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Synthesis of Novel Heterocyclic Derivatives from α-Lipoic Acid as Antibacterial Substances

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تحضير مركبات حلقية غير متجانسة جديدة مشتقة من حامض ألفا ليبويك كمواد مضادة للبكتيريا

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الملخص:
استخدم حامض الفا -ليبويك كمكون رئيسي في تحضير مركبات الكاربونيل الفا، بيتا غير المشبعة والتي تتفاعل مع الكواشف النيوكلوفيلية مثل (الهيدرازين ، الثايوريا واليوريا) لتحضير انواع مختلفة من المركبات الحلقية غير المتجانسة الملتحمة. تم اجراء العديد من القياسات الكيميائية والفيزيائية مثل قياس درجات الانصهار، ايضا استخدمت طرق التحليل الطيفي مثل طيف الاشعة تحت الحمراء و طيف الرنين النووي المغناطيسي (للبروتون والكاربون) لاثبات صحة تكوين المركبات المحضرة. تم اختبار الفعالية البايوجية ضد نوعين من البكتريا المرضية (المكورات العنقودية الذهبية- موجبة لصبغة كرام) و (الاشريكية القولونية- سالبة لصبغة كرام). اظهرت جميع المركبات المختبرة نشاطا مضادا للميكروبات افضل بكثير من المضادات الحيوية القياسية

الكلمات الدالة: 1،2-ثنائي ثايولان-3- حامض بنتانويك، تثبيط، حلقات ملتحمة غير متجانسة، ثايوريا، ثنائي مثيل سلفوكسايد.

Abstract
Lipoic acid was used as a key component in the production of α,β- unsaturated carbonyl compounds which react with nucleophilic reagents such as (hydrazine hydrate, thiourea and urea) to produce several types of fused heterocyclic derivatives. For many chemical and physical measurements, such as: melting point, FT-IR spectroscopy, as well as ^{1}H and ^{13}C-NMR spectroscopy used to proven the formation of synthesized compounds. Biological activity against two types of bacteria, Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative), was also investigated. All tested compounds demonstrated significantly better antimicrobial activity than standard antibiotics.

Keywords: 1,2-dithiolane-3-pentanoic acid, inhibition, fused heterocyclic, thiourea, dimethyl sulfoxide.

Introduction

Heterocyclic compounds form a category of organic compounds which feature one or more rings with heteroatoms. These are non-carbon atoms which include nitrogen, oxygen, or sulfur [1,2]. In addition to the three cited above, heterocycles may include other heteroatoms like phosphorus,

selenium, or even some transitional metals such as iron [3-5]. These motifs have fundamental importance in biochemistry, as they constitute important biomolecules such as DNA, RNA, hemoglobin, chlorophyll, and several vitamins [6-8]. Heterocyclic compounds are of great interest in medicinal chemistry because of their diverse biological activities which have led to a multitude of synthetic methodologies to access these pharmacologically important scaffolds. Fused heterocyclic compounds represent a critical class of organic molecules characterized by the sharing of two or more adjacent atoms between aromatic or non-aromatic rings, incorporating heteroatoms such as nitrogen, oxygen, or sulfur[9,10]. These systems exhibit remarkable chemical diversity, making them indispensable in pharmaceuticals, agrochemicals, and materials science. Fused heterocyclic compounds remain at the forefront of organic and medicinal chemistry due to their structural diversity and functional adaptability. Continued innovation in synthetic methodologies and interdisciplinary applications will further expand their utility in pharmaceuticals and beyond[11-14].

α-Lipoic acid or ALA is a short-chain fatty acid, a sulfur-containing compound, which has a bioactive enantiomer, and a biologically inactive S-(-) enantiomer, which is obtained artificially [15-17]. Alpha-lipoic acid, also called 1,2-dithiolane-3-pentanoic acid, an endogenous thiol antioxidant exerting a crucial influence on redox balance of the cell, is referred to as ALA [18,19]. ALA is made of an eight carbon chain which ends with a dithiolane ring (a cyclic disulfide) and contains a chiral carbon at the C3 position which renders it chiral and leads to the formation of two enantiomers [20,21]. Many studies have proven that both ALA and its reduced form, dihydrolipoic acid (DHLA), are strong free radical scavengers. These compounds prevent the development of numerous disorders by counteracting oxidative damage caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS) [22-24]. As a metabolic cofactor, ALA serves as a vital coenzyme for mitochondrial α-ketoacid dehydrogenase complexes. It helps in the oxidative decarboxylation of pyruvate and α-ketoglutarate in eukaryotic mitochondria and prokaryotic cytoplasm, and is a crucial component in the energy metabolism of the cell in the tricarboxylic acid (TCA) cycle (TCA) [25,26].

