Available online at www.sciencedirect.com
SCIENCE DIRECT
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 934–937

# Synthesis and evaluation of 2-anilino-3-phenylsulfonyl-6-methylpyridines as corticotropin-releasing factor$_1$ receptor ligands

Richard A. Hartz,[a,*] Argyrios G. Arvanitis,[a] Charles Arnold,[a] Joseph P. Rescinito,[a] Kimberly L. Hung,[a] Ge Zhang,[b] Harvey Wong,[c] David R. Langley,[a] Paul J. Gilligan[a] and George L. Trainor[a]

[a]*Discovery Chemistry, Bristol-Myers Squibb Company, Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*
[b]*Neuroscience Biology, Bristol-Myers Squibb Company, Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*
[c]*Department of Metabolism and Pharmacokinetics, Bristol-Meyers Squibb Company, Pharmaceutical Research Institute, 5 Research Parkway, Waalingford, CT 06492, USA*

Received 21 September 2005; revised 26 October 2005; accepted 28 October 2005
Available online 16 November 2005

**Abstract**—A novel series of 2-anilino-3-phenylsulfonyl-6-methylpyridines was synthesized and evaluated as corticotropin-releasing factor receptor ligands. Structure–activity relationship studies focused primarily on optimization of the 3-phenylsulfonyl group. Compounds within this series were identified which showed potent binding affinity for the $CRF_1$ receptor. Selected compounds were examined in a rat pharmacokinetic study and were found to have oral bioavailabilities ranging from 16 to 35%.


Corticotropin-releasing factor (CRF), a 41 amino acid neuropeptide, is an important regulator of the body's response to stress via modulation of the hypothalamic–pituitary–adrenal (HPA) axis. CRF was first isolated from ovine hypothalamus in 1981 and characterized by Vale and coworkers.[1] It was determined that the role of CRF in the hypothalamic–pituitary–adrenal axis is to act as an adrenocorticotropic hormone (ACTH) secretogogue via the $CRF_1$ receptors. ACTH in turn stimulates the release of glucocorticoids, such as cortisol, from the adrenal cortex. Elevated levels of glucocorticoids have been shown to exert negative feedback on CRF secretion at both the levels of the pituitary and hypothalamus.

CRF mediates its actions through two subtypes of 7-transmembrane G-protein coupled receptors, designated as $CRF_1$ and $CRF_2$ receptors.[2] $CRF_1$ receptors are expressed primarily in the rat brain, whereas $CRF_2$ receptors are found primarily in the rat periphery. Experiments with $CRF_1$ receptor knockout mice demonstrated the involvement of $CRF_1$ receptors in the stress response mediated by the HPA axis.[3] It was found that in the presence of increasing CRF levels, ACTH secretions do not increase in the pituitary cells of mice lacking the $CRF_1$ receptor.

Hypersecretion of CRF is associated with various endocrine and psychiatric disorders including depression, anxiety, and post-traumatic stress disorder.[2a,4] Clinical studies have shown that plasma levels of cortisol were elevated in a large number of depressed patients.[4c] A growing body of evidence continues to support the hypothesis that $CRF_1$ receptor antagonists offer significant therapeutic potential in the treatment of diseases resulting from elevated levels of CRF.[5]

A variety of small molecule $CRF_1$ receptor antagonists have been reported in the literature.[4a,6] Based on numerous previously disclosed reports, the pharmacophore model has been shown to include a required alkyl substi-

*Keywords*: Corticotropin-releasing factor; CRF; Phenylsulfone.
* Corresponding author. Tel.: +1 203 677 7837; fax: +1 203 677 7702; e-mail: richard.hartz@bms.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.10.097

tuent linked to a mono- or bicyclic core ring system generally via an aniline nitrogen (e.g., the diethylamino group in structure **1**, Fig. 1). We were interested in developing a novel chemotype by attempting to find a suitable replacement for this alkyl group. As illustrated in structure **2**, it was anticipated that a group on the 3-position of the pyridine ring could be designed as a suitable replacement for the dialkyl-amino group. It would be essential for this group to be oriented properly to achieve good binding affinity. A substituted phenylsulfonyl group was chosen based on its potential ability to achieve a favorable conformation due to hydrogen bonding of the sulfone oxygen with the neighboring aniline hydrogen (Figs. 1 and 2). This report discloses the synthesis, structure–activity relationships, and rat pharmacokinetic data for a novel series of 3-phenylsulfonyl pyridine-based compounds.

