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Houria Bentoumi, Sourour Tliba, Hacène K'Tir, Djawhara Chohra, Zineb Aouf, et al.. Experimental synthesis, biological evaluation, theoretical investigations of some novel benzoxazolinone based Schiff under eco-environmental conditions as potential antioxidant agents. *Journal of Molecular Structure*, 2022, 1270, pp.133986. 10.1016/j.molstruc.2022.133986 . hal-03961744

**HAL Id: hal-03961744**

**<https://hal.science/hal-03961744>**

Submitted on 29 Jan 2023

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# Experimental synthesis, biological evaluation, theoretical investigations of some novel benzoxazolinone based Schiff under eco-environmental conditions as potential antioxidant agents

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In this paper, we have developed a new, non-hazardous and eco-friendly access route for the synthesis of a novel Schiff bases containing 2-oxo-3H-benzoxazole scaffold 4(a-f) by lemon juice as natural catalyzed acid under solvent-free conditions. The chemical structures of the new synthesized compounds were elucidated on the basis of the FT-IR, <sup>1</sup>H and <sup>13</sup>C-NMR spectroscopic techniques and all molecules were isolated with moderate yields after shorter reaction times. Furthermore, a preliminary study on the *in vitro* antioxidant activity of some synthesized compounds was investigated. The biological activity results revealed that highest DPPH radical-scavenging activity was observed for compound 4e with an IC<sub>50</sub> of 2.13 µg.mL<sup>-1</sup>, more active than the standard ascorbic acid (IC<sub>50</sub> = 2.16 µg.mL<sup>-1</sup>). *In-silico* studies based on density functional theory (DFT) were realized to rationalize the biological activity with the structural and electronic properties of the 6-imino-2-oxo-3H-benzoxazoles. We using the molecular docking simulation to study the affinity and the possible binding mode of complexed ligand-protein. The synthesized molecules were tested to cross the clinical test by the ADMET prediction, these results indicated that the compounds 4(a-f) have excellent drug-likeness properties.

## Keywords:

Benzoxazolinone  
Antioxidant evaluation  
Nitric oxide synthase NOS  
DFT study  
Molecular docking

## 1. Introduction

In recent years, the interest in antioxidant agents, in relation to their medicinal properties, has increased significantly. They have been clearly described those antioxidants play a principal role in the defence mechanism against oxidative damage induced by free radicals and others reactive oxygen species (ROS) produced by cells [1,2]. In effect, their antioxidant properties can be attributed in part to the ability of this family of compounds to capture free radicals such as the hydroxyl radical (OH<sup>•</sup>), superoxide anion (O<sub>2</sub><sup>•-</sup>), as

well as non-radical molecules like hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), singlet oxygen (<sup>1</sup>O<sub>2</sub>) [3,4].

One of the most processes to combine oxygenase and reductase catalytic domains in one monomer is the using of the cytochrome P450-like hemoproteins dimeric, a nitric oxide synthase (NOS) enzyme. The development and identification of potential inhibitor of this enzyme is a great necessity and could be achieved *via* various strategies, one of them the use of known molecular debases to screen for agents that may have the same therapeutic effect [5-7].

The 2-oxo-3H-benzoxazole nucleus represents one of the important scaffolds in the field of medicinal chemistry, to develop new molecules with potential biological activities [8]. This pharmacophore has been incorporated into a wide variety of pharmaceutically interesting drug candidates, and has been used as lead

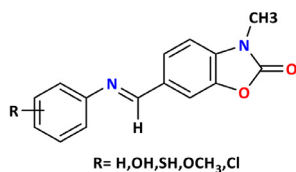


Fig. 1. Radical general structure of the synthesized Schiff bases 4(a-f).

structure in the design of novel antiviral compounds [9]. Several works on the benzoxazolone-based bioactive substances have led to the discovery of a number of derivatives endowed with various types of biological activities, such as antioxidant [10], anticancer [11], antibacterial and antifungal [12,13], anti-HIV [14] as well as analgesic and anti-inflammatory [15–17].

On the other hand, Schiff bases derivatives possessing an azomethine group ( $-N=CH-$ ), are among the most important class of compounds that have a wide variety of applications in many fields [18–20]. They have received much interest in biochemistry and medicinal chemistry due to their potential pharmacological properties, including antimicrobial [21–23], antioxidant [24,25], anticancer [26] and antiviral [27,28] activities.

Therefore, several strategies have been developed for the formation of the nitrogen–carbon double bond; this can be realized by the reaction of carbonyl compounds with primary amines under a variety of conditions in the presence of a catalytic amount of organic acid. However, this method has many drawbacks, strong acidic conditions and toxic organic solvents, lengthy reaction time [29,30].

Nowadays there are several citrus fruits; many of them are good for your health. Lemon has an enormous importance in our daily life; this fruit is an immense source of benefits gives us many vitamins. It contains high levels of vitamin C, also known as ascorbic acid. The main acid in lemon is citric acid, which makes up around 5 to 7% of lemon juice [31]. Lemon Juice has been explored recently as green solvent and catalyst in organic synthesis [32,33], catalyses the synthesis of dihydropyrimidinone, Knoevenagel reaction and the formation of Schiff bases [34–36]. Motivated by these interesting works and in continuation of our efforts toward development of useful green synthetic methodology [37–40], we report a successful approach for the preparation of some novel benzoxazolinonic Schiff bases (Fig. 1) as potential antioxidant agents in Lemon Juice as natural catalysed acid under solvent-free condition.

In addition, the field of the synthesis of new chemical molecules is currently often associated with a study by molecular modeling; a technique allowing not only to modify chemical properties and reactions, but also to manipulate models of 2D or 3D structures. Several methodological advances in theoretical chemistry, combined with increasing resources and computational methods, quantum chemistry calculations were carried out with optimizations of the complete geometry [41]. In this respect, we have performed *in-silico* studies, the structure-activity relationship of some Schiff bases benzoxazolinic, based on the electronic properties such as highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy and reactivity indices using the program Gaussian 09 and the hybrid B3LYP functional density with 6-31G (d,p) basis set. On the other hand, in order to explore the theoretical-experimental coherence, molecular docking were reported to appreciate the interaction of our molecules with its antioxidant target protein. Thus, to evaluate the promising pharmacokinetics/pharmacodynamics properties to identify that our compounds have a comparable result to the reference drug used in the study, we realised the theoretical ADMET analysis.

## 2. Materials and methods

### 2.1. Chemistry

Melting points were determined using a Köfler apparatus and are uncorrected. The structures of the synthesized compounds were elucidated by IR spectra measured by the KBr disc method with a FT-IR 8300S Shimadzu spectrometer. The  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra were measured in solutions on a Bruker AC 400 spectrometer using dimethylsulfoxide- $d_6$  and chloroform  $\text{CDCl}_3$  as solvents with TMS as internal standard, with chemical shifts reported as (ppm). Analytical thin layer chromatography was performed with commercial silica gel plates 60 F254 (Merck), and visualized with UV light, using ethyl acetate/cyclohexane (6:4, v/v) solvent system as eluent.

The synthesis and spectroscopic data of the known compounds 2-oxo-3H-benzoxazole derivatives 1, 2 and 3, were previously reported and prepared as cited in the literature [42–44].

#### 2.1.1. General procedure for extraction of lemon juice

The fresh lemons were cut with a knife, and then the pieces were squeezed to extract the juice. Then the juice was filtered through cotton / muslin and then through filter paper to remove lemon seed and obtain a clear juice used as a catalyst.

#### 2.1.2. General procedure for the preparation of 3-methyl-6-((E)-(arylimino)methyl)benzo[d]oxazol-2(3H)-ones 4(a-f)

The following procedures illustrate the general method used to convert the parent 3-methyl-2-oxobenzo[d]oxazole-6-carbaldehyde (3) into substituted 6-iminobenzoxazolone derivatives.

In a 100 mL flask, a suspension of 3-methyl-2-oxo-3H-benzoxazole-6-carbaldehyde (28 mmol) in a sufficient quantity of lemon juice (10 mL) is left under stirring, until obtaining a clear solution. After a few seconds of stirring, (28 mmol) of the aromatic amine derivative is added at room temperature in small portions. The reaction is followed by TLC, in order to determine the time and the end of the reaction. The precipitate formed is filtered off under vacuum, dried, and purified by recrystallized in ethanol absolute to get pure product.

