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Synthesis and structure–activity relationships of 2-(substituted phenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-ones acting as H_1-histamine antagonists

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Abstract

2-(Substituted-phenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-ones (**1**–**15**) showed dependence of the potency of the H_1-histamine antagonism on the *m*- and *p*-substituents suggesting that the aromatic moiety binds the receptor by a strong π-interaction. Electron-withdrawing substituents decrease the potency while the electron-donating alkyl substituents, enhancing the aryl HOMO energy, increase the antihistamine activity. The *m*-substituents with the capability to form hydrogen bonds, seems to share an extrainteraction with hydrogen accepting or donating groups of the histamine receptor and exhibits very high potency.

Keywords: 1,3-Thiazolidin-4-ones derivatives; H_1-Antihistamine activity

1. Introduction

The most important conclusion on the H_1-histamine antagonist model by QSAR and receptor mapping studies performed on both classical and non-classical H_1-antagonists suggests that there is a critical distance, around 6 Å, between a basic tertiary nitrogen atom and an aromatic ring [1–4]. The tertiary nitrogen and the aromatic system have been proposed to interact respectively, with the carboxy group of an aspartate (Asp^{311}) and the phenyl group of two different phenylalanines (Phe^{509} and Phe^{617}) belonging to the H_1-receptor protein [5,6]. While the main interaction is electrostatic, the phenyl–phenyl one is a π-stacking.

In a previous paper the synthesis and the H_1-antihistaminic activity of some 2-(substituted-phenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-ones [7–9] were reported. The dependence of the H_1-antihistaminic potency on the aromatic substituents suggested that the aryl group binds to the receptor by a strong π-interaction.

In order to investigate this binding, a new series of 2-(substituted-phenyl)-3-[3-(*N*,*N*-dimethylamino)-propyl]-1,3-thiazolidin-4-ones (Fig. 1) was synthesized, characterized and evaluated for its capacity to inhibit the contraction induced by histamine on guinea pig ileum.

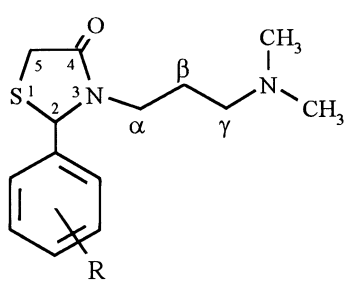

Fig. 1.

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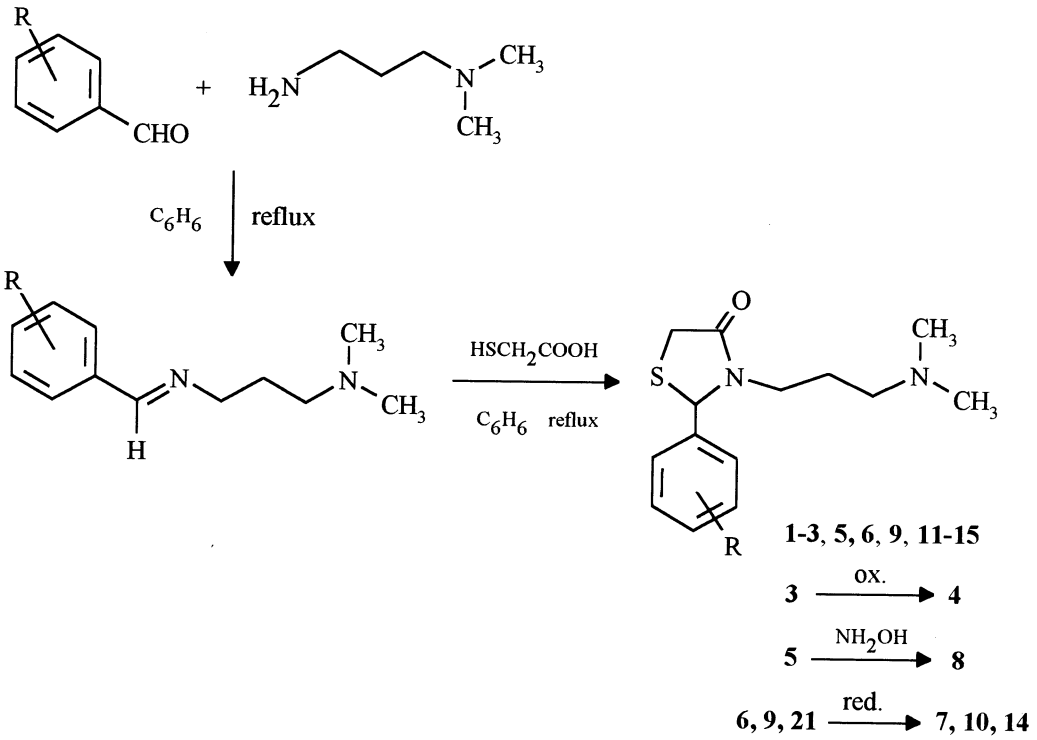

Scheme 1.

