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Rigidified 2-aminopyrimidines as histamine H_4 receptor antagonists: Effects of substitution about the rigidifying ring

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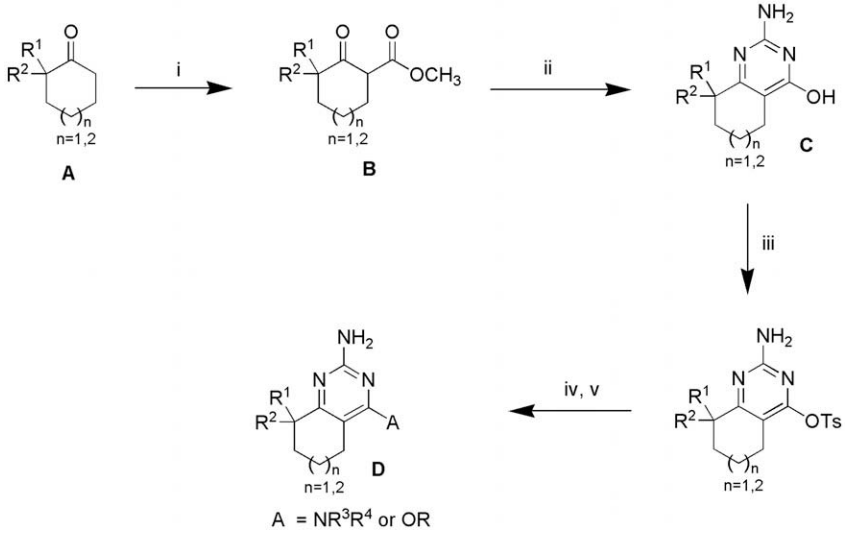
ABSTRACT

Three novel series of histamine H_4 receptor (H_4R) antagonists containing the 2-aminopyrimidine motif are reported. The best of these compounds display good in vitro potency in both functional and binding assays. In addition, representative compounds are able to completely block itch responses when dosed ip in a mouse model of H_4-agonist induced scratching, thus demonstrating their activities as H_4R antagonists.

The histamine H_4 receptor (H_4R) has attracted considerable interest from both academia and industry since its cloning several years ago.[1] H_4R has been found to be expressed in lymphocytes, mast cells, and dendritic cells,[2] and H_4 antagonists have been shown to block histamine-mediated shape change and chemotaxis of eosinophils and mast cells.[3] Thus, it has been proposed that antagonists of H_4R could be used to treat conditions arising from immune and inflammatory responses.[1c] Indeed, H_4 antagonists



Scheme 1. General preparation of compounds. Reagents and conditions: (i) NaH, dimethyl carbonate, reflux, 2 h; (ii) guanidine, DMF, 120 °C, overnight; (iii) TsCl, DMAP, Et_3N, CH_2Cl_2, rt, overnight; (iv) diamine or Boc-protected diamine, Et_3N, CH_3CN, reflux, 48 h; or hydroxylamine, KO*t*Bu, 0 °C to rt, THF, 48 h; (v) TFA, CH_2Cl_2, rt, 1 h.

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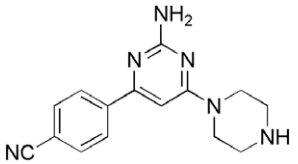
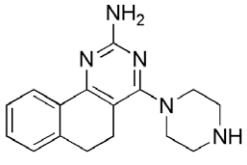
have been reported to be active in in vivo models of H_4-agonist induced itch[4] and ovalbumin-induced airway inflammation.[5] In addition, the antinociceptive activity of H_4 antagonists in models of inflammatory, postsurgical, osteoarthritic, and neuropathic pain has been reported by ourselves[6] and others.[7]

We recently disclosed some results of our studies of H_4R ligands containing the 2-aminopyrimidine moiety. We found that 6-aryl-2-aminopyrimidines, exemplified by **I**, can be potent antagonists of H_4 at both human and rat receptors but tend to suffer from problems with metabolism and off-target activity.[6a] Rigidification of the structure by including a new ring junction, such as in compound **II**, largely overcomes these issues while retaining much of the original potency, with the best potencies being obtained when the rigidifying ring is six- or seven-membered.[6b] We have also demonstrated that the aryl ring of **II** could be appended rather than fused to the rigidifying ring (e.g., **1**) with only a modest reduction in potency.



I
human H_4R pK_b = 8.53
rat H_4R pEC_{50} = 7.23 (64% eff.)

