Quantum Chemical Studies of Some Hydrazone Derivatives

Mahougbe T. A. Kpota Houngue[1], Maurice N'bouke[2], Bardieu Atchade[2], Rodrigue Chabi Doco[1], Urbain A. Kuevi[1], Gaston A. Kpotin[1], Salomé D. S. Kpoviessi[2], Yacole G. S. Atohoun[1], Michael Badawi[3], Jean-Baptiste Mensah[1]

[1]Laboratoire de Chimie Théorique et de Spectroscopie Moléculaire, Faculté des Sciences et Techniques, Université d'Abomey-Calavi, Cotonou, Bénin
[2]Laboratoire de Chimie Organique Physique et de Synthèse, Département de Chimie, Faculté des Sciences et Techniques, Université d'Abomey-Calavi, Cotonou, Bénin
[3]LCP-A2MC EA 4632, Université de Lorraine, Saint-Avold, France
Email: alice.kpotahoungue@fast.uac.bj

Abstract

By the functional B3LYP and M05-2X of DFT and in two bases set, more and more extended (6-311G and 6-311G (d, p)), theoretical study of antioxidant properties of four hydrazones was carried out. The calculations made concern the geometrical, spectroscopic and electronic parameters of the molecules. Analysis of the results relating to the geometrical parameters was carried out by calculating interatomic distances, relative errors between calculated values and those obtained experimentally by X-ray diffraction found in the literature. The ^{13}C NMR spectra were calculated by GIAO (Gauge Including Atomic Orbitals) methods, and the results were subjected to statistical analysis by calculating Mean Absolute Deviation (MAD), Root Mean. Square (RMS) and the correlation coefficient (R^2), in comparison with experimental spectra. The analysis of the results of calculations of various electronic parameters (hardness (η), softness (S), electronegativity (χ), electrophile index (ω), energy gap (HOMO-LUMO)) reveals that, overall, the methods M05-2X/6-311G (d, p) and B3LYP/6-311G (d, p) found that (R) - (−) - carvone salicylhydrazone (N_2) is the most antioxidant molecule of the four molecules and also classify them according to their stability. This confirms the results obtained on the antitrypanosomal activity, the toxicity, the cytotoxicity and the selectivity of the synthesized compounds.

Keywords

M05-2X, Antioxidant, Hydrazones, DFT

1. Introduction

Nowadays, hydrazones are an important class of biologically active compounds [1]. They have a large number of interesting pharmaceutical derivatives and are also important because of their use as reaction intermediates in organic synthesis [2]. In addition, these compounds have [3] [4] [5] antitripanosomal [6] [7], antiplasmodic [8] [9] antibacterial properties and are potential inhibitors for several enzymes [10] and DNA synthesis for cell growth [11]. Because of these different properties, they have acquired important places in medecinal chemistry. Some derivatives of hydrazones are marketed. For example, nifurtimox is used for the treatment of Chagas' disease [12] and nifuroxazide (D) as an intestinal antiseptic [13]. Hydrazones can act as polydentate ligands depending on the nature of the substitution attached to the hydrazone unit. It should also be noted that the complexing properties of hydrazones enhance the potency of drug candidates for these molecules. Indeed, ligands (hydrazones) act synergistically with transition metals to enhance their biological activities [14]. Hydrazones are also used as analytical reagents, for a coating of ink polymer, pigment, and fluorescent materials [15].

Numerous biological activities of hydrazones are well known. Among them are antibacterial [16], anticonvulsant [17], antifungal [18] and antipyretic activities [19]. Thanks to their very high bioactivity and the biological importance of the hydrazone group and these derivatives, it therefore appears necessary to design and synthetize new derivatives with the hydrazone pharmacophore and to evaluate their pharmacological activity.

The main objective of this work is to study theoretically the biological activities of hydrazones. It will specifically study the antioxidant properties of these molecules and compare the theoretical results with those published in the literature.

2. Material and Methods

Four hydrazones were studied in this study: (S) - (+) - carvone salicylhydrazone, (R) - (−) - carvone salicylhydrazone, (S) - (+) - carvone benzohydrazone, (R) - (−) - carvone benzohydrazone.

The four molecules were synthesized in the Laboratory of Physical and Synthetic Organic Chemistry (LACOPS) of the Department of Chemistry of the Faculty of Science and Technology (FAST) of the University of Abomey-Calavi (UAC).

The studied molecules constituting systems of more than four atoms, the implementation of the DFT with functional ones such as B3LYP and MO5-2X will make it possible to calculate the spectroscopic, electronic and thermodynamic quantities of our molecules with a good precision.

