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Discovery of 6-chloro-2-trifluoromethyl-7-aryl-7*H*-imidazo[1,2-*a*] imidazol-3-ylmethylamines, a novel class of corticotropin-releasing factor receptor type 1 (CRF_1R) antagonists

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ABSTRACT

A novel series of [6-chloro-2-trifluoromethyl-7-aryl-7*H*-imidazo[1,2-*a*]imidazol-3-ylmethyl]-dialkylamines was discovered as potent CRF_1R antagonists. The optimization of binding affinity in the series by the parallel reaction approach is discussed herein.

Corticotropin-releasing factor (CRF), a 41-amino acid neuropeptide produced by hypothalamic nuclei in brain, plays an essential role in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis and in the coordination of neuroendocrine, autonomic, behavioral and immune responses to stress.[1,2] The physiological effects of CRF are mediated through the known CRF_1 and CRF_2 receptor subtypes, of which the CRF_1 receptor is believed to play a pivotal role in stress-related responses.[3] A large body of pre-clinical and clinical data links CRF to psychopathology of a variety of stress-related dysfunctions, such as anxiety, depression, obsessive–compulsive and post-traumatic stress disorders.[4–7] It has been hypothesized that selective CRF_1R antagonists may be useful for the treatment of these illnesses.

A number of potent non-peptide CRF_1 antagonists have been reported over the past 15 years, reflecting significant efforts of many research groups in this area.[8–10] A thorough analysis of structure–activity relationships led to the postulation of a general CRF_1 antagonist chemotype.[8]

A large majority of these compounds contain either bicyclic or monocyclic core structures. As shown in Figure 1, a typical example of the former chemotype **1** consists of a heterobicyclic core, which possesses a basic sp^2-hybridized nitrogen atom, essential for hydrogen bonding between the receptor and the ligand. Attached to the core are a hydrophobic (usually dialkylamino) side chain R_2-Y-R_3 and a substituted phenyl or 3-pyridyl ring. The latter aromatic moiety possesses a 4-positional substituent R_5, which

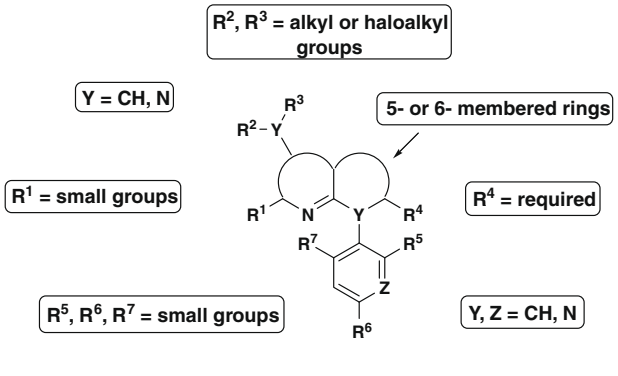

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Figure 1.

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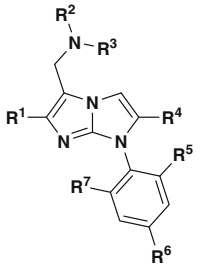


