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**Original paper**

# Pyridine and reduced pyridine analogues of 1,2,5-thiadiazoles as histamine $H_2$-receptor antagonists

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**Summary** — A series of 4-amino and 4-methylamino-3-[2-(pyridylmethylthio)ethylamino]-1,2,5-thiadiazole-1-oxides **6—11** and 1,1-dioxides **12—17** were prepared. Pharmacological testing using the histamine induced guinea pig atria chronotropic response indicated that the pyridyl substituent position was an important determinant of activity, since the relative activities within each isomeric series was 4-pyridyl > 3-pyridyl > 2-pyridyl. The activity exhibited by analogous 1-oxide and 1,1-dioxide analogues were similar. The C-4 substituent did not influence activity significantly since the corresponding 4-amino and 4-methylamino analogues showed similar activities, although the 4-amino analogues were marginally more active. Sodium borohydride reduction of the pyridyl compounds yielded the 1,2-dihydropyridyl analogues. Some structure—activity correlations are described.

**Résumé** — **Analogues pyridiniques et pyridiniques réduits de thiadiazoles-1,2,5: antagonistes du récepteur histamine-$H_2$.** *Une série d'amino-4 et de méthylamino-4[(pyridylméthylthio)-2-éthylamino]-3-thiadiazol-1,2,5-oxydes-1 (**6—11**) et dioxydes-1,1 (**12—17**) a été synthétisée. Les essais pharmacologiques portant sur la réponse chronotropique du cœur du cobaye, induit par l'histamine ont indiqué que la position du substituant pyridinique est un facteur déterminant pour l'activité, les activités relatives dans chaque série isomère étant pyridyl-4 > pyridyl-3 > pyridyl-2. L'activité montrée par les analogues oxyde-1 et dioxyde-1,1 est semblable. Le substituant en C-4 n'a pas affecté l'activité significativement puisque les analogues amino-4 et méthylamino-4 sont un peu plus actifs. La réduction des composés pyridiniques par le borohydrure de sodium a donné les analogues dihydro-1,2 pyridiniques. Une corrélation structure—activité est présentée.*

**$H_2$-receptor antagonists / 1,2-dihydropyridines / pyridines / thiadiazole derivatives**

## Introduction

The discovery of cimetidine and ranitidine and their clinical successes have provided both the rationale and stimulus for development of improved histamine $H_2$-receptor antagonists with enhanced activity, a longer duration of action and a lower potential for side effects [1—4]. A structural comparison of these drugs indicates three fundamental features which include a substituted heterocyclic ring containing a basic center linked by a common 2-thiabutyl spacer to polar hydrogen bonding acyclic cyanoguanidine or 1-nitro-2,2-diaminoethene end groups Y as illustrated by formula **1**. More recently, compounds which possess a cyclic 'urea equivalent' Y such as 3,4-diamino-1,2,5-thiadiazole-1-oxide and 1,1-dioxide [5, 6], isocytosine [1—4], aminocyclobut-1-ene-3,4-dione [4, 7], amino-1,2,4-triazole [4], amino-1,2,4,6-thiatriazine-1,1-dioxide [8], aminopyridone [7] or diaminofurazan [9] have been reported which exhibit a longer duration of action and enhanced activity relative to cimetidine, while still maintaining selective $H_2$-antagonist activity.

Het—$CH_2$—S—$CH_2CH_2$—Y **1**

Recently, we prepared compounds **1** in which the Het group was a pyridyl or 1,2-dihydropyridyl ring system and Y was —NHC(=NCN)NHMe and —NHC(=$CHNO_2$)N—. The pharmacological test results suggested that the charge distribution in the aromatic pyridyl or 1,2-dihydropyridyl ring was important to interaction with the $H_2$-receptor [10, 11]. It was, therefore, of interest to determine what effect incorporation of 3,4-diamino-1,2,5-thiadiazole-1-oxide and 1,1-dioxide cyclic 'urea equivalents' would have on $H_2$-antagonistic activity. We now describe the synthesis and/or $H_2$-antagonistic activity of **1** possessing pyridyl or 1,2-dihydropyridyl Het ring systems and 3,4-diamino-1,2,5-thiadiazole-1-oxide and 1,1-dioxide 'urea equivalents'.

