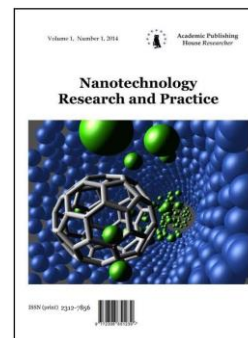


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Toxicity of a Series of Molecules Derived from Anilides: DFT Study

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Abstract

The objective of our work was to study 7 molecules derived from anilides, which enabled us to determine their geometric, structural, electronic and optical properties. And other shares using calculated parameters: Energy of the orbital borders, electronic affinity, index of the global electrophile and electronic chemical potential. The results obtained showed that the toxicity of these molecules is influenced with different degrees by several descriptors. We find that 3 molecules out of 7 studied are more toxic has been studied within the density functional theory (DFT) at the B3LYP/6-31(d,p) computational level.

Keywords: energy of the orbital borders, electronic affinity, index of the global electrophile and electronic chemical potential, DFT.

1. Introduction

Amide bonding is one of the most important chemical reactions. The usual routes to primary, secondary and tertiary amides mainly involve the treatment of activated acid derivatives, in particular acyl halides, acid anhydrides, esters, with ammonia or primary and secondary amines (Roughley, et al., 2011; Vogel et al., 1989). Starch is an important functional group and is an integral part of many pharmaceuticals, natural products, agrochemicals, refined chemicals and polymers, and the constituents of drugs (local anesthetics, antiarrhythmics, antivertiginous drugs, etc.). It is also the key binding fragment in the proteins and peptides of drug products (Pierrick et al., 2014; Jack et al., 2014; Carey et al., 2006; Humphrey et al., 1997).

Amides are divided into three classes according to the number of acyl groups carried by the nitrogen atom. Primary, secondary and tertiary amides are distinguished. Primary and secondary amides have higher melting and boiling points than tertiary amides, because in the first two types of amides there are intermolecular hydrogen bonds (Kevin et al., 2014).

As a result, many protocols have been developed for starch synthesis, including: catalytic condensation of carboxylic acids and amines and triphenyl borate as catalyst. This protocol is applicable for the synthesis of a wide range of starches providing excellent yields up to 92 % (Ghorpade et al., 2014).

- catalytic condensation of carboxylic acid and amine (starch) with arylboronic acid has been reported as an organo-catalyst for amide synthesis (Maki et al., 2014).

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• hydration of nitriles catalysed by Ag (I) N-heterocyclic (Ag (I) -NHC) is one of the classic reactions of organic synthesis to produce primary amides (NS Thirukovela et al., 2019). Among the known amide synthesis methods, condensation of carboxylic acid and amine (amidation) giving starch as a product and water as a by-product is an ideal method that is greener and more economical (Katkar et al., 2011; Maki et al., 2007).

• conversion of carboxylic acid by a combination of ammonium thiocyanate and potassium carbonate has made it possible to synthesize primary amides in the presence of 2,4,6-trichloro-1,3,5-triazine (Jaita et al., 2018).

• Conventional condensation of ammonia (NH₄SCN as a source of ammonia) with acyl chloride in the presence of an activator (Zhang et al., 2006).

• amidation of aldehydes with ammonium chloride or salts of amine hydrochloride has been developed for the synthesis of a wide variety of primary, secondary and tertiary amides with good yields, using cheap copper sulphate or copper oxide (I) as a catalyst (Ghosh et al., 2012).

• Most of these processes correspond to a reaction between an amine and an activated carbonyl compound and are similar to the method used to prepare esters.

The anilide derivatives naphthol-AS are synthesized following the coupling reaction between 2-hydroxy-3-naphthoic acid (Figure 1) and aniline derivatives (Table 1).

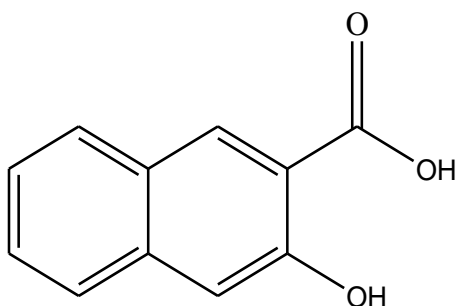


Fig. 1. Acide 2-hydroxy-3-naphtoïque

To address these problems related to the synthesis of amides, many new amide formation reactions have been developed (Esmail Eidi et al., 2016), such as primary amide transamidation (Tamura et al., 2012), oxidative amidation of aldehydes (Shie et al., 2003; Wang et al., 2008; Sarkar et al., 2010; Tillack et al., 2001; Muthaiah et al., 2010; Seo et al., 2010; Ghosh et al., 2012), catalytic acylation of amines with carboxylic acid (P. Tang. et al., 2010), haloarene aminocarbonylation (Dang et al., 2012), alkyne hydroamination (Chen et al., 2011), alcohol dehydrogenant starch (Gunanathan et al., 2007) and amidation of methylarenes with salts of amine hydrochloride, on magnetic nanoparticles (Nps) of CoFe₂O₄.

