Theoretical study on electronic and thermodynamic properties of the three isomers of some pyrido[4,3-e]-l,2,4-thiadiazine

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Abstract: The aim of present studies is to focus on the structural optimization, electronic, thermodynamic properties and tautomerism behavior of some pyrido[4,3-e]-l,2,4-thiadiazine l,l-dioxides (PDZ) as potassium channel openers by using density functional theory. The collected data showed that the substitution on the 3 position and pyrido-ring can be effective on the tautomerization constant and electronic properties. The data of DFT method show that the 4*H* (rather than 2*H* and C3-NH_2) tatomeric forms is preferentially adopted by this pyridothiadiazine derivative in the gas phase. Energy of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), chemical potential (μ), hardness (η), electrophilicity energy (ω) and nucleus-independent chemical shift (NICs) as electronic properties have been predicted. The effect of the substitute on the pyrido-ring on the aromaticity is more than the substitute on the NH_2 groups. Furthermore, density functional theory (DFT) calculations were carried out on the some of these compounds to investigate the deviation of the sulfone group on the 1 position of chair plane.

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Introduction

Potassium channels regulated by changes in intra cellular levels of adenosine triphosphate (ATP-sensitive K channels or K_{ATP} channels) and which link the membrane potential to the metabolic state of the cell have been described in a wide range of cell types including pancreatic B-cells (Cook, and Hales, 1984), and smooth muscle cells (Standen et al., 1989). A series of 3-alkylamino-4*H*-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxides structurally related to diazoxide and pinacidil were synthesized and tested as possible K_{ATP} channel openers on isolated pancreatic endocrine tissue as well as on isolated vascular, intestinal, and uterine smooth muscle (Cook, and Hales, 1984, Standen et al., 1989 and Quayle etal., 1997). Furthermore, the powerful inhibitors of some of these compounds on the insulin release from rat pancreatic B-cells were investigated (Pirotte et al., 1993 and de Tullio et al., 1996). Analogs of these compounds were identified as pancreatic B-cell K_{ATP} channel activators (Pirotte et al., 1994, Antoine et al., 1994, Lebrun et al., 1996, Pirotte et al., 1996). The chemistry and biological activity of one of the heterocyclic compounds as pyrido[4,3-e]-l,2,4-thiadiazine l,l-dioxides (PDZ) have attracted the attention of many researchers, and this led to the synthesis of a variety of pyridothiadiazine 1,1-dioxides derivatives.

Tautomerism is an important area of chemical study that has long been a challenge computationally, experimentally, and intellectually. For example, in 1950, Watson and Crick were able to propose the structure of DNA because they had the insight to focus on the keto-form base pairs rather than the enol-form tautomers (Watson, and Crick, 1953). Unfortunately, the complicating effects of tautomerism affect more than just the biochemical field; they also have a broad impact on analytical data interpretation and management for infrared (IR), Raman, UV/Vis, and nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS), and other analytical techniques .[11-21]

For the PDZs series of compounds, application of ^{1}H NMR, ^{13}C NMR, UV spectrophotometric analysis, X-ray crystallography data of individual pure enantiomers, show predominantly exist as a 4*H*-tautomer.[22-26] Furthermore Bernard Pirotte and co-worker synthesized some of the 3-alkylamino-4*H*-pyrido[4,3,e]-1,2,4-thiadiazine 1,1-dioxide & 7-chlorobenzothiadiazine and proposed that the 4*H*-tautomer exist (Pirotte et al., 1993).

However, in this context, we have carried out a systematic theoretical method to investigate the stability of three forms of PDZs and also study the equilibrium constant of the amine-imine equilibrium of these compounds. In addition, we have determined the HOMO, LUMO energy, chemical potential (μ),

chemical hardness (η) and global electrophilicity (ω) energy, and also nucleus-independent chemical shift (NICs) of the three isomers. According to the minimum electrophilicity principle (MEP) in chemical processes which is analogous to the maximum hardness principle (MHP),[27-31] the stable isomer is toward a state of minimum electrophilicity. Furthermore, the deviation of the sulfone group (SO_2 group) on the 1 position of chair plane was studied.

Theoretical backgrounds and computational techniques

The density functional theory (DFT) is one of the most important theoretical models to explain the science of solids and chemistry. A number of chemical concepts have correlated within the framework of DFT (Parr and Yang, 1995). The structural parameters calculated through the $\rho(r)$ concept, compare well, with the parameters calculated by the ψ concept.[33,34] Since this theory is simpler than quantum mechanics, the interest has grown in understanding the structure, properties, reactivity and dynamic of atoms, molecules and clusters using DFT. Global electrophilicity (ω), hardness (η), chemical potential (μ) energy, energy of HOMO, LUMO molecular orbital and aromaticity (NICs) are very important properties to characterize the reactive nature of atomic and molecular species that can be carried out by this method.

As far as is known (Parr and Yang, 1995); the electronic chemical potential (ECP) of a many electron system can be introduced in the framework of the density functional theory in two related ways. The first definition of ECP is based on the differential expression for the ground state electronic energy of a system (an atom, a molecule, etc.) equation 1,

$$dE = \mu dN + \int \rho(r)\, \delta\upsilon(r)\, dr \qquad (1)$$

that comes out of the dependence of the energy E on two independent variables: the number of electrons N and the external potential $\upsilon(r)$ due to nuclei. In the foregoing expression, quantities μ and $\rho(r)$ turn out to be very important. The latter represents the electron density of the system, and the former defined as $(\delta E/\delta N)$ is called ECP by the analogy with the chemical potential (μ) of ordinary macroscopic thermodynamics. The first definition of ECP assumes that E maybe determined as a smooth function of N by applying suitable interpolation methods (Kohn, et al., 1996). So, the three-point finite-difference approximation to μ for a system with the ionization potential I and electron affinity A is $-(I+A)/2$. This allows identifying ECP with the negative of the electronegativity of a system (Parr and Yang, 1995).

Using Koopmans' approximation can be simplified (Pearson 1987) to the calculation of the chemical potential energy (μ) and chemical hardness energy (η) by the following forms equations 2 and 3.

$$\mu = (\varepsilon_{LUMO} + \varepsilon_{HOMO}) / 2 \qquad (2)$$

$$\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO}) / 2; \qquad (3)$$

where the symbols have their usual meaning.

There has been a growing interest in classifying atoms and molecules with in empirical and theoretical scales of electrophilicity and nucleophilicity. From a theoretical point of view, the electrophilicity concept has attracted the attention of several authors.[37-41] It is based on a second order expansion of the electronic energy with respect to the charge transfer ΔN at fixed geometry. Since electrophiles are species that stabilize upon receiving an additional amount of electronic charge from the environment, there is a minimum of energy for a particular ΔN^* value. Using this simple idea, Parr et al. performed a variation calculation that led to the definition of the global electrophilicity index as $\omega = -\Delta E(\Delta N^*)$, which may be recast into the more familiar form (Parr et al., 1999) equation 4:

$$\omega = \frac{\mu^2}{2\eta} \qquad (4)$$

The global electrophilicity is defined in terms of the electronic chemical potential (μ) and the chemical hardness (η).

Computational methods

Structures of PDZs were built and optimized preliminarily with semi-empirical PM3 method using Hyper-Chem software.[39] These PM3 optimized structures were used as initial guess geometries for the ab initio calculations. Structural and electronic characteristics calculated for the B3LYP/6-311++G(d,p) optimized geometries were analyzed in the following sections. All computations were carried out using the Gaussian 98 package (Frisch et al., 1998). Compounds **1a**, **2a** and **3a** (both with X = Y = H) are considered as references to compounds in the comparative investigation of the effect of the substitution on the pyrido-ring and on the 3 position of amine groups optimized structures of three forms of PDZs. Charge density distributions for all PDZs were also studied using natural bond orbital (NBO) analysis of Weinhold.[41-43] Furthermore, the NICs calculations of the present systems have been performed by the use of Gaussian 98 package program (Frisch et al., 1998). To, we investigate the stability of the three isomers by comparative the minimum electrophilicity data.

