]pyrazine-2-amine (**30**) (34 mg, 0.1 mmol) in chloroform (1 mL) at 0 °C was added in portions *N*-chlorosuccinimide (20 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 2 h. Dichloromethane (5 mL) was added, and the solution was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. The residue was purified by preparative TLC (elution with hexane/ethyl acetate, 4:1) and gave the title compound **32** (28 mg, 74%). MS 373 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.14 (t, 3H), 1.55 (m, 2H), 1.70 (m, 2H), 2.46 (m, 2H), 4.05 (m, 1H), 4.93 (d, 1H), 7.24 (d, 1H), 7.30 (dd, 1H), 7.47 (d, 1H). HPLC (method 1): 98.3% purity. HPLC (method 2): 99.7% purity.

3-Iodo-6-ethyl-*N*-(1-ethylpropyl)-5-(2,4-dichlorophenyl)-pyrazin-2-amine (33). To a solution of 5-(2,4-dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl]pyrazine-2-amine (**30**) (51 mg, 0.15 mmol) in chloroform (1 mL) at 0 °C was added in portions *N*-iodosuccinimide (56 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 2 h. Dichloromethane (5 mL) was added, and the solution was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. The residue was purified by preparative TLC (elution with hexane/ethyl acetate, 5:1) to gave the title compound **33** (49 mg, 70%). MS 465 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.14 (t, 3H), 1.55 (m, 2H), 1.68 (m, 2H), 2.43 (m, 2H), 4.00 (m, 1H), 4.95 (d, 1H), 7.24 (d, 1H), 7.30 (dd, 1H), 7.46 (d, 1H). HPLC (method 1): 95.5% purity. HPLC (method 2): 96.0% purity.

3-Bromo-5-(2,4-dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl]-pyrazine-2-amine (34). To a solution of 5-(2,4-dichlorophenyl)-6-ethyl-[N-(1-ethyl)propyl]pyrazine-2-amine (**30**) (3.38 g, 10 mmol) in chloroform (50 mL) at 0 °C was added NBS in portions (1.8 g, 10 mmol). The reaction mixture was stirred at room temperature for 2 h, and solvents were evaporated under reduced pressure. The residue was dissolved in ethyl acetate (150 mL) and washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with hexane/ether 10:1) and gave the title compound **34** (3.87 g, 93%). MS 416 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.14 (t, 3H), 1.56 (m, 2H), 1.65 (m, 2H), 2.45 (m, 2H), 4.02 (m, 1H), 5.00 (d, 1H), 7.25 (d, 1H), 7.30 (dd, 1H), 7.46 (d, 1H).

5-(2,4-Dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl]-3-methoxypyrazine-2-amine (35). To a solution of 3-bromo-5-(2,4-dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl]pyrazine-2-amine (**34**) (4.16 g, 10 mmol) in NMP (20 mL) was added 25% (w/v) sodium methoxide in methanol (50 mL). The mixture was heated at 75 °C overnight, cooled, diluted with water, and extracted with 20% EtOAc in hexane (2 × 200 mL). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with hexane/ether 4:1) and gave the title compound **35** (3.12 g, 85%). MS 368 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.12 (t, 3H), 1.56 (m, 2H), 1.65 (m, 2H), 2.40 (q, 2H), 3.92 (s, 3H), 4.04 (m, 1H), 4.82 (d, 1H), 7.28 (m, 2H), 7.48 (d, 1H). HPLC (method 1): 96.7% purity. HPLC (method 2): 95.9% purity. The HCl salt of **35** had Mp 158 °C. Anal. Calcd for $C_{18}H_{24}ClN_3O$: C, 53.41; H, 5.98; N, 10.38. Found: C, 53.22; H, 6.33; N, 10.69.

5-(2,4-Dichlorophenyl)-3-ethoxy-6-ethyl-[*N*-(1-ethyl)-propyl]pyrazine-2-amine (36). To a solution of 3-bromo-5-(2,4-dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl]pyrazine-2-amine (**34**) (104 mg, 0.25 mmol) in NMP (1 mL) was added sodium ethoxide (68 mg, 1.0 mmol) in ethanol (2 mL). The mixture was heated at 75 °C overnight, cooled, diluted with water, and extracted with EtOAc (2 × 10 mL). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with hexane/ether 5:1) and gave the title compound **36** (47 mg, 49%). MS 383 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.10 (t, 3H), 1.37 (t, 3H), 1.55 (m, 2H), 1.68 (m, 2H), 2.36 (m, 2H), 4.05 (m, 1H), 4.33 (q, 2H), 4.81 (d, 1H), 7.24 (d, 1H), 7.26 (dd, 1H), 7.46 (d, 1H). HPLC (method 1): 95.7% purity. HPLC (method 2): 95.2% purity.

