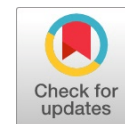


Molecular Docking, Simulation Against SARS-COV-2, Theoretical Study (DFT) and Superoxide Anion Scavenging by Cyclic Voltammetry of 2-Hydroxyphenyl Imino Naphthalen-2-ol

Noudjoud HOUAS, Siham KITOUNI, Assia TOUNSI



Abstract: The simulation in terms of enzymatic activity and the estimation of the process transfer of electronic active sites of the synthesized compound: 2-hydroxyphenyl imino naphthalen-2-ol (Schiff basis) required the use of valuable calculation programs such as the docking, for which we used the Arguslab program and the Gaussian endowed to the calculation of the functional density theory of the molecule studied. And as the experimental study designed under difficult, costly or sometimes impossible conditions, the docking program simulates the molecular binding of the protein target with the ligand, which can reveal the arrangement of the hydrogen and hydrophobic bonds that link the active sites and the ligand; it is an economical step in terms of time and money that can lead to the selectivity of the product of interest in drug manufacturing. In this context, we are currently focused on the study of the inhibitory effect of this molecule with the enzyme (6lu7) fighting against covid-19, and have compared it to the drug chloroquine. The obtained results show that the calculated Gibbs free energy with protease is -9.215 Kcal/mol, which is almost more inhibiting than chloroquine (-7.2652 Kcal/mol). The DFT method allowed us to estimate that the potentially positive sites easily cede an electron when they are brought into contact with oxidizing species during the reduction reaction. The study of the superoxide anion O_2^- scavenging activity via this product is performed practically by electrochemical way, the Gibbs standard energy (-16.9022 KJ/mol) explains that the reaction can spontaneously form very stable inactive species with the oxidizing ion.

Keywords: Antioxidant Activities, DFT Calculations, Molecular Docking, Schiff Bases.

I. INTRODUCTION

Schiff bases play a particular role in providing a wide exploitation of biological activities [1], such as antiviral activity [2], antifungal [3], antioxidant [4], anti-inflammatory [5], antitumor [6,7], anticancer [8,9], antibacterial activities [10,11], and antipyretic applications [12]; these famous compounds are known by the main formula $RN=CR'R''$ substrate [13] which can provide an amplifying electronic aspect and a flexibility of steric conformation when endowed with the proteins. Schiff bases are the most widely used organic compounds that coordinate with metal ions via an imine and have a wide variety of applications in many fields, including corrosion of carbon steel and catalytic oxidation [14,15].

Density functional theory (DFT) is a method of quantum computation that allows electronic structure to be studied in a principal manner; it is also used widely in chemistry, because of its possible application to systems of different sizes. In this context, we performed a calculation using the method assigned by the B3LYP levels included in the Gaussian 09 package program with 6-311G (d, p) basis set [16]. The purpose of this calculation is to determine the appropriate active sites contributing to the positive potential aspect that needs to access the reduction process in front of the oxidizing species; the energy of the reactivity of this molecule is estimated by the difference between the energies of the frontier orbitals LUMO and HOMO. The electrochemical study by cyclic voltammetry of the antioxidant activity against superoxide is carried out in order to reach an evaluation of the percentage of inhibition and the binding energy ΔG through the decrease in the intensity of the peaks, which undoubtedly defines the decrease in the quantity of superoxide radicals. The molecular docking simulation of the target SARS-CoV-2 main protease (M pro) is a theoretical approach that is used to deduce the efficiency of the enzymatic complexation of our product based on the Arguslab program; therefore, it predicts the selectivity of products with better binding affinity to be approved as a drug against covid-19. [17,18][42][43].

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II. EXPERIMENTAL

A. Instrumentation

The Electrochemical measurements were recorded using a VoltaLab40 PGZ301 potentiostat/galvanostat (Radiometer Analytical), equipped with a system of three-electrode consists of a saturated calomel electrode (SCE) as a reference electrode, a platinum wire as the counter electrode and a platinum disc as a working electrode. All measurements were carried out at room temperature.

B. Synthesis Process of Molecule

The synthesis of the studied molecule is referred by [19,20], proceeded with the reaction of 2-hydroxy naphthaldehyde and 2-amino phenol dissolved in toluene and heated progressively up to 100 °C for 1h at this temperature. The reaction was monitored by analytical thin layer chromatography (TLC); the crud solid was further washed with diethylether several times and offer a pure yellow imine.

