https://doi.org/10.31351/vol33iss(4SI)pp195-213

Molecular Docking Study, Synthesis and Preliminary Anti-inflammatory and Antimicrobial Properties of New Conjugate of Quinolone-Phenolic Derivatives

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Received 7/4/2024, Accepted 29/7/2024, Published 15/2/2025

Abstract

This research was designed focused on modification of the basic structure of quinolones by introducing ester group at C3 position; the design was made using Ligand Designer from Glide Schrodinger. A series of new conjugation derivatives (**IIa-Vb**) were synthesized by esterification of quinolones (ciprofloxacin, gatifloxacin, nalidixic acid, and norfloxacin) with two types of antioxidants (vanillin and sesamol) at C3 which was replaced by an ester group via a glycol linker.The synthesized compounds were checked and characterized by spectral techniques (^{1}HNMR, ATR-FTIR). Additionally, their pharmacological activities were examined. *In vivo*, the anti-inflammatory effect of the (**IIa-Vb**) compounds was estimated using a rat paw edema model, showing significant activity for the final compounds **IIa-Vb** from 2-5hrs. when compared to the DMSO (solvent and control).The new conjugation derivatives were further tested for their antimicrobial activity against both gram-positive and gram-negative bacteria using the well diffusion method according to the zone of inhibition for the eight synthesized final compounds , which showed the following results: with gram-negative bacteria (*Escherichia coli*): (**IIa-Vb**) at 100 mg/l; (**IIa-Vb**) at 50 mg/l; (**IIa-IVa and Vb**) at 25 mg/l; and (**IIa,IIb,IIIb and Vb**) at 12.5 mg/l concentrations give a high activity, (**IVb and Va**) at 25 mg/l and (**IIIa**)at 12.5 mg/l give a moderate activity, (**IVa ,IVb and Va**) at 12.5mg/l concentrations considered as inactive. For gram-positive bacteria (*Staphylococcus aureus*): (**IIa-IVa, Va and Vb**) at 100 mg/l; (**IIa-Vb**) at 50 mg/l; (**IIa-IIIb**, **Va and Vb**) at 25 mg/l; and (**IIa,IIb,IIIb and Vb**) at 12.5 mg/l concentrations give a high activity; (**IVb**) at 100 mg/l, (**IVa**) at 25 mg/l; and (**IIIa**) at 12.5 mg/l a moderately active; while (**IVb**) at 25 mg/l and (**IVa-Va**) at 12.5 mg/l are classified as inactive. According to antifungal activity against *Candida albicans*, when compared with the drug Fluconazole, only **IIa, IIb** and IVb highly active at 100 mg/l, while the final compounds (**IIa, IIb and IVb**) at 50 mg/l, and (**IIb**) at 25 mg/l showed a moderate activity; the other final compound is classified as inactive.ADME analysis of quasi-active molecules was performed and demonstrated an acceptable drug-like profile and desirable pharmacokinetic properties.

Keywords: ADME, anti-bacterial, Molecular Docking, Quinolone derivatives, Sesamol, Vanillin.

Introduction

The class of antibiotics known as fluoroquinolones includes ciprofloxacin (CP), moxifloxacin (MXF), and gatifloxacin. Antibiotics that inhibit the action of bacterial DNA Gyrase, adenosine triphosphate hydrolyzing Topoisomerase IV (3FV5), and /or prevent gyrase from detaching from the DNA[(1)].Topoisomerase II breaks, crosses over, and then seals both strands of the DNA chain to allow supercoiled DNA to relax [(2,3)]. Fluoroquinolones are a class of antibacterial agents with anti-inflammatory properties in addition to antibacterial effects; many people also face drug resistance because different types of microorganisms work through different mechanisms[(4)]. Researchers found that an increase in volume at C7 of the fluoroquinolone moiety was found. Reduce bacterial resistance by reducing efflux effects pump, there are also reports that this modification will bring improvements Anti-inflammatory effect[(5)].Fluoroquinolones have a broad spectrum of antibacterial activity were developed as a new class of synthetic antibiotics with potent bactericidal agents and broad-spectrum activity that are active against significant bacteria that cause a variety of diseases[(6)], such as urinary tract infections (UTIs)[(7),] chronic gastritis[(8)], Microbial keratitis (MK)[(9)], Infections of the upper and lower respiratory tracts (URTI and LRTI)[(10),] also prescribed to treat intestinal infections brought on by enteric pathogens[(11)], treatment in advance of

patients with immune problems, such as those with cancer or those undergoing renal transplant [9], cellulitis [12] ,Antimalarial activity[13-15].

Fluoroquinolone derivatives, such as fluoroquinolone hybrids, fluoroquinolone metal complexes, and other derivatives with antibacterial effectiveness[16] quinolone derivatives have been used as lead compounds in drug discovery efforts. Scientists modify the quinolone structure to develop new derivatives with improved properties, such as enhanced efficacy, reduced toxicity, and better pharmacokinetic profiles[17]. Several investigations were conducted to examine the anti-inflammatory[18] , anti-aging[19], anti-proliferative [20] , and antioxidant properties of phenolic compounds, which are naturally occurring in plants and can be used in health benefits in scientific terms[21], the hydroxyl group of phenolic compounds is linked to ester in the form of a chain of aromatic carbons containing drugs[22]. Natural phenolic components employed as promoities in the production of prodrugs, such as vanillin, sesamol, umbelliferon, and menthol[23], they exhibit antioxidant activity, as well as antibacterial, antifungal, and antioxidant action [24-26] .

Vanillin's neuroprotective, anti-carcinogenic, and antioxidant bioactive properties are becoming more widely recognized[27]. Vanillin is also a feasible choice for the treatment of neurological problems since it is rapidly absorbed, has no adverse effects even at high concentrations, and can cross the blood-brain barrier (BBB) [28]. Sesamol's therapeutic potential has been extensively researched, and the evidence strongly shows that it acts as a metabolic regulator with anti-aging, anti-mutagenic, anti-inflammatory, and chemo-preventive properties[29]. Numerous investigations have revealed that sesamol has potent anti-cancer properties. Because of its hydroxyl group, which is principally responsible for its antioxidant and anti-inflammatory properties, sesamol has multifunctional properties. A well-designed formulation promotes passive absorption of antioxidants and phenolic compounds from the intestinal lumen into the blood and lymphatic circulation, improving bioavailability considerably [30].Recently, the study of biological and pharmacological activity has established the heterocyclic chemistry of quinolines and that has shown to be an excellent scaffold. Nonetheless, quinoline derivatives were thoroughly investigated as bioactive substances [31].The computational methods employed in our work consist molecular docking studies, ADME (which include Adsorption, distribution, metabolism, excretion) molecular dynamics simulation which help and benefit to discovery of new lead compounds. Molecular docking plays an important role in the rational development of drugs. In the field of molecular modeling, docking is a method of predicting the preferred orientation of one molecule relative to a second molecule when brought together to form a stable complex. Molecular docking can be defined as an optimization problem describing the "best-fit" orientation of a ligand that binds to a specific target protein typically, it is used in the process of developing new drugs and identifies proteins responsible for the appearance or progression of disease in the body[32-35].

The objective of the present research is to synthesize a new derivative of different quinolines by linking different quinolone antibiotics (i.e. ciprofloxacin, gatifloxacin, nalidixic acid, and norfloxacin) with antioxidants (a: vanillin, b: sesamol), supported with molecular docking studies. The parent drug is modified using glycolic acid precursors (-OCH_2COO-) as shown in Figure 1.

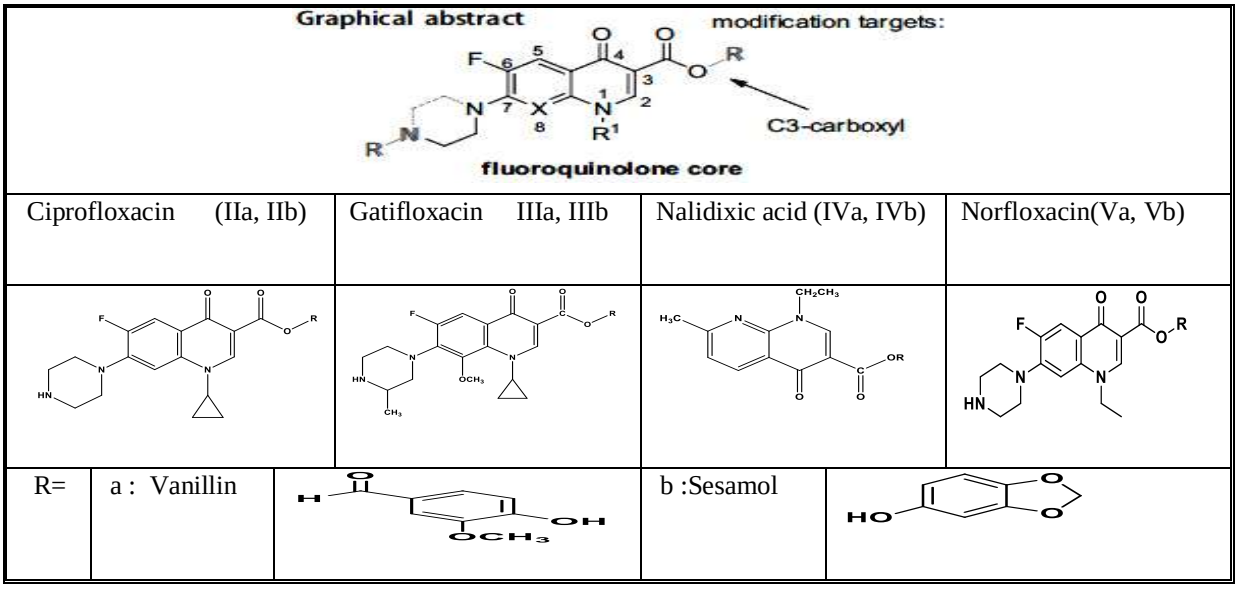


Figure 1. Modified position and chemical structure of drugs and antioxidants.

The emergence of bacterial resistance to current antibiotics necessitates the development of novel medicines to battle resistance. Many types of microbes have developed resistance to several antibiotics, which is a threat to global health[32] .

The most important pathogens are (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter species*), so research effort is required to satisfy the urgent demand for new antibiotic [34].

Materials and Methods

Fluoroquinolones and antioxidants were purchased from the Hyper Chem Company (China).Thin layer chromatography (TLC) was employed to monitor the progress of reactions; the mobile phase solvent systems used were A: chloroform: methanol (85:15), and B: chloroform: ethyl acetate: ether (10:5:1). The melting points were determined using an electronic melting point equipment (Stuart SMP30), and are uncorrected. (ATR-FTIR) (Shimadzu, Japan), was used to record the spectra ($v=cm^{-1}$) of the samples, at the college of Pharmacy-University of Baghdad. Dimethyl sulfoxide ($DMSO_{d6}$) was used as a solvent in the ^{1}HNMR spectra obtained, using a BRUKER model Ultrashield 500 MHz spectrometer.

1- Docking protocol [36-40]

Molecular docking of proposed eight new Quinolone derivatives was carried out using Maestro 11.5 Schrodinger software to select the derivatives that demonstrated good interactions with target protein with PDB (www.rscb.org). The following procedures are taken into account for molecular docking research. Preparation of Ligands Protein purification and refinement Receptor grid generation, PLD stands for protein-ligand docking.

