Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 1063–1066

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

USE OF THE SUZUKI REACTION FOR THE SYNTHESIS OF ARYL-SUBSTITUTED HETEROCYCLES AS CORTICOTROPIN-RELEASING HORMONE (CRH) ANTAGONISTS

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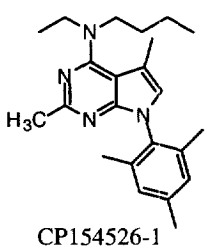
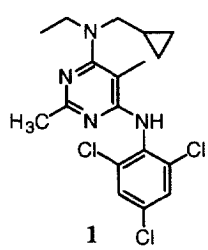
Received 9 December 1998; accepted 5 March 1999

Abstract: The Suzuki reaction has been used to synthesize a variety of aryl-substituted heterocyclic antagonists of the CRH_1 receptor. Examples with several different heterocyclic cores are potent CRH receptor ligands. © 1999

Based on a now substantial body of pharmacological and clinical evidence, there is anticipation that the modulation of the effects of corticotropin releasing hormone or factor (CRH or CRF) may eventually play a role in the treatment of depression or anxiety-related disorders.[1] This interest in CRH as a new important target for drug discovery is evidenced by the number of recent reports of small-molecule inhibitors of one (CRH_1) of the two known receptors of this hormone.[2-10] While derivatives of a variety of heterocyclic systems have shown activity as CRH_1 antagonists, many of these have structures in which a dialkylamine is linked through a heterocyclic core to a 2,4-disubstituted or 2,4,6-trisubstituted aromatic ring, including pyrrolopyrimidine CP154526-1 (K_i = 2.7 nM),[3] 4-anilinopyrimidine **1** (K_i = 2 nM),[4] triazolopyrimidine **2** (K_i = 3.7 nM),[5] and purine **3** (K_i = 3.5 nM).[5,8] In each of these examples, a different heterocyclic core holds in the same relative orientation a dialkylamine, a di- or trisubstituted aromatic ring, and a methyl group, all three of which are required for high receptor affinity.



CP154526-1



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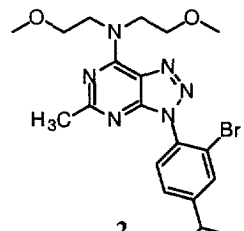

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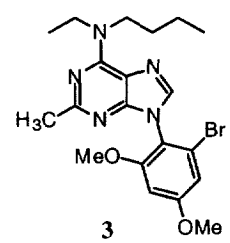

3

In addition to the four ring systems above, other monocyclic cores reported for CRH_1 antagonists include 1,3,5-triazines and 2-anilinopyrimidines;[6] bicyclic cores also include pyrazolopyrimidines.[7] In a recent

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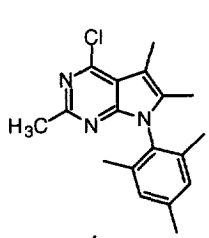
PII: S0960-894X(99)00133-X

communication we demonstrated that 4-aryl groups can replace the 4-(dialkylamino) substituents of 2-anilinopyrimidine CRH_1 antagonists.[9] In this report, we describe our use of the Suzuki reaction to synthesize a variety of compounds in which the dialkylamino group of other known classes of heterocyclic CRH_1 inhibitors are replaced with the o-(trifluoromethyl)phenyl group.

While originally developed for the synthesis of biaryls, the Suzuki reaction in recent years has also been used successfully to introduce aryl groups onto π-deficient heteroaromatic rings.[11,12] While either aryl bromides or iodides are required to react efficiently with arylboronic acids, heterocyclic chlorides are in many cases sufficiently reactive to undergo successful coupling reactions.

We and others have described the reaction of heterocyclic chlorides with dialkylamines to afford several series of potent CRH_1 antagonists. These heterocyclic chlorides include pyrrolopyrimidine **4**,[13] pyrazolopyrimidine **5**,[7] triazolopyrimidine **6**,[5] and 1,3,5-triazine **7**.[6] We now report that when each of these chlorides is reacted in turn with arylboronic acids under standard Suzuki reaction conditions the corresponding aryl substituted compounds are obtained.[14] For example, treatment of each of these chlorides with o-(trifluoromethyl)phenylboronic acid[15] afforded in yields of 50–80% the corresponding arylsubstituted heterocycles **8**, **9**, **10**, and **11**.



