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Synthesis, Characterization and computational study of N-Acylhydrazone derivatives

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Abstract

The N-Acylhydrazone of benzoic acid and their derivatives are important intermediates in organic synthesis and have widespread applications in the medicinal industry. The N-Acylhydrazone was prepared through the condensing the phenyl hydrazide derivatives which prepared from phenylmethyl ester, with benzaldehyde and then identified by physicochemical properties and spectral analysis; FT-IR and ^{1}HNMR.

Computation calculations studies by using Semi-empirical-PM3 method through a molecular structure with optimized geometry showed that there is a high correlation between dipole moment, Electron affinity (EA), ionization potential (IP), electronegativity, ClogP and hardness.

To Proof, the stability of N-Acylhydrazone derivatives by using Molecular orbital calculations supported a full description of the orbitals and the contributions of individual atoms. Highest occupied molecular orbital/lowest unoccupied molecular orbital energies and structures are demonstrated, calculation atomic charge and molecular electrostatic potential. Through the data obtained from the computational chemistry program, Hyper Chem 8, we were able to demonstrate that the N-acylhydrazone derivatives have a close values and within the limits of stability.

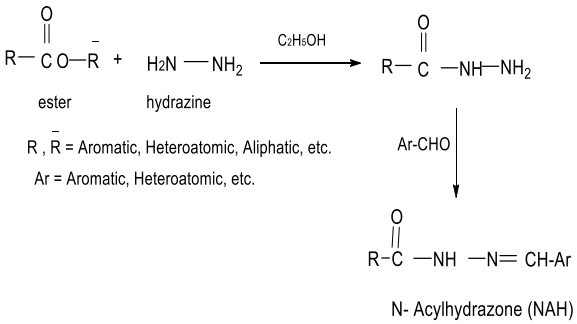
Keywords: N-Acylhydrazone, physicochemical properties, hydrazone Schiff's base

1. Introduction

Over the past two decades, the bioactive N-acylhydrazone (NAH) core has been one of the most ubiquitous functional groups in medicinal chemistry, and it has been identified in a huge number of hit and lead compounds that act on different types of molecular targets.[1]

Medicinal chemists have engaged in different efforts to synthesize new privileged small-molecule scaffolds by developing new and synthetic transformations using the powerful N-Acylhydrazone (NAH) core. The versatility of NAH in medicinal chemistry is depends on their ease of synthesis, as they are usually produced by a condensation reaction between aldehydes or ketones with hydrazides (scheme 1). NAH cores have also been extensively used as electrophiles in the production of nitrogen-containing compounds. [2]

These scaffolds have distinct H-bonding opportunities. there are two H-bond acceptor points (carbonyl oxygen and imine nitrogen) spaced by an H-bond donor (amide hydrogen). It is present in the structure of dantrolene, amid its rarity among approved drugs (scheme 2), the only medication available for the treatment of malignant hyperthermia [3]. Various drugs which have NAH structure which has a different activity[4-6]. In recent years, several studies have been published regarding the chemistry and bioactive lead scaffolds of N-acylhydrazones, and over time, this subject has grown in importance for the development of new, therapeutically useful bioactive NAH candidates [7-11]



Scheme (1): General synthesis of N-Acylhydrazone derivatives

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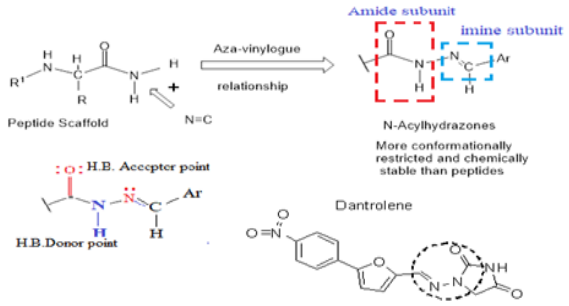

Scheme 2: NAH subunit as peptide mimic privileged structures.

Despite its peptide mimetic nature, the chemical stability of the NAH structure (1) against hydrolysis is demonstrated compared with isolated amide or imine functional groups.

The NAH structure enables the best study of its unique physicochemical profile and is therefore a valuable molecular framework in drug development and optimization[12]. Another advantage of this scaffold is that it is possible to strengthen or alter its bioactive profile through conformation shifts in NAH (1) derivatives.

