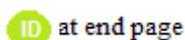




## The theoretical investigation of HOMO, LUMO, thermophysical properties and QSAR study of some aromatic carboxylic acids using HyperChem programming

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### ABSTRACT

Growing the molecular mechanism of chemicals, thermochemical and biological interactions is considered as the ultimate goal of computational chemistry. Some thermodynamic parameters such as free energy, entropy, dipole moment, binding energy, nuclear energy, electronics energy, heat of formation, and QSAR (quantitative structure activity relationship) properties of molecules like charge density, surface area grid, volume, LogP, polarizability, refractivity, molecular mass, and reactivity properties of molecules like HOMO (the highest occupied molecular orbital), LUMO (the lowest unoccupied molecular orbital), HUMO (the highest unoccupied molecular orbital)-LUMO gap, ionization potential and electron affinity were determined using the HyperChem 8.0.10 program. The computed QSAR parameters have a significant role in the estimation of the biological activity and metabolism in the human body.

**Keywords:** HyperChem 8.0.10, aromatic carboxylic acid, QSAR, HOMO-LUMO.

HyperChem programı kullanarak bazı aromatik karboksilik asitlerin HOMO, LUMO, termoplastik özellikleri ve QSAR incelemesinin teorik araştırılması

### ÖZ

Kimyasalların moleküler mekanizmasını geliştirmek, termokimyasal ve biyolojik etkileşimler hesaplamalı kimyanın temel amacı olarak düşünülmektedir. Moleküllerin serbest enerjisi, entropisi, dipol momenti, bağlanma enerjisi, nükleer enerjisi, elektronik enerjisi, oluşum ısısı gibi bazı termodinamik parametreleri ve yük yoğunluğu, yüzey alanı ızgarası, hacim, LogP, polarizasyon, kırılma, moleküler kütle gibi QSAR (kantitatif yapı aktivite ilişkisi) özellikleri, ve HOMO (en yüksek dolu moleküler orbital), ve LUMO (en düşük boş moleküler orbital), HUMO (en yüksek boş moleküler orbital)-LUMO enerji aralığı, iyonlaşma potansiyeli ve elektron afinitesi gibi reaktivite özellikleri, HyperChem 8.0.10 programı kullanılarak belirlenmiştir. Hesaplanan QSAR parametreleri, insan vücudundaki biyolojik aktivite ve metabolizmanın tahmininde önemli bir role sahiptir.

**Anahtar Kelimeler:** HyperChem 8.0.10, aromatik karboksilik asit, QSAR, HOMO-LUMO.

### 1. INTRODUCTION

Benzoic acid is a colorless crystalline solid and a simple aromatic carboxylic acid,<sup>1</sup> which was for a long time known as the source of a large number of synthesis of organic compounds.<sup>2-3</sup> Benzoic acid occurs naturally in many plants and serves as an intermediate in the

biosynthesis of many secondary metabolites.<sup>4-5</sup> Salts and esters of benzoic acid known as benzoates are used as food preservatives,<sup>6-7</sup> manufacture of alkyl resins and drilling mud additive, a rubber polymerization activator and retardant<sup>8</sup> and it has a great effect on growth performance, nutrient digestibility, nitrogen balance, gastrointestinal microflora and parameters of microbial

metabolism in piglets.<sup>9</sup> Many organic compounds were synthesized from benzoic acid in field of industries. Its use in the production of glycol benzoates for the application of plasticizer in adhesive formulations is increasing.<sup>10-12</sup> About 65% yield was obtained for traditional process. Most of the commercial benzoic acid is converted directly to phenol and caprolactam.<sup>13-14</sup> In United States of America, the production capacity of benzoic acid is estimated at 139,000 tons per year, which are used for both of the domestic and industrial uses as raw materials.

Benzoic acid is converted to its salts and esters for use as a preservative application in foods, drugs, and personal product. In case of the treatment of fungal skin disease, benzoic acid is the vital component of benzoin resin and ointments and other diseases such as tinea, ringworm, and athlete's foot.<sup>15-17</sup> On the other hand, the 2-nitrobenzoic acid, 2-chlorobenzoic acid, 2-methylbenzoic acid, and 2-hydroxybenzoic acids are the derivative of benzoic acid which is widely used in food industry, the pharmaceutical industry, chemical industry, agricultural land and with research purpose.<sup>18-19</sup> Due to estimate, the chemical and physical properties are a way of time and money. To save the time and cost, computational chemistry is the best tools to evaluate the chemical and biological properties.

Accordingly, an intimate relationship between the structure of a compound, in physicochemical, chemical reactivity, bioactivity, and biodegradation study should be computationally established as a "road map" of expectations, conditions of use, prediction and prevention.<sup>20-21</sup> In this context, the computational methods for modeling the chemical-biological interaction of a compound with organisms have become known as quantitative structure-activity relationships (QSAR) methods have come to the forefront.<sup>21-23</sup> Especially in the last two decade, a regulatory framework in variety of mareas such as, toxicological,<sup>24-25</sup> assessment of metabolic genotoxicity, screening of chemicals with bioaccumulation potential,<sup>26</sup> food and organic chemicals safety have been performed by computational analysis, and also thermophysical properties have been determined using computational programmes to save money and time. Considering their molecular structural relationship, HOMO, LUMO, and quantum chemical properties, and LogP plays a role in the determination of the chemical reactivity, biological activity and hydrophobicity and hydrophobicity of chemicals in relation with living cells activity and associated mechanistic interactions.

