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Synthesis and Characterization of 1,3,4-Thiadiazole-2-Thione Prepared from New Derivatives of Thiosemiacarbazide and Study of its Molecular Modeling

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Abstarct: Thiosemicarbazide (GI_1) was synthesized by reacting 4-aminobenzoic acid with CS_2 and 80% aqueous hydrazine. The prepared thiosemicarbazide (GI_1) is then annularly closed with potassium hydroxide (KOH) and carbon disulfide (CS_2) in ethanol as a solvent to produce a compound 1,3,4-thiadiazole-2-thione (GI_{27}), which was diagnosed by physical and spectral methods (infrared spectrum (FT-IR), proton nuclear magnetic resonance spectrum (^{1}H-NMR), and carbon (^{13}C-NMR), as well as their molecular modeling study.

Key points: Thiosemicarbazide, 1,3,4-thiadiazole-2-thione, Molecular modeling.

Introduction

Thiosemicarbazone compounds have the potential to have various biological activities against various germs and diseases, as they can be antibacterial[2.1] as well as viruses[3]. Thiosemicarbazone compounds are also antifungal[4]. Some thiosemicarbazone have also been found to be anti-cancer and herbicidal[5].

Heterocyclic compounds and their derivatives play an important and essential role in the pharmaceutical and industrial fields. Therefore, (65%) of the research presented in organic chemistry focused on the chemistry of heterocycles[6]. Heterocyclic compounds also have many benefits as therapeutic compounds, drugs, dyes, and polymeric additives [7].

1,3,4-Thiadiazole Compounds are one of the most widespread thiadiazole isomers in the pharmaceutical, industrial, and agricultural fields compared to other isomers due to the important biological effectiveness of these compounds and their derivatives[8]. Thiadiazole compounds have a wide range of vital activities, including their effectiveness as an antibacterial, antifungal, antiviral, antiepileptic, anti-diabetic, analgesic, and anti-inflammatory. Recent studies have indicated the importance of 1,3,4-thiadiazole in the discovery and development of anti-tumor drugs and various cancer cells [9].

Thiadiazole compounds are found in a number of clinically effective drugs available on the market, such as antitumor, Azetepa anti-cancer, diuretic Methazolamide, Cefazolin, Cefozopran as antibiotics, and antibacterial Sulphamethizole[10].

Experimental Part:

Devices and chemicals used: Infrared spectrometer (FT-IR) type Shimadzu Fourier Transform Infrared Spectrophotometer 8400S (KBr) Scale (4000-400)cm^{-1}, proton NMR spectrometer (^{1}H-NMR) and carbon (^{13}C-NMR) type (Varian-500MHz), fusion temperature meter type Electro thermal melting point Apparatus9300, the chemicals used in the research are equipped by companies (Fluk, BDH, Aldrich, Merck) where the materials were used directly without recrystallization to their high purity.

Materials and Methods:

Preparation of Thiosemicarbazide(GI_1)[11]:

Dissolve (0.01mol,1.37g) of the 4-aminobenzoic acid compound in 20 mL of absolute ethanol, then add(0.01mol,0.5g) of KOH to the solution and leave to stir until dissolved. Then (0.01mol,7.5mL) of carbon disulfide (CS_2) was added to an ice bath and gradually, the mixture was left for continuous stirring for 24 hours at room temperature, which ranged between(25-35)°C. After the completion of the reaction, a white solid was observed in the reaction mixture. (0.01mol,0.5mL) of aqueous hydrazine ($N_2H_4.H_2O$) 80%, and the mixture rose at a temperature of (80)°C for (4) hours. The mixture was concentrated and then cooled to (4)°C in an ice bath. 5 ml of a cold mixture (1:1) of hexane and dichloromethane was added to precipitate the product. Afterward, the precipitate was filtered and washed with 8 mL of hexane. A white precipitate was obtained and its melting point (201-203) was 80%, and it was recrystallized from absolute ethanol.