5-(2,4-Dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl]-3-methylpyrazine-2-amine (37). A solution of 3-bromo-5-(2,4-dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl] pyrazine-2-amine (**34**) (415 mg, 1.0 mmol) and $NiCl_2$(dppp) (27 mg, 0.05 mmol) in THF (5 mL) was cooled to 10−15 °C and methyl magnesium bromide (1 M, 2.0 mL, 2.0 mmol) was added dropwise. After the addition, the mixture was stirred for a further 2 h, cooled to 0 °C, and quenched by the dropwise addition of dilute aqueous acetic acid (5 mL). The mixture was extracted with ethyl acetate (2 × 10 mL), and the combined extracts washed with water (10 mL), aqueous sodium hydroxide (10 mL), and brine (10 mL). The residue was purified by flash chromatography (elution with hexane/ethyl acetate 10:1) and gave the title compound **37** (268 mg, 76%). MS 352 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.12 (t, 3H), 1.56 (m, 2H), 1.65 (m, 2H), 2.35 (s, 3H), 2.42 (m, 2H), 4.04 (m, 2H), 7.25 (d, 1H), 7.29 (dd, 1H), 7.46 (d, 1H). HPLC (method 1): 98.1% purity. HPLC (method 2): 96.8% purity.

5-(2,4-Dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl]-3-butylpyrazine-2-amine (38). A solution of 3-bromo-5-(2,4-dichlorophenyl)-6-ethyl-[*N*-(1-ethyl)propyl] pyrazine-2-amine (**34**) (208 mg, 0.50 mmol) and $NiCl_2$(dppp) (16 mg, 0.03 mmol) in THF (5 mL) was cooled to 10−15 °C and butyl magnesium chloride (1M, 1.0 mL, 1.0 mmol) was added dropwise. After the addition, the mixture was stirred for a further 2 h, and additional butyl magnesium chloride (1 M, 0.5 mL, 0.5 mmol) was added. The mixture was stirred for a further 2 h, cooled to 0 °C, and quenched by the dropwise addition of dilute aqueous acetic acid (10 mL). The mixture was extracted with ethyl acetate (2 × 15 mL), and the combined extracts washed with water (20 mL), aqueous sodium hydroxide (20 mL), and brine (20 mL). The residue was purified by flash chromatography (elution with hexane/ethyl acetate 19:1) and gave the title compound **38** (128 mg, 65%). MS 394 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.96 (m, 9H), 1.14 (t, 3H), 1.42 (m, 2H), 1.56 (m, 3H), 1.67 (m, 3H), 2.41 (brd, 2H), 2.61 (t, 2H), 4.14 (m, 2H), 7.26 (m, 2H), 7.46 (d, 1H). HPLC (method 1): 95.7% purity. HPLC (method 2): 96.4% purity.

[*N*-(1-Ethyl)propyl]-5-(2,4-dichlorophenyl)-3,6-dimethyl-pyrazine-2-amine (39). Starting from commercially available 2-chloro-3,6-dimethylpyrazine, and following the methods described above, the title compound **39** was prepared. MS 339 (M + 1), ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 6H), 1.6 (m, 4H), 2.2 (s, 3H), 2.4 (s, 3H), 4.05 (br, 2H), 7.25 (d, 1H), 7.3 (d, 1H), 7.45 (s, 1H). HPLC (method 1): 98.1% purity. HPLC (method 2): 96.3% purity.

5-Bromo-6-chloro-[*N*-(1-ethyl)propyl]pyrazine-2-amine (40). To 2-(3-pentylamino)-6-chloropyrazine (**27**) (4.09 g, 20.48 mmol) in chloroform (80 mL) at 0 °C was added NBS (3.65 g, 20.48 mmol) in portions. The mixture was stirred at 0 °C for 30 min, poured into saturated aqueous $NaHCO_3$ (100 mL), and extracted with further dichloromethane (2 × 125 mL). The combined extracts were washed with water (150 mL) and brine (150 mL), dried (sodium sulfate), and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate 19:1) and gave the title compound **40** (4.37 g; 77%). MS 279 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6H), 1.47 (m, 2H), 1.63 (m, 2H), 3.61 (m, 1H), 4.50 (m, 1H), 7.54 (s, 1H). Other fractions contained 3-bromo-6-chloro-[*N*-(1-ethyl)propyl]pyrazine-2-amine as a minor product (0.53 g, 9%). MS 279 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 6H), 1.53 (m, 2H), 1.66 (m, 2H), 3.98 (m, 1H), 5.08 (m, 1H), 7.52 (s, 1H).

