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Bioorganic & Medicinal Chemistry Letters 15 (2005) 4029–4032
Bioorganic & Medicinal Chemistry Letters

Synthesis and structure–activity relationship of imidazo[1,2-*a*]benzimidazoles as corticotropin-releasing factor 1 receptor antagonists

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Received 31 March 2005; revised 24 May 2005; accepted 7 June 2005
Available online 27 June 2005

Abstract—8-Aryl-1,3a,8-triaza-cyclopenta[a]indenes represent a novel series of high binding affinity corticotropin-releasing factor 1 receptor antagonists. Here, we report their synthesis, SAR, and pharmacokinetic properties of compound **8e** (K_i = 23 nM).

Corticotropin-releasing factor (CRF) is a 41-amino-acid neuropeptide secreted in the hippocampus. It imposes its physiological effects on depression and other neuropsychiatric disorders via the hypothalamic–pituitary–adrenal (HPA) axis.[1] The CRF receptor, a G-protein-coupled receptor, has two well-characterized subtypes (CRF1 and CRF2).[2] Compelling clinical evidence supports the hypothesis that overproduction of CRF may underlie the pathology of depression, anxiety, and stress-related disorders, and suggests that antagonists of CRF1R could be useful for the treatment of these conditions.[1]

As described in our preceding article,[3] we have synthesized 1-aryl-2,3-dihydro-imidazoimidazoles (**I**) (Fig. 1) as CRF1R antagonists. An exemplary compound (X,Y,Z = Me, R^1 = Et, R^2 = *n*Pr and R^3 = *c*PrCH$_2$) had relatively good binding affinity (K_i = 42 nM) and reasonable pharmacokinetic properties, and it demonstrated anxiolytic activity in a mouse canopy model. In the search for more potent compounds, we elaborated the core structure I with a phenyl ring as shown in Figure 1. In this article, we report our efforts on the design, synthesis, and SAR studies of a novel series of imidazo[1,2-*a*]benzimidazole CRF1R antagonists.

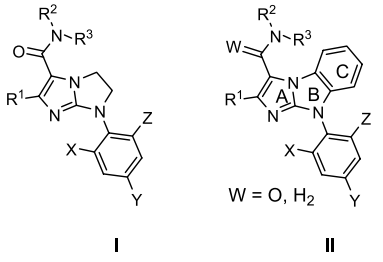

Figure 1. Small molecule CRF1R antagonists.

The synthesis of these compounds is outlined in Schemes 1 and 2. The reaction of substituted anilines **1** with *o*-fluoronitrobenzene **2** afforded *o*-nitroanilines **3**.[4] Reduction to the corresponding diamines **4** was effected by hydrogenation for 2,4,6-trimethyl-substituted anilines, and with $Na_2S_2O_4/NH_4OH$ for chloro- and bromo-substituted anilines to avoid reduction of the halides.[5] 2-Aminobenzimidazoles **5** were formed by the reaction of **4** with cyanogen bromide in ethanol at 150 °C,[6] followed by alkylation with ethyl bromoacetate in acetone

Keywords: Corticotropin-releasing factor 1; Antagonists; SAR; Pharmacokinetic properties.
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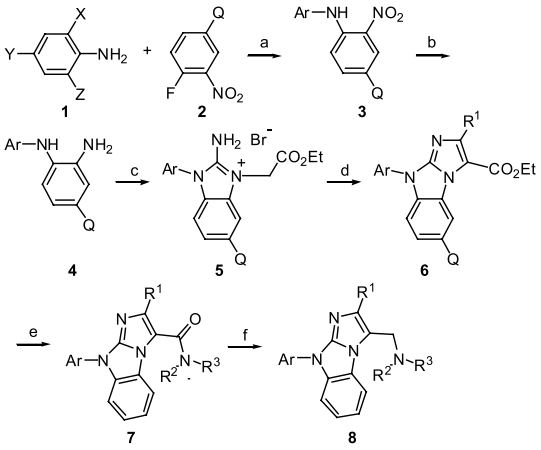
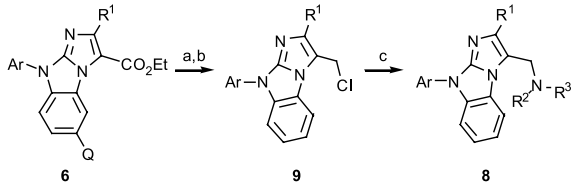
doi:10.1016/j.bmcl.2005.06.028



