Molecular Drug Design, Synthesis and Antibacterial study of Novel 4-Oxothiazolidin-3-yl Derivatives

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Abstract

New compounds containing 4-thiazolidinone pharmacophore 5(a) and (5b) have been synthesized. The chemical structures of the intermediate and final compounds were characterized and confirmed by using FT-IR and ^{1}H-NMR spectroscopy. All final compounds were tested against gram-positive and gram-negative bacteria using a well-diffusion technique for their ability as antimicrobial agents. The tested compounds 5a and 5b showed variable and modest antibacterial activity against gram-negative bacteria and gram-positive bacteria. Molecular docking simulations were studied to understand the molecular core. The results were achieved by docking, the most active compounds into the active site of protein of the bacteria which completely accorded with in vitro results.

Key words: Antibacterial, Molecular Docking Simulations, Heterocyclic, Thiazolidinone, Trimethoprim.

تصميم جزيئي وتحضير ودراسة مضادات بكتريا لمشتقات 4-اوكسوثايزوليدينون جديدة

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الخلاصة:

تم تصنيع سلسلة جديدة من المركبات التي تحتوي على الخاصية الدوائية 4-ثيازوليدينو ن(a,b5). ثم تمييز التركيب الكيميائي للمركبات الوسيطة والنهائية وتأكيده باستخدام التحليل الطيفي FT-IR و H-NMR 1 واختبار المركبات النهائية ضد البكتيريا إيجابية الجرام وسالبة الجرام باستخدام تقنية نشر جيد لقدرتها كعوامل مضادة للميكروبات. وأظهرت المركبات المختبرة (5 ب) و (5 أ) نشاطًا ضعيفا مضادًا للبكتيريا ضد البكتيريا سالبة الجرام والبكتيريا إيجابية الجرام مثل الإشريكية القولونية ،الراكدةالبومانية، المكورات العنقودية الذهبية ، والمكورات العقدية كدواء قياسي مقارنة مع تريميثوبريم. اضافة الى ذلك تمت دراسة محاكاة الإرساء الجزيئي لفهم اللب الجزيئي.وتم التاكد من النتائج عن طريق التحام المركبات في الموقع النشط لبروتين البكتيريا والتي تم تطابقها تمامًا مع النتائج المختبرية.

الكلمات المفتاحية: مضاد للالتهاب, محاكاةالارساء الجزيئي,الحلقية غير المتجانسة,ثايزوليدينون,ترايميثيبرم

Introduction

A microorganism or microbe, which may exist in organisms that own closest one cellular. Via a microscope, they appear to be balls, rods, or spirals. Some microorganism helps in meals digestion, can destroy disease-causing cells, and may offer the frame with wanted vitamins. However, infectious bacteria can affect us to a severe level. [1]They reproduce immensely fast in the frame freeing off toxins, the chemical that may harm the tissue and make us ill. Such as some

examples of bacteria; are Streptococcus, Staphylococcus, Acinetobacter and E. coli, which provide an upward push to the infection together with bacteremia, pneumonia, meningitis, endocarditis, urinary tract infection, and wound infections.[2]

Antibiotics are the usual remedy for these. However, the trouble of bacterial contamination similarly receives complex when coupled with the unfold of antibiotic-resistant microorganisms [3] even though it's miles actual that antibiotics and antimicrobials have revolutionized the treatment of infectious sicknesses, but the fast growth of antibiotics resistance has reached to an essential factor. Microorganisms have adapted defenses towards these antibiotics, despite the fact that we are developing more recent drugs.[4]

Heterocyclic compounds occupied a relevant role amongst those molecules that make lifestyles possible.Thiazolidinone derivatives possess interesting biological activities most likely presented to them due to strong aromaticity of the ring framework, which prompts to great in vivo stability and for the most part, an absence of toxicity for higher vertebrates, including humans when a different functional group that interacts with biological receptor are attached to an aromatic ring.[5, 6]

Thiazolidin4-ones are thiazolidine derivatives that belong to an essential institution of heterocyclic compounds in a five-member ring containing sulfur and nitrogen. [7]

Thiazolidin-4-one derivatives have received lots of attention due to their widespread applications in the chemotherapeutic field. They display a wide variety of biological activities such as Antimicrobial, Anti-inflammatory[8,9] Anti–Toxoplasma Gondii [10,11], and anti-HIV.[12,13] . The broad and potent activities of 4-thiazolidinones have established it as one of the naturally significant scaffolds. The presence of thiazolidinone rings in a wide range of known biologically active compounds has inspired researchers to synthesize several compounds containing this ring. [14]