Material and methods:

All chemicals and solvents used in the synthesis were of analytical grade and obtained from commercial suppliers, including Merck (Darmstadt, Germany), BDH Chemicals (Poole, UK), Fluka (Buchs, Switzerland), and Sigma-Aldrich (St. Louis, MO, USA). Solvents were purified and dried according to standard protocols prior to use.

Synthesis of compound (1)

In a round-bottomed flask,(0.02 mol) of lipoic acid was dissolved in (30 mL) of the prepared $POCl_3$ with continuous stirring. Then (0.02 mol) of thiosemicarbazide was added in batches. After completing the addition, the reaction mixture was heated in a water bath at 85°C for (10 hours). The reaction was monitored using thin layer chromatography (TLC), which proved the completion of the reaction and the end of the starting material. The reaction mixture was cooled, crushed ice was added, and the resulting precipitate was neutralized using (10% KOH). The precipitate was filtered and recrystallized using absolute ethanol to give a pale yellow precipitate with a melting point of (188-189°C). The percentage was 95%

Synthesis of compound (2)

In a suitable round-bottomed flask equipped with a reflective condenser, (4 mmol) of compound **(1)** with (2 mmol) of triethylamine TEA dissolved in (15 mL) of dioxane were adding with continuous stirring, then gradually and dropwise (2 mmol) of chloroacetyl chloride was added. The mixture was refluxed for (15 hours). The reaction was controlled by TLC. When the completion of the reaction was proven, the reaction mixture was cooled, evaporated, washed with

distilled water, dried, and recrystallized with ethanol to obtain a browen precipitate at melting point of (198-199°C) and 76% .

Synthesis of compound (3)

A mixture was formed by dissolving (5 mmol) of compound **(2)** in (25mL) of acetone, then potassium thiocyanate (10mmol) was added to the reaction mixture with refluxing for (6 hours). The progress of the reaction was monitored by TLC then, the resulting product was cooled, the solvent was evaporated, and (25mL) of distilled water was added with continuous stirring. The precipitate was filtered using filter paper and washed with distilled water. It was recrystallized with ethanol to give white crystals of compound (3) at a melting point of (204-202°C) and a yield of 70%.

Synthesis of compounds (4-6)

In a suitable round-bottomed flask, (2 mmol) of the previously prepared compound **(3)** was mixed with (4 mmol) of one of the aromatic aldehyde substitutes and solution consist of (4 mmol) of anhydrous sodium acetate in (10 mL) of acetic acid. The reaction mixture was refluxed for (7 hours). The completion of the reaction was monitored by TLC, after which the reaction product was cooled, filtered, and washed with distilled water. The precipitate was dried and recrystallized from ethanol.

Synthesis of compounds (7-9)

In a suitable round-bottomed flask equipped with a reflecting condenser, (2 mmol) of one of the compounds **(4-6)** was dissolved in (10 mL) of ethanol, then (6 mmol) of 80% aqueous hydrazine was added. The reaction mixture was refluxed for (6 hours) after adding a few drops of concentrated hydrochloric acid. The completion of the reaction was monitored by TLC, then the product was cooled and crushed ice was added The precipitate was filtered, dried, and purified by column chromatography using (Hexane: EtOAc 5:1) to give the target compounds.

Synthesis of compounds (10-11)

These two compounds were prepared by mixed (2 mmol) of compounds **(4 and 6)** with (4 mmol) of thiourea in the presence of potassium hydroxide (0.5 gm) in ethanol(10 mL). The reaction mixture was refluxed for (8 hours) and the completion of the reaction was monitored by TLC. The resulting solution was left for 24 hours and concentrated under vacuum pressure. The precipitate was filtered, washed with water, dried and purified by column chromatography using (Hexane: EtOAc 5:1).

