Specificity for the H_2 receptor was established through in vitro models. In the guinea pig atrium model, **1a–e** did not antagonize the chronotropic response to isoprenaline (β-adrenergic receptor) at concentrations up to 3×10^{-6} M. Likewise, the contractile responses to histamine (H_1 receptor) and methacholine (muscarinic receptor) in the guinea pig ileum were not blocked by **1a–e**.

Gastric antisecretory activity, after oral adminstration, was determined in dogs with a gastric fistula under histamine stimulation, as previously described.[17] For intravenous evaluation, the compounds were given immediately prior to histamine, and secretion was then measured as previously described.[17] ED_{50} values and confidence limits for the period of maximum effectiveness (0–30 min after histamine administration) are recorded in Table I. The test compounds were solubilized in aqueous vehicle with 1 equiv of HCl for both routes of administration.

The 1-oxide **1b** was similar in potency after intravenous administration to the corresponding 1,1-dioxide **1c**. Examples **1b,c** were some 300 times more potent iv and 30–50 times more potent po than cimetidine and about 8 times more potent than ranitidine both iv and po. The tiotidine analogue, **1d**, was approximately 450 times as potent as cimetidine. Surprisingly, the cimetidine analogue **1f** was significantly less potent than cimetidine, suggesting that H_2-receptor affinity depends on cooperative and dependent interactions of the three molecular substructures (vide supra) with the receptor. The approximately tenfold lower activity of the NCH_3 analogue **1a** compared with **1b** illustrates a trend of superior potency for unsubstituted analogues in this series.

Compounds **1a–e** were studied also for their ability to displace [^{3}H]-5α-dihydrotestosterone from rat prostate cytosol in vitro[18] and were found to have significantly less affinity than cimetidine[18,19] for these androgen receptors. In contrast to cimetidine,[20] these compounds did not inhibit mixed-function hepatic oxidases as assessed by potentiation of hexabarbital sleeping time in mice.[21] The compounds **1a–e** were negative in the Ames bacterial mutagenicity test using five *S. typhimurium* strains with and without metabolic activation by liver microsomal enzymes from rats pretreated with Aroclor 1254.[22]

Furthermore, since the most potent analogues in this series lack the *N*-methyl substituent in the urea equivalent group, they cannot give rise to a methylating species if nitrosated gastrointestinally. In addition, under WHO[23] and other nitrosating conditions, **1b** yields only the acid hydrolysis product, the corresponding 4-OH derivative.[24] In contrast, cimetidine in vitro yields an isolatable, mutagenic *N*-nitrosoguanidine derivative.[25]

In summary, members of the series of thiadiazole oxide histamine H_2 receptor antagonists show potential for clinical development as potent gastric antisecretory agents with a reduced likelihood of cimetidine-type side effects.[26]

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1,2,5-Thiadiazole 1-Oxide and 1,1-Dioxide Derivatives. A New Class of Potent Histamine H_2-Receptor Antagonists[1]

Sir:

The discovery of histamine H_2-receptor antagonists led to the development of cimetidine, which is widely used as an effective inhibitor of gastric acid secretion in the treatment of duodenal ulcers and related conditions.[2,3] More recently, the development of ranitidine,[4] tiotidine,[5] etintidine,[6] and oxmetidine[7] has demonstrated the po-

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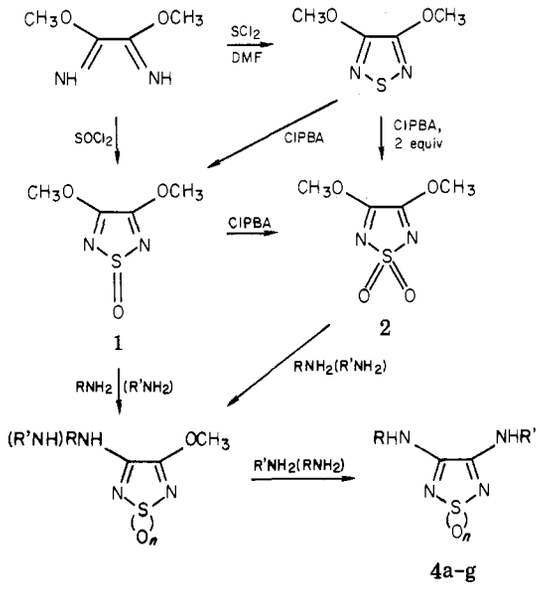
Scheme I



tential for an increase in potency relative to cimetidine while maintaining high H_2-receptor specificity. These H_2 antagonists are 2–6 times more potent than cimetidine as inhibitors of gastric acid secretion and, in addition, all have the same duration of action[6,7] when compared at equieffective doses.

