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TOXICITY AND SPR /SAR PROPERTIES OF ORGANOPHOSPHORUS INSECTICIDES USED IN AGRICULTURE

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ABSTRACT

The application of computational methods on the organophosphorus derivatives shows that, these toxic compounds will not have problems with oral bioavailability. The toxicity of Organophosphorus insecticide depends upon the nature and the environment of the bonds with different receptors. The P-O bond plays a very important role in the process of the poisoning action inside the body.

Calculated values of bond lengths, charges, dipole moments, heats of formation, drug-likeness and SPR/SAR properties, are reported in terms of the biological property/toxicity of organophosphorus insecticides, using the following quantum methods, ab initio/HF, and DFT/ B3LYP and PM3 method.

Keywords: Organophosphorus insecticide, structure, toxicity, drug-likeness, QSPR.

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1. INTRODUCTION

Quantum chemistry methods play an important role in obtaining molecular geometries and predicting various properties[1]. Especially for molecules that are built from electronegative elements, Quantum chemistry helps us obtain highly accurate physical properties, Expensive

ab initio/HF correlation methods are usually required[2-4]. Although DFT (density functional theory) methods offer an inexpensive alternative of computational methods that could handle relatively large molecules.[5-11] Quantitative Structure-Property/Activity Relationships (QSPR/QSAR) are attempts to correlate properties derived from molecular structure[12-14] with a chemical or biochemical activity.

Organophosphorus compounds are organic molecules based on phosphorus[15]. They are used primarily in pest control as an alternative to chlorinated hydrocarbons that persist in the environment. Some organophosphorus compounds are highly effective insecticides, although some other are extremely toxic to human, including sarin and VX nerve agents[16].

The organophosphorus compounds are powerful acetylcholinesterase inhibitors and they include a large number of modern insecticides used in agriculture. Modern organophosphorus insecticides[17] are compounds of pentavalent phosphorus[18] of the general structure sown in figure 1.The P-O bond plays a very important role in the process of the poisoning action inside the body[19]. Therefore the toxicity depends upon the nature and the environment of this bond[20].

Drug-likeness is a qualitative approach used in drug design, which is determined from the electronic structure before the substance is synthesized and tested. The calculation of the drug property can provide us with a better hypothesis of the biological activity of some molecules. The theoretical calculation of certain properties of a molecule can give us crucial information about the parameters, which are essential to show certain biological activity. Lipinski's rule of five (ROF) is a rule of MPO methods to estimate drug-likeness or determine a chemical compound with a certain biological activity that would make the drug likely to be orally active in humans[19].

The ROF is based on four chemical properties of molecules, molecular weight (MW), logP, number of hydrogen-bond donors (HBD), number of –OH and –NH and the number of hydrogen-bond acceptors (HBA) , number of oxygen and nitrogen atoms.

A ‘flag’ is set if a molecule’s MW is bigger than 500, logP is bigger than 5, number of its HBD not exceeds 5 and the number of its HBAs not exceeds 10. Because the values of scoring points for property values are multiples by five, this rules has been called the ‘Rule of Five.’ The total number of violations is the ROF-Score lies between ‘0’ and ‘4’ [20].

2. MATERIALS AND METHODS

All calculations were performed by using HyperChem 8.03 software[21]. The geometries of O,O-dimethyl O-phenyl phosphorothioate and its derivatives, were first fully optimized by molecular mechanics, with MM+ force-field (rms = 0.001 Kcal/Å). Further geometries were fully re-optimized by using PM3 method[22]. After that, a parallel study has been made by using Gaussian 09 software [23] ,with HF/6-31G (d,p) and B3LYP/6-31G (d,p).

The calculation of properties SAR/SPR is performed by the module (QSAR Properties, version 8.0). QSAR Properties is a module that of HyperChem software, allows calculating some properties commonly used in QSPR /QSAR studies. The calculations are empirical, and so, generally fast. The calculated results have been reported in the present work.

