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المجلة العراقية لبحوث السوق وحماية المستهلك

GEOMETRY OPTIMIZATION OF COUPLING ALLIN -METFORMIN USING DFT/B3LYP MOLECULAR MODELLING TECHNIQUE

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ABSTRACT

This researchpaper includes the incorporation of Alliin at various energy levels and angles With Metformin using Gaussian 09 and Gaussian view 06. Two computers were used in this work. Samples were generated to draw, integrate, simulate and measure the value of the potential energy surface by means of which the lowest energy value was (-1227.408au). The best correlation compound was achieved between Alliin and Metformin through the low energy values where the best place for metformin to bind was through (CH_2-). This is considered to be very useful for the industrial application of drugs.

This level of calculation was used for physical and quantum properties such as total energy, HOMO and LUMO orbitals energies, and power gap. Besides, the calculation of FT-IR spectra in the range 400-4000 cm-1 was calculated in addition to the essential vibrational frequencies and the intensity of the vibrational bands. Moreover, the chemical displacement of the ^{1}H and ^{13}C NMR of the compound in the ground state was studied.

Keywords: Alliin, metformin, computational chemistry, molecular modeling technique.

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الوضعية الفراغية المثلى لاقترن الالين مع الميثفورمين باستخدام تقنية النمذجة الجزيئية DFT/B3LYP

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الخلاصة

تضمن البحث دمج الألبين في مستويات طاقية وزوايا مختلفة مع الميتفورمين باستخدام برامج كاوسين 09 والكاوسين 06 باستخدم جهازي كمبيوتر لهذا الغرض، اذ تم إنشاء عينات لرسم ودمج ومحاكاة وقياس قيمة سطح الطاقة الكامنة التي بوساطتها تم تحديد أقل قيمة للطاقة (وحدة ذرية 1227.408-)، كما تم الحصول على أفضل مركب للارتباط بين Alliin وMetformin من خلال قيم الطاقة المنخفضة التي يكون أفضل مكان لارتباط الميتفورمين بالرابطة من خلال (CH_2-)، والذي يعتبر مفيد جدا للتطبيقات الصناعية في مجال صناعة وتحضير الأدوية، وتم استخدام هذا المستوى من الحساب للخصائص الفيزيائية والكمية مثل الطاقة الإجمالية وطاقات المدارات HOMO و LUMO وفجوة الطاقة، كما تم حساب أطياف FT-IR للمركب في النطاق 400-4000 سم$^{-1}$، وكذلك الترددات الاهتزازية الأساسية وشدة النطاقات الاهتزازية فضلا عن دراسة الازاحة الكيميائية ^{1}H و ^{13}C NMR للمركب في الحالة الأرضية.

الكلمات المفتاحية: البينن ميتفورمين، الكيمياء الحاسوبية، تقنية النمذجة الجزيئية.

INTRODUCTION

Metformin has been on the market for more than 50 years and has been developed as th e first line agent of choice for the treatment of type 2 diabetes. In this sense, the joint recommendations released by the American diabetes association and the European diabetes research association clearly and consistently recommend that this agent should be used in diagnosis alongside lifestyle modification **(Wild 2004; Nathan 2009; Nathan2009)**. It has recently been estimated that this disease affects about 6 percent of the world's adults. As a result, there is a substantially elevated risk of vascular disease in patients, broad arteries (macrovascular, i.e. cerebrovascular, coronary and peripheral artery disease) and narrow arteries (microvascular, i.e. retinopathy, neuropathy and nephropathy) can be impaired **(Mayor 2006; Papanas 2009)**. A further bonus is that metformin is safe and successful in being able to. It can be paired with all other ant diabetic oral agents **(Papanas 2009)**. Metformin, like phenformin, is a derivative of guanidine, the active ingredient in goat's rue, which was empirically used to cure diabetes in goats. About the middle ages **(Krall 1957)**. Metformin is easily spread after ingestion, without binding to plasma proteins. Unlike phenformin, metformin is not metabolized by the liver and is excreted by the kidneys without modification **(Scheen 1997)**. Allicin is a sulfur containing volatile compound present in white garlic (*Allium sativum* L.) and in other species of allium, such as elephant garlic (*A. ampeloprasum* L.), wild garlic (*A. ursinum* L.), field garlic (*A. vineale* L.) and alpine leek (*A. victorialis* L.). It is believed to be one of the most bioactive organosulfate species. In fact, allicin is the thiosulfinate that is most abundant in fresh garlic, usually. It accounts for 70% (w/w) (approximately 0.4% by fresh mass) of the overall thiosulfinates **(Horev-Azaria 2009)**. In one clove of fresh garlic, roughly 4-5 mg of allicin is detected and its presence is readily noticeable because of its distinctive odor **(Rybak 2004)**. Depending on the temperature and pH of the mixture, allicin is rapidly metabolized into several other secondary compounds until it is produced **(Fujisawa 2008)**. Due to lower pH, the presence of vinegar in garlic formulations has indicated an improvement in allicin shelf life. Thus, allicin half-life was observed to be 10-17 days at pH 5-6 **(Wang 2015)**. Allicin has shown several therapeutic effects, such as CVD protection, antioxidant, anticancer, antimicrobial, anti-asthmatic, immune regulator, blood pressure lowering and anti lipidemic **(Chan 2013; Wang 2017)**. To the best of our understanding, the theoretical measurement and impact on molecular geometry (bond length,

