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Potential Histamine H_2-Receptor Antagonists: Ranitidine Analogues Containing "Semicarbazono Equivalent" Groups

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Some ranitidine analogues containing "semicarbazono equivalent" groups were synthesized and tested for their H_2-antagonistic *in vitro* activity.

Potentielle Antagonisten der Histamin H_2-Rezeptoren: Ranitidin–ähnliche Produkte, die semikarbazonäquivalente Gruppen enthalten.

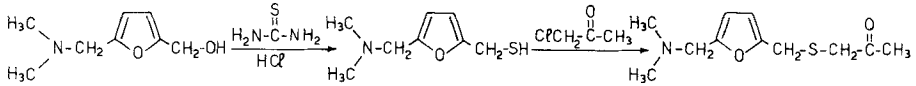
Einige dem Ranitidin ähnliche Produkte, die semikarbazonäquivalente Gruppen enthalten, wurden synthetisiert und auf ihre H_2-antagonistische *in vitro* Aktivität geprüft.

It is known that many potent H_2-inhibitors have in common the following structural pattern: a central chain (generally a 2-thiabutane-1,4-diyl group), linking a substituted aromatic ring (generally a substituted heterocyclic system) with an acyclic or cyclic "urea equivalent" group[1,2].

In this paper we describe the synthesis and the study of the *in vitro* H_2-antagonist activity of the series of products **5 a–f** in which a 5-(dimethylamino)methyl substituted furan ring is joined by a 4-methyl-2-thiabutane-1-yl-4-ylidene chain to a "semicarbazono equivalent" group.

We selected to synthesize this class of compounds on the basis of the observation that some guanylhydrazono structures show adrenergic neurone blocking activities similar to those of some parent guanidine derivatives (for example: Clonidine and Guanabenz)[3].

The common intermediate for the preparation of the products is [5-(dimethylamino)methyl-2-furyl]methylthio-2-propanone **(3)**. This compound can be easily obtained from [5-(dimethylamino)methyl-2-furyl]methanol **(1)**.



1 **2** **3**

The reaction of **3** with the appropriate hydrazine derivatives **4** gives the products **5a–f**. **5b** and **5d** can also be obtained by action on the hydrazone **6** of methylisocyanate and methylisothiocyanate, resp.

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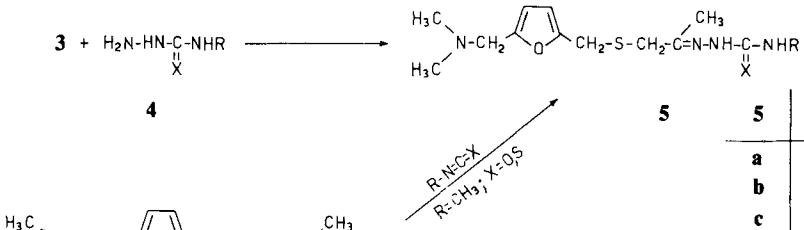
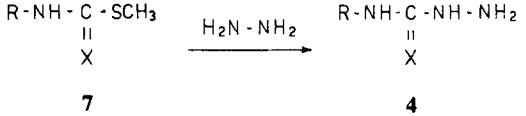


5	X	R
a	O	H
b	O	CH_3
c	S	H
d	S	CH_3
e	$CH\,NO_2$	CH_3
f	$N\text{-}NO_2$	H

All hydrazine derivatives condensed with **3** are well known products with the only exception of (1-methylamino-2-nitroethenyl)hydrazine **(4e)**, synthesized with the following procedure:



4;7	X	R
e	$CHNO_2$	CH_3
f	NNO_2	H

4f, already described in lit.[4], was also obtained by the same procedure.

The X-ray analysis of the structure **5e** was carried out in order to have some indications on the configuration of the –C=N– bond and on the conformations of the $-NH-(C=CHNO_2)-NH-CH_3$ moiety and the whole molecule in the solid state (see Figure 1)[5].

