Egypt.J.Chem. **Vol. 63**, No.7. pp. 2591- 2603 (2020)

Egyptian Journal of Chemistry
http://ejchem.journals.ekb.eg/

Design, Synthesis and Antibacterial Study of New Agents Having 4-Thiazolidinone Pharmacophore

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A NEW series of compounds containing 4-thiazolidinone pharmacophore 5(a-d) have been synthesized. The chemical structure of the intermediate and final compounds was 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 5b and 5c showed comparable antibacterial activity against gram-negative bacteria and gram-positive bacteria like Escherichia coli, Acinetobacter bumannii, Staphylococcus aureus, and Streptococcus pyougenes as a standard drug compared with Trimethoprim. 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.

Keywords: Antibacterial, Molecular Docking Simulations, Heterocyclic, Thiazolidinone, Trimethoprim.

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 diseases. 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.1,3,4-thiadiazole 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

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Received 3/10/2019; Accepted 13/12/2019
DOI: 10.21608/ejchem.2019.17518.2088

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]

A few syntheses techniques of 4-thiazolidinones are widely reported. 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. Patel synthesized a series of 4-thiazolidinone compounds, exhibiting marked antibacterial activity against *streptococcus pyogenes* and *Staphylococcus aureus*. [17]

Therefore, a series of 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. The synthesized compound expected to have good antibacterial activity compared to Trimethoprim via the molecular docking approach. Molecular docking is a prevailing tool in drug discovery to expect the conformation and evaluation binding energy of a Ligand docked into the active site of the target enzyme(s)[18]. This method typically consists of first: approximating possible energy states of the complex (protein-ligand) and second: to compute free binding energy (FEB) standards of fore mentioned complexes which can be associated with biological activities[19]. Docking study or in silico designs is a valuable tool to determine the residues (amino acid) which incorporated into the binding of a lead drug applicant to the active site 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 ^{1}H- 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)

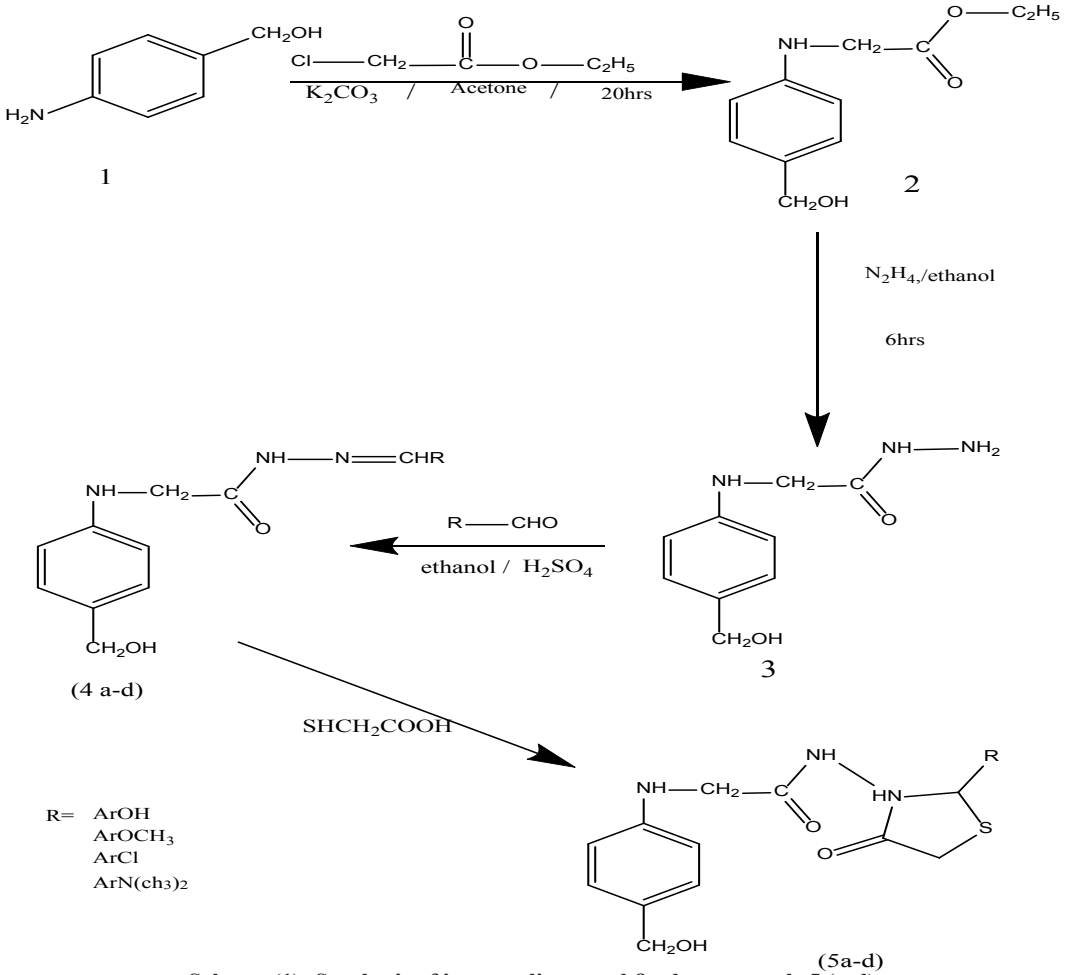
Compound 2: Synthesis of {ethyl (4-(hydroxymethyl) phenyl) glycinate}:

