ELSEVIER

Intramolecular C-H--O interaction between lactam oxygen and N-alkyl protons

Vincenzo Barone,* Adele Bolognese,† Gaetano Correale,‡ Maria Vittoria Diurno,‡ Isabel Gomez-Monterrey,‡ and Orazio Mazzoni‡

**Dipartimento di Chimica, Università di Napoli "Federico II", Napoli, Italy*
†Dipartimento di Chimica Organica e Biologica, Università di Napoli "Federico II", Napoli, Italy
‡Dipartimento di Chimica Farmaceutica e Tossicologica, Università di Napoli "Federico II", Napoli, Italy

We report evidence of an unusual C-H--O interaction between an α-methylene hydrogen of the alkylamine chain of substituted (N,N-dimethylamino)propyl-azetidinones, substituted (N,N-dimethylamino)propyl-thiazolidinones and substituted (N,N-dimethylamino)propyl-thiazinone and the lactam carbonyl oxygen. NMR analysis results, supported by molecular mechanic predictions, were in agreement with ab initio calculations. The observed interaction shorting the nitrogen–nitrogen distance in the H_1-histamine antagonist, 2-(4-methylphenyl)-3-[3-(N,N-dimethylamino)propyl]-1,3-thiazolidin-4-one (1) could explain its fitting with the H_1-antihistaminic pharmacophoric model and the high antihistaminic activity. © *2001 by Elsevier Science Inc.*

Keywords: 1,3-Thiazolidin-4-ones derivatives, Unusual C-H--O interactions

INTRODUCTION

Hydrogen bonding, especially the intramolecular variety, often plays a significant role in influencing the molecule conformation. Although research has discovered hydrogen bonding by the C-H group, few types of C-H bonds have been found that are polarized enough to form hydrogen bonds [1,2]. During a study on a recently synthesized series of 2-(substituted-phenyl)-3-[3-(*N,N*-dimethylamino) propyl]- 1,3-thiazolidin-4-ones[3–5] active as H_1-histamine antagonists, ^{1}H NMR data showed that the geminal protons of the three methylene groups, α, β, and γ, belonging to the alkylaminic side chains of series are not equivalent and are coupled to each other in a gauche-anti conformation (**1**, Figures 1 and 2). The chemical shift difference (~0.9 ppm) between the geminal α-CH_2 protons is very large and could be ascribed to an unusual intramolecular interaction, such as a hydrogen bond, between the amidic oxygen of the thiazolidinone ring and a hydrogen of the α-CH_2.

Corresponding author: Professor A. Bolognese, Università di Napoli Federico II, Dipartimento di Chimica Organica e Biologic, Napoli, Italy.

RESULTS

Because of the importance of the stabilizing role of such a CH--O interaction, a study was performed to explain and generalize what was observed in the thiazolidinone derivatives. Compounds **2**, **3** and **5**–**12** with different lactam rings, chain length, and substituents were synthesized to investigate the effects of these differences on the CH--O bond strength (Figure 1). The experimental section reports general synthetic procedures and characterization of all new compounds on the basis of physicochemical and spectral data and elemental analysis. Table 1 lists the chemical shift values of alkylaminic chain protons and the H_a-H_b differences and shows that methylene protons are equivalent in the achiral compounds, whereas they are diastereotopic in the chiral ones. Moreover, the H_a-H_b difference appears depending on cycle width. ^{13}C-^{1}H heteronuclear long-range coupling investigation performed on chiral and nonchiral thiazolidinones showed strong coupling between the carbonyl carbon and the α-CH_2 signals. COSY and NOESY experiments on the chiral thiazolidinones showed the interactions of the low field hydrogen (H_a) of α-CH_2 with the low field hydrogen of 5-CH_2 AB system of the thiazolidinone ring (H_A) and with the hydrogens of γ-CH_2. Furthermore the heterocyclic C_2-H showed a strong interaction with the low field hydrogen of β-CH_2 system (H_d). These results suggest that N-alkyl chain of chiral thiazolidinones stays in a α-β gauche β-γ anti-conformation where the dihedral angle between carbonyl group and one of α-CH_2 hydrogens is different from the other one. In the nonchiral compounds, the N-alkyl chain lies in the same conformation of the chiral compounds, but the