## 1.1. Theoretical background

### 1.1.1. Fundamentals of thermodynamics

Thermodynamics is a branch of physics and physical chemistry where describe the properties of the general

macroscopic physical systems and their theory of evolution, and it calculates all types of changes and heat in the physical and chemical processes.<sup>27</sup> The different activities of living occur with the conservation of energy which is governed by the physical law of altering one form of energy to another.<sup>28</sup>

A thermodynamic system consists of definite macroscopic region or space in the universe. This system has a specific volume consisting of molecules and atoms with continuous movement and concussion by the interaction with the external surrounding. The internal properties and its interaction with the surrounding determine the system behavior.<sup>29</sup>

The thermodynamics systems are of three types taking into account the interaction with the external environment which are: (i) Closed system: only the transfer of energy but not mass across the boundary. (ii) Open system: Transfer of both mass and energy across the boundary. (iii) Isolated system: Do not transfer both mass and energy across the boundary.

From above all three, a thermodynamic system of all living organisms is the open system and biological process is the irreversible thermodynamic process where the change of energy and mass take place. A thermodynamic system, when steady state, is called an equilibrium system where all the parameters do not vary with respect to time, and change by the surrounding involving the mass transport. A thermodynamic system can switch from initial state through the intermediate state to final state which is called transformation of state or thermodynamics process.<sup>30-31</sup>

Some properties like temperature (T), refractive index (n), density ( $\rho$ ) and hardness of an object ( $\eta$ ) are intensive properties, and also some properties like the mass (m), and the volume (V) are extensive properties. Surface area and some external parameters dependence of the thermodynamic system on the environment like pressure, temperature, density, electrical polarization, the coefficient of the tension of a liquid.<sup>32</sup>

### 1.1.2. Molecular modeling

Molecular modeling which is a useful implement in many fields such as chemistry, physics, biology, medicine, and pharmacy allows graphical representation of a molecular configuration and calculation of physicochemical properties and biological properties. In the pharmacological researchs, drug design, biological chemistry, and molecular biology, to do continuous researchs and design new molecules by molecular modeling of computational software has become easy. Instigated in various molecular modeling programs, these methods are used to determine the properties of drugs, and bioactive molecule found in the draft before the actual synthesis. Molecular modeling methods are numerous, mostly relying on the principles of quantum mechanics and Schrödinger's equation solving.<sup>33</sup>

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The most important methods that are used in molecular modeling programs are *ab-initio* methods, semi-empirical methods,<sup>34</sup> Density function theory.<sup>35</sup>

The most important methods of semi-empirical: AM1, PM3. In addition of the methods mentioned above, in recent years there was an expansion of the two methods, the method of molecular dynamics and Monte Carlo method, which refers to theoretical models that takes an intermediate between theory and experiment, called numerical methods.<sup>36</sup>

Among the most used molecular modeling programs, the common software is named Spartan, Gaussian, and HyperChem. Most molecular modeling techniques are worked based on the principles of quantum mechanics and Schrödinger's equation solving. Depending on the parameters molecular system has been studied that is intended to be obtained by choosing one or another method.<sup>37</sup>

## 2. COMPUTING MATERIALS AND METHODS FOR SIMULATION

HyperChem 8.0.1 is a path of molecular modeling program which permits to build and analyze different molecular structures and determine their physicochemical, thermo-chemical, and biological properties. To performing this work, a high core i7 computer, and HyperChem software were used.

The PM3 method is derived from Parametric Method number 3 from computational chemistry and included in the semi-empirical method for the quantum calculation of molecular structure. PM3 was used the Hamiltonian and it is parameterized to reproduce a large number of molecular properties.<sup>38</sup>

In order to create the spatial chemical structure of each calculated molecule, the two-dimensional structure of the molecule shall be built step-by-step by drawing. Then hydrogen atoms are automatically added from building option and chemical structure is automatically adjusted from model build option. In the first step, the optimization of main structure, bond length, bond order, and partial charges were obtained.

For optimization, MP3 from semi empirical method was ran up and running the option computing using the algorithm Polak–Ribiere was done with maximum gradient set at 0.001 kcal mol<sup>-1</sup> for calculation of free energy, entropy, dipole moment, binding energy, nuclear energy, electronics energy, heat of formation, the energy of frontier orbitals, HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital), and QSAR properties of molecules like charge density, surface area grid, volume, LogP, polarizability, refractivity, molecular mass.

## 3. RESULTS AND DISCUSSION

### 3.1. Optimized structure

A representation of the molecular structure optimized which contains the values of the reactivity indices is called the reactive molecular diagram. The optimized structure of optimized molecules using the HyperChem 8.0.10 software is represented in [Figures 1 and 2](#).

The symmetry is a very powerful tool established on the basis of HyperChem. The benzoic acid, 2-nitrobenzoic acid, 2-chlorobenzoic acid, 2-methylbenzoic acid, and 2 hydroxybenzoic acids are considered as the class symmetry, the molecules of this group are planar and they have only one element of symmetry and the plane of the molecule.

### 3.2 The atomic charges computed by HyperChem

It is seen from [Figure 3](#) that the negative charges are located near C and O atoms (the highest negative value is -0.404 in O, -0.10 atom) and the positive charges are located near H atoms (the highest positive value is 0.450).

