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Preparation, evaluation, and identification of the biological, laser, and nanoscale activity and computational chemistry of some 3,2-dihydroquinoxolin-4-on compounds derived from 4-aminotetrahydropyrane

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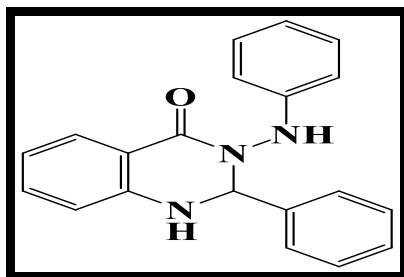
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Abstract---This research prepares heterocyclic compounds by the compound [G1] from the reaction of 2-chloroaceto-hydrazide with 4-amino-tetrahydropyrane in absolute ethanol with drops of triethylamine 3 (C₂H₅)₃N. Then the hydrozones [G7-G2] were prepared from the [G1] reactor with some substituted benzaldehyde in absolute ethanol using an acidic medium. Derivatives of 2,3-dihydroquinoxoline 4-on [G8-G13] were prepared by the reaction of the hydrozones [G2-G7] with anthranlic acid using 4,2-dioxane as a solvent then adding sodium carbonate to get rid of the residual acid used. After purification of the product, the prepared compounds were characterized by some spectroscopic methods, such as infrared (IR), proton nuclear magnetic resonance (NMR) [¹H and carbon NMR] ¹³C, as well as the study of the thermal stability of some 3,2-dihydroquinoxolin 4 compounds using the laser, obtaining nanoparticles, determining their shapes and sizes, the computational chemistry of all the prepared compounds, in addition to identifying the melting and purity degrees of the prepared compounds following the course of the reactions by thin layer chromatography (TLC). The biological activity of some prepared compounds was studied against some types of negative and positive gram stain bacteria, negative bacteria, [Gr-ve] *Escherichia coli* and *Klebsiella pneumonia* and gram positive bacteria [Gr+ve] *Staphylococcus aureus* and *Staphylococcus epidermidis*. The antibiotic amoxicillin was used as a control sample and some of the prepared compounds showed good inhibitory activity against the bacteria used.

Keywords---hydroquinoxaline and 4-amino-tetrahydropyran, cyclic closure reactions, hydrazones.

Introduction

The hydrazides are considered intermediates of wide importance, the general composition of any hydrazide is as follows $R-CO-NHNH_2$, although in the absence of an acyl group, such a type of compound is called hydrazine (Abbood S. S. & .A, 2016). It enters in the preparation of many heterocyclic organic compounds (Shamsabadi & Chudasama, 2017), the most important of which are the derivatives of 4,3,1-oxadiazole(Sharba, Al-Bayati, Aouad, & Rezki, 2005), 4,3,1-thiadiazole (Al-Iedani, Majeed, & Rashid, 2015)and 4,2,1-triazole(Al-Ajely & Yaseen, 2017). The hydrazides are also effective compounds, it has antimicrobial activity(Zhong, Wang, Cheng, Wang, & Liu, 2018), is used as an agent against tuberculosis(Lihimes, 2015) and stops immunodeficiency. In addition, it is used as a pesticide (Rahaman & Hossain, 2019)and works in acidic media as corrosion inhibitors in light steel(Shetty, 2018). Hydroquinoxalines consist of a hexagonal ring that includes two nitrogen atoms and a carbonyl group and when it contains a carbonyl group in the 4-position, it is called dihydroquinoxaline-4-on.



Lasers(A. Dalaf, Jumaa, & Salih, 2021)

The concept of laser rays expresses an abnormal source of light, where these rays are in the form of very narrow lines of light. Lasers are very useful and important in the fields of technology, industries, and others . There are several types of lasers, and they all share the same characteristics. In lasers, the material that produces the laser is excited by a process of pumping electrons from the ground level to a higher level (excited state). Electrons are used to pump out a strong flashlight or by electrical discharge. Pumping works are conducted to supply the largest possible number of electrons to the highest energy level, and thus the laser material includes a number of atoms with excited electrons. Then it is called the excited atom. The number of excited atoms in the laser material is greater than the number of unexcited laser atoms

Experient

The devices used

All solvents and reagents were obtained from commercial sources and used without further purification. Melting points were determined using capillary tubes

without correction, the electrical device used to measure the melting points is of automatic melting point/SMP40 electrode meter. Shimadzu Fourier Transform Infrared Spectrophotometer FT-IR 8400 was determined using Varian with a power of 400 MHz, and the spectra of the NMR-1H- ¹³C. The prepared compounds were bombarded with a Nd:YAG laser device and the SME nanometers were determined.

Compound preparation [G₁](Ghaisas & Patel, 2018)

(0.14 mol, 13.58 gm) of 2-chloroacetohydrazide prepared previously in paragraph (2-3) was dissolved in (40 ml) of absolute ethanol and 6 drops of triethylamine were added to (0.14 mol, 14 gm 14.5 ml) of 4 - Amino tetrahydropyran. The mixture was raised for 9 hours with continuous stirring and the completion of the reaction was confirmed using TLC technology. The mixture was left to cool, then the white precipitate was filtered and recrystallized with chloroform and dried at a temperature of 50 C. The percentage of the product was 43% and its melting point was (220-222 C) and the retardation factor was R_f 0.88.

Preparation of hydrozones [G₂-G₇](Jarrahpour, 2019; S.H.Rohane, 2019; Yousif, Jabbar, & Al-zahawi, 2022)

(1.5gm, 0.0094mol) of compound [G₁] is dissolved in (20ml) of absolute ethanol and added to (0.0094mol) of aldehydes (-cinnamaldehyde/-4,3-dichlorobenzaldehyde/-4,2-dimethoxybenzaldehyde/-4-methylthiobenzaldehyde/-4,2 dihydroxybenzaldehyde/3-methoxy-4-hydroxybenzaldehyde. After adding 4-3 drops of icy acetic acid, the mixture was Reflected for 6-9 hours and the completion of the reaction was confirmed by using TLC technology and after the completion of the reaction, the resulting mixture was slowly cooled and filtered. The precipitate was collected, recrystallized with absolute ethanol and dried at 50 °C.

Preparation of some 3,2-Dihydroquinoxoline 4-ON derivatives [G₈-G₁₃](Thomas-Hillman, Laybourn, Dodds, & Kingman, 2018)

(0.0004mol) of some of the prepared compounds [G₂-G₇] was dissolved in (10ml) of 4,2-dioxane and added to (0.0004mol, 0.055gm) of anthranilic acid dissolved in (5ml) 4,2-dioxane. Then the mixture was refluxed from 14 to 16 hours, and the completion of the reaction was confirmed using TLC technology. The mixture was cooled and treated by washing the mixture with sodium bicarbonate (10%), filtered, washed with cold water, recrystallized with absolute ethanol. This is followed by drying it at 50°C. Table (1) shows some physical properties, percentage and R_f of the prepared compounds [G₂-G₁₃]

Comp. No.	Ar	Molecular Formula/ M.Wt g/mol	Color	M.P. (°C)	Yield (%)	T.R	R _f
Comp. No.	Ar	Molecular Formula/ M.Wt g/mol	Color	M.P. (°C)	Yield (%)	T.R	R f

G₂		C₁₅H₁₉N₃O₂ 273	Orange	193-195	85	9	0.83
G₃		C₁₃H₁₅N₃O₂Cl₂ 316	Pall yellow	200-202	82	8	0.79
G₄		C₁₅H₂₁N₃O₄ 307	Yellow	218-220	71	7	0.76
G₅		C₁₅H₁₉N₃O₂S 293	Green	207-209	69	6	0.75
G₆		C₁₃H₁₇N₃O₄ 279	Yellow	213-215	65	9	0.69
G₇		C₁₄H₁₉N₃O₄ 293	Green	215-217	77	7	0.79
G₈		C₂₂H₂₄N₄O₃ 392	Pall brown	245-247	70	14	0.71
G₉		C₂₀H₂₀N₄O₃Cl₂ 435	Dark yellow	235-237	69	16	0.64
G₁₀		C₂₂H₂₆N₄O₅ 426	Yellow	242-244	86	14	0.83
G₁₁		C₂₁H₂₄N₄O₃S 412	Pall yellow	238-240	68	15	0.63
G₁₂		C₂₀H₂₂N₄O₅ 398	Brown	238-240	88	16	0.87
G₁₃		C₂₁H₂₄N₄O₅ 412	Dark Brown	202-204	81	16	0.79

laser beam effect(YASS & Ayed, 2020)

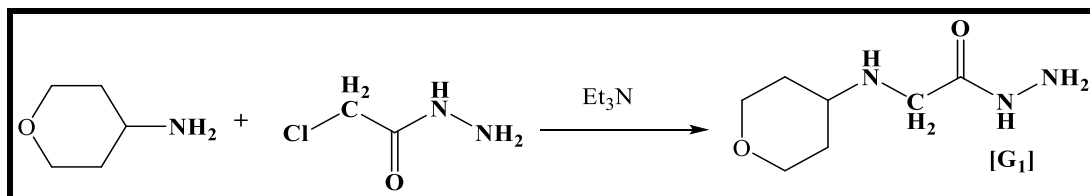
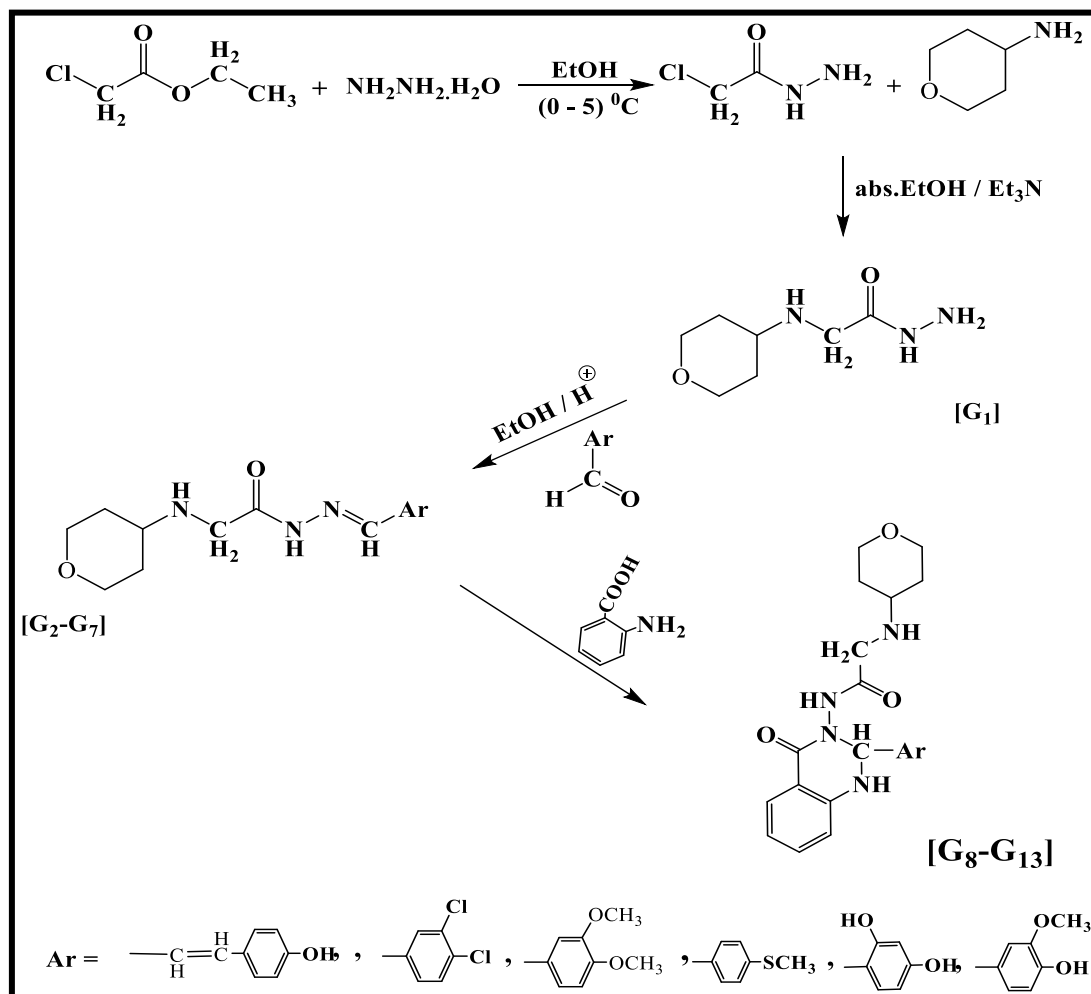
The samples were irradiated by a irradiated neodymium nanosecond laser system (Nd:YAG laser) that produces a pulsed nanosecond laser. The samples were irradiated with harmonic generation (532nm) and energy (800 mJ) and frequency (5 Hz) laser pulses of (15-30) seconds and delivered and the distance between the laser source and samples was (10 cm). Also, the incident laser radiation was perpendicular to the samples using a concave quartz lens. Its focal length is (100mm).