The main synthetic routes to 1,3-thiazolidine-4-ones involve three components that are an amine, a carbonyl compound, and a mercapto-acid. [15]The reactions start with the formation of an imine (the nitrogen of amine attacks the carbonyl of aldehyde or ketone), which undergoes attack by a generated sulfur nucleophile, and followed by intramolecular cyclization on the elimination of water. [16]

N.B. [17] Patel synthesized a series of 4-thiazolidinone compounds, exhibiting marked antibacterial activity against *streptococcus pyogenes* and *Staphylococcus aureus*.

Therefore, some new 4-thiazolidinone derivatives have been synthesized by using 4-amino benzyl alcohol as a starting material and evaluated for their antibacterial activity against gram-positive and gram-negative bacteria. Compared to Trimethoprim by molecular d ocking, the synthesized compound expecte d to have weak antibacterial activity. Molecular docking is a dominant drug system that anticipates the conformation and measurement of a Ligand's binding energy at the active position of the target enzyme(s)[18]. This method typically involves first: approximating potential energy states of the complex (protein ligand), and second: calculating Free Binding Energy standards (FEB) of the complexes described above that can be related to biological activities [19]. Dockingstudyorinsilicois a valuable tool fo r evaluating residues (amino acid) that are i ntegrated into the applicant's binding to the active area of a target enzyme [20].

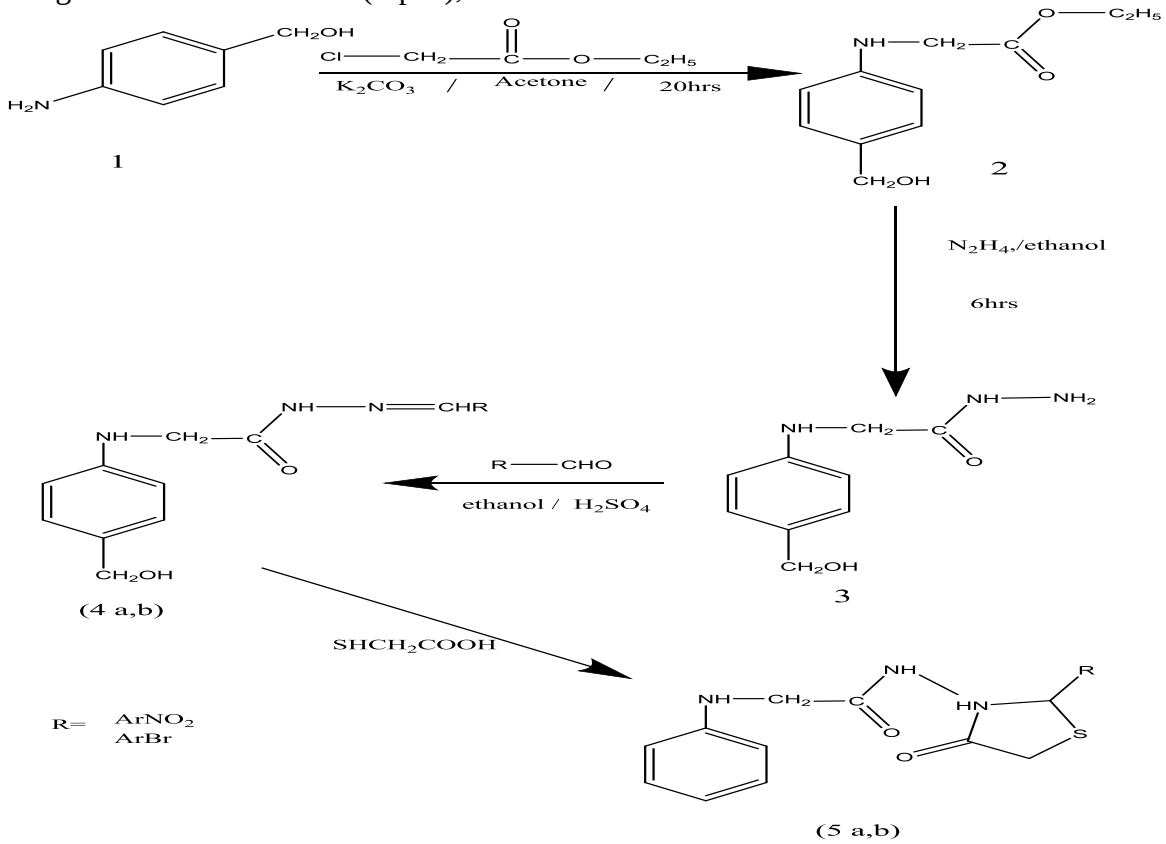
Experimental

Materials and Methods

The synthetic compounds utilized for the synthesis and the solvents used for the purification, recrystallization as well as analysis of synthesized products were