Preparation 1,3,4-Thiadiazole-2-thione (GI_{27})[12]:

Dissolve (0.01mol,2.11g) of compound(GI_1) and (0.02mol,1.12g) of potassium hydroxide (KOH) in (30mL) of ethanol solvent, then, (3 mL) of carbon disulfide (CS_2) was gradually added, the reaction mixture increased for (16) hours until the release of hydrogen sulfide gas (H_2S) stopped [tested with wet paper from lead acetate solution]. After the reaction is complete, the reaction mixture is cooled and then the reaction mixture is poured into cold water and neutralized with 10% HCl. The formed precipitate was filtered, washed with distilled water, and dried. A zero-color precipitate and its melting point (230-232) were obtained and the output was 60%, and it was recrystallized from the absolute ethanol solvent.

Results and Discussion:

Preparation and Characterization of Thiosemicarbazide derivative:

Thiosemicarbazide derivative (GI_1) was prepared by reacting the 4-amino-benzoic acid compound with CS_2 disulfide and aqueous hydrazine ($N_2H_4.H_2O$ 80%).

The resulting compound was characterized by; some characteristics; environmental physics such as (color and melting point) and through some spectral methods (^{13}C-NMR, ^{1}H-NMR, FT-IR), where the infrared spectrum (FT-IR) showed absorption beams at (3292),(3367)cm^{-1} back to stretch (NH_2), and also appeared(absorption beam at)pain (1674)cm^{-1} back to stretch: (C=O) Carboxyl group, with the appearance of (absorption beams at)range (1517-1596)cm^{-1} back to stretch: (C=C) Aromaticity, in addition to the appearance of absorption beams at(3066) cm^{-1} back to stretch (C-H) Aromaticity, with the appearance of (absorption beam) at (3112)cm^{-1} back to stretch (N-H), adding to the absorption beam at (2500-3500)cm^{-1} back to (OH) (Carboxyl group). As shown in Figure (1).

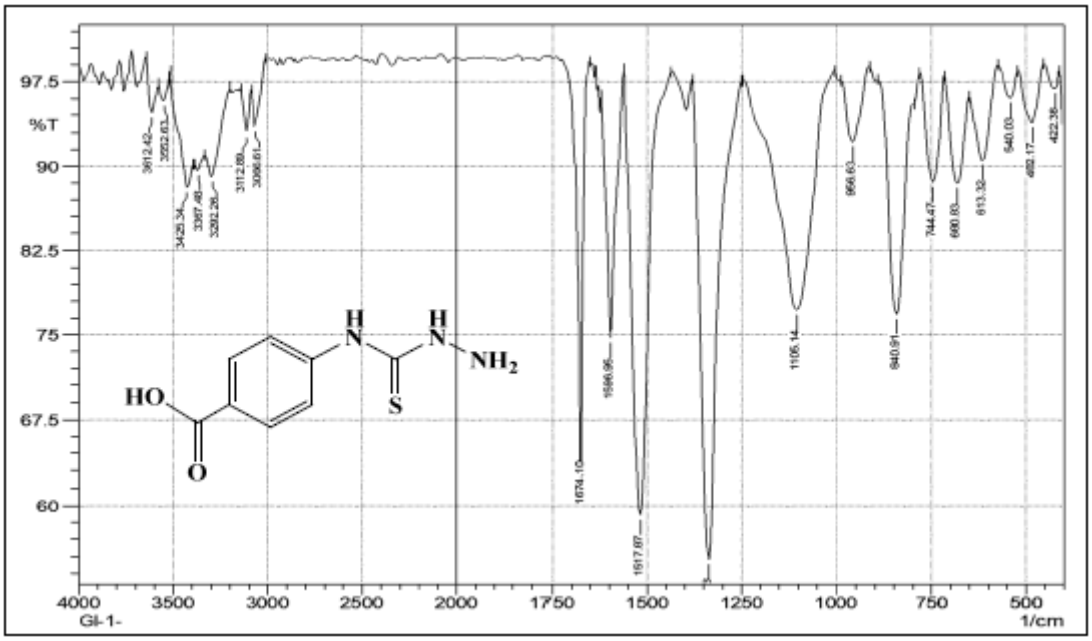


Figure (1) represents the infrared spectrum of the compound (GI_1)