3. RESULTS AND DISCUSSION

3.1. Geometric and electronic structure of basic structure of the organophosphorus compounds

The basic structure of the organophosphorus compounds: is O, O-dimethyl O-phenyl phosphorothioate. Present results concerning bond length values for O,O-dimethyl O-phenyl phosphorothioate (Table 1) and charge densities (Table 2) and angles of O,O-dimethyl O-phenyl phosphorothioate (Table 3).

From these computing results a good correlation can be seen between the ab initio, PM3, and DFT for bond lengths, and angles, also the charge densities calculated by these methods are approximately similar.

Table 1. Bond lengths (angstrom) of O,O-dimethyl O-phenyl phosphorothioate

Bond length	PM3	ab initio/HF (6-31G**)	DFT/B3LYP (6-31G**)
C1-C2	1.406	1.381	1.395
C2-C3	1.388	1.384	1.393
C3-C4	1.392	1.386	1.396
C1-O	1.368	1.384	1.396
O-P	1.691	1.584	1.610
P-S	1.928	1.924	1.934
P-Omethoxy	1.705	1.583	1.619
Omethoxy-Cmethoxy	1.390	1.422	1.438

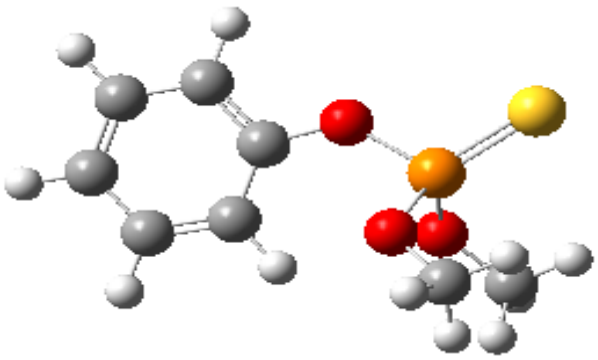


Fig.1. 3D Conformation of O,O-dimethyl O-phenyl phosphorothioate (Gauss View 3.09)

Table 2. Net charge distribution for O,O-dimethyl O-phenyl phosphorothioate

Atoms	PM3	ab initio/HF (6-31G**)	DFT/B3LYP (6-31G**)
P	1.841	1.411	1.048
S	-0.676	-0.512	-0.402
O	-0.497	-0.742	-0.553
Omethoxy	-0.589	-0.683	-0.531
C1	0.166	0.371	0.322
C2	-0.143	-0.145	-0.106
C3	-0.071	-0.149	-0.095
C4	-0.140	-0.152	-0.800
Cmethoxy	0.110	-0.034	-0.090

Table 3. Angles in degree of O,O-dimethyl O-phenyl phosphorothioate

Atoms	PM3	ab initio/HF (6-311G**)	DFT/B3LYP (6-311G**)
C1-C2-C3	119.148	118.927	119.382
C2-C3-C4	120.544	120.443	120.341
C3-C4-C5	119.952	119.751	119.477
C1-O-P	131.866	126.247	130.529
O-P-S	113.819	112.882	113.889
O-P-Omethoxy	99.688	105.871	101.125
P-Omethox-Cmethox	119.956	123.663	122.759

The molecular electrostatic potential **(**MESP) yields information on the molecular regions that are preferred by an electrophile or nucleophile. Any chemical system creates an electrostatic

potential around itself. When a positive charge volume unit is used as a probe, it feels the attractive or repulsive forces in the regions where the electrostatic potential is respectively negative or positive [24]. It has been found a very useful tool in the investigation of the correlation between the electronic structure and the physiochemical property relationship of molecules including biomolecules and drugs [24-28]. The red and blue regions in the MESP map refer to regions of negative and positive potential and correspond to electron rich and poor regions respectively and the green color signifies neutral electrostatic potential [29].

