Bioorganic & Medicinal Chemistry Letters 18 (2008) 4486–4490

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

2-Arylpyrimidines: Novel CRF-1 receptor antagonists

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ARTICLE INFO

Article history:
Received 29 May 2008
Revised 13 July 2008
Accepted 14 July 2008
Available online 18 July 2008

Keywords:
CRF-1
Anxiety
Depression
2-Arylpyrimidine

ABSTRACT

The design, synthesis and structure–activity relationship studies of a novel series of CRF-1 receptor antagonists, the 2-arylpyrimidines, are described. The effects of substitution on the aromatic ring and the pyrimidine core on CRF-1 receptor binding were investigated. A number of compounds with K_i values below 10 nM and lipophilicity in a minimally acceptable range for a CNS drug ($cLogP < 5$) were discovered.

Corticotropin releasing factor (CRF), a 41-amino acid peptide originally isolated by Vale in 1981 from ovine brain extract, is the prime regulator of the hypothalamic-pituitary-adrenal (HPA) stress–response.[1] CRF exerts its biological functions through activation of its receptors CRF-1 and CRF-2, both of which belong to the class B subfamily of G-protein coupled receptors.[2] While the benefits of blocking the CRF-2 receptor remain uncertain, evidence from preclinical animal models and early clinical studies suggests that antagonism of the CRF-1 receptor has the potential to produce therapeutically useful anxiolytic and antidepressant effects.[3] The first small molecule CRF-1 receptor antagonists disclosed in the late 1990s, and subsequently well characterized, include CP-154,526[4] and SSR125543A.[5] These early analogues were very potent in vitro and demonstrated efficacy in animal models but are generally highly lipophilic ($cLogP > 7$) and poorly water soluble. Clinical development of compounds of this nature has often been hindered by issues including unattractive pharmacokinetics, extensive tissue accumulation, undesirably long elimination half-life, and adverse events. In the ensuing years, efforts have focused on reducing the lipophilicity of these molecules to values considered more suitable for a CNS drug ($cLogP$ of between 2 and 5).[6] Successful approaches have included the replacement of the hydrophobic side-chain with a more polar group, for example, DMP696[7] or substitution of the lipophilic pendant phenyl ring by an amino-heterocycle, for example, R121919[8a] and MTIP[8b] (Fig. 1).

Notably, R121919 demonstrated efficacy in treating patients with depression in an open-label phase IIa clinical trial.[9] While this strategy provided an antagonist with improved drug-like properties, R121919 did not progress further into development due to

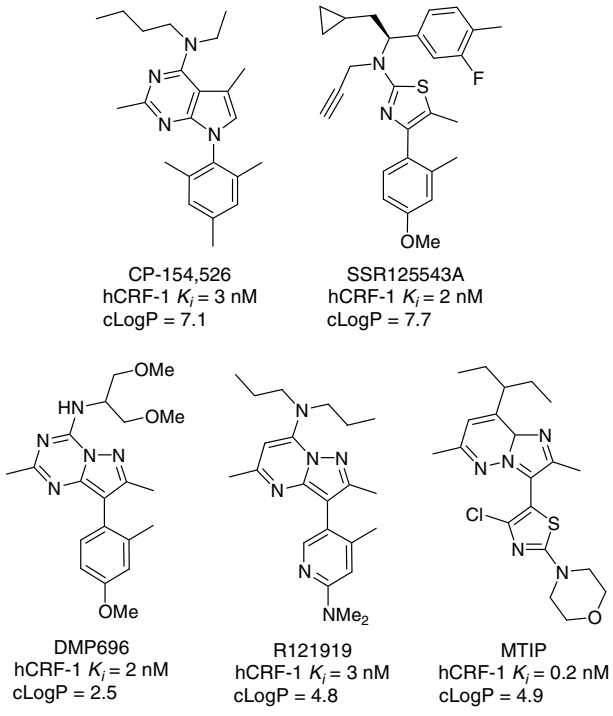

Figure 1. Structures of representative CRF-1 receptor antagonists.

