Bioorganic & Medicinal Chemistry Letters 25 (2015) 956–959

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Diaminopyrimidines, diaminopyridines and diaminopyridazines as histamine H_4 receptor modulators

Brad M. Savall *, Steven P. Meduna, Kevin Tays, Hui Cai †, Robin L. Thurmond, Patricia McGovern, Michael Gaul, Bao-Ping Zhao ‡, James P. Edwards

Janssen Pharmaceutical Research & Development, LLC, 3210 Merryfield Row, San Diego, CA 92121, United States

ARTICLE INFO

Article history:
Received 17 November 2014
Revised 8 December 2014
Accepted 9 December 2014
Available online 23 December 2014

Keywords:
Histamine H_4
Antagonists
Pyrimidine
Pyridine
Pyridazine

ABSTRACT

Previously disclosed H_4 receptor modulators, the triamino substituted pyridines and pyrimidines, contain a free primary amino ($-NH_2$) group. In this Letter we demonstrate that an exocyclic amine (NH_2) is not needed to maintain affinity, and also show a significant divergence in the SAR of the pendant diamine component. These *des*-NH_2 azacycles also show a distinct functional spectrum, that appears to be influenced by the diamine component; in the case of the 1,3-amino pyrimidines, the preferred diamine is the amino pyrrolidine instead of the more common piperazines. Finally, we introduce 3,5-diamino pyridazines as novel histamine H_4 antagonists.

The histamine H_4 receptor is a 390 amino acid G-protein coupled receptor that is implicated in the treatment of inflammatory diseases such as asthma and allergic rhinitis based on the expression of the H_4 receptor on eosinophils, mast cells, dendritic cells and other leukocytes.[1,2] JNJ 7777120 (**1**), the prototypical H_4 carboxamide derived antagonist, has served as a useful pharmacological tool, however the rapid metabolism makes it less than ideal as an in vivo tool.[3,4] Recently, there have been several reports from multiple groups on pyrimidine and pyridine based H_4 antagonists,[5,6] including our recent reports on several new histamine H_4 antagonist chemotypes. For example, the tricyclic aminopyrimidines typified by JNJ 40279486 (**2**), the 6-alkyl-2,4-diamino pyrimidines, such as JNJ 39758979 (**3**), and the related 2-amino azacycles, such as the triamino pyridines (**4**) and pyrimidines (**5**–**6**).[7–9] Previously disclosed H_4 receptor modulators, the triamino substituted pyridines (**4**) and pyrimidines (**5**, **6**) contain a free $-NH_2$ group as a common structural motif. In this paper we disclose a series of diamino substituted pyridine (**7**–**11**) and pyrimidines (**12**–**16**) without a free $-NH_2$ group demonstrating a free $-NH_2$ group is not required for H_4 histamine receptor modulation. In addition we disclose a series of diamino pyridazines (**17**–**19**), a new series of H_4 histamine receptor modulators (Fig. 1).

Chemistry: Scheme 1 describes a representative synthetic route used to prepare the 2,4-diamino pyridines. Commercially available 2-fluoro-4-bromopyrimidine (**20**) was combined with a primary amine and stirred in THF at room temperature to provide a high yield of the 2-amino substituted 4-bromopyridine (**21**). The use of a Pd catalyzed Buchwald–Hartwig amination[10] to install the diamine component delivered the desired analogs (**7**–**11**) in moderate to high yield. For the compounds with BOC groups, the BOC was removed by the use of 6 N HCl in formic acid, followed by azeotropic removal of the formic acid with methanol on a rotary evaporator.

Scheme 2 outlines the syntheses of the 2,4-diamino pyrimidines. Starting with commercially available 2,4-dichloropyrimidine (**22**), the diamine component selectively added at the 4-position when heated in the presence of di-isopropyl ethylamine in isopropyl alcohol at 160 °C in the microwave. Heating of **23** with excess primary amine in isopropyl alcohol at 160 °C in isopropanol under microwave irradiation provided the desired diamino substituted product. Removal of the BOC group with 4.0 M HCl in dioxane provided the final products (**12**–**16**).

Scheme 3 shows the synthesis of the pyridazine series of compounds. Combining 3,5-dichloropyridazine (**24**) with a diamine in THF at room temperature for 12 h led to very selective reaction at the 5-position to provide intermediate 3-chloropyridazines (**25**). The 3-chloro was not nearly as reactive as the 5-chloro and the second displacement required the use of a Pd mediated coupling protocol. BOC groups were removed by the use of 6 N HCl

* Corresponding author.
E-mail address: bsavall@its.jnj.com (B.M. Savall).
† Current addresses: WuXi AppTec, San Diego, CA, United States.
‡ Current addresses: WuXi AppTec (WuHan) Co., Ltd, United States.

