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FROM HISTAMINE TO IMIDAZOLYLALKYL-SULFONAMIDES: THE DESIGN OF A NOVEL SERIES OF HISTAMINE H3-RECEPTOR ANTAGONISTS.

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Abstract: Histamine was converted to a selective histamine H_3-receptor antagonist by capping the primary amine with 2-naphthalenesulfonyl chloride. Higher receptor affinity and lower variability in the data from the various bioassays were achieved with the 2-naphthalensulfonamides of histamine homologues.

Introduction

Blockade of the action of histamine has been a beneficial therapeutic route for a number of disease states, throughout the twentieth century. The commercially available histamine receptor antagonists act at H_1- and H_2-receptor subtypes. The therapeutic potential of drugs acting at the third histamine receptor subtype, H_3,[1] has yet to be realised.[2] Our search for novel H_3-receptor antagonists began with the natural receptor hormone, histamine, and the hope that it would be possible to disentangle the elements responsible for affinity and efficacy. The importance of the imidazole group has been demonstrated by most of the successful inventors of histamine H_3-receptor antagonists, which has left the aminoalkyl portion of histamine as the site of greatest variation and exploration.[3] The alkyl chain has commonly been extended by one or more carbon atoms or incorporated into a cyclic system. The amine group has either been incorporated into or replaced by one of a large number of polar groups. In the majority of cases, the polar group has served to link the alkyl chain, or its equivalent, to a lipophilic "capping" group. The nature of the optimum lipophilic capping groups has varied with the polar groups.

Our initial interest was to develop histamine H_3-receptor antagonists specifically designed to act at receptors located in the peripheral nervous system. The sulfonamide group is ubiquitous in medicinal chemistry and its presence is often associated with increased bioavailability and increased water solubility relative to other polar groups, such as amides. The sulfonamide group offers a high degree of metabolic stability and a high density of hydrogen bond donor and acceptor sites. Thus, we sought to incorporate these properties into a series of novel compounds [4,5] by capping the amino terminus of histamine with a variety of sulfonyl chlorides. We made a similar examination of higher homologues of histamine.[4]

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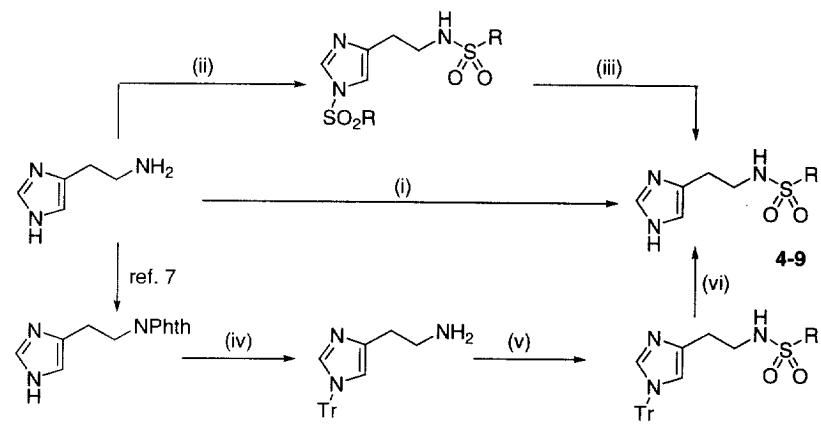
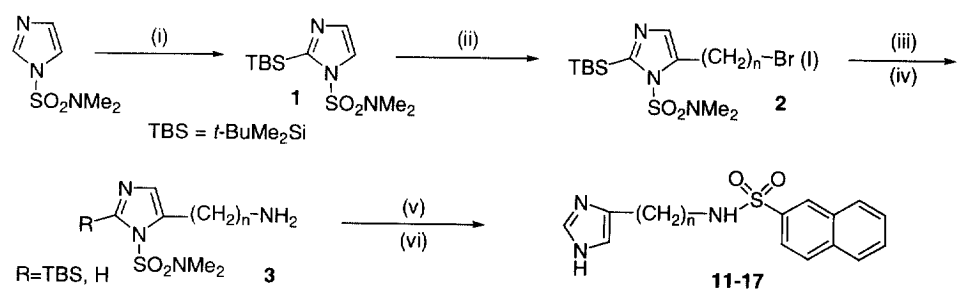
Chemistry

