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Identification of a Novel, Orally Bioavailable Histamine H_3 Receptor Antagonist Based on the 4-Benzyl-(1*H*-imidazol-4-yl) Template

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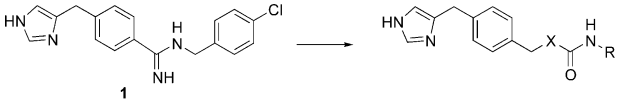
Abstract—A novel series of histamine H_3 receptor antagonists, based on the 4-benzyl-(1*H*-imidazole-4-yl) template, incorporating urea and carbamate linkers has been prepared. Compound **3j** is a selective H_3 antagonist and demonstrates excellent oral plasma levels in the rat and monkey.

Allergic rhinitis is a debilitating disease that affects 10–30% of the US population.[1] Although the sneezing, rhinorrhia, and pruritus associated with this disease are adequately treated with H_1 antihistamines, the nasal congestion that often accompanies it is not.[2] Current therapies for the treatment of congestion include oral decongestants such as pseudoephedrine, topical decongestants such as oxymetazoline, and nasal steroids. These treatments are effective, but all have drawbacks. Therefore, new methods for the treatment of nasal congestion should be an important therapeutic advance.

Recent evidence supports the idea that the combination of an H_1 antagonist with an H_3 antagonist acts as a nasal decongestant.[3] During a nasal allergic reaction, the actions of histamine released from mast cells are not blocked by H_1 antihistamines alone, which primarily prevent plasma extravization and mucus secretion. In the periphery, H_3 receptors found on sympathetic nerves modulate sympathetic neurotransmission.[4–6] Mast cell derived histamine may contribute to nasal congestion by promoting vascular engorgement (i.e., vasodilatation) through activation of prejunctional H_3 receptors that regulate the release of norepinephrine, an endogenous neurotransmitter that maintains vascular tone. H_3 blockade should reestablish the release of norepinephrine and result in vasoconstriction (decongestion). This hypothesis has been demonstrated in a histamine-driven cat model of nasal congestion.[7] Based on this data, we have undertaken a project to discover a novel, selective H_3 antagonist that can be used in combination with an H_1 antihistamine for the treatment of the nasal congestion associated with seasonal or perennial allergic rhinitis. This paper describes the synthetic efforts that have led to the identification of a novel, orally bioavailable H_3 antagonist based on the 4-benzyl-(1*H*-imidazol-4-yl) scaffold.[8]

Initial efforts from our lab identified the novel amidine **1** as a potent and selective H_3 antagonist in vitro using guinea pig brain membranes.[8] Additionally, **1** was active in vivo in a guinea pig model[9] when dosed intravenously ($ED_{50} = 0.3$ mg/kg).



1

K_i (H_3) = 16 nM
ED_{50} (guinea pig) = 0.3 mg/kg, i.v.
AUC (p. o., 10 mg/kg) = 0 h•ng/mL (rat)

3 X = N
5 X = O

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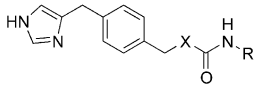
However, when dosed orally in the rat, the plasma AUC of **1** was zero. We reasoned that the poor plasma levels observed with **1** might be due to its dibasic nature, which could potentially decrease its absorption, and that removal of one of the basic groups might lead to improved pharmacokinetics. Because the 4-substituted imidazole ring is usually necessary for good H_3 activity,[10] we focused our efforts on replacing the amidine moiety with neutral linkers. A survey of a number of potential linkers and chain lengths led to the identification of the ureas **3** and carbamates **5** as moieties that conferred good H_3 potency and novelty. Members of the structural classes **3** and **5** were prepared and tested for H_3 binding affinity and oral pharmacokinetics.

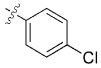
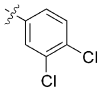
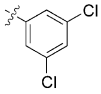
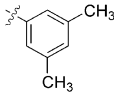
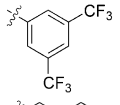
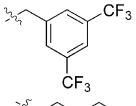
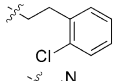
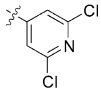
Scheme 1 outlines the synthesis of the urea and carbamate analogues **3** and **5**. The synthesis of the key intermediate **2** has been previously described (Tr is triphenylmethyl).[8] Reduction of the nitrile of **2** using Raney-nickel gave the primary amine. Reaction of the amine with a variety of isocyanates and deprotection gave the ureas **3**. The carbamate analogues **5** were prepared from **2** via hydrolysis of the nitrile to the carboxylic acid followed by esterification. The ester was reduced to the carbinol and reacted with an isocyanate to give the carbamate **5** after deprotection. Compounds were evaluated for H_3 binding affinity using guinea pig brain membranes as described by Korte et al.[11]