bond angle and dihedral angle), IR spectra and various molecular properties such as molecular electrostatic potential (MESP), mulliken charge charge distribution, global descriptors of reactivity (chemical hardness, softness, chemical potential, electron potential, mulliken charge distribution **(Glossman-Mitnik 2013)**. Charge transport models have been seen to be very largeuseful in identifying useful in identifying and recognizing qualitatively specific dimensions of chemical reactions that have arisen through donor-acceptor processes **(Chattaraj 2005)**.

MATERIAL AND METHODS

Experimental

apparatus

A different characteristic computers have been used depending on the required features of computational programs calculation such as:

Laptop CORE i7 (Model HP-Pavilion, Processor Int ® core™i7-4500 CPU @ 1.80GHZ 2.40GHZ RAM 8.00GB System type 64 bit operation system (windows 7) Hard 1 tera.

Laptop CORE i7 Model HP-Pc Processor Int ® core™i7-3520 CPU @ 2.90GHZ 2.90 GHZ RAM 16.00GB System type 64 bit operation system (windows 7) Hard 1 tera**.**

PROGRAMS

The programs have been used was Gaussian ®09 W Version 9.5 copyright © 1995-13 Gaussian, Inc., and GaussView 6.0.16 (64-bit Windows) Version Copyright (c) Semichem, Inc. 2000-2016

METHODOLOGY

The ground-state geometries were optimized using a DFT/ B3LYP/ 6-311G **(Vosko 1980; Becke 1993; Perdew 1988)** on Gaussian 09 software package **(Frisch 2009)** and Gauss view molecular visualization **(Dennington 2009)**. None of the frequency calculations generating imaginary frequencies indicate that the optimized geometries are true energy minima. The total energy, electronic and nuclear energies were calculated for correlation of Allin with Metformin, such as (HOMO, LUMO), can energy and the different between them (Egap) for the stable structure. The vertical excitation energy, wave length, with the electronic transition energy of Allin with Metformin and the single point were obtained by using time-dependent density functional theory TD/DFT with B3LYP calculations **(Lee 1988; Zhou 1989)**. The electronic absorption spectra of the Allin with Metformin are calculated and simulated with DFT/ B3LYP/ 6-311G level in vacuum.

RESULTS AND DISCUSSION

Quantum mechanics calculations of the correlation of allin with metformin geometry optimization for compounds

In this study, the best compound was chosen, through the lowest value of the potential energy. metformin was binding to the allin through the carboxyl group (-OH) and the potential energy (-1152.191 atomic unit) as in (Figure 1a), as well as the binding through the group of (CH_2). With a potential energy (-1227.408 atomic unit), as in (Figure 1b), it was found through the lower energy values that the best place for metformin to bind to the bond is through (CH_2-). The properties of the compound were studied by:

The bond length and angles

The simple way to describe the length of the bond between two atoms involving two nu clei is roughly the sum of the covalent radii of the two atoms **(Mulliken 1955).** Bond energies and bond lengths depend on multiple variables for covalent bonds, such as electron affinities, atom weights, variations in their electronegativity, and the overall molecule composition. There is a general tendency that the shorter the length of the bond, the higher the energy of the bond. The similarities and molecular symmetry are seen by identical bond length. In the both molecules the bond length in the S-C, C-N are 1.78, 1.70. The measured of the bond length for a theoretical prepared compound as in (Figure 2) using the gaussian/ DFT/ B3LYP/ 6-311G program, which includes building the molecule in the best possible way geometry optimization shown in (Table 1) and (Figure 3).

Table(1): Bond lengths and angles for compound by DFT / B3LYP / 6-311G.