- > 3-methyl-6-((E)-(phenylimino)methyl)benzo[d]oxazol-2(3H)-one (4a)  
MF:  $\text{C}_{15}\text{H}_{12}\text{O}_2\text{N}_2$ , MW: 252.27, light brown powder, Mp: 188–190 °C, yield: 51%. IR (KBr,  $\text{cm}^{-1}$ ): 2954 ( $\text{CH}_3$ ), 1774 ( $\text{C}=\text{O}$ ), 1623 ( $\text{C}=\text{N}$ ), 1602–1585 ( $\text{C}=\text{C}$ ).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.48 (s, 3H,  $\text{CH}_3$ -N), 7.05–7.89 (m, 8H, Ar-H), 8.46 (s, 1H,  $\text{CH}=\text{N}$ ).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.3 ( $\text{CH}_3$ -N), 107.8, 109.1, 120.9, 126.1, 126.2, 129.2, 131.8, 134.4, 143.0 ( $\text{CH}_{\text{Ar}}$ ), 158.9 ( $\text{C}=\text{O}$ ), 151.6 ( $\text{N}=\text{C}$ ).
- > 6-((E)-(2-mercaptophenylimino)methyl)-3-methylbenzo[d]oxazol-2(3H)-one (4b)  
MF:  $\text{C}_{15}\text{H}_{12}\text{O}_2\text{N}_2\text{S}$ , MW: 284.34, white powder, Mp: 252–254 °C, yield 78 %. IR (KBr,  $\text{cm}^{-1}$ ): 2943–2981 ( $\text{CH}_3$ ), 1774 ( $\text{C}=\text{O}$ ), 1612 ( $\text{C}=\text{N}$ ), 1557 ( $\text{C}=\text{C}$ ).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.48 (s, 3H,  $\text{CH}_3$ -N), 7.05–7.89 (m, 7H, Ar-H), 8.46 (s, 1H,  $\text{CH}=\text{N}$ ).  $^{13}\text{C NMR}$  (100MHz,  $\text{CDCl}_3$ ):  $\delta$  28.3 ( $\text{CH}_3$ -N), 107.8, 117.4, 120.3, 124.2, 125.9, 126.5, 127.2, 129.9, 130.6, 133.4, 144.8, 153.2 ( $\text{CH}_{\text{Ar}}$ ), 166.9 ( $\text{C}=\text{O}$ ), 154.6 ( $\text{N}=\text{C}$ ).
- > 6-((E)-(4-methoxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3H)-one (4c)  
MF:  $\text{C}_{16}\text{H}_{14}\text{O}_3\text{N}_2$ , MW: 282.29, white powder, Mp: 202–204 °C, yield 66 %. IR (KBr,  $\text{cm}^{-1}$ ): 2889–2954 ( $\text{CH}_3$ ), 1762 ( $\text{C}=\text{O}$ ), 1604 ( $\text{C}=\text{N}$ ), 1578 ( $\text{C}=\text{C}$ ).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.48 (s, 3H,  $\text{CH}_3$ -N), 3.87 (s, 3H,  $-\text{O}-\text{CH}_3$ ), 6.95–7.88 (m, 7H, Ar-H), 8.49 (s, 1H,  $\text{CH}=\text{N}$ ).  $^{13}\text{C NMR}$  (100MHz,  $\text{CDCl}_3$ ):  $\delta$  28.3 ( $\text{CH}_3$ -N), 55.5 ( $\text{CH}_3$ -O), ( $\text{CH}_3$ -Ar), 108.9, 114.4, 122.2, 125.9, 129.9, 133.4, 142.4, 144.2, 154.0 ( $\text{CH}_{\text{Ar}}$ ) 162.0( $\text{C}=\text{O}$ ), 156.9 ( $\text{N}=\text{C}$ ).

- > 6-((E)-(4-hydroxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3H)-one (4d)  
 MF: C<sub>15</sub>H<sub>12</sub>O<sub>3</sub>N<sub>2</sub>, MW: 268.27, white powder, Mp: 270–272 °C, yield 53%. IR (KBr, cm<sup>-1</sup>): 3421 (OH), 2916–2947 (CH<sub>3</sub>), 1760 (C=O), 1605 (C=N), 1581 (C=C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 3.38 (s, 3H, CH<sub>3</sub>-N), 3.33 (s, 1H, OH), 6.79–7.82 (m, 7H, Ar-H), 8.61 (s, 1H, CH=N). <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>): δ 28.7 (CH<sub>3</sub>-N), 108.2, 109.5, 116.1, 122.9, 126.1, 131.9, 134.6, 142.8, 142.9, 154.5 (CH<sub>Ar</sub>), 156.6 (N=C), 156.9 (C=O).
- > 6-((E)-(2-hydroxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3H)-one (4e)  
 MF: C<sub>15</sub>H<sub>12</sub>O<sub>3</sub>N<sub>2</sub>, MW: 268.27, yellow powder, Mp: 250–252 °C, yield 64%. IR (KBr, cm<sup>-1</sup>): 3421 (OH), 2920 (CH<sub>3</sub>), 1775 (C=O), 1620 (C=N), 1585 (C=C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 3.39 (s, 3H, CH<sub>3</sub>-N), 6.82–8.16 (m, 7H, Ar-H), 8.74 (s, 1H, CH=N), 8.95 (s, 1H, OH). <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>): δ 28.7 (CH<sub>3</sub>-N), 108.7, 109.3, 116.4, 118.9, 119.9, 127.2, 127.9, 131.8, 134.9, 137.6, 142.8, 152.0 (CH<sub>Ar</sub>), 154.6 (N=C), 158.5 (C=O).
- > 6-((E)-(5-chloro-2-hydroxyphenylimino)methyl)-3-methylbenzo[d]oxazol-2(3H)-one (4f)  
 MF: C<sub>15</sub>H<sub>11</sub>O<sub>2</sub>N<sub>2</sub>Cl, MW: 302.71, yellow powder, Mp: 276–278 °C, yield: 58%. IR (KBr, cm<sup>-1</sup>): 3390 (O-H), 2696 (CH<sub>3</sub>), 1766 (C=O), 1627 (C=N), 1605–1589 (C=C), 748 (C-Cl). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 3.33 (s, 3H, CH<sub>3</sub>-N), 6.89–8.13 (m, 6H, Ar-H), 8.76 (s, 1H, CH=N). <sup>13</sup>C-NMR (100MHz, CDCl<sub>3</sub>): δ 28.7 (CH<sub>3</sub>-N), 109.3, 117.8, 118.9, 123.4, 127.1, 127.5, 131.5, 135.2, 138.9, 142.8, 150.9 (CH<sub>Ar</sub>), 154.5 (N=C), 160.2 (C=O).

## 2.2. Antioxidant evaluation

### 2.2.1. General procedure for evaluation of DPPH radical activity

Free radical scavenging activity of the investigated compounds against stable radical (DPPH) was determined spectrophotometrically, and estimated as previously described with some minor modifications [45]. A 200 µg.mL<sup>-1</sup> stock solution of the selected compounds was prepared by dissolving 0.2 mg of each compound in 2 mL of ethanol, followed by serial dilution into five lower concentrations. For the free radical stock solution, 7.09 mg of DPPH was dissolved in ethanol and diluted to prepare 0.23 µg.mL<sup>-1</sup> of DPPH solution. Final concentration of compounds with varied final concentration (6.25, 12.5, 25, 50 and 100 µg.mL<sup>-1</sup>) was added and mixed rapidly, at an equal volume, to ethanolic solution of DPPH and incubated in the dark at room temperature for 30 min. All tests were repeated three times, ascorbic acid (vitamin C) was used, as a positive control in our assays.

