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Configurational and conformational analysis of some fully substituted imidazolidinic compounds: a theoretical study

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Abstract

Configurational and conformational analysis were performed using ab initio and semi-empirical molecular orbital methods in order to obtain structural, electronic and energetic information about three previously synthesized imidazolidine derivatives, namely: 3-benzyl-5-benzylidene-imidazolidine-2,4-dione (**5**), 3-benzyl-5-benzylidene-2-thioxo-imidazolidine-4-one (**6**), 5-benzylidene-3-(2-oxo-2-phenyl-ethyl)-2-thioxo-imidazolidine-4-one (**7**) and other two new proposed imidazolidine derivatives: 3-benzyl-5-benzylidene-4-thioxo-imidazolidine-2-one (**8**) and 3-benzyl-5-benzylidene-imidazolidine-2,4-dithione (**9**). Important aspects related to structure activity relationship are highlighted.

Keywords: Imidazolidines; Thioxo-imidazolidines; Configurational and conformational analysis; Ab initio; Semi-empirical

1. Introduction

Since hydantoin or imidazolidine-2,4-dione ring **1** (Scheme 1) was discovered by Bayer in 1861 [1], a large set of imidazolidine derivatives have been synthesized showing a wide range of biological activities like anticonvulsant [2], antischistosomal [3], tuberculostatic [4], etc. The first thioxo-hydantoin, the 2-thioxo-imidazolidin-4-one **2** was prepared in 1890 by Klason [5].

Edward [6] proposed that the polarity modification between imidazolidine-2,4-diones and 2-thioxo-imidazolidin-4-one are associated to the larger polarization of the thiocarbonyl bond comparing to that on the carbonyl bond. It is justified in terms of the larger difficulty of the sulfur atom to form a π-bond to the carbon atom. The contribution of this effect seems to exceed the higher electronegative effect of the oxygen atom.

During the last decades, the effect produced by the structural modification on the biological activity of the imidazolidine derivatives **1**–**4** has been the subject of great interest [7]. For example, the phenytoin (5,5-diphenyl-imidazolidine-2,4-dione) is currently used as the main anticonvulsant drug in epileptic crises, especially in partial and tonic–clonic convulses [8] being considered an essential drug by the World Health Organization (WHO) [9]. The 2-thioxo-imidazolidine-4,5-dione shows anticonvulsant activity [2] and hypnotic-sedative effect [10].

The biological activity showed by imidazolidine bioisosters is also extended to human been parasites like trematodeos of *Schistosoma* generous. Schistosomiasis is an old serious disease first identified by Theodor Bilharz in Egypt in 1851 [11]. According to WHO, there are about 200 million people who have this disease in 70 different countries [11].

Initially, Luttermoser and Bond [3] showed that phenytoin and its analogous 5-(4-chlorophenyl)-5-methyl-imidazolidine-2,4-dione present activity against adult worms of *Schistosoma mansoni* produced in mices

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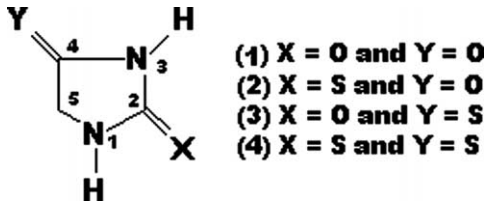
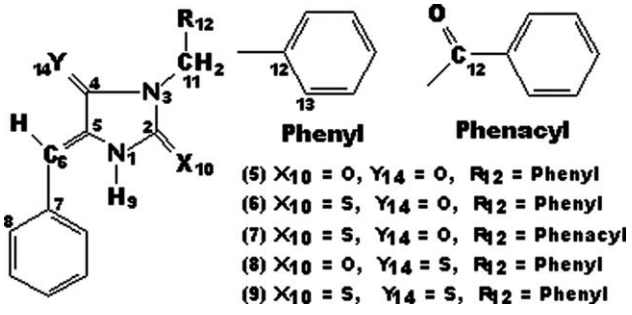


Scheme 1. Structure of imidazolidine-2,4-dione (**1**), 2-thioxo-imidazolidin-4-one (**2**), 4-thioxo-imidazolidin-2-one (**3**) and imidazolidine-2-4-dithione (**4**).

containing schistosome. Further studies by Benazet and Leroy [12] and by Werbel and Elslager [13] have shown that 5-(2,4,5-trichlorophenyl)-imidazolidine-2,4-dione and the 1-(5-nitro-thiophen-3-yl)-imidazolidine-2-thione also present activity against *S. mansoni*.

Recently, a new series of imidazolidines and thioxo-imidazolidines (Scheme 2), namely 3-benzyl-5-benzyliden-imidazolidine-2,4-dione **5**, 3-benzyl-5-benzylidene-2-thioxo-imidazolidine-4-one **6** and 5-benzylidene-3-(2-oxo-2-phenyl-ethyl)-2-thioxo-imidazolidin-4-one **7**, 3-benzyl-5-benzylidene-4-thioxo-imidazolidin-2-one **8**, 3-benzyl-5-benzylidene-imidazolidine-2,4-dithione **9** derivatives showing activity against *S. mansoni* were chosen by our group following the classic concept of bioisosterism [14]. In the last decade we have successfully synthesized compounds belonging to the series **5** [15], **6** [16] and **7** [17], whereas those belonging to **8** and **9** are being of synthesis in our laboratory.