In the case of this work, the studied molecules being of large size, we chose to use the base of Pople [20], the 6-311G (d, p). The structures of these molecules are as follows (Figure 1 and Figure 2). All theoretical calculations were
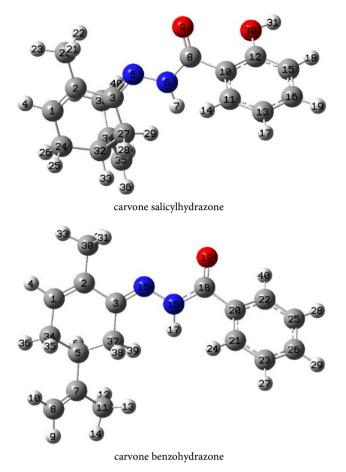
carvone salicylhydrazone

carvone benzohydrazone

Figure 1. Spatial representation of molecules.
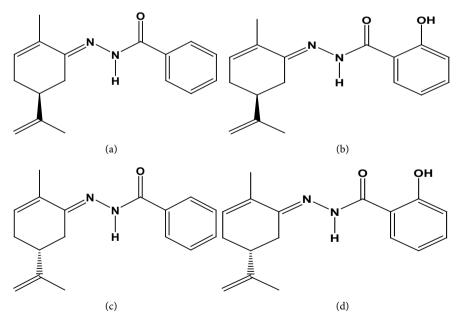

(a)

(b)

(c)

(d)

Figure 2. Structure of the four molecules. (a) Structure of (S) - (+) - carvone benzohydrazone (M_1); (b) Structure of (S - (+) - carvone salicylhydrazone (M_2); (c) Structure of (R) - (−) - carvone benzohydrazone (N_1); (d) Structure of (R) - (−) - carvone salicylhydrazone (N_2).

performed using the Gaussian 09 program [21] and the Gauss View 5.0.8 read interface. The work was carried out in the Laboratory of Theoretical Chemistry and Molecular Spectroscopy (LACTHESMO) of the Department of Chemistry of the Faculty of Science and Technology (FAST) of the University of Abomey-Calavi. The calculations are carried out on the server located at Metz Laboratory of Chemistry and Physics Approaches Multi-Scale Complex Environments of the University of Lorraine in France.

2.1. Structural Study of Molecules

For molecule with several degrees of freedom, the potential energy surface is a hyper-surface with several minima and maxima. The maxima correspond to transition states and the minima to equilibrium geometries or conformations of the molecule. In a state of minimal energy, the vibration frequencies of the molecule are all positive. The lowest of minima called global minima, represents the most stable conformation of the studied system. For each of the molecules studied, by the B3LYP and M05-2X functions of the DFT, geometric parameters relating to a minimum energy state were calculated, in the base 6-311G (d, p).

Also the relative error associated with the calculation of each parameter was evaluated. The lower this relative error, the closer the calculated theoretical value is to the experimental data.

The experimental data considered to evaluate the relative errors related to the calculation of the geometrical parameters of the molecules are those of hydrazide (see **Figure 3**).

2.2. Spectroscopic Study of Molecules

The ^{1}H NMR and ^{13}C NMR spectra of molecules were calculated with respect to DMSO (dimethylsulfoxide) taken as a reference molecule by the [23] approach. In order to appreciate the functional and the most suitable basis for carrying out the study of the biological properties of molecules, the calculated values of various parameters studied were compared with the corresponding experimental data. For this purpose, error discrepancies were calculated for some of the parameters examined and for others, we exploited statistical quantities such as Mean Absolute Deviation (MAD), Root Mean Square (RMS) and the correlation coefficient R^2. The calculations were performed at the GIAO level (Gauge Including Atomic Orbitals) with the two functional B3LYP and M05-2X, in the
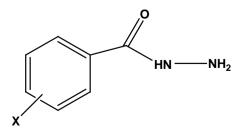

Figure 3. Structure of hydrazide [22].

base 6-311G (d, p). Calculations were made using the GIAO method.

1) *Mean Absolute Deviation* (*MAD*)

$$\text{MAD} = \frac{1}{N} \sum_{i=1}^{N} \left| \delta_{iexp} - \delta_{ical} \right|$$

2) *Root Mean Square* (*RMS*)

$$\text{RMS} = \sqrt{\frac{\sum_{i=1}^{N} \left(\delta_{iexp} - \delta_{ical} \right)^2}{N}}$$

3) *correlation coefficient* R^2

$$R^2 = \frac{\sum_{i=1}^{N} \left(\delta_{iexp} - \overline{\delta_{iexp}} \right) \cdot \left(\delta_{ical} - \overline{\delta_{ical}} \right)}{\sqrt{\sum_{i=1}^{N} \left(\delta_{iexp} - \overline{\delta_{iexp}} \right)^2 \cdot \sum_{i=1}^{N} \left(\delta_{ical} - \overline{\delta_{ical}} \right)^2}}$$

These three statistical quantities must build us on suitability of the combination Method/Base judicious for the study carried out. More lowly the values of MAD and RMS are, closer the theoretical results are to the experimental data, and the more convenient are the functional and the base. And, a value of the correlation coefficient (R^2) close to 1, indicates a good quality of the theoretical results.