The histamine derivatives were prepared from histamine itself, using one of three routes (Scheme 1). The sulfonamides were prepared directly, although in frequently low yields, from the reaction of histamine with a single equivalent of the sulfonyl chloride.[6] The use of two equivalents of the sulfonyl chloride resulted in sulfonylation of the imidazole, and the additional sulfonyl group was subsequently removed under basic conditions.[6] A more protracted, but less capricious route, relied on the differential protection of the two reactive nitrogen atoms. Phthalimoyl histamine was prepared from histamine according to literature precedent.[7] The imidazole nitrogen was protected with a trityl group, and the primary amine was unmasked. The sulfonamide was formed in the usual manner, and deprotection of the imidazole under acidic conditions led to the final compounds. The relative merits of each route depend on the sulfonyl chloride and we have used all three, as the syntheses necessitated.



Scheme 1. (i) RSO_2Cl (1 equiv.), Et_3N, DMF; (ii) RSO_2Cl (2 equiv.), Et_3N, CH_2Cl_2; (iii) Na_2CO_3, H_2O, EtOH; (iv) (a) Ph_3CCl, Et_3N, CH_2Cl_2, (b) $NH_2NH_2.H_2O$, EtOH, reflux; (v) RSO_2Cl, Et_3N, CH_2Cl_2; (vi) CF_3CO_2H.



Scheme 2. (i) (a) *n*-BuLi, THF, (b) TBSCl; (ii) (a) *n*-BuLi, THF, (b) $Br(CH_2)_nBr$ ($Cl(CH_2)_nI$); (iii) KNPhth, DMF, 100°C; (iv) $NH_2NH_2.H_2O$, EtOH, reflux; (v) 2-NaphthSO_2Cl, Et_3N, CH_2Cl_2; (vi) 2M HCl, EtOH, reflux.

The key amines (**3**) for the histamine homologues were prepared according to an established route (Scheme 2),[8] although the approach has evolved sufficiently in our hands to be worthy of further comment. 1-

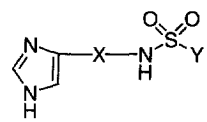
(*N*,*N*-Dimethylsulfamoyl)imidazole can be converted in a one-pot procedure to the alkylated compounds **2**. However, we achieved greater efficiency and more reproducible yields when the 2-silyl protected compound **1** was isolated, and the alkylation step was performed as a separate reaction. The differential reactivity of α-chloro-ω-iodoalkanes is a desirable feature, but in practice these reagents require a separate synthesis and the alkylations were achieved in a satisfactory manner with commercially available α,ω-dibromoalkanes. The product was usually accompanied by a small amount of dimer, from which it was easily separated. The alkylated product **2** is reported to react with potassium phthalimide to give, on deprotection, compound **3** (R=TBS).[8] However, we found that this reaction usually occurred with extensive removal of the silyl group. With two equivalents of wet potassium phthalimide complete desilylation was observed. The use of dried solvents and reagents resulted in a mixture of the two products. However, both the silylated (**3**, R=TBS) and desilylated (**3**, R=H) materials were carried successfully through the remainder of the synthesis. The amines **3** were converted to sulfonamides and deprotected.