received from the commercial suppliers (Iraq, BDH-England, HimediaIndia, Merck-Germany, Fluka AG Switzerland, and Sigma-Aldrich, Germany). The melting points of the synthesized compounds measured by using open capillary method with Electric melting points apparatus, IR bands were recorded using FTIR Shimadzu (Japan), One-dimensional 1H- NMR, spectra were recorded using a Bruker (Avance) 400 MHZ NMR and 300 MHZ instruments using tetra-methyl silane (TMS) as an internal standard.

The chemical synthesis of target compounds was achieved following the procedure shown in the (scheme 1)



Scheme (1): Synthesis of intermediates and final compounds 5(a,b)

Compound 2: Synthesis of {ethyl (4-(hydroxymethyl) phenyl) glycinate}:

A mixture of 4-amino benzyl alcohol (14mmole,1.8 g), anhydrous potassium carbonate (15mmole,2.07 g) and Sodium iodide (0.3 mmol,0.050 g) in acetone 15 ml was refluxed at 60 °C for 3-4 hours then ethyl chloroacetate (5mmole,0.5 ml) was added and continue the reflux for 18 hours. The mixture then filtered and excess of acetone, then removed by distillation. The remaining filtrate was washed with 5% HCl and dried over anhydrous sodium sulfate, and the resultant collected liquid was evaporated under reduced pressure to give pure compound. [21]

The percentage yield is 85%, M.P. 73-74 ° C, FT-IR band absorption characteristic C = O ester stretch in 1735cm-1, C-O-C ester stretch at 1180 cm-1. ^{1}H-NMR spectra showed a singlet for $CH_2C{=}O$ at 3.38 (δ, ppm) while the CH_2-CH_3 show quartet at 3.63 (δ, ppm) as well as a triplet at 1.16 for CH_3 group.

Compound 3: Synthesis of 2-((4-(hydroxymethyl) phenyl) amino) acetohydrazide

(6mmol, 1.4g) of compound **2** was dissolved in (15 ml) ethanol and (14 ml, 0.7ml) of hydrazine hydrate (90%) was added. The reaction mixture was stirred at room temperature overnight. The next day,

the solvent was removed under reduced pressure and the crude product was washed with ether under stirring to get the products in the pure state. [22]
The percent yield 70%, M.P. 114-116 °C. FTIR characteristic absorption bands of υNH-NH_2 stretching at 3307 and 3024cm^{-1} and υ C=O is stretching of amide at 1670cm^{-1}. ^{1}H-NMR spectra showed broad singlet for NH_2 protons of hydroxide at 4.06 (δ, ppm), broad singlet for NH proton at 5.73 (δ, ppm) and singlet for the NH proton of hydroxide at 8.31 (δ, ppm).

Compound 4a: Synthesis of 2-((4-(hydroxymethyl) phenyl) amino)-N'-(4-nitrobenzylidene) acetohydrazide.
(1mmol,0.195g) of compound **5** and (1.1mmol) appropriate aromatic aldehydes in absolute ethanol (25ml) were heated under reflux on a water bath for (6hrs.) at 80°C, during the refluxing period 2-3 drops of sulfuric acid were added. The solvent was evacuated under reduced pressure to a possible extent and residue was poured into ice-cooled water to get the product. It was filtered, washed with cold water and dried. The crude product was purified by recrystallization from ethanol. [23]

Compound **4a**: The percent yield is 70%, M.P. 154-155 °C. FT-IR characteristic absorption bands of υ NH stretching of amide at 3290 cm^{-1}, υ C=O is stretching of amide at 1627cm^{-1}, υ C=N is stretching of isoxazole at 1597cm^{-1} and NO_2 asymmetric stretching at 1508 cm^{-1}. ^{1}H-NMR spectra showed singlet of N=CH-Ar proton at 8.55 (δ, ppm), broad singlet for NH-N amide proton at 11.07 (δ, ppm),