Table 1 gives the structures and H_3 binding affinity for urea analogues **3** and carbamate analogues **5**.[11] The initial conclusion to be drawn from these data is that a urea or carbamate linker is a suitable replacement for the amidine group in **1**. Therefore, in agreement with the observation of others,[12] a basic moiety in the side chain of this series of H_3 antagonists is not necessary for good H_3 binding. This observation is consistent with a recently proposed pharmacophore model in which the amidine moiety of a homologue of **1** did not interact with two putative hydrogen-bonding sites on the H_3 receptor.[13] Apparently, it is not so much the basic nature of the linker that matters as the spacial orientation it imposes on the molecule. As further corroboration of this hypothesis, both the urea and carbamate linkers generally display similar H_3 binding profiles for the same R group.

The nature and position of the substituents around the aromatic ring of the carbamate and urea also play a role in the binding profile of these analogues. Compounds that lack an aromatic group **R** or in which the aromatic ring is unsubstituted or ortho substituted were less active (e.g., **3a**,**e** and **5b**). Optimum binding was obtained with substituents in the 3- or the 3,5-positions of the aromatic ring for both the urea and carbamate analogues (e.g., **3d**, **5d**, **3g**, **3i**, **3j**, **5j**, and **3p**). Spacing the aromatic ring an additional one or two carbons from the linker decreased potency (e.g., **3m**, **3n**, and **3o**). Heterocyclic substitution was also unfavorable if the heterocycle was unsubstituted (e.g., **3p** and **3q**). However, introduction of the 3,5-substitution pattern on the heterocycle reestablishes a good binding profile (e.g., **3r**).

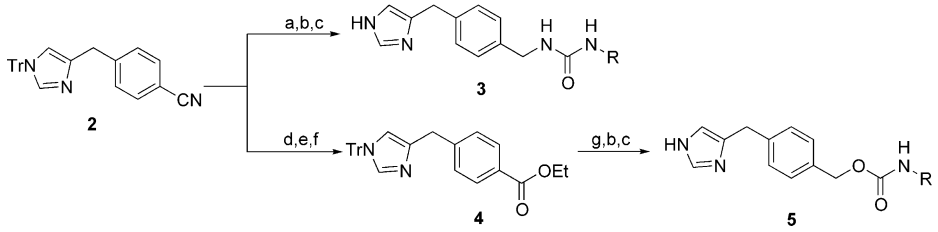
Table 1. H_3 binding affinity of compounds **3** and **5**



Example no.	X	R	K_i (nM)[a]
3a	NH	H	NA[b]
5b	O		37
3c	NH		21
5c	O		25
3d	NH		6
5d	O		7
3e	NH		32
3f	NH		18
3g	NH		5
3h	NH		16
3i	NH		7
5i	O		18
3j	NH		4
5j	O		5
3k	NH		9
3l	NH		22
3m	NH		NA
3n	NH		90
3o	NH		430
3p	NH		NA
3q	NH		270
3r	NH		3

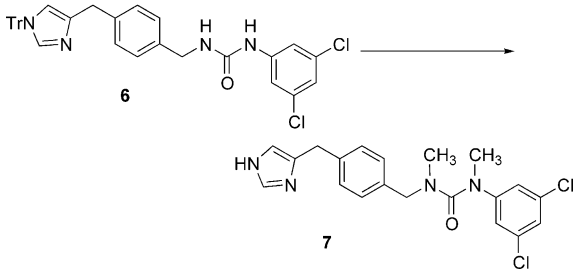
[a]H_3 binding K_i values are the average of at least two independent determinations. The assay-to-assay variation was generally ±2-fold. The average K_i for the standard H_3 antagonist thioperamide in this assay is 7.3±0.7 nM.

[b]NA = Less than 50% inhibition when screened at 1 μg/mL.[11]

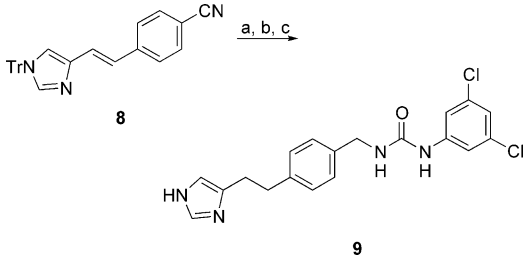


Scheme 1. Reagents and conditions: (a) H_2, Ra-Ni, MeOH/NH_3, 85%; (b) RNCO, pyridine; (c) 1 N HCl/MeOH; (d) 2 N NaOH, EtOH; (e) H_2SO_4, EtOH; (f) trityl chloride, Et_3N, 57% for steps d, e, and f; (g) DIBAl-H, THF, 94%. See Table 1 for the definition of R.