Scheme 1. Reagents and conditions: (a) KF, 180 °C, 48–72 h, 20–100%. (b) i—1 atm H_2, Pd/C (10%), EtOAc, rt, 4 h, 80–85%; or ii—$Na_2S_2O_4$, THF/H_2O/concd NH_4OH (1:1:1), rt, 16 h, 60–80%. (c) i—BrCN, EtOH, 150 °C, 40 min; ii—1.2 equiv $BrCH_2CO_2Et$, acetone, 65 °C, 16 h. 70–95%. (d) 2.5 equiv R^1CO_2Na, $(R^1CO)_2O$, 150–180 °C, 20 h, 40–76%; (e) R^2NHR^3, $AlMe_3$, PhMe, 80 °C, 14 h, 60–90%; (f) Red-Al, PhMe, rt, 24 h, 50–70%.



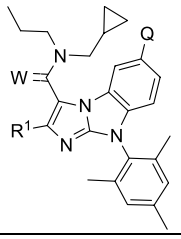
Scheme 2. Reagents and conditions: (a) 5 equiv *i*-Bu_2AlH, PhMe, 0 °C, 1 h, 80–100%. (b) 2 equiv $SOCl_2$, CH_2Cl_2, 0 °C, 1 h; (c) 5 equiv R^2NHR^3.HCl, 7 equiv *i*-Pr_2NEt (or 5 equiv R^2NHR^3, 2 equiv *i*-Pr_2NEt, MeCN, rt, 1 h, then chlorides **9**, rt, 24 h, 50–70% for two steps.

at reflux. Condensation with acetic, propionic, or trifluoroacetic anhydride along with the respective sodium salt at 160 °C afforded esters **6**.[7] Because of the volatility of trifluoroacetic anhydride (bp = 40 °C), esters **6** where $R^1 = CF_3$ were prepared in a sealed bomb. Weinreb amidation[8] of esters **6** formed amides **7**, and the Red-Al reduction of amides **7** afforded amines **8**.[9]

Amines **8** could also be efficiently synthesized in a parallel fashion (Scheme 2) using a variety of secondary (and primary) amines. This was especially convenient, since the CRF1R is tolerant of diversity in this area. The DIBAL-H reduction of esters **6** cleanly afforded the corresponding alcohol with minimal workup.[10] These alcohols were treated with $SOCl_2$ briefly to form chlorides **9** that, after concentration in vacuo, were treated with a variety of secondary amines in acetonitrile to give amines **8** in good yields.

Initial SAR studies focused on amide (Fig. 1, II, W = O) versus amine (Fig. 1, II, W = H_2) functionality, preferences for the small alkyl group on the A ring (R^1), and fluoro substitution on the C ring. CRF1R-binding affinities were determined as described previously,[11] and the results are summarized in Table 1.

Table 1. *h*CRF1R-binding affinities of amides **7a–e** and amines **8a–e**



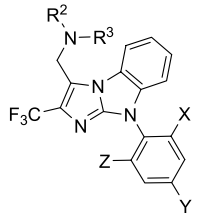
Compound	R^1	W	Q	K_i (nM)
7a	Me	O	H	360
7b	Me	O	F	1180
7c	Et	O	H	570
7d	Et	O	F	930
7e	CF_3	O	H	3560
8a	Me	H_2	H	20
8b	Me	H_2	F	59
8c	Et	H_2	H	21
8d	Et	H_2	F	150
8e	CF_3	H_2	H	23

In the related dihydroimidazoimidazole series,[3] amides displayed better potency than corresponding amines. However, in this series, amines showed a >10-fold potency advantage (**8a–e** vs. **7a–e**). This is similar to what was seen with a previous series of arylaminothiazoles.[13] For amines (W = H_2), there was a little difference when R^1 was Me, Et, or CF_3 (**8a**, **8c**, and **8e**). However, long-term hydrolytic stability was only ensured when at least one electron withdrawing group ($R^1 = CF_3$) was present on the core.[13] Therefore, it was hoped that, instead of the rather lipophilic CF_3 at R^1, a single fluorine on the C ring would permit methyl or ethyl substitution at R^1. Although **8b** and **8d** were sufficiently stable (data not shown), fluorination resulted in a 3- to 8-fold loss of potency for amines and amides (**8b**,**d** vs. **8a**,**c**).

