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4-CHLOROBENZYL SULFONAMIDE AND SULFAMIDE DERIVATIVES OF HISTAMINE HOMOLOGUES: THE DESIGN OF POTENT HISTAMINE H_3 RECEPTOR ANTAGONISTS

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Abstract: 4-Chlorophenylmethanesulfonamide and (4-chlorobenzyl)sulfamide derivatives of histamine homologues were prepared and found to be potent and selective histamine H_3 receptor antagonists. High receptor affinity and low differences in the data from the bioassays were achieved with the imidazol-4-ylbutyl analogues.

Introduction

Pharmacological evidence for the histamine H_3 receptor was first reported in1983,[1] and many selective antagonists and agonists have since been developed. [2,3] The histamine H_3 receptor has been identified in the central and peripheral nervous systems, and it has been shown to modulate the release of not only histamine, but also several other neurotransmitters. This breadth of possible interactions has created the current level of interest in selective ligands. The therapeutic potential of drugs acting through the histamine H_3 receptor is recognised,[3] and it is evident, from recent reports of early clinical trials, that realisation of this potential is actively being pursued.[4] Our initial aim was to develop histamine H_3 receptor antagonists designed to act specifically at receptors located in the peripheral nervous system. To this end, we have prepared a series of novel histamine H_3 receptor antagonists incorporating the polar sulfonamide group, the 2-naphthalenesulfonamide derivatives of histamine and its homologues (**Figure 1**, m=2–10).[5]

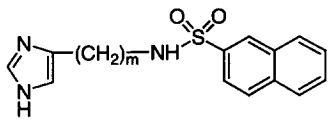

Figure 1

In addition to being selective for the histamine H_3 receptor, with sub-micromolar affinity, members of this series displayed low differences in the apparent affinity measured in the various bioassays, an important

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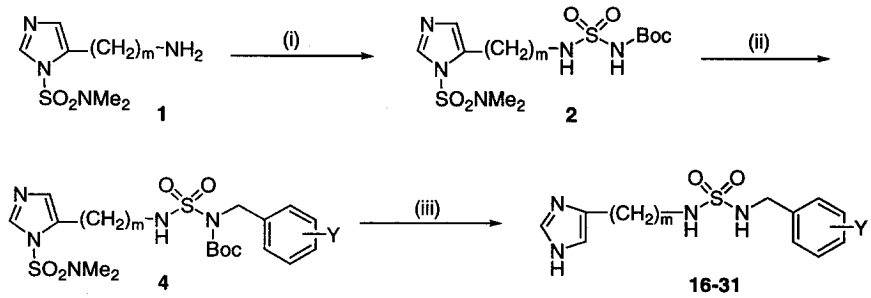
criterion in the evaluation of antagonists. The value of the sulfonamide group has been recently realised by others,[6] who have reported closely related examples that further exemplify our initial invention.[7]

It was found for the 2-naphthalenesulfonamides that there was an optimum length of the imidazolylalkyl chain, both in terms of antagonist affinity and low inter-assay differences in the biological data. An exploration of the sulfonamide substituent was undertaken for the optimal homologues, and it emerged that the 4-chlorobenzyl group provided distinct advantages over the 2-naphthalene or other carbocyclic groups.[7] The 4-chlorobenzyl group has also been the chosen cap for the polar group in the histamine H_3 receptor antagonists clobenpropit[8] and GR 175737.[9] We would like to report, herein, the optimisation of the sulfonamide series through the introduction of the 4-chlorobenzyl group, and its extension to a further series based on the sulfamide group, $-NHSO_2NH-$. The sulfamide was conceived as a more polar alternative to the sulfonamide, with an additional site for functionalisation. Given that both amides[10,11] and ureas[12] have been used in equivalent fashion as histamine H_3 receptor antagonists, it was envisaged that sulfonamides and sulfamides would bear a similar relationship.

Chemistry

The sulfonamides **5–15** were prepared from imidazol-4(5)-ylalkyl-amines (**1**) according to the procedure used for the 2-naphthalenesulfonamides.[5,7] The amines **1** were also the starting point for the sulfamides **16–31** (**Scheme 1**). The key reaction in this sequence was the conversion of the amines **1** to the *t*-butyloxycarbonyl protected sulfamides **2**. In the manner of an existing method,[13] chlorosulfonylisocyanate [CAUTION] was allowed to react with *t*-butanol to give sulfamoyl chloride **3**, which was used to functionalise the amines **1**. The sulfamides were obtained in yields of, typically, 40–60%. Alkylation of **2** occurred selectively at the more acidic NH, and deprotection of the resulting *N,N'*-dialkylsulfamides **4**, under acidic conditions, gave the target compounds **16–31**.



