



Novel organophosphonates based on the pyrazole moiety as potent antimicrobial agents: synthesis, characterization, molecular docking studies, and DFT calculations

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Abstract

In the present study, trimethoxy-oxaphosphol-pyrazol-3-one and dimethyl-pyrazoloxobutylphosphonate derivatives were produced when chalcones incorporated pyrazolone ring **1a,b** interacted with trimethyl phosphite in a free solvent setting with palladium acetate acting as a catalyst. However using dialkyl phosphites resulted in a phosphonate derivative. Moreover, organophosphonate derivatives have been prepared via the reaction of pyrazole substrates and dialkyl phosphites. On the other hand, bis(dimethylamino) phosphorylpropanoyl methane and bis(dimethylamino) phosphorylpropanoyl benzene were prepared through the reaction of 5-pyrazolones with hexamethylphosphinetriamine. Spectroscopic analysis was performed to confirm the structure of all new compounds. The in-vitro antibacterial and antifungal activities for all new synthesized compounds were carried out. The obtained results are compared with the reference antibiotics namely, Neomycin (bactericide) and Cyclohexamide (fungicide). Additionally, all of the substances under study showed good to moderate activity compared to the standards, according to the Minimum Inhibitory Concentration (MIC) measurements. The geometry of the compounds was adjusted using density function theory (DFT) at B3LYP using 6-311 G (d,p) basis in order to investigate the electronic characteristics and reactivity of all the compounds under study. Additionally, by inhibiting Dihydropteroate synthase, the molecular docking methodology shows the antibacterial activity of the created compounds, and all of the designed compounds have demonstrated notable drug-like properties.

Keywords. Chalcones; oxaphosphole; molecular docking; DFT; antimicrobial agents; MIC.

1- Introduction:

Phosphonate derivatives represent an important and versatile class of organophosphorus compounds with wide-ranging biological applications, particularly in medicinal chemistry. Their distinctive chemical features, such as the presence of a stable C–P bond and the ability to mimic biological phosphate esters [1], make them attractive scaffolds for the development of new antimicrobial agents [2-5]. The incorporation of phosphonate functionalities into organic frameworks can significantly enhance lipophilicity, improve metabolic stability, and modulate biological activity [6, 7]. Figure 1 showed some of active phosphonate drugs.

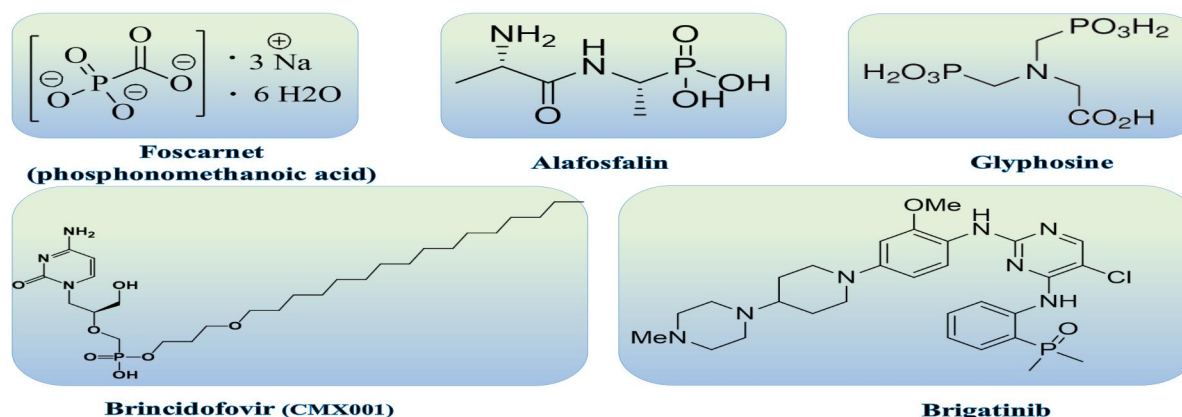


Figure 1: Structures of biologically active phosphonate drugs.

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Within this domain, chalcone-based frameworks have drawn considerable attention due to their remarkable pharmacological versatility. Chalcones, characterized by the α,β -unsaturated carbonyl system, exhibit diverse biological activities, including antibacterial, antifungal, anti-inflammatory, and anticancer properties [8-10]. The conjugation of chalcone skeletons with heterocycles such as pyrazole has been reported to further improve their potency and selectivity [11, 12]. Pyrazole-containing chalcones benefit from the synergistic combination of two bioactive motifs: the pyrazole nucleus, known for its antimicrobial, anti-tubercular, and anti-parasitic activities [13, 14], and the chalcone moiety, which can disrupt microbial enzymatic systems and membrane functions [15, 16].

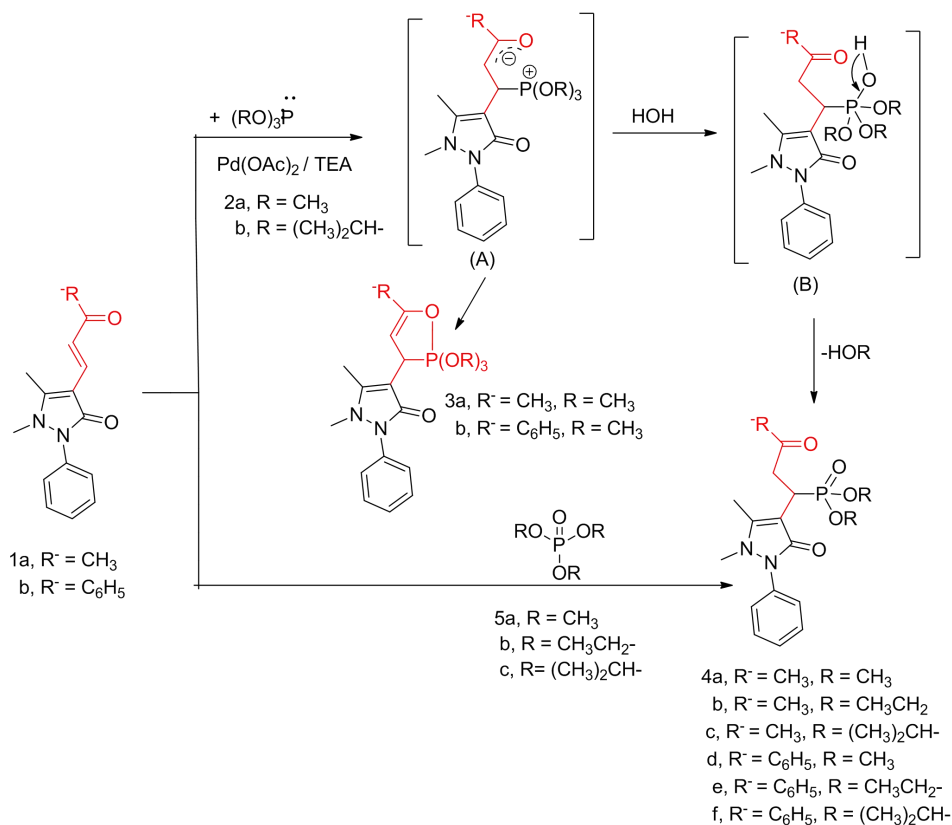
Previous studies have demonstrated that structural modifications, such as the introduction of phosphonate groups into chalcone-pyrazole hybrids, can lead to novel molecular entities with enhanced antimicrobial properties. This is attributed to the dual mechanism: (i) the electrophilic chalcone α,β -unsaturated carbonyl group, capable of interacting with nucleophilic residues in microbial enzymes, and (ii) the phosphonate group, which can mimic natural phosphate substrates and interfere with microbial metabolic pathways [17]. Given the rising threat of antimicrobial resistance, the design and synthesis of such hybrid molecules represent a promising strategy in drug discovery. Therefore, the present study focuses on the synthesis of novel chalcone derivatives containing pyrazole rings functionalized with phosphonate groups. The antimicrobial activities of the synthesized compounds will be evaluated against selected Gram-positive and Gram-negative bacterial strains, as well as pathogenic fungi, with their efficacy compared to established reference antibiotics. According to many applications of organophosphorus compounds as phosphorus-based organocatalysis and its applications in medicinal chemistry, production of phosphonates of pharmaceutical purposes. Density functional theory had been used to simulate the electronic properties of novel compounds. Frontier molecular orbitals, NBO, dipole moments and different electronic descriptors were all inspected through computational investigation. In addition to validate the DFT pharmacokinetics and molecular docking study.