Compounds of hydrazide-hydrazones are not only intermediate but rather effective organic compounds. The use of the active hydrogen portion -CONHN = CH- azomethine group is used as intermediates in the coupling of products. [13]

Preparing N-acylhydazone derivatives and diagnosing them firstly, then studying their stability using computational chemistry by calculation thermodynamic parameters such as bonding Energy, free energy, entropy, dipole moment, nuclear energy, electric power, formation heat, and calculated quantum structure-activity relationship properties such as charge density, surface area grid, length, CLogP, polarization, refractivity, molecular mass, and molecular reaction properties As HOMO (highest unoccupied molecular orbital), LUMO (lowest unoccupied molecular orbit), E gap [E_{HUMO}-E_{LUMO}], the ionization potential and electron affinity were determined using HyperChem 8.0.10 software.

HyperChem 8.0.1 program is molecular modeling software that could be used for calculating and studying the physicochemical, thermochemical, and biological properties of molecules at their equilibrium geometries. The semi-empirical quantum mechanical method (PM3) was used for calculating these physical properties [14].

Growing the molecular mechanism of chemicals, thermochemical and biological interactions is considered as the ultimate goal of computational chemistry. To save time and cost, computational chemistry is the best tools to evaluate the chemical and biological properties.

2. Experimental

2.1. Material and methods

All the chemicals were supplied from Merck, Sigma-Aldrich and have been carried forward without further purification. Melting points were determined by open glass capillary method on a SMP 30 Stuart apparatus. FT-IR spectra were recorded on a FT-IR 84005, SHIMADZU and ^{1}H-NMR spectra (500 MHz) was measured at university of Tahran.

2.2. Synthetic Procedure

2.2.1. Synthesis of Methyl benzoate- I [15]

Benzoic acid (1.22 g, 0.01 mol) was dissolved in methanol (25 mL) in a 100 mL round bottomed flask and 3 mL of conc.H_2SO4 was added. The resulting solution was refluxed for 6 hours. Progress of the reaction was monitored by TLC using ethyl acetate : hexane (3 : 7) as eluent. After completion of the reaction , the mixture was poured on to crushed ice, then treated by 10 % $NaHCO_3$ until the solution become pH 8. Then extracted with ethyl acetate (3 X 10 mL) and afterwards dried using anhydrous magnesium sulfate and evaporated the solvent. Colorless, b.p.198-199 ºC; IR (KBr) (cm^{-1}) 1735 (C=O), 3105(Ar-H) ; ^{1}H-NMR ($CDCl_3$) δ: 8.025 (Ar-H; d., Ha, Ha), 7.58 (Ar-H; d. , 1Hc), 7.39(Ar-H, t., Hb, Hb), 3.89 (s, 3H).

2.2.2. Synthesis of Methyl 4-Hydroxybenzoate-II [16]

To a mixture of 4-Hydroxybenzoic acid (1.52 g, 0.01 mol) and methanol (35 mL) in a 100 mL round bottomed flask and 3 mL of conc.H_2SO_4 was added. The resulting solution was refluxed for 8 hours. The mixture was poured on to crushed ice, then treated by 10% $NaHCO_3$ until the solution become pH 8. Extracted with acetone (3 X 10 mL) then evaporated. Collected the product. White needles, m.p.125-127 ºC; IR (KBr) (cm^{-1}) 3301(-OH), 1682(C=O), ^{1}H-NMR ($CDCl_3$):δ 10.3(s,1H, OH), 7.8 (Ar-H, d., Ha,Ha), 6.85 (Ar-H, d., Hb,Hb) 3.78 (s, 3H).

