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Comparative Computational Studies of 1,4-Diformyl-piperazine and 1,4-Dithionyl-Piperazine

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The molecular properties known to play an essential role in drug-receptor interaction of substructures models of bioactive molecules have been studied using chemical quantum calculations. 1,4-Diformyl-piperazine and 1,4-dithionyl-piperazine have been used as models to probe conformational behaviors and some electronic properties of substructure of some tri-substituted piperazine showing dual anti-PAF and anti-HIV-1 activities. The derivatives containing sulfur atoms present different bioactivities compared to those containing oxygen atoms. On the basis of the results, substitution of an oxygen atom by a sulfur atom induces changes in some activation energies when the conformers have similar structures. This substitution causes also changes in the molecular shape, electronic potentials, partial charges distribution, HOMO and LUMO energies.

Keywords: Conformational analysis, 1,4-Diformyl-piperazine, 1,4-Dithionyl-piperazine, Rotational barrier, Nitrogen inversion barrier, HOMO-LUMO gap

INTRODUCTION

The infection of central nervous system (CNS) by human immunodeficiency virus-1 (HIV-1) results on neurological complications named acquired immunodeficiency syndrome dementia complex (ADC). ADC is a consequence of neuronal cell injury, inflammatory syndrome, and HIV replication which are related to high levels of platelet-activating factor (PAF) in CNS [1-4]. These can explain the tests of PAF receptor antagonists as anti-HIV drugs [5-7]. Potent dual anti-PAF and anti-HIV-1 activities were discovered for numerous tri-substituted piperazine [7-12]. Martin *et al.* were first to show the anti-HIV action of the PAF receptor antagonist PMS-601 1 (Fig. 1) [11]. Since then, numerous compounds with dual anti-PAF and anti-HIV activities were developed by replacing the carbamate function by other organic functions [10] and modifying one or the two 3,4,5-trimethoxybenzoyl groups [8-9]. Serradji *et al.* showed that the replacement of the two oxygen atoms of carbonyl groups by sulfur atoms gives the compound 2 (Fig. 1) which presents better dual activities than 1. They also noted that substitution of the oxygen atom by sulfur increases the anti-PAF activity and lipophilicity (compound 2, 3 and 4 (Fig. 1)) independent of the position of substituted oxygen atom. However, the transformation of the amide function to thioamide in N4-position is necessary to obtain anti-HIV active molecules (compounds 2 and 4). In these cases, obtained molecules present anti-HIV activity close or better than 1 [9].

It is well established to interpret the drug-receptor interactions using the "lock and key" model [13-14]. So, Serradji *et al.* explained that differences between anti-HIV

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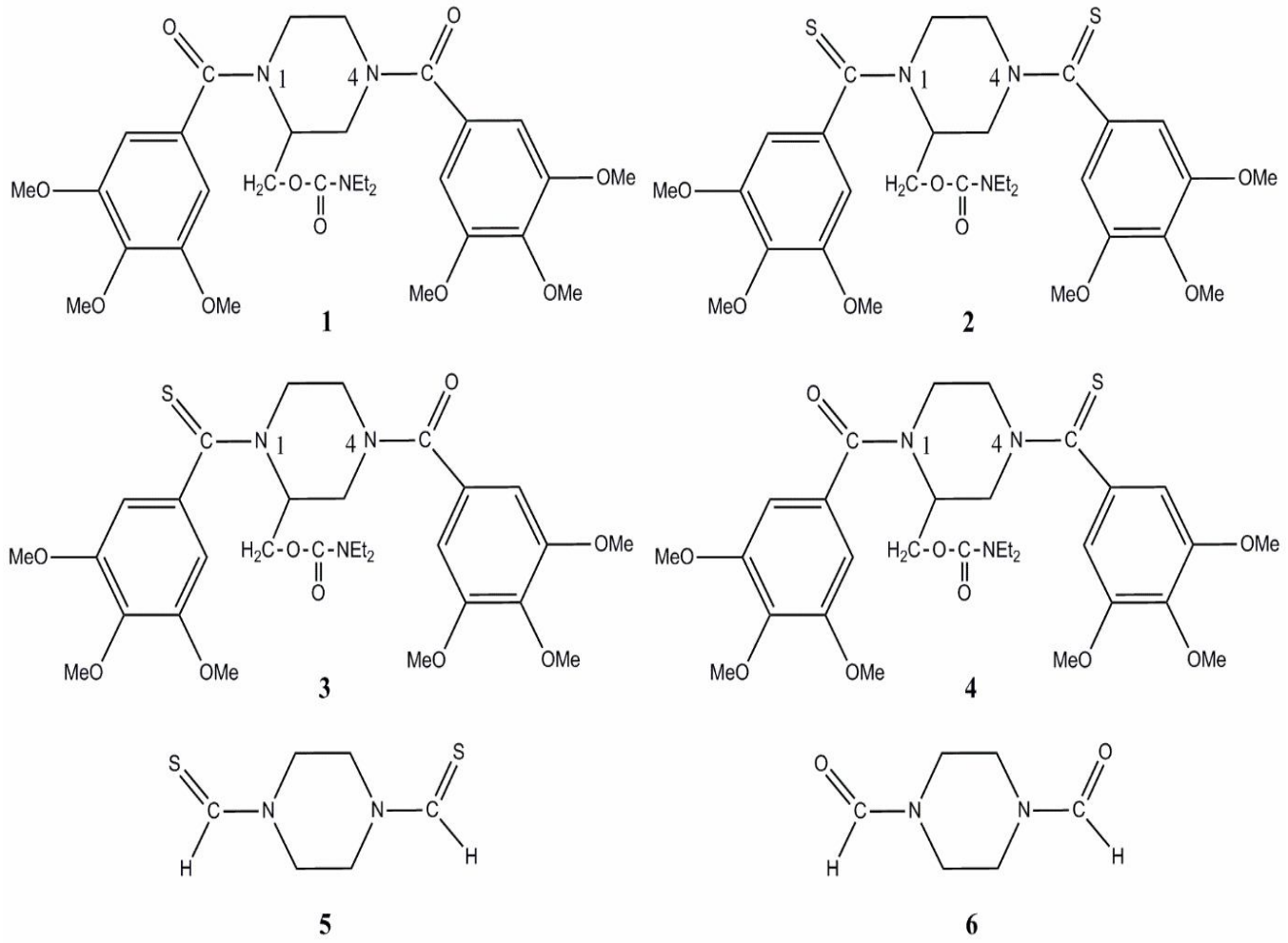


Fig. 1. Compounds 1, 2, 3, 4, 5 and 6.

activities of molecules 1, 2, 3 and 4 are due to differences of interactions between sulfur atom and carbamate group within these molecules [9]. Furthermore, it is well known that this group is mostly involved in anti-HIV activity [7]. Their quantum calculations results showed that molecules 1, 2, 3 and 4 exhibit different conformational flexibilities. Indeed, the interconversion between conformers of 1 and 3 are easier than those of 2 and 4 [9]. Consequently, it has been deduced that intramolecular interactions, such as hydrogen bonding, between carbamate and thioamide groups are stronger than those between carbamate and amide groups. It is noted that their obtained theoretical results did not interpret clearly the experimentally obtained bioactivity results [9]. It is worth noting that used quantum chemistry methods are insufficient to study the non covalent intramolecular interactions in 1, 2, 3 and 4. More sophisticate methods are therefore needed. However, the four studied molecules possess a large number of electrons then the use of sophisticated methods may not be possible. Moreover, Serradji *et al.* did not explain why the transformation of the amide in thioamide, at N4-position only, inhibits the anti-HIV activity [9].

Oxygen and sulfur are chalcogens belonging to two successive rows of the periodic table. The sulfur atom has a larger valence radius than oxygen and its electronegativity is close to that of carbon. Correspondingly, one might expect

that the C=S bond should be longer and less polarized than C=O bond. So, the interactions of C=O bond with its environment in carbonyl compounds differ from that of C=S bond in thiocarbonyl compounds, inducing differences between the shapes of the more stable conformers and electronic density distribution of the two types of compounds. This latter difference can be used to explain why carbonyl compounds and thiocarbonyls interact differently with other molecules or active sites. The molecules 1, 2, 3 and 4 involve amide and/or thioamide organic functions. So, the rotation about the amide or thioamide C-N bond plays a non-negligible role in their conformational behavior. Thioamide compounds (2, 3, 4) are expected to exhibit higher rotational barriers around the C-N bond than amide compounds (1, 3, 4) [15-18].