2- Results and Discussion

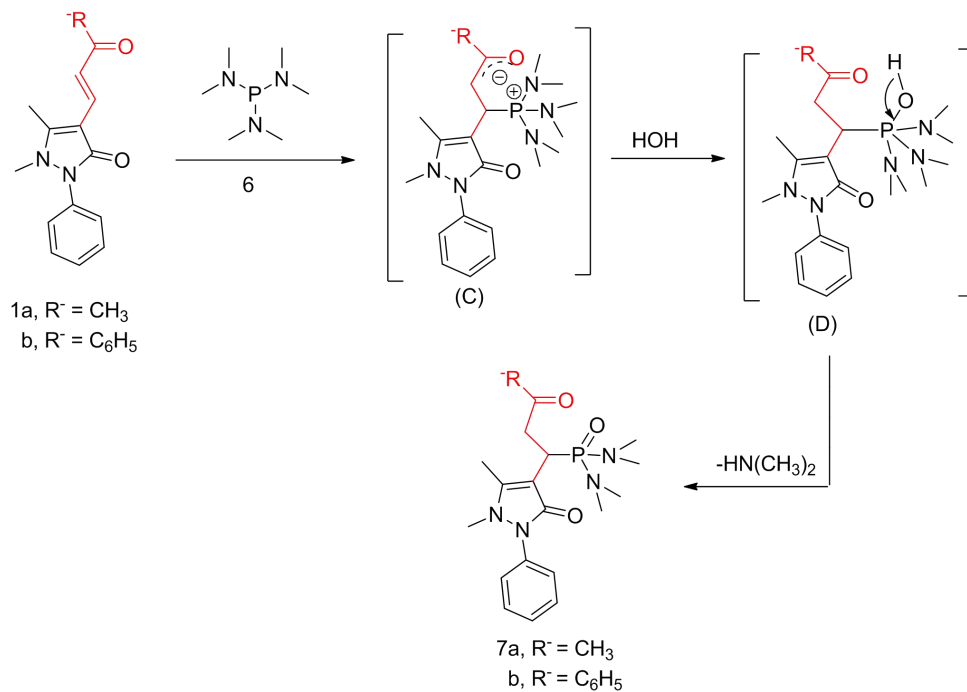
2.1. Chemistry

Reactions of α,β -unsaturated carbonyl compounds with different organophosphorus reagents were studied previously to prepare bioactive compounds for pharmaceutical purposes [18-25]. Moreover, oxobutenylpyrazolone and oxophenylpropenylpyrazolone with alkylphosphites are also discussed for synthesizing chalcone precursors containing phosphonate moiety and screening their antimicrobial activities. Therefore, when 1,5-dimethyl-4-(3-oxobut-1-en-1-yl)-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**1a**) reacts with trimethyl phosphite (**2a**) without solvent in the presence of palladium acetate as a catalyst gave two products **3a** and **4a**. The reaction proceeded *via* nucleophilic attack by **2a** on both carbonyl-C and double C=C of chalcone **1a** to form the intermediate dipolar adduct (A) which undergoes ring closure affords phospholane derivative **3a** [26, 27]. Due to unavoidable moisture the intermediate (A) can be hydrolyzed to form dialkyl phosphonate derivative **4a** through the extrusion of alcohol molecule. Besides, when oxophenylpropenylpyrazolone **1a** was reacted with TAP gave **3b** and **4b** (scheme 1). The chemical structures of **3a** and **4a** were assured using microanalyses and several spectroscopic data.

On the other side, when two α,β -unsaturated compounds **1a** and **1b** reacted with triisopropylphosphite (TIP, **2b**) gave the corresponding **4b** and **4f** respectively. Moreover, the reaction of dialkylphosphites (**5a-c**) and chalcones (**1a,b**) is also studied. When chalcones (**1a,b**) reacted with dimethyl- (**5a**), diethyl- (**5b**) and diisopropylphosphite (**5c**), the corresponding phosphonate derivatives (**4a-f**) were performed (scheme 1). Furthermore, hexamethylphosphinetriamine (**6**) was permitted to react with **1a,b** resulting in the unequivocally formation of **7a,b**, respectively (scheme 2). The phosphonates derivatives **7a,b** were formed through phosphorus atom of the aminophosphine **6** on the most interacting center, the methine carbon of starting materials **1a,b** which results in the formation of the dipolar adduct (C). While the addition of a water molecule (atmospheric moisture) to the intermediate (C) that producing intermediate (D) leads to form final products **7a,b** *via* $\text{HN}(\text{CH}_3)_2$ molecule was expelled.



Scheme 1. Synthesis of dialkyl phosphonate derivatives **3(a,b)**, **4(a-f)** and **5(a-c)**.



Scheme 2. Synthesis of dialkyl phosphonate **7(a,b)**.

2.2 Biological Evaluation

Antimicrobial activity

Table 1. The antimicrobial activity of the new compounds against different tests.

Microorganism	Gram Stain Reaction	Inhibition Clear Zone (mm)													
		Compound No												Reference antibiotics	
		1a	1b	3a	3b	4a	4b	4c	4d	4e	4f	7a	7b	Neomycin	Cycloheximide
<i>Staphylococcus aureus</i>	Positive	0	12	0	13	0	0	24	17	19	20	19	17	29	0
<i>Escherichia coli</i>	Negative	15	12	0	0	0	0	28	0	23	24	0	17	26	0
<i>Candida albicans</i>	Yeast	0	0	0	0	0	0	29	13	21	19	15	18	27	0
<i>Aspergillus niger</i>	Fungus	15	14	14	17	15	0	23	0	0	14	13	0	0	30

In most developing countries, pathogenic bacteria are responsible for the main causes of hazards to public health. Therefore, Starting 5-pyrazolones **1a**, **1b** and all newly synthesized compounds **3a**, **3b**, **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **7a** and **7b** were assessed for antibacterial activities *in vitro* against *Staphylococcus aureus* ATCC 6538-P as G+ve bacteria, *Escherichia coli* ATCC 25933 as G-ve bacteria, *Candida albicans* ATCC 10231 as yeast and *Aspergillus niger* NRRL as filamentous fungus test microbe using cup agar diffusion method in comparison to Neomycin as anti-bacterial drug and cycloheximide as anti-fungal drug and the minimum inhibitory concentrations (MIC) for the more active compounds (**4c-f**) and **7b** were determined, too.

Table 2. Minimum inhibition concentration (MIC) of **4c-f** and **7b** against different test microbes

Sample	<i>Staphylococcus aureus</i> MIC (µg/ml)	<i>Escherichia coli</i> MIC (µg/ml)	<i>Candida albicans</i> MIC (µg/ml)
4c	312.5	156.25	78.12
4e	312.5	78.12	156.25
4f	156.25	156.25	156.25
7b	156.25	156.25	78.12

As shown in Table 1 and 2, the anti-bacterial results showed that all of the tested compounds had moderate to good efficacy against G+ve and G-ve of the pathogenic bacteria and they also showed their inhibition zones. Compound **4c** is potent for *Escherichia coli* with MIC 78.12 (µg/ml) [28, 29] which has activity closely related the two reference antibiotics (Neomycin and cycloheximide) and the other compounds (**4e**, **4f** and **7b**) had a moderate effect with MIC, 156.25 (µg/ml). In case of *Staphylococcus aureus* pathogen, the results of the MIC of these compounds (**4c**, **4f** and **7b**) showed moderate activity (312.5, 312.5, 156.25 and, 156.25 µg/ml, respectively) and the others (**3a**, **b** and **4a**, **b**) are inactive against two types of bacteria. On the other hand, Compounds **4c** and **7b** showed potent antifungal activity against yeast *Candida albicans* with MIC 78.12 (µg/ml). In addition, two compounds **4d** and **4e** revealed a moderate activity valued 156.25 and 156.25 [30] (µg/ml) with *Candida albicans*. In a comparison with the starting materials **1a**, **b**, compound **4c** is the most potent antibacterial pyrazolone derivative due to the presence of isopropyl-group which might be responsible for the activity [31]. On the other side, the most potent antifungal activity related to compounds **4c** and **7b** that contains two *N*-dimethyl groups which enhance the activity of antifungal property [32, 33]. So, the chain length of alkyl group

improves the antimicrobial activity. The potential activities of the new compounds can be controlled by the cell outer layers of these [34] two types of bacteria. Gram (+) bacteria has an inadequate and permeable peptidoglycan layer as their outer barrier. Therefore, drug components can pass through the Gram (+) bacteria's cell wall. However, the cell wall of Gram (-) bacteria are composed of a multilayered peptidoglycan and phospholipidic membrane that is impervious to drug components [35]. Nevertheless, compounds (**4c**, **4e**, **4f** and **7b**) have a good activity against *E. coli* due to their potent structure that docked in the active site.