Bond length		Angles		Dihedral angle	
Bond	**values**	**angles**	**values**	**Dihedral angle**	**values**
R(1,2)	1.78	A(2,1,5)	109.4712	D(5,1,2,3)	144.8995
R(1,5)	1.4696	A(2,1,10)	109.4712	D(5,1,2,14)	67.7724
R(1,10)	1.78	A(5,1,10)	109.4712	D(5,1,2,15)	-152.6719
R(2,3)	1.54	A(1,2,3)	140.676	D(10,1,2,3)	-95.1005
R(2,14)	1.07	A(1,2,14)	85.0281	D(10,1,2,14)	-172.2276
R(2,15)	1.07	A(1,2,15)	80.8806	D(10,1,2,15)	-32.6719
R(3,4)	1.54	A(3,2,14)	85.7788	D(2,1,10,11)	-60.0
R(3,6)	1.47	A(3,2,15)	80.3865	D(2,1,10,13)	120.0
R(3,16)	1.07	A(14,2,15)	137.2949	D(5,1,10,11)	60.0
R(4,9)	1.2584	A(2,3,4)	84.646	D(5,1,10,13)	-120.0
R(4,15)	1.3598	A(2,3,6)	84.6864	D(1,2,3,4)	79.3658
R(4,16)	1.704	A(2,3,16)	138.1037	D(1,2,3,6)	-140.4172
R(4,30)	1.43	A(4,3,6)	138.8677	D(1,2,3,16)	146.7708
R(6,7)	1.0	A(4,3,16)	79.2806	D(14,2,3,4)	156.2316
R(6,8)	1.0	A(6,3,16)	82.6717	D(14,2,3,6)	-63.5514
R(10,11)	1.3552	A(3,4,9)	120.0	D(14,2,3,16)	-136.3634
R(10,13)	1.07	A(3,4,15)	72.5694	D(15,2,3,4)	16.7806
R(11,12)	1.07	A(3,4,30)	120.0	D(15,2,3,6)	156.9976
R(11,17)	1.47	A(9,4,15)	71.6766	D(15,2,3,16)	84.1856
R(17,18	1.0	A(9,4,30)	120.0	D(1,2,15,4)	-166.6338
R(17,19)	1.47	A(15,4,30)	127.8743	D(3,2,15,4)	-21.3659
R(19,20)	1.47	A(3,6,7)	109.4712	D(14,2,15,4)	-94.2924
R(19,21)	1.2936	A(3,6,8)	109.4712	D(2,3,4,9)	42.245
R(20,24)	1.47	A(7,6,8)	109.4712	D(2,3,4,15)	-13.5777
R(20,27)	1.0	A(1,10,11)	120.0	D(2,3,4,30)	-137.755
R(21,25)	1.0	A(1,10,13)	120.0	D(6,3,4,9)	-33.3542
R(22,24)	1.2936	A(11,10,13)	120.0	D(6,3,4,15)	-89.1768
R(22,25)	1.5899	A(10,11,12)	120.0	D(6,3,4,30)	146.6458
R(22,26	1.0	A(10,11,17)	120.0	D(16,3,4,9)	-98.8908
R(23,24)	1.47	A(12,11,17)	120.0	D(16,3,4,15)	-154.7135
R(23,28)	1.0	A(2,15,4)	116.6794	D(16,3,4,30)	81.1092
R(23,29)	1.0	A(11,17,18)	109.4712	D(2,3,6,7)	-51.8508
R(30,31)	0.96	A(11,17,19)	109.4712	D(2,3,6,8)	68.1492

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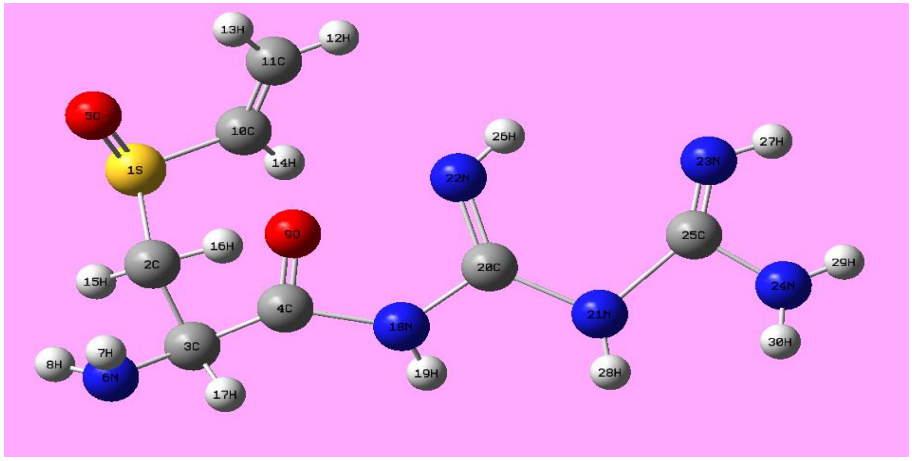

Figure (1a): Geometry optimization for binding metformin with allin through OH group by DFT / B3LYP / 6-311G.