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 relaxed 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 quarter 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]



Scheme (1): Synthesis of intermediates and final compounds 5 (a-d)

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 {N›-(4-(dimethylamine) benzylidene) -2-((4-(hydroxymethyl) phenyl) amino) acetohydrazide}.

(1mmol,0.195g) of compound **3** 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]3-diamine] are synthesize by Microwave irradiation, Reflux, Stirring and Grinding methods. Compared with all this method of synthesis of Schiff base ligand the Microwave irradiation has great virtue. Microwave irradiation synthesis does not only require the least time, but also has the greatest yield. A Schiff base was synthesized from p-Chlorobenzaldehyde and o-Phenylenediamine. Metal complexes of the Schiff base were prepared from chloride salts of Ni (II

Compound 4a: N'-(4-(dimethylamino) benzylidene) -2-((4-(hydroxymethyl) phenyl) amino) acetohydrazide

The percent yield is 75%, M.P. 169-170°C. FT-IR characteristic absorption bands of υ NH stretching of amide at 3304 cm^{-1}, υ C=O is stretching of amide at 1662cm^{-1}, υ C=N is stretching of isoxazole at 1608cm^{-1} and aromatic $CN(CH_3)_2$ stretching at 1367 cm^{-1} and ^{1}H-NMR spectra showed singlet of N=car proton at 8.53

(δ, ppm), broad singlet for NH-N amide proton at 9.68 (δ, ppm),

Compound 4b: 4-(hydroxymethyl) phenyl) amino) -N›(4methoxybenzylidene) acetohydrazide.

The percent yield is 83%, M.P. 150-151°C. FT-IR characteristic absorption bands of υ NH amide stretching at 3053cm^{-1}, υ C=O is stretching of amide at 1618 cm^{-1} and υ C=N is stretching of isoxazole at 1620cm^{-1}. ^{1}H-NMR spectra showed singlet for N=CH-Ar proton at 8.66 (δ, ppm), singlet for NH-N proton of amide at 9.97 (δ, ppm).

Compound 4 c: N›-(4-hydroxybenzylidene) -2-((4-(hydroxymethyl) phenyl) amino) acetohydrazide.

The percent yield is 65%, M.P. 196-170 °C. FT-IR characteristic absorption bands of υ NH amide stretching at 3245cm^{-1}, υ C=O is stretching of amide at 1674cm^{-1}, υ C=N isoxazole stretching at 608cm^{-1} .

Compound 4 d: N'-(4-chlorobenzylidene) -2-((4-(hydroxymethyl) phenyl) amino) acetohydrazide

The percent yield is 63%, M.P. 161-162°C. FT-IR characteristic absorption bands of υ NH amide stretching at 3367cm^{-1}, υ C=O amide stretching at 1683cm^{-1}, υ C=N isoxazole stretching at 1616cm^{-1}. ^{1}H-NMR spectra showed singlet of N=CH-Ar proton at 8.27 (δ, ppm), broad singlet for NH-N proton of amide at 11.58 (δ, ppm).