6-Chloro-5-(2,4-dichlorophenyl)-[*N*-(1-ethyl)propyl]-pyrazine-2-amine (41). To a solution of 5-bromo-6-chloro-[*N*-(1-ethyl)propyl]pyrazine-2-amine (**40**) (2.63 g, 9.44 mmol) and tetrakis-(triphenylphosphine)palladium(0) (273 mg, 0.23 mmol) in DME (100 mL) at room temperature under a nitrogen atmosphere was added 2,4-dichlorobenzeneboronic acid (1.90 g, 10 mmol) and an aqueous solution of sodium carbonate (1.0 M, 20 mL). The mixture was heated at 90 °C for 14 h, diluted with 0.1 N sodium hydroxide (100 mL), and extracted with hexane/ether (1:1, 3 × 150 mL). The combined extracts were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (elution with hexane/ethyl acetate 19:1 and then 10:1) to give the title compound **41** (3.55 g, 94%). MS 345 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H), 1.53 (m, 2H), 1.68 (m, 2H), 3.74 (m, 1H), 4.65 (d, 1H), 7.32 (m, 2H), 7.49 (s, 1H), 7.82 (s, 1H).

3-Bromo-6-chloro-5-(2,4-dichlorophenyl)-[*N*-(1-ethyl)-propyl]pyrazine-2-amine (42). To a solution of 6-chloro-5-(2,4-dichlorophenyl)-[*N*-(1-ethyl)propyl]pyrazine-2-amine **41** (550 mg,

1.6 mmol) in chloroform (5 mL) at 0 °C was added in portions NBS (315 mg, 1.76 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with dichloromethane (20 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with hexane/ether 24:1) and gave the title compound **42** (586 mg, 86%). MS 424 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.58 (m, 2H), 1.70 (m, 2H), 4.00 (m, 1H), 5.20 (d, 1H), 7.30 (s, 2H), 7.50 (s, 1H).

6-Chloro-5-(2,4-dichlorophenyl)-3-ethyl-[*N*-(1-ethyl)propyl]pyrazine-2-amine (43). To a solution of 3-bromo-6-chloro-5-(2,4-dichlorophenyl)-[*N*-(1-ethyl)propyl]pyrazine-2-amine **42** (423 mg, 1.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (27 mg, 0.02 mmol) in DME (10 mL) at room temperature under a nitrogen atmosphere was added ethane boronic acid (370 mg, 5 mmol) and an aqueous solution of sodium carbonate (1.0 M, 10 mL). The mixture was heated at 90 °C for 14 h and additional ethane boronic acid (370 mg, 5 mmol) was added. The mixture was heated at 90 ⊠C for 28 h, diluted with 0.1 N sodium hydroxide (100 mL), and extracted with hexane−ether (1:1, 3 × 25 mL). The combined extracts were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (elution with hexane/ethyl acetate 25:1) to give the title compound **43** (183 mg, 49%). MS 373 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H), 1.30 (t, 3H), 1.56 (m, 2H), 1.70 (m, 2H), 2.65 (t, 2H), 4.08 (m, 1H), 4.35 (d, 1H), 7.32 (d, 1H), 7.33 (s, H), 7.48 (d, 1H).

5-(2,4-Dichlorophenyl)-3-ethyl-6-methyl-[*N*-(1-ethyl)propyl]pyrazine-2-amine (44). A solution of 6-chloro-5-(2,4-dichlorophenyl)-3-ethyl-[*N*-(1-ethyl)propyl]pyrazine-2-amine (**43**) (180 mg, 0.48 mmol) and $NiCl_2$(dppp) (17 mg, 0.03 mmol) in THF (5 mL) was cooled to 10−15 °C and methyl magnesium bromide (1 M, 1 mL, 1.0 mmol) was added dropwise. After the addition, the mixture was stirred for a further 16 h, cooled to 0 °C, and quenched by the dropwise addition of aqueous acetic acid (5 mL). The mixture was extracted with ethyl acetate (3 × 10 mL) and the combined extracts washed with water (10 mL), aqueous sodium hydroxide (1 M, 10 mL), and brine (15 mL). The combined extracts were dried (Na_2SO_4), evaporated, and the residue purified by preparative TLC (elution with hexane/ethyl acetate, 4:1) to give the title compound **44** (98 mg, 58%). MS 353 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.28 (t, 3H), 1.54 (m, 2H), 1.67 (m, 2H), 2.20 (s, 3H), 2.65 (q, 2H), 4.13 (m, 2H), 7.27 (d, 1H), 7.31 (d, 1H), 7.48 (s, 1H). HPLC (method 1): 97.1% purity. HPLC (method 2): 98.3% purity.

