Synthesis and Antihistaminic Activity of Some Thiazolidin-4-ones

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A new series of 2-(4- and 3-substituted phenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-ones were synthesized, characterized, and evaluated for their ability to inhibit the contractions induced by histamine on guinea pig ileum. The measurement of pA_2 values suggested that the reported compounds showed H_1-antagonism. The more active compounds **5**, **9**, and **13** exhibited activity close to that of mepyramine.

Introduction

Several chemical classes of drugs, such as ethylenediamines, aminoethyl ethers, propyl- and propenylamines, phenothiazines, piperidines, and piperazines, are H_1-histamine antagonists[1] and have been discovered to have remarkable chemical and geometric similarities.[2,3]

The present paper reports the synthesis and pharmacological evaluation, in vitro, of antihistaminic activity of a new series of 2-phenyl-3-[3-(*N*,*N*-dimethylamino)-propyl]-1,3-thiazolidin-4-ones, having some geometric similarity with substituted propylamines (as pheniramine).

Results and Discussion

Chemistry. The described thiazolidinones were prepared, in good yield, by addition of α-mercaptoacetic acid to 3-benzylidene-*N*,*N*-dimethylpropylamine in refluxing benzene[4] (Scheme I). The free bases were recovered and converted into the crystalline hydrochlorides (**1–7** and **9–15**, Table I). Compound **8** was prepared by reduction of **7**.

The thiazolidinones were characterized by their chemical and spectroscopic properties (IR, ^1H NMR) and elemental analysis.

X-ray data on compound **7**, which furnished the more available crystals, showed that the protons C(5)-H_A and C(2)-H are at the same depth (+0.8 Å) on the thiazolidinone plane and that the sulfur atom is at −0.3 Å, giving rise to a slight envelope conformation. The conjugation between C=O and the amide nitrogen is evident from the value of the bond lengths N(1)–C(2) (1.343 Å). The finding that the amide group N(1)–C(2)–O(1) is coplanar with C(3), C(4), and C(1) and also with one of the two hydrogens on C(4) is noteworthy. Moreover, a perspective view of **7** (Figure 1a) shows that the distances between the four sites of thiazolidinones **1–15** fit the four points of the pharmacophore proposed by Naruto et al.[3] (Figure 1a–c).

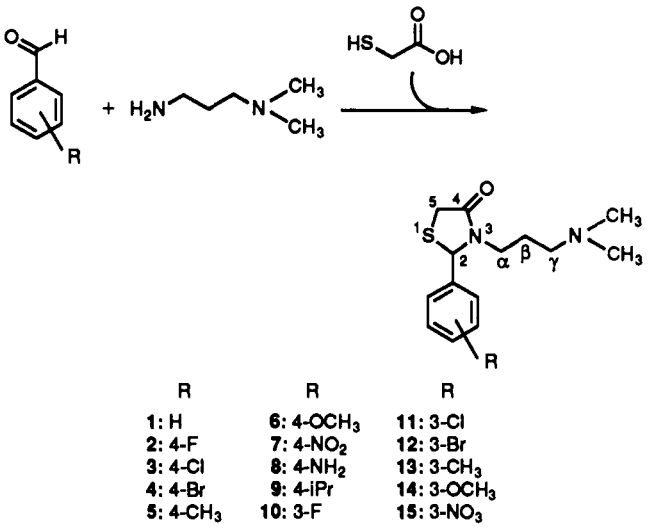
Pharmacology

The racemic mixtures of compounds were tested in vitro for histamine H_1-antagonist activity by measurement of the inhibition of the histamine-induced contractions on the isolated guinea pig ileum.[5] The activities were expressed as IC_{50} values and are reported in Table II.

The competitive H_1-receptor antagonism was evaluated by pA_2 data summarized in Table II and the potency of antagonistic effect of the tested compounds was compared to the activity of mepyramine.

According to current research on antihistamine drugs, four elements are required for the histamine H_1-receptor pharmacophore: two π sites, a basic nitrogen in a geometrically triangular arrangement, and a site for a heteroatom capable of hydrogen bonding.[2,3,6]

Scheme I



R	R	R
1: H	**6**: 4-OCH_3	**11**: 3-Cl
2: 4-F	**7**: 4-NO_2	**12**: 3-Br
3: 4-Cl	**8**: 4-NH_2	**13**: 3-CH_3
4: 4-Br	**9**: 4-iPr	**14**: 3-OCH_3
5: 4-CH_3	**10**: 3-F	**15**: 3-NO_3

