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NOVEL H_3 RECEPTOR ANTAGONISTS. SULFONAMIDE HOMOLOGS OF HISTAMINE

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Abstract: Sulfonamides derived from 4(5)-(ω-aminoalkyl)-1*H*-imidazoles containing chain lengths of three- to five-carbons were synthesized. Good to moderate H_3 receptor binding affinities were observed for several butyl and pentyl homologs, whereas binding affinities were considerably weaker in the propyl series. Separation of the imidazole ring and the sulfonamide unit by a four- or five-carbon tether afforded potent H_3 receptor antagonists.
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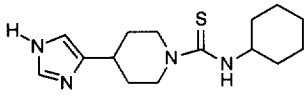
Introduction: To date three major subtypes of histamine receptors have been identified: H_1, H_2, and H_3. The pharmacology regarding the H_1 and H_2 receptor subtypes has been known since the 1960's,[1] however, elucidation of the H_3 receptor by Arrang and coworkers in 1983 is still a relatively new discovery and the precise consequence of inhibiting this receptor has not been fully determined.[2] One of the functions that has been established for the H_3 receptor is its role in the regulation of various neurotransmitters.[3] These receptors which are located on prejunctional nerve terminals in both the central and peripheral nervous systems, have been found to differ significantly in their pharmacology from the H_1 and H_2 subtypes.[4] This finding was borne out from the discovery that thioperamide **I** is a potent and selective H_3 receptor antagonist.[5] However, the thiourea moiety present in **I** has raised toxicology concerns that have hindered determining its possible therapeutic value in a clinical setting.[6]



I, Thioperamide

Subsequently, a great deal of structure–activity relationship (SAR) work has taken place in an effort not only to find a suitable replacement to **I**, but to also understand more accurately the complete physiological functions of this receptor. At the time we initiated our research, there had been only two accounts in the patent literature that investigated the use of sulfonamide derivatives based on the natural ligand histamine as possible H_1 agonists.[7] While a wide range of functionalities has since been evaluated in the development of H_3 antagonists, none has employed the use of sulfonamides in their design.[8] With our present understanding that homologs of histamine behave as H_3 receptor antagonists,[9] coupled with the absence of sulfonamides in SAR development, we set out to fill this gap.[10] Our primary interest in identifying a safe and selective H_3 antagonist was based on the premise that H_3 receptors are present in lung tissue which suggests that they can be regulated to control certain respiratory conditions, such as asthma;[2a] this paper describes some of our results along those lines.

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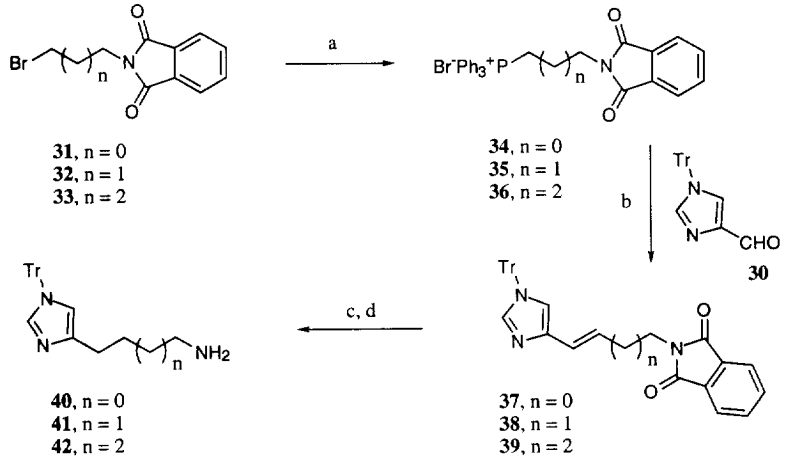
Chemistry: A concise, and high yielding 5 step synthetic sequence similar to that devised by Griffith[11] was employed to prepare the 4(5)-(ω-aminoalkyl)-1*H*-imidazole targets illustrated in Schemes 1–3. Treatment of the commercially available N-(2-bromoethyl)phthalimide, N-(3-bromopropyl)phthalimide, or N-(4-bromobutyl)-phthalimides with triphenylphosphine in CH_3CN provided the corresponding phosphonium salts **34–36**, which were coupled with the imidazole aldehyde **30** to give the Wittig olefination products **37–39** in excellent yield. Hydrogenation of the olefinic bond with 10% Pd/C, followed by liberation of the phthalimide moiety with hydrazine provided the requisite propyl, butyl and pentyl alkylamino-1*H*-imidazoles **40–42**.