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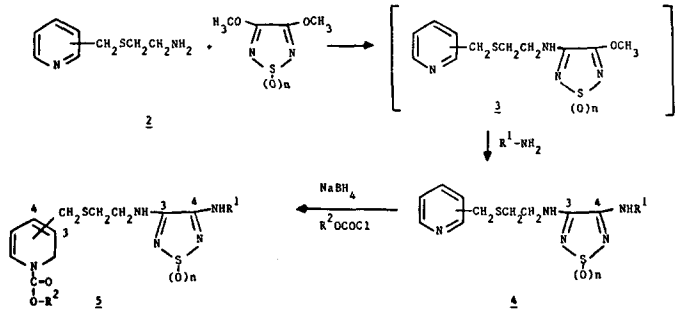
## Chemistry

The synthesis of the target 4-amino and 4-methylamino-3-[2-(pyridylmethylthio)ethylamino]-1,2,5-thiadiazole-1-oxide ($n$ = 1) or 1,1-dioxide ($n$ = 2) **4**, and the corresponding 1,2-dihydropyridyl analogs **5** is outlined in Scheme 1 and summarized in Table I. Thus, reaction of the (2-aminoethylthiomethyl)pyridines **2a—c** with 3,4-dimethoxy-1,2,5-thiadiazole-1-oxide or the 1,1-dioxide afforded the corresponding 3-[2-(pyridylmethylthio)ethylamino]-4-methoxy-1,2,5-thiadiazole-1-oxides or 1,1-dioxides **3** which were not isolated.

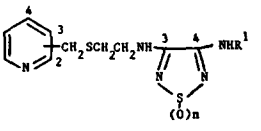


**Scheme 1.** **a**: 4-pyridyl; **b**: 3-pyridyl; **c**: 2-pyridyl; $R^1$ = $CH_3$, H; $R^2$ = $CH_3$, Ph; $n$ = 1, 2.

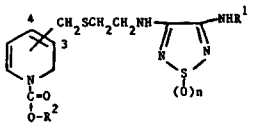
The immediate reaction of **3** with methanolic methylamine or ammonia gave the respective 4-amino and 4-methylamino-3-[2-(pyridylmethylthio)ethylamino]-1,2,5-thiadiazole-1-oxide or 1,1-dioxide **4** in 57—81% yield. The sodium borohydride reduction of the pyridine derivatives **4a—b** in the presence of phenylchloroformate or methylchloroformate in methanol at — 65°C [12, 13] gave the respective 1,2-dihydropyridyl analogues **5** in 41—63% yield as illustrated in Scheme 1 and summarized in Table I. The regiospecific attack by borohydride anion at the C-2 position of the intermediate 3-substituted pyridinium salts of **4** to yield 3-substituted-1,2-dihydropyridyl analogues **5** is consistent with previously reported reductions using sodium borohydride [10, 11].

The 300 MHz $^1$H NMR spectrum of the 1-methoxycarbonyl-4-substituted-1,2-dihydropyridyl analogue **20** in $CDCl_3$ at 25°C exhibited dual resonances for H-5, H-3 and H-6 at $\delta$ 5.24 and 5.30, 5.46 and 5.52 and 6.82 and 6.9, respectively, due to the presence of two rotamers which differ in configuration around the nitrogen-to-carbonyl bond. The difference in configuration is likely due to restricted rotation around the N—CO (carbamate) bond, due to its double bond character [14, 15]. The presence of rotamers was confirmed, since acquisition of the spectrum at 60°C induced coalescence of the dual resonances to a single resonance at $\delta$ 5.26, 5.47 and 6.83 for H-5, H-3 and

**Table I.** 4-Amino and 4-methylamino-3-[2-(pyridylmethylthio)ethylamino]-1,2,5-thiadiazole-1-oxides, 1,1-dioxides **4** (**6—17**) and 4-amino and 4-methylamino-3-[2-(1,2-dihydropyridylmethylthio)ethylamino]-1,2,5-thiadiazole-1,1-dioxides **5** (**18—25**).