The configuration of the –C=N– bond is *E* and the conformation of the diamino-nitro-ethene substructure is *Z,Z,E* (see Fig. 1). The whole molecular conformation is open contrary to what was found in other H_2-antagonists containing a thioether chain[6–9].

Pharmacology

The activity of the products as histamine H_2-receptor antagonists has been evaluated on guinea-pig isolated atria[10] (see Table 1).

The preparation was mounted in a 50 ml bath containing *Krebs* solution, oxygenated and kept at 31 °C. Histamine cumulative log concentration-response curves were obtained in the presence of increasing concentrations of these compounds. The parallelism of the regression lines was tested by *Student*'s t test[11]. The ED_{50}'s of histamine were obtained by interpolation of the linear regressions and the ratios of equiactive concentrations of histamine in the presence and absence of antagonist were calculated at 50 % of the effect.

All compounds produce no modification of the spontaneous contraction frequency when tested alone and cause a parallel dose-related rightward shift of histamine log concentration-response lines without affecting their maximum.

The regressions of log(dose ratio-1) Vs log concentration of antagonist were calculated by the least squares method: pA_2 values are reported in table 1.

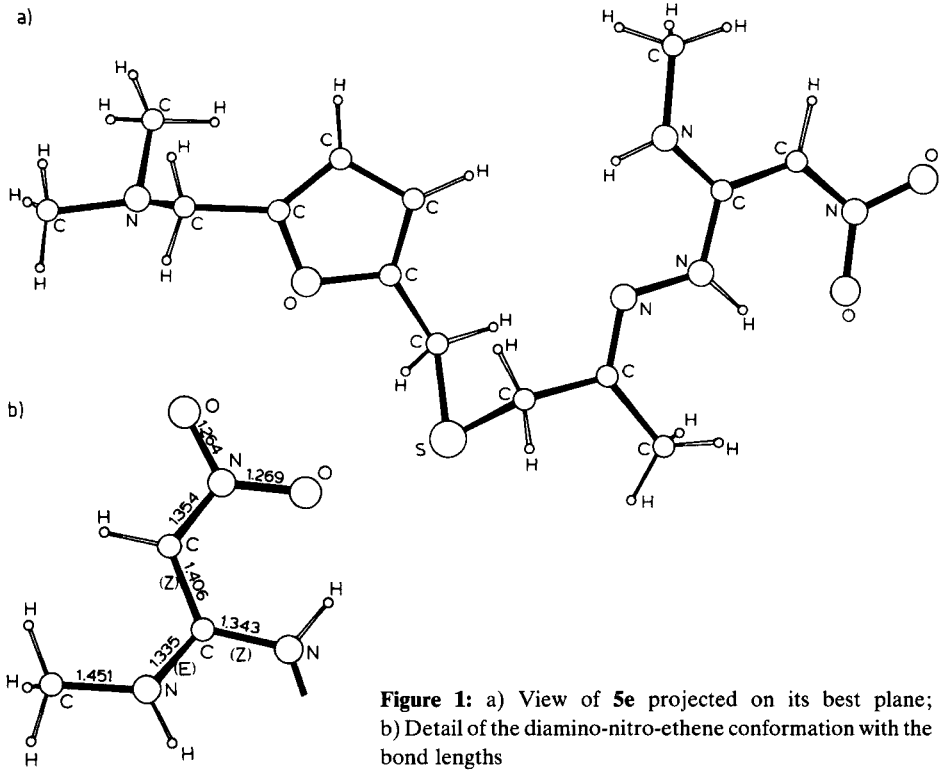


Figure 1: a) View of **5e** projected on its best plane; b) Detail of the diamino-nitro-ethene conformation with the bond lengths

These results show that all compounds are histamine H_2-receptor antagonists but their potency is very weak. The methylthiosemicarbazone **5d** appears to be the most active analogue of the series.

As far as **5e** is concerned, this product is $\sim 10^3$ times less potent than the parent ranitidine. The previously discussed results of the X-ray analysis suggest that conformational features could play an important role in the weak activity of this product.

