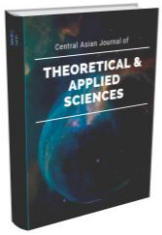

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Article

Synthesis, Theoretical Calculation Properties and Biological Activity Evaluation of Some Oxazolidinone derivatives

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Abstract: The synthesis of oxazolidinone derivatives from the Schiff bases which were previously prepared is described in this research paper and involves various substituents on the benzene ring at position para as mentioned in the experimental part. For the determination of structure and purity of the synthesized compounds, FT-IR, 1H-NMR and 13C-NMR spectroscopy analyses and elemental analysis have been carried out. In addition, theoretical calculation was done by using the Gaussian software to find out the most stable spatial conformation of the compounds at their lowest energy level. Therefore, stabilization energy, dipole moment, and frontier molecular orbital energies of the compounds were calculated including the calculation of energy of Highest Occupied Molecular Orbital (HOMO) and energy of Lowest Unoccupied Molecular Orbital (LUMO) and energy gap (ΔE Egap). Also, the effect of the substituents on stability of the compounds was investigated according to HOMO-LUMO energy gap. In addition, the biological activity of the compounds was studied. Compound H2 possessed a unique and strong inhibitory activity against bacteria, whereas compound H3 possessed a weak antibacterial activity. However, compounds H1, H4, and H5 did not possess any antibacterial activity.

Keywords: Heterocyclic Compounds, Oxazolidinone, Computational Chemistry, E.Coli Bacteria

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1. Introduction

The heterocyclic compounds with the unique property of ring structure containing at least one hetero atom have fascinated chemists and scientists through the ages. The word heterocyclic is a composite of two words: “heteros” which means different and “kyklos” which means ring. This denotes the uniqueness of the heterocyclic compound. The hetero atoms like nitrogen, oxygen, sulfur, and others give special characteristics to the heterocyclic compounds [1]. Chemistry is one of the key sciences that has made a huge contribution to our perception of the natural world. The area that can be considered one of the most interesting and useful in this discipline is the area that is dedicated to the study of heterocyclic compounds. Heterocyclic compounds are the basis for the formation of a wide range of organic compounds both in nature and synthetically. In this article, we will examine the peculiarities of these substances and discuss their importance for various fields of science and engineering. Also, the reactivity of heterocyclic compounds does not end in medicines alone [2]. There are many applications of these compounds in terms of material science as well, because they can be used as conducting polymers, semiconductors and organic dyes. Their use for catalysts and ligands' synthesis has made organometallic chemistry much more productive and prosperous [3]. The oxazolidinones are capable of undergoing asymmetric synthesis to form heterocycles and intermediates in industry [4]. The intermediates are critical in the development of biological active substances, such as monoamine oxidase inhibitors [5], antibiotics anticancer drugs, natural products and medicinal drug design [6-7]. Oxazolidinones moiety incorporation

into sulfonamide has been investigated thoroughly in a number of research works. Some of these studies have demonstrated that sulfamoyloxazolidinones are indeed very interesting compounds because of their different pharmacological properties [8-9]. The term "antibiotic" was coined in 1941 by Selman Waksman to refer to any small chemical compound synthesized by a microorganism that can inhibit the growth of other microorganisms. In the decades from 1940 to 1960, known as the golden age of antibiotics, penicillin, streptomycin, tetracycline, and chloramphenicol were discovered. Nevertheless, due to the development of bacteria resistance, all these antibiotics and many others have become virtually useless [10-11]. As defined by the WHO (World Health Organization), antimicrobial resistance is characterized by the evolution of microorganisms (including viruses, bacteria, parasites, and fungi) that make the medicines used to combat the infections they cause ineffective [12]. The resistance to diverse microorganisms is a serious public health issue, as is the fast spread of multidrug resistant bacteria [13-14]. Computational and Theoretical Chemistry in the Chemistry Department encompasses not only the design of theoretical and computational concepts, but also the application of such concepts to problems of interest for chemistry and biophysics. One of the main objectives of the group led by Markus Meuwly is to design numerical algorithms and computational strategies that will provide insight into the energetics and dynamics of chemical reactions in complex systems and apply them to chemically and biologically interesting systems [15-22]. Other research efforts focus on the design of fast algorithms for the in silico screening of organometallic compounds [8]. The study of small-molecule dynamics in chromatography systems [23-25] and quantum nuclear effects in clusters and molecules [26-27].

2. Materials and Method

2.1. Experimental

All chemical reagents in high purity were purchased from Fluka and Merck companies and used with no additional purification. All the compounds were characterized by comparison of their physical properties with reported samples in the literature. The FT-IR spectrum of the samples was recorded on a Shimadzu FT-IR 8400S spectrometer in the region 400–4000 cm^{-1} using pressed KBr discs. ^{1}H-NMR and ^{13}C-NMR spectra using Bruker instrument operated at 400 MHz frequency

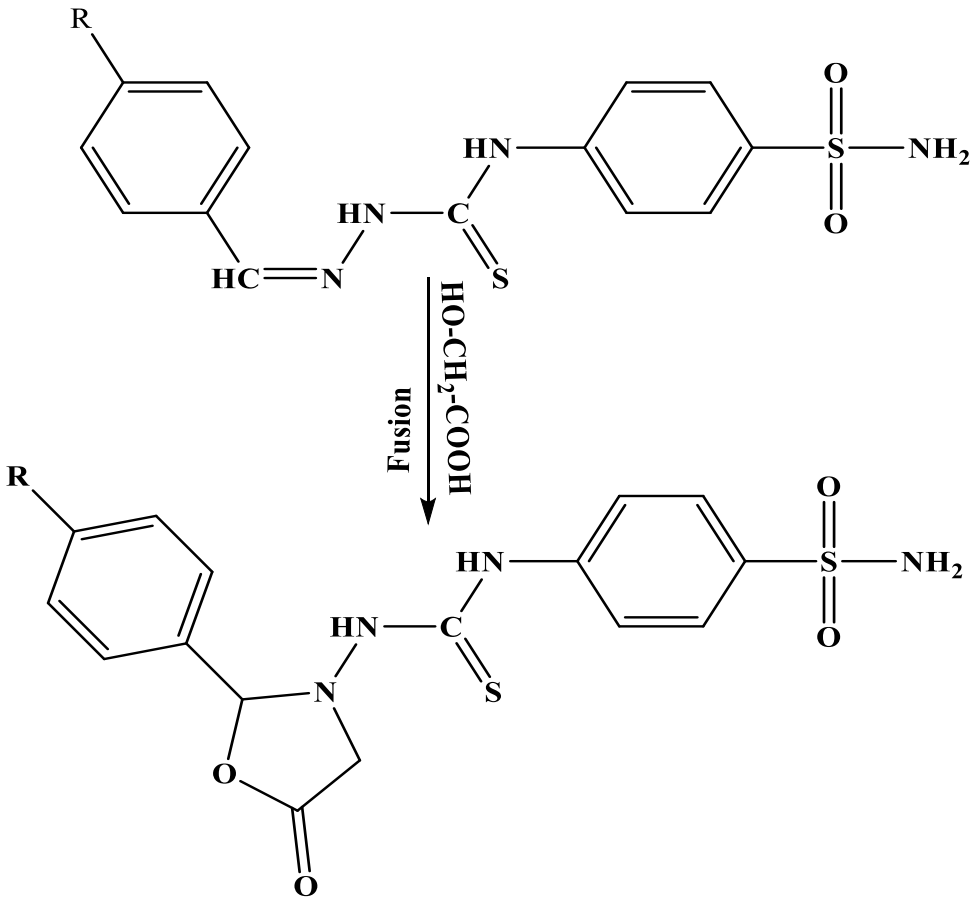
2.2. Computational method

All the computations have been carried out using Hartree-Fock (HF) method in the Gaussian 09 W software application package, Geometry Optimization of ground states for these materials in the gas phase was done using Gaussian 09W program package and using the Semi-empirical and Basis set AM1 approximation method,the following compounds were studying:

(H_1)[4-(3-(2-(4-hydroxyphenyl)-5-oxooxazolidin-3-yl)thioureido)benzenesulfonamide]
(H_2)[4-(3-(2-(4-nitrophenyl)-5-oxooxazolidin-3-yl)thioureido)benzenesulfonamide]
(H_3)[4-(3-(2-(4-chlorophenyl)-5-oxooxazolidin-3-yl)thioureido)benzenesulfonamide]
(H_4)[4-(3-(2-(4-(dimethylamino)phenyl)-5-oxooxazolidin-3-yl)thioureido)benzenesulfonamide]
(H_5)[4-(3-(5-oxo-2-phenyloxazolidin-3-yl)thioureido)benzenesulfonamide].

2.3. preparation Oxazolidinone derivatives derivatives

In this experiment, a combination of the synthesized hydrazone compound[28] (0.004 mol) and hydroxyacetic acid (0.004 mol) was placed in a heat resistant glass beaker without using any solvent. The mixture was slowly heated until melting while stirring continuously for 14-25 minutes, when there was a notable difference in the color and consistency of the reactants. The product obtained was then purified through recrystallization with ethanol.