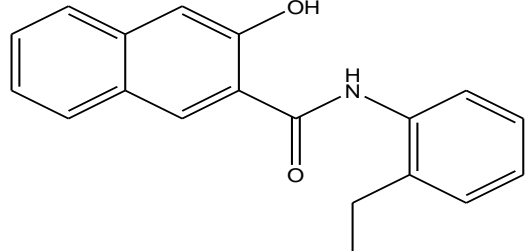
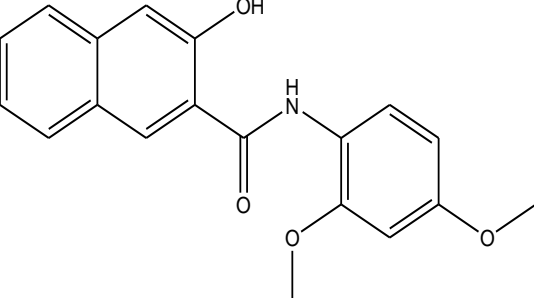
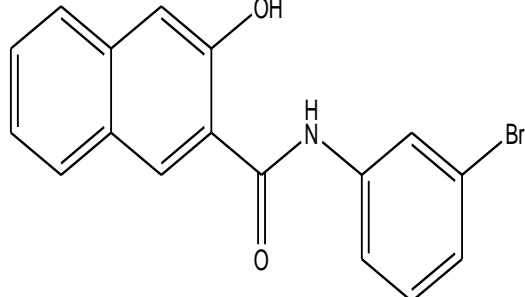
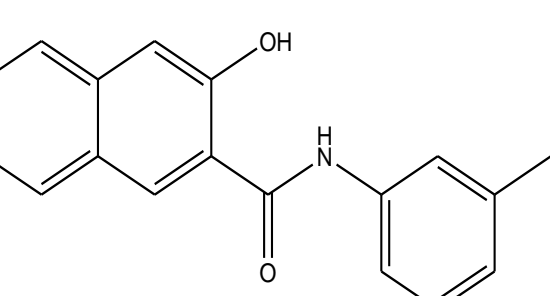
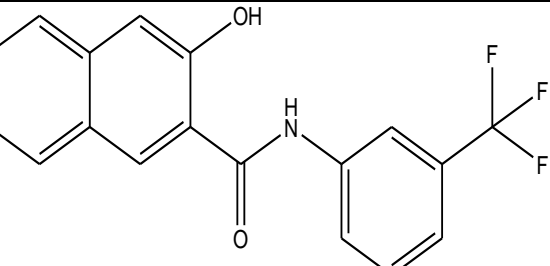
Amides are generally considered to be compounds with low solubility in water; they are much less soluble in water than acids and alcohols because of their non-ionic character, these compounds can give and accept both hydrogen bonds. Amides undergo hydrolysis at a slower rate than esters. The hydrolysis of the ester, when placed in an aqueous alcoholic solvent in the presence of a base, can be done within a few hours, under the same reaction conditions, it can take days (or more) for a structurally similar amide (Carey et al., 2006).

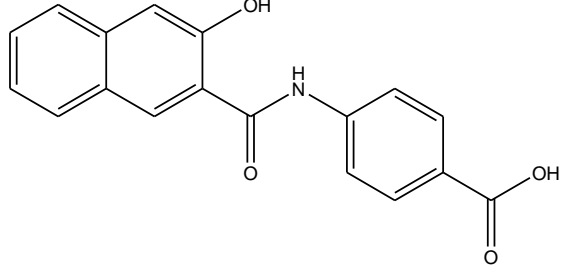
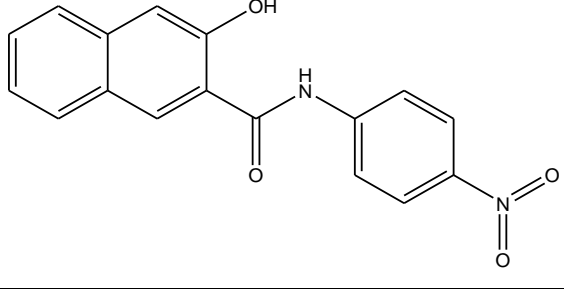
2. Methods of calculation

GAUSSIAN 09 (Gaikwad et al., 2015) and GAUSS VIEW 5.0.9 (Dong et al., 2018) are used as before for all calculations (Wan, et al., 2018). The structures were drawn in the GAUSSIAN software GAUSS VIEW 5.0.9 (Dong et al., 2018). The initial structures were cleaned several times to obtain a standardized geometry. For each product was then subjected to successive optimizations using semi-empirical methods (PM3), Hartree-Fock and DFT in conjunction with appropriate base sets. The final optimization of these molecules is carried out by the method DFT/B3LYP/ 6-311G (d, p).

The toxicity of 7 molecules derived from anilides is given in the Table 1 are following after the experimental work of S. A. Chicu et al (Chicu et al., 2011).

Table 1. The toxicity of 7 molecules derived from anilides

Molecules	Chemical Formula	Toxicity
1	 <chem>CCCC1=CC=C(NC(=O)c2cc(O)ccc21)C=C</chem>	5,44
2	 <chem>COc1cc(OC)cc(NC(=O)c2cc(O)ccc21)c1</chem>	5,47
3	 <chem>BrC1=CC=C(NC(=O)c2cc(O)ccc21)C=C</chem>	3,65
4	 <chem>Cc1ccc(NC(=O)c2cc(O)ccc21)cc1</chem>	4,29
5	 <chem>FC(F)(F)c1ccc(NC(=O)c2cc(O)ccc21)cc1</chem>	3,85