Synthesis of the 2-anilino-3-phenylsulfonyl-6-methylpyridine derivatives is illustrated in Scheme 1 below. Commercially available 2-hydroxy-6-methylpyridine **3** was treated with powdered iodine in a water/$CH_2Cl_2$ mixture in the presence of $NaHCO_3$ to give a 5:2:1:1 ratio of 3-iodopyridine **4**, starting material **3**, 5-iodo, and 3,5-diiodopyridine, respectively. The mixture was recrystallized from EtOAc to give the 3-iodoisomer (**4**) in >95% purity. 3-Iodopyridine **4** was then coupled with various substituted thiophenols in the presence of NaH and 20% CuI in DMF at 120 °C to give the corresponding sulfide. Subsequent treatment with $POCl_3$ afforded compound **5** in good yield. Compound **5** was oxidized

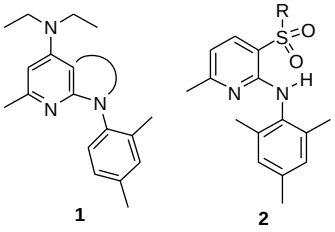


**Figure 1.** Design of novel 3-phenylsulfonyl pyridine-based compounds.

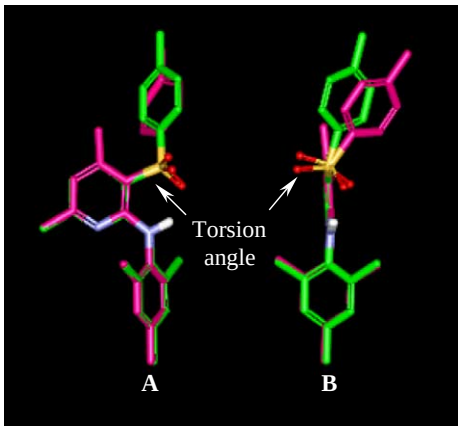
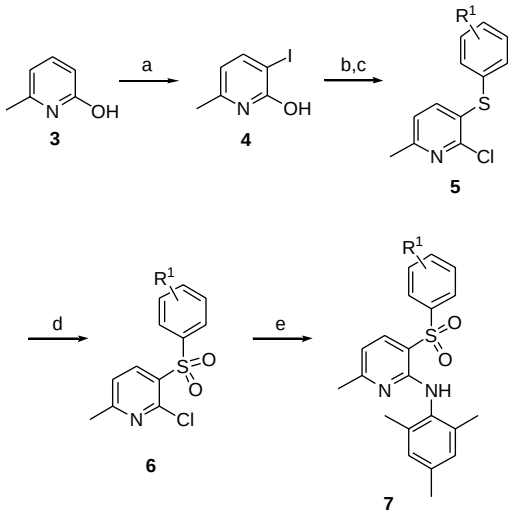



**Figure 2.** Overlay of compounds **7d** (magenta) and **7e** (green) as viewed from the front (left) and side (right). B is rotated 90° relative to A.

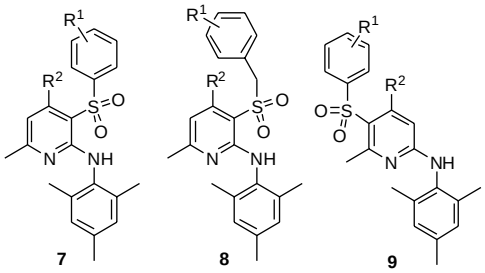


**Scheme 1.** Reagents and conditions: (a) $I_2/CH_2Cl_2$, $NaHCO_3/H_2O$, 35–40%; (b) substituted thiophenol, NaH, CuI (20 mol %), DMF, 120 °C, 71–92%; (c) $POCl_3$, 61–71%; (d) *m*-CPBA, $CH_2Cl_2$, 88–96%; (e) 2,4,6-trimethylaniline $(CH_2OH)_2$, reflux, 33–69%.

to the corresponding sulfone (**6**) in high yield with *m*-CPBA. Sulfone **6** was subsequently coupled with 2,4,6-trimethylaniline (6 equiv) in refluxing ethylene glycol for 16 h to give the adduct **7**, which was isolated by chromatography.