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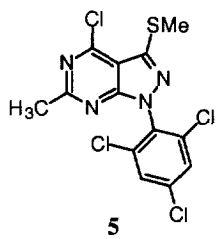

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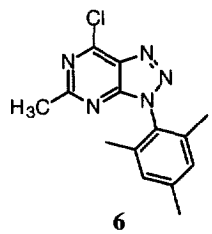

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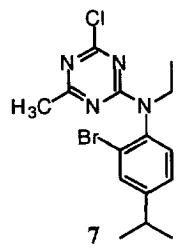

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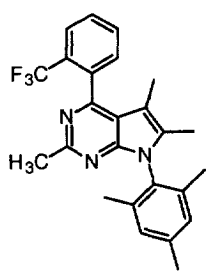
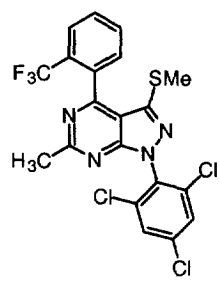
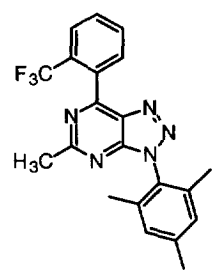


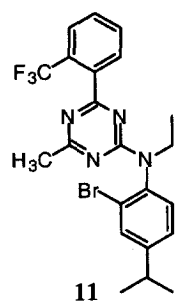
8
K_i = 9.7 nM



9
K_i = 33.4 nM



10
K_i = 168 nM

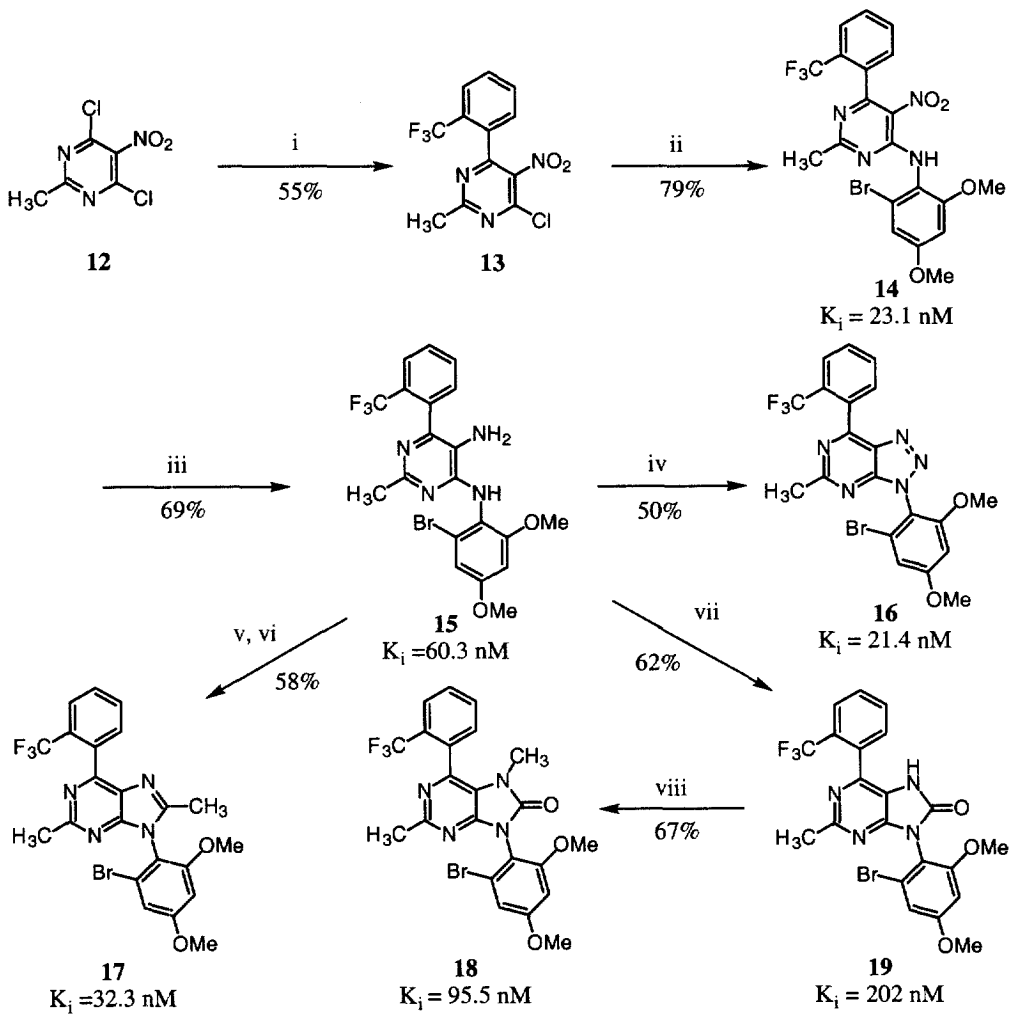


11
K_i = 5.5 nM

In our recent communication on 4-aryl-2-anilinopyrimidines, o-(trifluoromethyl)phenyl was shown to be the optimal aryl replacement for the dialkylamino group. We now report that its introduction onto three of the above four heterocycles resulted in potent antagonists of the CRH_1 receptor. While triazolopyrimidine **10** exhibited less receptor affinity than the other three compounds, we felt that its activity could be improved significantly by replacing the N-mesityl group, which we knew to be suboptimal in this series, with 2-bromo-4,6-dimethoxyphenyl. Since this would require a Suzuki reaction on a substrate containing both an arylbromide and a

heterocyclic chloride, we circumvented the expected selectivity problem by utilizing the coupling reaction earlier in the synthetic sequence as is depicted in the reaction scheme below.

Coupling of 4,6-dichloro-2-methyl-5-nitropyrimidine **12**[5] with o-(trifluoromethyl)phenylboronic acid afforded **13** as the major product with a lesser amount of diarylated product formed. Displacement of the remaining chlorine with 2-bromo-4,6-dimethoxyaniline and reduction of the nitro group gave 5-aminopyrimidine **15**. Nitrous acid mediated cyclization of **13** afforded N-(2-bromo-4,6-dimethoxyphenyl)triazolopyrimidine **16**, which had tenfold greater affinity for the CRH_1 receptor than the N-(trimethylphenyl)triazolopyrimidine **10**. Key intermediate **15** was also converted by conventional chemistry into additional heterocyclic systems, 8-methyl-