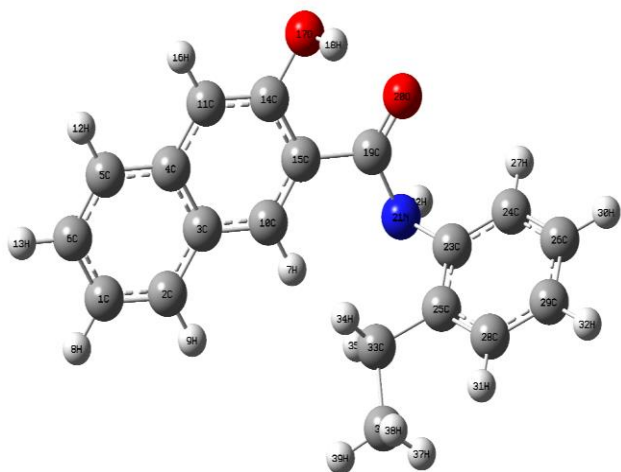
6		3,28
7		3,85

3. Results and discussions

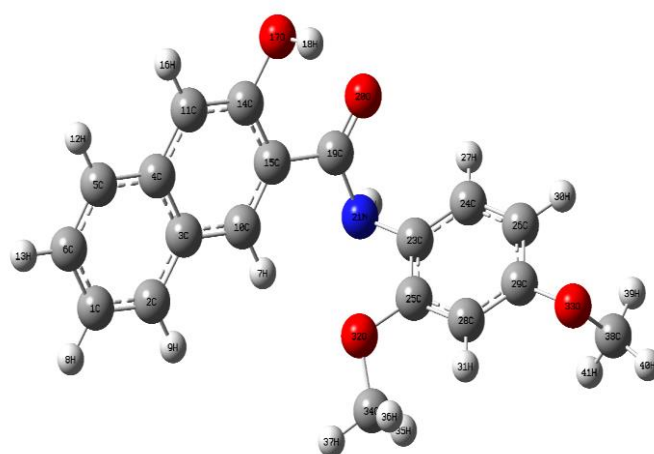
3.1. Optimized geometry and structures of the studied molecules

From the optimized structures, we can determine all the parameters relating to the geometry of the molecules, namely: interatomic distances, angles, dihedral angles, torsion angles, etc. In this work, the geometries of the optimized structures were obtained using the corrected gradient functionality of Becke, Lee, Yang and Parr (B3LYP) (Parr et al., 1989) exchange and correlation with the base 6-311G (Castro et al., 1998).

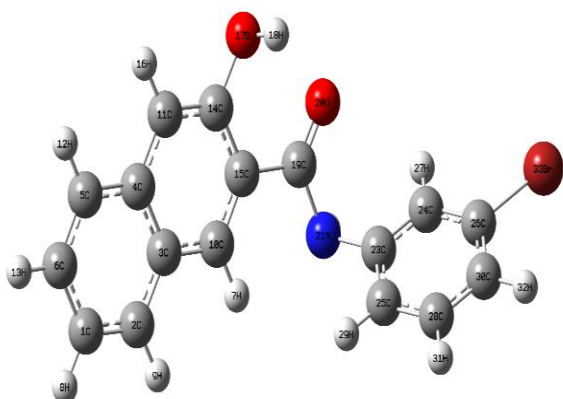
Molecule 1



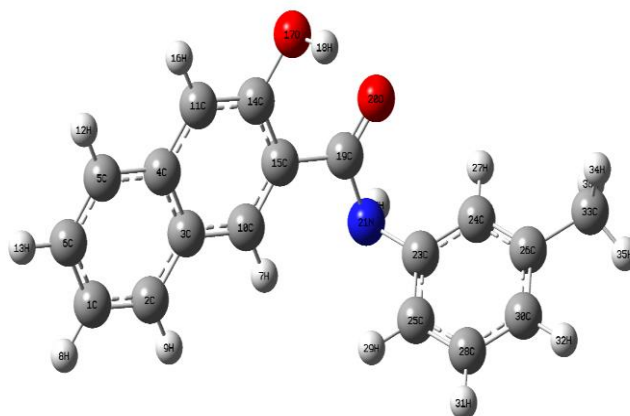
Molecule 2



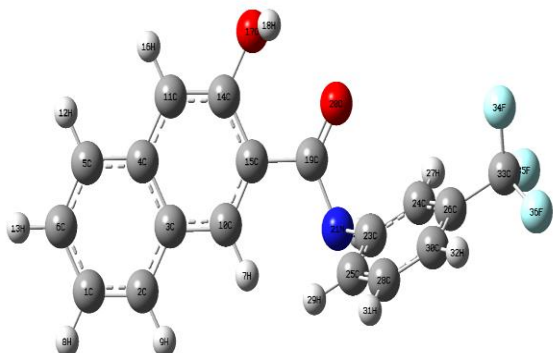
Molecule 3



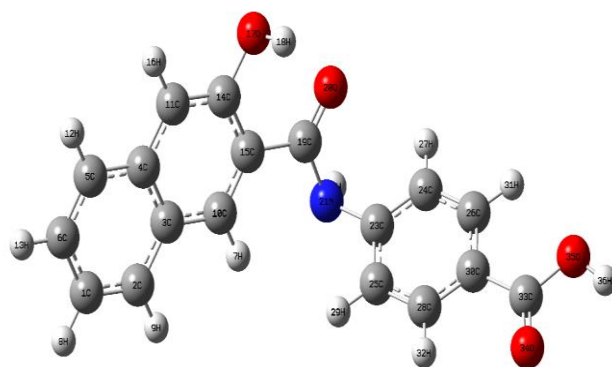
Molecule 4



Molecule 5



Molecule 6



Molecule 7

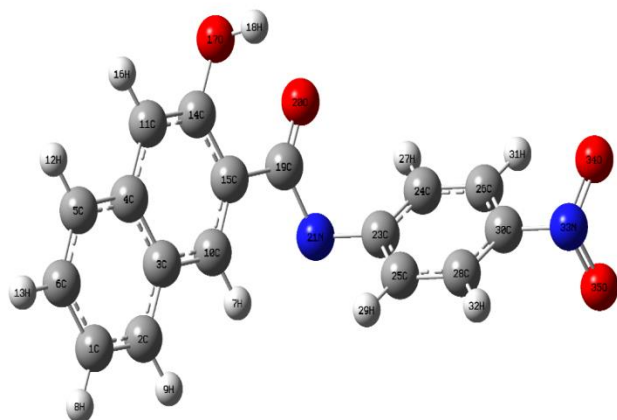


Fig. 2. Optimized structures of the studied molecules

3.2. Electronic properties of the studied molecules

The structures of all the compounds studied are optimized with the DFT method (Wan et al., 2018) using the software Gaussian 09 (Frisch et al., 2009), the function B3LYP (Becke et al., 1998) and the base 6-31G (d) (Castro et al., 1998), the results obtained are grouped in Table 2.