2.3. Study of Electronic Properties

For each of the molecules denoted ArOH, the calculated electronic parameters were:
- The energy of the highest occupied molecular orbital (Ehomo).
- The energy of the lowest molecular orbital vacant (Elumo).
- The $Gap_{(\text{HOMO-LUMO})} = E_{\text{lumo}} - E_{\text{homo}}$, [24].
- The hardness (η) which expresses the resistance of a molecule to the change of its number of electrons or to the charge transfer. The harder the hardness, the less reactive the molecule is [25]:

$$\eta = \frac{(IP - EA)}{2}$$

- Softness (S), defined as the inverse of hardness [26]:

$$S = \frac{1}{2\eta}$$

- Electronegativity (χ), which measures the tendency of a chemical species to attract electrons [27]:

$$\chi = \frac{(IP + EA)}{2}$$

- The electrophilic index (ω), which represents the stabilizing energy of a molecule saturated by electrons coming from its surroundings [28]:

$$\omega = \frac{\chi^2}{2\eta}$$

The dipole moment (μ) of a molecule expresses the value of its great polarity. It constitutes a very important index of reactivity which makes it possible to define the biological properties related to the interaction with the active sites of the molecule. In fact, the polar molecules are defined by a non-zero dipole moment whereas the apolar ones are defined by a zero dipole moment [29].

3. Results and Discussions

The results from this section constitute a theoretical tool for geometric, spectroscopic and electronic characterization of four hydrazones by quantum chemistry methods. It consisted in calculating the geomeric, spectroscopic, and electronic parameters relating to transformations to which they can lend themselves.

3.1. Structural Study of Each Molecule

Tables 1-4 show the experimental and calculated values of some geometric parameters (lengths) of the (R) - (−) - carvone benzohydrazone molecule, the (S) - (+) - carvone benzohydrazone, (R) - (−) - carvone salicyldrazone and (S) - (+) - carvone salicyldrazone, on the one hand, and related relative errors, on the other hand. Analysis of these tables will make a comparative study of the experimental and calculated values.

Analysis of the results in Table 1 shows that, in general, the calculated values of the interatomic distances are very close to the experimental data for the two functional ones when we consider the (R) - (−) - carvone benzohydrazone.

The analysis of the results in Table 2 shows that, in general, the calculated values of the interatomic distances are very close to the experimental data for the two functional ones when we consider the (S) - (+) - carvone benzohydrazone.

At the end of the results of Table 3, in general, the calculated values of the interatomic distances are very close to the experimental data for the two

Table 1. Experimental and calculated values of some interatomic distances of the (R) - (−) - carvone benzohydrazone and the corresponding relative errors.

δ (ppm)	EXP (ppm) [22]	B3LYP		M05-2X	
		X	Δx	x	Δx
$C^{10}C^{11}$	1.39	1.40	0.01	1.39	0.01
$C^{11}C^{13}$	1.39	1.39	0.00	1.39	0.00
$C^{13}C^{16}$	1.39	1.39	0.00	1.39	0.00
$C^{15}C^{16}$	1.47	1.40	0.07	1.39	0.07
$C^{15}C^{12}$	1.39	1.39	0.00	1.39	0.00
$C^{12}C^{10}$	1.38	1.39	0.01	1.39	0.01
$C^{10}C^{8}$	1.50	1.51	0.01	1.50	0.01
$C^{8}O^{9}$	1.22	1.21	0.01	1.21	0.01
$C^{8}N^{6}$	1.36	1.39	0.03	1.38	0.03
$N^{6}N^{5}$	1.39	1.36	0.04	1.35	0.04

Table 2. Experimental and calculated values of some interatomic distances of (S) - (+) - carvone benzohydrazone and the corresponding relative errors.

δ (ppm)	EXP (ppm) [22]	B3LYP		M05-2X	
		X	Δx	x	Δx
$C^{10}C^{11}$	1.39	1.40	0.01	1.39	0.00
$C^{11}C^{13}$	1.39	1.39	0.00	1.39	0.00
$C^{13}C^{16}$	1.39	1.39	0.00	1.39	0.00
$C^{15}C^{16}$	1.47	1.40	0.07	1.39	0.08
$C^{15}C^{12}$	1.39	1.39	0.00	1.39	0.00
$C^{12}C^{10}$	1.38	1.39	0.01	1.39	0.01
$C^{10}C^{8}$	1.50	1.51	0.01	1.50	0.01
$C^{8}O^{9}$	1.22	1.21	0.01	1.21	0.01
$C^{8}N^{6}$	1.36	1.39	0.03	1.38	0.02
$N^{6}N^{5}$	1.39	1.35	0.04	1.35	0.04

Table 3. Experimental and calculated values of some interatomic distances of (R) - (−) - carvone salicylhydrazone and the corresponding relative errors.