R = 4-OH(H_1) ,4- NO_2 (H_2) , 4-Cl (H_3), 4-$N(CH_3)_2$ (H_4) , 4-H (H_5)

Scheme 1. Synthesis pathway for the compounds H_1-H_5.

Table 1. Summarized some physical properties

Comp. No.	Color	m.p.	Yeild %
H_1	yellow	235-237	71
H_2	Brown	287-289	74
H_3	White	276-278	80
H_4	orange	254-256	77
H_5	Light red	263-265	79

3. Results and Discussion

3.1. Synthesis of Schiff base compounds

In this paper, several Schiff base compounds were synthesized and were used as the starting materials for the preparation of various Schiff bases compounds [29]. A careful analysis of the FT-IR spectra for **(H_1)** illustrated in the first figure gives a perfect match of structural arrangement in relation to the functional groups of the desired organic compound illustrated in the second figure. At the high frequency range, an extensive and strong overlapping band appears in the (3200-3500) cm^{-1} range. These bands comprise characteristic absorption peaks at (3382, 3271, and 3213) cm^{-1} and are associated with the stretching vibrations of phenolic hydroxyl (O-H) bond, as well as the amine and amide (N-H) bonds that are found in the thiourea functional group and sulfonamide group, respectively. In addition, the peak at 3084cm^{-1} corresponds to the stretching vibration of aromatic C-H bond while peaks at (2910 and 2816) cm^{-1} correspond to the stretching vibrations of symmetric and asymmetric aliphatic C-H bonds, respectively. As far as the unique sulfonamide group of the molecule is concerned, the asymmetric stretching of the sulfonyl group (asymmetric S=O) shows up as a sharp absorption peak at 1349 cm^{-1}, whereas the symmetric stretching (symmetric S=O) is seen in the region of (1159 and 1142) cm^{-1}. Also, the sharp peaks at 1269 and 1220 cm^{-1} correspond to the stretching of the

carbon-oxygen (C-O) and carbon-sulfur (C=S) bonds in the thiourea group, respectively. The fingerprint peaks obtained for out-of-plane bending at (837 and 771) cm^{-1} indicate that there is indeed a para-di substituted pattern in the benzene rings within the molecule, thereby establishing that the formation of the proposed structure is complete.

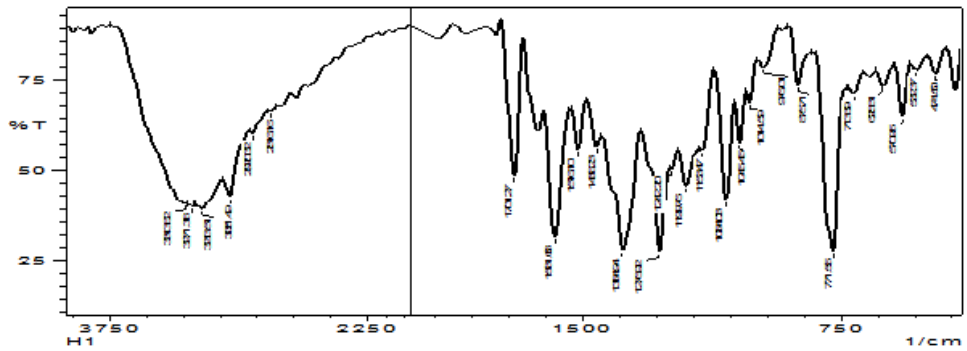


Figure 1. FT- IR spectrum of **H_1** compound

The proton nuclear magnetic resonance (H-NMR) spectrum illustrated for compound (**H_1**) gives the accurate structural information about the organic compound depicted in the second diagram. The spectrum was obtained using deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent and its appearance is a sharp residual solvent peak having a chemical shift value of 2.51 ppm along with the small water (H_2O) signal at around 3.33 ppm, When considering the chemical shifts from low field to high field (downfield to upfield), there is a distinct sharp singlet on the far left side (delta = 11.27 ppm) whose integration corresponds to a single proton. The signal is undoubtedly the hydroxyl proton (-OH) from the phenolic ring, because the ring exhibits great acidity and electronic deshielding due to the withdrawing power of the aromatic ring. After that, two distinct and characteristic broad downfield signals can be found at 9.44 ppm and 8.76 ppm which integrate to give a single proton. These signals correspond to the two amino protons (-NH-) from the thiourea linker, whose separation in chemical shifts and downfield shifts are due to the withdrawing effect of the thiocarbonyl (-C=S) group, On moving on to the discussion about aromatic regions, there are two distinct para-substituted aromatic groups that have been observed with overlapping peaks in the range from 6.72 ppm to 7.89 ppm to account for all the aromatic groups present in the molecule. The protons that are located ortho to the electron withdrawing group of sulfonamide are observed to be downfield shifted to 7.88 ppm and 7.46 ppm respectively and the total number of protons involved is four. On the other hand, the protons of the phenyl ring that has an electron donating hydroxyl group have been observed to be upfield in the range of 7.24 ppm and 6.72 ppm and their integration is perfect. The end sulfonamide group (-SO_2NH_2) has been observed as a broad signal along with the aromatic region at approximately 7.22 ppm and an integration value of two protons. In the upfield aliphatic region, a very distinct signal indicative of the presence of the ring structure of oxazolidin-4-one is observed. In addition to this, the methine proton (-CH-) between the oxygen atom and the aromatic ring gives rise to a very prominent singlet signal at δ6.12 ppm with an integration of one proton. The reason for such an extreme downfield signal for an aliphatic proton is the combination of both the electron withdrawing effects due to the neighboring oxygen atom and the phenyl ring. Lastly, the methylene protons (-CH2) of the oxazolidinone ring appear as a very distinct sharp singlet at δ3.85 ppm with an integration of two protons.

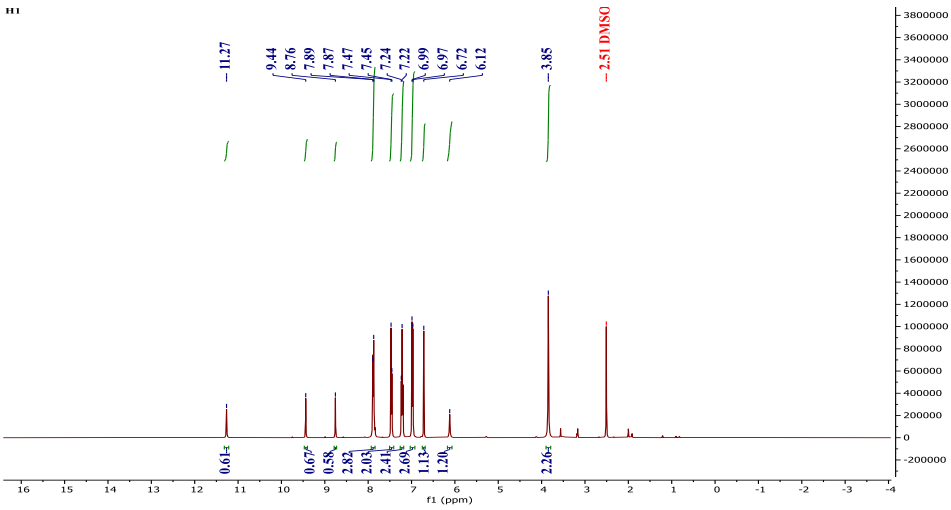


Figure 2. [1]H.NMR spectrum of **H**[1] compound

The [13]C-NMR attached below indicates a group of characteristic peaks whose exact correlation is based on the chemical structure of the target compound**(H**[1]**)**. These peaks result from the differences in the electronic environment surrounding each carbon atom in the molecule.Starting from the most downfield part, there is an intense signal at 184.07 ppm for the thiocarbonyl carbon (C=S) due to the highly electron-withdrawing character of the sulfur atom. This is then followed by a peak of the carbonyl carbon (C=O) of the oxazolidin-4-one ring at 177.26 ppm. There is another set of peaks in the aromatic range between 125.40 ppm and 138.98 ppm, which represent eight peaks, showing that there are two symmetric benzene rings: the 4-hydroxyphenyl and 4-sulfonamidophenyl rings. Shifting into the aliphatic zone, the next clear peak that is seen is at 96.35 ppm corresponding to the methine carbon (CH) of the oxazolidine ring. This peak has an unusual downfield shift for normal alkanes since it is located directly between oxygen and nitrogen atoms, aside from being connected to the aromatic ring. Next is the methylene carbon (CH2) of the same ring, seen at 56.50 ppm. This peak has a downfield shift because of its close location with respect to the nitrogen atom and carbonyl. Lastly, the multiplet peak ranging from 39.35 ppm to 40.60 ppm corresponds to 39.98 ppm and indicates the presence of the solvent used for the experiment, which is deuterated dimethyl sulfoxide (DMSO-d6).

