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Original Reserach Article

Synthesis, Characterization, Biological Activity, Laser Effect and Molecular Docking of Tri-Imidazole-4-One Derivatives

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Abstract: This study focuses on the synthesis of Imidazole-4-one derivatives (F11–F15) through the reaction of three equivalents of the amino acid alanine with one equivalent of Schiff bases. The structural confirmation of the synthesized compounds was carried out using various physical and spectroscopic techniques, including FT-IR, ^{1}H, ^{13}C-NMR, and elemental analysis. Additionally, melting point measurements and purity assessments were performed, while the reaction progress was monitored using Thin-Layer Chromatography (TLC). The laser activity of the synthesized compounds was evaluated using a helium-neon laser in the visible spectrum, with exposure durations of 15, 30, 45, and 60 seconds, and the resulting physical changes were analyzed. Furthermore, the antibacterial activity of the prepared compounds was tested against two bacterial isolates: Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive). Standard antibiotics—amoxicillin, ampicillin, and ciprofloxacin—served as reference controls. Moreover, molecular docking studies were conducted on selected compounds (F12 and F13) to assess their interaction with E. coli using the Molecular Operating Environment (MOE) software (2009).

Keywords: Imidazole-4-one, Schiff bases, Laser activity, Biological activity, Molecular docking.

1. INTRODUCTION

Imidazole compounds are among the important classes in organic chemistry, as they are characterized by the presence of a heterogeneous five-membered ring containing two nitrogen atoms in non-adjacent positions [1]. These compounds are the focus of many scientific research due to their diverse chemical and biological properties that give them wide applications in several fields such as medicine, industrial chemistry, and agriculture [2]. Structurally, imidazole consists of a heterogeneous five-membered ring, where the two nitrogen atoms are in positions 1 and 3 relative to each other [3], and this arrangement gives imidazole unique properties compared to other heterogeneous rings [4]. The strong hydrogen bond is one of the most important properties of imidazole compounds [5], as it enables these compounds to bind effectively with proteins and nucleic acids, making them essential in the design of drugs and pharmaceutical preparations [6]. Imidazole compounds have been prepared by several methods, including the addition of amino acids to Schiff bases [7]. One of the most famous applications of imidazole compounds is their use in the manufacture of medical drugs [8]. Many antifungal drugs are based on the imidazole nucleus, such as miconazole and clotrimazole [9], which are commonly used to treat fungal infections [10]. In addition, imidazole compounds are used in the development of antibacterial and antiparasitic drugs [11] and have shown effectiveness in treating diseases such as malaria and complicated bacterial infections [12]. Imidazole compounds are also part of the structures of many pharmaceutical compounds that act as inhibitors of certain enzymes, which opens new horizons in the treatment of chronic diseases such as cancer and hypertension [13]. In addition to medical applications, imidazole compounds are widely used in the chemical industry, especially in the field of chemical manufacturing [14]. Imidazole is used as a catalyst in polymerization reactions and the manufacture of resins [15], as well as in the manufacture of paints and dyes [16]. Imidazole compounds exhibit high chemical and thermal stability, making them suitable for use in harsh

industrial environments [16]. The presence of two nitrogen atoms in the structure gives them a high ability to react as a strong base or as a reducing agent in many chemical reactions [17]. In addition, imidazole compounds are used in the development of new materials with distinctive properties, such as electrically conductive polymeric materials [18], which are used in organic electronics and advanced materials [19]. Recent studies have helped to reveal new uses for these compounds in the design of nanomaterials and biochemical sensors [20], which contributes to future developments in nanotechnology [21]. The significant role of imidazole compounds in analytical chemistry cannot be overlooked, as they are used as complexing agents for metal analysis [22], and as reagents in spectroscopic analysis, in addition to their role in improving the accuracy and effectiveness of chemical analyses in laboratories [23]. Imidazole is also used in chromatographic separation techniques and amino acid analysis [24], which enhances its vital role in modern analytical chemistry [25]. Imidazole's are multifaceted compounds that are essential components in many scientific and industrial fields [26]. The unique properties of these compounds, in terms of chemical stability and high reactivity [27], give them a distinguished position among other organic compounds [28]. Ongoing research in this field remains promising to expand the range of potential applications of imidazole compounds, enhancing their importance in the scientific and industrial future [29].

2. Experimental:

2.1 Materials and Instruments:

All chemicals were sourced from Fluka, Aldrich, and BDH. Melting points were determined using an Electrothermal 9300 apparatus. FT-IR (400–4000 cm^{-1}) a Shimadzu 8400S. NMR Bruker 400 MHz instrument. Autoclave from Raypa steam sterilizer. Heraeus D-63450 incubator. Helium-Neon laser with a 1 mW power and an 808 nm wavelength.

2.2. Preparation of imidazole-4-one derivatives (F11-F15)

Mix (0.005 mol) of the Schiff bases dissolved in (30 ml) of ethanol with (0.015 mol, 1.336 g) of the amino acid alanine dissolved in (25 ml) of the same solvent, and the mixture was raised for (9-12) hours, and the completion of the reaction was confirmed using (TLC), then filtered and recrystallized with dioxane [30, 31], the physical properties as shown in Table (1).