Table I

no.	R	formula	% yield	mp, °C
1	H	$C_{14}H_{20}N_2OS$·HCl	33	191–192
2	4-F	$C_{14}H_{19}FN_2OS$·HCl	66	200–201
3	4-Cl	$C_{14}H_{19}ClN_2OS$·HCl	50	206–207
4	4-Br	$C_{14}H_{19}BrN_2OS$·HCl	42	189–190
5	4-CH_3	$C_{15}H_{22}N_2OS$·HCl	30	187–188
6	4-OCH_3	$C_{15}H_{22}N_2O_2S$·HCl	30	180–181
7	4-NO_2	$C_{14}H_{19}N_3O_3S$·HCl	35	229–230
8	4-NH_2	$C_{14}H_{21}N_3OS$·HCl	61	235–236
9	4-iPr	$C_{17}H_{26}N_2OS$·HCl	46	189–190
10	3-F	$C_{14}H_{19}FN_2OS$·HCl	78	207–208
11	3-Cl	$C_{14}H_{19}ClN_2OS$·HCl	40	205–206
12	3-Br	$C_{14}H_{19}BrN_2OS$·HCl	66	212–213
13	3-CH_3	$C_{15}H_{22}N_2OS$·HCl	92	198–199
14	3-OCH_3	$C_{15}H_{22}N_2O_2S$·HCl	66	170–171
15	3-NO_2	$C_{14}H_{19}N_3O_3S$·HCl	29	150–151
1a	H	$C_{13}H_{19}N_2OS$·HCl	40	226–227
1b		$C_{13}H_{19}N_3OS$·HCl	35	166–167

Table II. Histamine Antagonist Activity in Vitro on Guinea Pig Ileum[a]

no.	IC_{50}, μM	$pA_2 \pm 0.2$	no.	IC_{50}, μM	$pA_2 \pm 0.2$
1	20	7.4	10	3.1	6.4
2	24	7.1	11	2.2	6.2
3	21	5.6	12	60	6.4
4	2.3	7.4	13	5.0	7.7
5	1.2	8.3	14	25	6.4
6	>100	5.0	15	>100	5.4
7	>100	5.2	1a	>100	
8	40	6.0	1b	>100	
9	1.0	8.7			

[a] Mepyramine $pA_2 = 9.0$

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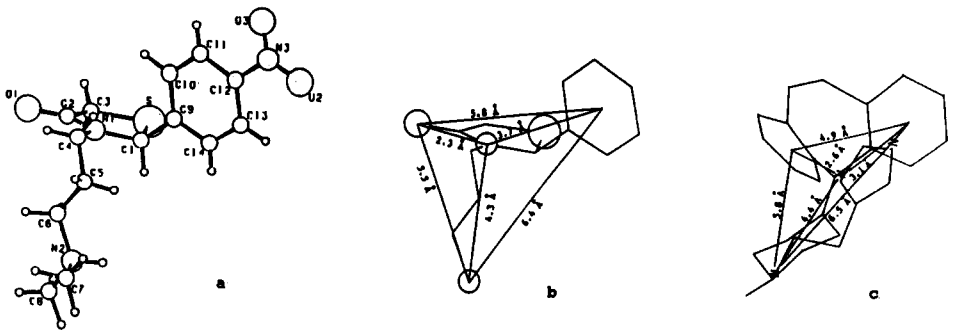

Figure 1. (a) X-ray structure of 7; (b) interatomic distances between the four pharmacophoric points in 7; (c) relative arrangement of the pharmacophoric groups as proposed by Naruto.[3]

Table III. NMR Data of 1,3-Thiazolidinones (D_2O, in δ, J in Hz)

			AB system							
no.	2-Ph	2-H	5-H_A[a]	5-H_B[a]	α-CH_2 (two p)[b]	β-CH_2 (p)	δ-CH_2 (t)	$N(CH_3)_2$	CH_3	-CH-
1	7.47	5.86	3.97	3.80	3.46, 3.07	1.74	2.99	2.77		
2	7.47 (d), 7.17 (d)	5.85	3.93	3.78	3.43, 3.04	1.72	3.01	2.77		
3	7.43 (d), 7.42 (d)	5.83	3.91	3.78	3.45, 3.01	1.75	2.98	2.79		
4	7.58 (d), 7.32 (d)	5.81	3.91	3.77	3.43, 3.01	1.73	2.98	2.77		
5	7.30 (d), 7.27 (d)	5.78	3.90	3.76	3.40, 3.05	1.69	2.94	2.75	2.31 (s)	
6	7.42 (d), 7.02 (d)	5.81	3.94	3.80	3.40, 3.10	1.72	2.98	2.76	3.82 (s)	
7	8.23 (d), 7.62 (d)	5.98	3.97	3.79	3.56, 3.05	1.82	3.05	2.80		
8	7.27 (d), 6.84 (d)	5.74	3.91	3.76	3.37, 3.10	1.68	2.95	2.75		
9	7.30 (d), 7.27 (d)	5.74	3.85	3.72	3.30, 2.98	1.66	2.89	2.67	1.11 (d)	2.82 (e)
10	7.45 (d), 7.25 (t) 7.25 (s), 7.20 (d)	5.84	3.93	3.76	3.47, 3.03	1.75	2.99	2.77		
11	7.49 (s), 7.38 (m)	5.81	3.93	3.76	3.44, 3.01	1.74	2.98	2.77		
12	7.65 (s), 7.58 (d) 7.38 (t), 7.34 (d)	5.79	3.93	3.77	3.44, 3.05	1.72	3.00	2.77		
13	7.34 (t), 7.28 (s) 7.25 (d), 7.24 (d)	5.79	3.94	3.77	3.43, 3.02	1.72	2.97	2.75	2.32 (s)	
14	7.38 (t), 7.04 (d) 7.03 (d), 6.99 (s)	5.80	3.92	3.76	3.44, 3.02	1.73	2.97	2.77	3.80 (s)	
15	8.26 (s), 8.23 (d) 7.84 (d), 7.65 (t)	5.98	3.97	3.82	3.55, 3.01	1.81	3.05	2.81		
1a	7.53	5.86	3.96	3.81	3.76, 3.36	3.15	3.01	2.87		
1b	8.56, 7.45	5.88	3.97	3.77	3.58, 3.03	1.84	3.06	2.81		