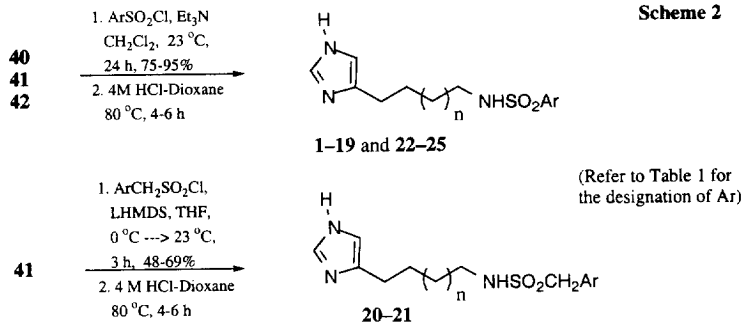
Scheme 1[a]



[a]Reagents and Conditions: (a) Ph_3P, CH_3CN, reflux, 24 h, 95% (b) aldehyde **30**, *t*-BuOK, THF, 0 °C ---> 60 °C, 3 h, 92% (c) 10% Pd/C, THF/MeOH (5:1, v/v), H_2, 45 psi, 1 h, 73% (d) NH_2NH_2, EtOH, 80 °C, 3 h, 92%

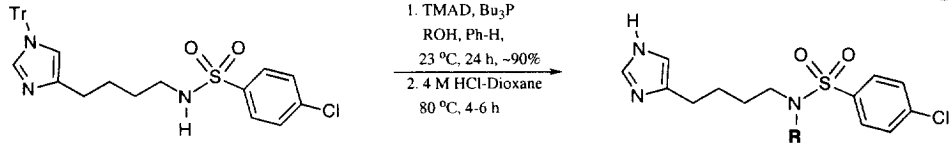
The aryl sulfonamides **1–19** and **22–25** were assembled in standard fashion from the corresponding amines **40–42** using Et_3N in CH_2Cl_2. Poor yields of the benzyl sulfonamides **20–21** were obtained by the above method, and were subsequently prepared using LHMDS in THF which afforded the targets in 48–69% yield.

Scheme 2



The three N-alkylated derivatives **26–28** were prepared by treating compound **43** under modified Mitsunobu conditions using TMAD (N,N, N',N'-tetramethylazodicarboxamide) and Bu_3P in benzene, with the appropriate alcohol providing the alkylated sulfonamides **44–46** in high yield.[12] Twenty-eight different sulfonamides were prepared to evaluate their hydrophobic and electronic effects (Tables 1 and 2).[13]