Bioassay tests developed by our group have proven the ability of such compounds **1**–**3** against *S. mansoni* [18]. Unfortunately, the biological target of these compounds is unknown at present time. Therefore, searches by improved drugs are strongly dependent on the information about structural, electronic and energetic parameters of these ligants. So, we report a systematic semi-empirical and ab initio configurational and conformational analysis of **5**–**9** in this paper. Their electronic and energetic profiles as a function of the conformational analysis are presented and



Scheme 2. Structure of 3-benzyl-5-benzylidene-imidazolidine-2,4-dione (X=O, Y=O, R=C_6H_5) **5**, 3-benzyl-5-benzylidene-2-thioxo-imidazolidin-4-one (X=S, Y=O, R=C_6H_5) **6**, and 5-benzilidene-3-(2-oxo-2-phenylethyl)-2-thioxo-imidazolidin-4-one (X=S, Y=O R=C_6H_5CO) **7**, 3-benzyl-5-benzylidene-4-thioxo-imidazolidin-2-one (X=O, Y=S, R=C_6H_5) **8** and 3-benzyl-5-benzylidene-imidazolidine-2,4-dithione (X=S, Y=S, R=C_6H_5) **9**.

the possible implications to Structure Property Relationships are discussed.

2. Calculations

A quick inspection in Scheme 2, call the attention for two possible configurational isomers *E* and *Z* around the C=C exocyclic moiety. Besides, different relative positions of H9 and R12 relative to the plane of the heterocycle ring are possible. Therefore, initially, a full geometry optimization using the semi-empirical AM1 method [19] was employed to calculate all possible combination of conformations for both *E* and *Z* configurational isomers of **5**. Following, the most stable AM1 conformation (relative to the most stable configurational isomer) of **5** was used for an ab initio full geometry optimization at the RHF/3-21G** [20] level for **5**–**9**. After that frequency calculations were performed and no imaginary frequency was observed. For all calculations we used the GAUSSIAN 94 program [21]. In all cases the internal default criteria of GAUSSIAN 94 were used. The computations were carried out on PC's (1.4 GHz, 40 GB of HD and 512 MB of RAM).

3. Results and discussion

In Fig. 1 the AM1 heat of formation for different conformations (see Table 1) of optimized both *E* and *Z* configurational isomers are shown.

This figure clearly shows that the *Z* form is predicted to be 3.80 kcal mol^{-1} more stable than the corresponding *E* form by the AM1 method. In particular, the lowest 5.3 and 5.6 **Z** isomers (see Table 1 and Fig. 1) are associated with

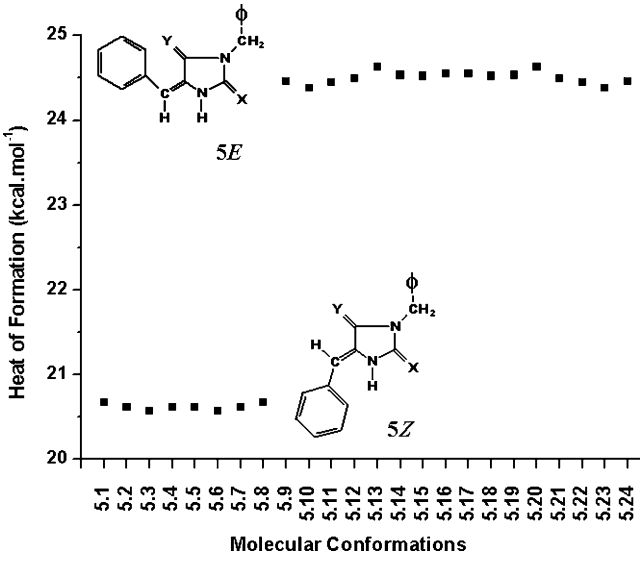


Fig. 1. Heat of formation of **5** calculated by the AM1 method for different conformations of both *E* and *Z* configurational isomers are shown.

Table 1
Optimized AM1 dihedral angles, in degrees, of 3-benzyl-5-benzylidene-imidazolidine-2,4-dione (**5**)

Molecular conformation	Dihedral angle (degrees)			
	C5C6C7-C8	H9N1C2-O10	C4N3C11-C12	N3C11-C12C13
5.1	140.0	29.6	79.0	104.9
5.2	140.0	29.1	90.3	−104.6
5.3	139.7	28.8	−88.1	105.0
5.4	139.8	28.4	−76.6	−104.6
5.5	−139.8	−28.4	76.6	104.6
5.6	−139.7	−28.8	88.1	−104.9
5.7	−139.9	−29.0	−91.0	104.7
5.8	−140.0	−29.6	−79.0	−104.9
5.9	140.9	−27.0	77.6	101.9
5.10	141.2	−27.2	88.2	−105.6
5.11	141.4	−27.7	−91.9	104.1
5.12	141.5	−28.5	−80.1	−105.2
5.13	142.0	26.6	80.2	102.6
5.14	142.3	25.8	91.7	−105.3
5.15	−140.2	25.6	−88.2	104.5
5.16	142.5	25.5	−77.3	−104.4
5.17	−142.5	−25.7	77.3	104.4
5.18	−142.4	−25.7	88.2	−104.5
5.19	−142.3	−25.9	−91.8	105.3
5.20	−141.9	−26.6	−80.2	−102.5
5.21	−141.6	28.4	80.1	105.1
5.22	−141.4	27.7	91.9	−104.2
5.23	−141.3	27.1	−88.2	105.7
5.24	−140.9	27.0	−77.6	−101.9

the up and down position (±29°) of H9 over the heterocycle plane. From Table 1 one can observe that the phenyl ring at C6 (see Scheme 2) assumes different conformations (±60°) relative to each H9 position. These results are in agreement with Boyd's theoretical prediction of partial free rotation (ca. ±20°) of the phenyl group on the closely related system, the *Z* form of benzylidene rhodanine (structure **4** in [22]).