From the optimized structures of each molecule, we directly determined the total energy E_{tot} , the energy of the highest molecular orbital occupied E_{HOMO} , the energy of the lowest vacant molecular orbital E_{LUMO} .

In addition to these descriptors, we calculated: the E_{gap} energy, the PCE chemical potential, the chemical hardness η , the global electrophile index, the global nucleophilia index N and the electronegativity.

3.3. Energy of boundary orbitals

According to the calculation we determined the energy of the orbital borders for each molecule. The following table shows the HOMO and LUMO energy for the 7 molecules.

Table 2. Energy of boundary orbitals (in eV) for different compounds

COMPOUNDS	HOMO ENERGY (eV)	LUMO ENERGY (eV)
1	-0.2184	-0.0755
2	-0.2256	-0.073
3	-0.2239	-0.0842
4	-0.2194	-0.0774
5	-0.2268	-0.0886
6	-0.2258	-0.0902
7	-0.2316	-0.1166

Therefore we have determined the HOMO/LUMO boundary orbital energy as illustrated in the following Figure 3.

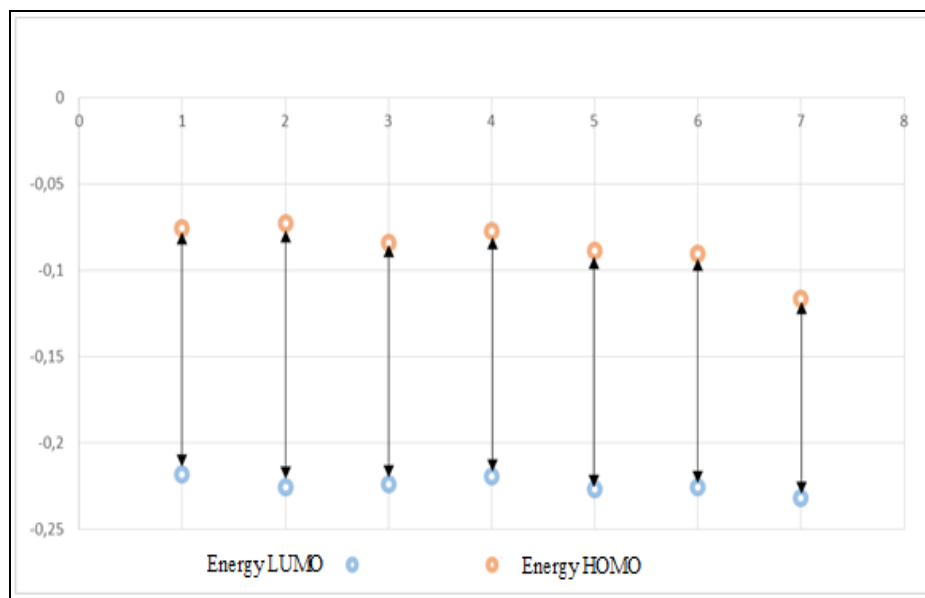


Fig. 3. HOMO/LUMO boundary orbital energy

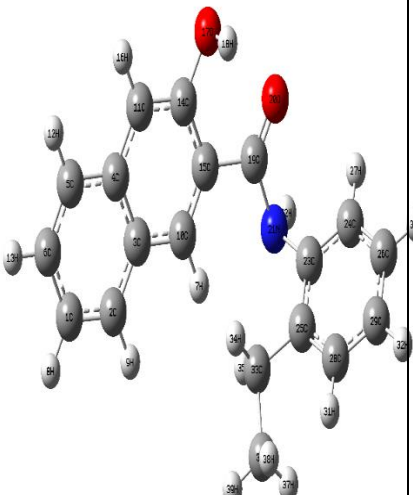
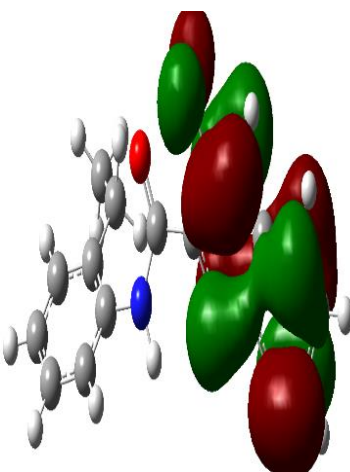
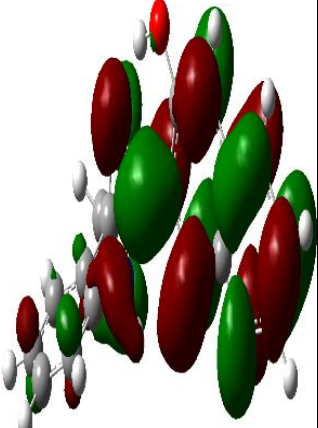
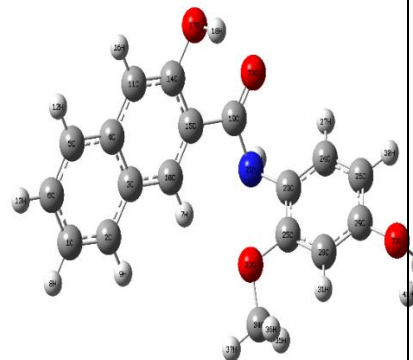
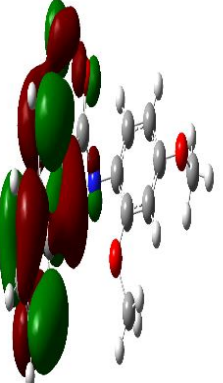
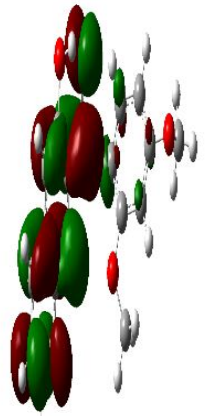
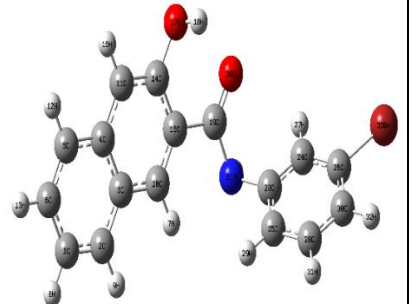
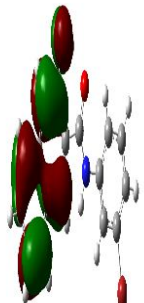