Results and discussion

The effect of centric perturbation of a heteroatom to the central ring, and/or substitution of a heteroatom or hetero-group with the hydrogens of well-known aromatic compounds has always found application in both theoretical and experimental studies. In the present article, all possible pyridothiadiazine 1,1-dioxides derivatives and their substituted have been

investigated theoretically by the application of B3LYP/6-311++G(d,p) level of theory in order to judge their stabilities of three tautomers forms, electronic, thermodynamic properties and aromaticity. The general structures of three isomers of PDZs are shown in Figure 1, where the numbering scheme used to describe these structures is also introduced. Analysis of the optimized structures of three isomers of PDZs shows that the six-membered ring that fused to pyrido-ring adopts a *boat* conformation, flattened at 1 position toward an envelope conformation, with a *pseudo-axial* orientation of the two oxygen atoms on the 1 position. In table 1 the optimized lengths of the N4-H, N5-H6,7, N2-H, C3-N5, N4=C3, N4-C3, N2-C3, N2=C3, C3=N5, C3-N5, S1-N2, S1-C10 and S1=O8,9 bonds that play a role in the activities of PDZs are listed. The optimum values of the N2–C3–N4, C10–S1–N2, and C3–N2–S1 bond angles denoted by α, β, and γ, respectively, are reported in table 2.

The DFT are calculated for the formation and the equilibrium reaction enthalpies. The DFT are also calculated for free energies of three forms of pyridothiadiazine 1,1-dioxides derivates and tautomeric equilibrium constants are given in tables 7 and 8.

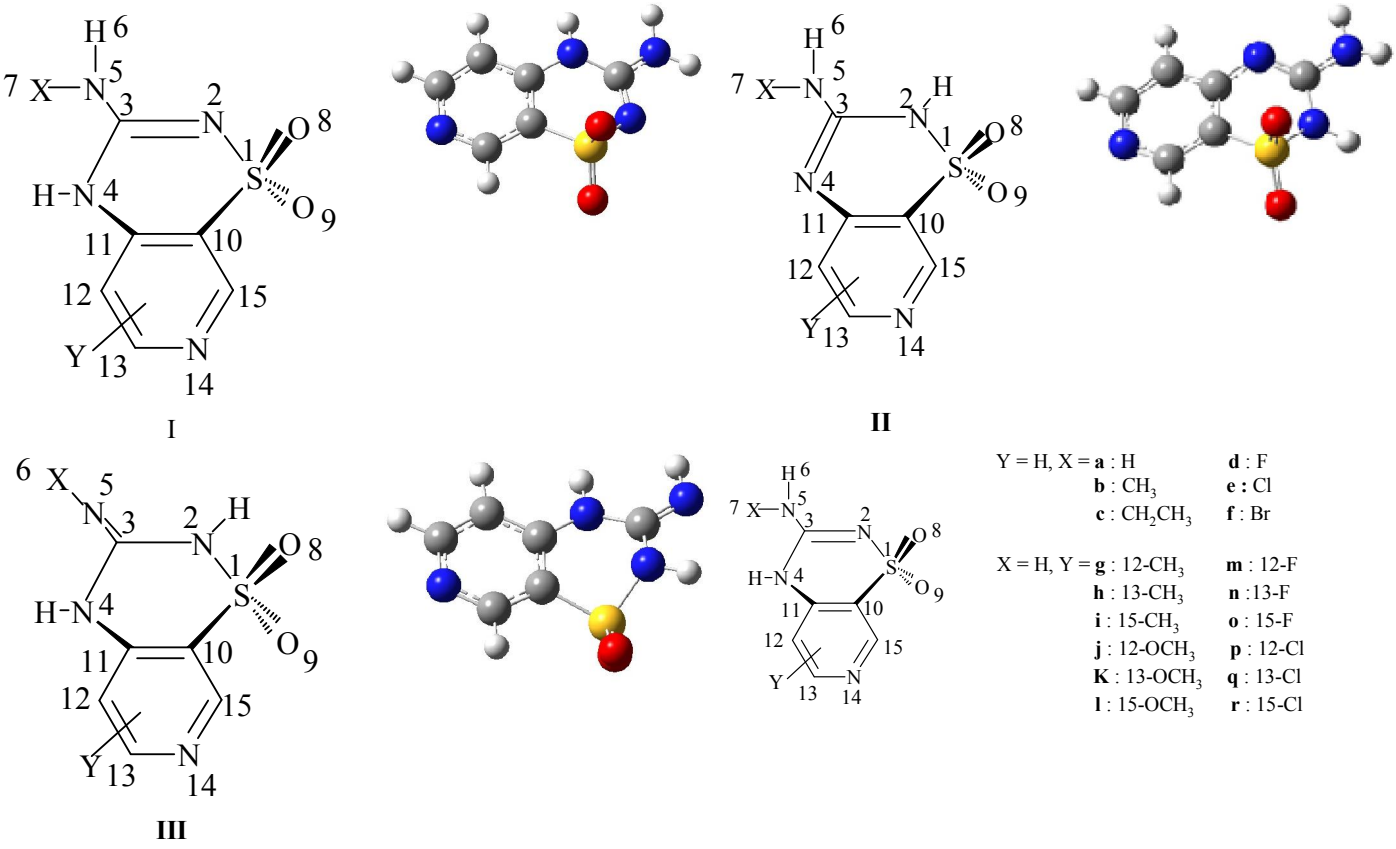

Figure 1. General structures of the 4*H*- pyridothiadiazine 1,1-dioxides (**I**), 2*H*- pyridothiadiazine 1,1-dioxides (**II**) and 2*H*,4*H*-pyridothiadiazine 1,1-dioxides (**III**) and those derivatives conformation and the numbering scheme used in this work.

Table 1. Selected B3LYP/6-311++G(d,p) optimized geometrical parameters obtained for bond lengths of three isomers of PZDs. (bond lengths are given in Å)

				Isomer I				
Comp.	N4-H	N5-H6,7	N4-C3	C3-N5	N2=C3	S1-N2	S1-C10	S1=O8,9
a	1.009	1.010,1.009	1.384	1.372	1.292	1.662	1.787	1.461,1.455
b	1.008	1.009	1. 382	1. 361	1. 301	1. 658	1.788	1.463,1 .455
c	1.008	1.010	1. 382	1. 361	1. 301	1. 658	1.788	1.463, 1.455
d	1.011	1.019	1. 365	1.403	1. 287	1. 685	1.788	1.452, 1.458
e	1.010	1.015	1. 369	1. 393	1. 291	1 .681	1.787	1.453, 1.459
f	1.010	1.016	1. 370	1. 390	1. 292	1. 680	1.787	1.453, 1.459

g	1.009	1.009, 1.010	1.384	1.373	1.291	1.662	1.787	1.461,1 .455
h	1.009	1.009, 1.010	1.384	1.374	1.291	1.663	1.785	1.455,1 .461
i	1.008	1.010, 1.010	1.376	1.375	1.291	1.665	1.798	1.456, 1.462
j	1.011	1.008,1.009	1.380	1.371	1.293	1.661	1.789	1.461,1.455
k	1.009	1.009, 1.010	1.384	1.373	1.291	1.663	1.782	1.462,1.456
l	1.009	1.011, 1.011	1.378	1.379	1.288	1.670	1.796	1.459,1.453
m	1.010	1.008,1.009	1.385	1.366	1.293	1.660	1.791	1.454,1.460
n	1.009	1.008, 1.009	1.388	1.369	1.291	1.661	1.787	1.454,1.460
p	1.009	1.010, 1.010	1.381	1.374	1.289	1.666	1.800	1.451,1.458
o	1.010	1.010, 1.010	1.383	1.369	1.294	1.665	1.792	1.454,1.460
q	1.009	1.010, 1.010	1.383	1.371	1.293	1.667	1.788	1.454,1.460
r	1.009	1.010, 1.010	1.378	1.374	1.289	1.664	1.809	1.452,1.458