[a] $J_{A,B}$ = 16 Hz. [b] J_{gem} = 12 Hz; $J_{\alpha,\beta}$ = 7 Hz; $J_{\beta,\delta}$ = 7 Hz; $J_{2,5A}$ = between 1.5 and 2 Hz; s = singlet, d = doublet, t = triplet, p = pentuplet, e = seven peak multiplet.

The activity data, reported in Table II, suggest that the length of the alkylamine chain (three methylenes) is critical, because the compounds with two methylenes were inactive [i.e., 2-phenyl-3-[2-(*N*,*N*-dimethylamino)ethyl]-1,3-thiazolidin-4-one (**1a**) and another not reported].

On the basis of the reported results, in the series of thiazolidinones (**1**–**15**), it seems that the four elements of the pharmacophore proposed by Naruto[3] are present. The 4-carbonyl and the C(2)-phenyl group could mimic the two π sites, the tertiary protonated nitrogen represents the anionic binding site, and the nitrogen atom of thiazolidine ring could correspond to the heteroatom capable of hydrogen bonding. Also the interatomic distances, evaluated on the X-ray structure, are in good agreement with the distances of the four sites of the pharmacophore.

The replacement on the C(2) of the phenyl group by a pyridine ring gives rise to less active compounds [i.e., 2-(pyridin-4-yl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-one (**1b**)], suggesting that a basic site disturbs the system. Actually, compound **8**, containing a 4′-amine group, showed low activity.

In regard to the substituent effect on the C(2)-phenyl group, it is noteworthy that the activity does not seem to be affected by the nature (electron-donating or electron-withdrawing) of the substituents in the 4′ position. However, bulky groups on 4′ increase the activity. Generally, 3′-substituted compounds did not show noticeable differences. Compound **9**, with its bulky electron-donating 4′-isopropyl group, achieved the best results.

Experimental Section

Melting points were determined with a Kofler apparatus and are uncorrected. The elemental analysis (C, H, and N) of the reported compounds agrees with the calculated values and was within ±0.4% of theoretical values. Electron impact (EI) mass spectra were obtained at 70 eV on a VG ZAB 2F spectrometer.

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The purity of the compounds was checked by ascending TLC on Merck's precoated silica gel plates (0.25 mm) with fluorescent backing.

The IR spectra were taken on a Perkin-Elmer 399 spectrophotometer in KBr. The C=O stretching lies between 1705 and 1710 cm^{-1}.

^1H NMR spectra (data reported in δ) were recorded on a Bruker 270 MHz spectrometer with Me_4Si as internal reference.

The ^1H NMR analysis of the reported compounds (Table III) showed the prochiral α-CH_2 on the 3-(*N*-alkylamino) chain as an AB system approaching an AX system, with chemical shifts lying at about δ 3.5 and 3.0 ppm (J_{AB} = 12 Hz). The difference between the chemical shifts of these geminal protons can be caused by the diamagnetic anisotropy of the carbonyl group deshielding the proton lying at lower field, while the other proton would be located in the shielding region of ring current of phenyl on C(2) of the thiazolidinone system,[7] as is supported by the X-ray structure of **7** (Figure 1a).