([G₁₃-G₂]: تحضير المركبات 1 مخطط)

Results and Discussion

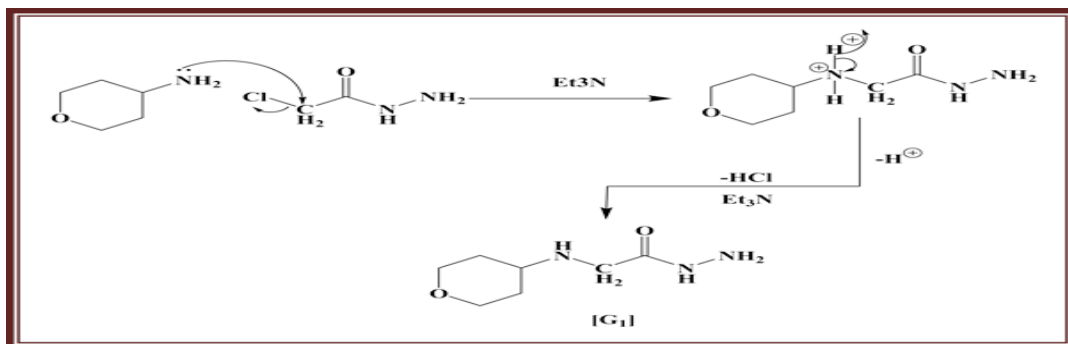
[G1] Compound diagnosis:

The compound [G1] was prepared by reacting one mole of 4-amino-tetrahydropyran with one mole with 2-chloroacetohydrazide in an alkaline medium using absolute ethanol as a solvent, as in the following equation:-



The reaction was confirmed by observing the changes in the physical properties of the melting point and the large change in color, as well as conducting the R_f test on the results. This showed a single clear spot on the thin layer chromatography

(TLC) plate. Tetrahydro-2H-pyran-4-yl (amino) acetohydrazid, according to the known mechanism (1) in the following scheme (2):

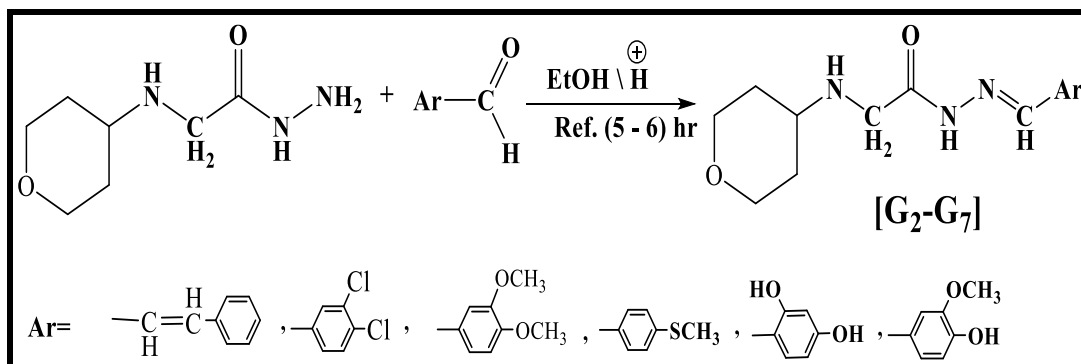


Scheme 2: Mechanism of preparing the compound [G1]

When studying the infrared (FT-IR) spectrum of the compound [G1], two stretching bands (NH₂) were observed, which appeared as a bisect band of intensity at (3211) cm⁻¹ and at (3243) cm⁻¹, and the emergence of a strong band for the band (C = O) Amida at (1666) cm⁻¹. Two symmetrical and asymmetrical stretching bands appeared for the aliphatic group (C-H) sharp and medium-intensity bundles at (2831) and (2891) cm⁻¹, and a strong bundle of the (N-N) bond appeared at (1030) cm⁻¹, and a strong (C-O-C) band at (1286) cm⁻¹, where these bands were identical to what is found in the literature (17) as in Figure (1) which shows the IR spectrum of the compound [G1]. The NMR spectrum appeared in Figures (2) and (3).

2: Hydrazoneate diagnosis [G7-G₂] :

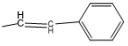
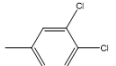
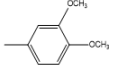
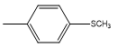
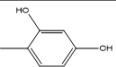
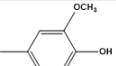
Hydrazones [G7-G₂] were prepared from the reaction of 1 mole of aromatic benzaldehyde substitutes with 1 mole of compound [G1] in the presence of ethanol as a solvent (Sykes, 1986) as shown in the following equation:



When studying the infrared (IR) spectrum of the prepared hydrazones [G7-G₂], it was noticed that the stretching bands of the amine group (NH₂) that appeared at (3211) and (3243) cm⁻¹ belonging to the compound [G1] disappeared. Also, a band appeared as medium stretching at (1631-1633) cm⁻¹ due to group (C=N) with the appearance of two absorption bands at the range (1577-1591) cm⁻¹ and (1516-

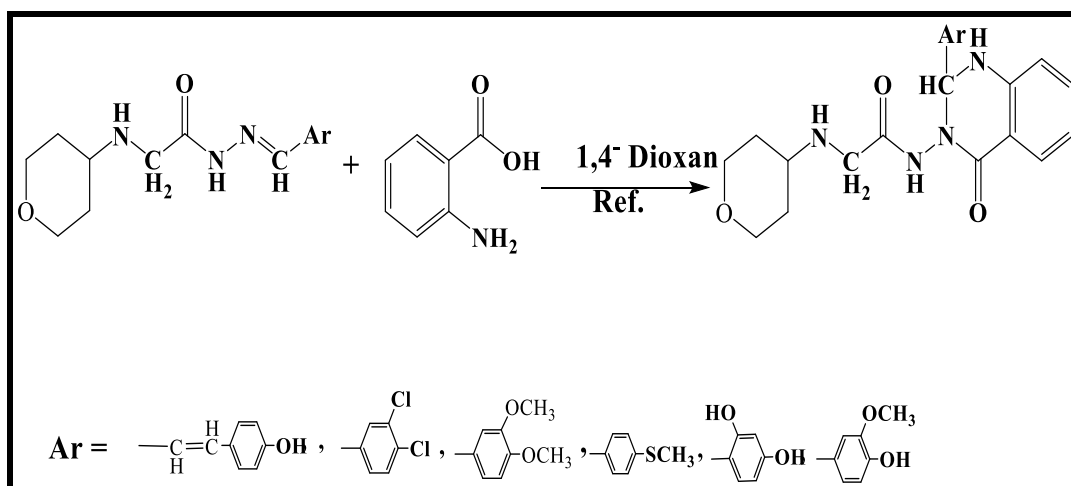
1558) cm^{-1} due to the stretching of the aromatic ($\text{C}=\text{C}$) bond. In addition, absorption bands at the range (3051-3053) cm^{-1} are due to the stretching of the aromatic ($\text{C}-\text{H}$) bond, and absorption bands at the range (2922-2966) cm^{-1} and (2833-2856) cm^{-1} are due to the asymmetric and symmetrical stretching of the ($\text{C}-\text{H}$) bond, respectively. Aliphatic with absorption bands at the range (3201-3205) cm^{-1} is caused by the stretching of the (NH) bond and the appearance of medium intensity absorption bands at the range (1286-1288) cm^{-1} belonging to the group ($\text{C}-\text{O}-\text{C}$). Also, strong intensity bands appeared at the range (1695). - 1666) cm^{-1} belonging to the group ($\text{C}=\text{O}$) and the two figures (4) (5) show the infrared spectrum of the two compounds [G4, G2] as a model where these bands were close to what is found in the literature(Vogel, 1989).

