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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

Dmitry Zuev *, Vivekananda M. Vrudhula, Jodi A. Michne, Bireshwar Dasgupta, Sokhom S. Pin, Xiaohua Stella Huang, Dedong Wu †, Qi Gao, Jie Zhang ‡, Matthew T. Taber, John E. Macor, Gene M. Dubowchik *

Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA

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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

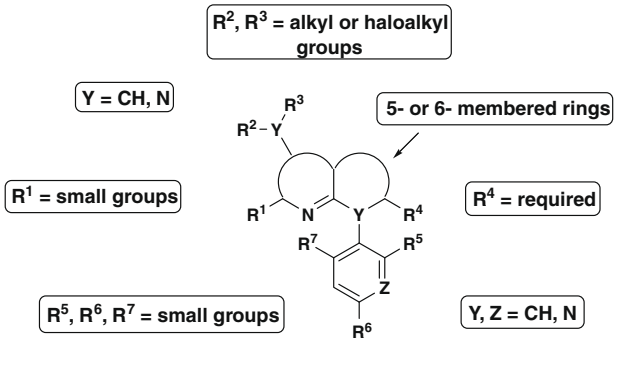

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Figure 1.

* Corresponding authors. Tel.: +1 203 677 6714; fax: +1 203 677 7702.
E-mail addresses: dmitry.zuev@bms.com (D. Zuev), gene.dubowchik@bms.com (G.M. Dubowchik).
† Present address: AstraZeneca PLP, 1800 Concord Pike, Wilmington, DE 19850, USA.
‡ Present address: Aventis Pharmaceuticals, PO Box 6800, Bridgewater, NJ 08807-0800, USA.

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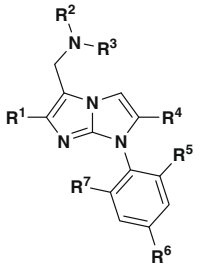

Amine Library: Optimize Activity Based on Available Amines

Bicyclic Core: Develop Efficient Synthesis

Aryl Library: Modulate Steric and Electronic Properties of Aryl Ring

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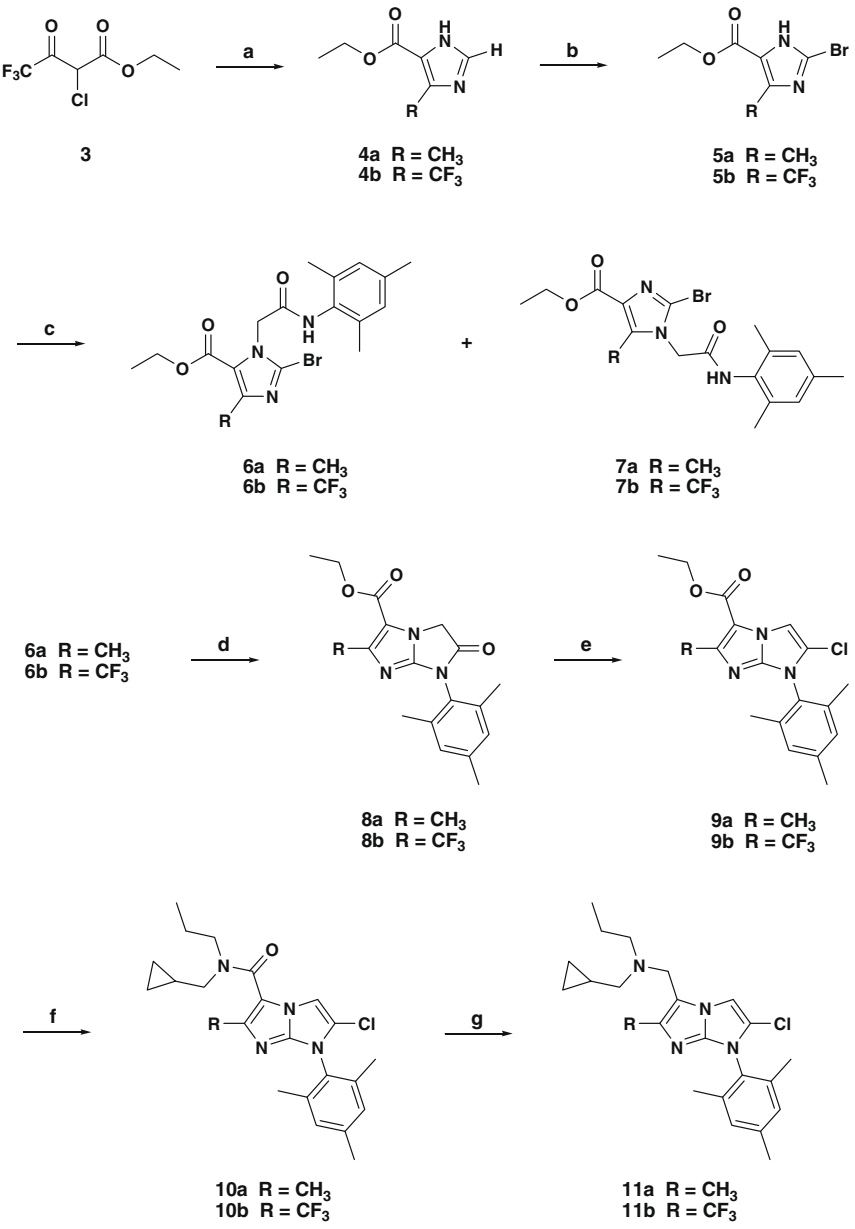
Figure 2.

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%.