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Diaminopyrimidines, diaminopyridines and diaminopyridazines as histamine H_4 receptor modulators

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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

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0960-894X/

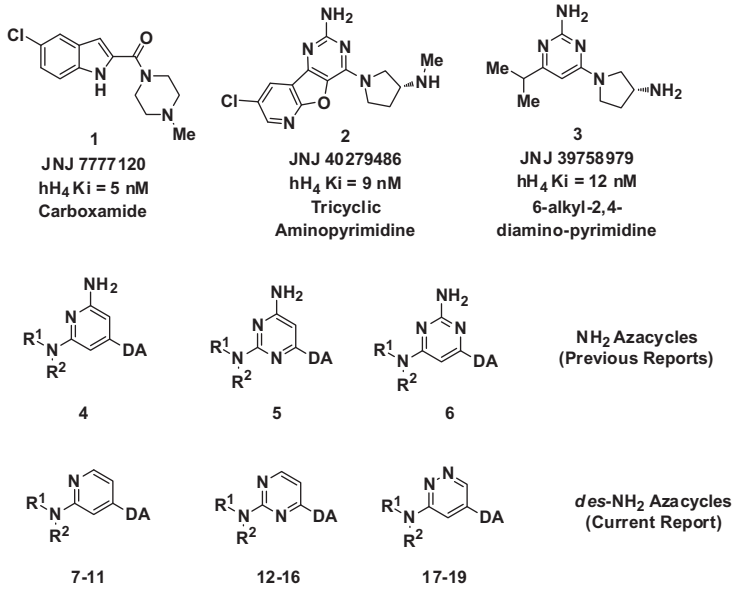


Figure 1. Selective histamine H_4 receptor antagonists. DA refers to a substituted piperazine or aminopyrrolidine. R^1R^2N and DA are defined by Figure 2 and Tables 1–6.

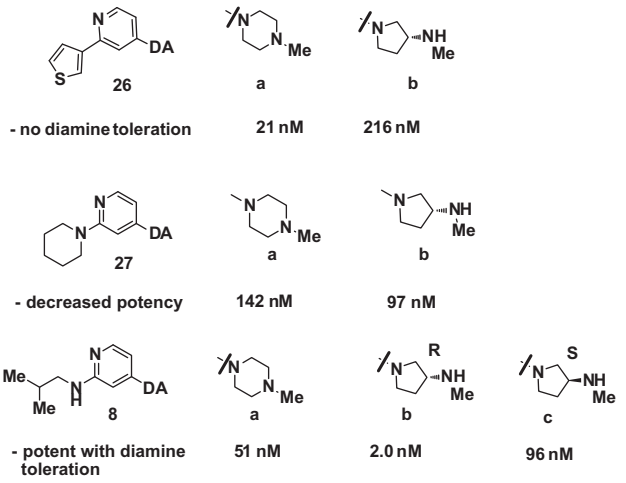
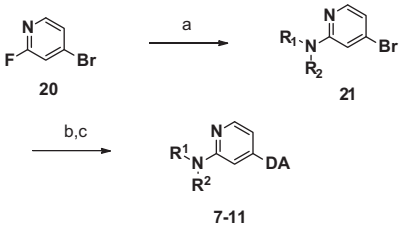
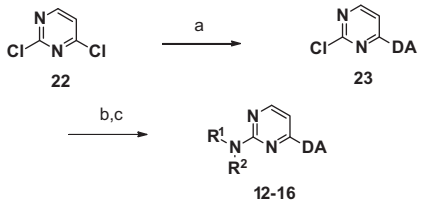


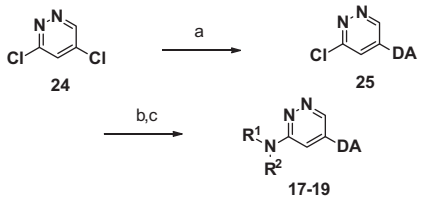
Figure 2. Lead design DA refers to a substituted piperazine or aminopyrrolidine.



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.

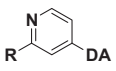
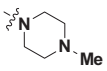
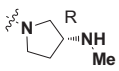
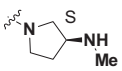
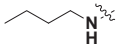
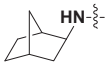


Scheme 3. Reagents and conditions: DA refers to a substituted piperazine or aminopyrrolidine. (a) R^1R^2NH, THF, 23 °C 12 h; (b) diamine, DIEA, (toluene, DME or *t*-BuOH), 65–100 °C 1–24 h; (c) 6.0 $HCl_{(aq)}$, formic acid, 16–69% combined steps a–c.