2.3. DFT study:

Optimized Geometry:

The optimized geometry of novel synthesized structures from **1(a,b)**, **3 (a,b)**, **4 (a-f)** and **7 (a,b)** derivatives were studied in gas phase via B3LYP/ 6-311G (d,p) method. The optimized molecular structures of all compounds were presented in Figure 2.

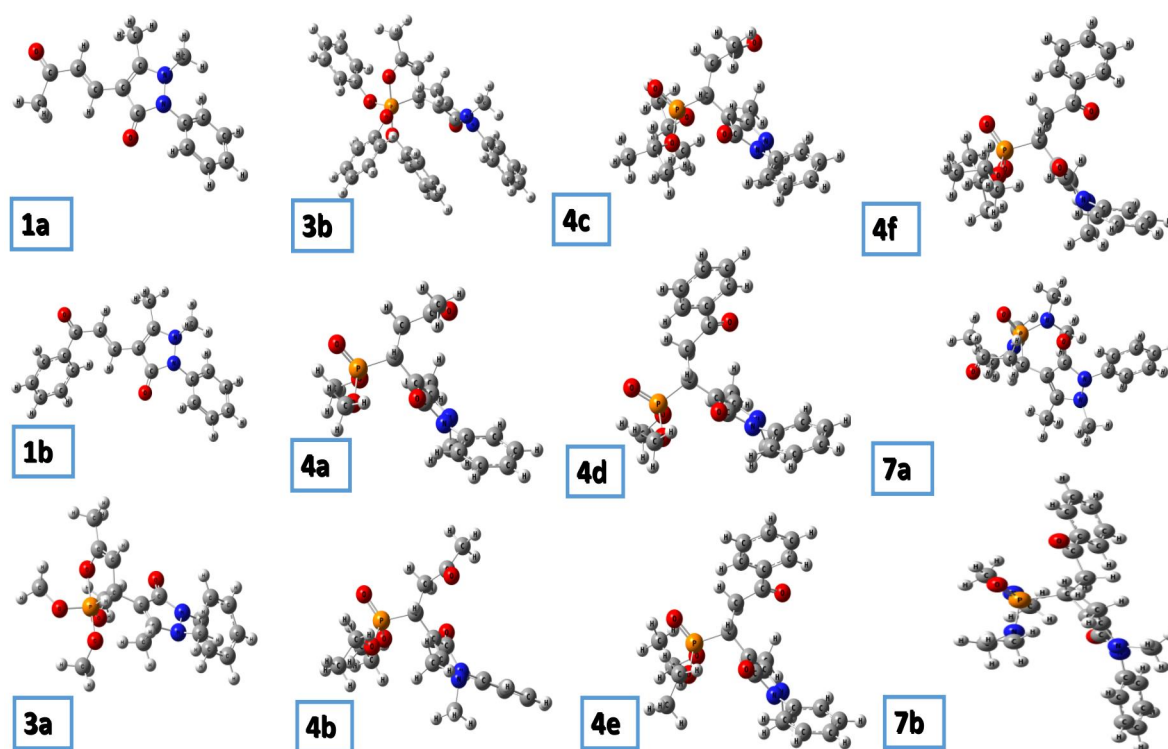


Figure 2. The optimized molecular structure of novel dimethyl-trimethoxy-oxaphosphol-pyrazol-3-one and dimethylpyrazoloxobutylphosphonate derivatives, as a ball-and-stick model colored by atom.

Frontier molecular orbitals and global reactivity descriptors

The structures of all new synthesized compounds have been fully optimized via DFT/B3LYP/6-311G (d,p) level of theory in order to study the electronic behavior of the compounds and hence their chemical reactivity. The highest occupied molecular orbital (HOMO) and the Lowest unoccupied molecular orbital (LUMO) were studied to show the electronic effects properties based on DFT studied in order to evaluate the structural properties of the new compounds [36, 37]. The HOMO is related to the electrons in the outermost orbital and tends to donate electrons, meanwhile the LUMO is the orbital without outermost electrons and tends to gain electrons. The HOMO energy represents ionization energy and the LUMO represents electron activation energy. The energy different between the HOMO and LUMO energies is known as energy gap (ΔE) which represents the chemical reactivity and stability of the compounds. The smaller the band gap the more active will be the compounds. The HOMO and LUMO shapes illustrate the mode of interaction of the synthesized molecules based on electronic

interaction properties which illustrate the intramolecular charge transfer. In the present study the physical descriptors had been detected to illustrate the reactivity of the phosphorus compounds based on the energy of HOMO and LUMO orbitals as shown in figure 2 and their values were presented in table 3.

The HOMOs of starting pyrazolone (**1a** and **1b**) are localized over the whole molecule, meanwhile the LUMO is located at pyrazone moiety. Compound **3a** had the smallest band gap due to complete separation of HOMO and LUMO nodes. The HOMO of **3a** is localized mainly on phosphonate part and the LUMO is over pyrazolone part with destabilization of LUMO and stabilization of HOMO compared with **1a** and **1b**. Although the phenyl group of **3b** leads to stabilize the HOMO and destabilize the LUMO and increasing of the band gap and both HOMO and LUMO were located at pyrazolone-phosphonate moieties. The new class of derivatives from (**4a-4e**), the HOMOs are delocalized over pyrazolone derivatives and the LUMOs were localized over pyrazolone moiety, except for phenyl-R' substituted compounds (**4d-4f**), the LUMOs were located over phenyl group. The band gaps showed values (from 4.11 eV to 5.08) in which HOMOs energies were destabilized and LUMOs energies were stabilized, especially with phenyl-R' substitutions. The phosphor-propanoyl (**7a** and **7b**) derivatives were new classes of compounds that show HOMOs with different circulation figures as both have HOMOs over phosphonates and LUMOs over pyrazolone in case of **7a** and phenyl in case of **7b**. The band gap values are moderated compared to references (**1a** and **1b**) and other phosphorus material (**3a-4f**).

Table 3. Theoretical Energy Calculations and Dipole Moment of the Studied Compounds.

ID	E _{total} (eV)	energy (eV)			I	A	η	S	μ	X
		E _{HOMO}	E _{LUMO}	ΔE						
1a	-841.367	-6.216	-2.174	4.042	6.216	2.174	-2.021	-0.495	-1.587	4.195
1b	-1033.145	-6.206	-2.222	3.985	6.206	2.222	-1.992	-0.502	-1.611	4.214
3a	-4586.465	-5.517	-0.755	4.761	5.517	0.755	-2.381	-0.420	-0.878	3.136
3b	-5242.165	-5.731	-0.901	4.830	5.731	0.901	-2.415	-0.414	-0.950	3.316
4a	-1646.324	-6.074	-0.997	5.077	6.074	0.997	-2.538	-0.394	-0.999	3.536
4b	-1567.667	-5.289	-0.686	4.602	5.289	0.686	-2.301	-0.435	-0.843	2.987
4c	-1646.324	-6.042	-0.981	5.061	6.042	0.981	-2.530	-0.395	-0.990	3.511
4d	-1680.788	5.061	-1.798	4.150	-5.061	1.798	3.429	0.292	-1.399	-1.631
4e	-1759.448	-5.932	-1.790	4.142	5.932	1.790	-2.071	-0.483	-1.395	3.861
4f	-1838.106	-5.928	-1.816	4.112	5.928	1.816	-2.056	-0.486	-1.408	3.872
7a	-1527.871	-5.985	-1.056	4.929	5.985	1.056	-2.465	-0.406	-1.028	3.520
7b	-1719.642	-5.913	-1.634	4.279	5.913	1.634	-2.140	-0.467	-1.317	3.773

