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In-silico Studies, Synthesis and Preliminary Biological Evaluation of New Fluoroquinolones-antioxidants Hybrid Compounds

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Abstract

Fluoroquinolones are one of the most promising types of antibacterial that is used to treat sever types of infection due to their broad spectrum of activity. This research was designed in a way that focused on modification of the basic structure of fluoroquinolones by introducing new functionality ester group at the C3 position 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-IVb) compounds was estimated using a rat paw edema model, showing significant activity for the final compounds IIa-IVb from 2-5hrs. when compared to the DMSO (solvent and control).The new hybrid 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 six synthesized final compounds , which showed the following results: with gram-negative bacteria (*Escherichia coli*): (IIa-IVb) at 100 mg/l; (IIa-IVa) at 50 mg/l; (IIa, IIb &IIIb) at 25 mg/l; and (IIa, IIb, IIIb &IVa) at 12.5 mg/l concentrations give high activity; (IVb) at 50 mg/l; (IIIa, IVa, & IVb) at 25 mg/l; and (IIIa) at 12.5 mg/l give moderate activity; (IVb) at 12.5 mg/l concentrations are considered inactive. For gram-positive bacteria (*Staphylococcus aureus*): (IIa-IVa) at 100 mg/l; (IIa-IVb) at 50 mg/l; (IIa-IVb) at 25 mg/l; and (IIa, IIb, IIIb &IVa) at 12.5 mg/l concentrations give high activity; (IVb) at 100 mg/l; and (IIIa) at 12.5 mg/l moderately active; while (IVb) at 12.5 mg/l is classified as inactive. According to antifungal activity against *Candida albicans*, when compared with the drug Fluconazole, the final compounds (IVb) at 100 mg/l, (IIa, IVa & IVb) at 50 mg/l, and at 25 mg/l showed moderate activity; the other final compounds are classified as inactive.

Keywords: ADME, Anti-Bacterial, Menthol, Molecular Docking, Fluoroquinolones Derivatives, Umbelliferone.

Introduction

Fluoroquinolones (FQs) including ciprofloxacin, gatifloxacin, and norfloxacin have the ability to targeting DNA gyrase, hydrolyzing adenosine triphosphate, DNA relaxes in response to ATP-dependent Topo II activity, belongs to topoisomerase II (topo II) of eukaryotic DNA or DNA decatenation driven by ATP for the type's class topo IV, or eubacterial topoisomerase IV.[(1,2)] Despite their antibacterial effectiveness, many people develop medication resistance because various organisms have different methods of action; The incorporation of the fluorine atom at C6, the piperazinyl ring at C7, and cyclopropyl at N1. increased the potency of quinoline derivatives to suppress the activity of E. *coli* gyrase significantly; the addition of fluoride improved the pharmacokinetic profile of FQs.; also, they indicate that this alteration will result in improved anti-inflammatory effects in addition to decreasing undesired side effects [(3)] . Fluoroquinolones have broad-spectrum as antibacterial with activity against mycobacteria, anaerobes, and both Gram-positive and Gram-negative bacteria ;they cause that through interfering with the enzymes DNA gyrase and topo-isomerase IV, preventing the production of nucleic acids by bacteria, and breaking bacterial chromosomes[(4,5)].They are utilized to treat infectious disorders include bone and joint infections, skin and soft tissue infections, respiratory tract infections, gastrointestinal infections, gynecological infections, sexually transmitted diseases, urinary tract infections, and prostatitis, respiratory tract infections including acute bacterial exacerbation of chronic bronchitis, bacterial sinusitis, community-acquired pneumonia and hospital-acquired pneumonia [(6)].

The treatment of immunocompromised patients with febrile neutropenia can also benefit from the use of several fluoroquinolones[(7)], the complicated urinary tract infections such as rectal and genitourinary gonorrhea without sequelae, chronic bacterial prostatitis, cystitis, and pyelonephritis[(8)], skin and other soft tissue infections such as treatment of severe bacterial skin infections and skin structure