Isomer II

Comp.	N2-H	N5-H6,7	N4=C3	C3-N5	N2-C3	S1-N2	S1-C10	S1=O8,9
a	1.012	1.009,1.010	1.296	1.369	1.383	1.712	1.766	1.456,1.456
b	1.013	1.008	1.299	1.360	1.390	1.711	1.767	1.457,1.456
c	1.013	1.009	1.299	1.359	1.391	1.710	1.767	1.457,1 .456
d	1.013	1.020	1.279	1.408	1.381	1.715	1.770	1.453, 1.454
e	1.013	1.013	1.283	1.389	1.387	1.712	1.769	1.453, 1.455
f	1.013	1.013	1.285	1.385	1.387	1.712	1.767	1.454, 1.455
g	1.012	1.010, 1.009	1.296	1.369	1.382	1.713	1.766	1.456, 1.456
h	1.012	1.100, 1.009	1.295	1.370	1.383	1.713	1.763	1.456,1 .456
i	1.012	1.010, 1.009	1.293	1.370	1.380	1.709	1.775	1.457,1.457
j	1.012	1.010, 1.009	1.294	1.370	1.384	1.710	1.769	1.456,1.456
k	1.012	1.010, 1.009	1.294	1.370	1.384	1.713	1.760	1.457,1.457
l	1.012	1.010, 1.009	1.296	1.370	1.376	1.718	1.771	1.456,1.454
m	1.013	1.010, 1.009	1.297	1.365	1.383	1.712	1.770	1.455,1.455
n	1.013	1.010, 1.009	1.297	1.366	1.382	1.713	1.764	1.455,1.455
o	1.013	1.010, 1.009	1.298	1.366	1.378	1.715	1.773	1.454,1.452
p	1.013	1.010, 1.009	1.297	1.365	1.382	1.712	1.770	1.455,1.455
q	1.013	1.010, 1.009	1.297	1.366	1.383	1.713	1.765	1.455,1.455
r	1.013	1.010, 1.009	1.296	1.366	1.377	1.712	1.784	1.454,1.453

Isomer III

Comp.	N2-H	N4-H	N4-C3	C3=N5	N2-C3	S1-N2	S1-C10	S1=O8,9
a	1.016	1.009	1.400	1.271	1.401	1.709	1.776	1.454,1.457
b	1.016	1.008	1.399	1.268	1.407	1.709	1.778	1.459,1.454
c	1.016	1.008	1.399	1.268	1.407	1.709	1.778	1.455,1.459
d	1.017	1.011	1.374	1.293	1.390	1.724	1.778	1.452,1.455
e	1.017	1.012	1.377	1.290	1.396	1.720	1.777	1.452,1.456
f	1.017	1.012	1.379	1.289	1.398	1.720	1.777	1.453,1.456
g	1.016	1.008	1.400	1.271	1.400	1.709	1.776	1.454,1.458
h	1.016	1.009	1.399	1.271	1.401	1.710	1.773	1.454,1.458
i	1.016	1.009	1.396	1.271	1.397	1.706	1.786	1.455,1.458
j	1.016	1.010	1.397	1.271	1.402	1.709	1.777	1.454,1.458
k	1.016	1.009	1.399	1.271	1.401	1.710	1.769	1.455,1.455
l	1.016	1.008	1.398	1.272	1.395	1.713	1.783	1.458,1.452
m	1.016	1.010	1.401	1.269	1.402	1.709	1.780	1.453,1.457
n	1.016	1.009	1.402	1.270	1.401	1.709	1.775	1.453,1.457
o	1.016	1.009	1.400	1.270	1.397	1.709	1.786	1.450,1.456
p	1.016	1.010	1.402	1.269	1.401	1.707	1.780	1.453,1.457
q	1.016	1.009	1.402	1.270	1.401	1.709	1.776	1.453,1.457
r	1.016	1.009	1.398	1.270	1.395	1.707	1.797	1.450,1.456

A review of the data reported in table 1 shows that the bond lengths in the three isomers of the PDZs compounds are very close, while they are dependent on the type of the substituent at the 3 position and on the pyrido-ring. However, one cannot observe pure trend could be extracted for individual contributions.

Comparative data which reported in the table 2, show that α and γ bond angles in the three isomers are close to each but β bond angle in the isomer **I** is more than two other isomers. It seems that this trend related to the balance between donor-acceptor interactions of substitution with electron pairs of the S atom.

Table 2. Selected B3LYP/6-311++G(d,p) optimized geometrical parameter obtained for bond angles of three isomer of PDZs. (angles are given in degrees)

Comp.	Isomer I			Isomer II			Isomer II		
	α (°)	β (°)	γ (°)	α (°)	β (°)	γ (°)	α (°)	β (°)	γ (°)
a	126.1	102.7	121.5	124.3	96.3	120.7	113.6	96.0	120.7
b	125.3	101.9	120.0	123.6	96.0	120.0	113.7	95.9	119.5
c	125.2	101.9	120.0	123.5	96.0	120.1	113.6	95.9	119.6
d	128.4	101.5	118.7	126.4	96.6	119.9	116.7	95.5	118.1
e	127.2	101.5	119.1	125.6	97.0	120.3	115.4	95.5	118.9
f	126.9	101.5	119.2	125.0	96.7	120.4	115.0	95.5	119.1
g	126.2	102.8	119.6	124.3	96.4	120.4	113.6	96.1	120.5
h	126.2	102.8	119.8	124.4	96.3	120.8	113.6	96.0	120.7
i	125.8	103.5	121.4	124.1	97.4	121.7	113.0	96.9	121.4
j	125.9	102.9	120.4	124.2	96.5	120.1	113.5	96.2	121.2
k	126.3	102.7	121.2	124.5	96.2	120.5	113.8	97.0	120.6
l	126.2	102.9	122.9	124.4	96.5	123.0	113.2	96.2	122.6
m	125.7	102.6	121.8	124.2	96.4	120.7	113.4	96.0	121.2
n	126.0	102.6	121.4	124.3	96.2	120.7	113.6	95.9	120.6
o	125.9	102.3	122.3	124.3	96.1	122.3	113.2	95.7	121.7
p	125.8	102.1	121.0	124.2	96.4	120.3	113.6	96.0	120.7
q	125.9	102.0	120.0	124.3	96.2	120.8	113.6	95.8	120.6
r	125.8	103.1	122.6	123.9	96.6	122.2	112.7	96.1	121.9

Vibration analysis

Vibration analysis was carried out on the optimized geometries of the PDZs at Beke[s] 3-parameter exact exchanges functional (B3) combined with gradient corrected correlation functional of Lee-Yang-Parr (LYP) by implementing the 6-311++G(d,p) as triple split valance basis set. The harmonic frequencies calculated for PDZs along with their IR intensities (given in parentheses) are reported in table 3. Analysis of the data reported in the table 3 shows that the calculated vibrational frequencies of S1-N2, N2=C3, N2-C3, N4-H, N2-H, N5-H6,7, S1=O8,9, N4=C3 and C3=N5 depend on the type and position of the substituent on 3 position and on the pyrido-ring. Furthermore, the angles α, β and γ can affect the vibrational frequencies of these bonds.

Table 3. Calculated harmonic frequencies (cm^{-1}) (IR intensities) obtained for the B3LYP/6-311++G(d,p) optimized structures of PDZs.