Synthesis of thiazolidine-4-one analogs 5 (a-d):

A mixture of (3ml) Thioglycolic acid and (1mmol) of either compound **4 (a-d)** 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]4-bis(6-(substituted phenyl

Compound 5a: -(2-(4-(dimethylamino) phenyl) -4-oxothiazolidin-3-yl) -2-((4-(hydroxymethyl) phenyl)
Amino) acetamide:

The percent yield is 65%, M.P. 109-110°C. FT-IR characteristic absorption bands of υ NH stretching of amide at 3379cm^{-1}, υ C=O is stretching of thiazolidinone at1732cm^{-1}, υ C=O is stretching of amide at 1650cm^{-1} and υ C-S stretching band at 1130cm^{-1}.^{1}H-NMR spectra showed doublet of doublet for the CH2 proton of thiazolidinone at C5 in the range of 3.49-3.66 (δ, ppm), singlet for the CH proton of thiazolidinone at C2 at 5.18 (δ,ppm), broad singlet for NH-N proton of amide at 7.31 (δ,ppm).

Compound 5b: 2-((4-(hydroxymethyl) phenyl)amino)-N-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl) acetamide:

The percent yield is 65%, M.P. 91-92 °C. FT-IR characteristic absorption bands of υ NH stretching of amide at 3350cm^{-1}, υ C=O is stretching of thiazolidinone at1734cm^{-1}, υ C=O is stretching of amide at 1674cm^{-1}, aromatic C-OCH$_3$ stretching at 1259 cm^{-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 3.60-3.75 (δ, ppm), singlet for the CH proton of thiazolidinone at C2 at 5.34 (δ, ppm), broad singlet for NH-N proton of amide at 8.64 (δ,ppm)

*Compound 5c: 2-((4-(hydroxymethyl) phenyl)amino)-N-(2-(4-hydroxyphenyl)-4-o*xothiazolidin-3-yl)acetamide:

The percent yield is 50%, M.P. 112-113°C. FT-IR characteristic absorption bands of phenolic OH stretch overlap with υ NH stretching of amide at 3300-3288cm^{-1}, υ C=O is stretching of thiazolidinone at1716cm^{-1}, υ C=O is stretching of amide at 1635cm^{-1} and υ C-S stretching band at 1236cm^{-1}. ^{1}H-NMR spectra showed doublet of doublet for the CH2 proton of thiazolidinone at C5 in the range of 3.54-3.92 (δ, ppm) singlet for the CH proton of thiazolidinone at C2 at 5.25 (δ,ppm), broad singlet for NH-N proton of amide at 11.03 (δ,ppm).

Compound 5d: N-2 (4chlorophenyl)4oxothiazolidin3yl)2 ((4 (hydroxymethyl) phenyl) amino) acetamide .

The percent yield is 76%, M.P. 120-121°C. ,FT-IR characteristic absorption bands of υ NH stretching of amide at 3446cm^{-1}, υ C=O is stretching of thiazolidinone at1718cm^{-1}, υ C=O is stretching of amide at 1678cm^{-1}, υ C-S stretching band at 1226cm^{-1} and aromatic C-Cl at 815cm^{-1}. ^{1}H-NMR spectra showed doublet of doublet for the CH2 proton of thiazolidinone at C5 in the range of 3.40-3.58 (δ, ppm), singlet for the CH proton of thiazolidinone at C2 at 5.84 (δ, ppm), broad singlet for NH-N proton of amide at 11.23 (δ, ppm).

Biological action

The preliminary antibacterial of the synthesized compound 5 (a-d) has been done. Bacterial isolates: The antimicrobial activity of

the final compounds were done in the Biology Department /College of the Pharmacy/ University of Al-Mustansiriyah.

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 pyogenes* and the others are gram-negative *Acinetobacter 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-d) & 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.

Results and Discussion

The synthesis of the target compounds **5(a-d)** through their intermediates accomplished effectively. Preliminary pharmacological study as antibacterial: Trimethoprim used as a reference, DMSO used as a control and the synthesized compounds **5 (a-d)** were screened for their antibacterial activity against gram-negative bacteria*: Escherichia Coli &, Acinetobacter bumannii* and gram-positive bacteria *Staphylococcus aureus & Streptococcus pyogenes* 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, compound **5c** had action practically equivalent to Trimethoprim against *E. Coli* and better than Trimethoprim against *Acinetobacter, and S. Pyougenes* while compound **5d** had the least one comparison to Trimethoprim, on the other hand, compound **5b** had better acted than Trimethoprim on *streptococcus pyogenes* and equivalent to the standard drug in *Acinetobacter bumanni.*

In a comparison with the antibacterial results among the tested compounds, compound 5c is the best one as an antibacterial activity, then compound **5b** comes next to it in all concentrations against Gram-negative and positive bacteria.