**6—17**



**18—25**

| No. | Point of attachment | $R^1$ | $R^2$ | $n$ | Reaction time (h) | Crystn solvent or $R_f$ | Yield (%) | mp (°C) | Formula[a] |
|---|---|---|---|---|---|---|---|---|---|
| **6** | C-4 | $CH_3$ | — | 1 | 3 | 0.5[b] | 65 | oil | $C_{11}H_{15}N_5OS_2$ |
| **7** | C-3 | $CH_3$ | — | 1 | 3 | 0.55[b] | 69 | oil | $C_{11}H_{15}N_5OS_2$ |
| **8** | C-2 | $CH_3$ | — | 1 | 3 | 0.4[b] | 57 | oil | $C_{11}H_{15}N_5OS_2$ |
| **9** | C-4 | H | — | 1 | 3 | $CH_3OH$ | 79 | 173 | $C_{10}H_{13}N_5OS_2$ |
| **10** | C-3 | H | — | 1 | 3 | $CH_3OH$ | 72 | 155 | $C_{10}H_{13}N_5OS_2$ |
| **11** | C-2 | H | — | 1 | 3 | $CH_3OH$ | 62 | 130 | $C_{10}H_{13}N_5OS_2$ |
| **12** | C-4 | $CH_3$ | — | 2 | 3 | $CH_3OH$ | 73 | 187 | $C_{11}H_{15}N_5O_2S_2$ |
| **13** | C-3 | $CH_3$ | — | 2 | 3 | $CH_3OH$ | 57 | 90 | $C_{11}H_{15}N_5O_2S_2$ |
| **14** | C-2 | $CH_3$ | — | 2 | 3 | $CH_3OH$ | 81 | 165 | $C_{11}H_{15}N_5O_2S_2$ |
| **15** | C-4 | H | — | 2 | 3 | $CH_3OH$ | 80 | 80 | $C_{10}H_{13}N_5O_2S_2$ |
| **16** | C-3 | H | — | 2 | 3 | $CH_3OH$ | 65 | 70 | $C_{10}H_{13}N_5O_2S_2$ |
| **17** | C-2 | H | — | 2 | 3 | $CH_3OH$ | 64 | 65 | $C_{10}H_{13}N_5O_2S_2$ |
| **18** | C-4 | $CH_3$ | Ph | 2 | 5 | 0.5[b] | 57 | 216[c] | $C_{18}H_{21}N_5O_4S_2$ |
| **19** | C-4 | H | Ph | 2 | 6 | 0.38[b] | 47 | 230[c] | $C_{17}H_{19}N_5O_4S_2$ |
| **20** | C-4 | $CH_3$ | $CH_3$ | 2 | 3 | 0.6[b] | 67 | 220[c] | $C_{13}H_{19}N_5O_4S_2$ |
| **21** | C-4 | H | $CH_3$ | 2 | 4 | 0.4[b] | 48 | 248[c] | $C_{12}H_{17}N_5O_4S_2$ |
| **22** | C-3 | $CH_3$ | Ph | 2 | 6 | 0.45[b] | 42 | 238[c] | $C_{18}H_{21}N_5O_4S_2$ |
| **23** | C-3 | H | Ph | 2 | 8 | 0.4[b] | 41 | 270 | $C_{17}H_{19}N_5O_4S_2$ |
| **24** | C-3 | $CH_3$ | $CH_3$ | 2 | 4 | 0.55[b] | 56 | 260[c] | $C_{13}H_{19}N_5O_4S_2$ |
| **25** | C-3 | H | $CH_3$ | 2 | 6 | 0.44[b] | 63 | 253 | $C_{12}H_{17}N_5O_4S_2$ |

[a]Compounds **6—8** and **11** were analyzed for C, H, N, O and S using high resolution mass spectrometry. Compounds **9**, **10**, **12—17** and **20** were analyzed for C, H and N and compounds **18**, **19** and **21—25** were analyzed for N by combustion analysis. Compounds **18—25** were analyzed as the dihydrogen hexachloroplatinate salts. The results were within ± 0.4% of theoretical values.
[b]Chloroform:methanol (4:1, v/v) as development solvent.
[c]Dihydrogen hexachloroplatinate salt (mp, decomposition).

H-6, respectively. The original spectrum was obtained upon cooling the sample to 25°C. The $^1H$ NMR spectra for the remaining 1,2-dihydropyridyl analogues **18**, **19**, **21**—**25** also showed dual resonances for the 1,2-dihydropyridyl olefinic protons in $CDCl_3$ at 25°C.