3-Bromo-5-(2,4-dichlorophenyl)-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (45). To a solution of 6-chloro-5-(2,4-dichlorophenyl)-[*N*-(1-ethyl)propyl]pyrazine-2-amine (**41**) (2.12 g, 5 mmol) in NMP (15 mL) was added sodium methoxide in methanol (1 M, 15 mL, 15 mmol). The mixture was heated at 75 °C for 24 h, cooled, diluted with water (100 mL), and extracted with 50% EtOAc in hexane (2 × 100 mL). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue was redissolved in chloroform (50 mL) and NBS (1.07 g, 6 mmol) was added in portions. The mixture was stirred for 4 h, diluted with dichloromethane (100 mL), washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (100 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with hexane/ether 49:1) and gave the title compound **45** (1.53 g, 73%). MS 419 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.60 (m, 2H), 1.70 (m, 2H), 3.89 (s, 3H), 3.92 (m, 1H), 4.98 (d, 1H), 7.27 (dd, 1H), 7.34 (d, 1H), 7.44 (d, 1H).

5-(2,4-Dichlorophenyl)-[*N*-(1-ethyl)propyl]-3,6-dimethoxypyrazine-2-amine (46). To a solution of 3-bromo-5-(2,4-dichlorophenyl)-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (**45**) (333 mg, 0.8 mmol) in 1-methyl-2-pyrrolidinone (5 mL) was added sodium methoxide (1 M, 3.0 mL, 3.0 mmol). The resulting mixture was then heated to 80 °C for three days. The mixture was then diluted with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with water (3 × 25 mL) and brine (25 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with hexane/ethyl acetate 29:1) and gave the title compound **46** (192 mg, 65%). MS 371 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.56 (m, 2H), 1.68 (m, 2H), 3.86 (s, 3H), 3.94 (s, 3H), 3.95(m, 1H), 4.82 (d, 1H), 7.27 (dd, 1H), 7.40 (d, 1H), 7.44 (d, 1H). HPLC (method 1): 95.7% purity. HPLC (method 2): 97.0% purity.

3-Methyl-5-(2,4-dichlorophenyl)-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (47). A solution of 3-bromo-5-(2,4-dichlorophenyl)-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (**45**) (100 mg, 0.24 mmol) and $NiCl_2$(dppp) (9 mg, 0.015 mmol) in THF (4 mL) was cooled to 10−15 °C and methyl magnesium bromide (1M, 0.6 mL, 0.6 mmol) was added dropwise. After the addition, the mixture was stirred for a further 12 h, cooled to 0 °C, and quenched by the dropwise addition of aqueous acetic acid (3 mL). The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined extracts washed with water (10 mL), aqueous sodium hydroxide (1 M, 10 mL), and brine (15 mL). The combined extracts were dried (Na_2SO_4) and evaporated, and the residue purified by preparative TLC (elution with hexane/ethyl acetate, 4:1), to give the title compound **47** (40 mg, 47%). MS 355 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 6H), 1.59 (m, 2H), 1.68 (m, 2H), 2.36 (s, 3H), 3.85 (s, 3H), 4.04 (m, 1H), 4.09(m, 1H), 7.26 (dd, 1H), 7.36 (d, 1H), 7.42 (d, 1H). HPLC (method 1): 98.2% purity. HPLC (method 2): 96.3% purity.

5-(2,4-Dichlorophenyl)-[*N*-(1-ethyl)propyl]-3-methoxy-6-methylpyrazine-2-amine (48). Following analogueous procedures, the title compound **48** was prepared. MS 355 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.6 (m, 4H), 2.15 (s, 3H), 3.9 (s, 3H), 4.05 (m, 1H), 4.8 (br d, 1H), 7.3 (s, 2H), 7.45 (s, 1H). HPLC (method 1): 97.7% purity. HPLC (method 2): 96.4% purity. The HCl salt of **48** had Mp 143−145 °C. Anal. Calcd for $C_{17}H_{21}Cl_2N_3O$: C, 57.63; H, 5.97; N, 11.86. Found: C, 57.31; H, 6.28; N, 11.60.