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doi:10.1016/j.bmcl.2008.07.063

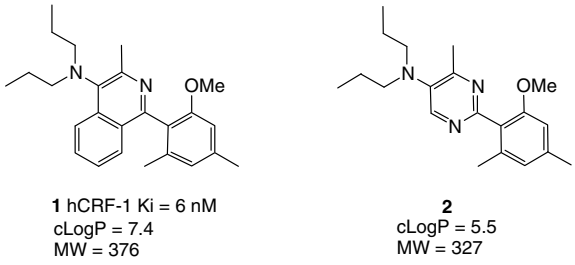


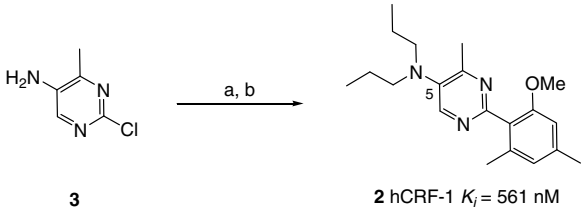
Figure 2. Design of 2-arylpyrimidines as CRF-1 receptor antagonists.

hepatotoxicity issues. A number of other CRF-1 receptor antagonists are reportedly in clinical development at the present time.

We recently described a series of isoquinolines, such as **1**, that demonstrated strong CRF-1 receptor antagonism (Fig. 2).[10] The suboptimal, physicochemical (high lipophilicity and low aqueous solubility), and poor pharmacokinetic profiles of this series rendered its members unsuitable for further development. To increase hydrophilicity and improve general pharmacokinetic properties, we considered replacing the bicyclic quinoline core of **1** with a less lipophilic, monocyclic core such as the 2-arylpyrimidine **2**. The synthesis and SAR of the 2-arylpyrimidines as CRF-1 receptor antagonists are described herein.

The synthesis of pyrimidine **2** is outlined in Scheme 1. Reductive amination of 2-chloro-4-methyl-5-aminopyrimidine (**3**)[11] with propionaldehyde allowed introduction of the di-*N*-propylamine moiety at C-5. Subsequent Suzuki coupling provided the desired pyrimidine **2** in modest yield. It should be noted that throughout the course of the study, the coupling of unactivated 2-chloro-pyrimidines with 2,6-disubstituted aryl boronic acids[12] was very sluggish, and excess of both boronic acid and palladium catalyst, and prolonged reaction times were necessary to achieve even moderate yields of desired product. The unsubstituted pyrimidine **2** had an encouraging affinity (K_i = 561 nM) for the CRF-1 receptor,[13] despite being considerably less active than the corresponding isoquinoline **1** (K_i = 6 nM).

In order to design a strategy to enhance the affinity of **2**, the structures of SSR12543A and **2** were aligned using GASP software, and local minimum energy conformations were computed.[14] Figure 3 shows a good overlay for the low-energy conformations of these two compounds, especially at the pendant aryl ring, the central hydrogen bond acceptor, and the lipophilic top side-chain. The key feature lacking in **2** appears to be a group flanking the pyrimidine. The introduction of a small alkoxy substituent at the vacant ring position on the heterocycle seemed to be an attractive strategy to fill this pocket. The repulsion between the lone pairs on the oxygen and the adjacent pyrimidine nitrogen appears to further restrict the low-energy conformational space, and confer additional rigidity that was expected to be beneficial.



Scheme 1. Reagents and conditions: (a) CH_3CH_2CHO, $NaBH(OAc)_3$, HOAc, CH_2Cl_2, RT (76%); (b) $ArB(OH)_2$, 2M K_2CO_3, $Pd(PPh_3)_4$, PhMe, 85 °C (35%).