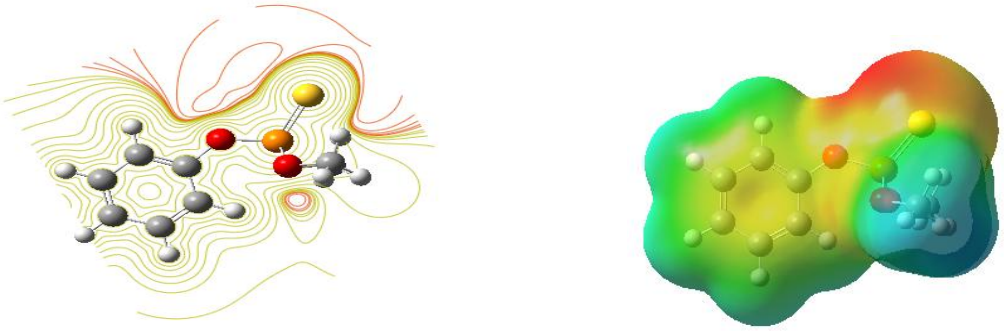
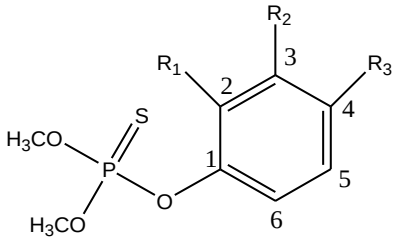


Fig.2. 2D MESP and 3D MESP contour map for O,O-dimethyl O-phenyl phosphorothioate (GaussView 3.09)

The MESP surface map for O,O-dimethyl O-phenyl phosphorothioate shows that the region near the sulfur atom is rich with electrons due to the red color that refers to a negative potential. In the other hand, the region near the carbon atoms is more yellow which indicates a less negative potential than the previous one. The green region around hydrogen atoms refers to a neutral electrostatic potential, but the blue regions near the methyl groups signifies a slight deficient in electrons which indicates that these regions bear the maximum brunt of positive charges.

3.2. Effect of the substitution on the base structure

In table 4 we studied the energies of O,O-dimethyl O-phenyl phosphorothioate and (methyl, nitro) substituted O,O-dimethyl O-phenyl phosphorothioate (Fig. 3), which are: heat of formation, dipole moment (μ), HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital), and their difference (ΔE). In table 5, charge densities of these compounds are reported.



Series

(A). R1=R2=R3= H
(B). R1=CH3, R2=R3=H
(C). R1=R3=H, R2=CH3
(D). R1=R2=H, R3=CH3
(E). R1=NO2, R2=R3=H
(F). R1=R3=H, R2=NO2
(G). R1=R2=H, R3=NO2

Fig.3. Scheme of O,O-dimethyl O-phenyl phosphorothioate systems

We note that the heat of formation approximately 8 kcal/mol is increased at each addition of methyl group, in the base compound O,O-dimethyl O-phenyl phosphorothioate.

For these compounds the negative charge on sulfur is increased except for compound B, also, on oxygen the negative charge is increased (Table 5).

In methyl-substituted O,O-dimethyl O-phenyl phosphorothioates the O,O-dimethyl O-(4-methyl-phenyl) phosphorothioate (compound D) shows greatest positive charge on 1st position carbon (0.284) which leads to nucleophilic substitution (Table 5).

This is further supported by the least HOMO-LUMO energy gap (0.227) (Table 4) which depicts the chemical reactivity of the compound, the higher is the HOMO-LUMO energy gap, the lesser is the flow of electrons to the higher energy state , making the molecular hard and less reactive.

On the other hand in lesser HOMO-LUMO gap, that is easy flow of electrons to the higher energy state making it soft and reactive (HSAB). Hard bases have highest occupied molecular orbitals (HOMO) of low energy, and hard acids have lowest unoccupied molecular orbitals (LUMO) of high energy[30].

We also note that the methyl substituent (donor effect) has the effect of decreasing the energy of the HOMO and LUMO (Table 4).

We have studied nitro-substituted O,O-dimethyl O-phenyl phosphorothioates, along the same line of methyl-substituted O,O-dimethyl O-phenyl phosphorothioates for a comparative study. We note that the heat of formation is increased approximately 7 kcal/mol at each addition of nitro group, for these compounds the negative atomic charge on sulfur is decreased, but, on oxygen the negative atomic charge is increased (Table 5).