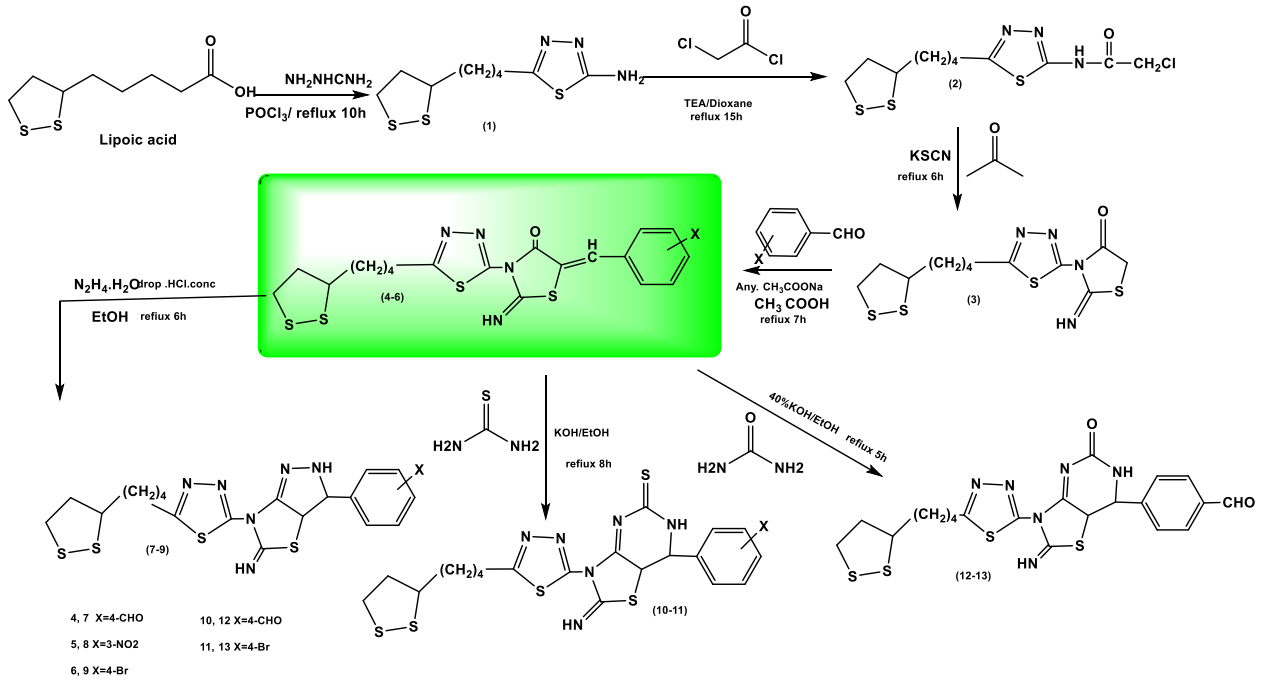
Synthesis of compounds (12-13)

A mixture of compounds **(4 and 6)** (2 mmol) with urea (4 mmol) in (10 mL) ethanol was stirring, then slowly and with continuous stirring add (5 mL) of aqueous potassium hydroxide solution (40%). The reaction mixture was refluxed in a water bath (80-90°C) for (5 hours). After the reaction is complete, cool the product and add it to iced water and neutralize it by adding dilute hydrochloric acid. Filter the precipitate formed, wash with water, dry, and purified by column chromatography using(Hexane: EtOAc5:1).

Comp.NO	X	m.p.	yield %	colour
H4	4-CHO	243-245	63	Reddish-brown
H5	3-NO_2	254-256	55	Black
H6	4-Br	232-234	64	Dark-brown
H7	4-CHO	249-251	90	Yellow

H8	3-NO_2	221-223	70	Brown
H9	4-Br	215-217	72	Beige
H10	4-CHO	289-291	87	Reddish-brown
H11	4-Br	223-225	75	Brown
H12	4-CHO	286-288	75	Light-Brown
H13	4-Br	175-177	83	Brown

Table 1: Physical properties for compounds (4-13)



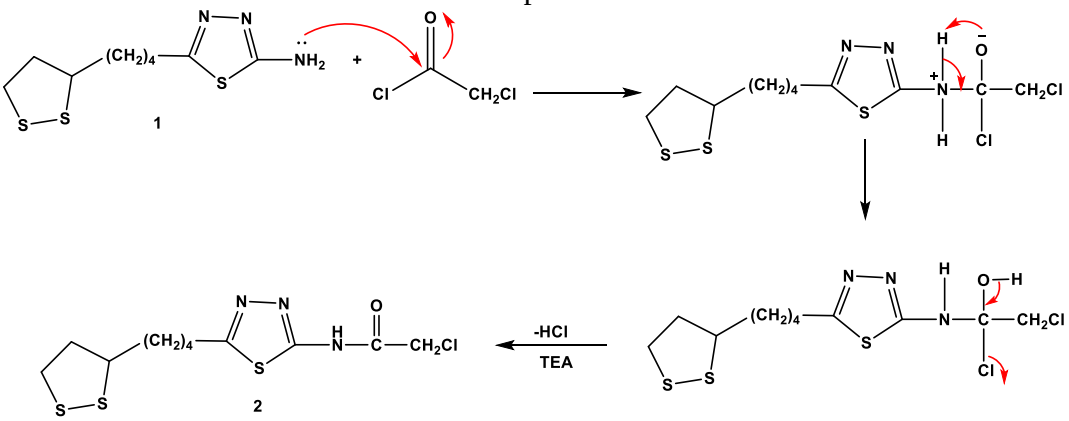
Scheme (1): synthesis of compounds (1-13)

