

## DFT Study, POM Analyses and Molecular Docking of Novel Oxazaphosphinanes: Identification of Antifungal Pharmacophore Site

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**Abstract:** A computational Petra/Osiris/Molinspiration/DFT(POM/DFT) based model has been developed for the identification of physico-chemical parameters governing the bioactivity of series of oxazaphosphinanes derivatives **1a-1f** containing potential antifungal O,N-pharmacophore. A molecular docking study was performed in order to evaluate synthesized compounds, their possible antifungal properties, and their interactions in the binding site. Molecular docking studies revealed that the compounds **1a-1f** have the potential to become lead molecules in the drug discovery process. The six compounds **1a-1f** analyzed here were previously synthesized by our group.

**Keywords:** oxazaphosphinane; DFT; Petra/Osiris/Molinspiration (POM) analyses; molecular docking

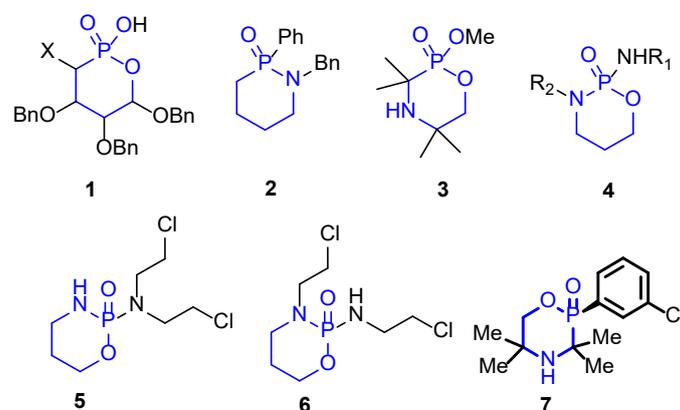
### ■ INTRODUCTION

The 6-membered P-heterocycles have attracted considerable attention from the scientific community because of their wide biological activities spectrum [1]. Examples cited in the literature include oxazaphosphinanes **1** with antiproliferative properties [2-3], azaphosphinane **2**, which has been shown to be effective as a biodegradable insecticide [4], and antitumoral [5-6] as alkylating agent drugs such as cyclophosphamide and ifosfamide **5**, **6**.

Research teams have described the synthesis of a series of oxazaphosphinane **3**, an analog of hydroxybupropion, which has been evaluated as an antidepressant agent [7]. In the past 20 years, significant effort has been devoted to the synthesis of a particular family of organophosphorus compounds: such as **4** [8] and (±)-2-aryl-3,3,5,5-tetramethyl-[1,4,2]-oxazaphosphinanes **7** [6].

Among methods used of quantum mechanics, density functional theory (DFT) methods that have been

widely used in many studies because of the smaller computational resources needed to describe very large systems. Specially, they have been found to be efficient in the description of systems dominated by hydrogen bonding interactions [9].



**Fig 1.** Examples of important bioactive oxazaphosphinanes and their derivatives

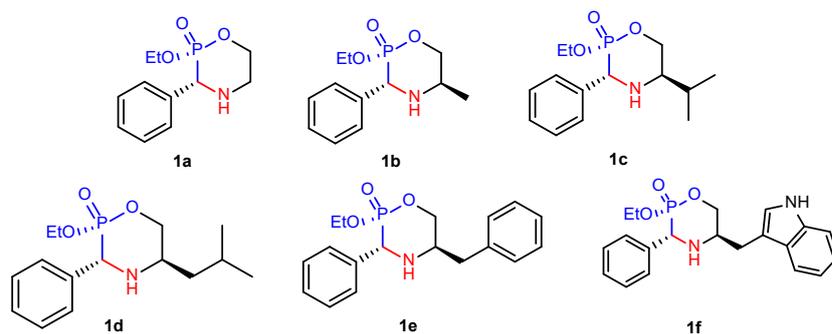


Fig 2. Chemical structure of studied compounds

Recently, DFT has been accepted by the quantum chemistry community as a cost-effective approach for the computation of molecular structure, vibration frequencies, and energies of chemical reactions. Many studies have shown that molecular modeling has had a profound effect on procedure modeling through a better understanding of the fundamental physical and chemical interactions, through forming the basis for predicting physico-chemical properties of molecules that are difficult to calculate using experimental procedures [10].

