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Identification of a Dual Histamine H_1/H_3 Receptor Ligand Based on the H_1 Antagonist Chlorpheniramine

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Abstract—Combining the first generation H_1 antihistamine chlorpheniramine (**1**) with H_3 ligands of the alkylamine type has led to the identification of compound **9d**, a dual ligand of both the H_1 and H_3 receptors.

The histamine H_3 receptor is a presynaptic autoreceptor that controls the release of histamine as well as other neurotransmitters such as acetylcholine and norepinephrine.[1] Most of the interest in the therapeutic use of H_3 receptor antagonists and agonists has been in the CNS area, including treatment of cognition disorders, obesity, and sleep-related disorders.[2] We, however, have been interested in their use for the treatment of allergic diseases, in particular nasal congestion. We previously demonstrated that the combination of the selective H_1 antagonist chlorpheniramine (**1**) with the selective H_3 antagonist thioperamide prevented congestion in a histamine-driven model of nasal congestion in the cat.[3] We became interested in determining if a dual antagonist of these receptors could be designed. There is ample precedent in the histamine literature that supports the concept of dual antagonism in which one of the receptors is the H_1 receptor. These include, among others, dual PAF/H_1 antagonists, NK_1/H_1 antagonists, H_1/H_2 antagonists and LTD_4/H_1 antagonists.[4] Recently, examples of dual H_1/H_3 antagonists have also been reported although these were not originally designed to be dual antagonists.[5] This paper describes our efforts towards the identification of a dual antagonist of the H_1 and H_3 receptors based on the first-generation H_1 antagonist chlorpheniramine.

Chlorpheniramine (**1**) is a potent antagonist of the human H_1 receptor ($K_i = 2$ nM).[6] Our approach for the design of dual H_1/H_3 ligands based on chlorpheniramine envisioned the coupling of H_3 ligands of the alkylamine class (**2**)[7] via the amine moieties that are common to both (Fig. 1). Optional linking groups on either side of the amine moiety provided further opportunity to introduce diversity into the molecules.

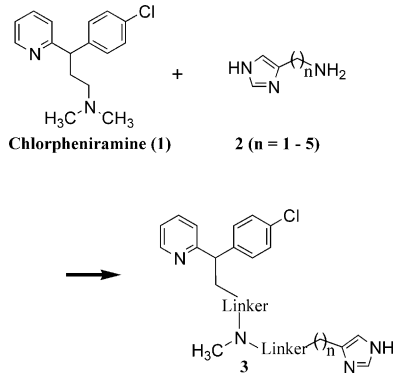

Figure 1.

The preparations of the putative dual H_1/H_3 ligands are given in the following Schemes. Analogues in which $n = 2$ or 4 possessing either an amide linker or a straight alkyl chain were prepared as shown in Schemes 1 and 2 (exemplified for $n = 4$). Wittig olefination of the known ketone **4** gave a 1:1 mixture of olefin isomers **5**. Although these could be separated via column chromatography, the mixture was reduced directly to give the ester **6**. The ester **6** was converted to the amides **7** by treatment with the Weinreb reagent[8] formed from the alkylamine[7] and Me_3Al. Removal of the triphenylmethyl (Tr) protecting group on the imidazole ring