### 3.3. Bond length

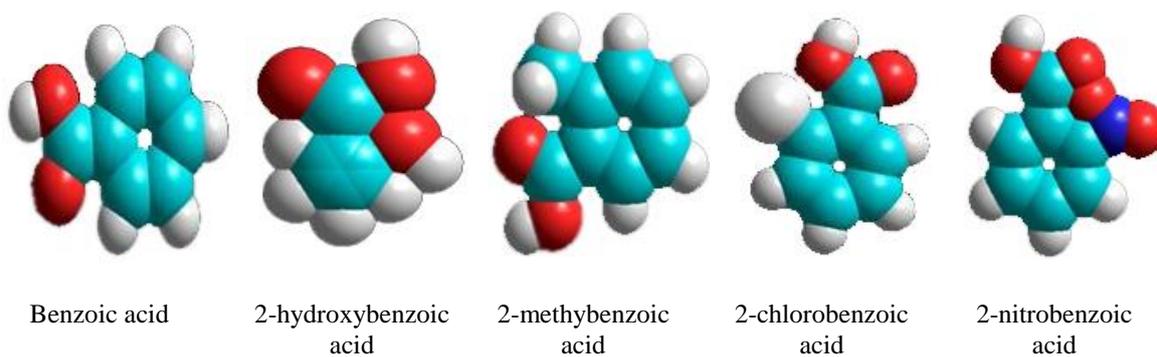
In general, the bond length between two atoms is approximately the sum of the covalent radii of the two atoms. For covalent bonds, bond energies and bond lengths depend on many factors like electron affinities, sizes, electro-affinity of atoms involved in the bond, differences in their electronegativity, and the overall structure of the molecule shown in [Figure 4](#). There is a general trend in that the shorter the bond length, the higher the bond energy. Similar bond length indicates the similarity and molecular symmetry.

### 3.4. Bond order

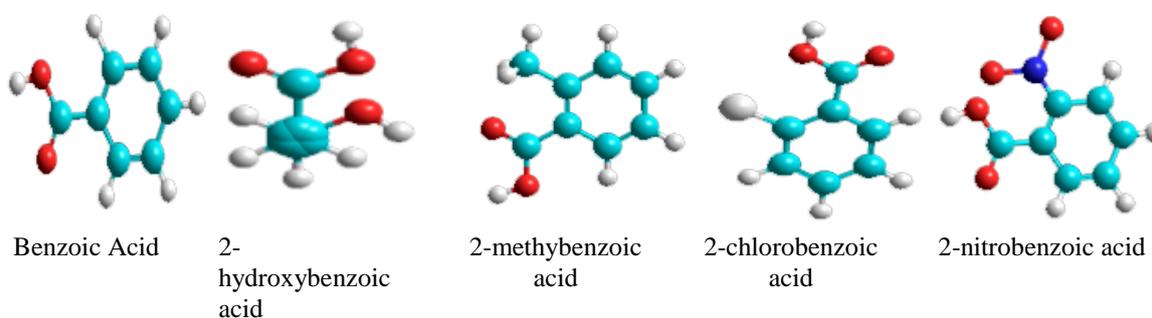
The higher the bond order indicates the stronger the pull between the two atoms and the shorter the bond length. The shorter bond length indicates the higher required energy. Bond orders in different molecules optimized by HyperChem are shown in [Figure 5](#).

### 3.5. HOMO-LUMO

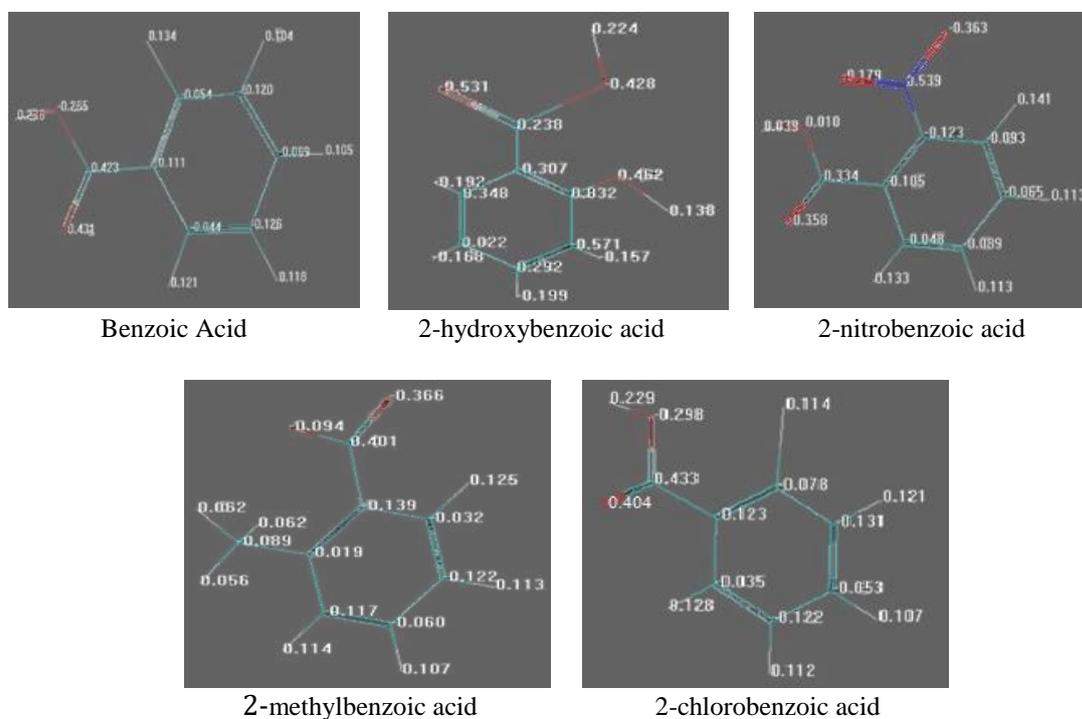
The energy levels of the molecular orbitals order HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) for different aromatic carboxylic acid molecules give information on the possible electronic transition. The HOMO and LUMO also indicate the electrophilic and nucleophilic attraction in the molecule. The LUMO-HOMO gap is the most important parameter for the chemical reactivity. The shorter LUMO-HOMO gap is considered as the high reactivity, they are highlighted in [Figure 6](#) (color: green is the positive value and blue is the negative value).<sup>39-40</sup>



