

NOVEL H₃ RECEPTOR ANTAGONISTS. SULFONAMIDE HOMOLOGS OF HISTAMINE

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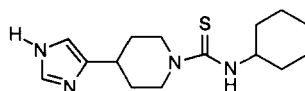
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Abstract: Sulfonamides derived from 4(5)-(ω-aminoalkyl)-1*H*-imidazoles containing chain lengths of three- to five-carbons were synthesized. Good to moderate H₃ receptor binding affinities were observed for several butyl and pentyl homologs, whereas 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 H₃ receptor antagonists.

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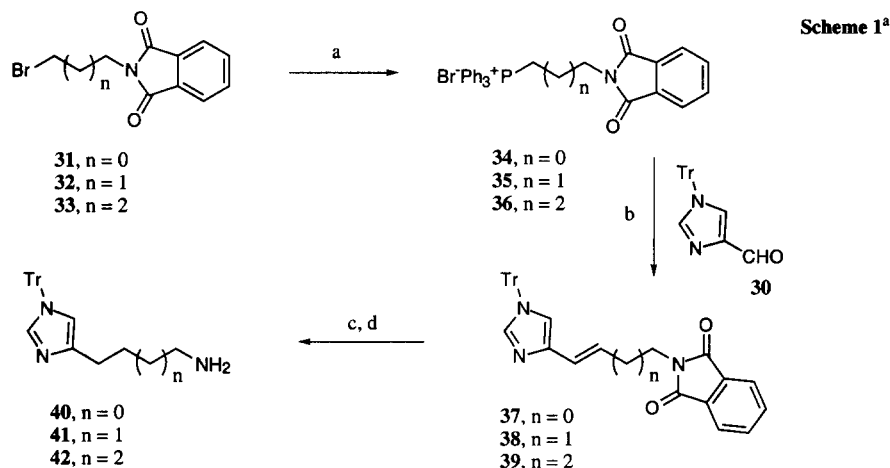
Introduction: To date three major subtypes of histamine receptors have been identified: H₁, H₂, and H₃. The pharmacology regarding the H₁ and H₂ receptor subtypes has been known since the 1960's,¹ however, elucidation of the H₃ receptor by Arrang and coworkers in 1983 is still a relatively new discovery and the precise consequence of inhibiting this receptor has not been fully determined.² One of the functions that has been established for the H₃ receptor is its role in the regulation of various neurotransmitters.³ These receptors which are located on presynaptic nerve terminals in both the central and peripheral nervous systems, have been found to differ significantly in their pharmacology from the H₁ and H₂ subtypes.⁴ This finding was borne out from the discovery that thioperamide **I** is a potent and selective H₃ 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

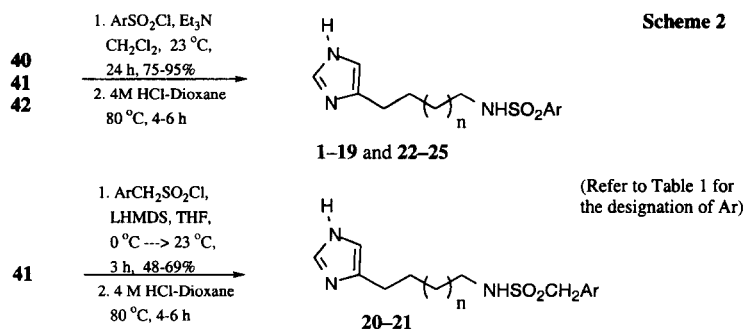
Subsequently, a great deal of structure–activity relationship (SAR) work has taken place in an effort not only to find a suitable replacement to **I**, but to also understand more accurately the complete physiological functions of this receptor. At the time we initiated our research, there had been only two accounts in the patent literature that investigated the use of sulfonamide derivatives based on the natural ligand histamine as possible H₁ agonists.⁷ While a wide range of functionalities has since been evaluated in the development of H₃ antagonists, none has employed the use of sulfonamides in their design.⁸ With our present understanding that homologs of histamine behave as H₃ 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 H₃ antagonist was based on the premise that H₃ 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.

