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# Synthesis and Evaluation of Imidazo[1,5-*a*]pyrazines as Corticotropin Releasing Hormone Receptor Ligands

Richard A. Hartz,[a,*] Paul J. Gilligan,[a,*] Kausik K. Nanda,[a] Andrew J. Tebben,[a] Larry W. Fitzgerald[b,†] and Keith Miller[b]

[a]*DuPont Pharmaceuticals Company, Chemical and Physical Sciences, Experimental Station, PO Box 80500, Wilmington, DE 19880, USA*
[b]*DuPont Pharmaceuticals Company, CNS Diseases Research, 500 S Ridgeway Ave., Glenolden, PA 19036, USA*

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**Abstract**—A novel series of imidazo[1,5-*a*]pyrazines was synthesized and evaluated as corticotropin releasing hormone (CRH) receptor ligands. SAR studies focused primarily on dialkylamino side chain optimization. SAR of the aryl and small alkyl substituents was also explored. 

Corticotropin releasing hormone (or factor) is a 41 amino acid neuropeptide that serves as the primary regulator of the hypothalamic–pituitary–adrenal axis.[1,2] Hypersecretion of CRH is associated with a variety of endocrine and psychiatric disorders, including depression,[3] anxiety,[1,3] anorexia nervosa,[3] and post traumatic stress disorder.[3] CRH levels were found to be elevated in the cerebrospinal fluid of depressed patients relative to that of a control group.[4] In addition, elevated plasma adrenocorticotropin (ACTH) and cortisol levels have also been found in a large subset of depressed patients.[1,5] CRH receptors are distributed throughout the central and peripheral nervous systems. Two receptor subtypes have been identified and designated as $CRH_1$ and $CRH_2$, each with distinct anatomical localization. Within the $CRH_2$ receptor subtype class three splice variants—α, β, and γ—have been cloned and sequenced.

Preclinical and clinical data suggest that CRH antagonists may be useful for the treatment of depression. Pioneering studies with CP-154,526 (**1**) indicated that this small molecule CRH antagonist had activity in rat models for anxiety or depression.[6] More recently, the results of the first human open-label study of a small molecule $CRH_1$ receptor antagonist, R-121,919, were reported.[7] Reductions in depression and anxiety scores were noted using both patient and clinician ratings; however, no control patients were involved in this study. The data also suggested that R-121,919 does not impair corticotropin and cortisol release with or without an exogenous CRH challenge, indicating that its mode of action does not compromise the stress–hormone system. Thus, it appears that small molecule $CRH_1$ receptor antagonists have considerable therapeutic potential for the treatment of anxiety and depression in humans.

A series of triazolopyridines represented by **2** ($K_i = 3.6$ nM, human) was reported to be potent $CRH_1$ receptor antagonists.[8] Given the good potency of **2**, it was of interest to explore a series of closely related compounds in our continuing search for novel CRH antagonists. An imidazo[1,5-*a*]pyrazine scaffold with a novel substitution pattern ($N^3$-aryl-1-alkyl-$N^8$,$N^8$-dialkyl-3,8-diamine; e.g., **3f**) was chosen for exploratory studies (Fig. 1). The choice of substituents in the imidazo[1,5-*a*]pyrazine series was based on previous SAR results in the triazolopyridine series, where compound **2** was one of the most potent compounds in that series.

It was envisioned that the imidazo[1,5-*a*]pyrazine heterocyclic ring system could be used in place of the triazolopyridine scaffold with the five- and six-membered rings of the core heterocycle transposed relative to **2**. A proposed overlay is shown in Figure 2.[9] At the outset of this study, it was not known what impact the altered electronic properties of the core heterocycle would have on the biological activity of these compounds.

The general route employed for the preparation of this series of $N^3$-aryl-1-alkyl-$N^8$,$N^8$-dialkyl-imidazo[1,5-*a*]pyr-

*Corresponding authors. Tel.: +1-302-695-1236; fax.: +1-302-695-1173 (R.A.H.); e-mail: richard.a.hartz@dupontpharma.com;
tel.: +1-302-695-1439; fax: +1-302-695-1173 (P.J.G.); e-mail: paul.j.gilligan@dupontpharma.com
†Present address: 301 Henrietta Street, Kalamazoo, MI 49007-4940, USA.