Ligand instruction

The Schrödinger ligand instruction was completed with the aid of the Lig Prep panel utility, comprising a series of measures that perform conversion of second systems to 3-D shape, practice shape correction by reducing the right bond angles and distances, and maximize the structure via pressure-subject OPLS3.

Protein preparation and its refinement

Protein is the most crucial issue in molecular docking research, and it is essential to reduce the power of protein molecules before docking studies with ligands. Both proteins for ligand docking assessment were produced with the aid of the protein practice wizard device, which was used to import proteins for the protein information bank. Proteins obtained from the Protein Data Bank (PDB), big companies, and other resources often contain missing hydrogen, partial costs, aspect chains, and whole loops regions. To overcome all of these restrictions, the proteins were pre-processed, which was accomplished by setting the following parameters: Upload hydrogen and make zero order metal bonds. The generation of disulfide bonds, using top to fill gaps in aspect chains, using top to fill in missing loops, removing water above 5.00Å, and crating of the kingdom using Epik: PH 7.0+/- 2.zero.

Receptor grid generation

Before approaching a virtual display with waft, grid generation needs to be completed. The shape and features of the receptor are represented in a grid by area, which allows for more precise scoring of ligand poses throughout time. Flow generates grids for each conformation of receptors that undergo more than one conformation during binding to guarantee that viable actives are not missing. Receptor grid generation requires a "prepared" structure: an all-atom structure with appropriate bond orders and formal charges. In most cases, the preparation process can be performed automatically using the Protein Preparation Wizard.

Protein-ligand docking simulation

Docking was completed with the aid of the general Precision (SP) mode, and refining was accomplished with the aid of the greater precision (XP) mode. The ligand docking technique predicts ligand shape and orientation (posing) inside the targeted binding site, facilitating identification of interactions of ligand atoms with amino acids of proteins. The ligand docking concluded in the following steps: first, the Ligand docking program was selected from the software menu. Following the receptor grid, select Browse and choose the created receptor grid. The flavone Lig Prep report was then browsed and entered into ligands to be docked. Subsequently, the ligand and the protein grid are formed below three headings. The receptor, website, and constraints determine the size of the grid container wherein the ligand is expected to dock.

ADME studies

To test the drug resemblance of the proposed compounds, the produced ligands are subject ligand base ADME prediction. Setting the software to identify the most similar drug molecules, QIK Prop examined the output data for the drug ability of the generated compounds. The top-ranked compounds were subjected to drug-like property prediction using Lipinski's rule of five and the ADME Descriptors calculation using Qikprobe software (Utilizing an authorized Glide module as Maestro software by Schrodinger's modeling software version 13.0135). Different molecular properties, such as the number of hydrogen bond acceptors and donors, are considered in Lipinski's rule of five[41]. The aim of the study is to get knowledge of the main pharmacokinetic properties of compounds, such as aqueous solubility, intestinal absorption, systemic distribution, metabolism, excretion, and hepatotoxicity, among many other descriptors for ADME.

Chemical synthesis

Synthesis of antioxidant-chloroacetic chloride (Ia-b) [35]

An appropriate amount of each antioxidant (a-vanillin and b-sesamol) (0.001 mol, 1.5 g and 0.001mol, 1.38g), respectively, was mixed with trimethylamine (0.001mol, 1.4ml), 25ml of dichloromethane was placed into the mixture using round bottom flask, and then the mixture was cooled to -10°C, using an ice bath.

A mixture of chloroacetylchloride (0.001mol/0.8ml) in chloroform 25ml was prepared and was added drop-wise to the antioxidant mixture over a period of 1h. The temperature of the reaction mixture was kept at -10ºC, during the addition, and stirred overnight. Then wash using separatory funnel with; 5% HCl (3×50 ml), 5% NaOH (3×50 ml), and brine solution (2×25ml). The mixture was collected by evaporating the solvent using a hot air stream. Then recrystallization of the resultant compound with petroleum ether (60-80) and ethyl acetate (25:1)

Synthesis of quinolones-antioxidant compounds (IIa-Vb) [42]

A suitable amount of each Ia-b 0.001 mol (a:1.5 g and b :1.38g) together with different quinolone 0.001mol (II:ciprofloxacin, 3.31g, III:gatifloxacin,3.75g , IV: nalidixic acid, 2.32g, and V :Norfloxacin, 3.19g) respectively, in trimethylamine (0.001mol, 1.4ml) in 250 ml using round bottom flask, NaI (0.001mol, 1.5g) and DMF was added also to round bottom flask, the mixture was kept stirring in the refrigerator for overnight at 25°C. Following the 12 h stirring the resultant mixture was poured onto a crushed ice, then, extraction with chloroform (4X25ml) was and separation of the organic layer by using 2% sodium thiosulphate (3×50ml), 5% HCl (3×50 ml), 5% NaOH (3×50 ml), brine solution (2×25ml) The solvent was evaporated to obtain the final products (quinolone antioxidant) using a hot air stream. Recrystallization with petroleum ether (60-80) °C and ethyl acetate (25:1).

Pharmacological studies

Anti-inflammatory activity [33,43,44]

The experiment protocol was performed under authorization, and the synthesized derivatives, IIa-Vb, were estimated for their acute anti-inflammatory activity using egg-white method converting edema in albino rats (AR) and compared with diclofenac sodium 3 mg/ kg as a reference medicine. The basis for screening the anti-inflammatory effects them is the reduction in the thickness of paw edema.

Method

Sixty white albino rats weighing (160-200g) were attained from the / Baghdad University animal house and kept in the Iraqi Center for Cancer and Medical Genetics Research, they were housed under standard conditions with marketable chaw as food and ad libitum water. Inflammation was measured at the start and throughout the short time course by subcutaneous injection of egg whites into the rat paw under standard acclimation conditions.

These rats were aimlessly sorted into 10 groups each group consisting of six rats: Group A: Six rats injected intra-peritoneally (IP) with propylene glycol considered as control. Group B: Six rats were injected with the reference drug (Diclofenac sodium 3mg/Kg dissolved in propylene glycol[43].The**(C,D,E,F,G,H,I,J**) Groups: Six rats from each group were injected with prepared compounds dissolved in propylene glycol in the doses shown in the Table1.

A 0.05ml subcutaneous injection of undiluted egg-white material into the plantar side of the left-hand paw for the rats' hind paws may cause substantial skin discomfort, due to dominant inflammation. Thirty minutes after administration of the desired compounds or the vehicle, the paw width was measured using a Vernier caliper at intervals of (0, 30, 60, 120, 180, 240, and 300) minutes, respectively, after drug administration.

Calculation of the dose [46,47]

The doses of these target compounds were calculated according to the following equation:

$$\frac{\textit{Dose of reference compound}}{\textit{M.wt of reference compound}} = \frac{\textit{Dose of tested compound}}{\textit{M.wt of tested compound}}$$

Diclofenac sodium is given at a dose of 3 mg/kg, were the intended compounds are calculated in the equation as shown in Table 1.

Table 1. The molecular weights and doses for Diclofenac and the intended compounds

Compounds	M.Wt	Rat dose(mg/kg)
Diclofenac sodium	318.1	3
IIa	523.516	4.937
IIb	509.486	4.804
IIIa	567.564	5.352
IIIb	553.534	5.220
IVa	424.405	4.002
IVb	410.375	3.870

Va	511.501	4.823
Vb	497.471	4.691

Antimicrobial activity [48-51]

In vitro, the final synthesized compounds (**IIa-Vb**) were tested against two bacteria species, gram-positive was *Staphylococcus aureu*s, gram-negative was *Escherichia coli*, and fungi species was *Candida albicans;* Ciprofloxacin was used as a reference for antibacterial activity, Fluconazole was used as an antifungal, and DMSO was used as a solvent (negative control).

One-liter Mueller-Hinton agar made from commercially available powder after weighing the compounds with a sensitive balance at a rate of 1000 mg/ml, they were dissolved in the DMSO solution by stirring, and kept at room temperature (RT) for 18 h, until complete dissolution, at which point reducing concentrations of 100mg to 12.5 mg were obtained .Bacterial inoculum was prepared and inoculated by overnight activating bacteria from stock cultures in nutrient broth.

Bacterial inoculum was prepared by diluting activated bacteria with sterile D.W to achieve cell concentration of about 1.5108 cells /ml, the turbidity of bacteria solution was visually adjusted to 0.5 McFarland standard *via* wicker ham card, and the obtained inoculum was streaked directly on agar plates (MHA) After inoculating microbes, and loading material into agar wells, Petri dishes were incubated in a laboratory incubator for 24 h, at a temperature of 35-37°C, and the MIC activity was determined by measuring the diameter of inhibition zones around the holes loaded with solutions with a transparent ruler in millimeters (mm)[51,52].

Results and Discussion

1-Docking end result shows that binding of ligand to protein occurs as consistent with carried out constriction with interplay with preferred way. Excellent docking score and float rating of newly designed quinolines der-ivatives (IIa-Vb) were as compared the usage of docking score and glide rating and potential strength. Both of (IVb and Vb) had been maximum docking score as anti-inflammatory activity whereas (IIa, IIIa, IIIb, and IVa) maximum docking score as anti-bacterial activity, the results of docking, i.e., the binding mode, docked pose, and binding free energy were studied to evaluate the interaction between the amino acids residues of the proteins COX-1 and COX-2 and our synthesized ligands. As proven in both Tables (2 and 3) also Figure (2 and 3).

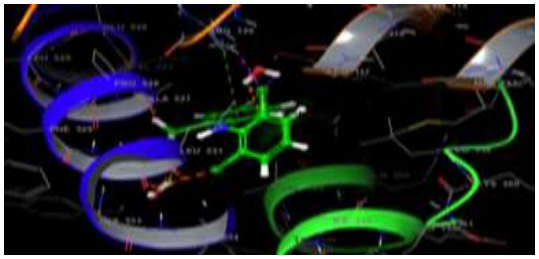
Table 2. Anti-inflammatory Docking Scores of docked Ligands (IIa-Vb) with Cyclooxygenase-1 (PDB Code: 4O1Z); and Cyclooxygenase-2 (PDB Code: 4m11), using Diclofenac as a Reference

Symbol Kcal/ mol	**Cox1** **ΔG (Kcal/mol)**	**Cox2** **ΔG (Kcal/mol)**
Diclofenac	-5.950	-6.809
IIa	- -	- -
IIb	-2.024	-5.394
IIIa	- -	-0.440
IIIb	-1.479	-3.099
IVa	-3.088	-5.887
IVb	-6.024	-7.279
Va	9.702	-2.141
Vb	-4.209	-6.979