infections [9], bone and joint infections caused by Enterobacter species [10], adults receiving empiric antibiotic treatment for infectious diarrhea[11], and typhoid by Salmonella species (Enterica serovars typhi) [12], intra-abdominal infections (when used with metronidazole) astargeted therapy following bacterial identification[13]. It is believed that the more recent fluoroquinolones generation makes sense as an alternative to conventional antibiotics, particularly in cases where penicillin and macrolide allergies also along with lincosamide and streptogramin group resistant [14,15]. Since fluoroquinolone-resistant bacteria have become a greater threat to human health in recent years, structural modifications to fluoroquinolones to boost their efficacy and reduce their side effects are essential. [16]. In drug development efforts, fluoroquinolones derivatives have been employed as lead molecules[17], researchers alter the quinoline structure to create novel compounds with superior features, such as good efficacy, less toxicity, and give better pharmacokinetics[18] ; they explore various therapeutic properties, Several research have examined the anti-inflammatory activities[19],analgesic effects[20], Alzheimer's disease treatment[21],anticonvulsant[22],antioxidants effect[23], anticancer activities[24], also it found its activity in decreasing blood cholesterol level in mice[25]. Natural phenolic components that are employed as promoieties in the manufacture of prodrugs exhibit antioxidant activity such as sesamol , umbelliferone ,vanillin and menthol[26-28]. They have antioxidant ,antimicrobial and antifungal properties[29].Menthol shows good potential properties in skin wound healing , also show biological activity both in vivo and in vitro, including analgesic, antibacterial, anti-inflammatory, anti-pruritic, anticancer, and antifungal properties[30,31], with regard to umbelliferone has potential biological activities *in vivo* and *invitro* and demonstrates large pharmacological activities as antioxidant, antiulcerogenic, antibacterial, antidiarrheal, and mutagenic[32], also it has antitumor, anti-inflammatory activity and anti-hyperlipidemia properties[33].The computational techniques within our study include molecular docking studies, and ADME (absorption, distribution, metabolism, and excretion), all of which aid in the search for new lead compounds. Molecular docking is essential to the logical creation of pharmaceuticals; also, it is used in molecular modeling that predicts a molecule's preferred orientation with respect to another molecule when they combine to form a stable complex. An optimization problem that describes the "best-fit" orientation of a ligand that binds to a certain target protein is known as molecular docking. It typically aids in the discovery of novel medications and indicates the proteins that cause illnesses. [34, 35] Through combining some types of fluoroquinolones antibacterial, such as ciprofloxacin, gatifloxacin, and Norfloxacin, with menthol and umbelliferon as antioxidants, we hope to produce novel derivatives of various quinolines. The parent medication is changed utilizing glycolic acid (-OCH_2COO-) precursors to produce more effective and secure derivatives and synthesized 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 are supplied from Shanghai Macklin Biochemical Company (China). Solvent and other reagents for the reaction were purchased from the pharmacy college's chemical store/university of Baghdad. The reactions were detected using thin layer chromatography (TLC), two mobile solvent systems are used (A: chloroform: methanol (85:15), B: chloroform: ethyl acetate: ether (10:5:1). All melting points in this investigation were determined using an electronic melting point device (Stuart SMP30). ATR-FTIR (Schimadzu, Japan) was developed via the thin film method. using dimethyl sulfoxide ($DMSO_{d6}$) as a solvent, ^{1}H-NMR spectra were obtained on a BRUKER model Ultrashield 500 MHz spectrophotometer, molecular docking study was performed at the College of Pharmacy/ University of Baghdad, by using Schrodinger software.

Molecular docking

The interactions between synthesized quinoline derivatives (IIa-IVb), COX-2, and E. *coli* Topoisomerase IV receptors (PDB ID: 4m11 and 3Fv5, respectively) were investigated using the Schrödinger Maestro software version. The study also examined the interactions of diclofenac and ciprofloxacin with the same receptors. Understanding the molecular mechanisms behind these drugs' interaction with the COX-2 and E. *coli* Topoisomerase IV receptors was the main objective of this investigation; this would provide crucial information about their binding patterns and their uses as pharmaceuticals. In order to get the ligands prepared to perform the molecular docking study, LigPrep was used in the lab. LigPrep improves ligand structures for docking simulations by generating 3D ligand representations using the Build Panel.To allow protein docking, the Protein Data Bank supplied the crystallographic structures