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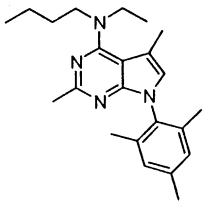
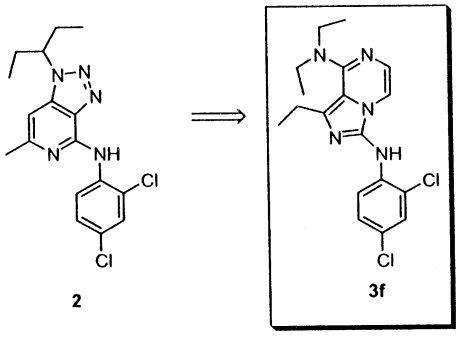
azine-3,8-diamines is described in Scheme 1. The synthesis begins with 2-chloropyrazine. The aryl ring was deprotonated and acylated according to a procedure developed by Queguiner to afford desired alcohol **5**.[10] The secondary alcohol was treated with methanesulfonyl chloride followed by displacement of the resulting mesylate with sodium azide to give **6**. Reduction of the azide with triphenylphosphine afforded the corresponding amine, which was subsequently treated with an aryl isocyanate to furnish urea **7**. Urea **7** was readily cyclized upon treatment with $POCl_3$ to form the imidazole ring.[11] The yield for this reaction was quite variable depending on the workup conditions employed. The optimized workup procedure involved removal of the $POCl_3$ by evaporation under reduced pressure. The residue was then taken up in ethyl acetate, cooled to 0 °C, and was treated with a solution of 1 N NaOH to afford the desired product (**8**) in good yield (>70%).[12] In some cases, the aniline was alkylated at this point. Finally, the chloride was displaced with a variety of alkyl amines to furnish the desired product (**3**).



**1** (CP-154,526)



**2** **3f**

**Figure 1.** Development of the imidazo[1,5-*a*]pyrazines as $CRH_1$ receptor ligands.

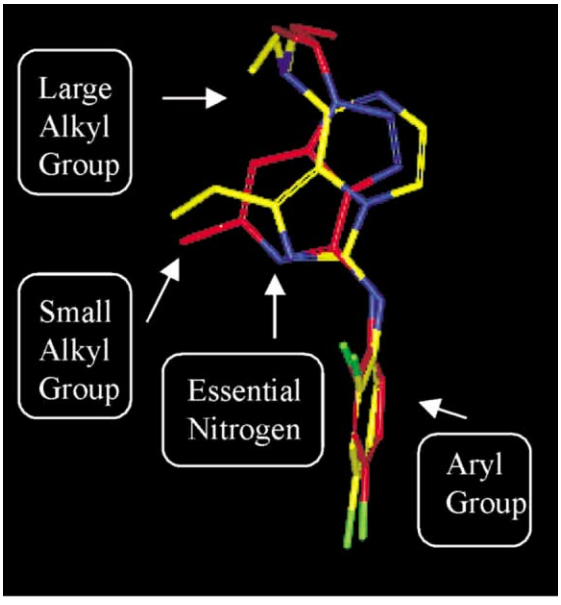


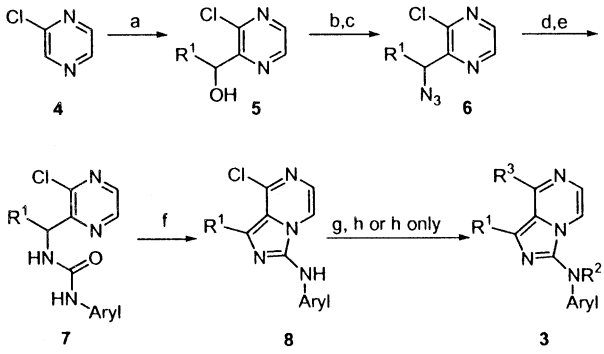

**Figure 2.** Overlay of compounds **2** and **3f**.

The CRH receptor binding affinities for this series of imidazo[1,5-*a*]pyrazines are shown in Table 1. Binding affinities were determined by displacement of [$^{125}$I]Tyr-*o*-CRF from rat frontal cortex homogenates by our test compounds.[13] α-Helical $CRF_{9-41}$ was found to have a $K_i = 7.6 \pm 0.8$ nM ($n = 3$) in this assay.