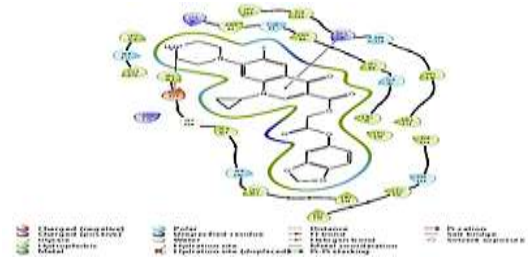
2Dstructure
Diclofenac

3D structure
Diclofenac

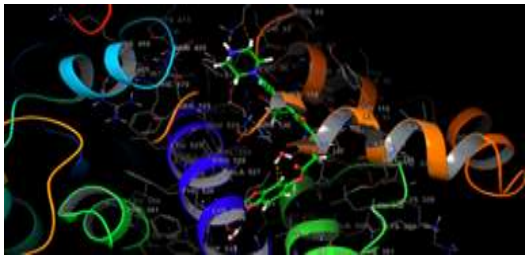
IIa



IIa

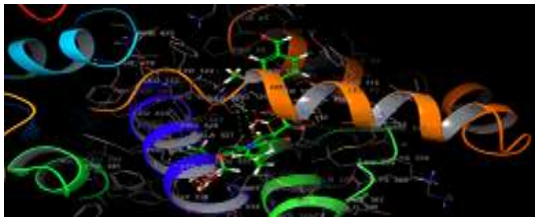


IIb



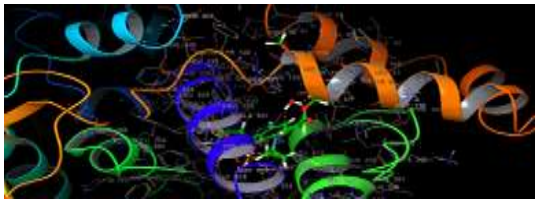
IIb

IIIa



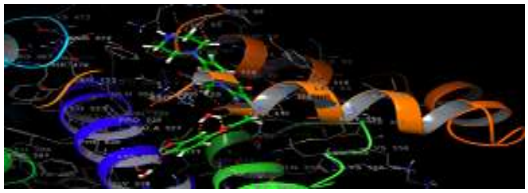
IIIa

IIIb



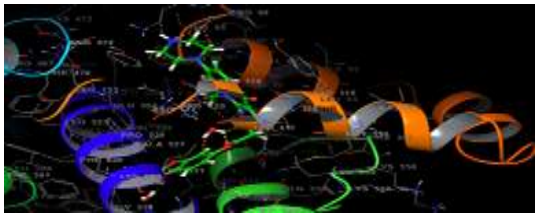
IIIb

IVa

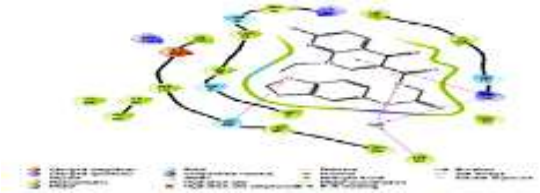


IVa

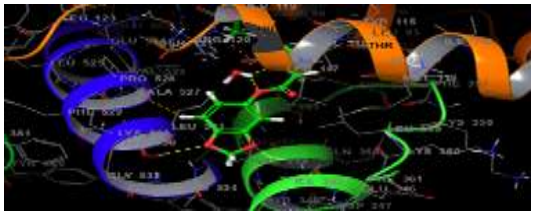
IVb



IVb



Va



Va

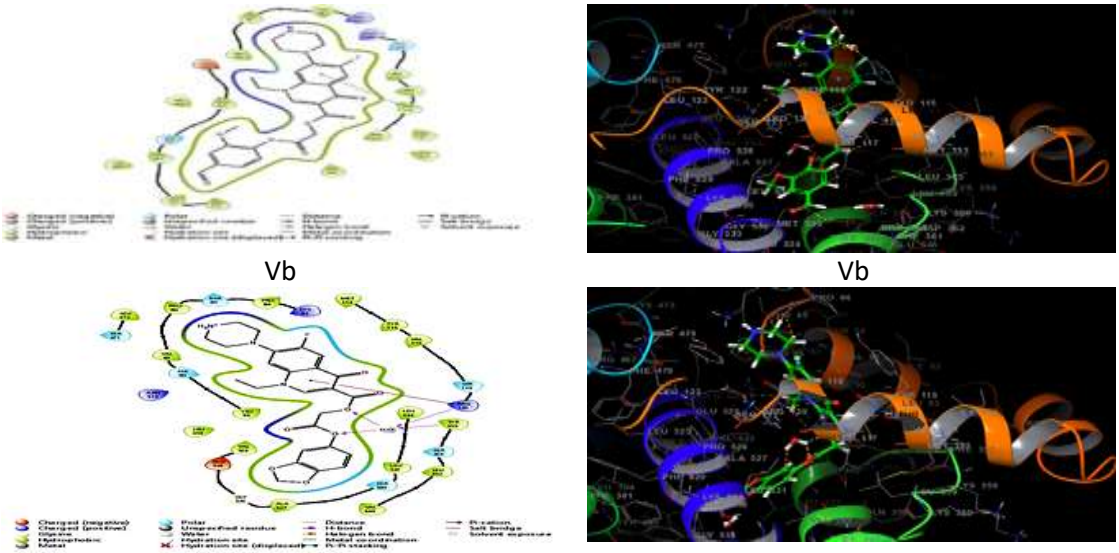
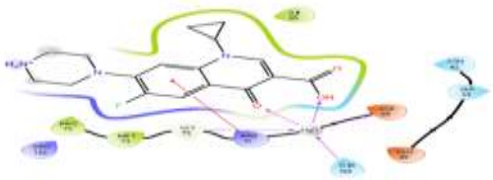


Figure 2. Anti-inflammatory docking/2D and 3D structure for compounds.

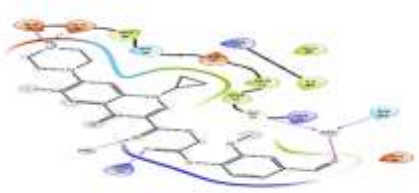
Table 3. Anti-bacterial docking scores: protein/ *E. coli* Topoisomerase IV co-complexed with inhibitor (PDB code 3FV5), Ciprofloxacin as reference

Symbol Kcal/ mol	Docking score
Ciprofloxacin (reference)	-5.500
IIa	-6.502
IIb	-3.632
IIIa	-5.740
IIIb	-6.645
IVa	-6.844
IVb	-3.099
Va	-4.603
Vb	-4.953

2D structure
Ciprofloxacin

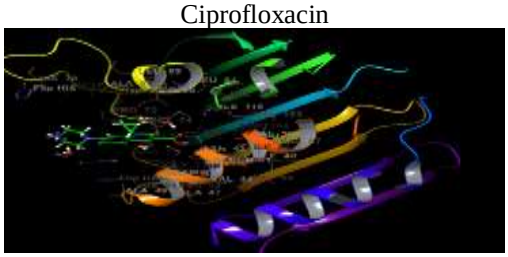


IIa



IIb

3D structure
Ciprofloxacin



IIa

IIb

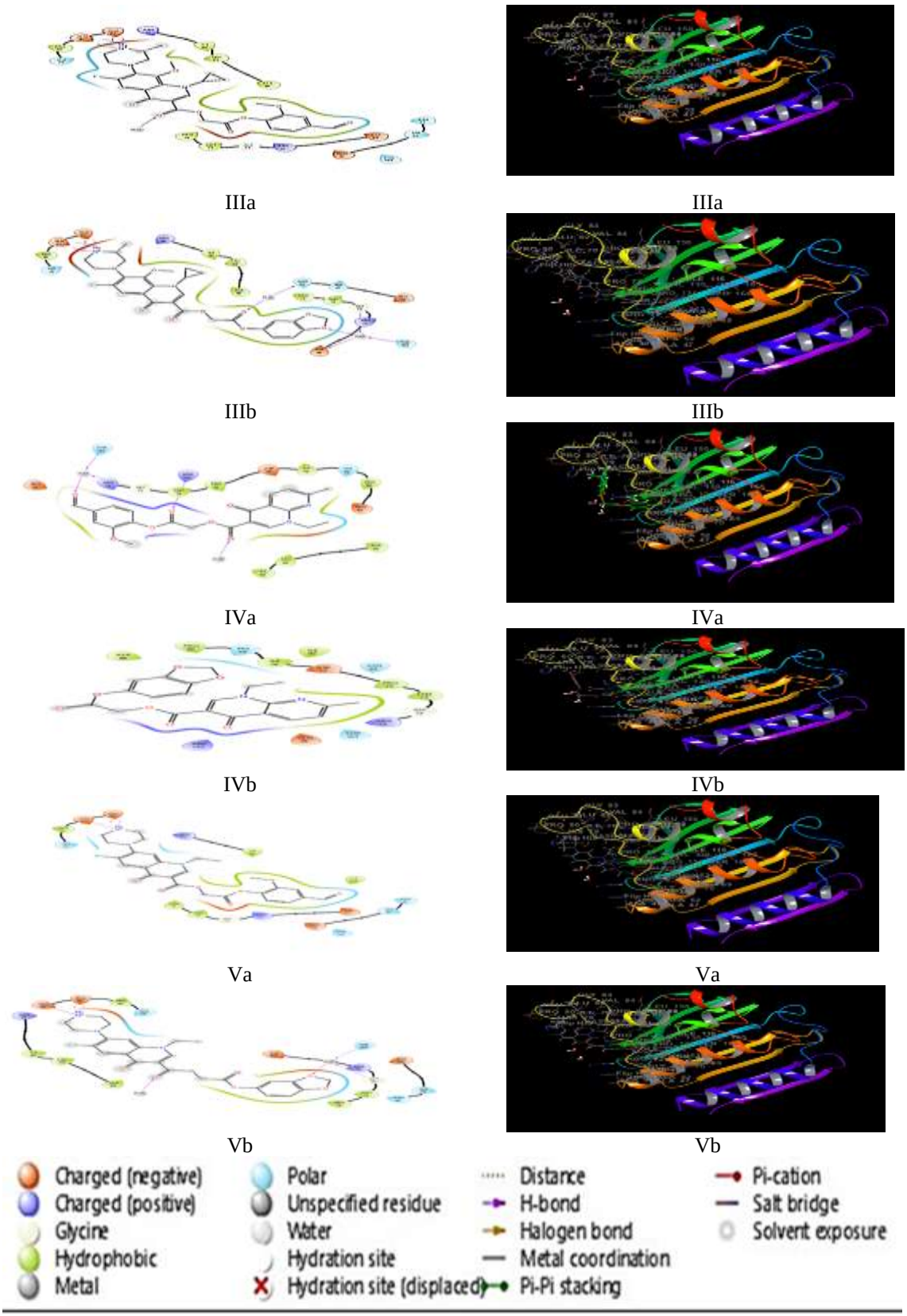


Figure 3. Anti-bacterial docking/2D and 3D structure for compounds.