C. Electrochemical Process

In electrochemical process, there are several types of phenomena associated with an electric charge transfer at the interfaces formed by the contact of electrodes and an electrolyte, the chemical transformation is carried out with the oxidation-reduction.

D. Mathematical Description of Reaction Steps

This method allows the rapid detection of the existence of different reaction steps by only playing on the scanning rate [21]. The case of a reversible system is given by the equation Randles and Sevcik: [22]:

$$I_p = 2.68 \cdot 10^5 n^{3/2} AD^{1/2} v^{1/2} C$$

$$\Delta E_p = E_{pa} - E_{pc} = 0.057/n \quad \text{At } 25^\circ \text{C}$$

Where, I_p : peak current (μA).

n : number of electrons involved in the electrochemical reaction.

A : electrode surface (cm^2).

D : diffusion coefficient of the electroactive species ($\text{cm}^2 \cdot \text{s}^{-1}$).

C : electroactive species concentration (mM).

v : scan rate ($\text{V} \cdot \text{s}^{-1}$).

For the irreversible system: [23]

$$I_p = 2.99 \cdot 10^5 n (\alpha n)^{1/2} AD^{1/2} v^{1/2} C$$

Where, α : transfer coefficient.

E. Scavenging Superoxide Radical using Cyclic voltammetric Method

Superoxide is an anionic free radical with the chemical formula $\text{O}_2^{\cdot-}$. It is formed by one-electron reduction of dioxygen (O_2) [24] which is presented abundantly in nature; it is qualified as one among of dangerous species that can destabilize our life system [25]. Recently the cyclic voltammetry is used to determine the antioxidant activity in confrontation of this radical. This electrochemical method consists in generating the radical by the reduction process of the dissolved oxygen in aprotic solvents [26,27].

a. Procedures

In an electrochemical cell, we placed 20 mL of a solution containing the supporting electrolyte Bu_4NBF_4 (0.1M) dissolved in DMF on which immersed three electrodes; this solution was saturated by dry air in the case of scavenging activity [28-30]. However, the study of the reaction mechanism and the nature of the electrochemical transfer regime adopted at the surface of the working electrode of the analyzed product was only performed in the absence of oxygen by bubbling with nitrogen in solution. Measurement of superoxide radical scavenging activity was based on the method of Le Bourvellec et al. [31] with slight modification in experimental conditions. The effect of inhibition of compound was checked by the addition of different concentrations to blank test. The percentage inhibition of tested product was calculated using the following equation:

$$RSA_{\text{O}_2^{\cdot-}} \% = \frac{I_p^o - I_p}{I_p^o} \times 100$$

Where I_p^o and I_p are the intensity of peaks without and with the analyzed compound respectively.

F. Computational of Quantum Chemical Parameters with DFT

The geometric optimization of the compound was performed using the Gaussian program [32], based on the density functional theory (DFT), with Lee-Yang-Parr correlation functional (B3LYP) at basis sets 6-311G (d,p) [33,34]. The quantum chemical parameters of the investigated compound as gap energy which defines the reactivity of the molecule is evaluated at low value of the energy difference between the LUMO and HOMO orbitals.

G. Molecular Docking

Molecular docking study was performed in order to determine binding affinity of the present ligand against SARS-CoV-2 main protease (M pro). The crystalline form of this protein is evoked by Liu, X et al [35], labeled 6LU7 and extracted from the PDB protein data base, has been used in similar studies [36-38][44]. Molecular docking simulation was executed by Arguslab 4.0.1 program [39], where the docking parameters were adapted as the dimensions of the binding site bounding box dimensions equal to: $12 \times 21 \times 21 \text{ \AA}^3$. The graphical data of the enzyme complex is visualized using Discovery Studio 4.0 client software [40].

III. RESULTS AND DISCUSSION

A. Spectral Study of 2-Hydroxyphenyl Imino Naphthalen-2-ol (HINP)

M.p (262°C), 99.6% yield.

FT-IR ν (cm^{-1}): ν_{OH} (3661.58), $\nu_{\text{C-H(aromatic)}}$ (2993,2903.74), $\nu_{\text{C=N}}$ (1612.91), δ_{OH} (1236.42).

NMR ^1H (400 MHz, DMSO- d_6), (δ) ppm: 6.98-7.94 (m, 10 H, aromatic protons); 8.37, 8.39 (s, 2H, OH), 9.50 (s, H, N=CH). NMR ^{13}C (400 MHz, DMSO- d_6), (δ): 108.2-149.9 (m, 16 C, aromatic carbons), 178.06. (CH=N).