Results and Discussion

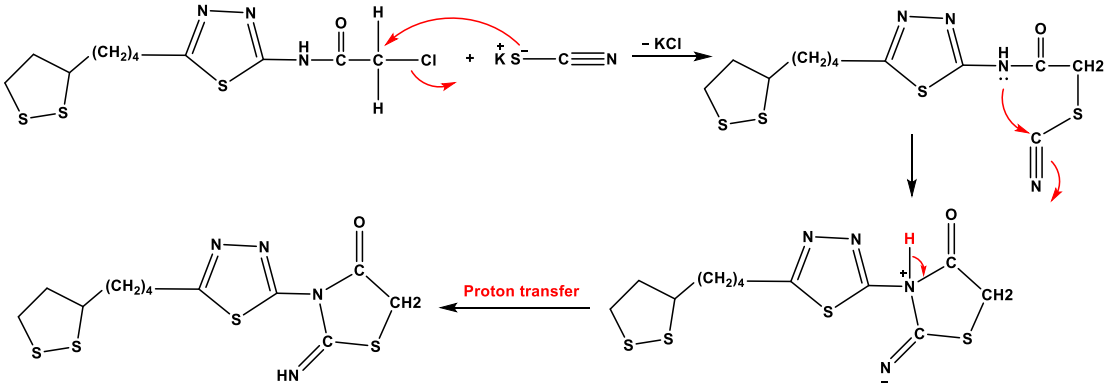
Various nucleophilic reagents, including hydrazine hydrate, thiourea and urea were reacted with α-β unsaturated carbonyl compounds to afford the corresponding fused heterocyclic derivatives, (compounds 1-13), as outlined in Scheme (1). The structures of all synthesized compounds were confirmed using Fourier-transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (^{1}H NMR), carbon-13 nuclear magnetic resonance (^{13}C-NMR), and elemental analysis. Among the tested compounds, 3a demonstrated superior antibacterial activity against both Staphylococcus aureus and Escherichia coli, while other derivatives also exhibited significant antimicrobial effects.

Compound *5-(4-(1,2-dithiolan-3-yl)butyl)-1,3,4-thiadiazol-2-amine* (1) was synthesized via reaction of α-lipoic acid with thisemicarbazide in presence of $POCl_3$. It was used as starting material and play a key role to prepare fused heterocyclic compounds. The structure of the synthesized compound was confirmed by (IR,^{1}H and ^{13}C-NMR) spectroscopy. The spectrum of IR showed two bands at 3254 and 3098 cm^{-1} belong to primary NH_2 group, 2919, 2853 cm^{-1} for stretching of aliphatic C-H group, also band at 1621 cm^{-1} refers to C=N group. The ^{1}H-NMR gave a single signal at 1.32 ppm refers to (2H for NH_2 group), a triplet at 2.69 ppm *J*= 8.0 refers

to CH_2 in the chain next to thiadiazole ring. The ^{13}C-NMR gave signals at 170.4, 169.5, 61.4 and 40.5 ppm refer to two(C=N, thiadiazole ring)and two (C-S) respectively. The treatment of compound (1) with chloroacetyl chloride in 1,4-dioxane in presence of TEA gave the resulting ***N-(5-(****4-(1,2-dithiolan-3-yl)butyl)-1,3,4-thiadiazol-2-yl)-2-chloroacetamide* (2). The IR spectra showed the absence band for (NH_2) while appear absorption band at 1674cm^{-1} belong to (C=O) group. The band at 3318 cm^{-1} was designated for secondary amine (N-H), the characteristic (C-Cl) moiety was distinguished at 641cm^{-1}. ^{1}H-NMR showed two singlets at 5.38 and 4.34 ppm belong to one proton in (N-H) and two protons in (CH_2-Cl) groups respectively, C^{13}-NMR gave signals at 172.6, 157.5 ppm for two (C=N) and 172.0 ppm for (C=O) group. The reaction mechanism was follow the steps:



Compound*N-(5-(4-(1,2-dithiolan-3-yl)butyl)-1,3,4-thiadiazol-2-yl)-2-iminothiazolidin-4-one* (3) was prepared by dissolving the compound (2) prepared in the previous step in acetone, then potassium thiocyanate was added to the reaction mixture. The reaction process can be explained by the following mechanism:



Spectroscopic methods were used to prove the chemical structure of the prepared compound, as the infrared (IR) spectrum showed the basic frequency bands present in the compound, where a stretching band appeared at 3289 cm^{-1} due to the (N-H) group in the compound, as well as the symmetric and asymmetric stretching bands of the aliphatic (C-H) group at frequencies of 2923 and 2853 cm^{-1}in addition to the stretching band of the lactam carbonyl group at 1694 cm^{-1}, as well as a stretching band due to the (C=N) group in the thiadiazole ring at frequencies of 1664 cm^{-1}. ^{1}H and ^{13}C-NMR data gave signal as singlet at 6.65ppm refer to (N-H) proton, another singlet at 4.01ppm belong to two protons (CH_2); (C=O) group appeared at 176.4ppm, two (C=N) groups 176.2, 159.9 ppm while signal at 160.4 for (C=NH). Compound (3) was used with an aromatic aldehyde substitute and in the presence of an anhydrous sodium acetate solution with acetic acid as the solvent to prepare *Alpha-beta unsaturated carbonyl compounds* (4-6) The prepared compounds were characterized spectroscopically, as the infrared (IR) spectrum gave

absorption bands belonging to (C=O) groups in the range of (1693-1697 cm^{-1}) and frequencies belonging to the (C=C) bond stretching bands in the range of (1604-1612 cm^{-1}) . The compounds were also identified by magnetic resonance spectra (^{1}H and ^{13}C-NMR). Compound (6) as a model of the prepared compounds, gave the following signals: a single signal at (9.39 ppm) due to the proton of the (N-H) group and two double signals at (7.58 ppm) and (7.26 ppm) representing to the four protons of the aromatic ring the coupling constant value was (J = 7.5 Hz). The proton of the double bond outside the ring it gave a single signal at (5.73 ppm). Also, the ^{13}C-NMR spectrum of the same compound gave the following signals at chemical shifts: 161.5, 176.3, 175.8, belonging to the groups (C=O), (C=NH), (C=N) respectively. The carbon atoms belonging to the aromatic ring, they gave signals at chemical shifts (132.2, 131.9, 130.4, 124.9 ppm). The carbon atoms belonging to the double bond, their signals appeared at chemical shifts (132.1and120.2 ppm).

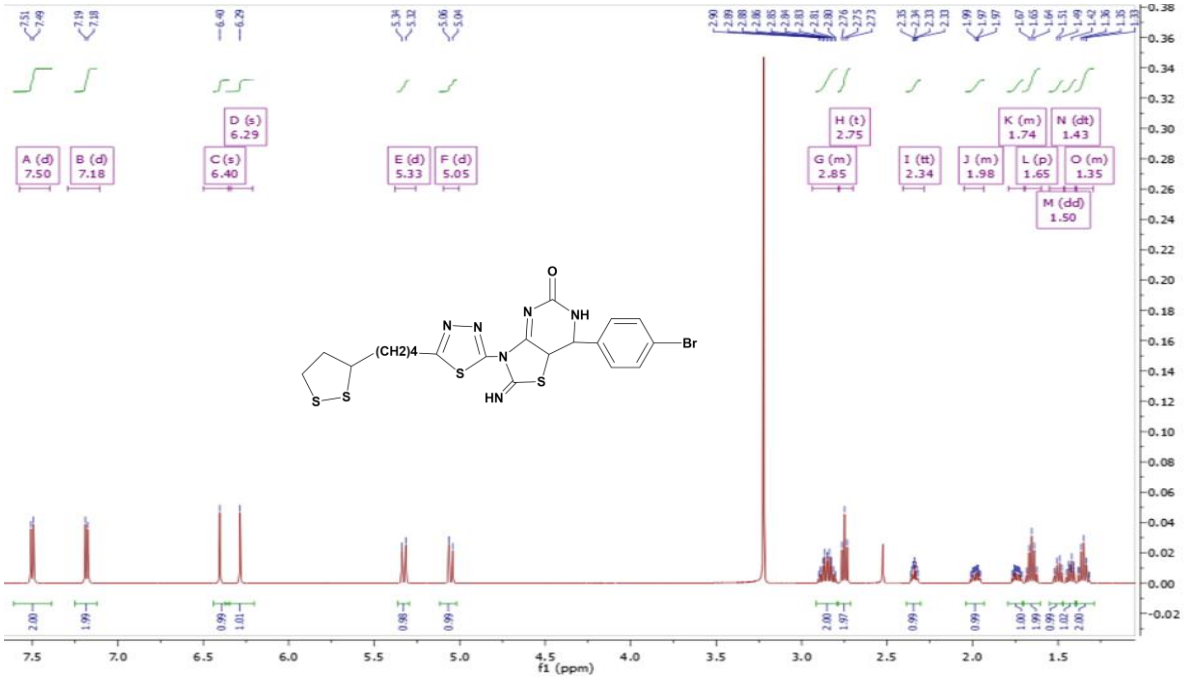


Figure 1: ^{1}H-NMR for compound (6)