2.2.3. Synthesis of Methyl 4-Chlorobenzoate-III [17]

To a mixture of 4-Chlorobenzoic acid (1.70g, 0.01 mol) in (30 mL) methanol in a 100 mL round bottomed flask and 3 mL of conc.H_2SO_4 were added. The resulting solution was refluxed for 12 hour. The product was diluted with ice water and extracted with acetone (3 X 10 mL). The organic layer was dried over anhydrous magnesium sulphate. Collected the product. White crystals, m.p.44.5-45 ºC; IR (KBr)(cm^{-1}) 1715(C=O), ^{1}H-NM ($CDCl_3$):δ 7.89 (Ar-H, d., Ha, Ha),7.60 (Ar-H, d., Hb,Hb), 3.89 (s,3H)

2.2.4. Synthesis of Methyl 4-Aminobenzoate-IV [18]

To 4-amino benzoic acid (0.01 mol, 1.51 gm) and methanol (30mL) in a 100 mL round bottomed flask and 3 mL of conc H_2SO_4 were added. The solution was refluxed for 6 hours. After completion of the reaction, and the crude product was diluted with ice water and extracted with ethyl acetate (3 X 10 mL). The organic layer was dried over anhydrous magnesium sulphate and the solvent was evaporated. Off-white crystals, m.p.109-110.5 ºC; IR (KBr) (cm^{-1}) 3466, 3371(asy. ,sym. NH_2), 1681(C=O); ^{1}H -NMR ($CDCl_3$):δ 4.8 (s,2H, -NH_2), 7.83(d,2H, Ha, Ha), 6.62(d, 2H, Hb,Hb), 3.85(s, 3H).

2.2.5. General methods of Synthesis Benzohydrazide derivatives (V-VIII) [19]

The mixture of Methyl benzoate ester derivatives (I, II, III, IV) (0.01mol) respectively in ethanol (25 mL) and hydrazine hydrate (90%) (0.5 mL, 0.012 mol) was taken in a flat bottomed flask and refluxed for 3 hourS. The reaction mixture was cooled at room temperature, it was filtered and washed thoroughly with cooled water to get the crude of product. Recrystallized from ethanol.

The all data IR and ^{1}HNMR for the products are very closed.

Benzohydrazide derivative (V): m.p 115℃, IR (KBr) (cm^{-1}) 3329 (NH), 3055(C-H aromatic), 1643 (C=O), ^{1}H-NMR ($CDCl_3$):δ 9.5(1H,s, NH), 7.9(2H, d, Ha, Ha¯, Ar-H), 7.5(2H, triplicate, Hb, Hb¯, Ar-H), 7.6(1H, d, Hc), 4.4(2H,s, NH_2).

4-Hydroxybenzohydrazide derivative (VI): m.p 268℃; IR (KBr) (cm^{-1}) 3356(OH), 3325(NH), 1635 (C=O); ^{1}H-NMR ($CDCl_3$):δ 9.6(1H, s, OH), 9.4(1H,s,NH), 7.5(2H,d. , Ha, Ha¯, Ar-H), 6.8(2H, d., Hb ,Hb¯, Ar-H), 4.9(2H,s, NH_2).

4- Chlorobenzohydrazide derivative (VII): m.p.166℃; IR (KBr) (cm^{-1}) 3320 (NH), 3089 (Ar-H), 1660 (C=O), 1645 (C=C), ^{1}H-NMR ($CDCl_3$):δ 9.65(1H,s,NH), 7.9(2H,d., Ha,Ha¯, Ar-H), 7.55(2H,d., Hb,Hb¯, Ar-H), 4.5(1H,s, NH_2) .

4-Aminobenzohydrazide derivative (VIII) : m.p.226℃; IR (KBr) (cm^{-1}) 3428, 3348 (Asym., Sym. 4-NH_2), 3274(NH), 1622(C=O),3056(Ar-H), ^{1}H-NMR ($CDCl_3$):δ 9.65(1H,s ,NH), 5.54 (2H,d.,Ha,Ha¯, Ar-H), 6.54 (2H,d., Hb,Hb¯, Ar-H), 5.48(2H,s, 4-NH_2), 4.5(2H, s,NH-NH_2).

2.2.6. General procedure for the synthesis of N-Acylhydrazone derivatives (IX- XII)[20,21]

The diverse substituted N-Acylhydrazone derivatives were synthesized by reacting the appropriate substituted benzohydrazide derivatives (V-VIII) (0.1mol) and one equivalent of aromatic benzaldehyde (0.1mol) with 2 mL glacial acetic acid in ethanol (20 mL). The reaction mixture was stirred and refluxing for 3 hours. After completion of reaction mixture, the crude product was recrystallized from ethyl acetate to give the pure product . In general final products were confirmed by the absence of signals for the hydrazide protons (–CONHNH$_2$), which were at δ = 9.22 –9.68 (–CONH–) and at 4.40–4.9 ppm (–NH_2), and the aldehyde proton appearance (N=CH-) at δ = 8.32- 8.7 ppm which belong to acylimine of N-Acylhydrazone derivatives.