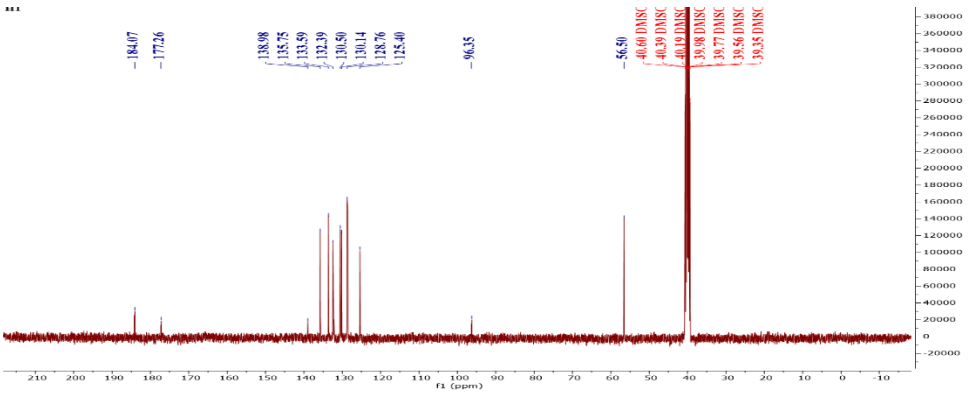


Figure 3. [13]CNMR spectrum of **H**[1] compound

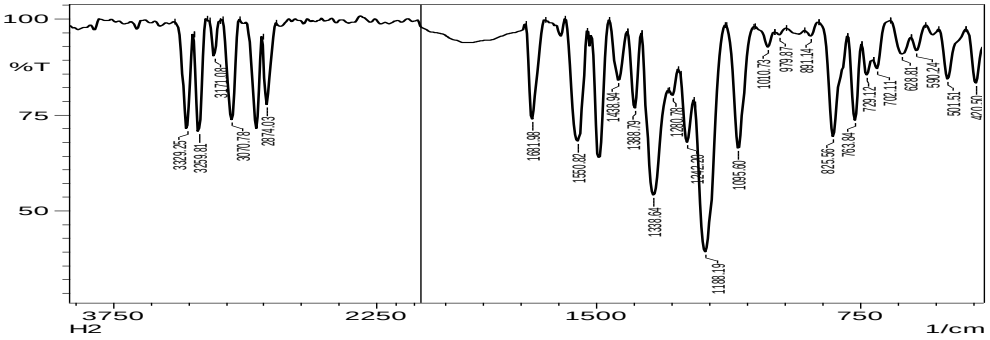


Figure 4. FT- IR spectrum of **H**2 compound

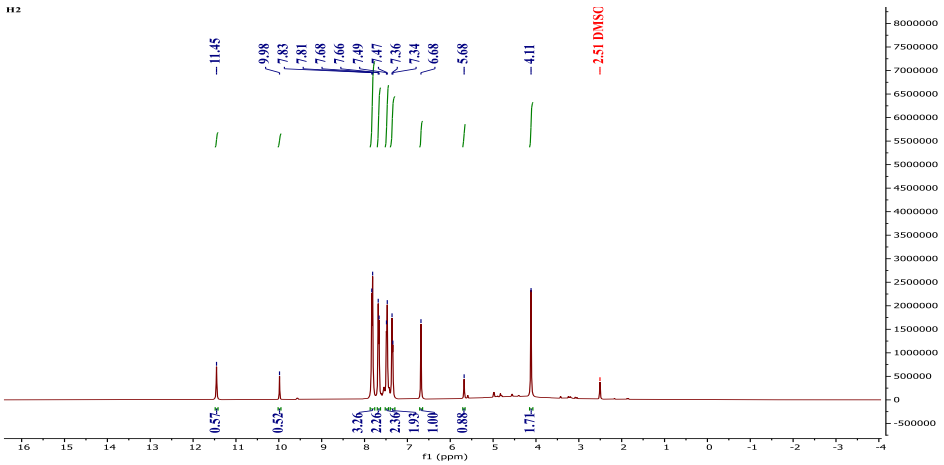


Figure 5. [1]H.NMR spectrum of **H**2 compound

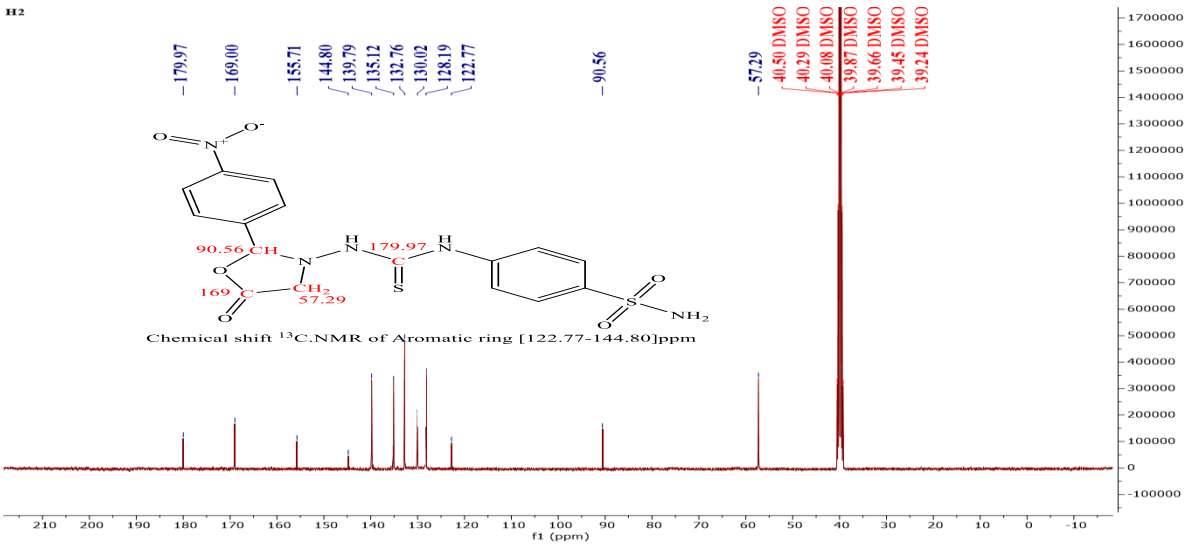


Figure 6. [13]CNMR spectrum of **H**2 compound

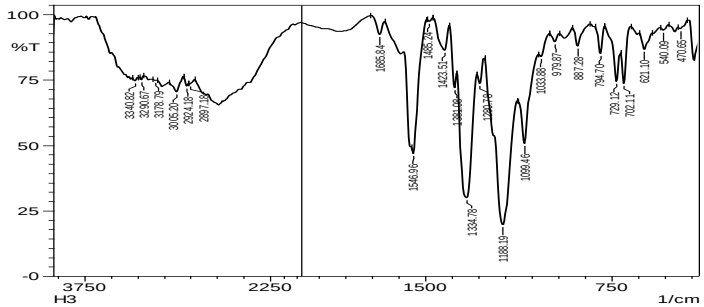


Figure 7. FT- IR spectrum of **H**3 compound

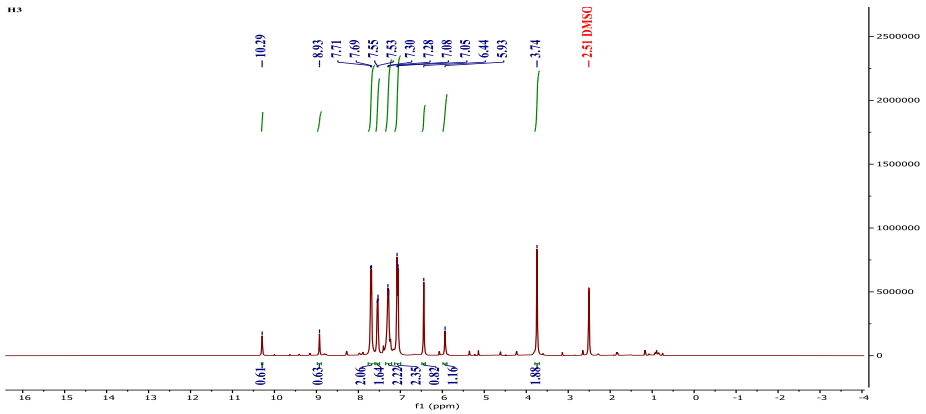


Figure 8. [1]H.NMR spectrum of **H**3 compound

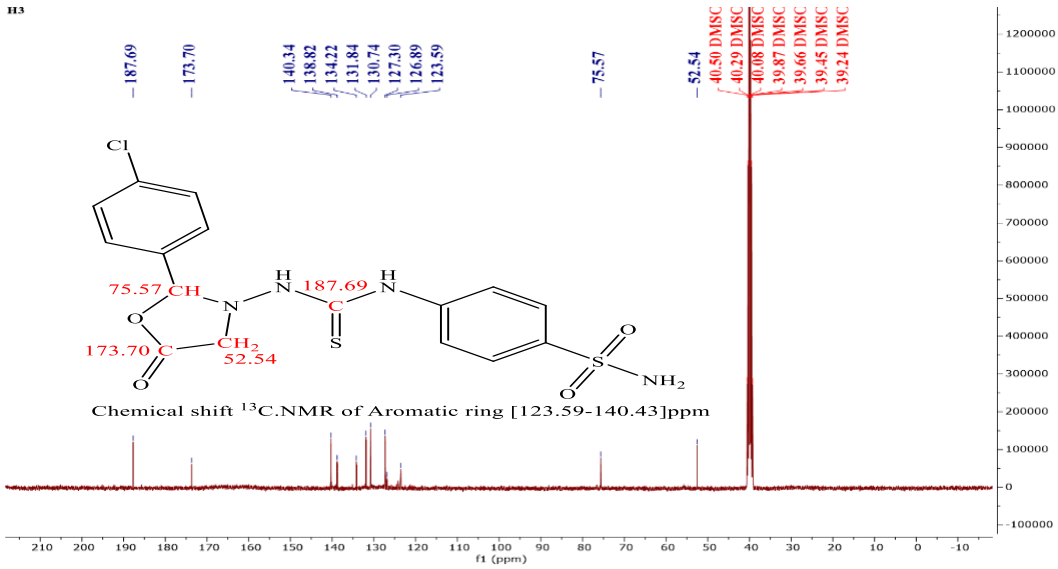


Figure 9. [13]CNMR spectrum of **H**3 compound

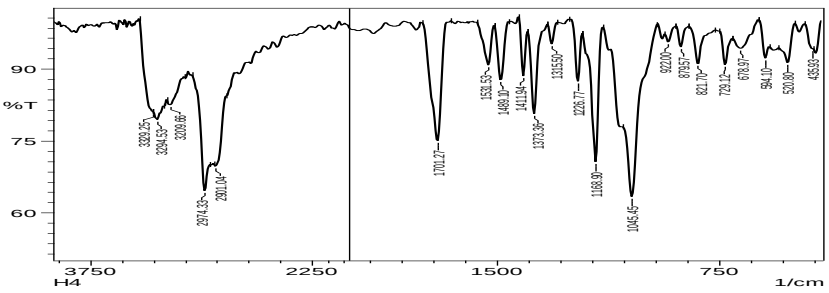


Figure 10. FT- IR spectrum of **H**4 compound

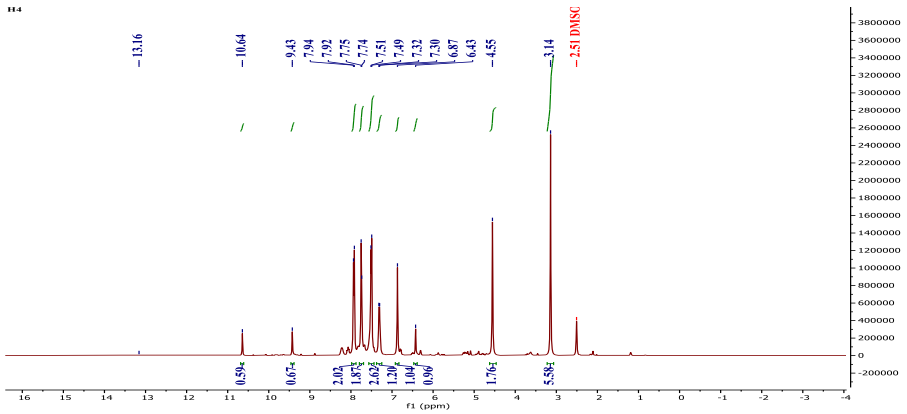