δ (ppm)	EXP (ppm) [22]	B3LYP		M05-2X	
		X	Δx	x	Δx
$C^{10}C^{11}$	1.39	1.40	0.01	1.39	0.01
$C^{11}C^{13}$	1.39	1.39	0.00	1.39	0.00
$C^{13}C^{16}$	1.39	1.39	0.00	1.39	0.00
$C^{15}C^{16}$	1.47	1.40	0.07	1.39	0.08
$C^{15}C^{12}$	1.39	1.39	0.00	1.39	0.00
$C^{12}C^{10}$	1.38	1.39	0.01	1.39	0.01
$C^{12}O^{30}$	1.50	1.51	0.01	1.50	0.00
$C^{10}C^{8}$	1.39	1.36	0.03	1.36	0.03
$C^{8}O^{9}$	1.22	1.21	0.01	1.21	0.01
$C^{8}N^{6}$	1.36	1.39	0.03	1.38	0.03
$N^{6}N^{5}$	1.39	1.35	0.04	1.35	0.04

functional with respect to (R) - (−) - carvone salicylhydrazone.

The analysis of results of Table 4 shows that, in general, calculated values of the interatomic distances are very close to the experimental data for the two functional ones by considering (S) - (+) - carvone salicylhydrazone.

At this stage of the calculations, we do not find any significant difference between structural results given by the two functional ones. Since the theoretical calculations are carried out in the gaseous phase and taking into account the effects of solvents on the atoms, the comparison of certain theoretical results with those of the experimental ones will be made on the basis of the statistical parameters obtained.

Table 4. Experimental and calculated values of some interatomic distances of (S) - (+) - carvone salicylhydrazone and the corresponding relative errors.

δ(ppm)	EXP (ppm) [22]	B3LYP		M05-2X	
		X	Δx	x	Δx
$C^{10}C^{11}$	1.39	1.40	0.10	1.39	0.00
$C^{11}C^{13}$	1.39	1.39	0.00	1.39	0.00
$C^{13}C^{16}$	1.39	1.39	0.00	1.39	0.00
$C^{15}C^{16}$	1.47	1.40	0.07	1.39	0.07
$C^{15}C^{12}$	1.39	1.39	0.00	1.39	0.00
$C^{12}C^{10}$	1.38	1.39	0.01	1.39	0.01
$C^{12}O^{30}$	1.50	1.51	0.01	1.50	0.00
$C^{10}C^{8}$	1.39	1.36	0.03	1.36	0.03
$C^{8}O^{9}$	1.22	1.21	0.01	1.21	0.01
$C^{8}N^{6}$	1.36	1.39	0.03	1.38	0.03
$N^{6}N^{5}$	1.39	1.36	0.03	1.35	0.03

3.2. Spectroscopic Study: Case of the ^{13}C NMR Spectra of the Molecules

In Table 5 and Table 6 are grouped the chemical shift values (δ in ppm) of carbon atoms at the approximation levels M05-2X/6311G (d, p) and B3LYP/ 6311G (d, p) for each of the four molecules and the corresponding experimental values.

Since the theoretical calculations are carried out in the gaseous phase and do not take into account the effects of solvents on the atoms, the comparison of theoretical results of Table 5 and Table 6 with those of the experimental ones will be done on the basis of the statistical parameters obtained (Table 7).

The values of absolute mean deviation (MAD), standard deviation (RMS) and correlation coefficient (R^2), relative to the ^{13}C experimental and theoretical NMR spectra of each of the molecules, were calculated by functional B3LYP and M05-2X using the GIAO method. The results are shown in Table 7.

These results show that all correlation coefficient values are close to unity (1). This means that approximations taken into account in the calculation methods used are good. However, it can be generally observed that the absolute average deviation values calculated by the functional B3LYP are lower than those calculated by the functional M05-2X. For the calculated standard deviation values, the same trend is observed. The standard deviation values calculated by the functional B3LYP are lower than those calculated by the functional M05-2X. Finally, the functional M05-2X and the base 6-311G (d, p) seem really suitable for calculating the ^{13}C NMR spectrum of the (R) - (−) - carvone benzohydrazone, of (S) - (+) - carvone benzohydrazone, (R) - (−) - carvone salicylhydrazone and (S) - (+) - carvone salicylhydrazone.

Table 5. δ (ppm) Experimental and Calculated 13C NMR for (R) - (−) - and (S) - (+) - carvone benzohydrazone by the method GIAO/B3LYP and GIAO/M05-2X.

(R) - (−) - carvone benzohydrazone				(S) - (+) - carvone benzohydrazone			
δ (ppm)	EXP (ppm) [9]	6-311G (d, p)		δ (ppm)	EXP (ppm) [9]	6-311G (d, p)	
		B3LYP	M05-2X			B3LYP	M05-2X
C20	157.68	161.66	168.62	C18	20.44	20.43	12.41
C2	33.16	38.01	28.07	C7	20.45	24.63	15.68
C3	29.47	33.98	23.68	C3	31.73	32.62	22.51
C36	153.99	161.66	166.87	C2	29.47	39.04	29.77
C27	151.80	154.64	160.50	C20	110.32	42.52	41.43
C24	147.67	149.86	158.39	C1	40.10	45.79	36.65
C30	133.87	136.62	145.83	C22	116.77	47.41	36.37
C8	20.45	20.09	12.59	C26	33.16	47.88	38.11
C33	132.28	68.42	58.49	C5	40.10.	49.73	146.44
C10	40.10	42.93	32.82	C23	133.87	51.54	42.09
C11	130.85	55.39	168.62	C8	132.28	70.40	59.85
C12	116.77	47.92	36.53	C25	119.59	138.30	39.71
C13	119.59	51.56	47.05	C34	148.67	150.97	159.68
C15	117.95	49.61	41.55	C37	153.99	151.91	158.44
C16	110.32	47.38	35.74	C11	157.68	158.25	166.29
C32	20.44	20.55	9.14	C30	161.80	162.41	167.73