The C(5)-methylenic protons, H_A and H_B, of the thiazolidinone ring appeared as an AB system with a geminal proton coupling J_{AB} of 16 Hz. The A proton, lying at lower field, showed a small coupling (J = 2 Hz) with the C(2)-H signal. This long-range coupling takes place through the eclipsing lone pair of the sulfur atom with the C-H_A bond of the thiazolidinone ring. The H_B proton appeared at higher field owing to the shielding effect of the nearly coplanar sulfur orbital.[8,9]

General Procedure for the Preparation of 2-(Substituted phenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-ones (1-7 and 9-15). An equimolar mixture (0.01 mol) of substituted benzaldehydes and *N*,*N*-dimethylpropylamine (0.01 mol) in dry benzene (50 mL) was refluxed until no more water was collected in a Dean-Stark trap. α-Mercaptoacetic acid (0.01 mol) was added, dropwise, to this crude mixture, and the reaction was carried out at reflux temperature until stoichiometric amount of water was collected.

The mixtures, cooled and evaporated in vacuo, afforded pale yellow oils, which were dissolved in anhydrous ethanol (20 mL). Ether (20 mL), saturated with HCl, was added to these solutions. White powders were collected and recrystallized with absolute ethanol, to yield the thiazolidin-4-one hydrochlorides (**1-7, 9-15**).

N,*N*-Dimethylethylamine and pyridine-4-carboxaldehyde were used, respectively, in the preparation of **1a** and **1b**.

2-(4-Aminophenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-one (8). 2-(4-Nitrophenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-one (**7**) (0.005 mol) was dissolved in an ethanol-water mixture (50 mL, 3:2, v/v). Iron filings and glacial acetic acid (1 mL) were added, and the mixture was refluxed for 3 h. It was cooled and filtered, made alkaline by sodium carbonate, and extracted ($CHCl_3$). The organic layer, evaporated in vacuo, afforded the crude base which was converted to the corresponding hydrochloride.

Guinea Pig Ileum in Vitro Assay for H_1-Receptor Histamine Antagonism. The assay was performed on ileum of either sex (weighing ~250 g) Percentage inhibition for guinea pig[5] was calculated on the response caused by 0.5 μM histamine in the absence of drugs. Six observations were carried out for each drug concentration. The results, IC_{50}, listed in Table II, are reported as concentration of drug causing 50% inhibition of the submaximal contractions induced by histamine.

The dissociation constant (K_B), for pA_2 value calculations ($pA_2 = -\log K_B$), was evaluated according to the method of Schild,[10] from the equation $K_B = B/(x - 1)$, where x is the respective ratio of concentrations of histamine needed to produce half-maximal responses in the presence and absence of different concentrations (B) of antagonists. pA_2 values, reported in Table II, are the average of five observations.

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Registry No. **1**, 141955-94-4; **1** base, 141956-11-8; **1a**, 141956-09-4; **1a** base, 141956-26-5; **1b**, 141956-10-7; **1b** base, 141956-27-6; **2**, 141955-95-5; **2** base, 141956-12-9; **3**, 141955-96-6; **3** base, 141956-13-0; **4**, 141955-97-7; **4** base, 141956-14-1; **5**, 141955-98-8; **5** base, 141956-15-2; **6**, 141955-99-9; **6** base, 141956-16-3; **7**, 141956-00-5; **7** base, 141956-17-4; **8**, 141956-01-6; **8** base, 141956-18-5; **9**, 141956-02-7; **9** base, 141956-19-6; **10**, 141956-03-8; **10** base, 141956-20-9; **11**, 141956-04-9; **11** base, 141956-21-0; **12**, 141956-05-0; **12** base, 141956-22-1; **13**, 141956-06-1; **13** base, 141956-23-2; **14**, 141956-07-2; **14** base, 141956-24-3; **15**, 141956-08-3; **15** base, 141956-25-4.

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Communications to the Editor

Probing the Molecular Basis of Resistance to Pyrimethamine by Site-Directed Mutagenesis

Rational drug design is based on understanding the principles of molecular recognition which govern receptor-ligand interactions. Recently, investigations of the mechanism of action and design of selective inhibitors for dihydrofolate reductase (5,6,7,8-tetrahydrofolate:$NADP^+$ oxidoreductase, EC 1.5.1.3; DHFR) have been greatly facilitated by advances in X-ray crystallography, recombinant-DNA technology, and molecular modeling techniques.[1-3] The enzyme, by catalyzing the NADPH-dependent reduction of 7,8-dihydrofolate (H_2F) to tetrahydrofolate (H_4F), is primarily responsible for the maintenance of essential intracellular cofactor pools of key importance for biosynthetic reactions requiring one-carbon unit transfer. Consequently, the synthesis of highly specific anti-folates has been spectacularly successful in producing powerful therapeutic agents.[3] For example, pyrimethamine is 1400-fold more active against the malaria enzyme isolated from *Plasmodium berghei* than the rat liver enzyme.[4] The basis for this specificity has been

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