Rational Design, Synthesis, and Structure−Activity Relationships of Aryltriazoles as Novel Corticotropin-Releasing Factor-1 Receptor Antagonists

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Following the discovery of the very high binding affinity of 4-anilinopyrimidines against corticotropin-releasing factor receptor-1 (CRF_1) (e.g., **1**, $K_i = 2$ nM), a new series of triazoles bearing different groups has been synthesized and evaluated. The compounds were prepared by cyclizations of *N*-acyl-*S*-methylisothioureas with alkylhydrazines or by cyclizations with hydrazine followed by alkylation. While members of this series showed potent binding affinity against CRF_1 receptor, there were important differences between the different regio- (**7** and **12**) and stereoisomeric aryltriazoles where the R^1 or R^2 side chain in **7** has an asymmetric center. In terms of overall potency, aryltriazole analogues such as **7r** bearing an *N*-(α-branched benzyl)-*N*-propylamino side chain were the most potent, followed by analogues such as **7a**, with an *N*-bis(cyclopropyl)methyl-*N*-propylamino side chain, and analogues such as **7m**, with an *N*-(α-branched aliphatic)-*N*-propylamino side chain. While the *N*-propyl group was crucial for high potency, we hypothesized that the terminal methyl mimicked the 5-methyl of pyrazolo-[1,5-*a*]pyrimidines **3** and **4**. Correlation of the low-energy conformers of compounds of type **3** and **7** generated by computational analyses was very good. The size and shape of the *N*-alkyl group dramatically changed the potency of the triazoles, which is in contrast to the SAR seen for bicyclic CRF_1 antagonists. In general, the *S*-enantiomer was much more potent than the corresponding *R*-isomer. Furthermore, to a limited extent in the aryltriazole series the substituent on the 5-phenyl ring changed the potency up to 9-fold. (*S*)-1-Methyl-3-[*N*-(4-fluorophenylpentyl)-*N*-propyl]amino-5-(2-methoxy-4-dichlorophenyl)-1*H*-[1,2,4]triazole [(*S*)-**7r**] showed very potent binding affinity ($K_i = 2.7$ nM) to CRF_1 receptors with an IC_{50} of 49 nM in a cAMP inhibition assay.

Introduction

Corticotropin-releasing factor (CRF), a 41 amino acid neuropeptide isolated from mammalian brain,[1] has been implicated in the mediation of the integrated physiological response to stress.[2] CRF acts by direct interaction with cell surface receptors known as CRF receptors, which are members of the superfamily of seven transmembrane proteins that signal across the cellular membrane through G proteins.[3] Two distinct CRF receptors have thus far been cloned, CRF_1 and CRF_2 receptors (including three splice variants, $CRF_{2(a)}$, $CRF_{2(b)}$, and $CRF_{2(c)}$). Inhibition of the CRF_1 receptor has been shown to reduce the ACTH level in plasma.[4] Most importantly, CRF is involved in a wide spectrum of central nervous system mediated effects that suggest that this peptide plays an important role within the brain, especially during stress.[5] Because of this diversity of action, potent competitive antagonists of CRF have been extremely useful in the study of the physiologic and pathophysiologic role of CRF.[6] Ultimately, it is hoped that such antagonists will play a major role in the management of some stress-related disorders such as anxiety and depression.[7]

In recent years, several different classes of compounds have been reported as CRF receptor antagonists.[8] We recently disclosed that anilinopyrimidines,[9] anilinotriazines,[10] 3-phenylpyrazolo[1,5-*a*]pyrimidines,[11] and 3-pyridylpyrazolo[1,5-*a*]pyrimidines[12] such as compounds **1**−**5**, are potent antagonists of the CRF_1 receptor (Figure 1).[13] Part of our research program has been directed toward the development of other analogues in series related to **1** as potential antagonists of the CRF_1 receptor.[14] In the present paper, we describe the rational design, synthesis, biological profile, and structure−activity relationships (SAR) of a further class of compounds containing an aryltriazole moiety as the structural element in their molecules as highly potent and selective CRF_1 receptor antagonists.

In the course of our search for CRF_1 receptor antagonists via SAR studies around the core structure of **1**, we identified triazole **6** as a potent antagonist.[15] Conceptually, compound **6** resulted from compound **2** simply by extrusion of a carbon from the triazine nucleus. Removal of the nitrogen linker between two aromatic moieties of **6**, among other changes, led to compounds **7b** and **7c**, which showed only very weak activity (**7c** had a K_i of 3.4 μM, Figure 1).[16] Nevertheless, by adding another cyclopropyl group on the side chain of the amino

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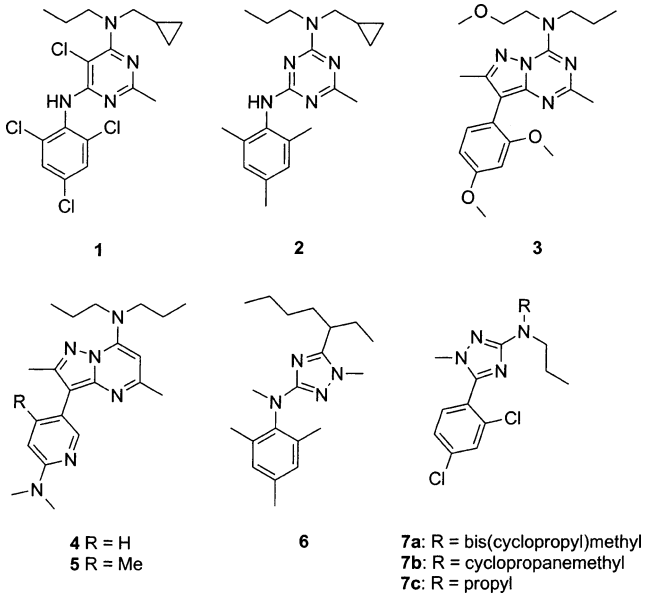


Figure 1. Examples of small molecule CRF antagonists.

group (compound **7a**) we discovered another series of aryltriazoles that were novel and potent CRF_1 receptor antagonists. The chemistry and CRF_1 receptor binding of compound **7a** and its analogues are the subjects of this paper and are described below.

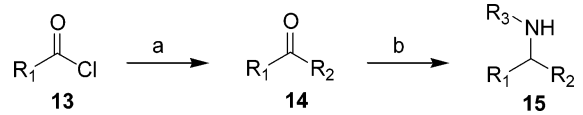
Chemistry

The required 3-aryltriazoles **7** were prepared as depicted in Scheme 1. Substituted benzoyl thiocyanates **8** were synthesized[17] by reactions of substituted benzoyl chlorides with thiocyanate salt in THF or acetone at room temperature. Reaction of acyl thiocyanates **8** with secondary amines gave the desired *N*-acylthioureas **9**,[18] which were converted to the corresponding benzoyl-*S*-methylisothioureas **10** by reaction with iodomethane.[19] Compounds **10** could also be synthesized in one-pot from acyl chlorides. Thus, treatment of a solution of sodium thiocyanate in acetone with substituted benzoyl chlorides at room temperature, followed by addition of dialkylamines and then methyl iodide/sodium carbonate, gave the corresponding *N*-benzoyl-*S*-methylisothioureas **10** in good to excellent yields. Cyclization of benzoyl-*S*-methylisothiourea **10** with hydrazine gave the triazole **11**. Cyclizations of **10** with methylhydrazine afforded triazoles **7** as predominant products. Alkylations of **11** with methyl iodide or ethyl iodide in the presence of sodium hydride gave a mixture of two isomers, **7** and **12**, which were separated by chromatography on silica gel. The isomeric structures were assigned on the basis of NMR analysis as well as NOE NMR experiments of **7a** and **12a**.

α-Branched secondary amines **15** were prepared by using titanium(IV) chloride mediated reductive aminations between primary amines and ketones **14**,[20] which could be readily prepared via copper-catalyzed condensations of Grignard reagents with acid chlorides.[21] (Scheme 2).