Experimental Part

MP: capillary apparatus, uncorr. All compounds were routinely checked by IR, ^{1}H-NMR (Varian T-60), ms and HPLC: the spectra are in accordance with the proposed structures. The NMR spectra of **5e** and **4e** show a predominant presence of the nitroethylene tautomer[12]; in the NMR spectrum of **5f** we were unable to detect a NH signal. In all NMR spectra 3-H and 4-H protons on the furan ring appear almost as a doublet of doublets (dd) with central lines more or less partially degenerated.

[5-(Dimethylamino)methyl-2-furyl]methanol **(1)**

1 was prepared according to the method reported in ref.[13] for the synthesis of [5-(dialkylamino)methyl-2-furyl]methanol derivatives. B.p. 113° C/3 torr (Lit.[14] 110–111° C/3 torr); NMR ($CDCl_3$/TMS

Table 1: *H_2-antagonistic activity of* **5b–f** *and of ranitidine*

Compound	pA_2	95 % CL	Number of experiments
5b	4.22	4.77–3.67	16
5c	4.18	4.62–3.74	16
5d	4.70	4.73–4.66	22
5e	3.97	4.20–3.74	21
5f	3.98	4.23–3.73	18
ranitidine	7.12	7.83–6.41	18

5a was not tested.

int.) δ (ppm) = 2.20 (6H, s, $N(CH_3)_2$), 3.40 (2H, s, CH_2-N), 4.50 (2H, s, CH_2-O), 5.12 (1H, s, O-H), 6.15 (2H, dd, 3-H,4-H). $C_8H_{13}NO_2$ (155.19) Calcd.: C 61.9 H 8.44 N 9.0 Found: C 61.7 H 8.3 N 8.9.

[5-(Dimethylamino)methyl-2-furyl]methanethiol **(2)**

A stirred solution of 19 g (0.25 mol) thiourea in 40 ml 6N-HCl was combined with 38 g (0.25 mol) **1**. This mixture was heated at 65–70 °C for 4.5 h and then was left at room temp. for 22 h. After neutralization with sodium hydroxide dissolved in a small amount of water, the solution was steam distilled. The distillate was extracted with ethyl acetate. Solvent removal gave an oil, yield 75 %. An analytical sample was purified by distillation in a nitrogen atmosphere. B.p. 84 °C/2 torr (Lit.[15] 109–113 °C/9 torr; Lit.[16] hydrobromide, m.p. 129–130°); NMR ($CDCl_3$/TMS int.) δ (ppm) = 1.98 (1H, s, SH), 2.25 (6H, s, $N(CH_3)_2$), 3.40 (2H, s, CH_2-N), 3.70 (2H, s, CH_2-S); 6.07 (2H, dd, 3-H,4-H). $C_8H_{13}NOS$ (171.25) Calcd: C 56.1 H 7.65 N 8.2 Found: C 55.9 H 7.9 N 8.0.

[5-Dimethylamino)methyl-2-furyl]methylthio-2-propanone **(3)**

To a stirred and ice-cooled solution of 6.8 g (0.10 mol) sodium ethoxyde in 50 ml ethanol, 17.1 g (0.10 mol) **2** was added dropwise in a nitrogen atmosphere. 9.3 g (0.1 mol) chloroacetone was then added gradually under vigorous stirring. The mixture was evaporated in vac. and the residue was extracted with chloroform. Solvent removal gave an oil which was purified by distillation, yield 74 %. B.p. 102 °C/0.2 torr; IR (neat): 1705 cm^{-1} (C=0); NMR ($CDCl_3$/TMS int.) δ (ppm) = 2.18 (3H, s, CH_3C=0), 2.23 (6H, s, $N(CH_3)_2$), 3.17 (2H, s, CH_2-C=0), 3.30 (2H, s, CH_2-N), 3.65 (2H, s, CH_2-S), 6.08 (2H, dd, 3-H, 4-H). $C_{11}H_{17}NO_2S$ (227.31) Calcd: C 58.1 H 7.54 N 6.2 Found: C 58.3 H 7.8 N 6.2.