N-benzylidenebenzohydrazide (IX): m.p.165-166℃; IR(KBr) (cm^{-1}) 3320 (NH), 1666.5 (C=O), 1539.2 (C=N);^{1}H-NMR($CDCl_3$):δ 9.22 (1H,s,NH), 8.329 (1H,s,N=CH),7.93(4H,multip.,Ha,Ha¯ & benzylidine) , 7.54 (6H, multiple, Hb,Hb¯, benzylidine).

N-benzylidene-4-hydroxybenzohydrazide derivative (X): 159-160℃; IR (KBr) (cm^{-1}) 3352 (OH), 3322(NH), 3075(Ar-H), 1664.5 (C=O), 1530.2 (C=N); ^{1}H-NMR ($CDCl_3$):δ 9.68(1H,s,OH), 9.23 (1H,s,NH),8,555(1H,s,N=CH),7.76(2H,d.,benzylidine), 7.58(3H,s,benzylidine), 6.88(2H,d.,Hb,Hb¯, Ar-H).

N-benzylidene-4-chlorobenzohydrazide derivative (XI):147-148℃;IR (KBr) (cm^{-1}) 3320 (NH), 3090 (Ar-H), 1665 (C=O), 1650 (C=N), ^{1}HNMR($CDCl_3$):δ 9.48(1H,s,NH),8.37(1H,s,N=CH),7.93 (4H, multiple, HaHa¯, benzylidine), 7.58(4H,multip.,HbHb¯ , benzylidine), 6.88(2H,d., Hb,Hb¯ ,Ar-H).

4-amino-N-benzylidenebenzohydrazide derivative (XII): 170-172℃; IR (KBr) (cm^{-1}) 3427, 3347 (Asym., Sym. 4-NH_2), 3270 (NH), 1625(C=O), 1540(C=N), ^{1}H-NMR ($CDCl_3$):δ 9.481(1H,s, NH), 8.37(1H,s, N=CH), 7.93(2H,d.,benzylidine), 7.54 (5H,multip.,HaHa¯ & benzylidine),6.54(2H,d.,HbHb¯) , 5.48(2H,s, NH_2).

3. Result and Discussion

3.1. Chemistry

The acid hydrazide was prepared by esterification of benzoic acid derivatives followed by treatment with hydrazine hydrate in absolute ethanol. The final product derivatives (IX-XII) were prepared by reaction of benzoic acid hydrazide with the aromatic aldehyde to form imines with nucleophilic condensation to the aldehydes. In the first stage of the reaction, preparation benzoic acid ester derivatives then followed by replacement methyl ester group by hydrazide. A nucleophilic attack from nitrogen hydrazide derivatives on the carbonyl group of aldehyde, carbinolamine is formed and followed by water dehydration. The steps of reaction accelerated by acid catalysts. Carefully adjust the acidity of pH is necessary since there must be adequate acid to give an appropriate protonated form of benzaldehyde equilibrium concentration, as shown in Scheme 3.

3.2. Computational studies

Molecular electronic structure has arrived an enormous amount of awareness by chemists and has become a key stone of modern chemical research. Several articles employed the PM3 method in medicinal chemistry research. [22] The optimized geometries calculated by PM3 were used as strategy to obtain N-Acylhydrazone using the HyperChem 8.0.10 software is represented in Figure1, and the data listed in table 1 showed the highest atomic charge of all NAH derivatives IX- XII. Studies of the stable structures can form a strategy to rationalize important aspects of medicinal compounds.