***N*-(1-Ethyl)propyl-6-methoxypyrazine-2-amine (49).** To a solution of 2-(3-pentylamino)-6-chloropyrazine (**27**) (20.0 g, 100 mmol) in DMF (150 mL) at room temperature was added sodium methoxide (13.5 g, 250 mmol). The resulting solution was heated at 75 °C for 20 h, evaporated, poured into water (250 mL), and extracted with ethyl acetate (3 × 200 mL). The combined extracts were dried, washed with water (5 × 200 mL) and brine (250 mL) (Na_2SO_4), and evaporated to afford the title compound **49** (18 g, 92%). MS 196 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 6H), 1.50 (m, 2H), 1.64 (m, 2H), 3.62 (m, 1H), 3.83 (s, 3H), 4.24 (m, 1H), 7.40 (s, 1H), 7.42 (s, 1H).

3-Bromo-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (50). To a solution of *N*-(1-ethyl)propyl-6-methoxypyrazine-2-amine (**49**) (25 g, 128 mmol) in chloroform (400 mL) at 0 °C was added NBS (23 g, 129 mmol) in portions. The mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was diluted with chloroform (200 mL), washed with saturated $NaHCO_3$ (250 mL), water (250 mL), and brine (250 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with dichloromethane/hexane 2:1 gradient to 1:1 and then hexane/ether 1:1). The first fractions contained 3,5-dibromo-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (**51a**) (9.9 g, 22%). MS 354 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 6H), 1.58 (m, 2H), 1.65 (m, 2H), 3.84 (m, 1H), 3.98 (s, 3H), 4.82 (brd, 1H). Later fractions contained the desired 3-bromo-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (**51b**) (10.2 g, 29%). MS 275 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 6H), 1.56 (m, 2H), 1.66 (m, 2H), 3.87 (s, 3H), 3.92 (m, 1H), 4.85 (d, 1H), 7.18 (s, 1H). Final fractions contained 5-bromo-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (**50**) (7.4 g, 21%). MS 275 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 6H), 1.48 (m, 2H), 1.62 (m, 2H), 3.60 (m, 1H), 3.92 (s, 3H), 4.24 (d, 1H), 7.20 (s, 1H).

3-Ethyl-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (52). To a stirred solution of 3-bromo-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (**50**) (19.6 g, 71 mmol) in THF (250 mL) at 0 °C, and under a nitrogen atmosphere, was added [1,3-bis(diphenylphosphino)propane]dichloronickel(II) (2.2 g, 4 mmol). After 10 min, ethylmagnesium bromide (2.0 M in THF, 100 mL, 200 mmol) was added dropwise, and the mixture was allowed to return to room temperature. After 2 h, aqueous ammonium chloride (200 mL) was added dropwise, and the mixture extracted with ether (3 × 200 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (elution with hexane/ether 4:1) and gave the title compound **52** (10.7 g, 64%). MS 237 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 6H), 1.27 (t, 3H), 1.52 (m, 2H), 1.63 (m, 2H), 2.57 (q, 2H), 3.88 (s, 3H), 4.01 (m, 2H), 7.38 (s, 1H). Later fractions contained the reduction product *N*-(1-ethyl)propyl-6-methoxypyrazine-2-amine **49** (4 g, 29%).

3-Ethyl-[*N*-(1-ethyl)propyl]-5-bromo-6-methoxypyrazine-2-amine (53). A solution of 3-ethyl-[*N*-(1-ethyl)propyl]-6-methoxypyrazine-2-amine (**52**) (9.0 g, 38 mmol) in chloroform (150 mL) was cooled to 0 °C, and NBS (6.8 g, 38 mmol) was added in portions. After the addition, the mixture was stirred for 1 h and allowed to warm to room temperature. The mixture was diluted with chloroform (200 mL), washed with saturated $NaHCO_3$ (200 mL), water (200 mL), and brine (250 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (elution with hexane/ether 9:1) and gave the title compound **53** (11.2 g, 98%). MS 303 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 6H), 1.23 (t, 3H), 1.52 (m, 2H), 1.65 (m, 2H), 2.57 (q, 2H), 3.88 (m, 1H), 3.92 (s, 3H), 4.05 (m, 2H).