The most important orbitals in determining chemical reactivity are the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). The energy difference between the HOMO and LUMO, means the band gap, can sometimes be useful to measure of the molecule excitability, the smaller energy, the more easily it will be excited [11-14]. In the past few years, there have been some theoretical studies of oxazaphosphinane using molecular modeling [15-16].

The aim of our work is the theoretical study of reactivity and to determine energies, dipole moments and vibrational study of six novel oxazaphosphinanes [17] (Fig. 2), using the density functional theory method (DFT). POM (Petra/Osiris/Molinspiration) analyses have been executed with the aim of evaluating the performance of physico-chemical properties of tested compounds. As a result, an antifungal *O,N*-pharmacophore site is identified. A docking study was carried out to achieve the interaction on the active site.

## ■ COMPUTATIONAL METHODS

The studied compounds were optimized with DFT by program package GAUSSIAN 09 using the B3LYP/6-

31G(d) method. The B3LYP density functional method is one of the most commonly Hybrid functional used, which stands for Becke, 3 parameters, Lee-Yang-Parr [18]. We employed well established *in silico* tools POM Osiris, Petra, and Molinspiration, validated with about 7000 drug molecules available in databases [19].

The inaugural molecular docking program, DOCK, developed by Kuntz and co-workers, has a long history of new advances and accomplishments in the field of structure-based design. We briefly present methods for preparing the system and performing pose reproduction experiments in the program DOCK. First, the molecular surface of the receptor absent hydrogen atoms and the ligand was determined using the DMS [20] program, then, the DOCK accessory programs sphgen [21] and show box were used to generate spheres and box within the ligand binding site. The DOCK accessory program GRID [22] was used to precompute energy interactions between a dummy probe atom and all receptor atoms on a 0.3 Å resolution grid within the box. Finally, for pose reproduction experiments, the ligands were treated as flexible based on the FLX protocol (standard flexible docking) by Mukherjee et al. [23].

## ■ RESULTS AND DISCUSSION

### DFT Studies

The molecular geometry of oxazaphosphinanes and the nature of their substituents are often correlated with their stability and their reactivity. In order to specify the relationship between the experimental results of the activities with the structure of the molecules and to evaluate this relationship, theoretical studies were carried out by molecular modeling. Thus, modeling

gives some important and necessary information on the structure and reactivity of oxazaphosphinane.

### Geometry optimization

The optimization of different structures has been obtained by Gaussian 09 [24] using the B3LYP/6-31G(d) [25-26] method. The optimized geometries were used to calculate the level of energy HOMO, LUMO, and gap. The structures of the six compounds obtained after geometric optimizations in the DMSO solvent are shown in Fig. 3.

The values of hydrophobicity coefficient (log P) thus energetic levels of the (HOMO, LUMO), gap energies, total energy, dipolar moment ( $\mu$ ) and linear polarizability

( $\alpha_{\text{Tot}}$ ) calculated by DFT method using B3LYP/6-31G(d) in the gas phase and DMSO solvent are presented in Table 1.

The compound **1e** has the highest gap energy in both gas phase and DMSO; it is more stable and less active. In the gas phase, **1a** is the more active compound, while in the DMSO solvent, the more active compound is **1f**. The results in Table 1 show that the gap energy ( $\Delta E_{\text{gap}}$ ) is inversely proportional to the dipolar moment.

### Chemical reactivity

In order to understand the activities of titled compounds, the conceptual density functional theory (DFT) was employed to obtain the chemical reactivity