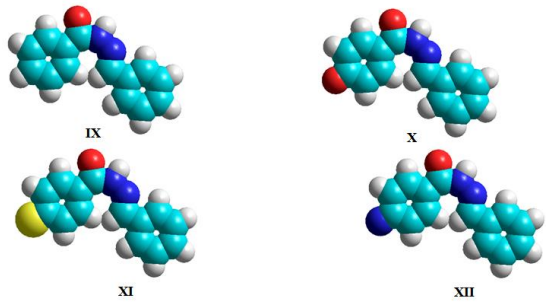

Figure 1. Optimized structure representing ball shape, Color: cyan is carbon, Red is oxygen, nitrogen is blue, white is hydrogen, chlorine is yellow

The distribution of atomic charge has a major effect on the (Electrostatic potential and. Dipole moment. Show the results are close or approximately identical to calculate the atomic charge, the atomic charge vehicles account generally affects the extent of the effectiveness of the derivative and the active sites in the compound as the increased charge of the atomic negative or positive value indicates to increase the effectiveness of this atom, also results indicate that the effectiveness is in the atoms of hydrazone bond (-CO-NH-N=CH-) of most derivatives. Both X and XII derivatives have proximately similar data which belong to the presence of the donating group (OH, NH_2), loin pair of a heteroatom.

In general, the length of the bond between two atoms is roughly the sum of the two atoms' covalent radii. Bond energies and bond lengths depend on several variables for covalent bonds, such as electron affinities, sizes, electro-affinity of the atoms involved in the bond, variations in their electronegativity, and the overall molecule structure seen in Figure 3. All derivatives contain the active and specific group (-CO-NH-N=CH-) that found the bonds approximately the same length bond indicating that they have the same tendency and bond energy, but when compared to the same molecule, a difference was found between the length of the bond C=O with C=N (1.215,1.30) respectively, that C=O is shorter than C=N because O is more electronegativity than N.

Some physical properties of the molecules studied in this research were calculated; such as the energies(ev) of the high Occupied Molecular Orbital (E_{HOMO}) and the Lower Unoccupied Molecular Orbital (E_{LUMO}). The HOMO and LUMO of a molecule play important roles in intermolecular interactions, through the interaction between the HOMO of the drug with the LUMO of the receptor and vice versa.

The region bounded by the HOMO orbital measuring the character electron–donor derivative, and the LUMO measuring the electron acceptor character. From these definitions, two important features can be observed: the higher the energy of the HOMO, the greater the electron–donor capacity and the lower the energy of the LUMO lower the resistance to accept electrons. [23-25]

The most important parameter for chemical reactiv ity is the LUMO-HOMO gap. [26,27] The shorter ΔE (LUMO-HUMO) gap is called reactivity, as seen in Figure 4.

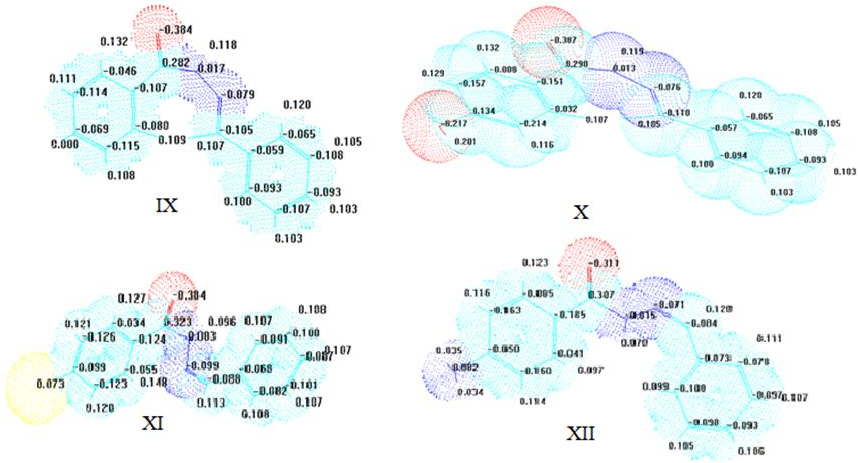

Figure 2. The atomic charges of (-CO-NH-N=CH-) in N-Acyl hydrazone derivatives .