Journal of Molecular Graphics and Modelling 19, 318–324, 2001

655 Avenue of the Americas, New York, NY 10010
1093-3263/01/$–see front matter
PII S1093-3263(00)00078-4

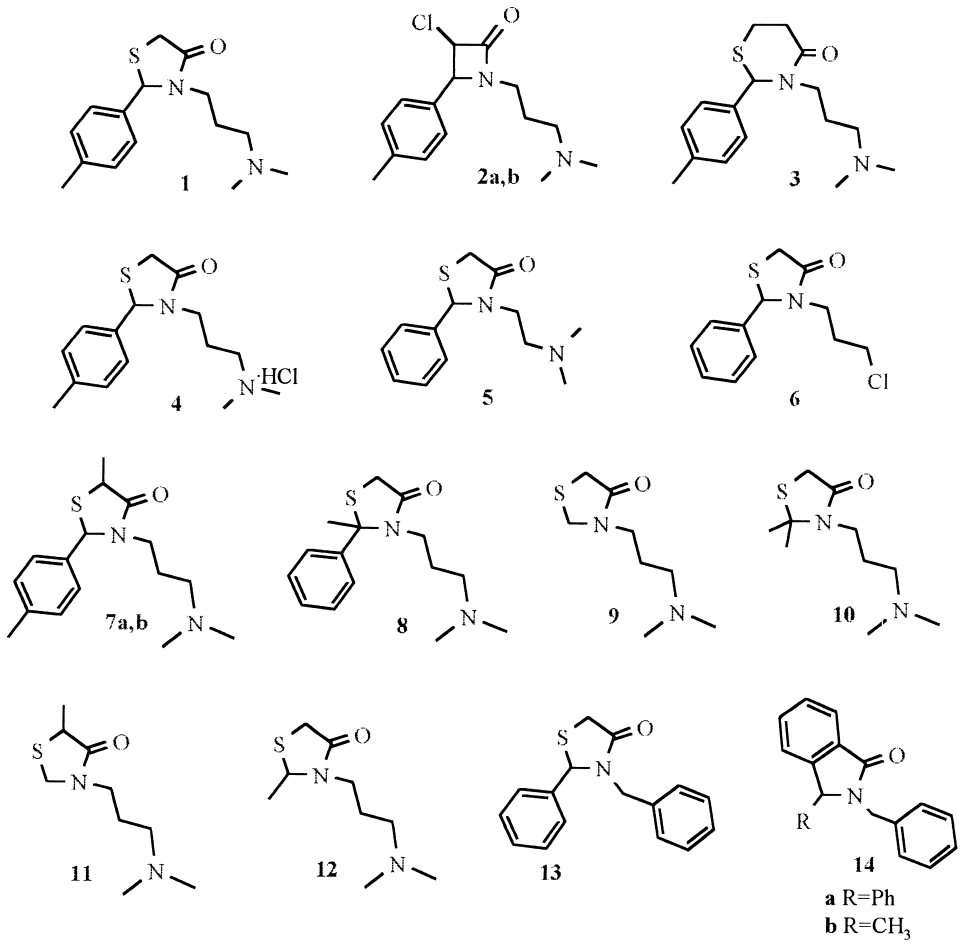

Figure 1. Thiazolidinone, azetidinone and thiazinone structures synthesized to study C-H--O interaction.

α-CH_2 hydrogens give rise only to a signal owing to the equivalence of two sides of the thiazolidinone plane. In this situation the ^{1}H NMR signals will be the average of signals arising from equivalent populations of enantiotopic conformers. Figure 2 shows the best conformation of **1** that agrees with the NMR results.

DISCUSSION

To investigate these results and to justify the origin of the large H_a-H_b nonequivalence, the geometries of thiazolidinones **1** and **5–12** were generated within SYBYL[6] starting from the relevant internal coordinates determined for 2-(4-nitrophenyl)-3-[3-(*N*,*N*-dimethylamino) propyl]-1,3-thiazolidin-4-one hydrochloride by X-ray diffraction.[1] X-ray data showed that the H-C_α-N_3-C_4═O atoms lie on the same plane, that the C_4═O--H-C_α distance is 2.33 Å, shorter than van der Waals radii, and that the C_4═O--H angle is 110°. Molecular mechanics calculations of the low-energy conformations of all derivatives were carried out by TRIPOS force field[6] of SYBYL. Geometry optimizations were realized with the semiempirical quantum-mechanical method AM1,[7] available in the MOPAC program[8] (default settings; keyword: "MMOK"). Two low energy conformers (I and II) of **1** and **5**–**12**, showed a gauche-anti conformation of the alkylamine chain and the H-C_α-N_3-C_4═O

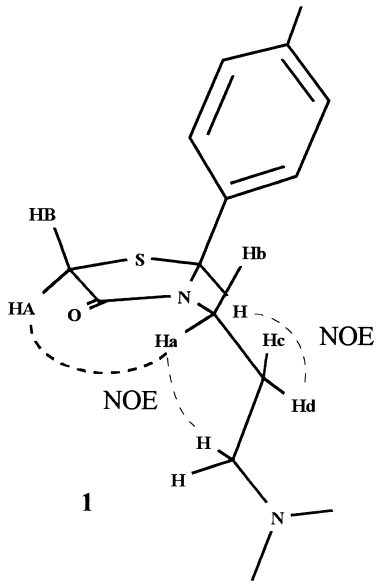

Figure 2. NOE interaction detected by COSY and NOESY experiments on **1.**

Table 1. ^{1}H NMR data of α,β and γ-CH_2 protons of 1-3 and 5-13 in C_6D_6 and 25°C (multiplet center) and of 4 in D_2O.

H_a-H_b difference	cpd	α-CH_2		β-CH_2		γ-CH_2	
		H_a	H_b	H_c	H_d	H_e	H_f
0.96	**1**	3.70	2.74	1.54	1.41	2.03	1.91
0.59	**2a**	3.48	2.89	1.65		2.24	
0.55	**2b**	3.46	2.89	1.59		2.16	
1.63	**3**	4.31	2.68	1.88	1.69	2.35	2.02
0.36	**4**	3.43	3.07	1.69		2.94	
1.25	**5**	3.80	2.55	2.21	1.97		
0.85	**6**	3.44	2.59	1.54	1.44	2.97	2.91
0.85	**7a**	3.60	2.75	1.57		2.18	
0.90	**7b**	3.65	2.75	1.64		2.18	
0.64	**8**	3.55	2.91	1.86	1.70	2.05	
0.00	**9**	3.13		1.41		2.01	
0.00	**10**	3.14		1.68		2.09	
0.12	**11**	3.20	3.08	1.40		1.99	
0.69	**12**	3.53	2.84	1.52	1.37	2.04	1.96
1.84	**13**	4.66	2.82				
1.75	**14a**[a]	5.42	3.67				
1.05	**14b**[a]	5.20	4.15				

