

Design, Green Synthesis, Molecular Docking, Anti-inflammatory and Antioxidant Effect of a New Drug

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ABSTRACT

This work has been devoted to the synthesis of α -hydroxyphosphonates derivative by two methods: classical and microwave method the physicochemical characterization of this molecule was carried out by the spectroscopic methods (UV-vis, and IR). The anti-inflammatory effect of our molecule was evaluated in silico using a molecular docking of our molecule with JAK1 and JAK2. The antioxidant effect was evaluated in silico using a molecular docking of our molecule with PRDX5. Lipinski's rules, absorbance and toxicity of our molecule were compared with two types of drugs. This study allowed it was concluded that the resulting compound has significant anti-inflammatory and antioxidant activity.

Keywords: Microwave Radiation, Electromagnetic Spectrum, Green Chemistry, α -hydroxyphosphonates, JAK1, JAK2, Anti-inflammatory Activity, Antioxidant Activity.

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Abbreviations

JAK1 and 2: Protein Janus kinase 1 and 2.

PRDX5: Peroxiredoxin 5.

DH4NPMP: Diethyl [hydroxy(4-nitrophenyl) methyl] phosphonate.

ASA: Ascorbic Acid.

MOE: Molecular Operating Environment.

Introduction

Phosphonates are among the most important chemical substances for man in his daily life, they are widely used in different fields, notably in the pharmaceutical industry particularly as effective drugs against cancer, aids and inflammatory diseases and in the food industry, in corrosion inhibition, in catalysis, water treatment. The α -hydroxyphosphonates in particular are considered an important class of phosphonates, their structures are similar to that of amino acids. Are low toxicity and biologically active compounds. Recently,

the synthesis of α -hydroxyphosphonate derivatives has attracted significant attention owing to their role as promising precursors in organophosphorus compound synthesis and the formation of organometallic complexes α -hydroxyphosphonates have also piqued considerable interest due to their demonstrated potent biological activities. These compounds exhibit a broad spectrum of captivating and valuable properties, making them appealing for applications in pharmaceutical chemistry as antibiotic, antiviral and anticancer agents. Additionally, α -hydroxyphosphonates were used as active ingredients in pesticides and herbicides. One of the current primary challenges is the development of synthetic methods that are environmentally friendly, aiming to design green chemical transformations and clean technologies. Discovery of a new effective is a costly and time-consuming process. The

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cost of success is very high because many drug candidates fail. One of the possibilities to reduce costs and improve efficiency in current drug discovery processes is to use computer-aided drug design. The objective of our work is the synthesis of new α -hydroxyphosphonate derivatives by the conventional method and by microwave irradiation, its identification by different methods of physico-chemical analysis and subsequent demonstration of its anti-inflammatory and antioxidant activity in Silico and in vitro. In order to prepare the product, we use a reflux assembly reaction, for this reaction we need these essential products: Chloride of cobalt hexahydrate; 4-nitrobenzaldehyde; diethylphosphite and dichloroethane. In an Erlenmeyer flask we mix (0.5 g) of Chloride of cobalt hexahydrate then we add 0.97 g of 4-nitrobenzaldehyde; 3 ml of dichloroethane then 1.3 ml of diethylphosphite. The mixture is stirred strongly at a temperature of 60°C under a N₂ atmosphere, leave it for 48 hours and you will notice its color changing to a blue and we stop the reaction. During the past fifteen years there is a tremendous growth and efforts to prepare organic, inorganic and organometallic compounds via green chemical approach. Green chemistry efficiently utilizes natural resources (ideally renewable ones), removes waste, and keep away from the use of hazardous or toxic reagents and solvents. In the best of situations, reaction times have been lowered from hours or days to minutes. The goal of the current investigation was to clarify the meaning, mechanism, and potential significance of microwave-assisted phosphonate synthesis. Microwave activation results from two contributions [1-4]: One of purely thermal origin resulting from molecular agitation caused by the reversal of dipoles with alternations of the electric field [5]. Microwave irradiation heating developed in the field of organic synthesis from the work of Gedye and Giguere in 1986 [6-8].