Table (2) Infrared absorption results (cm^{-1}) for [G7-G2] hydrazones derivatives

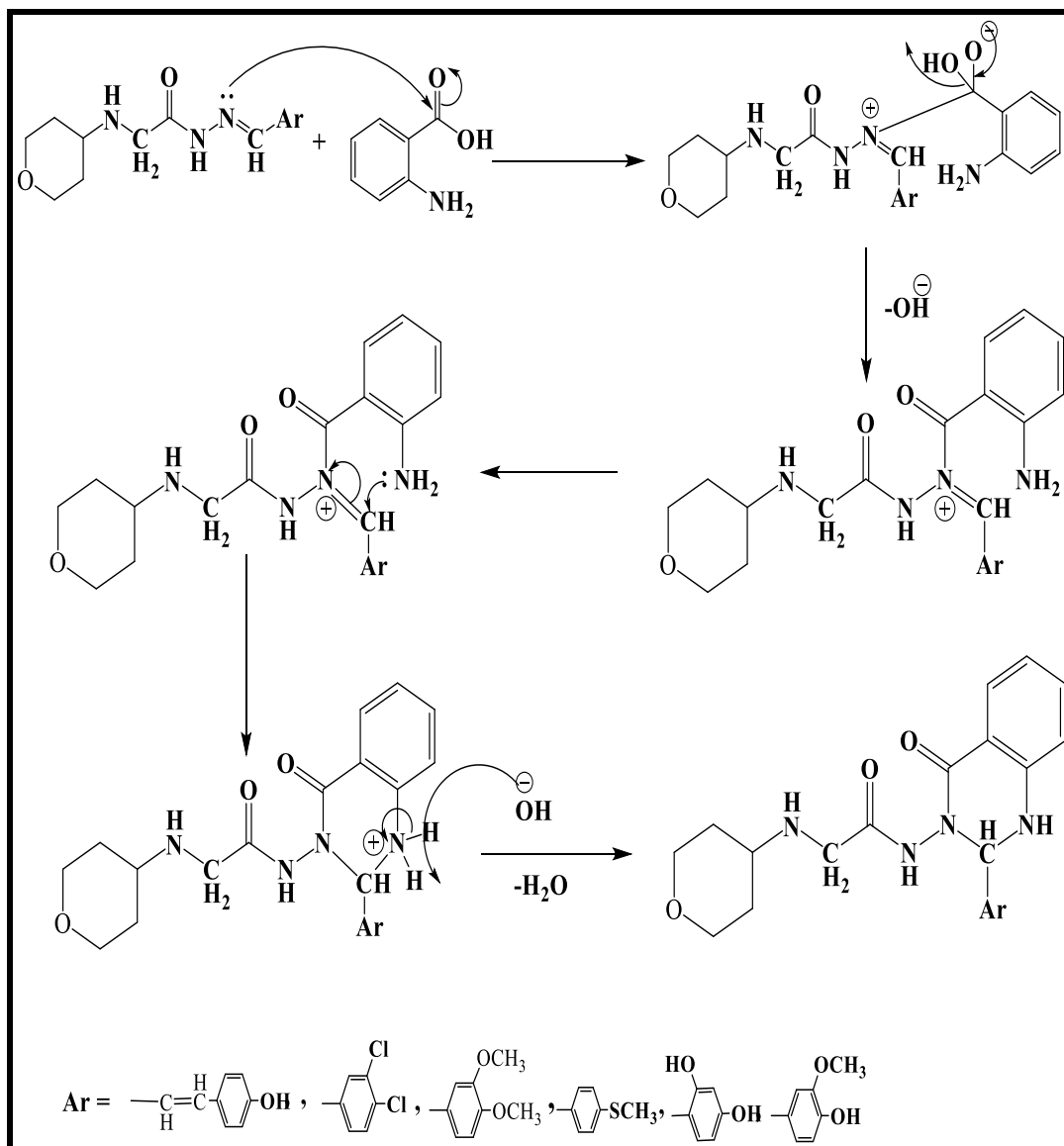
Comp. No.	Ar	IR (KBr) cm^{-1}						v (N-H)	Others
		v (C=N)(Sheiff	v (C-H) Arom. Aliph.	v (C=C) Arom.	v (C-O-C)	v (C=O) Amid	v (C-N) (N-N) Amid		
G ₂		1633	3053 2930 2837	1577 1531	1286	1670	1155 1076	3205	v (C=C-)1640 v (H-C=C)3003
G ₃		1631	3051 2935 2856	1577 1531	1288	1666	1166 1089	3205	v (C-Cl) 866
G ₄		1633	3053 2933 2837	1577 1531	1286	1670	1157 1095	3205	v (C-O-C)1031
G ₅		1631	3053 2922 2833	1591 1558	1288	1695	1170 1091	3201	v (C-S)1008
G ₆		1633	3053 2931 2847	1577 1531	1286	1670	1157 1078	3203	v (OH) 3560
G ₇		1633	3053 2966 2848	1583 1516	1288	1670	1124 1085	3201	OHv 3456

4: Diagnosis of 3,2-Dihydroquinoxolin 4-on. derivatives [G₈-G₁₃]

The derivatives of 2-3, dihydroquinoxolin 4-on [G14-G19] were prepared from the reaction of one mole of the prepared hydrazones [G2-G7] with one mole of anthranlic acid in 1,4-dioxane as a solvent to give a heterocyclic hexagonal ring of 3,2 derivatives Dihydroquinoxoline 4-on [G8-G13], and as shown in the following equation:



The mechanism for preparing 3,2-dihydroquinoxolin-4-one derivatives is summarized in three steps: the first involves the process of nucleophilic attack on the carbonyl carbon atom by the nitrogen electron pair of the azomethine group ($\text{C}=\text{N}$), and the second step occurs by deleting the (OH) group of the carboxylic acid. To activate our new nucleophilic center to attack the unshared electronic double of the (NH_2) group on the aromatic ring and close the ring forms a heterogeneous hexagonal ring consisting of two nitrogen and four carbon atoms. In the third step, a proton is deleted from the deleted hydroxyl group as in the following diagram that shows the mechanism (Sykes, 1986) to prepare derivatives of 3, 2-dihydroquinoxoline 4-un [G13-G8]:

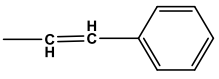
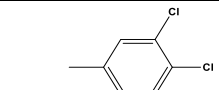
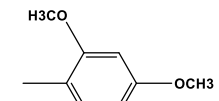
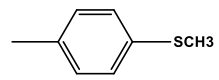
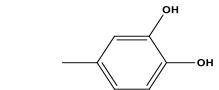
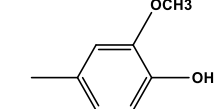


Scheme 3: Mechanism of preparation of 3,2-dihydroquinoxolin 4-on derivatives [G8-G13].

When studying the infrared spectrum, it was noticed that the medium beam disappeared at $(1631-1633) \text{ cm}^{-1}$, which belongs to the group $(\text{C}=\text{N})$, and a strong beam appeared at frequency $(1658-1676) \text{ cm}^{-1}$ $(1685-1693) \text{ cm}^{-1}$ that belonged to the group $(\text{C}=\text{N})$. Stretching of the carbonyl-lactam bond $(\text{C}=\text{O})$, a sharp absorption band was observed at the range $(3299-3386) \text{ cm}^{-1}$ due to the stretching of the (NH) bond, with the appearance of a medium band at the range $(3205-3215) \text{ cm}^{-1}$ belonging to the $(\text{N}-\text{H})$ group. The absorption bands appeared at the range $(3033-3062) \text{ cm}^{-1}$ due to the stretching of the aromatic $(\text{C}-\text{H})$ bond, as well as the appearance of absorption bands at the range $(2923-2929) \text{ cm}^{-1}$

(2813-2898) cm^{-1} due to the stretching of the Aliphatic (C-H) bond. Two bands emerged at the range (1604-1623) cm^{-1} and (1542-1591) cm^{-1} due to the vibration of the aromatic (C = C) bond, and the presence of medium-intensity bands belonging to the group (C-O-C) was observed at the range (1244- 1249) cm^{-1} , and the same middle band at the range (1141-1168) cm^{-1} belongs to the (C-N) group appeared. Other bands at the range (1054-1089) cm^{-1} appeared and attributed to the stretching of the (N-N) bond, and these bands were an approach to what is found in the literature (Sorates, 1980), and as in Table (3), which shows the results of infrared absorption (cm^{-1}), for the two compounds [G10, G8] and each (10) (11) as a model for the group.

Table (3) results of infrared absorption (cm^{-1}) for the derivatives of 3, 2-dihydroquinoxaline 4-en [G13-G8].

Comp. No.	Ar	IR (KBr) cm^{-1}							
		ν (C=O) Amide Lactam	ν (C-O-C)	ν (C-H) Arom., Aliph.	ν (C=C)	ν (N-H)	ν (C-N)	ν (N-N)	Others
G ₈		1668 1693	1245	3037 2927 2896	1604 1569	3352 3215	1141	1089	ν (-C=C) 1654 ν (HC=C) 3011
G ₉		1676 1695	1245	3033 2925 2898	1623 1564	3359 3211	1168	1087	ν (C-Cl) 935
G ₁₀		1676 1693	1249	3033 2923 2813	1612 1560	3352 3217	1141	1054	ν (C-O-C) 1024
G ₁₁		1662 1685	1245	3037 2927 2898	1606 1591	3386 3205	1141	1089	C-S ν 837
G ₁₂		1658 1687	1245	3062 2927 2896	1614 1591	3340 3205	1147	1065	ν (OH) 3531
G ₁₃		1668 1693	1244	3041 2929 2898	1604 1542	3299 3209	1141	1089	ν (OH) 3510

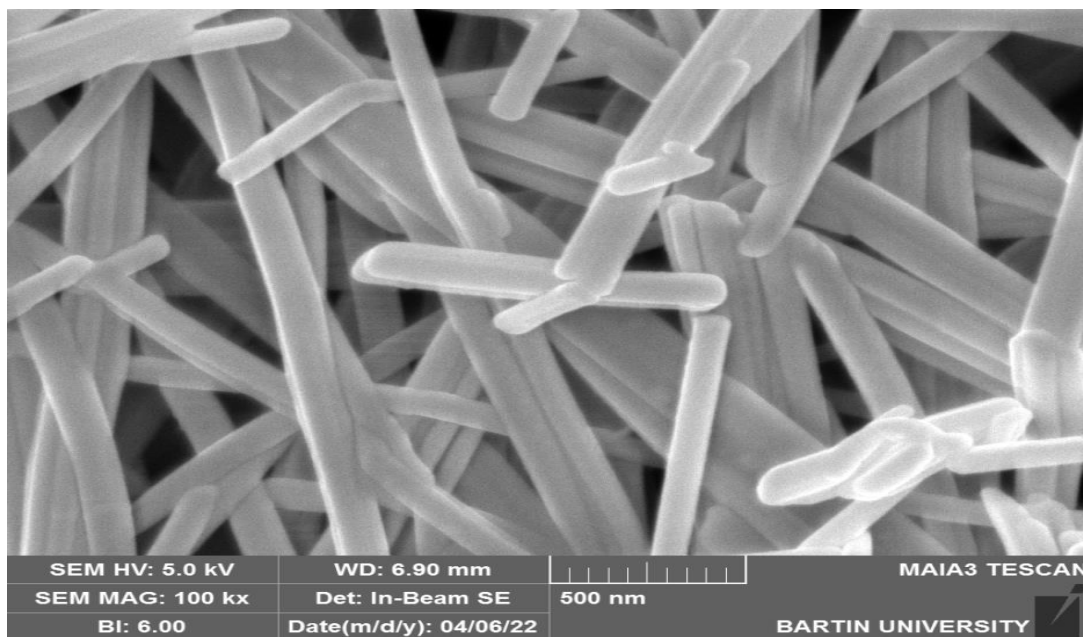
Effect of laser rays on some prepared compounds