of receptors. Specifically, we retrieved structures with PDB IDs 4m11 (COX-2) and 3Fv5 (E. *coli* Topoisomerase IV). These structures were prepared for the docking research using the protein preparation wizard. Adding hydrogen atoms and removing solvent molecules were part of the preparation processes to provide a clean and suitable environment for the docking simulations. The goal was to minimize the protein-ligand complexes and ensure that the bound ligands were in conformations within the protein-binding region that were energetically valuable. A molecular docking was generated by comparing to the bound ligands that cocrystallized; these grids helped define the potential binding sites within the catalytic sites of the target proteins (COX-2 and E. *coli* Topoisomerase IV). This was essential in directing the docking simulations.As a part of the validation process for the docking protocol, diclofenac (in COX-2) and ciprofloxacin (in E. *coli* Topoisomerase IV) were redocked into the catalytic sites of the proteins. The successful occupation of the similar binding pockets by these reference ligands as seen in the crystallographic structures further supports the accuracy of the docking methodology.The molecular docking simulations employed the glide standard-precision (SP) mode. The docking process involved compounds IIa-IVb, as well as diclofenac and ciprofloxacin. For each molecule, the docking simulations generated and saved two potential binding poses, utilizing the SP mode. This strategy made it possible to investigate various ligand orientations and conformations within the binding sites, which aided in the identification of the binding modes that are most potentially advantageous. This method has been demonstrated to be useful in predicting the binding mechanism of small-molecule inhibitors to their target proteins [36-39].

ADME studies

The study made use of the highly accurate QikProp module of Maestro-Schrodinger, a software that is well-known for being user-friendly, precise, and quick in predicting crucial descriptors that aid in understanding how drugs are absorbed, distributed, metabolized, excreted, and their potential toxicity (ADME), which help to optimize the pharmacokinetics and pharmaceutical properties of intended compounds that give an expressed proteome capable of binding high-affinity ligands with characteristics like drugs and whose activity is affected by them; also described genes that produce physiologically significant proteins, the activity of which is regulated by ligands of high affinity [40,41].

Chemical synthesis

- ***Synthesis of antioxidant- chloroacetyl chloride (Ia-b) as intermediates***

An appropriate amount of each antioxidant (a-menthol and b-umbelliferone) (0.001 mol, 1.56 g and 0.001 mol, 1.6 g), respectively, was mixed with trimethylamine (0.001 mol, 1.4 ml). 25 ml of dichloromethane was placed into the mixture in a round bottle flask, and then the mixture of clear color solution was cooled to -10 °C using an ice bath.A mixture of chloroacetylchloride (0.001 mol/0.8 mL) in chloroform 25 ml was prepared and was added drop-wise to the antioxidant mixture over a period of 1 h. The temperature of the reaction mixture was kept at -10 °C during the addition and stirred overnight. Then wash the clear mixture using a separatory funnel with 5% NaOH (3.50 ml), 5% HCl (3.50 ml), and Brine solution (2.25 ml). 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) [42]. The R_f values were obtained from running TLC using (chloroform: methanol 8.5:1.5) as solvent system. Compound (Ia) Yield =78%, R_f =0.65, IR (v=cm^{-1}): 2954.95, 2924.09 and 2870.08 (C-H str. of CH_2 and CH_3), 1755.22 and 1735.93 (C=O) stretching vibration of ester, 1261.45 (*asym* C-O-C)str., 790.81 and 702.09 (C-Cl)str. Compound (Ib) Yield = 70%, R_f = 0.70 IR (v=cm^{-1}): 3078.39 and 3024.38 (ArC-H) str., 2970.38 ,2916.37 and 2850.79 (C-H str. of CH_2 and CH_3), 1766.80 and 1728.22 (C=O) stretching vibration of ester,1651.07 1616.35(Lactone- C=O)Str., 1556.20 and 1513.07 (Ar C=C)str., 1265.30 (*asym* C-O-C)str., 790.81 and 752.24 (C-Cl)str..

- ***Synthesis of fluoroquinolones - antioxidant compounds (IIa-IVb)***

A suitable amount of each Ia-b 0.001 mol (a:1.56 g and b :1.6g) together with different fluoroquinolones 0.001mol (II:ciprofloxacin, 3.31g, III:gatifloxacin, 3.75g, and IV:Norfloxacin, 3.19g) respectively, in trimethylamine (0.001mol, 1.4ml) in 250ml round bottle flask(RBF), NaI (0.001mol, 1.5g) and DMF was added also into (RBF), the mixture was kept stirring in the refrigerator for overnight at 25°C. Following the 12 h stirring the resultant mixture was poured on to a crushed ice, then, extraction with chloroform (4X25ml) was and separation of the organic layer by using 2% sodium thiosulphat (3×50ml), 5% NaOH (3×50 ml), 5% HCl (3×50 ml), and 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) and ethyl acetate (25:1).[43] The R_f values obtained from running TLC using (chloroform: methanol 8.5:1.5) as a solvent system.