	Isomer I				
Comp.	N4-H	N2=C3	N5-H6,7	S1=O8,9	S1-N2
a	3612.6 (40.7)	1687.4 (638.6)	3579.9 (82.5)	1300.5 (189.1)	800.8 (87.0)
b	3630.7 (43.4)	1666.7 (784.6)	3633.1 (82.9)	1294.1 (202.1)	804.2 (117.1)
c	3632.5 (43.1)	1663.3 (86.3)	3611.4 (68.4)	1293.5 (209.3)	799.4 (117.2)
d	3603.9 (84.1)	1670.8 (320.7)	3519.5 (66.0)	1312.3 (136.4)	779.6 (97.7)
e	3604.7 (65.9)	1656.6 (352.5)	3555.1 (83.0)	1309.6 (165.0)	772.4 (117.0)
f	3602.2 (61.6)	1649.1 (330.7)	3553.6 (79.3)	1143.5 (227.4)	844.5 (116.0)
g	3614.2 (43.6)	1689.6 (708.3)	3584.4 (90.1)	1126.7 (179.6)	801.0 (96.8)
h	3601.0 (68.9)	1680.7 (554.0)	3570.0 (79.6)	1125.7 (229.8)	835.0 (37.7)
i	3626.9 (54.3)	1692.3 (599.0)	3564.6 (72.5)	1122.1 (153.2)	791.7 (70.2)
g	3609.7 (72.9)	1686.3 (670.0)	3588.8 (92.4)	1112.0 (145.8)	790.1 (80.4)
k	3620.6 (50.9)	1682.1 (580.1)	3567.3 (78.9)	1106.3 (235.6)	808.6 (56.0)
l	3623.7 (53.1)	1695.1 (575.1)	3564.3 (73.4)	1117.9 (117.0)	800.0 (64.51)
m	3623.3 (41.5)	1687.2 (589.3)	3579.5 (80.7)	1112.1 (189.6)	792.4 (82.2)
n	3613.6 (37.6)	1687.7 (625.1)	3577.2 (79.8)	1123.3 (171.7)	797.1 (79.7)
o	3624.4 (49.0)	1687.0 (560.2)	3564.8 (69.0)	1116.4 (152.9)	796.3 (61.9)
p	3601.5 (74.5)	1681.1 (578.5)	3583.2 (80.5)	1115.7 (137.4)	789.4 (75.11)
q	3613.6 (38.4)	1687.3 (666.2)	3579.3 (81.5)	1129.5 (185.0)	800.6 (105.4)
r	3628.4 (42.1)	1695.8 (602.9)	3560.9 (63.0)	1133.1 (146.9)	787.8 (75.4)

	Isomer II					
Comp.	N2-H	N2-C3	N4=C3	N5-H6,7	S1=O8,9	S1-N2
a	3587.6 (88.6)	1000.7 (27.4)	1674.1 (437.5)	3570.9 (71.6)	1140.1 (135.7)	831.7 (32.1)
b	3583.0 (60.7)	981.2 (11.0)	1652.7 (316.6)	3631.2 (61.1)	1138.3 (185.1)	817.7 (38.7)
c	3583.5 (54.7)	1015.1 (13.4)	1649.4 (288.7)	3613.2 (61.4)	1134.8 (149.8)	821.6 (16.3)
d	3580.9 (110.7)	1030.2 (3.5)	1684.3 (330.6)	3488.4 (42.4)	1140.5 (123.6)	780.6 (27.9)
e	3585.5 (104.7)	1033.2 (10.1)	1667.5 (371.2)	3566.1 (56.8)	1139.0 (175.5)	806.5 (57.5)
f	3587.6 (105.7)	1030.5 (10.9)	1658.4 (335.3)	3572.3 (49.9)	1137.7 (181.3)	846.7 (39.3)
g	3588.5 (89.5)	1027.1 (8.1)	1027.1 (507.8)	3571.1 (65.5)	1130.3 (67.5)	826.7 (39.4)
h	3588.7 (90.0)	1030.2 (8.5)	1030.2 (381.1)	3570.4 (70.3)	1132.9 (184.2)	834.5 (35.6)
i	3588.6 (90.2)	1008.1 (22.9)	1008.1 (486.7)	3569.3 (69.8)	1138.9 (25.3)	841.5 (41.7)

g	3587.9 (89.1)	1001.1 (41.4)	1001.1 (586.6)	3567.2 (67.0)	1133.4 (67.8)	827.8 (34.3)
k	3590.2 (90.7)	1004.2 (68.3)	1004.2 (278.3)	3568.7 (69.5)	1135.8 (226.3)	836.0 (45.5)
l	3588.6 (90.3)	1013.4 (47.0)	1013.4 (369.0)	3570.6 (70.3)	1141.1 (50.9)	837.5 (27.7)
m	3585.9 (96.9)	1007.6 (9.6)	1674.7 (529.0)	3573.0 (81.2)	1131.6 (79.1)	827.6 (32.3)
n	3587.9 (96.8)	1017.3 (23.2)	1676.7 (293.9)	3574.6 (78.6)	1136.9 (213.0)	816.6 (18.0)
o	3587.4 (99.1)	999.0 (32.4)	1674.5 (337.5)	3574.7 (78.3)	1148.6 (111.4)	822.5 (24.9)
p	3585.9 (98.3)	1005.6 (20.1)	1671.4 (578.3)	3572.8 (77.9)	1135.6 (234.1)	841.9 (33.7)
q	3587.1 (102.4)	1009.2 (17.1)	1673.0 (450.4)	3574.4 (78.6)	1145.1 (71.0)	833.0 (31.6)
r	3587.1 (99.2)	1016.2 (35.2)	1675.6 (489.5)	3573.8 (79.4)	1141.2 (114.5)	833.5 (27.9)
			Isomer III			
Comp.	N4-H	N2-H	N2-C3	C3=N5	S1=O8,9	S1-N2
a	3627.4 (44.2)	3554.5 (91.5)	973.9 (116.4)	1728.6 (628.5)	1144.7 (142.1)	870.4 (76.8)
b	3633.7 (50.1)	3547.0 (83.7)	946.1 (31.4)	1744.5 (711.4)	1140.6 (69.5)	844.6 (67.8)
c	3633.9 (51.2)	3548.1 (79.3)	980.0 (77.0)	1739.9 (811.8)	1144.5 (145.0)	829.4 (49.3)
d	3611.2 (95.8)	3545.7 (98.7)	999.1 (51.0)	1702.1 (420.5)	1146.7 (135.5)	813.5 (47.8)
e	3583.0 (82.3)	3544.7 (96.2)	993.4 (62.6)	1682.7 (626.5)	1146.0 (140.8)	863.8 (94.5)
f	3564.2 (85.6)	3545.6 (87.9)	991.9 (68.2)	1674.8 (695.9)	1145.7 (143.9)	859.4 (96.5)
g	3638.4 (43.3)	3554.6 (91.7)	972.6 (82.8)	1726.8 (628.3)	1119.2 (140.6)	852.9 (10.4)
h	3628.4 (40.8)	3554.1 (92.1)	991.9 (86.1)	1727.0 (640.4)	1137.9 (209.1)	878.1 (25.1)
i	3629.7 (43.2)	3557.6 (92.2)	993.3 (97.9)	1730.3 (651.5)	1121.2 (78.7)	876.9 (23.3)
g	3617.6 (69.5)	3555.5 (93.0)	972.8 (89.2)	1725.7 (684.9)	1124.7 (111.4)	876.8 (17.8)
k	3628.4 (41.0)	3554.2 (92.5)	989.3 (36.2)	1726.9 (624.4)	1142.3 (248.5)	878.8 (34.1)
l	3632.2 (46.0)	3558.9 (90.2)	995.5 (11.7)	1728.2 (630.9)	1118.6 (109.7)	871.7 (24.4)
m	3622.2 (70.2)	3553.6 (95.3)	1383.3 (151.8)	1732.9 (651.7)	1121.5 (120.8)	880.3 (18.2)
n	3626.5 (46.7)	3552.7 (34.4)	1353.0 (193.9)	1731.8 (586.6)	1141.5 (122.8)	881.0 (20.9)
o	3628.6 (48.8)	3556.3 (96.2)	1353.7 (87.8)	1732.4 (607.6)	1124.0 (88.5)	874.8 (18.1)
p	3604.9 (60.5)	3553.0 (97.6)	1351.9 (242.9)	1731.5 (637.3)	1135.0 (244.0)	876.0 (31.1)
q	3625.6 (45.4)	3553.1 (98.6)	1350.4 (255.4)	1731.2 (625.1)	1149.5 (80.1)	878.3 (16.3)
r	3627.6 (47.4)	3558.6 (97.8)	1358.5 (193.1)	1734.2 (639.0)	1120.6 (70.8)	874.1 (15.6)

Analysis of the data that reported in this table shows that υ S1=O8,9 of isomers **I, II** and **III** are different. It seems that the hybridization of the N2 atom can be affect on the frequency of S=O group. According to data in the table 3, one can observe that the υ S1-N2 of isomer **III** is larger than the isomer **I** and **II**. (υ S1-N2 **III** > **II** > **I**). The difference refers to the hybridization of N2 atom.