Compound 4b: N'-(4-bromobenzylidene)-2-((4-(hydroxymethyl)phenyl) amino) acetohydrazide
The percent yield is 78%, M.P. 213-218 °C. FT-IR characteristic absorption bands of υ NH amide stretching at 3248cm^{-1}, υ C=O is stretching of amide at 1683 cm^{-1} and υ C=N is stretching of isoxazole at 1625cm^{-1}. ^{1}H-NMR spectra showed a singlet for N=CH-Ar proton at 8.79 (δ, ppm), singlet for NH-N proton of amide at 11.58 (δ, ppm).

Synthesis of thiazolidine-4-one analogs 5 (a,b):
A mixture of (3ml) Thioglycolic acid and (1mmol) of either compound **4 (a,b)** was heated at (60°C) for 20 hours, Ethyl acetate (5ml) was added to the reaction mixture; the organic layer was washed with saturated sodium bicarbonate (3x20ml). Dried with anhydrous sodium sulfate, and concentrated to give oil using a rotary evaporator. The oil washed with ether to give the last compounds. [24]

Compound 5a: 2-((4-(hydroxymethyl) phenyl) amino)-N-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl) acetamide.
The percent yield is 65%, M.P. 109-110 °C. FT-IR characteristic absorption bands of υ NH stretching of amide at 3377cm^{-1}, υ C=O is stretching of thiazolidinone at1718cm^{-1}, υ C=O is stretching of amide at 1681cm^{-1} and υ C-S stretching band at 1220cm^{-1}.^{1}H-NMR spectra showed doublet of doublet for the CH2 proton of thiazolidinone at C5 in the range of 3.76-3.98 (δ, ppm), singlet for the CH proton of thiazolidinone at C2 at 5.97 (δ, ppm), broad singlet for NH-N proton of amide at 8.31 (δ,.ppm).

Compound 5b: N-(2-(4-bromophenyl)-4-oxothiazolidin-3-yl)-2-((4-(hydroxymethyl)phenyl)amino)acetamide The percent yield is 65%, M.P. 91-92 °C. FT-IR characteristic absorption bands of υ NH stretching of amide at 3369cm^{-1}, υ C=O is stretching of thiazolidinone at1712cm^{-1}, υ C=O is stretching of amide at 1681cm^{-1}, and υ C-S stretching band at 1166cm^{-1}. ^{1}H-NMR spectra showed doublet of doublet for the CH2 proton of thiazolidinone at C5 in the range of 3.72-3.96 (δ, ppm), singlet for the CH proton of thiazolidinone at C2 at 5.78 (δ, ppm),

broad singlet for NH-N proton of amide at 11.27 (δ, ppm)

Biological action

The preliminary antibacterial of the synthesized compound 5(a,b) has been done.

Bacterial isolates: The antimicrobial activity of the final compounds was done in the Biology Department /College of the Pharmacy/ Mustansiriyah University

A preliminary antibacterial activity has been carried out according to Well Diffusion Method: The synthesized compounds have been contemplated for their antimicrobial activity in vitro against four tested bacteria. Four species of bacteria were used to assay the bacteriological activity of compounds in this study, two of them are gram-positive *Staphylococcus aureus & Streptococcus pyougenes* and the others are gram-negative *Acenetobactor bumanni & Escherichia coli*, they were isolated from different clinical sources. The bacterial diagnosis based on a morphological examination, biochemical tests, and diagnostic kits. Trimethoprim was used as a standard drug for antibacterial activity.

Preparation of serial dilutions of the newly synthesized compounds:

1. Dissolve (0.005g) for each compound in DMSO (5ml) (the stock solution 1000µg/ml).
2. Dilute 2.5 ml of the stock solution by addition of (2.5 ml) of DMSO to it. (500µg/ml) (1st dilution).
3. Dilute (2.5 ml) of 1st dilution by addition of (2.5 ml) of DMSO to it. (250µg/ml) (2nd dilution).
4. Dilute (2.5 ml) of 2nd dilution by the addition of (2.5 ml) of DMSO to it. (125µg/ml) (3rd dilution).
5. Dilute (2.5 ml) of 3rd dilution by addition of (2.5 ml) of DMSO to it. (62.5µg/ml) (4th dilution).