**Figure 1.** Optimized structure representing ball shape, Color: Red is oxygen, cyan is carbon, white is hydrogen, nitrogen is blue, chlorine is white in large size.



**Figure 2.** Optimized structure in the cylinder shape, Color: Red is oxygen, cyan is carbon, white is hydrogen, nitrogen is blue, chlorine is white in large size.



**Figure 3.** The atomic charges in the molecules computed by HyperChem.

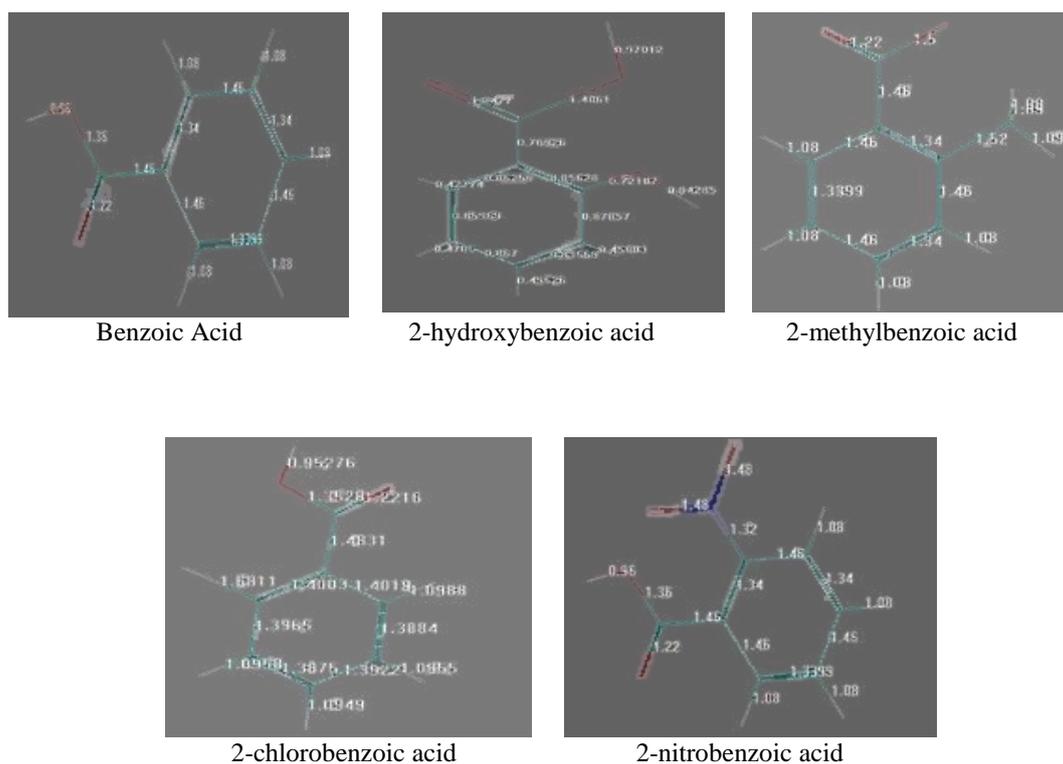


Figure 4. Bond length in different molecules optimized by HyperChem.