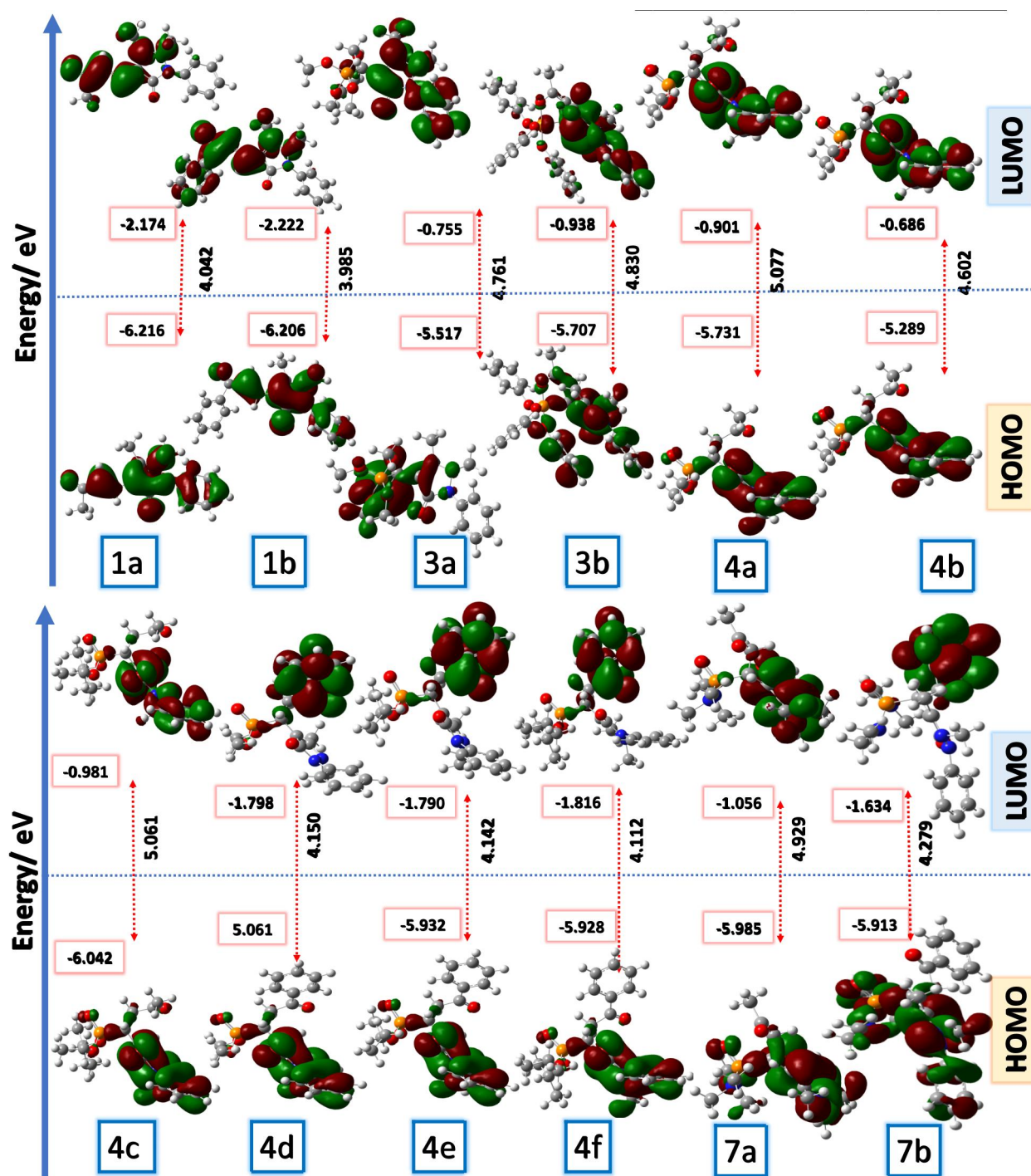


Figure 3. Frontier molecular orbitals for all novel dimethyl-trimethoxy-oxaphosphol-pyrazol-3-one and dimethylpyrazoloxobutylphosphonate derivatives calculated in gas phase at B3LYP/6-311G (d,p) method; Energy level of HOMOs and LUMOs and E_{gap} (ΔE).

Molecular Electrostatic Potential (MEP) Maps

Molecular electrostatic potential (MEP) is a very powerful tool utilized to determine the reactive regions of nucleophilic and electrophilic attacks on a molecular system based on their charge distribution and polarization along with capability of Hydrogen-bond formation. It can be generated by mapping the electrostatic potential on to the isoelectron density surface of the molecule, which gives us the possibility to determine the distribution of the electronic charge over all the structure. Essentially, MEP mapping remains a useful way to give a clear imagination of the system and therefore its interaction with its environment as well as the biological recognition

processes.[38] In the present study, the MEP maps of all compounds show good nucleophilic behavior based on the color map presented in figure 3. The colors denote the reactivity of the region; blue is most positive electrostatic potential, red (represent electrophilic reactivity) > orange > yellow > green > blue (nucleophilic reactivity). From the MEP plots it was presumed that all phosphonate derivative parts showed high electropositive potential (red) and the *N-N* group of pyrazolone possessed slightly low electropositive region (blue). Accordingly, the phosphonate group of all new synthesized compounds support electrophilicity pyrazolone moiety promotes nucleophilicity.

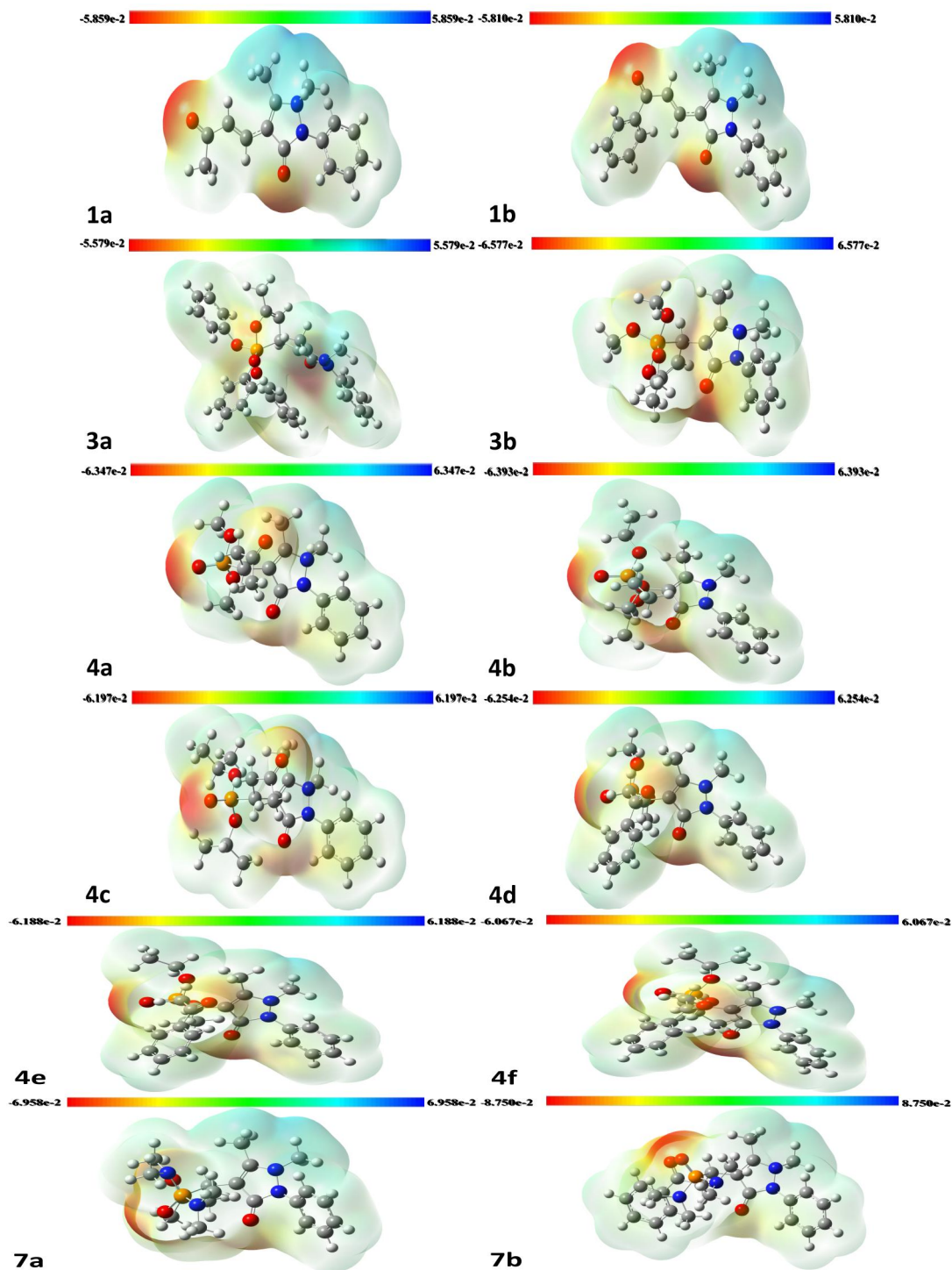
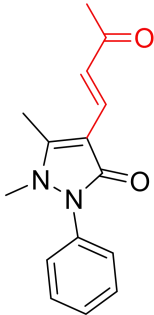
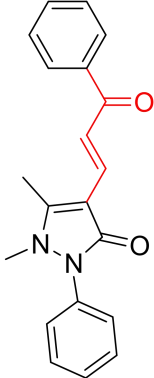
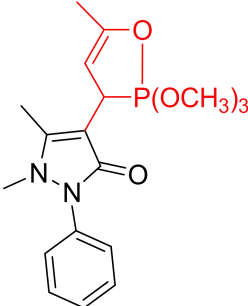