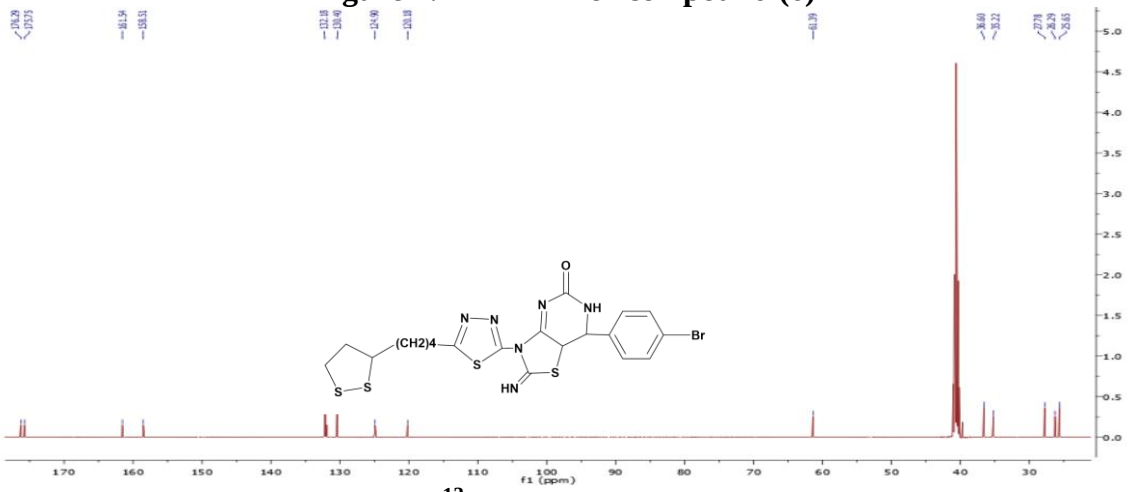


Figure 2: ^{13}C-NMR for compound (6)

These compounds (7-9) were prepared by reacting compounds (4-6) with one of the nucleophilic reagents (hydrazine hydroxide) in the presence of ethanol containing hydrochloric acid. The mechanism includes a nucleophilic attack by the amine group in hydrazine on the carbonium atom in the (C=C) group to give the Michael addition product (1,4), then attack of the free electron doublet of the other nitrogen atom on the carbonyl group to give the (1,2) product, followed by the removal of the water molecule. In the presence of hydrochloric acid, an oxidation process occurs for the pyrazoline ring to give the pyrazole compounds The compounds were characterized by infrared (IR) spectrum, where it was observed that the absorption bands that were due to the carbonyl groups (C=O) and the double bond (C=C) that were evident in the compounds (4-6) disappeared, while new bands appeared, which provided evidence for the chemical structures of the newly prepared compounds, as absorption bands due to the stretching of the (C=N) group in the pyrazole ring appeared in the range (1619-1622 cm^{-1}) as well as the stretching bands of the (C-S-C) bond at the frequencies (827-675cm^{-1}) ^{1}H-NMR data for compound (8) showed two doublet at 8.16 and 7.3 ppm belong to four protons aromatic ring , two singlets refer to protons (NH) groups at 6.19 and 6.05 ppm respectively also two doublet at 4.70, 4.65 ppm with coupling constant (J = 10.8, 10.6 Hz) for (C-H) group in the ring

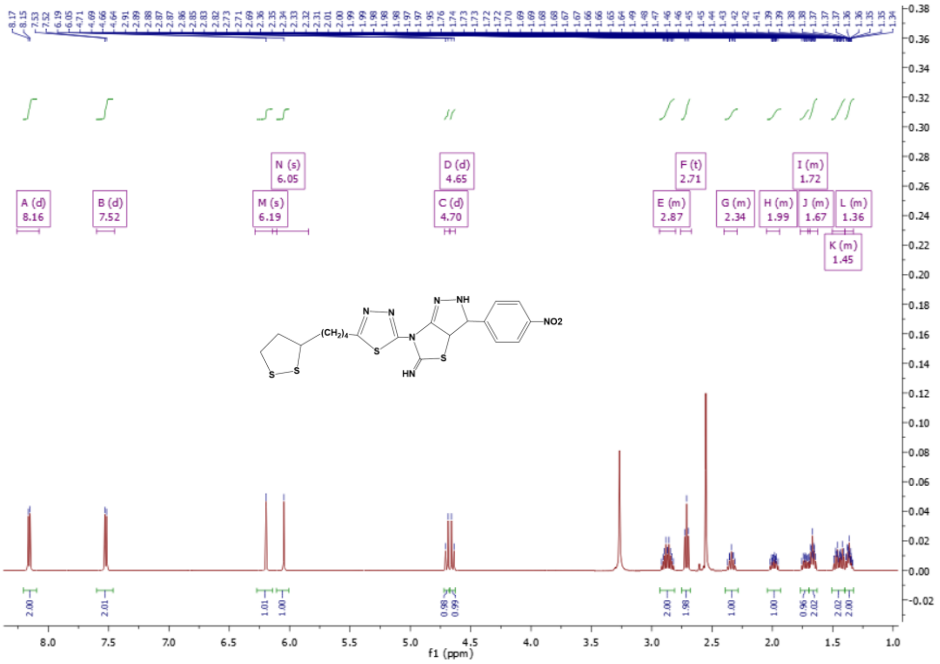


Figure 3: H-NMR for compound (8)