When studying the proton magnetic nuclear resonance spectrum (^{1}H-NMR) of the compound (GI_1), it showed a single signal at the site (2.51) ppm of the solvent protons (DMSO-d ^{6}), and a single signal at the chemical displacement (3.84) ppm of the amine group protons (-NH_2/2H), and the emergence of multiple signals within the range (6.47-7.57) ppm of the aromatic ring protons (Ar-CH/4H), with the emergence of a single signal at the site (8.62) ppm of the amine group proton (CS-NH-N/1H), and the emergence of a single signal at the site (10.20) ppm of the amine group proton (Ar-NH-/1H), as well as the emergence of a single signal at the site (11.31) representing the carboxyl group (OH/1H). As shown in Figure (2).

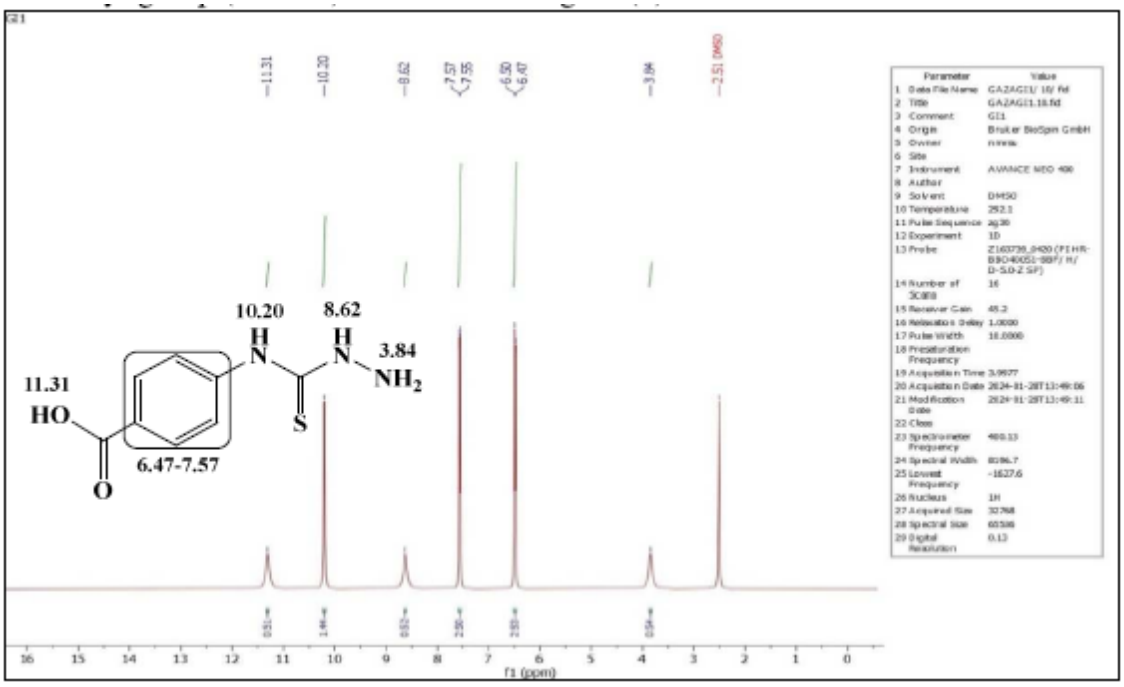


Figure (2) represents the NMR spectrum of the proton J of the compound (GI_1)

When studying the carbon magnetic nuclear resonance spectrum (^{13}C-NMR) of compound (GI_1), it showed a multiple signal at chemical displacement (40.48-39.23) ppm back to solvent carbon atoms (DMSO-d^{6}), and single signals at chemical displacement (152.20,131.39,116.53,113.02) ppm back to aromatic ring carbon atoms (C-H-Ar), with a single signal at chemical displacement (170.19) ppm back to carbonyl group carbon atom (C=O) benzoic acid, as well as a single signal at chemical displacement (181.32) ppm back to carbon group carbon atom (C=S). As shown in Figure (3).