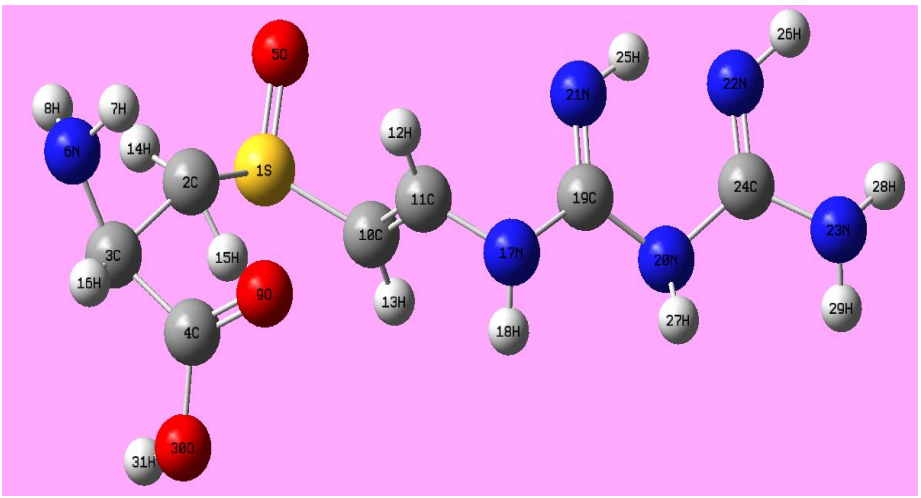

Figure (1b): Geometry optimization for binding metformin with allin through CH_2 group by DFT/ B3LYP/ 6-311G.

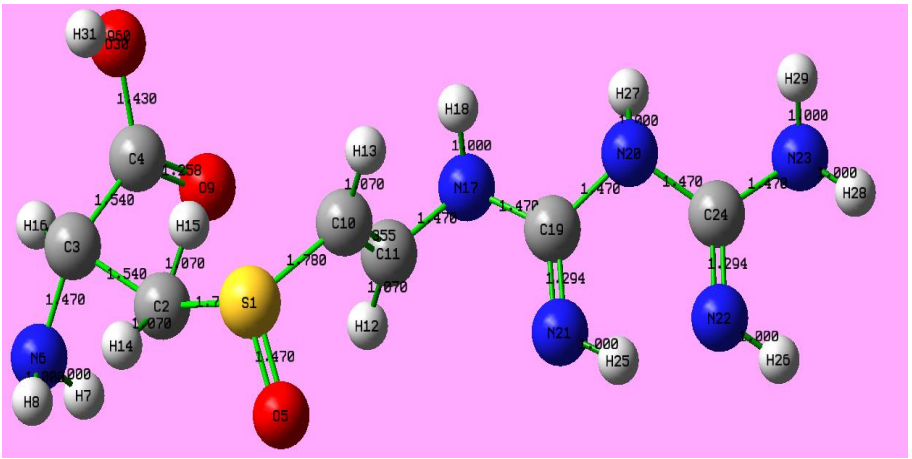

Figure (2): Bond lengths for binding metformin with allin through CH_2 group by DFT/ B3LYP/ 6-311G.

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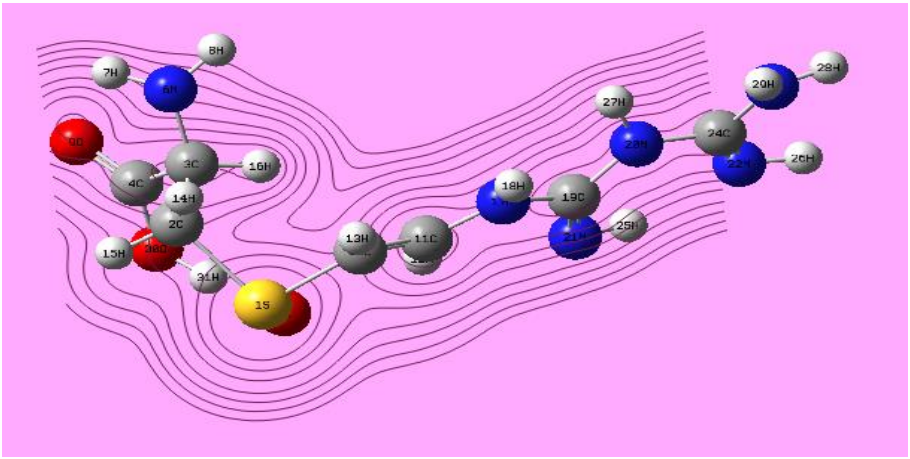
Molecular Electrostatic Potential