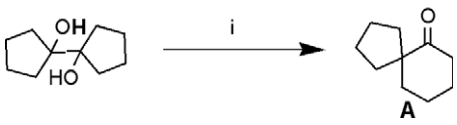


II
human H_4R pK_b = 7.58
rat H_4R pEC_{50} = 7.62 (52% eff.)

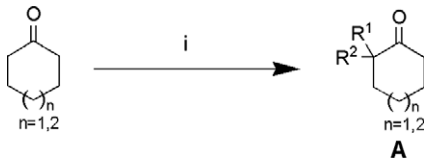
Intrigued by the in vitro results obtained with **1**, and in an effort to further understand the SAR of such compounds, we prepared a series of similar rigidified analogs with substitution(s) about the rigidifying ring. The results of this campaign are presented in this communication.

Synthesis of the compounds in this study proceeded according to the general synthetic scheme in Scheme 1. Ketone **A**, available commercially or prepared according to Scheme 2 or 3, was converted to the corresponding 1,3-dicarbonyl **B** with sodium hydride and dimethyl carbonate. Reaction of **B** with guanidine with heating in DMF afforded hydroxypyrimidine **C**, which upon tosylation and reaction with a diamine or hydroxylamine yielded compound **D**. For those diamines that were Boc-protected, a final deprotection step with TFA removed the Boc group.

Ketone **A** with *spiro*-cyclopentyl substitution alpha to the carbonyl was prepared via pinacol rearrangement of bi(cyclopentane)-1,1′-diol, as outlined in Scheme 2. With other *spiro*-cycloalkyl substitution, or with bis-alkyl or bis-benzyl substitution, the required ketones were prepared according to Scheme 3.[8]



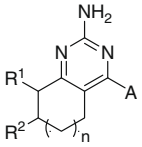
Scheme 2. Synthesis of *spiro*-cyclopentyl compounds **A**. Reagents and conditions: (i) $(CH_3O)_3CH$, BF_3–OEt_2, −20 °C to rt, 2 h.

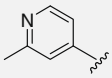
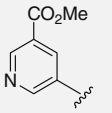
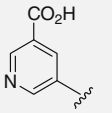


Scheme 3. Synthesis of compounds **A** with other *spiro*-cycloalkyl substitution or with bis-alkyl or bis-benzyl substitution. Reagents and conditions: (i) KO*t*Bu, electrophile, *t*BuOH, rt, overnight (electrophiles: 1-chloro-5-iodopentane, MeI, EtI, BnBr, or 1,2-bis(bromomethyl)benzene).

The in vitro results at H_4R are shown in Tables 1–3, with the functional assays being run as previously described.[6] In an earlier publication,[6b] we demonstrated that compounds with a rigidifying cycloalkyl ring are potent at H_4, with six- or seven-membered rings being preferred and roughly equivalent to each other in terms of

Table 1
Summary of in vitro potency at histamine H_4 receptors[a]



Compd	R^1	R^2	n	A	Human H_4 FLIPR pK_b ± SEM or pEC_{50} ± SEM (% eff)	Rat H_4 FLIPR pK_b ± SEM or pEC_{50} ± SEM (% eff)
1	Ph	H	2		7.24 ± 0.02	7.26 ± 0.07
2	H	H	2		6.57 ± 0.02	6.46 ± 0.11 (80%)
3	Ph	H	2		7.88 ± 0.27	8.24 ± 0.24
4	Ph	H	1		7.52 ± 0.11	7.28 ± 0.21 (49%)
5	Ph	H	1		8.04 ± 0.06	7.61 ± 0.10 (47%)
6	Ph	H	1		7.34 ± 0.03	<7.34[b]
7	Ph	H	2		7.88 ± 0.05	7.51 ± 0.08
8	Ph	H	2		7.57 ± 0.05	7.26 ± 0.06 (84%)
9	Ph	H	2		7.59 ± 0.08	7.97 ± 0.20
10		H	2		6.31 ± 0.05	6.37 ± 0.02
11		H	2		5.63 ± 0.07	<5.44[b]
12		H	2		5.37 ± 0.005	<4.91[b]
13	H	Ph	2		7.17 ± 0.06	7.37 ± 0.13
14	H	Ph	2		6.61 ± 0.05	6.84 ± 0.16
15	H	Ph	2		7.15 ± 0.09	7.73 ± 0.15

[a] $n \geqslant 2$.
[b] $n = 1$.