Molecular docking

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 (5c). All synthesized compounds were docked into the active site of receptors. Their binding interaction template and orientation with amino acid residues were investigated. All compounds have a chiral center and this generated two isomers of each compound (R & S).

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

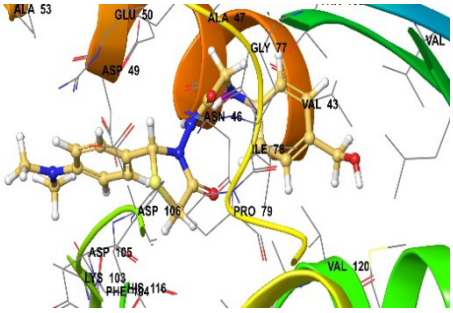
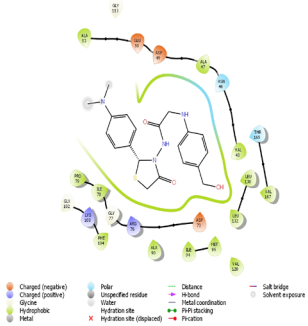
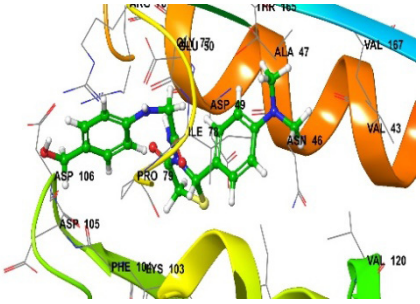
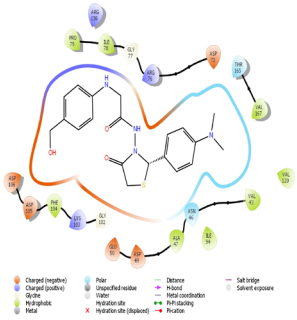
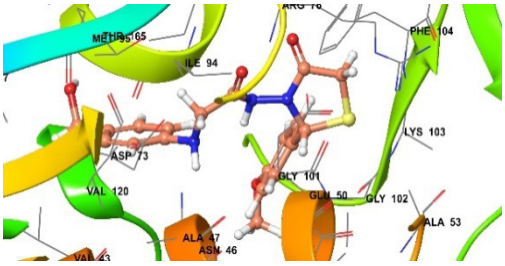
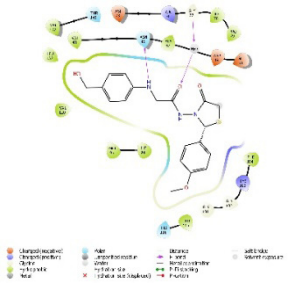
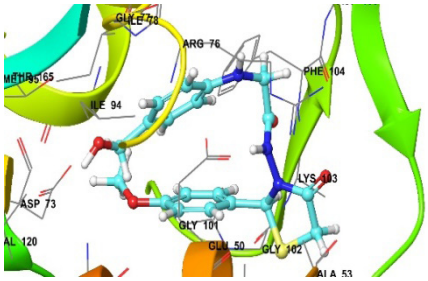
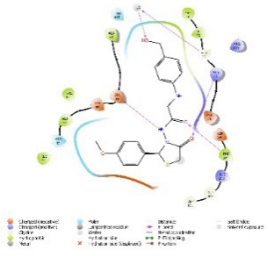
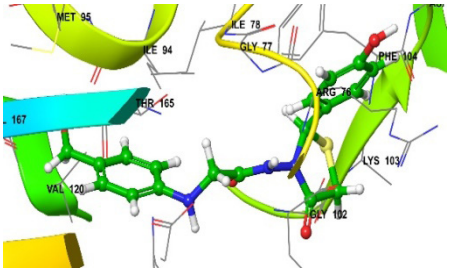
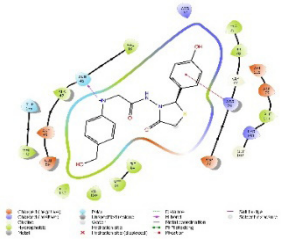
Comp. No.	Conc. (µg/ml)	Inhibition zone(mm)			
		Gram-negative		Gram-positive	
		Escherichia coli	Acinetobacter	Staphylococcus aureus	Streptococcus pyogenes
Trimethoprim	500	26	20	28	16
	250	22	18	24	10
	125	16	14	20	6
	62.5	10	10	14	2
DMSO	Pure	----------	----------	----------	----------
5a	500	6	12	6	4
	250	4	6	4	2
	125	2	6	4	2
	62.5	2	2	1	1
5b	500	14	20	18	14
	250	10	18	18	10
	125	10	14	12	10
	62.5	10	8	10	10
5c	500	20	24	20	14
	250	20	20	18	12
	125	18	16	16	10
	62.5	10	14	10	6
5d	500	4	10	4	2
	250	2	10	2	2
	125	2	8	2	2
	62.5	1	2	1	1