In this communication we report our discovery of the 3,4-diamino-1,2,5-thiadiazole *S*-oxides as novel pharmacophores for selective H_2-receptor antagonist activity. The incorporation of either heterocyclic moiety in place of the usual cyanoguanidine and 1,1-diamino-2-nitroethylene moieties greatly enhances the potency relative to cimetidine and, in some examples, results in a longer duration of action. We have prepared a large number of compounds to confirm this finding,[1,8] and we present here a few examples to demonstrate the potential of this new class of H_2 antagonists.

The 1,2,5-thiadiazole *S*-oxides **4a–g** were synthesized according to the method outlined in Scheme I. The oxidation of 3,4-dimethoxy-1,2,5-thiadiazole[9] with 1 equiv of *m*-chloroperoxybenzoic acid (ClPBA) in methylene chloride at ambient temperature gave the monoxide **1**, mp 135–137 °C after recrystallization from *i*-PrOH, in 87% yield. Anal. ($C_4H_6N_2O_3S$) C, H, N, S. Use of 2 equiv of ClPBA with 3,4-dimethoxy-1,2,5-thiadiazole or 1 equiv with the monoxide **1** at reflux temperature gave the dioxide **2**, mp 187–191 °C after recrystallization from MeOH, in 46% and 70% yields, respectively. The dioxide **2** may also be prepared by the method of Wen et al.[10] Alternatively, the monoxide **1** was more readily prepared in 87% yield directly from dimethyl oxaldiimidate and thionyl chloride with 2 equiv of pyridine. Compound **1** or **2** then was treated sequentially in methanol at 0–5 °C with the appropriate amines (RNH_2 and $R'NH_2$ or $R'NH_2$ and RNH_2) to give the corresponding 3,4-di(substituted-amino)-1,2,5-thiadiazole *S*-oxides **4a–g**.

Compounds **4a–g** were evaluated as antagonists of the positive chronotropic action of histamine in the isolated guinea pig right atrium and as inhibitors of gastric acid secretion in the pylorus-ligated rat. As noted in Table I,

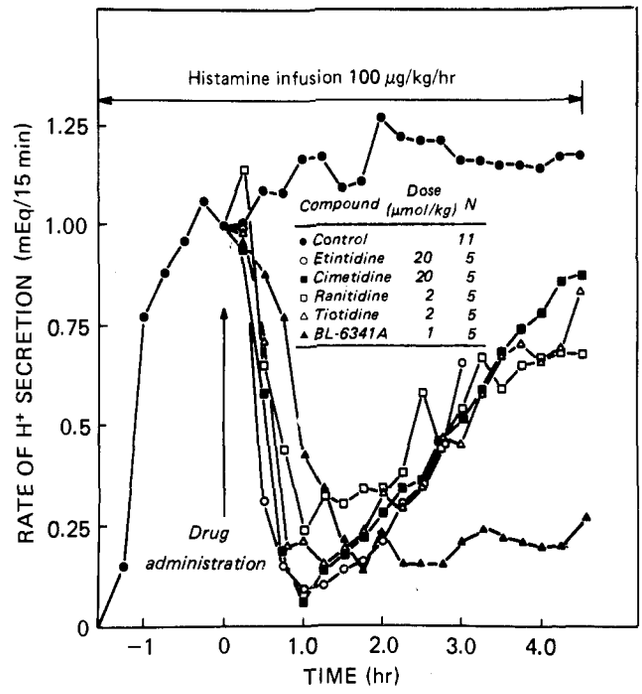


Figure 1. Duration of gastric antisecretory effects following approximately equieffective oral doses of etintidine (○), cimetidine (■), ranitidine (□), tiotidine (△), and BL-6341A (**4e**) (▲) as compared to the control (●) in the histamine-stimulated Heidenhain pouch dog. Each data point is the mean of the number (*N*) of animals indicated.

the thiadiazole compound **4a**, which contains the imidazole moiety present in cimetidine, shows only weak activity in both these models. However, when an exocyclic basic group is attached to a heterocyclic or phenyl group as shown in compounds **4b–g**, then an exceptionally high degree of both in vitro and in vivo activity is observed with the 1,2,5-thiadiazole derivatives. This new series of compounds confirms earlier findings[4,5] that the imidazole ring is not essential for specific and potent H_2-antagonist activity. In fact, in this new series, the imidazole ring is actually detrimental to the activity.

The primary amino derivatives where R′ = H are generally more active than the corresponding substituted amines.[8] In addition, we have found comparable pharmacological activity with both the 1-oxide and 1,1-dioxide derivatives, although the dioxides tend to be slightly more active. This activity may be related to the excellent electron-withdrawing property of the oxidized thiadiazole ring system which is clearly manifested in the acidic nature of the hydroxy thiadiazole oxides.[10] Furthermore, the activities obtained for compounds **4b–g**, as indicated in Table I, suggest that the oxidized 1,2,5-thiadiazole moiety is essential for the observed significant increase in activity and that structure–activity relationships are governed by the exact nature of the substituents RNH_2 and $R'NH_2$. This subject will be discussed in future publications.