The molecule with a larger energy gap compared to others would be is more stable. HOMO/LUMO boundary orbitals play a special role (Hoffmann et al., 1969):

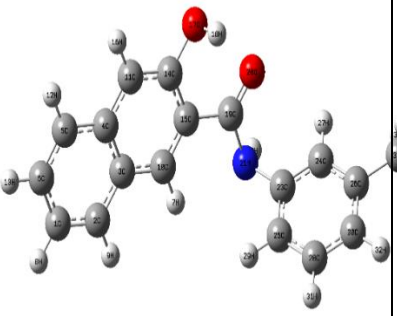
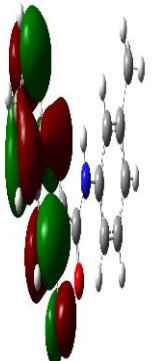
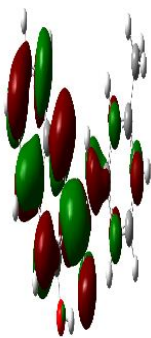
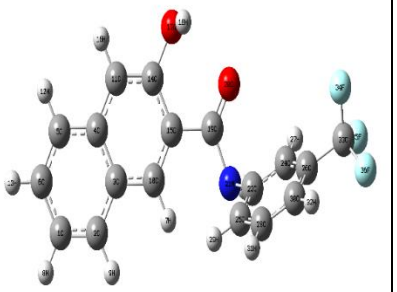
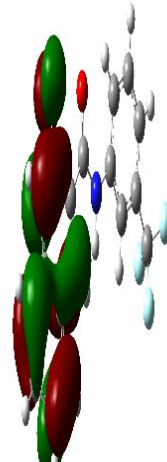

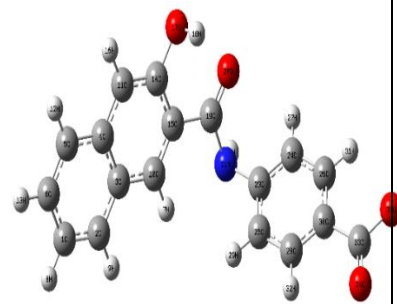
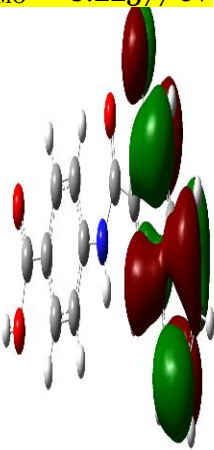
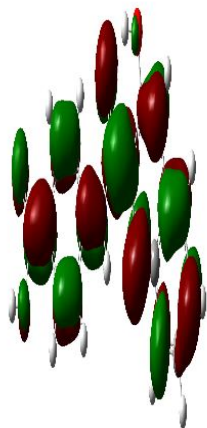
• HOMO translates the electro-donor character of the molecule. The higher the energy of this OM the more easily the molecule will yield electrons.

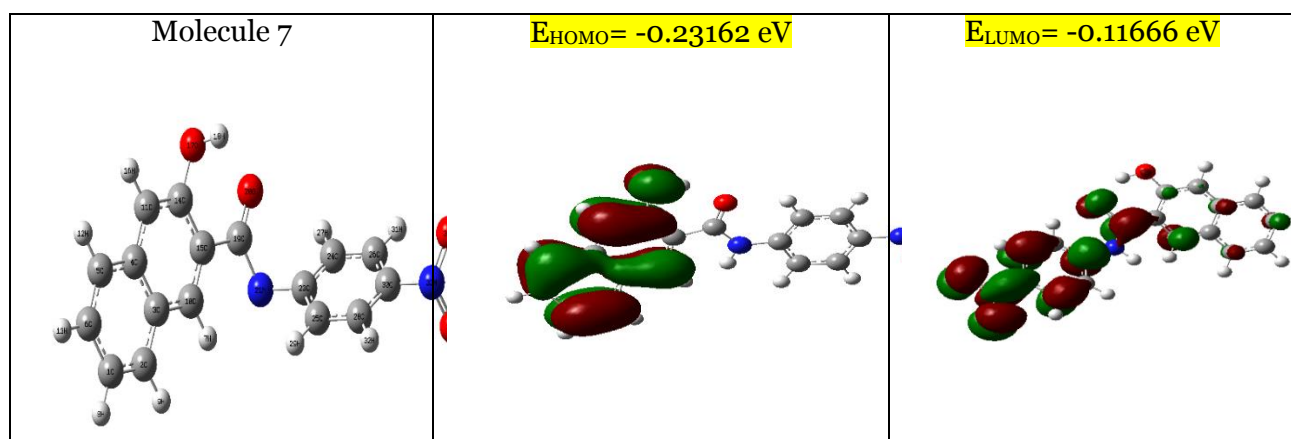
• LUMO translates the electroacceptor character of the molecule. The weaker the energy of this OM the more easily the molecule will accept electrons

The following table shows the geometrics and the energy of the molecules

Table 4. Energy of borders HOMO/LUMO orbital

Molecule	Energy	Energy
Molecule 1 	$E_{\text{HOMO}} = -0.21842 \text{ eV}$	$E_{\text{LUMO}} = -0.07547 \text{ eV}$
		
Molecule 2 	$E_{\text{HOMO}} = -0.22559 \text{ eV}$	$E_{\text{LUMO}} = -0.07302 \text{ eV}$
		