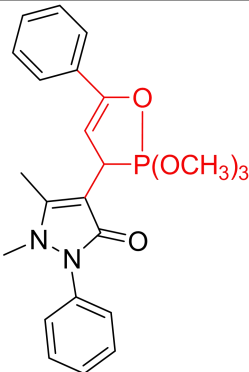
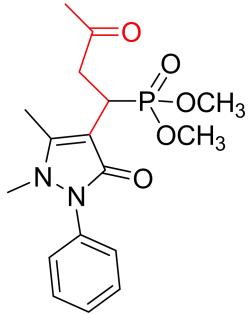
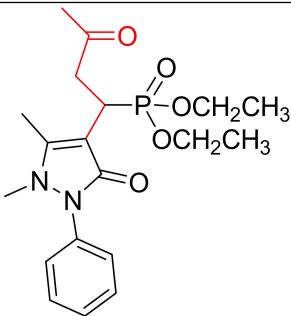
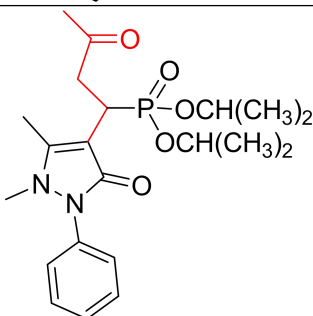
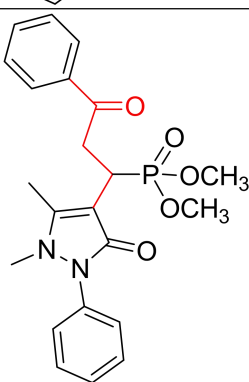
Figure 4. Generated molecular electrostatic potential (MEP) maps of all studied compounds.

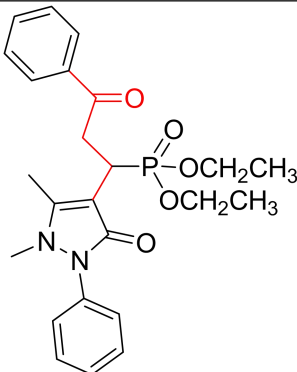
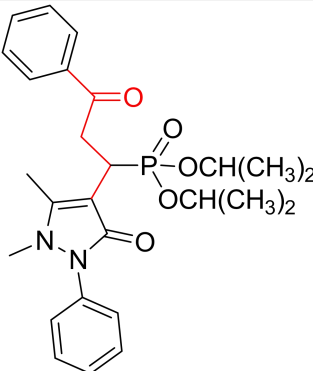
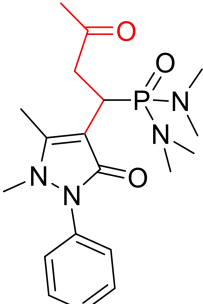
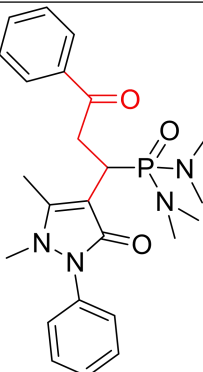
2.4. Molecular docking study

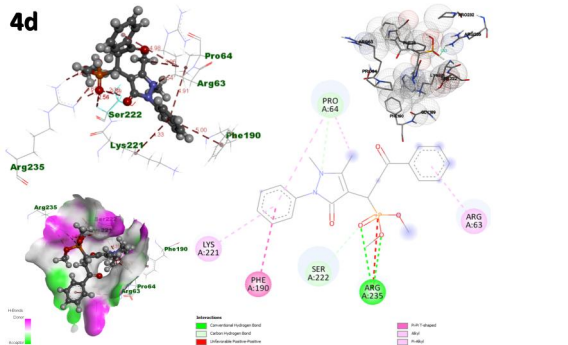
Molecular docking studies were carried out for all the synthesized compounds to evaluate the binding energies with dihydropteroate (DHPS). The dihydropteroate synthase is one of the enzymes involved in the bacterial folate synthesis pathway. The folate synthesis pathway is an essential pathway for synthesizing amino acids.[39, 40] The DHPS had two characteristic binding sites: the first one binds with dihydropterin pyrophosphate (DHPP) and the second one binds with p-amino benzoic acid (pABA).[41, 42] The most important amino acids residues for the first type which interact with protein moiety are (Asp96, Asn115, Asp185, Lys221 and Arg235). Meanwhile, the second serious of amino acids that interact with pABA moiety are (Phe190, Lys221 and Ser222).[43, 44] All the synthesized compounds were found to have strong interaction with the with hydropteroate (DHPS) with inhibition constant range from (4.19-560.27 μM) as shown in table 4. All compounds show H-bond interaction with Arg235 and some Pi-Pi interaction with other amino acids. Except for the high potent compounds **4c**, **4e**, **4f** and **7b**, they have another strong H-bond interaction with Lys221 and more Pi-Pi interactions. This is the reason why their potency as antimicrobial agents were very high compared to other derivatives. The formed H-bonds visualized to oriente with the whole active site as depicted in figure 6.

Table 4. Docking score and binding energy (kcal/mol) of studied ligands with the referent ligand.

No.	Code number	Chemical structure	Binding Energy (μM)	Ki	RMSD
	1a		-6.74	11.47	44.34
	1b		-7.34	4.19	43.10
	3a		-5.9	45.21	41.27

	3b		-7.35	4.11	42.01
	4a		-6.37	21.43	41.80
	4b		-7.16	5.61	43.36
	4c		-6.10	33.78	42.77
	4d		-7.33	4.25	42.70

	4e		-5.41	107.52	45.89
	4f		-4.44	560.27	45.10
	7a		-5.98	41.03	42.99
	7b		-6.79	10.59	43.13



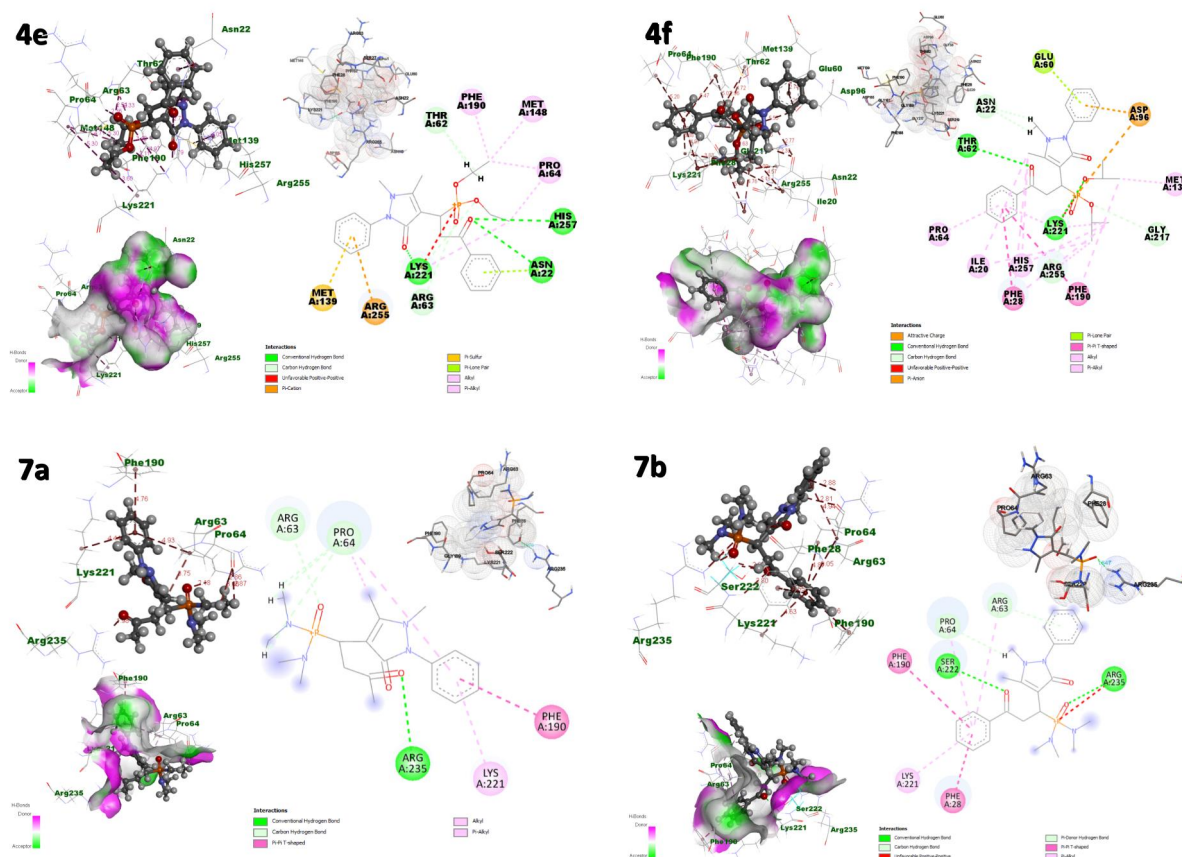


Figure 5. 3D and 2D Docking pose of docked derivatives into DHPS; A: compound 3a (purple), B: compound 3b (pink), C: compound 3c (green) and D: compound 3d (orange). H-Bond interactions shown in green line.