Microwave technology was applied to the synthetic reaction to shorten the reaction time and increase the yields of Diethyl [Hydroxy (4-nitroPhenyl) Methyl] Phosphonate derivatives. As expected, when the mixture of diethylphosphite and 4-nitrobenzaldehyde in dichloromethane was irradiated with microwaves, the reaction was completed in 3 to 4 min with higher yields compared with the conventional mode of heating.

Materials and Methods

The UV-Vis spectrum of the DH4NPMP was measured at room temperature in the range 200-900 nm in distilled water using a JASCO V680 spectrometer. Infrared spectrum was recorded using a FT-IR 4200 JASCO spectrometer, in the wavenumber range 600-4000cm⁻¹, at room temperature. The basic principle behind the heating in a microwave oven resides to the interaction of the charged particles of the reaction material with electromagnetic waves of particular frequency. The phenomena of producing heat by electromagnetic irradiation are either by collision or by conduction, sometimes even by both [1].

The figure1 show the mechanism of heating process in conventional and microwave process.

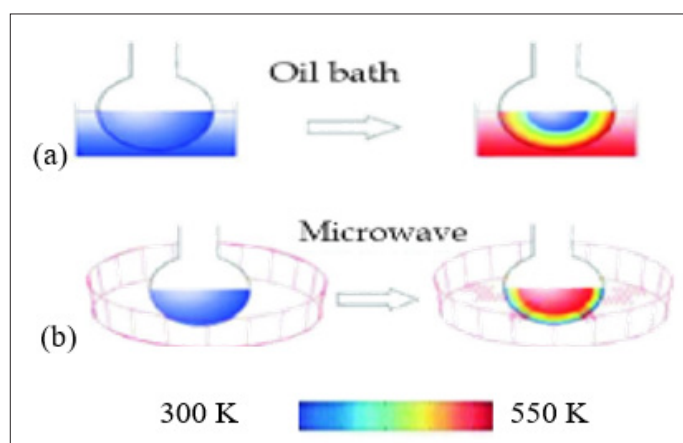


Figure1: Mechanism of heating process.

- (a): In the oil bath heated tube, the reaction mixture in contact with vessel wall. Vessel wall is heated first.
(b): Microwave irradiation raises the temperature of whole volume of reaction mixture as the figure above shows.

This study was conducted on a computer equipped with 16 GB RAM, an Intel i7-7600U processor (2.8 GHz) with Radeon™ Graphics, running a 64-bit operating system. Molecular modeling and docking studies were performed using the Molecular Operating Environment (MOE) software developed by Chemical Computing Group. Additional software, including ChemDraw for molecular structure construction and Gaussian 09 for molecular optimization, was used to support the computational analysis. The study also utilized scientific databases, which are systems designed to store, organize, and manage large amounts of structured data, facilitating efficient data retrieval, analysis, and management. Two types of protein are used in this work, Janus kinase 1 (JAK1, PDB code: 6BBU) is a human tyrosine kinase involved in cytokine signaling through the JAK/STAT pathway, regulating immune and cellular responses, and Janus kinase 2 (JAK2, PDB code: 3EYH) regulates several signaling pathways, particularly those involved in inflammatory and immune responses.

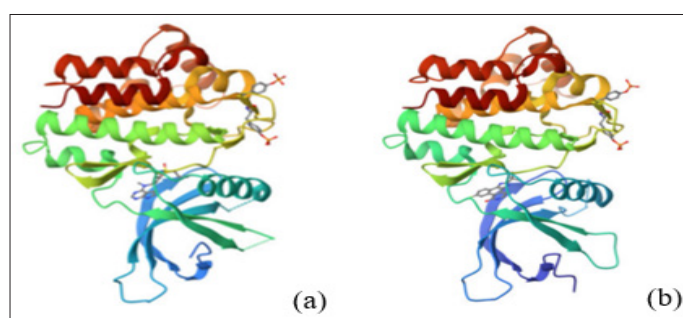


Figure 2: Simplified model of the crystal structure of (a) JAK1 and (b) JAK2 proteins.