Several experimental and computational studies, dealing with comparison between compounds containing C-O bonds and those containing C-S bonds, have been reported in the literature. Egsgaard and co-workers used mass spectrometric technique to show that C=S bonds are thermodynamically less stable than C=O bonds [19]. Some experimental and computational studies showed that the basicities of thiocarbonyls are more pronounced than those of carbonyls [20]. Fabian and co-workers showed that sulfur shifts n-π^* transition into the visible spectrum [21]. There are also interesting differences in reactivity between carbonyl and thiocarbonyl derivatives [22-23].

The present study aims to explore computationally some properties of N,N-dithionyl-piperazine 5 and N,N-dicarbonyl-piperazine 6, in order to highlight their differences and similarities. These two compounds present the same base structure as the two molecules 1 and 2, which show different dual anti-PAF and anti-HIV activities. Since molecules 5 and 6 are simple and less complex than 1 and 2, their computational studies can be done with usual computation resources. Correlations between differences in structural and electronic properties of 5 and 6 and differences in the bioactivities of 1 and 2 are investigated. The commercial compound 1,4-diformylpiperazine 6 has been widely used to synthesize some bioactive molecules [24-25]. Some of its structural, electronic and spectral properties were experimentally and computationally studied [26]. To the best of our knowledge, the compound 5, named 1,4-dithiocarbaldehyde-piperazine has not been synthesized before. However, it can be obtained by direct thionation of 6 [27] or using Lawesson's reagents [28].

COMPUTATION DETAILS

All quantum calculations were performed using Gaussian09W [29]. At the density functional theory (DFT) level, the hybrid functional of B3LYP was principally used [30]. The functional M062X was also tested [31]. Some MP2 calculations were performed and the results were compared with those obtained using DFT calculations. Pople's 6-31G(d,p), 6-31G++(d,p) [32], Dunning's correlation-consistent, and polarized valence double-zeta cc-pvdz [33-34] basis sets were used. The quantum calculations results are collected and analyzed using GaussView5.0 package [35]. The conformation search was performed by full geometrical optimization and relaxed scan of dihedral angles. All key compound structures were identified as minimum or transition state on the potential energy surfaces by vibrational frequency calculations. All minimums presented real frequencies, while transition states had one imaginary frequency. In some quantum chemistry calculations, the solvent effects were taken into account using the continuum PCM model.

RESULTS AND DISCUSSION

Conformational Analysis

The conformational behavior of compounds 5 and 6 depends on the conformations of piperazine ring, nitrogen inversion and rotation about amide (thioamide) C-N bond. Piperazine rings and amide groups are common substructures of 5 and 6 and of 1, 2, 3 and 4 as well. Therefore, the comparison of the conformational behaviors of 5 and 6 can be considered as a key step in the comparison of the conformational properties of 1, 2, 3 and 4 in order to explain the differences in their bioactivities [9].

Piperazine Ring Dihedral Angles Rotation

In general, the more stable conformers of saturated six-membered heterocyclic rings are the ones having chair-like forms. In the case of piperazine (1, 4-Diazacyclohexane), the boat-like conformers are energetically unfavorable [36] due to the short distance between nitrogen atoms (gauche

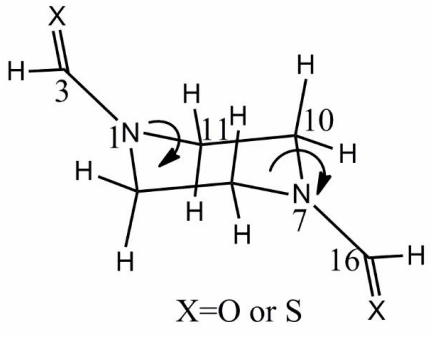


Fig. 2. equatorial/axial exchange.

effect). The boat-like conformers can be stabilized when the piperazine ring is multi-substituted, as shown from the results obtained by Serradji *et al.* using modest quantum calculation methods for molecules 1, 2, 3 and 4 **[**9]. Parlak *et al.* considered only the chair conformation, which is well known to be a global minimum on the potential energy surface, in their 6 studies [26]. Some other important conformers, such as boat, skew, half-chair, and envelope can also be considered. Therefore, it is possible to conclude from our tests, using the MP2, DFT/M062X and DFT/B3LYP methods, that the non-covalent interactions between the two carbonyls and between the two thionyls did not stabilize the latter conformers of 5 and 6, respectively. Based on the results of all the methods used, shown in Table 1, the skew conformers are local minimums. Accordingly, the present study has focused on the chair conformers of 5 and 6.

Axial/Equatorial Exchange

In the chair-like conformers of N-substituted piperazine, the group can be linked to the nitrogen atoms, either at the axial or equatorial positions, leading to equatorial-equatorial (ee), axial-axial (aa) and equatorial-axial (ea) conformational isomers. The interconversion between these isomers can be performed using two different modes. The first mode is a simple nitrogen inversion and the second one is ring flipping from one of the two nitrogen atoms. The theoretical results published by Khodabendeh *et al.* on axial/equatorial exchange in piperidines show that the second route is energetically unfavored [37]. So, the approach of Parlak *et al.* [26] was used through which the nitrogen inversion is applied to move the thionyl in 5 and carbonyl in 6 from the equatorial position to the axial position and *vice versa*.

The compounds 5 and 6 are thioamide and amide, respectively. The most structural characteristic properties of amides are the planarity of the structure of nitrogen atom and its bonded atoms, the shorter C-N bond lengths than those in amines, and the larger C-O bond lengths than those in aldehydes [38]. These are explained by a resonance between the nitrogen lone pair (n_N) and the carbonyl p orbital (π_{CO}). In this interaction, the lone pair electrons of nitrogen are delocalized across the amide group leading to a partial double-bond character of the C-N bond. So, it is expected that in the most stable conformers of 5 and 6 the thiocarbonyls and carbonyls would not be effective in equatorial or axial positions, but in intermediate positions. Consequently, the equatorial/axial exchange through nitrogen inversion is hindered. It is worth mentioning that this hindrance is different in thioamide 5 from that in the amide 6. To compare the axial/equatorial exchange in 5 and 6 we explored their potential energy surfaces by varying the dihedral angle C11-C10-N7-C16 from -180° to -70°, by an increment of 10°. For each value α_j = -180 + 10j, with j $\in$ [0, 10] of the latter angle the dihedral C10-C11-N1-C3 was incremented from α_j to -80° by 10° (Fig. 2). The relaxed scans were performed at the B3LYP/6-31G++(d,p) level of theory resulting in 66 different conformational isomers. Only one minimum was identified for both compounds.

As shown in Fig. 3, the potential energy surfaces have the shape of a well. In order to estimate the depth of the well, three high energy points, denoted ee, aa and ea, were chosen. Then, the energy differences were estimated