The free radical scavenging activity of each solution was then calculated as percent inhibition (%RSC) according to the following equation:

$$\%RSC = 100 * \frac{(A_{\text{blank}} - A_{\text{sample}})}{A_{\text{blank}}} \quad (1)$$

Where  $A_{\text{blank}}$  is the absorbance of the control reaction (containing all reagents except the test compound) and  $A_{\text{sample}}$  is the absorbance of the test compound. The values of IC<sub>50</sub>, defined as the effective concentration at which 50% of the radicals were scavenged and were calculated to evaluate the antioxidant activities.

### 2.3. Theoretical investigate

In this study, various *in silico* approaches such as density functional theory (DFT), molecular docking and ADMET analysis have been reported to elucidate the reactivity and selectivity of our organic reactions, thus to predict the drug-receptor interactions that hold a protein and a ligand together in a bound state and to estimate likelihood of our synthesized products to pass the clinic trials.

**Table 1**  
Newly synthesized 6-iminobenzoxazole derivatives 4(a-f).

Compounds	R	Time (min)	Yield %
4a	H	7	51
4b	2-SH	5	78
4c	4-OMe	10	66
4d	4-OH	5	53
4e	2-OH	10	64
4f	2-OH,5-Cl	5	58

### 2.3.1. Ligand preparations

We transferred from Chemdraw 3D software (Chem-Draw, 2019) to Gaussian 09 software (Gaussian 09) as an MDL mol file, All the 3D chemical structures of the synthesized molecules. Using Gaussian software 09 with semi-empirical method AM1, we pre-optimized all structures and then they were optimized using Density Functional Theory (DFT) method using the basis set B3LYP/6-31G(d,p) [46–47] to obtain the most stable conformation, which was also used to elucidate global and local reactivity indices, also thermodynamic parameters. Molecular electrostatic potential (MEP) maps of the optimized structure were calculated and generated with Gaussview 05 software. In order to analysis the affinity of ligands atoms into active site of the protein, all the optimized structures were combined in one database on MOE 2015 software (Molecular Operating Environment).

### 2.3.2. Protein preparation

The crystal structure of nitric oxide synthase NOS at a resolution of 2.35 Å, was saved from the protein databank (<http://www.rcsb.org>) with their PDB identification code (PDB ID: 1m8d Table 1). Using default parameters included in MOE software, the sequence of the protein was corrected by removing cofactors. After that, the protein structure was prepared by correcting the missing bonds, which were broken in X-Ray diffraction, and then the hydrogen atoms were added. The active site was searched using the site finder tool.

## 3. Results and discussion

### 3.1. Chemistry

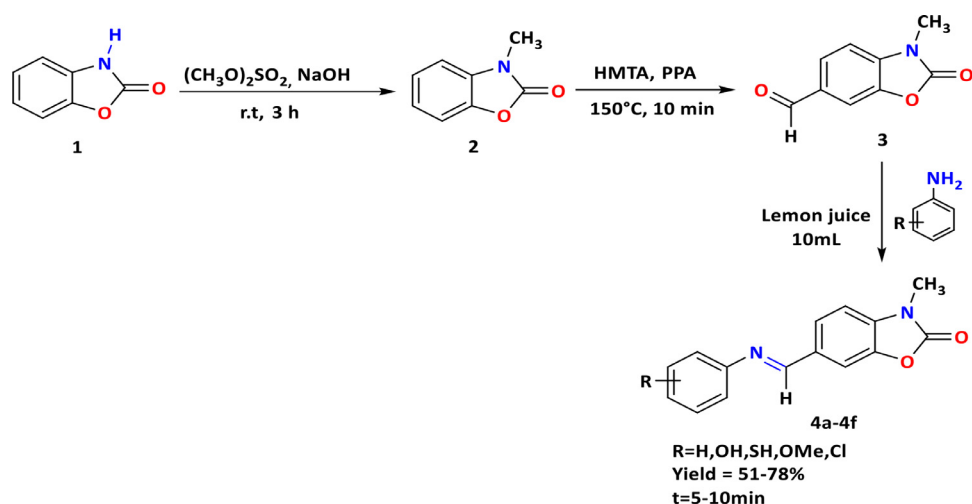
In our research program focused on the synthesis of novel Schiff bases benzoxazolone derivatives with very timely methods [48–49]. The synthesis pathway illustrating our approach for the synthesis of the title compounds is given in (Scheme 1). Starting materials (1, 2 and 3), were synthesized according to the literature method [42–44]. The condensation of 3-methyl-6-carbaldehyde-2(3H) benzoxazolinone (28 mmol) and various primary amines (28 mmol) was examined in a Lemon Juice (10 ml) at room temperature to give the target compounds with an azomethine group at the 6-position of the benzoxazole ring 4(a-f).

The findings has shown that the use of lemon juice under catalyst-free condition, has resulted in the formation of the desired Schiff bases derivatives in shorter reaction times (5–10 min) and moderate yields (51–78%) (Table 1).

Therefore, this new approach is more eco-friendly, involving mild reaction conditions and simple workup compared to traditional methods in the synthesis of 3-methyl-imino-2(3H) benzoxazolinone previously published [48].

### 3.2. Antioxidant Activity

The antioxidant activity of the compounds 4(d-f) was investigated and evaluated for their free radical scavenging activity using



Scheme 1. Synthesis of 6-iminobenzoxazole derivatives.

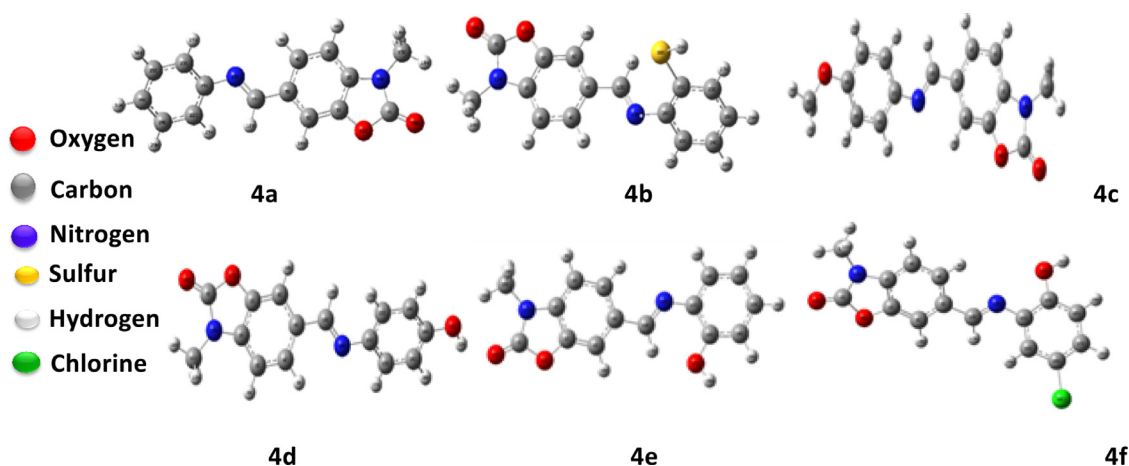


Fig. 2. Optimized structure of titled compounds obtained at B3LYP/6-31G (d,p) level in gas phase.

Table 2  
Radicals scavenging activities of compounds (4d, 4e, 4f) and reference compound ascorbic acid.

Compounds	%RSC					
	6.25 $\mu\text{g.mL}^{-1}$	12.5 $\mu\text{g.mL}^{-1}$	25 $\mu\text{g.mL}^{-1}$	50 $\mu\text{g.mL}^{-1}$	100 $\mu\text{g.mL}^{-1}$	IC <sub>50</sub>
4d	5.46	21.24	48.33	60.65	78.44	3.39
4e	23.12	48.33	77.63	83.35	86.35	2.13
4f	7.53	20.72	42.32	45.91	73.46	3.68
Ascorbic acid	9.37	65.27	70.80	94.08	94.53	2.16

the radical DPPH (2,2-diphenyl-2-picrylhydrazylhydrate). The IC<sub>50</sub> was calculated for each compound with ascorbic acid as standard compound, and the results are summarized in (Table 2).

The studied compounds showed activity in the range of 2.13–3.68  $\mu\text{g.mL}^{-1}$  (Table 2). The Compound 4e (IC<sub>50</sub> = 2.13  $\mu\text{g.mL}^{-1}$ ) showed highest activity, more active than the standard ascorbic acid (IC<sub>50</sub> = 2.16  $\mu\text{g.mL}^{-1}$ ).