2.3. Measuring the laser effectiveness of prepared compounds

The laser effectiveness of prepared compounds (F11-F15) was measured using a visible helium-neon laser. Compounds were irradiated for various time intervals (15, 30, 45, 60 seconds), and physical properties and changes in the prepared compounds were observed [32, 33].

2.4. Biological activity study

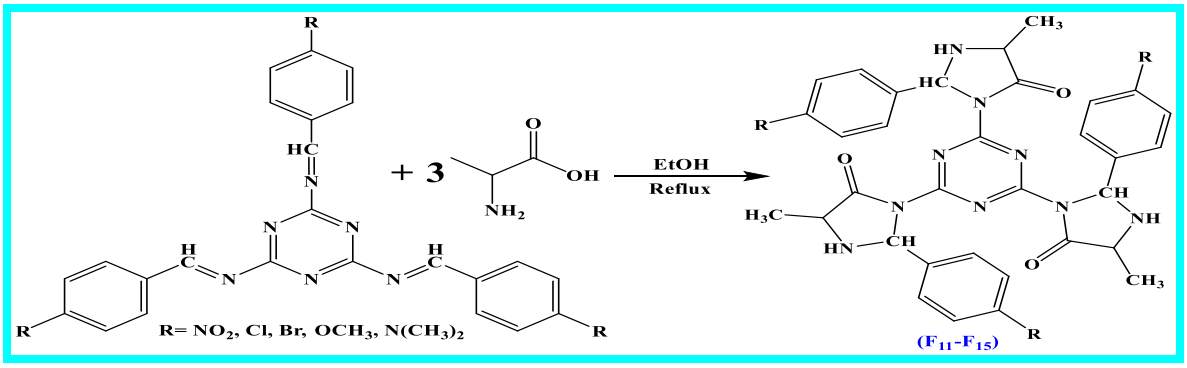
This study utilized two pathogenic bacterial strains: the Gram-positive Staphylococcus aureus and the Gram-negative Escherichia coli [34]. Solutions of (F11–F15) were prepared at concentrations of 25, 50, and 75 mg/mL using (DMSO) as the solvent [35], and the diffusion-drilling method was used on Mueller-Hinton agar [36]. After incubation, the results were analyzed the following day to determine the sensitivity of the bacterial isolates to the tested compounds [37].

2.5. Molecular docking study of some prepared compounds

The molecular docking study of the prepared compounds (F12, F13) was conducted against Escherichia coli using the MOE program (2009). To ensure the most stable spatial conformation, energy minimization was performed to achieve the lowest steric hindrance energy [38]. The 3D structure of Escherichia coli was retrieved from the Protein Data Bank, and the docking simulations were carried out on a high-performance computer [39]. Due to the computational intensity of these simulations [40], an advanced system with fast, multi-core processors was used to efficiently process large molecular structures and complex atomic interactions [41].

3. RESULTS AND DISCUSSION

In this study, Imidazole-4-one derivatives (F11-F15) were synthesized by reacting one mole of Schiff bases with three moles of amino acid alanine, as depicted in Scheme 1.



Scheme 1: Route of prepared compounds (F11-F15)

3.1. Characterization of Schiff bases derivatives (F1-F5) by FT-IR, ^{1}H-NMR and ^{13}C-NMR

The characterization of imidazole-4-one derivatives (F1-F5) was conducted using (FT-IR), (^{1}H-NMR), and (^{13}C-NMR) to confirm the structural integrity of the synthesized compounds.

The FT-IR spectrum provided valuable insights into the functional groups present in the derivatives. Notably, the disappearance of the azomethine (C=N) band, typically observed in Schiff bases, indicates a successful structural transformation. Instead, a new absorption band appeared within the range of 3194-3217 cm^{-1}, corresponding to the stretching vibration of the NH bond, confirming the presence of an imidazole ring. Additionally, absorption bands observed in the range 3053-3093 cm^{-1} were attributed to the stretching of aromatic C-H bonds [42], while two bands appearing in the ranges 2943-2997 cm^{-1} and 2822-2891 cm^{-1} corresponded to the stretching vibrations of aliphatic C-H bonds, reinforcing the presence of both aromatic and aliphatic moieties. Furthermore, a strong absorption band was detected between 1690-1699 cm^{-1}, indicating the presence of a carbonyl (C=O) group. This confirms the retention of the imidazole-4-one core structure. Another absorption band in the range 1624-1629 cm^{-1} was assigned to the stretching of the (C=N) bond within the azine ring, which plays a crucial role in the stabilization of the compound. Additionally, aromatic (C=C) stretching vibrations were observed at 1581-1595 cm^{-1} and 1480-1494 cm^{-1} [43], indicating the presence of conjugated aromatic systems. The absorption band at 1236-1269 cm^{-1} was attributed to the stretching vibration of the C-N bond [44], further supporting the successful synthesis of the imidazole-4-one derivatives. These findings are summarized in Table (2) and illustrated in Figures (1) and (2).