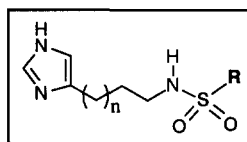
Chemistry: A concise, and high yielding 5 step synthetic sequence similar to that devised by Griffith¹¹ was employed to prepare the 4(5)-(ω-aminoalkyl)-1*H*-imidazole targets illustrated in Schemes 1–3. Treatment of the commercially available *N*-(2-bromoethyl)phthalimide, *N*-(3-bromopropyl)phthalimide, or *N*-(4-bromobutyl)phthalimides with triphenylphosphine in CH₃CN 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**.



^aReagents and Conditions: (a) Ph₃P, CH₃CN, 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), H₂, 45 psi, 1 h, 73% (d) NH₂NH₂, 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 Et₃N in CH₂Cl₂. 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.

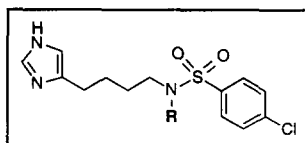


**Table 1.** H₃ Receptor Affinity and Antagonist Activity for Substituted Sulfonamide Analogs.

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- <i>p</i> -CH ₃	2	17	0	7.6	16% ^e
4	phenyl- <i>p</i> - <i>t</i> -Bu	1	45.5	30	-	-
5	phenyl- <i>p</i> - <i>t</i> -Bu	2	16.5	32	7.8	~3
6	phenyl- <i>p</i> - <i>t</i> -Bu	3	5	14	8.0	40% ^e
7	phenyl- <i>p</i> -OCH ₃	2	51	-	-	-
8	phenyl- <i>p</i> -Cl	1	380	21	-	-
9	phenyl- <i>p</i> -Cl	2	9	48	7.9	2.2
10	phenyl- <i>p</i> -Cl	3	11.5	37	7.0	~3
11	phenyl- <i>m</i> -Cl	2	8.5	0	7.6	8% ^e
12	phenyl- <i>p</i> -F	2	20.5	19	6.8	-
13	phenyl- <i>p</i> -CF ₃	2	10	1	8.4	~3
14	phenyl- <i>p</i> -OCF ₃	2	7	0	8.0	na
15	phenyl- <i>p</i> -OCF ₃	3	24.3	1	8.0	-
16	phenyl- <i>p</i> -NO ₂	1	93	36	-	-
17	phenyl- <i>p</i> -NO ₂	2	16.5	24	7.7	na
18	phenyl- <i>p</i> -NO ₂	3	5.5	25	8.1	2.7
19	phenyl- <i>p</i> -NH ₂	2	99	-	-	-
20	CH ₂ -phenyl	2	6	3	7.5	17% ^e
21	CH ₂ -phenyl- <i>o</i> -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 [³H]N^α-methylhistamine binding to guinea-pig brain membranes, ref 14. (b) Determined by an H₁ histamine-mediated bronchospasm, ref 16. (c) H₃ -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. ED₅₀ and pA₂ values were not obtained for compounds with H₃ 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 H₃ binding affinity. However, while the K_i and pA₂ 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 H₃ 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 H₃/H₁ 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 H₁ antagonists are lipophilic in nature^{2c} and compound **28** possesses two highly polar imidazole functions.

**Table 2.** H₃ 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- <i>p</i> -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) ED₅₀ 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 H₃ antagonists, and may serve as useful tools to further aid in the understanding of the H₃ 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 CH₂Cl₂ solution (5 mL) containing the amine **41** (457 mg, 1.2 mmol) and Et₃N (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 silica gel and eluted with 25% EtOAc–hexane increasing gradually to 100% EtOAc. The product was collected as a white foam 520 mg (94%). ¹H NMR (300 MHz, CDCl₃) 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 C₃₂H₃₀N₃O₂ClS: 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 CH₂Cl₂, and dried under vacuum to afford the hydrochloride salt as a hygroscopic foam. ¹H NMR (300 MHz, CD₃OD) 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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