Initially the SAR of a series of compounds with a 4,6-dimethylpyridine core was studied[7] (Table 1). CRF receptor binding affinities were determined by displacement of [$^{125}$I]Tyr-o-CRF from rat frontal cortex homogenates by our test compounds.[8] α-Helical $CRF_{9–41}$ was found to have a $K_i = 7.6 \pm 0.8$ nM ($n = 3$) in this assay. The unsubstituted phenyl analog **7a** and 2-methyl

**Table 1.** Structure–activity relationships of the $R^2$ substituent and phenylsulfone group



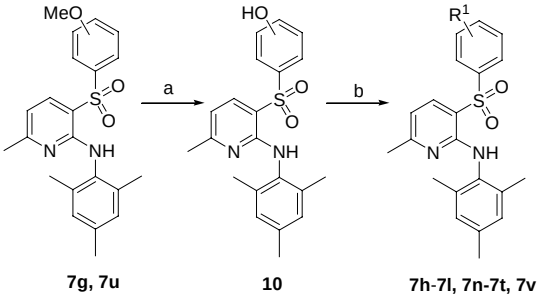
| Compound | $R^1$ | $R^2$ | Mean $K_i$ (nM)[a] |
|---|---|---|---|
| **7a** | H | Me | >10,000[b] |
| **7b** | 2-Me | Me | >10,000[b] |
| **7c** | 3-Me | Me | 5170 ± 160 |
| **7d** | 4-Me | Me | 1778 ± 741 |
| **7e** | 4-Me | H | 145 ± 44 |
| **8** | 4-Cl | H | 857 ± 120 |
| **9** | 4-Me | H | >10,000[b] |

[a] Data are averaged from a minimum of two replicates unless otherwise noted. The standard deviation is also reported.
[b] Single determination.

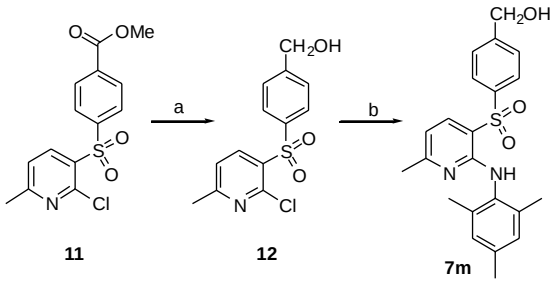
substituted analog **7b** were inactive in the binding assay. Movement of the methyl substituent to the 3- and 4-positions however resulted in a progressive improvement in binding affinity (**7c** and **7d**). Replacement of the methyl group at $R^2$ with a hydrogen further improved the binding affinity (**7e**, $K_i = 145$ nM). Replacement of the 4-methylphenylsulfonyl group with a 4-chlorobenzylsulfonyl group resulted in a decrease in binding affinity (compare **7e** with **8**). In addition to the 3-phenylsulfone structural motif, the 5-phenylsulfone structural motif was also examined. Attachment of the benzenesulfone moiety at the 5-position (**9**) resulted in loss of binding affinity to the $CRF_1$ receptor.

Modeling studies were conducted to better understand these results. Figure 2 depicts the overlaid, minimized structures of compounds **7d** (magenta) and **7e** (green). The global minimum for each compound was identified using a systematic grid search followed by CHARMM minimization[9] using the CFF98 force field.[10] The results show that the sulfone oxygen is capable of hydrogen bonding with the neighboring aniline N-H. The measured distance between the sulfone oxygen and aniline N-H is 1.77 Å in structure **7d** and 1.89 Å in structure **7e**. Possibly, the lack of binding affinity of compound **9** is due to the inability of the 5-phenylsulfone group to be held in a favorable conformation by a hydrogen bonding interaction. Furthermore, the presence of a methyl group at the 4-position on the pyridine core of **7d** apparently forces the neighboring 3-phenylsulfone group in a suboptimal confirmation relative to compound **7e**. The torsion angle in compound **7d** is 140° versus 162° for compound **7e** (Fig. 2).

In an attempt to enhance the binding affinity of this series of compounds, an effort was made to further explore the SAR on the phenylsulfonyl group. The primary focus of this effort was the preparation of analogs at the 4-position based on the initial results reported in Table 1. To this end, the methyl ether analogs of **7** (**7g** and **7u**) were heated in 48% HBr at 110 °C for 24 h to furnish, after washing with diethyl ether, the corresponding phenols in excellent yield (Scheme 2). The phenols were then alkylated under standard conditions ($K_2CO_3$, NaI, and MeCN) to afford the desired products generally in good yield. In addition, compound **7m** was prepared by DIBAL reduction of **11** followed by coupling with 2,4,6-trimethylaniline (Scheme 3).

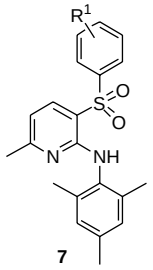



**Scheme 2.** Reagents and conditions: (a) HBr (48%), 110 °C, 90–97%; (b) $R^1X$, NaI, $K_2CO_3$, $CH_3CN$, heat, 53–92%.