The study of the electrostatic potential of the molecule gives clear pictures of the electronic density distribution of the molecular systems. As a result, it is possible to predict and verify the highly effective electrochemical sites as well as the positive charge centers **(Bastos 2017)**. By drawing the peripheral surface (2D-Contours) and total charge density, theoretical chemistry plays a major role in explaining many complex interactions that relate to nucleophilic and electrophilic reactions by expressing the characteristics of the HOMO (Highest Occupied Molecular Orbital). One of Lewis and LUMO bases (Lowest Unoccupied Molecular Orbital) for Lewis acids **(Drissi 2015)**. The calculations of the electrostatic potential enable us to know the effective locations between the interacting molecules, that is, the interaction between (HOMO) and (LUMO) that have a great influence in directing many chemical reactions **(Sharma 2019)**. (Figure 3 and 4) shows the chemically effective sites and the most likely sites for the binding between metformin and allin.



Figure(3): Total charge density-2 Dfor compound by DFT/ B3LYP/ 6-311G.

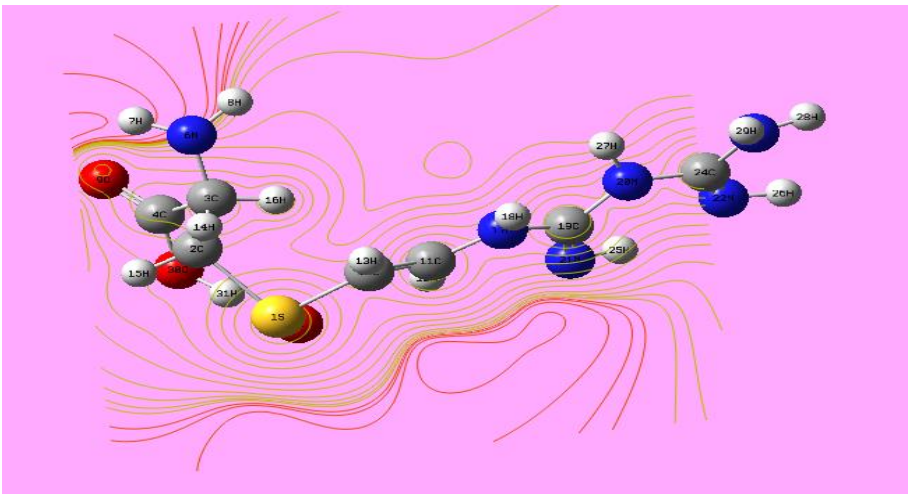


Figure (4): Electrostatic potential for orbital (HOMO) from (2 D Contours).

The energy potential of single molecules

The results showed that the energy potential of the allin and metformin molecule was (-874.55 atomic unit) and (-354.018 atomic unit) respectively. The most accurate energy values are the relative energies obtained by subtracting the total primary energies from the result of

the primary calculations; and the output is the final energy. Thus, the difference in energy between the formed complexes as well as the dissociation energies can be calculated with high precision. The complex energy was calculated for lower energy structures:

$$E = E_{complex} - (E_{Allin} + E_{metformen}) \ldots\ldots\ldots\ldots (1)$$

Where:
E: is represent the final bonding energy.

$E_{complex}$: is the primary complex energy.

$E_{metformin}$, E_{Allin}: is represents the primary compounds energies.

The energy change is an indication of the active energy behind the formation of the complex between Allin and metformin in terms of correlation through the CH_2. The greater the negative change in the energy change, the more stable the linkage to the formation of the complex.

Dipole Moment

The dipole moment is meant to be one of the properties of the molecule that results from the separation of charges. The dipole moment is the one that can distinguish the effective groups in the molecular spectra since the molecules that possess such moment are effective in the spectrum and vice versa, and the value of the dipole moment depends on the presence of Electron-withdrawing and donating(-COOH, $-NH_2$)groups in the molecule **(Bastos 2017)**. The dipole moment of the prepared compound was calculated using the Gaussian / DFT / B3LYP / 6-311G program shown in (Table 2).