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

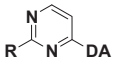
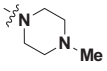
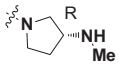
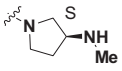
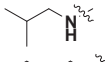
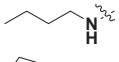
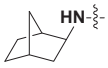
During the follow up efforts to our initial screening campaign, we identified the thiophene substituted pyridine (**26a**), as a reasonably potent histamine H_4 receptor ligand (21 nM) (Fig. 2). Replacing the *N*-methyl piperazine (**26a**) with other amines, such as (*R*)-aminomethyl pyrrolidine (**26b**), 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

Table 1

#	 7-11	 a	 b	 c
7			19 nM	
8		51 nM	2 nM	96 nM
9		176 nM	7 nM	109 nM
10		16 nM	4 nM	33 nM
11			1.0 nM	6 nM

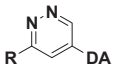
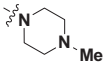
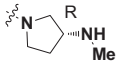
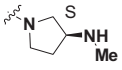
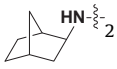
DA refers to a substituted piperazine or aminopyrrolidine.

Table 2

#	 12-16	 a	 b	 c
12		117 nM	8 nM	118 nM
13		69 nM	2 nM	134 nM
14		55 nM	3 nM	
15		63 nM	2 nM	45 nM
16		86 nM	0.8 nM	8 nM

DA refers to a substituted piperazine or aminopyrrolidine.

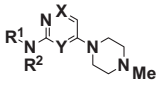
Table 3

#	 17-19	 a	 b	 c
17		10,000 nM	55 nM	389 nM
18		824 nM	6 nM	240 nM
19		365 nM	8 nM	5 nM

DA refers to a substituted piperazine or aminopyrrolidine.

diamine trends. Specifically, the (*R*)-amino pyrrolidine derivatives (**7**–**11b**) were nearly an order of magnitude more potent relative to the corresponding piperazines (**7**–**11a**). Although the (*R*)-enantiomer was more potent than the (*S*)-enantiomer, at least one derivative (**11c**) with an (*S*)-pyrrolidine was under 10 nM.

Table 4
Functional activity of the *N*-methylpiperazine compounds



#	R^1R^2N	X	Y	K_i[a] (nM)	EC_{50}[b] (nM)	α[c]	pA2[d]
12a		CH	N	117	112	0.67	—
8a		CH	CH	146	—	0.50	—
13a		CH	N	69	84	0.69	—
14a		CH	N	33	91	0.71	—
10a		CH	CH	25	—	0.80	—
15a		CH	N	63	75	0.72	—
16a		CH	N	31	20	0.63	—

[a] Displacement of [^{3}H]histamine from the recombinant histamine H_4 receptor. K_i values are the geometric mean of three or more independent determinations and calculated according to Cheng and Prusoff.[8]
[b] Compounds with K_i >100 nM not tested in functional assays.
[c] Compounds with α >0.40 were not tested in the pA2 assay.
[d] Antagonism of histamine inhibition of forskolin-stimulated cAMP-mediated reporter gene activity in SK-N-MC cells expressing the human histamine H_4 receptor. Detailed experimental for EC_{50} and pA_2 determinations included in Ref. 9.

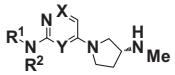
This trend of amino pyrrolidines being more potent than the piperazines translated to the pyrimidine series (Table 2). This series had similar trends to the pyridine series in terms of overall potency and also in the trends of the diamines. Specifically, the (*R*)-aminopyrrolidine was more potent than the (*S*)-enantiomer, though the inclusion of a lipophilic secondary amine resulted in enhanced affinity for both the (*R*)- and (*S*)-aminopyrrolidines (**16b** and **16c**, respectively).

Finally, we investigated the pyridazine series (Table 3); which was unique in several respects. In all three series, the piperazines were less active than the pyrrolidine counterparts, however in the pyridazine series the discrepancy was more dramatic and none of the piperazine derivatives (**17**–**19a**) were under 100 nM, with most being in the micromolar range. For example, with isobutylamine at the 3-position and an *N*-Me piperazine at the 5 position (**20a**), the affinity is >10,000 nM, while the corresponding *N*-Me pyrrolidine (**17b**) is 55 nM. This series overall was less potent than the other two series, though the combination of a lipophilic amine at the 3 position with either an (*R*)- or (*S*)-aminomethyl pyrrolidine at the 5 position delivered single digit nanomolar compounds (**19b**, **c**).

Thus far we have only focused on the affinity of the various series without discussing the functional activity of the ligands. At this point, it is more instructive to look at the diamines and how they impact the functional activity. As such, Tables 4–6 are configured to compare the effect of the diamines across the various series. Table 4 shows that the pyridine derivatives (**8a**, **10a**) tested as partial agonists with α-values between 0.5 and 0.8. A similar trend was noticed for the pyrimidines (**12a**–**16a**) where all of the piperazines tested behaved as partial agonists with α-values between 0.6 and 0.7. As mentioned above, the piperazine derivatives in the pyridazine series did not possess sufficient potency to be tested in the functional assays.