In nitro-substituted O,O-dimethyl O-phenyl phosphorothioates, the O,O-dimethyl O-(3-nitro-phenyl) phosphorothioate (compound F) is predicted to be the most reactive with least HOMO-LUMO energy gap (0.159) (Table 5), the 1st position shows maximum positive charge (0.341) which refers to nucleophilic attack.

The O,O-dimethyl O-(3-nitro-phenyl) phosphorothioate is predicted to be the most reactive with least HOMO- LUMO energy gap of all O,O-dimethyl O-phenyl phosphorothioates.

Table 4. Energies of O,O-dimethyl O-phenyl phosphorothioate and its derivatives

Compound	System	Heat of formation (kcal/mol)	-HOMO (a.u.)	-LUMO (a.u.)	ΔE (a.u.)	μ(D)
A	O,O-dimethyl O-phenyl phosphorothioate	-127.152	0.235	0.005	0.230	3.744
B	O,O-dimethyl O-(2-methyl-phenyl) phosphorothioate	-136.969	0.238	0.009	0.229	5.175
C	O,O-dimethyl O-(3-methyl-phenyl) phosphorothioate	-135.536	0.238	0.009	0.229	2.516
D	O,O-dimethyl O-(4-methyl-phenyl) phosphorothioate	-135..892	0.237	0.010	0.227	2.889
E	O,O-dimethyl O-(2-nitro-phenyl) phosphorothioate	-135.201	0.248	0.087	0.161	5.636
F	O,O-dimethyl O-(3-nitro-phenyl) phosphorothioate	-133.435	0.254	0.095	0.159	4.946
G	O,O-dimethyl O-(4-nitro-phenyl) phosphorothioate	-135.677	0.256	0.093	0.163	5.303

Heat of formation by P M3, HOMO, LUMO, ΔE and μ by DFT.

Table 5. Net atomic charges for O,O-dimethyl O-phenyl phosphorothioate and its derivatives

compound	A	B	C	D	E	F	G
P	1.048	1.058	0.979	0.979	1.011	0.973	0.971
S	-0.402	-0.372	-0.410	-0.410	-0.347	-0.378	-0.389
O	-0.553	-0.572	-0.557	-0.557	-0.582	-0.557	-0.558
O-methoxy	-0.531	-0.533	-0.482	-0.482	-0.535	-0.480	-0.521
C1	0.322	0.249	0.288	0.284	0.350	0.341	0.320
C2	-0.106	0.116	-0.105	-0.072	0.236	-0.123	-0.088
C3	-0.095	-0.139	0.107	-0.133	-0.089	0.224	-0.100
C4	-0.800	-0.074	-0.112	0.133	-0.093	-0.088	0.252
C5	-0.095	-0.105	-0.097	-0.137	-0.079	-0.104	-0.101
C6	-0.106	-0.088	-0.098	-0.091	-0.100	-0.082	-0.107
C-methoxy	-0.090	-0.087	-0.094	-0.094	-0.100	-0.093	-0.095
C-methyl	-	-0.378	-0.0388	-0.382	-	-	-
N	-	-	-	-	0.361	0.391	0.386
O-nitro	-	-	-	-	-0.383	-0.390	-0.394

Net charge calculated by DFT

3.3. Study of Structure-Property/activity Relationship

We have studied six physical-chemical properties of organophosphorus insecticides (eleven compounds) by HyperChem software.

For example, Scheme 4 shows the favored conformation in 3D of the compound 1. In the future we will continue this work by a quantitative model QSAR.

QSPR/ QSAR properties are, van der Waals molecular volume, the log of the octanol-water partition coefficient (logP), polarizability, solvent-accessible surface bounded of the molecule and molecular mass (M). Calculation of logP is carried out using atomic parameters derived by Viswanadhan and coworkers[31]. Computation of molar refractivity was made via the same method as logP. Ghose and Crippen presented atomic contributions to the refractivity [32].