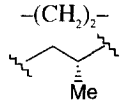
Results and Discussion

The compounds were evaluated in the guinea pig isolated ileum assay,[9a] in which H_3-receptors mediate inhibition of neurogenic contractions,[9b] and radioligand binding assays using guinea pig cerebral cortex and guinea pig ileal longitudinal muscle myenteric plexus (LMMP) membranes.[10] The radioligand binding ileal LMMP assay was developed to reduce any inter-tissue receptor differences as a potential source of the disparity between the functional and binding assays. Data for histamine and the selective H_3-receptor agonist (*R*)-α-methyl-histamine[11] are given in the Table. For both agonists the affinity measured in the cortex binding assay was greater than the $p[A]_{50}$ value from the ileum functional assay. Moreover, this difference was still apparent for these two agonists on using common tissue for the functional and binding assays, and for (*R*)-α-methyl-histamine it was substantial. Although the difference could be attributed to a number of sources, it is well-established that agonists can express high affinity binding in radioligand binding assays.[12] Previously,[10a] we have examined several ligands that were described in the literature[13,14] either as H_3-receptor agonists or antagonists on these assays. We found that the agonists and several of those pre-classified as antagonists expressed differences between the assays. In fact closer examination of some of the 'antagonist' ligands revealed that they expressed partial agonist activity at the H_3-receptor.[14,15,16] Therefore, we concluded that the difference between functional and radioligand binding assays could be viewed a measure of efficacy inherent in the molecules, even if agonism was not always detectable in the functional assay.[17] As it is well-known that the expression of efficacy is tissue-dependent,[18] we sought to design ligands with minimal residual efficacy to avoid the possible expression of inappropriate agonist activity in other experimental or clinical situations. Thus, in our search for an antagonist, we set both a low inter-assay difference and a high receptor affinity as our primary criteria for compound evaluation and selection.

We prepared many sulfonamide derivatives of histamine and representative examples (**4–9**) are given in the Table. The methanesulfonamide **4** behaved as a partial agonist in the functional guinea pig ileum assay. However, the efficacy of the natural hormone was effectively overcome by the higher sulfonamides, most notably the 2-naphthalenesulfonamide **9**. The functional/radioligand binding assay difference, which was in the order of 1 log unit throughout this series, was brought into sharp relief by *trans*-styrenesulfonamide **6**.

Table. Sulfonamide derivatives of histamine and its homolgues.



Cpd[a, b]	X	Y	G.P. Cortex $pK_i \pm SEM$ (n)[c]	G.P. LMMP $pK_i \pm SEM$ (n)[d]	G.P. Ileum $pK_B' \pm SEM$[e]
histamine	–	–	9.84±0.14 (6)	7.98±0.16 (7)	7.15±0.16[f,g]
(*R*)-α-methyl-histamine	–	–	10.07±0.16 (8)	9.82±0.09 (9)	7.94±0.10[f,g]
4	$-(CH_2)_2-$	Me	7.07±0.33 (6)	6.73±0.14 (4)	4.77±0.15[h,i]
5	$-(CH_2)_2-$	Bn	5.73±0.13 (4)	5.54±0.15 (4)	<5.00
6	$-(CH_2)_2-$	-CH=CHPh	6.94±0.04 (4)	7.26±0.09 (4)	<5.50
7	$-(CH_2)_2-$	$-CH_2$-2-naphth	6.31±0.22 (5)	5.94±0.11 (4)	<5.00
8	$-(CH_2)_2-$	$-(CH_2)_2C_6H_{11}$	7.79±0.22 (5)	7.55±0.21 (4)	5.87±0.21
9	$-(CH_2)_2-$	2-naphth	7.85±0.10 (5)	7.77±0.16 (4)	6.70±0.10
10		2-naphth	8.99±0.26 (6)	8.44±0.27 (3)	6.02±0.10[f,g,i]
11	$-(CH_2)_3-$	2-naphth	7.85±0.20 (6)	—	5.93±0.12
12	$-(CH_2)_4-$	2-naphth	7.64±0.10(5)	7.42±0.07 (3)	6.81±0.18
13	$-(CH_2)_5-$	2-naphth	7.83±0.05 (5)	7.50±0.06 (3)	6.96±0.10
14	$-(CH_2)_6-$	2-naphth	7.60±0.15 (4)	7.49±0.25 (3)	7.11±0.24
15	$-(CH_2)_7-$	2-naphth	7.30±0.11 (4)	7.40±0.24 (3)	6.88±0.10
16	$-(CH_2)_8-$	2-naphth	5.99±0.16 (4)	6.97±0.16 (3)	6.62±0.08
17	$-(CH_2)_{10}-$	2-naphth	6.86±0.16 (4)	7.07±0.17 (3)	5.79±0.13