[a]Spectrum recorded in carbon tetrachloride.[9]

atoms lying on the same plane in agreement with an attractive interaction between the carbonyl oxygen and an α-CH_2 hydrogen (Figure 3). When X = Y, the two thiazolidinone planes are equal, I and II have the same energy and are equally probable, and ^{1}H NMR spectrum shows only one α-CH_2 signal. When $X \neq Y$, $H_a \neq H_b$, the two low-energy minimized conformers, I and II, contribute differently to the H_a and H_b shifts, and ^{1}H NMR spectrum shows two α-CH_2 signals. According to the energy difference in **1** ($\Delta E = 1$ kcal/mol; I constitutes approximately 80%, and II 20%), the dominance of I agrees with the NOESY results (Figure 2) and X-ray data.[3] NMR experiments performed in a temperature range of 25–50 °C showed no temperature-dependent chemical shift, reflecting a stable population distribution. Moreover, nonprotic solvents, such as benzene, seem to increase the reported conformational preference, whereas water weakens it, pushing the two α-CH_2 signals (^{1}H NMR data of **4**) very close. All data are in agreement with the reported C-H--O interaction.[2] In conclusion, the hydrogen–oxygen interaction, resulting in a low field H_a, plays the same role in chiral and achiral thiazolidinones stabilizing low-energy conformers. In the chiral compounds these two conformers are pseudo-diastereoisomers, whereas in nonchiral compounds they are enantiotopic forms. This attractive interaction is not affected by substituent effects, steric hindrance, or shielding-deshielding effects, so it appears similar to an electrostatic interaction as in a hydrogen bond. In fact, in **9** as in **10,** the α-CH_2 signals lie at 3.13 and at 3.14 δ, whereas in **8** and **12** the C-H_a signals lie at 3.55 and 3.53 δ excluding any inductive and steric effect on the alkyl chain chemical shifts.[8] 2-Substituted and unsubstituted thiazolidinones as azetidinones **2a**, **b** and thiazinone **3**, showed the same N-alkylaminic chain conformation. Figure 4 shows a generic lactam and the optimized structures of **1**, **2**, and **3** obtained from the SYBYL program. In the azetidinones **2** as in the thiazinone **3** the α-CH_2 hydrogens are diastereotopic and, the calculated angles C_α-N_3-C_4 of **1**, C_α-N_1-C_2 of **2**(**a**, **b**) and C_α-N_3-C_4 of **3** were, respectively, 123°, 130°, and 119° (Figure 4). The hydrogen–oxygen distances were 2.3, 2.8, and 2.2 Å showing that the thiazinone geometry could allow the best hydrogen interaction. According to this, the chemical shift difference between the H_a and H_b in **3** is larger (1.65 δ) than in the corresponding five and four member rings of **1** and **2** (0.96 and 0.65 δ), respectively. On the basis of these results, it seems reasonable that azetidinone, thiazolidinone, and thiazinone systems sufficiently influence the polar-

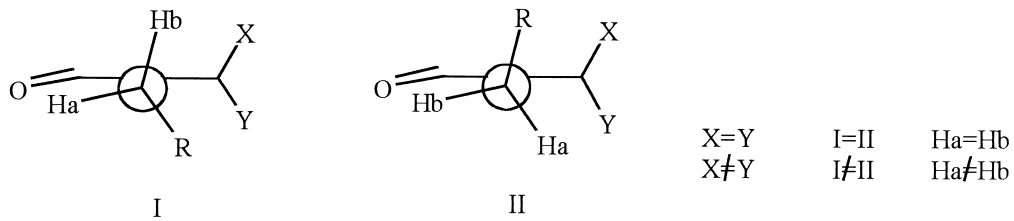

Figure 3. Two low energy thiazolidinone conformers contributing differently to the α-CH_2 shifts.

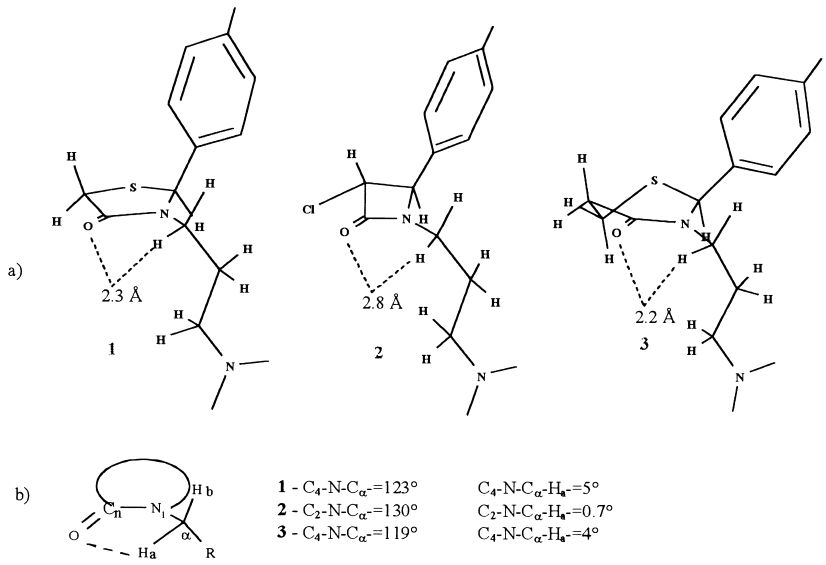

*Figure 4. (a) **1**, **2** and **3** structures represent the minimum energy conformers obtained from SYBYL package. (b) Generic N-alkyl lactam structure. C_4-N-C_α and C_4-N-C_α-H_a didehral angles are reported.*