Figure 11. [1]H.NMR spectrum of **H**4 compound

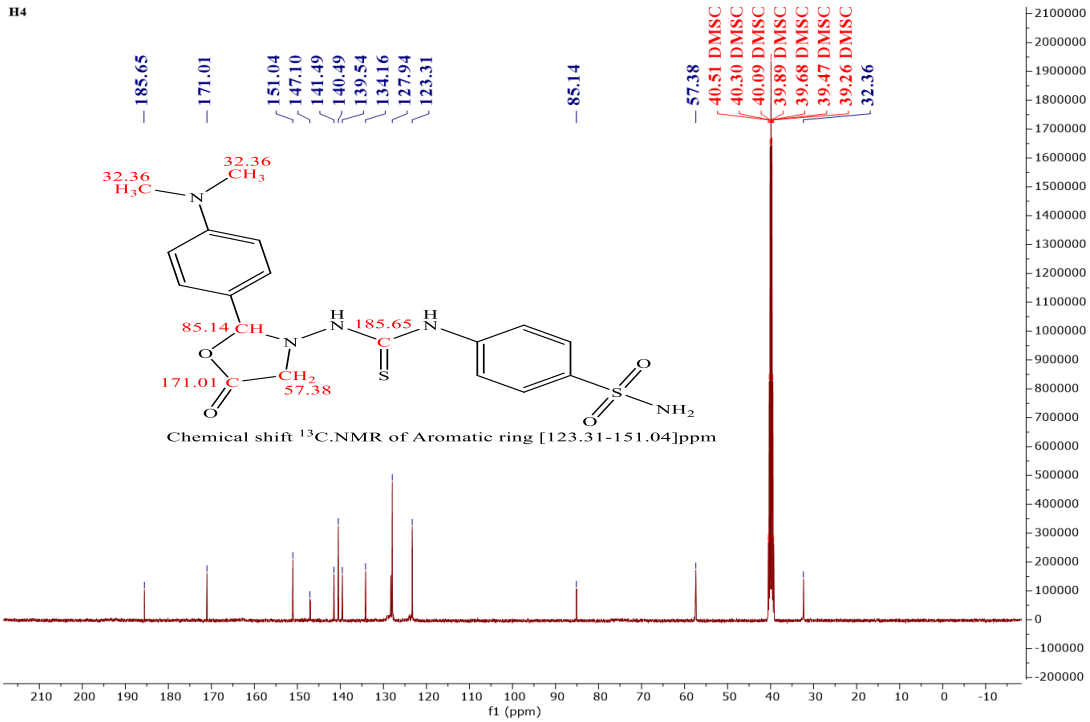


Figure 12. ^{13}CNMR spectrum of **H4** compound

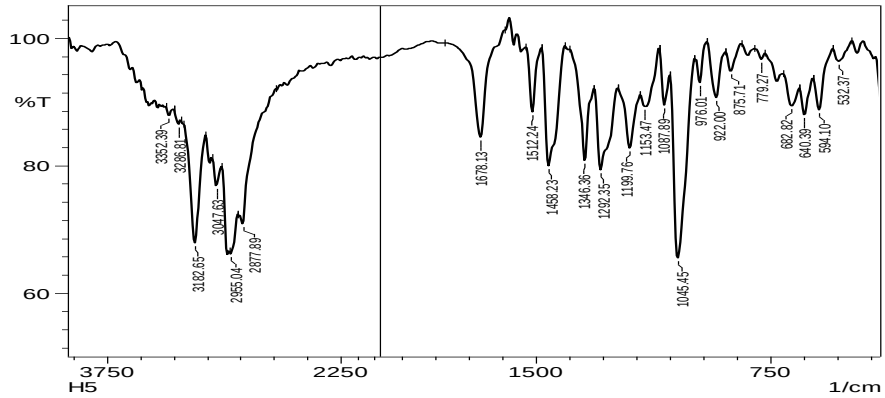


Figure 13. FT- IR spectrum of **H5** compound

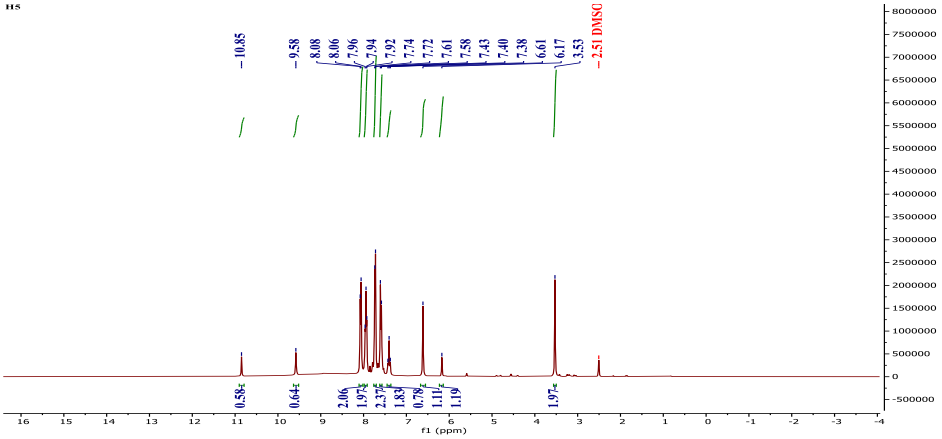


Figure 14. ^{1}H.NMR spectrum of **H5** compound

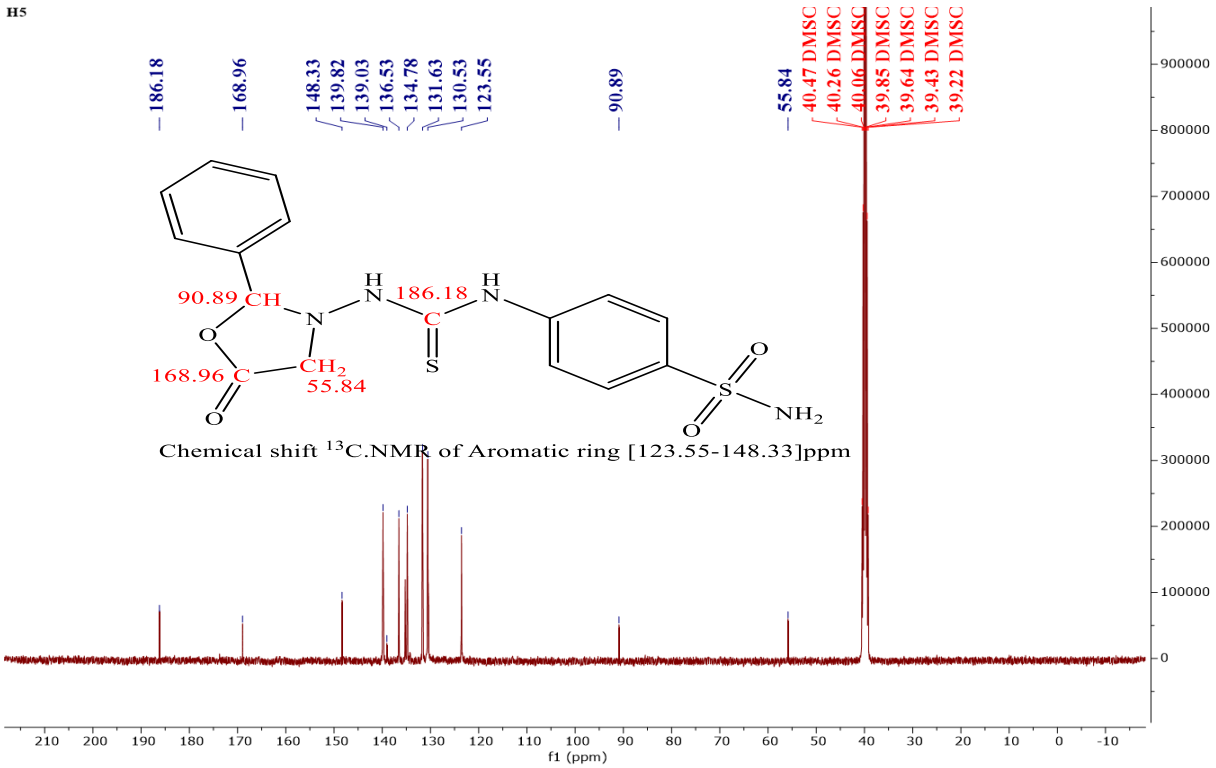


Figure 15. ^{13}CNMR spectrum of **H5** compound

Table 2. FT-IR characteristic absorption of prepared compound

Comp	νNH2 (cm-1)		νSO2 (cm-1)		νCH alph (cm-1)	νC-HArom (cm-1)	νOH (cm-1)	Others (cm-1)
	asym	sym	asym	sym				
H2	3329	3259	1311	1188	2874	3070	-------	C=CAr (1508-1499) NO2asym(1388) NO2 sym(1508) C=O(1681) C-HAr (3095)
H3	3340	3290	1334	1150	2924	3095	-------	C=O(1685) CHOxa(2897) C=CAr (1546-1381) C=S (1495) C-HAr (3099)