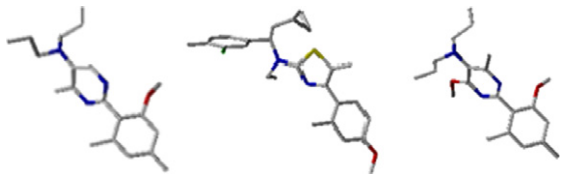
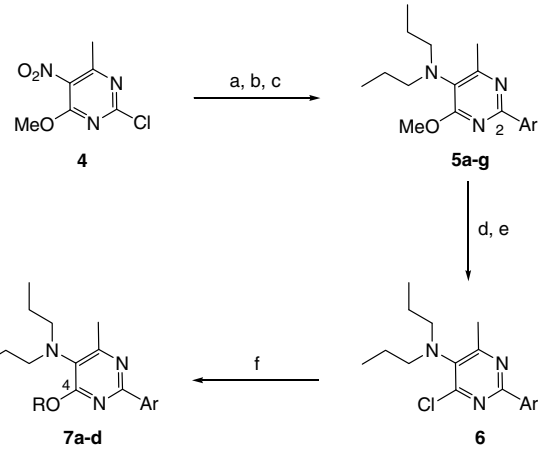


Figure 3. Minimized structures of **2**, SSR125543A, and the 4-methoxy pyrimidine derivative of **2**.

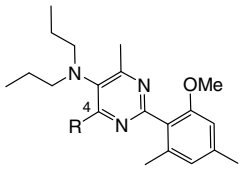


Scheme 2. Reagents and conditions: (a) $ArB(OH)_2$, 2 M K_2CO_3, $Pd(PPh_3)_4$, PhMe, 85 °C (55–77%); (b) H_2, Pd/C, EtOH (77–100%) or $Na_2S_2O_4$, NH_4OH, THF, H_2O, (68%); (c) CH_3CH_2CHO, $NaBH(OAc)_3$, HOAc, CH_2Cl_2, RT (82%); (d) **5a**, cHCl, 100 °C (100%); (e) $POCl_3$, 90 °C (77%); (f) ROH, NaH, DMSO, 100 °C (57–69%).

The readily available 2-chloro-4-methoxy-5-nitro-6-methylpyrimidine (**4**)[15] proved to be a suitable starting material in this regard (Scheme 2). Suzuki coupling of the 5-nitropyrimidine **4** was considerably more facile than for the 5-aminopyrimidine and gave moderate to good yields of the corresponding 2-arylpyrimidines. Hydrogenation of the nitro group followed by reductive alkylation with an excess of propionaldehyde gave the desired methoxypyrimidines **5a–g** in good yields. Acidic hydrolysis of **5a** (Ar = 2-methoxy-4,6-dimethylphenyl), then treatment with phosphorus oxychloride yielded the chloro-pyrimidine **6**. The chloride was susceptible to displacement by alkoxides in hot DMSO to provide the corresponding 4-alkoxypyrimidines **7a–d** in moderate yields.

The effects of alkoxy substitution at the 4-position are summarized in Table 1. The 2-methoxy-4,6-dimethylphenyl, 5-dipropyl amine, and 6-methyl substituents were kept constant to allow comparison with the unsubstituted pyrimidine **2** (K_i = 561 nM). A significant increase in affinity was observed upon incorporation

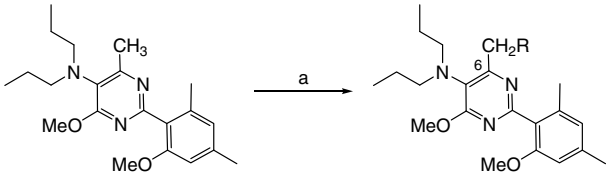
Table 1
Effects of the 4-substituent on CRF-1 receptor binding



2, 5a, 6, 7a-d

Compound	R	K_i (nM)	cLog*P*
1	—	6	7.4
2	H	561	5.5
5a	OMe	15	6.4
6	Cl	33	6.2
7a	OEt	16	6.9
7b	O^{n}Pr	53	7.5
7c	O^{i}Pr	>5000	7.3
7d	OCH_2CH_2OH	1610	5.6

K_i values are the mean of 3 independent experiments.