[a] Satisfactory ^1H NMR spectra and elemental analyses were obtained for all new compounds. [b] Compounds **4-17** were tested as maleic acid salts [c] $pK_i \pm SEM$ values were estimated from n separate competition experiments in which [^{3}H]-(*R*)-α-methylhistamine was used to label histamine H_3-binding sites in guinea pig cortical homogenates. [d] $pK_i \pm SEM$ values were estimated from n separate competition experiments in which [^{3}H]-(*R*)-α-methylhistamine was used to label histamine H_3-binding sites in guinea pig ileum LMMP homogenates. [e] $pK_B' \pm SEM$ values were estimated from single shifts of (*R*)-α-methylhistamine concentration–effect curves in the isolated, electrically-stimulated, guinea pig ileum assay, in at least four separate tissues, in which the compounds behaved as surmountable antagonists. [f] $p[A]_{50}$. [g] Full agonist (α=100%) relative to the maximum response of (*R*)-α-methylhistamine. [h] Partial agonist. Compound **4** produced small, but definable responses. [i] The responses of compounds **4** and **10** could be abolished by treatment with a selective concentration of the competitive and reversible H_3-receptor antagonist thioperamide (1μM, which is equivalent to 340-fold the K_B in this assay[9a]). This is consistent with results obtained from a similar experiment with thioperamide, using (*R*)-α-methylhistamine as the selective H_3-receptor agonist.

For **6** the affinity values in the binding assays were comparable to the other compounds, but the compound was inactive in the functional assay at the concentration tested. This may be a consequence, at least in part, of residual efficacy of the molecule. From compounds such as **5**, **7** and **8**, it became apparent that the affinity was dependent on both the nature and disposition of the terminal group. The 2-naphthalenesulfonamide **9** was pre-eminent among the histamine derivatives, and furthermore it was shown to be more than 200 fold selective for the H_3-receptor subtype over the H_1- and H_2-receptor subtypes.[19]

Simple substitution of the alkyl chain of histamine did not further the search for a suitable antagonist,[4] but one example warrants further comment. We reported above that making the 2-naphthalenesulfonamide of histamine (**9**) turned the natural hormone into an antagonist. The same transformation was carried out on (*R*)-α-methylhistamine, and a compound that remained a powerful agonist was produced (**10**). It may be noted that the difference between the radioligand binding and the functional assays was much greater for this agonist (2.5 log units) than it was for its antagonist counterpart (1 log unit), giving further strength to our view on the origins of the differences. The structure of the H_3-receptor remains to be determined and it is only possible to speculate on the chemical nature of the efficacy trigger. However, compounds such as these may eventually further our understanding of the molecular function of this receptor.

We hypothesised that the inter-assay differences for these early compounds may be a consequence of residual efficacy, which could not be detected in the functional assay. For homologues of histamine a simultaneous diminution of efficacy and an increase in affinity has been observed on increasing the length of the alkyl chain.[8] It was hoped that homologues of the histamine sulfonamides would not only have higher affinity but also greater consistency across the assays. The 2-naphthalenesulfonamide group was the most effective cap in the histamine series, and it was chosen as the basis for the extended imidazolylalkyl sulfonamides (Table).

The data from the two radioligand binding assays showed little variation across the series of histamine homologues. Lower affinities, particularly in the functional assay, and higher inter-assay differences were obtained for the shorter and longer compounds (**11** and **17**). Both the lowest inter-assay differences and the highest affinities were observed for compounds of intermediate chain length. This may be illustrated by compound **14**, for which the affinity in the radioligand binding assays was in the order of 0.5 log unit higher than that measured in the functional assay, whereas the corresponding difference for the histamine derivative **9** was in the order of 1 log unit. In compound **14** we have achieved our initial aim of developing a potent H_3-receptor antagonist, based on the polar sulfonamide group, with low inter-assay differences.

We have demonstrated that potent and selective histamine H_3-receptor antagonists may be produced by capping the aminoalkyl arm of histamine and its homologues with 2-naphthalenesulfonyl chloride. We have highlighted further instances where affinity values in the functional assay do not correlate with those from the radioligand binding assays, and we have reported that the length of the chain between the imidazole and the sulfonamide may be a factor in determining the magnitude of the difference. Clearly, compounds with a low or

insignificant difference, such as **14**, merited further synthetic exploration. These studies will be discussed in a forthcoming article.