Taking the *Z* configurational isomer as the most stable form, the energy barrier associated with the movement of H9 over the imidazolidinic plane was also calculated to **5** at the AM1 level. Thus, the plot between the AM1 heat of formation versus the dihedral angle O10–C2–N1–H9 is shown in Fig. 2.

From this plot, one can see that the H9 atom is predicted to be out-of-heterocycle plane by ca. 30°. The energy barrier is narrow ca. 0.6 kcal mol^{-1}. Therefore, it seems to be a good approach to consider the N–H inversion movement as free.

As cited above the first ab initio calculations were started from the AM1 minimum conformer of **5**. The energy barrier related to the R12 positions (see Scheme 2) around the heterocycle plane was investigated at RHF/3-21G** level for the five systems **5**–**9**. The curves of the relative energy versus the dihedral angle C4–N3–C11–C12 are shown in Fig. 3.

From this figure, one can note that there exist two minima associated to the benzyl or phenacyl group displayed at approximately 90 and −90°, i.e. above and below the ring plane, respectively. Our HF/3-21G** calculations predict minima structures with the benzyl group at N3 position for the systems containing the sulfur atom at X10 (**6**, **7** and **9**) pointing out different compared to **5** and **8**. In fact, the dihedral angle C4—N3—C11—C12 on the minima structures for **6**, **7**, and **9** value −83.9°, −80.9°, and −81.6°, whereas for **5** and **8** value 86.9°, 91.4°, respectively. These results compare with those of Benassi

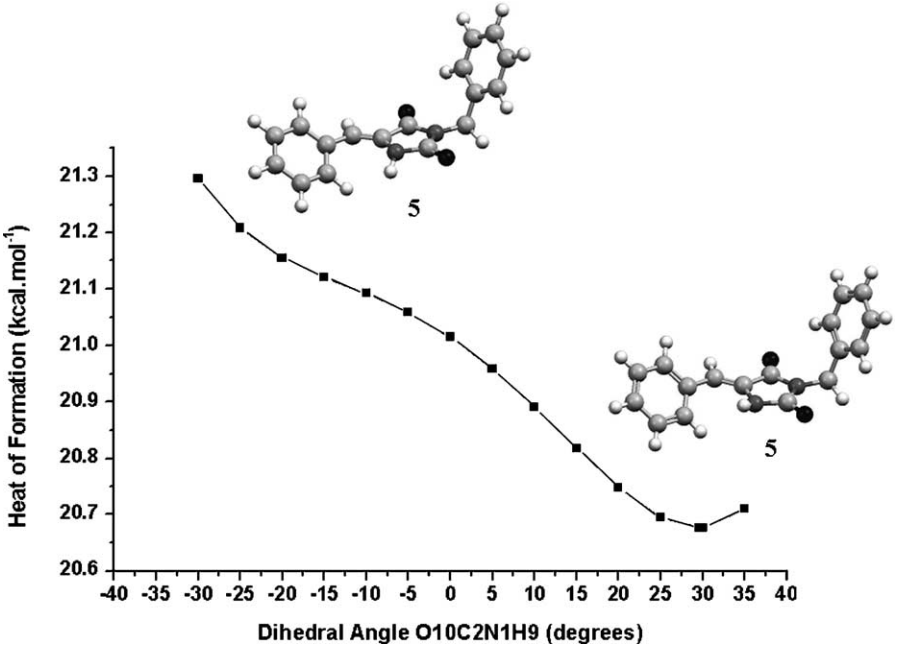


Fig. 2. Energy barrier as the dihedral angle O10–C2–N1–H9 change in **5**.

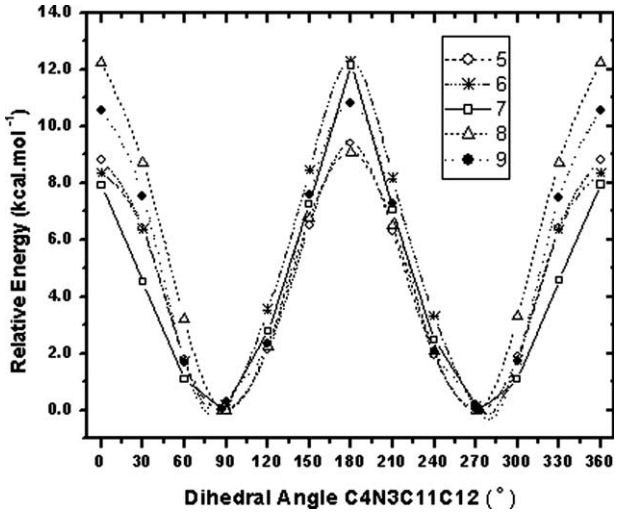


Fig. 3. Relative energy versus the dihedral angle C4–N3–C11–C12. The reference energy was the minimum energy structure, with RHF/3-21G** energy and dihedral angle of −905.5951718 hartree and 86.93° in **5**, −1226.8044801 hartree and −83.91° in **6**, −1338.902089 hartree and −80.86° in **7**, −1226.804502 hartree and 91.39° in **8**, −1548.0110007 hartree and −81.56° in **9**.