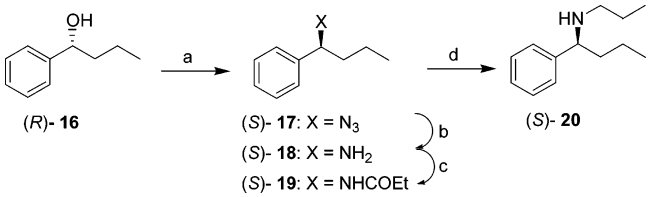
Both enantiomerically pure (*S*)- and (*R*)-1-phenylbutylamines [(*S*)-**20** and (*R*)-**20**] were prepared according to Scheme 3 from the corresponding (*R*)-(+)- and (*S*)-(−)-1-phenyl-1-butanols [(*R*)- and (*S*)-**16**, commercially available with ee's of 98% and 99%, respectively). Thus, treatment of (*R*)-**16** with diphenylphosphoryl azide and DBU in toluene afforded the corresponding (*S*)-1-phenylbutyl azide (*S*)-**17** with inversion of the chiral center.[22] Catalytic hydrogenation of the azide (*S*)-**17** with Pd/C gave (*S*)-1-phenylbutaylamine (*S*)-**18**,[23] which was converted to the corresponding amide (*S*)-**19** and then reduced with $LiAlH_4$ to afford (*S*)-*N*-(1-phenylbutyl)-*N*-propylamine (*S*)-**20** in 62% overall yield. (*R*)-*N*-(1-phenylbutyl)-*N*-propylamine (*R*)-**20** was prepared in a similar manner from the corresponding (*S*)-(−)-1-phen-

Scheme 2[a]



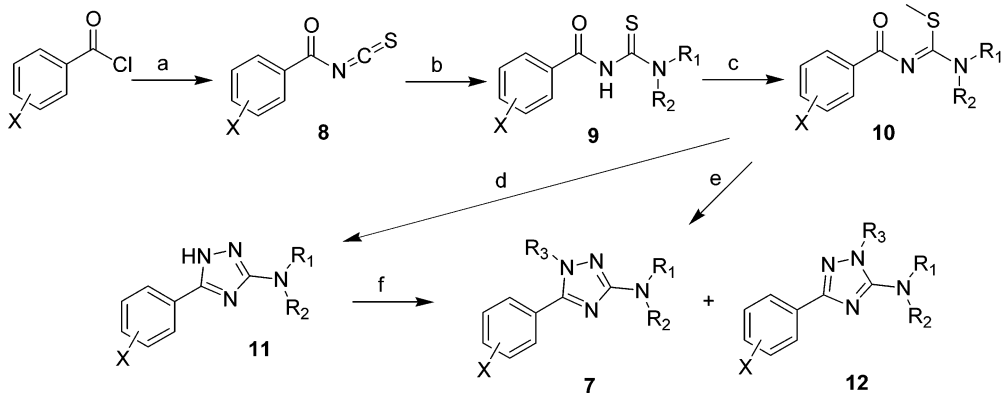
[a] Reagents: (a) R^2MgCl/THF/CuI; −35 °C; (b) $R^3NH_2/TiCl_4$/0 °C/CH_2Cl_2 then $NaBH_3CN$/MeOH.

Scheme 3[a]



[a] Reagents (a) $(PhO)PON_3$/DBU/toluene; (b) Pd/C, H_2/EtOH; (c) $EtCOCl/Et_3N/CH_2Cl_2$ then $LiAlH_4$/THF.

Scheme 1[a]



[a] Reagents: (a) $NaSCN/Me_2CO$; (b) R^1R^2NH/THF; (c) MeI/Na_2CO_3/THF; (d) NH_2NH_2/EtOH, reflux; (e) R^3NHNH_2/EtOH, reflux; (f) R^3X/NaH/THF.

yl-1-butanol in a 51% overall yield. The chiral purity of these two amines was confirmed by preparing the corresponding Mosher's amides, the proton and fluorine NMR spectra of which showed no detectable appearance of the other isomer (>95% chiral purity). Enantiomerically pure aminotriazoles were also obtained by separation of the enantiomeric mixtures using chiral HPLC (see Experimental Section).

Results and Discussion

The inhibition of [^{125}I]-[Tyr^0]sauvagine binding to cells expressing the human CRF_1 receptor was used to identify specific receptor antagonists in a radioligand binding assay. Full dose−response curves were determined for each compound having greater than 50% inhibition at $10^{-5}\mu$M concentration in the single point screen. The resulting K_i's for potent compounds are listed in Table 1 and in most cases are an average of at least two such determinations.

The 3-[*N*-bis(cyclopropyl)methyl-*N*-propylaminotriazole derivative **7a** (CRF_1 $K_i = 9$ nM, CRF_2 $K_i > 10$ μM) is a potent inhibitor and shows functional activity as determined by inhibition of CRF-stimulated cAMP production ($IC_{50} = 90$ nM) in a rat pituitary assay. However, during the efforts to synthesize the corresponding hydrochloride and mesylate salts of these compounds for formulation purposes, we found that the *N*-bis(cyclopropyl)methyl group was labile under acidic conditions. Because of this finding, we embarked on a program focused on identifying acid-stable replacements for this group that would also maintain or improve the CRF_1 activity of **7a**.

Previous SAR of the dialkylaminotriazoles suggested the importance of the methyl group at the 1-position of triazole. It was found that introduction of groups larger than methyl resulted in significant loss of activity (e.g., ethyl analogue **7d**, $K_i = 80$ nM), perhaps indicating a position of bulk intolerance in the pharmacophore. That some level of lipophilicity is required is supported by the fact that the corresponding des-methyl analogue showed activity only in the micromolar range (**11a**, $K_i = 4.5$ μM). Furthermore, the regioisomer (**12a**) of **7a** was completely inactive at the CRF_1 receptor.

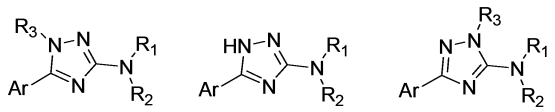
We investigated the role of an aliphatic chain or an aromatic ring as potential replacements for the bis-(cyclopropyl)methyl group. A 1-methyltriazole library of about 200 compounds was synthesized from over 80 commercially available dialkylamines using the robust chemistry described above. It quickly became apparent to us that compounds generated from simple straight-chain secondary amines had little success. For example, replacement of the *N*-bis(cyclopropyl)methyl group of **7e** ($K_i = 28$ nM) with a cyclopropylmethyl or a propyl group resulted in compounds **7g** and **7h**, respectively, with drastically attenuated activity or no activity at all. Conservative replacement of the bis(cyclopropyl)methyl group with bis(isopropyl)methyl afforded an analogue with a 30-fold loss of activity (**7f**, $K_i = 910$ nM), which possibly suggested a better shape complementarity of the cyclopropyl rings with the receptor. However, one of the compounds from this library caught our attention. Compound **7i**, which is a very close analogue of **7h** ($K_i = >10\,000$ nM), showed moderate activity with a K_i of 690 nM. After confirming this result, the importance of the α-branched alkyl group was recognized and thus justified a more detailed study.

Previous work with the pyrazolo[1,5-*a*]pyrimidines showed that a dialkylamino or α-branched primary amino group at the 7-position of the bicyclic nucleus is essential for high binding affinity.[11] Prompted by computational analysis of the pharmacophore of both compounds **3** and **7** (see discussion below), and also by the binding affinity of **7i**, triazoles containing an α-branched alkylamino group were prepared. Substitution of the α-methyl group in R_1 of **7i** by a simple phenyl ring led to great improvement in activity (**7k**, $K_i = 26$ nM), while pentyl substitution afforded an analogue with similar activity (**7m**, $K_i = 46$ nM). The combination of a butyl or a pentyl group with a phenyl group resulted in very active compounds (**7q** and **7l**, K_i's = 14 and 6.8 nM, respectively).

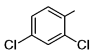
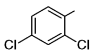
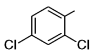
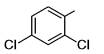
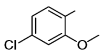
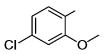
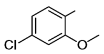
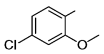
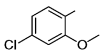
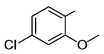
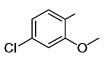
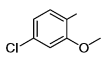
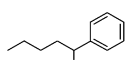
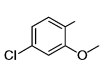
On the other side, replacement of the R_2 propyl group of **7k** with a smaller ethyl group led to an almost 6-fold loss of activity (**7j**, $K_i = 150$ nM). Similarly, replacement with a cyclopropylmethyl or a 2-methoxyethyl group resulted in at least a 6-fold decrease in activity (**7n** and **7o** compared with **7m**). These results suggested a propyl group was optimal at this site and it matched our pharmacophore hypothesis (see discussion below). Substituents on the phenyl side chain in R_1 were further explored to define the SAR in this region. A small fluorine atom in the para-position was well-tolerated (compare **7l**, $K_i = 6.8$ nM, with **7r**, $K_i = 7.3$ nM) as was the larger and more lipophlic trifluoromethyl substituent (compare **7k**, $K_i = 26$ nM, with **7p**, $K_i = 12$ nM). Several substituted aryl groups other than the 2,4-dichloro- and 2-methoxy-4-chlorophenyl moiety at the 3-position of the triazole were studied for the SAR. Among them, the 2-methyl-4-methoxyphenyl group led to triazole analogues with comparable activities (**7s**, **7t**, and **7u**, $K_i = 14$, 61, and 6.9 nM respectively), while with the more hydrophilic 2,4-dimethoxyphenyl and 2-chloro-4,5-dimethoxyphenyl groups, a trend toward decreased binding activities was observed (**7v**, **7w**, and **7x**, K_i's = 120, 24, and 84 nM, respectively).