The ^{1}H-NMR spectrum of compound (F14) was recorded using DMSO-d6 as a solvent. A multiplet signal observed in the range 6.69-7.85 ppm was attributed to the protons of the aromatic rings, confirming the aromatic nature of the synthesized compound. A distinct single signal at 6.44 ppm was assigned to the proton of the (CH) group in the imidazole ring, providing further evidence of the core imidazole structure [45]. Additionally, a single signal at 6.37 ppm corresponded to the proton of the (NH) group in the imidazole ring, reinforcing the observations made in the FT-IR spectrum. A single signal at 3.47 ppm was attributed to the presence of water (H_2O) within the sample, while another single signal at 3.35 ppm was assigned to the proton of the methoxy (OCH_3) group, indicating the presence of alkoxy substituents. Interestingly, a quadruple signal at 3.21, 3.19, 3.18, and 3.15 ppm was observed, which was attributed to the protonation of the (CH) groups within the imidazole ring [46]. A signal at 2.47 and 2.48 ppm corresponded to residual protons of the solvent (DMSO-d6). Finally, a doublet signal at 1.00 and 0.98 ppm was attributed to the protonation of methyl (CH_3) groups, indicating the presence of alkyl substituents within the compound. These findings are illustrated in Figure (3).

The ^{13}C-NMR spectrum of compound (F14) was also recorded using DMSO-d6 as a solvent. A prominent signal at 170.22 ppm was attributed to the carbonyl (C=O) carbon, confirming the presence of the imidazole-4-one structure. Another significant signal at 166.19 ppm corresponded to the carbon of the (C=N) bond in the azine ring, further verifying the structural features observed in the FT-IR spectrum [47]. A multiplet signal appearing in the range 116.75-151.94 ppm was assigned to the carbons of the aromatic rings, indicating the retention of aromaticity in the synthesized derivatives. Additionally, two distinct signals at 114.98 ppm and 110.23 ppm were assigned to the carbon atoms of the (CH) groups within the imidazole rings, further corroborating the formation of the expected framework. A signal at 60.75 ppm was attributed to the carbon of the methoxy (OCH_3) groups, confirming the presence of alkoxy functionality [48]. Furthermore, a signal appearing between 39.07-40.74 ppm corresponded to the carbon of the solvent (DMSO-d6). Finally, a signal at 25.94 ppm was assigned to the carbon of the methyl (CH_3) groups, reinforcing the presence of alkyl substituents in the compound [49]. The observed results are summarized in Figure (4). The results obtained from FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopic analyses confirm the successful synthesis of the Schiff base derivatives (F1-F5). The disappearance of the azomethine (C=N) band in FT-IR, along with the appearance of new absorption bands corresponding to NH, C=O, and C=N in the imidazole and azine rings, supports the proposed structural transformation. The ^{1}H-NMR and ^{13}C-NMR spectra further validate the presence of aromatic, aliphatic, and functionalized groups within the synthesized compounds, reinforcing their structural integrity and chemical identity. These findings confirm the successful characterization of the derivatives, paving the way for further investigations into their potential applications.

3.2. Laser Activity Measurement Results for Compounds

During the first 15, 30, and 45 seconds, no changes were observed in any of the compounds' physical properties, indicating that short-duration laser exposure did not significantly affect the molecular structure. At 60 seconds, all compounds exhibited noticeable changes, including: A decrease in melting points, suggesting bond breakage or structural modifications [50]. Altered Rf values, indicating changes in molecular polarity or interactions with the stationary phase. Slight color changes, which could be due to the formation of new compounds or degradation products. These findings suggest that prolonged laser exposure induces chemical modifications, possibly through bond dissociation, rearrangement, or degradation of functional groups [51].

A. Compound F11 in 60s: Significant increase in Rf value (0.46 → 0.68) suggests increased compound mobility, possibly due to the formation of less polar degradation products. Melting point decreased (284-286°C → 267-269°C), indicating a structural breakdown or lower-molecular-weight fragments forming. Color remained orange, implying that the chromophoric structure may have remained mostly intact despite structural changes. Laser exposure at 60s likely caused partial degradation, leading to the formation of smaller or altered molecular fragments.

B. Compound F12 in 60s: Rf value decreased (0.58 → 0.41), suggesting the formation of more polar degradation products or a structural rearrangement. Melting point decreased (236-238°C → 215-217°C), indicating thermal decomposition or chemical transformation. Color darkened (Light Brown → Brown), likely due to oxidation or conjugation changes. Longer laser exposure may have increased molecular polarity, possibly due to hydrolysis, oxidation, or formation of new functional groups [52].

C. Compound F13 in 60s: Significant increase in Rf (0.49 → 0.73) suggests the formation of less polar fragments. Melting point dropped (255-257°C → 232-234°C), indicating potential molecular degradation. The color remained yellow, meaning no drastic chromophoric changes occurred. Laser exposure may have caused structural breakdown while preserving the compound's overall conjugated system [53].