2. Chemistry

The thiazolidinones **1**–**15**, reported in Scheme 1 and Table 1, were synthesized by addition of mercaptoacetic acid to *N*-(substituted-benzylidene)-*N*′,*N*′-dimethyl-1,3-diaminopropane in refluxing benzene. Radziszewski oxidation of **3** afforded **4**, while **8** was obtained by treatment of **5** with hydroxylamine. Compounds **7**, **10** and **14** were obtained by reduction of the corresponding nitro derivatives **6**, **9** and **21**, respectively. The substituted aldehydes used to prepare the compounds **6** and **9** were synthesized according to the procedures reported in Section 4.

The products were characterized by their spectroscopic properties (IR, ^{1}H NMR) and elemental analysis.

The ^{1}H NMR data of compounds **1**–**15**, reported in Table 2, and the NOESY experiments, in agreement with the X-ray data, suggested that the chain lies in a *gauche* (α–β CH_2)-anti (β–γ CH_2) conformation. This spatial arrangement reduces the distance between the aromatic ring and the tertiary nitrogen compared with the distance of an all-*anti* conformation. According to the current reports, this conformation satisfies the requirement of a 6 Å distance that gives rise to good electrostatic and π interaction of the basic nitrogen and of the phenyl ring with the corresponding areas of receptor.

3. Results and discussion

Thiazolidinones **1**–**15** as free bases were converted into the corresponding hydrochlorides for the pharmacological assays. The H_1-antihistaminic activity of the synthesized compounds was evaluated in vitro by measuring their ability to inhibit the histamine-induced contractions of isolated guinea-pig ileum [10] and reported, as pA_2 values, in Table 3. The results were

Table 1
1,3-thiazolidin-4-ones (**1**–**15**)

Comp.	R	Formula	Yield	M.p. (°C)
1	4-OH	$C_{14}H_{20}N_2O_2S$	45	208–9
2	4-N(Me)$_2$	$C_{16}H_{25}N_3OS$	58	168–9
3	3-CN	$C_{15}H_{19}N_3OS$	40	227–8
4	3-CONH$_2$	$C_{15}H_{21}N_3O_2S$	70	224–5
5	3-CHO	$C_{15}H_{20}N_2O_2S$	32	275–6
6	4-NO$_2$, 3-Me	$C_{15}H_{21}N_3O_3S$	42	200–1
7	4-NH$_2$, 3-Me	$C_{15}H_{23}N_3OS$	60	230–1
8	3-CHNOH	$C_{15}H_{21}N_3O_2S$	57	200–1
9	3-NO$_2$, 4-Me	$C_{15}H_{21}N_3O_3S$	48	218–9
10	3-NH$_2$, 4-Me	$C_{15}H_{23}N_3OS$	65	248–9
11	4-OC$_3$H$_7$	$C_{17}H_{26}N_2O_2S$	68	173–4
12	4-C$_2$H$_5$	$C_{16}H_{24}N_2OS$	62	156–7
13	4-NHCOMe	$C_{16}H_{23}N_3O_2S$	65	226–7
14	3-NH$_2$	$C_{14}H_{21}N_3OS$	62	170–1
15	4-*t*But	$C_{18}H_{28}N_2O_2S$	70	253–4

Table 2
^{1}H NMR data of 1,3-thiazolidinones [a]