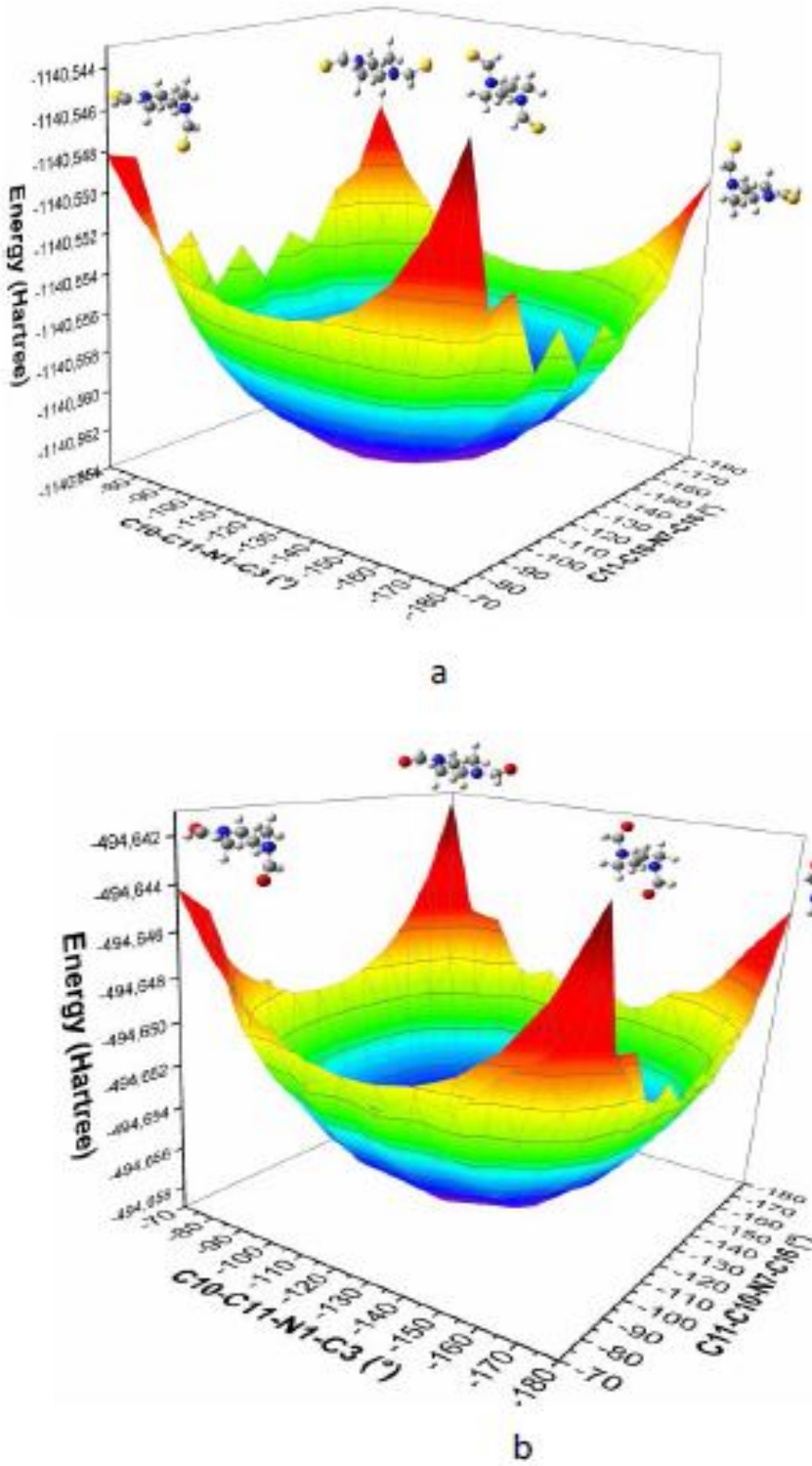


Fig. 3. Axial/equatorial exchange potential energy surfaces of 5 (a) and 6 (b) obtained using B3LYP/6-31G++(d,p).

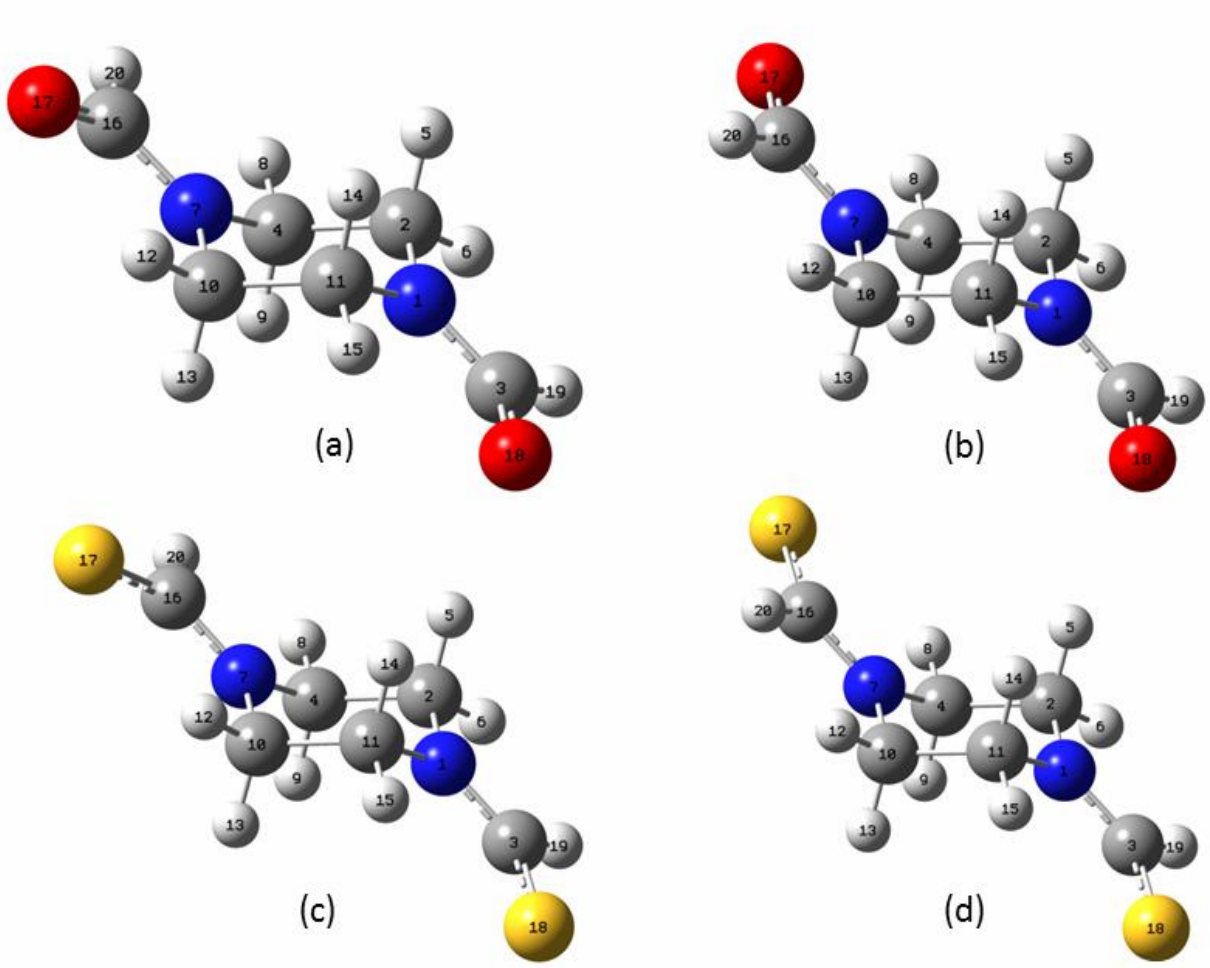


Fig. 4. The optimized structures at B3LYP/6-31++G(d,p) and atomic numbering. (a) *Cis* conformer of 6, (b) *Tran* conformer of 6, (c) *Cis* conformer of 5 and (d) *Tran* conformer of 5.

between each high energy point and the minimum point, at different levels of precision. From the results presented in Table 2, one can note small effects of basis sets on the well depth in the cases of the two compounds. The MP2 method decreases the well depth indicating the importance of the correlation between electrons. This was found to be in consistence with the established observation that the well depth decrease is more pronounced in the compounds containing sulfur atom. The energy differences between high energy points and the global minimum turned out to be larger for 5 than for 6. Therefore, it can be concluded that the substitution of the oxygen atom by the sulfur atom gives larger well depths.