Three different alkyl substituents were investigated at the $R^1$ position, which is believed to fit into a small hydrophobic pocket of the pharmacophore model.[3] An ethyl group was found to be optimal (cf. **3f** vs **3a** and **3j**). The SAR at $R^2$ was probed with hydrogen, methyl, and ethyl groups. There was no clear trend in binding affinity among these three substituents.

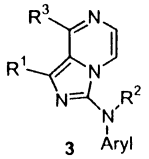
A more detailed investigation of the SAR at the $R^3$ position was undertaken in an effort to optimize the binding affinity and protein binding properties. The $R^3$ substituent is believed to fit into a large hydrophobic pocket of the receptor. Structure–activity relationship studies on previous series found that the large hydrophobic pocket is capable of accommodating a variety of alkyl substituents, thus providing the opportunity to optimize binding affinity and physical properties.[3] Inspection of the results shown in Table 1 reveals that, in general, the optimal substituent at $R^3$ is diethylamine, with the most potent compound in the series being **3f** ($K_i = 127$ nM). Compounds with a dipropylamino substituent at $R^3$ were slightly less potent, all other substituents being equal. However, analogues with smaller (e.g., **3h**) or larger (e.g., **3c**) alkyl substituents were significantly less potent.

Two different substituents were investigated at the aryl position. The 2,4-dichlorophenyl and 2,4,6-trimethylphenyl substituents were chosen based on optimized




**Scheme 1.** Reagents and conditions: (a) *n*-BuLi, TMPH, THF then $R^1CHO$, 49–68%; (b) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C to rt, 88–99%; (c) $NaN_3$, DMF, rt, 79–86%; (d) $PPh_3$, $H_2O$, THF, 50 °C; (e) ArNCO, $Et_3N$, EtOH, 67–89%, two steps; (f) $POCl_3$, 75 °C, 43–97%; (g) NaH, $R^2I$, DMF, 90%; (h) $R^2NH$, pyridine, 85 °C, 50–90%.

**Table 1.** Rat receptor binding affinities of imidazo[1,5-*a*]pyrazines




**3**

| Compd | $R^1$ | $R^2$ | $R^3$ | Aryl | Mean $K_i$ (nM, rat)[a] | *n* |
|---|---|---|---|---|---|---|
| **3a** | Me | H | $NEt_2$ | 2,4-$Cl_2$–Ph[b] | 485±250 | 3 |
| **3b** | Me | H | $NPr_2$ | 2,4-$Cl_2$–Ph | 597±228 | 3 |
| **3c** | Me | H | NH(3-pentyl) | 2,4-$Cl_2$–Ph | >3000 | 3 |
| **3d** | Me | Me | $NPr_2$ | 2,4-$Cl_2$–Ph | 1361±830 | 2 |
| **3e** | Me | Et | $NPr_2$ | 2,4-$Cl_2$–Ph | 671±126 | 2 |
| **3f** | Et | H | $NEt_2$ | 2,4-$Cl_2$–Ph | 127±45 | 5 |
| **3g** | Et | H | $NPr_2$ | 2,4-$Cl_2$–Ph | 223±110 | 3 |
| **3h** | Et | Et | $NMe_2$ | 2,4-$Cl_2$–Ph | 2884±720 | 3 |
| **3i** | Et | Et | $NPr_2$ | 2,4-$Cl_2$–Ph | 1540±30 | 3 |
| **3j** | Pr | H | $NEt_2$ | 2,4-$Cl_2$–Ph | 825±274 | 3 |
| **3k** | Pr | H | $NPr_2$ | 2,4-$Cl_2$–Ph | 492±260 | 3 |
| **3l** | Pr | Me | $NEt_2$ | 2,4-$Cl_2$–Ph | 324±3.8 | 3 |
| **3m** | Pr | Me | $NPr_2$ | 2,4-$Cl_2$–Ph | 623±207 | 3 |
| **3n** | Pr | Et | $NMe_2$ | 2,4-$Cl_2$–Ph | 2420±1445 | 4 |
| **3o** | Pr | Et | $NEt_2$ | 2,4-$Cl_2$–Ph | 2220±947 | 3 |
| **3p** | Et | H | $NEt_2$ | 2,4,6-$Me_3$–Ph | 143±1 | 2 |
| **3q** | Et | H | $NPr_2$ | 2,4,6-$Me_3$–Ph | 173±49 | 3 |
| **3r** | Pr | H | $NEt_2$ | 2,4,6-$Me_3$–Ph | 1140±61 | 3 |
| α-Helical $CRF_{9-41}$ | | | | | 7.6±0.8 | 3 |