### 3.3. Theoretical investigation

#### 3.3.1. Structure-activity relationship study (SAR)

Nowadays, in theoretical chemistry, several approaches *in silico* have been reported to describe the structure activity relationship. One of most calculations methods, based on the correlation

of systems comprising a large number of electrons is Density Functional Theory (DFT) [50]. It's usually selected to represent the potent qualitative and semi-quantitative model for describing chemical reactivity in terms of quantum theory, almost at the cost of a Hartree-Fock calculation [51].

#### 3.3.2. Geometry optimization

Several quantum chemistry calculations for Schiff bases compounds have already been published in the literature [52], the optimization of different structures was performed out by Gaussian 09 at the B3LYP/6-31G (d,p) level. The (Fig. 2) shows the structure of our compounds obtained after the geometry optimization in the gas phase.

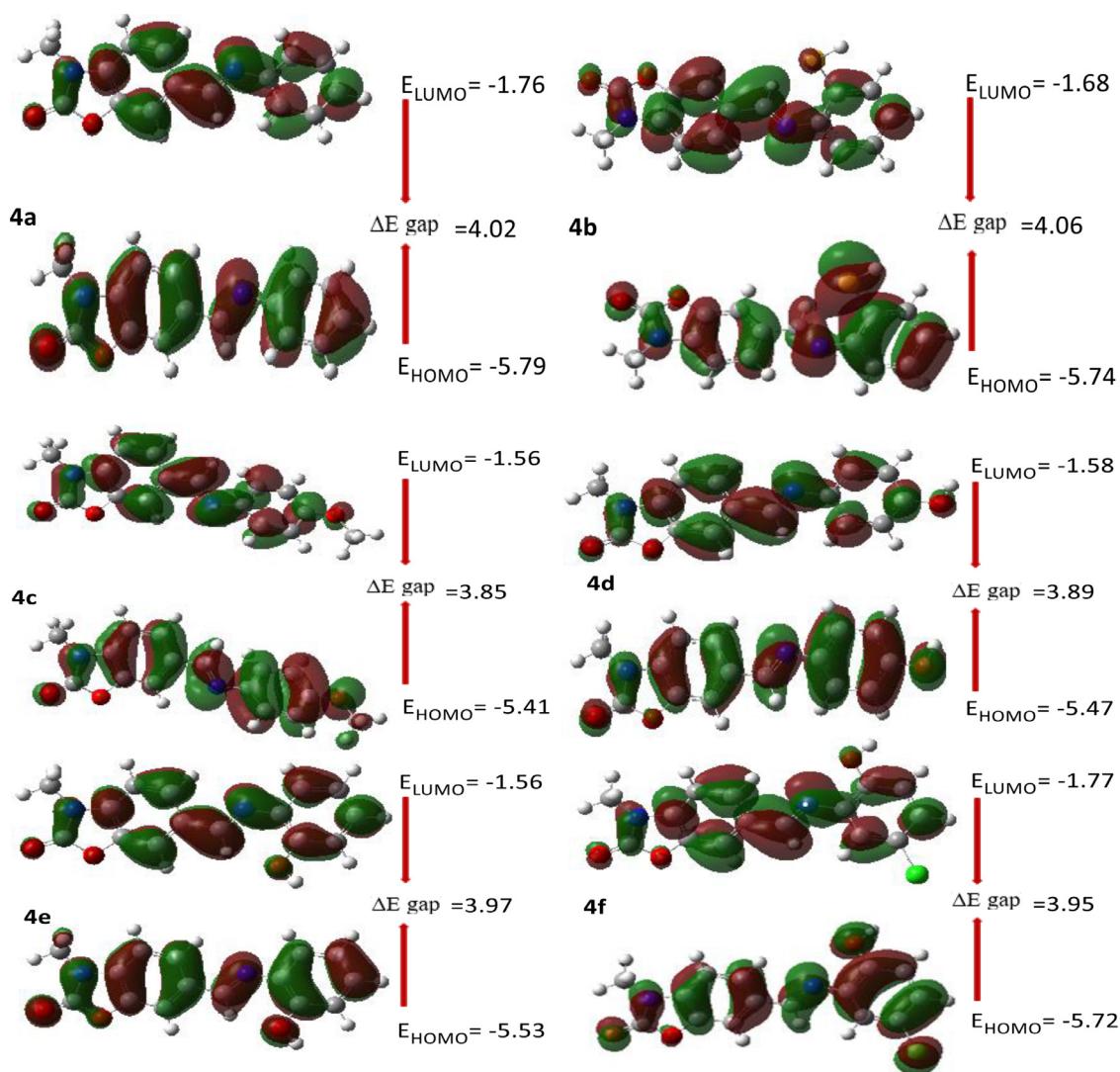


Fig. 3. 3D representation of HOMO, LUMO and their energy gap ( $\Delta E$  gap) of the studied molecules 4(a-f).

### 3.3.3. Frontier molecular orbital (FMO) analysis

The representation 3D of the frontier molecular orbital LUMO and HOMO calculated in the gas phase for the different imines are signified in (Fig. 3).

The energy difference between HOMO and LUMO is termed energy gap and is a significant stability index. Great energy gap makes a molecule less polarisable, less reactive and highly stable while insignificant energy gap makes a molecule more polarisable, more reactive and less stable [53]. The values of (HOMO, LUMO) level of energy, gap energy and total energy and dipolar moment ( $\mu$  total) as well as linear polarizability ( $\alpha_{\text{TOT}}$ ) are described in (Table 3)

As we can observe from the results of (Table 3), the energy gap in the increasing order of study compounds is found to be  $4c > 4d > 4f > 4e > 4a > 4b$ . Compound 4c has the lowest gap (3.85 eV) and the most values of linear polarizability (231.3 Bhor<sup>3</sup>). Therefore, it is less stable and more lipophilic and reactive.

### 3.3.4. Analysis of the global and local reactivity index

Since the 1981, Parr and Yang reported some reactivity descriptors to provide a precise theoretical framework to often ill-defined concepts to characterize chemical reactivity [54]. This proposed model has been judged as the most effective and still seems

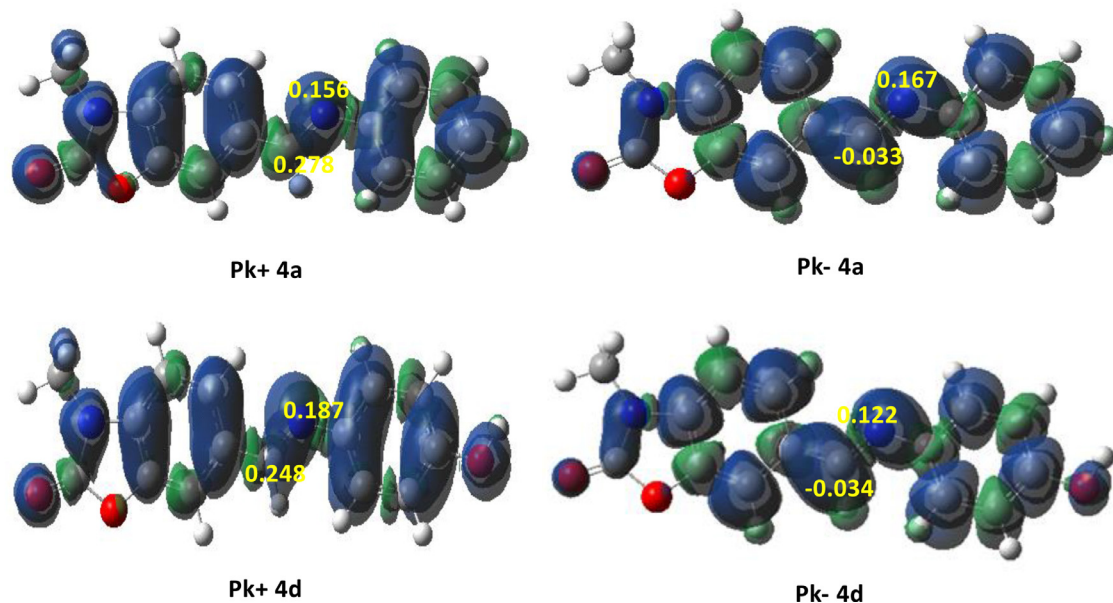
Table 3

The calculated parameters of compounds 4a-4f obtained at B3LYP/6-31G (d,p) level in gas phase.