This type of compounds (10-11) was prepared by mixing (4-6) with thiourea in the presence of a basic medium of potassium hydroxide, a system of heterogeneous fused rings were obtained. The chemical structures of the prepared compounds were proven by identifying them using the infrared (IR) spectrum where the appearance of new absorption bands was observed, which belong to the basic groups entering into the composition of the compounds, as the spectrum showed stretching bands for (N-H) groups as well as (C=N) in the range (3338-3337 cm^{-1}), (3136-3165 cm^{-1}), (1556-1563 cm^{-1}) respectively. The nuclear magnetic resonance spectroscopy (^{1}H-NMR) was also used to confirmed the formation of compounds, compound (10) was selected as a model for these compounds the spectrum gave a single signal at chemical shift (9.91 ppm) for the aldehyde proton in the phenyl ring, while the four protons of the aromatic ring gave two signals at chemical shift (7.82, 7.40 ppm), and the protons of secondary amine (N-H) gave single as signals at (7.66, 7.52 ppm) while the thiopermidine ring protons gave a signal as doublet to

each proton at (5.55, 5.48 ppm) and the value of the coupling constant was (J = 6.2 Hz). ^{13}C-NMR gave a good information belong to the compound (10) as shown in figure (5)

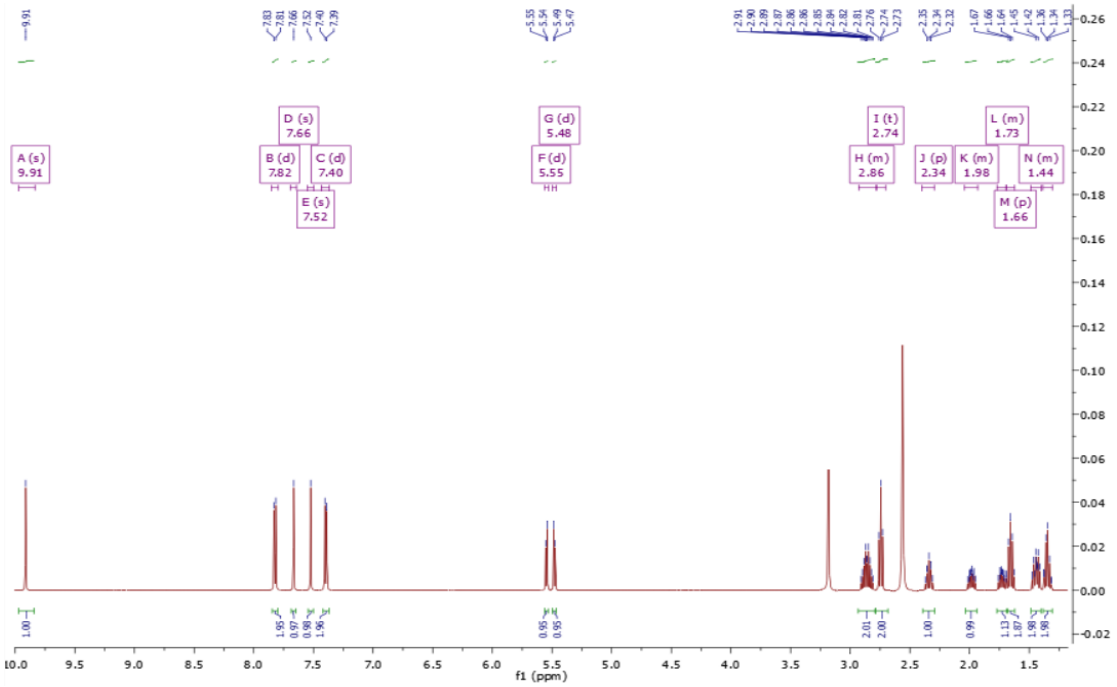


Figure 4: H-NMR for compound (10)