Looking at the aminopyrrolidines, there was a range of functional activity across the series. In the aminopyridines, the

Table 5
Functional activity of (*R*)-3-aminomethyl pyrrolidine compounds



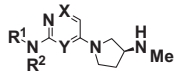
#	R^1R^2N	X	Y	K_i[a] (nM)	EC_{50}[b] (nM)	α[c]	pA2[d]
7b		CH	CH	19	3162	—	8.5
12b		CH	N	8.0	25	0.70	—
8b		CH	CH	2.0	—	—	9.2
13b		CH	N	3.4	15	0.42	—
17b		N	CH	55	3160	0.22	7.8
9b		CH	CH	18	48	0.60	—
14b		CH	N	3.4	4.0	0.62	—
10b		CH	CH	1.2	>10,000	—	9.0
15b		CH	N	2.0	86	0.53	—
18b		N	CH	6.0	—	—	8.0
11b		CH	CH	0.4	>10,000	—	11.2
16b		CH	N	0.8	3162	—	10.1
19b		N	CH	8.5	1000	0.14	8.0

[a] Displacement of [^{3}H]histamine from the recombinant histamine H_4 receptor. K_i values are the geometric mean of three or more independent determinations and calculated according to Cheng and Prusoff.[8]
[b] Compounds with K_i >100 nM not tested in functional assays.
[c] Compounds with α >0.40 were not tested in the pA2 assay.
[d] Antagonism of histamine inhibition of forskolin-stimulated cAMP-mediated reporter gene activity in SK-N-MC cells expressing the human histamine H_4 receptor. Detailed experimental for EC_{50} and pA_2 determinations included in Ref. 9.

(*R*)-enatiomer provided antagonists with the branched isopropylamine (**7b**), isobutylamine (**8b**), aminocyclopentane (**10b**), and [2.2.1]-bicycloheptyl amine (**11b**) but a partial agonist in the case of the linear *n*-butylamine (**9b**). In the case of the pyrimidines, all of the (*R*)-pyrrolidines (**12b**–**15b**) were partial agonists with α-values between 0.4 and 0.8 with the exception of and [2.2.1]-bicycloheptyl amine (**16b**). In the pyridazine series, only the [2.2.1]-bicycloheptyl amine derivative (**19b**) had sufficient potency and functionally behaved as an antagonist of the H_4 receptor.

Although the (*S*)-aminomethyl pyrrolidines were generally less potent than the (*R*)-aminopyrrolidines, in the limited number of examples where the potency warranted functional testing, all (*S*)-aminomethyl pyrrolidines behaved as antagonists. It is interesting that for all three cores, the combination of [2.2.1]-bicycloheptyl amine and an (*S*)-aminopyrrolidine provided functional antagonists (**11c**, **16c**, **19c**).

Table 6
Functional activity of (*S*)-3-aminomethyl pyrrolidine compounds



#	R^1R^2N	X	Y	K_i[a] (nM)	EC_{50}[b] (nM)	α[c]	pA2[d]
10c		CH	CH	34	>10,000	—	7.4
11c		CH	CH	5.6	>10,000	—	9.0
16c		CH	N	8.3	>10,000	—	8.1
19c		N	CH	5.0	>10,000	—	8.1

[a] Displacement of [^{3}H]histamine from the recombinant histamine H_4 receptor. K_i values are the geometric mean of three or more independent determinations and calculated according to Cheng and Prusoff.[8]
[b] Compounds with K_i >100 nM not tested in functional assays.
[c] Compounds with α >0.40 were not tested in the pA2 assay.
[d] Antagonism of histamine inhibition of forskolin-stimulated cAMP-mediated reporter gene activity in SK-N-MC cells expressing the human histamine H_4 receptor. Detailed experimental for EC_{50} and pA_2 determinations included in Ref. 9.

There have been several reports of exocyclic NH_2-amino heterocycles as ligands for the histamine H_4 receptor. In this Letter we demonstrate that the NH_2 can be replaced with hydrogen if a free NH is available on the opposite side of the basic heterocyclic nitrogen and maintain H_4 receptor affinity. We further elaborated these '*des*-NH_2' series to show that *N*-methyl piperazine derivatives behaved as partial agonists while (*R*)- and (*S*)-amino pyrrolidine provided for a range of functional activity. Interestingly, the combination of the lipophilic [2.2.1]-bicycloheptyl amine and an (*S*)-aminopyrrolidine provided potent antagonists in all three series. This provides a range of functional activity across multiple chemotypes each of which are undergoing additional profiling.

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