Amine Library: Optimize Activity Based on Available Amines

Bicyclic Core: Develop Efficient Synthesis

Aryl Library: Modulate Steric and Electronic Properties of Aryl Ring

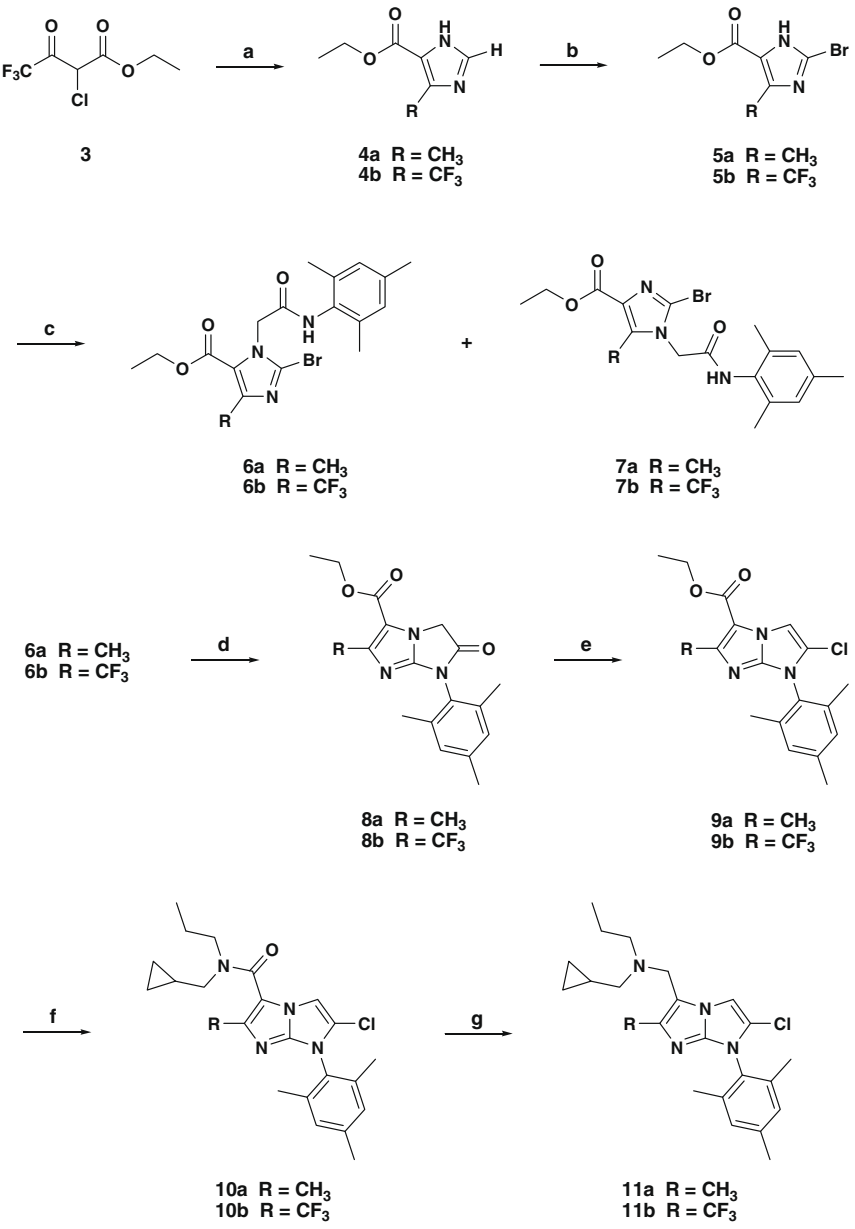
2

Figure 2.

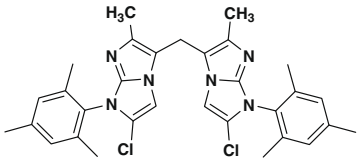
interacts with a hydrophobic pocket of the CRF_1 receptor, as well as 2- and/or 6-positional substituents R_4 and R_6, and is required for the maintenance of an orthogonal binding conformation.

Based on these general considerations, we designed imidazo[1,2-*a*]imidazole derivatives **2** as novel CRF_1R antagonists (Fig. 2). Our goal was to develop an efficient synthesis of the heterocyclic core of the molecule with a late stage introduction of diversity elements. The proposed approach would allow us to effectively optimize the potency of the target compounds by a systematic modulation of the steric and electronic properties of aryl rings as well as by the utilization of a wide variety of available amines.

The synthetic pathway towards imidazo[1,2-*a*]imidazole derivatives **2** is illustrated in Scheme 1. While methyl imidazole **4a** was commercially available, trifluoromethyl analog **4b** was prepared by condensation of ethyl 2-chloro-4,4,4-trifluoro-3-oxobutanoate **3** with formamide.[11] Bromination of **4a** and **4b** with NBS provided bromoimidazoles **5a** and **5b**, which were alkylated with 2-bromo-*N*-mesitylacetamide[12] in the presence of DBU to yield products **6a** and **6b**. We found that the regioselectivity of *N*1 versus *N*3 alkylation of bromoimidazoles **5a** and **5b** was highly dependent