Table 6. δ (ppm) Experimental and Calculated 13C NMR for (S) - (+) and (R) - (−) - carvone salicylhydrazone by the method GIAO/B3LYP and GIAO/M05-2X.

(S) - (−)- carvone salicylhydrazone				(R) - (+)- carvone salicylhydrazone			
δ (ppm)	EXP (ppm) [9]	6-311G (d, p)		δ (ppm)	EXP (ppm) [9]	6-311G (d, p)	
		B3LYP	M05-2X			B3LYP	M05-2X
C18	20.45	18.78	08.67	C20	162.85	161.92	169.85
C22	148.00	19.87	09.23	C27	152.78	154.54	159.99
C7	29.10	26.68	17.79	C2	20.44	38.12	169.85
C3	148.52	132.40	166.87	C3	20.45	34.54	24.41
C2	147.17	139.01	30.29	C35	31.73	68.80	59.20
C1	107.20	47.00	158.39	C32	29.47	136.89	145.56
C26	163.15	148.04	35.43	C24	148.52	150.17	158.06
C21	36.16	49.83	38.58	C7	40.10	166.00	159.99
C20	31.75	54.46	48.46	C8	16.77	20.95	13.43
C23	40.10	60.16	53.01	C9	33.16	161.60	39.73
C25	33.16	64.95	55.63	C10	40.10	48.40	44.92
C8	40.70	70.11	58.41	C11	33.87	50.10	40.28
-	-	-	-	C12	32.28	20.66	12.91
-	-	-	-	C13	119.59	60.46	51.87
-	-	-	-	C15	48.67	65.87	58.30
-	-	-	-	C16	53.99	48.22	37.19
-	-	-	-	C34	17.68	20.63	09.62

Table 7. Values of the statistical quantities calculated for each of the four molecules by the method GIAO/B3LYP and GIAO/M05-2X.

BASES	MAD		RMS		R^2	
	B3LYP	M05-2X	B3LYP	M05-2X	B3LYP	M05-2X
N_1	6.52	8.13	9.15	11.46	0.936	0.945
N_2	4.53	5.21	7.17	8.65	0.949	0.936
M_1	4.31	4.43	6.12	7.96	0.908	0.951
M_2	4.22	3.13	6.02	7.12	0.918	0.925

3.3. Study of Electronic Parameters of Molecules

Table 8 summarizes the values of the electronic parameters (electronic affinities (EA), ionization energy (IP), hardness (η), softness (S), electronegativity (χ), electrophile index (ω), gap d (HOMO-LUMO)) calculated at the approximation level M05-2X/6-311G (d, p) and B3LYP/6-311G (d, p).

3.4. Study of the Stability of Molecules

It is found that the four molecules do not have the same values of the electronic parameters.

Note that:

✓ hardnes of the four molecules are weak and almost equal, which would mean that it is easy for these molecules to exchange electrons with the environment.

✓ Gap (HOMO-LUMO) of the enantiomer (R) - (−) - carvone salicylhydrazone is greater than the Gap (HOMO-LUMO) relative to enantiomer (S) - (+) - carvone salicylhydrazone. With B3LYP/6-311G (d), p) method; therefore (R) - (−) - carvone salicylhydrazone is more stable than (S) - (+) - carvone salicylhydrazone. As for the enantiomers of the benzohydrazone, they have the same values of the Gap, so same stability with this method. Similarly, we find that (R) - (−) - carvone benzohydrazone is more stable than (S) - (+) - carvone salicylhydrazone and (R) - (−) - carvone salicylhydrazone is more stable than (S) - (+) - carvone benzohydrazone.

✓ However, (S) - (+) - carvone salicylhydrazone is less stable than the other three compounds.

✓ On the other hand, with the method M05-2X/6-311G (d, p), the enantiomers of the carvone salicylhydrazone have the same stability. It is the same for the enantiomers of carvone benzohydrazone. In addition, the enantiomers of carvone salicylhydrazone are more stable than those of carvone benzohydrazone.

3.5. Study of Antioxidant Properties

On the basis of these series of results, the following observations can be made:

➢ With the method B3LYP/6-311G (d, p), Gap values (HOMO-LUMO) were obtained in ascending order: (S) - (+) - carvone salicylhydrazone, (R) - (−) -

Table 8. Values calculated at the approximation levels B3LYP/6-311G (d, p) and M05-2X/6-311G (d, p) of the electronic descriptors.