A review of the data reported in table 3 shows that the υ N4-H of isomer **III** is more or less than the N4-H of **I** isomer, this trend related to the bond force because the bond lengths of N4-H in two isomer are close to each. To, the υ N2-H of isomer **II** is more or less than the N2-H of **III** isomer, this different related to the resonance of N2 with C=N bond.

Natural bond orbital analysis (NBO)

It is important to recall that in the NBO analysis the electronic wave function is interpreted in terms of a set of occupied Lewis and a set of unoccupied non-Lewis localized orbitals (Reed et al., 1988). The NBO analysis is a sufficient approach to investigate the effect of the stereoelectronic interactions on the stability, reactivity and dynamic behaviors of chemical compounds.[43-50] However, in this section, the NBO electric charges calculated for selected atoms including S1, N2, N4, N5, S1=O8, S1=O9, N4-H, N2-H, N5-H6 and N5-H7 which are important in the chemical reactivity are listed in table 4. Furthermore, the electric dipole moment (μ_M) of the PDZs, are also listed in this table.

Table 4. Natural bond orbital (NBO) analysis of the atomic charges and electric dipole moments (μ_M) (Debye) calculated for three isomers of PDZs using B3LYP/6-311++G(d,p) method.

	Comp.	N4-H	N4	N2	S1	S1=O8	S1=O9	N5-H6	N5-H7	μ_M (D)
	a	0.99	-0.59	-0.79	2.22	3.12	3.12	1.20	1.17	9.72
	b	1.00	-0.60	-0.81	2.22	3.12	3.12	1.02	-	10.62
	c	1.00	-0.60	-0.81	2.22	3.12	3.12	1.03	-	10.93
	d	1.01	-0.58	-0.75	2.21	3.09	3.10	0.58	-	6.86
	e	1.01	-0.59	-0.76	2.21	3.10	3.10	1.08	-	7.63
	f	1.01	-0.59	-0.76	2.21	3.10	3.10	1.08	-	7.95
	g	1.00	-0.60	-0.79	2.22	3.12	3.12	1.20	1.17	10.22
Isomer I	**h**	0.99	-0.59	-0.79	2.22	3.12	3.12	1.20	1.17	9.81
	i	1.00	-0.60	-0.79	2.21	3.12	3.12	1.20	1.17	8.85
	g	1.02	-0.60	-0.80	2.22	3.12	3.12	1.19	1.17	10.72
	k	0.99	-060	-0.60	2.22	3.12	3.12	1.20	1.17	8.64
	l	1.00	-0.60	-0.79	2.22	3.11	3.12	1.20	1.17	8.53
	m	1.01	-0.59	-0.80	2.22	3.11	3.12	1.20	1.17	8.26
	n	0.99	-0.59	-0.79	2.22	3.12	3.12	1.19	1.17	9.19
	o	1.00	-0.60	-0.79	2.22	3.11	3.11	1.20	1.17	11.03

	p	1.02	-0.60	-0.79	2.21	3.11	3.11	1.19	1.17	8.24
	q	1.00	-0.60	-0.79	2.22	3.11	3.11	1.19	1.17	8.98
	r	1.00	-0.60	-0.79	2.22	3.11	3.11	1.20	1.17	10.55
	Comp.	N2-H	N4	N2	S1	S1=O8	S1=O9	N5-H6	N5-H7	μ_M (D)
	a	1.29	-0.58	-0.86	2.22	3.11	3.10	1.17	1.19	5.88
	b	1.28	-0.59	-0.86	2.22	3.11	3.10	0.99	-	6.75
	c	1.28	-0.59	-0.86	2.22	3.11	3.10	1.00	-	7.07
	d	1.31	-0.52	-0.87	2.22	3.11	3.09	0.58	-	2.90
	e	1.31	-0.54	-0.87	2.22	3.11	3.09	1.03	-	4.06
	f	1.30	-0.54	-0.87	2.22	3.11	3.09	1.10	-	4.46
	g	1.29	-0.58	-0.86	2.22	3.11	3.10	1.17	1.19	6.29
	h	1.29	-0.58	-0.86	2.22	3.11	3.10	1.17	1.19	5.54
Isomer II	**i**	1.29	-0.58	-0.86	2.22	3.12	3.10	1.17	1.19	5.12
	g	1.29	-0.56	-0.86	2.22	3.11	3.10	1.17	1.19	5.86
	k	1.29	-0.58	-0.86	2.22	3.12	3.10	1.17	1.19	3.96
	l	1.29	-0.58	-0.86	2.23	3.11	3.11	1.17	1.19	3.97
	m	1.29	-0.57	-0.86	2.22	3.11	3.09	1.17	1.19	5.24
	n	1.29	-0.58	-0.86	2.22	3.11	3.10	1.17	1.19	6.64
	o	1.29	-0.58	-0.86	2.22	3.10	3.10	1.17	1.19	7.32
	p	1.29	-0.57	-0.86	2.22	3.11	3.09	1.17	1.19	5.41
	q	1.29	-0.58	-0.86	2.22	3.11	3.10	1.17	1.19	6.57
	r	1.29	-0.58	-0.86	2.22	3.11	3.10	1.17	1.19	6.95
	Comp.	N4-H	N2-H	N4	N2	S1	S1=O8	S1=O9	N5-H	μ_M (D)
	a	1.01	1.29	-0.61	-0.86	2.21	3.09	3.10	1.04	6.15
	b	1.02	1.28	-0.61	-0.85	2.21	3.09	3.10	-	6.43
	c	1.02	1.28	-0.61	-0.85	2.21	3.09	3.10	-	6.38
	d	1.03	1.27	-0.60	-0.84	2.21	3.08	3.09	-	4.22
	e	1.03	1.27	-0.60	-0.84	2.21	3.08	3.09	-	4.64
	f	1.03	1.27	-0.60	-0.84	2.21	3.08	3.09	-	4.76
	g	1.02	1.29	-0.61	-0.86	2.21	3.09	3.10	1.04	6.75
	h	1.01	1.29	-0.61	-0.86	2.21	3.09	3.10	1.04	6.59
Isomer III	**i**	1.01	1.29	-0.61	-0.86	2.21	3.09	3.10	1.04	5.46
	j	1.03	1.29	-0.61	-0.86	2.21	3.09	3.10	1.04	7.64
	k	1.01	1.29	-0.61	-0.86	2.21	3.10	3.10	1.04	6.02
	l	1.01	1.29	-0.60	-0.86	2.22	3.09	3.10	1.04	6.12
	m	1.02	1.30	-0.61	-0.86	2.21	3.09	3.09	1.03	4.55
	n	1.01	1.29	-0.61	-0.86	2.21	3.09	3.10	1.03	5.07
	o	1.01	1.30	-0.60	-0.86	2.22	3.09	3.09	1.03	7.47
	p	1.03	1.29	-0.61	-0.86	2.21	3.09	3.09	1.03	4.70
	q	1.01	1.29	-0.60	-0.86	2.21	3.09	3.10	1.03	5.09
	r	1.01	1.30	-0.60	-0.86	2.22	3.09	3.09	1.04	6.97

It is considered that through-space interactions of the substituent on the NH_2 groups and pyrido-ring can be affect on the charge density of these atoms. In the three isomers, charge density on the N2 atom is more or less than N4 atom. However, the charge densities on the S1, S1=O8 and S1=O9 atoms in the corresponding **I**, **II** and **III** isomers are very close. Analysis of the data shows that the charge densities on these atoms depend on the type and position of the substituent on the pyrido-ring and NH_2 group. Inductive and resonance effects and through-space interactions of the substituent on the different positions can be affecting on the charge densities.