and co-workers [23] for the closely related system, 3-benzyl-5-methyl-imidazolidine-2,4-dione, calculated at HF/3-21G level where the benzyl group assumes dihedral angles values ca. ±90° relative the heterocycle ring plane. For each system, the energy difference between the two minima is predicted to be very small, 0.04, 0.20, 0.21, 0.02 and 0.05 kcal mol^{-1} for **5**–**9**, respectively. However, the predicted barrier height associated with R12 anticlockwise rotation (i.e. looking from N3 to C11 with the R12 group passing close the C4=Y14 bond) is 8.82, 8.36, 7.91, 12.26 and 10.57 kcal mol^{-1} for **5**–**9**, respectively. On the other hand, this barrier height is predicted for the R12 clockwise rotation (i.e. R12 passing close the C2=X10 bond) as 9.41, 12.28, 12.15, 9.09, 10.81 kcal mol^{-1} for **5**–**9**, respectively. It shows that the introduction of the sulfur atom at positions X10 or Y14 of the imidazolidine ring increases the barrier height, because repulsive interaction, therefore introducing an energetic asymmetry for the benzyl group rotation around the N3–C11 in **5**. Besides, the introduction of the sulfur atom at Y14 leads to a decrease in the barrier height at the dihedral angle C4–N3–C11–C12 = 180° when compared to the system where Y14 is the oxygen atom. For example, this barrier goes from 9.41 to 9.09 kcal mol^{-1} going from **5**→**8** whereas it goes from 12.28 to 10.81 kcal mol^{-1} going from **6**→**9**, respectively. This slight stabilization may be explained in terms of the carbon–sulfur/carbon–oxygen polarizability. Thus, in **8** the canonical ($^{-}$S14–C4=N3^{+}–C11) structure has a larger N3–C11 bond length compared to **5**. Indeed, a close inspection on the calculated maximum energy structures (i.e. those with the dihedral angle C4–N3–C11–C12 = 180°) show that the predicted bond lengths for **5** and **8** corresponding to C4=O14 and C4–S14 value 1.209 Å and 1.636 Å, to N3–C4 value 1.379 and 1.361 Å and to N3–C11 value 1.481 and 1.486 Å, respectively. A similar tendency can be visualized to similar bond lengths in **6** and **9**. Concerning the other maximum structure at C4–N3–C11–C12 = 0.0° it is also interesting to note that the barrier height of **6** is lower than **5** (see Fig. 3). Here the same above cited effect can be used to explain the results. Observe that the predicted bond lengths for **5** and **6** associated to C2=O10 and C2=S10 value 1.207 Å and 1.650 Å, to C2–N3 value 1.395 and 1.379 Å and to N3–C11 value 1.481 and 1.488 Å, respectively. Again, the same tendency can be visualized between **8** and **9**.

In Fig. 4, the optimized structures associated to the minima and the maximum (C4–N3–C11–C12 = 180°) relative energies are shown for **5**–**7** (the structures for **8** and **9** are very similar and are not shown here).

Although one could suppose that the barrier height at C4–N3–C11–C12 = 0.0 or 180.0° for **7** should be even higher compared to **6**, a quick analysis of Fig. 4 can explain the discrete energy decreasing for these two dihedrals (0.4 and 0.1 kcal mol^{-1}, respectively,) due to the flexibility for rotation of the phenacyl group around the C11–C12 single bond close to the transition state conformation.

In order to strengthen our findings about the structures of 3-benzyl-5-benzylidene-imidazolidine derivatives, a search on the crystallographic database 'Cambridge Structural Database 2003' (CSD) [24–26] was conducted. We were mainly interested to localize all the structures containing imizadolidine and thioxo-imidazolidine rings. Only three files of related structures were found. Two of them are associated to the 3-(4-bromobenzyl)-5-(4-fluorobenzylidene)imidazolidine-2,4-dione **10** [27] and 3-benzyl-5-(2-fluorobenzylidene)imidazolidine-2,4-dione **11** [28] both published previously by two of us and another one is associated to the 5-(4-dimethylaminobenzylidene)-2-thioxo-imidazolidin-4-one **12** [29] (Scheme 3).

Table 2 shows mainly geometric parameters of these structures experimental (**10**–**12**), those of our corresponding structures **5** and **6**, as well as those for **7**–**9**. From this table, it is possible to observe that the bond lengths and the bond angle deviations do not exceed 0.03 Å and 1.0°, respectively. Because of the crystal bulk effect, it is possible to find the calculated and crystal dihedral angles quite different. For example, the calculated C8–C7–C6–C5 dihedral angle in **5** values 141.8° and the corresponding dihedral in **10** and **11** provide the values of −179.3° and −161.5°, respectively. However, it is interesting to observe the agreement for the C4–N3–C11–C12 dihedral angle in **5** which values 87.0° and the corresponding dihedral in **10** and **11** which have the values of 93.4 and 86.5°, respectively.