Having established the best side chains of the 1-methyltriazoles for CRF activity, we next examined the effects of the chirality of the α-branched alkylamino groups. First, we separated the racemic mixture **7u** into its enantiomeric isomers (*S*)-**7u** and (*R*)-**7u**. These two individual enantiomers were then tested for CRF activity. Not surprisingly, one of the enantiomers showed an increase in binding activity [(*S*)-**7u**, $K_i = 5.7$ nM] compared to its racemic mixture, while the other enantiomer was over 50-fold less active [(*R*)-**7u**, $K_i = 350$ nM] than its counterpart. To establish the absolute configuration of compounds of this series, we synthesized the two individual enantiomers (*S*)-**7t** and (*R*)-**7t** from (*S*)- and (*R*)-1-phenylbutanols as described in Scheme 3. The results showed that (*S*)-**7t** ($K_i = 9.0$ nM) was much more active than (*R*)-**7t** ($K_i = 380$ nM). A number of triazoles containing chiral amines with the (*S*)-configuration required for high potency were then synthesized from the corresponding enantiomerically pure amines or separated from their racemic mixtures by chiral HPLC. Their CRF binding affinities and cAMP inhibitory activities were determined, and the results are listed

Table 1. Structure−Activity Relationships of Arytriazoles **7**, **11**, and **12**



7 **11** **12**

No.	Compound	Ar	R^3	R^2	R^1	K_i (nM)(n)[a]
1	**7a**		Me			9.2 ± 1.8 (4)
2	**7d**		Et			80 ± 14 (2)
3	**11a**		H			4500 (1)
4	**12a**		Me			>10,000 (1)
5	**7e**		Me			28 ± 13 (3)
6	**7f**		Me			910 (1)
7	**7g**		Me			2600 (1)
8	**7h**		Me			>10,000 (1)
9	**7i**		Me			690 ± 73 (3)
10	**7j**		Me			150 (1)
11	**7k**		Me			26 ± 9 (2)
12	**7l**		Me			6.8 ± 4.8 (4)
13	**7m**		Me			46 ± 44 (3)
14	**7n**		Me			440 ± 310 (2)
15	**7o**		Me			280 ± 38 (2)
16	**7p**		Me			12 ± 9 (3)
17	**7q**		Me			14 ± 2 (2)
18	**7r**		Me			7.3 ± 7.9 (3)
19	**7s**		Me			14 ± 11 (3)
20	**7t**		Me			61 (1)
21	**7u**		Me			6.9 ± 3.8 (6)
22	**7v**		Me			120 ± 16 (2)
23	**7w**		Me			24 ± 11 (4)
24	**7x**		Me			84 ± 8 (2)

[a] Number of determinations

in Table 2. In general, the (*S*)-enantiomers are at least 20−40-fold more active than their corresponding (*R*)-isomers.

Compounds (*S*)-**7l** and (*S*)-**7r** had K_i's of 4.0 and 2.7 nM binding affinity to CRF_1, respectively, and were not active in a CRF_2 receptor-binding assay. In addition, the compounds inhibited CRF-stimulated adenylyl cyclase activity in rat cortical homogenates with IC_{50} values of 56 and 49 nM, respectively. They formed stable hydrochloride salts in good yields, and these salts had moderate water solubility. Compound **7r** in racemic form was subjected to a 72 h pharmacokinetic study,

Table 2. Binding Affinity and Adenylase Cyclase Inhibitory Activity of Some (*S*)- and (*R*)-Triazole HCl Salts

HCl salt	yield (%)	K_i (nM) (*n*)[c]	IC_{50} (cAMP, nM) (*n*)[d]
(*S*)-**7l**	63	4.0 ± 1.0 (3)	56 ± 20 (3)
(*S*)-**7p**	90	5.2 ± 1.8 (3)	120 ± 25 (3)
(*S*)-**7q**	78	6.3 ± 3.2 (3)	91 ± 36 (4)
(*S*)-**7r**	67	2.7 ± 1.5 (5)	49 ± 10 (4)
(*S*)-**7s**	69	11.7 ± 2.9 (3)	270 ± 74 (3)
(*S*)-**7t**	74[a]	9.0 ± 2.0 (2)	120 (1)
(*S*)-**7u**	30[b]	5.7 ± 3.5 (5)	92 ± 55 (5)
(*S*)-**7v**	71	22 ± 14 (3)	240 ± 47 (4)
(*S*)-**7x**	70	16.3 ± 12.6 (3)	240 ± 86 (4)
(*R*)-**7p**	58[b]	428 ± 147 (3)	*e*
(*R*)-**7r**	68	46 ± 6 (3)	*e*
(*R*)-**7t**	51	380 (1)	*e*
(*R*)-**7u**	30[b,c]	350 ± 140 (4)	*e*

[a] Formation of the HCl salt was unsuccessful; characterized as the free base. [b] Separated by chiral HPLC. [c] Formation of HCl salt was unsuccessful; characterized as the free base. [d] Number of determinations. [e] Not measured.

Table 3. Pharmacokinetic Study of Compound **7r**

iv (1 mg/kg)	
CL	27.7 mL/min/kg
V	7.8 L/kg
$t_{1/2}$	3.3 h
B/P	20%
po (2 mg/kg)	
t_{max}	0.5 h
C_{max}	290 ng/mL
AUC(0−*t*)	1013 ng h/mL
F	84%

the results of which are shown in Table 3. This compound was shown to have excellent oral bioavailability, a modest brain/plasma ratio, a good half-life, and a large volume of distribution.

Computational Analysis of Pharmacophore

The potential overlay of low-energy conformers of several compounds of type **3** and **7** was examined to better understand the comparisons between the pharmacophore responsible for the CRF activity of the 1-methyl-3-dialkylamino-5-aryltriazole series **7** and those of other known small molecule CRF antagonists. These analyses were performed using the software package MedChem Explorer from MSI, running on a Silicon Graphics R10000 workstation. Conformational analyses of the triazoles and pyrazolopyrimidines in Figure 2 were carried out using CFF (moderate convergence) for energy minimizations. Given the fact that the potency of **7l** (K_i = 4.0 nM) was comparable to those of **2** and **3** (K_i = 4 nM) and that its ethyl and des-methyl analogues were significantly less active, we hypothesized that a nearly orthogonal conformation of the 3-aryl group attached to the triazole ring afforded the best activity. This concept is commonly accepted for anilinopyrimidines and pyrazolo[1,5-*a*]pyrimidines and other bicyclic CRF antagonists.[24] All of the low-energy conformations of aryl triazoles displayed a dihedral angle between the phenyl ring and pyrimidine plane of about 46°. On the basis of this hypothesis, the dichlorophenyl group of **7l** and the 2,4-dimethoxyphenyl group of **3** were superimposed, as were the 1-methyltriazole ring of **7l** and the 5-methylpyrazolo moiety of **3**. The resulting overlay of

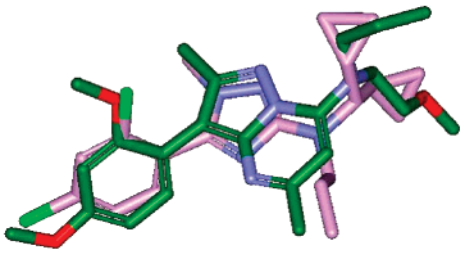


Figure 2. Molecular overlay of triazole **7l** (pink) and pyrazolo[1,5-*a*]pyrimidine **3** (green).

the other moieties of **7l** and **3** revealed a perfect relationship between the *N*-propyl group of the triazole **7l** and the 5-methyl group of pyrazolo[1,5-*a*]pyrimidine **3**, and between the *N*-(1-phenyl)pentyl group of **7l** and the *N*-propyl-*N*-(2-methoxyethyl)amino side chain of **3**. The nitrogen at the 4-position of the 1-methyltriazole **7l** perfectly mimicked the very important 4-nitrogen of the pyrazolo[1,5-*a*]pyrimidine **3** as a hydrogen-bond acceptor.

Conclusions

The above results summarized from a large number of triazole derivatives of the potent CRF_1 receptor antagonists **7** show that the high potency of **7a** is not unique, with derivatives possessing appropriate combinations of substituted phenyl and dialkylaminotriazole substitutions having similar K_i's for binding affinity of the CRF_1 receptor. An efficient synthetic route has been developed for rapid SAR studies on the designed triazoles, via cyclizations of acyl-*S*-methylisothioureas either with alkylhydrazines or with hydrazine followed by alkylation.

In conclusion, a new series of triazoles as potent CRF_1 receptor antagonists was designed and synthesized and their activity as CRF_1 receptor antagonists was evaluated. While the triazoles bearing a bis(cyclopropyl)-methyl group are acid-labile, compounds of type **7** with an α-branched benzyl group show very high binding affinity and stability, compound (*S*)-**7r** having a K_i of 2.7 nM in binding and an IC_{50} of 49 nM in inhibition of cAMP production in a rat pituitary assay.

Experimental Section

Chemistry. HPLC mass spectra (HPLC MS) were recorded on a Hewlett-Packard Series 1100 MSD using an ODS-AQ column and electrospray ionization (CI). Conditions employed were 100% 0.05% TFA/water to 90% MeCN/0.05% TFA/water over 3 min with a total run time of 3.5 min. Purities quoted below represent UV purities recorded at 220 and 254 nm, respectively. Proton NMR spectra were recorded on a Varian Mercury 300 instrument at 300 MHz; chemical shifts were reported in ppm (δ) from an internal tetramethylsilane standard in deuteriochloroform. Coupling constants (*J*) were reported in hertz (Hz). Gas chromatography−mass spectroscopy (GC−MS) were obtained using a Hewlett-Packard 5890 Series II GC linked to a Hewlett-Packard 5972 Mass Selective Detector. Elemental analyses were carried out by NuMega Resonance Laboratories, San Diego, CA. Solvents and reagents were purchased from commercial sources and used without purification. Chromatography was performed on silica gel using the solvent systems indicated. Chiral chromatography for all compounds was carried out using a Chiralpak AD 20 μM (Daicel) column with a 99/1 mixture of hexanes/ethanol. Anhydrous magnesium sulfate ($MgSO_4$) was used to dry the organic layer from extractions and evaporation was achieved

in vacuo using a rotary evaporator followed by evacuation with a vacuum pump.

