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New products

Inhibitors of gastric acid secretion: *N*-sulphonyl formamidines in a series of new histamine H_2-receptor antagonists

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Summary — A series of 19 new *N*-sulphonyl formamidines have been synthesized and evaluated as inhibitors of gastric acid secretion. Compounds **4a** and **4n** were the most active and were selected for further pharmacological and toxicological studies.

Résumé — **Inhibiteurs de la sécrétion d'acide gastrique: *N*-sulfonylformamidines, série de nouveaux antagonistes du récepteur histaminique H_2.** *Une série de 19 nouvelles* N-*sulphonylformamidines a été synthétisée et essayée comme inhibiteur de la sécrétion d'acide gastrique. Les composés les plus actifs,* ***4a*** *et* ***4n****, ont été sélectionnés afin de poursuivre leur développement pharmacologique et toxicologique.*

sulphonyl formamidines / histamine H_2-receptor antagonists / anti-secretory drugs

Introduction

The discovery of burimamide by Black *et al.* [1] in 1972 provided the first example of an antagonist of histamine H_2-receptors. Structural changes of this model led to more potent antagonists, such as metiamide [2], cimetidine [3], ranitidine [4] and tiotidine [5].

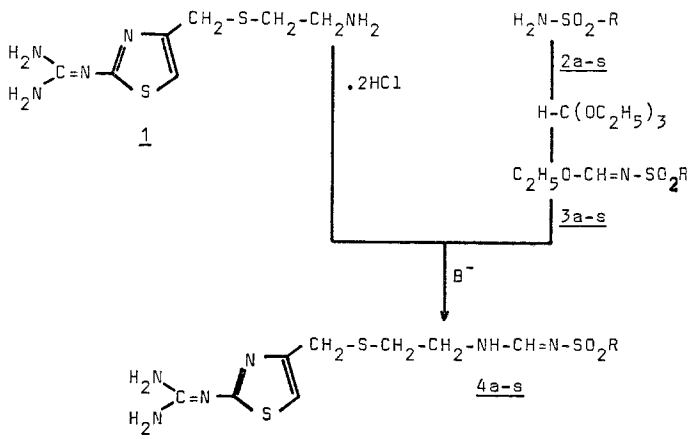
The successful therapeutic use of cimetidine stimulated the search for new antagonists of histamine H_2-receptors; etintidine [6], oxmetidine [7], famotidine [8], and mefentidine [9] resulted from these investigations and claimed to have a higher potency or a longer duration of action.

In general, the structures of these products show three fundamental substructures: a heterocycle containing an endocyclic or exocyclic basic moiety, a four-membered side chain (CH_2—S—CH_2—CH_2), and an H-bonding group.

This report describes a novel class of histamine H_2-receptor antagonists characterized by the presence of an *N*-sulphonyl formamidine substructure. The preparation of the obtained compounds is described and the pharmacological data are discussed in relation to their chemical structure.

Synthesis

The synthesis steps for the preparation of *N*-sulphonyl formamidines are illustrated in Scheme 1.



Scheme 1. R = (see Table I).

Intermediate **1** [10] is known in the chemistry of histamine H_2-antagonists. Sulphonamides **2a**—**s** were obtained from the corresponding sulphonic acid chloride and ammonia; when the acid chloride was not commercially available, it was prepared by reacting the aromatic derivative with chlorosulphonic acid [11]. The treatment of **2a**—**s** with triethyl *ortho*formate leads to the *N*-sulphonyl formimidates **3a**—**s** [12]. Compounds **4a**—**s** were synthesized by reacting the amine **1** with the corresponding imidates **3a**—**s** in a polar solvent, such as methanol (Table I).

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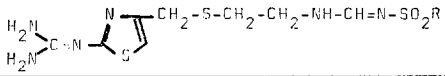
Table I. Structure and chemical data for *N*-sulphonyl formamidines.