[5(Dimethylamino)methyl-2-furyl]methylthio-2-propanone semicarbazone **(5a)** *and thiosemicarbazone* **(5c)**

5a and **5c** were prepared according to usual procedures from **3** and semicarbazide or thiosemicarbazide.

5a: recrystallized from water m.p. 110-111 °C, NMR (DMSO/TMS int.) δ (ppm) = 1.83 (3H, s, C-CH_3), 2.10 (6H, s, $N(CH_3)_2$), 3.23 (2H, s, CH_2-C=), 3.33 (2H, s, CH_2-N), 3.63 (2H, s, CH_2-S), 6.15 and 6.25 ((4H), s, 3-H,4-H and broad s, NH_2), 9.10 (1H, broad s, NH-N=). $C_{12}H_{20}N_4O_2S$ (284.37) Calcd: C 50.7 H 7.09 N 19.7 Found C 50.6 H 7.35 N 19.7.

5c: recrystallized from ethyl acetate m.p. 96–97 °C; NMR (DMSO/TMS int.) δ (ppm) = 1.93 (3H, s, C-CH_3), 2.13 (6H, s, $N(CH_3)_2$), 3.27 and 3.33 ((4H), s, CH_2-C and s, CH_2-N), 3.63 (2H, s, CH_2-S),

6.13 (2H, dd, 3-H, 4-H), 7.53 (1H, broad s, NHH), 8.10 (1H, broad s, NHH), 10.02 (1H, broad s, NH-N=). $C_{12}H_{20}N_4OS_2$ (300.43) Calcd: C48.0 H 6.71 N 18.7 Found C 48.1 H 6.9 N 18.8.

[5-(Dimethylamino)methyl-2-furyl]methylthio-2-propanone methylsemicarbazone **(5b)***and methylthiosemicarbazone* **(5d)**

A solution of 7.9 g (0.035 mol) **3** in ethanol was slowly added dropwise to 35 g (0.70 mol) hydrazine hydrate, stirred and ice-cooled. The reaction mixture was kept at room temp. for 30 min and then extracted with ether. The organic layers, washed with a little water and dried on magnesium sulphate, were evaporated under reduced pressure at room temp. The oil residue **6**, dissolved in acetonitrile, was added dropwise to a stirred solution of 1.98 g (0.035 mol) methylisocyanate in 10 ml acetonitrile. Solvent removal and recrystallization from ether-petroleum ether 40–60° gave **5b** as white crystals, yield 77 %; m. p. 59–60 °C; NMR (DMSO/TMS int.) δ (ppm) = 1.80 (3H, s, C-CH_3), 2.12 (6H, s, N(CH_3)$_2$), 2.66 (3H, d, J=5Hz, N-CH_3), 3.25 (2H, s, CH_2-C=), 3.33 (2H, s, CH_2-N), 3.63 (2H, s, CH_2-S), 6.17 (2H, dd, 3-H,4-H), 6.58 (1H, broad m, NH-C), 9.10 (1H, broad s, NH-N=). $C_{13}H_{22}N_4O_2S$ (298.40) Calcd: C 52.3 H 7.43 N 18.8 Found: C 52.5 H 7.7 N 18.7.

Similarly was prepared **5d**, yield 88 %, recrystallized from isopropyl ether, m.p. 77–78 °C; NMR (DMSO/TMS int.) δ (ppm) = 1.93 (3H, s, C-CH_3), 2.12 (6H, s, N (CH_3)$_2$), 2.97 (3H, d, J=5Hz, N-CH_3), 3.30 and 3.33 ((4H), s, CH_2-C and s, CH_2-N), 3.67 (2H, s, CH_2-S), 6. 15 (2H, dd, 3-H,4-H), 8.15 (1H. broad m, NH-C), 10.00 (1H, broad s, NH-N). $C_{13}H_{22}N_4OS_2$ (314.46) Calcd: C 49.7 H 7.05 N 17.8 Found: C 49.4 H 7.2 N 17.6. **5b** and **5d** can also be prepared by the usual methods from **3** and methylsemicarbazide or methylthiosemicarbazide.