This process was done for all the synthesized compounds 5(a,b) & for Trimethoprim drug which was used as a standard.

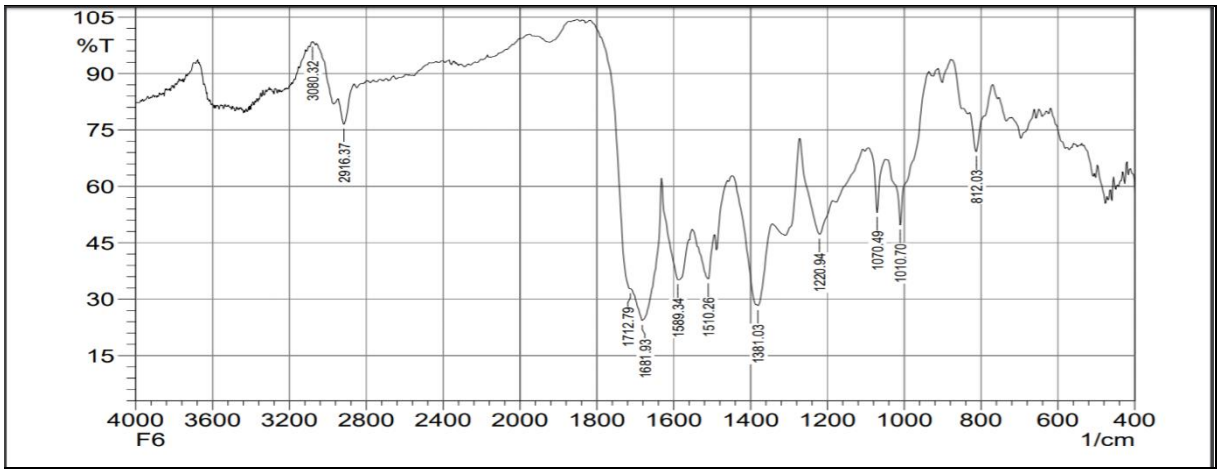
Sensitivity Assay: The antibacterial activity of each derivative was determined by agar well diffusion assay and carried out by using pure culture for all species of bacteria, an inoculum of bacteria was the first subculture in brain heart infusion broth and incubated at 37°C for 18-24 hour. After incubation, a loopful of each species transferred to a tube containing 3 mL normal saline and vortex well. The concentration of (1.5×108 CFU/mL) was obtained by using McFarland turbidity standard (number 0.5) of each bacterium inoculated by use glass spreader on the surface of Mueller Hinton Agar (MHA) plates previously prepared. The plate was allowed to dry and punched wells (five) in diameter of 6 mm. into agar. Subsequently, in each agar plate of tested bacteria five wells were made and (100µl) of dilutions of the derivatives (500,250,125 and 62.5) introduced into wells on the MHA plate. DMSO used as a negative controller. The plates were kept warm at 37 °C for 24 hours and the antimicrobial action was estimated by determining the diameter of the inhibition zone.[25] The evaluation of antibacterial action was based on the extent of the diameter of the inhibition zone formed all over the place of the well as shown in table 1.

Table 1: Antibacterial activity of Trimethoprim and compounds 5(a-d) against tested bacteria:

Comp. No.	Conc. (µg/ml)	Inhibition zone(mm)			
		Gram-negative		Gram-positive	
		Escherichia coli	Acinetobacter	Staphylococcus aureus	Streptococcus pyougenes
Trimethoprim	500	26	20	28	16
	250	22	18	24	10
	125	16	14	20	6
	62.5	10	10	14	2
DMSO	Pure	----------	----------	----------	----------
5a	500	4	8	4	2
	250	3	6	2	2
	125	2	4	2	2
	62.5	2	2	2	1
5b	500	3	10	2	4
	250	2	8	2	2
	125	2	6	2	1
	62.5	1	8	2	1

Results and Discussion

The synthesis of the target compounds **5(a,b)** through their intermediates accomplished effectively. And this can be seen in the IR charts by the formation of υ C=O stretching of thiazolidinone at1712cm^{-1}, υ C=O stretching of amide at 1681cm^{-1} and υ C-S stretching band at 1220cm^{-1}as shown in figure(1).In addition, ^{1}HNMR results assure the formation of compound 5a &5b by the appearance of a doublet of doublet for the CH_2 proton of thiazolidinone at C5 in the range of 3.76-3.98 (δ, ppm) and singlet for the CH proton of thiazolidinone at C2 at 5.78-5.97 (δ, ppm) in figure(2).