About Amide (Thioamide) C-N Bond Rotation

In the most stable conformers, the carbonyl groups of 6 and thionyl groups of 5 are on either sides of the symmetry plane of piperazine containing two nitrogen atoms. The conformational isomers under consideration are called transoides and noted Tran. When the thionyl (5) or carbonyl (6) groups are in the same side of the latter plane, the conformer is named cisoide and noted *Cis* [9]. The two conformers of *Cis* and *Tran* of 5 and 6 compounds can be characterized by the values of C10-N7-C16-O17(S17) and

Table 1. Relative Stabilization of Chair and Skew Conformers of 5 and 6 Estimated at Different Level of Precision

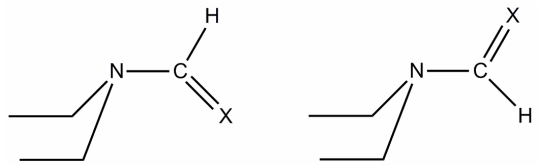
Method		Compounds	Energies (Hartree)		ΔE
			Chair-like conformer	Skew conformer	(kcal mol^{-1})[a]
B3LYP	6-31G(d,p)	5	-494.636933	-494.628033	-5.6
		6	-1140.552509	-1140.544514	-5.0
	6-31G++(d,p)	5	-494.658252	-494.649472	-5.5
		6	-1140.563331	-1140.555433	-5.0
	cc-pvdz	5	-494.649901	-494.640888	-5.7
		6	-1140.590389	-1140.582233	-5.1
M062X	6-31G++(d,p)	5	-494.441857	-494.434217	-4.8
		6	-1140.331445	-1140.324730	-4.2
	cc-pvdz	5	-494.462401	-494.454867	-4.7
		6	-1140.379768	-1140.373203	-4.1
	aug-cc-pvdz	5	-494.498434	-494.491264	-4.5
		6	-1140.406737	-1140.400627	-3.8
MP2	6-31G(d,p)	5	-493.195366	-493.187792	-4.7
		6	-1138.362229	-1138.355077	-4.5
	6-31G++(d,p)	5	-493.227700	-493.221007	-4.2
		6	-1138.387309	-1138.381961	-3.4
	cc-pvdz	5	-493.213587	-493.206301	-4.6
		6	-1138.413193	-1138.406758	-4.0
	aug-cc-pvdz	5	-491.728906	-491.717800	-7.0
		6	-1138.505846	-1138.501841	-2.5

[a]$\Delta E = E_{\text{Chair-like conformer}} - E_{\text{Skew conformer}}$.

C11-N1-C3-O18(S18) dihedral angles. In the *Cis* conformer, these angles have the same value close to 0°, whereas their difference is about 180° in the Tran conformer (Fig. 4). The results presented in Table 3 show that all used methods found the *Tran* conformation more stable than *Cis* for both 5 and 6. The small values of the energy differences between the two conformers are interpreted as weak interactions between the carbonyl or thionyl groups, due to the large distances between their atoms. Small effects of the substitution of oxygen atom by sulfur one is noted. A

Table 2. The Well Depth of Axial/Equatorial Exchange Potential Surfaces of 5 and 6 Estimated at Different Levels of Precision

Méthode	ΔE (well depth) (Kcal mol^{-1})					
	6			5		
	aa	ea	Ee	aa	ea	ee
B3LYP/6-31G (d,p)	9.7	8.5	8.8	11.8	9.3	9.4
B3LYP/6-31++G (d,p)	10.4	8.7	8.5	12.1	9.3	8.8
B3LYP/6-31++G(d,p)//B3LYP/cc-pvdz	9.8	8.6	8.7	11.8	9.4	9.4
B3LYP/6-31++G(d,p)//MP2/6-31G(d,p)	6.6	6.9	8.5	7.6	7.1	9.0
B3LYP/6-31++G(d,p)//MP2/6-31++G(d,p)	7.1	7.0	8.0	7.0	6.6	8.2
B3LYP/6-31++G(d,p)//MP2/cc-pvdz	5.9	6.5	7.8	6.8	6.8	8.8



TS1 **TS2**

Fig. 5. The Transition states in the about C-N bond rotation of 5 (X = S) and 6 (X = O).

negligible effect of the basis sets used was also noted. So, it can be concluded that the 6-31G(d,p) basis set is sufficient to estimate the relative stabilities of the two conformers. We note that the MP2 method slightly increases the energy differences between the *Tran* and *Cis* conformers. This effect is more pronounced in the case of sulfur containing compound 5 and can be explained by the best representation of electronic correlation in MP2 method.

The polarizable continuum model (PCM) of water and n-octanol [39] were used to investigate the effects of aqueous and biological media on the conformational behaviors of 5 and 6. We used the Gaussian09W default values of solvent dielectric constants which are 78.35 for water and 9.86 for n-octanol [29]. It should be noted that in continuum model of water and n-octanol, the two conformers have equivalent stabilities. Water has a more pronounced effect than n-octanol. An explicit solvent model should be used to improve the representation of the solvent effects. Due to the hydrogen bond interaction between solute and solvent molecules, the results can be completely different from those obtained in gas phase using continuum model. This finding has also been reported by Anik Sen et al. as they studied the solvent effect on the conformational behavior of piperazine [40].

The hindered rotation about C-N bond converts *Tran* to *Cis* conformer. To compare this transition in 5 et 6, a scan, where the dihedral angle C10-N7-C16-O17(S17) varies from 0° to 360° in increments of 5°, was performed at the B3LYP/6-31G++(d,p) level of theory. Two different transition states were expected (Fig. 5). Because of the non-bonded intramolecular interactions in both transition states their activation energies should be different. Both transition

Table 3. Differences between the Energies of Conformers *Cis* and *Tran* of 5 and 6 in Gas Phase and Water and n-octanol Solvents Utilizing B3LYP/6-31G (d,p) Method

Medium	Method	Compound	Conformer	E (Hartree)	$\Delta E = E_{Tran} - E_{Cis}$ (kcal mol^{-1})
Gas phase	B3LYP/6-31G(d,p)	6	*Cis*	-494.636436	0.3
			Tran	-494.636933	
		5	*Cis*	-1140.551673	0.5
			Tran	-1140.552509	
	B3LYP/6-31++G(d,p)	6	*Cis*	-494.657678	0.4
			Tran	-494.658252	
		5	*Cis*	-1140.562521	0.5
			Tran	-1140.563331	
	B3LYP/cc-pvdz	6	*Cis*	-494.649420	0.3
			Tran	-494.649901	
		5	*Cis*	-1140.589577	0.5
			Tran	-1140.590388	
	MP2/6-31G(d,p)	6	*Cis*	-493.194841	0.3
			Tran	-493.195366	
		5	*Cis*	-1138.361492	0.5
			Tran	-1138.362229	
	MP2/6-31++G (d,p)	6	*Cis*	-493.227122	0.4
			Tran	-493.227700	
		5	*Cis*	-1138.386558	0.5
			Tran	-1138.387309	
	MP2/cc-pvdz	6	*Cis*	-493.213130	0.3
			Tran	-493.213587	
		5	*Cis*	-1138.412463	0.5
			Tran	-1138.413193	
Water	B3LYP/6-31G(d,p)	6	*Cis*	-494.651456	0.0
			Tran	-494.651483	
		5	*Cis*	-1140.571704	0.1
			Tran	-1140.571805	
n-octanol	B3LYP/6-31G(d,p)	6	*Cis*	-494.649317	0.1
			Tran	-494.649437	
		5	*Cis*	-1140.568590	0.2
			Tran	-1140.568860	