A series of aminomethyltrifluoromethylimidazoles using a small set of amine substituents was prepared next to probe the requirement for 2,4- versus 2,4,6-aryl substitution on the pendant aryl ring. In some fused bicyclic aromatic CRF antagonist chemotypes, 2,4,-disubstitution resulted in high affinity binding, while in others activity was greatly diminished.[14] This appeared to depend on the presence of a substituent on the B ring that projected into the 'ortho-space' of the pendant aryl ring, presumably helping to enforce an orthogonal conformation. As given in Table 2, 2,4,6-trisubstitution (**8e–g**) is clearly preferred for this core structure, with the bulkier substituents on **8h–j** provided some advantage over the smaller chlorines in **8k–m**.

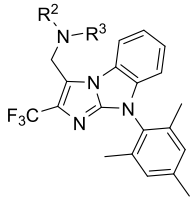
Lastly, we explored some SAR of the aminomethyl side chains. Additional polar atoms were avoided since their presence abolished the activity in related series.[3,13] The results are summarized in Table 3. Interestingly, while 'benzyl-like' cyclopropylmethyl-containing compounds showed better binding potency than cyclopropylethyl compounds (**8f** vs. **8aa**, **8o** vs. **8cc**, and **8n** vs. **8ff**), phenylethyl derivatives were clearly superior to benzyl-containing compounds (**8g** vs. **8ll** and **8x** vs. **8jj**). Clearly,

Table 2. The effects of aryl substitutions on *h*CRF1R-binding affinities



Compound	X	Y	Z	R^2	R^3	K_i (nM)
8f	Me	Me	Me	*c*PrCH$_2$	*c*PrCH$_2$	11
8e	Me	Me	Me	*c*PrCH$_2$	*n*Pr	23
8g	Me	Me	Me	PhCH$_2$CH$_2$	*n*Pr	250
8h	Br	*i*-Pr	H	*c*PrCH$_2$	*c*PrCH$_2$	54
8i	Br	*i*-Pr	H	*c*PrCH$_2$	Pr	150
8j	Br	*i*-Pr	H	PhCH$_2$CH$_2$	*n*Pr	410
8k	Cl	Cl	H	*c*PrCH$_2$	*c*PrCH$_2$	240
8l	Cl	Cl	H	*c*PrCH$_2$	*n*Pr	370
8m	Cl	Cl	H	PhCH$_2$CH$_2$	*n*Pr	1600

Table 3. The effects of amine substitutions on *h*CRF1R-binding affinities



Compound	R^2	R^3	K_i (nM)
8n	*c*PrCH$_2$	CF$_3$CH$_2$	7.1
8o	*c*PrCH$_2$	CF$_3$CH$_2$CH$_2$	13
8p	*c*BuCH$_2$	*n*Pr	26
8q	*c*PrCH$_2$	Et	28
8r	*c*PrCH$_2$	CF$_3$CF$_2$CH$_2$	34
8s	*c*BuCH$_2$	CF$_3$CH$_2$	53
8t	CF$_3$CH$_2$CH$_2$	*n*Pr	68
8u	CF$_3$CF$_2$CH$_2$	*n*Pr	75
8v	CF$_3$CH$_2$	*n*Pr	75
8w	Allyl	Allyl	138
8x	PhCH$_2$CH$_2$	Et	249
8y	CF$_3$CH$_2$CH$_2$	CF$_3$CH$_2$	291
8z	PhCH$_2$CH$_2$	PhCH$_2$CH$_2$	333
8aa	*c*PrCH$_2$CH$_2$	*n*Pr	362
8bb	PhCH$_2$	CF$_3$CH$_2$CH$_2$	428
8cc	*c*PrCH$_2$CH$_2$	CF$_3$CH$_2$CH$_2$	457
8dd	PhCH$_2$	Me	573
8ee	PhCH$_2$CH$_2$	CF$_3$CH$_2$CH$_2$	618
8ff	*c*PrCH$_2$CH$_2$	CF$_3$CH$_2$	653
8gg	Et	*n*Bu	704
8hh	PhCH$_2$CH$_2$	CF$_3$CH$_2$	744
8ii	*c*PrCH$_2$CH$_2$	Et	1412
8jj	PhCH$_2$	Et	2774
8kk	PhCH$_2$CH$_2$	Et	3388
8ll	PhCH$_2$	*n*Pr	4049
8mm	PhCH$_2$	*n*Bu	7708

and as seen in our other studies,[3,13] the binding pocket available for these residues is comparatively small and favors aromatic character. Trifluorination of the other side chain (R^3) was preferred to a greater (**8n** vs. **8q**) or lesser extent (**8e** vs. **8o**).