B. Electrochemical Study

▪ Electrochemical Properties

The voltammogram of supporting electrolyte Bu_4NBF_4 (0.1M) in DMF solution (blank test) is adjusted along the interval from -1000 mV/ECS to 1600 mV/ECS, in order to ensure the inert process of electron transfer carried out by three electrodes in the absence of oxygen [Fig.1](#).

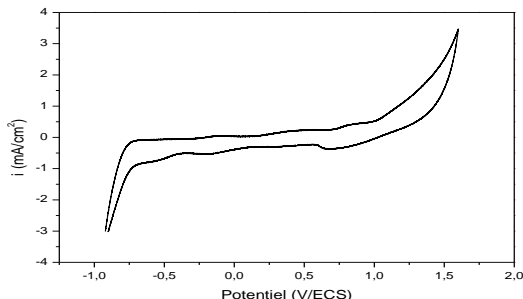


Fig. 1: Cyclic Voltammogram of the Supporting Electrolyte DMF- Bu_4NBF_4 , 0.1 M with a Scan Rate, $\nu = 20 \text{ mV/s}$, Including the Activity Range [-1000- 1600 mV/ECS]

The analyzed product shows voltammograms which differ in the shape of plots at each variation in the scanning speed, as shown in [Fig.2](#).

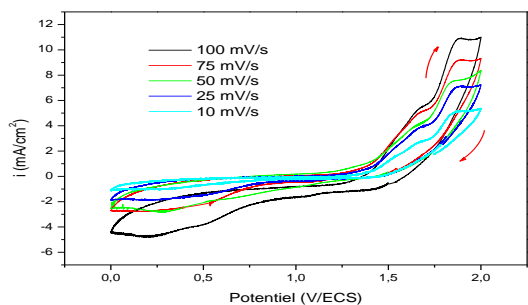


Fig. 2: Cyclic Voltammograms of Tested Product at Different Scan Rates in the Presence of Bu_4NBF_4 - DMF (0.1M), Activity Range [0-2000 mV/ECS].

The result illustrates an anodic peak situated at 1889 mV/ECS and its cathodic peak corresponding to 217 mV/ECS; according to the potential difference, the system is considered to be irreversible. The study of the charge transfer on the electrode surface was carried out at different rates and is collected in [Table.1](#). By discrimination of the nature of

reaction and the mechanism of the limiting step constituted at the surface of the electrode, we can establish the regime of electronic transfer as follows: HINP leads to a semi rapid reaction governed by pure diffusion. [Fig \(3, 4\)](#).

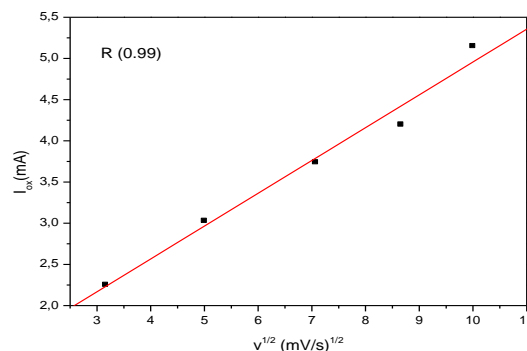


Fig. 3: Evolution of the Current Intensity Upon Variation of Rate

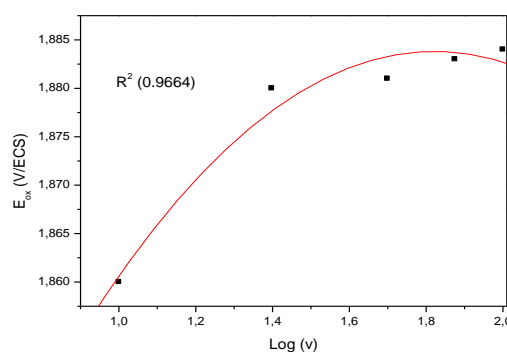


Fig. 4: Evolution of the Potential Upon Variation of Rate

C. Superoxide Radical Scavenging Via Cyclic Voltammetry

The voltammogram of the blank test in the presence of oxygen records the redox couple $\text{O}_2/\text{O}_2^{\cdot-}$, confirms that the oxidation-reduction process of this couple is irreversible [41]

The antioxidant capacity is also evaluated by adding different concentrations of the sample to the initial solution. The remarkable decrease in the intensity of the oxygen radical peak reflects a decrease in the concentration of which can be translated the effective inhibitor that characterizes our study product. [Fig.5](#) and [Table.2](#).