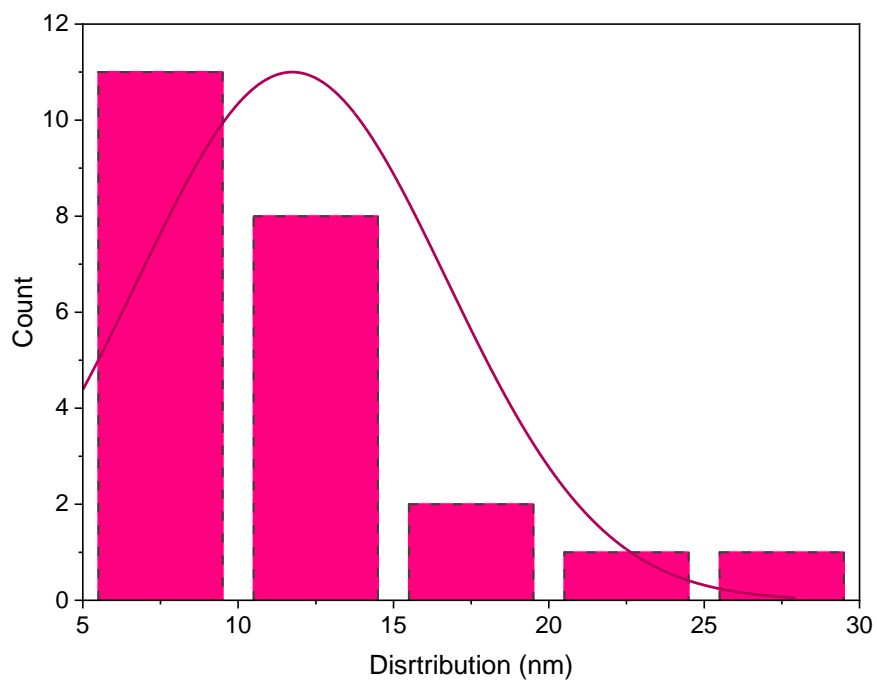
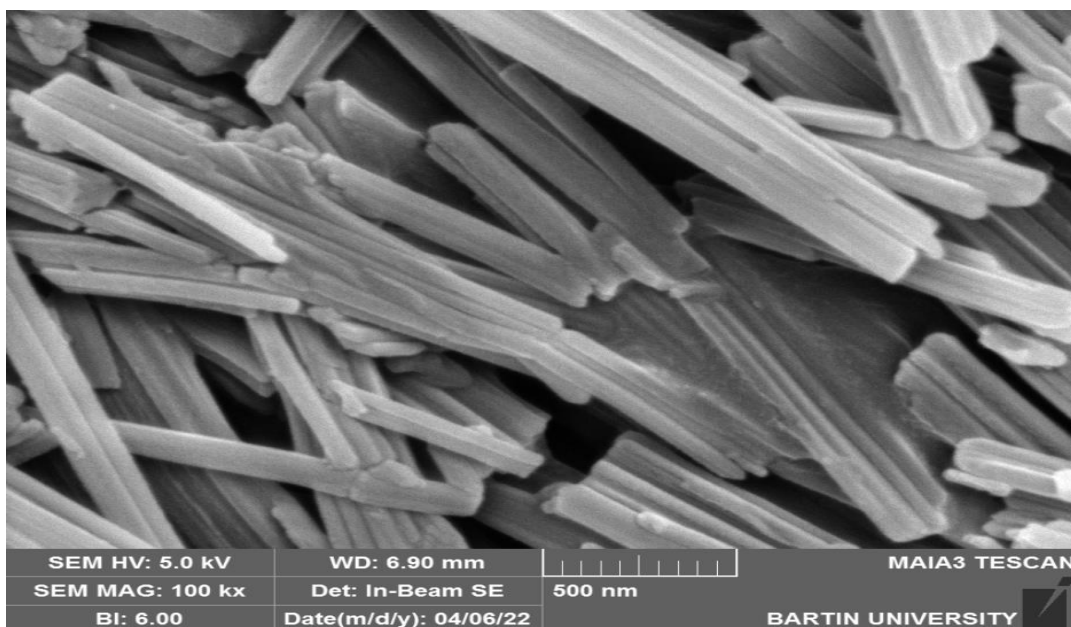
It was noted that the samples were not affected by laser beams in terms of identifying the degree of melting point and color, meaning that the compounds are stable and did not decompose (A. H. Dalaf & Jumaa, 2020) as in the following table:

Table (4): Effect of laser rays on some prepared compounds
SME nanoscale measurements

Comp. No.	15 S		30S	
	M.P. °C	Color	M.P. °C	Color
G ₈	245-247	Pall brown	245-247	Pall brown
G ₉	235-237	Dark yellow	235-237	Dark yellow
G ₁₀	242-244	Yellow	242-244	Yellow
G ₁₁	238-240	Pall yellow	238-240	Pall yellow
G ₁₂	238-240	Brown	238-240	Brown
G ₁₃	202-204	Dark Brown	202-204	Dark Brown

The measurement shown in Figures 1 and 2 showed regular geometric structures, which were in the form of fibres. The measurement proved that the diameters of these fibers were within the range 5-30 nm. Yet, the distribution of nanosizes in Figure 3 shows that the most fibers were within the range 5-15 nm.





Biological activity of some prepared compounds(Ronald, 2010):

The biological activity of some of the prepared compounds was evaluated, as the heterocyclic compounds had varying biological activity against gram-positive and gram-negative bacteria.

The effect of the prepared compounds in this research was evaluated on four types of bacteria, namely:

1. *Escherichia coli*
2. *Klebsiella pneumonia*
3. *Staphylococcus aureus*
4. *Staphylococcus epidermidis*

Table (5): Antibacterial activity of some prepared tetrazol compounds on the growth of a number of positive and negative bacteria (the diameter of the inhibition circle is measured in mm)

Comp. No.	Conc. mg/ml	<i>E. Coil</i>	<i>K. Pneumonia</i>	<i>S. Aureus</i>	<i>S. Epidermidis</i>	Inhibition Zone(mm)
G ₈	25	-	-	-	-	0
	50	+	++	+	+	1-4
	100	++	++	++	++	2-4
G ₉	25	-	-	-	-	0
	50	+	+	+	+	1-2
	100	++	++	++	++	2-4
G ₁₀	25	-	-	-	++	0
	50	+	+	++	++	1-4
	100	+++	++	++	+++	2-4
G ₁₁	25	-	-	-	-	0
	50	+	++	++	++	1-4
	100	++	++	++	+++	2-5
G ₁₂	25	-	-	+	+	1-2
	50	+	+	++	+	1-4
	100	+++	++	++	++	3-4
G ₁₃	25	+	+	+	+	1-2
	50	++	+	++	++	1-4
	100	+++	+++	+++	+++	4-5

= (-) No inhibition = (++)

(+) inhibition 1 – 2 mm = (+++)

2 – 4 mm inhibition

4 – 5 mm inhibition

Computational Chemistry(A)

To accomplish a specific research requires several factors, including: the nature of the molecule and the type of data to be studied, the availability of some practical data may be required by some methods. Also, practical capabilities and computers existed with high specifications so that the work can be completed in the least possible time, bypassing some limitations, including the size of the molecule, the number of its atoms, etc.

Table No. (6) Computational chemistry values for some prepared tetrazol compounds

Code	Property (Kcal)								Dipole moment (Debye)	Energy KJ
	E _{HOMO}	E _{LUMO}	E _{HOMO-LUMO}	I	A	μ	H	Ω		
G ₈	- 1.846239 02	- 3.4653 6878	1.61912 976	1.846 23902	3.465 36878	2.655 8039	- 0.809 56488	- 0.2652 92507	0.72 7584	- 2.8944 3682
G ₉	- 2.084698 55	- 3.5677 2935	1.48303 08	2.084 69855	3.567 72935	2.826 21395	- 0.741 5154	- 0.2038 593	1.40 2794	- 2.0540 0816
G ₁₀	- 7.539069 68	- 3.4344 4193	- 4.10462 775	7.539 06968	3.434 44193	5.486 75580 5	2.052 31387 5	4.3221 65059	4.65 7243	- 6.2481 7313
G ₁₁	- 1.817082 4	- 3.1242 3629	1.30715 389	1.817 0824	3.124 23629	2.470 65934 5	0.653 57694 5	- 0.1395 91886	1.57 5346	- 1.2637 1661
G ₁₂	- 8.257572 18	- 3.4430 8479	- 4.81448 739	8.257 57218	3.443 08479	5.850 32848 5	2.407 24369 5	6.9747 74611	3.37 4229	- 7.0789 2315
G ₁₃	- 1.822288 94	- 3.3838 3437	1.56154 543	1.822 28894	3.383 83437	2.603 06165 5	0.780 77271 5	- 0.2379 81879	2.38 2041	- 6.7096 9607