- ***Compound (IIa) 2-((2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl 1-cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate***

Light yellow powder, yield=86%, M.P.= (160-162)°C ,R_f = 0.84 **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., 1735.39 and 1701.22 (ester C=O) str., 1624.06 (ketone C=O)str, 1585.49 and1535.34 (Ar C=C)str., 1172.72 and 1149.57 (C-F) str.**^{1}HNMR(500 MHz, DMSO$_{d6}$; δ,ppm) :** 0.27-0.99 (m,9H,CH_3), 1.26 (d,4H, cyclopropyl ring), 1.52 (s,1H, Isopropyl group), 1.67-1.89 (m,1H, cyclohexane ring), 2.11 (dd,2H, cyclohexane ring), 2.53-2.57 (m,4H, cyclohexane ring), 260-264 (m,1H, Isopropyl group), 3.65 (s,1H, piperazine ring), 4.30 (t,4H, piperazine ring), 4.55 (t,4H, piperazine ring), 4.63 (quintet ,1H, cyclopropyl group), 4.99 (dd,1H, cyclohexane ring), 7.43 (s,2H, CH_2) 7.77 (s,1H, Ar-H), 7.82 (s,1H, Ar-H), 8.55 (s,1H, pyridin-4(1H)-one).

- ***Compound (IIb) 2-oxo-2-((2-oxo-2H-chromen-7-yl)oxy)ethyl 1-cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate***

Light yellow powder, yield=84%, M.P. = (168-170)°C , R_f =0.87 **, IR(v=cm^{-1}):** 3082.25 and 3059.10 (Imino moiety of piprazinyl)str., 2962.66 and 2831.50 (C-H of CH_2 and CH_3)str., 1755.22 and1728.22 (ester C=O) str., 1654.92 (ketone C=O)str., 1624.06 (Lactone- C=O)Str., 1566.20 and1500.62 (Ar C=C)str., 1242.16 (*asym* C-O-C)str. of ether, 1114.86 and1095.57 (C-F) str..**^{1}HNMR(500 MHz, DMSO$_{d6}$; δ,ppm) :** 1.26 (d,4H, cyclopropyl ring), 2.48 (s,1H, piperazine ring), 2.86 (t,4H, piperazine ring), 3.66 (t,4H, piperazine ring), 4.82 (Quintet ,1H, cyclopropyl group), 5.71 (s,2H, CH_2), 6.47 (s,1H, Ar-H), 6.77 (d,1H, 5,6-dihydro-2H-pyran-2-one), 7.19 (d,1H, Ar-H), 7.31 (s,1H, Ar-H), 7.54 (d,1H, Ar-H), 7.78 (d,1H, 5,6-dihydro-2H-pyran-2-one), 7.93 (s,1H, Ar-H), 8.54 (s,1H, pyridin-4(1H)-one).

- ***Compound (IIIa) 2-((2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl 1-cyclo-propyl-6-fluoro-8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylate***

Light yellow powder, yield=86%, M.P. = (155-156)°C , R_f =0.82,**IR(v=cm^{-1}):** 3068.11 (Imino moiety of piprazinyl)str., 2951.09 , 2931.80 , 2870.08 and 2846.93 (C-H of CH_2 and CH_3)str., 1735.93 (ester C=O) str., 1616.35 (ketone C=O)str., 1585.49 and 1535.34 (Ar C=C)str., 1230.58 (*asym* C-O-C)str. of ether, 1168.86 and 1149.57 (C-F) str.. **^{1}HNMR(500 MHz, DMSO$_{d6}$; δ,ppm) :** 0.81-1.04 (m,9H,CH_3), 1.36 (d,4H, cyclopropyl ring), 1.45 (Septet,1H, Isopropyl group), 1.55-1.60 (m,1H, cyclohexane ring), 1.69 (dd,2H, cyclohexane ring), 1.88 (d,3H, piperazine ring) , 2.15-2.19 (m,4H, cyclohexane ring), 3.02-3.23 (m,1H, isopropyl ;β to ester group), 3.42 (s,1H, piperazine ring), 3.44-3.49 (m,1H, piperazine ring), 3.54 (t,2H, piperazine ring), 3.77 (t,2H, piperazine ring), 3.82 (d,2H, piperazine ring), 4.33 (Quintet,1H, cyclopropyl ring), 4.46 (s,3H,OCH_3), 4.57 (dd,1H, cyclohexane ring α to methyl group), 4.75 (s,2H, methylene group (α –C to ester)), 7.63 (s,1H, Ar-H), 8.48 (s,1H, pyridin-4(1H)-one).