ADME Studies

The ADME properties for the final compounds (IIa-Vb) predicted *in vitro* in silico by using Schrödinger suit, taking different pharmacokinetic parameter, the molecular weight of the final compounds shown in the range of 410.382 and 567.57. Dipole moment between 6.071-12.375. Number of hydrogen bond donors that, in a fluid arrangement of the mixtures, the solute would provide to water atoms given in the range of 0-1. Number of hydrogen bonds that the compounds' fluid arrangement's solute would recognize from water particles given in the range of 9.5-12.25. QPlogPo/w is used to analyze the estimation of the lipophilicity (octanol-water partition coefficient). Lipophilicity is thought to be the significant physical characteristic that promotes excellent adsorption and ideal molecular permeability through passive spread. Generally, high lipophilicity values carry a considerable danger of toxicity associated with metabolic clearance, while low renal clearance may be encouraged by lipophilicity levels; the compounds showed good QPlogPo/w values. Several possible metabolic reactions of the substances show in the range of 1-3. It is evident that some of the final compounds complies with Lipinski's five rules in range of 0-2. The excellent oral bioavailability shown with these final compounds is 39-87%. Therefore, the majority of the compounds in silico ADME screening findings fall within the advised ranges. We believe that in silico ADME prediction results could support the ongoing development of the medication candidates. (Table 4)

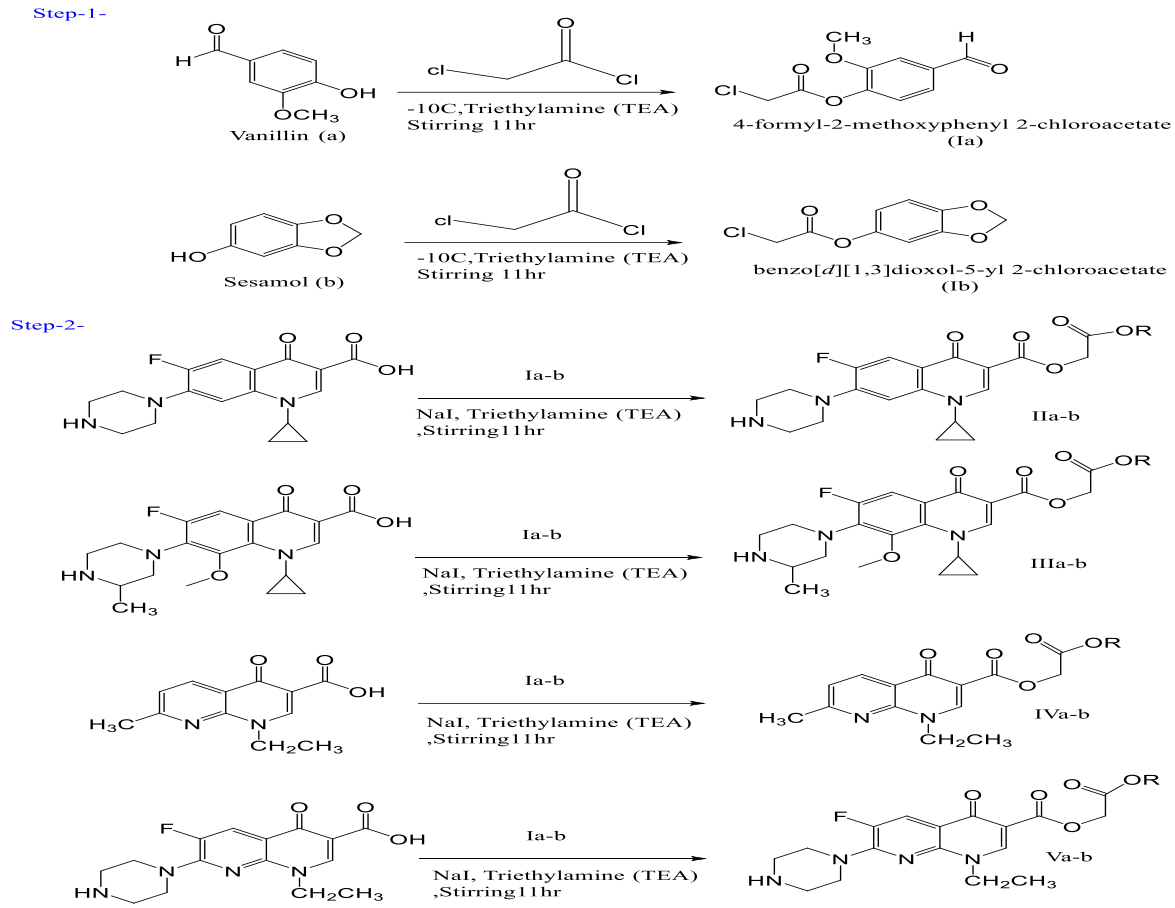
Table 4. *In silico* ADME prediction results of the final compounds.

Compounds	M.wt	Dipole	Donor HB	Accept HB	QPlogPo/w	#metab	Rule of Five	%Human oral absorption
IIa	523.517	10.471	1	12.25	1.761	2	1	42.568
IIb	509.49	12.05	1	11	2.42	1	1	59.568
IIIa	567.57	8.465	1	13	2.359	3	2	39.005
IIIb	553.543	11.642	1	11.75	2.982	2	2	56.194
IVa	424.409	8.236	0	10.75	1.553	3	0	70.423
IVb	410.382	6.071	0	9.5	2.018	2	0	87.232
Va	511.506	12.375	1	12.25	1.963	3	1	46.24
Vb	497.479	11.495	1	11	2.287	2	0	71.662
Recommended values	130-725	1-12.5	0-6	2-20	-2-6.5	1-8	Max4	>80% is high <25% is poor

-**MWt**: Molecular weight of the molecule.-**Dipole:** Computed dipole moment. - **HBD:** Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution.-HBA**:** Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution**.** -**QPlogP o/w:** Predicted logarithm octanol/water partition coefficient.-**#metab:** Number of likely metabolic reactions. - **Rule of Five**: Number of violations of Lipinski's rule of five. - **%Human oral absorption**: Percentage of oral absorption.

Chemical synthesis

The synthesized compounds IIa-Vb was obtained successively ; the overall process for synthesizing the intermediates and targeted compounds were depicted in Scheme 1.



Scheme 1. Synthesis of intermediates Ia-b and targeted compounds IIa-Vb

The synthesis of the intermediate as antioxidant-chloroacetyl chloride- (Ia-b) were synthesized from two types of antioxidant (a-vanillin and b-sesamol) with chloroacetylchloride .The conversion of chloroacetyl chloride into ester, will occur through nucleophilic acyl substitution reactions which involve tetrahedral intermediate [47,53,54].

Nucleophilic substitution occurs selectively at the acyl carbon atom in α-chloroacetyl chloride because of the greater reactivity of nucleophiles toward acid chlorides compared to alkyl chlorides. The reasons for this selectivity are attributed to the differences in the electrophilicity of the two carbon atoms in α- chloroacetyl chloride. Electronically, the carbonyl carbon has two electron-withdrawing groups – the oxygen doubly bonded to it and the (-Cl) bonded to it. On the other hand, the carbon in – CH_2Cl has only one electron withdrawing group (-Cl). Besides electronics, steric factors also play a role in this selectivity. It is easier for the nucleophile to attack the carbon of the planar carbonyl group in the acid chloride than to attack the tetrahedra carbon in the – CH_2Cl group. The R_f and FT-IR spectral data of intermediates as shown below:

Compound (Ia) Yield = 85%, m.p. = 68-70 °C, R_f = 0.87, IR (v=cm^{-1}): 3078.39 and 3055.24 (Ar-C-H)str., 2920.23, 2877.79 and 2831.50 (C-H Str of CH_2 and CH_3), 2762.06 (aldehyde-COH)str, 1778.37 (C=O ester)str, 1689.64 (aldehyde-C=O) str., 1600.59, 1593.20 and1508.33 (ArC=C)str,1265.30 (asym C-O-C) str., 779.24 and 759.95 (C-Cl)str.

Compound (Ib) Yield = 75%, m.p.= 50-52 °C, R_f = 0.84, IR: 3086.11 and 3005.10 (ArC-H) str , 2951.09 and 2912.51 (C-H of CH_2)str., 1762.94 C=O-ester)str,1558.48, 1543.05 and 1504.48 ,(Ar C=C)str., 1242.16 (asym C-O-C)str., 752.24 (C-Cl)str..

The above results indicated to the disappearance of broad bands at (3320-3170) cm^{-1} and (3362-3197) cm^{-1} respectively and to the revealed band sat 1724.36, 1693.50) cm^{-1} and (1759.08 and 1716.65) cm^{-1} respectively which attributed ester(C=O)str.

Synthesis of Target Compounds (IIa-Vb)

The target compounds were synthesized according to the following steps:

1- Finkelstein reaction, halo-de-halogenation takes place by replacement of chloride with iodide by reacting the chlorinated ester (resulted from step1) with anhydrous NaI in order to remove iodide in the next step which is easier than that of chloride due to its low electronegativity.

2- Mixing the iodinated ester with quinolones in presence of TEA in DMF [53,55]

Compound (IIa): 2-(4-formyl-2-methoxyphenoxy) -2-oxoethyl 1-cyclopropyl-6-fluoro-4-oxo-7- (piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate

Off white powder, yield=87%,m.p. = 189-190 °C , R_f = 0.86 IR(v=cm^{-1}): 3059.10 (ArC-H)str., 2962.66, 2941.26 and 2912.51), (C-H of CH_2 and CH_3)str, 2760.87 (aldehyde CO-H)str, 1724.36,1693.50(ester C=O) str, 1654.92 (aldehyde-C=O)str, 1624.06(ketone C=O)str, 1581.63, 1546.91 and 1504.48(Ar C=C)str,1257.59 ,1211.30 (asym C-O-C)str.

^{1}HNMR(500 MHz, $DMSO_{d6}$; δ,ppm) : 1.29 (d,4H, cyclopropyl ring), 2.71 (m,1H, piperazine ring), 2.87 (m,4H ,piperazine ring), 3.68 (m,4H, piperazine ring), 3.84 (s,3H, OCH_3), 4.12 (Quintet,1H, cyclopropyl group), 5.08 (s,2H,CH_2) , 6.96 (s,1H, Ar-H), 7.37 (d,1H, Ar-H), 7.58 (s,1H,Ar-H),7.88 (d1H, Ar-H), 7.99 (s,1H, Ar-H), 8.66 (s,1H, 1-cyclopropylpyridin-4(1H)-one group), 9.74 (s,1H, CHO).

Compound (IIb): 2-(benzo[d][1,3]dioxol-5-yloxy)-2-oxoethyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate

white powder, yield=86%,m.p.=(197-198)°C, R_f = 0.85, IR(v=cm^{-1}): 3047.53 (Imino moiety of piperazinyl) str,2943.37 , 2916.37 and 2857.61(C-H of CH_2)str, 1759.08 and 1716.65(ester C=O)str,1624.06 and 1600.92 (carboxylic-C=O)str, 1562.34 and 1508.33(Ar C=C)str,1249.87(asym C-O-C)str., 1168.86 and 1134.14 (C-F) str.

^{1}HNMR(500 MHz, $DMSO_{d6}$; δ,ppm) : 1.28 (d,4H, cyclopropyl ring), 2.53 (m,1H, piperazine ring), 3.36 (m,4H, piperazine ring),3.53(m,4 ,piperazine ring), 3.86 (Quintet, 1H , cyclopropyl ring), 5.86 (s,2H,CH_2) , 6.08 (s,1H, Ar-H) , 6.35 (s,2H,CH_2), 6.67 (s,1H,Ar-H), 6.94 (d,1H,Ar-H), 7.63 (d,1H,Ar-H), 7.95 (s,1H,Ar-H), 8.67(s,1H, 1- cyclopropylpyridin-4(1H)-one group) .

Compound (IIIa): 2-(4-formyl-2-methoxyphenoxy)-2-oxoethyl 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydro quinoline -3-carboxylate

Light yellow powder, yield=86%,m.p.= (161-163) °C, R_f =0.82, IR(v=cm^{-1}): (3078.39) Imino moiety of pipra-zinyl)str, 2966.52 , 2949.89 and 2850.79) (C-H CH_2 and CH_3)str, 2754.35 (-aldehyde-COH) str,1766.80(ester-C=O)str,1693.50 (-aldehyde-HC=O)str, 1616.35(conj. ketone C=O)str,1585.49 and1535.34(ArC=C)str, 1265.30 (asym C-O-C)str, 1114.86 and1060.85 (C-F) str.