Descriptors	Gas phase					
	4a	4b	4c	4d	4e	4f
$E_{\text{HOMO}}$ (eV)	-5.79	-5.74	-5.41	-5.47	-5.53	-5.72
$E_{\text{LUMO}}$ (eV)	-1.76	-1.68	-1.56	-1.58	-1.56	-1.77
$ \Delta e_{\text{gap}} $ (eV)	4.02	4.06	3.85	3.89	3.97	3.95
$E$ (u.a)	-877	-1236	-593	-914	-914	-1373
$\mu_{\text{total}}$ (D)	4.09	3.34	4.31	4.06	3.50	4.80
$\alpha_{\text{TOT}}$ (Bhor <sup>3</sup> )	202.6	207.2	231.3	214.9	213.4	222.05

the most promising [55]. Currently to describe the reactivity of molecules two types of chemicals reactivity descriptors are used, one of these descriptors is global index, which are based on predictions of electronic properties. The second descriptor is local index which using to study of selectivity.

*Analysis of global properties.* As global properties, a large number of reactivity indices have been suggested in the literature, we must mention that the chemical potential  $\mu$  and the hardness  $\eta$  are the two global descriptors from which other global indices can be eval-



**Fig. 4.** 3D maps of ASDs for the cation and anion radicals of compounds 4a and 4d with the values of the nucleophilic  $P_{K^-}$  and electrophilic  $P_{K^+}$  Parr functions.

**Table 4**

Calculated values of the global reactivity descriptors for synthesized imines 4(a-f) studied by B3LYP / 6-31G (d, p) level in gas phase.

Gas Phase						
Descripteurs	4a	4b	4c	4d	4e	4f
IP	5,79	5,81	5,74	5,41	5,53	5,72
EA	1,76	1,67	1,68	1,56	1,58	1,77
$\mu$	-3,77	-3,71	-3,49	-3,53	-3,55	-3,74
X	3,77	3,71	3,49	3,53	3,55	3,74
$\eta$	2,01	2,03	1,92	1,94	1,98	1,97
S	0,49	0,49	0,51	0,51	0,50	0,50
$\omega$	3,54	3,39	3,15	3,20	3,16	3,55
N	3,69	3,74	4,07	4,01	3,95	3,76

uated such as the global softness S or the global electrophilic index  $\omega$ . Herein, we have also calculated the global indices of molecular system (Table 4) using B3LYP/6-31+G (d, p) level of DFT theory from the energy HOMO and LUMO levels according to the following equations:

Electrophilicity index [56]

$$\omega = \mu^2 / (2\eta) \quad (2)$$

To determine this electrophilicity, we calculated the chemical potential [57]. Which is a negative value and chemical hardness [58].

$$\mu = -\chi (E_{\text{HOMO}} + E_{\text{LUMO}}) / 2 \quad (3)$$

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

Molecular softness [59], nucleophilicity index [60].

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

$$N = E_{\text{HOMO}} - E_{\text{HOMO}}(\text{TCE}) \quad (6)$$

The small values of chemical potential were observed with compounds 4a, and 4f with ( $\mu = -3.77, -3.74$ ) respectively. This results could partly describe the molecules as strong electron-acceptor reagents. While the higher values of chemical potential

**Table 5**

Local electrophilic and nucleophilic indices for the compounds 4a and 4d calculated by DFT at the B3LYP / 6-31G level (d, p).

Atom	4a		4d	
	C-11	N-13	C-11	N-13
$P_{K^+}$	0.278949	0.156326	0.248335	0.187161
$P_{K^-}$	-0.033948	0.167439	-0.03476	0.122758

( $\mu = -3.49$ ) and the low values of chemical hardness  $\eta = 1.92$  were observed with compound 4c, it will act as strong electron-donor molecule.

Also, the minimum values of electron affinity (EA = 1.56, 1.58 eV) and ionization energy (IP = 5.41, 5.53 eV) were observed with compounds 4d and 4e implies a larger tendency of the atom to accept an extra electron and indicate a high antioxidant activity which are in agreement with DPPH test.

The values of nucleophilicity and electrophilicity of the studied Schiff base allows them to be classified as strong electrophilic  $> 1.5$  [61] and nucleophilic  $> 3$  reagents [62]. Thus, 4a and 4f are a good electrophile species ( $\omega = 3.54, \omega = 3.55$ ) and 4c is a good nucleophile species with  $N = -4.07$ .

*Analysis of locals properties.* According to Domingo's polar model [63], the static indices of local electrophilic  $\omega_k$  ( $P_{K^+}$ ) [64] and local nucleophilic  $N_k$  ( $P_{K^-}$ ) [65] are reliable descriptors for the prediction of the most favored electrophilic-nucleophilic interaction for the chemical formation of a chemical bond between two atoms. The electrophilic and nucleophilic Parr functions represented by the expressions  $\omega_k = \omega \cdot P_{K^+}$  and  $N_k = N \cdot P_{K^-}$  [64] are respectively the local electrophilic  $\omega_k$  and local nucleophilic  $N_k$  indices, where  $P_{K^+}$  and  $P_{K^-}$  have been obtained by analyzing the Mulliken atomic spin density (ASD) of the anion radical and the cation radical of the compounds (Fig. 4).

Analysis of the Parr function data for the synthesized Schiff bases 4a and 4d as an example shows that the local electrophilic indice is mainly concentrated on the C-11 carbon atom (Table 5), which indicates that this atom is the most electrophilic center in the molecule. On the other hand, the local nucleophilic index concentrated on the nitrogen atom N-13, allowed us to say

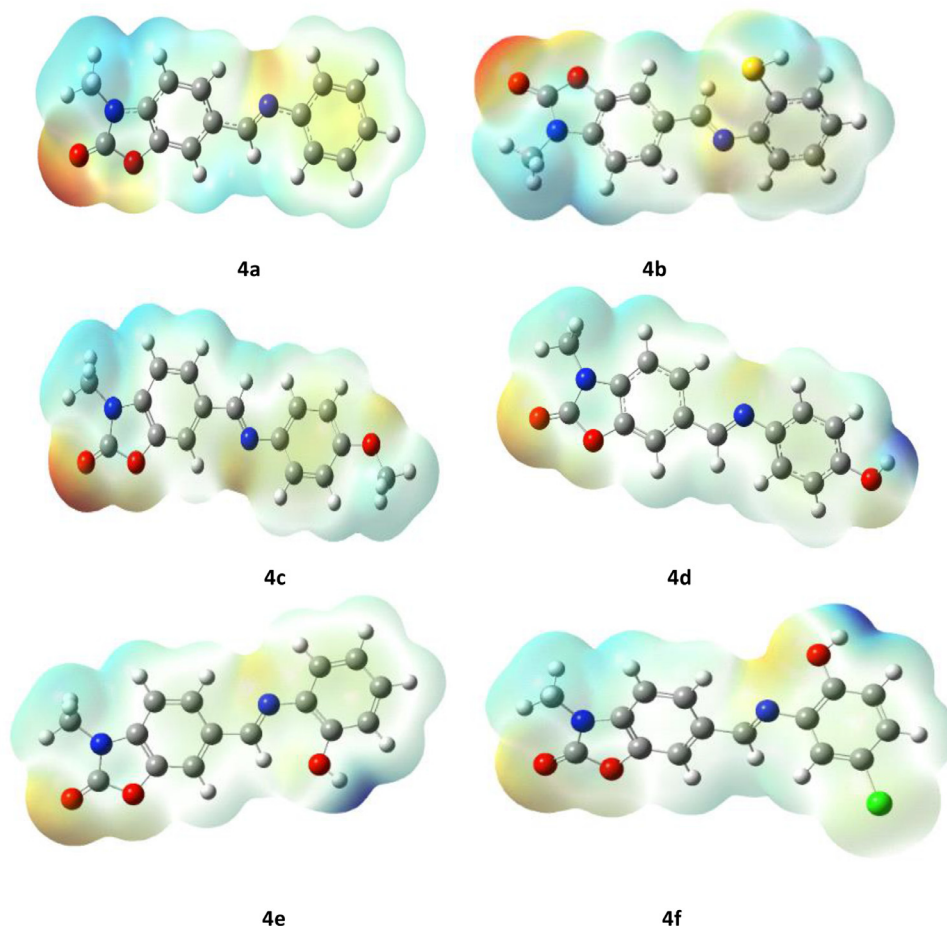


Fig. 5. 3D map of molecular electrostatic potential density in gas phase for the synthesized Schiff bases 4(a-f).

that nitrogen is the most nucleophilic center for our described products.