ization of the C-H bond[10–12] acting as electron-withdrawing group on the side N-alkylic chain and allow the development of an attractive intramolecular interaction between C_α-H_a and the carbonyl oxygen. To gain further insight into the electronic origin of the behavior of these molecules, we performed a number of quantum mechanical computations by the Gaussian 98 package[13] using the very reliable PBE0 density functional[14] and the 6-311G(d,p) basis set,[15] which provide essentially converged results at the DFT level.[16] In a first step, we have fully optimized the geometries of **1** and of the two model compounds 3-methyl-1,3-thiazolidin-4-one (**15a**) and 3-ethyl-1,3-thiazolidin-4-one (**15b**) as shown in Figure 5. In all cases, the most stable conformer has one of the α-CH_2 hydrogens in the plane of the thiazolidinone ring and a short O–H distance (2.333, 2.328, and 2.306 Å, respectively), which is quite close to the molecular mechanics result. Analogous computations for **15b** in aqueous solution by the C-PCM model[17] show that environmental effects do not alter the structure of these compounds significantly. Next, the net atomic charges of **15b** have been obtained by a number of different procedures, including Mulliken[18,19] and natural bond orbital (NBO)[20] population analyses, fitting of the molecular electrostatic potential (MEP)[21,22] and atomic polar tensor (APT)(Table 2).[23] Whereas the different procedures give widely different charges, all the methods agree in indicating that the α-methylene unit is more positive than the β-methyl group. Moreover, a significant Coulombic interaction is operative between the oxygen atom and the α-CH_a hydrogen. The NBO analysis also allows a dissection of the interactions between different localized orbitals into physical significant terms. In the present case, the most significant (and conformation-dependent) interaction occurs between an oxygen lone-pair and the C-Ha σ^* bond orbital. This interaction thus contributes to further stabilize conformers with the C-H_a bond lying in the ring plane. Further studies will be performed on this topic. This C-H--O interaction, which is similar to a hydrogen bond, stabilizes a gauche-anti spatial arrangement of the alkylaminic chain of 2-(substituted-phenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-one series, thereby reducing the distance between the two nitrogens; this geometry can dramatically affect H_1-histamine antagonism.[24,25] H_1–histamine antagonist thiazolidinones,[3,5,26] as the majority of potent antihistamines, are tertiary amines and exist at physiological pH with the nitrogen of the side chain protonated. Nevertheless, when they interact with a receptor,[26,27] it can be a nonaqueous milieu where the hydrogen-bond constrained conformation is reasonable. Better fitting with the receptor site can be responsible for the high H_1–histamine receptor affinity.

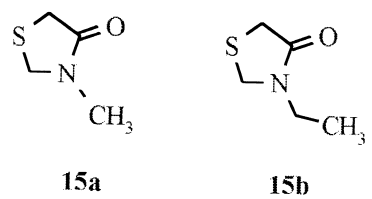

Figure 5. 1,3-thiazolidinones used for quantum mechanical computations.

MATERIALS AND METHODS

The IR spectra were taken on a Perkin-Elmer 1760-X IFT (Perkin Elmer Corp., Norwalk, CT USA) spectrophotometer in potassium bromide. The ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Fourier-transform Bruker

Table 2. Net atomic charges of 15b obtained by different procedures

	Mulliken	ESP	NBO	APT
qO	−0.388	−0.514	−0.602	−0.794
qN	−0.420	−0.249	−0.474	−0.802
qH_a	0.162	0.056	0.234	0.162
qCH_2	0.141	0.254	0.226	0.351
qCH_3	0.066	−0.062	0.018	−0.002

spectrometer AMX 500 equipped with a Bruker X-32 computer, using the UXNMR software package (Unix Software (ver. 950901) developed by Bruker Analytische Messtechnik GmbH, Rheinstetten, Germany). Standard pulse sequences were employed for DEPT and COSY. Phase sensitive NOESY spectra were measured with a mixing time t_m 800 ms, while HMQC and HMBC were optimized for $^1J_{C\text{-}H}$ = 135 Hz and $^{2,3}J_{C\text{-}H}$ = 8 and 10 Hz, respectively. To enhance the results, nitrogen was bubbled through the sample to remove oxygen. Electron impact (ei) mass spectra were obtained at 70 eV on a VG ZAB 2F spectrometer. The purity of the compounds was checked by ascending tlc on Merck's precoated silica-gel plates (0.25 mm) (Merck Eurolab, Milano, Italy).

Preparation of 1,3-thiazolidin-4-ones (1, 5–6, 8–13) and of 1,3-thiazin-4-one (3).

General Procedure

An equimolar mixture (0.01 mol) of aldehyde or ketone and appropriate alkylamine (0.01 mol) in dry benzene (50 ml) was refluxed until no more water was collected in a Dean-Stark water separator. α-Mercaptoacetic acid (0.01 mol) (β-mercaptopropionic acid for compound **3**) 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 the crude compounds as pale yellow oils that were purified by TLC (Silica gel, Merck 0.5 mm; eluent: *n*-exane:ethanol:TEA, 10:3:2, vv). The compound **13** was collected as white powder after purification.