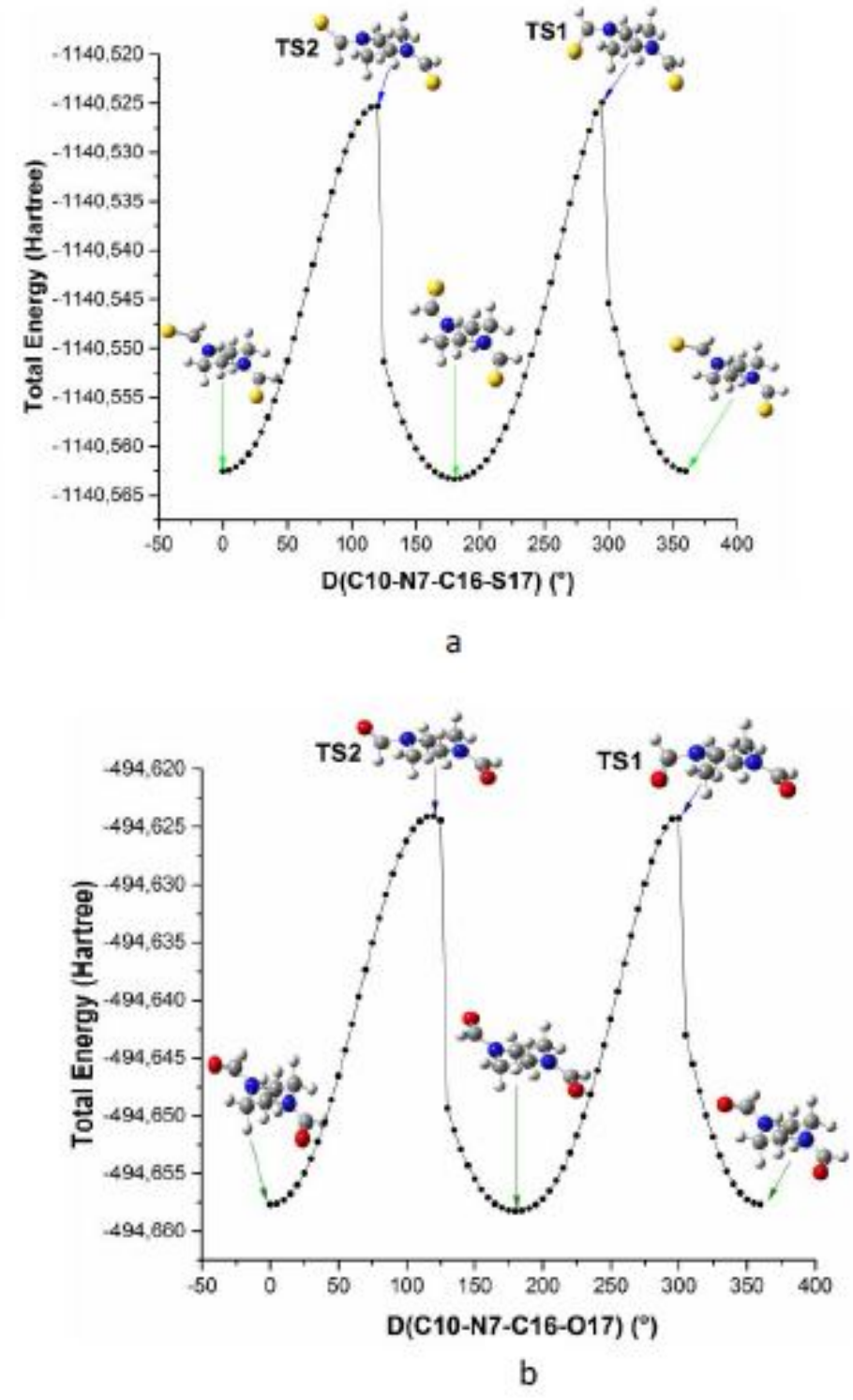


Fig. 6. Potential curves concerning the rotation about C-N bonds of 5 (a) and 6 (b) obtained at the B3LYP/6-31G(d,p) method.

states are characterized by the plane containing nitrogen and carbonyl atoms to be somewhat perpendicular to the plane containing the four heterocycle carbon atoms. We noted them by TS1 and TS2 as shown in Fig. 5. We have identified the transition states and estimated the rotational barriers. Figure 6 shows the potential energy curve of the rotation about C-N obtained for 5 and 6 at the B3LYP/6-31++G(d,p) level of theory. Table 4 illustrates a comparison of the rotational barriers of the two compounds with those of some other compounds collected from the literature.

It is worth noting that regardless of the type of the method used 6 exhibits a higher rotation barrier than 5. These findings are in good agreement with those reported in several previous theoretical and experimental studies [15-16-18]. The substitution of oxygen by sulfur increases the rotational barrier. This effect is more pronounced in 6 than that in formamide, acetamide and N,N-Dimethylformamide. This difference can be attributed to the cyclic hindrances of geometry relaxation in compound 6. Contrary to the literature results of acyclic amides, our results show that the transition states TS1 and TS2 have equivalent stabilities. We think that TS1 is less stable in cyclic amides than in linear ones. This can be explained by the more significant steric effect in cyclic amides. The methods used show that 6 has same rotational barrier in water and in n-octanol. The effects of water on the rotational barrier of 5 are larger than those in n-otanol. Rotational barriers increase in both solvents. The continuum solvent models can be insufficient because they do not take into account the specific interactions, such as hydrogen bonding, between 5 or 6 with solvent molecules. The explicit solvent model can provide completely different results.

Structural Properties

In order to explore the structural differences between 5 and 6 we compare their geometrical parameters in *Cis* and *Tran* conformers. Table 5 shows some bond lengths, bond angles and dihedral angles of the *Cis* and *Tran* conformers of 5 and 6. Some experimental structural data of other compounds collected from the literature are also shown in this table. So, they can be compared to those theoretically obtained at B3LYP/6-31G(d,p) level of the studied compounds.

The bond lengths calculated are comparable to available experimental data. The bond length between piperazine nitrogen and carbone atom of carbonyl or thionyl has a partial double bond character. This character is slightly more important in the case of sulfur containing compound 5. Similar results were obtained by Wiberg *et al.* for formamide and thiformamide [15]. These findings may partially explain why rotation barrier about C-N bond is larger in 5 than that in 6. The optimized bond length of C-C in the piperazine ring falls in the range 1.532-1.537 Å for all compounds and conformers. This result is in good agreement with an analogous molecule in which the length of the C-C bond is about 1.511 Å [43]. As expected, the C-S bond is larger than the C-O bond, which is consistent with the literature data. Consequently, it can be concluded that compound 5 has larger molecular dimensions and volume. It is well known that molecular volume is used as a descriptor for QSAR model. Therefore, the differences in bioactivities of 1 and 2 can partially be related to molecular volume difference between 5 and 6. In the *Tran* conformer of 6 all C-N bonds of piperazinic ring have the same bond length. In the *Cis* conformer the piperazine C-N bonds near carbonyl groups are slightly larger than the others. This outcome may be attributed to the effect of the interactions between the two carbonyl groups. The interactions between the two thionyl groups in *Cis* conformer of 5 do not affect the piperazine C-N bond lengths. The sum of the three bond angles around nitrogen atoms are about 360°, confirming the planarity and the sp^2 hybridization of this atom in both compounds. The substitution of the oxygen atom by the sulfur atom has an impact on the values of the N-C-O(S) bond angles (125.3° and 128.4° in 6 and 5, respectively). The same observation was noted for the dihedral angle, since the values of O17-C16-N7-C4 and O18-C3-N1-C11 are around 0.8° and -0.8°, respectively, whereas those of S17-C16-N7-C4 and S18-C3-N1-C11 are about 0.4° and -0.4°, respectively.

Dipole Moment

Table 6 summarizes the dipole moment values of *Cis* and *Tran* conformations of the 5 and 6 compounds obtained at the B3LYP/6-31G(d,p) level of theory.

As expected, since the *Tran* conformations are centro-symmetric, their dipole moments are null. On the other hand, the *Cis* conformations are not centro-symmetric and

Table 4. About C-N Bond Rotational Barriers of 5 and 6 Compared to those of other Amides

Compounds	Solvent	Methods	Transition state nature	Rotational barriers (Kcal mol^{-1})
Thioformamide	Gas phase	MP2/6-31+G(d)	TS1	18.8[a]
		MP2/6-31+G(d)	TS2	21.2[a]
Thioacetamide	Gas phase	MP2/6-31G(d,p) //RHF/6-31G(d,p)	TS1	18.1[b]
			TS2	20.2[b]
		MP2/6-31G(d,p)//MP2/6-31G(d,p)	TS1	17.3[b]
5	Gas phase	B3LYP/6-31G(d,p)	TS2	24.2
		B3LYP/6-31++G(d,p)		23.4
		B3LYP/cc-pvdz		24.0
		MP2/6-31G(d,p)		20.8
		MP2/6-31++G(d,p)		19.8
		MP2/cc-pvdz		20.9
	PCM-Water	B3LYP/6-31G(d,p)		27.4
	PCM-n-octanol	B3LYP/6-31G(d,p)		26.8
	Gas phase	B3LYP/6-31G(d,p)	TS1	24.5
		B3LYP/6-31++G(d,p)		23.7
		B3LYP/cc-pvdz		24.2
		MP2/6-31G(d,p)		20.9
		MP2/6-31++G(d,p)		19.9
		MP2/cc-pvdz		20.6
	PCM-Water	B3LYP/6-31G(d,p)		28.7
	PCM-n-octanol	B3LYP/6-31G(d,p)		28.0

Table 4. Continued

6	Gas phase	B3LYP/6-31G(d,p)	TS2	21.5
		B3LYP/6-31++G(d,p)		21.1
		B3LYP/cc-pvdz		20.9
		MP2/6-31G(d,p)		19.7
		MP2/6-31++G(d,p)		19.2
		MP2/cc-pvdz		18.5
	PCM-Water	B3LYP/6-31G(d,p)		22.4
	PCM-n-octanol	B3LYP/6-31G(d,p)		22.3
	Gas phase	B3LYP/6-31G(d,p)	TS1	21.2
		B3LYP/6-31++G(d,p)		21.0
		B3LYP/cc-pvdz		21.1
		MP2/6-31G(d,p)		19.0
		MP2/6-31++G(d,p)		18.7
		MP2/cc-pvdz		18.4
	PCM-Water	B3LYP/6-31G(d,p)		23.2
	PCM-n-octanol	B3LYP/6-31G(d,p)		22.9
Formamide	Gas phase	MP2	TS1	17.3[a]
			TS2	19.7[a]
		Experimental	-	13.5[c]
Acetamide		MP2/6-31G(d,p)//RHF/6-31G(d,p)	TS1	13.9[b]
		Experimental	-	13.3[c]
N,N-dimethylformamide		Experimental		13.9[c]

[a]From reference 15. [b]From reference 16. [c]From reference 41.