Scheme 3



43

26, R = CH_3
27, R = CH_2Ph-*p*-Cl
28, R = $CH_2(CH_2)_3$-imidazole

Results: The data provided in Table 1 illustrate several key points. Evaluation of the target compounds as inhibitors of [^{3}H]N$^\alpha$-methylhistamine binding to guinea-pig brain membranes[14] reveals the importance of chain length and binding affinity. For example, focus on the three series that contain the *p*-*t*-butylsulfonamides **4–6**, the *p*-chlorosulfonamides **8–10**, and the *p*-nitrosulfonamides **16–18**. In each of these examples, the chain length was varied from three to five carbons while keeping the sulfonamide moiety constant. The H_3 binding affinities in each of these examples was poor when n = 1, with the weakest K_i value being observed for the *p*-chlorosulfonamide **8**. Increasing the chain length to four carbons (n = 2) improved binding by 2.7x in the *t*-butyl case **4** --> **5**, and 5.6x in the *p*-nitro case **16** --> **17**, and 42x in the *p*-chloro case **8** --> **9**. A further improvement in binding affinities was realized in going from a four- to a five-carbon tether (n = 3); For example, both the *t*-butyl case **5** --> **6** and the *p*-nitro case **17** --> **18** improved by about 3-fold, whereas, the *p*-chloro case **9** --> **10** remained constant. Next, a notable difference in K_i values was observed between compounds containing an electron-withdrawing group and an electron-donating substituent on the aromatic ring. For instance, the *p*-methoxy derivative **7** and the *p*-amino compound **19** both have weaker K_i values by at least a factor of three compared to the other benzene sulfonamide derivatives containing a four-carbon linker. Both heteroaromatic sulfonamides **22** and **24**, displayed slightly weaker binding affinities relative to the benzenesulfonamides containing a butyl spacer. For comparison purposes, the isopropyl sulfonamide **25** was prepared in the butyl series and exhibited comparable binding activity with several of the aromatic sulfonamides. Moreover, none of the derivatives in Table 1 displayed any appreciable affinity for the H_1 receptor. Interestingly, of the fifteen antagonists that possessed pA_2 values above 7.0, only five of those compounds were active as H_3 antagonists *in vivo*.[15] This observation is not unusual, since *in vitro* functional activity does not always translate to the *in vivo* model. A good example of this phenomenon is observed between the *t*-butyl derivatives **5** and **6**, wherein the K_i and pA_2 values for **5** are slightly weaker relative to **6**, but **5** displays better *in vivo* activity.

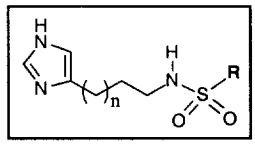


Table 1. H_3 Receptor Affinity and Antagonist Activity for Substituted Sulfonamide Analogs.

Compd	R	n	K_i (H_3) (nM)[a]	K_i (H_1) (%)[b]	pA_2[c]	ED_{50} (mg/kg)[d]
1	phenyl	2	10.5	5	7.5	na
2	phenyl	3	24.5	19	7.2	-
3	phenyl-*p*-CH_3	2	17	0	7.6	16%[e]
4	phenyl-*p*-*t*-Bu	1	45.5	30	-	-
5	phenyl-*p*-*t*-Bu	2	16.5	32	7.8	~3
6	phenyl-*p*-*t*-Bu	3	5	14	8.0	40%[e]
7	phenyl-*p*-OCH_3	2	51	-	-	-
8	phenyl-*p*-Cl	1	380	21	-	-
9	phenyl-*p*-Cl	2	9	48	7.9	2.2
10	phenyl-*p*-Cl	3	11.5	37	7.0	~3
11	phenyl-*m*-Cl	2	8.5	0	7.6	8%[e]
12	phenyl-*p*-F	2	20.5	19	6.8	-
13	phenyl-*p*-CF_3	2	10	1	8.4	~3
14	phenyl-*p*-OCF_3	2	7	0	8.0	na
15	phenyl-*p*-OCF_3	3	24.3	1	8.0	-
16	phenyl-*p*-NO_2	1	93	36	-	-
17	phenyl-*p*-NO_2	2	16.5	24	7.7	na
18	phenyl-*p*-NO_2	3	5.5	25	8.1	2.7
19	phenyl-*p*-NH_2	2	99	-	-	-
20	CH_2-phenyl	2	6	3	7.5	17%[e]
21	CH_2-phenyl-*o*-NO_2	2	42	-	-	-
22	N-Me-(3)-imidazole	2	43	-	-	-
23	2-thienyl	1	550	-	-	-
24	2-thienyl	2	45	-	-	-
25	isopropyl	2	22	0	7.2	-

(a) Inhibition of [^{3}H]N$^\alpha$-methylhistamine binding to guinea-pig brain membranes, ref 14. (b) Determined by an H_1 histamine-mediated bronchospasm, ref 16. (c) H_3 -antagonist potency of electrically stimulated guinea-pig ileum, ref 15. (d) Determined in the CNS hypertension model, ref 17. na = not active; No inhibition was observed at 3 mg/kg dosing. (e) Per cent inhibition obtained at 3 mg/kg dosing. ED_{50} and pA_2 values were not obtained for compounds with H_3 K_i values >20 nM.