## Pharmacological Results and Discussion

The chronotropic response of guinea pig atria to the $H_2$-agonist histamine is blocked by the competitive antagonist cimetidine and related analogues [16]. A chronotropic $H_2$-antagonism test consists of exposing guinea pig atria to increasing doses of the $H_2$-agonist. A parallel shift of the dose—response curve to the right at drug concentrations which have no effect on the resting heart rate serves as the criterion for competitive $H_2$-antagonism [17—19]. A number of selected compounds were tested, and their biological test results are reported in Table II.

The amino-1,2,5-thiadiazoles **9**—**17** were studied to determine the effects of the pyridyl ring, the pyridyl substituent position, the oxidation state of the thiadiazole sulfur atom and methyl substitution on the 4-amino substituent upon $H_2$-antagonist activity. Compounds **4** possessing a 3-amino-1,2,5-thiadiazole 'urea equivalent' were selected for this investigation, since the aminothiadiazole oxide moiety, which acts as an electron acceptor, has a greater acidity than the cyanoguanidine group which could result in enhanced receptor affinity, *viz* hydrogen bonding [6]. It has been reported that the $H_2$-antagonist effect of compounds possessing 'urea equivalents', such as aminonitropyrroles and aminonitropyridones, may be due to interaction with the $H_2$-receptor by hydrogen-bonding, and the strength of this interaction is determined by the dipoles ability to align with the receptor [7]. The enhanced activity of 1,2,5-thiadiazole oxide analogues could therefore be due, at least in part, to their dipole effects. Furthermore, the rigid conformation of the amino-1,2,5-thiadiazole ring system does not allow for tautomeric species which is the case for cyanoguanidine [20] and 1-nitro-2,2-diaminoethene [21] acyclic 'urea equivalents'. Compounds **4** could theoretically adopt an intramolecularly folded structure stabilized by a hydrogen bond between the pyridine nitrogen and the weakly acidic hydrogens of the diaminothiadiazole oxide moiety [22] analogous to that reported for the clinically useful histamine $H_2$-receptor antagonist cimetidine [23, 24].

The test results indicate that the point of attachment of the pyridyl ring substituent is an important determinant of activity, since the relative activities within the three isomeric series investigated were 4-pyridyl > 3-pyridyl > 2-pyridyl (**9** > **10** > **11**, **12** > **13** > **14**, **15** > **16** > **17**). In contrast, previous studies for thiourea, cyanoguanidine [10] and 1-nitro-2,2-diaminoethene [11] 'urea equivalents' showed that the relative activities within an isomeric series was 2-pyridyl > 4-pyridyl > 3-pyridyl. These results suggest that affinity for the $H_2$-receptor is due to co-operative and dependent interactions of the molecular substructures (pyridyl ring, 'urea equivalents') [20]. A comparison of the relative activities of the isomeric series **9**—**11** with **15**—**17** indicates comparable pharmacological activities with both the 1-oxide and 1,1-dioxide analogs, although the 1,1-dioxides tend to be slightly more active. The observation that the oxidation state of the thiadiazole sulfur atom is not a major determinant of activity is consistent with earlier studies for heterocyclic ring systems other than pyridyl [5, 6]. The nature of the C-4 thiadiazole substituent did not alter activity significantly. The activities of the C-4 methylamino analogues **12**—**14** were similar to those of the corresponding C-4 amino analogues **15**—**17** although the latter compounds were generally slightly more active. The 1-phenoxycarbonyl- and 1-methoxycarbonyl-1,2-dihydropyridyl analogues **18**—**25** were not evaluated as histamine $H_2$-receptor antagonists due to their chemical instability which could contribute to erroneous structure—activity correlations.

In summary, the relative order of activity within the three isomeric series of compounds tested was 4-pyridyl > 3-pyridyl > 2-pyridyl. The C-4 pyridyl compounds **9**, **12** and **15** were more active than the clinically effective drug cimetidine.