^{1}HNMR(500 MHz, $DMSO_{d6}$; δ,ppm) : 1.8 (d,3H,CH_3), 2.08 (d,4H, cyclopropyl ring) , 2.27 (s,1H, piperazine ring), 2.70-2.86 (m,1H, piperazine ring), 2.95 (m,2H, piperazine ring), 3.22 (m,2H ,piperazine ring) , 3.68 (d,2H, piperazine ring), 3.81 (s,3H, OCH_3), 3.85 (s,3H, OCH_3), 4.17 (Quintet ,1H, cyclopropyl ring), 5.36 (s,2H, CH_2) , 7.24 (d,1H ,Ar-H), 7.38 (s,1H, Ar-H), 7.59 (d,1H,Ar-H) , 7.93 (s,1H Ar-H), 8.63 (s,1H, pyridin-4(1H)-one), 9.76 (s,1H, CHO) .

Compound (IIIb): 2-(benzo[d][1,3]dioxol-5-yloxy) -2-oxoethyl 1-cyclopropyl-6-fluoro-8-methoxy-7-(3- methylpiperazin-1-yl)-4-oxo-1,4-dihydro quinoline -3-carboxylate

Light yellow powder, yield=86%, m.p.=(178-179) °C , R_f = 0.83, IR(v=cm^{-1}): 3082.25 (Imino moiety of pipra-zinyl)str,2978.09,2893.22 and 2839.22 (C-H of CH_2 and CH_3)str, 1759.08 and 1735.50(ester-C=O)str, 1616.35 (conj ketone C=O) str,1581.63 ,1535.34 and1500.62(ArC=C), 1246.02(asym C-O-C) str, 1134.14 and 1033.85 C-F)str.

^{1}HNMR(500 MHz, $DMSO_{d6}$; δ,ppm) : 1.66 (d,3H, piperazine ring), 1.98 (d,4H, cyclopropyl ring), 2.06 (s,1H, piperazine ring) , 2.54-2.90 (m.1H, piperazine ring), 3.19 (m,2H, piperazine ring), 3.41(m,2H ,piperazine ring) , 3.65 (d,2H, piperazine ring), 3.83 (s,3H, OCH_3), 4.47 (Quintet ,1H, cyclopropyl ring), 5.92 (s,2H,CH_2) , 6.07 (s,2H,CH_2) ,6.56 (d,1H, Ar-H), 6.66 (s,1H, Ar-H,) , 6.86 (d,1H, Ar-H),7.62 (s,1H, Ar-H) ,8.57 (s,1H ,pyridin-4(1H)-one).

Compound (IVa): 2-(4-formyl-2-methoxyphenoxy)-2-oxoethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate

Light brown (Sticky), yield=51%,m.p=(49-50) °C, Rf =0.90, IR(v=cm^{-1}): 3016.67 (Ar C-H)str., 2970.38 , 2920.23 and 2877.79 (C-H of CH_2 and CH_3)str, 2738.92 (aldehyde- COH str,1739.79 (ester-C=O)str, 1693.50 (aldehyde-HC=O)str, 1612.49 (conj.ketone C=)str., 1546.91 and1500.62(ArC=C)str., 1261.45 and1234.44(asym C-O-C) str.

^{1}HNMR (500 MHz, $DMSO_{d6}$; δ,ppm) : 1.37 (t,3H,CH_3-CH_2), 2.48 (s,3H, CH_3) , 3.85 (s,3H, OCH_3) , 4.49 (q,2H, CH_3-CH_2), 5.36 (s,2H, CH_2), 6.97 (d ,1H ,Pyridine ring),7.34 (d,1H, Ar-H), 7.38 (s,1H, Ar-H) , 7.42 (d,1H, Ar-H), 7.61(d,1H ,Pyridine ring), 8.45 (s,1H ,pyridin-4(1H)-one) , 9.74 (s,1H, CHO) .

Compound (IVb): 2-(benzo[d][1,3]dioxol-5-yloxy)-2-oxoethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate

Light brown powder, yield=76%, m.p. = (160-162)°C , R_f = 0.89 ,IR(v=cm^{-1}):: 3086.11 and 3005.10 (Ar C-H)str., 2954.95 and 2916.37 (C-H of CH_2 and CH_3)str, 1766.80 and 1685.79 (ester C=O)str 1608.63 (ketone-C=O)str, 1585.49, 1546.91 and

1504.48 (Ar C=C) str., 1257.59 and 1226.73(asym C-O-C)str.

^{1}HNMR (500 MHz, $DMSO_{d6}$; δ,ppm) : 1.35 (t,3H ,CH_3-CH_2), 2.69 (s,3H, CH_3), 4.46 (q,2H, CH_3-CH_2), 5.36 (s,2H, CH_2) , 6.11 (s,2H,CH_2), 6.79 (d,1H ,Pyridine ring) , 6.92 (d,1H, Ar-H), 6.96 (s,1H,Ar-H), 6.99 (d,1H,Ar-H) , 7.04 (d,1H, Pyridine ring) , 8.48 (s,1H ,pyridin-4(1H)-one).

Compound (Va): 2-(4-formyl-2-methoxyphenoxy)-2-oxoethyl 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate

Off white powder, yield=86%,m.p=(181-183)°C, R_f = 0.88, IR(v=cm^{-1}): 3055.24 (ArC-H)str., 2981.95, 2958.80 and 2862.36 (C-H of CH_2 and CH_3)str., 2723.49 (aldehyde-CO-H)str., 1735.93 and 1681.93 (ester C=O)str., 1624.06(aldehyde HC=O) str, (1589.34 and 1504.48) (ArC=C)str., 1261.45 (asym-C-O-C)str., 1122.57 and 1060.85 (C- F) str.

^{1}HNMR(500 MHz, $DMSO_{d6}$; δ,ppm) : 1.39 (t,3H, CH_3-CH_2), 2.67 (m,1H, piperazine ring), 2.95 (m,4H, piperazine ring), 3.66 (m,4H, piperazine ring), 3.83 (s,3H, OCH_3), 4.57 (q,2H,CH_3-CH_2), 5.07 (s,2H, CH_2), 7.09 (s,1H, Ar-H) , 7.36 (1d,H, Ar-H) , 7.40 (s,1H, Ar-H) , 7.61 (d,1H, Ar-H) , 7.92 (s,1H, Ar-H) , 8.67 (s,1H, pyridin-4(1H)-one) , 9.74 (s,1H, CHO).

Compound (Vb): 2-(benzo[d][1,3]dioxol-5-yloxy)-2-oxoethyl 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate

White powder, yield=86%,m.p= (187-188) °C, R_f=0.90, IR(v=cm^{-1}): 3055.24(Ar C-H)str., 2970.38, 2935.66 and 2862.36 (CH of CH_2 and CH_3)str, 1759.08 ,1735.93 and 1705.07 (ester C=O)str, 1624.06 (ketone-C=O) str overlapping with NH bending vibration of quinolones, 1519.91 and 1500.62 (Ar C=C) str., 1253.73 (asym C-O-C)str., 1176.58 and 1157.29 (C-F) str.

^{1}HNMR(500 MHz, $DMSO_{d6}$; δ,ppm) : 1.39 (t,3H, CH_3-CH_2), 2.36 (m,1H, piperazine ring), 3.13 (m,4H, pipera-zine ring) ,3.47 (m,4H, piperazine ring) 4.58 (q,2H, CH_3-CH_2), , 5.87 (s,2H, CH_2), 6.09 (s,1H, Ar-H) , 6.18 (s,2H,-CH_2), 6.59 (s,1H, Ar-H ,6.66 (d,1H, Ar-H) , 6.93 (d,1H, Ar-H) ,7.88 (s,1H, Ar-H) , 8.64 (s,1H, pyridin-4(1H)-one.).

The IR spectrum of compound IIa-Vb indicated the disappearance of broad band of OH group of: Ciprofloxacin (3255.84-3209.55) cm^{-1}, Gatifloxacin (3371.57-3216.58) cm^{-1}, Nalidixic acid (3226.73-3255.24) cm-1and Norfloxacin (3332.10 - 3276.58) cm^{-1} and the appearance of band attributed ester(C=O)str. for IIa-Vb respectively:{(1724.36 ,1693.50) , (1759.08 and 1716.65), (1766.80), (1759.08 and 1735.50), (1782.23 and 1720), 1766.80 and 1685.79), (1735.93 and 1681.93) and (1759.08, 1735.93 and 1705.07) cm^{-1} ;on the other hand, the interpretation of the ^{1}HNMR spectrum for compounds IIa-Vb revealed a singlet peak due to the (CH_2 α to ester group) at δ=(ppm) : 5.08, 5.86, 5.36, 5.92, 5.36, 5.36, 5.07 and 5.87 respectively and there is no peak appeared at the range of proton of carboxylic group . All the inferences mentioned above provide evidence of the occurrence of the association and the success of the preparation of the compounds.

Pharmacological studies

Anti-inflammatory assessment of the tested compound [58]. In comparison experimental chemicals with control (propylene glycol 50%), they all displayed thinner paws thickness

Table 5. The anti-inflammatory activity of final quinolone derivatives (IIa-Vb), using an egg-white, and induced paw edema in rat; propylene glycol as control and Diclofenac as standard compound

Paw Thickness (mm±SD)							
Time (hrs.)	**0 hr.**	**0.5 hr.**	**1 hr.**	**2 hr.**	**3hr.**	**4hr.**	**5 hr.**
control	4.38 ±0.03	4.61 ±0.02	5.95 ±0.03	7.56 ±0.5	7.65 ±0.03	6.87 ±0.02	6.46 ±0.11
Standard	4.33 ±0.02	4.47 ±0.02	5.89 ±0.04	6.24 ±0.02*^{a}	6.00 ±0.01*^{a}	5.72 ±0.01*^{a}	5.14 ±0.02*^{a}
IIa	4.33 ±0.02	4.56 ±0.02	5.91 ±0.04	6.14 ±0.01*^{a}	5.88 ±0.03*^{a}	5.67 ±0.02*^{a}	5.10 ±0.04*^{a}
IIIa	4.50 ±0.01	4.57 ±0.01	5.86 ±0.01	6.55 ±0.04*^{b}	6.31 ±0.4*^{b}	6.30 ±0.01*^{b}	5.72 ±0.01*^{b}
IVa	4.41 ±0.02	4.55 ±0.02	5.84 ±0.03	6.21 ±0.01*^{a}	5.95 ±0.01*^{a}	5.70 ±0.02*^{a}	5.12 ±0.01*^{a}
Va	4.44 ±0.03	4.56 ±0.02	5.89 ±0.03	6.89 ±0.02*^{c}	6.77 ±0.01*^{c}	6.57 ±0.02*^{c}	6.14 ±0.02*^{c}
IIb	4.39 ±0.01	4.54 ±0.02	5.86 ±0.04	6.05 ±0.01*^{a}	5.84 ±0.03*^{a}	5.65 ±0.02*^{a}	5.04 ±0.01*^{a}
IIIb	4.41	4.54	5.84	6.50	6.35	6.15	5.65