### 3.3.5. Molecular electrostatic potential (MEP)

The molecular electrostatic potential has become a current guide to the electrostatic interactions between molecules. In this computational study, we determined the molecular electrostatic potential (MEP) of titled molecules 4(a-f) with DFT method in B3LYP/6-31G (d,p) for the optimized geometries. The results of MEP for the investigated molecules are presented in (Fig. 5).

Therefore, the red and yellow areas represent the negative regions indicates the site for electrophilic attack, the blue area show the positive regions determines the site of nucleophilic reaction and the green color illustrates the regions of zero potential.

The azomethine group (C=N) and the carbonyl atoms (C=O) in the oxazole ring represents the most electronegative regions (yellow and red colors respectively) of all Schiff bases compounds, and can be confirmed as a distinct site of electronegativity attack. The hydroxyl and thiol atoms of compounds 4d, 4e and 4b have a positive charge (blue region), which can act as nucleophilic centers.

### 3.3.6. Thermodynamic parameters

The thermodynamic statistics can be used to estimate the ways of chemical reactivity according to the second law of thermodynamics in thermo chemical field, from which the association between energy, structural and reactivity characteristics of the molecules can be explained. Therefore thermodynamical parameters of Schiff bases were described at B3LYP/6-31+G (d,p) level of theory in gas phase, the values total energy (E<sub>tot</sub>), enthalpy and

Table 6

Thermodynamic parameters [E<sub>tot</sub> (u.a), S and Cv (Cal.mol<sup>-1</sup>.K<sup>-1</sup>), H and G (Kcal.mol<sup>-1</sup>)], for synthesized imines 4(a-f) calculated by DFT at the B3LYP / 6-31G (d, p) level.

	4a	4b	4c
E(tot)	-838	-1236	-953
S	126	137	139
H	-526192	-776051	-598034
Cv	59.601	65.879	68.759
G	-526230	-776092	-598076
	4d	4e	4f
E(tot)	-914	-914	-1373
S	132	134	139
H	-573389	-573387	-861787
Cv	64.323	64.328	68.161
G	-573428	-573427	-861829

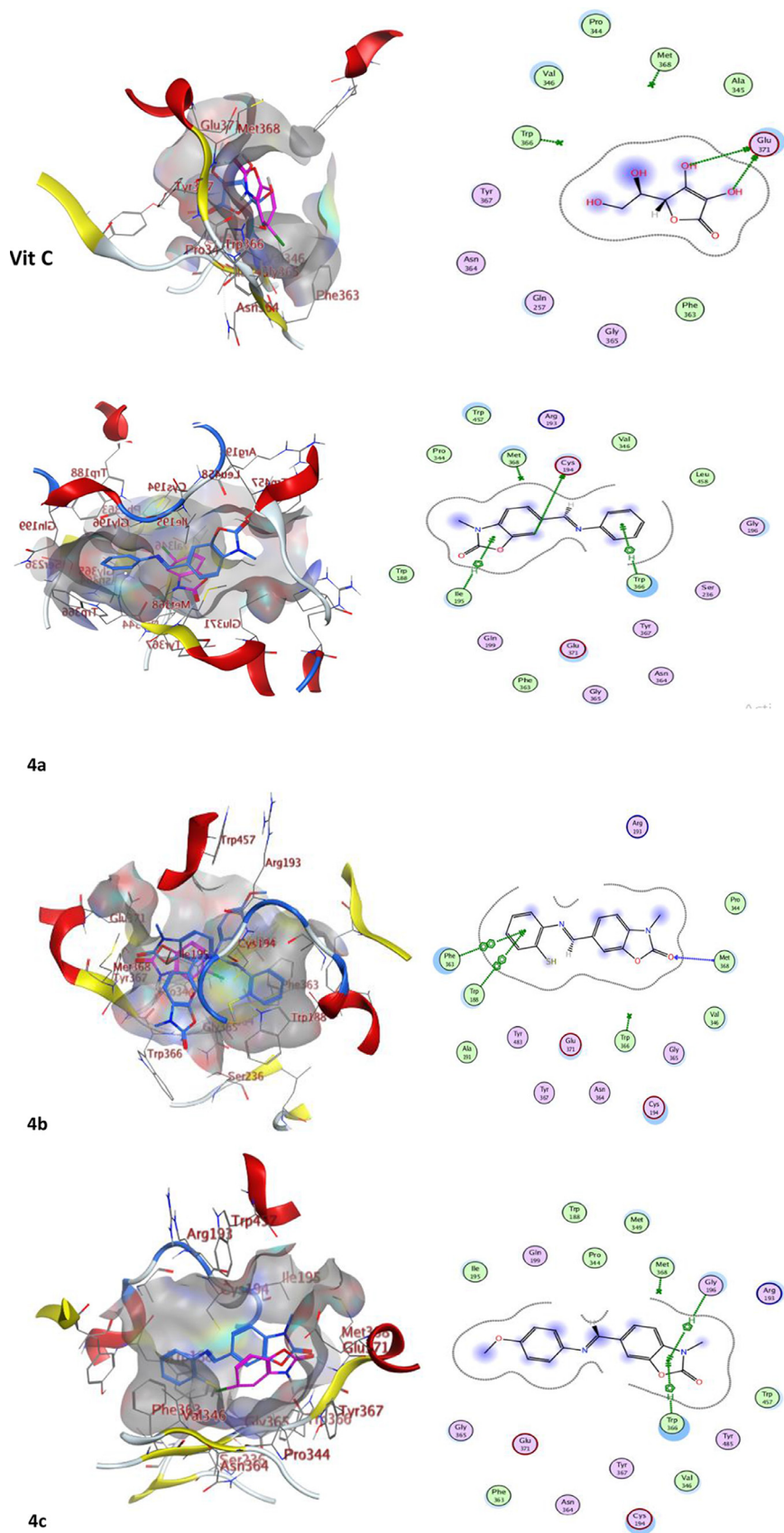
free gibbs energy, specific heat and entropy have been computed (Table 6).

We can notice by thermodynamic conveniences that the synthesized Schiff bases compounds are less stable, thus confirming the experimental results that we have found.

### 3.4. Binding affinities, amino acids interaction of the ligands into nitric oxide synthase (NOS)

A specific protein nitric oxide synthase NOS were identified as target for antioxidants compounds. This study was approved out in order to describe in silico antioxidants activity of our compounds





**Fig. 6.** 2D, 3D schematic representations of the NOS catalytic site. Interaction between Schiff bases ligands 4(a-f) and NOS.