Scheme 1. Reagents and conditions: (a) $HCONH_2$, H_2O, 135 °C, 2 h, 24%; (b) NBS, 1,2-dichloroethane, 85 °C, 4 h, 85%; (c) 2-bromo-*N*-mesitylacetamide, DBU, toluene–acetone, 55 °C, overnight, 88–90%; (d) Ag_2CO_3 or AgOTf, tetramethylenesulfone, 150 °C, 73%; (e) $POCl_3$, 55 °C, 15 min, 50–80%; (f) Me_3Al, *N*-(cyclopropylmethyl)propan-1-amine, toluene, reflux, 14 h, 68–100%; (g) Red-Al, toluene, rt, overnight, 64%.



12

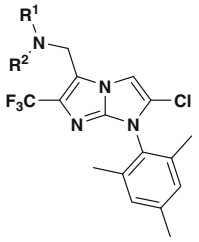
Figure 3.

on the nature of the *C*4-substituent. While the alkylation of methyl imidazole **5a** displayed virtually no stereoselectivity,[13] the alkylation of trifluoromethyl imidazole **5c** was completely *N*1-regiospecific.[14] Silver salt assisted cyclization of **6a** and **6b** in sulfolane furnished constrained imidazoles **8a** and **8b**. Heating of the latter compounds with phosphorus trichloride at 150 °C in a high-pressure vessel then provided 6-chloroimidazo[1,2-*a*]imidazoles **9a** and **9b**. The trimethylaluminum promoted amidation[15] of **9a** and **9b** with *N*-(cyclopropylmethyl)propan-1-amine yielded amides **10a** and **10b**, which were converted to the corresponding amines **11a** and **11b** by Red-Al reduction[16] in toluene.

It soon became evident that the presence of another electron-withdrawing group at the imidazo[1,2-*a*]imidazole core was necessary to ensure chemical stability. Indeed, a trifluoroacetate salt of methyl derivative **11a**, upon exposure to acetonitrile, suffered the loss of its amino side chain, undergoing spontaneous dimerization[17] to form compound **12** (Fig. 3). In contrast, trifluoromethyl derivative **11b** was chemically stable under the described conditions.[18]

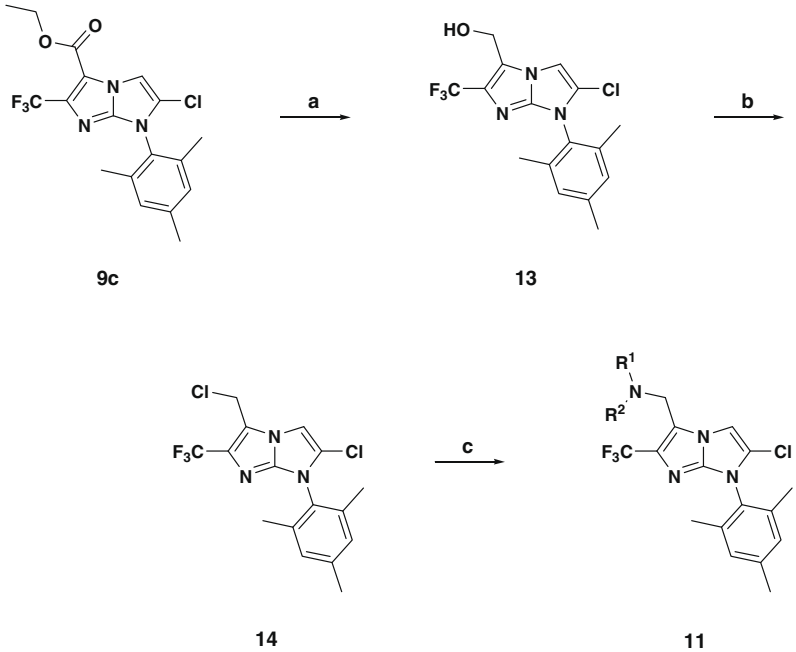
We found the Weinreb amidation/Red-Al reduction sequence to be inconvenient for rapid parallel synthesis of amines **11**, due to the moisture-sensitivity of both reactions and tedious aqueous work-ups. As an alternative, ester **9b** was quantitatively reduced to alcohol **13** with DIBAL-H, followed by the conversion of the latter to chloromethyl intermediate **14** by reaction with thionyl chloride (Scheme 2). Alkylation of both primary and secondary amines[19] with **14** in acetonitrile in the presence of Hünig's base cleanly produced the corresponding monoalkylated products without any detectable over alkylation.[20] The reaction occurred at room temperature and was usually completed within 15 min. For convenience, no aqueous work up was necessary, as the homogeneous reaction mixture could be directly injected into a reversed phase preparative HPLC system for purification.[21]