H4	3329	3245	1337	1158	2901	3099	-------	C=O(1701) CHOxa(2897) C=CAr(1531-14011) C=S (1255) CH2CH3asym(2974) CH2CH3 sym(2901)
H5	3352	3286	1346	1153	2800	3047	-------	C=O(1678) CHOxa(2955-2877) C=CAr (1512-1458) C=S (1045)

Table 3. ^{1}H.NMR.Chemical Shift δ ppm of [H_2, H_3,H_4 and H_5]

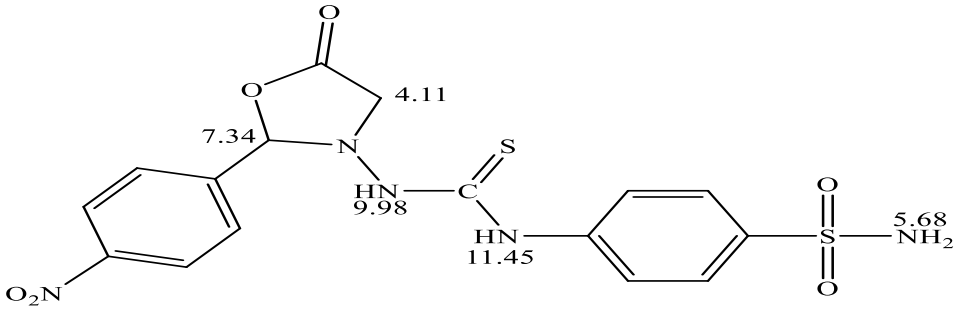
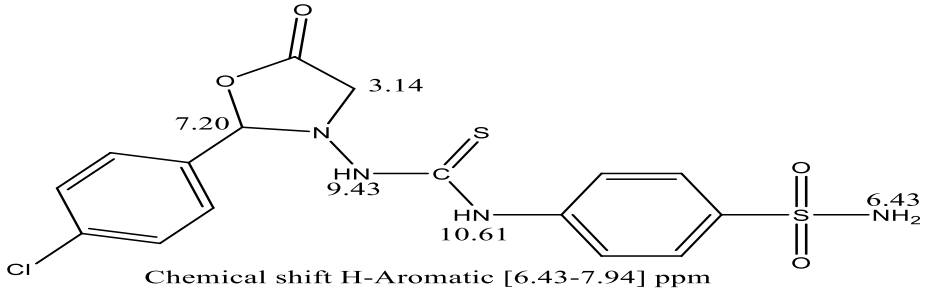
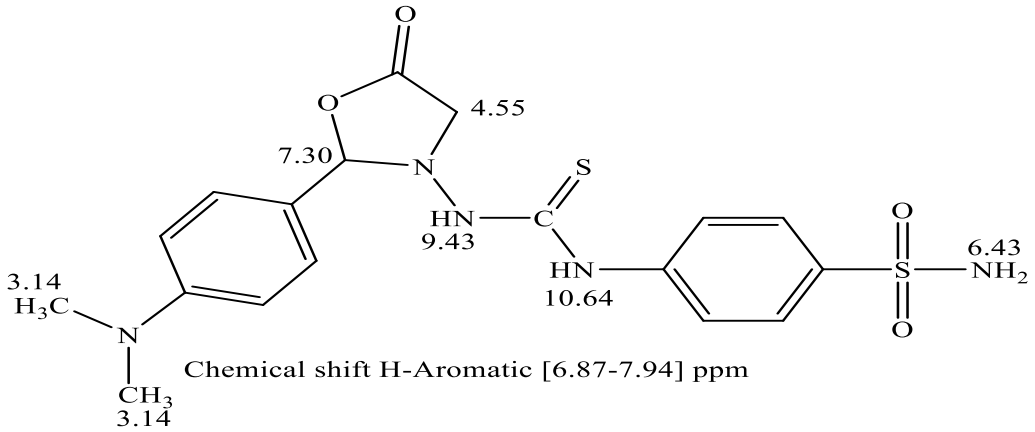
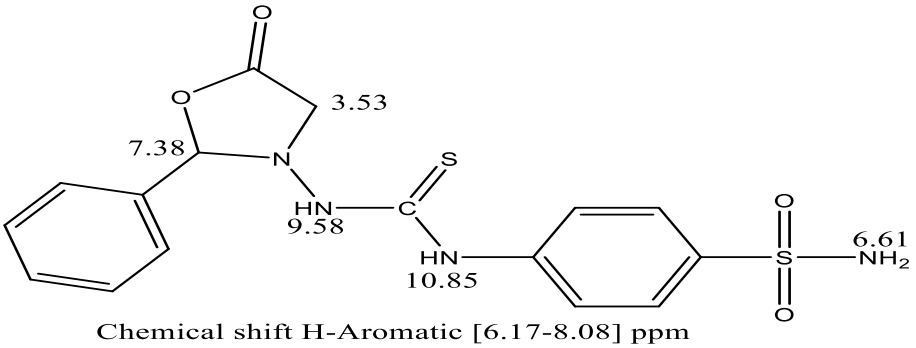
Comp.No	Structure
H_2	 Chemical shift H-Aromatic [6.68-7.83] ppm
H_3	 Chemical shift H-Aromatic [6.43-7.94] ppm
H_4	 Chemical shift H-Aromatic [6.87-7.94] ppm
H_5	 Chemical shift H-Aromatic [6.17-8.08] ppm

Table 4.[13]C.NMR.Chemical Shift δ ppm of [H_2, H_3,H_4 and H_5]