Compd.	R	yield %	mp[a], °C	crystn solvent	formula[b]	H¹-NMR[k] δ (DMSO)
4a		54.5	143-145	MeOH	$C_{15}H_{20}N_6O_2S_3$[c]	2.3(s,3H),2.54(t,2H),3.3(m,2H), 3.52(s,2H),6.36(s,1H),6.8(br,4H), 7.5(m,4H),8.1(d,1H),8.06(br,1H).
4b	$-CH_3$	37	110-112[i]	Me_2CO	$C_9H_{16}N_6O_2S_3.HCl$[c]	2.54(t,2H),2.84(s,3H),3.4(m,2H), 3.78(s,2H),7.26(s,1H),7.98(d,1H), 8.32(br,4H),8.85(br,1H).
4c		75.3	152-154	MeOH	$C_{14}H_{18}N_6O_2S_3$[c]	2.6(t,2H),3.38(m,2H),3.54(s,2H), 6.42(s,1H),6.84(br,4H),7.6(m,5H), 8.16(s,1H),8.9(br,1H).
4d		51	75-78	MeCN	$C_{14}H_{17}ClN_6O_2S_3$[d]	2.56(t,2H),3.38(m,2H),3.52(s,2H), 6.38(s,1H),6.78(br,4H),7.6(m,4H), 8.12(s,1H),9.4(br,1H).
4e		60.4	90-93[i]	EtOH	$C_{14}H_{17}N_7O_4S_3HCl$[e]	2.6(t,2H),3.4(m,2H),3.7(s,2H), 7.08(s,1H),8.2(m,9H),9.35(br,1H).
4f		47	160-170	i.PrOH	$C_{15}H_{17}N_6O_4S_3K$[c]	2.63(t,2H),3.45(m,2H),3.54(s,2H), 6.42(s,1H),7.20(br,4H),7.82(m,4H), 8.15(s,1H),9.75(br,1H).
4g		12.5	130-144	MeOH	$C_{12}H_{17}N_9O_3S_4$[c]	2.19(s,3H),2.57(t,2H),3.45(m,2H), 3.55(s,2H),6.42(s,1H),6.80(br,4H), 8.25(s,1H),-.45(br,1H).
4h		81	152-155	AcOEt	$C_{16}H_{21}N_7O_3S_3$[c]	2.05(s,3H),2.56(t,2H),3.38(m,2H), 3.52(s,2H),6.38(s,1H),6.8(br,4H), 7.68(m,4H),8,08(s,1H),8.86(br,1H), 10.24(s,1H).
4i		48.5	87-89	MeOH	$C_{16}H_{20}N_6O_4S_3$[c]	2.58(t,2H),3.40(m,2H),3.53(s,2H), 3.86(s,3H),6.38(s,1H),6.80(br,4H), 7.82-8.14(m,4H),8.18(s,1H),9.05 (br,1H).
4j		82.7	180-182	MeOH	$C_{16}H_{23}N_7O_2S_3$[c]	2.56(t,2H),2.95(s,6H),3.3(m,2H), 3.52(s,2H),6.4(s,1H),6.64-7.56 (m,8H),8.05(s,1H),8.6(br,1H).
4k		49	126-130[i]	MeOH	$C_{15}H_{21}N_7O_4S_4.HCl$[c]	2.6(t,2H),3.1(s,3H),3.4(m,2H), 3.75(s,2H),7.1(s,1H),7.3-8.8(m,4H), 8.15(d,1H),8,35(br,4H),9.1(d,1H), 10.3(br,1H).
4l		86.7	175-177	EtOH	$C_{14}H_{17}N_7O_4S_3$[c]	2.58(t,2H),3.4(m,2H),3.52(s,2H), 6.40(s,1H),6.78(br,4H),7.7-8.4 (m,6H).
4m		11.6	181-184[j]	Me_2CO	$C_{15}H_{20}N_6O_4S_4.C_4H_4O_4$[c]	2.58(t,2H),3.26(s,3H),3.4(m,2H), 3.55(s,2H),6.06(s,2H),7(s,1H), 7.68-8.22(m,9H),9.1(br,1H).
4n		59	107-110	AcOEt	$C_{14}H_{17}BrN_6O_2S_3$[c]	2.58(t,2H),3.45(m,2H),3.55(s,2H), 6.4(s,1H),6.8(br,4H),7.7(s,4H), 8.15(s,1H),9(br,1H).
4o		60	149-153	MeOH	$C_{16}H_{23}N_7O_2S_3$[c]	2.58(t,2H),2.9(s,6H),3.4(m,2H), 3.52(s,2H),6.38(s,1H),6.78-7.4 (m,8H),8.1(s,1H),8.8(br,1H).
4p		23	89-94[j]	AcOEt	$C_{15}H_{21}N_7O_4S_4.C_4H_4O_4$[c]	2.56(t,2H),3(s,3H),3.4(m,2H), 3.8(s,2H),6.1(s,2H),7.05(s,1H), 7.45-7.6(m,4H),8.17(br,5H), 9(br,1H).
4q		81.8	145-149	MeOH	$C_{16}H_{22}N_6O_2S_3$[g]	1(t,3H),2.5(m,4H),3.25(m,2H), 3.4(s,2H),6.25(s,1H),6.7(br,4H), 7.5(s,2H),8.00(s,1H),8.7(br,1H).
4r		57	104-108[i]	H_2O	$C_{15}H_{20}N_6O_2S_4.HCl$[f]	2.5(s,3H),2.56(t,2H),3.35(m,2H) 3.8(s,2H),7.05(s,1H),7.3-7.7(m,4H), 8.1(d,1H),8.3(br,4H),12.5(br,1H).
4s		52	165-170[j]	MeOH	$C_{15}H_{20}N_6O_3S_3C_4H_4O_4$[h]	2.6(t,2H),3.45(m,2H),3.7(s,2H), 3.8(s,3H),6.1(s,2H),6.9(s,1H), 7-7.8(m,4H),8.1(br,5H),8.7(br,1H).