Figure(1): FT-IR spectrum of compound (5a)

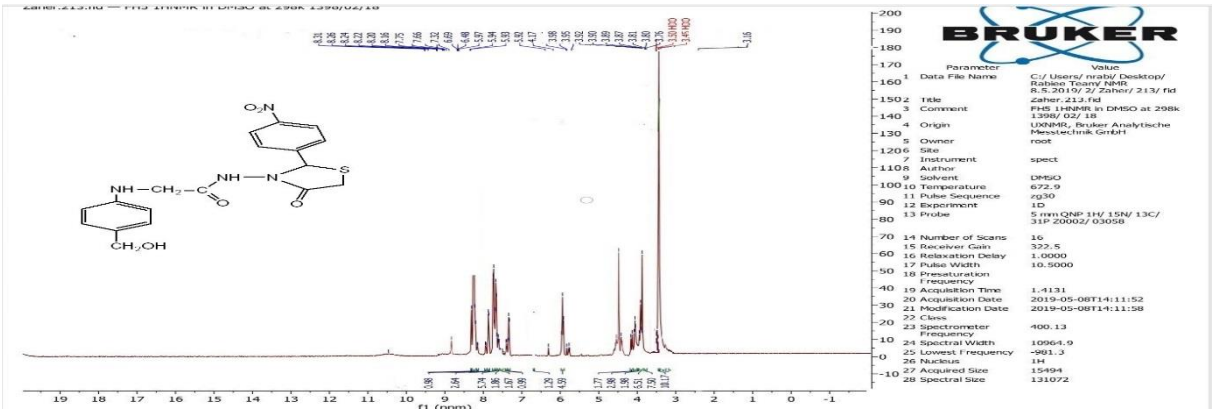


Figure (2): H1-NMR Spectrum of compound (5a)

Preliminary pharmacological study as antibacterial: Trimethoprim used as a reference, DMSO used as a control and the synthesized compounds **5 (a, b)** was screened for their antibacterial activity against gram-negative bacteria*: Escherichia coli & ,Acenetobactor bumanni* and gram-positive bacteria *Staphylococcus aureus & Streptococcus pyougenes* at concentrations of (62.5,125, 250 & 500 µg/ml) aside from the control which used in the pure state. Table 1 illustrates the inhibition zone in (mm) for each concentration of all tested compounds.

In general, both compounds had low antibacterial activity in comparison to Trimethoprim. However, compound 5b had a varied and modest effect against Acenetobactor but still less than Trimethoprim.