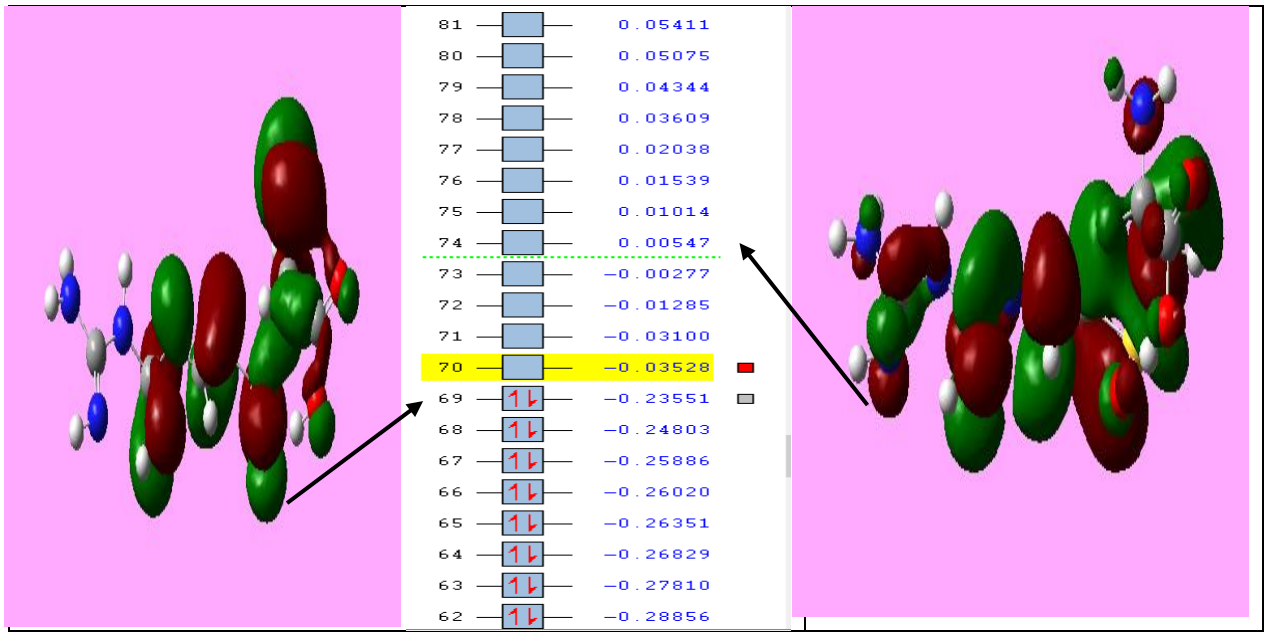
Table(2): Dipole moment (Debye) of prepared compound by DFT / B3LYP / 6-311G.

Dipole Moment Debye	Total Dipole	Dipole x	Dipole y	Dipole z
compound	7.3792	-4.3316	4.4221	-4.0167

The dipole moment of the molecule is the result of the different groups in the molecule based on the coordinates (z, y, x) and through the above table it is clear that the compound is in three dimensions and not one level.

Higher and lower energy orbital(HOMO-LUMO)

HOMO represents the highest occupied molecular orbital, as it represents the ionization potential, which represents the lowest energy to remove the electron from the outer orbital and the compound turns into an oxidation state. LUMO is lowest unoccupied molecular orbital as it represents the electronic affinity, which represents the lowest energy for electron gain in a unoccupied orbital .It is through the energy values of the highest and lowest orbital that the energy gap that is important to know the stability and effectiveness of the compound is calculated **(Hadanu 2019; Huang 2020**) (Figure 5).