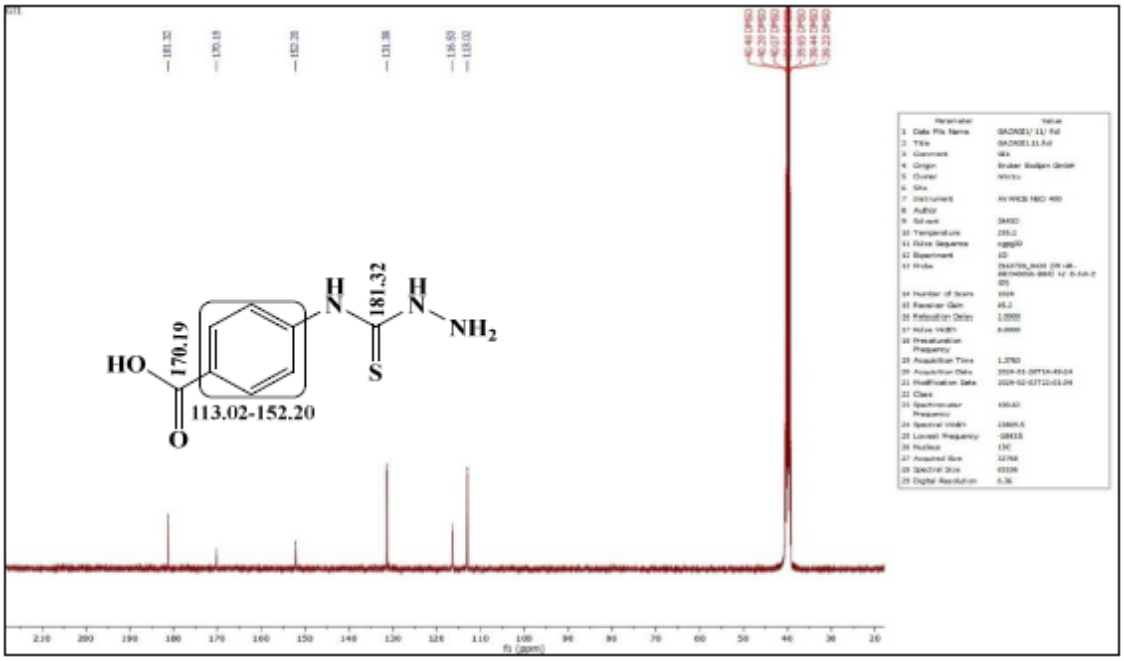


Figure (3) represents the nuclear magnetic resonance spectrum of the compound (GI_1)

Preparation and Characterization of Derivative 1,3,4-Thiadiazole-2-thione :

Compound 1,3,4-thiadiazole-2-thione (GI_{27}) was prepared by reacting the prepared thiosimicarbazide (GI_1) with CS_2 in the presence of KOH and using ethanol as a solvent.

The derivative of 14,3, -thiadiazole-2-thione prepared (GI_{27}) was diagnosed through some physical properties such as (color and melting point) and through some spectral methods (^{13}C-NMR, ^{1}H-NMR, FT-IR), where infrared spectra (FT-IR) measurements showed the disappearance of the two amine group stretch bundles (NH_2) that appeared at (3292),(3367)cm^{-1} returning to the compound [GI_1], while in the spectrum an absorption bundle was observed at the site (1635)cm^{-1} that returned to the stretch of (C=N) returning to the thiadiol ring, in addition to the absorption at site (3346)cm^{-1} that returned to the stretch (N-H) of the thiadiol ring, in addition to the absorption at site (3225)cm^{-1} that returned to the stretch (N-H) outside the thiadiol ring, in addition toat the (1170)cm^{-1} that returned to the (C=S)[13]. As shown in Figure (4).