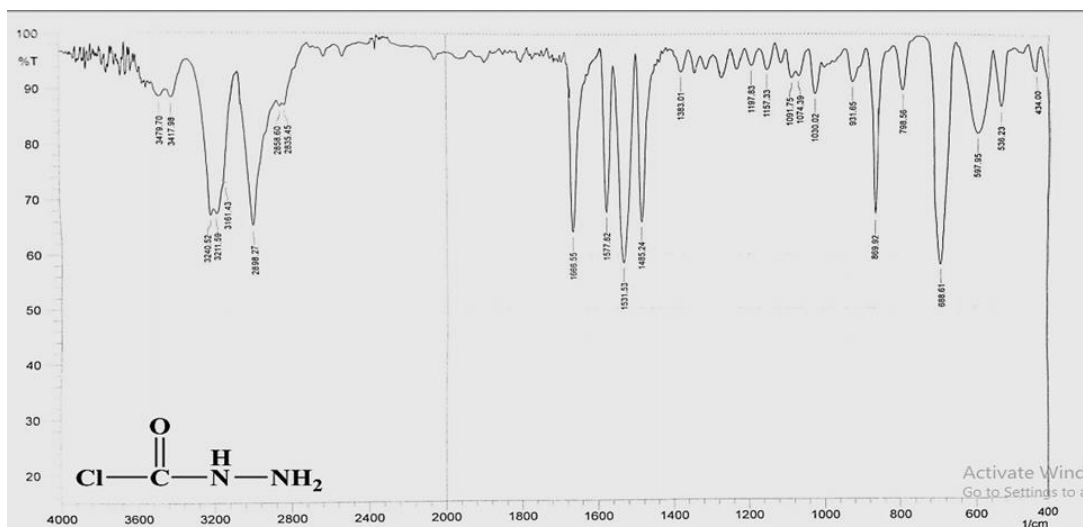
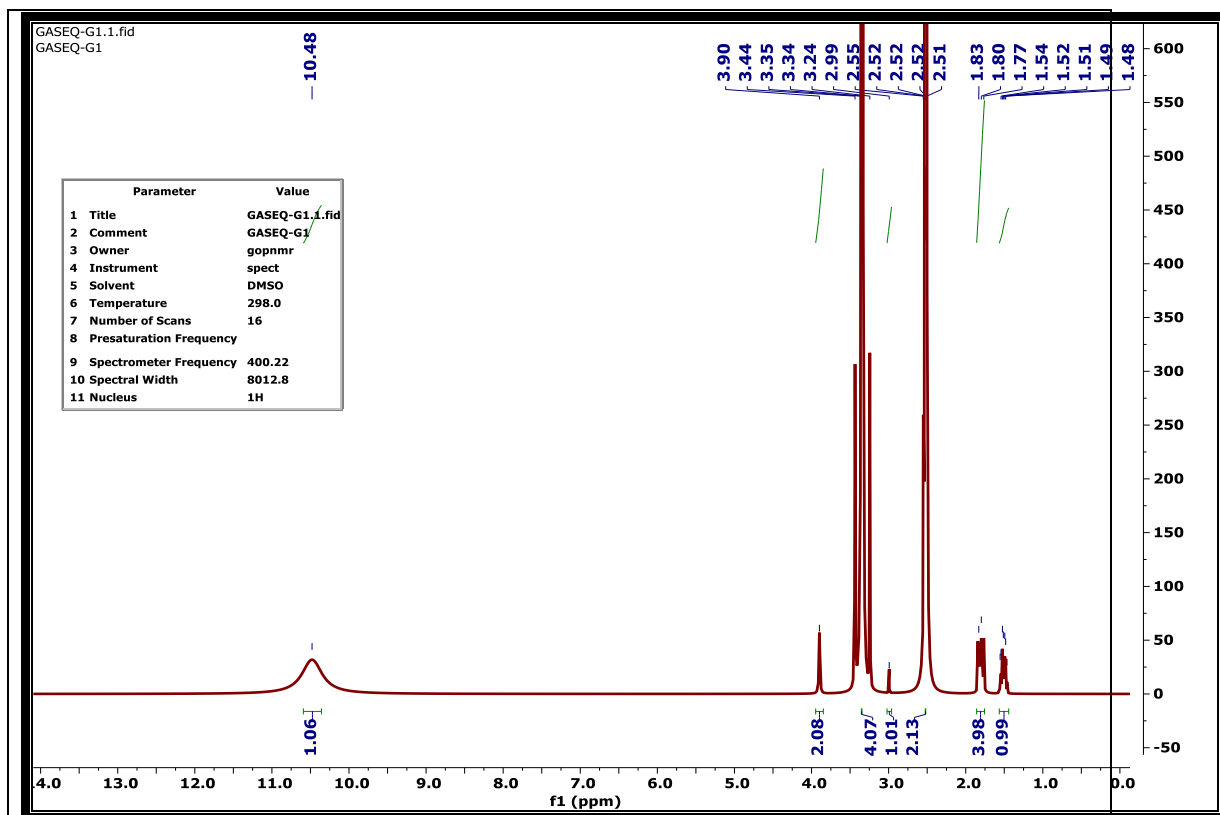
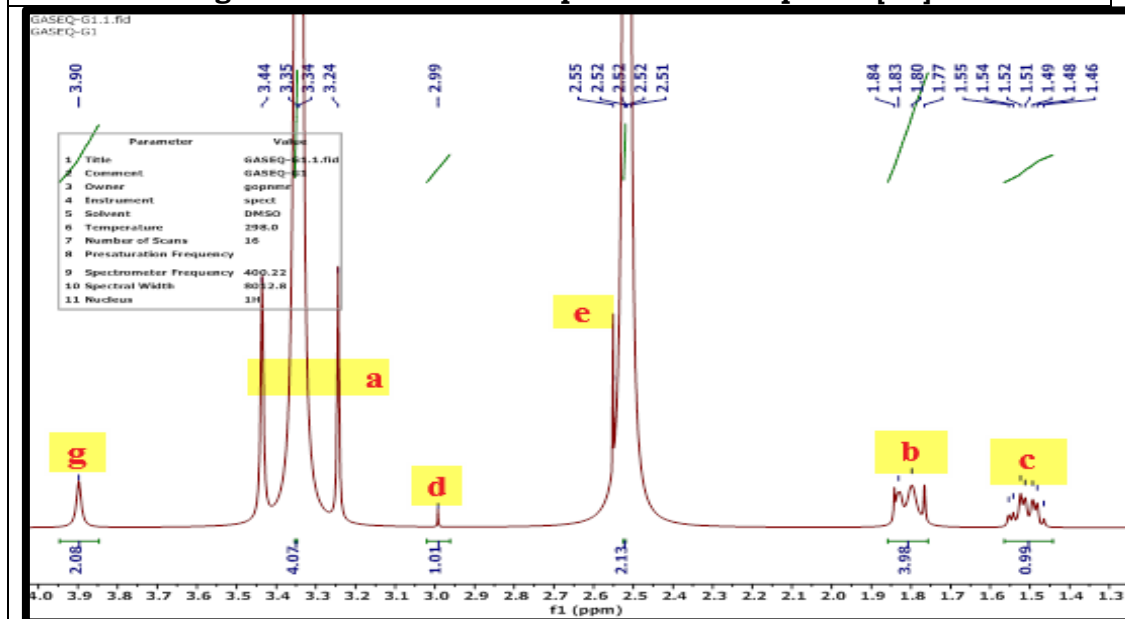


Figure 3: Infrared spectrum of compound [G1].

Figure 4: Proton ¹H-NMR spectrum of compound [G1].

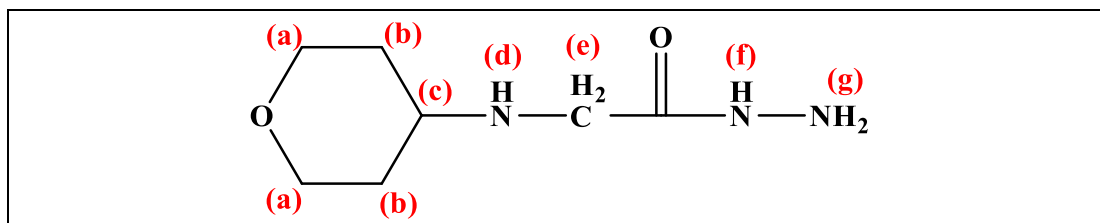


Figure 4: NMR spectrum of the 13C proton for compound [G1].

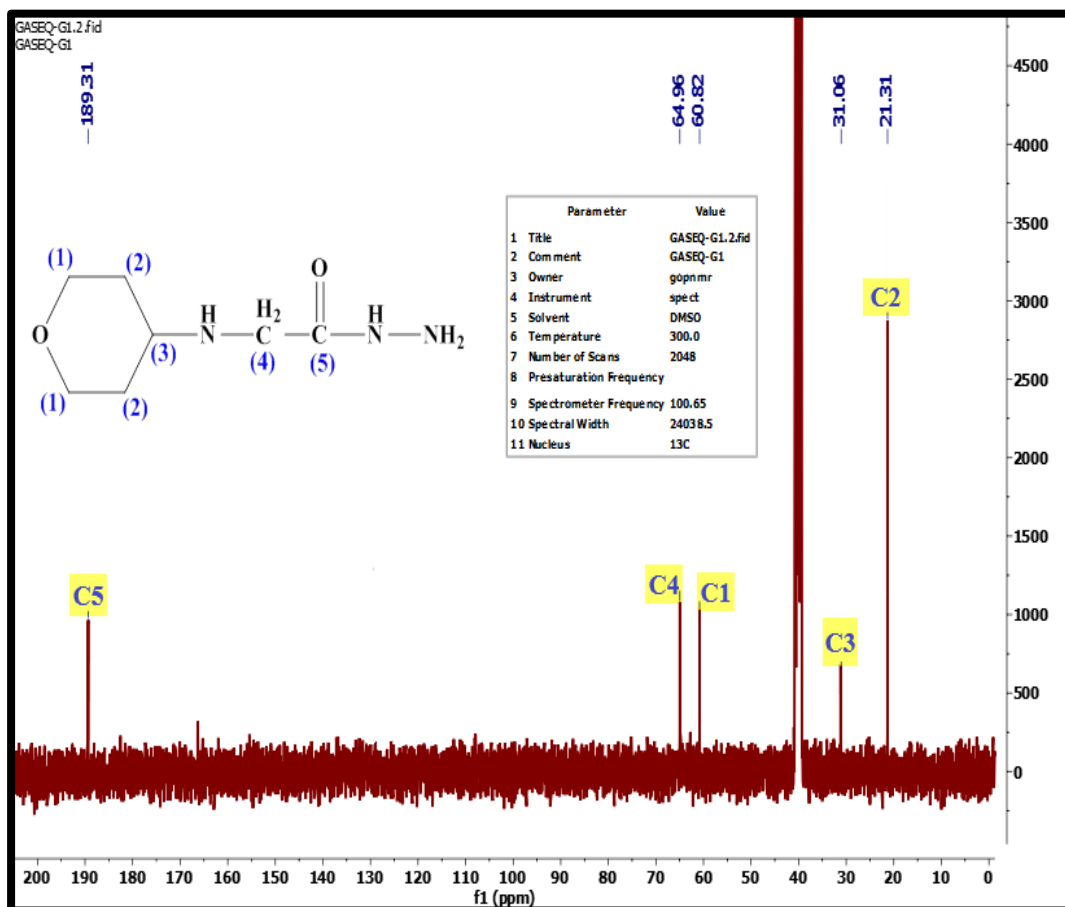


Figure 5: The proton NMR spectrum of the compound [G1].

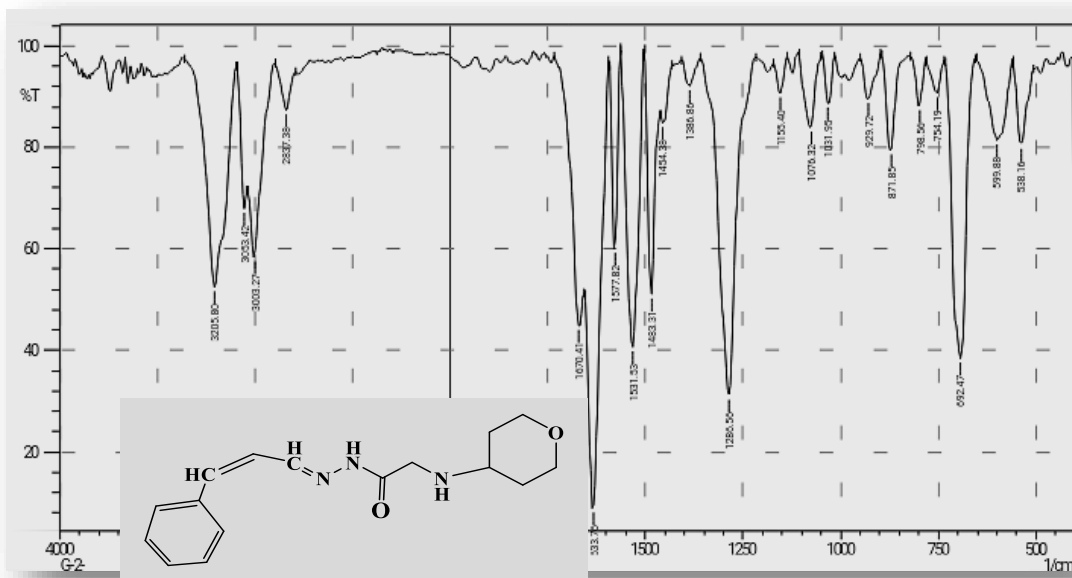


Figure 6: Infrared spectrum of the compound [G2]