D. Compound F14 in 60s: Rf value increased (0.60 → 0.75), indicating a shift toward lower polarity. Melting point reduced (268-270°C → 247-249°C), signifying molecular fragmentation. Color deepened from Light Orange to Orange, possibly due to changes in electronic structure. Laser exposure altered molecular weight or polarity, leading to minor chromophoric changes.

E. Compound F15 in 60s: Rf value decreased (0.55 → 0.46), suggesting the formation of more polar degradation products. Melting point decreased (202-204°C → 180-182°C), indicating structural decomposition. Color lightened from Dark Orange to Orange, implying subtle changes in conjugation. Laser exposure may have caused oxidation or the formation of oxygen-containing functional groups, increasing polarity [54], as illustrated in Table (4).

Laser exposure caused a decrease in melting points, changes in Rf values, and slight color variations, indicating bond breakage, structural rearrangements, and possible formation of new compounds. These effects suggest oxidation, reduction, or thermal decomposition. Laser irradiation may serve as a tool for controlled chemical transformations, with further analysis needed to confirm specific molecular changes.

3.3. Analysis of the Antibacterial Activity of the Compounds (F11–F15)

F11 showed the highest activity against E. coli, with an inhibition zone of 10 mm at 75 mg/mL. This suggests that F11 has a strong antibacterial effect, possibly due to interactions between its functional groups and bacterial components. F12, F13, and F15 exhibited minimal activity, with inhibition zones not exceeding 2 mm, even at the highest concentration. F14 demonstrated weak antibacterial activity, with inhibition observed only at 75 mg/mL (4 mm). Standard antibiotics showed moderate activity, with inhibition zones ranging from 2 mm to 5 mm at the highest concentration. The blank disk exhibited no inhibition, confirming that the solvent (DMSO) did not contribute to bacterial inhibition [55]. The activity of F11 at 75 mg/mL (10 mm) was significantly higher than all tested antibiotics, suggesting that this compound could be a strong candidate for further antibacterial studies. The other compounds (F12–F15) were significantly less effective than Amoxicillin, Ampicillin, and Ciprofloxacin [56]. F11 again exhibited the strongest inhibition, reaching 10 mm at 75 mg/mL, like its effect on E. coli. F14 displayed moderate activity, showing an inhibition zone of 5 mm at 75 mg/mL, suggesting some effectiveness against S. aureus. F12, F13, and F15 showed weak activity, with inhibition zones not exceeding 2 mm at any concentration. The standard antibiotics performed well, with inhibition zones reaching up to 7 mm (Amoxicillin) at 75 mg/mL [57]. The blank disk showed no inhibition, confirming that bacterial inhibition was solely due to the test compounds. F11 at 75 mg/mL (10 mm) demonstrated greater inhibitory activity than Amoxicillin (7 mm), Ampicillin (6 mm), and Ciprofloxacin (5 mm), making it the most promising compound against S. aureus. F14 also displayed moderate antibacterial activity, potentially warranting further study. The antibacterial activity of the compounds was dose-dependent, with inhibition zones increasing as the concentration rose from 25 to 75 mg/mL [58]. The results suggest that F11 is the most potent compound against both E. coli and S. aureus, surpassing even the standard antibiotics at 75 mg/mL. Gram-positive bacteria (S. aureus) were generally more susceptible to the compounds than Gram-negative (E. coli). This aligns with expectations, as Gram-negative bacteria have an additional outer membrane that can restrict compound penetration. F12, F13, and F15 exhibited poor activity, indicating that their chemical structures may not be highly effective against these bacterial strains [59], as presented in Table (4) and Figures (5, 6).

3.4. Molecular docking study for some compounds

The values of the docking score and the root mean square deviation (RMSD) were calculated as shown in Table (5). Compound (F12) interacts with amino acid residues in the active site through two alkyl bonds linking LEU171 and ALA184 with the methyl group substitution on the ring [60], along with a Pi-Alkyl bond involving VAL172 and the aromatic ring's electron

pairs [61-64], as in Figure (7). Meanwhile, Compound (F13) engages with active site residues through four types of bonds: three hydrogen bonds connecting GLY20, GLY106, and ASN24 with the carbonyl oxygen of the five-membered ring [65-67]; two alkyl bonds linking ALA185 with the ring's bromine atom; two Pi-Alkyl bonds involving LEU178, PHE182, and the ring's bromine atom; and a halogen bond with ASN186 and the ring's bromine atom [68], as in Figure (8).

Table (1): Some physical properties of Schiff bases derivatives.

Comp.	R	Molecular Formula/ M.Wt g/mol	Color	Time (h)	M.P ^{0}C	R*f*	Yield %
F11	NO_2	$C_{33}H_{30}N_{12}O_9$ / 738.68	Orange	10	284-286	0.46	75
F12	Cl	$C_{33}H_{30}N_9O_3Cl_3$ / 707.01	Light brown	12	236-238	0.58	78
F13	Br	$C_{33}H_{30}N_9O_3Br_3$ / 840.38	Yellow	9	255-257	0.49	60
F14	OCH_3	$C_{36}H_{39}N_9O_6$ / 693.77	Light orange	9	268-270	0.60	74
F15	$N(CH_3)_2$	$C_{39}H_{48}N_{12}O_3$ / 732.89	Dark orange	12	202-204	0.55	76

Table (2): FT-IR absorption results for Schiff bases derivatives by KBr (cm-1).