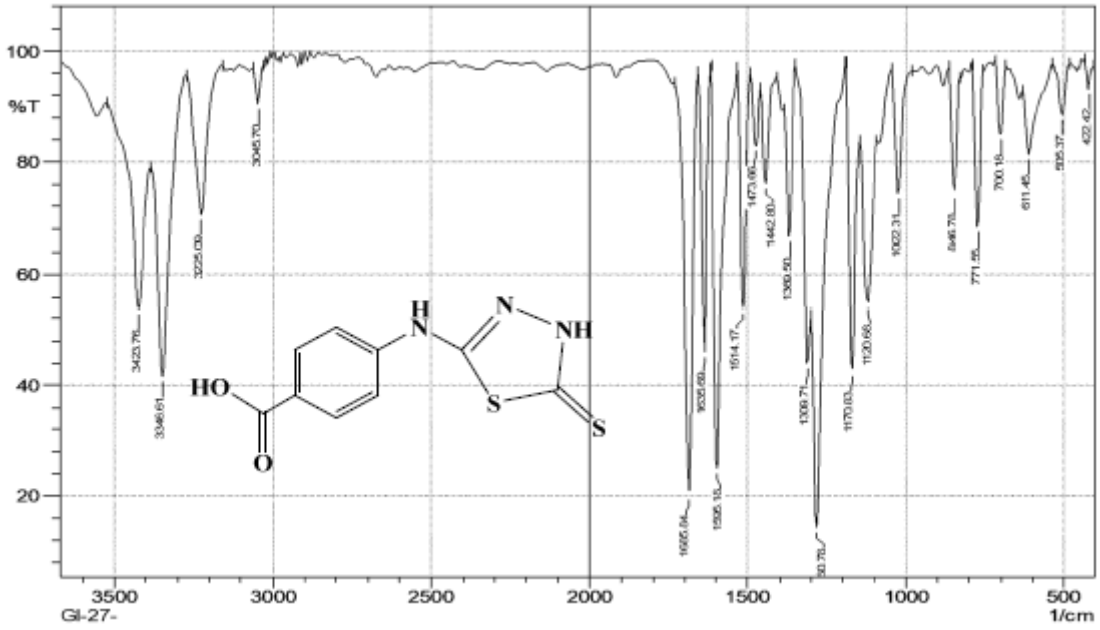


Figure (4) represents the infrared spectrum of the compound (GI_{27})

When studying the proton magnetic nuclear resonance spectrum (^{1}H-NMR) of the compound (GI_{27}), it showed a sharp single signal at the site (2.51) ppm belonging to the solvent protons (DMSO-d^6), and multiple signals within the range (6.54-7.60) ppm representing the aromatic ring protons (Ar-CH/4H), and a single signal at the chemical displacement (10.16) ppm belonging to the amine group proton (-NH-/1H), in addition to the emergence of a single signal in the region (11.50) representing the carboxyl group proton (OH/1H), with the emergence of a single signal in the region (13.07) representing the amine group proton (-NH-/1H) thiazole-2-thione ring. As shown in Figure (5).