Molecule 3 	$E_{\text{HOMO}} = -0.22389 \text{ eV}$	$E_{\text{LUMO}} = -0.08421 \text{ eV}$
		

<p>Molecule 4</p> 	<p>$E_{\text{HOMO}} = -0.21936 \text{ eV}$</p> 	<p>$E_{\text{LUMO}} = -0.07743 \text{ eV}$</p> 
<p>Molecule 5</p> 	<p>$E_{\text{HOMO}} = -0.22675 \text{ eV}$</p> 	<p>$E_{\text{LUMO}} = -0.08862 \text{ eV}$</p> 
<p>Molecule 6</p> 	<p>$E_{\text{HOMO}} = -0.22577 \text{ eV}$</p> 	<p>$E_{\text{LUMO}} = -0.09024 \text{ eV}$</p> 



We have computed adiabatic IP and adiabatic EA for seven Molecules presented in the following Table 5. Value deviates from the mean value are highlighted by underline. IP: Ionization potential, EA: Electron affinity, μ : Chemical potential, χ : Electronegativity, η : Chemical hardness, σ : Chemical softness ($1/\eta$), ω : Electrophilicity index and Energy gap.

Table 5. Electronic properties of the studied molecules

Molecules	μ (eV)	A (eV)	η (eV)	S (eV)	ω (Ev)	E gap (eV)
1	-0.0714	0.0755	0.1429	3.4989	0.0178	0.1429
2	-0.0763	0.0731	0.1526	3.2765	0.0190	0.1526
3	-0.0698	0.0842	0.1397	3.5790	0.0174	0.1397
4	-0.0711	0.0774	0.1421	3.5211	0.0177	0.1421
5	-0.0691	0.0886	0.1382	3.6179	0.0172	0.1382
6	-0.0678	0.0902	0.1356	3.6873	0.0169	0.1356
7	-0.0574	0.1166	0.1149	4.3493	0.0143	0.1149

3.4. Energy gap

According to the graph analysis (Figure 4), molecule 2 has a higher gap energy than other molecules, so molecule 2 has a lower and more stable conductivity.

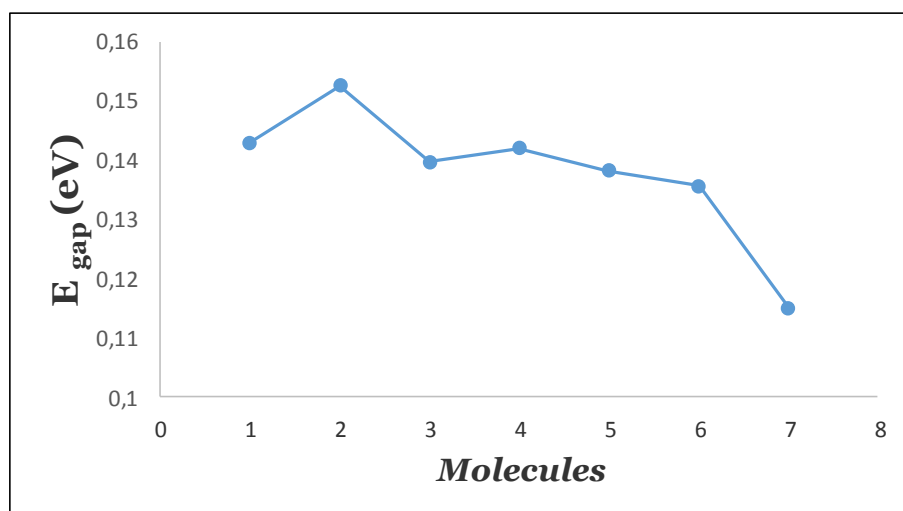


Fig. 4. Energy gap

3.5. Electronic chemical potential

The electronic chemical potential determines the direction of electron transfer during condensation between two molecules. According to the calculation of the chemical potential of the molecules (Figure 5), we observe that molecule 2 has a greater electronic potential than the other. This implies that the electron transfer will take place in molecule 2.

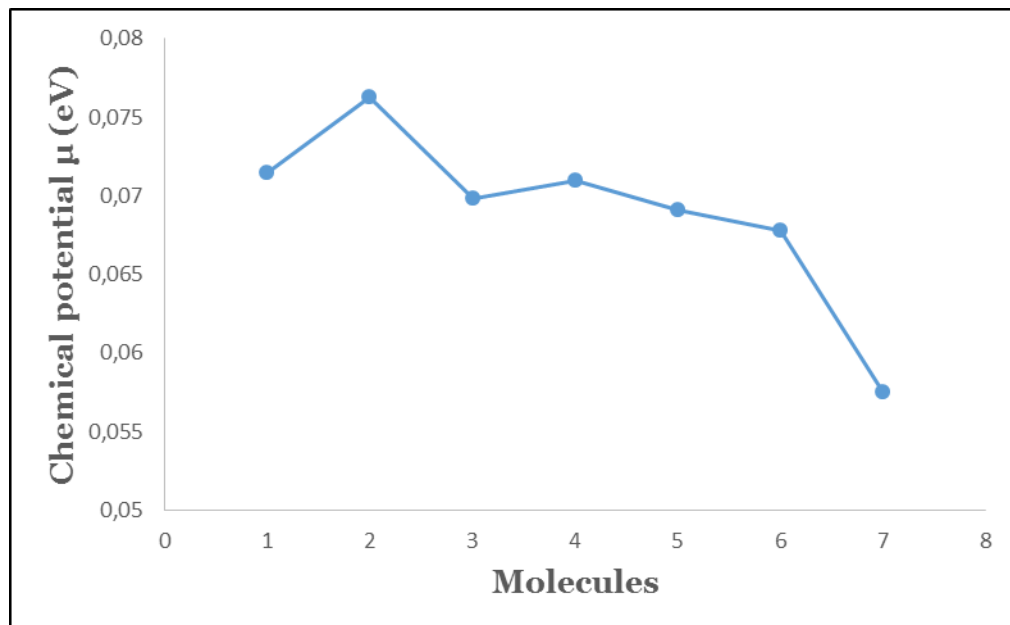


Fig. 5. Electronic chemical potential

3.6. Hardness and Softness

Hardness gives an idea of the relative duration of a molecule to store electrons in its environment. According to the curve (Figure 6) we have molecule 2 at a greater hardness compared to other molecules, so molecule 2 holds more electrons in its environment compared to other molecules. Softness (Figure 6) is the easiness with which the cationic A^+ molecule can receive electrons, or anionic A^- to lose electrons. So molecule 2 is difficult to receive or lose electrons.