The solvent-accessible surface and Van der Waals-surface-bounded are based on a grid method developed by Bodor et al.[33] using the atomic radii of Gavezzotti[34].

The polarizability was calculated from additivity settings given by Miller [35] with a precision of 3%. The hydration energy is a key factor determining the stability and toxicity of different molecular conformations[36]. The calculation is based on exposed surface area, and employs the surface area as computed by the approximate method (above), weighted by atom type.

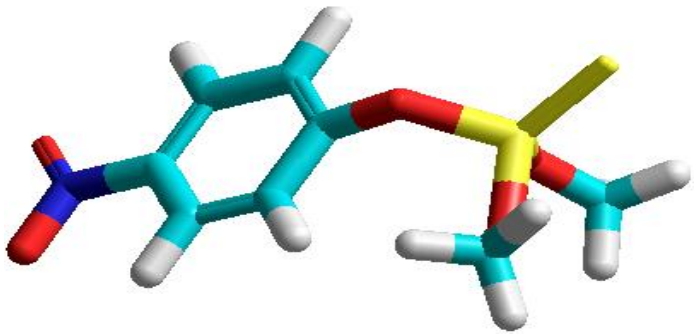
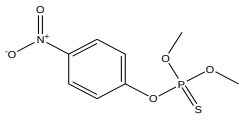
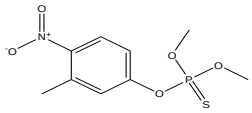
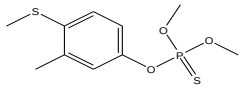
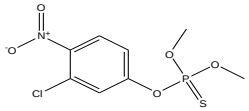
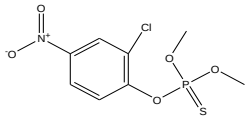
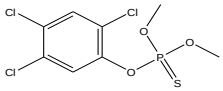
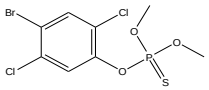
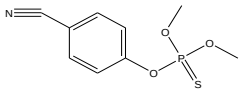
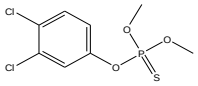
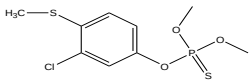
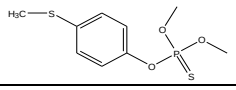


Fig.4. 3D Conformation of compound 1 (HyperChem 8.03)

3.2.1. Structural comparison of organophosphorus insecticides

Based on our conclusions on the effect of substitution on the O,O-dimethyl O-phenyl phosphorothioate molecule, we chose a series of O,O-dimethyl O-phenyl phosphorothioates (organophosphorus insecticides), which are a class of heterocyclic synthetic compounds. Initially, we performed a structural comparison of this series (Table 6). We used molecular mechanics, with MM+ force-field to calculate the stable conformations of this series. In a window of 2kcal/mol, only one favored conformations is found, for each structure. These molecules have a strong conformational flexibility, with regard to macrolide type[37-42].

Table 6. Organophosphorus insecticides: O,O-dimethyl O-phenyl phosphorothioate derivatives

Compound	O,O-dimethyl O-phenyl phosphorothioate derivatives	
1	O,O-dimethyl O-(4-nitro-phenyl) phosphorothioate	
2	O,O-dimethyl O-(4-nitro-3-methyl-phenyl) phosphorothioate	
3	O,O-dimethyl O-(3-methyl-4-methylsulfanyl-phenyl) phosphorothioate	
4	O,O-dimethyl O-(3-chloro-4-nitro-phenyl) phosphorothioate	
5	O,O-dimethyl O-(2-chloro-4-nitro-phenyl) phosphorothioate	
6	O,O-dimethyl O-(3,4,6-trichloro-phenyl) phosphorothioate	
7	O,O-dimethyl O-(3,6-dichloro-4-bromo-phenyl) phosphorothioate	
8	O,O-dimethyl O-(4-cyano-phenyl) phosphorothioate	
9	O,O-dimethyl O-(4,5-dichloro-phenyl) phosphorothioate	
10	O,O-dimethyl O-(4-methylsulfanyl-5-chloro-phenyl) phosphorothioate	
11	O,O-dimethyl O-(4-methylsulfanyl-phenyl) phosphorothioate	