Table. 1: Evaluation of I_{ox} and E_{ox} as a Function of Rate Variance, $\nu^{1/2}$ and $\text{Log}(\nu)$

ν (mV/s)	100	75	50	25	10
$\nu^{1/2}$	10	8.66	7.071	5	3.162
$\text{Log}(\nu)$	2.00	1.875	1.699	1.398	1.00
I_{ox} (mA)	5.15	4.198	3.739	3.029	2.252
E_{ox} (mV/ECS)	1.889	1.868	1.858	1.845	1.827

Table. 2: Evaluation of the Percentage of Inhibition Related to the Current Intensity of the Anodic Peak

	Current Intensity I_{ox} (mA)	APR% θ_2	R^2	IC_{50} ($\mu\text{g/ml}$)
HINP	2.301			
	1.25	45.67		
	0.805	65.14	0.9	6.14
	0.418	80.96		
	0.398	82.70		

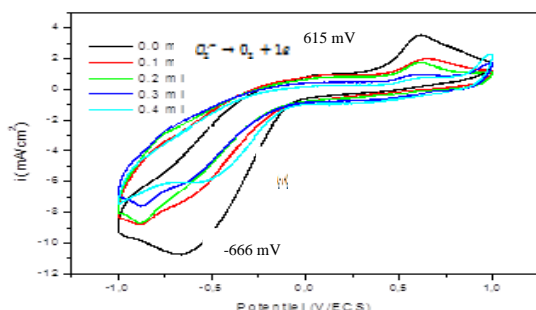


Fig. 5: Cyclic Voltammograms of DMF of Superoxide with and Without Tested Sample

a. Determination of thermodynamic parameters

The thermodynamic study of the capacity of superoxide radical scavenging of our antioxidant specie aims to determine the stability constant K_b and the standard Gibbs free energy ΔG° . These parameters are expressed by the following relationships:

$$\log\left(\frac{1}{C_{test}}\right) = \log K_b + \log\left(\frac{I_{pa}}{I_{pa}^0 - I_{pa}}\right)$$

$$\Delta G^\circ = -RT \ln (C_{solvent} K_b)$$

Where R is the constant of perfect gases (8.314 J K⁻¹ mol⁻¹). T (K) is the absolute temperature. $C_{solvent}$ is the molar concentration of DMF solvent.