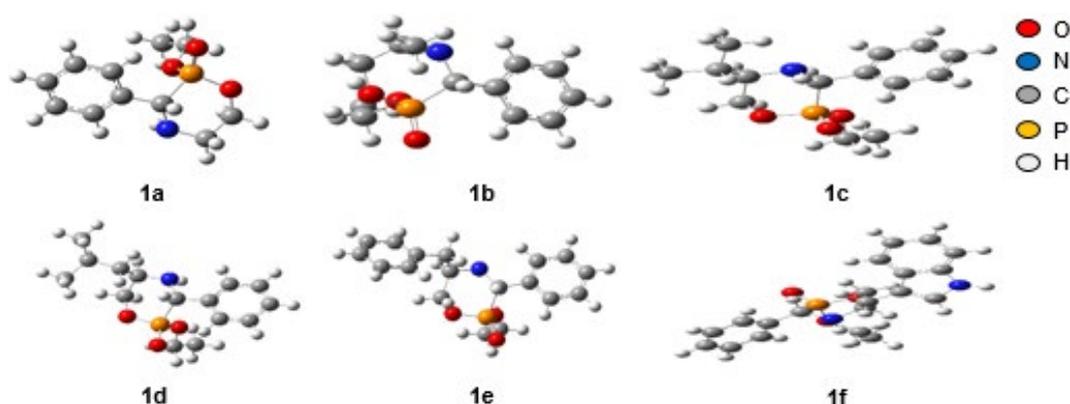


Fig 3. Optimized structures of titled compounds obtained at B3LYP/6-31G(d) level in DMSO

Table 1. The calculated parameters of compounds **1a-1f** obtained by the B3LYP/6-31G(d) method in the gas phase and DMSO solvent

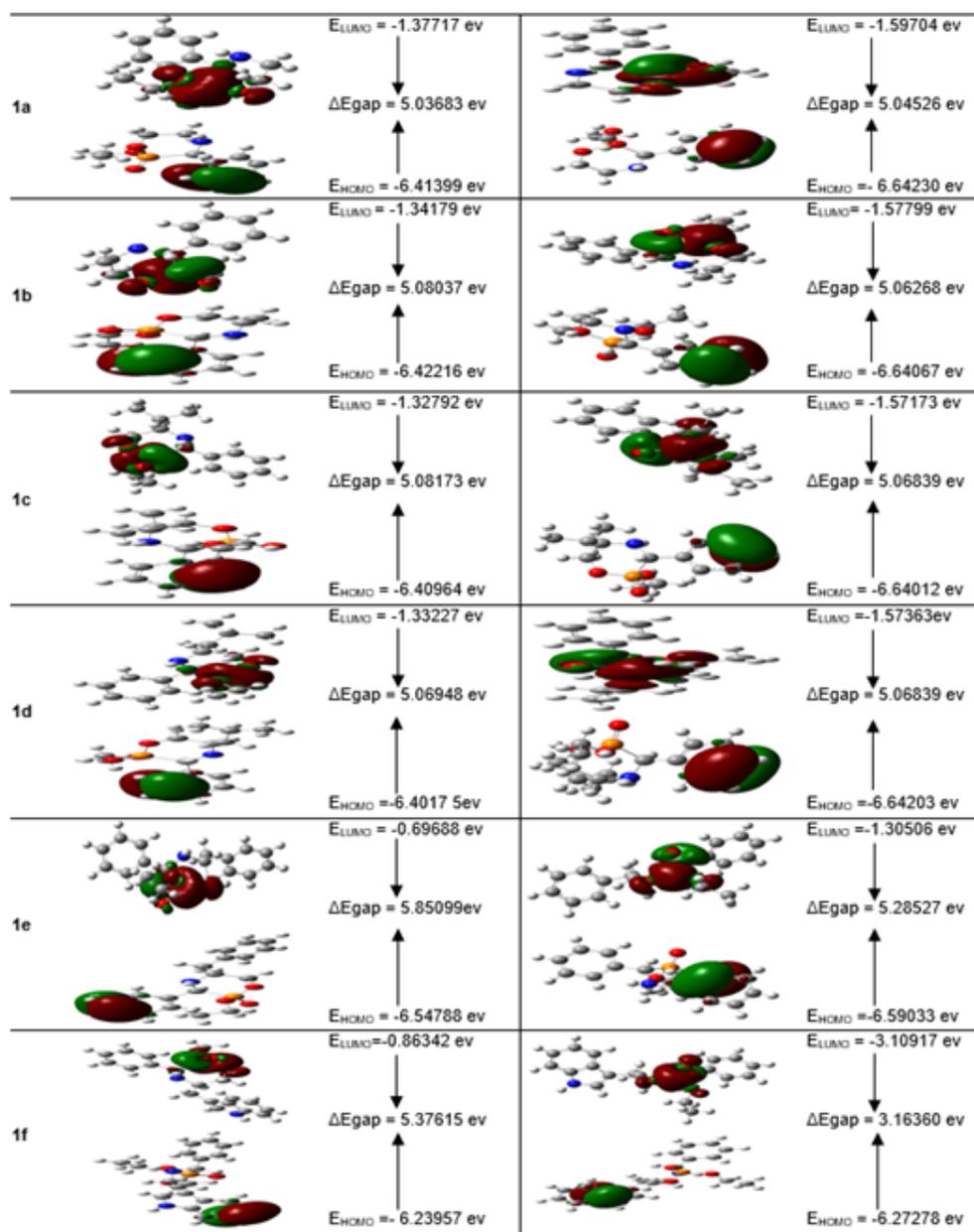
Descriptors	Gas phase					
	1a	1b	1c	1d	1e	1f
Log p	1.87	2.29	3.16	3.84	3.97	3.28
$\alpha_{\text{Tot}}$ (Bohr <sup>3</sup> )	141.33	151.78	173.78	185.18	211.95	239.34
$\mu$ (D)	4.0263	3.9571	3.9546	3.9755	2.7887	6.9136
$E_{\text{HOMO}}$ (eV)	-6.41399	-6.42216	-6.40964	-6.40175	-6.54788	-6.23957
$E_{\text{LUMO}}$ (eV)	-1.37717	-1.34179	-1.32792	-1.33227	-0.69688	-0.86342
$\Delta E_{\text{gap}}$ (eV)	5.03683	5.08037	5.08173	5.06948	5.85099	5.37615
E (u.a)	-1050.634	-1089.9483	-1168.573	-1207.884	-1320.994	-1452.557
Descriptors	DMSO					
	1a	1b	1c	1d	1e	1f
$\alpha_{\text{Tot}}$ (Bohr <sup>3</sup> )	182.41	196.09	224.11	237.84	272.91	313.01
$\mu$ (D)	5.8327	5.8691	5.7702	5.8942	4.5032	10.0717
$E_{\text{HOMO}}$ (eV)	-6.64230	-6.64067	-6.64012	-6.64203	-6.59033	-6.27278
$E_{\text{LUMO}}$ (eV)	-1.59704	-1.57799	-1.57173	-1.57363	-1.30506	-3.10917
$\Delta E_{\text{gap}}$ (eV)	5.04526	5.06268	5.06839	5.06839	5.28527	3.16360
E (u.a)	-1050.648	-1089.962	-1168.587	-1207.898	-1321.008	-1452.577