Molecules	B3LYP/6-311G (d, p)							
	E_{HOMO}	E_{LUMO}	Gap	χ	η	S	ω	μ
M_2	−0.21	−0.06	0.15	0.13	0.08	6.25	0.11	3.77
N_2	−0.22	−0.05	0.17	0.13	0.09	5.56	0.09	4.81
N_1	−0.22	−0.06	0.16	0.14	0.08	6.25	0.12	4.68
M_1	−0.22	−0.06	0.16	0.14	0.08	6.25	0.12	4.94
Molecules	M05-2X/6-311G (d, p)							
	E_{HOMO}	E_{LUMO}	Gap	χ	η	S	ω	μ
M_2	−0.28	−0.02	0.26	0.15	0.13	3.85	0.09	4.12
N_2	−0.27	−0.01	0.26	0.14	0.13	3.85	0.08	5.17
N_1	−0.27	−0.02	0.25	0.15	0.13	3.85	0.09	4.96
M_1	−0.27	−0.02	0.25	0.15	0.13	3.85	0.09	5.23

carvone benzohydrazone, (S) - (+) - carvone benzohydrazone, (R) - (−) - carvone salicylhydrazone. These results indicate that (S) - (+) - carvone salicylhydrazone and (R) - (−) - carvone benzohydrazone ((S) - (+) - carvone benzohydrazone) are more antioxidant than (R) - (−) -. -carvone salicylhydrazone. For the M05-2X/6-311G (d, p) method, however, (R) - (-) - carvone benzohydrazone and (S) - (+) - carvone benzohydrazone are more antioxidant than the (S) - (+) - carvone salicylhydrazone and (R) - (−) - carvone salicylhydrazone.

➤ The results obtained by the DFT methods B3LYP/6-311G (d, p) for the calculation of softness (S), found that the highest values were obtained for (S) - (+) - carvone salicylhydrazone, (R) - (−) - carvone benzohydrazone, and the (S) - (+) - carvone benzohydrazone thus displaying them as the best antioxidants of the four molecules. There really was not a difference in the results given by the method M05-2X/6-311G (d,p).

➤ With the B3LYP/6-311G (d, p) method, the lowest values of the electronegativity index (χ) were obtained for (S) - (+) - carvone salicyl-hydrazone and (R) - (−) - carvone salicylhydrazone. This makes (S) - (+) - carvone salicylhydrazone and (R) - (−) - carvone salicylhydrazone appear to be the most antioxidant of the four molecules. On the other hand, at the M05-2X/6-311G (d, p) approximation levels, the lowest index value was obtained for (R) - (−) - carvone salicylhydrazone. This compound is the most antioxidant by the method M05-2X/6-311G (d, p).

➤ Electrophilic index calculations (ω) carried out by the B3LYP/6-311G (d, p) method revealed that (S) - (+) - carvone salicylhydrazone and (R) - (−) - carvone salicylhydrazone are the most electrophilic and therefore the strongest antioxidants. In addition, (R) - (−) - carvone salicylhydrazone is more antioxidant than (S) - (+) - carvone salicylhydrazone.

➤ By calculations M05-2X/6-311G (d, p), it is rather the (R) - (−) - carvone

salicylhydrazone which appears as the most antioxidant molecules.

➢ Values of the dipolar moment obtained made it possible to note that the (S) - (+) - carvone salicylhydrazone is the most polar of the four molecules whatever the method of calculation used.

The analysis of the results of calculations of the various electronic parameters, electronic affinities, ionization energy, hardness, softness, electronegativity, electrophile index, energy gap (HOMO-LUMO) reveals that, overall, the methods M05-2X/6-311G (d, p) and B3LYP/6-311G (d, p) showed that (S) - (+) - carvone salicylhydrazone and the (R) - (−) - carvone salicylhydrazone are the most antioxidant molecules of the four. In addition, (R) - (−) - carvone salicylhydrazone (N_2) is more antioxidant than (S) - (+) - carvone salicyl-hydrazone (M_2). The difference in the antioxidant powers observed in (R) - (−) - carvone salicylhydrazone (N_2) and (S) - (+) - carvone salicylhydrazone (M_2) is due to the descriptors of (R) and (S) configurations.

4. Conclusions

Theoretical study of the antioxidant properties of the four hydrazones (R) - (−) - carvone benzohydrazone, (S) - (+) - carvonebenzohydrazone, (R) - (−) - carvone salicylhydrazone and ((S) - (+) - carvone salicylhydrazone) was carried out, by the functional groups B3LYP and M05-2X of the DFT, in the bases 6-311G and 6-311G (d, p). For this, different parameters have been calculated. It's about:

- Geometric parameters of the molecules. The comparison of the calculated values with experimental X-ray diffraction data from the literature did not tangibly retain one of the functionalities as the most suitable for the study.

- Spectroscopic parameters relating to the ^{13}C NMR spectra of the three molecules. The statistical analysis of chemical shift values calculated by the GIAO method revealed that the M05-2X functional appears to be the most appropriate for calculating the ^{13}C NMR spectrum of each molecule.