Scheme 1. (i) $ClSO_2NHBoc$ (**3**) (from $ClSO_2NCO$ [CAUTION] and *t*-BuOH), Et_3N, CH_2Cl_2; (ii) (a) NaH, DMF, (b) Y-$C_6H_4CH_2Br$; (iii) 2M HCl, EtOH, reflux.

In addition to the chemistry depicted in **Scheme 1**, the following points, which add flexibility to the synthetic strategy, may be noted. Several alternative routes have been reported for the synthesis of amines such as **1**,[6,14] and we have found that the conditions for the sulfamide synthesis are compatible with various groups used to protect the imidazole, such as triphenylmethyl. The alkylation reaction, used to introduce the benzyl group, was not appropriate for less reactive electrophiles. In these instances, alkylation was achieved using the Mitsunobu reaction with the corresponding alcohol.[15] Furthermore, this approach enabled the sulfamide-forming sequence to be reversed. In these cases, sulfamoylation of the amine of the tail group was followed by a Mitsunobu reaction with the appropriate imidazol-4(5)-ylalkan-1-ol.[7]

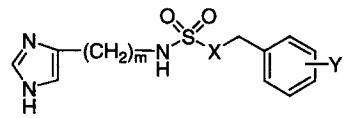
Results and Discussion

The compounds were evaluated in the guinea pig isolated ileum assay,[16a] in which histamine H_3 receptors mediate inhibition of neurogenic contractions,[16b] and in the radioligand binding assay using guinea pig ileal longitudinal muscle myenteric plexus (LMMP) membranes.[17] The choice and interpretation of the assays has been discussed previously,[5] and it is sufficient to note that, together with affinity, minimising the differences in the data between the assays was a primary consideration in evaluating these compounds. The results for the compounds under consideration are presented in **Table 1**.

In optimising the sulfonamide series, many lipophilic capping groups were used for several lengths of imidazol-4-ylalkyl chain.[7] For the 4-chlorophenylmethanesulfonamides, compounds **5–11**, the optimum length was reached at four methylene units (**6**). This was less distinct for the 2-naphthalenesulfonamides.[5] The jump in affinity on increasing the chain length from three (**5**) to four methylene units was followed by a more gradual decline from five to ten methylene units (**7–11**), a trend which was generally apparent in both assays. The impact of chain length on affinity, noted previously for the 2-naphthalenesulfonamides,[5] is readily apparent in the data from the ileum functional assay. For the 2-naphthalenesulfonamides it was also noted that compounds with the extremes of chain length displayed greater inter-assay differences than compounds with alkyl chains of four to seven methylene units. This is borne out by the ten-methylene compound (**11**). For the four-methylene chain, alternatives to equal the 4-chloro-substituent were not found (e.g. **12–15**). The affinities measured for compound **6** represented a thirty-fold improvement over the most potent of the 2-naphthalenesulfonamides. The 4-chlorobenzyl group was consequently chosen as the basis for the series of new sulfamide analogues.

Data from the bioassays for the 4-chlorobenzyl sulfamides of the histamine homologues (**Table 1, 16–22**) paralleled the analogous sulfonamides, with affinities reaching a maximum at an alkyl chain length of four methylene groups (**17**) and declining towards the longer chain lengths. For equal chain lengths, the affinities of the sulfamides were generally several fold greater than the sulfonamides, which was also the case on changing the benzyl substituent (**25, 26, 27, 28**). However, the maximum affinities were identical in both series. The importance of the position of the chloro-substituent was evident from the lower affinities measured for the 2- and 3-chloro variants (**24** and **23**, respectively).

Table 1. Phenylmethanesulfonamide and benzylsulfamide derivatives of histamine homolgues.