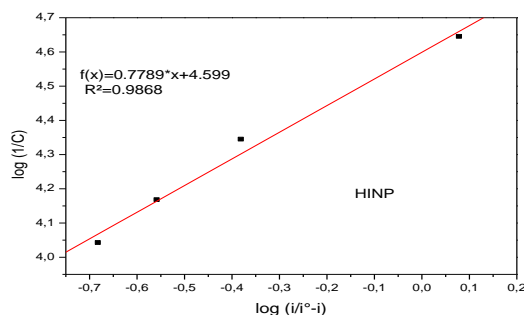


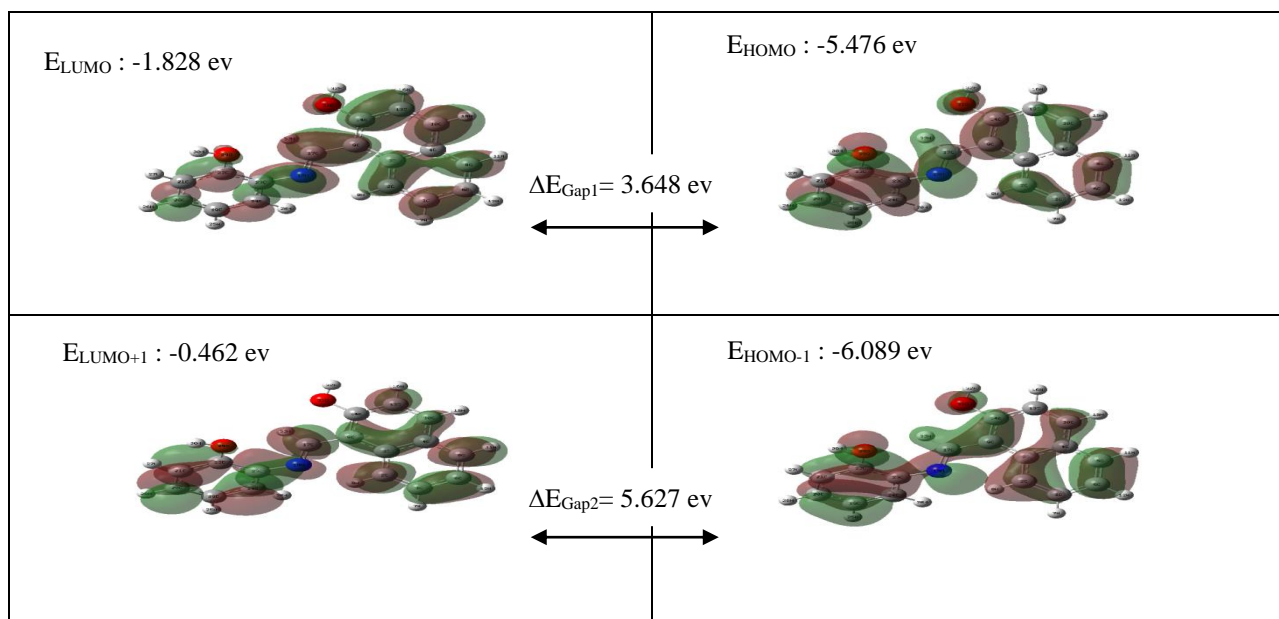
Fig. 6: Graphical Determination of the K_b Constant

From this linear graph the constant K_b is estimated at 39719.145 l/mol, while the energy ΔG° is (-16.9022 KJ/mol), as shown in Fig. 6. The high value of K_b and the negative sign of the energy allow us to state that the scavenging reaction is very stable and spontaneous.

D. Chemical Reactivity Study

Molecular orbitals are conceived to identify the electron transfer process as donor or acceptor, while the absolute gap between the two frontier orbitals assumes the chemical reactivity. Thus, the smaller gap energy reflects the high reactivity of a molecule.

It can be seen from the 3D plots Fig.7. that the frontier orbitals HOMO and LUMO cover entirely the molecule; for the Highlighted orbitals the hydroxyl moiety in the naphthalene side is the only one that is not covered at the level LUMO+1; however LUMO+2 is spread over the right part of the molecule and that the left part remains clearly naked; for HOMO-2 the covering is extended on the majority of the molecule while it is not uniform at the right side.



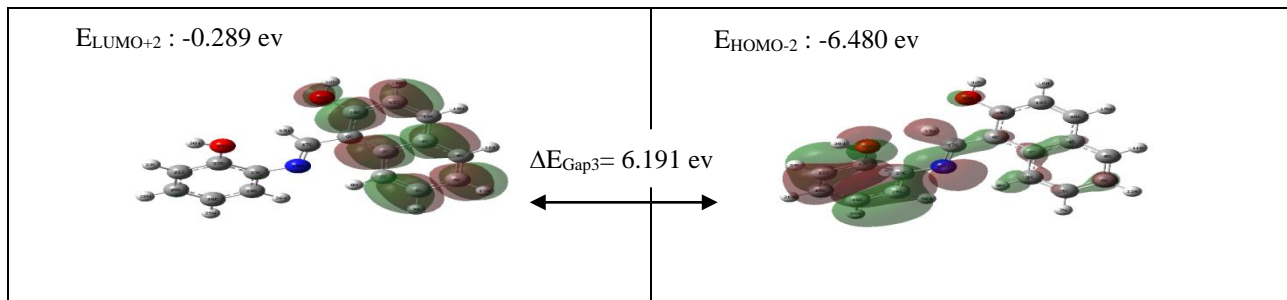


Fig. 7: Molecular Orbitals of the HINP and Related Gap Energies

Through the HOMO/LUMO energies we can explain that the first oxidation/reduction is displayed with ΔE_{Gap1} at 3.648 eV. Where the surface of electrostatic potentials mapped the active sites of the electrophilic reactivity (lowest density) which can easily give electrons on contact with oxidizing species, it is illustrated in blue color around hydrogen atoms H30 and H32 of the hydroxyl groups; these sites of positive potential confirm the effective antioxidant activity through the reduction process. [Fig.8.](#)