[a]Binding affinities were determined by displacement of [$^{125}$I]Tyr-*o*-CRF from rat frontal cortex homogenates by our test compounds. The standard deviation is also reported.
[b]Ph, phenyl.

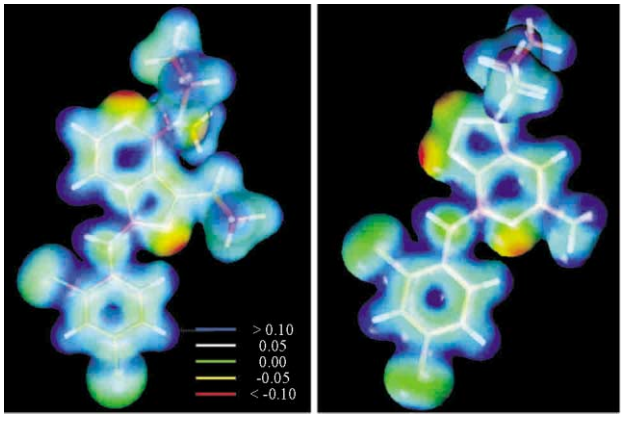



**Figure 3.** A comparison of the electrostatic potentials of **3f** and **2**.

SAR from previous work.[8] In this series, analogues with a 2,4,6-trimethylphenyl substituent were similar in potency to the corresponding analogues with a 2,4-dichlorosubstituted phenyl substituent (e.g., **3f** and **3p**).

In conclusion, a novel series of imidazo[1,5-*a*]pyrazines was synthesized and investigated as potential $CRH_1$ receptor antagonists. Several members of this series were found to have modestly potent $CRH_1$ receptor binding affinity. The most potent member within this series is **3f**. In addition, this study illustrates that the electronic properties of the core heterocycle may be critical to $CRH_1$ receptor binding affinity. Based on these results, it appears that the imidazo[1,5-*a*]pyrazine core is not a good bioisostere for the triazolopyridine moiety. Calculations[14] reveal significant differences in the electrostatic potential about the core heterocycles. (Fig. 3). Future studies are planned to further explore the correlation between the electronic properties of the core heterocycle with CRH receptor binding affinity.

## Acknowledgements

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graphy on neutral silica gel (Davisil Grade 643, 30% ethyl acetate in hexanes with 0.5% methanol > 50% ethyl acetate in hexanes with 0.5% methanol) to afford 8-chloro-*N*-(2,4-dichlorophenyl)-1-methyl-imidazo[1,5-*a*]pyrazine-3-amine (305 mg, 72% yield) as a yellow solid: mp 184–185 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, $J = 2.6$ Hz, 1H), 7.30 (d, $J = 5.1$ Hz, 1H), 7.19 (d, $J = 5.1$ Hz, 1H), 7.14 (dd, $J = 8.8$, 2.2 Hz, 1H), 6.97 (d, $J = 8.8$ Hz, 1H), 6.43 (s, 1H), 2.80 (s, 3H); LRMS (APCI) *m*/*e* 327.0 [$(M + H)^+$, calcd for $C_{13}H_{10}N_4Cl_3$ 327.0].

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