[a]Uncorrected.
[b]IRs were consistent with assigned structure.
[c]Elemental analysis (C, H, N) were within ± 0.4.
[d]H + 0.66; (C, N) were within ± 0.4.
[e]N —0.43; (C, H) were within ± 0.4.
[f]C —0.42; H + 0.29; N —0.46.
[g]1.1% water determined by the Karl Fischer iodometric titration was present. Found values for C, H, N were C 44.50, H 5.35, N 19.36 and were within ± 0.4 if corrected according to the water content.
[h]1.5% water determined by the Karl Fischer iodometric titration was present. Found values for C, H, N were C 41.04, H 4.62, N 15.06 and were within ± 0.4 if corrected according to the water content.
[i]Hydrochloride.
[j]Maleate.
[k]Proton shift assignments exemplified for **4a** were as follow: δ = 2.3 (3H, s, Ø—C*H*₃); 2.54 (2H, t, —S—C*H*₂—CH₂); 3.3 (2H, m, CH₂—C*H*₂—NH); 3.52 (2H, s, thiazole—C*H*₂—S); 6.36 (1H, s, thiazole); 6.8 (4H, br, guanidine); 7.5 (4H, m, aromatic); 8.1 (1H, d, NH—C*H*=N); 8.86 (1H

Discussion

The *N*-sulphonyl formamidines reported in Table I were evaluated as inhibitors of gastric acid secretion in histamine-stimulated perfused stomach of the rat, according to the method described by Ghosh and Schild [13] (Table II). ED_{50} values were recorded; compounds **4a, e, h, j, m, n,** showed the lowest values and matched those of ranitidine, while cimetidine values were lower than those of this new series of compounds.

Inhibition rates of the acid content in the rat stomach was measured 3 h after administering an oral dose of 100 mg/kg. Compounds showing better results are **4a, n,** which are as potent as cimetidine and ranitidine.

Compounds **4a, n,** were evaluated *in vitro* for histamine H_2-receptor antagonist activity, using the histamine-stimulated chronotropic response of the guinea pig atrium [14, 15]. pA_2 values were 7.03 and 7.12 for **4a** and **4n** respectively, *versus* 6.68 and 7.26 for cimetidine and ranitidine, respectively.