	±0.02	±0.02	±0.03	±0.01*[b]	±0.01*[b]	±0.03*[b]	±0.01*[b]
IVb	4.35 ±0.01	4.58 ±0.02	5.94 ±0.03	6.13 ±0.02*[a]	5.91 ±0.04*[a]	5.66 ±0.01*[a]	5.06 ±0.02*[a]
Vb	4.37 ±0.01	4.56 ±0.01	5.88 ±0.03	6.88 ±0.04*[c]	6.80 ±0.01*[c]	6.62 ±0.02*[c]	6.09 ±0.02*[c]

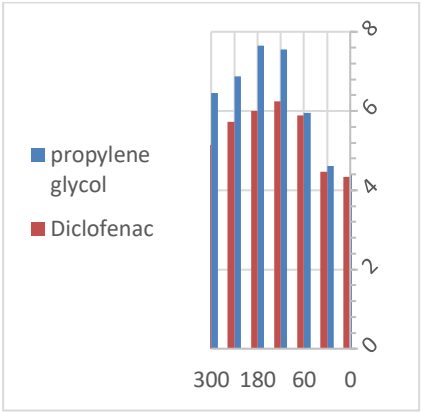
Different testing groups' non-identical superscripts (a, b, c) are evaluated as significantly different ($p \leq 0.05$).Data are expressed as mean ± SEM of mm paw thickness, n= number of animal, time (0) is time of injection of tested compounds time (30) minutes is time of injection of egg-white (induced of paw edema) , *significantly different with control ($p \leq 0.05$)

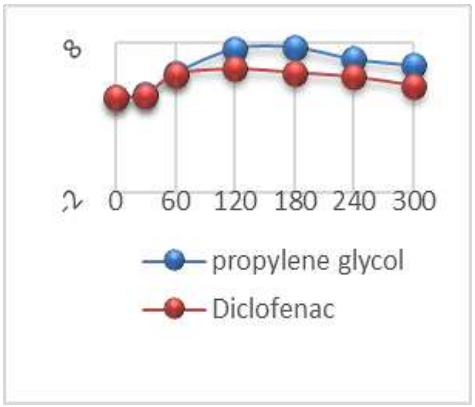
All tested compounds and standard drug showed significant activity in comparison with the control at 2hrs.time.

- (IIa, Iva, IIb and IVb) compounds showed comparable activity to standard drugs and significantly higher than control from time (2-5) hrs.
- (IIIa and IIIb) compounds showed lower activity than standard; and significantly higher activity than control from time (2-5) hrs.
- Finally; (Va and Vb) compounds showed lower activity than standard and all tested compounds and significantly Higher activity than control from time (2-5) hrs.

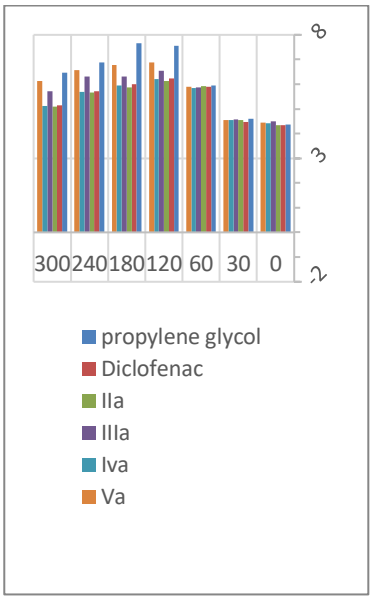
propylene glycol

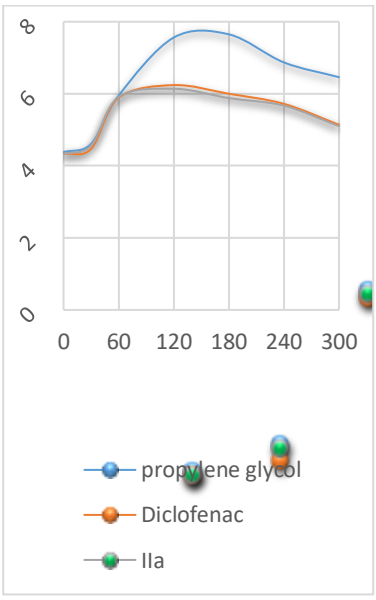
and diclofenac

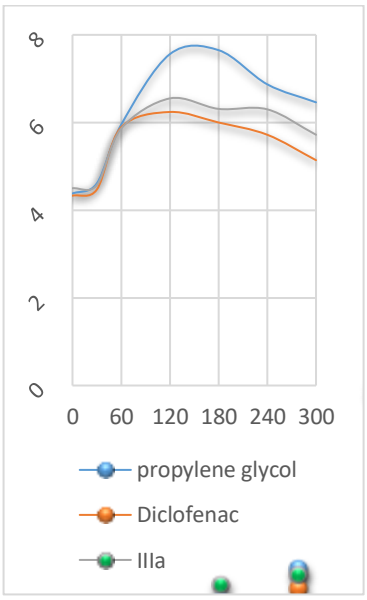


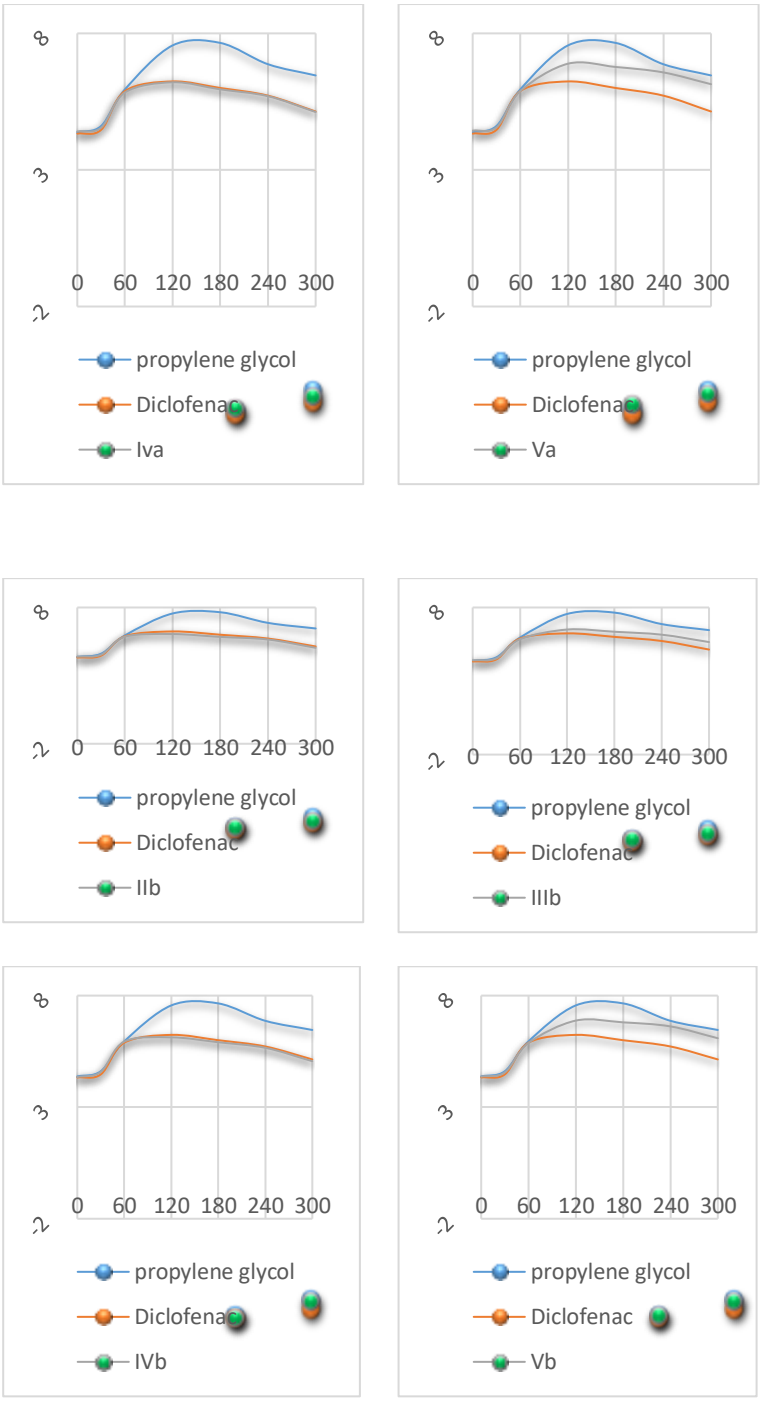


IIa ,IIIa ,Iva and Va









*All the synthesized derivatives (IIa-Vb) regarded as significant within (2-5) hrs.

Figure 3. Curves illustrates anti-inflammatory activities of final compounds in comparison with control and standard.

Antimicrobial biological study [52, 59]

The synthesized final compounds (Ia-Vb) were tested to evaluate their antimicrobial activity against gram negative, gram positive bacteria & fungi, this evaluation was done using well diffusion method, using the standard compounds :with anti-fungal agent was (fluconazole), while with antibacterial agent was (ciprofloxacin). DMSO was chosen as a solvent and as control. The increase of inhibition activity at lower concentrations compared to the absolute concentrations of the compounds due to greater diffusion of the compound molecules in the solvent [60, 61]. The results were expressed in MIC as shown in the Tables 6 and 7.

Table 6. Antimicrobial activity as of final compounds as Inhibition zone the inhibition zones of the chemical being tested are considered to be extremely active when they are more than 15 mm, moderately active when they are between 10 and 15 mm, barely active when they are between 5 and 10 mm, and inactive when they are less than 5 mm.

compounds	Zone of inhibition(mm)											
	Gram negative bacteria				Gram positive bacteria				Fungi			
	Escherichia coli				*Staphylococcus aureus*				*Candida albicans*			
	Conc.(mg/l)				Conc.(mg/l)				Conc.(mg/l)			
	100	**50**	**25**	**12.5**	**100**	**50**	**25**	**12.5**	**100**	**50**	**25**	**12.5**
Ciprofloxa-cin	39	30	20	17	40	35	30	20	2	0	0	0
Fluconazole	0	0	0	0	0	0	0	0	22	0	0	0
DMSO	0	0	0	0	0	0	0	0	0	0	0	0
IIa	30*	30*	30*	30*	24*	30*	35*	27*	17*	12	0	0
IIb	30*	30*	37*	40*	25*	35*	35*	32*	15*	12	10	0
IIIa	26*	29*	21*	14	25*	27*	21*	13	0	0	0	0
IIIb	30*	33*	29*	20*	23*	30*	29*	21*	0	0	0	0
IVa	29*	23*	29*	0	16*	22*	13	0	0	0	0	0
IVb	28*	17*	10	0	12	16*	0	0	18*	12	0	0
Va	25*	24*	14*	0	20*	25*	18*	0	0	0	0	0
Vb	30*	30*	25*	21*	20*	30*	30*	19*	0	0	0	0

Table 7. MIC values for quinolines derivatives.

compounds	Gram negative bacteria	Gram positive bacteria	Fungi
	Escherichia coli	*Staphylococcus aureus*	*Candida albicans*
	Conc.(mcg/ml)		
Ciprofloxacin	100	100	0
Fluconazole	0	0	50000
IIa	50	100	10000
IIb	50	50	10000
IIIa	100	100	0
IIIb	100	100	0
IVa	1000	1000	0
IVb	1000	1000	10000
Va	1000	1000	0
Vb	100	100	0

Conclusions

The docking study revealed that some of the newly synthesized derivatives exhibited superior alignment at the active site by interacting with all crucial amino acid residues. In-silico method adopted in the present study facilitated the identification of lead compounds, partly explaining their beneficial effects observed *in vivo* studies. The docking study's anti-inflammatory and antibacterial properties, along with the delta G results, align with conclusions from related *in vivo* investigations and demonstrate acceptable pharmacokinetic properties through virtual ADME studies. *In vivo* study for estimation of their anti-inflammatory activity; as illustrated in Table 5 and Figure 3, all synthesized derivatives (**IIa-Vb**) showed significant activity compared to the control from 2-5 h.