**Scheme 3.** Reagents and conditions: (a) DIBAL, $Et_2O$, 98%; (b) 2,4,6-trimethylaniline, $(CH_2OH)_2$, reflux, 55%.

**Table 2.** Structure–activity relationships of the $R^1$ substituent




| Compound | $R^1$ | Mean $K_i$ (nM)[a] |
|---|---|---|
| **7e** | 4-Me | 145 ± 44 |
| **7f** | 4-Et | 52 ± 22 |
| **7g** | 4-OMe | 198[b] |
| **7h** | 4-Oallyl | 119 ± 18 |
| **7i** | 4-$OCH_2$Ph | 32 ± 3 |
| **7j** | 4-$OCF_3$ | 268 ± 50 |
| **7k** | 4-$OC_3H_6CN$ | 635 ± 39 |
| **7l** | 4-$OC_4H_8CN$ | 395 ± 5 |
| **7m** | 4-$CH_2OH$ | 1078 ± 175 |
| **7n** | 4-$OCH_2$-(3,5-$OMe_2$)Ph | 34 ± 1 |
| **7o** | 4-$OCH_2$-(3-OMe)Ph | 58 ± 0.2 |
| **7p** | 4-$OCH_2$-(2-OMe)Ph | 17 ± 1.3 |
| **7q** | 4-$OCH_2$-(3-$CO_2$Me)Ph | 49 ± 25 |
| **7r** | 4-$OCH_2$-(3-CN)Ph | 75 ± 45 |
| **7s** | 4-$OCH_2$-(4-CN)Ph | 157 ± 8 |
| **7t** | 4-$OCH_2$-pyridin-2-yl | 250 ± 76 |
| **7u** | 3-OMe | 249 ± 4 |
| **7v** | 3-$OCH_2$Ph | 132[b] |

[a] Data are averaged from a minimum of two replicates unless otherwise noted. The standard deviation is also reported.
[b] Single determination.

**Table 3.** Rat pharmacokinetic parameters of selected 2-anilino-3-phenylsulfonyl pyridines

| | **7f** | **7i** | **7p** |
|---|---|---|---|
| iv (0.5 mg/kg) | | | |
| CL (L/h/kg) | 5.2 | 4.7 | 3.5 |
| $V_{ss}$ (L/h) | 25 | 10 | 8 |
| $t_{1/2}$ (h) | 5.1 | 3 | 3.5 |
| po (2.0 mg/kg) | | | |
| AUC (nM h) | 347 | 167 | 176 |
| $C_{max}$ (nM) | 72 | 42 | 48 |
| $F$% | 35 | 18 | 16 |

The SAR of various alkyl and alkoxy groups (compounds **7e**–**i**) indicates that, in general, the binding affinity improves as the size of the alkyl or alkoxy group increases within this set of compounds. However, analogs with a polar group incorporated within $R^1$ are less potent (compounds **7j**–**m**). This observation is not unlike results noted in previously reported series of $CRF_1$ receptor antagonists where it was found that polar functionality, in particular very acidic or basic moieties, is not well tolerated by the large lipophilic cavity of $CRF_1$ receptor.[11]

Since the highest affinity substituent was a benzyl ether (**7i**, $K_i = 32$ nM), an investigation was conducted to examine the SAR of various substituents on the benzyl group. Several compounds are included in Table 2 to illustrate the SAR trends observed. The 3,5-dimethoxy substituted benzyl group (compound **7n**) was somewhat more potent than the 3-methoxybenzyl group (compound **7o**). Moving the methoxy group to the 2-position (compound **7p**), however, further improved the binding affinity over **7n**. A methyl ester at the 3-position possessed similar activity to the corresponding methoxy group at this position (compare **7o** with **7q**). Replacement of the phenyl group with a 2-pyridin-2-yl group resulted in a decrease in binding affinity (compare **7t** with **7i**). The analog, where $R^1$ is a benzyl ether at the 3-position, was less potent than the corresponding analog at the 4-position (compare **7u** with **7g** and **7v** with **7i**).

Selected compounds were further assessed in a rat cassette study to determine their pharmacokinetic profile. Results of the rat pharmacokinetic studies are summarized in Table 3.[12] Examination of the iv data in Table 3 indicates that all three compounds have high clearance and modest half-lives. The data from oral dosing show that compounds **7f**, **7i**, and **7p** possess oral bioavailabilities of 35%, 18%, and 16%, respectively.

In conclusion, a novel series of 2-anilino-3-phenylsulfonyl-6-methylpyridines was synthesized and investigated as potential $CRF_1$ receptor antagonists. Members of this class of compounds were found to be potent ligands for the $CRF_1$ receptor. In addition, this study illustrates that a novel phenylsulfonyl tether from the 3-position of the pyridine core can serve as a replacement for the dialkylamino group present in structure **1**. Additional efforts are required to further optimize binding affinity and improve the pharmacokinetic profile of compounds in this series.