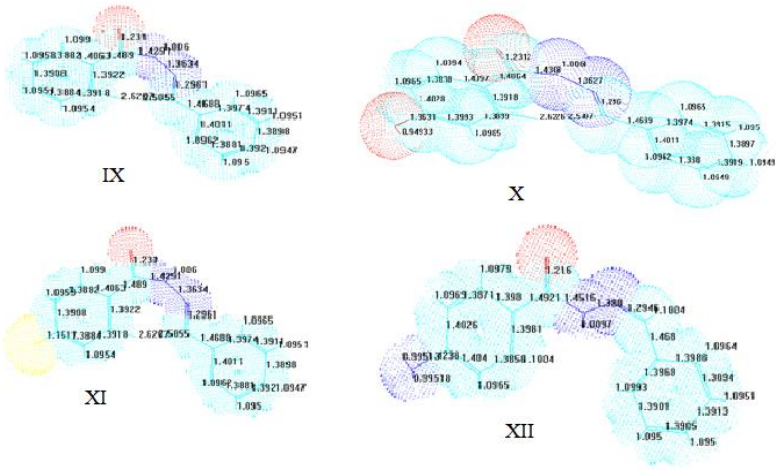

Figure 3. Bond length in different derivatives optimized by HyperChem.

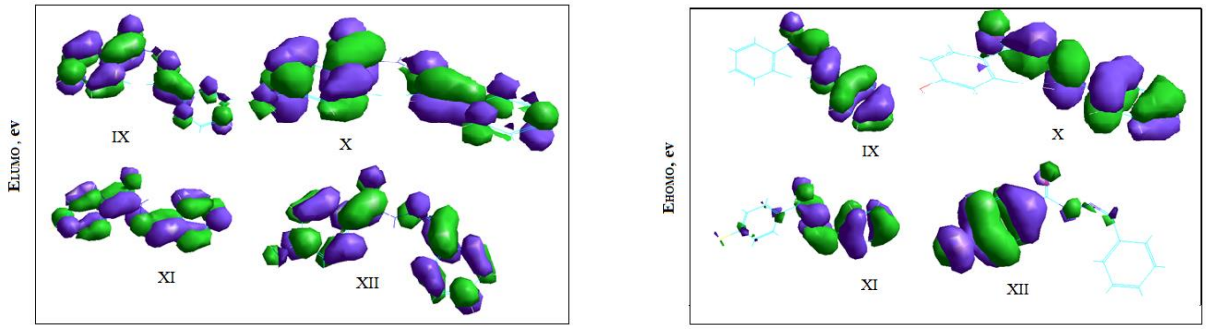

Figure 4. The frontier orbitals: a) LUMO and b) HOMO of N-Acylhydrazone derivatives.
(color: the positive value is green and the negative value is blue).

By using this energy gap(ΔE) for the purpose of comparison between the derivatives there was the necessary basic medication – powered teams could not rule out this derivative but the differences that emerged for all derivatives are relatively close, XII derivative more one. Chemical hardness signifies resistance towards deformation or polarization of the atom, ions, or molecules' electron cloud under small perturbation of chemical reaction. Hard molecules have a large energy gap and soft molecules have a small energy gap. Using Koopmans theorem for closed-shell compounds, η, μ and ω be defined as:

$$\eta = (E_{LUMO} - E_{HOMO})/2 \quad \text{----------} \quad 1$$

The electronic chemical potential of a molecule is known as the electronegativity negative and is determined using equation 2.

$$\mu = -(IP + Ea)/2 \quad \text{----------} \quad 2$$

So, the electronegativity of an element is the power of an atom of the element to attract an electron to itself when it is part of a derivative. If an atom has a strong tendency to acquire electron, it is said to be highly electronegative. Electronegativity is a very useful concept in chemistry and has numerous applications which include rationalization of bond energies and the type of reaction that substance undergoes and the prediction of the polarity of bonds in molecules. It can be related to the size and electronic configuration of the atom. show in table 2, the electron chemical potential data for all derivatives are close. Physically, μ determines the propensity of electrons to flee from an equilibrium system.

Table 1: Atomic charge calculation of N-Acyl ydrazone group in derivatives (IX, X, XI, XII)

-CONH-N=CH- Charge atoms	IX (H)	X (OH)	XI (Cl)	XII (NH_2)
O	- 0.382	- 0.311	- 0.304	- 0.311
C	0.326	0.307	0.299	0.307
N	- 0.004	- 0.008	- 0.007	- 0.010
H	0.096	0.061	0.061	0.061
N	- 0.092	- 0.078	- 0.082	- 0.075
C	- 0.092	- 0.075	- 0.070	- 0.08
H	0.113	0.096	0.096	0.095

Table 2. Data for HOMO, LUMO, LUMO- HOMO gap (ΔE) , IP ,EA, μ, η and ω.