3-(2-Dichlorophenyl)-5-(*N*-propyl-*N*-bis(cyclopropyl)-methylamino)-1*H*-[1,2,4]triazole (11a). 2,4-Dichlorobenzoyl chloride (4.19 g, 20 mmol) was added to a solution of NaSCN (1.78 g, 22 mmol) in acetone (50 mL) and the resultant suspension was heated at reflux for 1 h and then cooled to room temperature. *N*-Bis(cyclopropyl)methyl-*N*-propylamine (3.06 g, 20 mmol) was added and the mixture was stirred at room temperature overnight, after which time MeI (14 g, 10 mmol) was added and the mixture was heated at reflux for 6 h, cooled, and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (30% EtOAc/hexanes) to give *N*-(2,4-dichlorobenzoyl)-*N*′-bis-(cyclopropyl)methyl-*N*′-propyl-*S*-methylisothiourea (**10a**) (2.62 g, 33%) as an oil: MS (CI) *m/z* 399 (M + 1).

A solution of *N*-(2,4-dichlorobenzoyl)-*N*′-bis(cyclopropyl)-methyl-*N*′-propyl-*S*-methylisothiourea (**10a**) (80 mg, 0.2 mmol) and hydrazine (192 mg, 6 mmol) in ethanol was heated at reflux overnight, cooled, and poured into water (15 mL), and the mixture was stirred at room temperature. The resulting white solid was collected by filtration and washed with water to give, after drying in vacuo, **11a** (65 mg, 90%), as white solid: mp 148−9 °C; ^{1}H NMR ($CDCl_3$) δ 0.42 (m, 6H), 0.62 (m, 2H), 1.00 (t, J = 6.9 Hz, 3H), 1.10 (m, 2H), 1.80 (m, 2H), 3.05 (t, J = 6.5 Hz, 1H), 3.42 (m, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.48 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 365 (M + H). Anal. ($C_{18}H_{22}Cl_2N_4$) C, H, N.

1-Methyl-3-(*N*-propyl-*N*-bis(cyclopropyl)methylamino)-5-(2,4-dichlorophenyl)-1*H*-[1,2,4]triazole (7a) and 1-Methyl-3-(2,4-dichlorophenyl)-5-(*N*-propyl-*N*-bis(cyclopropyl)-methylamino)-1*H*-[1,2,4]triazole (12a). A solution of 3-(2-dichlorophenyl)-5-(N-propyl-*N*-bis(cyclopropyl)methylamino)-1*H*-[1,2,4]triazole (81 mg, 0.22 mmol) in dry THF was treated with NaH (44 mg) at room temperature for 20 min, followed by MeI (140 mg). The mixture was stirred for 2 h and TLC indicated two products. The mixture was evaporated and the products were separated by chromatography on silica gel (20% EtOAc/hexanes) to afford **7a** and **12a**.

7a: the major product, a colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.40 (m, 6H), 0.60 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H), 1.15 (m, 2H), 1.82 (m, 2H), 3.06 (t, J = 6.5 Hz, 1H), 3.40 (m, 2H), 3.60 (s, 3H), 7.35 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.56 (s, 1H); MS (CI) *m/z* 379 (M + H). Anal. ($C_{19}H_{24}Cl_2N_4$) C, H, N.

12a: the minor product, a colorless solid; ^{1}H NMR ($CDCl_3$) δ 0.17 (m, 2H), 0.26 (m, 2H), 0.46 (m, 2H), 0.55 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H), 1.06 (m, 2H), 1.46 (tq, J = 7.2, 7.2 Hz, 2H), 1.93 (t, J = 8.6 Hz, 1H), 3.35 (t, J = 7.2 Hz, 2H), 3.76 (s, 3H), 7.28 (dd, J = 8.2, 1.9 Hz, 1H), 7.47 (d, J = 1.9 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H); MS (CI) *m/z* 379 (M + H). Anal. ($C_{19}H_{24}Cl_2N_4$) C, H, N.

1-Ethyl-3-(*N*-propyl-*N*-bis(cyclopropyl)methylamino)-5-(2,4-dichlorophenyl)-1*H*-[1,2,4]triazole (7d) was prepared in a manner similar to the procedure described for **7a** using iodoethane: colorless solid; ^{1}H NMR ($CDCl_3$) δ 0.40 (m, 6H), 0.60 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H), 1.10 (m, 2H), 1.50 (m, 3H), 1.85 (m, 2H), 3.05 (t, J = 6.5 Hz, 1H), 3.43 (m, 2H), 3.83 (m, 2H), 7.30 (d, J = 7.5 Hz, 1H), 7.55 (s, 1H), 7.86 (d, J = 7.5 Hz, 1H); MS (CI) *m/z* 393 (M + H).

1-Methyl-3-(*N*-propyl-*N*-bis(cyclopropyl)methylamino)-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7e). 4-Chloro-*o*-anisic acid (1.8 g, 10 mmol) was suspended in CH_2Cl_2 (20 mL) and treated with $(COCl)_2$ (2 mL, ∼2 equiv) The mixture was stirred at room temperature for 1 h to give a clear solution. The solvent was concentrated in vacuo to give 4-chloro-*o*-anisoyl chloride as a white solid.

4-Chloro-*o*-anisoyl chloride (1.02 g, 5 mmol) was dissolved in THF (10 mL) and treated with a solution of NaSCN (440 mg, 5.5 mmol) in acetone (20 mL). The mixture was heated to reflux for 10 min. A solution of *N*-bis(cyclopropyl)methyl-*N*-propylamine hydrochloride (945 mg, 5.0 mmol) in CH_2Cl_2 (10 mL) was added, followed by Na_2CO_3 (1.2 g, 11 mmol), and the white suspension was heated at reflux for 16 h and then cooled to room temperature. MeI (1.42 g, 10 mmol) was added and the mixture was refluxed for 2.5 h. The resultant mixture was cooled and filtered through a silica gel pad, and the pad was washed with EtOAc. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (50% EtOAc/hexanes) to afford *N*-(2-methoxy-4-chlorobenzoyl)-*N*′-bis(cyclopropyl)methyl-*N*′-propyl-*S*-methylthioisourea (**10e**) (1.6 g, 81%) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ 0.49 (m, 6H), 0.72 (m, 2H), 0.98 (m, 3H), 1.12 (m, 2H), 1.94 (m, 2H), 2.47 (s, 3H), 3.10 (m, 1H), 3.61 (t, J = 6.6 Hz, 2H), 3.87 (s, 3H), 6.93 (s, 1H), 6.95 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 395 (M + H).

A mixture of *N*-(2-methoxy-4-chlorobenzoyl)-*N*′-bis(cyclopropyl)methyl-*N*′-propyl-*S*-methylthioisourea (**10e**; 40 mg, 1 mmol) and methylhydrazine (80 mg, 1.7 mmol) was heated at 100 °C for 15 h. The resultant mixture was purified silica gel chromatography (20% EtOAc/hexanes) to give **7e** (28 mg, 75%) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 0.40 (m, 6H), 0.60 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H), 1.12 (m, 2H), 1.80 (m, 2H), 3.08 (t, J = 6.5 Hz, 1H), 3.42 (m, 2H), 3.57 (s, 3H), 4.00 (s, 3H), 7.01 (s, 1H), 7.10 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 3.8, 5.9, 13.4, 23.4, 37.2, 48.2, 57.2, 66.7, 113.3, 118.1, 122.4, 133.9, 138.3, 151.1, 159.0, 166.6; MS (CI) *m/z* 375 (M + H). Anal. ($C_{20}H_{27}ClN_4O$) C, H, N.

1-Methyl-3-(*N*-propyl-*N*-bis(isopropyl)methylamino)-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7f) was prepared in a manner similar to the procedure described for **7e** using *N*-bis(isopropane)methyl-*N*-propylamine: 7.4 mg of colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3H), 0.92 (d, J = 7.2 Hz, 6H), 0.98 (d, J = 7.2 Hz, 6H), 1.83 (m, 2H), 2.08 (m, 2H), 3.12 (m, 2H), 3.53 (s, 3H), 3.83 (s, 3H), 3.85 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 1.8 Hz, 1H), 7.02 (dd, J = 8.4, 1.8 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H); MS (CI) *m/z* 379 (M + H); HPLC purity 100%, 95%.

1-Methyl-3-(*N*-cyclopropylmethyl-*N*-propylamino)-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7g) was prepared in a manner similar to the procedure described for **7e** using *N*-cyclopropanemethyl-*N*-propylamine: 12 mg of colorless solid; ^{1}H NMR ($CDCl_3$) δ 0.25 (m, 2H), 0.50 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H), 1.11 (m, 1H), 1.67 (m, 2H), 3.30 (d, J = 6.9 Hz, 2H), 3.45 (t, J = 7.5 Hz, 2H), 3.55 (s, 3H), 3.84 (s, 3H), 6.97 (d, J = 1.8 Hz, 1H), 7.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 335 (M + H); HRMS (EI) calculated for $C_{17}H_{23}ClN_4O$ *m/z* (MH^+) 335.1639, observed. 335.1633; HPLC purity 92%, 100%.