5-(2,4-Dichlorophenyl)-[*N*-(1-ethyl)propyl]-3-ethyl-6-methoxypyrazine-2-amine (54). To a solution of 3-ethyl-[*N*-(1-ethyl)propyl]-5-bromo-6-methoxypyrazine-2-amine (**53**) (101 mg; 0.33 mmol) and tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.017 mmol, 5 mol %) in DME (3 mL) under a nitrogen atmosphere was added 2,4-dichlorobenzeneboronic acid (95 mg, 0.5 mmol) and aqueous potassium carbonate (1.0 M, 0.75 mL). The mixture was heated at 75 °C for 15 h, diluted with water, and extracted with ethyl acetate (2 × 10 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (elution with hexane/ethyl acetate 19:1) and gave the title compound **54** (121 mg, 99%). MS 368 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.27 (t, 3H), 1.56 (m, 2H), 1.70 (m, 2H), 2.62 (q, 2H), 3.85 (s, 3H), 4.00 (m, 1H), 4.18 (d, 1H), 7.28 (d, 1H), 7.38 (d, 1H), 7.44 (s, 1H). HPLC (method 1): 98.7% purity. HPLC (method 2): 99.1% purity.

Following the methods described above, the following compounds were prepared:

*5-(2-Ethyl-4-methoxyphenyl)-6-ethyl-[N-(1-ethyl)propyl]-3-methoxypyrazine-2-amine (**55**).* MS 358 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.12 (m, 6H), 1.62 (m, 4H), 2.38 (q, 2H), 2.54 (q, 2H), 3.83 (s, 3H), 3.91 (s, 3H), 4.02 (m, 1H), 4.75 (d, 1H), 6.78 (dd, 2H), 6.86 (s, 1H), 7.12 (d, 1H). HPLC (method 1): 98.2% purity. HPLC (method 2): 96.9% purity. The HCl salt of **55** had Mp 138−139 °C. Anal. Calcd for $C_{21}H_{32}ClN_3O_2$: C, 64.02; H, 8.19; N, 10.67. Found: C, 63.92; H, 8.02; N, 10.77.

*5-(2-Methoxy-4-trifluoromethylphenyl)-6-ethyl-[N-(1-ethyl)propyl]-3-methoxypyrazine-2-amine (**56**).* MS 398 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.13 (t, 3H), 1.57 (m, 2H), 1.68 (m, 2H), 2.37 (q, 2H), 3.84 (s, 3H), 3.92 (s, 3H), 4.04 (m, 1H), 4.77 (d, 1H), 7.15 (s, 1H), 7.28 (d, 1H), 7.39 (d, 1H). HPLC (method 1): 97.7% purity. HPLC (method 2): 96.0% purity.

*6-Ethyl-3-methoxy-5-(4-methoxy-2-(trifluoromethyl)phenyl)-N-(pentan-3-yl)pyrazin-2-amine (**57**).* MS 399 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.09 (t, 3H), 1.52−1.62 (m, 2H), 1.64−1.71 (m, 2H), 2.33 (q, 2H), 3.88 (s, 6H), 4.01−4.06 (m, 1H), 4.75 (d, 1H), 7.07 (dd, 1H), 7.26−7.29 (br, 2H). HPLC (method 1): 99.7% purity. HPLC (method 2): 99.8% purity. The HCl salt of **57** had Mp 163−165 °C. Anal. Calcd for $C_{20}H_{27}ClF_3N_3O$: C, 55.36; H, 6.27; N, 9.68. Found: C, 64.23; H, 8.09; N, 9.88.

*5-(2-Chloro-4-(difluoromethoxy)phenyl)-6-ethyl-3-methoxy-N-(pentan-3-yl)pyrazin-2-amine (**58**).* MS 401 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.11 (t, 3H), 1.51−1.73 (m, 4H), 2.38 (q, 2H), 3.90 (s, 3H), 4.00−4.06 (m, 1H), 4.81 (d, 1H), 6.54 (t, 1H), 7.07 (dd, 1H), 7.25 (d, 1H), 7.32 (d, 1H). HPLC (method 1): 97.2% purity. HPLC (method 2): 96.4% purity.

*3-Methoxy-5-(2-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-N-(pentan-3-yl)pyrazin-2-amine (**60**).* MS 384 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 6H), 1.52−1.56 (m, 2H), 1.62−1.71 (m, 2H), 2.13 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 4.01−4.07 (m, 1H), 4.78 (d, 1H), 7.15 (s, 1H), 7.28 (d, 1H), 7.41 (d, 1H). HPLC (method 1): 96.6% purity. HPLC (method 2): 97.2% purity. The HCl salt of **60** had Mp 149−151 °C. Anal. Calcd for $C_{19}H_{25}ClF_3N_3O_2$: C, 54.35; H, 6.00; N, 10.01. Found: C, 54.72; H, 5.76; N, 9.83.

*5-(2-Chloro-4-(difluoromethoxy)phenyl)-3-methoxy-6-methyl-N-(pentan-3-yl)pyrazin-2-amine (**61**).* MS 387 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.49−1.72 (m, 4H), 2.14 (s, 3H), 3.92 (s, 3H), 4.01−4.07 (m, 1H), 4.82 (d, 1H), 6.54 (t, 1H), 7.08 (dd, 1H), 7.25 (d, 1H), 7.33 (d, 1H). HPLC (method 1): 99.4% purity. HPLC (method 2): 98.8% purity.