The electronic distribution over the heterocycle ring was evaluated through the analysis of the atomic Mulliken charges as shown in Fig. 5.

From this figure one can observe that the only atoms affected substantially over changes on the heteroatoms X10 and Y14 are those directly attached to them, i.e. C2 and C4 atoms, respectively. The presence of the sulfur atom on **6**–**9**

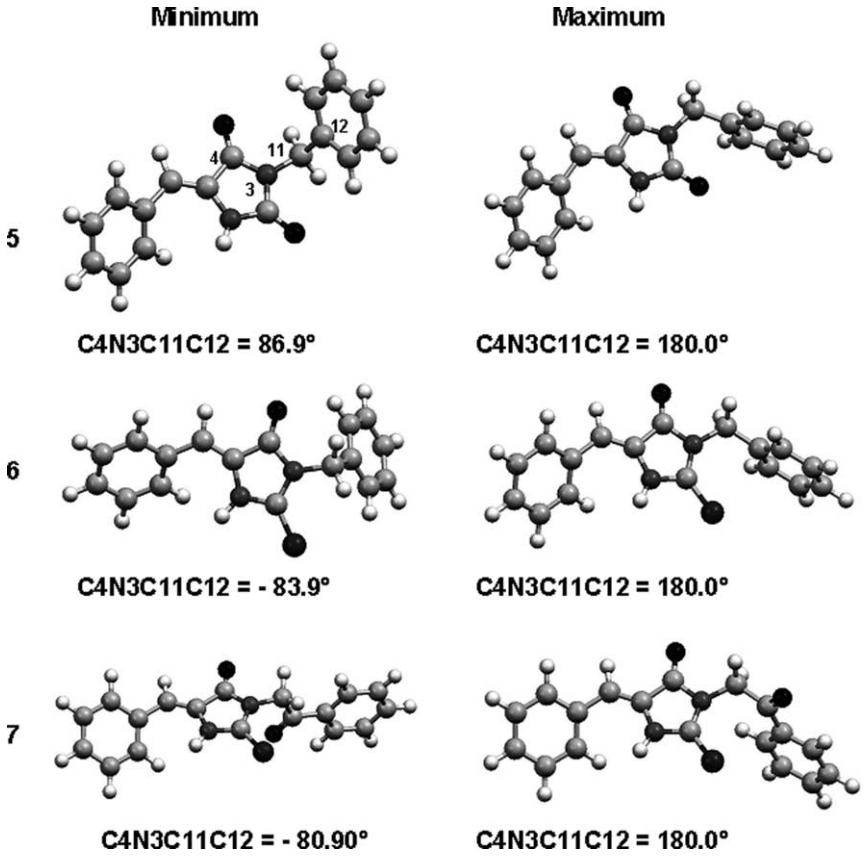


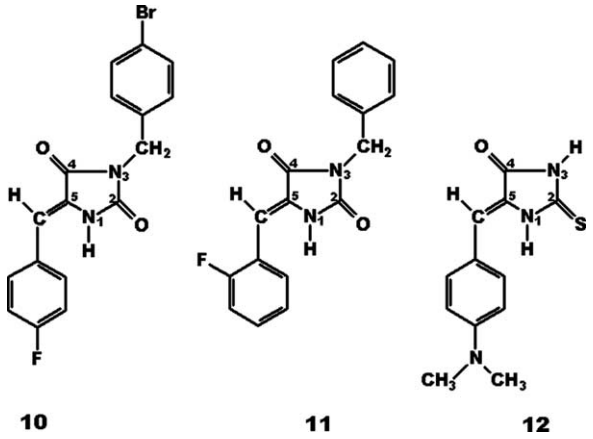
Fig. 4. Structures of minimum and maximum for **5**–**7**.

leads to a slight decrease the N1 and N3 atomic charges when compared to **5**. As consequence H9 becomes more acidic when the sulfur atom is present on the heterocycle ring.

Another parameter investigated during this conformation analysis was the electric dipole moment for which some aspects can be sorted. First, the symmetry partner as long as the dihedral angle C4–N3–C11–C12 change for the imidazoline and thioxo-imidazolidine derivatives may be observed in Fig. 6.

Second, the electric dipole moment values associated to the minima structures (ca. C4–N3–C11–C12 = 90 and −90°) for the imidazoline and thioxo-imidazolidine derivatives are not so different (ca. 3.0 D–4.00 D). The transition state structures (ca. C4–N3–C11–C12 = 0 and 180°) have the electric dipole moment values lower compared to the structures of minima energy. Except to **7**, the introduction of the sulfur atom increases the electric dipole moment for **6**, **8**, and **9**. Even containing the sulfur atom, the introduction of the phenacyl group in **7** decreases the value of the electric dipole moment compared to **5** on the minima energy conformation. Third, as the R12 group rotates around the N3–C11 bond, the maximum variation of the electric dipole moment does not exceed 0.8 D for **5** and 1.3 D for **6**, **8** and **9**. However, it is very interesting to observe that this variation may be as larger as 5.4 D for **7**. Since the electric dipole moment is a vectorial property, again the rotation around the C11–C12 bond leading the keto C=O group for a new orientation may explain this significant variance.