Table 1
*h*CRF$_1$R binding affinities of *N*,*N*-disubstituted aminomethylimidazo[1,2-*a*]imidazoles **11**



11

Compd	R^1	R^2	K_i (nM)
11b	*c*PrCH$_2$	*n*Pr	9.1
11c	*c*PrCH$_2$	CF$_3$CH$_2$	5.2
11d	*c*PrCH$_2$	Et	9.0
11e	*c*PrCH$_2$	CF$_3$CH$_2$CH$_2$	16
11f	*n*Pr	CF$_3$CH$_2$	8.3
11g	*n*Pr	CF$_3$CH$_2$CH$_2$	12
11h	*n*Pr	CH$_3$OCH$_2$CH$_2$	32
11i	*n*Pr	*n*Pr	69
11j	*n*Pr	CF$_3$CF$_2$CH$_2$	440
11k	*n*Bu	Et	78
11l	*n*Bu	Me	310
11m	Allyl	*n*Pr	4.5
11n	Allyl	Allyl	13
11o	Metallyl	Et	67
11p	*c*BuCH$_2$	*n*Pr	5.3
11q	*c*BuCH$_2$	CF$_3$CH$_2$	13
11r	*c*BuCH$_2$	Et	16
11s	*c*PrCH$_2$CH$_2$	CF$_3$CH$_2$	6.3
11t	*c*PrCH$_2$CH$_2$	Et	13
11u	*c*PrCH$_2$CH$_2$	*n*Pr	53
11v	*c*PrCH$_2$CH$_2$	CF$_3$CH$_2$CH$_2$	110



9c 13 14 11

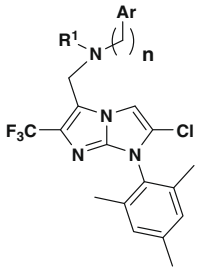
Scheme 2. Reagents and conditions: (a) DIBAL-H, THF, 0 °C to rt, 2 h, 100%; (b) $SOCl_2$, CH_2Cl_2, 0 °C, 30 min, 100%; (c) R^1R^2NH, Et_3N, CH_3CN, rt, 15 min, 50–95%.

The general approach presented in Scheme 2 was successfully applied to the parallel synthesis of a number of imidazo[1,2-*a*]imidazoles **11, 15–17** in generally good yields.[22] The CRF_1R binding affinities of these analogs were determined by displacement of [^{125}I] Tyr-*o*-CRF from *h*CRF_1R endogenously expressed on IMR-32 human neuroblastoma cells[23] and are summarized in Tables 1–4.

Initially, we investigated the effect of the amino side chain on binding potency of analogs **11** (Table 1). Cyclopropylmethyl amines **11b–e** displayed high binding affinity. While *n*-propyl derivatives **11f** and **11g** were nearly as potent as their cyclopropylmethyl analogs **11c** and **11e**, replacement of the cyclopropylmethyl group in **11b** with *n*-propyl resulted in almost 7.5-fold loss in activity for **11i**. Terminal trifluorination of the *n*-propyl side chain gave a sixfold advantage in potency for **11g** over **11i**; however, further introduction of fluorine atoms (as in **11j**) had an unfavorable effect on binding. Allyl derivative **11m** was the most potent compound in the series. The expansion of the cyclopropyl ring in **11b–d** to cyclobutyl did not result in a significant change in binding affinity for **11p–r**. However, the effect of homologation of the cyclopropylmethyl group appeared to be sensitive to the length of substituent R_2. In particular, while trifluoroethyl **11s** and ethyl **11t** derivatives were equipotent with **11c** and **11d**, significant loss in activity was observed for *n*-propyl **11u** and 3,3,3-trifluoropropyl **11v** analogs, compared to **11b** and **11e**.