descriptors, using the HOMO's and the LUMO's energy level (Fig. 4).

Electronegativity, noted  $\chi$ , is a chemical property that describes the ability of an atom to attract a shared pair of electrons (or electron density) towards itself [27]. Chemical hardness [28], noted  $\eta$ , is a measure of the resistance to change the electron cloud density of the chemical system, its reciprocal softness, noted  $S$ . The

electrophilicity index, noted  $\omega$ , is used to measure the stabilization in energy when the system acquires an additional electronic charge from the environment [29]. These different values are illustrated in Table 2.

Table 2 shows the reactivities of the new molecules. According to this, the compound **1e** has the highest chemical hardness and is more stable. In addition, the most active compound is **1a** in the gas phase and **1f** in



**Fig 4.** HOMO, LUMO orbitals and their energy gap ( $\Delta E_{\text{gap}}$ ) for **1a-1f** obtained at the B3LYP/6-31G(d) level using a contour threshold of 0.02 a.u. in the gas phase and DMSO solvent

**Table 2.** Calculated values of chemical hardness, electronegativity, Electronic chemical potential, and global values electrophilicity index for the compounds studied by B3LYP/6-31G(d)

	Gas phase					DMSO				
	$\eta$	s	$\mu$	$\chi$	$\omega$	$\eta$	s	$\mu$	$\chi$	$\omega$
<b>1a</b>	2.5198	0.3969	-3.8967	3.8967	3.0123	2.5226	0.3964	-4.1198	4.1198	3.3633
<b>1b</b>	2.5415	0.3935	-3.8831	3.8831	2.9660	2.5306	0.3952	-4.1089	4.1089	3.3361
<b>1c</b>	2.5415	0.3934	-3.8695	3.8695	2.9443	2.5334	0.3947	-4.1062	4.1062	3.3252
<b>1d</b>	2.5361	0.3943	-3.8667	3.8667	2.9497	2.5334	0.3947	-4.1089	4.1089	3.3307
<b>1e</b>	2.9252	0.3419	-3.6218	3.6218	2.2422	2.6422	0.3785	-3.9483	3.9484	2.9497
<b>1f</b>	2.6885	0.3720	-3.5511	3.5511	2.3456	1.5810	0.6325	-4.6912	4.6912	6.9552

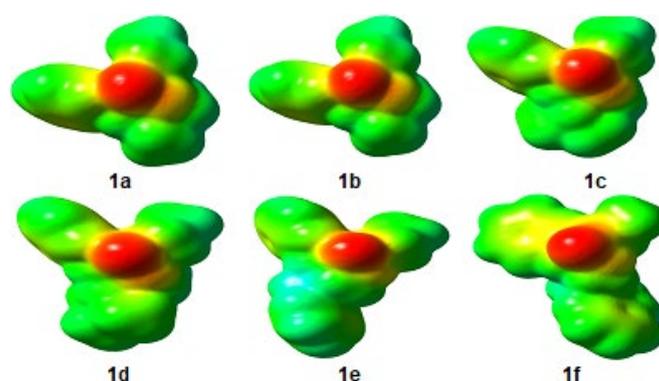
DMSO. In the gas phase, the compound **1a** has the highest  $\omega$  and  $\mu$  values, so it is the most susceptible molecule to nucleophilic attack.

#### Molecular electrostatic potential surface

The electrostatic potential maps are the energy of interaction of a positive charge (an electrophile) with the nuclei and electrons of a molecule. Negative electrostatic potentials indicate probable initial sites for the electrophilic attack. Enough small value of the electron density gives overall molecular size and shape. The electrostatic potential can be mapped onto a particular value of the total electron density by using color to represent the value of the potential. The regions of the molecule with negative values of the electrostatic potential are indicated by red color, while color blue indicates positive values of the potential. The green color corresponds to an intermediate potential situated between the two extremes (red and dark blue). The yellow and light blue color split the difference between the medium color (green) and the extremes (red/dark blue).

Based on these considerations, oxygen would be related with the red region of the diagram, and nitrogen would be found with the blue region; the phosphorus, carbon, and hydrogen situated between these two extremes, phosphorus in the yellow region and the green region for carbon and hydrogen (Fig. 5).

The molecular electrostatic potential's representation of title compounds that the oxygen atom (red region) presents the electrophilic attack site with high electron density; furthermore, analysis of the NBO charge in DMSO shows that phosphonyl oxygen atoms have an average charge of -0.871 in all compounds except in **1e** -0.864 and



**Fig 5.** Molecular electrostatic potential MESP for titled compounds on total density (Isovalue = 0.0004 a.u)

-0.869 in **1f**, as well as nitrogen amide, carried a charge of -0.699 in **1a**, -0.704 in **1b**, -0.703 in **1c**, -0.702 in **1d**, -0.702 in **1e** and an average charge of -0.629 in **1f**. On the other hand, MESP shows one major nucleophilic active centers at the proximity of hydrogens atoms related to nitrogen atom, with a NBO charge of 0.399 in **1a**, 0.401 in **1b**, 0.403 in **1c**, 0.401 in **1d**, 0.409 in **1e** and an average charge of 0.428 in **1f**, and another nucleophilic center in all compounds due to the presence of ethoxy group.

#### POM Analyses of Compounds (1a-1f)

For a molecule to be a potential drug, besides having a good biological activity, it must have good pharmacokinetic properties in human biological systems. To access the pharmacokinetic profile of the tested compounds, we employed Petra/Osiris/Molinspiration (POM) analyses. The results of theoretical toxicity risks of compounds **1a-1f**, which are calculated with the aid of the Petra/Osiris/Molinspiration (POM) program are shown in Table 3 [30-32]. Our findings reveal that all

synthesized compounds **1a-1f**, are not toxic and can be utilized as therapeutic agents.