Table 5. Structural Parameters of 5 and 6 in their *Tran* and *Cis* Conformers Optimized at B3LYP/6-31G(d,p) Density Functional Calculation

Parameters	Crystal[a;b;c;d]	B3LYP/6-31G (d,p)			
		6		5	
		Cis	*Tran*	*Cis*	*Tran*
Bond lenghts					
N1-C2	1.4629b	1.455	1.457	1.461	1.464
N7-C4		1.455	1.459	1.461	1.462
N1-C11	1.4629b	1.462	1.459	1.465	1.462
N7-C10		1.462	1.458	1.465	1.464
N1-C3	1.3391[a]/1.391[d]	1.367	1.367	1.349	1.348
N7-C16	1.3621c	1.367	1.367	1.349	1.348
C2-C4	1.511b	1.537	1.535	1.536	1.534
C10-C11	1.511b	1.533	1.535	1.532	1.534
C3-O18(S18)	1.2387[a]/1.2367[c]	1.219	1.219	1.655	1.656
C16-O17(S17)	1.224d	1.219	1.219	1.655	1.656
Bond angles					
C2-N1-C3	125.53[c]	122.9	123.2	122.2	122.4
C3-N1-C11	119.16[c]	121.0	120.7	123.4	123.1
C2-N1-C11	113.43[b]	116.1	116.1	114.4	114.5
C10-N7-C16	121.83[a]	121.0	123.1	123.4	122.4
C4-N7-C16	124.54[a]	122.9	120.7	122.2	123.1
C4-N7-C10		116.1	116.1	114.4	114.5
N1-C2-C4		110.0	110.3	110.2	109.9
N1-C11-C10		110.2	109.8	110.4	110.6
C2-C4-N7		110.0	109.8	110.2	110.6
N7-C10-C11		110.2	110.3	110.4	109.9
N1-C3-O18(S18)	121.45[a]	125.3	125.3	128.4	128.4
N7-C16-O17(S17)	121.76[c]	125.3	125.3	128.4	128.4

Table 5. Continued

Dihedral angles					
N7-C4-C2-N1		51.3	50.8	53.1	52.7
C4-C2-N1-C11		-54.3	-54.3	-55.2	-55.3
C2-N1-C11-C10		53.9	54.1	54.9	54.9
N1-C11-C10-N7		-50.3	-50.8	-52.3	-52.7
C11-C10-N7-C4		53.9	54.3	54.9	55.3
C10-N7-C4-C2		-54.3	-54.1	-55.2	-54.9
C16-N7-C10-C11	-133.4[a]	-124.4	-123.8	-123.6	-123.3
C16-N7-C4-C2	132.86[a]	124.0	124.1	123.3	123.7
C3-N1-C11-C10	-136.92[c]	-124.5	-124.0	-123.6	-123.7
C3-N1-C2-C4	137.76[c]	124.1	123.8	123.3	123.3
(S17)O17-C16-N7-C10	-4.88[a]	-0.7	178.8	-0.6	178.9
(S17)O17-C16-N7-C4	-178.37[a]	-178.9	0.8	-178.9	0.4
(S18)O18-C3–N1-C11	176.58[c]	-0.7	-0.8	-0.7	-0.4
(S18)O18-C3-N1-C2	9.51[c]	-179.0	-178.8	-179.0	-178.9

[a]1-[4-(4-Hydroxyphenyl)piperazin-1-yl]-ethanone: taken from Ref. [42]. [b]N,N-Dibenzoylpiperazine: taken from Ref. [43]. [c]1,4-Bis(2-diazoacetyl)piperazine: taken from Ref. [44]. [d]N,Ndimethylformamide: taken from Ref. [45].

Table 6. Dipole Moment of the *Cis* and *Tran* Conformers of 5 and 6 Calculated in Gas Phase at B3LYP/6-31G(d,p) Level and in Solution of n-octanol and Water

μ (Debey)		6		5	
		Cis	*Tran*	*Cis*	*Tran*
B3LYP/6-31G(d,p)	Gaz	4.1	0.0	4.8	0.0
	n-Octanol	5.2	0.0	6.9	0.0
	Water	5.4	0.0	7.3	0.0

present non-zero dipole moments. It can be deduced that *Tran* and *Cis* conformers exhibit different physisorption features and that they can be separated using chromatography techniques. Replacing the oxygen atom by the sulfur atom in the carbonyl function induces a small effect on the dipole moment. Both solvents, *i.e.* water and n-

octanol, increase the dipole moments of both compounds. The water solvent effect is more pronounced than that of n-octanol. The dipole moment of the *Cis* conformation of sulfur containing compound 5 is more sensitive to the solvent effect than 6. The obtained results indicated that 5 shall exhibit better solvation in polar solvent than 6.

Partial Charges Distribution

The atomic charges were calculated at B3LYP/6-31G(d,p) using Mulliken approximation**,** NBO analysis**,** and atomic polar tensors, APT, approaches. In Fig. 7 the partial atomic charges of the two compounds are compared. In agreement with electronegativity of the sulfur atom the thionyl groups are less polarized than carbonyl group. The substitution of oxygen atom by sulfur one induces a large decline in their partial charges and an increase of the partial charges of aldehyde hydrogen atom. These external atoms are supposed to play an important role in the binding of its molecules to the active site. This observation can be used to explain the bioactivity difference between compounds containing 5 and 6 as substructures. Proton NMR shielding is closely related to its surrounding electronic density. So, the hydrogen partial charges can be used to probe H NMR properties. It can be noted that all used population analysis approaches predict similar H NMR spectra for the two conformations: *Cis* and *Tran*. Also, despite the slow rotation about C-N, this technique not useful to estimate the *Cis*/*Tran* population ratio of 5 and 6 [17]. This ratio can be experimentally studied for the unsymmetrical molecules 1, 2, 3 and 4 and used to interpret their bioactivity differences. In agreement with the results published by Stewart *et al*., NBO population analysis approach results show clearly that the aldehyde proton is more shielded in thioamide compound of **6** than amide compound of 5 [17].