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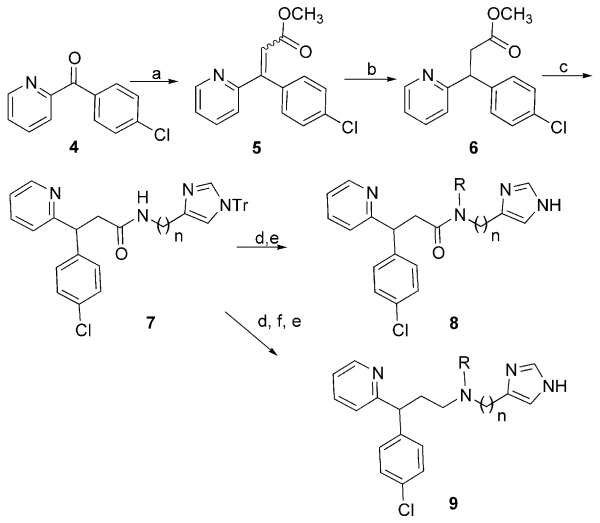
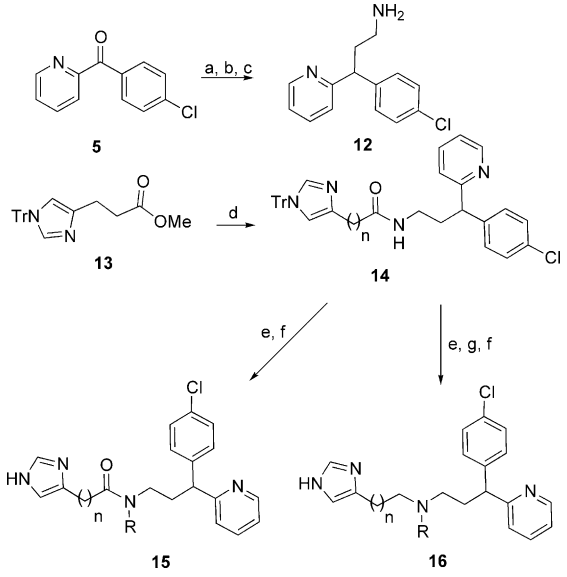
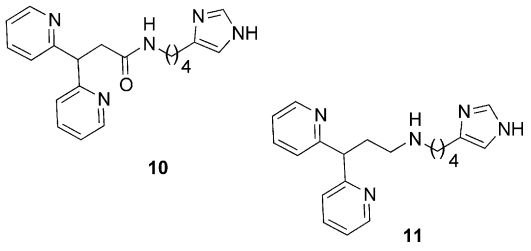
gave the amide analogues **8** (R = H). Alternatively, the amide nitrogen was alkylated followed by deprotection of the imidazole ring to give **8** (R = CH_3). Reduction of the amide **7** followed by deprotection gave the amine analogues **9**. In an analogous manner, amide **10** and amine **11** were prepared.



Scheme 1. (a) $Ph_3PCH_2CO_2CH_3Br$, NaH, THF, 92%; (b) Mg, MeOH, 45%; (c) Me_3Al, aminoalkyl imidazole, toluene, 77%; (d) NaH, MeI, THF, 67% (R = CH_3); (e) 1N HCl, EtOH, 95% (**7** to **8**), 100% (**7** to **9**); (f) $BH_3{\cdot}Me_2S$, THF, 100%.



Scheme 2. (a) Ph_3PCH_2CNBr, NaH, THF, 90%; (b) $NaBH_4$, *i*-PrOH, reflux, 78%; (c) $LiAlH_4$, Et_2O, reflux, 36%; (d) **12**, Me_3Al, toluene, 80%; (e) NaH, MeI, THF, 94% (for R = CH_3); (f) 1N HCl, EtOH, quantitative; (g) $LiAlH_4$, THF, 19%.



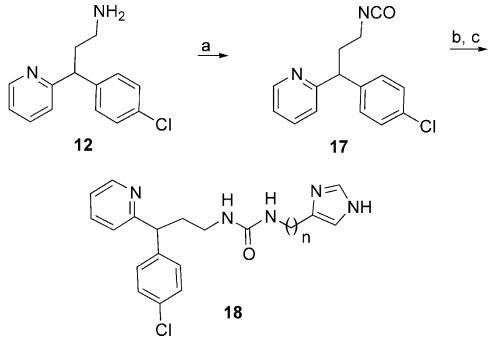
The three-carbon homologues were prepared starting from the known ester **13** (Scheme 2).[9] Horner–Wadsworth-Emmons olefination of **5** followed by reduction of the nitrile and double bond gave amine **12**. This amine was coupled with ester **13** using Weinreb chemistry to give amide **14**. Further manipulation in the same manner as that used to produce analogues in which $n = 2$ or 4 gave the desired targets **15** ($n = 2$) and **16** ($n = 2$).

The synthesis of urea and amidine linked analogues is given in Schemes 3 and 4. Amine **12** was converted to the isocyanate **17** and then coupled with 1-trityl-4-(4-aminobutyl)imidazole to give the urea analogue **18** ($n = 4$) after deprotection.