- ***Compound (IIIb) 2-oxo-2-((2-oxo-2H-chromen-7-yl)oxy)ethyl 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate***

Light yellow powder, yield=83%, M.P. = (158-159)°C , , R_f =0.85**, IR(v=cm^{-1}):** 3089.96 (Imino moiety of piprazinyl)str., 2970.38 , 2935.66 , 2885.51 and 2839.22 (C-H of CH_2 and CH_3)str., 1770.65 and 1732.08 (ester C=O) str., 1651.07 (ketone C=O)str., 1616.35 (Lactone- C=O)str., 1581.63 ,1543.05 , 1523.76 and 1500.62 (Ar C=C)str., 1230.58 (asym C-O-C)str. of ether, 1118.71 and 1091.71 (C-F) str.. **^{1}HNMR(500 MHz, DMSO$_{d6}$; δ,ppm):** 1.06 (d,3H, piperazine ring), 1.07 (d,4H, cyclopropyl ring), 1.90 (s,1H, piperazine ring), 2.09-2.18 (m,1H, piperazine ring), 2.79 (t,2H, piperazine ring), 3.76 (t,2H , piperazine ring), 4.01 (d,2H, piperazine ring), 4.12 (s,3H,OCH_3), 4.63 (Quintet ,1H, cyclopropyl ring), 5.96 (s,2H, methylene group (α –C to ester)), 6.50 (d,1H, 5,6-dihydro-2H-pyran-2-one), 6.60 (d,1H, Ar-H), 7.29 (s,1H, Ar-H), 7.63 (d,1H, Ar-H), 7.76 (s,1H, Ar-H), 7.80 (d,1H, 5,6-dihydro-2H-pyran-2-one), 8.59 (s,1H, pyridin-4(1H)-one) .

- ***Compound (IVa) 2-((2-isopropyl-5-methylcyclohexyl)oxy)-2-oxoethyl 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate***

Off white powder, yield=85%, M.P. =(185-187)°C , R_f =0.89 , **IR(v=cm^{-1}):** 3001.24 (Ar C-H)str., 2951.09 ,2924.09 and 2866.22 (C-H of CH_2 and CH_3)str., 1739.79 (ester C=O)str., 1620.21 (ketone-C=O)str., 1585.49 and 1535.34 (Ar C=C) str., 1257.59 (asym C-O-C)str., 1184.29 and 1172.72 (C-F) str.**^{1}HNMR(500 MHz, DMSO$_{d6}$; δ,ppm):** 0.76-0.99 (m,9H,CH3), 1.30 (Septet ,1H, Isopropyl ring), 1.43 (t,3H, CH_3-CH_2), 1.59-1.63 (m,1H, cyclohexane ring), 1.70 (dd,2H, cyclohexane ring), 1.79-1.88 (m,4H, cyclohexane ring), 1.90-1.97 (m,1H, C-H of isopropyl), 2.56 (s,1H, piperazine ring), 2.83 (t,4H, piperazine ring), 3.15 (t,4H, piperazine ring), 4.55 (dd,1H, cyclohexane ring), 4.65 (q,2H, CH_3-CH_2), 5.26 (s,2H,CH_2), 7.16 (s,1H, Ar-H), 7.86 (s,1H, Ar-H) , 8.69 (s,1H, pyridin-4(1H)-one) .