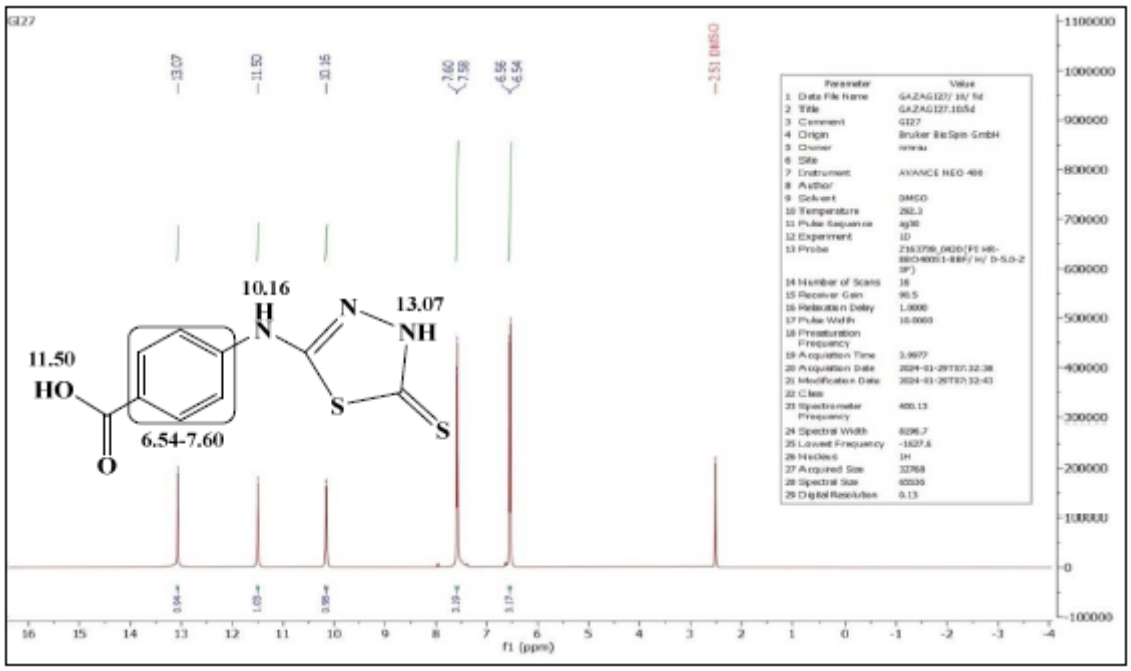


Figure (5) represents the NMR spectrum of the proton J of the compound (GI_{27})

When studying the carbon magnetic nuclear resonance spectrum (^{13}C-NMR) of compound (GI_{27}), it showed a multiple signal at chemical displacement (40.43-39.18) ppm back to the solvent carbon atoms (DMSO-d^6), and single signals at chemical displacement (152.72,131.71,117.38,113.24) ppm back to the aromatic ring carbon atoms (C-H-Ar), with a single signal at chemical displacement (155.96) ppm back to a carbon atom (-NH-C=N-) thiazole-2-thione ring, in addition to the emergence of a single signal at chemical displacement (181.32) ppm back to a carbon atom (C=S) thiazole-2-thione ring, and a single signal at chemical displacement (168.08) ppm back to a carbon atom (C=O) benzoic acid. As shown in Figure (6).