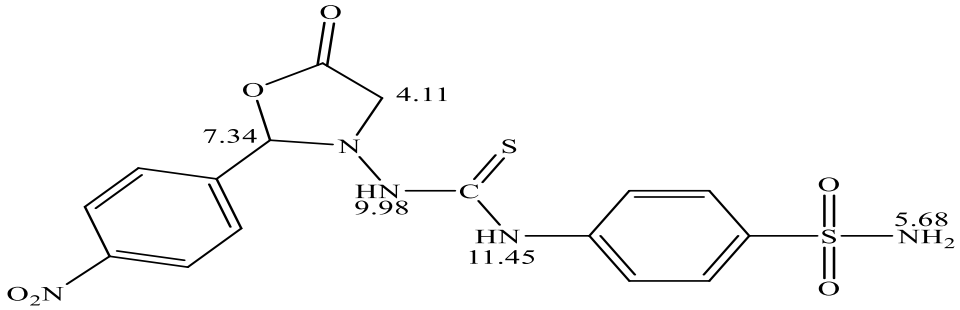
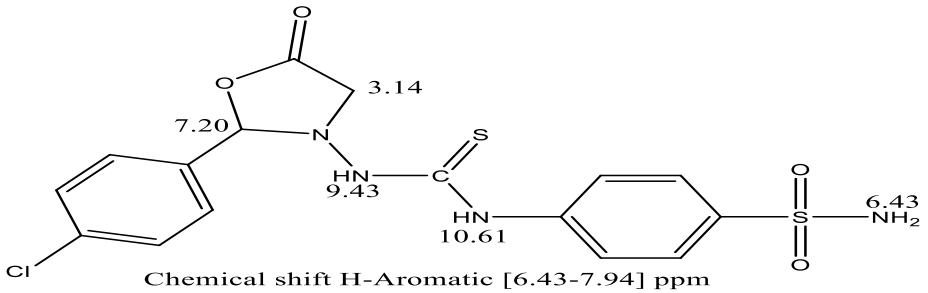
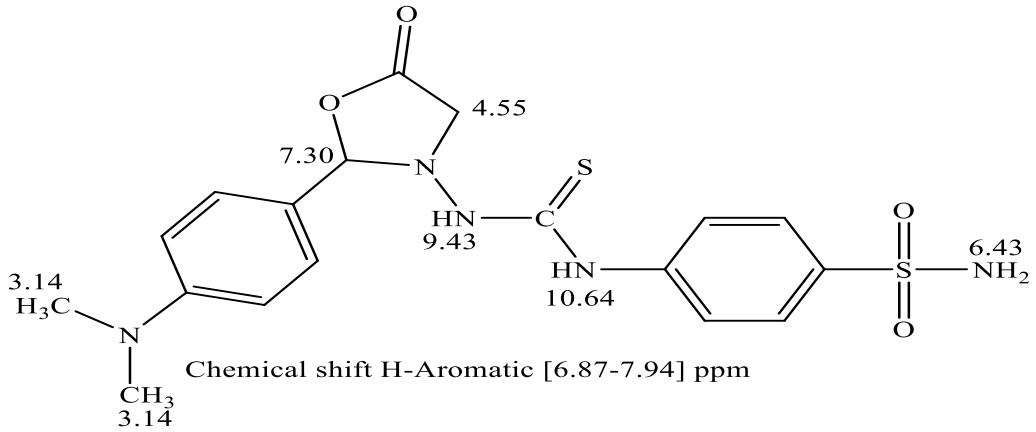
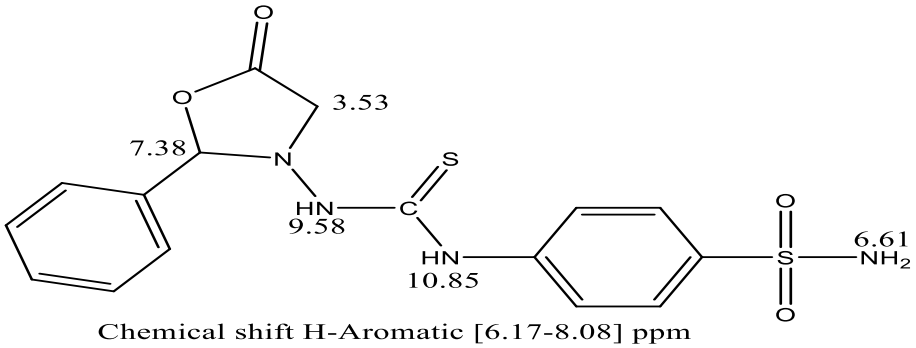
Comp.No	Structure
H_2	 Chemical shift H-Aromatic [6.68-7.83] ppm
H_3	 Chemical shift H-Aromatic [6.43-7.94] ppm
H_4	 Chemical shift H-Aromatic [6.87-7.94] ppm
H_5	 Chemical shift H-Aromatic [6.17-8.08] ppm

Table 5. Elemental Analysis

Comp	Calculated				Found			
No.	C%	H%	N%	S%	C%	H%	N%	S%
H_1	47.67	4.43	13.98	16.04	47.05	3.95	13.72	15.70
H_2	43.45	3.86	16.67	14.90	43.93	3.46	16.01	14.66
H_3	45.76	3.88	13.49	15.56	45.02	3.54	13.12	15.02
H_4	49.34	4.34	16.46	14.24	49.64	4.86	16.08	14.72
H_5	49.38	3.76	14.69	6.06	48.97	4.11	14.28	16.34

3.2 Theoretical Calculations [Geometric optimization of the compounds [H_1-H_5]

Theoretical calculations of the prepared Oxazolidinone derivatives have been accomplished utilizing the Gaussian 09W program package and using the Semi-empirical and Basis set AM1 approximation method. The 3D geometric structure of gas-phase for prepare compounds are shown in figures.In studying the total stabilization energy of the compounds, it becomes clear that the first compound, H_1, having the para-substituted hydroxyl group, has the lowest total stabilization energy of -7.45 kJ. This makes it the most thermodynamically stable compound compared to other derivative compounds studied. Next on the stability list is the chlorine-substituted compound, H_3 having energy of -4.83 kJ. The difference between the total energy of the derivatives is brought about by the different electronic character of the substituent groups. In particular, the effect brought about by the inductive and resonance of these groups helps in redistribution of the electron density throughout the oxazolidinone structure hence changing the energy of the molecule. Discussing the dipole moment analysis, we note that the dipole moment is the largest in compound H_2, due to the presence of the very electron withdrawing group nitro and amounts to 6.42 Debye. On the contrary, the dipole moment is minimal in the first compound H_1 and equals to 1.38 Debye. The values characterize the extent of intramolecular polarization; indeed, the stronger the withdrawing effect of the substituent, the greater its ability to shift electron density to one side of the molecule. This causes the separation of positive and negative charges centers, which results in increased polarization and dipole moment. In turn, the electron donating effect or interaction results in the equal distribution of the electron density and thus polarization decreases, which characterizes the solubility of the compounds and interaction with receptors. In relation to frontier molecular orbitals (HOMO and LUMO), the energy difference is the key parameter which can be used to assess the stability and hardness of the compound. It should be stated that molecule H_1 has the highest positive energy gap among all other studied molecules equal to 614.13(kJ/mol). (It should be pointed out that the negative values in other gaps obtained in the table are caused by the fact that the method of shallow subtraction was applied to the raw output data but only the absolute value reflects the hardness of the molecule). This means that compound H_1 has the highest level of stability and the lowest level of electron excitability which results in the low reactivity of the molecule. On the contrary, derivatives H_2, H_4 and H_5 have small and similar values of energy gaps from 484(kJ/mol) to 487 (kJ/mol). Inserting different groups to oxazolidinone analogs will affect their surface physical properties as well as the electronic configuration of the molecule. Electron withdrawing groups (EWG) increase polarity and reduce the energy gap (Egap) of the molecule, making it more reactive towards interaction. On the other hand, attachment of groups that enhance charge distribution in the molecule increases the energetic stability and orbital gap (HOMO-$LUMO_{gap}$) of the molecule. This information is helpful for the medicinal chemist to understand the behavior of these compounds since it will help them predict the biochemical interaction mechanism of these derivatives depending on the type of the substituent attached to the ring."

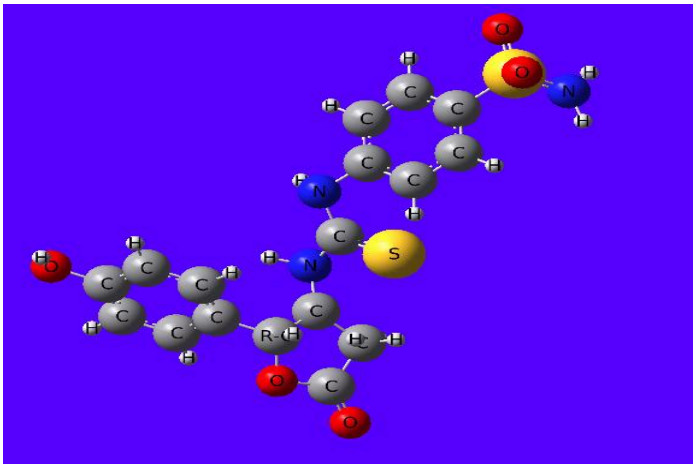


Figure 16. The optimized structure H_1.