## Experimental protocols

### Chemistry

Melting points were determined with a Buchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined

**Table II.** Antagonism of histamine-induced guinea pig atria chronotropic response.

| No. | Point of attachment | $R^1$ | $n$ | Histamine $H_2$-receptor antagonist activity $pA_2(\pm SE)$ | Slope of Schild plot |
|---|---|---|---|---|---|
| **9** | C-4 | H | 1 | 6.39(0.244) | 0.927 |
| **10** | C-3 | H | 1 | 5.62(0.138) | 1.076 |
| **11** | C-2 | H | 1 | 4.40(0.125) | 0.976 |
| **12** | C-4 | $CH_3$ | 2 | 6.31(0.359) | 1.042 |
| **13** | C-3 | $CH_3$ | 2 | 5.69(0.346) | 1.042 |
| **14** | C-2 | $CH_3$ | 2 | 4.78(0.189) | 1.045 |
| **15** | C-4 | H | 2 | 6.28(0.289) | 0.908 |
| **16** | C-3 | H | 2 | 5.78(0.181) | 0.981 |
| **17** | C-2 | H | 2 | 5.07(0.293) | 0.896 |
| Cimetidine | | | | 6.1[a] | |

[a]Literature value [16].

for solutions in deuterochloroform or deuterodimethylsulfoxide with tetramethylsilane (TMS) as the internal standard with a Varian EM-390 or Bruker AM-300 spectrometer. Mass spectra were measured with an AEI-MS-50 mass spectrometer and these exact mass measurements are in some cases used in lieu of elemental analyses (**6—8, 11**). Microanalytical analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of Alberta. Analyses indicated by the symbols of the elements were within ± 0.4% of theoretical values for **9, 10, 12—17, 20** (C, H, N) and **18, 19, 21—25** (N). The 1,2-dihydropyridinyl compounds **18—25** were analyzed as the dihydrogen hexachloroplatinate salts. Infrared spectrum (potassium bromide for solid products and films for oils) were measured on a Nicolet 5DX spectrometer. All of the products gave rise to a single spot on thin—layer chromatography (TLC), using a solvent system of low, medium and high polarity. Analytical TLC was performed using Whatman PE Sil G/UV 250 $\mu$m layer silica gel plates and preparative TLC was carried out using Camag DSF-5 silica gel G plates, 2.0 mm thick. The [(2-aminoethyl)thiomethyl]pyridines **2a—c** were prepared using the procedure reported previously [10]. 3,4-Dimethoxy-1,2,5-thiadiazole-1-oxide and 3,4-dimethoxy-1,2,5-thiadiazole-1,1-dioxide were prepared using the literature procedure [5].

*General synthesis of 4-amino- and 4-methylamino-3-[2-(pyridylmethylthio)-ethylamino]-1,2,5-thiadiazole-1-oxides 6—11 and 1,1-dioxides 12—17*

A solution of the [(2-aminoethyl)thiomethyl]pyridine **2a, b** or **c** (1.68 g, 0.01 mol) in methanol (30 ml) was added dropwise to a solution of 3,4-dimethoxy-1,2,5-thiadiazole-1-oxide (1.62 g, 0.01 mol) or 3,4-dimethoxy-1,2,5-thiadiazole-1,1-dioxide (1.78 g, 0.01 mol) in methanol (150 ml) and the reaction mixture was stirred at 25°C for 1 h to give products **3** which were used immediately without isolation, in the subsequent reaction. A solution of ammonia in methanol (0.01 mol) or methylamine (0.31 g, 0.01 mol) in methanol (20 ml) was added dropwise and the reaction was allowed to proceed at 25°C with stirring for 2 h prior to removal of the solvent *in vacuo*. Products **6—8** were purified by preparative silica gel TLC, using 2.0 mm thick plates, with chloroform:methanol (4:1, v/v) as the developing solvent. The product band (see $R_f$ values Table I) was extracted with chloroform:methanol (4:1, v/v). Products **9—17** were purified by recrystallization from methanol. The spectrometric data for compounds **6** and **12** which are representative of the title compounds are listed below.

*4-Methylamino-3-[2-(4-pyridylmethylthio)ethylamino]-1,2,5-thiadiazole-1-oxide 6.* IR (KBr): 1672 (CN) and 1023 (SO) $cm^{-1}$; $^1H$ NMR $\delta$: 2.68 (t, $J$ = 7 Hz, 2H, $SCH_2CH_2N$); 2.92 (d, $J$ = 4.4 Hz, 3H, $NHCH_3$); 3.51 (m, 2H, $SCH_2CH_2N$); 3.72 (s, 2H, 4-pyridyl—$CH_2$—S); 7.32 (d, $J_{2,3} = J_{5,6}$ = 6 Hz, 2H, H-3, H-5); 7.98 (br m, 1H, $NHCH_3$, exchanges with deuterium oxide); 8.18 (br m, 1H, $NHCH_2$, exchanges with deuterium oxide); 8.58 (d, $J_{2,3} = J_{5,6}$ = 6 Hz, 2H, H-2, H-6). Mass calcd. for $C_{11}H_{15}N_5O^{32}S_2$: 297.0719; found: 297.0723.