In the course of our optimization studies, we prepared and tested a number of arylalkyl imidazo[1,2-*a*]imidazoles **15**. (Table 2). The highest binding affinity was displayed by phenethyl ethyl amine **15r** (K_i = 6.0 nM), an almost 60-fold advantage over benzyl ethyl amine **15m**. *n*-Propyl **15q** and methyl **15s** analogs were, respectively, 3.5 and 25 times less potent than **15r**. Pyridyl-containing derivatives **15t–v** were less active than **15s**, suggesting that polar atoms in the side chain are not well-tolerated by the receptor for this chemotype. Surprisingly, more lipophilic fluoroethyl and fluoropropyl analogs **15w** and **15x** were significantly less potent than **15r** and **15q**. In the benzylamine series, the introduction of a fluorine atom on the phenyl ring of **15a** or **15h** did not result in significant changes in potency for **15b** and **15c** or **15k** and **15l**. However, *para*-chlorophenyl analogs **15e** and **15i** were 3.5 and 6 times more potent than **15a** and **15h**.

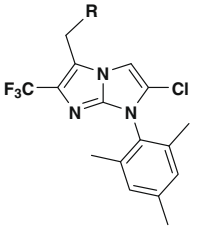
Table 2
hCRF_1R binding affinities of arylalkylaminoimidazo[1,2-*a*]imidazoles **15**



15

Compd	*n*	Ar	R^1	K_i (nM)
15a	1	Ph	$CF_3CH_2CH_2$	43
15b	1	*m*-F-C_6H_4	$CF_3CH_2CH_2$	49
15c	1	*p*-F-C_6H_4	$CF_3CH_2CH_2$	34
15d	1	*p*-F-C_6H_4	CF_3CH_2	160
15e	1	*p*-Cl-C_6H_4	$CF_3CH_2CH_2$	12
15f	1	Ph	*n*Bu	130
15g	1	Ph	Me	160
15h	1	Ph	*n*Pr	170
15i	1	*p*-Cl-C_6H_4	*n*Pr	28
15j	1	*p*-NO_2-C_6H_4	*n*Pr	150
15k	1	*m*-F-C_6H_4	*n*Pr	260
15l	1	*p*-F-C_6H_4	*n*Pr	350
15m	1	Ph	Et	350
15n	1	*m*,*p*-Di-Cl-C_6H_3	Et	580
15o	1	*o*-Me-C_6H_4	Et	4800
15p	1	2-Furanyl	Me	180
15q	2	Ph	*n*Pr	21
15r	2	Ph	Et	6.0
15s	2	Ph	Me	150
15t	2	2-Pyridyl	Me	4300
15u	2	3-Pyridyl	Me	1900
15v	2	4-pyridyl	Me	7600
15w	2	Ph	CF_3CH_2	350
15x	2	Ph	$CF_3CH_2CH_2$	1900

Table 3
hCRF_1R binding affinities of cyclic aminomethylimidazo[1,2-*a*]imidazoles **16**



16

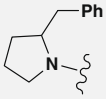
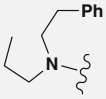
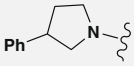
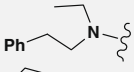
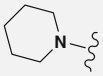
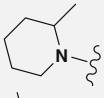
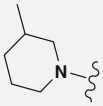
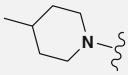
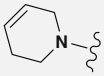
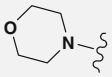
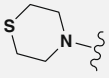
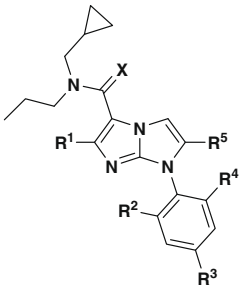
Compd	R	K_i (nM)
16a		>7000
15h		170
16b		190
15q		21
16c		610
15r		6.0
16d		1200
16e		1600
16f		5800
16g		3200
16h		760
16i		1700
16j		920