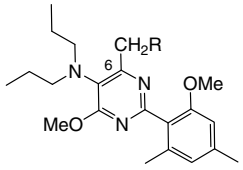
5a **8a-d**

Scheme 3. Reagents and conditions: (a) LDA, THF, −78 °C then electrophile (52–75%).

of the methoxy group at the 4-position (**5a**, K_i = 15 nM), although lipophilicity was significantly increased (*c*Log*P* = 6.4). The ethoxy-analogue **7a** was of a similar potency but further increases in chain length resulted in a loss in affinity (**7b**), while side-chain branching led to an inactive compound (**7c**). To increase hydrophilicity, the incorporation of polar functionality into the chain was investigated (**7d**) but since this approach resulted in a severe loss of potency, it was not pursued further.

In terms of affinity, the 4-methoxy substituent appeared optimal and was thus retained in the next series of analogues. Functionalization of the 6-position of the pyrimidine **5a** was achieved by deprotonation with LDA and subsequent trapping with an electrophile. Using this method, a number of 6-substituted analogues **8a**–**d** were prepared in moderate to good yields (Scheme 3).

Table 2
Effects of the 6-substituent on CRF-1 receptor binding

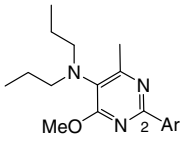


5a, 8a-d

Compound	R	K_i (nM)	*c*Log*P*
5a	H	15	6.4
8a	CH_3	22	7.0
8b	CH_2CH_3	76	7.5
8c	$CHOHCH_3$	1150	5.4
8d	$C(CH_3)_2OH$	604	5.8

K_i values are the mean of 3 independent experiments.

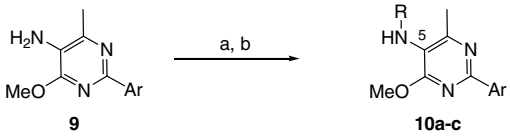
Table 3
Effects of the 2-aryl substituent on CRF-1 receptor binding



5a-g

Compound	Ar	K_i (nM)	*c*Log*P*
5a	2-Methoxy-4,6-dimethylphenyl	15	6.4
5b	2,4-Dichlorophenyl	>10,000	7.4
5c	2,4-Dimethoxyphenyl	507	5.8
5d	2,6-Dimethoxyphenyl	277	5.8
5e	2,4,6-Trimethylphenyl	354	7.1
5f	2-Methoxy-4,6-ditrifluoromethylphenyl	6	7.7
5g	2,6-Dimethoxy-4-chlorophenyl	2	5.9

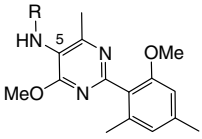
K_i values are the mean of 3 independent experiments.



9 **10a-c**

Scheme 4. Reagents and conditions: (a) $NaNO_2$, HCl, H_2O, 0 °C then KI, reflux (34%); (b) $Pd_2(dba)_3$, P^tBu_3, PhMe, (17–29%).

Table 4
Effects of the 5-substituent on CRF-1 receptor binding



10a-c

Compound	R	K_i (nM)	*c*Log*P*
5a	—	15	6.4
10a	^{n}Propyl	>10,000	5.3
10b	3-Pentyl	94	6.1
10c	$CH_2C(CH_3)_3$	>10,000	6.1

K_i values are the mean of 3 independent experiments.

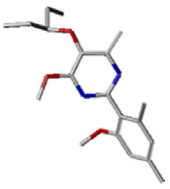
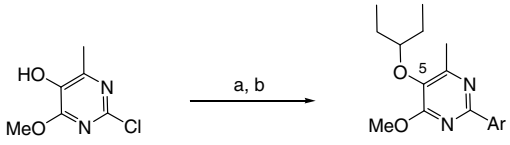


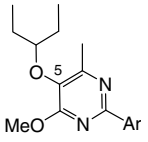
Figure 4. Minimum energy conformation of the dialkoxypyrimidine **12a**.



11 **12a-c**

Scheme 5. Reagents and conditions: (a) PPh_3, DEAD, propan-3-ol, THF, RT (72%); (b) $ArB(OH)_2$, 2 M K_2CO_3, $Pd(PPh_3)_4$, PhMe, 85 °C (35–57%).