Comp.	R	νN-H	νC-H Arom.	νC-H Aliph.	νC=O	νC=N	νC=C Arom.	νC-N	Others
F11	NO_2	3198	3067	2997, 2822	1690	1625	1589, 1494	1269	ν(NO_2) 1530, 1349
F12	Cl	3194	3053	2947, 2850	1697	1624	1581, 1483	1246	ν (C-Cl) 771
F13	Br	3200	3085	2978, 2891	1696	1629	1595, 1480	1236	ν (C-Br) 680
F14	OCH_3	3217	3093	2964, 2845	1693	1626	1587, 1489	1251	-------
F15	$N(CH_3)_2$	3198	3090	2943, 2887	1699	1624	1591, 1486	1260	-------

Table (3): Results of measuring the laser effectiveness of some prepared compounds

Comp.	15 S			30 S			45 S			60 S		
	Color	M.P ^{0}C	R*f*	Color	M.P ^{0}C	R*f*	Color	M.P ^{0}C	R*f*	Color	M.P ^{0}C	R*f*
F11	Orange	284-286	0.46	Orange	284-286	0.46	Orange	284-286	0.46	Orange	267-269	0.68
F12	Light brown	236-238	0.58	Light brown	236-238	0.58	Light brown	236-238	0.58	Brown	215-217	0.41
F13	Yellow	255-257	0.49	Yellow	255-257	0.49	Yellow	255-257	0.49	Yellow	232-334	0.73
F14	Light orange	268-270	0.60	Light orange	268-270	0.60	Light orange	268-270	0.60	Orange	247-249	0.75
F15	Dark orange	202-204	0.55	Dark orange	202-204	0.55	Dark orange	202-204	0.55	Orange	180-182	0.46

Table (4): Biological effectiveness of compounds and control treatments (inhibition in mm).

Comp. No.	*Escherichia coil*			*Staphylococcus aureus*		
Conc. mg/ml	**25**	**50**	**75**	**25**	**50**	**75**
F_{11}	**1**	**4**	**10**	**2**	**5**	**10**
F_{12}	**0**	**1**	**2**	**0**	**1**	**1**
F_{13}	**0**	**2**	**2**	**0**	**1**	**2**
F_{14}	**0**	**0**	**4**	**0**	**1**	**5**
F_{15}	**0**	**1**	**1**	**0**	**1**	**2**
Amoxicillin	**2**	**4**	**5**	**2**	**5**	**7**
Ampicillin	**2**	**3**	**5**	**2**	**4**	**6**
Ciprofloxacin	**1**	**2**	**5**	**2**	**3**	**5**
Blank disk	**0**	**0**	**0**	**0**	**0**	**0**

Table (5): Binding energy values of the prepared compounds.

Comp. No.	RMSD	Docking Score
F12	**0.048**	**-7.0**
F13	**0.022**	**-9.4**

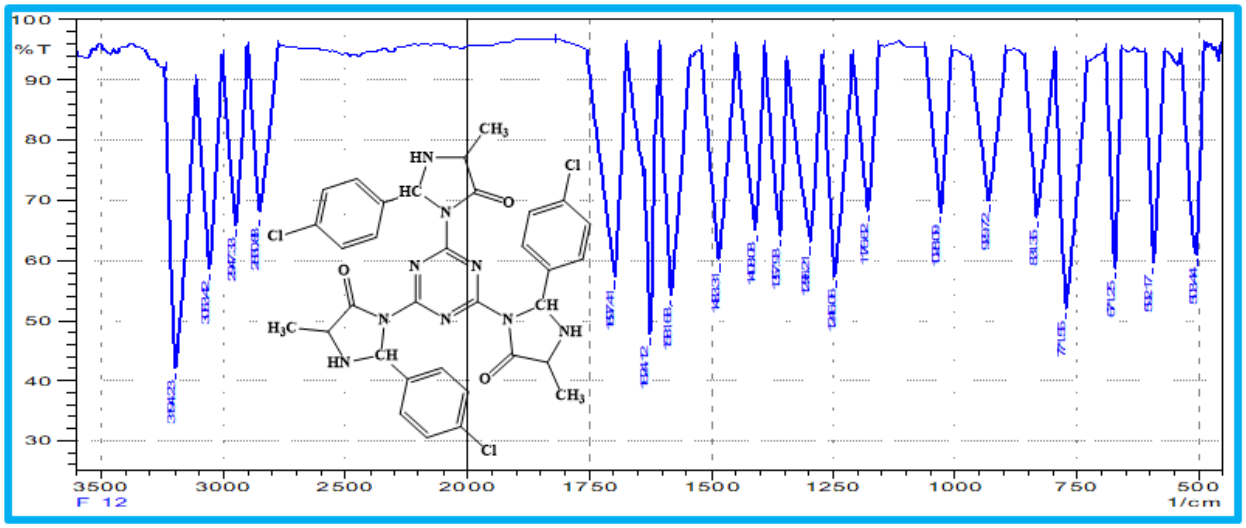


Figure (1): FT-IR spectrum of the compound (F12).