Table 4
*h*CRF$_1$R binding affinities *N*-cyclopropylamino-*N*-propylimidazo[1,2-*a*]imidazoles



Compd	X	R^1	R^2	R^3	R^4	R^5	K_i (nM)
10a	O	Me	Me	Me	Me	Cl	61
10b	O	CF_3	Me	Me	Me	Cl	33
11b	2H	CF_3	Me	Me	Me	Cl	9.1
17a	2H	CF_3	Me	Me	Me	H	470
17b	2H	CF_3	Me	Me	Cl	Cl	4.2
17c	2H	CF_3	Me	MeO	H	Cl	13

Imidazo[1,2-*a*]imidazoles **16a–c**, possessing cyclic amino side chains, displayed significantly lower binding affinities than corresponding acyclic amines **15q, 15r** and **15h** (Table 3). Olefin-containing **16h** was slightly more potent than its saturated analogs **16d**. The potency of methyl piperidines **16e–g** were inferior to that of unsubstituted analog **16d**. The introduction of the electronegative oxygen atom into the piperidine moiety of **16g** led to a decrease in the potency of **16i**, while the analogous substitution with sulfur marginally increased the potency of **16j**.

We also briefly investigated a variation in substituents at the aromatic ring of **2** on binding potency. Both 2-chloro-4,6-dimethylphenyl **17b** and 2-methoxy-4-methylphenyl **17c** analogs were nearly as potent as 2,4,6-trimethylphenyl derivative **11b** (Table 4). It should be noted, however, that the presence of the 6-chloro substituent at the imidazo[1,2-*a*]imidazole core was necessary for a molecule to sustain high binding affinity. For example, dechlorinated derivative **17a** was approximately 50-fold less active than **11b**. The presence of a polar amide functionality in the side chain of **10a** and **10b** led to a decrease in their binding affinities, compared to that of amine **11c**.

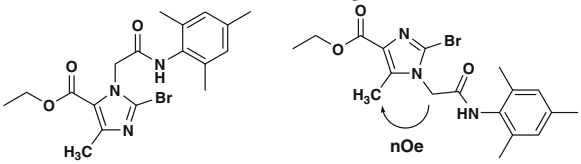
In summary, we designed and prepared 6-chloro-2-trifluoromethyl-7-aryl-7*H*-imidazo[1,2-*a*]imidazol-3-ylmethyl amines as potent CRF$_1$R receptor antagonists by selective monoamination of the common chloromethyl intermediate. The presence of the 2-trifluoromethyl group at the core was found to be necessary for chemical stability. Analogs with amino side chains containing small alkyl or cycloalkyl groups were found to have the highest binding affinities.

Acknowledgments

The authors are grateful to Daniel Smith and Henry Wong (BMS Chemical Synthesis, Wallingford, CT) for providing them with multi-gram quantities of ethyl 2-bromo-4-(trifluoromethyl)-1*H*-imidazole-5-carboxylate.