Table 4. Rat PK parameters for **8e** (10 mg/kg, p.o.; 2 mg/kg, i.v.)[a]

Cl	5.1 mL/min/kg
V_d	0.6 L/kg
$t_{1/2}$	4.1 h
$F_{p.o.}$	35%
AUC (plasma, p.o.)	11438 ng h/mL
C_{max}	2380 ng/mL
B/P (2 h)	0.03

[a] Dosing vehicle was 10/10/80 Cremphor/DMSO/water. Dosing volumes were 1 and 3 mL/kg for i.v. and p.o., respectively. Brain-to-plasma concentration ratio (B/P) was determined after i.v. administration.

Compound **8e** was chosen for in vivo pharmacokinetic profiling (Table 4). In rats, **8e** had a low plasma clearance, low volume of distribution, moderate terminal half-life, acceptable oral bioavailability, but essentially no brain penetration.

In summary, imidazo[1,2-*a*]benzimidazoles represent a new series of CRF1R antagonists with good receptor-binding affinities. Efforts to improve the physiochemical properties of this series to improve brain penetration will be reported shortly.

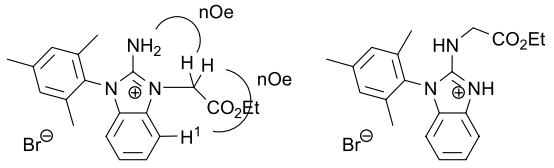
Acknowledgments

We thank Dr. John Macor and Dr. Joanne Bronson for critical reading of the manuscript.

References and notes

1. (a) Contoreggi, C.; Ayala, A.; Grant, S.; Eckelman, W.; Webster, E.; Rice, K. C. *Drug of Future* **2002**, *27*, 1093; (b) Páez-Pereda, M.; Arzt, E.; Stalla, G. K. *Expert Opin. Ther. Patents* **2002**, *12*, 1537; (c) Dinan, T. G. *Hum. Psychopharmacol. Clin. Exp.* **2001**, *16*, 89; (d) O'Brien, D.; Skelton, K. H.; Owens, M. J.; Nemeroff, C. B. *Hum. Psychopharmacol. Clin. Exp.* **2001**, *16*, 81.

2. Hauger, R. L.; Grigoriadis, D. E.; Dallman, M. F.; Plotsky, P. M.; Vale, W. W.; Dautzenberg, F. M. *Pharmacol. Rev.* **2003**, *55*, 21.
3. Han, X.; Michne, J. A.; Pin, S. S.; Burris, K.; Balanda, L. A.; Fung, L.; Fiedler, T.; Browman, K. E.; Taber, M. T.; Zhang, J.; Dubowchik, G. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3870.
4. Kulagowski, J. J.; Rees, C. W. *Synthesis* **1980**, 215.
5. Redemann, C. T.; Redemann, C. E. *Org. Syn. Coll. Vol.* **1955**, *3*, 69.
6. Scherz, M. W.; Fialeix, M.; Fischer, J. B.; Reddy, N. L.; Server, A. C.; Sonders, M. S.; Tester, B. C.; Webber, E.; Wong, S. T.; Keana, J. F. W. *J. Med. Chem.* **1990**, *33*, 2421, The structure of bromide **5a** was confirmed by ^{1}H NMR studies. First, the CH_2 in $-CH_2CO_2Et$ is a singlet, and there is no coupling between this CH_2 and NH; secondly, there are positive nOe observed between $-CH_2CO_2Et$ and $-NH_2$ and also H^1.