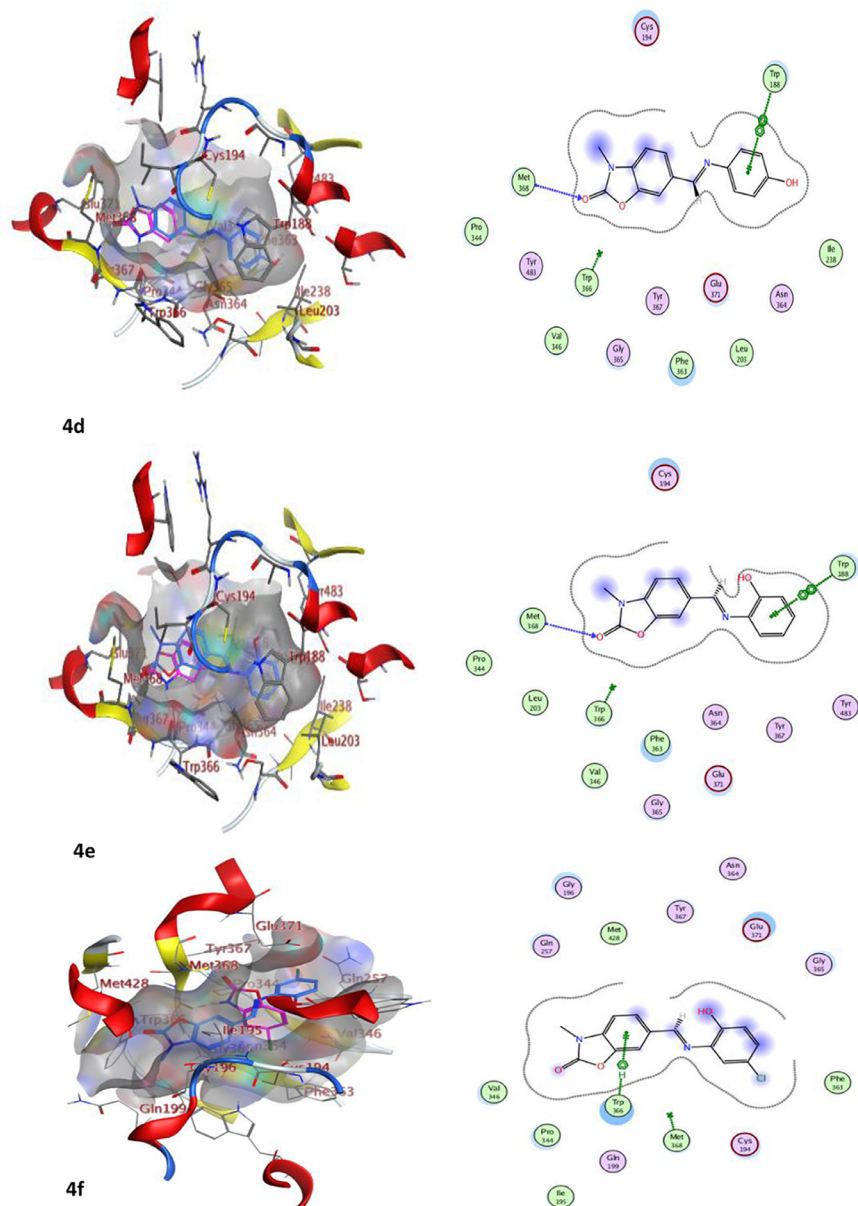


Fig. 6. Continued

previously synthesized, the important binding interactions of actively docked conformations are listed in (Table 7).

As shown in Table 7, all binding interactions of all compounds have in some case a similar hydrogen bonding, hydrophobic interaction, H- $\pi$  interactions and  $\pi$ - $\pi$  interactions. From the structure activity relationship, the scoring values of all compounds within the active site of above the protein can be used to explain the straight comparison of inhibitory potency and selectivity index profiles. The 4e, and 4d showed a stronger interaction with nitric oxide synthase (NOS) receptor than the other compounds with lowest scoring are  $-11.003$  and  $-9.1296$  kcal mol $^{-1}$  respectively, which explain that compound 4e and 4d have a similar antioxidants activity comparing by 4f. The best-docked conformations of 4(a-f) with receptor NOS are shown in (Fig. 6).

The compounds 4d and 4e bind to the nitric oxide synthase NOS through hydrogen bond and  $\pi$ - $\pi$  interactions with Met 368 and Trp 188 residues respectively compared with 4f. In addition, they showed other interactions as hydrophobic interactions, ionic, H- $\pi$  interactions. These results approve that the compound 4d and

4e can be considered as potential inhibitors of nitric oxide synthase NOS.

### 3.5. Ligand based druglikeness and ADME/toxicity

This analysis is realized to simplify the development of innovative drug compounds. To be approved the molecules must comply with the following Lipinski rules: molecular weight:  $\leq 500$ , number of hydrogen bond donors:  $\leq 5$ , number of hydrogen bond acceptors:  $\leq 10$ , lipophilicity (expressed in Log P):  $\leq 5$  and molar refractivity from 40 to 130. The results of this study are shown in (Table 8).

As shown in Table 8, the co-crystallized ligand has a molecular weight  $\geq 500$  g/mol, so it doesn't obey Lipinski's first rule. 4(a-f) and Ascorbic acid have respectively the following molecular weights: (252.27, 284.34, 282.29, 268.27, 268.27, 302.71, 176.12) g/mol, they have all a molecular weight  $\leq 500$ . These molecules have the following Topological Polar Surface Area (TPSA) values (47.50, 86.30, 56.73, 67.73, 67.73, 67.73, 107.22) ( $\text{\AA}$ ) $^2$  respectively, the lowest TPSA (20-130 ( $\text{\AA}$ ) $^2$ ) always give good results. By

**Table 7**

Docking results of compounds 4(a-f) for a potential inhibition of nitric oxide synthase.

	S (Kcal/mol)	Hydrogen bonds	Hydrophobic interactions	Ionic interactions	H- $\pi$ interactions	$\pi$ - $\pi$ interactions
A	-7.6620	Met 368, Trp 366	Ser436, Trp188, Pro 344, Ile198, Ser 236, Ala 433, Gly196, Gln199, Gly365, Asn364, Met428, Ile195, Phe 363, Val 346	Glu 371	/	/
B	-7.3345	Glu 371	Ala445, Gln257, Gly365, Tyr367, Asn364, Met428, Ile195, Phe 363, Tyr 367	/	/	/
4a	-8.5747	Cys 194	Trp188, Pro344, Val346, Ser236, Gly196, Gln199, Gly365, Asn364, Met368, Phe363, Tyr367, Trp457, Arg193, Leu458	Glu 371 Cys 194	Trp 366, Ile 195	/
4b	-8.7413	Met 368	Trp366, Pro344, Ile191, Val346, Gly365, Asn364, Tyr367, Arg193, Tyr483	Cys 194 Glu 371	/	Phe 363, Trp 188
4c	-9.4688	/	Trp188, Pro344, Trp485, Val346, Gln199, Met368 Gly365, Asn364, Met349, Ile 195, Arg193, Phe363, Tyr367, Tyr 485	Cys 194 Glu 371	Gly 196, Trp 366	/
4d	-11.003	Met 368	Leu203, Trp366, Pro344, Val346, Tyr483, Gly365, Asn364, Ile238, Phe363, Tyr 367	Cys 194 Glu 371	/	Trp 188
4e	-9.1296	Met 368	Leu203, Trp366, Pro 344, Gly 365, Asn 364, Tyr 483, Phe 363, Val346, Tyr 367	Cys 194 Glu 371	/	Trp 188
4f	-7.3657	/	Pro 344, Met 368, Gly196, Gln199, Gly365, Asn364, Met 428, Ile195, Phe363, Val 346 Tyr367, Gln257	Cys 194 Glu 371	Trp 366	/

Foot note: A: co-crystallized Ligand, B: ascorbic acid.

**Table 8**

Drug-likeness results of compounds 4(a-f).

Drug likeness properties	Vit C	4a	4b	4c	4d	4e	4f
Molecular weight g/mol	176.12	252.27	284.34	282.29	268.27	268.27	302.71
Consensus Log P o/w	-1.41	2.88	3.17	2.89	2.58	2.58	3.24
Log S	-0.10	-3.27	-4.24	-3.43	-3.33	-3.33	-3.97
NHBA	6	3	3	4	4	4	4
NHBD	4	0	0	0	1	1	1
Molar refractivity	35.12	75.43	82.68	81.92	77.45	77.45	82.46
Lipinski	YES	YES	YES	YES	YES	YES	YES
Ghose	NO	YES	YES	YES	YES	YES	YES
Veber	YES	YES	YES	YES	YES	YES	YES
Egan	YES	YES	YES	YES	YES	YES	YES
Muegge	NO	YES	YES	YES	YES	YES	YES
Bioavailability Score	0.56	0.55	0.55	0.55	0.55	0.55	0.55
Synthetic accessibility (SA)	3.47	2.96	2.93	2.96	2.91	2.94	2.92
TPSA (Å) <sup>2</sup>	107.22	47.50	86.30	56.73	67.73	67.73	67.73
N° of rotatable bonds	2	2	2	3	2	2	2

**Table 9**

The ADME/T test result of ligands (various pharmacokinetic and pharmacodynamic properties).