Comp.	2-Ph		2-H	AB system						R
				5-CH_A [b]	5-CH_B [b]	α-CH_2 [c]	β-CH_2	γ-CH_2	$N(CH_3)_2$	
1	7.13 (d)	6.66 (d)	5.58	3.79	3.69	3.58 2.79	1.64	2.28	2.21	
2	7.15 (d)	6.64 (d)	5.57	3.76	3.64	3.55 2.74	1.56	2.16	2.11	2.93 (s)
3	7.65 (d)	7.58 (s)	5.68	3.81	3.70	3.67 2.71	1.62	2.24	2.14	
	7.53 (t)	7.51 (d)								
4	7.80 (s)	7.79 (t)	5.69	3.83	3.69	3.61 2.78	1.57	2.17	2.10	6.80 (bs)
	7.46 (d)	7.45 (d)								
5	7.78 (d)	7.75 (s)	5.68	3.75	3.63	3.58 2.64	1.53	2.12	2.05	9.94 (s)
	7.51 (d)	7.49 (t)								
6	7.99 (d)	7.27 (d)	5.73	3.81	3.72	3.71 2.68	1.83	2.39	2.29	2.60 (s)
	7.26 (s)									
7	6.97 (s)	6.95 (d)	5.53	3.78	3.67	3.56 2.73	1.59	2.17	2.12	2.13(s)
	6.92 (d)									1.94(bs)
8	7.48 (s)	7.47 (d)	5.58	3.78	3.64	3.61 2.77	1.61	2.12	1.99	8.02 (s)
	7.37 (d)	7.28 (t)								
9	7.91 (s)	7.46 (d)	5.70	3.82	3.71	3.67 2.73	1.68	2.19	2.14	2.61 (s)
	7.38 (d)									
10	7.02 (d)	6.59 (d)	5.54	3.79	3.67	3.66 2.66	1.61	2.19	2.15	2.14 (s)
	6.57 (s)									1.90 (bs)
11	7.02 (d)	6.72 (d)	5.38	3.69	3.52	3.38 2.78	1.47	2.01	1.93	3.50(t) 1.53(m) 0.82(t)
12	7.21 (d)	7.18 (d)	5.63	3.79	3.68	3.58 2.77	1.64	2.33	2.25	2.63 (q) 1.21 (t)
13	7.35 (d)	7.25 (d)	5.64	3.78	3.66	3.59 2.71	1.59	2.20	2.13	7.68 (bs) 2.17 (s)
14	6.91 (t)	6.47 (d)	5.33	3.77	3.51	3.65 2.78	1.50	2.17	1.94	2.80 (bs)
	6.23 (s)	6.18 (d)								
15	7.37 (d)	7.22 (d)	5.64	3.79	3.68	3.58 2.78	1.62	2.33	2.23	1.29 (s)

[a] $CDCl_3$, chemical shifts in ppm.
[b] $J_{A,B} = 15$ Hz.
[c] $J_{a,b} = 13$ Hz, $J_{\alpha,\beta} = 7$ Hz, $J_{\beta,\gamma} = 7$ Hz, $J_{2,5A}$ = between 1.5 and 2 Hz.

compared with the activity of mepyramine and with previously synthesized thiazolidinones **16**–**22**.

The thiazolidinones **1**–**15** were also tested to investigate the anticholinergic ability to inhibit the acetylcholine induced contractions on guinea-pig ileum. No anticholinergic activity was detected for all compounds.

According to the previous pA_2 data on the phenyl substituent effect, the alkyl (Me [7], Et, *i*-Prop [7], *t*-But) substituted thiazolidinones (**19**, **12**, **16**, **15**) showed high values of H_1-antagonism (p$A_2 > 8$). The *para*-substituent effect was the most intensive (**19** was five times more active than **18**). The pA_2 values of the alkyl derivatives (Me < Et < *i*-Prop < *t*-But) suggested that a hydrophobic interaction is involved, probably in a lipophylic area.

On the contrary, the polar *p*-electron-donating groups as OCH_3 (**20**) < OC_3H_7 (**11**) < NH_2 (**17**) ≃ $N(Me)_2$ (**2**) ≃ OH (**1**), with large mesomeric effects, reduce the potency of the thiazolidinones as the electron-withdrawing halogens [7] and nitro group [7] (p$A_2 \leq 7$) do. Thiazolidinones **6** and **9** showed a low potency, dramatically affected by the presence of the strong electron-withdrawing nitro group, in spite of the positive influence of the methyl group. Moreover, the alkyl substituents, raising the energy of the HOMO [11], could increase the electron availability of the aromatic system to share the π-interaction.

The electron-donating 4-substituents NH_2 (**17**), OH (**1**), $N(Me)_2$ (**2**), OCH_3 (**20**) would exert a detrimental effect on activity, owing to their hydrophilic nature [12]. In opposition to the potency of **15** the inactivity of compound **11** is likely connected with the length of the OC_3H_7 group, which could be repelled by the steric

Table 3
H_1-antagonistic activity on guinea-pig ileum [a]