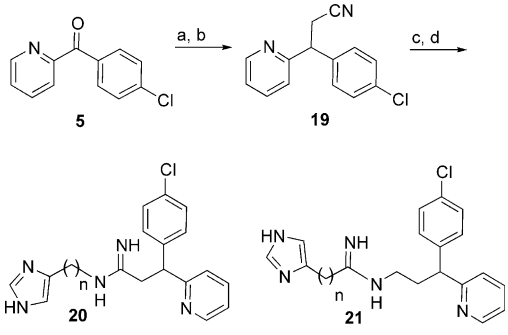
The amidine **20** ($n = 2$) was formed by reaction of the nitrile **19** with the Weinreb amide formed from 1-triphenylmethyl histamine and Me_3Al. Deprotection of the imidazole ring gave the target. In a similar manner, amidine **21** ($n = 3$) was prepared from amine **12** and trityl-protected 3-[4(5)-imidazolyl]butyronitrile.

Compounds were evaluated for H_3 binding affinity using guinea pig brain membranes as described by Korte et. al.[10] and for H_1 binding affinity using the procedure of Tran.[11] These data are presented in Table 1.

Examination of these data indicates that it is easier to maintain H_3 binding affinity than H_1 binding affinity in this series. For example, both neutral linkers like amides



Scheme 3. (a) Triphosgene, pyridine, 100%; (b) aminoalkylimidazole, pyridine, 50%; (c) 1N HCl, EtOH, 90%.



Scheme 4. (a) Ph_3PCH_2CNBr, NaH, THF, 90%; (b) $NaBH_4$, 2-propanol, reflux, 78%; (c) Me_3Al, 1-triphenylmethyl histamine, toluene; (d) 1N HCl, EtOH, 68% for steps c and d.

Table 1. H_1 and H_3 receptor binding affinity

Example No.	*n*	R	K_i (H_1, nM)[a]	K_i (H_3, nM)[a]
8a	2	H	N.A.[b]	16
8b	4	H	N.A.	1
8c	4	CH_3	N.A.	7
8d	2	CH_3	N.A.	1
9a	2	H	600	56
9b	4	H	254	10
9c	5	H	39	33
9d	4	CH_3	7	15
9e	5	CH_3	6	50
10	—	H	N.A.	1
11	—	H	N.A.	4
15a	2	H	N.A.	510
15b	2	CH_3	N.A.	260
16a	2	H	N.A.	240
16b	2	CH_3	10	120
18	4	—	920	23
20	2	—	N.A.	8
21	3	—	201	29

[a]Binding K_i values are the average of at least two independent determinations. The average K_i value for thioperamide in the H_3 assay is 7.3 ± 0.7 nM; the average K_i value for chlorpheniramine in the H_1 binding assay is 2.1 ± 0.2 nM.
[b]N.A., Less than 50% inhibition when screened at 1 μg/mL.[13]

and ureas (Examples **8a**–**d** and **18**) as well as analogues with a basic linker like an amine or amidine (Examples **9b**,**c**, **20** and **21**) display excellent affinity for the H_3 receptor. Interestingly, the amides appear to display higher receptor affinity then the corresponding amines (**8a**–**d** vs **9a**–**d**). Furthermore, binding affinity for the H_3 receptor is sensitive to the carbon chain length between the imidazole ring and the amine linker. The four carbon chain analogues are generally superior to the two, three or five carbon chains. This result differs somewhat from Timmerman's original work in a structurally similar alkylamine series where H_3 affinity peaked with the five-carbon linker.[7]

In contrast to the generally good H_3 binding affinity of this series, H_1 binding affinity is much more sensitive to the nature of the substrate. None of the compounds which incorporate a neutral linker (i.e., amide or urea) display significant H_1 binding affinity. However, incorporating a basic amine into the linking group restores H_1 binding affinity, which is optimum, when the linker is a tertiary amine (Examples **9d**, **9e** and **16b**). This result is consistent with the known structural requirements for a first generation H_1 ligand, namely that a basic amine, capable of interacting with the aspartic acid residue in transmembrane **3**, be present.[12]

In conclusion, a series of compounds has been prepared that combine known pharmacophores of the H_1 and H_3 receptors to determine if dual affinity for the H_1 and H_3 receptors by a single chemical entity is possible. This led to the identification of compounds that in general display very good affinity for the H_3 receptor, but much lower affinity for the H_1 receptor. However, compound **9d**, incorporating a tertiary amine as the linker, displays very good binding affinity for both the H_1 and H_3 receptors (7 and 15 nM, respectively). Compounds such as this may be useful additions to current therapies for the treatment of allergies and nasal congestion.

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