3. Experimental

3.1. Chemistry

Melting points were determined in open glass capillaries using an Electrothermal IA 9100 series digital melting point apparatus (Electrothermal, Essex, UK), and IR spectra were measured as KBr pellets with a PerkinElmer Infrared Spectrophotometer model 157. The ^1H , ^{13}C and ^{31}P NMR spectra were recorded in CDCl_3 or $[\text{d}_6]\text{DMSO}$ as solvents on a Jeol-500 spectrometer (^1H : 500 MHz; ^{13}C : 125 MHz), and the chemical shifts are recorded in δ values relative to TMS as internal reference. The mass spectra were recorded at 70 eV with a Kratos MS equipment or a Varian MAT 311A spectrometer. Elemental analyses were performed using an Elementar Vario E1 instrument. The reported yields are of pure isolated materials obtained by column chromatography on silica gel 60 (Merck).

General experimental

See supplementary file

Solvent-free synthesis of phosphonates

Compounds **1a**, **b** (1 mmol) and phosphorus compounds **2a,b**, **5a-c** and **6** (1.2 mmol) were added to Pd acetate (0.05 g) and the mixture was heated in an oil bath at 50°C . The progress of the reaction was monitored by *TLC*. After the reaction was complete, purification using column chromatography (ethyl acetate/n-hexane) to give **3a,b**, **4a-f** and **7a,b**.

1,5-Dimethyl-4-(2,2,2-trimethoxy-5-methyl-2,3-dihydro-1,2-oxaphosphol-3-yl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (3a)

This product was isolated from column chromatography using petroleum ether $60-80^\circ\text{C}$ / ethyl acetate (70: 30 v/v) as an eluent, pale yellow crystals, yield 25%, m.p: $141-143^\circ\text{C}$. IR (KBr, cm^{-1}): $\tilde{\nu} = 1681$ ($\text{C}=\text{O}$, pyrazolone), 991 ($\text{P}-\text{OCH}_3$). ^1H NMR (500 MHz, $\text{d}_6\text{-DMSO}$, δ , ppm): 7.28- 7.48 (m, 5 H, H-arom.), 4.18 (d, 1H, CH), 3.66-3.43 (m, 10 H, 3 OCH_3 + CH), 3.10 (s, 3 H, N- CH_3), 2.14 (s, 3H, CH_3), 1.18 (d, 3 H, O-C- CH_3). ^{13}C NMR (125

MHz, d_6 -DMSO, δ , ppm): 163.97 (C=O), 135.80-124.29 (arom. -C), 53.85 (OCH₃), 36.12 (*N*-CH₃), 14.84 (CH₃), 11.98 (CH₃). ³¹P NMR (200 MHz, d_6 -DMSO, δ , ppm): 33.27. MS (EI, 70 eV): *m/z* (%): 378 [M-2H]⁺, 3]. Anal. Calcd. for C₁₈H₂₅N₂O₅P (380.38). Calcd: C, 56.84; H, 6.62; N, 7.36; P, 8.14. Found: C, 56.77; H, 6.56; N, 7.31; P, 8.03.

1,5-Dimethyl-4-(2,2,2-trimethoxy-5-phenyl-2,3-dihydro-1,2-oxaphosphol-3-yl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (3b)

This product was isolated from column chromatography using pet.ether 60-80/ ethyl acetate (70: 30 v/v) as an eluent, pale yellow crystals, yield 25%, m.p: 214-216 °C. IR (KBr, cm⁻¹): $\tilde{\nu}$ = 1619 (C=O, pyrazolone), 1010 (P-OCH₃). ¹H NMR (500 MHz, d_6 -DMSO, δ , ppm): 8.04 - 7.35 (m, 10 H, H-arom.), 4.10 (d, 1H, CH), 3.21 (s, 10 H, 3 OCH₃ + CH), 3.21 (s, 3 H, *N*-CH₃), 2.47 (s, 3H, CH₃), 1.20 (s, 3 H, O-C-CH₃). ¹³C NMR (125 MHz, d_6 -DMSO, δ , ppm): 167.74 (C=O), 132.25-128.39 (arom.-C), 65.54 (OCH₃), 39.91 (*N*-CH₃), 19.18 (CH₃), 14.05 (CH₃). MS (EI, 70 eV): *m/z* (%) 441 [M-H]⁺, 1]. Anal. Calcd. for C₂₃H₂₇N₂O₅P (442.44). Calcd: C, 62.44; H, 6.15; N, 6.33; P, 7.00. Found: C, 62.36; H, 6.10; N, 6.28; P, 6.92

Dimethyl(1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-oxobutyl)phosphonate (4a)

This product was isolated from column chromatography using pet.ether 60-80/ ethyl acetate (70: 30 v/v) as an eluent, pale yellow crystals, yield 25%, m.p: 156-158 °C. IR (KBr, cm⁻¹): $\tilde{\nu}$ = 1743 (C=O, pyrazolone), 1589 (C=O, broad), 1238 (P=O), 1103 (P-OCH₃). ¹H NMR (500 MHz, DMSO- d_6 , δ , ppm): 7.45 - 7.25 (m, 5 H, H-arom.), 3.70-3.35 (m, 8 H, 2 OCH₃+CH₂), 3.29 (m, 1H J_{HP}= 10 Hz, CH-P), 2.99 (s, 3 H, *N*-CH₃), 2.25 (s, 3H, CH₃), 2.04 (s, 3 H, O-C-CH₃). ¹³C NMR (125 MHz, d_6 -DMSO, δ , ppm): 205.38 (CH₃-C=O), 164.51 (C=O), 129.17-123.65 (arom.-C), 53.06 (OCH₃), 36.11 (*N*-CH₃), 30.30 (CH₃), 11.99 (CH₃). ³¹P NMR (200 MHz, d_6 -DMSO, δ , ppm): 21.03. MS (EI, 70 eV): *m/z* (%) 365 [M-H]⁺, 2]. Anal. Calcd. for C₁₇H₂₃N₂O₅P (366.35). Calcd: C, 55.73; H, 6.33; N, 7.65; P, 8.45. Found: Calcd: C, 55.67; H, 6.28; N, 7.59; P, 8.38.

Diethyl(1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-oxobutyl)phosphonate (4b)

This product was isolated from column chromatography using pet.ether 60-80/ ethyl acetate (50: 50 v/v) as an eluent, colorless crystals, yield 25%, m.p:120-122 °C. IR (KBr, cm⁻¹): $\tilde{\nu}$ =1720 (C=O, pyrazolone), 1592 (C=O), 1181(P=O), 1118 (P-O-CH₂). ¹H NMR (500 MHz, d_6 -DMSO, δ , ppm): 7.97 - 6.98 (m, 5 H, H-arom.), 3.96 (q, 4 H, CH₂CH₂-O-), 3.06-1.93 (m, 12 H, CH-P + CH₂+ *N*-CH₃+2 CH₃), 1.14 (t, 6H, CH₃CH₂-O-). ¹³C NMR (125 MHz, d_6 -DMSO, δ , ppm): 195.42 (CH₃-C=O), 149.87 (C=O), 133.42-127.71 (arom.-C), 64.01 (CH₃CH₂-O-), 42.8 (*N*-CH₃), 39.5 (O=C-CH₃), 25.30 (CH₃), 10.58 (CH₃CH₂-O-). MS (EI, 70 eV): *m/z* (%) 395 [M+H]⁺, 21]. Anal. Calcd. for C₁₉H₂₇N₂O₅P (394.40). Calcd: C, 57.86; H, 6.90; N, 7.10; P, 7.85. Found: C, 57.75; H, 6.85; N, 6.95; P, 7.72.