3.2.2. Toxicity and SPR /SAR properties

Lipophilicity is a property that has an important role on solubility, absorption, distribution, metabolism, excretion and toxicity properties, so as pharmacological activity. Lipophilicity has been applied as a major drug property. It can be quickly measured or calculated. Lipophilicity has been correlated to many other properties, such as bioavailability, storage in tissues, permeability, volume of distribution, toxicity, plasma protein binding and enzyme receptor binding[43,44].

The toxicity of Organophosphorus insecticide depends upon the nature and the environment of the bonds or intermolecular forces (ligand-receptor) with different receptors. All types of intermolecular forces may be involved in the connection between a drug substance and its receptor (acceptor) for example: van der Waals bonds, electrostatic bonds, for example: Hydrogen bonds R - C = O.... H - NH.....X, and ovalent bonds R - S = O. . . H - S - X, R - S = S – X.

Log P value has been used to estimate the facility with which a compound will crows the blood-brain barrier by diffusion, experimentally, this is done by partitioning the molecule between water and the solvent n-octanol, determining the P value of the concentration of compound in n-octanol and that in water[45].

Table 7. QSPR /QSAR properties for O,O-dimethyl O-phenyl phosphorothioate derivatives.

compound	Molecular Volume ($Å^3$)	Molecular Surface ($Å^2$)	Molecular Mass (uma)	Partition coefficient (log P)	Hydration energy (kcal/mol)	Polarizability ($Å^3$)
1	692.59	436.39	263.20	-1.05	-12.48	21.97
2	734.21	459.89	277.23	-0.90	-10.78	23.81
3	770.65	472.95	278.32	1.20	-6.51	26.80
4	728.87	456.24	297.65	-1.28	-11.57	23.90
5	721.56	447.62	297.65	-1.28	-11.50	23.90
6	740.80	453.20	321.54	1.03	-5.89	25.91
7	757.06	462.50	365.99	1.30	-5.87	26.61
8	686.69	434.63	243.22	1.42	-11.66	21.98
9	710.49	447.22	287.10	1.25	-6.73	23.99
10	772.39	480.48	298.74	0.82	-6.96	26.89
11	735.13	461.95	264.29	1.04	-7.56	24.97

The values of polarizability are generally proportional to the values of surfaces and of volumes, the decreasing order of polarizability for these studied O,O-dimethyl O-phenyl phosphorothioates is: 7,6,10,4 and 5,9,3,2,11,1,8 (Table 7).

The order of polarizability is approximately the same one for volume and surface. This is explained by the relation between polarizability and volume, for the relatively non polar molecules.

The surface and the volume of distribution of these molecules are generally great than that of more polar molecules like beta-lactams. For example, Deleu et al. used TAMMO program [46]

on C13, C14 and C15/ surfactins having cores similar to the macrolides. They found that their surfaces vary from129 to 157 $Å^2$ [47], contrarily for these O,O-dimethyl O-phenyl phosphorothioates surfaces vary from 686.69 to 772.39 $Å^2$. These O, O-dimethyl O-phenyl phosphorothioates have a great variation of distribution volume, in particular compound **10,** which has volume: 480.48 $Å^3$ (Table 7).

The most important hydration energy in the absolute value, is that of the compound **7** (26.91 kcal/mol) and the weakest is that of compound **1** (21.97kcal/mol) (Table 7). Indeed in the biological environments the polar molecules are besieged by water molecules. Hydrogen bonds can be established between a water molecule and these molecules. The donor sites of proton interact with the oxygen atom of water and the acceptor sites of proton interact with the hydrogen atom.

The first correspond to the complex (ligand-receptor) with the strongest hydrogen bond. These hydrated molecules are dehydrated at least partially before and at the time of their interaction. These interactions of weak energy, which we observe particularly between drugs and receivers, are generally reversible[48].