Having established the 3-substitution or 3,5-disubstitution patterns as optimal on the aromatic ring of the urea or carbamate, and aniline analogues as superior to the corresponding benzyl or phenethyl derivatives, we next explored the SAR of the core region of this structure. We chose the potent urea analogue **3j** as the template for this investigation and prepared analogues **7**, **9**,[14] **12**, and **14** (Schemes 2–5).

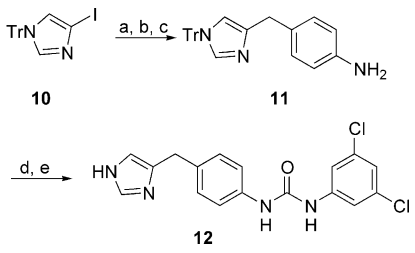


Scheme 2. (a) NaH, THF, CH_3I, 96%; (b) 1 N HCl, MeOH, 83%.

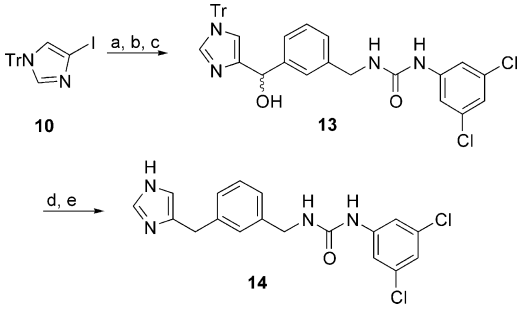


Scheme 3. (a) H_2, Ra-Ni, NH_3/MeOH; (b) 3,5-$Cl_2C_6H_4NCO$, CH_2Cl_2, 25% for two steps; (c) HCl/dioxane, 81%.

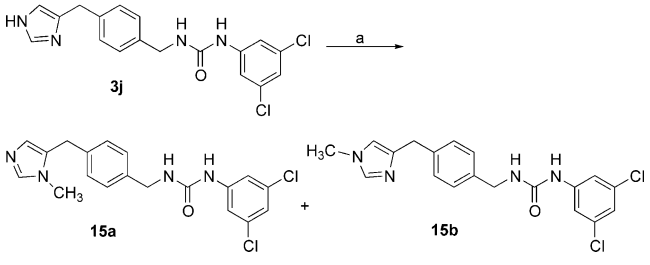
In general, the core region is not amenable to structural change. Methylation of the urea nitrogens led to a decrease in binding affinity (**7**, $K_i = 370$ nM). Elongation of the carbon chain between the imidazole and phenyl rings (**9**) or truncation of the chain between the central phenyl ring and the urea nitrogen (**12**) also led to decreased binding affinity ($K_i = 120$ nM and 36% inhibition at 1 μg/mL respectively[11]). Shifting the point of attachment on the central phenyl ring from a 1,4-configuration to a 1,3-configuration also had a negative impact on activity (**14**, 33% inhibition at 1 μg/mL[11]). These results are consistent with those seen for similar compounds in the amidine series.[8]



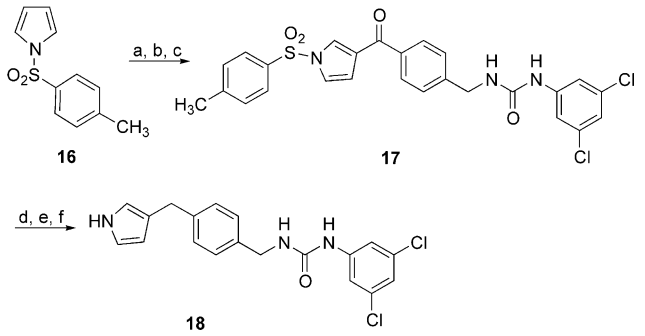
Scheme 4. (a) EtMgBr, CH_2Cl_2, 4-$NO_2C_6H_4CHO$, 75%; (b) Ac_2O, pyridine, CH_2Cl_2 (c) H_2, $Pd(OH)_2$/C, HOAc 50% for steps b and c; (d) HCl/ MeOH; (e) 3,5-$Cl_2C_6H_4NCO$, THF, 66% for steps d and e.