Diisopropyl(1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-oxobutyl) phosphonate (4c)

This product was isolated from column chromatography using pet.ether 60-80/ ethyl acetate (85: 15 v/v) as an eluent, pale yellow crystals, yield 25%, m.p: 236-238 °C. IR (KBr, cm⁻¹): $\tilde{\nu}$ =1635 (C=O, pyrazolone), 1592 (C=O, broad), 1222 (P=O), 1022 (P-O-CH). ¹H NMR (300 MHz, d_6 -DMSO, δ , ppm): 7.40 - 7.22 (m, 5 H, H-arom.), 4.51-4.53 (m, 2 H, 2 CH, isopropyl), 3.31-2.90 (m, 6 H, *N*-CH₃ + CH-P + CH₂), 2.36 (s, 3H, CH₃), 2.21 (s, 3 H, O-C-CH₃), 1.22-1.18 (m, 12 H, 4 CH₃, isopropyl). ¹³C NMR (125 MHz, d_6 -DMSO, δ , ppm): 183.85 (CH₃-C=O), 161.51 (C=O), 134.05-120.36 (arom.-C), 70.22 (-CH(CH₃)₂), 60.32 (CH₂), 33.19 (*N*-CH₃), 28.06 (O=C-CH₃), 23.84 (4 CH₃, isopropyl), 10.34 (CH₃). MS (EI, 70 eV): *m/z* (%) 422 [M]⁺, 8]. Anal. Calcd. for C₂₂H₃₁N₂O₅P (422.46). Calcd: C, 59.70; H, 7.40; N, 6.63; P, 7.33. Found: C, 59.64; H, 7.37; N, 6.55; P, 7.27.

Dimethyl(1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-oxo-3-phenylpropyl)phosphonate (4d)

This product was isolated from column chromatography using pet.ether 60-80/ ethyl acetate (85: 15 v/v) as an eluent, pale yellow crystals, yield 25%, m.p: 145-147 °C. IR (KBr, cm⁻¹): $\tilde{\nu}$ = 1639 (C=O, pyrazolone), 1592 (C=O), 1006 (P-OCH₃), 1295 (P=O). ¹H NMR (500 MHz, d_6 -DMSO, δ , ppm): 7.88 - 7.25 (m, 10 H, H-arom.), 4.22-4.17 (m, 1 H, CH), 3.52 (d, 8 H, (P-O-CH₃)₂), J_{CP}= 15 Hz + CH₂), 3.03 (s, 3H, *N*-CH₃), 2.47 (s, 3 H, CH₃). ¹³C NMR (125 MHz, d_6 -DMSO, δ , ppm): 184.24 (Ph-C=O), 161.09 (C=O), 136.09-127.44 (arom.-C), 67.26 (P(OCH₃)₂), 33.10 (*N*-CH₃), 25.3 (CH₃). MS (EI, 70 eV): *m/z* (%) 396 [M-CH₃OH]⁺, 23]. Anal. Calcd. for C₂₂H₂₅N₂O₅P (428.42). Calcd: C, 61.68; H, 5.88; N, 6.54; P, 7.23. Found: C, 61.55; H, 5.81; N, 6.49; P, 7.12.

Diethyl(1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-oxo-3-phenylpropyl)phosphonate (4e)

This product was isolated from column chromatography using pet.ether 60-80/ ethyl acetate (50: 50 v/v) as an eluent, colorless crystals, yield 25%, m.p: 106-108 °C. IR (KBr, cm⁻¹): $\tilde{\nu}$ = 1639 (C=O, pyrazolone), 1589 (C=O), 1261 (P=O), 1110 (P-OCH₂). ¹H NMR (300 MHz, d_6 -CDCl₃, δ , ppm): 7.71 - 6.98 (m, 10 H, H-arom.), 4.24-2.35 (m, 10 H, 2 CH₃CH₂-O- + CH₂+CH-+*N*-CH₃), 1.20 (t, 6 H, 2 CH₃CH₂-O-). ¹³C NMR (125 MHz, d_6 -DMSO, δ , ppm): 213.48 (Ph-C=O), 167.45 (C=O), 132.84-127.89 (arom.-C), 67.68, 38.30 (3 CH₂), 35.53 (*N*-

CH₃), 22.43 (CH₃) 11.27, 14.40 (2 O-CH₂-CH₃) MS (EI, 70 eV): m/z (%): 456 [M]⁺, 52]. Anal. Calcd. for C₂₄H₂₉N₂O₅P (456.47). Calcd: C, 63.15; H, 6.40; N, 6.14; P, 6.79. Found: C, 63.06; H, 6.32; N, 6.09; P, 6.68
Diisopropyl(1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-oxo-3-phenylpropyl) phosphonate (4f)

This product was isolated from column chromatography using pet.ether 60-80/ ethyl acetate (85: 15 v/v) as an eluent, pale yellow crystals, yield 25%, m.p: 280-282°C. IR (KBr, cm⁻¹): $\tilde{\nu}$ = 1681(C=O, pyrazolone), 1619 (C=O), 1207 (P=O), 1099 (P-O-CH). ¹H NMR (500 MHz, *d*₆-DMSO, δ , ppm): 7.40 - 7.22 (m, 10H, H-arom.), 4.51-4.53 (m, 2 H, 2 CH, isopropyl), 3.31-2.90 (m, 6 H, *N*-CH₃ + CH-P + CH₂), 2.36 (s, 3H, CH₃), 1.22-1.18 (m, 12 H, 4 CH₃, isopropyl). ¹³C NMR (125 MHz, *d*₆-DMSO, δ , ppm): 198.16 (Ph-C=O), 163.97 (C=O), 136.79-123.94 (arom.-C), 76.95 (-CH(CH₃)₂), 71.19 (CH₂), 35.53 (*N*-CH₃), 23.81 (4 CH₃, isopropyl), 11.50 (CH₃). MS (EI, 70 eV): m/z (%): 483 [M-H]⁺, 100]. Anal. Calcd. for C₂₆H₃₃N₂O₅P (484.52). Calcd: C, 64.45; H, 6.86; N, 5.78; P, 6.39. Found: C, 64.28; H, 6.77; N, 5.66; P, 6.29.

3-[Bis(dimethylamino)phosphoryl]-3-(2-phenyl-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazol-4-yl)propanoyl methane (7a)

This product was isolated from column chromatography using pet.ether 60-80/ ethyl acetate (85: 15 v/v) as an eluent, pale yellow crystals, yield 25%, m.p: 128-130 °C. IR (KBr, cm⁻¹): $\tilde{\nu}$ = 1720.(C=O, pyrazolone), 1592 (C=O), 1311, 755 (P-*N*(CH₃)₂), 1184 (P=O). ¹H NMR (500 MHz, *d*₆-DMSO, δ , ppm): 7.39 - 7.20 (m, 5 H, H-arom.), 2.48-2.24 (m, 23 H, 5 *N*-CH₃+ CO-CH₃ + CH₂-C-CH₃), 3.25 (d, 1 H, CH). MS (EI, 70 eV): m/z (%) 392 [M]⁺, 1]. Anal. Calcd. for C₁₉H₂₉N₄O₃P (392.43). Calcd: C, 58.15; H, 7.45; N, 14.28; P, 7.89. Found: C, 57.99; H, 7.38; N, 14.18; P, 7.78.

3-[Bis(dimethylamino)phosphoryl]-3-(2-phenyl-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazol-4-yl)propanoyl benzene (7b)

This product was isolated from column chromatography using pet.ether 60-80/ ethyl acetate (85: 15 v/v) as an eluent, pale yellow crystals, yield 25%, m.p: 151-153 °C. IR (KBr, cm⁻¹): $\tilde{\nu}$ = 1781 (C=O, pyrazolone), 1673 (C=O), 1353, 744 (P-*N*(CH₃)₂), 1245 (P=O). ¹H NMR (500 MHz, *d*₆-DMSO, δ , ppm): 7.65-7.22 (m, 10 H, H-arom.), 2.92-2.10 (m, 21 H, 5 *N*-CH₃+ CH₃ + CH₂ + CH). ¹³C NMR (125 MHz, *d*₆-DMSO, δ , ppm): 203.88 (Ph-C=O), 164.08 (C=O), 134.71-125.90 (arom.-C), 35.16-25.36 (P(*N*-CH₃)₃+ CH₂), 12.06 (CH₃). MS (EI, 70 eV): m/z (%) 423 [M-CH₃NH₂]⁺, 3]. Anal. Calcd. for C₂₄H₃₁N₄O₃P (454.50). Calcd: C, 63.42; H, 6.87; N, 12.33; P, 6.81. Found C, 63.33; H, 6.81; N, 12.27; P, 6.75.