According to these data, it seems that 4*H*-tatumer (**I** isomer) is more polar than two isomers. The dipole moments (μ_M) changed with the different substitution groups on the 3 position and different position on the pyrido-ring (From 6.859 D to 11.029 D for **I** isomer with different substituents on the 3 position and pyrido-ring). The dipole moments of the **II** and **III** isomers changed with the different substituents (From 2.900 D to 7.316 D and 4.219 D to 7.637 D respectively).

HOMO-LUMO energy

It is well-known that HOMO/LUMO (highest occupied or lowest unoccupied molecular orbital) and global electrophilicity/nucleophilicity energy interaction plays very important roles in chemical reaction. However, in this section, the HOMO and LUMO energies are calculated by B3LYP/6-311++G(d,p) method is shown below. According to equations (2), (3) and (4) one could calculate the chemical potential (μ), hardness (η) and global electrophilicity of these isomers. The data of this analysis are reported in the table 5.

Table 5. Calculated HOMO, LUMO, chemical potential (μ), hardness (η) and global electrophilicity (ω) energy values of three isomers of PDZs using B3LYP/6-311++G(d,p) method. (Energies are given in eV)

	Comp.	HOMO	LUMO	μ	η	ω
Isomer I	**a**	-6.46	-1.74	-4.60	5.74	1.85
	b	-7.29	-1.69	-4.49	5.61	1.80
	c	-7.24	-1.63	-4.44	5.61	1.77
	d	-7.89	-2.39	-5.14	5.50	2.39
	e	-7.78	-2.80	-5.31	4.98	2.83
	f	-7.76	-3.40	-5.58	4.35	3.56
	g	-7.37	-1.69	-4.54	5.71	1.80
	h	-7.37	-1.66	-4.52	5.72	1.77
	i	-7.37	-1.66	-4.49	5.72	1.77
	j	-7.08	-1.66	-4.38	5.44	1.77
	k	-7.10	-1.63	-4.38	5.47	1.74
	l	-7.08	-1.61	-4.36	5.47	1.71
	m	-7.62	-1.99	-4.79	5.61	2.07
	n	-7.67	-2.04	-4.84	5.63	2.10
	o	-7.59	-2.01	-4.82	5.58	2.07
	p	-7.65	-2.01	-4.84	5.63	2.07
	q	-7.70	-2.04	-4.87	5.66	2.10
	r	-7.54	-2.00	-4.76	5.58	2.01

	Comp.	HOMO	LUMO	μ	η	ω
Isomer II	**a**	-7.15	-1.91	-4.53	5.24	1.95
	b	-6.95	-1.79	-4.37	5.16	1.85
	c	-6.91	-1.76	-4.33	5.16	1.82
	d	-7.70	-2.37	-5.03	5.33	2.38
	e	-7.46	-2.29	-4.88	5.17	2.30
	f	-7.37	-2.74	-5.06	4.63	2.76
	g	-6.98	-1.85	-4.41	5.13	1.90
	h	-7.06	-1.81	-4.43	5.25	1.87
	i	-7.02	-1.79	-4.41	5.23	1.86
	j	-6.55	-1.82	-4.19	4.73	1.85
	k	-6.88	-1.66	-4.27	5.22	1.74
	l	-6.83	-1.75	-4.29	5.09	1.81
	m	-7.20	-2.13	-4.67	5.07	2.15
	n	-7.37	-2.05	-4.71	5.32	2.09
	o	-7.30	-2.12	-4.71	5.17	2.14
	p	-7.13	-2.13	-4.63	5.00	2.14
	q	-7.36	-2.10	-4.73	5.26	2.13
	r	-7.24	-2.08	-4.67	5.16	2.10

	Comp.	HOMO	LUMO	μ	η	ω
Isomer III	**a**	-7.38	-1.96	-4.67	5.42	2.02
	b	-7.14	-1.91	-4.52	5.24	1.95
	c	-7.12	-1.89	-4.50	5.22	1.94
	d	-7.55	-2.27	-4.91	5.28	2.29
	e	-7.41	-2.24	-4.82	5.20	2.25
	f	-7.33	-2.28	-4.80	5.05	2.28
	g	-7.27	-1.88	-4.58	5.39	1.94
	h	-7.28	-1.82	-4.55	5.45	1.90
	i	-7.27	-1.86	-4.57	5.40	1.93
	j	-7.00	-1.86	-4.43	5.14	1.91
	k	-7.26	-1.72	-4.49	5.53	1.82
	l	-7.19	-1.82	-4.51	5.37	1.89
	m	-7.53	-2.23	-4.88	5.30	2.24

n	-7.60	-2.13	-4.87	5.47	2.16
o	-7.55	-2.22	-4.89	5.33	2.24
p	-7.50	-2.22	-4.86	5.29	2.23
q	-7.59	-2.15	-4.87	5.44	2.18
r	-7.50	-2.18	-4.84	5.33	2.20

The HOMO and LUMO energies changed with the different group substitutions on the 3, 12, 13 and 15 positions. Furthermore, amine-imine form can affect on these energies that corresponding to the tautomers forms. Considering these calculated results, it can be concluded that the change of the HOMO and LUMO energies of PDZs is due to inductive and through resonance on the PDZs compounds.

According to the minimum electrophilicity principle (MEP) in chemical processes, that is analogous to the maximum hardness principle (MHP) [27-31,51,52] "the natural direction of a chemical reaction is toward a state of minimum electrophilicity. Recently, computational methods have begun to be employed in studying the calculation of the MEP of the many reactions. The minimum electrophilicity principle (MEP) successfully predicts the major products of these reactions, but in all of the considered reactions, with no exception, the main products have the less electrophilicity (Chattaraj 1996). Analysis of the data that reported in the table 5 predicts the most stable isomer is isomer **I**, with no exception compounds, because this isomer has the less electrophilicity. According to the electrophilicity data, one can propose this trend for stability of these three isomers the stability of isomer **I** > **II** > **III**). This trend is in good agreement with the experimental data.[22-26]

Nucleus-Independent Chemical Shift (NICs)

Magnetic criteria are based on this fact that π-electron ring current is induced when the system is exposed to an external magnetic field. Undoubtedly, the most widely used magnetic-based index, which is proposed by Schleyer and co-worker, is the Nucleus-Independent Chemical Shift (NICs) (Reed and Schleyer 1987). This index is defined as the negative value of the absolute shielding which is computed at the center (NICs (0)). In this work, one can obtain the NICs(0) for three isomers of the some PDZs and comparative aromaticity of pyrido-ring for these isomers by NICs(0) parameter. Data of NICs (0) for three isomers compounds are listed in table 6.

Table 6. Nucleus-Independent Chemical Shift (NICs (0)) analysis of the aromaticity parameter calculated for three isomers of PDZs using B3LYP/6-311++G(d,p) method.