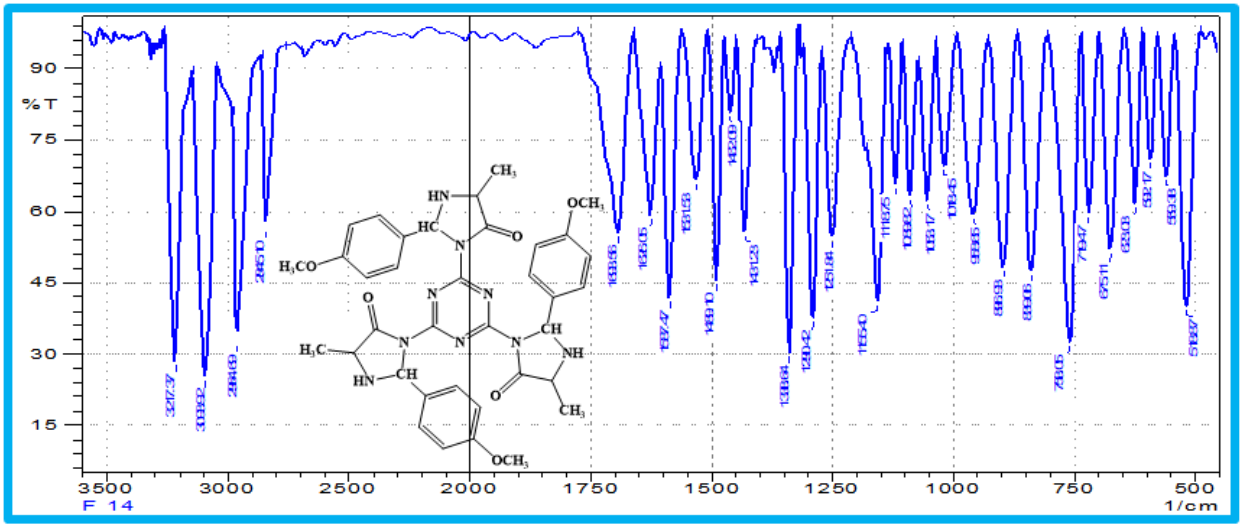


Figure (2): FT-IR spectrum of the compound (F14).

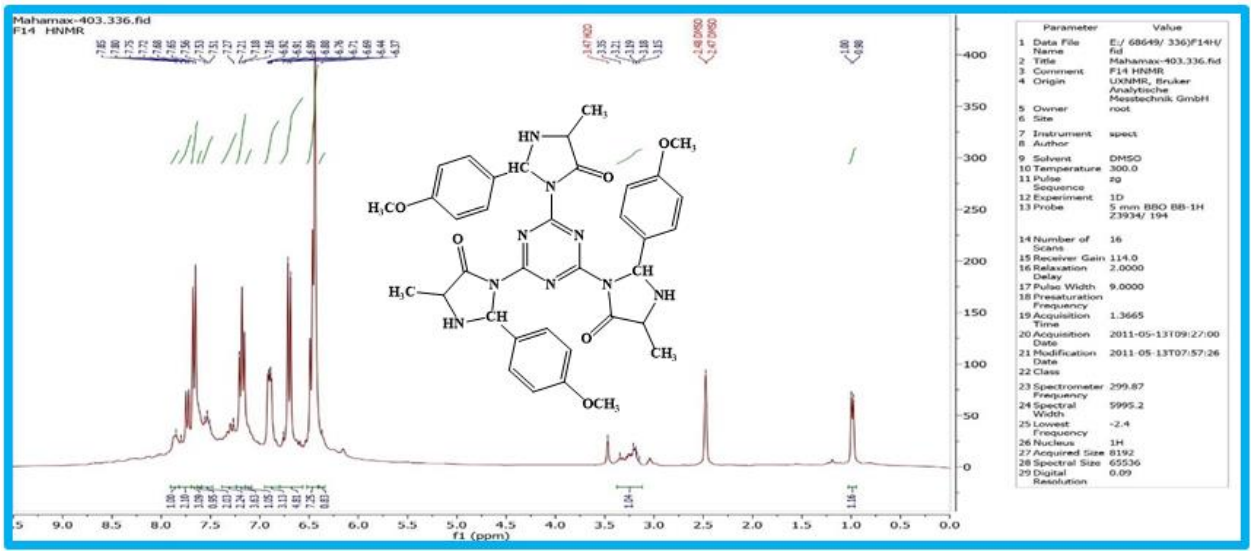


Figure (3): ^{1}H-NMR spectrum of the compound (F14).