Interestingly **1b** deserves pharmacomodulation (DS = 47%). The hydrophilicity character of each compound has been calculated. All of the compounds (**1a-1f**) have accepted *cLogP* values (*cLogP* < 3). The geometrical conformation of pharmacophore site is taken into consideration (Fig. 6). This is because it is flexible for all compounds (**1a-1f**). The absorption, distribution, characteristics, and bioactivity were proved to be dependent on the geometrical parameter and the aqueous solubility of each compound.

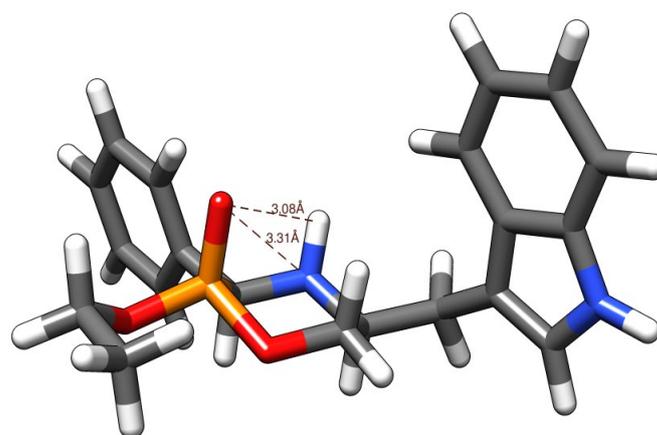
On the other hand, drug-likeness (DL) of (**1a-1f**) is not in the comparable zone with the used standard drug. The compounds (**1a-1f**) showed a high capacity to excellent DS as compared with **Ifosfamide** (Table 3).

Topological polar surface area (TPSA), i.e., surface belonging to polar atoms and molecular weight, is the descriptors that correlate with passive molecular transport through membranes that allow prediction of the route of transport of drugs through the barrier membranes the intestine and blood-brain barrier (BBB). All tested compounds have no violation of Lipinski rules (NV = 0). Prediction results of compounds (**1a-1f**) with molecular properties (GPCRL, ICM and enzyme inhibitors) are recorded in Table 4.

### Molecular Docking Study

From the previous results of the POM program, and with the aim of achieving the interaction on the active site, a docking study was carried out. Computer-based

molecular docking can facilitate the early stages of drug discovery through systematic prescreening of ligands (i.e., small molecules) for shape and energetic compatibility with a receptor (i.e., protein) prior to experimental evaluation [33-35]. Recently, small chemical ligands have been reported to inhibit cytochrome P450 sterol 14 $\alpha$ -demethylase in a wide spectrum of fungal species [36-38]. To understand the mechanism of action and antifungal activity of our synthesized analogues, molecular docking studies were employed using the crystal structure of human cytochrome P450 2E1 that was picked from the Protein Data Bank (CYP2E1; pdb code: 3e4e) (<http://www.rcsb.org/pdb>). The protein was processed, optimized, and minimized by using the protein preparation wizard of Schrodinger Suite by applying OPLS3 force field [39].



**Fig 6.** Identification antifungal *O, N*-pharmacophore site of compound **1f**

**Table 3.** Osiris calculations of toxicity risks of compounds (**1a-1f**)

Compounds	MW	Toxicity Risks <sup>[a]</sup>				Osiris calculations <sup>[b]</sup>			
		MUT	TUM	IRRI	REP	<i>cLogP</i>	<i>cLogS</i>	DL	DS
<b>1a</b>	241	■	■	■	■	1.01	-1.93	-30.92	0.47
<b>1b</b>	255	■	■	■	■	1.34	-2.31	-29.71	0.47
<b>1c</b>	283	■	■	■	■	2.01	-2.74	-31.38	0.45
<b>1d</b>	297	■	■	■	■	2.46	-3.01	-30.71	0.43
<b>1e</b>	331	■	■	■	■	2.78	-3.44	-30.32	0.41
<b>1f</b>	370	■	■	■	■	2.82	-3.98	-29.06	0.38
Ifosfamide(Holoxan®)	260	■	■	■	■	1.06	-1.89	-10,7	0.1

Highly toxic ■, Slightly toxic ■, Not toxic ■;

<sup>[a]</sup>MUT: Mutagenic, TUM: Tumorigenic, IRRIT: Irritant, RE: Reproductive effective. <sup>[b]</sup>Sol: Solubility, DL: Druglikness, DS: Drug-Score