(1-Methylamino-2-nitroethenyl)hydrazine **(4e)**

A solution of 3 g (0.02 mol) N-methyl-1-methylthio-2-nitroetheneamine[13] **(7e)** in 30 ml ethanol was combined with 2.36 ml of a 72 % hydrazine hydrate ethanolic solution. The reaction mixture was refluxed for 20 min and then cooled. The separated solid product was washed on the filter with a little cold ethanol, dried i. vac.; yield 87 %, and finally recrystallized from 90 % ethanol, m.p. 178–179 °C (dec.); NMR (DMSO/TMS int.) δ (ppm) = 2.70 (3H, d, J = 5Hz, N-CH_3), 2.78 (2H, broad s, NH_2), 6.47 (1H, s, CH), 7.62 (1H, broad m, NH-C), 10.03 (1H, broad s, NH-N). $C_3H_8N_4O_2$ (132.13) Calcd: C 27.3 H 6.10 N 42.4 Found: C 27.5 H 6.1 N 42.2.

[(N'-nitro)aminoiminomethyl]hydrazine **(4f)**

4f was prepared from S-methyl-N-nitroisothiourea **(7f)** according to the procedure used for the preparation of **4e**; yield 95 %, recrystallized from 50 % ethanol, m.p. 183–184 °C (dec.) [Lit.[4] 185 °C (dec.), 190 °C (dec.)].

[5-(Dimethylamino)methyl-2-furyl]methylthio-2-propanone-(1-methylamino-2-nitroethenyl)hydrazone **(5e)**

To a stirred solution of 1.32 g (0.01 mol) **4e** in 15 ml acetic acid, 2.3 g (0.01 mol) **3** was added dropwise. After 15 min the reaction solution was diluted with a little water, basified with anhydrous sodium carbonate and the resulting slurry extracted with ethyl acetate. The organic layers, reduced to a small volume i. vac., were filtered on a short silica gel column. The product obtained after solvent removal, yield 62 %, was recrystallized from isopropyl ether/ethyl acetate (9:1), m.p. 91–92 °C; NMR (DMSO/TMS int.) δ (ppm) = 1.93 (3H, s, C-CH_3), 2.12 (6H, s, N(CH_3)$_2$), 2.77 (3H, d, J=5Hz, N-CH_3), 3.33 (2H, s, CH_2-C=), 3.42 (2H, s, CH_2-N), 3.70 (2H, s, CH_2-S), 6.15 (2H, dd, 3-H, 4-H), 6.57 (1H, s, C=CH), 7.75 (1H, broad m, NH-C), 12.43 (1H, broad s, NH-N). $C_{14}H_{23}N_5O_3S$ (341.42) Calcd: C 49.3 H 6.79 N 20.5 Found: C 49.0 H 7.0 N 20.4.

[5-(Dimethylamino)methyl-2-furyl]methylthio-2-propanone-[(N'-nitro)aminoiminomethyl]hydrazone **(5f)**

This product was prepared from **3** and **4f** according to the procedure used for the preparation of **5e**; yield 82 %, recrystallized from ethyl acetate, m. p. 130–131 °C (dec.); NMR (DMSO/TMS int.) δ (ppm) = 1.95 (3H, s, C-CH_3), 2.12 (6H, s, $N(CH_3)_2$), 3.33 and 3.35 ((4H), s, CH_2-C= and s, CH_2-N), 3.68 (2H, s, CH_2-S), 6.15 (2H, dd, 3-H,4-H), 8.30 (2H, broad, s, NH_2). $C_{12}H_{20}N_6O_3S$ (328.39) Calcd: C 43.9 H 6.14 N 25.6 Found: C 43.7 H 6.3 N 25.2.

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[Ph 766]