Results/Discussion

Diethyl [hydroxy(4-nitrophenyl) methyl] phosphonate (DH4NPMP) was synthesized by reacting 4-nitrobenzaldehyde and diethyl phosphite in the presence of CoCl₂·6H₂O as a catalyst under a nitrogen atmosphere. The reaction was carried out at room temperature, and a blue color appeared after 48 hours, indicating product formation. Reaction progress was monitored by thin-

layer chromatography (TLC), and the catalyst was removed by filtration after adding dichloroethane. The organic phase was purified, dried with MgSO_4 , and evaporated under vacuum, yielding the final product with a 64% yield. DH4NPMP was synthesized in the same condition under microwave irradiation. A blue color appeared after 3 minutes, and the reaction progress was monitored by thin-layer chromatography (TLC) on silica gel with an 80% yield. The product was purified following the same procedure used for the classical synthesis method.

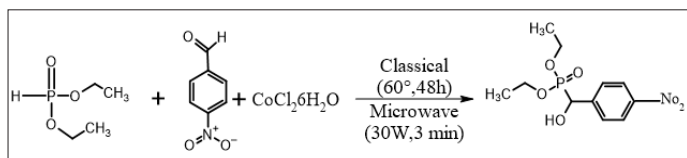


Figure 3: DH4NPMP synthesis scheme.

To plot the IR spectrum of DH4NPMP we used the standard program Origin 18, and was illustrated in figure 4. Their characteristic absorption bands and their assignments are collected in table 1. The IR spectrum of the DH4NPMP molecules shows the disappearance of the absorbance band located at 1705cm^{-1} correspond to the vibrations modes of $\nu(\text{C}=\text{O})$ characteristic of aldehyde. The appearance of a broad average band at 3284cm^{-1} characteristics of hydroxyl group and the appearance of the vibration bands $\nu(\text{P}=\text{O})$, $\nu(\text{P}-\text{O})$ and $\nu(\text{C}-\text{P})$ are located at 1203cm^{-1} , 1024cm^{-1} and 987cm^{-1} respectively, characteristic of the phosphonate group.

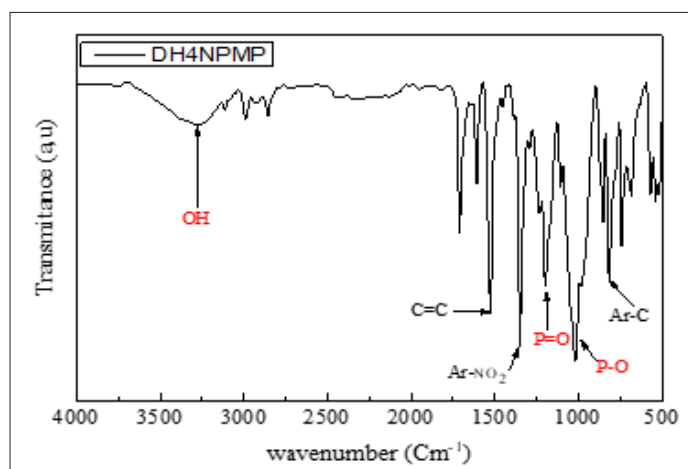


Figure 4: IR spectrum of DH4NPMP.

Table 1: Characteristic absorption bands and their assignments.

Wavenumber (cm^{-1})	Assignments
3284	O-H
2992	-CH ₃
2856	-CH ₂
1525	Ar-C=C
1345	Ar-NO ₂
1203	P=O
1110	C-C
1024	P-O

987	P-C
820	Ar-C

To plot the UV-vis spectrum of DH4NPMP we used the standard program Origin 18. The optical absorption spectrum of DH4NPMP and 4NBA (Figure 5) exhibits a strong absorption band around 271.99 nm assigned to the aromatic systems or electronic excitation in this region. In general, the absorption band of benzene are mainly located around 200 nm related to the energy required for $\pi-\pi$ transition. The absorption is negligible in visible range in the spectrum of 4NBA and DH4NPMP with a cut-off wavelength 289.6 nm and 320.7 nm respectively, which is sufficient for laser frequency doubling and other related optoelectronic applications in ultra violet domain.