The 1,2,5-thiadiazole 1-oxide compound **4e** (BL-6341A) is a competitive antagonist of H_2 receptors in the isolated guinea pig atrium with a pA_2 of 7.6 (7.2–8.2), which corresponds to 45 times the activity of cimetidine. Interaction of **4e** with H_1, pA_2 = 3.9 (3.7–4.2), and cholinergic receptors, pA_2 = 3.4 (3.2–3.6), in the isolated guinea pig ileum and β-adrenergic receptors, pA_2 = 4.3 (4.0–5.5), in the isolated rat uterus indicates high H_2-receptor specificity. One additional advantage that compounds **4e** and **4g** possess is extended duration of action. For example, compound **4e** at a single oral dose of 1 μmol/kg in the histamine-stimulated Heidenhain pouch dog, as shown in

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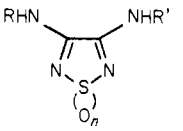
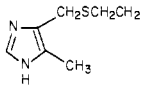
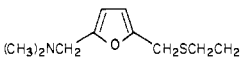
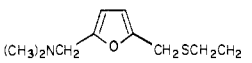
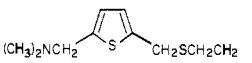
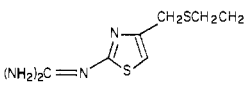
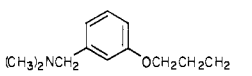
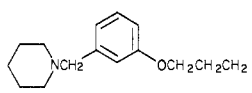
Table I. Structure and Pharmacological Activity of 1,2,5-Thiadiazole *S*-Oxide Derivatives



no.	R	R′	*n*	mp,[a] °C	formula[b]	isolated guinea pig atrium: K_B,[c] μM	2-h pylorus-ligated rat[d] ED_{50},[e] μmol/kg	2-h pylorus-ligated rat[d] potency ratio[f] (cimetidine = 1.0)
4a		CH_3	2	*g*	$C_{10}H_{16}N_6O_2S_2$	11.5	131 (32–464)	0.07
4b		H	2	156–158	$C_{12}H_{19}N_5O_3S_2$	0.035	0.016 (0.006–0.039)	425
4c		H	1	151–153	$C_{12}H_{19}N_5O_2S_2$	0.026	0.041 (0.015–0.125)	168
4d		CH_3	2	122–124	$C_{13}H_{21}N_5O_2S_3$	0.14	0.072 (0.019–0.32)	94
4e		H	1	207–208	$C_9H_{14}N_8OS_3 \cdot HCl$	0.027[h]	0.075 (0.049–0.12)	116
4f		H	1	162.5–163.5	$C_{14}N_{21}N_5O_2S$	0.065	0.066 (0.018–0.19)	142
4g		H	1	155.5–156.5	$C_{17}H_{25}N_5O_2S$	0.04	0.061 (0.019–0.24)	152

[a] Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. The reported melting points occurred with decomposition. [b] All compounds were analyzed for C, H, N, and S, and the results were within ±0.4% of theory. [c] Estimates of the apparent dissociation constants (K_B) were determined by the method of Furchgott, R. F. *Ann. N.Y. Acad. Sci.* 1967, *139*, 553, from the formula K_B = concentration of antagonist/dose ratio − 1. Parallel shifts in dose-response curves were obtained without depressing the maximal response at the antagonist concentration utilized, and the results are the means of three to five preparations tested with each antagonist. [d] Modified procedure of Shay, H.; Sun, D. C. H.; Gruenstein, M. *Gastroenterology* **1954**, *26*, 906. [e] The dose giving 50% inhibition administered subcutaneously. At least five rats were used at each dose level, and a minimum of five dose levels were utilized for determination of a dose-response curve, except for **4f** where three dose levels were used. ED_{50} values and 95% confidence limits indicated in parentheses were determined by Probit analysis according to Finnley, D. J. "Probit Analysis," 3rd ed.; University Press: Cambridge, England, 1971; Chapter 4. [f] Potency ratio relative to cimetidine = 1.0; the ED_{50} for cimetidine varied from 6.8 to 9.4 μmol/kg during the course of the studies. [g] Amorphous solid. [h] Derived from Schild plots (Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48) with 95% confidence limits of 0.006–0.057; for cimetidine a value of 1.2 μM (0.35–2.3) was obtained. Three concentrations of both antagonists with three to six preparations at each concentration were used. Competitive antagonism is indicated, since linear responses were obtained with both antagonists, and the slopes of the regression lines were not significantly different from unity.

Figure 1, is significantly longer acting than approximately equieffective doses of cimetidine, etintidine, ranitidine, and tiotidine. Whereas the latter compounds show only weak inhibitory activity after 4 h in this model, **4e** is still effective with greater than 50% inhibition 9 h postdose.[11]

These results indicate that members of this new class of H_2 antagonists warrant further evaluation of their therapeutic potential for the treatment of peptic ulcer disease.

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