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Synthesis and evaluation of carbamate and aryl ether substituted pyrazinones as corticotropin releasing factor-1 (CRF_1) receptor antagonists

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ABSTRACT

A series of pyrazinone-based compounds incorporating either carbamate or aryl ether groups was synthesized and evaluated as corticotropin-releasing factor-1 (CRF_1) receptor antagonists. Structure–activity relationship studies led to the identification of highly potent CRF_1 receptor antagonists **14a** (IC_{50} = 0.74 nM) and **14b** (IC_{50} = 1.9 nM). The synthesis, structure–activity relationships and in vitro metabolic stability properties of compounds in this series will be described.

Corticotropin releasing factor (CRF), a 41-amino acid neuropeptide first isolated and characterized by Vale et al.,[1] is secreted from the paraventricular nucleus of the hypothalamus, and is the primary physiological regulator of the hypothalamic–pituitary–adrenal (HPA) axis mediating the autonomic, endocrine and behavioral responses to stress.[2–4] CRF exerts its action in the pituitary by binding to CRF_1 receptors, resulting in the release of adrenocorticotropic hormone (ACTH), β-endorphin, and other proopiomelanocortin (POMC) derived peptides.[4] Increased levels of ACTH initiate the synthesis and release of adrenal corticosteroid hormones (e.g., cortisol), enabling the body to respond to the stressor. The increased levels of corticosteroid hormones also provide negative feedback to suppress the synthesis of additional CRF and ACTH, thereby restoring homeostasis of the HPA axis.

Two G-protein coupled CRF receptor subtypes have been identified and designated as CRF_1 and CRF_2.[5,6] These receptors are widely distributed throughout the central and peripheral nervous systems. It appears that the CRF_1 receptor subtype plays a significant role in the stress-related response. The heterogeneous distribution patterns of CRF_1 and CRF_2 receptors suggest distinct functional roles for these receptor subtypes. Studies suggest that increased level of CRF_1 mRNA in the hypothalamic paraventricular nucleus (PVN) due to various kinds of stress can be decreased by glucocorticoid treatment. However, the levels of CRF_2 mRNA in PVN were not affected by glucocorticoid treatment.[6]

Studies have also indicated that hypersecretion of CRF in the central nervous system is associated with a variety of psychiatric and stress-related illnesses including anxiety,[3] depression,[7] and post-traumatic stress disorder,[6] and that CRF_1 receptor antagonists may be useful for the treatment of these conditions.[4,6,8]

Numerous small molecule CRF_1 receptor antagonists have been reported in the literature. Some representative examples are shown in Figure 1. In preclinical studies **1** (DMP696)[9–11] was found to be efficacious in preclinical behavioral models for anxiety and depression. In an open label clinical trial with **2** (R121919),[12] it was reported that depressed patients showed reductions in depression symptoms, as rated by both patients and clinicians.[13,14] However, when **3** (CP-316,311) was tested in patients in a 6-week randomized, placebo-controlled trial for the treatment of major depression, it failed to show efficacy.[15] Likewise, when pexacerfont (**4**) was tested in a randomized, double-blind, active comparator and placebo-controlled clinical trial for generalized anxiety disorder, it also failed to show efficacy in patients.[16] Although the outcomes of these trials were mixed, there remains an urgent need for novel treatment approaches with a rapid onset of action for those suffering from anxiety and depression disorders. Efforts to discover additional small-molecule CRF_1 receptor antagonists suitable for

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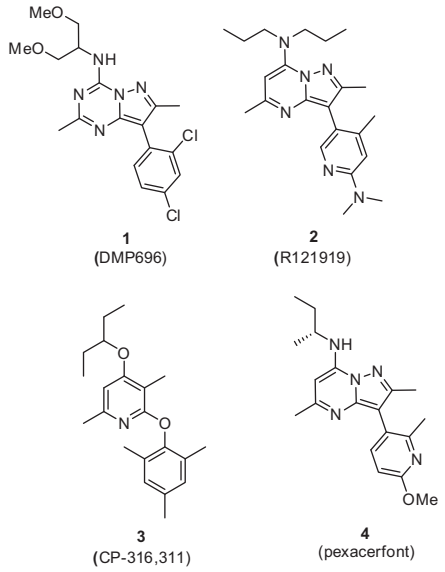

Figure 1. CRF_1 receptor antagonists.

testing in clinical trials, thus potentially offering a novel approach for the treatment of diseases such as anxiety and depression, have been the focus of a number of research groups.[17]