2-(4-Methylphenyl)-3-[2-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-one (1): ^{1}H NMR: 6.98 (2H, d; J = 8.1 Hz), 6.87 (2H, d; J = 8.1 Hz), 5.35 (1H, d; J = 1.9 Hz), 3.70 (1H, dd; J = 14.2, 6.4 Hz), 3.48 (1H, dd; J = 15.1, 1.9 Hz), 3.35 (1H, d; J = 15.1 Hz), 2.74 (1H, ddd; J = 14.2, 6.4 Hz), 2.03 (1H, ddd; 12.5, 5.3, 6.4 Hz), 2.01 (3H, s), 1.91 (1H, ddd; 12.5, 5.3, 6.4 Hz), 1.89 (6H, s), 1.54 (1H, m), 1.41 (1H, m); ^{13}C NMR: 178.8 (s), 38.7 (s), 137.5 (s), 129.6 (2C, d), 127.4 (2C, d), 67.0 (d), 63.5 (t), 56.8 (t), 45.1 (2C, q), 41.4 (t), 32.7 (t), 25.2 (t), 20.9 (q); mass spectrum, m/e M+ 278. *Anal.* Calcd. for $C_{15}H_{22}N_2OS$: C, 64.71; H, 7.96; N, 10.06. Found: C, 64.69; H, 7.94; N, 10.07.

2-(4-Methylphenyl)-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazin-4-one (3): ^{1}H NMR: 7.11 (2H, d; J = 8.0 Hz), 6.95 (2H, d; J = 8.0Hz), 5.65 (1H, s), 4.31 (1H, ddd; J = 13.1, 8.2, 7.9), 2.68 (1H, dt; J = 13.1, 7.5 Hz), 2.65 (1H, ddd; J = 17.5, 10.9, 6.35 Hz), 2.56 (1H, ddd; J = 17.5, 6.3, 6.4 Hz), 2.47 (1H, ddd; J = 13.6, 10.9, 6.1), 2.35 (1H, ddd; J = 12.1, 8.4, 6.5), 2.10 (3H, s), 2.02 (7H, s+m), 1.95 (1H, m), 1.88 (1H, m), 1.69 (1H, ddt; J = 13.4, 6.7, 6.5); **^{13}C** NMR: 170.77 (s), 140.6 (d), 129.7 (2C, d), 129.6 (2C, d), 61.01 (d), 54.87 (t), 44.82 (t), 43.25 (2C, q), 33.15 (t), 24.13 (t), 20.39 (t), 19.11 (q); mass spectrum, m/e M+ 292. *Anal.* Calcd. for $C_{16}H_{24}N_2OS$: C, 65.71; H, 8.27; N, 9.58. Found: C, 65.90; H, 8.24; N, 9.61.

2-Phenyl-3-[2-(*N*,*N*-dimethylamino)ethyl]-1,3-thiazolidin-4-one (5): ^{1}H NMR: 7.02 (5H, m), 5.67 (1H, d; J = 1.7 Hz), 3.80 (1H, dt; J = 14.2, 6.4 Hz), 3.45 (1H, dd; J = 15.1, 1.7 Hz), 3.36 (1H, d; J = 15.1 Hz), 2.55 (1H, ddd; J = 14.2, 6.4 Hz), 2.21 (1H, ddd; 12.5, 5.3, 6.4 Hz), 1.97 (1H, ddd; 12.5, 5.3, 6.4 Hz), 1.90 (6H, s); ^{13}C NMR: 170.77 (s), 140.6 (s), 129.0 (2C, d), 128.8 (d), 127.3 (2C, d), 63.7 (d), 57.0 (t), 45.3 (2C, q), 40.4 (t), 32.6 (t) mass spectrum, m/e M+ 250. *Anal.* Calcd. for $C_{13}H_{18}N_2OS$: C, 62.37; H, 7.25; N, 11.14. Found: C, 64.20; H, 7.23; N, 11.16.

2-Phenyl-3-(3-chloropropyl)-1,3-thiazolidin-4-one (6): ^{1}H NMR: 7.01 (3H, d+t; J = 8.8 Hz), 6.94 (2H, d; J = 8.7 Hz), 5.12 (1H, d; J = 1.8 Hz), 3.44 (1H, ddd; J = 13.8, 7.3, 7.0 Hz), 3.35 (1H, dd; J = 15.7, 1.7 Hz), 3.26 (1H, d; J = 15.7 Hz), 2.97 (1H, ddd; J = 10.5, 6.3, 2.0 Hz), 2.91 (1H, ddd; J = J = 10.5, 6.3, 1.8 Hz), 2.59 (1H, dt; J = 13.8, 7.3, 7.0 Hz), 1.54 (1H, seven peak multiplet), 1.44 (1H, seven peak multiplet); ^{13}C NMR: 170.83 (s), 140.11 (s), 129.10 (3C, d), 127.26 (2C, d), 63.62 (d), 42.15 (t), 40.81 (t), 32.46 (t), 30.11 (t); mass spectrum, m/e M+ 255, (M+2) 257. *Anal.* Calcd. for $C_{12}H_{14}ClNOS$: C, 56.35; H, 5.52; N, 5.48. Found: C, 56.32; H, 5.50; N, 5.47.