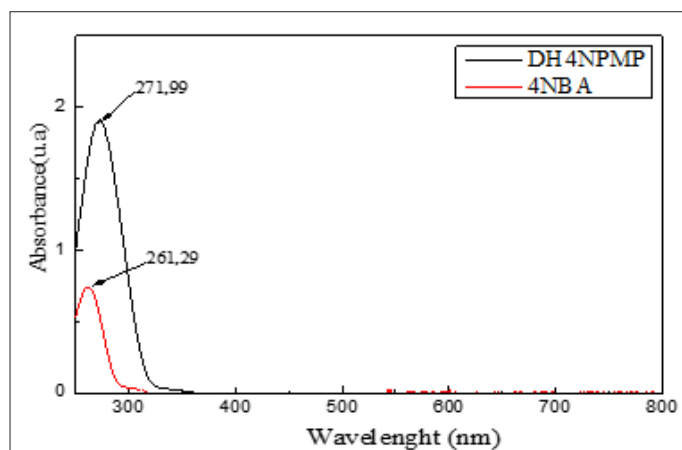


Figure 5: UV-Vis Absorption Spectrum.

In order to choose the therapeutic targets for our ligand, we used the Swiss Target software. The result obtained is illustrated in table 2. Among the targets given by the software, we chose two targets, which are JAK1 and JAK2 to test the anti-inflammatory and one target, which are PRDX5 to test antioxidant effect of our synthesized molecule.

Table 2: Bioactivity of DH4NPMP.

Target	Common name	ChEMBL ID	Target class
Tyrosine-protein kinase	JAK1	P23458	Kinase
Tyrosine-protein kinase	JAK2	O60674	Kinase
Peroxiredoxin 5	PRDX5	P30044	Peroxidases

The docking analysis showed that DH4NPMP exhibited stronger and more diverse interactions with both JAK1 and JAK2 proteins than Aspirin (ASA) [9,10]. In JAK1, DH4NPMP formed two H-donor bonds with Arg1007 and Glu566, as well as one H-acceptor interaction with Gly962, indicating a stable binding mode. In contrast, Aspirin formed only one H-donor bond with Asn1008 and weaker π -related interactions with Lys908 and Gly884. For JAK2, DH4NPMP displayed an H-donor bond with Arg1007 and two H- π interactions involving Arg1007 and His855, suggesting favorable ligand-protein stabilization. Conversely, Aspirin formed a single H-donor bond with Pro950

and one H- π interaction with Leu881, indicating fewer binding contacts. Although Aspirin showed slightly lower RMSD values (0.74 Å for JAK1 and 1.44 Å for JAK2), DH4NPMP established a greater number of hydrogen-bonding and π -interactions, suggesting stronger binding affinity and potentially better inhibitory activity toward both JAK1 and JAK2 proteins.