Comp.	R	pA_2 [b]	Comp.	R	pA_2 [b]
1	4-OH	6.4	**12**	4-C_2H_5	8.8
2	4-$N(Me)_2$	6.3	**13**	4-NHCOMe	7.2
3	3-CN	5.7	**14**	3-NH_2	7.3
4	3-$CONH_2$	11.4	**15**	4-*t*But	9.5
5	3-CHO	11.7	**16** [c]	4-*i*Pro	9.0
6	4-NO_2, 3-Me	5.7	**17** [c]	4-NH_2	6.0
7	4-NH_2, 3-Me	9.3	**18** [c]	3-Me	7.7
8	3-CHNOH	11.2	**19** [c]	4-Me	8.3
9	3-NO_2, 4-Me	6.4	**20** [c]	4-OMe	5.0
10	3-NH_2, 4-Me	11.3	**21** [c]	3-NO_2	5.4
11	4-OC_3H_7	5.5	**22** [c]	4-NO_2	5.2

[a] Mepyramine p$A_2 = 9.0$.
[b] ± 0.2.
[c] Reported in Ref. [7].

boundaries of the lipophilic area which probably has the feature of a restricted cleft.

The strong H_1-antihistaminic activity ($pA_2 > 11$) showed by **4**, **5** and **8**, expected to be less active, needs a different interpretation. In fact, the electron-withdrawing substituents $CONH_2$, CHO and CHNOH make the thiazolidinones more active than the other electron-withdrawing substituted derivatives and more active also than the alkyl substituted ones.

This behavior might depend on the capability of the $CONH_2$, CHO and CHNOH groups to be involved in hydrogen-bond interactions in the binding site.

Actually, the above quoted mapping receptor studies of H_1-receptor suggest that Asn^{508} is present in proximity of the Phe^{509} and could promote the binding by interaction with the 3-substituents $CONH_2$, CHO and CHNOH as hydrogen bond accepting/donating group [5].

In fact, the 3,4-disubstituted thiazolidinones **7** and **10** showed higher potency than the corresponding monosubstituted methyl or amino thiazolidinones. The 100 times increase in activity observed going from **7** (4-NH_2, 3-Me) to its positional isomer **10** (3-NH_2, 4-Me), may reflect favorable interactions involving the 3-NH_2 (hydrogen bond) and the 4-Me (HOMO energy enhancement) groups.

In conclusion, whenever the phenyl moiety of the thiazolidinones interacts with a complementary area of the H_1-receptor, this π interaction is enhanced by not hydrophilic substituents increasing the HOMO energy and is affected by the size of the 4-alkyl substituent. The 3-arylsubstituent capable of hydrogen-bonding, probably lying at suitable distance from Asn^{508}, seems to produce a strong additional interaction, thus enhancing the potency. In this perspective, the hypothesis of an additional hydrogen bond between the electronegative atom of the 3-substituent and a neighboring site of the H_1-histamine receptor, could explain the high H_1-antihistaminic activity of **4**, **5** and **8**. Moreover, this result highlights another aspect of the H_1-histamine receptor and supports the early hypothesis of Nauta et al. on the possibility of hydrogen bonding between a hydrophilic aminoacidic residue and some antihistaminic drugs [2].

4. Experimental

4.1. Chemistry

Melting points of thiazolidinones hydrochlorides reported in Table 1 were determined with a Kofler apparatus and are uncorrected. The elemental analyses (C, H and N) of the reported compounds are within $\pm 0.4\%$ of theoretical values. Electron impact (EI) mass spectra were obtained at 70 eV on a VG ZAB 2F mass spectrometer. The purity of the compounds was checked by ascending TLC on F_{254} Merck precoated silica-gel plates (0.25 mm) with fluorescent backing.

IR spectra were taken on a Perkin–Elmer 399 spectrophotometer in KBr. The C=O stretching occurs at 1705–1710 cm^{-1} for the thiazolidinones **1**–**15**. The $CONH_2$ stretching of the compound **4** lies at 3350–3170 and 1646 cm^{-1}.

^1H NMR data reported in Table 2 were recorded in $CDCl_3$ on a Bruker 500 MHz spectrometer with Me_4Si as internal reference. Chemical shifts are given in ppm and coupling constants in Hz.

4.1.1. 2-(Substituted-phenyl)-3-[3-(N,N-dimethylamino)-propyl]-1,3-thiazolidin-4-one (*1*–*3*, *5*, *6*, *9*, *11*–*15*)

General procedure. An equimolar mixture (10 mmol) of substituted benzaldehydes and 3-(*N*,*N*-dimethyl amino)-1-propylamine (10 mmol) in dry benzene (50 ml) was refluxed until no more water was collected in a Dean–Stark water separator. Mercaptoacetic acid (0.01 mol) was added, dropwise, to this crude mixture, and the reaction was carried out at reflux temperature until stoichiometric water was collected.