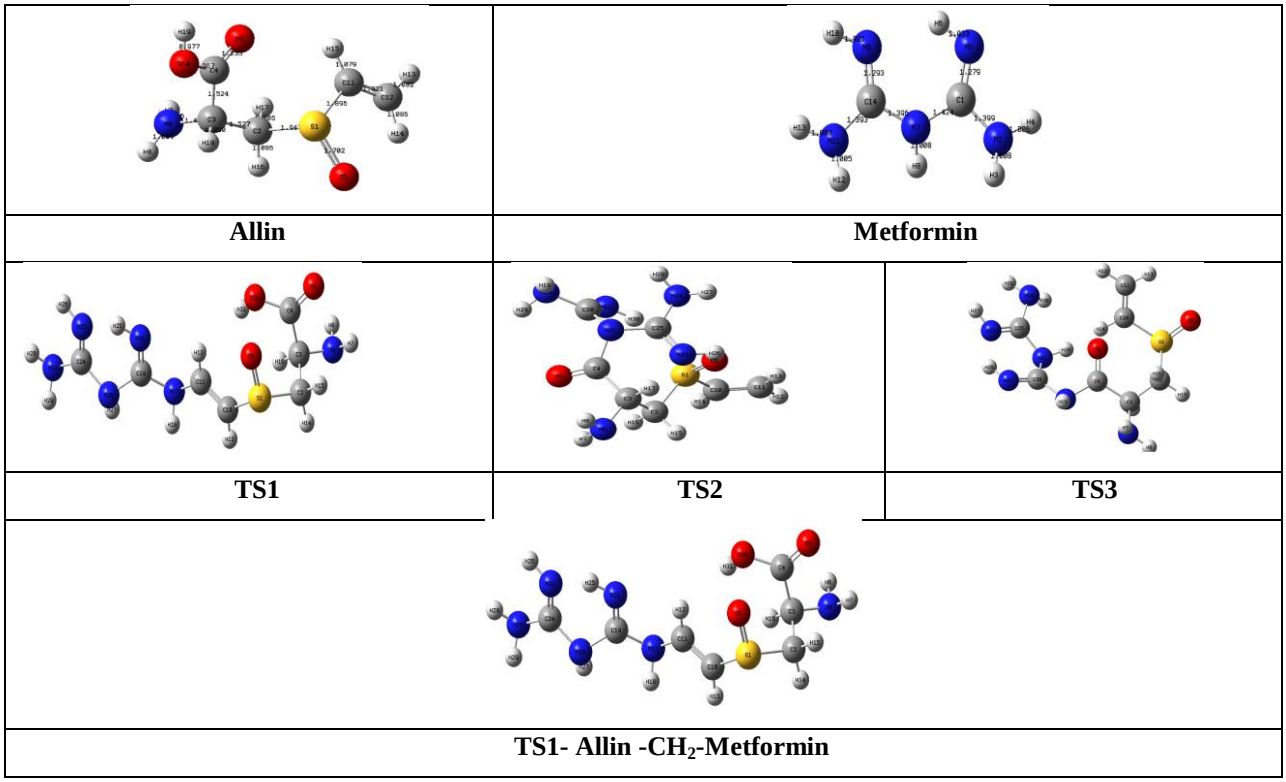


EHOMO= - Egap=0.24098 ELUMO=0.005

Figure (5): Represents 3D of the highest and lowest orbital of the molecules allin-metformin.

The best binding for allin-metformin

Transition state calculations, in shown in (Figure, 6), show that's the first transition state is the real transition state due to the lower energy (-1227.408 atomic unit)by DFT/ B3LYP for binding Allin-Metformine**.**



Figure(6): Transition state of the best binding for allin-metformin.

Theoretical identification of allin-metformin compound

In this study, identification of compound by using infrared spectroscopy, NMR spectroscopy and UV-visible spectroscopy.

Infrared spectra

This technique is very important to identification the compound studied in this research, where absorption packages are followed for groups and from the vibration spectra, which gives a great indication of the occurrence of consistency between allin and metformin **(Rudyk 2019; El-Azhary 1998)**. The compound spectrum showed the following beams as in (Figure 7).

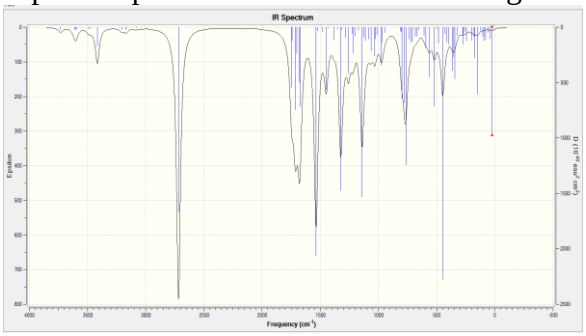


Figure (7): infrared spectrum of the compound in this study.

NMR spectra

The NMR spectra of the compound 1H-NMR where the NMR spectrum was marked by the appearance of multiple signals (multiples) as well as the spectrum of the compound (Figure 8).