1-Methyl-3-(*N*-dipropylamino)-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7h) was prepared in a manner similar to the procedure described for **7e** using dipropylamine: 12 mg of colorless solid; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.5 Hz, 6H), 1.66 (m, 4H), 3.35 (t, J = 7.5 Hz, 4H), 3.54 (s, 3H), 3.83 (s, 3H), 6.96 (d, J = 1.8 Hz, 1H), 7.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 323 (M + H); HRMS (EI) calculated for $C_{16}H_{23}ClN_4O$ *m/z* (MH^+) 323.1639, observed 323.1642; HPLC purity 100%, 100%

1-Methyl-3-(*N*-propyl-*N*-*sec*-butylamino)-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7i) was prepared in a manner similar to the procedure described for **7e** using *N*-(1-methylpropyl)-*N*-propylamine: 22 mg; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.0 Hz, 6H), 1.15 (d, J = 6.9 Hz, 3H), 1.42−1.71 (m, 4H), 3.22 (m, 2H), 3.53 (s, 3H), 3.82 (s, 3H), 4.11 (m, 1H), 6.94 (s, 1H), 7.02 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 337 (M + H); HRMS (EI) calculated for $C_{17}H_{25}ClN_4O$ *m/z* (MH^+) 337.1795, observed 337.1796; HPLC purity 100%, 100%.

1-Methyl-3-[*N*-(1-phenylpropyl)-*N*-ethylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7j) was prepared in a manner similar to the procedure described for **7e** using *N*-(1-phenylpropyl)-*N*-ethylamine: 36 mg; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 7.2 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H), 2.05 (m, 2H), 3.20 (q, J = 7.2 Hz, 2H), 3.57 (s, 3H), 3.87 (s, 3H), 5.39 (t, J = 6.9 Hz, 1H), 6.98 (d, J = 1.8 Hz, 1H), 7.05 (dd, J = 8.1, 1.8 Hz, 1H), 7.25 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H), 7.43 (d, J = 8.1 Hz, 1H);

MS (CI) *m/z* 385 (M + H); HRMS (EI) calculated for $C_{21}H_{25}ClN_4O$ *m/z* (MH^+) 385.1795, observed 385.1778; HPLC purity 99%, 100%.

1-Methyl-3-[*N*-(1-phenylpropyl)-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7k) was prepared in a manner similar to the procedure described for **7e** using *N*-(1-phenylpropyl)-*N*-propylamine: 17.2 mg; ^{1}H NMR ($CDCl_3$) δ 0.74 (t, J = 7.8 Hz, 3H), 1.01 (t, J = 6.9 Hz, 3H), 1.26 (m, 2H), 2.03 (m, 2H), 3.04 (t, J = 7.0 Hz, 2H), 3.56 (s, 3H), 3.86 (s, 3H), 5.38 (t, J = 7.0 Hz, 1H), 6.98 (s, 1H), 7.03 (d, J = 8.0 Hz, 1H), 7.30 (m, 3H), 7.41 (m, 3H); MS (CI) *m/z* 399 (M + H); HPLC purity 94%, 94%.

1-Methyl-3-[*N*-(1-phenylpentyl)-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7l) was prepared in a manner similar to the procedure described for **7e** using *N*-(1-phenylpentyl)-*N*-propylamine: 22.5 mg; ^{1}H NMR ($CDCl_3$) δ 0.74 (t, J = 7.8 Hz, 3H), 0.90 (t, J = 6.5 Hz, 3H), 1.41 (m, 6H), 2.00 (m, 2H), 3.03 (t, J = 7.5 Hz, 2H), 3.56 (s, 3H), 3.86 (s, 3H), 5.44 (t, J = 7.0 Hz, 1H), 6.98 (d, J = 1.8 Hz, 1H), 7.05 (dd, J = 8.1, 1.8 Hz, 1H), 7.29 (m, 3H), 7.42 (m, 3H); MS (CI) *m/z* 427 (M + H); HPLC purity 100%, 100%.

The corresponding stereoisomerically pure *S*- and R-enantiomers were obtained by separation of the enantiomeric mixture **7l** using chiral HPLC. The *S*-isomer was converted to the corresponding HCl salt as described below.

(*S*)-1-Methyl-3-[*N*-(1-phenylpentyl)-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole Hydrochloride [(*S*)-7l HCl]. The enantiomerically pure (*S*)-**7l** was dissolved in diethyl ether and a solution of 1.0 M HCl in diethyl ether (1 equiv) was added. The precipitate was filtered and washed with diethyl ether to afford the hydrochloride salt (63%) as a white powder: ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.3 Hz, 3H), 0.91 (t, J = 6.9 Hz, 3H), 1.19−1.31 (m, 2H), 1.45 (m, 4H), 2.05 (m, 2H), 3.35 (m, 2H), 3.70 (s, 3H), 3.90 (s, 3H), 5.55 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 1.8 Hz, 1H), 7.19 (dd, J = 8.7, 1.8 Hz, 1H), 7.34 (m, 3H), 7.45 (m, 2H), 7.72 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 427 (M + H). Anal. ($C_{24}H_{32}Cl_2N_4O$) C, H, N.

1-Methyl-3-[*N*-(1-ethylpentyl)-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7m) was prepared in a manner similar to the procedure described for **7e** using *N*-(1-ethylpentyl)-*N*-propylamine: 8.6 mg; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 6H), 0.92 (t, J = 7.5 Hz, 3H), 1.30 (m, 4H), 1.53 (m, 4H), 1.69 (m, 2H), 3.11 (t, J = 7.5 Hz, 2H), 3.54 (s, 3H), 3.84 (s, 3H), 4.03 (m, 1H), 6.96 (d, J = 1.8 Hz, 1H), 7.03 (dd, J = 8.1, 1.8 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H); MS (CI) *m/z* 379 (M + H); HRMS (EI) calculated for $C_{20}H_{31}ClN_4O$ *m/z* (MH^+) 379.2265, observed 379.2249; HPLC purity 100%, 100%.

1-Methyl-3-[*N*-(1-ethylpentyl)-*N*-cyclopropylmethylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7n) was prepared in a manner similar to the procedure described for **7e** using *N*-(1-ethylpentyl)-*N*-cyclopropanemethylamine: 8.6 mg; ^{1}H NMR ($CDCl_3$) δ 0.26 (m, 2H), 0.50 (m, 2H), 0.87 (t, J = 6.9 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.30 (m, 5H), 1.54 (m, 4H), 3.09 (d, J = 6.1 Hz, 2H), 3.55 (s, 3H), 3.84 (s, 3H), 4.03 (m, 1H), 6.96 (d, J = 1.8 Hz, 1H), 7.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 391 (M + H); HRMS (EI) calculated for $C_{21}H_{31}ClN_4O$ *m/z* (MH^+) 391.2265, observed 391.2258; HPLC purity 100%, 100%.

1-Methyl-3-[*N*-(1-ethylpentyl)-*N*-(2-methoxyethyl)amino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7o). This was prepared in a manner similar to the procedure described for **7e** using *N*-(1-ethylpentyl)-*N*-(2-methoxyethyl)-amine: 8.6 mg, ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H), 1.29 (m, 4H), 1.54 (m, 4H), 3.38 (s, 3H), 3.40 (t, J = 7.2 Hz, 2H), 3.54 (s, 3H), 3.62 (t, J = 7.2 Hz, 2H), 3.84 (s, 3H), 4.04 (m, 1H), 6.97 (d, J = 1.8 Hz, 1H), 7.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 395 (M + H); HRMS (EI) calculated for $C_{20}H_{31}ClN_4O_2$ *m/z* (MH^+) 395.2214, observed 395.2219; HPLC purity 100%, 100%.

1-Methyl-3-[*N*-{1-(4-trifluoromethylphenyl)propyl}-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]-triazole (7p) was prepared in a manner similar to the procedure described for **7e** using *N*-[1-(4-trifluorophenyl)-propyl-*N*-propylamine: 24.8 mg; ^{1}H NMR ($CDCl_3$) δ 0.77 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H), 1.53 (m, 2H), 2.06 (m, 2H), 3.04 (t, J = 7.5 Hz, 2H), 3.57 (s, 3H), 3.87 (s, 3H), 5.39 (t, J = 6.8 Hz, 1H), 6.99 (d, J = 1.8 Hz, 1H), 7.06 (dd, J = 8.1, 1.9 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 9.3 Hz, 2H), 7.55 (d, J = 9.3 Hz, 2H); MS (CI) *m/z* 467 (M + H); HPLC purity 97%, 100%.

The corresponding *S*- and *R*-enantiomers were separated by chiral HPLC column. (*S*)-**7p** $[\alpha]^{20}_D = -151.3$ (0.47, CH_2Cl_2). (*R*)-**7p** $[\alpha]^{20}_D = +158.7$ (*c* 0.51, CH_2Cl_2).

The *S*-isomer was converted to its hydrochloride salt in a manner similar to the procedure described for **7l**.

(*S*)-1-Methyl-3-[*N*-{1-(4-trifluoromethylphenyl)propyl}-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]-triazole hydrochloride [(*S*)-7p HCl]: white powder, 90% yield; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H), 1.35 (m, 1H), 1.54 (m, 1H), 2.11 (m, 2H), 3.30 (m, 2H), 3.70 (s, 3H), 3.94 (s, 3H), 5.66 (1H, t, J = 8.1 Hz), 7.06 (d, J = 1.8 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 7.20 (dd, J = 8.1, 1.5 Hz, 1H), 7.6 (4H, br s); MS (CI) *m/z* 467 (M + H). Anal. ($C_{23}H_{27}Cl_2F_3N_4O$) C, H, N.