References and Notes

1. Arrang, J.-M.; Garbarg, M.; Schwartz, J. C. *Nature* **1983**, *302*, 832.
2. Leurs, R.; Blandina, P.; Tedford, C.; Timmerman, H. *TiPS* **1998**, *19*, 177.
3. The design and development of histamine H_3-receptor antagonists has been the subject of a recent review: Stark, H.; Schlicker, E.; Schunack, W. *Drugs Fut.* **1996**, *21*, 507.
4. James Black Foundation patent publication number WO 97/29092, **1997**.
5. Following the patent,[4] a report of sulfonamide homologues of histamine has appeared. Wolin, R.; Connolly, M.; Afonso, A.; Hey, J. A.; She, H.; Rivelli, M. A.; Williams, S. M.; West, Jr., R. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2157.
6. (a) Altman, J.; Shoef, N.; Wilchek, M.; Warshawsky, A. *Isr. J. Chem.* **1986**, *27*, 29. (b) Warshawsky, A.; Altman, J.; Khana, R.; Arad-Yellin, R.; Deshe, A.; Hasson, H.; Shoef, N.; Gottlieb, H. *Synth.* **1989**, 825.
7. Emmett, J. C.; Holloway, F.H.; Turner, J. L. *J. C. S. Perkin I* **1979**, 1341.
8. Vollinga, R. C.; Wiro, W. M. P. B.; Leurs, R.; Timmerman, H. *J. Med. Chem.* **1995**, *38*, 266.
9. (a) Watt, G. F.; Hamilton, L. C.; Shankley, N. P.; Black, J. W. *Br. J. Pharmacol.* **1997**, *122*, 434P. (b) Trzeciakowski, J. P. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 874.
10. (a) Harper, E. A.; Shankley, N. P.; Black, J. W. *Br. J. Pharmacol.* **1997**, *122*, 430P. (b) Harper, E. A.; Gardner, B.; Griffin, E. P.; Shankley, N. P.; Black, J. W. *Br. J. Pharmacol.* **1997** *122*, 431P.
11. Arrang, J.-M.; Garbarg, M.; Lancelot, J.-C.; Lecomte, J.-M.; Pollard, H.; Robba, M.; Schwartz, J. C. *Nature* **1987**, *327*, 832.
12. Kent, R. S.; De Lean, A.; Lefkowitz, R. J. *Mol. Pharmacol.* **1980**, *17*, 14.
13. Stark, H.; Purand, K.; Hüls, A.; Ligneau, Garbarg, M.; Schwartz, J.-C.; Schunack, W. *J. Med. Chem.* **1996**, *39*, 1220.
14. Low, C. M. R.; Vinter, J. G.; Kalindjian, S. B.; Pether, M. J. *Br. J. Pharmacol.* **1997**, *122*, 433P.
15. Watt, G. F.; Sykes, D. A.; Roberts, S. P.; Shankley, N. P.; Black, J. W. *Br. J. Pharmacol.* **1997**, *122*, 435P.
16. Schlicker, E.; Kathmann, M.; Bitschau, H.; Marr, I.; Reidemeister, S.; Stark, H.; Schunack, W. *Naunyn-Schmeideberg's Arch. Pharmacol.* **1996**, *353*, 482.
17. Harper, E. A.; Shankley, N. P.; Black, J. W. *Br. J. Pharmacol.* **1997** *122*, 429P.
18. Kenakin, T. P.; Beak, D. *J. Pharmacol. Exp. Ther.* **1980**, *213*, 406.
19. Histamine H_1-receptor assay:[9a,20] compound **9** was found to be inactive at 30μM in the guinea pig isolated ileum assay. Histamine H_2-receptor assay:[21] compound **9** was found to be inactive at 30μM in the guinea pig right atrium assay.
20. Watt, G. F.; Shankley, N. P.; Black, J. W. *Br. J. Pharmacol.* **1995** *114(suppl.)*, 260.
21. Angus, J. A.; Black, J. W. *Circ. Res.* **1980**, *65*, 1.