Compounds	IX	X	XI	XII
E_{HOMO}, ev	- 8.84022	- 8.82667	- 9.02973	- 8.96381
E_{LUMO}, ev	- 0.75521	- 0.72760	- 0.81263	- 0.48175
ΔE,(LUMO-HOMO)	8.08501	8.09907	8.2171	8.48206
Ionization Energy (IE)	8.84022	8.82667	9.02973	8.96381
Ionization chemical potential (IP), ev	- 8.84022	- 8.82667	- 9.02973	- 8.96381
Electron affinity(Ea), ev	0.75521	0.72760	0.81263	0.48175
Electronic chemical potential (μ)	-4.79771	-4.77713	-4.92118	-4.72278
Chemical hardness (η)	4.42011	4.049535	4.10855	4.24103
Electrophilicity (ω)	2.6037	2.8177	2.9472	2.6296

The global electrophilicity index (ω), as seen in equation 3, is determined using the electronic chemical potential and chemical hardness.

$$\omega = \mu^2/2\eta \qquad \text{----------} \qquad 3$$

The XI derivative is more electrophilicity than other derivatives.

The ionization energy (IE) correlated with a higher energy orbital full of electrons (HOMO), high energy ionization values mean high molecular stability, thus increased stability of Cl and NH_2 derivatives and on the other hand, low ionization energy means high molecule efficiency, hence increased reactivity for H and OH. More efficiency compared to the low ionizing energy of the molecule. [28]

Electron affinity(Ea), refers to the capability of ligand to accept one electron from a donor.

The properties of the individual atom were proposed by Robert Mulliken i.e., an atom with high ionization energy (IE) and a high electron affinity (Ea) likes to acquire electron than to lose electron when it is part of a compound, i.e highly electronegative. Conversely, the atom with low ionization energy and electron affinity tends to lose electron rather than gain them i.e. electropositive. This observation motivated the definition of the Mulliken electronegativity.[29]

The physicochemical properties of molecules, such as their lipophilicities and polar surface areas (PSAs) play important roles in determining biological responses and are commonly used to study the structure-activity relationships of bioactive molecules in medicinal chemistry. [30, 31]

The results showed that derivative XII has a high value for Dipole moment, shown in table 3, 5.544 Debye. So the derivative XII which contain NH_2 group more dipolar moment and polarity than substituted by OH group (is expected result).

These parameters are now well-accepted major experimental and theoretical tools for drug design and discovery.

The binding energy of XII derivative is more than others derivatives, which related positively with dipole moments. Heat of formation for derivative X is less value, 8.427 $Kcal.mol^{-1}$ which make the more stable one, then XI, XII and I , respectively.

The biological activity of derivative can be estimated on the basis of the energy difference ΔE frontier orbitals. This difference, ΔE represents the electronic excitation energy which is possible in a molecule shown in Table 4 and Figure 5.

According the mechanism of biological activity and agents of bioactive molecules, the positive charge end of molecules is responsible to damage the membrane of pathogens .[32] To kill to pathogens, the region of molecules was used the positive charge area of the molecule. In this case, the most important factors is explained that the higher surface area having positive charge is considered as the high biological activity.

Here, E1=Electrostatic potential energy in positive value, E2=Electrostatic potential energy in negative value and ΔE= Electrostatic potential energy difference of two level.

From quantıtatıve structure-actıvıty relatıonships, (QSAR) Correlation of the molecular structure or properties is derived from a molecular structure with a particular chemical or biochemical activity. This method is widely used in pharmaceutical chemistry in the environment and the search for certain properties. show QSAR study are given in Table 5.

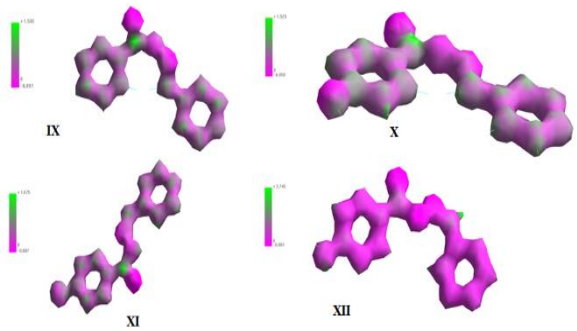

Figure 5 . The 3D geometry of the distribution electrostatic potential.