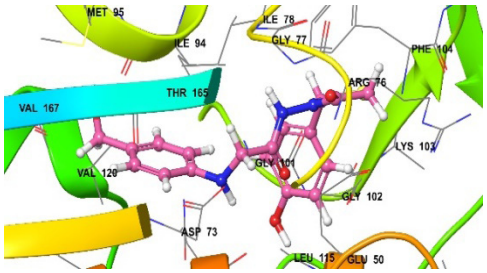
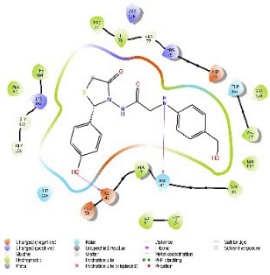
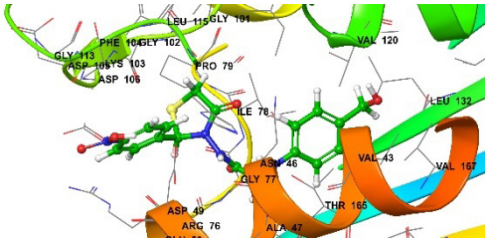
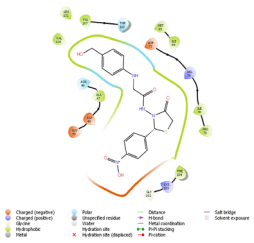
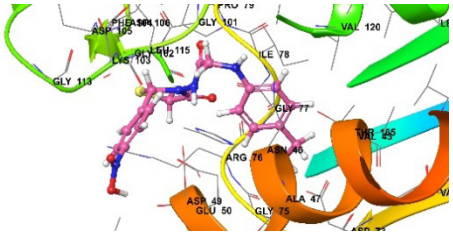
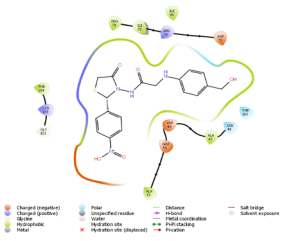
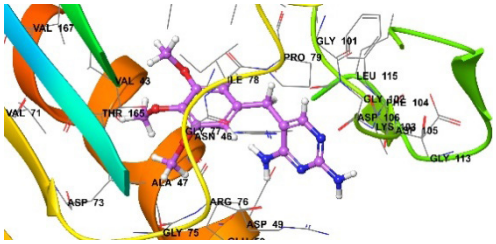
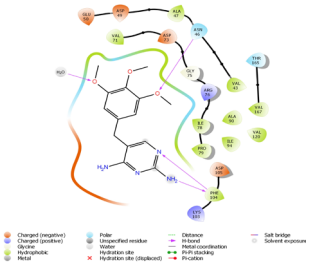
Comparing with trimethoprim as a positive control. The result is matched to biological experimental activity result as showing in (Table 3). The binding affinity within the range of (-7.03 to – 7.39 kcal/mole). Moreover, many H-bond interactions appear between compounds and amino acids in the active site which increased binding affinities such as the H-bonds between ASN54 and ASP81 with ketone and hydroxy of compound 5b R, respectively as well as hydrophobic interactions.

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. Docking score within a range of (-7.36 to -8.31 kcal/mol). In addition, many H-bond interactions are appearing such as the H-bonds between ASN46 and GLY77 with amid and ketone hydroxy of compound 9b R, respectively.

It is clear from (Table 2) and (Table 3) that compounds 5a, 5d (R & S) have no interactions with the specific amino acid required for the biological activity. The 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	
5a R			-1.22
5a S			-1.51
5b R			-7.36
5b S			-7.72
5c R			-8.31

5c S			-8.02
5d R			-1.07
5d S			-1.13
Trimethoprim			-9.01

DME studies

The synthesized compounds have been evaluated for the prediction of reasonable absorption, distribution, metabolism, and excretion (ADME) properties. The ADME of our combined analogs was considered by efficient and accurate tools by using Maestro software and successfully predicting the physical and pharmaceutical properties of the synthesized compounds. Several parameters have been established using Qikprop and their recommended values, which are summarized in Table (4).