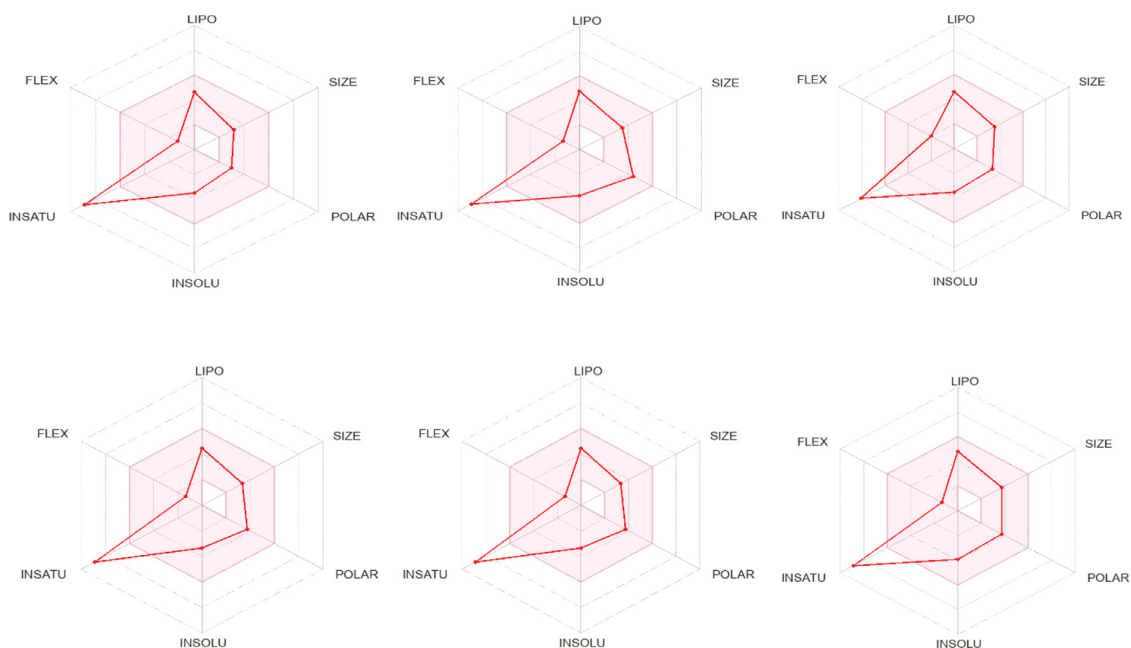
Class	Properties	Vit C	4a	4b	4c	4d	4e	4f
Absorption	Caco-2 permeability	-0.482	1.334	1.308	1.346	1.112	0.931	1.022
	Pgp-inhibitor	NO	NO	NO	NO	NO	NO	NO
	Pgp-substrate	NO	YES	YES	NO	YES	YES	YES
	Skin permeability	-3.14	-2.52	-2.76	-2.31	-2.70	-2.83	-2.85
	Human intestinal Absorption (HIA)	39.71	99.13	92.98	97.79	93.35	93.91	92.95
Distribution	BBB (blood-Brain Barrier)	-1.031	0.188	0.234	0.109	-0.256	-0.248	-0.479
	VDss	-0.092	-0.378	0.282	0.022	-0.037	0.094	0.178
Metabolism	CYP450 2D6 Substrate	NO	NO	NO	NO	NO	NO	NO
	CYP450 3A4 Substrate	NO	NO	YES	YES	NO	YES	YES
	CYP450 2C19 inhibitor	NO	YES	YES	YES	YES	YES	YES
	CYP450 1A2 inhibitor	NO	YES	YES	YES	YES	YES	YES
	CYP450 2C9 inhibitor	NO	NO	YES	NO	YES	YES	YES
	CYP450 2D6 inhibitor	NO	NO	NO	NO	NO	NO	NO
	CYP450 3A4 inhibitor	NO	NO	YES	NO	YES	NO	NO
Toxicity	hERG (hERG Blockers)	NO	NO	NO	NO	NO	NO	NO
	Maximum Tolerated Dose	1.386	1.282	0.262	-0.127	0.352	0.156	0.241
	Acute oral toxicity	1.298	2.492	2.06	2.14	1.931	1.939	2.161

comparing the lipophilicity (Log P) values of molecules, we find, they all show very good results  $\leq 5$  and can be easily absorbed in body.

Though, acid ascorbic and Schiff bases 4 (a-f) have NHBA values of (6, 3, 3, 4, 4, 4) and NHBD (4, 0, 0, 0, 1, 1, 1) respectively, also molar refractivity (35.12, 75.43, 82.68, 81.92, 77.45, 77.45, 82.46). Therefore, we can observe that compounds 4a-f are suitable by the five Lipinski rules. The results of Egan, Ghose's and Muegge's rules confirmed that the synthesized Schiff bases could be considered as good drugs bioactive compounds.

The bioavailability radar of Schiff bases evaluated using the swissADME web tool is presented in (Fig. 7). They revealed that schiff bases 4a-4f had better physicochemical profiles makes them suitable for oral administration. However, these compounds had high unsaturation indicated by an offshoot of one of the saturations (INSATU) vertex.

In silico screening software of pharmacokinetic and pharmacodynamic properties were designated by ADME/T analysis (Table 9). In absorption part, Caco-2 permeability and Human intestinal Absorption (HIA) showed that 4(a-f) and ascorbic acid are easily



**Fig. 7.** Oral bioavailability Radar of Schiff bases 4(a-f).

absorbed in intestine. In addition, when we looked at our Pgp-glycolprotein data, we confirmed that the 4(a-f) are easily absorbed in the cell.

Predicting the skin permeability (SP) rate as a vital metric for transdermal drug delivery is important in the pharmaceutical, cosmetics, and agrochemical industries. Consequently, as show in table, all examined compounds have a higher skin permeability (SP) rate.

In the distribution part, the BBB (Blood-Brain-Barrier) is a barrier that protects the brain from outside substances. The BBB is one of the most critical pharmacological characteristics that can assist reduce side effects and toxicity while also increasing therapeutic efficacy. Based on our findings, we reported that all compounds 4(a-f) have a higher capacity to pass into the brain. According to the results of the metabolism section, the 4(a-f) are also considered as potential inhibitors of cytochrome P450 1A2, P450 2C19 and P450 2C9.

In this investigation, it was discovered that substances with a high lipophilicity have lesser retention, increased BBB permeability, and a higher SP rate.

As a final point, in the toxicity part, we confirmed that the compounds 4(a-f) current negative test. This ADMET analysis demonstrated that the synthesized compounds have higher drugs-likeness.

#### 4. Conclusion

In this article, we are reporting an environmentally benign approach with shorter reaction times and high purity for the synthesis of Schiff bases containing 2 (3H) benzoxazolone moiety in lemon juice under solvent free conditions. Therefore, this solvent-free, non-hazardous and economic approach for organic synthesis, make this method attractive for the synthesis of potential biologically active molecules. Preliminary antioxidant activity by DPPH method for three phenolic Schiff bases (4d, 4e and 4f) was evaluated and the  $IC_{50}$  value was determined for every compound revealed that the compound 4d showed promising antioxidant activity, compared to the ascorbic acid, used as a standard compound.

On the other hand, a theoretical study has also been performed using the DFT/B3LYP method and 6-31G (d,p) basis set in gas phase to explain the reactivity behaviors of the products 4a-4f. Global

and local properties, molecular electrostatic potential and Thermodynamic parameters based on the HOMO and LUMO level analyses, were discussed. The molecular docking and ADMET results proved that the synthesized target compounds could be used as a lead for new antioxidant agents. Based on these results, we hope that could make an additional contribution and a solid platform for future studies in the development of novel potential antioxidant agents.

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