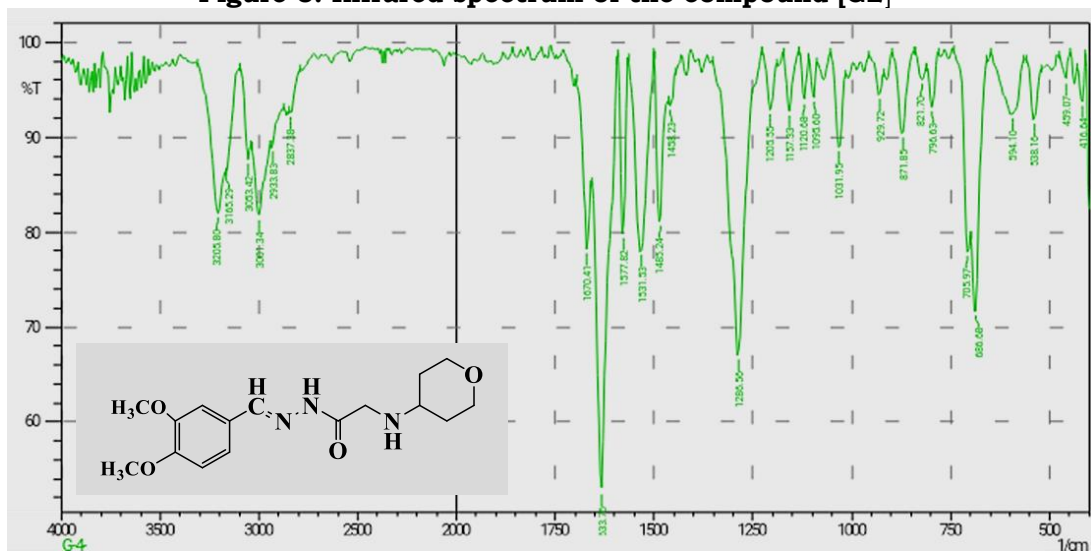
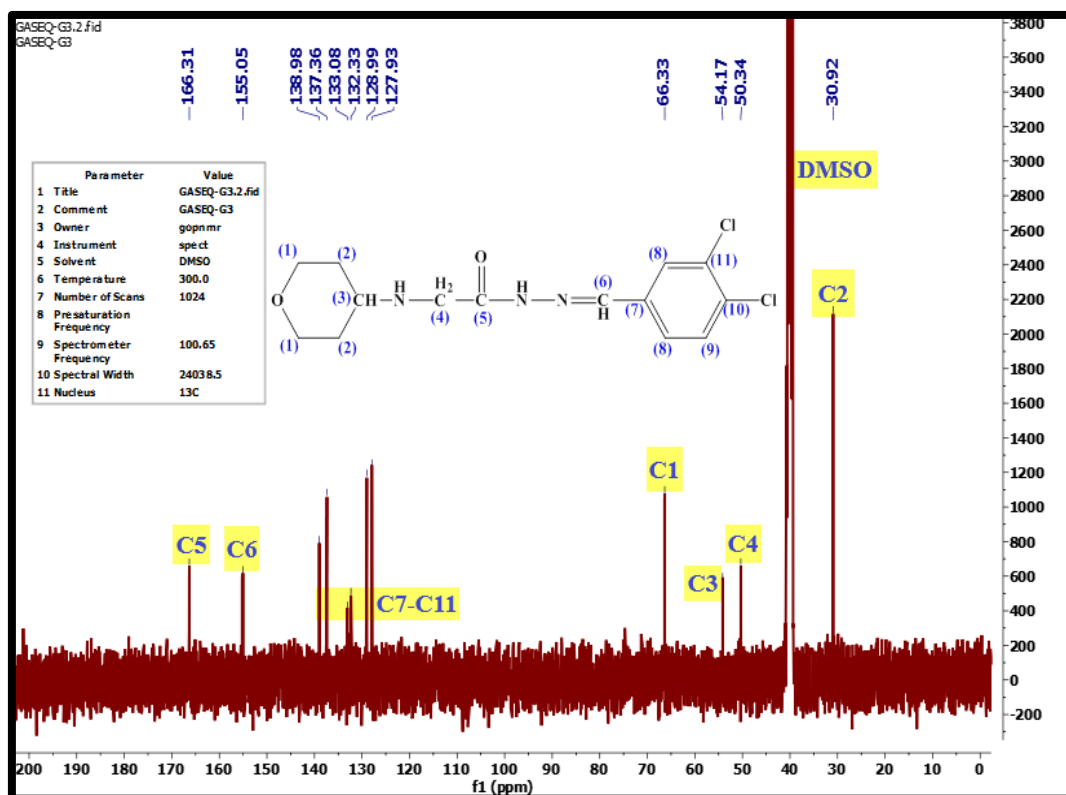


Figure 7: Infrared spectrum of the compound [G4]



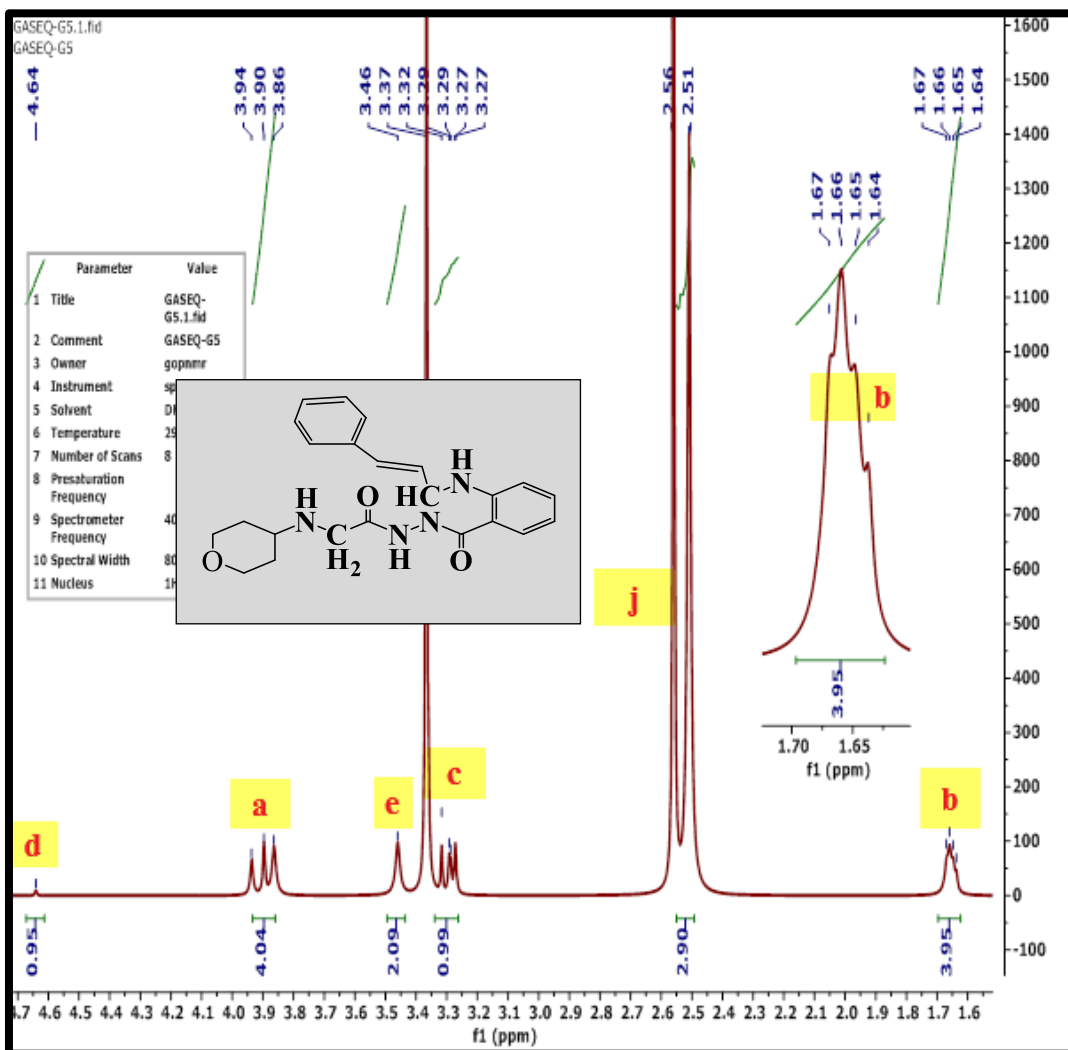


Figure 9: The proton NMR spectrum of the compound [G5].

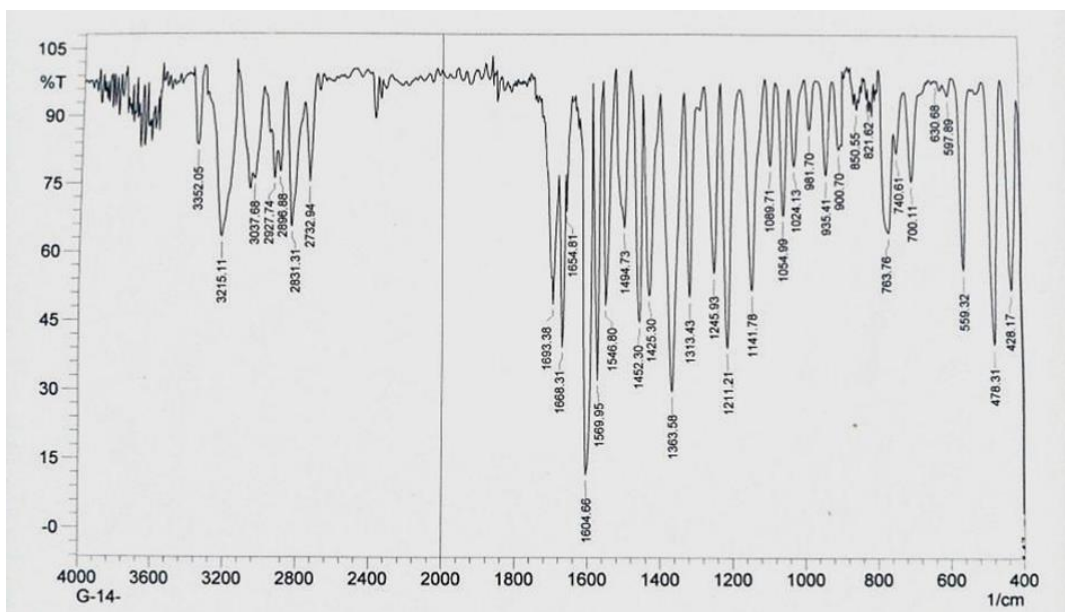


Figure 10: Infrared spectrum of the compound [G8].