- Electronic parameters such as hardness (η), softness (S), electronegativity (χ), electrophilic index (ω), energy gap (HOMO-LUMO) of the molecules. The theoretical results obtained have shown that (R) - (−) - carvone salicyl-hydrazone (N_2) is the most antioxidant molecule of the four and also classified according to their stability. The experimental results are confirmed by the theoretical results. The method M05-2X/6-311G (d, p) appears best indicated in the calculation of electronic parameters.

In perspective, we plan to:

- To enhance the biological activity of the compounds by formation of the metal complexes.

- To carry out quantum-chemical studies on the complexes formed.

References

[1] Ali, R., Marella, A., Alam, T., Naz, R., Akhter, M., Shaquiquzzaman, Saha, R., Tanwar, O., Alam, M. and Hooda, J. (2012) Review of Biological Activities of Hydrazones. *Indian Journal of Pharmaceutical Sciences*, **23**, 193-202.

[2] Rollas, S. and Kaymakçıoğlu, K.B. (2002) Synthesis, Characterization and Evaluation of Antituberculosis Activity of Some Hydrazones. *Farmaco*, **57**, 595-599. https://doi.org/10.1016/S0014-827X(02)01255-7

[3] Bedia, K.K., Elçin, O., Seda, U., Fatma, K., Nathaly, S., Sevim, R. and Dimoglo, A. (2006) Synthesis and Characterization of Novel Hydrazide-Hydrazones and the Study of Their Structure-Antituberculosis Activity. *European Journal of Medicinal Chemistry*, **41**, 1253-1261. https://doi.org/10.1016/j.ejmech.2006.06.009

[4] Özkay, Y., Tunali, Y., Karaca, H. and Isikdag, I. (2010) Antimicrobial Activity and a SAR Study of Some Novel Benzimidazole Derivatives Bearing Hydrazone Moiety. *European Journal of Medicinal Chemistry*, **45**, 3293-3298. https://doi.org/10.1016/j.ejmech.2010.04.012

[5] Jatav, V., Mishra, P., Kashaw, S. and Stables, J. (2007) Synthesis and CNS Depressant Activity of Some Novel 3-[5-Substituted 1,3,4-Thiadiazole-2-yl]-2-Styryl Quinazoline-4(3H)-Ones. *European Journal of Medicinal Chemistry*, **1**, 7.

[6] Troeberg, L., Chen, X., Flaherty, T.M., Morty, R.E., Cheng, M., Hua, H., Springer, C., McKerrow, J.H., Kenyon, G.L., Lonsdale-Eccles, J.D., Coetzer, T.H. and Cohen, F.E. (2000) Chalcone, Acyl Hydrazide, and Related Amides Kill Cultured Trypanosoma Brucei Brucei. *Molecular Medicine*, **6**, 660-669.

[7] Glinma, B., Kpoviessi, S.D.S., Gbaguidi, F.A., Kapanda, C.N., Bero, J., Leclercq, J.Q., Moudachirou, M., Poupaert, J., Accrombessi, G.C., Gachomo, E.W., Moussa, L.B. and Kotchoni, S.O. (2014) Trypanocidal and Cytotoxic Evaluation of Synthesized Thiosemicarbazones as Potential Drug Leads against Sleeping Sickness. *Molecular Biology Reports*, **41**, 1617-1622. https://doi.org/10.1007/s11033-013-3008-2

[8] Xia, Y.L., Fan, C.-D., Zhao, B.X., Zhao, J., Shin, D.S. and Miaom, J.Y. (2008) Synthesis and Structure-Activity Relationships of Novel 1-Arylmethyl-3-Aryl-1H Pyrazole-5-Carbohydrazide Hydrazine Derivatives as Potential AGENTS against A549 Lung Cancer Cells. *European Journal of Medicinal Chemistry*, **43**, 2347-2353. https://doi.org/10.1016/j.ejmech.2008.01.021

[9] Atchade, B., Kpoviessi, D.S.S., Gbaguidi, F.A., Glinma, B., Ahoussi, L.A., Gbenou, L.A., Accrombessi, G.A., Frederick, R. and Poupaert, J.H. (2015) Synthesis, Characterization, Purity Verification, Antiplasmodial Activity and Toxicity against Artemia Salina Leach of Salicylhydrazones and p-Tosylhydrazones from S-(+)-Carvone and Arylketones. *Journal of Chemical and Pharmaceutical Research*, **7**, 318-326.

[10] Xu, J., Cole, D.C., Chang, C.P., Ayyad, R., Asselin, M., Hao, W., Gibbons, J., Jelinsky, S.A., Saraf, K.A. and Park, K. (2008) Inhibition of the Signal Transducer and Activator of Transcription-3 (STAT3) Signaling Pathway by 4-oxo-1-Phenyl-1,4-Dihydroquinoline-3-Carboxylic Acid Esters. *Journal of Medicinal Chemistry*, **51**, 4115-4121. https://doi.org/10.1021/jm701271y

[11] Sreeja, P.B., Kurup, M.R.P., Kishore, A. and Jasmin (2004) For the Synthesis of Related Compounds and for Related Work. *IUCr Journals*.