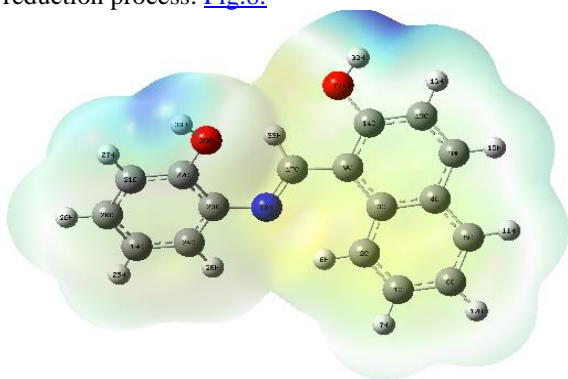


Fig. 8: Molecular Electrostatic Potential Map of the HINP Compound

The atomic charges are probably appreciated in [Table.3.](#)

Table. 3: Mulliken Atomic Charges of HINP Determined by DFT using B3LYP Levels with 6-311G (d, p) basis Set

Atom	Charge	Atom	Charge
C1	-0.0922530	N18	-0.3738150
C2	-0.0398820	C19	-0.1007550
C3	-0.0524190	C20	-0.0929140
C4	-0.0530200	C21	-0.1137010
C5	-0.0631820	C22	0.1767960
C6	-0.0851700	C23	0.0688960
H7	0.0918520	C24	-0.0628660
H8	0.1272350	H25	0.0895930
C9	-0.1479970	H26	0.0909210
C10	-0.0415050	H27	0.0824080
H11	0.0800020	H28	0.0983050
H12	0.0897890	O29	-0.3703270
C13	-0.0956110	H30	0.2480470
C14	0.1777990	O31	-0.3647980
H15	0.0873150	H32	0.2507050
H16	0.0859500	H33	0.1117520
C17	0.1928480		

E. Molecular Docking Analysis

The molecular docking of M^{Pro} receptors with HINP ligand was executed to define the appropriate best conformation of the ligand within amino acid target, while the minimal binding energy describes the highest inhibition stability. [Fig. 9.](#)

The docking results of the ligand HINP with the target 6lu7 show that ligand bind inside of enzyme, so it promoted an interesting inhibitory effect that due to different favorable non-covalent interactions responsible for the complexation

with the active sites; this simulation suggested a single hydrogen bond with the active site His164 and four interactions according to the hydrophobic mode two of them are linked with the same site Cys44, one with Pro52, and the last one bind with His41. As well, the low Gibbs free energy ($\Delta G_{binding}$) attests to the better binding affinity compared with chloroquine, it is therefore estimated at (-9.215 Kcal/mol), which can approve the reliability of its use in covid-19 therapy.

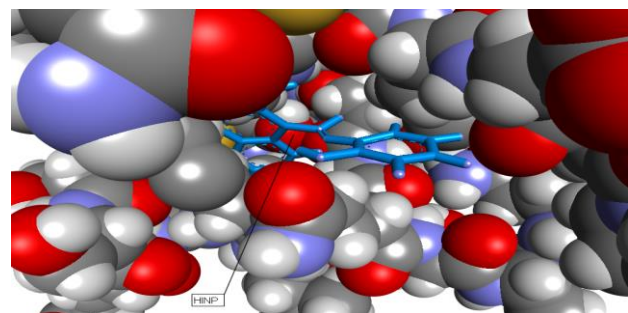
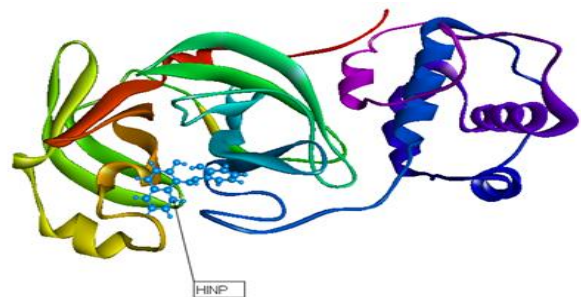


Fig. 9: Docking Presentation of the Ligand with the SARS-CoV-2 Main Protease, Visualized by Discovery Studio 4.0 Client Software

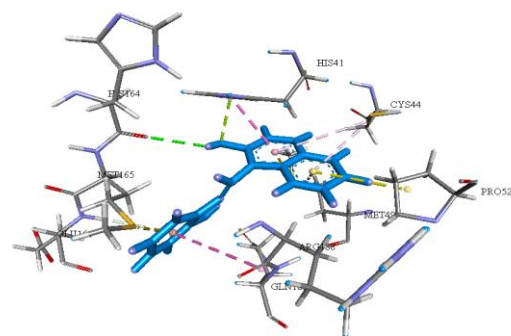


Fig. 10: Map Binding-Interaction Diagrams of HINP Ligand with SARS-CoV-2 Main Protease