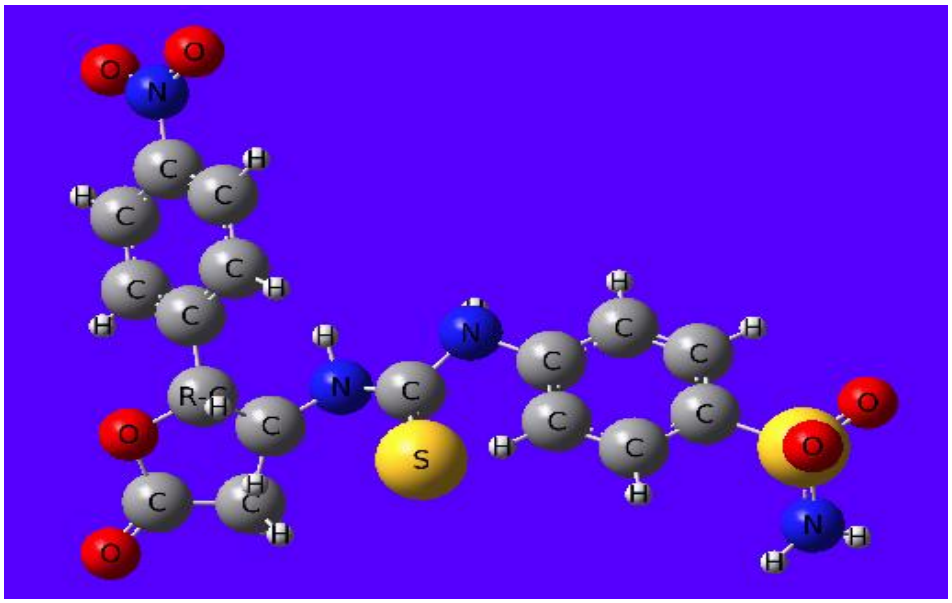


Figure 17. The optimized structure H_2.

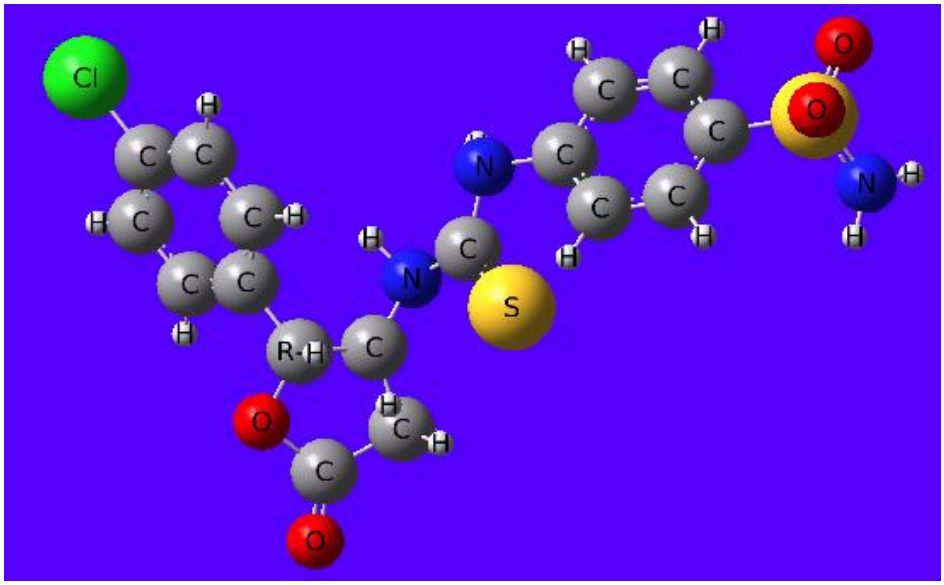


Figure 18. The optimized structure H_3.

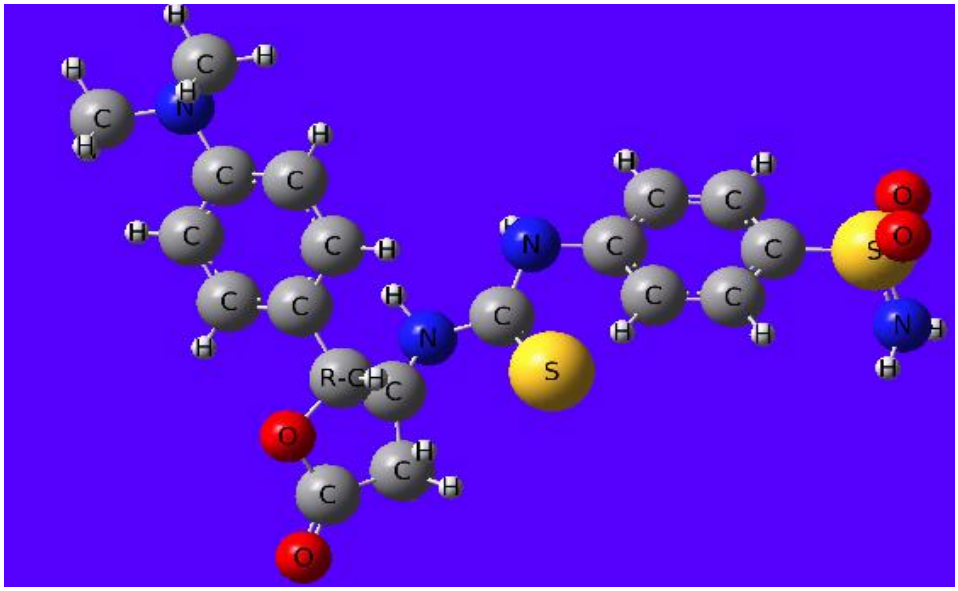


Figure 19. The optimized structure H_4.

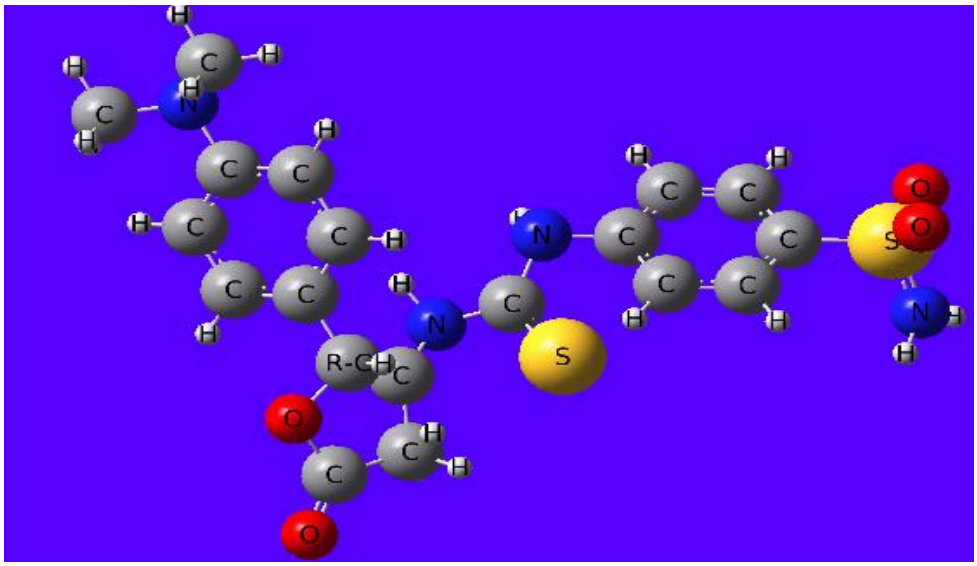


Figure 20. The optimized structure H_5.

3.3 Biological Activity Evaluation

The biological activity of the synthesized compounds was examined on different types of bacteria: *Staphylococcus*, and *E.Coli bacteria*. Also, the biological activity of several substances was investigated "Evaluation of biological activity revealed that the H_1,H_4 and H_5 compounds do not exhibit any significant inhibition.", This is the primary assay that tests for antibacterial activity of the biological compound (H_2) against the growth-positive strain of Escherichia coli (E. coli) as shown in bellow figure 21 and figure 22. The plate has a three-compartmental division to determine the inhibitory activity of the organic compound at varying concentrations. The organic compound contains the oxazolidinone moiety with a nitrophenyl functional group attached, linked through thiourea and sulfonamide bioisosteres. The mechanism behind the formation of the clear zones of inhibition around the chemical sample discs is based on the capacity of this mixture to diffuse in water inside the agar gel medium and thus prevent the growth or even kill the bacterial cells in the region of the disc. Mechanistically, this unique activity can be explained by the presence of the structural synergy of this substance where the sulfonamide group functions as an antimetabolite by competing with the structure of para-aminobenzoic acid (PABA) molecules. As a result, the inhibition of the enzyme dihydropteroate synthase takes place and consequently the whole process of the synthesis of folic acid that is required for the bacterial cell growth and replication is inhibited. Additionally, the presence of the oxazolidinone ring and the active nitro group increases the permeability of the substance across the cell wall and cytoplasmic membrane of Gram-negative bacteria via the pores and inhibits the initial stages of the bacterial protein synthesis by interacting with the ribosome. There are three well-defined, clearly visible zones of inhibition around the tested compounds on the plate. From the scientific point of view, it means that this compound—in certain concentrations or derivatives (C1, C2, and C3)—has the capacity to inhibit bacterial proliferation and kill it in those areas surrounding the compound, thanks to its active substance spreading out through the medium and poisoning the bacteria. Compound (H_2) has the structure of a complex system of a combination of several pharmacological functional groups, which have antimicrobial effects, namely the oxazolidinone group with the nitrophenyl group and the sulfonamide group with the amine group connected by the thiourea group. The scientific reason for the biological activity seen on the plate lies in the possibility of penetration of these functional groups into the Gram-positive bacterial cell wall and inhibition of important biological processes inside the cells such as protein synthesis and folic acid synthesis. Figure 23 below depicts a laboratory study of the effect of an antimicrobial agent through the agar well diffusion test (or disk diffusion test), where the surface of the solid nutrition medium was inoculated with Gram-negative bacteria, such as E.coli, to grow a uniform bacterial lawn. The test plate has depicted clear, circular zones around the