(*R*,*S*)-1-propylamino-1-(2-methoxyphenyl)butane (*R*,*S*)-20. *n*-Butyrophenone (1.48 g, 10 mmol) and propylamine (5.4 mL, 38.5 mmol) were dissolved in CH_2Cl_2 (70 mL) and cooled to 0 °C. Titanium(IV) chloride (15.4 mL, 1 M solution in toluene, 15.4 mmol) was added dropwise and the mixture was stirred for 16 h. A solution of $NaCNBH_4$ (1.45 g, 23.1 mmol) in MeOH (110 mL) was added and the mixture was stirred overnight, after which time LC−MS showed disappearance of the starting material. The solvent was evaporated and the residue was partitioned between 3 N sodium hydroxide solution and ether. Following filtration through Celite, the organic layer was separated, dried, and evaporated in vacuo to afford the title compound (1.03 g, 47% over two steps) as a yellowsh oil which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6.9 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 1.20 (m, 2H), 1.43 (m, 2H), 1.62 (m, 2H), 2.39 (m, 2H), 3.56 (dd, J = 7.5, 5.7 Hz, 1H), 7.28 (m, 5H); MS (CI) *m/z* 192 (M + H).

1-Methyl-3-[*N*-(1-phenylbutyl)-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7q) was prepared in a manner similar to the procedure described for **7e** using (*R*,*S*)-1-propylamino-1-(2-methoxyphenyl)butane, which was synthesized as described above: 2.9 mg; ^{1}H NMR ($CDCl_3$) δ 0.74 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H), 1.44 (m, 4H), 1.97 (m, 2H), 3.05 (m, 2H), 3.56 (s, 3H), 3.86 (s, 3H), 5.47 (t, J = 6.8 Hz, 1H), 6.98 (d, J = 1.8 Hz, 1H), 7.05 (dd, J = 8.1, 1.8 Hz, 1H), 7.27 (m, 3H), 7.40 (m, 2H), 7.42 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 413 (M + H); HPLC purity 100%, 100%.

(*S*)-1-propylamino-1-phenylbutane (*S*)-20. To a solution of (*R*)-(+)-1-phenyl-1-butanol **16** (7.5 g, 50 mmol) in toluene (80 mL) was added diphenylphosphoryl azide (13.0 mL, 60 mmol) followed by DBU (9.0 mL, 60 mmol). The mixture was stirred for 16 h, after which time TLC indicated disappearance of the starting material. The mixture was poured on to water and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and evaporated. Chromatography of the residue (5% EtOAc/hexanes) afforded (S)-1-azido-1-phenylbutane **17** (7.0 g, 80%) as an oil, which was hydrogenated in 2 h at 40 psi in a 1:1 mixture of EtOAc/ethanol (80 mL) using 10% Pd−C (1.5 g) as catalyst. The mixture was filtered and evaporated to afford (*S*)-1-amino-1-phenylbutane **18** (5.4 g, 90%) as an oil. This amine (3.4 g, 22.8 mmol) in CH_2Cl_2 (40 mL) was treated with triethylamine (8.2 mL, 59.2 mmol), cooled to 0 °C, and propionyl chloride (2.6 mL, 29.6 mmol) was added dropwise. After 2 h, the mixture was poured onto water and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and evaporated. Chromatography of the residue on silica gel (50% EtOAc/hexanes) afforded (*S*)-1-propinoylamido-1-phenylbutane **19** (4.7 g, 100%) as a white solid. This amide (4.7 g, 22.8 mmol) in THF (50 mL) was treated with $LiAlH_4$ (2.61 g, 68.8 mmol) and the mixture was heated at reflux for 7 h. After cooling, the mixture was quenched successively with water (4.0 mL), 1 N NaOH (4.0

mL), and then water (8.0 mL) and stirred. The mixture was dried, filtered, and evaporated to afford (*S*)-1-propylamino-1-phenylbutane [(*S*)-**20**, 3.76 g, 86%] as a clear oil: ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 6.9 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H), 1.21 (m, 2H), 1.42 (m, 2H), 1.62 (m, 2H), 2.38 (m, 2H), 3.56 (dd, J = 8.4, 6.2 Hz, 1H), 7.28 (m, 5H); MS (CI) *m/e* 192 (M + H); $[\alpha]^{20}_D$ = −46 (*c* 0.77, CH_2Cl_2).

The corresponding (*R*)-1-propylamino-1-phenylbutane [(*R*)-**20**; 1.65 g, 51% overall yield) was prepared in a similar manner starting from (*S*)-(−)-1-phenylbutanol: ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6.9 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 1.21 (m, 2H), 1.42 (m, 2H), 1.62 (m, 2H), 2.39 (m, 2H), 3.55 (dd, J = 8.4, 6.2 Hz, 1H), 7.28 (m, 5H); MS (CI) *m/e* 192 (M + H); $[\alpha]^{20}_D$ = −50 (*c* 0.6, CH_2Cl_2).

(*S*)-1-methyl-3-[*N*-(1-phenylbutyl)-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole [(*S*)-7q HCl]. To a solution of 2-methoxy-4-chlorobenzoyl thioisocyanate (0.60 g, 2.64 mmol) in THF (5 mL) was added dropwise a solution of (*S*)-1-propylamino-1-phenylbutane (0.53 g, 2.77 mmol) in THF (5 mL). The mixture was stirred at room temperature for 10 min, after which time TLC (20% EtOAc/hexanes) indicated disappearance of the starting material. Powdered sodium carbonate (0.29 g, 2.77 mmol) was added, followed by methyl iodide (0.31 mL, 5.54 mmol), and the mixture was heated at 70 °C for 6 h. Following evaporation of the solvent, silica gel chromatography (50% EtOAc/hexanes to 80% EtOAc/hexanes) afforded the S-methylated thiourea (1.12 g, 98%) as an oil. Methyl hydrazine (1.0 mL) was added and the mixture was heated at 100 °C for 2 h, after which time HPLC−MS indicated disappearance of the starting material. The reaction mixture was cooled and then poured onto water. The aqueous layer was extracted twice with EtOAc and the organic layer was washed with brine, dried, and evaporated. Silica gel chromatography (20% EtOAc/hexanes) afforded (*S*)-1-methyl-3-[*N*-(1-phenylbutyl)-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole as an oil [(*S*)-**7q**; 0.74 g, 70% from the benzoyl thioisocyanate].

The above free base was dissolved in diethyl ether and a solution of 1.0 M HCl in diethyl ether (1.8 mL, 1.8 mmol) was added. The precipitate was filtered and washed with diethyl ether to afford the title compound (0.63 g, 78%) as a white powder: ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H), 1.26 (m, 1H), 1.46 (m, 3H), 2.02 (m, 2H), 3.32 (m, 2H), 3.69 (s, 3H), 3.69 (s, 3H), 3.93 (s, 3H), 5.58 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 1.8 Hz, 1H), 7.19 (dd, J = 8.4, 1.8 Hz, 1H), 7.31 (m, 3H), 7.45 (m, 2H), 7.73 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 413 (M + H). Anal. ($C_{23}H_{30}Cl_2N_4O\cdot H_2O$) C, H, N.

1-Methyl-3-[*N*-{1-(4-fluorophenyl)pentyl}-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole (7r) was prepared in a manner similar to the procedure described for **7e** using *N*-[1-(4-fluorophenyl)pentyl]-*N*-propylamine: 12.4 mg; ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 6.2 Hz, 3H), 1.40 (m, 6H), 1.98 (m, 2H), 2.99 (t, J = 6.2 Hz, 2H), 3.57 (s, 3H), 3.83 (s, 3H), 5.41 (t, J = 6.3 Hz, 1H), 6.98 (m, 3H), 7.04 (d, J = 8.1 Hz, 1H), 7.39 (m, 3H); MS (CI) *m/z* 445 (M + H); HPLC purity 98%, 100%.

The hydrochloride salt of **7r** was also prepared in a manner similar to the procedure described for **7l**.

1-Methyl-3-[*N*-{1-(4-fluorophenyl)pentyl}-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole hydrochloride [7r HCl]: white powder, 68% yield; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 6.9 Hz), 1.38 (m, 4H), 1.48 (m, 2H), 2.03 (m, 2H), 3.29 (m, 2H), 3.69 (s, 3H), 3.93 (s, 3H), 5.84 (t, J = 6.3 Hz, 1H), 7.02 (m, 2H), 7.19 (dd, J = 8.4, 1.8 Hz, 1H), 7.45 (m, 1H), 7.71 (d, J = 8.1 Hz); ^{13}C ($CDCl_3$) δ 164.1, 160.9, 157.9, 156.1, 146.1, 141.0, 135.3, 133.7, 130.0, 129.9, 122.0, 115.6, 115.3, 112.9, 61.0, 56.6, 46.4, 37.6, 31.3, 28.7, 22.8, 21.5, 14.0, 11.1; MS (CI) *m/z* 445.2 (M + H). Anal. $C_{24}H_{30}ClFN_4O\cdot HCl$.