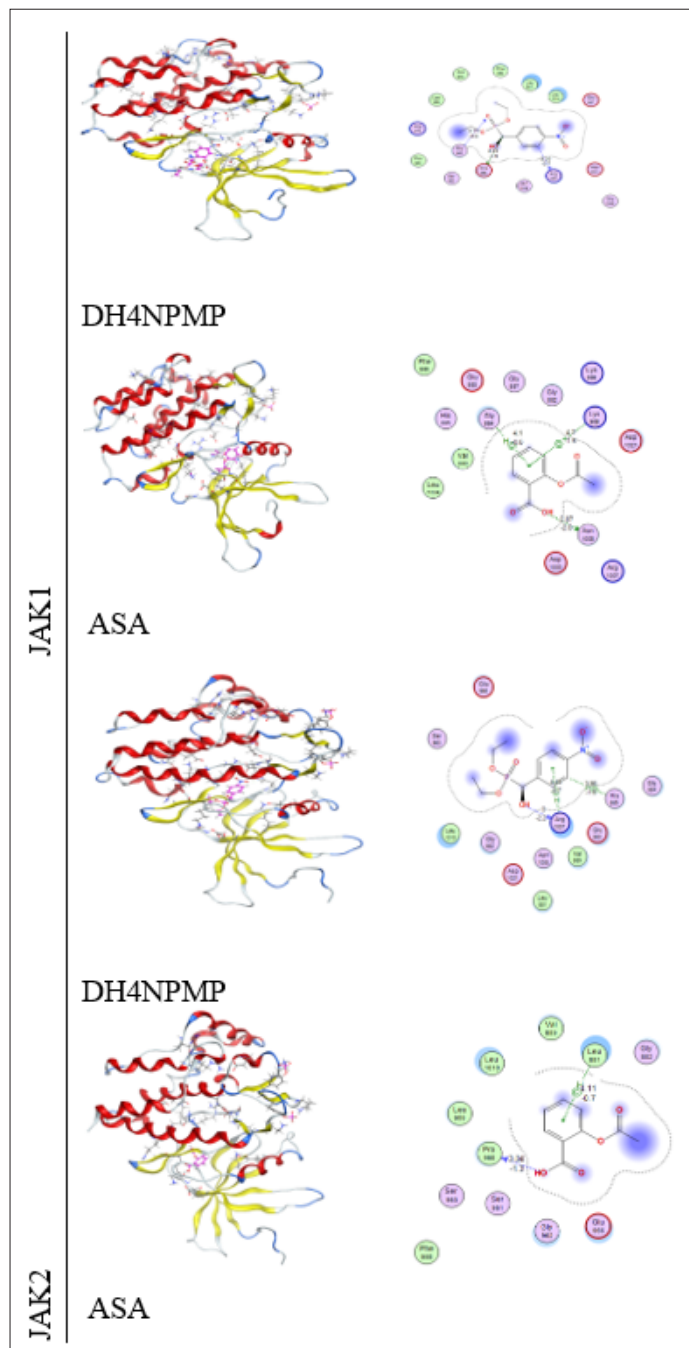


Figure 6: Best 2D and 3D position of the DH4NPMP and Aspirin (ASA) inhibitor in the JAK1 and JAK2 proteins.

The docking results showed that DH4NPMP formed multiple and diverse interactions with PRDX5, including two H-donor bonds with Glu18 and Glu91, as well as one H-acceptor interaction with Gly92, indicating a strong and stable binding profile. In contrast, BHT exhibited only a single H- π interaction with Glu91, where its aromatic ring interacted with the residue, suggesting fewer binding contacts compared to DH4NPMP.

Although both ligands interacted with Glu91, DH4NPMP displayed a more extensive interaction network across different residues, indicating a potentially stronger affinity for PRDX5 than BHT.

Table 3: Molecular docking results and interactions.

Proteins	Ligands	Score (Kcal/mol)	RMSD	Interactions		
				Atom	residue	Types of interactions
JAK1	DH4NPMP	-6.098	1.004	O30 C11	Gly962 Glu566	H-acceptor H-donor
	ASA	-4.70	0.74	Cycle Cycle	Gly884 Lys908	H- π H- π
JAK2	DH4NPMP	-5.95	1.40	C11 Cycle	Arg1007 Arg1007	H-donor H- π
	ASA	-4.50	1.44	Cycle O	Leu881 Pro950	H- π H-donor

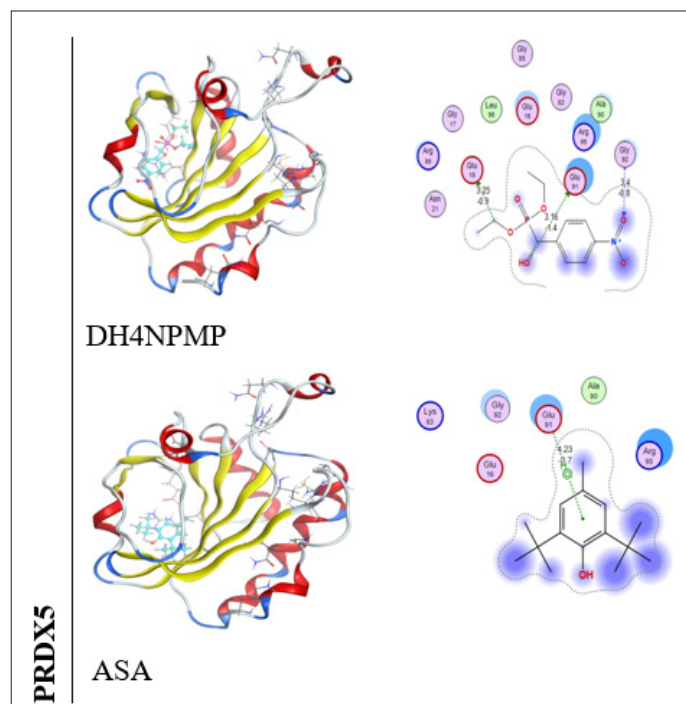


Figure 7: Best 2D and 3D position of the DH4NPMP and BHT inhibitor in the PRDX5 protein.