Admitting that the imidazoline and thioxo-imidazolidine derivatives here investigated interact with the same biological target, throughout the same mechanism and making some orbital interaction to him, it seem appropriate to analyze the frontier orbitals of the ligants. Since in this



Scheme 3. Structural representation of 3-(4-bromobenzyl)-5-(4-fluorobenzylidene) imidazolidine-2,4-dione **10**, 3-benzyl-5-(2-fluorobenzylidene)imidazolidine-2,4-dione **11** and 5-(4-dimethylaminobenzylidene)-2-thioxo-imidazolidin-4-one **12**.

Table 2
RHF/3-21G** geometric parameters of **5–9** and the corresponding experimental X-ray diffraction values of **10–12**

Parameter	Calculated RHF/3-21G**					Experimental X-ray diffraction		
	5	**6**	**7**	**8**	**9**	**10**[a]	**11**[b]	**12**[c]
Bond lengths (Å)								
N1–H9	0.986	0.986	0.986	0.986	0.987	0.965	0.948	1.043
C2=X10	1.208	1.649	1.648	1.208	1.651	1.224	1.216	1.645
C4=Y14	1.209	1.209	1.205	1.635	1.630	1.212	1.213	1.219
C5=C6	1.318	1.320	1.319	1.321	1.324	1.345	1.328	1.351
N3–C11	1.466	1.475	1.446	1.475	1.481	1.459	1.465	–
N1–C2	1.379	1.364	1.360	1.365	1.351	1.350	1.362	1.357
C2–N3	1.388	1.374	1.375	1.403	1.389	1.377	1.376	1.380
N3–C4	1.374	1.387	1.390	1.356	1.374	1.379	1.375	1.375
C4–C5	1.492	1.482	1.481	1.490	1.479	1.477	1.483	1.465
C5–N1	1.401	1.402	1.403	1.405	1.405	1.398	1.392	1.399
Planar angles (°)								
N1–C2–N3	105.76	106.14	105.99	105.55	155.82	108.34	107.50	106.47
C2–N3–C4	112.72	112.24	112.44	112.85	112.38	110.48	110.99	111.16
N3–C4–C5	104.88	104.98	104.69	104.96	104.97	105.44	105.59	105.37
C4–C5–N1	104.96	104.37	104.47	105.01	104.47	105.18	104.80	105.04
C4–N3–C11	124.18	122.04	121.74	126.50	123.89	125.66	125.14	–
N3–C11–C12	111.15	111.82	109.55	111.86	112.28	112.22	111.91	–
C11–C12–C13	119.93	120.51	117.42	119.69	120.17	121.32	119.56	–
Dihedral angles (°)								
C7–C6=C5–C4	178.94	178.50	178.46	178.80	178.61	−178.34	117.31	−175.46
C8–C7–C6=C5	141.81	141.91	140.24	138.20	139.26	−179.30	−161.51	159.31
C4–N3–C11–C12	86.93	−83.91	−80.86	91.39	−81.56	93.35	86.49	–
N3–C11–C12–C13	85.75	−99.73	−178.02	76.38	−70.93	96.05	75.29	–

[a] 3-(4-Bromobenzyl)-5-(4-fluorobenzylidene)imidazolidine-2,4-dione, see Ref. [27].
[b] 3-Benzyl-5-(2-fluorobenzylidene)imidazolidine-2,4-dione, see Ref. [28].
[c] 5-(4-Dimethylaminobenzylidene)-2-thioxo-imidazolin-4-one, see Ref. [29].

work we have performed only Hartree-Fock calculations we should focus our attention only to the energy level associated to the Highest Occupied Molecular Orbital (HOMO). Thus, in Fig. 7 the HOMO energy level is compared for the five systems as the R12 group rotates around the N3–C11 bond.

According this parameter one may observe that the introduction of the sulfur atom on the heterocyclic ring (like