*5-(2-Chloro-4-ethoxyphenyl)-3-methoxy-6-methyl-N-(pentan-3-yl)-pyrazin-2-amine (**62**).* MS 365 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.43 (t, 3H), 1.50−1.58 (m, 2H), 1.62−1.71 (m, 2H), 2.14 (s, 3H), 3.92 (s, 3H), 4.02−4.08 (m, 1H), 4.76 (d, 1H), 6.84 (dd, 1H), 6.98 (d, 1H), 7.22 (d, 1H). HPLC (method 1): 96.9% purity. HPLC (method 2): 97.4% purity.

*5-(2-Methoxy-4-trifluoromethoxyphenyl)-[N-(1-ethyl)propyl]-3-ethyl-6-methoxypyrazine-2-amine (**63**).* MS 414 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H), 1.25 (t, 3H), 1.59 (m, 2H), 1.69 (m, 2H), 2.62 (q, 2H), 3.80 (s, 3H), 3.87 (s, 3H), 4.00 (m, 1H), 4.10 (d, 1H), 6.80 (s, 1H), 6.89 (d, 1H), 7.39 (d, 1H). HPLC (method 1): 98.4% purity. HPLC (method 2): 99.1% purity.

*5-(2-Chloro-4-methoxyphenyl)-3-ethyl-6-methoxy-N-(pentan-3-yl)-pyrazin-2-amine (**64**).* MS 365 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.27 (t, 3H), 1.52−1.74 (m, 4H), 2.63 (q, 2H), 3.81 (s, 3H), 3.87 (s, 3H), 3.98−4.02 (m, 1H), 4.09 (d, 1H), 6.85 (dd, 1H), 6.98 (d, 1H), 7.33 (d, 1H). HPLC (method 1): 95.9% purity. HPLC (method 2): 96.3% purity. The HCl salt of **64** had Mp 152−153 °C. Anal. Calcd for $C_{19}H_{26}ClN_3O_2$: C, 62.71; H, 7.20; N, 11.55. Found: C, 62.99; H, 7.54; N, 11.41.

*5-(2-Chloro-4-(difluoromethoxy)phenyl)-3-ethyl-6-methoxy-N-(pentan-3-yl)pyrazin-2-amine (**65**).* MS 401 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 6H), 1.25 (t, 3H), 1.49−1.61 (m, 2H), 1.63−1.77 (m, 2H), 2.63 (q, 2H), 3.88 (s, 3H), 3.95−4.04 (m, 1H), 4.19 (d, 1H), 6.50 (t, 1H), 7.07 (dd, 1H), 7.22 (d, 1H), 7.43 (d, 1H). HPLC (method 1): 98.7% purity. HPLC (method 2): 99.1% purity.

***N*-(1-Ethyl)propyl-6-methylpyrazine-2-amine (66).** A solution of 2-(3-pentylamino)-6-chloropyrazine (**27**) (625 g, 3.14 mol) and $NiCl_2$(dppp) (17 g, 31.4 mmol) in THF (5 L) was cooled to 10−15 °C and methyl magnesium bromide (3 M, 2.4 L, 7.2 mol) was added at a rate so as to maintain the internal temperature at 10−15 °C. After the addition, the mixture was stirred for a further 6 h, cooled to 0 °C in an ice bath, quenched by the dropwise addition of methanol (190 mL), and then aqueous acetic acid (10% solution v/v, 3.8 L). The mixture was stirred until homogeneous and extracted with toluene (2 × 2 L). The combined extracts were washed with water (3 L), aqueous sodium hydroxide (0.2 M, 3 L) and brine (3 L). The combined extracts were dried (Na_2SO_4), evaporated, and distilled (121−123 °C at 1 mmHg) to afford the title compound **66** (530 g, 87%). MS 180 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 6H), 1.47 (m, 2H), 1.62 (m, 2H), 2.34 (s, 3H), 3.59 (m, 1H), 4.32 (m, 1H).