*4-Methylamino-3-[2-(4-pyridylmethylthio)ethylamino]-1,2,5-thiadiazole-1,1-dioxide 12.* IR (KBr): 3370 (NH), 1632 (C=N) and 1163 ($SO_2$) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$: 2.66 (t, $J$ = 7 Hz, 2H, $SCH_2CH_2N$); 2.94 (s, 3H, $NCH_3$), 3.56 (t, $J$ = 7 Hz, 2H, $SCH_2CH_2N$); 3.84 (s, 2H, 4-pyridyl—$CH_2$—S); 7.44 (d, $J_{2,3} = J_{5,6}$ = 5.4 Hz, 2H, H-3, H-5); 8.58 (d, $J_{2,3} = J_{5,6}$ = 5.4 Hz, 2H, H-2, H-6); 8.74 (br s, 2H, NH, exchange with deuterium oxide). *Anal.* ($C_{11}H_{15}N_5O_2S_2$) C, H, N.

*General synthesis of 4-amino and 4-methylamino-3-{2-[4-(3-)1-phenoxycarbonyl-(1-methoxycarbonyl)-1,2-dihydropyridylmethylthio]ethylamino}-1,2,5-thiadiazole-1,1-dioxides 18—25*

Sodium borohydride (0.114 g, 3 mmol) was added to a solution of 4-amino or 4-methylamino-3-{2-[4-(3-)-pyridylmethylthio]ethylamino}-1,2,5-thiadiazole-1,1-dioxide **12, 13, 15** or **16** (1 mmol) in absolute methanol (20 ml) precooled to — 65°C. A solution of phenylchloroformate or methylchloroformate (1 mmol) in anhydrous diethylether (5 ml) was added dropwise with stirring. The reaction was allowed to proceed at — 65°C with stirring for the time specified in Table I. The reaction mixture was poured onto ice and extracted with chloroform (3 × 10 ml). The combined chloroform extracts were washed with water (3 × 5 ml), dried ($Na_2SO_4$) and the solvent was removed *in vacuo* at 25°C to yield the respective 1,2-dihydropyridyl derivatives **18—25**. Products **18—25** were purified on silica 2 mm thick gel plates with chloroform:methanol (4:1, v/v) as the developing solvent. The band containing the product (see $R_f$ values listed in Table I) was extracted with chloroform:methanol (4:1, v/v).

Some spectrometric data for compound **20**, which is representative of the other 1,2-dihydropyridyl derivatives prepared are listed below.

*4-Methylamino-3-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridylmethylthio]ethylamino}-1,2,5-thiadiazole-1,1-dioxide* **20**. IR (film): 1155 ($SO_2$), 1704 ($CO_2$) and 3345 (NH) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 2.76 (t, $J$ = 7 Hz, 2H, $SCH_2CH_2N$); 3.14 (br s, 5H, pyridyl—$CH_2$—S, $NCH_3$); 3.68 (br m, 2H, $CH_2CH_2N$, changes to a t, $J$ = 7 Hz after deuterium oxide exchange); 3.83 (s, 3H, $CO_2CH_3$); 4.52 (d, $J$ gem = 3.4 Hz, 2H, H-2); 5.24 and 5.30 (two d, $J$ = 8 Hz, 1H total, H-5); 5.46 and 5.52 (two br s, 1H total, H-3); 6.82 and 6.90 (two d, $J$ = 8 Hz, 1H total, H-6); 7.88 and 7.96 (two br s, 2H, NH, exchange with deuterium oxide). *Anal.* ($C_{13}H_{19}N_5O_4S_2$) C, H, N.

### Pharmacology

The compounds listed in Table II were evaluated using the previously reported procedure to determine antagonism of the histamine-induced guinea pig atria chronotropic response [10].

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