Compound **7** does not possess any donor site of proton, but it has eight acceptor sites of proton (3O, 1P, 1S, 2Cl, 1Br). On the other hand, compound **1** does not possess any donor site, but it possesses seven acceptor sites of proton (5O, 1P, and 1S). The first having higher value, it has one more acceptor site of protons. This property assists the first compound, not only by fixing on the receptor but in addition activates it. So, it is an agonist ligand, consequently a better distribution in fabrics.

All (log P) of studied molecules have optimal values. For good oral bioavailability, the log P must be greater than zero and less than 3 ($0 < \log P < 3$). For log P too high, the drug has low solubility and a log P too low; the drug has difficulty penetrating the lipid membranes[49].

Compounds **4** and **5** present the low coefficient of division (-1.28). When the coefficient of division is rather low, so consequently a better gastric tolerance. Compounds **8** and **7** which have respectively higher values 1.42 and 1.30, have capacities to be dependent on plasmatic proteins.

3.2. 3. Drug-likeness calculation on the basis of Lipinski rule of five

Drug-likeness appears as a promising paradigm to encode the balance amongst the molecular

properties of a bioactive compound and its pharmacokinetics and ultimately optimizes their absorption, distribution, metabolism and excretion, and toxicity (ADME-Tox). The empirical conditions to satisfy Lipinski's rule and manifest a high oral bioavailability involve a balance between the solubility of a compound and its permeability through the different biological barriers[50,51]. These parameters permit ascertaining oral absorption or membrane permeability that happen when the evaluated molecule follows Lipinski's rule of five since, molecular weight (MW) ≤ 500 Da, an octanol-water partition coefficient log P ≤ 5, H-bond donors (HBD) ≤ 5 and H-bond acceptors (HBA) ≤ 10.

Molecules that violate more than one of these rules may have problems with bioavailability. Therefore, this rule develop some structural parameters relevant to the computational prediction of the oral bioavailability, is widely used in designing new drugs.[50] The total number of violations is the ROF-Score, which lies between 0 and 4 [52].

The computational results (Table 8) indicate that all the toxic compounds agree with Lipinski rules, whish that all these bioactive compounds would not have problems with oral bioavailability.

Table 8. Lipinski's rule for drug likeliness of O,O-dimethyl O-phenyl phosphorothioate derivatives

Compound	Molecular Mass (uma)	Partition coefficient (log P)	HBD	HBA	Scoring Lipinski's rule
1	263.20	-1.05	0	6	4
2	277.23	-0.90	0	6	4
3	278.32	1.20	0	3	4
4	297.65	-1.28	0	6	4
5	297.65	-1.28	0	6	4
6	321.54	1.03	0	3	4
7	365.99	1.30	0	3	4
8	243.22	1.42	0	4	4
9	287.10	1.25	0	3	4
10	298.74	0.82	0	3	4
11	264.29	1.04	0	3	4

Molecular Mass and Log P calculated by HyperChem 8.06

4. CONCLUSION

The present work studied the molecular proprieties and toxicity of O, O-dimethyl O-phenyl phosphorothioates. The ab initio/HF, DFT/B3LYP and PM3 method can be used quite satisfactorily in predicting the biological activity, chemical reactivity and the effect of substitution of either donor or acceptor electron. O,O-dimethyl O-(3-nitro-phenyl) phosphorothioate is predicted to be the most reactive with least HOMO- LUMO energy gap of all O,O-dimethyl O-phenyl phosphorothioates.

The toxicity of Organophosphorus insecticide depends upon the nature and the environment of the bonds or intermolecular forces (ligand-receptor) with different receptors. O, O-dimethyl O-(2-nitro-phenyl) phosphorothioate presents the higher value of dipole moment. Compounds **4** and **5** present the lower coefficient of division (Log P); as a consequence, they have the best gastric tolerance. Toxic compound **7** has important hydration energy; it has a better distribution in fabrics. The application of Lipinski rules on the studied 1.2.5-oxadiazole derivatives shows that, these organophosphorus compounds will not have problems with oral bioavailability in the human body.

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