Cpd[a,b]	m	X	Y	G.P. LMMP $pK_I \pm SEM$ (n)[c]	G.P. Ileum $pK_B \pm SEM$[d]
5	3	—	4-Cl	—	6.29±0.12
6	4	—	4-Cl	8.53±0.17 (3)	8.62±0.22
7	5	—	4-Cl	7.94±0.06 (3)	7.33±0.10
8	6	—	4-Cl	7.95±0.03 (3)	8.01±0.15
9	7	—	4-Cl	7.44±0.03 (3)	7.36±0.11
10	8	—	4-Cl	7.27±0.14 (3)	6.64±0.21
11	10	—	4-Cl	7.23±0.11 (3)	<5.0
12	4	—	4-Br	—	7.68±0.26
13	4	—	4-CF_3	—	7.89±0.15
14	4	—	4-F	—	7.32±0.14
15	4	—	4-Ph	—	8.10±0.16
16	3	NH	4-Cl	7.28±0.04 (4)	7.04±0.09
17	4	NH	4-Cl	8.56±0.14 (3)	8.68±0.16
18	5	NH	4-Cl	8.23±0.10 (3)	8.20±0.17
19	6	NH	4-Cl	8.36±0.06 (3)	8.77±0.08
20	7	NH	4-Cl	8.15±0.04 (4)	8.37±0.15
21	8	NH	4-Cl	7.88±0.09 (3)	7.37±0.18
22	10	NH	4-Cl	6.02±0.15 (3)	<5.0
23	4	NH	3-Cl	—	7.86±0.12
24	4	NH	2-Cl	—	6.42±0.33
25	4	NH	4-Br	8.71±0.08 (3)	8.91±0.19
26	4	NH	4-CF_3	8.58±0.12 (3)	8.48±0.04
27	4	NH	4-F	7.84±0.08 (3)	7.70±0.09
28	4	NH	4-Ph	8.12±0.15 (3)	8.32±0.15
29	4	NH	4-I	8.68±0.27 (3)	8.49±0.21
30	4	NH	4-OMe	7.58±0.15 (3)	7.06±0.20
31	4	NH	H	—	7.01±0.16

[a] Satisfactory ^1H NMR spectra and elemental analyses were obtained for all new compounds. [b] All compounds were tested as maleic acid salts [c] $pK_I \pm SEM$ values were estimated from n separate competition experiments in which [^3H]-(*R*)-α-methylhistamine was used to label histamine H_3 binding sites in guinea pig ileum LMMP homogenates. [d] $pK_B' \pm SEM$ values were estimated from single shifts of (*R*)-α-methylhistamine concentration–effect curves in the guinea pig isolated, electrically-stimulated, ileum assay, in at least four separate tissues, in which the compounds behaved as surmountable antagonists.

The absence of the 4-chloro-substiuent was deleterious, as judged by compound **31**. However, in contrast to the sulfonamide series, some alternative 4-substituents were well tolerated. In particular, the 4-bromo compound (**25**) was among the most potent members of the sulfamide series, whereas the affinity of the 4-bromo sulfonamide (**12**) in the ileum functional assay was in the order of ten-fold less that of its 4-chloro-counterpart (**6**). The affinities of the compounds with smaller (**31** and **27**) or electron-donating substituents (**30**) were significantly lower than those of compound **17**.

It is evident that the sulfonamide and sulfamide groups are equally suitable as polar linkers between the imidazol-4-ylalkyl and lipophilic capping groups necessary for selective H_3 receptor antagonists.[2] Alkyl chain length has been shown to be an important factor in determining affinity and inter-assay differences. A possible rationale for the observed trends may be that the alkyl chain governs the spatial disposition of the imidazole and 4-chlorobenzyl groups. The optimal disposition was possible at four methylene groups, and the decline in potency with increasing chain length may be attributed to the increasing entropy involved in organising longer chains. From the close correlation in the behaviour of the two series, it may be suggested that the additional NH of the sulfamides did not contribute greatly to the effective length of the alkyl chain. The roles of the imidazole group, the alkyl chain, the polar linker, and the 4-chlorobenzyl group seem, therefore, to be distinct and, to a degree, separable.

In conclusion, we have achieved highly potent H_3 receptor antagonists, with affinities across our bioassays in the nanomolar range. This represents a considerable improvement on the earlier 2-naphthalenesulfonamides. The biological data for these benzyl compounds showed low inter-assay differences, satisfying our selection criteria detailed elsewhere.[5] Additionally, the sulfonamide **6** and the sulfamide **17** were shown to be more than eight thousand-fold selective for the H_3 receptor subtype over the H_1- and H_2 receptor subtypes.[18] The in vitro properties of compounds bearing sulfonamide and sulfamide groups are comparable, and the effect of the additional NH of the sulfamide on the in vivo characteristics is the subject of ongoing investigations.

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