[12] Matysiak, J. and Opolski, A. (2006) Synthesis and Antiproliferative Activity of N-Substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles. *Bioorganic & Medicinal Chemistry*, **14**, 4483-4489. https://doi.org/10.1016/j.bmc.2006.02.027

[13] Küçükgüzel, S.G., Mazi, A., Sahin, F., Öztürk, S. and Stables, J.P. (2003) Synthesis and Biological Activities of Diflunisal Hydrazide-Hydrazones. *European Journal of Medicinal Chemistry*, **38**, 1005-1013. https://doi.org/10.1016/j.ejmech.2003.08.004

[14] Badiger, S., Kundapur, R., Jain, A., Kumar, A., Pattanshetty, S., Thakolkaran, N., Bhat, N. and Ullal, N.K.S. (2012) Self-Medication Patterns among Medical Students in South India. *Australasian Medical Journal*, **5**, 217-220.

[15] El-Tabl, A.S., El-Saied, F.A. and Al-Hakimi, A.N. (2008) Spectroscopic Characterization and Biological Activity of Metal Complexes with an ONO Trifunctionalized Hydrazone Ligand. *Journal of Coordination Chemistry*, **61**, 2380-2401. https://doi.org/10.1080/00958970801914041

[16] Özdemir, Ü., Arslan, F. and Hamurcu, F. (2010) Synthesis, Characterization, Antibacterial Activities and Carbonic Anhydrase Enzyme Inhibitor Effects of New Arylsulfonylhydrazone and Their Ni(II), Co(II) Complexes. *Spectrochimica Acta Part A*, **75**, 121-126. https://doi.org/10.1016/j.saa.2009.09.052

[17] Kaushik, D., Khan, S.A., Chawla, G. and Kumar, S. (2010) N'-[(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl) methylene] 2/4-Substituted Hydrazides, Synthesis and Anticonvulsant Activity. *European Journal of Medicinal Chemistry*, **45**, 3943-3949. https://doi.org/10.1016/j.ejmech.2010.05.049

[18] Cui, Z., Yang, X., Shi, Y., Uzawa, H., Cui, J., Dohi, H. and Nishida, Y. (2011) Molecular Design, Synthesis and Bioactivity of Glycosyl Hydrazine and Hydrazone Derivatives: Notable Effects of the Sugar Moiety. *Bioorganic & Medicinal Chemistry Letters*, **21**, 7193-7196. https://doi.org/10.1016/j.bmcl.2011.09.068

[19] Cocco, M.T., Congiu, C., Lilliu, V. and Onnis, V. (2006) Synthesis and *in Vitro* Antitumoral Activity of New Hy-drazinopyrimidine-5-carbonitrile Derivatives. *Bioorganic & Medicinal Chemistry*, **14**, 366-372. https://doi.org/10.1016/j.bmc.2005.08.012

[20] Hehre, W.J., Radom, L., Schleyer, P.R. and Pople, J.A. (1986) *Ab Initio* Molecular Orbital Theory. Wiley, New York.

[21] Frisch, M.J., *et al.* (2009) Gaussian 09. Revision A.02, Gaussian, Inc., Wallingford.

[22] Benmansour, B.H.Y. (2015) Thèse: Synthèse, étude physico-chimique et activité biologique des complexes de cuivre et/ou nickel dérivés d'Hydrazone et Thiadiazole.

[23] Becke, A.D. (1993) The Role of Exact Exchange. *The Journal of Chemical Physics*, **98**, 5648-5653. https://doi.org/10.1063/1.464913

[24] Zhang, G. and Musgrave, C.B. (2007) Comparison of DFT Methods for Molecular Orbital Eigenvalue Calculations. *The Journal of Physical Chemistry A*, **111**, 1554-1561.

[25] Bonin, K.D. and Kresin, V.V. (1997) Electric-Dipole Polarizabilities of Atoms Molecules and Clusters. World Scientific, Singapore. https://doi.org/10.1142/2962

[26] Medjdoub, G.A. (2012) Contribution à l'étude de la réactivité chimique à l'aide de la DFT conceptuelle. Application à la chimie des hétérocycles.

[27] Morrel, H., Chattaraj, P.K. and Sengupta, S.J. (2006) Electrophilicity Index. *The Journal of Physical Chemistry*, **103**, 6122.

[28] Payán, G., Sergio, A., Norma, F.-H., Antonino, P.-H., Manuel, P.-M. and Daniel, G.-M. (2010) Computational Molecular Characterization of the Flavonoid Rutin. *Chemistry Central Journal*, **4**, 12-17. https://doi.org/10.1186/1752-153X-4-12

[29] Conde, J.P. and Moura-Ramos, J.J. (1986) Study of Conformational Equilibria by Dipole Moment Measurements. *Journal of Chemical Education*, **63**, 823-826.