The data represented in Table 2 indicate the acidic sulfonamide hydrogen can be replaced with a methyl group as in compound **26** without altering the H_3 binding affinity. However, while the K_i and pA_2 values for the N-methyl derivative **26** are slightly better than for compound **9**, the *in vivo* functional activity did not carry through in this case.[18] In contrast to the N-methyl example, incorporation of a *p*-chlorobenzyl moiety tends to diminish the H_3 binding activity by a factor of ~2x. Surprisingly, when the sulfonamide hydrogen is replaced with a second 4(5)-(4-aminobutyl)-1*H*-imidazole unit (compound **28**) a sharp decline in the H_3/H_1 selectivity ratio (16:1) is observed as the binding affinity towards both receptor subtypes improves. This observation is contrary to what one might expect, since most H_1 antagonists are lipophilic in nature[2c] and compound **28** possesses two highly polar imidazole functions.

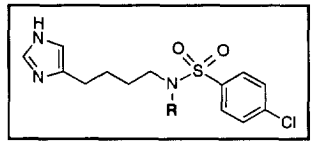


Table 2. H_3 Receptor Affinity and Antagonist Activity for N-alkylated Sulfonamide Analogs.

Compd	R	$K_i(H_3)$ (nM)	$K_i(H_1)$ (%)	pA_2	ED_{50} (mg/kg)
9	H	9	48	7.9	2.2
26	CH_3	4	32	8.3	43%[b]
27	CH_2-Phenyl-*p*-Cl	24	45	7.8	3
28	$CH_2(CH_2)_3$-imidazole	2.5	40 nM[a]	8.1	-

Refer to Table 1 for references to the assay protocols. (a) K_i value is reported as a nM concentration. (b) ED_{50} value is reported as a per cent inhibition at 3 mg/kg dosing.

In summary, we have demonstrated that butyl and pentyl homologs of histamine containing a sulfonamide moiety are potent and selective H_3 antagonists, and may serve as useful tools to further aid in the understanding of the H_3 receptor.

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13. Representative procedure for the preparation of 4-chloro-N-[4-(1*H*-imidazole-4-yl)butyl]benzene-sulfonamide: Compound **9**. To a CH_2Cl_2 solution (5 mL) containing the amine **41** (457 mg, 1.2 mmol) and Et_3N (0.42 mL, 3.0 mmol) was added 4-chlorobenzenesulfonyl chloride (211 mg, 1.0 mmol) at 22 °C. After the reaction mixture was stirred for 18 h, the contents were loaded directly onto a column of silca gel and eluted with 25% EtOAc–hexane increasing gradually to 100% EtOAc. The product was collected as a white foam 520 mg (94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 2H, *J* = 8.6 Hz), 7.44 (d, 2H, *J* = 8.5 Hz), 7.06–7.38 (m, 16H, trityl), 6.49 (s, 1H), 5.71 (m, 1H), 2.95 (q, *J* = 6.2, 12.4 Hz), 2.47 (t, *J* = 7.0 Hz), 1.45–1.65 (m, 4H). MP = 167.5–168.5. MS (FAB, M+H) 556. Anal. calc for $C_{32}H_{30}N_3O_2ClS$: C, 69.11; H, 5.44; N, 7.56; S, 5.76. Found C, 69.10; H, 5.66; N, 7.54; S, 5.98. The above compound was treated with 4 M HCl (1.6 mL, 6.5 mmol) in dioxane (10 mL) and heated to 80 °C for 4 h. The product precipitated out of solution as gummy residue coating the inside of the flask. The mixture was cooled to 22 °C and the solvent was decanted from the residue. The residue was rinsed with EtOAc, and then with CH_2Cl_2, and dried under vacuum to afford the hydrochloride salt as a hygroscopic foam. ^{1}H NMR (300 MHz, CD_3OD) δ 8.8 (s, 1H), 7.9 (d, 2H, *J* = 8.6 Hz), 7.7 (d, 2H, *J* = 8.6 Hz), 7.3 (s, 1H), 3.0 (t, 2H, *J* = 7.3 Hz), 2.8 (t, 2H, *J* = 7.5 Hz), 1.8 (m, 2H), 1.6 (m, 2H). MS (CI, M + H) 314.

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18. Preliminary pharmacokinetic data obtained for compound **9** indicates that the serum half life of 4.3 h is consistant with the observed *in vivo* ED_{50} value.