5a **NOT**

7. (a) Spasov, A. A.; Larionov, N. P.; Sibiryakova, T. B.; Verovskii, V. E.; Anisimova, V. A.; Dudchenko, G. P.; Baldenkov, G. N.; Men'shikov, M. Y. *Khim.-Farm. Zh.* **1998**, *32*, 17; (b) Anisimova, V. A.; Kuz'menko, T. A.; Spasov, A. A.; Bocharova, I. A.; Orobinskaya, T. A. *Pharm. J. Chem.* **1999**, *33*, 361.
8. Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
9. All new compounds gave satisfactory analytical data. For **5a** (Ar = 2,4,6-trimethylphenyl, Q = H): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.28 (br s, 2H), 7.40 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.14 (s, 2H), 6.87 (d, J = 7.8 Hz, 1H), 5.73 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H); 2.41 (s, 3H), 2.01 (s, 6H), 1.34 (t, J = 7.2 Hz, 3H). For **6a** (Ar = 2,4,6-trimethylphenyl, Q = H, R = CF_3): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.76–8.73 (m, 1H), 7.43–7.34 (m, 2H), 7.08 (s, 2H), 7.01–6.98 (m, 1H), 4.54 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.99 (s, 6H), 1.50 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 147.0, 139.9, 139.1 (q, J = 39 Hz), 136.9, 135.7, 129.7, 129.5, 128.0, 125.4, 125.0, 121.9, 120.9 (q, J = 268 Hz), 116.4, 110.6, 61.4, 21.0, 17.6, 14.0. For **7a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86–7.82 (m, 1H), 7.23–7.19 (m, 2H), 7.02 (s, 2H), 6.89–6.86 (m, 1H), 3.69 (t, J = 7.0 Hz, 2H), 3.49 (d, J = 6.9 Hz, 2H), 2.39 (s, 3H), 2.35 (s, 3H), 1.98 (s, 6H), 1.74–1.65 (m, 2H), 1.16–1.06 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H), 0.59–0.53 (m, 2H), 0.23–0.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.7, 139.2, 137.0, 136.8, 135.2, 129.8, 129.6, 128.8, 124.8, 123.4, 121.0, 114.2, 113.1, 110.2, 51.1, 48.5, 21.0, 17.7, 15.4, 14.1, 11.2, 10.1, 3.7; Mass spec.: 428.32 $(MH)^+$. For **8f**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09–8.06 (m, 1H), 7.37–7.33 (m, 2H), 7.04 (s, 2H), 6.97–6.94 (m, 1H), 4.95 (s, 2H), 3.27–3.16 (m, 4H), 2.22 (s, 3H), 1.96 (s, 6H), 1.87–1.79 (m, 2H), 1.23–1.20 (m, 1H), 0.97 (t, J = 7.2 Hz, 3H), 0.84–0.80 (m, 2H), 0.46–0.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.3 (q, J = 36.8 Hz), 148.4, 140.0, 137.0, 135.8, 129.8, 128.2, 128.0, 125.6, 123.9, 122.8 (q, J = 270 Hz), 122.0, 111.1, 110.3, 57.4, 53.1, 45.9, 21.1, 17.6, 17.3, 11.0, 5.5, 4.9; Mass spec.: 469.30 $(MH)^+$.
10. For a description of the workup procedures, see Han, X.; Corey, E. *J. Org. Lett.* **2000**, *2*, 2543.
11. Membranes were prepared from IMR-32 cells as previously described[12] and incubated with [^{125}I]Tyr-*o*-CRF (100 pM) and increasing concentrations of test compound for 100 min at 25 °C (assay bufffer: 50 mM Tris (pH 7.2), 10 mM $MgCl_2$, 0.5% BSA, 0.005% Triton X-100, 0.01 mg/mL aprotinin, and 0.01 mg/mL leupeptin). Assays were stopped by the addition of ice-cold buffer. Nonspecific binding was defined with 0.01 mM *o*-CRF. These compounds are full antagonists of the CRF1R, as determined by their ability to inhibit CRF-stimulated *c*AMP production in IMR-32 cells.[12] Compound **8e** was also tested against the CRF2R and found to have $IC_{50} > 10$ μM.[15]
12. Dieterich, K. D.; DeSouza, E. B. *Brain Res.* **1996**, *733*, 113.
13. Dubowchik, G. M.; Michne, J. A.; Zuev, D.; Schwartz, W.; Scola, P. M.; James, C. A.; Ruediger, E. H.; Pin, S. S.; Burris, K.; Balanda, L. A.; Gao, Q.; Wu, D.; Fung, L.; Fiedler, T.; Browman, K. E.; Taber, M. T.; Zhang, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3997.
14. (a) Kehne, J. H.; Maynard, G. D.; De Lombaert, S.; Krause, J. E. *Ann. Rep. Med. Chem.* **2003**, *38*, 11; (b) Grigoriadis, D. E.; Haddach, M.; Ling, N.; Saunders, J. *Curr. Med. Chem.—Central Nervous System Agents* **2001**, *1*, 63; (c) Gilligan, P. J.; Robertson, D. W.; Zaczek, R. *J. Med. Chem.* **2000**, *43*, 1641; (d) Keller, P. A.; Elfick, L.; Garner, J.; Morgan, J.; McCluskey, A. *Bioorg. Med. Chem.* **2000**, *8*, 1213.
15. Suman-Chauhan, N.; Carnell, P.; Franks, R.; Webdale, L.; Gee, N. S.; McNulty, S.; Rossant, C. J.; Van Leeuwen, D.; MacKenzie, R.; Hall, M. D. *Eur. J. Pharmacol.* **1999**, *379*, 219.