Scheme 5. (a) EtMgBr, CH_2Cl_2, 4-NCC_6H_4CHO, 66%; (b) H_2, Ra-Ni, NH_3/MeOH, 99%; (c) 3,5-$Cl_2C_6H_4NCO$, THF, 50%; (d) NaI, Me_2SiCl_2, acetone/CH_2Cl_2, 54%; (e) maleic acid, MeOH/CH_2Cl_2, 92%.

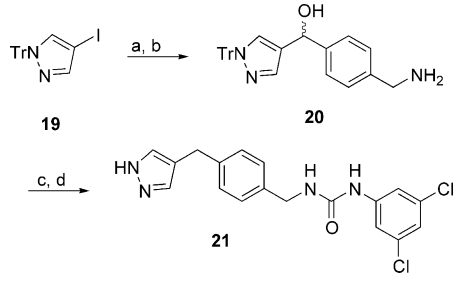


Scheme 6. (a) CH_3I, CH_2Cl_2/MeOH, Et_3N, 40 °C, 19%.

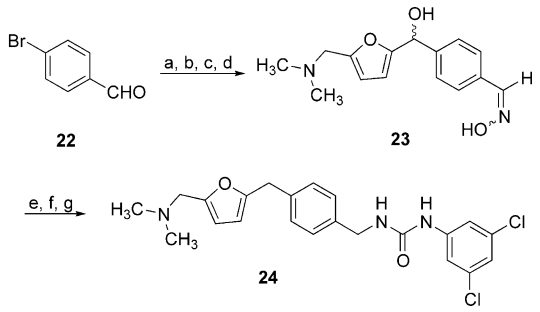


Scheme 7. (a) $AlCl_3$, dichloroethane, 4-NCC_6H_4COCl, 54%; (b) H_2, Ra-Ni, $MeOH/NH_3$, 49%; (c) 3,5-$Cl_2C_6H_4NCO$, THF, 73%; (e) $NaBH_4$, MeOH/THF, 99%; (e) Me_2SiCl_2, NaI, CH_2Cl_2/acetone, 72%; (f) NaOH, MeOH/dioxane/H_2O, 69%.

We next turned our attention to the imidazole moiety. Despite some recent, notable exceptions,[15] it is generally true that a 4-substituted imidazole ring is necessary for good H_3 binding affinity and that substitution of the ring or replacement with other heterocycles leads to loss of activity.[10] This was indeed the case with this series as substitution of the imidazole nitrogens with methyl (**15a** and **b**, Scheme 6)[16] or replacement of the imidazole ring by other heterocycles such as pyrrole **18** (Scheme 7), pyrazole **21** (Scheme 8) or the furan moiety found in the H_2 receptor antagonist ranitidine, **24** (Scheme 9), abolished activity.



Scheme 8. (a) *t*-BuLi, THF/Et_2O, 4-NCC_6H_4CHO, 55%; (b) H_2, Ra-Ni, $MeOH/NH_3$, 91%; (c) 3,5-$Cl_2C_6H_4NCO$, THF, 88%; (d) Me_2SiCl_2, NaI, CH_2Cl_2/acetone, 53%.



Scheme 9. (a) $HOCH_2CH_2OH$, *p*-TSA, toluene, 95%; (b) Mg, THF, 5-dimethylaminomethylfuraldehyde, 19%; (c) HCl/H_2O/MeOH; (d) $NH_2OH{\cdot}HCl$, MeOH, 36% for steps c and d; (e) H_2, Ra-Ni, EtOH, 90% crude; (f) 3,5-$Cl_2C_6H_4NCO$, THF, 36%; (g) TFA, Et_3SiH, CH_2Cl_2, 65%.

Table 2. Pharmacokinetic parameters for **3j**

	Rat	Monkey
Dose (mg/kg)[a]	10	3
AUC (μg·h/mL)	18.1	12.6
C_{max} (μg/mL)	1.5	1.7
$t_{1/2}$ (h)	—	4.4
Bioavailability	—	44%

[a]Crystalline **3j** dosed in methyl cellulose.

Based on its favorable H_3 binding affinity, **3j** was further screened against other G-protein coupled receptors, including the H_1, H_2, and M_{1-5} receptors and was inactive at the highest dose tested (1 μM).[17] It did however show α_{2a} activity (207 nM), dopamine uptake antagonism (805 nM) and imidazoline I_2 activity (155 nM). The oral pharmacokinetics of **3j** were ascertained in the rat and monkey (Table 2). Unlike the amidine **1**, the urea **3j** exhibited very good pharmacokinetics in both the rat and monkey.