Comp.	**Isomer I**		**Isomer II**		**Isomer III**	
	NICs(0)	δ NICs(0)	NICs(0)	δ NICs(0)	NICs(0)	δ NICs(0)
a	-8.270	-	-7.817	-	-7.924	-
b	-8.109	-0.162	-7.250	-0.566	-8.072	0.148
c	-8.339	0.069	-7.584	-0.232	-7.871	-0.053
d	-8.459	0.189	-8.118	0.301	-8.293	0.369
e	-8.299	0.029	-8.068	0.251	-7.584	-0.339
f	-8.163	-0.107	-7.921	0.104	-7.945	0.021
g	-8.424	0.156	-7.727	-0.090	-8.044	0.120
h	-7.921	-0.350	-6.845	-0.971	-7.640	-0.284
i	-7.930	-0.340	-7.466	-0.351	-7.555	-0.369
j	-9.607	1.337	-8.897	1.081	-9.582	1.659
k	-8.336	0.065	-8.131	0.315	-8.068	0.144
l	-7.948	-0.322	-7.150	-0.666	-7.698	-0.226
m	-10.296	2.025	-9.657	1.840	-10.214	2.290
n	-9.747	1.477	-8.451	0.634	-9.397	1.473
o	-9.619	1.348	-9.104	1.287	-9.211	1.287
p	-8.830	0.560	-8.107	0.291	-8.474	0.551
q	-8.717	0.447	-8.290	0.474	-8.538	0.615
r	-8.300	0.030	-8.005	0.189	-8.176	0.252

$\delta NICs(0) = NICs(0)_{unsubstituted} - NICs(0)_{substitued}$

According to the results of NICs calculations of unsubstituted and substituted PDZs derivatives, it is clear that the system becomes less aromatic by the substitution confirming the above explanation. (With no exception) Furthermore, analysis of data reported in the table 6 show that the isomer **I** is less aromatic

than two isomers and one can be proposed this trend for the aromaticity of three isomers. (With no exception) (Isomer **I** > **III** > **II**).

Thermochemical analysis and Tautomerism

It was stated in the literature that **I** form (i.e. 4*H*-tautomer) of PDZs predominates over the **II** and **III** forms (de Tullio et al., 1995). The DFT calculated of the formation enthalpies (ΔH^{o}_{f}), Gibbs free energy (ΔG^{o}_{f}) and tautomeric equilibrium constant based on the equilibrium reaction given in Figure 2. These calculation was carried out on the optimized geometries of the PDZs at B3LYP/6-311++G(d,p) level and below reaction (Eq.5). These values are reported in tables 7 and 8.

$$a\ C\ (s) + b\ H_2\ (g) + c\ N_2\ (g) \rightarrow \text{product} \qquad 5$$

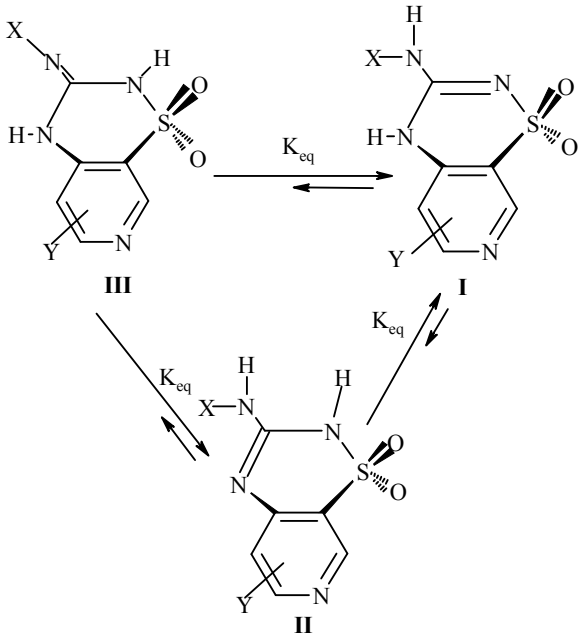

Figure 2. different possible tautomeric forms for 3-alkylamino-pyrido[4,3-e]-1,2,4 thiadiazine 1,l dioxides

Table 7. The formation and the equilibrium reaction enthalpies ΔH°_{f}, ΔH°_{eq} of some three forms of PDZs calculated based on the B3LYP/6-311++G(d,p) method.

Comp.	ΔH^{o}_{f} (kJ mol^{-1})			ΔH^{o}_{eq} (kJ mol^{-1})		
	I	**II**	**III**	I ⇌ II	I ⇌ III	II ⇌ III
a	-1112.8	-1109.2	-1083.8	3.6	29.0	25.4
b	-1265.4	-1262.5	-1237.1	2.8	28.2	25.4
c	-1447.0	-1443.4	-1419.3	3.5	27.6	24.1
d	-1099.4	-1068.2	-1109.4	31.2	-10.0	-41.2
e	-1014.1	-991.2	-1018.6	22.9	-4.5	-27.4
f	-978.0	-955.5	-979.9	22.4	-2.0	-24.4
g	-1984.2	-1981.5	-1955.8	2.7	28.3	25.7
h	-2025.2	-2021.1	-1996.9	4.1	28.3	24.2
i	-2026.5	-2017.3	-1992.9	9.3	33.6	24.4
j	-2205.5	-2183.5	-2174.9	22.0	30.6	8.6
k	-2240.0	-2234.5	-2212.2	5.5	27.7	22.2
l	-2232.0	-2227.1	-2201.0	4.9	31.0	26.2
m	-1299.1	-1289.1	-1268.1	10.0	31.0	21.0
n	-1328.1	-1326.4	-1298.7	1.7	29.3	27.7
o	-1317.6	-1314.1	-1284.6	3.5	33.0	29.5
p	-1141.3	-1126.4	-1106.8	14.9	34.8	19.5
q	-1149.2	-1143.9	-1116.3	5.3	32.9	27.6
r	-1130.5	-1127.3	-1097.8	3.2	32.7	29.5

Table 8. The formation and the equilibrium reaction Gibbs free energies $\Delta G°_f$, $\Delta G°_{eq}$ and tautomeric equilibrium constants of some three forms of PDZs calculated based on the B3LYP/6-311++1G(d,p).

Comp.	$\Delta G°_f$ (kJ mol^{-1})			$\Delta G°_{eq}$ (kJ mol^{-1})			tautomeric equilibrium constants (K_T)		
	I	**II**	**III**	I ⇌ II	I ⇌ III	II ⇌ III	K_T (I,II)	K_T (I,III)	K_T (II,III)
a	-1112.8	-1109.2	-1083.8	4.4	31.2	26.9	0.17	3.42*10^{-6}	1.94*10^{-5}
b	-1265.4	-1262.5	-1237.1	2.4	29.0	26.5	0.38	8.30*10^{-6}	2.28*10^{-5}
c	-1447.0	-1443.4	-1419.3	2.8	28.7	25.9	0.32	9.37*10^{-6}	2.90*10^{-5}
d	-1099.4	-1068.2	-1109.4	29.3	-9.2	-38.5	7.35*10^{-6}	40.91	5.56*10^{8}
e	-1014.1	-991.2	-1018.6	20.8	-3.3	-24.0	0.00	3.79	1.60*10^{4}
f	-978.0	-955.5	-979.9	20.4	-0.5	-20.8	0.00	1.22	4.41*10^{4}
g	-1984.2	-1981.5	-1955.8	2.8	30.8	28.0	0.32	4.02*10^{-6}	1.24*10^{-5}
h	-2025.2	-2021.1	-1996.9	5.2	30.9	25.8	0.12	3.86*10^{-6}	3.02*10^{-5}
i	-2026.5	-2017.3	-1992.9	8.8	34.8	26.0	0.03	8.00*10^{-7}	2.78*10^{-5}
j	-2205.5	-2183.5	-2174.9	22.8	173.5	150.7	0.00	4.00*10^{-31}	3.95*10^{-27}
k	-22440.0	-2234.5	-2212.2	6.1	30.2	24.1	0.09	5.12*10^{-6}	5.99*10^{-5}
l	-2232.0	-2227.1	-2201.0	4.9	32.7	27.8	0.14	1.87*10^{-6}	1.35*10^{-5}
m	-1299.1	-1289.1	-1268.0	40.0	62.6	22.7	9.82*10^{-8}	1.08*10^{11}	0.00
n	-1328.1	-1326.4	-1298.7	2.7	32.1	29.3	0.34	2.38*10^{-6}	7.35*10^{-6}
o	-1317.6	-1314.1	-1284.6	3.5	34.7	31.1	0.24	8.33*10^{-7}	3.56*10^{-6}
p	-1141.3	-1126.4	-1106.8	13.9	35.3	21.4	0.00	6.54*10^{-7}	0.00
q	-1149.2	-1143.9	-1116.3	4.4	33.7	29.3	0.17	1.25*10^{-6}	7.35*10^{-6}
r	-1130.5	-1127.3	-1097.8	3.6	34.7	31.0	0.23	8.33*10^{-7}	3.70*10^{-6}

The analysis of these data show that tautomer **I** (i.e. 4*H*-tautomer) is more stable than two other isomers. In all of the considered tautomerism, with no exception, isomer **II** is more stable than isomer **III**. However, the theoretical data are in agreement with the spectrophotometric analysis. X-ray crystallography data of these enantiomers show that they exist predominantly as a 4*H*-tautomer.