- ***Compound (IVb) 2-oxo-2-((2-oxo-2H-chromen-7-yl)oxy)ethyl 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate***

Light yellow powder, yield=82%, M.P. = (198-200)°C , R_f =0.88 , **IR(v=cm^{-1}):** 3055.24(Imino moiety of piprazinyl)str., 2951.09 , 2900.94 and 2835.36 (C-H of CH_2 and CH_3)str., 1762.94 , 1724.36 and 1697.36 (ester- C=O)str., 1651.07 (conj ketone C=O) str., 1616.35 (Lactone-C=O)str., 1562.34 ,1530 and 1508.33 (Ar C=C) str., 1253.73 and 1242.16 (asym C-O-C)str., 1126.43 and 1014.56 (C-F) str.. **^{1}HNMR(500 MHz, DMSO$_{d6}$; δ,ppm):** 1.39 (t,3H, CH_3-CH_2)**,**

2.06 (s,1H, piperazine ring)**,** 2.70 (t,4H, piperazine ring), 3.57 (t,4H, piperazine ring), 4.55(q,2H, CH_3-CH_2), 4.99 (s,2H,CH_2), 6.19 (s,1H, Ar-H), 6.48 (d,1H, 5,6-dihydro-2H-pyran-2-one), 6.77 (d,1H, Ar-H), 7.31 (s,1H, Ar-H), 7.50 (d,1H, Ar-H), 7.88 (s,1H, Ar-H), 7.93 (d,1H, 5,6-dihydro-2H-pyran-2-one), 8.69 (s,1H, pyridin-4(1H)-one) .

Pharmacological studies

Anti-inflammatory activity[43-46]

In vivo, an albino rats were used in anti-inflammatory study, in which a reduction in paw edema thickness is the main indicator in the experimental medication for assessment activity of the synthesized compound, Within the Iraqi Center for Cancer and Medical Genetics Research, forty-eight white albino rats weighing between 160 and 200g were housed. Baghdad University Animal House provided these rats. Under normal acclimation environments, the animals were fed in a commercial chaw and had free access to water. The inflammation was assessed at the beginning and during the short period of the experiment by injecting egg whites subcutaneously into the rat paw. Ten animal groups, each consisting of six rats, were present:

Group A: six rats served as control; and were treated with the vehicle (propylene glycol 50% v/v).

Group B: six rats treated with diclofenac sodium in a dose of 3mg/ kg, suspended in propylene glycol 50%

Groups (**C, D, E, F, G, H**): Six rats per group received injections of prepared substances that were dosed and dissolved in propylene glycol as shown in table 1.For the rats' hind paws, a 0.05 ml subcutaneous injection of an undiluted egg-white substance into the plantar side of the left hand paw may result in significant skin, the discomfort because of dominating inflammation. A Vernier caliper was used to measure the paw width at intervals of 0, 30, 60, 120, 180, 240, and 300 minutes, respectively, following drug delivery of the desired compounds or the vehicle, thirty-minutes after the injection.

Calculation of the dose

The following equation [47] was used to calculate the recommended doses of these intended compounds:

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

Equation is used to determine the intended compounds, as indicated in Table 1.

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

Compounds	M.wt(g/mol)	Rat dose(mg/kg)
Diclofenac sodium	318.1	3
IIa	527.636	4.976
IIb	533.506	5.031
IIIa	571.684	5.391
IIIb	577.554	5.446
IVa	515.621	4.862
IVb	521.491	4.918

Antimicrobial activity

In vitro, the minimum inhibitory concentration (MIC) of the synthesized compounds (IIa-IVb) was tested against two bacterial species: Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli*. Additionally, the antifungal activity was assessed against *Candida albicans*. Ciprofloxacin was used as a reference for antibacterial activity, while fluconazole was used as an antifungal reference, with DMSO serving as a solvent (negative control) [48, 49].

To prepare 1 liter of Mueller-Hinton agar from commercially available powder, the compounds were weighed using a sensitive balance at a concentration of 1000 mg/ml and dissolved in DMSO. The solution was stirred and left at room temperature for 18 hours to ensure complete dissolution, followed by the preparation of serial dilutions ranging from 100 mg to 12.5 mg [50, 51].For bacterial inoculum preparation and inoculation, bacterial species were activated overnight from stock cultures in nutrient broth. The bacterial inoculum was prepared by diluting the activated bacteria with sterile distilled water to achieve a cell concentration of approximately 1.5×10^8 cells/ml. The turbidity of the bacterial solution was visually adjusted to a 0.5 McFarland standard using a Wickerham card. The inoculum was then streaked directly onto Mueller-Hinton agar (MHA) plates using sterile cotton swabs. Wells (holes) with a diameter of 6 mm were created on the surface of these plates, where the solutions were loaded [52-54].After inoculating the microbes and loading the material into the agar wells, the Petri dishes were incubated in a laboratory incubator at 35-37 °C for 24 hours. The MIC activity was determined by measuring the diameter of the inhibition zones around the wells loaded with solutions using a transparent ruler, recorded in millimeters [50].