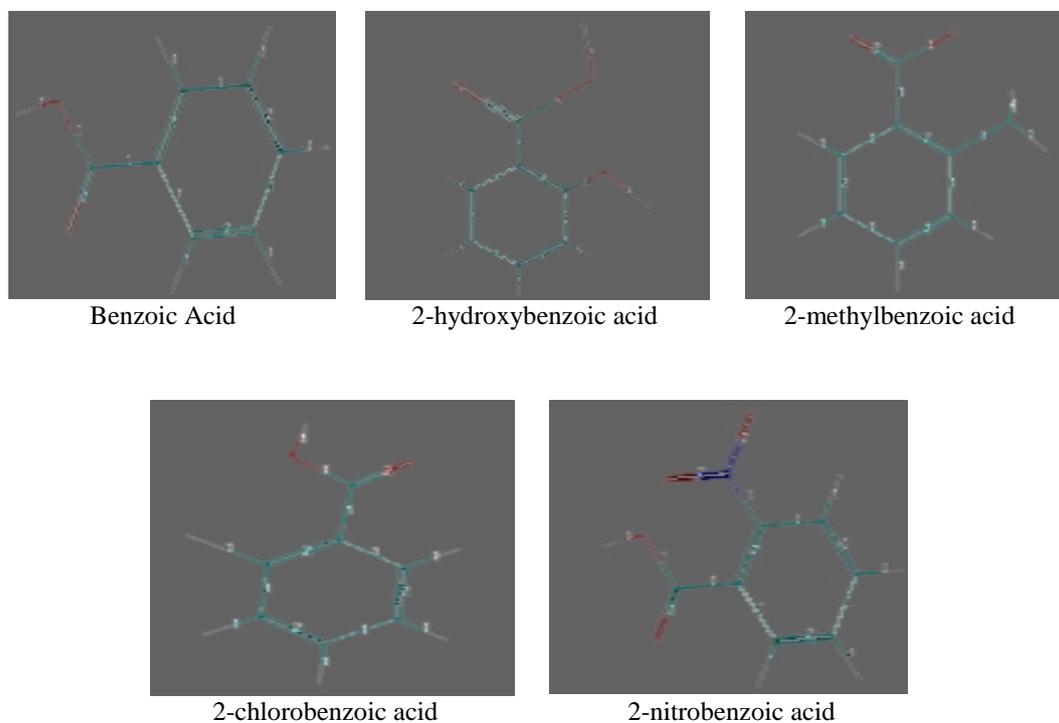
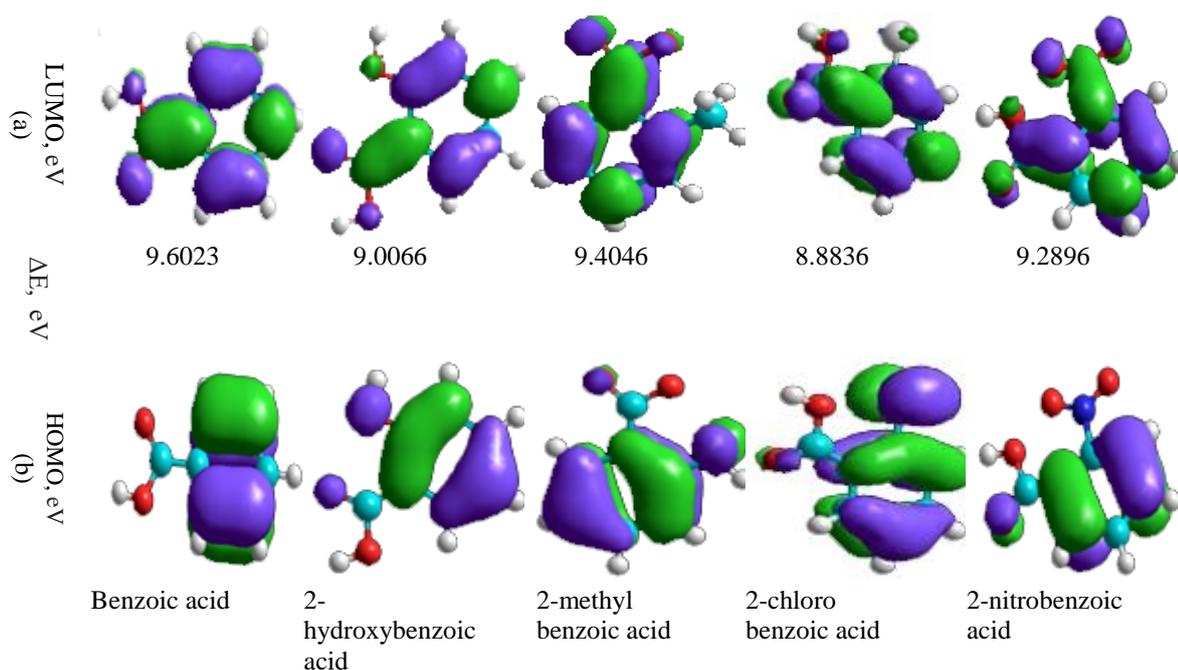


Figure 5. Bond order in different molecules optimized by HyperChem.



**Figure 6.** The frontier orbitals: a) LUMO and b) HOMO.

**Table 1.** Data for HOMO, LUMO, IP, EA, and LUMO- HOMO gap ( $\Delta E$ )

	Benzoic acid	2-hydroxybenzoic acid	2-methylbenzoic acid	2-chlorobenzoic acid	2-nitrobenzoic acid
HOMO, eV	-10.1358	-9.5180	-10.0681	-9.5955	-10.8299
LUMO, eV	-0.5335	-0.5114	-0.6635	-0.7119	-1.5403
$\Delta E$ , (LUMO-HOMO)	9.6023	9.0066	9.4046	8.8836	9.2896
Ionization potential (I), eV	-10.1358	-9.5180	-10.0681	-9.5955	-10.8299
Electron affinity (A), eV	-0.5335	-0.5114	-0.6635	-0.7119	-1.5403

In the Figure 6, all of molecules have almost near HOMO LUMO gap that is from 8.88 to 9.60 eV.

The electrophilic (Positive charge groups or atoms) attack to the most likely to the atomic site with a high density of orbital HOMO, while nucleophilic (Negative charge groups or atoms) attack LUMO that is correlated with atomic high-density of orbital LUMO.

The ionization potential (I) and electron affinity (A) have been estimated from the HOMO and LUMO energy values like as IP = Negative of the energy of HOMO, and EA = Negative of the energy of LUMO (Table 1).

### 3.6. Thermophysical properties

Thermophysical properties optimized from HyperChem are given in Table 2.