Table 4: Molecular docking results and interactions.

Proteins	Ligands	Score (Kcal/mol)	RMSD	Interactions		
				Atom	residue	Types of interactions
JAK1	DH4NPMP	-5.46	1.04	C13 C11 O35	Glu18 Glu91 Gly92	H-donor H-donor H-acceptor
	BHT	-4.34	1.40	Cycle	Gly91	H- π

Using Lipinski's rule as a reference, which is commonly used to evaluate the drug-likeness of compounds, we compare the values obtained for each compound (Table 5).

Table 5: Lipinski Rule analysis of DH4NPMP and ASA. (Original 2024).

Formula	C ₁₁ H ₁₆ NO ₆ P	C ₁₄ H ₂₁ N ₅ O ₂ S	C ₁₈ H ₁₆ FN ₃ O	C ₉ H ₈ O ₄	Lipinski Rules
Ligands	DH4NPMP	Native Ligand of JAK1	Native Ligand of JAK2	ASA	
Property	Values				
MW (g/mol)	289.07	323.14	309.13	180.04	≤500
nHA	7	7	4	4	<10
nHD	1	2	2	1	<5
TPSA (Å ²)	98.9	90.98	61.54	63.6	<140
Log P(Log mol/L)	1.039	1.769	4.048	1.168	<5
Volume	236.275	305.558	312.415	177.642	
Density	1.098	1.058	0.989	1.013	
nHet	8	8	5	4	

Using Lipinski's rule as a reference, which is commonly used to evaluate the drug-likeness of compounds, we compare the values obtained for each compound (Table).

Table 6: Lipinski Rule analysis of DH4NPMP and BHT.

Formula	C ₁₁ H ₁₆ NO ₆ P (DH4NPMP)	C ₇ H ₅ O ₂ -(Native Ligand of PRDX5)	C ₁₄ H ₂₂ O (BHT)	Lipinski Rules
Property	Values			
MW (g/mol)	289.07	128.08	206.17	≤500
nHA	7	2	1	<10
nHD	1	1	1	<5
TPSA (Å ²)	98.9	37.3	20.23	<140
Log P Log mol/L	1.039	1.946	4.565	<5
Volume	236.275	136.016	243.025	
Density	1.098	0.942	0.848	
nHet	8	2	1	

We start with the molecular weight, the compounds respect the Lipinski rule, because their molecular weights are less than 500 g/mol. This indicates that they have an appropriate molecular size to be considered as potentially pharmacologically favorable compounds. When it comes to hydrogen bond acceptors (HBAs), compounds also meet Lipinski's rule because they have fewer than 10 HBA groups. This suggests that they may be capable of establishing appropriate interactions with other molecules in a biological context. On the other hand, when it comes to hydrogen bond donors (HBD), this may have an influence on the ability of the compound to form specific bonds in a biological environment. Regarding the octanol-water partition coefficient (LogP), the compounds meet Lipinski's rule, as they have a LogP less than 5. This value suggests adequate solubility in hydrophobic and hydrophilic solvents. For total polar surface area (TPSA), compounds comply with Lipinski's rule, as their TPSA is less than 140 Å². This indicates a moderate total polar surface area, which may be favorable from a pharmacological point of view. We can say that the compounds meet the majority of the criteria of Lipinski's rule. However, it is important to note that Lipinski's rule is a rule of thumb and there are many other factors to consider when evaluating a compound's viability

and effectiveness as a drug potential. Through these results we can say that the DH4MPMP ligand could be used as a drug in comparison with the inhibitors of the three proteins which are already marketed.

Conclusion

In conclusion, this study highlights the potential of α-hydroxyphosphonates as promising therapeutic agents for diseases associated with oxidative stress and inflammation. It also emphasizes the value of computational drug discovery approaches as essential tools in the early stages of rational drug design. The encouraging in silico findings support further experimental investigations to validate the biological activity and assess the pharmacological safety of these compounds through in vitro and in vivo studies.

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