**Table 4.** Molinspiration calculations of compounds (**1a-1f**)

Compounds	Molinspiration calculations <sup>[a]</sup>				Drug-likeness <sup>[b]</sup>					
	TPSA	NONH	NV	VOL	GPCRL	ICM	KI	NRL	PI	EI
<b>1a</b>	48	1	0	216	-0.62	0.39	-0.64	-0.90	0.04	0.26
<b>1b</b>	48	1	0	232	-0.52	0.25	-0.69	-0.86	0.06	0.27
<b>1c</b>	48	1	0	266	-0.34	0.18	0.50	-0.68	0.34	0.32
<b>1d</b>	48	1	0	282	-0.22	0.21	-0.44	-0.43	0.46	0.37
<b>1e</b>	48	1	0	304	-0.04	0.31	-0.19	-0.39	0.45	0.36
<b>1f</b>	63	1	0	333	0.15	0.37	0.04	-0.35	0.45	0.41
Ifosfamide(Holoxan®)	42	1	0	209	-0.71	-0.45	-0.65	-1.02	-0.29	0.55

<sup>[a]</sup>TPSA: Total molecular polar surface area; NONH: number of OH---N or O---NH interaction, NV: number of violation of five Lipinsky rules; VOL: volume. <sup>[b]</sup>GPCRL: GPCR ligand; ICM: Ion channel modulator; KI: Kinase inhibitor; NRL: Nuclear receptor ligand; PI: Protease inhibitor; EI: Enzyme inhibitor

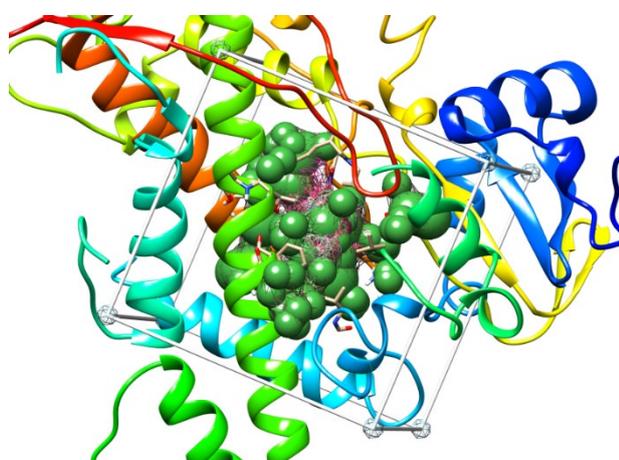
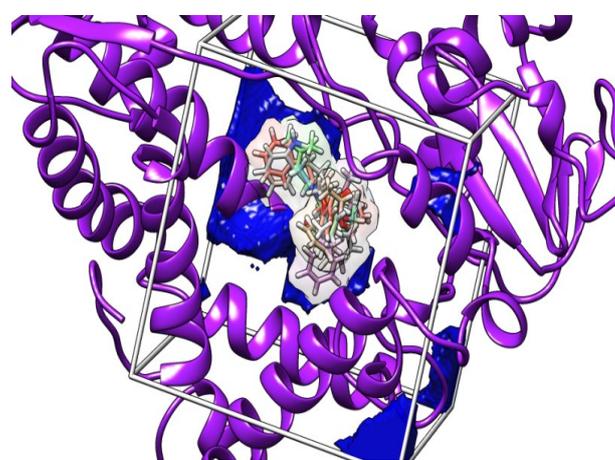
In the docking study, the 6 compounds mentioned above were prepared using open babel [40] software and docked into the catalytic site of the human cytochrome P450 (Fig. 7). Docking studies revealed that oxazaphosphinanes derivatives prove interesting stability inside the cavity, with remarkable superimposition (Fig. 8). All compounds were ranked by the total energy of predicted pose in the binding site (Table 5). Otherwise, the 6 derivatives interact with active site residues mainly through hydrogen bonds, as well as hydrophobic interactions.