The pharmacological results obtained enhance the potential of the *N*-sulphonyl formamidine substructure as a component of general structures exhibiting an antagonist activity of histamine H_2-receptors. A series of alkyl or aryl sulphonyl formamidines was prepared, allowing the evaluation of the effect of different monosubstitutions in the benzene ring of these derivatives. It was observed that the best results were recorded when the monosubstitution was in the *para* position (**4a** and **4n**).

Experimental protocols

Chemistry

Melting points (uncorrected) were determined on a Gallenkamp digital thermometer MFB-595. IR and ^1H NMR were recorded with a Beckman infrared spectrophotometer Acculab-4 and a Bruker NMR-spectrophotometer WP80-CW (tetramethylsilane (TMS) as the internal standard). Analytical results for C, H, N were obtained within $\pm$ 0.4% of the theoretical values. Melting points, crystallization solvents and ^1H NMR of end products are shown in Table I.

General method for the preparation of sulphonyl formimidates
Sulphonamide (1 mol) and triethyl *ortho*formate (5 mol) were heated at 110°C for 2 h. The formed ethanol and the excess triethyl *ortho*-formate were removed by distillation. The resulting residue was purified by several methods: 1) distillation at P = 0.1—0.5 mm Hg; 2) addition of *n*-hexane and separation of the solid by filtration; and 3) crystallization in a suitable solvent, preferably absolute ethanol.

Ethyl benzenesulphonyl formimidate ***3c***
Benzenesulphonamide (15.7 g, 0.1 mol), triethyl *ortho*formate (74.1 g, 0.5 mol) and *p*-toluenesulphonic acid (0.1 g) were heated in an oil bath at 120°C for 5 h. The formed EtOH and the excess triethyl *ortho*-formate were distilled at P = 12 mm Hg. The residue was distilled

Table II. Pharmacological data for *N*-sulphonyl formamidines.

Compd.	Inhibition[a] of histamine-stimulated gastric secretion ED_{50}(μmol/kg, i.v.) ± SEM	Inhibition of basal gastric secretion[b] 100 mg/kg, *p.o.* (3 h after adm.)	Effect on histamine-induced chronotropism pA_2
4a[g]	0.7 ± 0.2	+++[c]	7.03 (6.74—8.24)
4b	1.1 ± 0.2	—	
4c	1.8 ± 0.4	—	
4d	1.2 ± 0.7	++	
4e	0.6 ± 0.4	—	
4f	2.9 ± 0.9	+	
4g	3.4 ± 2.3	—	
4h	0.5 ± 0.3	0	
4i	1.3 ± 0.8	++	
4j	0.8 ± 0.5	0	
4k	1.2 ± 0.6	0	
4l	1.5 ± 0.9	+	
4m	< 0.75	+	
4n[h]	0.4 ± 0.1	+++[d]	7.12 (6.92—7.42)
4o	—	++	
4p	—	+	
4q	—	++	
4r	—	+	
4s	—	+	
Cimetidine	3.6 ± 0.9	+++[e]	6.68 (6.45—7.04)
Ranitidine	0.5 ± 0.2	+++[f]	7.26 (7.07—7.51)

[a]Number of assays (n) between 5 and 9.
[b]Inhibition scale: 0 = < 10%; + = 10—40%; ++ = 40—70%; +++ = 70—100%.
[c]ED_{50} = 63 ± 8.8 (n = 80).
[d]ED_{50} = 8.5 ± 3.2 (n = 386).
[e]ED_{50} = 42 ± 5.5 (n = 394).
[f]ED_{50} = 16 ± 6.2 (n = 386).
[g]Slope **4a** = 0.94.
[h]Slope **4n** = 0.96.

at $P = 0.4$ mm Hg. 15.9 g of ethyl benzenesulphonyl formimidate were obtained under distillation at 140—145°C. Analysis ($C_9H_{11}NO_3S$), C, H, N, S. IR, NMR.