Reagents and conditions: (i) *o*-(trifluoromethyl)phenylboronic acid, $(Ph_3P)_4Pd$, benzene, 1 M Na_2CO_3, reflux; (ii) 2-bromo-4,6-dimethoxyaniline, diisopropylethylamine, dioxane, reflux; (iii) Fe, HOAc, MeOH, reflux; (iv) $NaNO_2$, HOAc, H_2O, CH_2Cl_2; (v) $CH_3C(OEt)_3$, HCl, dioxane; (vi) xylene, reflux; (vii) phosgene, toluene, reflux; (viii) MeI, KOH, MeOH.

purine **17**, which has tenfold less affinity than a dialkylamino analog **3**, and the 8-oxopurines **18** and **19**, which exhibit only modest activity for the CRH_1 receptor. Intermediate 4-anilinopyrimidines **14** and **15**, which can be considered aryl-analogs of the class of 5-substituted 4-anilinopyrimidine CRH_1 antagonists exemplified by **1**, also exhibited substantial affinity for the CRH_1 receptor.

Thus we have demonstrated that for CRH_1 antagonists in seven different heterocyclic series, the dialkylamino group can be replaced with an o-trifluoromethylphenyl substituent, generally with little or no loss of receptor affinity.[16]

Acknowledgements: The authors gratefully acknowledge Anne Marshall, Sue Keim, Carol Krause, John Patterson, David Rominger, and Cindy Rominger for *in vitro* binding studies.

References and Notes

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16. Receptor binding was determined by displacement of ^{125}I-tyr-ovine-CRH from cloned human $hCRH_1$ receptors expressed in 293EBNA cells. For a detailed description of the isolation of cell membranes containing cloned human CRH_1 receptors for use in the binding assay as well as a description of the binding assay itself see ref 6. K_i values are the average of at least two determinations for K_i < 50 nm, otherwise they are single determinations. Selected compounds (**8**, **14**, and **16**) were shown to be silent antagonists in that they completely inhibited CRH-stimulated adenylyl cyclase activity in membranes from rat cortex without any effect by themselves (data not shown).