Getting the highest binding affinity is the strongest drug molecule and contributes to computer-focused molecules. By using the fitness of the drug, which will bind to the target molecule during the docking process, we can discover the drug binding affinity and the second approach is to use Gibbs free energy measurements. According to the more negative value, we can consider a more effective drug. As seen from Table 5, it is found that the binding energy, which is almost close (Kmol-1.mol.) in most forms of N-Acylhydrazone derivatives(IX, X, XI, XII).

In the case of the biological activity of a molecule, the essential parameter is assumed to be the surface area. The larger surface area of a molecule's charge will destroy more pathogens. The charged distribution from electrostatic potential completely depends on the surface area.

The greater surface area of the positive charge indicates greater biological activity. As seen in Table 5, all derivatives have the same surface region, so the same biological behavior is shown. from results data, Volume and surface area share the same effect in binding affinity.

The energy of hydration is characterized as the energy consumed in the water when the material is dissolved. The lower energy of hydration is known to be the greater potential to dissolve in water so that it behaves as hydrophilic and forecasts the drug's strongest properties. The derivatives for X and XII are -14.3 and -11.7 kcal.mol^{-1}, respectively.

Both hydrophilicity and hydrophobicity play an important role in biochemical interactions and bioactivity. Hydrophobic drugs, 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 5, it can be seen calculated (ClogP) values all above 1, so are more hydrophobic, but chloro derivative which one more hydrophobicity and then hydroxyl derivative. While without substituted phenyl ring is less one.[33]

Table 3. Thermophysical properties optimized from HyperChem.

Compounds	IX	X	XI	XII
Total energy (kcal/mol^{-1})	-56718.9344	- 6497.6465	- 63670.4304	- 60824.0477
Free energy (kcal/mol^{-1})	-56718	- 63497.6	- 63670.40	- 60824
Entropy (kcal/mol^{-1})	0.0	0.0	0.0	0.0
Heat capacity (kcal mol^{-1} .degree^{-1})	0.0	0.0	0.0	0.0
Dipole moment, Depye	4.119	3.373	3.641	5.028
RMS gradient(Kcal mol^{-1})	0.009921	0.00728	0.008134	0.006564
Binding energy (Kcal mol^{-1})	- 3247.54778	-3354.37406	- 3232.441823	- 3417.078219
Heat of formation (kcal mol^{-1})	55.69522033	8.427930	47.68947705	51.26678
Nuclear energy, (kcal mol^{-1})	293026.700213	317904.1973	314250.9177	317345.599
Electronic energy, (kcal mol^{-1})	-349745.004617	-381401.7438	- 377921.3516	- 378169.647

Table 4. Data of electrostatic potential energy difference of two levels.

Derivatives	IX	X	XI	XII
E1	+ 1.591	+ 1.529	+ 1.675	+ 2.745
E2	- 0.097	- 0.050	- 0.087	- 0.061
ΔE	1.494	1.479	1.588	2.684

Table 5. Chemical-Physical properties of N-Acylhydrazone derivatives.

Compounds	IX	X	XI	XII
Partial charge	0.0	0.0	0.0	0.0
Surface area [grid]	439.37	470.89	478.60	477.14
Volume, Å^3	703.84	744.95	764.35	758.54
Hydration Energy	- 6.7	- 14.36	- 7.14	- 11.74
CLog P	2.27	3.14	3.94	2.64
Refractivity, Å^3	75.26	69.44	72.55	72.45
Polarizability	26.13	26.77	28.06	27.49
Mass(amu)	224.26	240.26	258.71	239.28

4. Conclusion

N-Acylhydrazone derivatives were prepared. All the products were charecterized. Theoretical computational of stability NAH derivatives, features of the electronic charge density distribution were studies. The estimation of the dipole moments and electrostatic potential of NAH with substituted hydroxy, chloro , amino function groups and related with stability. The electronegativity and electropositivity of substituted group comparison with hydrogen were estimated. Some of physicochemical properties were estimated to prove the stability of hydrazone derivatives.

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