Deviation of the S1atom from the boat plane (N2–C3–C10–C11)

Since deviations of the S1 atom of the heterocyclic ring of the PDZs (referenced to the plane containing N2, C3, C10 and C11 atoms) from the boat plane can be affect on the rate of tautomerism, aromaticity and pharmacological properties, calculations and analyses of these deviations are described in this section. These calculations are based on the geometries and trigonometrics given in Figures 3 and 4.

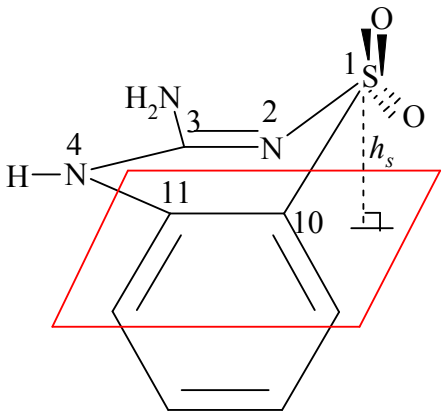

Figure 3. General geometry defining the deviation of the S1 atom from the boat plane (N2–C3–C10–C11) in the PDZs.

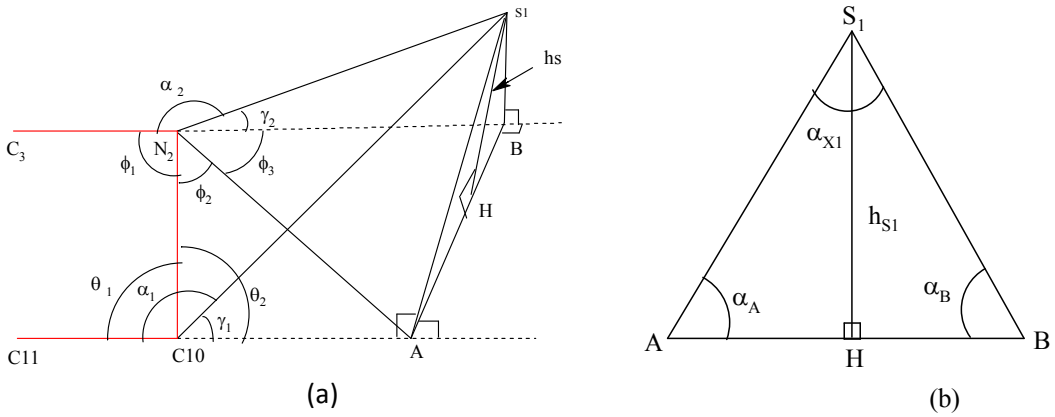

Figure 4. **a** The trigonometric frame used for the calculation of the deviation of the S1 atom (the height h_S) from the N2–C3–C10–C11 plane (Figure 3), and **b** a closer view of the triangle defining the height of the S1 atom (h_S) from the N2–C3–C10–C11 plane as shown in (**a**)

$$\gamma_1 = 180 - \alpha_1 \quad (6)$$

$$\gamma_2 = 180 - \alpha_2 \quad (7)$$

$$\theta_2 = 180 - \theta_1 \quad (8)$$

$$C_6A = C_{10}S_1 \cos \gamma_1 \quad (9)$$

$$C_2B = N_2S_1 \cos \gamma_2 \quad (10)$$

$$C_1A = C_{10}S_1 \sin \gamma_1 \quad (11)$$

$$S_1B = N_2S_1 \sin \gamma_2 \quad (12)$$

$$N_2A = (C_{10}A^2 + N_2C_{10}^2 - 2\ C_{10}A \times N_2C_{10} \times \text{Cos}\ \theta_2)^{1/2} \quad (13)$$

In triangle $C_{10}N_2A$:

$$Cos(\varphi_2) = \frac{(N_2C_{10})^2 + (N_2A)^2 - (C_{10}A)^2}{2\ C_{10}N_2 \times N_2A} \quad (14)$$

$$\varphi_3 = 180 - (\varphi_1 + \varphi_2) \quad (15)$$

In triangle BN_2A:

$$AB = (N_2A^2 + N_2B^2 - 2\ N_2A \times N_2B \times \text{Cos}\ \varphi_3)^{1/2} \quad (16)$$

In triangle S_1AB:

$$Cos(\alpha_B) = \frac{S_1B^2 + AB^2 - S_1A^2}{2\ S_1B \times AB} \quad (17)$$

In triangle S_1HB:

$$S_1H = S_1B \times \text{Sin}(\alpha_B) \quad (18)$$

Table 8. Values of the deviations h_S (S1) (A°) from the boat plane (C2–N3–C5–C6) based on the geometries given in Figures. 3 and 4 calculated by using relations (6–18) for PDZs compounds.

Comp.	**Isomer I**	**Isomer II**	**Isomer III**
	h_{S1} (Å)	h_{S1} (Å)	h_{S1} (Å)
a	0.4182	0.6066	0.7328
b	0.5193	0.6491	0.7474
c	0.5219	0.6484	0.7452
d	0.5068	0.6113	0.7517
e	0.5195	0.5995	0.7498
f	0.5229	0.6112	0.7498
g	0.4243	0.6030	0.7343
h	0.4005	0.6019	0.7284
i	0.4042	0.5874	0.7175

j	0.4137	0.6049	0.7245
k	0.4233	0.6050	0.7327
l	0.2984	0.5707	0.6836
m	0.4341	0.6147	0.7343
n	0.4308	0.6087	0.7373
o	0.3836	0.5922	0.71423
p	0.5111	0.6077	0.7378
q	0.5073	0.6084	0.7370
r	0.3578	0.6057	0.7287

Analysis of the data reported in the table 8 show that, the deviation of the isomer **III** is most that two isomers and one can predict this trend for increasing of h_s (deviation of S1 atom) from the boat plane (C2–N3–C5–C6).

Furthermore, all data presented in this paper show that an increase in stability of the isomer **I** toward other isomers is due a decrease to h_s and an increase the though resonance.

Conclusion

1. The results of computations at ab initio (B3LYP) and level of theory carried out on the conformational analysis of three isomers of some PDZs are in agreement with the X-ray crystallographic data. Furthermore, the most stable isomers of PZDs compound according to theoretical and experimental data is 4*H*-tautomer.
2. The comparison among global electrophilicity shows that the isomer **III** is less stable due to the increasing electrophilicity.
3. According to the thermodynamic data, in all of the considered tautomerism, with no exception, one can predict this trend for stability of these isomers **I>II>II**). The stability is in agreement with experimental observation, since the products isolated are the most favorable 4*H*-tautomer.
4. A comparison of the Nucleus-Independent Chemical Shift (NICs (0)) data with deviation of $h_{s,}$ data, show that aromaticity data are in agreement with the deviation of the S1 atom fro boat plane. It seems the stability of these isomers are due to the deviation of the S1 atom from boat plane, because an increasing of the h_s cause a decrease in the though resonance. However, among the three possible products, the one isomer with the double bond (N2=C3) in conjugation to the S1 atom was found to be more stable than the other isomers.
5. Finally, one may use these theoretical data for the synthesis of the many PZDs compounds, because these data are in agreement to experimental results.

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