Molecular Electrostatic Potential

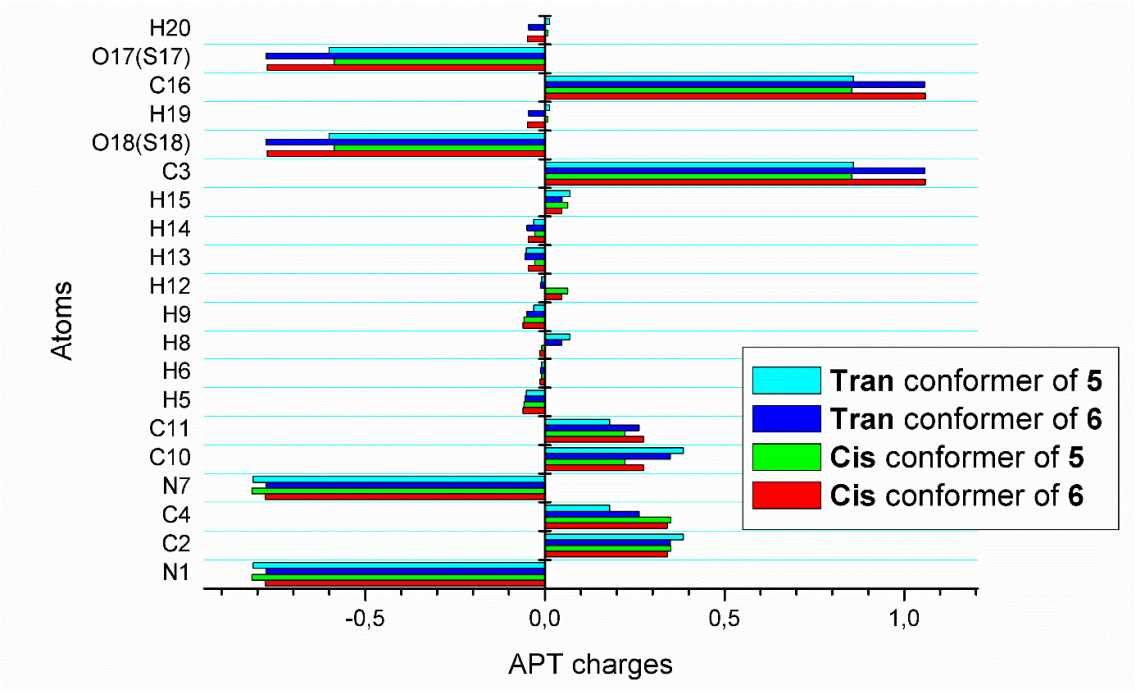
Molecular electrostatic potential (ESP) at a point of the space gives an indication of the net electrostatic effect induced at that point by the total charge distribution (electron + nuclei) of the molecule in a given conformation. ESP correlates with dipole moments, partial charges and electronegativity. It is also used to explain the bioactivities of molecules. In addition, it provides a visual method to understand the relative polarity of the molecule. In Fig. 8, the different values of the electrostatic potential are represented by different colors; red represents the regions of the most negative electrostatic potential, blue represents the regions of the most positive electrostatic potential, and green represents the region of zero potential. The calculated 3D ESP contour map shows the negative regions mainly over the oxygen and sulfur atoms. The positive regions are over the hydrogen atoms. Net differences are observed between the 3D ESP shapes and intensities of 5 and 6 at their both *Cis* and *Tran* conformations. These results are in the opposite of results of Serradji *et al.* [9]

HOMO-LUMO Analysis

The energies of highest occupied molecular orbital *(HOMO)* and lowest unoccupied molecular orbital *(LUMO)* and their energy gaps show the tendency of molecules, like 1, 2, 3, 4, 5 and 6, to have charge transfer interactions with other molecules, as active sites. So, bioactivities of molecules can be related to the properties of the frontier orbitals. The HOMO and LUMO energies and their difference of 5 and 6 have been calculated using the B3LYP/6-31G (d,p) method, and presented in Table 7. The LUMOs' energies of 5 are near zero and negative. This indicates that 5 can receive electrons from other molecules through charge transfer interactions. Therefore, compound 5 has a higher tendency to undergo charge transfer than 6. The HOMO-LUMO energy gap decreases when the oxygen atom is substituted by sulfur atom. A similar observation was noted by Kenneth et al. in studying the $n \rightarrow \pi^*$ transition in small carbonyl and thiocarbonyl derivatives [46]. It is supposed that the compounds 5 and 6 absorb ultraviolet radiations. Sulfur shifts the corresponding electronic transition about 2.3 eV to the red. Compared to the results published by Kenneth *et al*., it can be deduced that the six-membred ring hindrance increases the transition energy about 2 eV [46]. As observed in Fig. 9, the LUMO is delocalized on all the atoms, however, the substitution of oxygen by sulfur atom decreases the piperazine ring participation in the HOMO orbital which is destabilized.

CONCLUSIONS

The substitution of oxygen atom by a sulfur atom induces some changes in the anti-PAF and anti-HIV



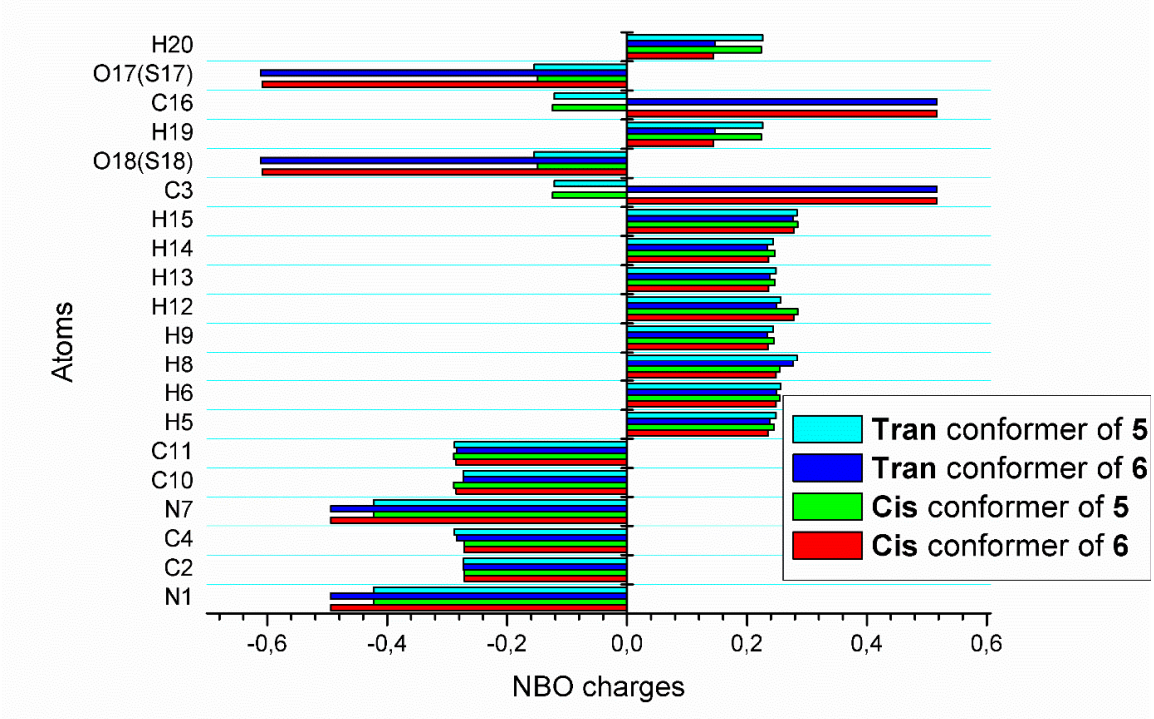


Fig. 7. Graphical representation of the partial atomic charges of 5 and 6 in their *Cis* and *Tran* conformations, calculated at B3LYP/6-31G(d,p) using Mulliken approximation, NBO analysis, and APT approaches.

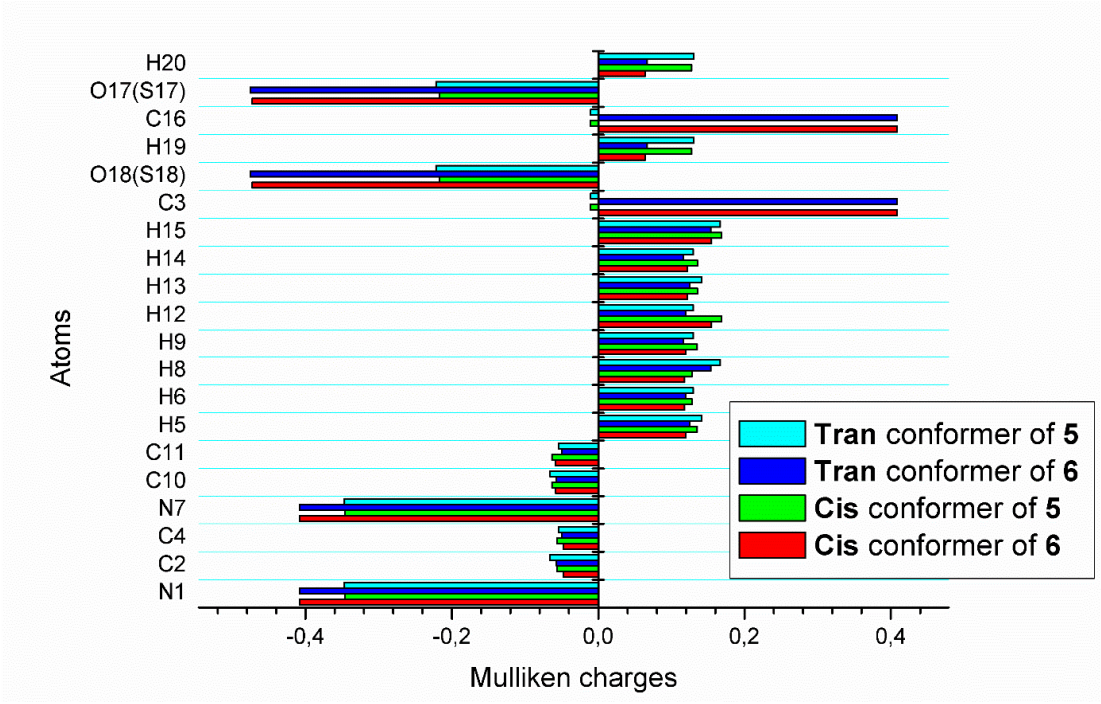


Fig. 7. Continued.