The reaction was carried out using the general method and the obtained residue was recrystallized in absolute EtOH. mp: 73—75°C. IR (KBr): 3100, 3000, 1590, 1320, 1280, 1150, 1080, 905, 650 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.3 (t, 3H); 4.3 (c, 2H); 7.4—7.9 (m, 4H); 8.42 (s, 1H). Analysis ($C_9H_{10}ClNO_3S$), C, H, N, Cl, S.

Ethyl m-N,N-*dimethylamino benzenesulphonyl formimidate* ***3o***
The reaction was carried out using the general method and the oily residue was used without subsequent purification. IR (KBr): 1580, 1370, 1300, 1260, 1130, 1080, 625 cm^{-1}. ^1H NMR (DMSO): δ 1.32 (t, 3H); 2.99 (s, 6H); 4.18 (dd, 3H); 7.17—8.62 (m, 4H); 8.48 (s, 1H).

General method for the preparation of N-*sulphonyl formamidines*
Compound **1** was suspended in MeOH and the base was released by the addition of the stoichiometric quantity of KOH/MeOH. The resulting suspension was filtered off and the corresponding sulphonyl formimidate was added onto the filtrate. The reacting mixture was stirred for 2 h at room temperature. The resulting formamidine was isolated by the procedure illustrated below for compound **4a**.

N-p-*Toluenesulphonyl*-N′-[*2*-[[[*2*-[*(aminoiminomethyl)amino*]-*4-thiazol*]-*methyl*]*thio*]*ethyl*]*formamidine* ***4a***
Compound **3** (3.04 g, 0.01 mol) was suspended in 10 ml of MeOH and treated with 12 ml of KOH/MeOH (1.66 M). The mixture was stirred for 30 min, filtered off and ethyl *p*-toluenesulphonyl formimidate (2.27 g, 0.01 mol) was added to the filtrate. The reaction mixture was stirred for 2 h at room temperature to crystallize a solid **(4a)** which was filtered off and washed with methanol. 3.1 g were obtained; mp: 143—145°C. Analysis ($C_{15}H_{20}N_6O_2S_3$), C, H, N, S, IR, NMR.

4a hydrochloride was prepared by suspension in water, addition of the stoichiometric quantity of 1 M hydrochloride and lyophilization of the resulting solution.

Pharmacology

Histamine-stimulated gastric secretion in the rat
The method described by Ghosh and Schild [13] was used. The test drugs were rapidly injected into the left femoral vein. Each animal was given a single dose and each dose was tested in 2—10 animals.

Gastric secretion p.o. *in the rat*
Sprague—Dawley female rats weighing 180 ± 20 g were used. The animals were starved and kept in metabolism cages for 48 h before starting the experiment and had free access to an aqueous solution containing 8% saccharose and 0.2% NaCl. The test drugs, suspended in 0.25% (p/v) bacto-agar, were administered through gastric cannulation 3 h before killing the animals by stretching—fracture of the cervical vertebrae. Then, the abdomen was opened, the stomach was clamped just above the pyloric sphincter and the esophagus clamped just above the cardia; the whole stomach was excised after sectioning the duodenum and esophagus 1 cm from the clamps. Then, the esophagus was cannulated to flow 10 ml of distilled water into the stomach. After gently stirring, the stomach contents, the rumen was punctured and the stomach contents were removed, then filtered and centrifuged (5000 rpm) for 15 min at 20°C. The remaining acid was titrated with 0.01 M NaOH, using an auto-burette (ABU 12) connected to a TTT60 titrator connected in turn to a PAM-62 pH meter (pH 7.02). The value of acid titrated in control animals' stomachs ($n = 244$) was 26.6 ± 1.1 μeq of HCl ($\bar{x}$ ± SEM).

Isolated guinea pig atrium
The method described by the Staff of the Department of Pharmacology, University of Edinburgh [16] was used.

After an initial 90 min period of incubation, histamine was cumulatively added to the organ bath just before and 45 min later, using the ½ $\log_{10}$ interval described by Van Rossum [14]. Each preparation was used for one single concentration and 3—4 preparations were used for each concentration; 4 concentrations/drug were determined. pA_2 was measured according to the method of Arunlakshana and Schild [17]: $\log (DR - 1) = \log B$.

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