### 3.7. Characterization by NMR

The  $^1\text{H}$  NMR spectroscopy analysis in view of shielding and shift plotting, coupling and shielding tensor which are given in Figure 7. In measurements of nuclear magnetic moments, a correction must be made

for the magnetic field ascending from the motions of the molecular electrons which are induced by the externally applied field. The "chemical effect" which is considered as the chemical shift commonly, was used now for structural determination of molecules. The calculation of the second order paramagnetic contribution is used for shielding calculation perturbation theory. The chemical shift or magnetic shielding as a number associated with each resonant nucleus, in reality, the shielding is a tensor quantity. The shielding phenomena have to be described by a shielding tensor instead of a scalar number to easily calculate the structure of molecules. In Figure 7, if

shields and shift consists of three bars at which blue indicates the shielding, green indicates the chemical shift of proton and paste color indicates the tau. On the other hand, the shielding tensor different color indicates the different proton environment. In the last view, the proton coupling indicates the proton-proton coupling by different color bar.

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**Table 2.** Thermophysical properties optimized from HyperChem

Properties	Benzoic acid	2-hydroxybenzoic acid	2-methyl benzoic acid	2-chloro benzoic acid	2-nitrobenzoic acid
Total energy, (kcal mol <sup>-1</sup> )	-348030.6	-41446.25	-38253.4	-41751.5	-51653.70
Free energy, (kcal mol <sup>-1</sup> )	-348030.6	-41446.1	-38253.4	-41751.5	-51653.70
Entropy, (kcal mol <sup>-1</sup> deg <sup>-1</sup> )	0	0	0	0	0
Heat capacity, (kcal mol <sup>-1</sup> deg <sup>-1</sup> )	0	0	0	0	0
Dipole moment, (D)	0	0	0	0	0
RMS gradient, (kcal mol <sup>-1</sup> )	0.9482	0.093	0.6339	0.2354	4.5660
Binding energy, (kcal mol <sup>-1</sup> )	-1694.629	-1664.2025	-1975.9445	-1674.881	-1865.970
Heat of formation, (kcal mol <sup>-1</sup> )	-66.2537	23.3164	-72.8905	-70.0334	-57.9941
Nuclear energy, (kcal mol <sup>-1</sup> )	113121.321	134964.4467	141280.465	139147.969	195423.2914
	4		9	9	
Electronic energy, (kcal mol <sup>-1</sup> )	-146925.93	-176413.38	-179533.85	-180899.50	-247076.30