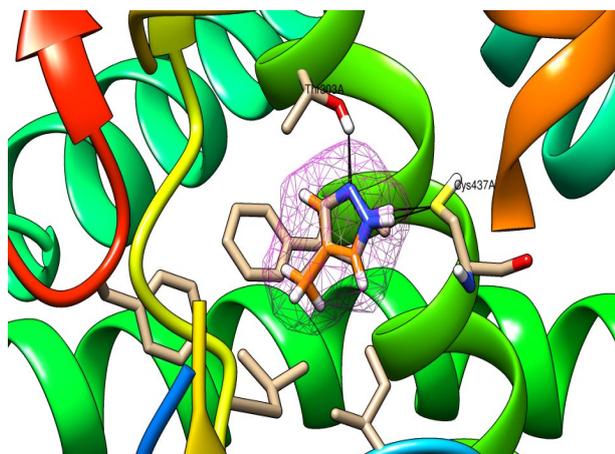
Compound **1f**, which has the least binding total energy (-41.319 kcal/mol) is most favorable, with the most interesting interaction inside the pocket. Fig. 10 shows that compound **1f** was docked to the pocket of human cytochrome P450. Compound **1f** formed 4 hydrogen bonds

with the residues of Cys437 and Thr303, 2 hydrogen bonds as a donor with the nitrogen atom, and 2 others as an acceptor with the oxygen atom. Otherwise, 3 hydrophobic interactions occur with the residues of Phe430, Phe298, and Ile115, which makes it the most stable ligand.

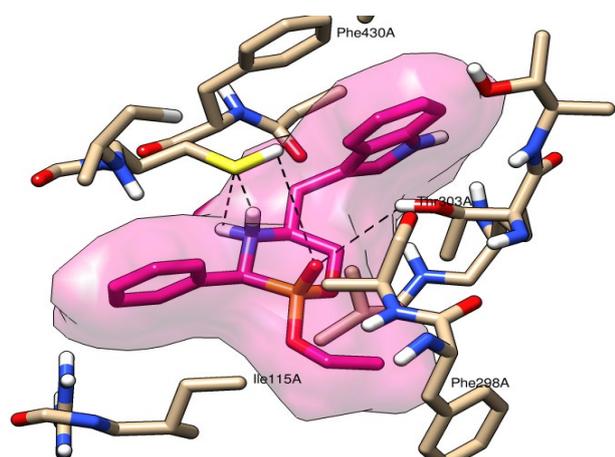
**Table 5.** Ranking of the six oxazaphosphinanes derivatives after docking study

Compounds	Total energy (kcal/mol)	Docking score
<b>1a</b>	-22.892	-4.728
<b>1b</b>	-28.506	-4.457
<b>1c</b>	-32.58	-5.112
<b>1d</b>	-33.413	-4.271
<b>1e</b>	-38.496	-6.219
<b>1f</b>	-41.319	-9.949
Ref ligand (4PZ)	-37.21	7.123

**Fig 7.** The active site of the human cytochrome P450 (Green spheres)**Fig 8.** Super imposition of the six oxazaphosphinanes derivatives in the cavity after docking calculation



**Fig 9.** Conserved active site architecture after self-docking for the co-crystallized ligand (4PZ). Hydrogen bonding interactions are shown in black



**Fig 10.** Binding model of compound **1f** in the binding pocket of human cytochrome P450. The amino acid residues and compound **1f** are shown as stick models, H-bonds are shown as black dashed lines

Prior to the docking analysis, a self-docking evaluation of the main cytochrome-inhibitor X-ray complexes has been carried out using the Dock v6.9 program [41]. The use of this program resulted to be the most reliable as it showed the lower average root-mean-square deviation (RMSD) (Fig. 9).

## ■ CONCLUSION

This work reports the computational analysis of a new series of oxazaphosphinane derivatives. The geometry of all synthesized compounds was optimized with DFT/B3LYP methods using 6-31G(d) basis to

determine tasks that coordinate electron density with energy. Our findings reveal that all synthesized compounds, **1a-1f**, are not toxic and can be utilized as therapeutic agents. All oxazaphosphinane derivatives represent an important antifungal *O,N*-pharmacophore site, which needs a separated supplementary antifungal screening. The nature of the pharmacophore site assignment of the oxazaphosphinane compounds was based on their docking and Petra/Osiris/Molinspiration (POM) analyses.

## ■ ACKNOWLEDGMENTS

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