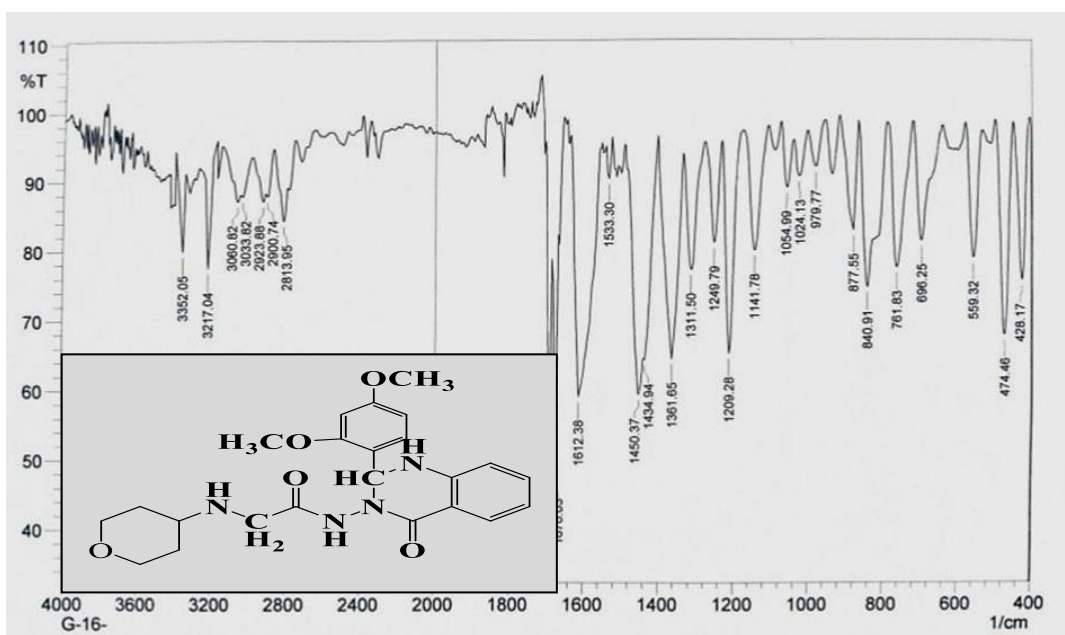


Figure 11: Infrared spectrum of compound [G10]

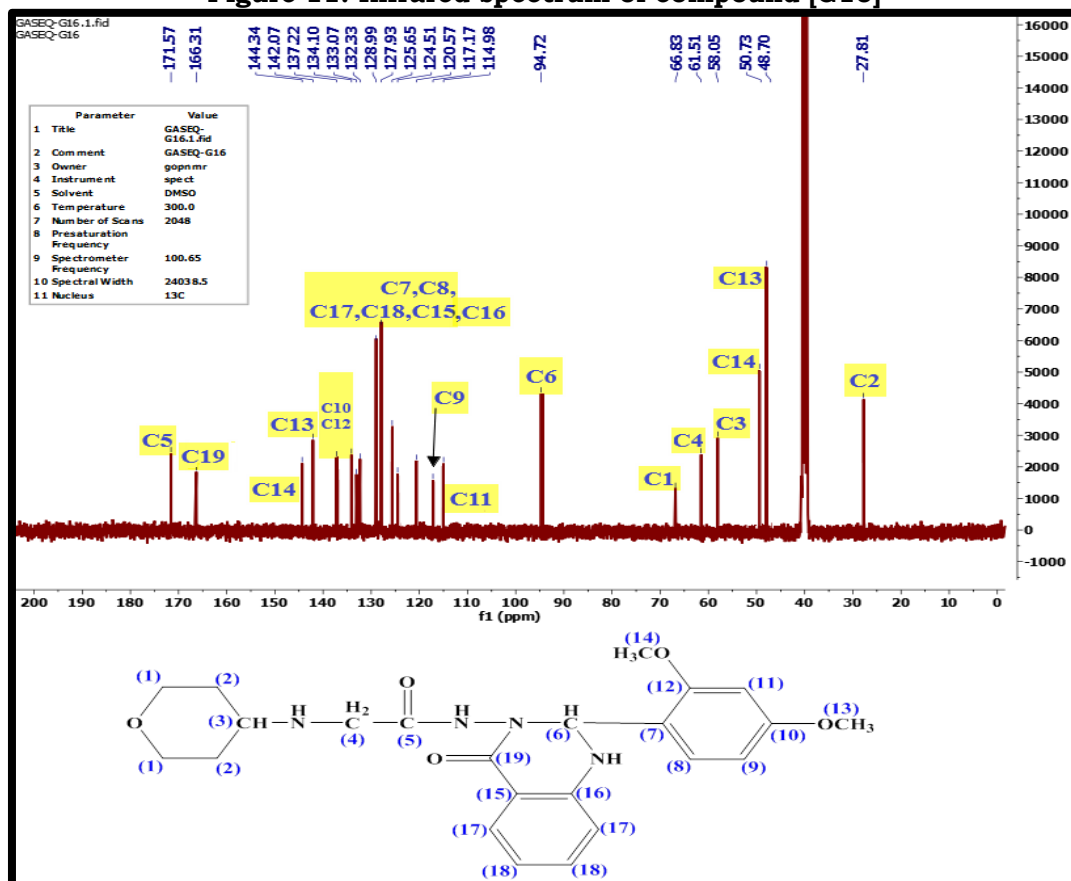
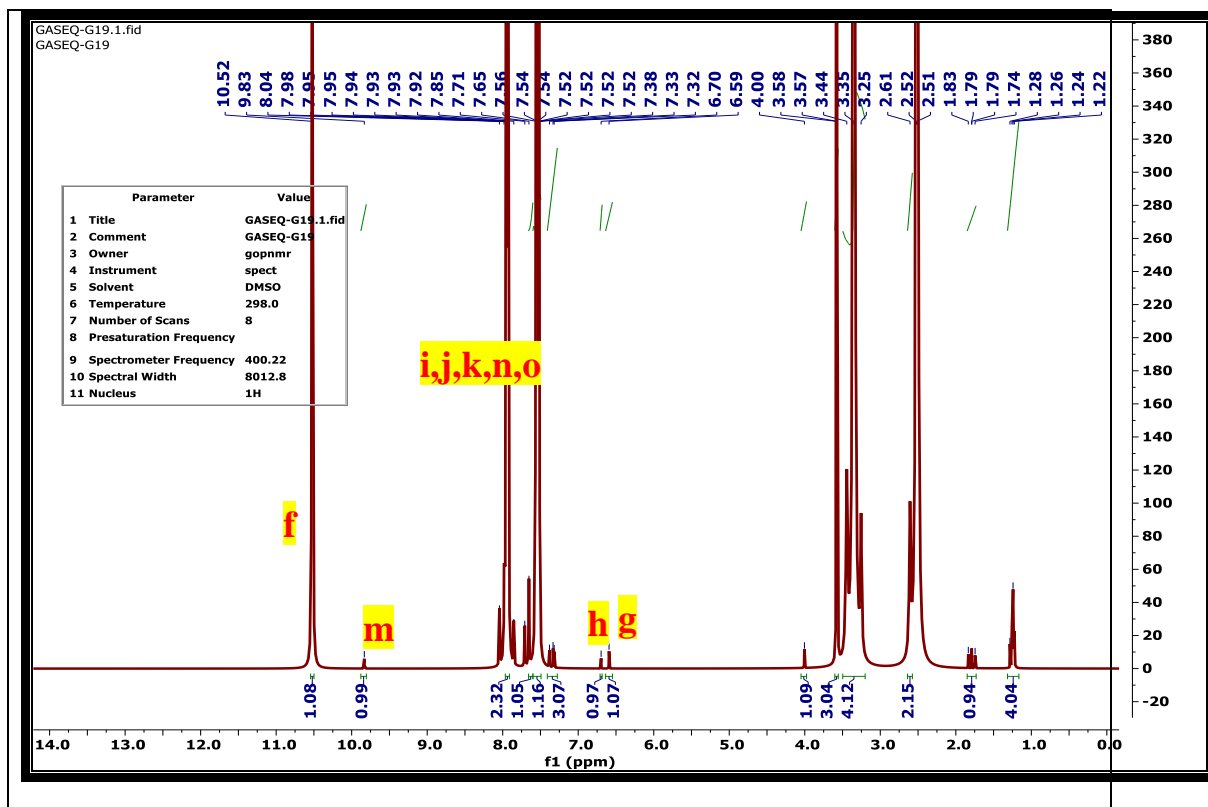


Figure 12: Carbon NMR spectrum of the compound [G8].



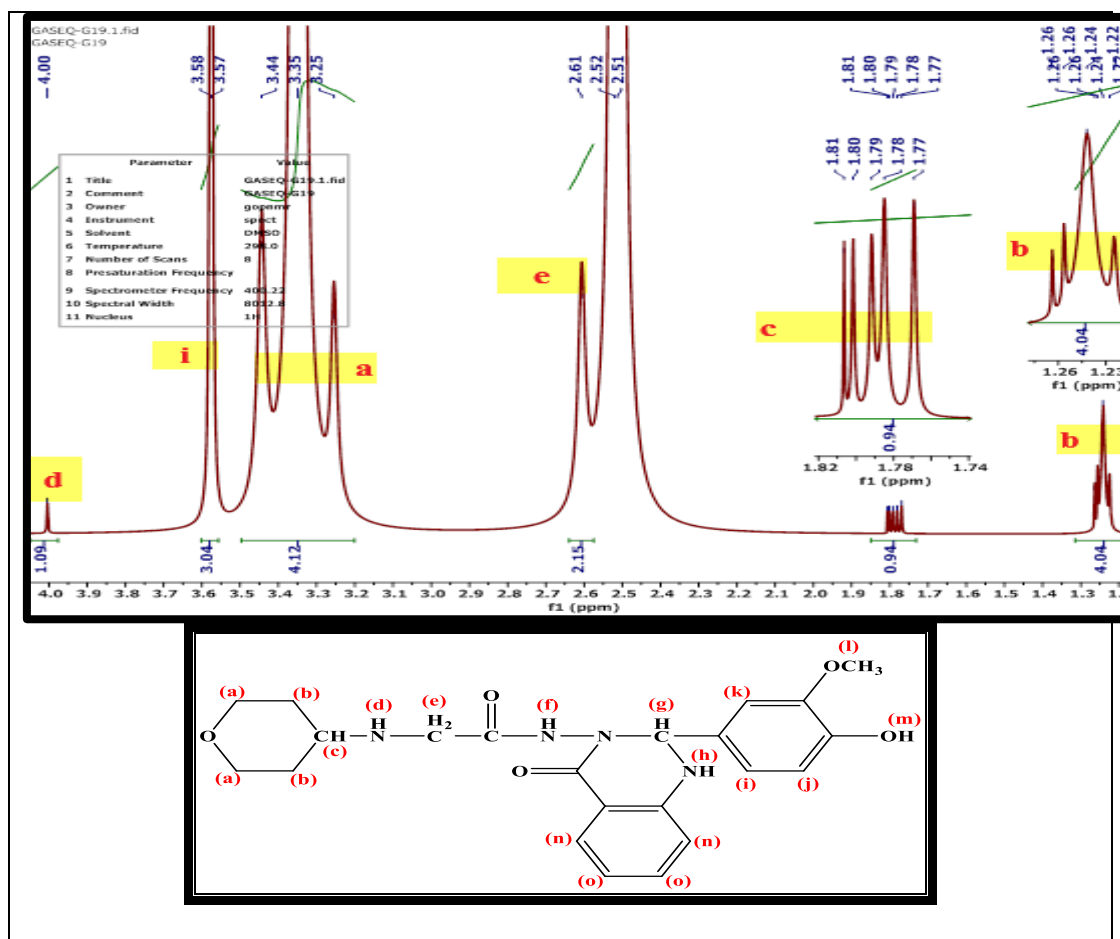


Figure 13: The proton NMR spectrum of the compound [G12]