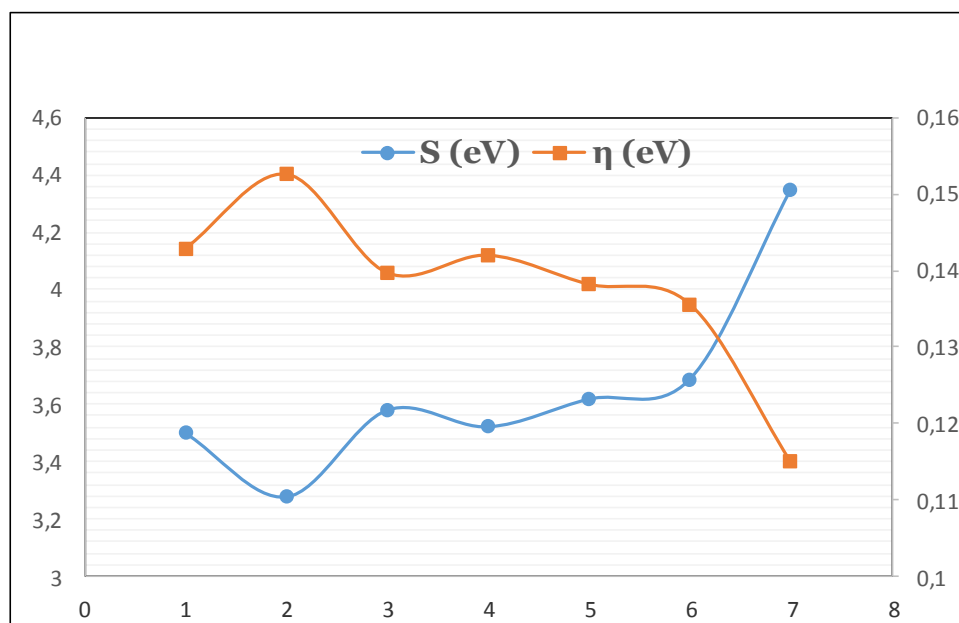


Fig. 6. Hardness and softness

3.7. Index of the global electrophile

The index of the global electrophile of a molecule is the number of electrons it can acquire by an electrophile, if it is immersed in a cloud of free electrons. The value of the number of electrons acquired and the resulting energy stabilization would allow the electrophilic power of two species to be compared.

According to the curve (Figure 7), molecule 2 has a larger global electrophilic index value compared to other molecules, so it is more stable than the other molecules.

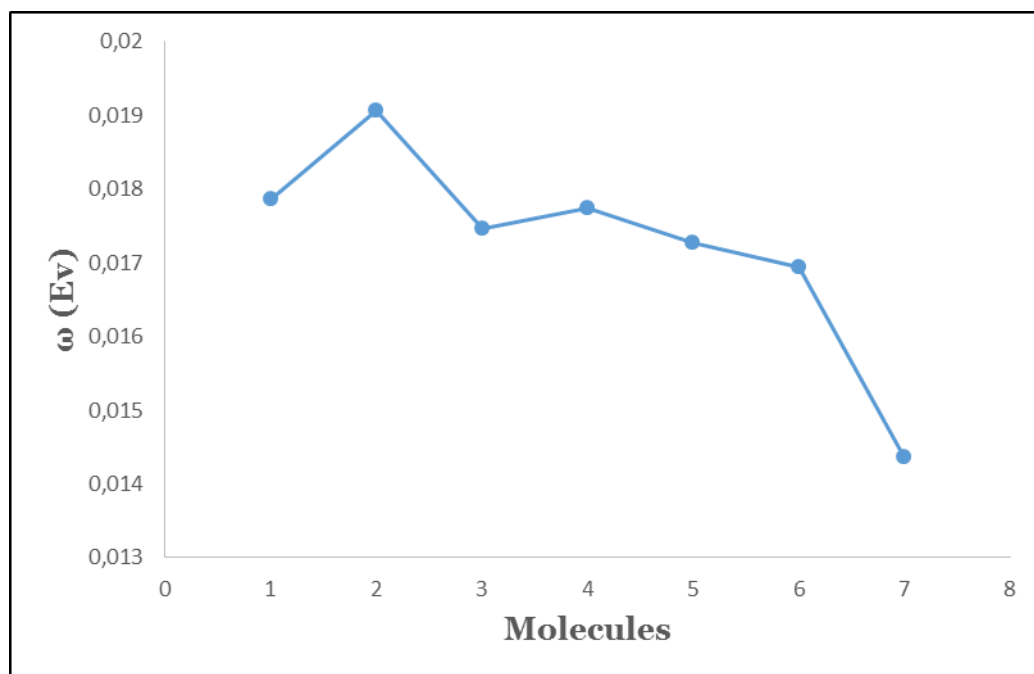


Fig. 7. The index of the global electrophile

3.8. Electronic affinity

Electronic affinity refers to the ability of a neutral atom or molecule to capture an additional electron. Molecule 2 has a lower electronic affinity than other molecules, so this implies that molecule 2 is more stable (Figure 8).