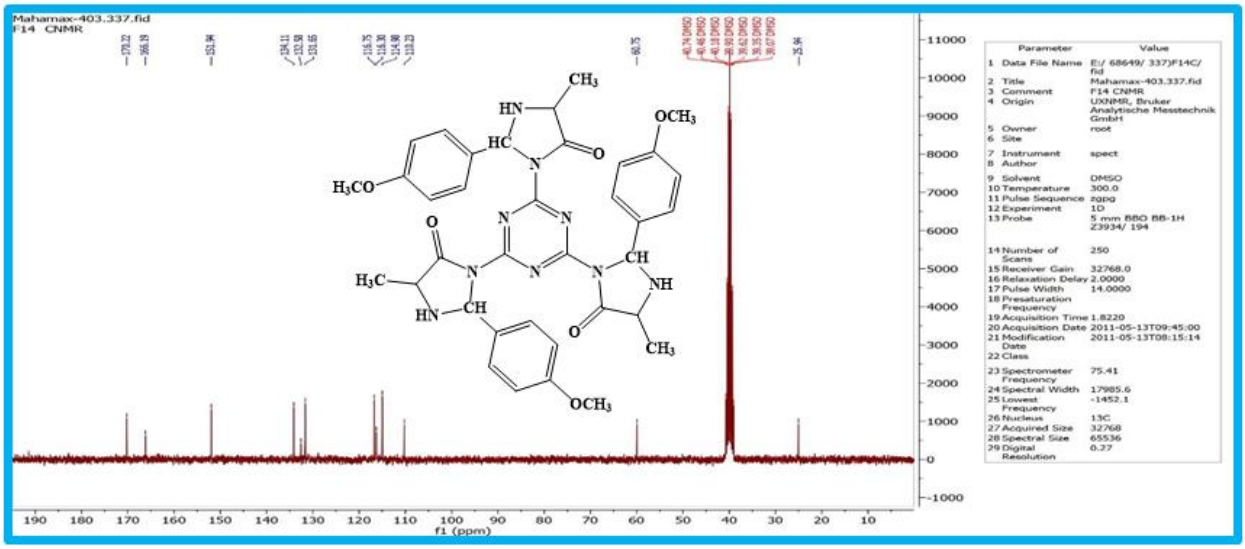


Figure (4): ^{13}C-NMR spectrum of the compound (F14).

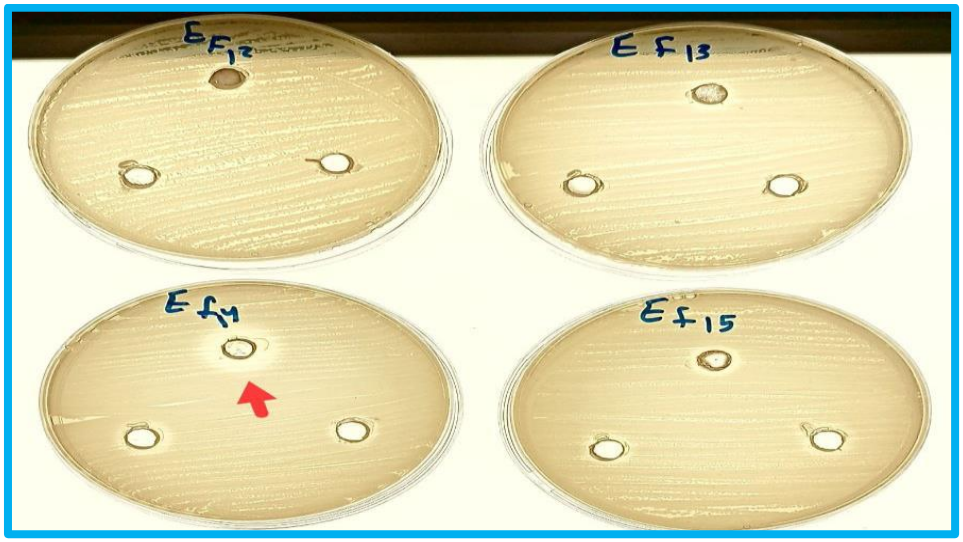


Figure (5): Inhibitory activity of some prepared compounds against E. Coli bacteria.