According to the recorded values in the Table (4) and (5), which obvious that all synthesized compounds are inactive to the CNS, not crossing the Blood-Brain barrier and have good aqueous solubility with no violation to the five rules of Lipinski.

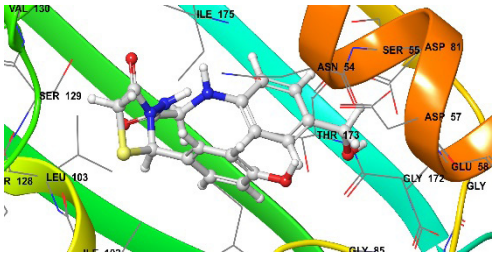
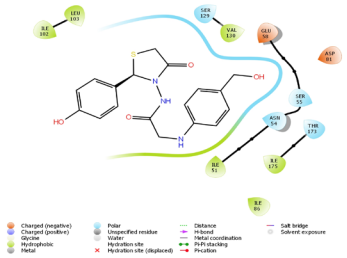
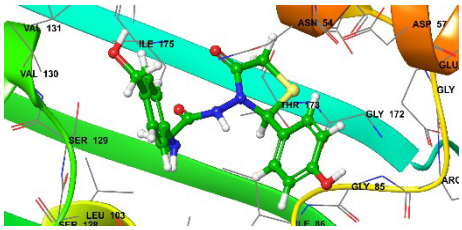
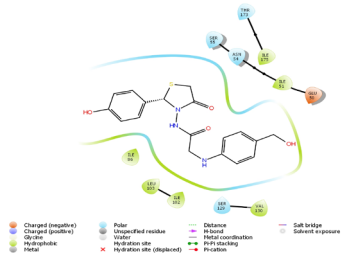
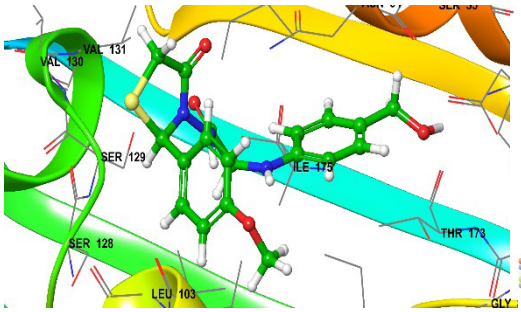
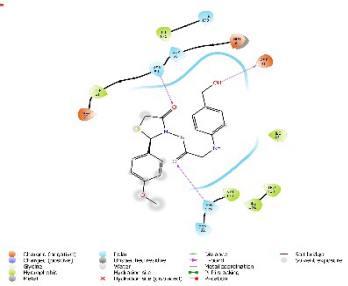
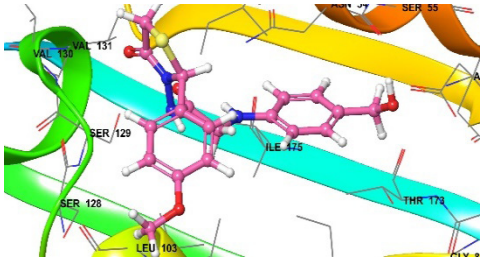
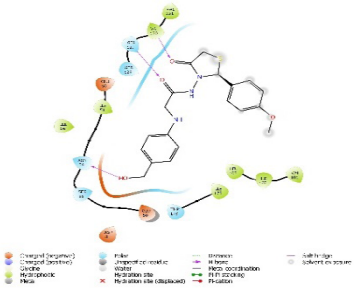
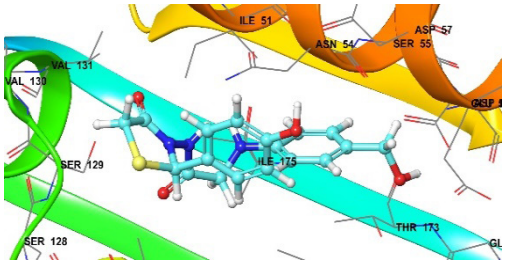
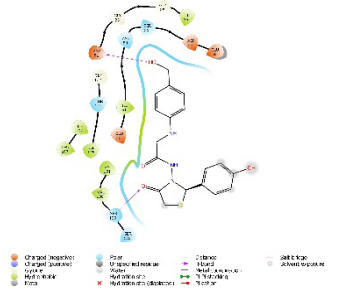
Regarding predicted human oral absorption, compounds 5c have medium values which are lower than 80%, while compounds 5a,5b,5d have high oral absorption with percent values, which are higher than 80 %.