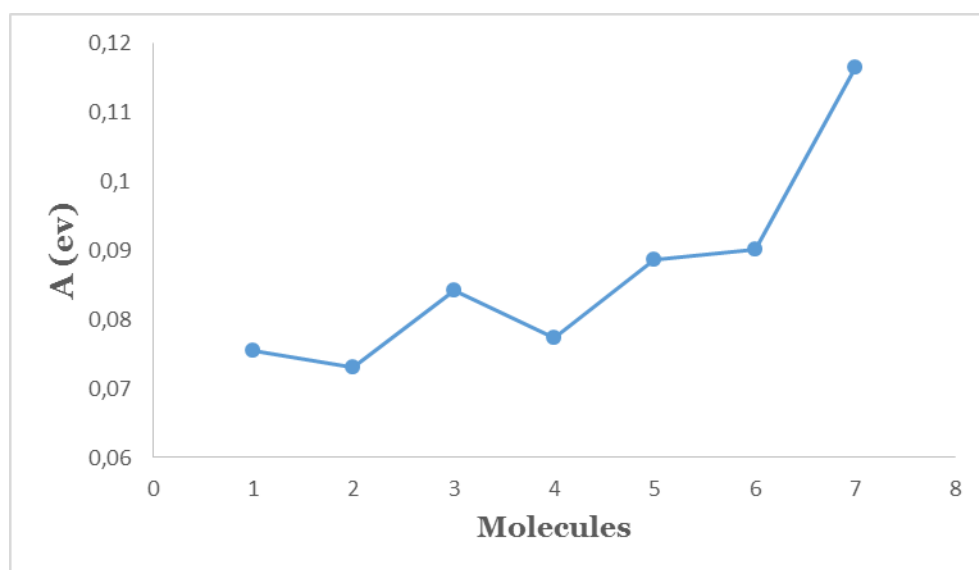


Fig. 8. Electronic affinity

3.9. Thermodynamic parameters

We determined for each molecule the enthalpy H, entropy S and free enthalpy G.

- Enthalpy H is the sum of the internal energy of a system and the product of its pressure by its volume.

- Entropy S, it characterizes the degree of disorder or unpredictability of the information content of a system.

Table 6. Thermodynamic parameters

Molecule	ΔH (Cal/mol)	ΔS (Cal/mol/K)	ΔG (Cal/mol)
1	-939.138	138.585	-42237,468
2	-1089,268	152.428	-46509,812
3	-3434.073	136.080	-43985,913
4	-899.861	136.144	-41470,773
5	-1197.634	147.362	-45111,510
6	-1049.120	140.954	-43053,412
7	-1065.052	140.183	-42839,586

According to the free enthalpy calculation, the free enthalpy G-curve is plotted for each molecule (Figure 9).

We determined the enthalpy of 7 derived anilide molecules and we found that molecule 2 has a lower energy. This result means that molecule 2 is thermodynamically more stable.

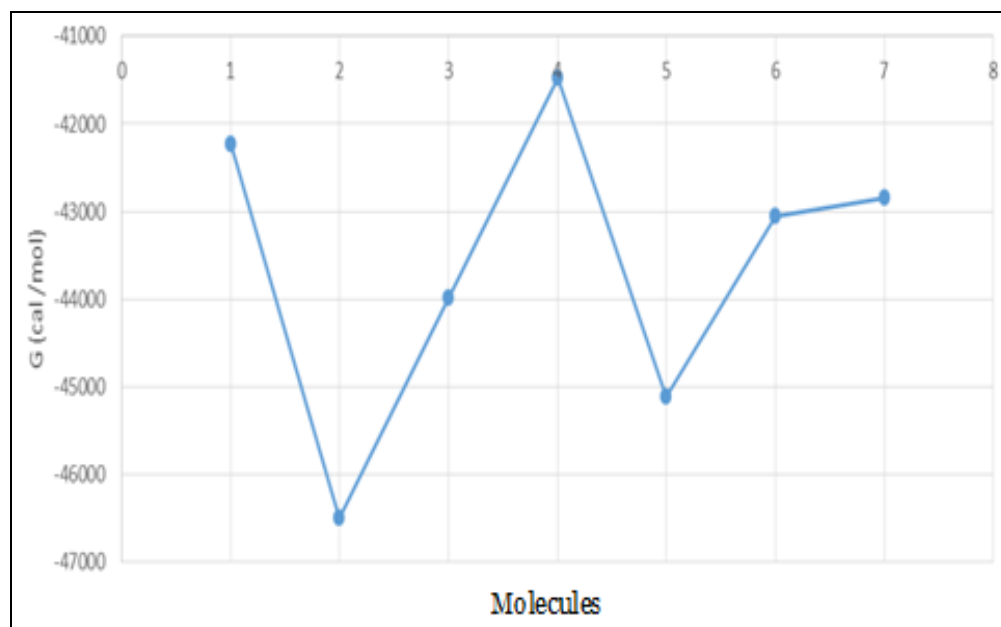


Fig. 9. Free enthalpy of molecules

5. Conclusion

This work has demonstrated the concordance between our results from quantum chemistry on the one hand and those of the team of Sergiu Adrian et al from experience.

In fact, our two teams found that 3 out of 7 molecules studied are more toxic. In addition, the two teams found the same rows of toxicity for these 3 molecules.

The parameters responsible for increasing toxicity are diversified: the energy of the highest molecular orbital occupied EHOMO, the energy of the lowest vacant molecular orbital E LUMO, the Egap energy, the ionization energy I, the electronic affinity A, the electronic chemical potential PCE, the chemical hardness η , the global electrophilic index, the global nucleophilic index N and electrolyte.

The quantum chemistry offers researchers and industrialists alike new horizons.

6. Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper. Also, they declare that this paper or part of it has not been published elsewhere.

7. Acknowledgments

The authors are thankful for Laboratory of Chemical Process and Applied Materials. Sincere thanks are also due for Prof. Adil Belhaj, Department of Physique, Faculty of Science, Mohammed V University, Rabat, for valuable comments for the manuscript.

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