The mixtures, cooled and evaporated in vacuo, afforded, as pale yellow oils, the free bases of **1**–**3**, **5**, **6**, **9**, **11**–**15**, which were dissolved in anhydrous ethanol (20 ml). Diethyl ether (20 ml), saturated with HCl, was added to these solutions. White powders were collected and, recrystallized by absolute ethanol, yielded the thiazolidin-4-one hydrochlorides.

4.1.2. 3-Methyl-4-nitro- and 4-methyl-3-nitrobenzaldehydes (*23*, *24*)

General procedure. The benzaldehydes **23** and **24** were synthesized to prepare thiazolidinones **6** and **9** by oxidation of the corresponding benzyl alcohols. To the yellow complex, formed by mixing CrO_3 (3.2 g) to pyridine (60 ml) at 0°C, the 3-nitro, 4-methyl or 3-methyl, 4-nitro benzylalcohol (20 mmol) was added. The mixture, stirred for 30 min at 0°C and heated at 50°C for 2 h, was filtered and the solution was evaporated in vacuo and chromatographed on a silica gel column using chloroform as eluent. The fraction containing the aldehydes recovered and evaporated in vacuo yielded **23** and **24**, respectively, both as pale-yellow crystals.

23: ^1H NMR ($CDCl_3$): 10.09 (1H, s), 8.46 (1H, d, $J = 8.0$), 7.87 (1H, d, $J = 1.3$), 7.86 (1H, dd, $J = 8.0$, 1.3), 2.67 (3H, s). M.p. 65–66°C. MS, m/z: 165 (M^+). *Anal*. $C_8H_7NO_3$: (C, H, N). Yield 38%.

24: ^1H NMR ($CDCl_3$): 9.59 (1H, s), 8.46 (1H, d, $J = 1.6$), 8.03 (1H, dd, $J = 7.8$, 1.6), 7.55 (1H, d, $J =$ 7.8), 2.70 (3H, s). M.p. 94–95°C. MS, m/z: 165 (M^+). *Anal*. $C_8H_7NO_3$: (C, H, N). Yield 45%.

*4.1.3. 2-(4-Amino-3-methyl-phenyl)-3-[3-(N,N-dimethylamino)propyl]-1,3-thiazolidin-4-one (**7**), 2-(3-amino-4-methyl-phenyl)-3-[3-(N,N-dimethylamino)-propyl]-1,3-thiazolidin-4-one (**10**) and 2-(3-amino-phenyl)-3-[3-(N,N-dimethylamino)propyl]-1,3-thiazolidin-4-one (**14**)*

To a solution of **6**, **9** or 2-(3-nitrophenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-one (**21**) (10 mmol) in ethanol (15 ml), glacial acetic acid (5 ml) and Fe filings (4 g) were added. The reaction mixture, after stirring at reflux temperature for 4 h, was diluted with HCl 2 N and extracted with chloroform. The aqueous layer, alkalinized with NaOH 2 N and extracted with diethyl ether, afforded **7**, **10** and **14**, respectively.

*4.1.4. 2-(3-Carbamoyl-phenyl-3-[3-(N,N-dimethyl-amino)-propyl]-1,3-thiazolidin-4-one (**4**)*

To a stirred mixture of NaOH (1 g in pellets) in *n*-butanol (50 ml) and **3** (10 mmol) 33% H_2O_2 (1 ml) was added. After 10 min at room temperature, the reaction mixture was filtered and the filtrate evaporated in vacuo yielded the crude **4**, that was purified by TLC (0.50 mm) on silica gel using triethylamine:*n*-hexane:ethanol 3:10:2 v/v.

*4.1.5.2-(3-Hydroxyimino-phenyl)-3-[3-(N,N-dimethyl-amino)propyl]-1,3-thiazolidin-4-one (**8**)*

A mixture of thiazolidinone **5** (10 mmol) and hydroxylamine (2 ml of 50% aqueous solution), in benzene (100 ml) was refluxed for 4 h using a Dean–Stark water separator. When no more water was separated, the mixture was evaporated in vacuo to yield the crude **8** that was purified as indicated in the general procedure.

4.2. Pharmacology

4.2.1. Guinea-pig ileum in vitro assay for H_1-receptor histamine antagonism

The assays were performed on ileum of either sex guinea-pigs weighing ~ 250 g [10]. The dissociation constants (K_B) for pA_2 value calculations were evaluated, according to Schild [13], 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; $pA_2 = -\log K_B$. The pA_2 values, reported in Table 3, are the average of six measurements.

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