The eight designed derivatives were successfully synthesized with acceptable yields, and their ^{1}HNMR and ATR-FTIR spectroscopy investigations proved significant. All these results support the potential use of these derivatives in pharmaceutical applications to combat worldwide health problems, particularly antibiotic resistance. Additionally, the synthesized compounds exhibited considerable antibacterial activity. The final synthesized derivatives **IIa-Vb** demonstrated superior antibacterial activity, exhibiting significant antibacterial activity against gram-negative bacteria (*Escherichia coli*) compared to the reference drug (ciprofloxacin with gram-negative bacteria (*Escherichia coli*): (**IIa-Vb**) at 100 mg/l; (**IIa-Vb**) at 50 mg/l; (**IIa-IVa and Vb**) at 25 mg/l; and (**IIa, IIb**, **IIIb**, **and Vb**) at 12.5 mg/l concentrations give a high activity, (**IVb and Va**) at 25 mg/l and (**IIIa**)at 12.5 mg/l give moderate activity,

(**IVa, IVb, and Va**) at 12.5mg/l concentrations considered as inactive. For gram-positive bacteria (*Staphylococcus aureus*): (**IIa-IVa**, **Va**, **and Vb**) at 100 mg/l; (**IIa-Vb**) at 50 mg/l; (**IIa-IIIb**, **Va**, **and Vb**) at 25 mg/l; and (**IIa**, **IIb**, **IIIb and Vb**) at 12.5 mg/l concentrations give high activity; (**IVb**) at 100 mg/l , (**IVa**) at 25 mg/l; and (**IIIa**) at 12.5 mg/l moderately active; while (**IVb**) at 25 mg/l and (IVa-Va) at 12.5 mg/l are classified as inactive. According to the antifungal activity against *Candida albicans*, when compared with the drug Fluconazole, only **IIa**, **IIb**, and **IVb** highly active at 100 mg/l, while the final compounds (**IIa**, **IIb**, **and IVb**) at 50 mg/l, and (**IIb**) at 25 mg/l showed a moderate activity; the other final compound is classified as inactive. ADME analysis of quasi - active molecules was performed and demonstrated an acceptable drug-like profile and desirable pharmacokinetic properties.

Acknowledgment

The authors are grateful to the College of Pharmacy/ University of Baghdad; for all the facilities to conduct the research.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

The authors declare that they have no received financial support from an Institution.

Ethics Statements

The authors declare that their study does not need ethical approval from an ethics committee.

Author Contribution

Both authors contributed to the research study design and practical application of the research strategy for the preparation of target compounds for which FTIR and ^{1}HNMR tests were conducted on, and interpretation of their results. As well as conducting antimicrobial and anti-inflammatory tests and discussing their results; also, both authors reviewed the complete research writing in terms of scientific and linguistic formulation.

References

1. Spencer AC, Panda SS. DNA Gyrase as a Target for Quinolones. Biomedicines [Internet]. 2023 Jan 27; 11(2):371. Available from: https://www.mdpi.com/2227-9059/11/2/371.
2. Swedan HK, Kassab AE, Gedawy EM, Elmeligie SE. Design, synthesis, and biological evaluation of novel ciprofloxacin derivatives as potential anticancer agents targeting topoisomerase II enzyme. J Enzyme Inhib Med Chem. 2023;38(1):118–37. https:// doi.org/ 10. 1080/14756366.2022.2136172.
3. Struga M, Roszkowski P, Bielenica A, et al. N-Acylated Ciprofloxacin Derivatives: Synthesis and In Vitro Biological Evaluation as Antibacterial and Anticancer Agents. ACS Omega. 2023;8(21):18663–84.
4. Kabir S, Tahir Z, Mukhtar N, Sohail M, Saqalein M, Rehman A. Fluoroquinolone resistance and mutational profile of gyrA in pulmonary MDR tuberculosis patients. BMC Pulm Med. 2020;20(1):1–6.
5. Ajjah NT, Naser NH, Alard AAA, Diwan MF. Design , Synthesis , Docking Study and Preliminary Pharmacological Assessment of New Norfloxacin Analogues Having Thiazole Nucleus. J Biochem Technol. 2020;11(2):58–67.
6. Brar RK, Jyoti U, Patil RK, et al. Fluoroquinolone antibiotics: An overview. Adesh Univ J Med Sci Res [Internet]. 2020 Jul 23 [cited 2022 Jul 17];2(1):26–30. http://aujmsr.com/fluoroquinolone-antibiotics-an- overview-2
7. Millanao AR, Mora AY, Villagra NA, et al. Biological effects of quinolones: A family of broad-spectrum antimicrobial agents. Vol. 26, Molecules. 2021. 1–42.
8. Sukumaran DP, Abdulla MH. Can bio-nanotechnology be effective against multi drug resistant (MDR) pathogens? Appl Multifunct Nanomater [Internet]. 2023, 1,;475–98. https://linkinghub.elsevier.com/ -retrieve/pii/B9780128205570000084
9. Herbert R, Caddick M, Somerville T, McLean K, et al. Potential new fluoroquinolone treatments for suspected bacterial keratitis. BMJ Open Ophthalmol. 2022;7(1). 34-41
10. Naqvi SAR. 99mTc-labeled antibiotics for infection diagnosis: Mechanism, action, and progress. Chem Biol Drug Des. 2022;99(1):56–74.
11. Terreni M, Taccani M, Pregnolato M. New antibiotics for multidrug-resistant bacterial strains: Latest research developments and future perspectives. Molecules. 2021;26(9). 20-32
12. ALOthman ZA, Badjah AY, Alsheetan et al Enantiomeric resolution of quinolones on crown ether CSP: Thermodynamics, chiral discrimination mechanism and application in biological samples. J Chromatogr B Anal Technol Biomed Life Sci . 2021;1166:12255. https://doi.org/10.1016/j.jchromb.2021.122550
13. Zhao Y-Q, Li X, Guo H-Y, Shen Q-K, Quan Z-S, Luan T. Application of Quinoline Ring in Structural Modification of Natural Products. Molecules. 2023;28(18):6478.
14. Scelfo C, Menzella F, Fontana M, Ghidoni G, Galeone C, Facciolongo NC. Pneumonia and invasive pneumococcal diseases: The role of pneumococcal conjugate vaccine in the era of multidrug resistance. Vaccines. 2021;9(5).
15. Dube PS, Legoabe LJ, Beteck RM. Quinolone: a versatile therapeutic compound class. Mol Divers 2022;(0123456789). https:// doi.org/ 10.1007 /s11030-022-10581-8

16. Jia Y, Zhao L. The antibacterial activity of fluoroquinolone derivatives: An update (2018–2021). Eur J Med Chem. 2021;224:113741. https://doi.org/10.1016/j.ejmech.2021.113741

17. Senerovic L, Opsenica D, Moric I, Aleksic I, et al. Quinolines and quinolones as antibacterial, anti-fungal, anti-virulence, antiviral and anti-parasitic agents. Adv Exp Med Biol. 2020;1282:37–69.

18. Zhao D, Jiang Y, Sun J, Li H, Huang M, Sun X, et al. Elucidation of The Anti-Inflammatory Effect of Vanillin In Lps-Activated THP-1 Cells. J Food Sci. 2019;84(7):1920–8.

19. Arruda HS, Neri-Numa IA, Kido LA, Maróstica ,et al. Recent advances and possibilities for the use of plant phenolic compounds to manage ageing-related diseases. J Funct Foods. 2020;75(June):104203.: https://doi.org/10.1016/j.jff.2020.104203

20. do Carmo MAV, Granato D, Azevedo L. Antioxidant/pro-oxidant and antiproliferative activities of phenolic-rich foods and extracts: A cell-based point of view .1st ed. Vol. 98, Advances in Food and Nutrition Research. Elsevier Inc.; 2021. 253–280 .http://dx.doi.org/10.1016/bs.afnr.2021.02.010

21. Rahman M, Rahaman S, Islam R, Rahman F, Mithi FM, Alqahtani T, et al. Role of Phenolic Compounds in Human Disease : Current. Molecules. 2022;27(233):1–36.

22. Cheng Y-L, Lee C-Y, Huang Y-L, Buckner CA, Lafrenie RM, Dénommée JA, et al. We are IntechOpen , the world ' s leading publisher of Open Access books Built by scientists , for scientists TOP 1 %. Intech. 2016; 11 (tourism): 13. https:// www. intechopen. com/ books/ advanced -biometric-technologies /liveness-detection -in-biometrics

23. Manish S. Junagade, Anju Goyal. 'Mutual Prodrug' and approach to increase the effectiveness of Non-Steroidal Anti-inflammatory Drugs. World J Biol Pharm Res. 2021;1(1):035–45.

24. Manessis G, Kalogianni AI, Lazou T, Moschovas M, Bossis I, Gelasakis AI. Plant-derived natural antioxidants in meat and meat products. Antioxidants. 2020;9(12):1–30.

25. Mohammed1 ZB, Omar2 TN, Mohammed ZB. Chemical Design, Synthesis And Biological Evaluoation Of Mutual Prodrug Of Gabapentin With Different Types Of Phenolic And Alcoholic Antioxidants. Syst Rev Pharm. 2021;12(1):858–68.

26. Yaşa H. Synthesis, characterization, and evaluation of antioxidant activity of new γ- and δ-imino esters. Turkish J Chem. 2018;42(4):1105–12.

27. Arya SS, Rookes JE, Cahill DM, Lenka SK. Vanillin: a review on the therapeutic prospects of a popular flavouring molecule. Adv Tradit Med. 2021;21(3):415–31. https://doi.org/10.1007/s13596-020-00531-w

28. Iannuzzi C, Liccardo M, Sirangelo I. Overview of the Role of Vanillin in Neurodegenerative Diseases and Neuropathophysiological Conditions. Int J Mol Sci. 2023;24(3).

29. Majdalawieh AF, Mansour ZR. Sesamol, a major lignan in sesame seeds (Sesamum indicum): Anti-cancer properties and mechanisms of action. Eur J Pharmacol .2019;855:75–89.: https://doi.org/ 10.1016 /j.ejphar.2019.05.008

30. Nair AB, Dalal P, Kadian V, Kumar S, Garg M, Rao R, et al. Formulation Strategies for Enhancing Pharmaceutical and Nutraceutical Potential of Sesamol: A Natural Phenolic Bioactive. Plants. 2023;12(5).

31. Golea L, Chebaki R, Laabassi M, Mosset P. Synthesis, characterization of some substituted Quinolines derivatives: DFT, computational, in silico ADME, molecular docking and biological activities. Chem Data Collect. 2023;43,. https://doi.org/10.1016/j.cdc.2022.100977

32. Jubeh B, Breijyeh Z, Karaman R. Antibacterial prodrugs to overcome bacterial resistance. Molecules. 2020;25(7):1–16.

33. Raauf AMR, Omar TNA, Mahdi MF, Fadhil HR. Synthesis, molecular docking and anti-inflammatory evaluation of new trisubstituted pyrazoline derivatives bearing benzenesulfonamide moiety. Nat Prod Res. 2022;1–21.