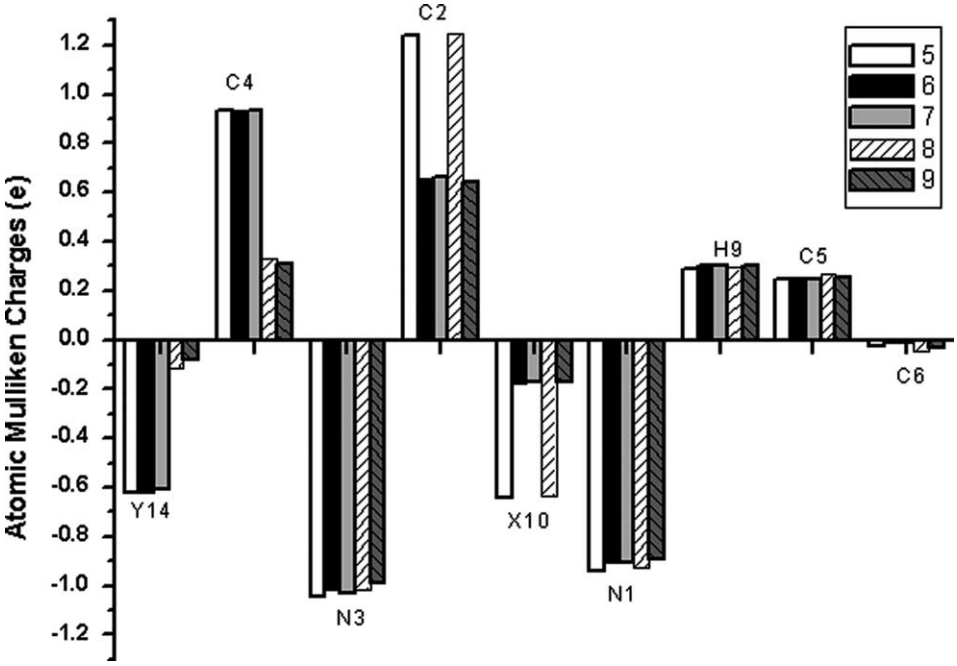


Fig. 5. Atomic Mulliken charges over the heterocycle ring and the exocyclic atoms in **5–9**.

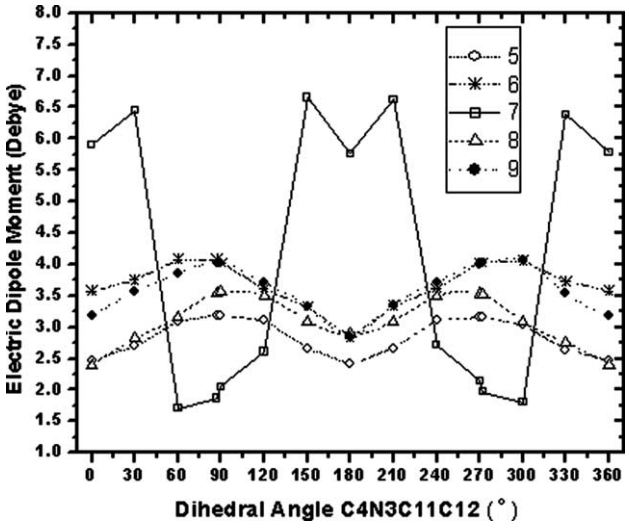


Fig. 6. Dipole moment as the dihedral angle C4–N3–C11–C12 changes in **5–9**.

in **6–9**) increases the HOMO energy level in approximately 0.3 eV relative to **5**. Therefore, compounds **6–9** are predicted to exhibit a larger susceptibility to electrophilic attack than **5**. Finally, it is curious to observe that the HOMO orbital energy has its lower values on the corresponding total energy minima (ca. C4–N3–C11–C12 = 90° and −90°) for **5**, **6**, **8** and **9**, however, it is not true for **7**. However, all systems containing at least one sulfur atom on the heterocylce ring have close HOMO energy values between −8.43 and −8.48 eV.

4. Conclusions

From the semi-empirical AM1 and ab initio HF/3-21G** calculations, it was possible to conclude that: (i) the *Z* isomer is the most stable, (ii) the N–H bond is free to invert in the heterocycle plane, (iii) there exist two minima to the benzyl or phenacyl group related to positions above and below the molecular heterocycle plane, (iv) the introduction of the sulfur atom on X10 leads to the minima structure with the benzyl group below the heterocycle plane; (v) the sulfur atoms in X10 or Y14 lead to lower energy barrier around N3–C11 bond, (vi) because the larger polarizability of the sulfur atom compared to the oxygen atom, the canonical structure $^{-}$S14–C4=N3^{+}–C11 may explain the larger stabilization of the maximum structure of **8** at C4–N3–C11–C12 = 180° compared to **5**. A symmetrical situation occurs for these systems involving the stabilization of the maximum structure at C2–N3–C11–C12 = 0° and the canonical structure $^{-}$S10–C2=N3^{+}–C11. The introduction of the sulfur atom increases the electric dipole moment and becomes less negative the HOMO orbital energy. These last two parameters exhibits a symmetry profile (relative to the heterocycle ring plane) concerning the rotation of R12 around the N3–C11 bond. The phenacyl group at R_{12} leads to the larger variations on the electric dipole moment and the HOMO energy level. Naturally, all the structure–properties relationships discussed above should be take in account on the design of new imidazolidine derivatives against *S. mansoni*.

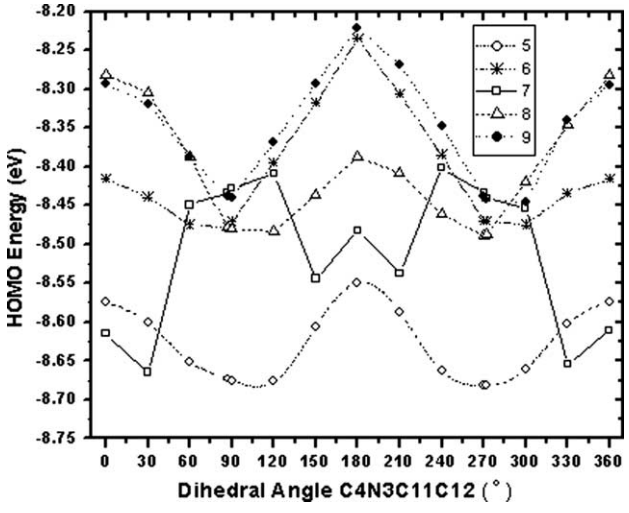


Fig. 7. HOMO energy as the dihedral angle C4–N3–C11–C12 changes in **5–9**.