regions where the chemical agent was added; these zones are scientifically referred to as zones of inhibition. This region does not have any growth of bacteria at all as a result of diffusion of the chemical agent in the agar that inhibits bacterial growth. A clear diameter of these halos indicates the high efficiency of inhibition of the tested compound, which shows the ability of this chemical substance to effectively penetrate the bacteria wall and inhibit the vital components inside. When connecting this activity to the structure of the chemical compound presented in the second picture, it becomes clear that this chemical substance is smartly built with several functional groups that increase its efficiency of inhibition of bacteria E. coli. This compound consists of the sulphonamide group (SO_2NH_2), which is connected with a benzene ring – this is the key part of the chemical structure responsible for inhibition of the enzyme dihydropteroate synthase, preventing bacteria from folic acid synthesis and therefore from synthesis of the genetic material and nucleic acids within the bacteria.Additionally, the compound includes a five-membered oxazolidinone ring containing a chlorophenyl substitution. This group belongs to the class of chemical structures known for their binding to bacterial ribosomes' subunit and inhibition of bacterial protein synthesis at the early stages of it. Moreover, inclusion of the central thiourea linker (NH-CS-NH) increases polar properties of the compound and its ability to form strong hydrogen connections with elements of bacterial cell membranes and enzymes. It makes the whole structure even more lipophilic (fat soluble) because of the presence of the chlorine atom in the substitution of the phenyl group. This provides easy permeability and penetration into the complex cell structure of Gram-negative E. coli bacteria that has the additional membrane layer. It is evident that Compound H_3 shows a dense and homogenous bacterial growth (Bacterial Law) on the entire surface of the nutrient media Figure 24. At the center of each section, there is a well where the concentration of the chemical compound has been added. Around these wells, there are clear zones where there is absolutely no bacterial growth at all; these zones are scientifically referred to as Zones of Inhibition. These zones have come about as a result of the diffusion of the compound in a radial manner from the center of the well to the surrounding areas. When its diffused concentration becomes equal to or above the MIC for the microbe, it inhibits the bacteria from growing in that zone. When comparing this biological effect with the chemical structure of this compound presented in the second figure, one can notice that this molecule consists of highly active structural and pharmacophoric units that provide strong inhibitory efficiency of this compound towards Staphylococcus bacteria. Indeed, this compound contains an oxazolidinone ring that is substituted with 4-chlorophenyl group; this is the structural motif, which is famous for its high permeability into the thick cell wall of Gram-positive bacteria and inhibition of their essential proteins' synthesis. Moreover, thiourea bridge (thiosemicarbazide / thiourea core) is connected with the previous ring through nitrogen atom; the bond of thiourea is represented by HN-C(=S)-HN and has a key role in providing the increase in affinity and binding to the bacterial receptor and generation of oxidative stress in the bacterial cell. In addition, this molecule has sulfonamide group at the para position (SO_2NH_2), which is responsible for the inhibition of bacterial folic acid synthesis enzymes. Bacterial inhibition effectiveness, based on the clear zones' diameters in all the three sections, is a sign that this substance has good and impressive efficacy against Staphylococcus bacteria. These zones have very sharp and clear boundaries, which prove the effective inhibition of bacteria's growth in the given concentrations without any appearance of resistant bacteria in the inhibition zones. The similarity of the zone sizes in the three sections is an evidence of the stability of the substance, its ability to diffuse easily in the nutrient agar and reproduce the positive result. Such powerful effect proves the great potential of this substance as an antibacterial agent, capable of destroying staphylococcal strains due to high efficacy in disruption of their key systems.

Figure 21 .Anti fungi activity of H_2 compounds against [*E.Coli*]

Figure 22 .Anti fungi activity of H_2 compounds against [*Staphylococcus*]

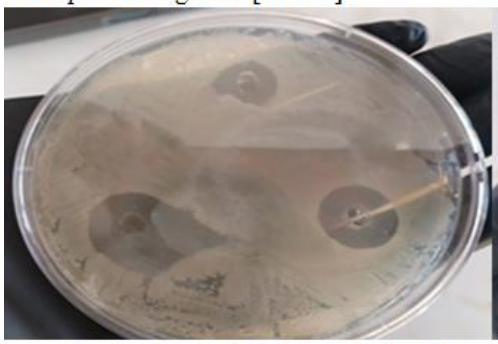


Figure 23 .Anti fungi activity of H_3 compounds against [*E.Coli*]

Figure 24 .Anti fungi activity of H_3 compounds against [*Staphylococcus*]

Table 6. Zone of Inhibition in Millimeters for Biological Activity

Sample. No	S.aureus Gram +			A.baumanii Gram -		
	100	**50**	**25**	**100**	**50**	**25**
H_1	n.a	n.a	n.a	n.a	n.a	n.a
H_2	23	15	10	12	10	10
H_3	18	13	10	10	5	5
H_4	n.a	n.a	n.a	n.a	n.a	n.a
H_5	n.a	n.a	n.a	n.a	n.a	n.a
Negative control	n.a			n.a		
Positive Control	30			13		

4. Conclusion

This research covers a variety of directions, such as the organic synthesis and biological evaluation of oxazolidinones obtained via Schiff bases. It is proved that the synthesis of five oxazolidinone derivatives (H1–H5) by means of clean, solvent-free chemistry was successful. The accuracy of the data is proven by the precise coincidence of the results of the Fourier-transform infrared spectroscopy (FT-IR), 1H-nuclear magnetic resonance 1H-NMR}, and 13C-NMR spectrometry, as well as microelemental analysis. Spectral analysis shows the formation of the five-membered ring oxazolidinone and the bonds of the disulfonamide and thiourea fragments, in which the chemical shift of the methine and methylene fragments is emphasized in the influence of the substituent environment. Theoretical calculations conducted with the use of Gaussian 09 program using the Hartree-Fock method and AM1 approximation from the physicochemical point of view indicate the key role played by the nature of the para-substituents for stability and stereochemistry of the molecules. In particular, it has been found out that the most stabilized compound is H1 containing the electron donor hydroxyl substituent, which is characterized by the minimum value of total stabilization energy (-7.45 kJ). It means that this molecule is the most stable one and the least sensitive to electronic excitation due to the largest HOMO-LUMO energy gap (614.13 kJ/mol). On the contrary, electron-withdrawing substitutes, such as the nitro group in compound H2, cause an increase of internal molecular polarization, which is characterized by the maximum dipole moment of 6.42 Debye. The above-mentioned variation in the structure and stereochemistry of

these two compounds affects their biological action against E. coli, Staphylococcus, and A. baumannii. The evaluation of the antibacterial activity through the agar disk diffusion method showed the presence of considerable variation in the inhibitory efficiency. It was found that the only compound which demonstrated the powerful and unique inhibitory action was compound H2, which recorded the well-defined inhibitory zones with a diameter of up to 23 mm against Gram-positive bacteria and 12 mm against Gram-negative bacteria at the highest concentration. Such biological effectiveness of compound H2 is due to the synergism in its structural and pharmaceutical properties of oxazolidinone ring, nitrophenyl group, and sulfonamide group joined through the thiourea bridge. Sulfonamide group is an antimetabolite that blocks the dihydropteroate enzyme, which results in the blocking of the synthesis of folic acid necessary for bacterial cell growth and replication. At the same time, the nitro group and oxazolidinone ring provide increased penetration of the compound into cell membranes and inhibition of the early stage of bacterial protein synthesis in the ribosomes. Moreover, compound H3 with a chlorine atom exhibited biological activity ranging from weak to moderate, showing inhibition diameters of 18 mm and 10 mm towards Staphylococcus and E. coli, respectively. This is attributed to the contribution of chlorine atom in increasing lipophilicity, enabling the passage through the thick and complicated cell wall of bacteria. On the other hand, the biological activity of inhibition completely disappeared in the cases of compounds H1, H4, and H5 since these did not show any biological activity against the tested bacteria. Based on the above integrated results, the conclusion of the study is modification of the electronic and steric properties of oxazolidinone ring through adding withdrawing or donating groups would be the key to the control of stability, dipole moment and penetrability of the compound into bacteria. This study provides a promising scientific platform for drug and medicinal chemist to understand the biochemical interaction mechanism. Thus, some of these derivatives especially compound H2 could become a cornerstone for developing novel antibacterial drugs against microbial resistance challenge.

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