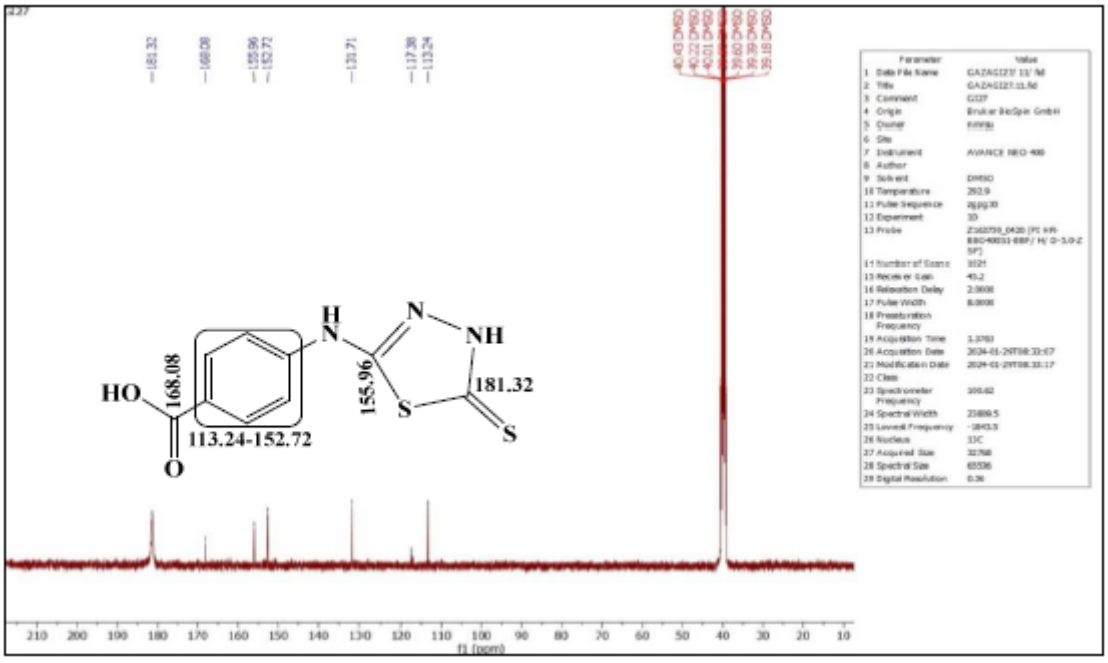
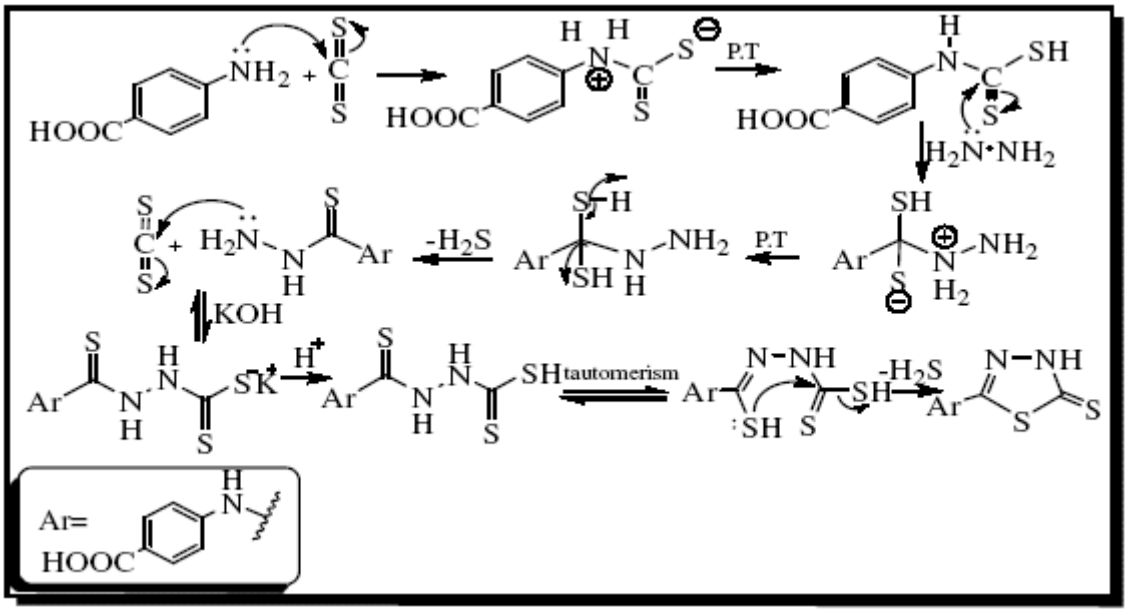


Figure (6) represents the NMR spectrum ofthe compound (GI_{27})

Equation(interaction):

Mechanical, Interaction:

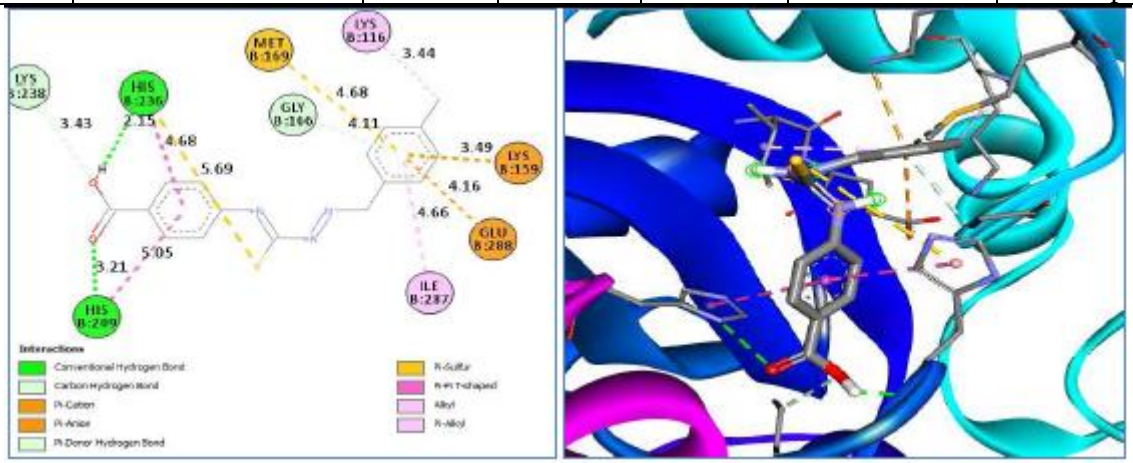


Molecular Modeling:

Molecular modeling of derivatives with high inhibition efficacy against pathological E.coli bacteria was performed, and the enzyme biotin carboxylase was chosen because it plays an important role in the metabolism of fats, proteins, and carbohydrates, and thus its inhibition contributes to the reduction or prevention of the growth of these bacteria. AutoDockTools was used to identify the Grid box for the enzyme represented by the symbol (PDB:ID:**3jzf**).1.5.6 Its dimensions were (40,40,40) (X,Y,Z) and its position coordinates (36.578, -24.476, 39.415) (X,Y,Z), while each of the derivatives (GI_1,GI_{27}) and pictures (7,8) show the overlap between the protein and these derivatives:

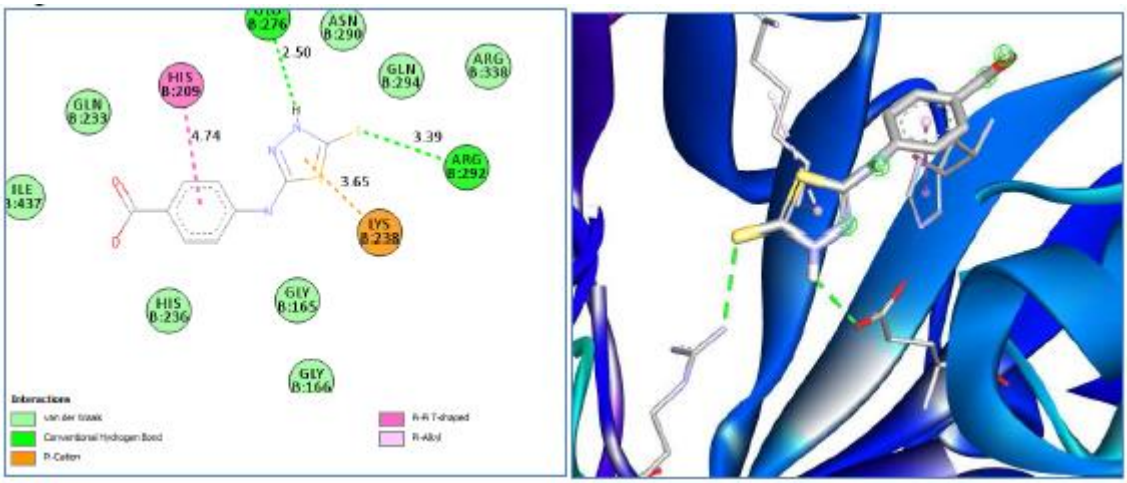
The following table shows the results of molecular anchoring of compounds effective against **E.coli** bacteria

Comp No.	Affinity (Kcal/mol)	RMSD l.b. (A°)	RMSD u.b. (A°)	Distance (A°)	Main residue	Type of H-bond
GI_1	-7.0	3.762	4.683	3.215 2.151	B:HIS209 B:HIS236	H-Donor H-Acceptor
GI_{27}	-6.2	7.224	8.465	3.389 2.497	B:ARG292 B:GLU276	H-Donor H-Acceptor



Figure(7) represents the two-dimensional (right) and three-dimensional(left) structure of the molecular cohesion of the GI1 derivative interference with the binding site of the protein (PDB:ID**: 3jzf**)

Compound **GI$_1$** was overlapped at a docking score value of -7.0 Kcal/mol and a single hydrogen bond appeared between Lys:B:238 and the hydroxyl group, as shown in the figure above.



Figure(8) represents the two-dimensional structure 2D(right) and 3D(left) of the molecular docking of the GI27 derivative interference with$_{the}$ binding site of the protein (PDB:ID**: 3jzf)**

Compound **GI$_{27}$** was overlapped at a docking score value equal to -6.2 Kcal/mol and showed two hydrogen bonds between Glu:B:276 with the NH group and arg:B:292 with the SH group in addition to some other correlations.

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