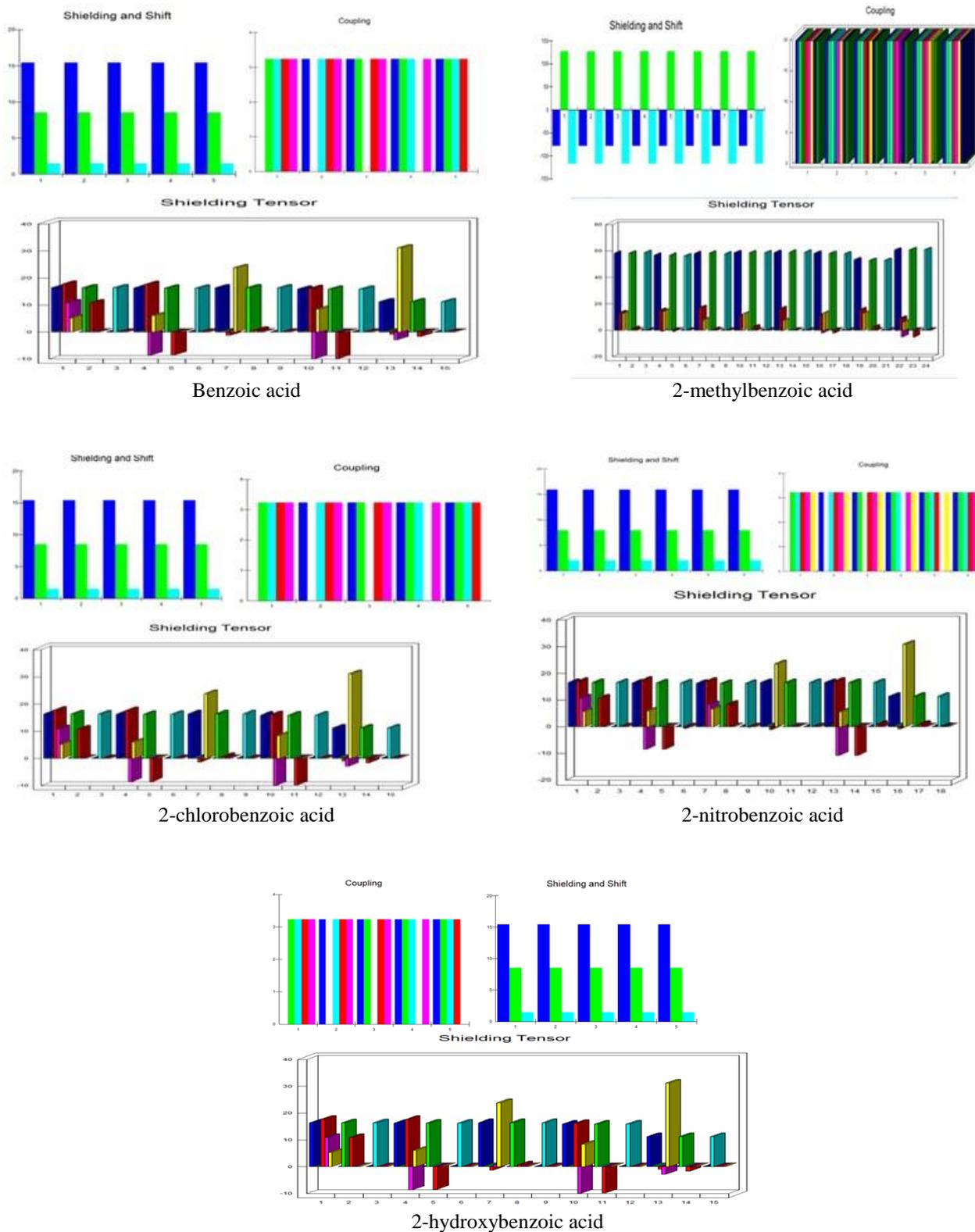
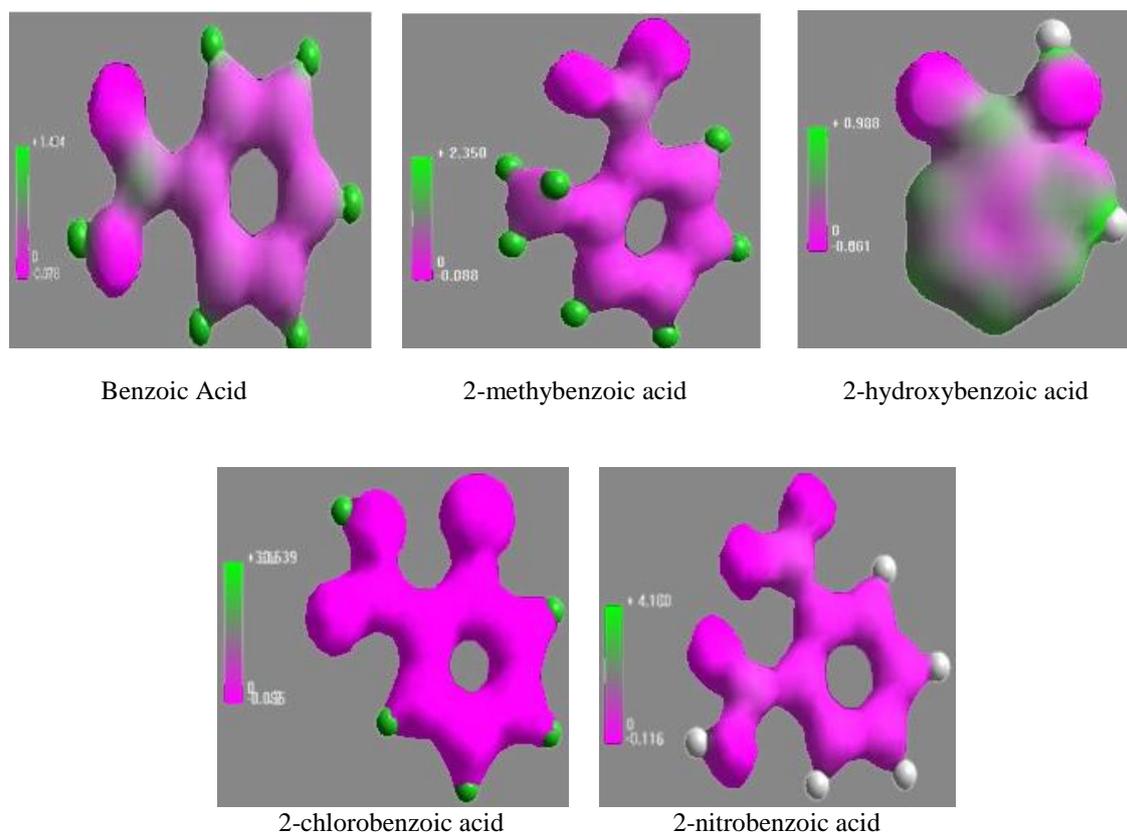


Figure 7. Shielding and shift, coupling and shielding tensor.



**Figure 8.** The 3D geometry of the distribution electrostatic potential.

**Table 3.** Data of electrostatic potential energy difference of two levels

	<b>Benzoic acid</b>	<b>2-hydroxy benzoic acid</b>	<b>2-methyl benzoic acid</b>	<b>2-chloro benzoic acid</b>	<b>2-nitro benzoic acid</b>
E1	1.434	2.350	0.988	30.539	4.180
E2	0.078	0.088	0.061	0.095	0.116
$\Delta E$	1.358	2.262	0.927	30.44	4.064

Here, E1= Electrostatic potential energy in positive value, E2= Electrostatic potential energy in negative value, and  $\Delta E$ = Electrostatic potential energy difference of two level.

### 3.8. Biological activity of optimized molecules

#### 3.8.1. The distribution electrostatic potential due to 3D mapped structure

The stability of the studied molecular structure is given by the higher negative values of total energy. The biological activity of a compound can be estimated on the

basis of the energy difference ( $\Delta E$ ) frontier orbitals. This difference,  $\Delta E$  represents the electronic excitation energy of molecule. According to the mechanism of antimicrobial activity and antimicrobial agents of bioactive molecules, the positive charge end of molecules is responsible for damage the plasma membrane of pathogens.<sup>41</sup> To kill the different human pathogenic microorganisms, the charge region of molecules was used as the biological active part in the molecule. In this case, the most important factors are explained that the higher surface area and higher positive and negative charge is considered as the high antimicrobial active molecule. The electrostatic potential in view of the 3D mapped structure