The corresponding *S*- and *R*-enantiomers of **7r** were separated by chiral HPLC: (*S*)-7r $[\alpha]^{20}_D$ = −128.9 (*c* 0.66, CH_2Cl_2); (*R*)-7r $[\alpha]^{20}_D$ = +124.6 (*c* 0.70, CH_2Cl_2).

The *S*-isomer was converted to the hydrochloride salt in a manner similar to the procedure described for **7l**.

***(S)*-1-Methyl-3-[*N*-{1-(4-fluorophenyl)pentyl}-*N*-propylamino]-5-(2-methoxy-4-chlorophenyl)-1*H*-[1,2,4]triazole hydrochloride [(*S*)-7r HCl]**: white powder, 67% yield, ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H), 1.39 (m, 6H), 2.03 (m, 2H), 3.31 (m, 2H), 3.69 (s, 3H), 3.94 (s, 3H), 5.90 (t, J = 7.6 Hz, 1H), 7.03 (dd, J = 8.4, 8.4 Hz, 2H), 7.05 (*d* = 1.8 Hz, 1H), 7.19 (dd, J = 8.4, 1.8 Hz, 1H), 7.46 (dd, J = 8.7, 5.4 Hz, 2H), 7.72 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 445 (M + H). Anal. ($C_{24}H_{31}Cl_2FN_4O$) C, H, N.

1-Methyl-3-[*N*-{1-(4-trifluoromethylphenyl)propyl}-*N*-propylamino]-5-(2-methyl-4-methoxyphenyl)-1*H*-[1,2,4]-triazole (7s) was prepared in a manner similar to the procedure described for **7e** using 2-methyl-4-methoxybenzoic acid and *N*-[1-(4-trifluoromethylphenyl)propyl]-*N*-propylamine: 28.6 mg; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 3H), 1.06 (t, J = 7.5 Hz, 3H), 1.36 (m, 1H), 1.54 (m, 1H), 2.12 (m, 2H), 2.40 (s, 3H), 3.35 (m, 2H), 3.70 (s, 3H), 3.86 (s, 3H), 5.64 (t, J = 7.2 Hz, 1H), 6.89 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.61 (s, 4H); MS (CI) *m/z* 447 (M + H); HPLC purity 98%, 100%.

The corresponding *S*- and *R*-enantiomers were separated by chiral HPLC and the *S*-isomer was converted to the hydrochloride salt in a manner similar to the procedure described for **7l**.

***(S)*-1-Methyl-3-[*N*-{1-(4-trifluoromethylphenyl)propyl}-*N*-propylamino]-5-(2-methyl-4-methoxyphenyl)-1*H*-[1,2,4]-triazole hydrochloride [(*S*)-7s HCl]:** white powder, 69% yield; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H), 1.38 (m, 1H), 1.55 (m, 1H), 2.13 (m, 2H), 2.40 (s, 3H), 3.23−3.39 (m, 2H), 3.69 (s, 3H), 3.86 (s, 3H), 5.67 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.90 (s, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.61 (4H, br s); MS (CI) *m/z* 447 (M + H). Anal. ($C_{24}H_{30}ClF_3N_4O\cdot 0.5H_2O$) C, H, N.

1-Methyl-3-[*N*-(1-phenylbutyl)-*N*-propylamino]-5-(2-methyl-4-methoxyphenyl)-1*H*-[1,2,4]triazole (7t) was prepared in a manner similar to the procedure described for **7e** using 2-methyl-4-methoxybenzoic acid and *N*-(1-phenylbutyl)-*N*-propylamine: 4.0 mg; ^{1}H NMR ($CDCl_3$) δ 0.75 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 1.48 (m, 4H), 2.00 (m, 2H), 2.29 (s, 3H), 3.04 (t, J = 8.4 Hz, 2H), 3.57 (s, 3H), 3.83 (s, 3H), 5.50 (t, J = 7.3 Hz, 1H), 6.80 (m, 2H), 7.26 (m, 4H), 7.40 (d, J = 7.8 Hz, 2H); MS (CI) *m/z* 393 (M + H); HPLC purity 100%, 100%.

(*S*)-1-Methyl-3-[*N*-(1-phenylbutyl)-*N*-propylamino]-5-(2-methyl-4-methoxyphenyl)-1*H*-[1,2,4]triazole [(*S*)-7t] was prepared in a manner similar to the procedure described for (*S*)-**7q** using 2-methyl-4-methoxybenzoic acid and (*S*)-1-propylamino-1-phenylbutane **20** (formation of the HCl salt was not successful): colorless solid, 74% yield; ^{1}H NMR ($CDCl_3$) δ 0.75 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 1.48 (m, 4H), 2.00 (m, 2H), 2.29 (s, 3H), 3.04 (t, J = 8.4 Hz, 2H), 3.57 (s, 3H), 3.83 (s, 3H), 5.50 (t, J = 7.3 Hz, 1H), 6.81 (m, 2H), 7.26 (m, 4H), 7.40 (d, J = 7.8 Hz, 2H); MS (CI) *m/z* 393 (M + H); HPLC purity 100%, 100%; $[\alpha]^{20}_D$ = −149.1 (*c* 0.48, CH_2Cl_2). Anal. ($C_{24}H_{32}N_4O$) C, H, N.

(*R*)-1-Methyl-3-[*N*-(1-phenylbutyl)-*N*-propylamino]-5-(2-methyl-4-methoxyphenyl)-1*H*-[1,2,4]triazole [(*R*)-7t] was prepared in a manner similar to the procedure described for (*S*)-**7q** using 2-methyl-4-methoxybenzoic acid and (*R*)-1-propylamino-1-phenylbutane **20**: colorless oil, 72% yield; ^{1}H NMR ($CDCl_3$) δ 0.75 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 1.48 (m, 4H), 2.01 (m, 2H), 2.29 (s, 3H), 3.04 (t, J = 8.4 Hz, 2H), 3.57 (s, 3H), 3.83 (s, 3H), 5.50 (t, J = 7.3 Hz, 1H), 6.81 (m, 2H), 7.26 (m, 4H), 7.40 (d, J = 7.8 Hz, 2H); MS (CI) *m/z* 393 (M + H); HPLC purity 100%, 100%; $[\alpha]^{20}_D$ = +149.7 (*c* 0.52, CH_2Cl_2).

1-Methyl-3-[*N*-(1-phenylpentyl)-*N*-propylamino]-5-(2-methyl-4-methoxyphenyl)-1*H*-[1,2,4]triazole (7u) was prepared in a manner similar to the procedure described for **7e** using 2-methyl-4-methoxybenzoic acid and *N*-(1-phenylpentyl)-*N*-propylamine: 24.7 mg; ^{1}H NMR ($CDCl_3$) δ 0.74 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H), 1.42 (m, 6H), 1.95 (m, 2H), 2.29 (s, 3H), 3.04 (t, J = 7.5 Hz, 2H), 3.57 (s, 3H), 3.84 (s, 3H), 5.48 (t, J = 7.3 Hz, 1H), 6.77 (m, 2H), 7.27 (m, 4H), 7.40 (m, 2H); MS (CI) *m/z* 407 (M + H); HPLC purity 100%, 100%.

The corresponding *S*- and *R*-enantiomers were separated by chiral HPLC in a manner similar to the procedure described for **7l**. Conversion of the *S*-isomer to the hydrochloride salt was not successful.

***(S)*-1-Methyl-3-[*N*-(1-phenylpentyl)-*N*-propylamino]-5-(2-methyl-4-methoxyphenyl)-1*H*-[1,2,4]triazole [(*S*)-7u]**: colorless solid, 30% yield; ^{1}H NMR ($CDCl_3$) δ 0.74 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H), 1.42 (m, 6H), 1.96 (m, 2H), 2.29 (s, 3H), 3.04 (t, J = 7.5 Hz, 2H), 3.57 (s, 3H), 3.84 (s, 3H), 5.48 (t, J = 7.3 Hz, 1H), 6.77 (m, 4H), 7.27 (m, 2H), 7.40 (m, 2H); MS (CI) *m/z* 407 (M + H); $[\alpha]^{20}_D = -126.6$ (*c* 0.54, CH_2Cl_2). Anal. ($C_{25}H_{34}N_4O \cdot 0.25EtOAc$) C, H, N.

***(R)*-1-Methyl-3-[*N*-(1-phenylpentyl)-*N*-propylamino]-5-(2-methyl-4-methoxyphenyl)-1*H*-[1,2,4]triazole [(*R*)-7u]**: colorless solid, 22% yield; ^{1}H NMR ($CDCl_3$) δ 0.74 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H), 1.43 (m, 6H), 1.96 (m, 2H), 2.29 (s, 3H), 3.04 (t, J = 7.5 Hz, 2H), 3.57 (s, 3H), 3.84 (s, 3H), 5.48 (t, J = 7.3 Hz, 1H), 6.77 (m, 4H), 7.26 (m, 2H), 7.40 (m, 2H); MS (CI) *m/z* 407 (M + H); $[\alpha]^{20}_D = +138.7$ (*c* 0.47, CH_2Cl_2).