2-Methyl-2-phenyl-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-one (8): ^{1}H NMR: 7.08 (2H, t; J = 7.5 Hz), 7.06 (1H, t; J = 7.5 Hz), 7.01 (2H, d; J = 7.5 Hz), 3.55 (1H, ddd; J = 10.9, 5.4, 5.2 Hz), 3.48 (1H, d; J = 17.5 Hz), 3.42 (1H, d; J = 17.5 Hz), 2.91 (1H, ddd; J = 10.9, 5.4, 5.2 Hz), 2.05 (2H, m), 2.02 (6H, s), 1.86 (1H, m), 1.79 (3H, s), 1.70 (1H, m); ^{13}C NMR: 171.57 (s), 143.91 (s), 128.88 (2C, d), 125.95 (2C, d), 71.08 (d), 57.28 (t), 45.38 (2C, q), 42. 09 (t), 32.98 (q), 28.46 (t), 26.74 (t); mass spectrum, m/e M+ 278. *Anal.* Calcd. for $C_{15}H_{22}N_2OS$: C, 64.71; H, 7.96; N, 10.06. Found: C, 64.52; H, 7.92; N, 10.09.

3-(*N*,*N*-dimethylamino)propyl-1,3-thiazolidin-4-one (9): ^{1}H NMR: 3.75 (2H, bs), 3.21 (2H, bs), 3.13 (2H, t; J = 6.9 Hz), 2.01 (2H, t; J = 6.9 Hz), 1.99 (6H, s), 1.41 (2H, p; J = 6.9 Hz); ^{13}C NMR: 170.25 (s), 56.79 (t), 47.21 (t), 45.41 (q), 45.34 (q), 42.63 (t), 32.18 (t), 25.57 (t); mass spectrum, m/e M+ 188. *Anal.* Calcd. for $C_8H_{16}N_2OS$: C, 51.03; H, 8.57; N, 14.88. Found: C, 51.23; H, 8.55; N, 14.86.

2-Dimethyl-3-(*N*,*N*-dimethylamino)propyl-1,3-thiazolidin-4-one (10) ^{1}H NMR: 3.29 (2H, s), 3.14 (2H, dd; J = 7.8 Hz), 2.09 (2H, t; J = 6.9 Hz), 2.03 (6H, s), 1.68 (2H, m), 1.20 (6H, s); ^{13}C NMR: 170.02 (s), 66.70 (s) 57.22 (t), 45.28 (2C, q), 40.09 (t), 32.11 (t), 30.23 (2C, q), 27.39 (t); mass spectrum, m/e M+ 216. *Anal.* Calcd. for $C_{10}H_{20}N_2OS$: C, 55.52; H, 9.32; N, 12.95. Found: C, 55.48; H, 9.30; N, 12.96.

5-Methyl-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-one (11): ^{1}H NMR: 3.76 (1H, dd; J = 15.9, 1.1 Hz), 3.71 (1H, dd; J = 15.9, 1.4 Hz), 3.54 (1H, dq; J = 6.9, 1.4 Hz), 3.20 (1H, ddd; J = 14.0, 7.3, 7.0 Hz), 3.08 (1H, ddd; J = 14.2, 7.3, 7.0 Hz), 1.99 (2H, t; J = 6.9 Hz), 1.98 (6H, s), 1.45 (3H, dd; J = 6.9, 1.1 Hz), 1.40 (2H, p; J = 7.3, 6.9 Hz); ^{13}C NMR: 172.89 (s), 56.75 (d), 45.31 (2C, q), 45.22 (t), 42.89 (t), 41.45 (t), 25.51 (t), 19.72 (q);. mass spectrum, m/e M+ 202. *Anal.* Calcd. for $C_9H_{18}N_2OS$: C, 53.43; H, 8.97; N, 13.85. Found: C, 53.50; H, 9.00; N, 13.83.

2-Methyl-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-one (12): ^{1}H NMR: 4.21 (1H, dq; J = 5.9, 1.6 Hz), 3.53 (1H, ddd; J = 13.4, 7.3, 2.0 Hz), 3.27 (1H, dd; J = 15.9, 1.6 Hz), 3.16 (1H, d; J = 15.9 Hz), 2.84 (1H, ddd; J = ; J = 13.4, 7.3, 2.0 Hz), 2.04 (1H, m) 1.99 (6H, s), 1.96 (1H, m), 1.52 (1H, m), 1.37 (1H, m), 1.02 (3H, d; J = 5.9 Hz); ^{13}C NMR: 171.50 (s), 56.84 (t), 56.42 (d), 45.28 (2C, q), 40. 2 (t), 32.01 (t), 25.71

(t), 23.02 (q); mass spectrum, m/e M+ 202. *Anal.* Calcd. for $C_9H_{18}N_2OS$: C, 53.43; H, 8.97; N, 13.85. Found: C, 53.48; H, 8.99; N, 13.81.

2-Phenyl-3-benzyl-1,3-thiazolidin-4-one (13): ^{1}H NMR: 6.50 (8H, m), 6.33 (2H, m), 4.66 (1H, d; J = 14.7 Hz), 4.61 (1H, d; J = 1.7 Hz), 2.95 (1H, dd; J = 15.4, 1.7 Hz), 2.82 (1H, d; J = 14.7 Hz), 2.79 (1H, d; J = ; J = 15.4); ^{13}C NMR: 170.71 (s), 140.20 (s), 136.33 (s), 129.05 (2C, d), 128.88 (d), 128.58 (2C, d), 128.40 (d), 128.00 (2C,d), 127.30 (2C,d), 62.53 (d), 46.20 (t), 32.56 (t); mass spectrum, m/e M+ 269; Mp 142-3 °C. *Anal.* Calcd. for $C_{16}H_{15}NOS$: C, 71.34 ; H, 5.61 ; N, 5.20: Found: C, 71.35 H, 5.59; N, 5.18.