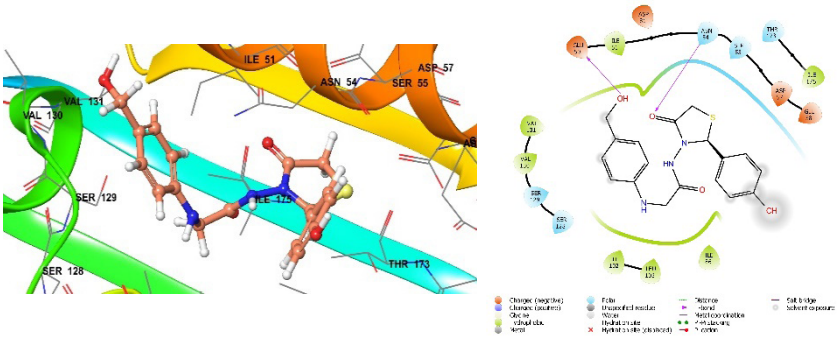
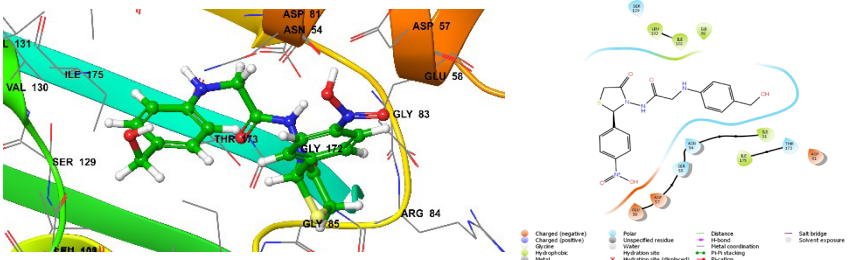
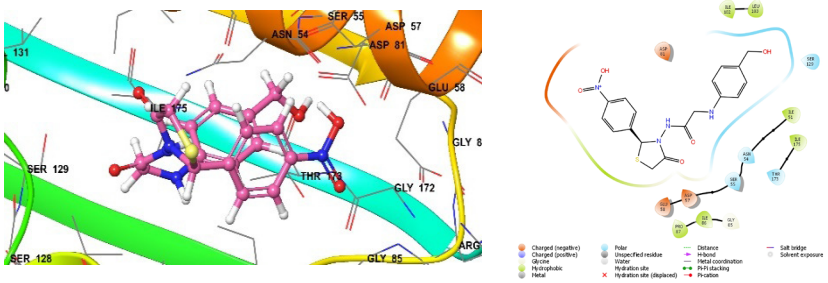
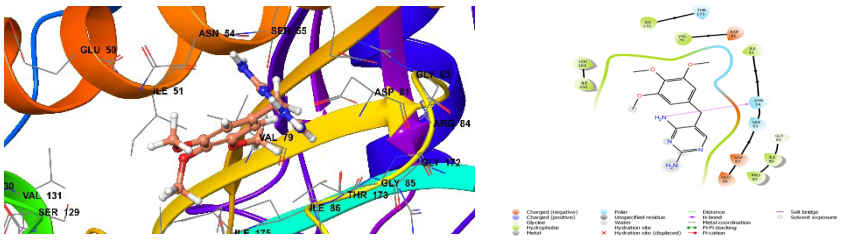
Conclusion

In this study, we conclude that:

1. The synthesis of the designed compounds has been effectively accomplished.
2. Characterization and identification of the synthesized compounds were verified by the assurance of physical properties (melting

TABLE 3. Compounds inside the active site of *S. aureus* Gyrase B (PDB ID; 3G7E) surrounded by amino acids with docking score.

Compound	Compound as ball and stick, receptor as ribbon	Ligand interaction view of compound	Docking Score in kcal/ mol
5a R			-1.43
5a S			-1.25
5b R			-7.03
5b S			-7.37
5c R			-7.23

5c S			-7.39
5d R			-0.75
5d S			-0.92
Trimethoprim			-8.46

point and description), FT-IR spectroscopy and ^{1}H-NMR spectra.