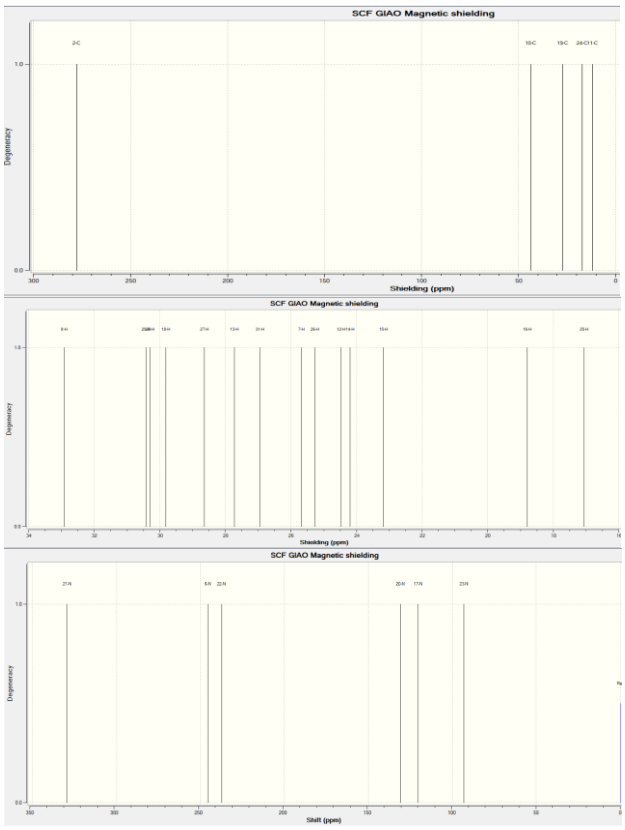


Figure (8): NMR spectrum of C, N, H of compound in this study.

Electronic spectra

Theoretical electronic spectra are shown as delicate lines (Sharp) using the DFT density function at the B3LYP levels and with a base of 6-31 1G which shows the transfer of electrons in the compound as in (Figure, 9) because the theoretical calculations give only electronic transmission lines, without rotational and vibratory transfers using the law of electronic transitions only, that the electronic spectrum of the compound has shown a very clear absorption package at (814nm) due to electronic transitions of the type (n-π *) and it belongs to the non-bonding electronics in the atoms (N, S, O) and an absorption package at (878 nm) returns to electronic transfers from The type (* π-π) refers to the electrons of the alternatebonds in the methyl group **(Tagore, 2020, Khalid, 2019)**. From the theoretical study, the wavelength, excitation energy and frequency strength are calculated as in (Table, 3).

Table (3): The wavelength, excitation energy and frequency strength of the theoretically prepared compound.

Wavelength (λ)	frequency strength(ℱ)	Energy (Eev) DFT	orbital contributor
878.47	0.0010	1.4114	67-70
814.53	0.0029	1.5222	68-70

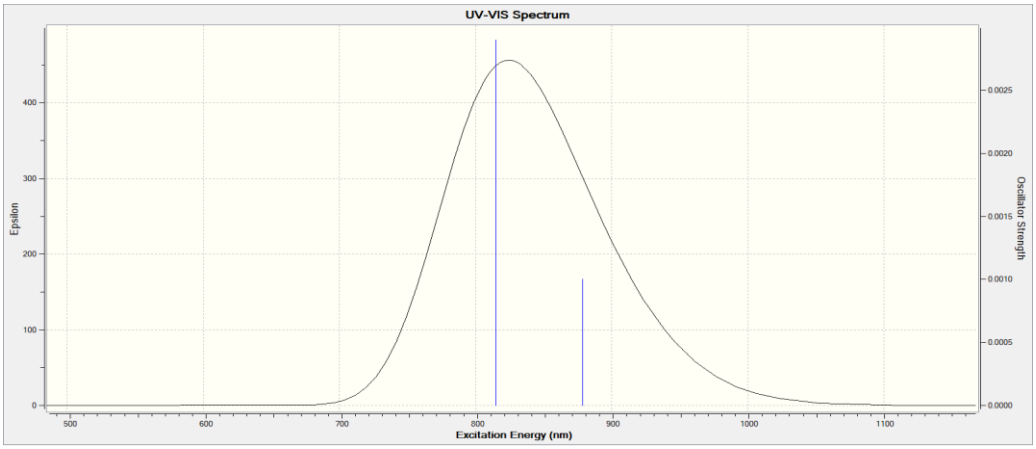


Figure (9): The UV -visible spectrum of the allin-metformin compound.

CONCLUSIONS

1. The bond lengths of compound are very important in the load of charge transfer between donor sit and acceptor sit.
2. A small value of the energy gap is (0.24098) implies low electronic stability and high reactivity of allin toward binding with metformine.
3. The first suggested transition state is more probable than other transition stats to give up the final product for binding allin with metformine.
4. Metformin was binding to the allin through the carboxyl group (-OH) and the potential energy (-1152.191 atomic unit), as well as the binding through the group of (CH_2). With a potential energy (-1227.408 atomic unit), found through the lower energy values that the best place for metformin to bind to the bond is through (CH_2-).

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