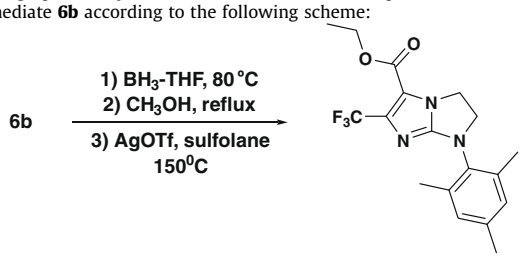
References and notes

1. Owens, M.; Nemeroff, C. B. *Pharmacol. Rev.* **1991**, *43*, 425.
2. Grigoriadis, D. E.; Haddach, M.; Ling, N.; Saunders, J. *Curr. Med. Chem. CNS Agents* **2001**, *1*, 63.
3. Takahashi, L. K. *Neurosci. Behav. Rev.* **2001**, *25*, 627.
4. Kasckow, J. W.; Baker, D.; Geracioti, T. D. *Peptides* **2001**, *22*, 845.
5. Holsboer, F. *J. Psychiatr. Res.* **1999**, *33*, 181.
6. Banki, C. M.; Karmasci, L.; Bissette, G.; Nemeroff, C. B. *Eur. Neuropsychopharmacol.* **1992**, *2*, 107.
7. Webster, E. L.; Torpy, D. J.; Elenkov, I. J.; Chrousos, G. P. *Ann. N.Y. Acad. Sci.* **1998**, *840*, 21.
8. Dzierba, C. D.; Hartz, R. A.; Bronson, J. J. *Ann. Rep. Med. Chem.* **2008**, *43*, 3–23.
9. Muller, M. B.; Wurst, W. *Trends Mol. Med.* **2004**, *8*, 409–415.
10. Gilligan, P. J.; Robertson, D. W.; Zaczek, R. *J. Med. Chem.* **2000**, *43*, 1641.
11. Lee, L. F.; Schleppnik, F. M.; Howe, R. K. *J. Heterocycl. Chem.* **1985**, *22*, 1621.
12. Byrnes, E. W.; McMaster, P. D.; Smith, E. R.; Blair, M. R.; Boyes, R. N.; Duce, B. R.; Feldman, H. S.; Kronberg, G. H.; Takman, B. H.; Tenthorey, P. A. *J. Med. Chem.* **1979**, *22*, 1171.
13. The assignment of structures of alkylation products **6a** and **7a** was made on the basis of the NOE studies. Particularly, a positive NOE effect was observed between the protons of the *C*4-methyl and *N*3-methylene groups in **7a**. No such effect was seen in the studies with analog **6a**:

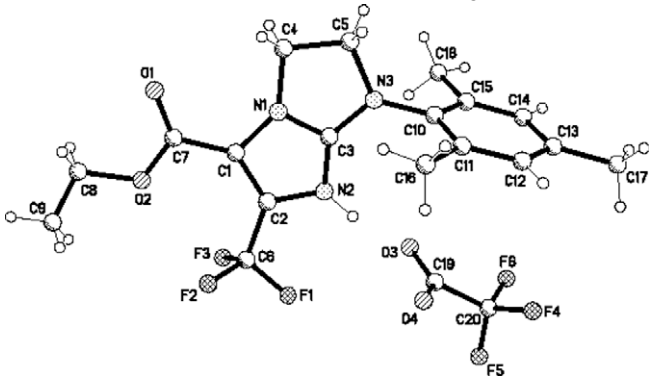


6a **7a**

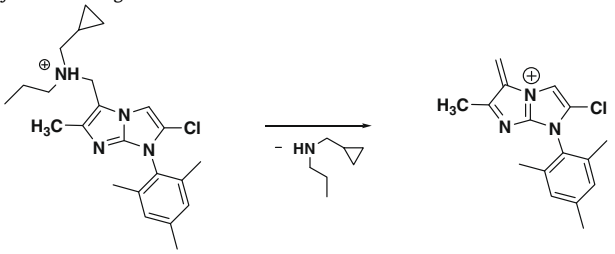
14. The *N*1-regiospecificity of alkylation of **5b** was evidenced by an X-ray crystallographic analysis of the mono TFA salt of compound **18**, derived from intermediate **6b** according to the following scheme:



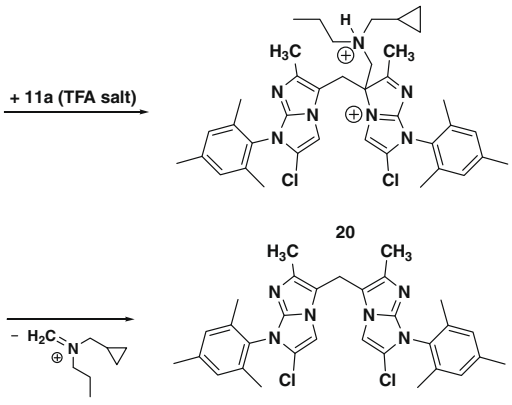
18



The X-ray crystal structure of **18** was deposited with Cambridge Crystallographic Data Centre (deposition number—CCDC 773714).
15. Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
16. Malek, J. *Org. React.* **1988**, *36*, 249.
17. Analytical data for **12** (double TFA salt): ^{1}H NMR (CD_3OD, 500 MHz) δ 2.05 (s, 12H), 2.36 (s, 6H), 2.40 (s, 6H), 4.52 (s, 2H), 7.21 (s, 4H), 7.48 (s, 2H), 7.78 (s, 2H). Mass spec.: 558.21 (MH^+). In accordance with the related examples[24] reported in the literature, the dimerization of **11a** to **12** is believed to proceed by the following mechanism:



11a (TFA salt) **19**



18. This stabilizing effect of the trifluoromethyl group has been previously observed in related systems: see (a) Dubowchik, G. M.; Michne, J. A.; Zuev, D.; Schwartz, W.; Scola, P. M.; James, C.; Ruediger, E.; Pin, S.; Burris, K. D.; Balanda, L.; Gao, Q.; Fung, L.; Fiedler, T.; Browman, K. E.; Taber, M. T.; Zhang, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3997; (b) Han, X.; Michne, J. A.; Pin, S. S.; Burris, K. D.; Balanda, L. A.; Fung, L. K.; Fiedler, T.; Browman, K. E.; Taber, M. T.; Zhang, J.; Dubowchik, G. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3870.
19. Some of the utilized amines were commercially available, while the others were prepared according to the published procedure: see Dubowchik, G. M.; Michne, J. A.; Zuev, D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3147.
20. All new compounds gave satisfactory analytical data. For **11c** (mono TFA salt): ^{1}H NMR (CD_3OD, 500 MHz) δ 0.12 (m, 2H), 0.55 (m, 2H), 0.98 (m, 1H), 2.01 (s, 6H), 2.39 (s, 3H), 2.60 (d, J = 6.5 Hz, 2H), 3.36 (m, 2H), 4.21 (s, 2H), 7.12 (s, 2H), 7.61 (s, 1H). Mass spec.: 492.96 (MH^+).
21. Preparative HPLC Conditions: column XTERRA 30 mm × 150 mm S5; injection volume, 2000 μL; solvent A, CH_3OH (10%)/H_2O (90%)/TFA (0.1%); solvent B, CH_3OH (90%)/H_2O (10%)/TFA (0.1%); starting% B, 30; final% B, 100; flow rate 25 mL/min; gradient time, 20 min; end time, 25 min.
22. The purity of analogs **11**, **15**–**17** was found to be >90% by reversed phase analytical LC–MS analysis under following conditions: column—PHENOMENEX-LUNA 4.6 × 50 mm S10; solvent A, CH_3OH (10%)/H_2O (90%)/TFA (0.1%); solvent B, CH_3OH (10%)/H_2O (90%)/TFA (0.1%); starting% B, 0; final% B, 100; flow rate 4 mL/min; gradient time, 2 min; end time, 3 min.
23. Membranes were prepared from transformed IMR-32 cells as previously described,[25] and incubated with [^{125}I]Tyr-*o*-CRF (100 pM) and increasing concentrations of test compound for 100 min at 25 °C (assay buffer: 50 mM Tris (pH 7.2), 10 mM $MgCl_2$, 0.5% BSA, 0.005% Triton X-100, 10 μg/mL aprotinin and 10 μg/mL leupeptin. Assays were stopped by addition of ice-cold wash buffer (50 mM Tris, pH 7.4 and 0.2% BSA). Non-specific binding was defined with 10 μM *o*-CRF. The present compounds are full antagonists of the CRF_1R as determined by their ability to inhibit CRF stimulated cAMP production in IMR-32 cells.
24. (a) Kamel, M. M.; Nabih, I.; Nasr, M. E.; Abbasi, M. M. *Pharmazie* **1985**, *40*, 622; (b) Abbasi, M.; Nasr, M.; Zoorob, H. H.; Michael, J. M. *J. Heterocycl. Chem.* **1978**, *15*, 649; (c) Frydman, R. B.; Reil, S.; Frydman, B. *Biochemistry* **1971**, *10*, 1154; (d) Burke, W. J.; Nasutavicus, W. A.; Weatherbee, C. *J. Org. Chem.* **1964**, *29*, 407.
25. Dieterich, K. D.; DeSouza, E. B. *Brain Res.* **1996**, *733*, 113.