## Acknowledgments

The authors gratefully acknowledge Anne Marshall and Susan Keim forin vitro binding studies.

## References and notes

1. Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. *Science* **1981**, *213*, 1394.
2. (a) Gilligan, P. J.; Hartig, P. R.; Robertson, D. W.; Zaczek, R. In *Annual Reports in Medicinal Chemistry*, Bristol, J. A., Ed.; Academic: San Diego, 1997; Vol. 32, pp 41–50.; (b) DeSouza, E. B.; Grigoriadis, D. E. In *Psychopharmacology; The Fourth Generation of Progress*, Bloom, F. E., Kupfer, D. J., Eds.; Raven: New York, 1995; pp 505–517; (c) Kostich, W. A.; Chen, A.; Sperle, K.; Largent, B. L. *Mol. Endocrinol.* **1998**, *12*, 1077; (d) Chen, R.; Lewis, K. A.; Perrin, M. H.; Vale, W. W. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8967; (e) Perrin, M. H.; Donaldson, C. J.; Chen, R.; Lewis, K. A.; Vale, W. W. *Endocrinology* **1993**, *133*, 3058.
3. Smith, G. W.; Aubry, J.-M.; Dellu, F.; Contrarino, A.; Bilezekijian, L. M.; Gold, L. H.; Chen, R.; Marchuk, Y.; Hauser, C.; Bentley, C. A.; Sawchenko, P. E.; Koob, G. F.; Vale, W.; Lee, K.-F. *Neuron* **1998**, *20*, 1093.
4. (a) Gilligan, P. J.; Robertson, D. W.; Zaczek, R. *J. Med. Chem.* **2000**, *43*, 1641; (b) Nemeroff, C. B.; Widerlov, E.; Bissette, G.; Wallens, H.; Karlsson, I.; Eklund, K.; Kilts, C. D.; Loosen, P. T.; Vale, W. *Science* **1984**, *226*, 1342; (c) Owens, M. J.; Nemeroff, C. B. *Pharmacol. Rev.* **1991**, *43*, 425.
5. (a) Chen, Y. L.; Mansbach, R. S.; Winter, S. M.; Brooks, E.; Collins, J.; Corman, M. L.; Dunaiskis, A. R.; Faraci, W. S.; Gallaschun, R. J.; Schmidt, A.; Schultz, D. W. *J. Med. Chem.* **1997**, *40*, 1749; (b) Mansbach, R. S.; Brooks, E. N.; Chen, Y. L. *Eur. J. Pharmacol.* **1997**, *323*, 21; (c) Arborelius, L.; Skelton, K. H.; Thrivikraman, K. V.; Plotsky, P. M.; Schulz, D. W. J. *Pharmacol. Exp. Ther.* **2000**, *34*, 171; (d) Zobel, A. W.; Nickel, T.; Künzel, H. E.; Ackl, N.; Sonntag, A.; Ising, M.; Holsboer, F. *J. Psychiatr. Res.* **2000**, *34*, 171.
6. (a) Keller, P. A.; Elfick, L.; Garner, J.; Morgan, J.; McCluskey, A. *Bioorg. Med. Chem.* **2000**, *8*, 1213; (b) McCarthy, J. R.; Heinrichs, S. C.; Grigoriadis, D. E. *Curr. Pharm. Des.* **1999**, *5*, 289.
7. Compounds with a 4,6-dimethylpyridine core analogous to compound **6** were purchased from Bionet via Ryan Scientific, PO Box 845, Isle of Palms, SC 29451.
8. De Souza, E. B. *J. Neurosci.* **1987**, *7*, 88.
9. Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4*, 187.
10. Maple, J. R.; Hwang, M.-J.; Jalkanen, K. J.; Stockfisch, T. P.; Hagler, A. T. *J. Comp. Chem.* **1998**, *19*, 430.
11. Gilligan, P. J.; He, L.; Culp, S.; Fitzgerald, L.; Tam, S. W.; Wong, Y. N. *Bioorg. Med. Chem.* **1999**, *7*, 2321.
12. Compounds **7f**, **7i**, and **7p** were co-administered intravenously to Sprague–Dawley rats ($n = 3$) at a dose of 0.5 mg/kg for each compound. In addition, the same set of compounds was administered to rats ($n = 3$) orally at a dose of 2 mg/kg. Plasma samples were collected at 0, 0.1, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h post-dose for the intravenous experiment, and at 0, 0.5, 1, 2, 4, 6, 8, and 24 h post-dose for the oral experiment. Drug concentrations were determined in the plasma samples using LC/MS/MS.