In conclusion, exchanging the basic amidine linker of **1** with a neutral urea or carbamate linker led to the identification of a new series of H_3 receptor antagonists exemplified by the urea **3j**. Compound **3j** is a potent and selective H_3 receptor antagonist showing no activity against the H_1 or H_2 receptors. More significantly, **3j** displays good oral pharmacokinetics in the rat and monkey, which supports the hypothesis that the basic amidine moiety was the source of the poor pharmacokinetic profile seen in **1**. The full biological profile of **3j** will be published in due course.

Acknowledgements

The authors would like to thank the Drug Metabolism and Pharmacokinetics group for determining the pharmacokinetic profile of compounds **1** and **3j**.

References and Notes

1. Galant, S. P.; Wilkinson, R. *Formulary* **1999**, *34*, 1016.
2. Spector, S. *J. Aller. Clin. Immunol.* **1999**, *103*, S386.
3. McLeod, R. L.; Egan, R. W.; Cuss, F. M.; Bolser, D. C. Hey, J. A. In *Progress in Respiratory Research*; Hansel, T. T., Barnes, P. J., Eds.; Karger: Basel, 2001; Vol. 31, p 133.
4. Koss, M. C.; Hey, J. A. *Naunyn Schmiedeberg's Arch. Parmacol.* **1992**, *346*, 208.
5. McLeod, R. L.; Gertner, S. B.; Hey, J. A. *Br. J. Pharmacol.* **1993**, *110*, 553.
6. McLeod, R. L.; Gertner, S. B.; Hey, J. A. *Gen. Pharmacol.* **1996**, *27*, 1001.
7. McLeod, R. L.; Mingo, G. G.; Herczku, C.; DeGennaro-Culver, F.; Kreutner, W.; Egan, R. W.; Hey, J. A. *Am. J. Rhinol.* **1999**, *13*, 391.
8. Aslanian, R.; Brown, J. E.; Shih, N.-Y.; Mutahi, M. wa; Green, M. J.; She, S.; Del Prado, M.; West, R.; Hey, J. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2263.

9. Hey, J. A.; Del Prado, M.; Egan, R. W.; Kreutner, W.; Chapman, R. W. *Br. J. Pharmacol*. **1992**, *107*, 347.
10. De Esch, I. J.; Timmerman, H.; Menge, W. M. P. B.; Nederkoorn, P. H. J. *Arch. Pharm. Pharm. Med. Chem*. **2000**, *333*, 254.
11. Korte, A. K.; Myers, J.; Shih, N.-Y.; Egan, R. W.; Clark, M. A. *Biochem. Biophys. Res. Commun*. **1990**, *168*, 979. Compounds are screened at a concentration of 1 μg/mL and those demonstrating greater than 50% inhibition are submitted for a K_i determination.
12. See for example Stark, H.; Sadek, B.; Krause, M.; Huls, A.; Ligneau, X.; Ganellen, C. R.; Arrang, J.-M.; Schwartz, J.-C.; Schunack, W. *J. Med. Chem*. **2000**, *43*, 3987.
13. De Esch, I. J. P.; Mills, J. E. J.; Perkins, T. D. J.; Romeo, G.; Hoffmann, M.; Wieland, K.; Leurs, R.; Menge, W. M. P. B.; Nederkoorn, P. H. J.; Dean, P. M.; Timmerman, H. *J. Med. Chem*. **2001**, *44*, 1666.
14. Compounds **8** and **10** are prepared according to ref 8 and Aslanian, R. G.; Green, M. J.; Shih, N.-Y. U.S. Patent 5,578,616 and Aslanian, R. G. U.S. 5,990,147.
15. (a) Ganellin, C. R.; Leurquin, F.; Piripitsi, A.; Arrang, J.-M.; Garbarg, M.; Ligneau, X.; Schunack, W.; Schwartz, J.-C. *Arch. Phar. Med. Chem*. **1998**, *331*, 395. (b) Meier, G.; Apelt, J.; Reichert, U.; Graßmann, S.; Ligneau, X.; Elz, S.; Leurquin, F.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W.; Stark, H. *Eur. J. Pharm. Sci*. **2001**, *13*, 249. (c) Linney, I. D.; Buck, I. M.; Harper, E. A.; Kalindjian, S. B.; Pether, M. J.; Shankley, N. P.; Watt, G. F.; Wright, P. T. *J. Med. Chem*. **2000**, *43*, 2362.
16. The imidazole isomers **15a** and **15b** are separated using silica gel chromatography eluting with 90% CH_2Cl_2/10% MeOH saturated with NH_3.
17. Screened by MDS Panlabs, PO Box 26–127, Taipei, Taiwan (106), ROC.