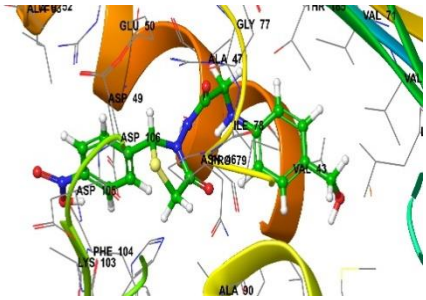
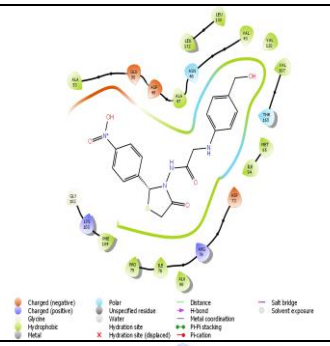
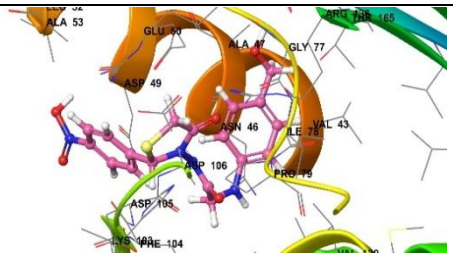
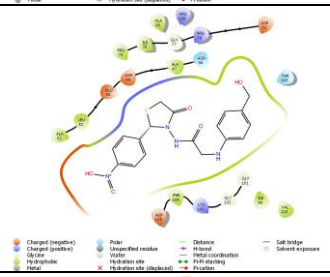
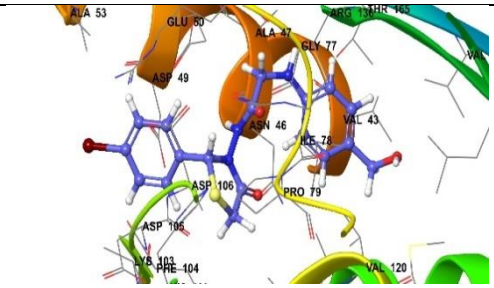
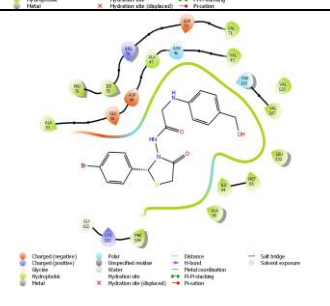
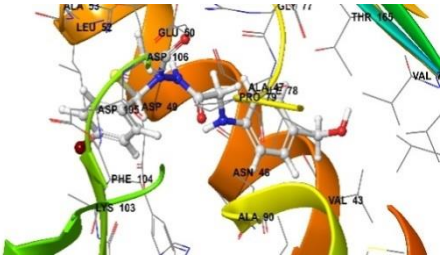
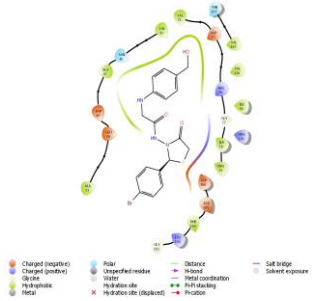
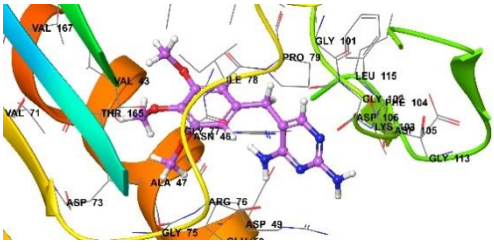
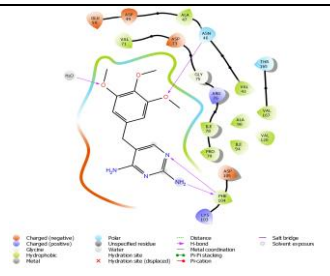
In a comparison with the antibacterial results among the tested compounds, compound 5b is better than compound **5a** as antibacterial activity**,** and both of them are inferior to the standard drug in all concentrations against Gram-negative and positive bacteria.

The crystal structure of *S. Aureus* and *E. coli* and DNA Gyrase B X-ray crystal structures were obtained from the Protein Data Bank by (Pdb id: 3G7B and 3G7E) and binding dynamics with the inhibitor compounds (5b) and (5a). They were docked into the active site of receptors. Their binding interaction template and orientation with amino acid residues were investigated.

The reason for choosing Trimethoprime as positive standard because it gives high score when docked in the DNA Gyrase B protein of bacteria in addition it resembles the compounds 5(a-f) due to that CH_2OH is isoster of NH_2 in Trimethoprime. The result is matched to biological experimental activity result as showing in (Table 2). For *E Coli.* Docking result, the most important interactions inside the active site amino acids are Ile 78, Gly 77, Thr 165 and Asp 73 were reported from references. These amino acids have appeared in ligand interaction views which approve the binding position and orientation inside active site.

It is clear from (table 2) that compounds 5a, 5b have no interactions with the specific amino acid required for the biological activity and molecular docking analysis was in an agreement with the experimental results.

Table (2): Compounds inside the active site of *E. coli* Gyrase B (PDB ID; 3G7E) surrounded by amino acids with docking score.

Compound	A compound as ball and stick, receptor as ribbon	Ligand interaction view of the compound	Docking Score in kcal/Mol
5a R			-1.26
5a S			-1.42
5b R			-1.17
5b S			-1.19
Trimethoprim			-9.01

Conclusion

In this study, we conclude that the synthesis of the designed compounds has been effectively accomplished with the characterization and identification of the compounds accomplished by the assurance

of physical properties (melting point and description), FT-IR spectroscopy and ^{1}H-NMR spectra. The anti-bacterial assessment of the final products with the incorporation of the electron-withdrawing group (NO_2& Br) displays lower activity in comparing with trimethoprim. In addition, all compounds were docked inside the active site of E. *coli* and DNA Gyrase B crystal structure using the Maestro software package. Furthermore, compared with experimental results, the docking score approves binding ability surrounded by residues of amino acids

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