3. The anti-bacterial assessment of the final products with the incorporation of electron-donating groups (OCH_3 & N $(CH_3)_2$) display remarkable activity more than an electron-withdrawing group (Cl).

4. 4. All active compounds were docked inside each active site of *S. Aureus* and *E. coli* and DNA Gyrase B crystal structure using the Maestro software package. Comparing with experimental results, the docking score approves binding ability surrounded by residues of amino acids.

Acknowledgment

NONE

TABLE 4: Different Parameters Tested by Using QikProp with their Recommended Values.

Property or Descriptor	Description	Range or recommended values
QPlogBB	Predicted brain/blood partition coefficient.	−3.0 - 1.2
CNS	Predicted central nervous system activity.	−2 (inactive), +2 (active)
QPlogPw	Predicted water/gas partition coefficient.	4.0 – 45.0
QPlogPo/w	Predicted octanol/water partition coefficient.	−2.0 – 6.5
QPlogS	Predicted aqueous solubility, log S. S in mol dm^{-3}.	−6.5 – 0.5
CIQPlogS	Conformation-independent predicted aqueous solubility.	−6.5 – 0.5
QPlogHERG	Predicted IC_{50} value for blockage of HERG K^+ channels.	concern below −5
QPPCaco	Predicted apparent Caco-2 cell permeability in nm/sec.	<25 poor, >500 great
QPlogKhsa	Prediction of binding to human serum albumin.	−1.5 – 1.5
Human Oral Absorption	Predicted qualitative human oral absorption.	1, 2, or 3 for low, medium, or high.
Percent Human Oral Absorption	Predicted human oral absorption on 0 to 100% scale.	>80% is high <25% is poor
Rule Of Five	Number of violations of Lipinski's rule of five.	maximum is 4

TABLE 5. The ADME Properties of the Synthesized Compounds

Name	CNS	QPlogPw	QPlogPo/w	QPlogS	CIQPlogS	QPlogHERG	QPPCaco	QPlogBB	QPlogKhsa	Human Oral Absorption	Percent Human Oral Absorption	Rule Of Five	Rule Of Three
5a R	-2	14.33	3.13	-5.68	-4.86	-6.29	327.55	-1.47	0.16	3	90.27	0	1
5a S	-2	14.31	3.10	-5.64	-4.86	-6.26	326.49	-1.46	0.15	3	90.09	0	1
5b R	-2	14.13	2.80	-5.08	-4.70	-6.19	337.94	-1.40	0.03	3	88.65	0	1
5b S	-2	14.12	2.79	-5.05	-4.70	-6.17	338.39	-1.39	0.02	3	88.53	0	1
5c R	-2	15.78	1.95	-4.40	-4.39	-5.83	111.80	-1.83	-0.13	2	75.05	0	1
5c S	-2	15.98	1.98	-4.61	-4.39	-6.15	104.01	-1.94	-0.13	2	74.63	0	1
5d R	-2	13.45	3.15	-5.32	-5.06	-5.89	370.32	-1.06	0.11	3	91.36	0	0
5d S	-2	13.66	3.19	-5.58	-5.06	-6.21	339.05	-1.16	0.13	3	90.96	0	0
TRIM.	-2	12.07	0.91	-2.84	-3.59	-4.14	386.27	-1.19	-0.28	3	78.59	0	0

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تصميم وتحضير ودراسة مضادات بكتريا تحتوي على الخاصية الدوائية -4ثايزوليدينون

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تم تصنيع سلسلة جديدة من المركبات التي تحتوي على الخاصية الدوائية ٤-ثيازوليدينون(٥أ- ث). ثم تمييز التركيب الكيميائي للمركبات الوسيطة والنهائية وتأكيده باستخدام التحليل الطيفي FT-IR و H-NMR[١] واختبار جميع المركبات النهائية ضد البكتيريا إيجابية الجرام وسالبة الجرام باستخدام تقنية نشر جيد لقدرتها كعوامل مضادة للميكروبات. وأظهرت المركبات المختبرة ٥ ب و ٥ ج نشاطًا 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 أكثر المركبات نشاطًا في الموقع النشط لبروتين البكتيريا والتي تم تطابقها تمامًا مع النتائج المختبرية.