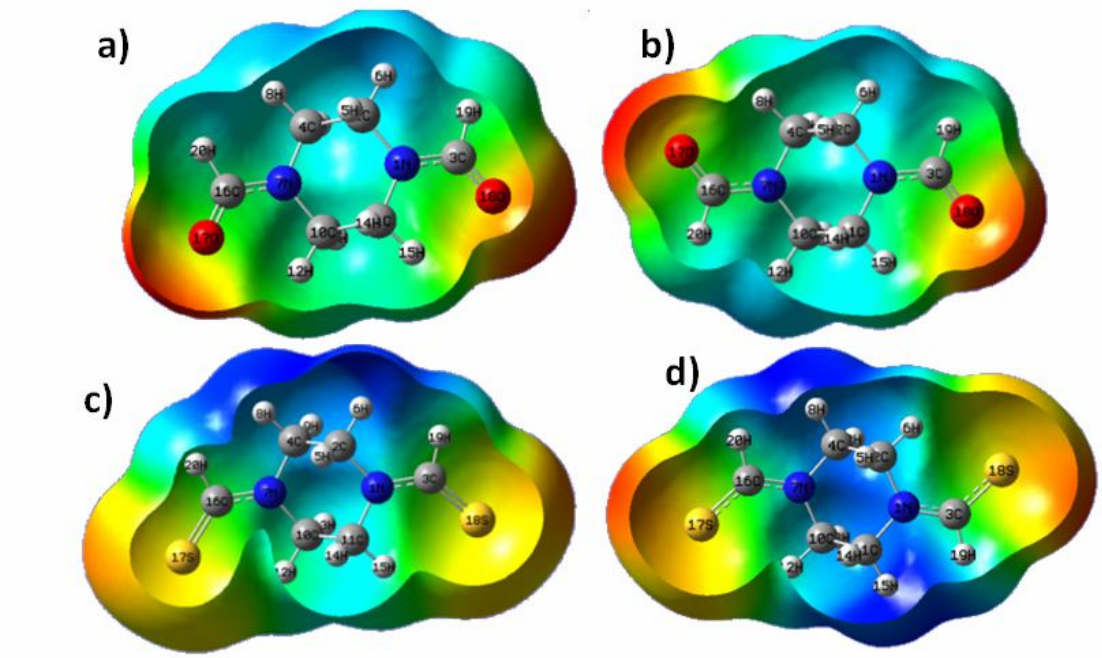


Fig. 8. The molecular electrostatic potentials surface for (a) conformer *Cis* of 6, (b) conformer *Tran* of 6, (c) conformer *Cis* of 5 and (d) conformer *Tran* of 5 calculated in gas phase at B3LYP/6-31G(d,p) level.

Table 7. HOMO and LUMO Energies in eV of 5 and 6 in their Conformers *Cis* and *Tran* Obtained Using B3LYP/6-31G(d,p) Method

	6		5	
	Cis	*Tran*	*Cis*	*Tran*
HOMO (eV)	-6,60	-6,60	-5,91	-5,93
LUMO (eV)	0,36	0,36	-1,26	-1,28

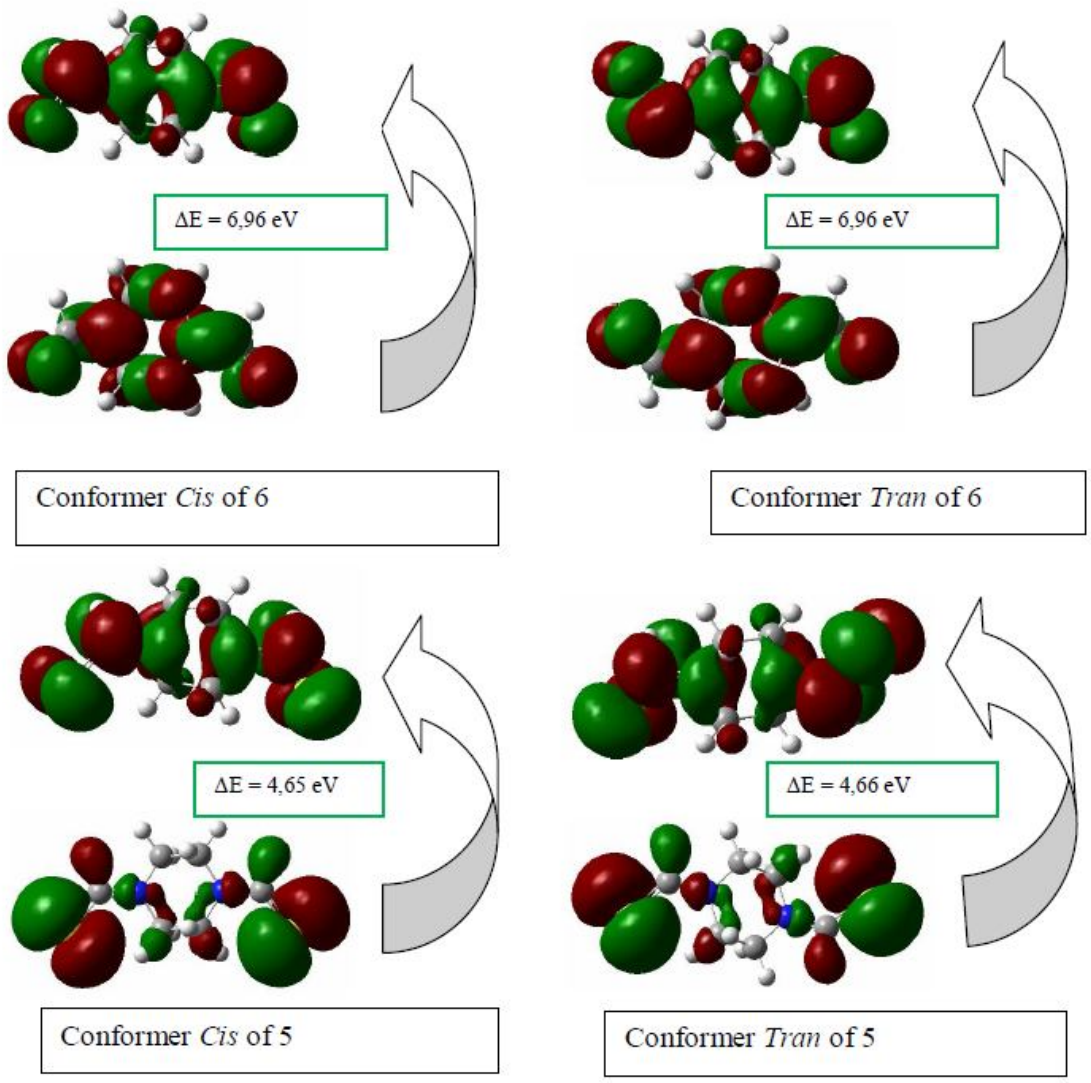


Fig. 9. HOMO and LUMO plot and HOMO-LUMO gap of 6 and 5 in their conformations *Cis* and *Tran*.

bioactivities of piperazine derivatives. It suggests that 5 and 6 could be simple but well informative models of the base substructures of theses bioactive compounds. We compared their structural and electronic properties which play key roles in the drug-receptor interactions. It was shown that oxygen-containing compound 6 and its sulfur-containing analogue 5 have similar conformational behaviors. However, compound 5 exhibits higher activation energies, indicating its less flexibility than 5. Both compounds 5 and 6 have equivalent shapes, but the former has less great molecular volume. These findings can be used to explain why the compound containing 5 as substructure (2) show better anti-HIV activity than the compound containing 6 as substructure (1). The substitution of oxygen atom by sulfur modifies the electronic density distribution of the HOMO and LUMO orbitals and decreases the LUMO orbital energy which can cause changes in the interaction of the molecule with the receptor.

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