Table 5
Effects of the 2-aryl substituent of 5-alkoxy pyrimidines on CRF-1 receptor binding



12a-c

Compound	Ar	CRF-1 K_i (nM)	AtT_{20} IC_{50} (nM)	*c*Log*P*
1	—	6	12	7.4
5g	—	2	1	5.9
12a	2-Methoxy-4,6-dimethyl	8	19	5.5
12b	2,6-Dimethoxy-4-chloro	9	7	5.0
12c	2,6-Dimethoxy-4 -difluoromethyl	9	—	4.5

IC_{50} values are the mean of 3 independent experiments.

Table 6
Pharmacokinetic profiles of **1**, **5g**, and **12b** in Sprague–Dawley rats (20 mg/kg po and 3 mg/kg iv)

Compound	Solubility (μg/mL)[a]	F (%)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	C_l (mL/min/kg)	V_d (L/kg)
1	<0.5	5	387	0.7	5.4	14.5	13
5g	27	2	210	0.6	2.8	21	12
12b	28	6	194	1.8	8.3	13.6	14

[a] Determined in 0.1 N HCl.

The CRF-1 receptor binding affinities of these 6-substituted analogues are summarized in Table 2. A small increase in chain size (**8a**) afforded a compound of similar potency to **5a** but further increases in chain length (**8b**) led to a decrease in affinity. The introduction of secondary (**8c**) and tertiary (**8d**) alcohol functionality resulted in a decrease in activity.

A number of substituted 2-aryl analogues of the 4-methoxypyrimidines were prepared (Schemes 2 and 5a–g) and their CRF-1 receptor binding affinities are shown in Table 3. To achieve maximal CRF-1 binding affinity in the isoquinoline[10] series a 2,4,6-trisubstitution on the aryl ring was required. This also proved to be the case in the pyrimidine series.[16] Replacing the 2-methoxy-4,6-dimethylphenyl (**5a**, K_i = 15 nM) by 2,4-dichlorophenyl (**5b**) led to a complete loss in activity. Likewise, only modest affinity was found for the 2,4- and 2,6-dimethoxyphenyl analogues (**5c** and **5d**). Reverting to 2,4,6-trisubstitution and replacing the 2-methoxy group of **5a** with methyl (**5e**, K_i = 354 nM) resulted in a considerable loss in affinity, underscoring the importance of the 2-methoxy substituent in this series. Reintroduction of the 2-methoxy and replacement of both methyl groups with trifluoromethyl groups gave an increase in affinity (**5f**, K_i = 6 nM) but also lipophilicity ($c\mathrm{Log}P$ = 7.7). In an attempt to increase the hydrophilicity, while retaining the potency of **5f**, the trifluoromethyl groups were replaced by less lipophilic substituents such as a second *ortho*-methoxy and a *para*-chloro. The resulting compound, **5g**, had excellent CRF-1 receptor binding affinity (K_i = 2 nM) and lower lipophilicity ($c\mathrm{Log}P$ = 5.9).

A limited number of secondary amines were also investigated at the 5-position. The 5-aminopyrimidine **9** was converted to the corresponding 5-iodopyrimidine and subsequent Buchwald amination gave the 5-aminopyrimidines **10a–c** in low yields (Scheme 4).

The modifications to the 5-position are summarized in Table 4. A complete loss in activity was observed following removal of a propyl group (**10a**) although α-branching (e.g., 3-pentyl amine **10b**) recovered activity (K_i = 94 nM). Increasing the steric bulk (**10c**), however, brought about a complete loss in binding.

The conformational control enabled by adjacent lone pair repulsions can be taken advantage of further by replacing the 5-aminoalkyl group with an α-branched alkyl ether. The calculated minimum energy conformation of a representative (e.g., **12a**, Fig. 4) indicates that the combination of lone pair and steric interactions may place the alkyl chain in the desired lipophilic pocket.