1-Methyl-3-[*N*-(1-phenylbutyl)-*N*-propylamino]-5-(2,4-dimethoxyphenyl)-1*H*-[1,2,4]triazole (7v) was prepared in a manner similar to the procedure described for **7e** using 2,4-dimethoxybenzoic acid and *N*-(1-phenylbutyl)-*N*-propylamine: 1.2 mg; ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7.8 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H), 1.44 (m, 4H), 2.01 (m, 2H), 3.03 (t, J = 7.5 Hz, 2H), 3.56 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 5.48 (t, J = 7.8 Hz, 1H), 6.53 (d, J = 2.1 Hz, 1H), 6.58 (dd, J = 8.1, 2.1 Hz, 1H), 7.21 (m, 1H), 7.30 (m, 2H), 7.40 (m, 3H); MS (CI) *m/z* 409 (M + H); HPLC purity 85%, 86%.

(*S*)-1-Methyl-3-[*N*-(1-phenylbutyl)-*N*-propylamino]-5-(2,4-dimethoxyphenyl)-1*H*-[1,2,4]triazole hydrochloride [(*S*)-7v HCl] was prepared in a manner similar to the procedure described for (*S*)-**7q** using 2,4-dimethoxybenzoic acid and (*S*)-1-propylamino-1-phenylbutane: white solid, 71% yield; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H), 1.27 (m, 1H), 1.46 (m, 3H), 2.02 (m, 2H), 3.32 (m, 2H), 3.67 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 5.60 (t, J = 8.4 Hz, 1H), 6.54 (d, J = 2.1 Hz, 1H), 6.71 (dd, J = 8.7, 2.4 Hz, 1H), 7.31 (m, 3H), 7.46 (m, 2H), 7.74 (d, J = 8.7 Hz, 1H); MS (CI) *m/z* 409 (M + H). Anal. ($C_{24}H_{33}ClN_4O_2$) C, H, N.

1-Methyl-3-[*N*-{1-(4-fluorophenylpentyl}-*N*-propylamino]-5-(2,4-dimethoxyphenyl)-1*H*-[1,2,4]triazole Hydrochloride (7w) was prepared in a manner similar to the procedure described for (*S*)-**7q** using 2,4-dimethoxybenzoic acid and *N*-[1-(4-fluorophenyl)pentyl]-*N*-propylamine: white solid, 81% yield; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H), 1.40 (m, 6H), 1.97 (m, 2H), 2.99 (t, J = 7.0 Hz, 2H), 3.57 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 5.43 (t, J = 6.5 Hz, 1H), 6.51 (d, J = 1.8 Hz, 1H), 6.58 (dd, J = 8.1, 1.8 Hz,-1H), 6.98 (t, J = 8.5 Hz, 2H), 7.40 (t, J = 8.5 Hz, 2H), 7.74 (d, J = 8.1 Hz, 1H); MS (CI) *m/z* 441 (M + H). Anal. ($C_{25}H_{33}FN_4O_2$) C, H, N.

1-Methyl-3-[*N*-(1-phenylbutyl)-*N*-propylamino]-5-(2-chloro-4,5-dimethoxyphenyl)-1*H*-[1,2,4]triazole (7x) was prepared in a manner similar to the procedure described for **7e** using 2-chloro-4,5-dimethoxybenzoic acid and *N*-(1-phenylbutyl)-*N*-propylamine: 3.9 mg; ^{1}H NMR ($CDCl_3$) δ 0.74 (t, J = 7.3 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H), 1.50 (m, 4H), 2.02 (m, 2H), 3.03 (t, J = 7.0 Hz, 2H), 3.56 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 5.40 (t, J = 6.8 Hz, 1H), 6.48 (s, 1H), 6.54 (s, 1H), 7.28 (m, 3H), 7.43 (m, 2H); MS (CI) *m/z* 443 (M + H); HPLC purity 100%, 100%.

(*S*)-1-Methyl-3-[*N*-(1-phenylbutyl)-*N*-propylamino]-5-(2-chloro-4,5-dimethoxyphenyl)-1*H*-[1,2,4]triazole hydrochloride [(*S*)-7x HCl] was prepared in a manner similar to the procedure described for (*S*)-**7q** using 2-chloro-4,5-dimethoxybenzoic acid and *S*-1-propylamino-1-phenylbutane: white solid, 70% yield; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.8 Hz, 3H), 0.99 (t, J = 7.8 Hz, 3H), 1.29 (m, 1H), 1.46 (m, 3H), 2.04 (m, 2H), 3.25−3.45 (m, 2H), 3.76 (s, 3H), 3.94 (s, 3H), 4.04 (s, 3H), 5.57 (t, J = 7.5 Hz, 1H), 6.98 (s, 1H), 7.33 (m, 4H), 7.55 (m, 2H); MS (CI) *m/z* 443 (M + H). Anal. ($C_{24}H_{32}Cl_2N_4O_2$) C, H, N.

CRF_1 Binding Assay. Full-length human CRF_1 receptor cDNA was subcloned into the mammalian expression vector pCDM7amp and transfected into mouse fibroblast Ltk$^-$ cells. Cell clones isolated by limiting dilution were screened for high-level expression of human CRF_1 receptor by whole cell sauvagine-stimulated cAMP assay as previously described. The clone L/hA6-4E10 was expanded in culture, and cell membranes were prepared from frozen pellets of 5×10^7 cells as described.[25] Cell pellets were resuspended and homogenized in tissue buffer (1× Dulbecco's phosphate-buffered saline without Ca^{2+} or Mg^{2+} supplemented with 10 mM $MgCl_2$ and 2 mM EGTA) at a ratio of 10 mL of tissue buffer per 5×10^7. The homogenate was centrifuged at 800*g* for 10 min. The supernatant was transferred to a new tube and centrifuged at 38 000*g* for 20 min at 4 °C. The resulting pellet was resuspended in fresh tissue buffer and stored at −80 °C or used immediately in the binding assay. Binding assays were conducted in polypropylene 96-well microtiter plates with each well receiving (in order) 50 μL of tissue buffer (with or without various dilutions of competing compounds), 50 μL of [^{125}I]-[Tyr^0]-sauvagine (NEX 306; NEN), and 100 μL of membrane suspension (5−10 μg of protein). The mixture was incubated for 2 h at room temperature and then rapidly filtered onto GF/C filter plates which had been presoaked with 1% polyethyleneimine and prerinsed with PBS containing 1% BSA and 0.01% Triton X-100. The membranes were washed four times on the filter plate with 200 μL of rinse buffer (1× Dulbecco's phosphate-buffered saline without Ca^{2+} or Mg^2 supplemented with 0.01% Triton X-100). Plates were dried and counted for radioactivity using scintillation fluid and a TopCount liquid scintillation counter (Packard). Nonspecific binding was determined in the presence of 1 μM human urocortin. Displacement binding curves were generated from the data using the curve-fitting program Prism 3.0 (GraphPad Software). K_i values were derived from IC_{50} values using the Cheng−Prusoff equation.[26]

CRF_1 Adenylate Cyclase Assay. Cells expressing human CRF_1 were seeded into 96-well microtiter tissue culture plates (10^4 cells/well) and grown overnight. The culture medium was aspirated, and the cells were washed once with PBS. Each well received assay medium (DMEM without phenol red supplemented with 1 mM isobutylmethylxanthine, pyruvate, HEPES, l-glutamine) with or without various dilutions of competing compounds followed by sauvagine (2 nM final concentration). After a 30 min incubation at 37 °C, cells were lysed and total cAMP was determined using a chemiluminescent immunoassay kit (Tropix-PE Biosystems, Bedford, MA).

Pharmacokinetics. The pharmacokinetics and blood−brain barrier (BBB) penetration of NBI-42862 was determined in male Sprague−Dawley rats following an intravenous (iv, N = 3/time point) and oral (po, N = 3/time point) dose of 1 and 2 mg/kg, respectively. The dosing solution was prepared in purified water and filtered through a 0.2 μm Nylon filter before administration (2 mL/kg) via tail vain (iv) or a gavage (po). Terminal blood and brain tissue samples were taken at predetermined times for composite sampling. All plasma and tissue samples were flash frozen in liquid nitrogen within 10 min of sampling and stored in −70 °C or below until analysis. The bioanalytical method applied for the measurement of test articles in plasma along with added internal standard consisted of precipitation with 200 μL of acetonitrile from 50 μL of plasma, centrifugation, and recovery of the supernatant, drying down in a vacuum and then reconstitution in acetonitrile−water solutions before introducing into an LC−MS/MS system for analysis. The lower limit of quantification (LLOQ) for the analytical methods was 5 ng/mL of test article in plasma. The bioanalytical method applied for the measurement of test articles in brain tissue along with added internal standard consisted of homogenizing half of the brain tissue (longitude cut) in 2 mL of acetonitrile/water (50:50), centrifugation, and recovery of the supernatant before introduction into an LC−MS/MS system for analysis. The LLOQ for the analytical methods was 0.5 ng/g of test article in brain tissue. All pharmacokinetic parameters were calculated from a non-compartmental model in the WinNonlin program. The brain-

to-plasma ratio was obtained by comparing brain AUC to plasma AUC.

Supporting Information Available: Elemental analyses of relevant compounds and copies of ^{1}H NMR spectra and HPLC MS spectra used to confirm the optical purity of (*R*)- and (*S*)-(**20**). This material is available free of charge via the Internet at http://pubs.acs.org.

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