Common features shared by most of the reported small molecule CRF_1 receptor antagonists include a monocyclic or bicyclic heterocyclic aromatic scaffold containing a required sp^2-hybridized basic nitrogen, which serves as a key hydrogen bond acceptor (Fig. 2). This core heterocyclic ring system generally bears three substituents: a small substituent at R^1 (e.g., methyl, halo, cyano, etc.), which is believed to fit into a small lipophilic pocket; a larger group at R^2, which appears to fit into a large lipophilic pocket that can accommodate a wider variety of substituents, thus providing the potential opportunity to optimize binding affinity and physical properties; and an orthogonally oriented aryl or heteroaryl group attached to the core heterocycle by a carbon, nitrogen or oxygen atom (B, Fig. 2).[18] Various small molecule CRF_1 receptor antagonists have been reported with heterocyclic R^2 groups included to modulate potency and polarity. Examples in Figure 3 include the pyrazole **5** (emicerfont; $pIC_{50} = 7.2$), which also contains a hydrogen bond donor group,[19] the oxadiazole **6** ($pK_i = 8.2$)[20] and the phenyl-substituted 1,2,3,6-tetrahydropyridine **7** ($IC_{50} = 20$ nM).[21]

Previously, we reported the structure–activity-relationships (SAR) of a series of pyrazinone-based CRF_1 receptor antagonists[22–25] leading to highly potent and efficacious compounds such as **8**, and ultimately to the discovery of **9** (BMS-764459, Fig. 4).[24] Detailed SAR studies of the lower phenyl/pyridyl substituent and the small substituent (R^1), as well as a limited group of substituents at R^2 were described.

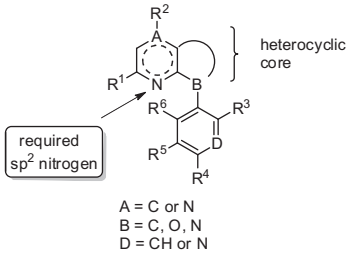

Figure 2. Common features shared by many reported small molecule CRF_1 receptor antagonists.

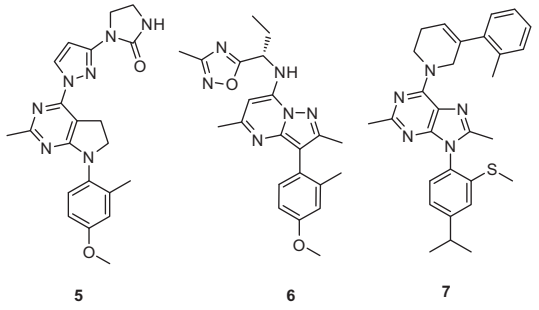

Figure 3. Structures of compounds **5**–**7**.

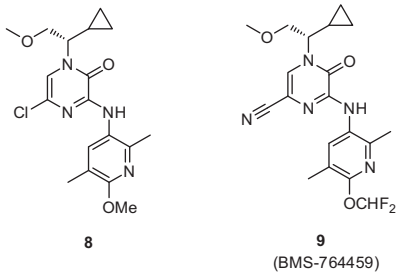

Figure 4. Structures of compounds **8** and **9**.

During the greater course of our investigation, SAR studies that included additional structural diversity at the upper R^2 substituent were also conducted. As part of this investigation, an attempt was made to incorporate a modest degree of polarity into the R^2 substituent to improve the physiochemical properties of these molecules and to further probe this region of the CRF_1 receptor to assess the tolerance for other functionalities.

In this Letter, the synthesis and SAR of pyrazinone-based CRF_1 receptor antagonists incorporating either carbamate or aryl ether functional groups within the R^2 substituent are described (Scheme 1). These target molecules could be rapidly prepared from a common alcohol intermediate (**10**). On the basis of previously described SAR for our pyrazinone-based chemotype, the cyclopropyl group at the branching position of R^2 was held constant.

The synthesis of a series of pyrazinones bearing ester, carbamate and aryl ether functional groups is illustrated in Schemes 1 and 2. The synthesis of **8** was previously described.[22] We observed that demethylation of the methoxy group in compound **8** could be effected in high yield by treatment with BBr_3. The resultant alcohol (**10**) was then converted to an ester by treatment with NaH and an acid chloride to afford compounds **11a**–**11e** in moderate yields. Treatment of alcohol **10** with NaH and various isocyanates at 0 °C resulted in the formation of carbamate analogs **11f**–**11l** and **11n**–**11p**. For analog **11m**, where no commercially available isocyanate was available, a two-step procedure was employed. Alcohol **10** was treated with 4-nitrophenylchloroformate and Et_3N to afford an activated carbonate intermediate which was subsequently treated with 3-(6-OMe-2-Me)-pyridylamine in the presence of HOBt to form the desired carbamate analog (**11m**).

Preparation of the 2-pyridyl ether analogs (**11q**–**11u**) was accomplished by alkylation of alcohol **10** with 2-bromopyridines in the presence of NaH to afford the desired pyridyl ether analogs in low to moderate yield. Preparation of the 3-pyridyl analog was carried out by conversion of alcohol **10** to the tosylate, followed by displacement with 3-hydroxypyridine in the presence of NaH to afford **11v**. As previously reported[22], it was found that there was little difference in the potency of enantiomers at the chiral center in the R^2 substituent in this pyrazinone chemotype; hence,