**Table 5.** Data of QSAR study

	<b>Benzoic acid</b>	<b>2-hydroxybenzoic acid</b>	<b>2-methyl benzoic acid</b>	<b>2-chloro benzoic acid</b>	<b>2"-nitro benzoic acid</b>
Partial charge (e)	0.0	0.0	0.0	0.0	0.0
Surface Area (grid)	280.25	313.13	297.04	294.48	305.75
Volume, Å <sup>3</sup>	407.24	461.61	450.99	442.41	457.69
Hydration Energy	-6.82	13.54	-6.07	-5.27	-11.47
LogP	0.98	-0.04	1.14	0.76	-3.70
Refractivity, Å <sup>3</sup>	36.98	38.58	41.24	41.67	42.17
Polarizability, Å <sup>3</sup>	12.99	13.63	14.28	14.92	14.83
Mass (amu)	122.12	138.12	136.15	156.57	162.12

indicates positive and negative charge region and the charged surface area in a molecule that is considered as the best tools to estimate the biological activity parameters.<sup>42</sup>

The three-dimensional geometry of molecular electrostatic potential distribution highlights the existence of three regions with increased electronegativity in which oxygen and chlorine atoms are involved, and which play a role in their coupling to different structures in which ions are positively charged. From Table 4, it is found that the 2-chlorobenzoic acid shows high electrostatic potential energy difference of two levels due to having chlorine and highly bioactive than nitrobenzoic acids.

The surface distribution of molecular electrostatic potential is an indicator of the specific reactive regions of the molecule given in Figure 8.

### 3. 9. Qquantitative structure-activity relationships (QSAR)

Correlation of the molecular structure or properties are derived from a molecular structure with a particular chemical or biochemical activity. This method is widely used in pharmaceutical chemistry in the environment and in the search for certain properties. Data of QSAR study are given in Table 5.

#### 3.9. 1. Binding Energy

The binding free energy of the optimized molecules is calculated by performing a docking process. The molecule with minimum binding energy will have the maximum binding affinity. The binding free energy of the designed molecules is obtained by eliminating the energy of the main molecule. Having the maximum binding affinity indicates as the best molecule for drug and leads molecules targeting computationally. We can find out the drug binding affinity by using the fitness of the drug, which can bind to the target molecule during the docking process and the second way is to use Gibbs free energy calculations. According to the more negative value, we can consider a more effective drug. As seen from Table 2, it is found that the binding energy, which is almost the same in benzoic acid, 2-hydroxybenzoic acid, and 2- chlorobenzoic acid from-to 1695 (kcal mol<sup>-1</sup>). On the other hand, the 2-methyl 1664 benzoic acid shows the higher binding energy of -1975.9445 where nitrobenzoic acid has -1865.970 (kcal mol<sup>-1</sup>).

#### 3.9.2. Surface area

In the case of the biological activity of a molecule, the surface area is considered as the important parameter. Greater charge surface area of a molecule can possible to kill more pathogens. The charged distribution from

electrostatic potential completely depends on the surface area. The greater positive charge surface area means the higher biological activity. As seen from Table 4, it is illustrated that 2-methylbenzoic acid and 2-chlorobenzoic acid are near 195 to 197 where 2-hydroxybenzoic acid has 313 and benzoic acid has 280.

### 3.9.3. Hydration Energy

The hydration energy is defined as the energy absorbed when the substance is dissolved in water. The lower hydration energy is considered as the greater capacity to dissolve in water so that it acts as the hydrophilic nature and predict the best properties of the drug. The 2-hydroxybenzoic acid and 2-nitrobenzoic acid are -11.0 to 13.0 kcal mol<sup>-1</sup> and all other are near about 6.00 kcal mol<sup>-1</sup>.

### 3.9.4. LogP

A negative value of LogP indicates the hydrophilicity and positive LogP indicates the hydrophobicity. The both of hydrophilicity and hydrophobicity play an important role in biochemical interactions and bioactivity. Hydrophobic drugs tend to be more toxic because, in general, are kept longer, have a wider distribution in the body, are somewhat less selective in their binding to molecules and finally are often extensively metabolized. Therefore ideal distribution coefficient for a drug is usually intermediate (not too hydrophobic nor too hydrophilic). From the data in Table 4, it can be seen that 2-hydroxybenzoic acid has -0.04 value that indicates lower hydrophobicity, and nitrobenzoic acid show a higher hydrophobicity. All other three molecules show hydrophilicity range from 0.98 to 1.15.

## 4. CONCLUSIONS

The semi-empirical PM3 method of the program HyperChem 8.010 was used to characterize and compute benzoic acid, 2- nitrobenzoic acid, 2-chlorobenzoic acid, 2-methylbenzoic acid, and 2- hydroxybenzoic acid. The physicochemical parameters and thermodynamic properties were estimated for a specific use to each molecule including 3D structure, bond lengths, the atomic charges, total energy, free energy, entropy, dipole moment, formation energy, binding energy, electrostatic energy, and nuclear energy.

The molecular descriptors QSAR provided the calculation of charge, surface area, volume, hydration energy, LogP, refractivity, polarizability, and molecular mass. The most important properties for biological chemistry, reactivity and drug design, the HOMO, LUMO, LUMO-HOMO gap, ionization potential, electron affinity, and electrostatic potential in case of the charge distribution in molecule were optimized and recorded using semi-empirical modeling methods.

The <sup>1</sup>H NMR was evaluated by molecular modeling programs. Obtaining by modeling the distribution of

molecular electrostatic potential reactive sites leads to the identification and characterization of the molecules. It is summarized that the resulted optimized molecules of aromatic carboxylic acid were developed a comparative study on their chemical reactivity, thermo-chemical profile and biological activity in view of theoretical studies.

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## Conflict of interest

Authors declare that there is no a conflict of interest with any person, institute, company, etc.

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