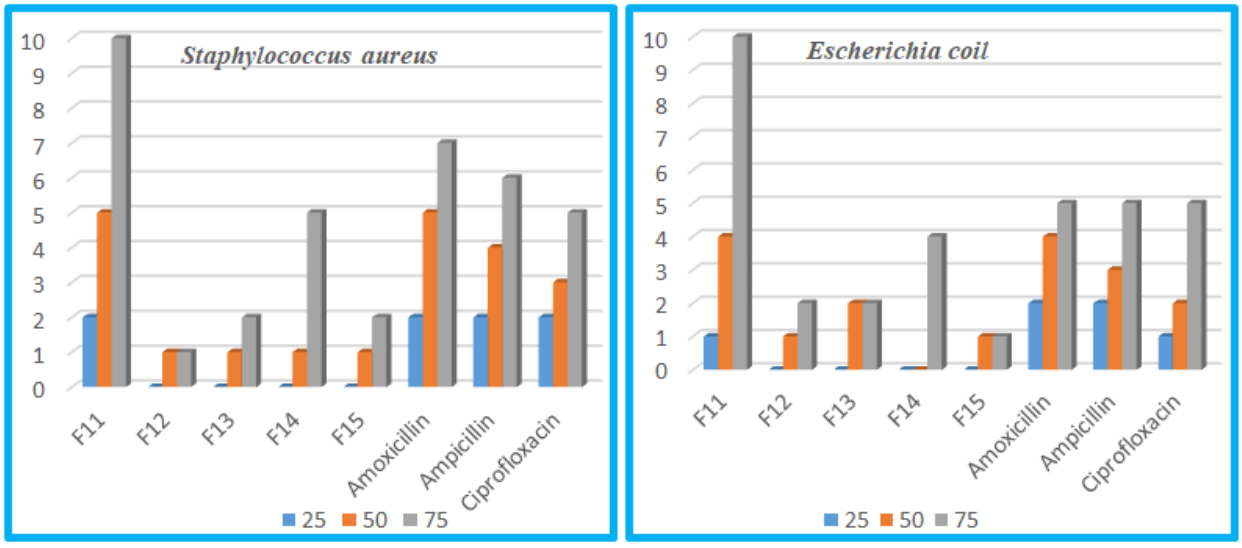


Figure (6): Inhibitory activity values of the prepared compounds against E. coil and S. aureus

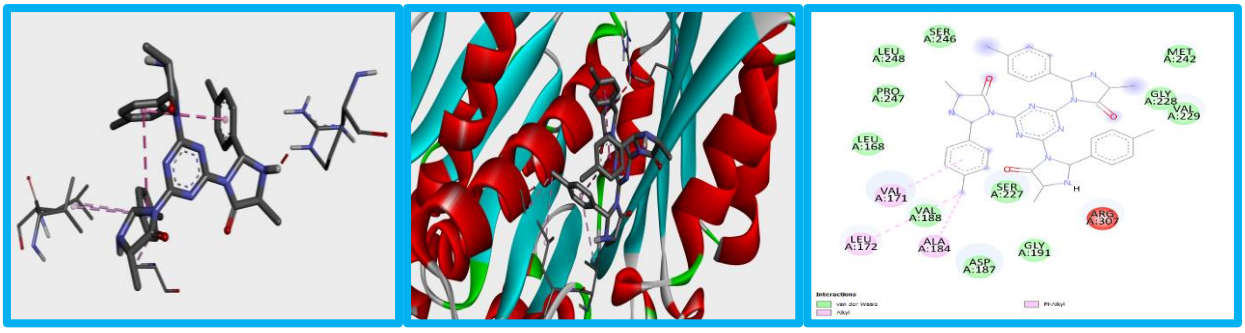


Figure (7): Interactions between compound (F12) in 3D, 2D dimensions

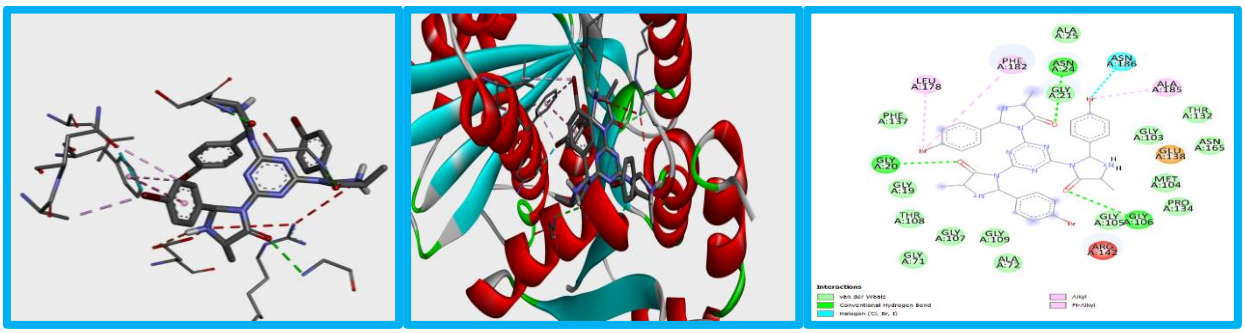


Figure (8): Interactions between compound (F13) in 3D, 2D dimensions

4. CONCLUSIONS

The similarity between the results of the molecular docking study and the practical result of the biological test confirms that the prepared compounds have good effectiveness against the bacteria used. Additionally, the stability of the prepared compounds against helium-neon laser radiation has been demonstrated.

5. RECOMMENDATIONS

We recommend completing studies and applications of the prepared compounds by knowing the properties of liquid crystals, selecting fungi and parasites and knowing the effect of the compounds on them, studying the possibility of using them as insecticides and using them as heavy metal removers in industries. It is also necessary to know new environmentally friendly methods and alternatives for preparing the compounds.

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