Table 4: Favorable Intermolecular Interactions of HINP Compared to Chloroquine

Molecule	Hydrogen Bond		Hydrophobic		ΔG Kcal/mol
	Interaction	Distance (Å)	interaction	Distance (Å)	
HINP	O-H...O:His164	2.96373	HIS41	3.666	-9.215
			Cys44	4.844	
			Cys44	4.133	
			Pro52	4.375	
Chloroquine	N...HN:Thr190	2.676	LEU167	5,06118	-7.265
			MET165	3,52587	
			MET165	3,17488	

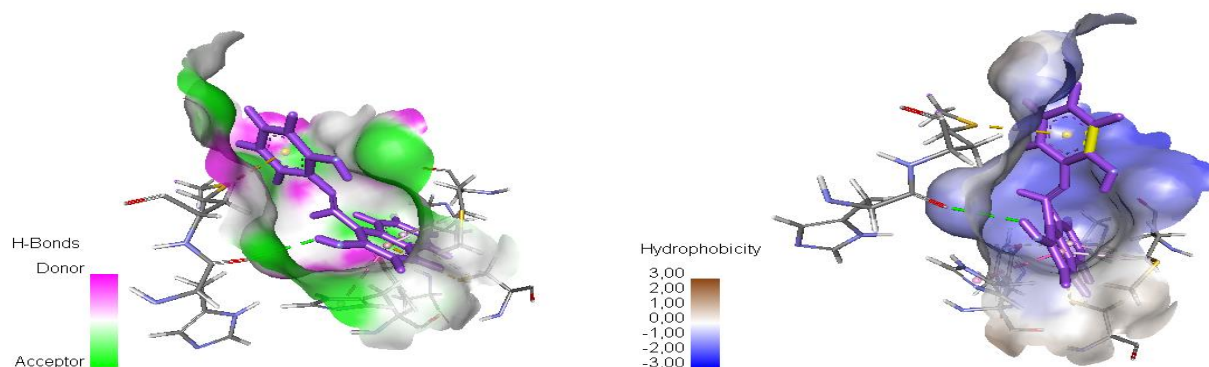


Fig. 11: Molecular Surfaces Colored by Hydrogen Bonds and Hydrophobicity

The physical properties of HINP- M^{pro} coordination such as hydrophobicity and hydrogen-bond, suggested that these interactions played an indispensable role in the binding of this ligand to the active site of receptor, which may contribute to the relatively low binding free energy. H-bonds acceptor/donor is generally reacted in aprotic solvents; for the hydrophobicity degree is usually quantified by the $\log P$ scale, a concept derived from the partition coefficient of complex between 1-octanol and water. It is estimated to be less than 3; detected in Fig. 11.

IV. CONCLUSION

The results obtained from the exploitation of the present imine compound considered as an inhibitor against oxidative species by cyclic voltammetry and also with the enzyme SARS-CoV-2 by simulation using the Arguslab program, show that HINP has an effective scavenging capacity against the superoxide radical estimated at 6.14 $\mu\text{g/ml}$ with a strong stable energy ΔG at (-16.9022 KJ/mol). Therefore this product behaves by a semi-rapid charge transfer controlled by diffusion. For enzymatic complexation, it is evident that the combination of intramolecular interactions leads to the formation of different bonds such as the hydrogen bond (His164) and four Hydrophobic bonds (HIS41, two with Cys44 and the last one is Pro52 site), while the binding energy is -9.215 Kcal/mol. The quantum parameters of the molecules associated with the DFT method are also processed in this work showed the reactivity ΔE_{Gap1} at 3.648 eV as well the positive sites implemented through the reduction reaction.

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DECLARATION STATEMENT

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Ethical Approval and Consent to Participate	No, the article does not require ethical approval and consent to participate with evidence.
Availability of Data and Material	Not relevant.
Authors Contributions	Noudjoud HOUAS: Writing, Synthesis and characterization, Project administration, Data curation, Formal analysis, Methodology and Resources, Theoretical studies and Review, Resources and Investigation. Siham KITOUNI: Contributed in experimental part. Assia TOUNSI: Contributed in the electrochemical study.

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