3.2. Methodology antimicrobial

The antimicrobial activity of the synthesized compounds was assessed against *Staphylococcus aureus* ATCC 6538-P as G+ve bacteria, *Escherichia coli* ATCC 25933 as G-ve bacteria, *Candida albicans* ATCC 10231 as yeast and *Aspergillus niger* NRRL as filamentous fungi test microbe using cup agar diffusion method. Samples were prepared by dissolving 5mg in 2ml of DMSO. Nutrient agar plates were used in case of bacterial and yeast test microbes whereas potato dextrose plates were used in case of fungal test microbe. Each plate was inoculated with 0.1ml of 10⁵cells/ml from each microbial stock. Then plates were kept at low temperature (4°C) for 2-4 hours to allow maximum diffusion. The plates were incubated at 37°C for 24 hours for bacteria and at 30°C for 48 hours for the fungus in upright position to allow maximum growth of the organisms. The antimicrobial activity of the test agent was measured by detecting the diameter of zone of inhibition expressed in millimeter (mm). The experiment was carried out more than once and the reported mean was recorded.

Determination of minimum inhibitory concentration (MIC) of tested compounds

Staphylococcus aureus ATCC 6538 (G+ve bacteria), *Escherichia coli* ATCC 25933 (G-ve bacteria) and *Candida albicans* ATCC 10231 were cultivated on nutrient broth medium. Cell pellets were collected by centrifugation under sterile condition after cultivating the test microbes for 24h. Cells were resuspended in sterile normal saline with optical density of 0.5 to 1.0 giving actual CFU number of about 10⁶ cell/ml. Resazurin solution was prepared (675 mg in 40 mL of sterile distilled water) and sterilized by filtration through membrane filter (pore size 0.22μm). 100 μL of the broth culture was distributed in all wells of the plate then 100 μL stock concentration of 2.5mg/mL from each purified compound was pipetted into the first row of the plate and then two fold dilution has been done up to tenth dilution. 10μL of resazurin indicator solution was added to each well and 10μL of bacterial suspension (10⁶cfu/mL) was added to each well. The plates were incubated at 37°C for 24 h. The colour change was then assessed visually. Any colour changes from purple to pink or colourless were recorded as positive. The lowest concentration at which colour change occurred was taken as the MIC value.

3.3. Computational Procedure:

DFT calculations

The current investigation discussed the optimization of novel dimethyl-trimethoxy-oxaphosphol-pyrazol-3-one and dimethylpyrazoloxobutylphosphonate derivatives using gaussian 16 program [45] for all computations. All the chemical structures from **1(a,b)**, **3 (a,b)**, **4 (a-f)** and **7 (a,b)** have been optimized using the B3LYP/6-311G(d,p) functional.[46-48] All compounds were in their minima with absence of imaginary frequency. Frontier molecular orbitals had been studied in the ground state to describe the electronic structural behavior of the synthesized compounds. Electrostatic potential maps[49] were analyzed to identify the interaction points of the compounds.

DFT based parameters such as, energy of HOMO (E_H), energy of LUMO (E_L), band gap (ΔE), absolute softness (S)[50]; which indicate the capability of the composite to form a covalent bonds, global hardness (η); that related to the struggle of the system to exchange electronic charge with the environment, electrophilicity index (ω); which describes how does the stabilization energy of a given system affected via gains an additional electronic charge from the surrounding, nucleophilicity index (N); that is the inverse of the electrophilicity, ($1/\omega$), chemical potential (μ); that regulates the tendency of the electrophile to accept more electronic charge, and are all calculated via DFT calculations.[51-53]

$$\Delta E = E_{LUMO} - E_{HOMO} \quad (1)$$

$$I = -E_{HOMO} \quad (2)$$

$$A = -E_{LUMO} \quad (3)$$

$$\eta = (E_{HOMO} - E_{LUMO})/2 \quad (4)$$

$$\sigma = 1/\eta \quad (5)$$

$$\mu = -(I + A)/2 \quad (6)$$

$$X = (I + A)/2 \quad (7)$$

Where, E_{HOMO} and E_{LUMO} represent the energies of HOMO and LUMO, respectively and ΔE , is the band gap.

Molecular docking study

The starting protein geometry of DHPS (Dihydroptorate Synthase of *Versinia pestis*, PDB ID 3TZF) was retrieved from the RCSB protein data bank (<http://www.pdb.org>) and following the next step to dock all the target geometry.

Ligand preparation

- The optimized geometry obtained from gaussian was prepared using discovery studio along with the protein structure downloaded from protein data bank. Hydrogen and Gastegier charges were added for the ligand.

Protein preparation

- The structure of Dihydroptorate (PDB ID: 3TZF) was obtained from the RCSB protein Data Bank (<https://www.rcsb.org/>). Discovery studio was used to identify and visualize the active compounds with protein. All the heteroatoms were removed and isolated from the 3TZF.pdb, to ensure that the receptor is free from any ligands before docking and hydrogen atoms were added to the typical geometry before docking. The solvent molecules in the protein were removed, hydrogen atoms, and Kollmann charges were added automatically via AutoDock software.

Receptor grid generation:

- A grid was generated using the Auto Dock 4.0 by selecting the active site residues in the protein (PDB ID: 3TZF).

Docking using AutoDock

- The interaction mode of all new synthesized compounds and were predicted in the active site of 3TZF through rigid docking using AutoDock v 4.0. The compounds were docked to the receptor using the default settings of the Lamarckian genetic algorithm. After docking, the individual binding conformations of each ligand were observed, and the interactions with the protein were studied. The best and the most energetically favorable conformation of each compound were selected based on the fitness function that was optimized by the genetic algorithm. The results of the docking studies were quantified in terms of the binding energy (kcal/mol). The predicted binding free energy was used as criteria for ranking the compounds.

4- Conclusion

The present study is considered an interesting approach to the synthesis of organophosphonate derivatives through the reaction of α , β -unsaturated compounds **1a,b** with alkyl phosphites (**2a,b** and **5a-c**) and phosphorus triamide **6**. When substrates **1a,b** reacted with trimethyl phosphite **2a** gave two products **3a,b** and **4a,b**. But in case of the reaction of **2b** and dialkyl phosphites **5a-c**, gave the corresponding organophosphonate derivatives **4c-f**. Moreover, tris(dimethylamino)-phosphine **6** can react with the same starting materials **1a,b** to give bis(dimethylamino)-phosphorylpropanoylethane and bis(dimethylamino)phosphoryl propanoylebenzene **7a,b** respectively. Furthermore, the newly synthesized compounds **4c**, **4e**, **4f** and **7d** are screened as antibacterial, antifungal and they showed a good activity. Using DFT protocol study, HOMO-LUMO gaps and various chemical reactivity descriptors have been studied and explain the reactivity of the compounds. The results showed that compounds **4e** and **4f** have a good chemical reactivity. The electrostatic potential mapped was discussed to show the predicted site for both electrophilic and nucleophilic attack which influence antimicrobial activity. Moreover, the docking studies had been done to support the experimental hypothesis for all target compounds which agreed with their detected antimicrobial and antifungal by means of good binding energy and inhibition constant. High docking score and more interaction was observed for **4e**, **4f** and **7b** indicated the high potency compared with the reference compound.

Declaration of Interest

No known competing of interests (financially and non- financially) or personal relationships influencing the reported work were declared by the authors in this paper.

Consent to participate

Not applicable

Consent for publication

Not applicable

Data Availability

Data is provided within the supplementary information files

Competing interests

No known competing interests (financially and non- financially) or personal relationships influencing the reported work were declared by the authors in this paper.

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Authors' contributions

Mansoura A. Abd-El-Maksoud, contributed to the preparation of newly designed organic compounds, writing the manuscript, and communicating with journals for publishing the manuscript. **Basma Ghazal**, Docking and DFT study, writing the manuscript. **Mohamed S. Abdel-Aziz**, contributed in antimicrobial activity for the newly prepared compounds and writing the manuscript. **Marwa El-Hussieny**, contributed the preparation of new designed organic compounds, writing the manuscript and communicates with journals for publishing the manuscript

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