The 5-(3-pentyloxy) analogues **12a–c** were prepared as outlined in Scheme 5. Mitsunobu reaction of the known pyrimidine **11**[17] with propan-3-ol and subsequent Suzuki coupling with a 2,4,6-trisubstituted aryl boronic acid gave the desired 2-aryl-5-alkoxypyrimidines **12a–c** in modest overall yields.

The binding affinities of the 5-(3-pentyloxy) analogues **12a–c** are summarized in Table 5. The 2-methoxy-4,6-dimethylphenyl analogue **12a** displayed excellent affinity (K_i = 8 nM), compared to the corresponding 3-pentyl amine **10b** (K_i = 94 nM), and significantly less lipophilicity than compounds of similar activity in the parent isoquinoline series, such as **1**. The effects of a second *ortho*-methoxy substituent on the aryl ring were then investigated and the 2,6-dimethoxy-4-chloro analogue **12b** and the 4-difluoromethyl analogue **12c** had similar affinities to **12a** but also a reduced lipophilicity ($c\mathrm{Log}P \leqslant 5$). At this point, it became important to determine the functional activity of these compounds at the CRF-1 receptor. Compounds **5a**, **12a**, and **12b** were found to inhibit sauvagine-stimulated cAMP accumulation in AtT_{20} cells expressing the CRF-1 receptor[18] with IC_{50}s that correlated well with binding affinity, thereby supporting that these compounds are indeed functional antagonists at the CRF-1 receptor.

The pharmacokinetic properties of the 5-aminoalkyl pyrimidine **5g** and the 5-alkoxy analogue **12b** were examined (Table 6). Disappointingly, despite lower lipophilicity and increased solubility relative to the isoquinoline **1**, both **5g** and **12b** exhibited moderate oral exposure in rats. The low-to-moderate clearance values suggest that the poor exposure was not due to metabolic liabilities, leaving limited absorption as a potential culprit.

In summary, we have described our efforts to overcome the liabilities of our recently described series of isoquinolines (e.g., **1**) as CRF-1 receptor antagonists. Their poor physicochemical properties (high lipophilicity, $c\mathrm{Log}P > 7$) contributed to unacceptable pharmacokinetic profiles. Our strategy to increase hydrophilicity invoked the replacement of the bicyclic quinoline with a less lipophilic, monocyclic pyrimidine core ($\Delta c\mathrm{Log}P$ = 1.9 between these two cores). Optimization of this new series with regard to CRF-1 receptor binding affinity and reduced lipophilicity led to the identification of compounds with K_i values below 10 nM and lipophilicity in a minimally acceptable range for a CNS drug ($c\mathrm{Log}P < 5$). However, the improvements in lipophilicity within this series did not translate into increased oral bioavailability, therefore hindering the progression of these otherwise potent antagonists. The results of our efforts to resolve these issues will be reported in due course.

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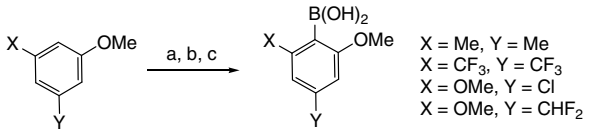
12. 2,4,6-Trimethylphenyl boronic acid was commercially available. 2-Methoxy-4,6-substituted aryl boronic acids were prepared by *ortho*-lithiation of the corresponding anisole, quenching with trimethyl borate and acid hydrolysis:



Reagents and (a) ^{n}BuLi, TMEDA, Et_2O, 0 °C to RT; (b) $(MeO)_3B$, −78 °C to RT; (c) 2 M HCl.

13. The affinity of the compounds described in this study for the CRF-1 receptor was determined by using a modified version of the assay described by Grigoriadis and De Souza by examining the displacement of ^{125}I-sauvagine from CRF-1 receptors endogenously expressed in IMR-32 human neuroblastoma cells; Grigoriadis, D. E.; De Souza, E. B. *Methods Neurosci.* **1991**, *5*, 510.
14. Molecular superimpositions using the GASP algorithm and energy minimizations using the MMFF94 force field were carried out with the Sybyl suite of programs: Tripos International, 1699 South Hanley Rd., St. Louis, MO 63144, USA.
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