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References

[1] A. Bayer, LIEBIGS Ann. Chem. 117 (1861) 178; H. Finkbeiner, J. Org. Chem. 30 (1965) 3414.
[2] (a) C. Dwivedi, T.K. Gupta, S.S. Parmar, J. Med. Chem. 15 (1972) 553;
(b) S.P. Singh, T.K. Auyong, S.S. Parmar, J. Pharm. Sci. 63 (1974) 960;
(c) N. Karali, A. Gürsoy, N. Terzioglu, S. Özkirimli, H. Özer, A.C.A. Ekinci, Arch. Pharm. Med. Chem. 331 (1998) 254.
[3] G.W. Luttermoser, H.W. Bond, J. Parasitol. 40 (1954) 33.
[4] S. Ozkirimli, O. Hamali, IL Farmaco 50 (1975) 65.
[5] P. Klason, P. Chem. Ztg. 14 (1890) 543.
[6] J.T. Edward, Chem. Org. Sulfur Compd. Eng. 2 (1966) 287.
[7] G.L. Jones, D.M. Woodbury, Drug Dev. Res. 2 (1982) 333.
[8] J.G. Hardman, L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Gilman, The Pharmacological Basis of Therapeutics, 10th ed., McGraw-Hill Professional Publishing, 2001.
[9] See www.who.org, Model List of Essential Drugs (EDL). 10th ed., 1997.
[10] S.K. Chaudari, M. Verma, A. Chatuvedi, S.S. Parmar, J. Pharm. Sci. 64 (1975) 615.

[11] WHO—World Organization Report of the WHO informal consultation on schistosomiasis control, Geneva, World Health Organization, 1998.(Document WHO/CDS/CPC/SIP/99.2)
[12] F. Benazet, J.P. Leroy, Bull. Soc. Pat. E 3 (1974) 287.
[13] L.M. Werbel, E.F. Elslager, J. Med. Chem. 20 (1977) 1569.
[14] E.J. Barreiro, Rev. Bras. Farm. 72 (1991) 2; E.J. Barreiro, Rev. Bras. Farm. 72 (1991) 34.
[15] E.L. Amorim, Master Science Dissertation, Universidade Federal de Pernambuco, 1990.
[16] S.M. Oliveira, Master Science Dissertation, Universidade Federal de Pernambuco, 2002.
[17] M.T.C. Lima, Master Science Dissertation, Universidade Federal de Pernambuco, 2003.
[18] M.C.P.A. Albuquerque, Doctoral Thesis, Universidade Federal de Pernambuco, 2002.
[19] M. Dewar, W. Thiel, J. Am. Chem. Soc. 99 (1977) 4499.
[20] J.S. Binkley, J.A. Pople, W.J. Hehre, J. Am. Chem. Soc. 102 (1980) 939.
[21] M.J. Frisch, G.W. Trucks, H.B. Schlegel, P.M.W. Gill, B.G. Johnson, M.A. Robb, J.R. Cheeseman, T. Keith, G.A. Petersson, J.A. Montgomery, K. Raghavachari, M.A. Al-Laham, V.G. Zakrzewski, J.V. Ortiz, J.B. Foresman, J. Cioslowski, B.B. Stefanov, A. Nanayakkara, M. Challacombe, C.Y. Peng, P.Y. Ayala, W. Chen, M.W. Wong, J.L. Andres, E.S. Replogle, R. Gomperts, R.L. Martin, D.J. Fox, J.S. Binkley, D.J. Defrees, J. Baker, J.P. Stewart, M. Head-Gordon, C. Gonzalez, J.A. Pople, GAUSSIAN 94 (Revision E.3) Gaussian, Inc., Pittsburgh PA, 1995.
[22] D.B. Boyd, J. Mol. Struct. (Theochem) 401 (1997) 227.
[23] R. Benassi, A. Bregulla, A. Friderich, D. Henning, M. Heydenreich, W. Mickler, E. Kleinpeter, G. Kempter, U. Schilde, F. Taddei, J. Mol. Struct. 441 (1998) 47.
[24] F.H. Allen, Acta Crystallogr. B 58 (2002) 380.
[25] I.J. Bruno, J.C. Cole, P.R. Edgington, M. Kessler, C.F. Macrae, P. McCabe, J. Pearson, R. Taylor, Acta Crystallogr. B 58 (2002) 389.
[26] F.H. Allen, W.D.S. Motherwell, Acta Crystallogr. B 58 (2002) 407.
[27] C.A. de Simone, J. Zukerman-Schpector, M.A. Pereira, L.-D. Cuong, I.R. Pitta, S.L. Galdino, E.L.C. de Amorim, Acta Crystallogr. Sect. C: Cryst. Struct. Commun. 51 (1995) 2620.
[28] C.A. de Simone, M.A. Pereira, C. Luu-Duc, I.R. Pitta, S.L. Galdino, E.H.C. Menezes, J. Zukerman-Schpector, Acta Crystallogr. Sect. C C52 (1996) 2771.
[29] J.S. Casas, A. Castineiras, N. Playa, A. Sanchez, J. Sordo, J.M. Varela, E.M. Vazquez-Lopez, Polyhedron 18 (1999) 3653.