http://dx.doi.org/10.1016/j.bmcl.2014.12.027
0960-894X/

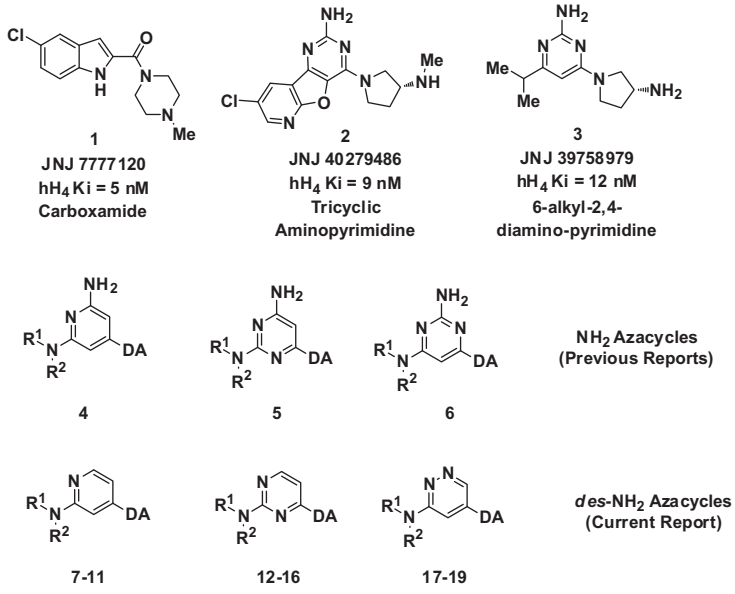


Figure 1. Selective histamine H_4 receptor antagonists. DA refers to a substituted piperazine or aminopyrrolidine. R^1R^2N and DA are defined by Figure 2 and Tables 1–6.

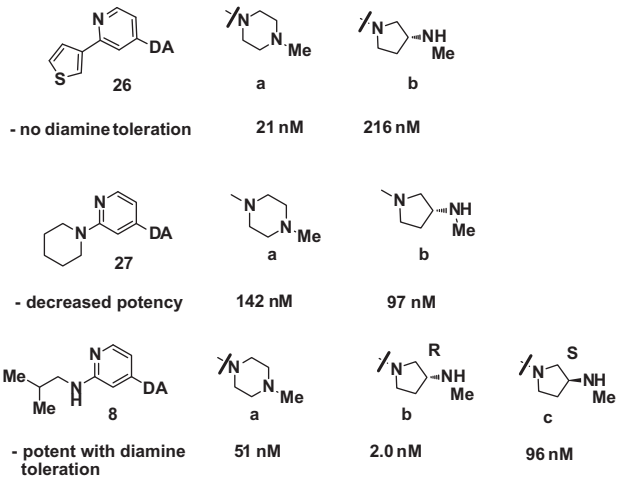
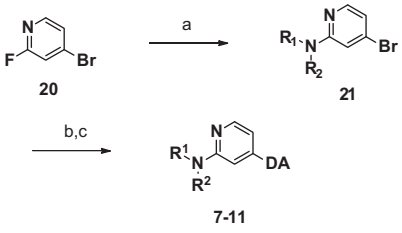
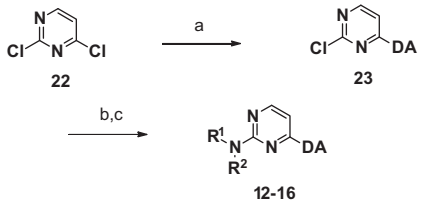


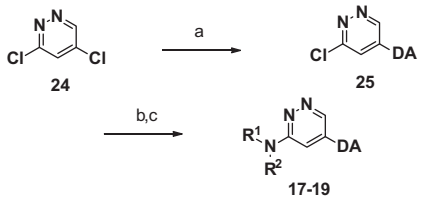
Figure 2. Lead design DA refers to a substituted piperazine or aminopyrrolidine.



Scheme 1. Reagents and conditions: DA refers to a substituted piperazine or aminopyrrolidine. (a) R^1R^2NH, THF, 23 °C 1–2 h; (b) diamine, LiHMDS, $Pd_2(DBA)_3$, X-PHOS, THF, 60 °C 1–2 h microwave (μW), (c) 4.0 M HCl/dioxane; 27–84% combined a and b steps.



Scheme 2. Reagents and conditions: DA refers to a substituted piperazine or aminopyrrolidine. (a) R^1R^2NH, DIEA, IPA, 100–160 °C 1–2 h microwave (μW); (b) diamine, DIEA, IPA, 100–160 °C 1–2 h μW; (c) 4.0 M HCl in dioxane, MeOH, 22–54% combined steps a–c.



Scheme 3. Reagents and conditions: DA refers to a substituted piperazine or aminopyrrolidine. (a) R^1R^2NH, THF, 23 °C 12 h; (b) diamine, DIEA, (toluene, DME or *t*-BuOH), 65–100 °C 1–24 h; (c) 6.0 $HCl_{(aq)}$, formic acid, 16–69% combined steps a–c.

in formic acid, followed by azeotropic removal of the formic acid with methanol on a rotary evaporator to provide the final products (**17**–**19**).

During the follow up efforts to our initial screening campaign, we identified the thiophene substituted pyridine (**26a**), as a reasonably potent histamine H_4 receptor ligand (21 nM) (Fig. 2). Replacing the *N*-methyl piperazine (**26a**) with other amines, such as (*R*)-aminomethyl pyrrolidine (**26b**), resulted in a loss of affinity. This lack of 'tolerance' for diamines other than *N*-methyl piperazine has been previously noted with other histamine H_4 receptor ligands such as JNJ 7777120. Replacement of the thiophene with a piperidine led to a reduction of potency for the *N*-methyl piperazine derivative (**27a**, K_i = 142 nM), but a slight increase in the case of the 3-aminomethylpyrrolidine (**27b**, K_i = 97 nM). Prompted by our previously reported observations in the containing pyrimidine series containing an $-NH_2$ (**5**–**6**), we investigated the secondary amines that provided an H-bond donor at the 2-position (e.g., **8a**–**c**). This change resulted in an ~3 fold boost in affinity for the piperazine (**8a**, K_i = 51 nM) and an ~20 fold boost for the amino pyrrolidine (**8b**, K_i = 2.0 nM). This series was further explored with other alkyl groups and diamines (Table 1) and continued the