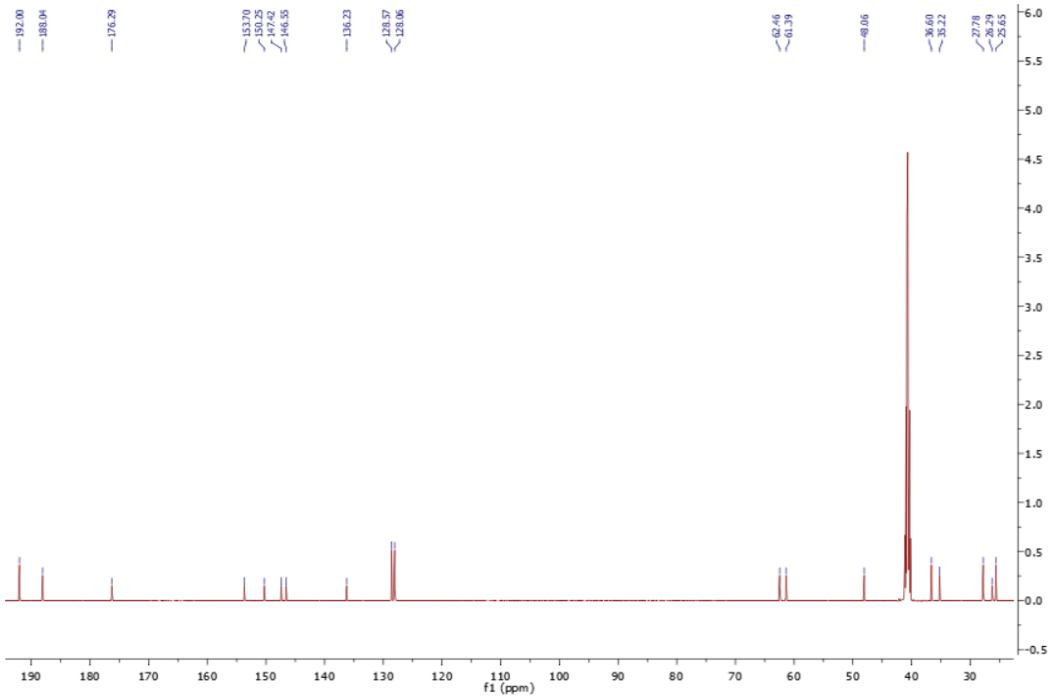


Figure 5: ^{13}C-NMR for compound (10)

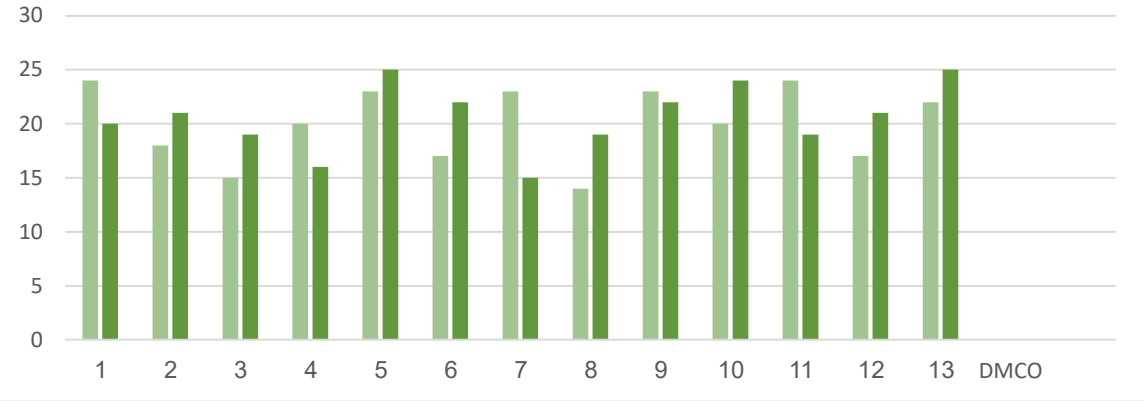
Compounds (12 and 13) were synthesized as above except using urea, the formation of target compounds proven by IR which showed bands refer to (C=O) groups at the rang of (1711-1661 cm^{-1}) another band refer to (C=N) group at (1625-1618 cm^{-1}). Again the ^{1}H-NMR for (13) gave

two doublet belong to the aromatic protons at (7.50 and 7.18 ppm) also (N-H) and (C= NH) singlet at (6.28, 6.40 ppm) respectively.

Biological study

The newly synthesized compounds (1-13) were screened for biological activity against S. aureus, E. coli Gram negative and positive using the disk diffusion method on agar plates, with the synthesized compounds dissolved in dimethyl sulfoxide (DMSO). The plates were incubated at 37°C for 24 hours, after which the inhibition zones were measured (in millimeters). The results demonstrated significant antibacterial efficacy for synthesized compounds as shown in figure (6) compounds gave an excellent activity against the two types of bacteria.

Figure 6 biological activity for the synthsized compounds



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