3-Methoxy-[*N*-(1-ethyl)propyl]-5-bromo-6-methylpyrazine-2-amine (67). *N*-(1-Ethyl)propyl-6-methylpyrazine-2-amine (**66**)

(570 g, 3 mol) was dissolved in glacial acetic acid (3 L) and cooled to 0 °C. Bromine (307 mL, 6 mol) was added at a rate such that the temperature of the reaction remained at room temperature or below. After the addition, the mixture was stirred for a further 1 h and water (4 L) and toluene (4 L) were added. The toluene layer was washed with water (3 L), aqueous sodium hydroxide (0.3 M, 3 L), aqueous Na_2SO_3 (0.1 M, 3 L), and water (3 L), and concentrated to give 3,5-dibromo-*N*-(1-ethyl)propyl-6-methylpyrazine-2-amine (852 g, 84%), MS 337 (M + 1), which was used without further purification. 3,5-Dibromo-*N*-(1-ethyl)propyl-6-ethylpyrazine-2-amine (564 g, 1.67 mol) was dissolved in methanol (1 L) and sodium methoxide (574 mL, 25 wt % in methanol) added dropwise. The mixture was heated to 65 °C for 16 h, cooled to 0 °C, and glacial acetic acid (53 mL) added. The mixture was concentrated and partitioned between water (1.5 L) and toluene (2.5 L). The toluene layer was collected, washed with water (1 L) and concentrated. The residue was purified by distillation (112−115 °C at 0.7 mmHg) and gave the title compound **67** (408 g, 85%). MS 289 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 6H), 1.46 (m, 2H), 1.61 (m, 2H), 2.38 (s, 3H), 3.94 (s, 3H), 4.62 (m, 1H).

5-(2-Methoxy-4-trifluoromethoxyphenyl)-[*N*-(1-ethyl)-propyl]-3-methoxy-6-methylpyrazine-2-amine (59). 3-Methoxy-[*N*-(1-ethyl)propyl]-5-bromo-6-methylpyrazine-2-amine (**67**) (380 g, 1.32 mol) was dissolved in toluene (2.5 L). 2-Methoxy-4-trifluoromethoxy-phenyl-boronic acid (342 g, 1.45 mol) and aqueous potassium carbonate solution (2 M, 1.3 L) were added, and the stirred solution was degassed with argon. Tetrakis(triphenylphosphine)palladium(0) (30 g, 25 mmol) was added, and the solution was heated at 85 °C for 12 h. The mixture was filtered through Celite, and the toluene layer washed with water (3 × 1 L) and concentrated. The residue was purified by distillation (157−158 °C at 0.6 mmHg) and gave the title compound **59** (476 g, 90%) as a clear viscous oil that crystallized on standing (Mp 45−47 °C). MS 400 (M + 1), ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 6H), 1.56 (m, 2H), 1.64 (m, 2H), 2.12 (s, 3H), 3.81 (s, 3H), 3.93 (s, 3H), 4.04 (m, 1H), 4.78 (d, 1H), 6.80 (s, 1H), 6.98 (d, 1H), 7.32 (d, 1H). HPLC (method 1): 98.1% purity. HPLC (method 2): 97.3% purity. Compound **59** (465.5 g, 1.16 mol) in ethyl acetate (2.32 L) was heated to 50−55 °C and *tert*-butyl methyl ether (2.3 L) added. The resulting solution was stirred for 0.5 h and toluenesulfonic acid monohydrate (230 g, 1.2 mol) was added in portions. The solution was stirred for 10 min at 50−55 °C and cooled in an ice bath for 2 h. The resulting solid was collected by filtration, washed with *tert*-butyl methyl ether (3 × 1 L) and dried in a vacuum oven at 85−90 °C for 2 h. The product was white and crystalline (612.5 g, 89.2%). Mp 162−4 °C. Anal. Calcd for $C_{26}H_{32}F_3N_3O_6S$: C, 54.63; H, 5.64; N, 7.35. Found: C, 54.58; H, 5.81; N, 7.09.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Procedures for the radioligand binding assay, IMR 32 whole cell functional assay, *ex vivo* receptor occupancy assay, ICV CRF-induced locomotor activity, restraint-stress-induced ACTH release, spontaneous locomotor activity, statistical analyses of behavioral data and Cerep selectivity profile for compound **59**. Data for reference compound **7**, in the icv CRF-enhanced locomotor activity, restraint stress-enhanced ACTH release and spontaneous locomotor activity, is also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS:

CRF, corticotropin releasing factor; HPA, hypothalamic-pituitary-adrenal; ACTH, adrenocorticotropic hormone; CNS, central nervous system; hERG, human ether-à-go-go related gene; TPGS, tocopheryl polyethylene glycol 1000 succinate; TLC, thin layer chromatography; NBS, *N*-bromosuccinimide; 9-BBN, 9-borabicyclo[3.3.1]nonane; cAMP, 3′-5′-cyclic adenosine monophosphate

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