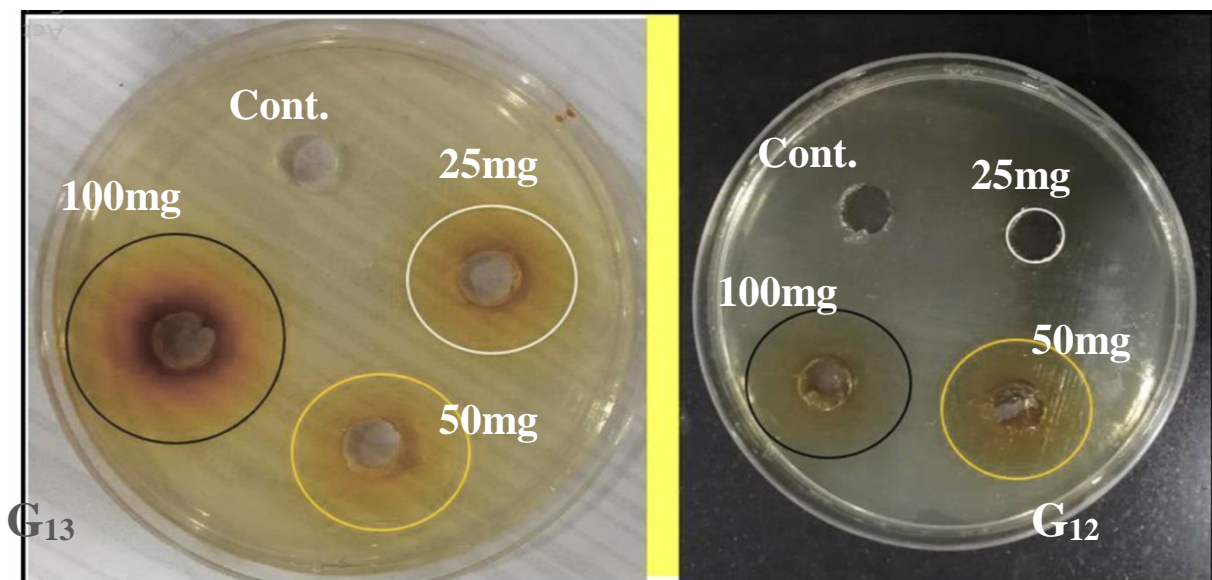
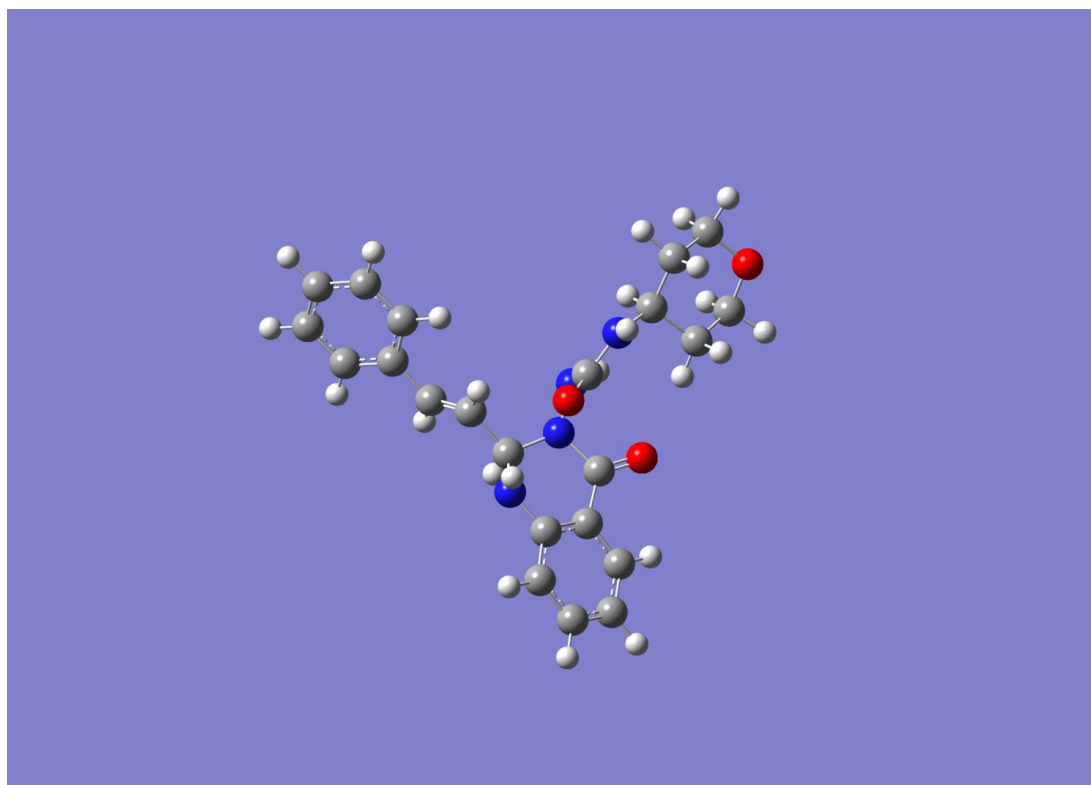
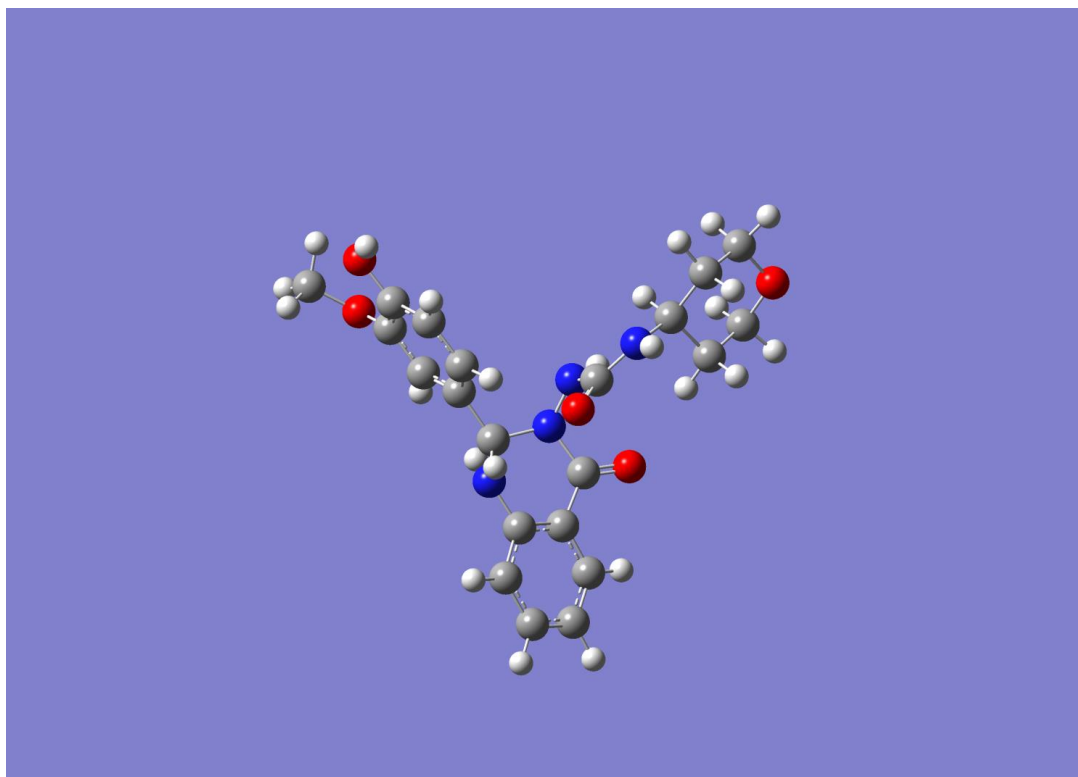
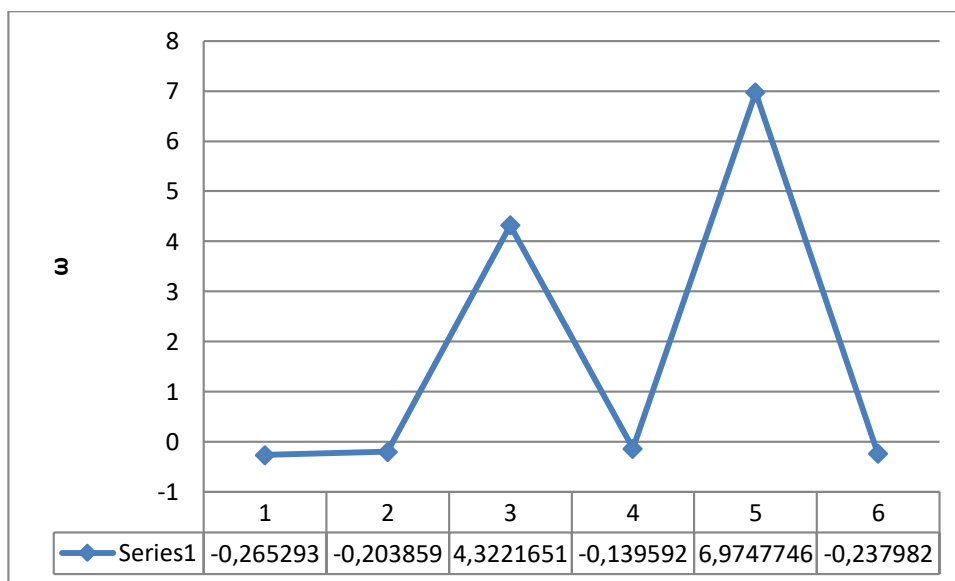


Figure (14): Inhibitory activity of the two compounds [G13-G12] against *Escherichia coli*



compound G₈

Compound G₁₃

Scheme (4) shows the values of the spherical electrophilic index of the prepared compounds] G₁₃-G₈[

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