Preparation of cis and trans 3-chloro-[3-(*N*,*N*-dimethylamino)propyl]-4-(4-methylphenyl)-azetidin-2-ones (2a, 2b)

An equimolar mixture (0.01 mol) of *p*-tolualdehyde and *N*,*N*-dimethyl-alkylamine (0.01 mol) in dry benzene (50 ml) was refluxed until no more water was collected in a Dean-Stark water separator. The crude mixture was extracted with a HCl 2N (100 ml). The aqueous line, alkalinized with NaOH and extracted with diethyl ether (50 ml), yielded a pale-yellow oil that was diluted with DMF (50 ml). Chloroacetyl chloride (0.01 mol) was added to the solution and the mixture, refluxed for 2 h, and evaporated *in vacuo*, which yielded the crude *trans* (**2a**) and *cis* (**2b**) azetidinones. **2a** and **2b** were separated and purified by TLC (Silica gel, Merck 0.5 mm; eluent: *n*-exane: ethanol:TEA, 10:3:2, vv)

3-Chloro-1-[3-(*N*,*N*-dimethylamino)propyl]-4-4-methyl-phenyl-azetidin-2-ones (2a, 2b): ***trans*-2a**- ^{1}H NMR: 7.20 (2H, d; J = 7.9), 7.16 (2H, d; J = 7.9), 4.50 (1H, d; J = 1.6), 4.44 (1H, d; J = 1.6), 3.48 (1H, dt; J = 7.0, 14.0), 2.89 (1H, dt; J = 7.0, 14.0), 2.33 (3H, s), 2.24 (2H, m), 2.14 (6H, s), 1.65 (2H, m); ^{13}C NMR: 163.62 (s), 139.44 (s), 132.01 (s), 129.83 (2C, d), 126.42 (2C, d), 66.03 (d), 63.01 (d), 56.64 (t), 45.15 (2C, q), 39.33 (t), 25.41 (t), 21.05 (q); mass spectrum, m/e M+ 280, (M+2) 282. *Anal.* Calcd. for $C_{15}H_{21}ClN_2O$: C, 64.16; H, 7.54; N, 9.98. Found: C, 64.61; H, 7.55; N, 9.93. ***cis*-2b** ^{1}H NMR: 7.14 (2H, d; J = 7.9), 7.08 (2H, d; J = 7.9), 5.01 (1H, d; J = 4.8), 4.86 (1H, d; J = 4.8), 3.46 (1H, dt; J = 7.0, 14.0), 2.91 (1H, dt; J = 7.0, 14.0), 2.29 (3H, s), 2.16 (2H, m), 2.07 (6H, s), 1.59 (2H, m) ^{13}C NMR: 160.51 (s), 140.32 (s), 128.13 (s), 127.81 (2C, d), 125.45 (2C, d), 66.01 (d), 58.02 (d), 50.93 (t), 44.63 (2C, q), 40.22 (t), 25.49 (t), 21.09 (q); mass spectrum, m/e M+ 280, (M+2) 282. *Anal.* Calcd. for $C_{15}H_{21}ClN_2O$: C, 64.16; H, 7.54; N, 9.98. Found: C, 64.62; H, 7.54; N, 9.91.

ACKNOWLEDGMENTS

We thank the Dr. Antonio Lavecchia for the molecular modeling and the Centro di Metodologie Chimico-Fisiche and the Centro Interdipartimentale di Metodologie Chimico-Fisiche of the University of Naples "Federico II" for the instrumental support. This work was supported by a grant of Regione Campania POP '94–'99 and of the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Roma).