34. Jubeh B, Breijyeh Z, Karaman R. Resistance of gram-positive bacteria to current antibacterial agents and overcoming approaches. Molecules. 2020;25(12).

35. Ashraf Z, Rafiq M, Seo SY, Babar MM, Zaidi NUSS. Synthesis, kinetic mechanism and docking studies of vanillin derivatives as inhibitors of mushroom tyrosinase. Bioorganic Med Chem [Internet]. 2015;23(17):5870–80. Available from: http://dx.doi.org/10.1016/j.bmc.2015.06.068.

36. Omar TNA, Mahdi MF, Al-Mudhafar MMJ, Zainabbassim. Synthesize of new ibuprofen and naproxen sulphonamide conjugate with anti-inflammatory study and molecular docking study. Int J Pharm Qual Assur. 2018;9(2):102–8.

37. Awinash C, Prafulla S. Molecular docking study and antibacterial activity of novel chalcone derivatives. Pharma Innov. 2020;9(1):39–42.

38. Mehta S, Pathak SR. In silico drug design and molecular docking studies of novel coumarin derivatives as anticancer agents. Asian J Pharm Clin Res. 2017;10(4):335–40.

39. Elekofehinti OO, Iwaloye O, Josiah SS, et al Molecular docking studies, molecular dynamics and ADME/tox reveal therapeutic potentials of STOCK1N-69160 against papain-like protease of SARS-CoV-2. Mol Divers . 2021; 25(3):1761–73. https://doi.org/10.1007/s11030-020-10151-w

40. Pattar SV, Adhoni SA, Kamanavalli CM, Kumbar SS. In silico molecular docking studies and

MM/GBSA analysis of coumarin-carbonodithioate hybrid derivatives divulge the anticancer potential against breast cancer. Beni-Suef Univ J Basic Appl Sci. 2020;9(1). 65

41. Pollastri MP. Overview on the rule of five. Curr Protoc Pharmacol. 2010;(SUPPL. 49):1–8.

42. Ramkrushnarao Chaple D, Pratyush K, Avhad DM, Chaple DR, Asnani AJ, Mohurle S, et al. Synthesis and Evaluation of Mutual Prodrugs of Ibuprofen As Non Steroidal Anti-Inflammatory Drugs With Antioxidants. 2020;9(5):1426–38. Available from: www.wjpps.com

43. Omar TN. Synthesis of anti-inflammatory aromatic Schiff bases Synthesis of Schiff Bases of Benzaldehyde and Salicylaldehyde as Anti-inflammatory Agents. Iraqi JPharmSci. 2007;16(2):5–11.

44. Kanaan SK, Omar TNA. Synthesis and Preliminary Anti-Inflammatory and Anti-Microbial Evaluation of New 4,5-Dihydro-1H-Pyrazole Derivatives. Iraqi J Pharm Sci. 2023;32(2):262–70.

45. Naser NH, Mahdi MF, Omar TN-A, Fadhil AA. Synthesis and preliminary pharmacological evaluation of new analogues of diclofenac as potential anti-inflammatory agents. Iraqi J Pharm Sci. 2011;20(1):25–32.

46. N â€“ A . Omar T. Synthesis and Preliminary Pharmacological Evaluation of Esters and Amides Derivatives of Naproxen as Potential Anti-Inflammatory Agents. Iraqi J Pharm Sci (P-ISSN 1683 - 3597 E-ISSN 2521 - 3512). 2017;22(1):120–7.

47. K MM. Synthesis characterization and Preliminary Pharmacological Evaluation of new 2-pyrazoline derivatives derived from resorcinol. J Popul Ther Clin Pharmacol. 2023;30(14):319–26.

48. Kamoon RA, Jawad Al-Mudhafar MM, Omar TNA. Synthesis, characterization and antimicrobial evaluation of new Azo compounds derived from sulfonamides and Isatin Schiff base. Int J Drug Deliv Technol. 2020;10(1):150–5.

49. K MM, Omar TN. Evaluation of New 2-Pyrazolines Derivatives Derived. 2023; 32(2):254–61.

50. Al-Nakeeb MR, Omar TNA. Synthesis, characterization and preliminary study of the anti-inflammatory activity of new pyrazoline containing ibuprofen derivatives. Iraqi J Pharm Sci. 2019;28(1):133–9.

51. Balouiri M, Sadiki M, Ibnsouda SK. Methods for in vitro evaluating antimicrobial activity: A review. J Pharm Anal [Internet]. 2016;6(2):71–9. Available from: http:// dx.doi. org/ 10. 1016 /j.jpha.2015.11.005

52. Kowalska-Krochmal B, Dudek-Wicher R. The minimum inhibitory concentration of antibiotics: Methods, interpretation, clinical relevance. Pathogens. 2021;10(2):1–21.

53. Assar S, Nosratabadi R, Khorramdel Azad H, Masoumi J, Mohamadi M, Hassanshahi G. A Review of Immunomodulatory Effects of Fluoroquinolones. Immunol Invest. 2021; 50(8):1007–26.:https://doi.org /10. 1080 /08 820139.2020.1797778

54. Fief CA, Hoang KG, Phipps SD, Wallace JL, Deweese JE. Examining the Impact of Antimicrobial Fluoroquinolones on Human DNA Topoisomerase IIα and IIβ. ACS Omega. 2019;4(2):4049–55.

55. Mohammed YW, Omar TN. Design, Synthesis and Antibacterial Evaluoation of mutual Prodrugs of Antioxidants With Different quinolone Antibiotics. Biochem Cell Arch. 2021;21(1):1759–68.

56. Kivinen in Patai: The chemistry of acyl halides, Interscience Publishers,New York, 1972; pp.177.

57. March, J.: Advanced organic chemistry (4th ed). John Wiley and Sons.1992;.438

58. K SK, Omar TN. Synthesis and Preliminary Pharmacological Evaluation of New Pyrazoline Derive from Different Heterocyclic Aldehydes. J Popul Ther Clin Pharmacol. 2023;30(14):311–8.

59. Praveen Kumar CH, Katagi MS, Samuel J, Nandeshwarappa BP. Synthesis, Characterization and Structural Studies of Novel Pyrazoline Derivatives as Potential Inhibitors of NAD+ Synthetase in Bacteria and Cytochrome P450 51 in Fungi. ChemistrySelect. 2023 Mar 28;8(12): e202300427.: https:// onlinelibrary. wiley. Com /doi/full/10.1002/slct.202300427

60. Najmuldeen ZD, Omar TNA. Synthesis and Evaluation of New Pyrazoline derivatives containing Sulfonamide Moiety as Anti-microbial and Anti-inflammatory Agents. J Res Med Dent Sci. 2023;11(01):1–10.

61. Wheeler WJ, Preston DA, Wright WE, Huffman GW, Osborne HE, Howard DP. Orally Active Esters of Cephalosporin Antibiotics. 3.1Synthesis and Biological Properties of Aminoacyloxymethyl Esters of 7-[D-(-)-Mandelamido]-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylic Acid. J Med Chem. 1979;22(6):657–61.

دراسة الالتحام الجزيئي والتخليق والخصائص الأولية المضادة للالتهابات والمضادة للميكروبات لمترافق جديد من مشتقات الكينولون-الفينول

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الخلاصة

تم تصميم هذا البحث بشكل يركز على تعديل البنية الأساسية للكينولونات عن طريق إدخال مجموعة الإستر في الموضع C3؛ تم التصميم باستخدام Ligand Designer من برنامج شرودنكر. تم تصنيع سلسلة من مشتقات الاقتران الجديدة (IIa-Vb) عن طريق استرة الكينولونات (سيبروفلوكساسين، جاتيفلوكساسين، حمض النالديكسيك، والنورفلوكساسين) مع نوعين من مضادات الأكسدة (فانيلين وسيسامول) عند C3 والتي تم استبدالها بمجموعة استر عبر جليكول. رابط.تم فحص المركبات المحضرة وتوصيفها بالتقنيات الطيفية الرنين النووي المغناطيسي والاشعة تحت الحمراء. بالإضافة إلى ذلك، تم فحص أنشطتها الدوائية. في الجسم الحي، تم تقدير التأثير المضاد للالتهابات لمركبات (IIa-Vb) باستخدام نموذج وذمة مخلب الفئران، مما يدل على نشاط كبير للمركبات النهائية IIa-Vb من ٢-٥ ساعات. عند مقارنتها بـ ثنائي مثيل السلفوكسيد (المذيب والتحكم). تم اختبار مشتقات الاقتران الجديدة بشكل إضافي لنشاطها المضاد للميكروبات ضد كل من البكتيريا إيجابية الجرام وسالبة الجرام باستخدام طريقة الانتشار الجيد وفقًا لمنطقة التثبيط للمركبات النهائية الثمانية المحضرة، والتي أظهرت النتائج التالية: مع البكتيريا سالبة الجرام(IIa-Vb) : بتركيز ١٠٠ ملغم/لتر؛ (IIa-Vb) عند ٥٠ ملغم/لتر؛ (IIa-IVa وVb) عند ٢٥ ملغم/لتر؛ و (IIa, IIb, IIIb و Vb) بتركيزات ١٢,٥ ملغم/لتر تعطي نشاطاً عالياً، (IVb و Va) بتركيز ٢٥ ملغم/لتر و (IIIa) بتركيز ١٢,٥ ملغم/لتر تعطي نشاطاً متوسطاً، (IVb, IVa و Va) بتركيزات ١٢,٥ ملغم/لتر تعتبر غير فعالة. بالنسبة للبكتيريا إيجابية الجرام: (IIa-IVa، Va وVb) بجرعة ١٠٠ ملغم/لتر؛ (IIa-Vb) عند ٥٠ ملغم/لتر؛ (IIa-IIIb، Va وVb) عند ٢٥ ملغم/لتر؛ و(IIa,IIb,IIIb وVb) بتركيزات ١٢,٥ ملغم/لتر تعطي نشاطاً عالياً؛ (IVb) عند ١٠٠ ملغم/لتر، (IVa) عند ٢٥ ملغم/لتر؛ و(IIIa) عند ١٢,٥ ملغم/لتر نشط بشكل معتدل؛ بينما (IVb) عند ٢٥ ملغم/لتر و(IVa-Va) عند ١٢,٥ ملغم/لتر يصنفان على أنهما غير نشطين. وفقًا للنشاط المضاد للفطريات ضد المبيضات البيضاء، بالمقارنة مع عقار فلوكونازول، فإن IIa وIIb وIVb فقط نشط للغاية عند ١٠٠ ملغم/لتر، في حين أن المركبات النهائية (IIa وIIb وIVb) عند ٥٠ ملغم/لتر و(IIb) عند ٢٥ ملغم/لتر أظهر نشاطاً معتدلاً؛ تم تصنيف المركب النهائي الأخر على أنه غير نشط. تم إجراء تحليل (عوامل الامتصاص، التوزيع، الايض، الطرح و السمية) للجزيئات شبه النشطة وأظهر شكلًا مقبولًا يشبه الدواء وخصائص حركية دوائية مرغوبة.

الكلمات المفتاحية: مشتقات الكينولون، الرسو الجزيئي، الحركية الدوائية، المضادة للبكتيريا، الفانيلين، السيسامول.