REFERENCES

1 Green, R.D. Hydrogen Bonding by C-H Groups. Wiley Interscience, New York, 1974.
2 Taylor, R., and Kennard, O. Crystallographic evidence for the existence of C-H···O, C-H···N, and C-H···Cl Hydrogen bonds *J. Am. Chem. Soc.*, 1982, 104, 5063–5070
3 Bolognese, A., Calignano, A., Diurno, M.V., Giordano, F., Mazzoni, O., and Piscopo, E. Synthesis and antihistaminic activity of some thiazolidin-4-ones. *J. Med. Chem.*, 1992, 35, 2910–2912
4 Bolognese, A., Diurno, M.V., Greco, G., Grieco, P., Mazzoni, O., Novellino, E., Perissutti E., and Silipo, C. Quantitative structure-activity relationships in a set of thiazolidin-4-ones acting as H_1 histamine antagonists. *J. Receptor. Res.*, 1995, 15, 631–635
5 Diurno, M.V., Greco, G., Mazzoni, O., Novellino, E., Calignano, A., La Rana, G., Barbieri A., and Bolognese, A. Synthesis and structure-activity relationships of 2-(substitutedphenyl)-3-[3-(*N*,*N*-dimethylamino) propyl]-1,3-thiazolidin-4-ones and related analogues acting as H_1-Histamine antagonists. *Med. Chem. Res.*, 1994, 4, 578–587
6 Clark, M., Cramer, R.D. III, and Van Opdenbosch, N. Validation of the General Purpose Tripos 5.2 Force Field. *J. Comp. Chem.*, 1989, 8, 892–1012.
7 Dewar, M.J.S., Zoebish, E.G., Healy, E.F., and Stewart, J.J.P. AM1: a new general purpose mechanical molecular model. *J. Am. Chem. Soc.*, 1985, 107, 3902–3909
8 Stewart, J.J.P. MOPAC (version 6.00), Quantum Chemistry Program Exchange (QCPE), Indiana University
9 Lewin, A. H., Lipowitz, J., and Cohen, T. A large chemical shift difference for geminal protons. *Tetrahedron Lett.*, 1965, 18, 1241–1245
10 Iesce, M.R., Cermola, F., Graziano, M.L., Cimminiello, G., and Scarpati, R. Photosensitized oxidation of furans. Part 16. Selective formation and chemical properties of 3H-1,2-dioxoles: a new class of cyclic peroxides. *J. Chem. Soc. Perkin Trans. I*, 1992, 1855–1858
11 Wiberg, K.B., Waldron, R.F., Schulte, J., and Saunders, M. Lactones. 1. X-ray crystallographic studies of nonanolactone and tridecalactone: nature of CH···O nonbonded interactions. *J. Am. Chem. Soc.*, 1991, 113, 971–977
12 Desiraju, G.R., and Sharma, C.V.K. C-H···O Hydrogen bonding and topochemistry in crystalline 3,5-dinitrocinnamic acid and its 1:1 donor-acceptor complex with 2,5-dimethoxycinnamic acid. *J. Chem. Soc., Chem. Commun.*, 1991, 1239–1241
13 Gaussian 98, (Revision A.7) Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E.; Robb, M.A., Cheeseman, J.R., Zakrzewski, V.G., Montgomery, J.A., Stratmann, R.E., Burant, J.C., Dapprich, S., Millam, J.M., Daniels, A.D., Kudin, K.N., Strain, M.C., Farkas, O., Tomasi, J., Barone, V., Cossi, M., Cammi, R., Mennucci, B., Pomelli, C., Adamo, C., Clifford, S., Ochterski, J., Petersson, G.A., Ayala, P.Y., Cui, Q., Morokuma, K., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Cioslowski, J., Ortiz, J.V., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Gomperts, R., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Gonzalez, C., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Andres, J.L., Head-Gordon, M., Replogle, E.S.,

and Pople, J.A. Gaussian 98, Gaussian, Inc., Pittsburgh, PA, 1999
14 Adamo, C., Barone, V. Toward reliable density functionals without adjustable parameters: the PBEO Model. *J. Chem. Phys.* 1999, 110, 6158–6170
15 Collins, J.B., Schleyer, P.v.R., Binkley, J.S., and Pople, J.A. Self-consistent molecular orbital methods. XVII. Geometries and binding energies of second-row molecules. A comparison of three basis set. *J. Chem. Phys.*, 1976, 64, 5142–5151
16 Scalmani, G., Brèdas, J.L., and Barone, V. Ab initio study of the gas-phase structure and electronic properties of M-CH_3 (M = Li, Na) and M-CCH (M = Li, Na, K): A combined post-Hartree-Fock and density functional theory study. *J. Chem. Phys.*, 2000, 112, 1178–1191
17 Barone, V., and Cossi, M. Quantum calculation of molecular energies and energy gradients in solution by a conductor solvent model. *J. Phys. Chem. A*, 1998, 102, 1995–2001
18 Mulliken, R.S. Electronic population analysis on LCAO-MO molecular wave functions. I. *J. Chem. Phys.*, 1955, **23,** 1833–40, 1841–1846
19 Mulliken, R.S. Electronic population analysis on LCAO-MO molecular wave functions. II. Overlap populations, bond orders and covalent bond energies, *J. Chem. Phys.*, 1955, 23, 1841–1846
20 Reed, A.E., Curtiss, L.A., and Weinhold, F. Intermolecular interactions from a natural bond orbital, donor-acceptor viewpoint. *Chem. Rev.*, 1988, 88, 899–926
21 Singh, U.C., and Kollman, P.A. Energy Component Analysis Calculations on Neutral Atom . · · Base Interactions *J. Comp. Chem.*, 1985, 6, 5–8
22 Basler, B.H., Merz, K.M. Jr., and Kollman, P.A. Atomic charges derived from semiempirical methods, *J. Comp. Chem.*, 1990, 11, 431–439
23 Cioslowski, J. A new population analysis based on atomic polar tensors. *J. Am. Chem. Soc.*, 1989, 111, 8333–8336
24 Naruto, S., Motoc, I., and Marshall, G.R. Computer-assisted analysis of bioactivity. *Eur. J. Med. Chem.*, 1985, 20, 529–532
25 Laak, A.M., Drooge M.J., Timmerman H., and Kelder, G.M. QSAR and molecular modeling studies on histamine H_1-receptor antagonists, *Quant. Struct.-Act. Relat.*, 1992, 11, 348–363
26 Diurno, M.V., Mazzoni, O., Correale, G., Gomez Monterrey, I., Calignano, A., La Rana, G., and Bolognese, A. Synthesis and antihistaminic activity of some thiazolidin-4-ones. *Il Farmaco*, 1999, 54, 579–583
27 Hoflack, J., Trumpp-Kallmeyer, S., and Hibert, M. Molecular modeling of G protein-coupled receptors. In: *3D QSAR in Drug Design. Theory, Methods and Applications.* H. Kubinyi, Ed., Escom, Leiden, 1993, 355–372