Results and Discussion

Numerous active drugs' binding reactions can be well understood by using molecular docking research. Molecular docking was used in this study to test eight compounds with anti-inflammatory and

antibacterial medications such as diclofenac against the COX-2 receptor and ciprofloxacin against the E. *coli* Topoisomerase IV receptor, as proven in Tables 2 and 3. Referring to diclofenac and ciprofloxacin, respectively, as reference ligands, the docking scores of the compounds were compared. The ligands' affinity for COX-2 was noted to be higher as the interaction of compound IIa and compound IVa for the E. *coli* Topoisomerase IV receptor.

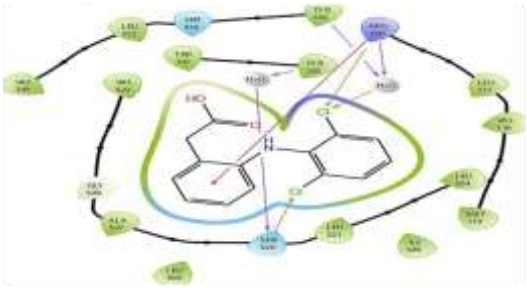
Table 2. Anti-inflammatory Docking Scores of docked Ligands (IIa-IVb) with Cyclooxygenase-2 (PDB Code: 4m11), Using Diclofenac as a Reference.

ID	Cox2 ΔG (Kcal/mol)	Types of interaction
diclofenac	-6.809	Halogen bond:SER530, ARG120 Pi-cation:ARG120
IIa*	-5.788	2H-Bond:ARG120, TYR355 Pi-cation:ARG120
IIb	-1.323	2H-Bond:ARG120, TYR122
IIIa	-1.455	π-π Stacking:TYR115
IIIb	-3.952	H-Bond: ARG120 π-π Stacking:TYR115
IVa*	-6.200	2H-Bond: ARG120, TYR355
IVb	-4.728	2H-Bond: ARG120, TYR355 Pi-cation: ARG120, PHE529

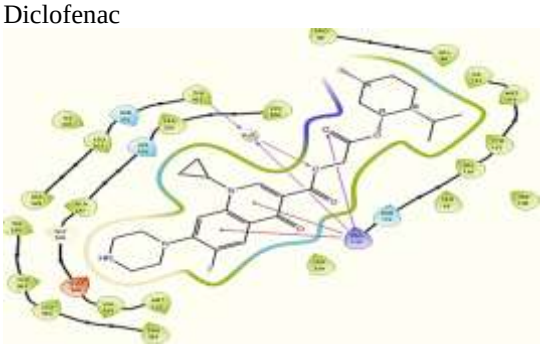
***Final synthesized compounds: IIa, IVa give moderate activity*.**

The interaction showed the synthesized compound IIa, and IVa produced significant result with two hydrogen bonds: ARG120 and TYR355, an important residue in both catalysis and binding processes. In the vivo study, as illustrated in Table 5 and Figure 3, all synthesized derivatives (IIa-IVb) showed significant activity compared to the control from 2-5 hrs.

2D structure

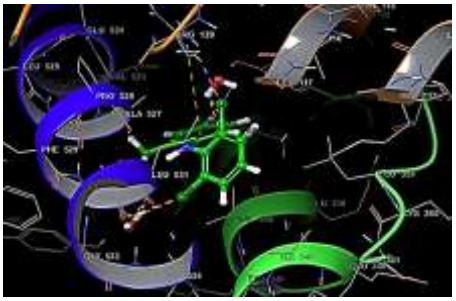


Diclofenac

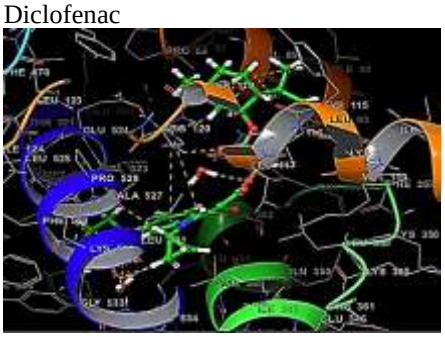


IIa

3D structure



Diclofenac



IIa

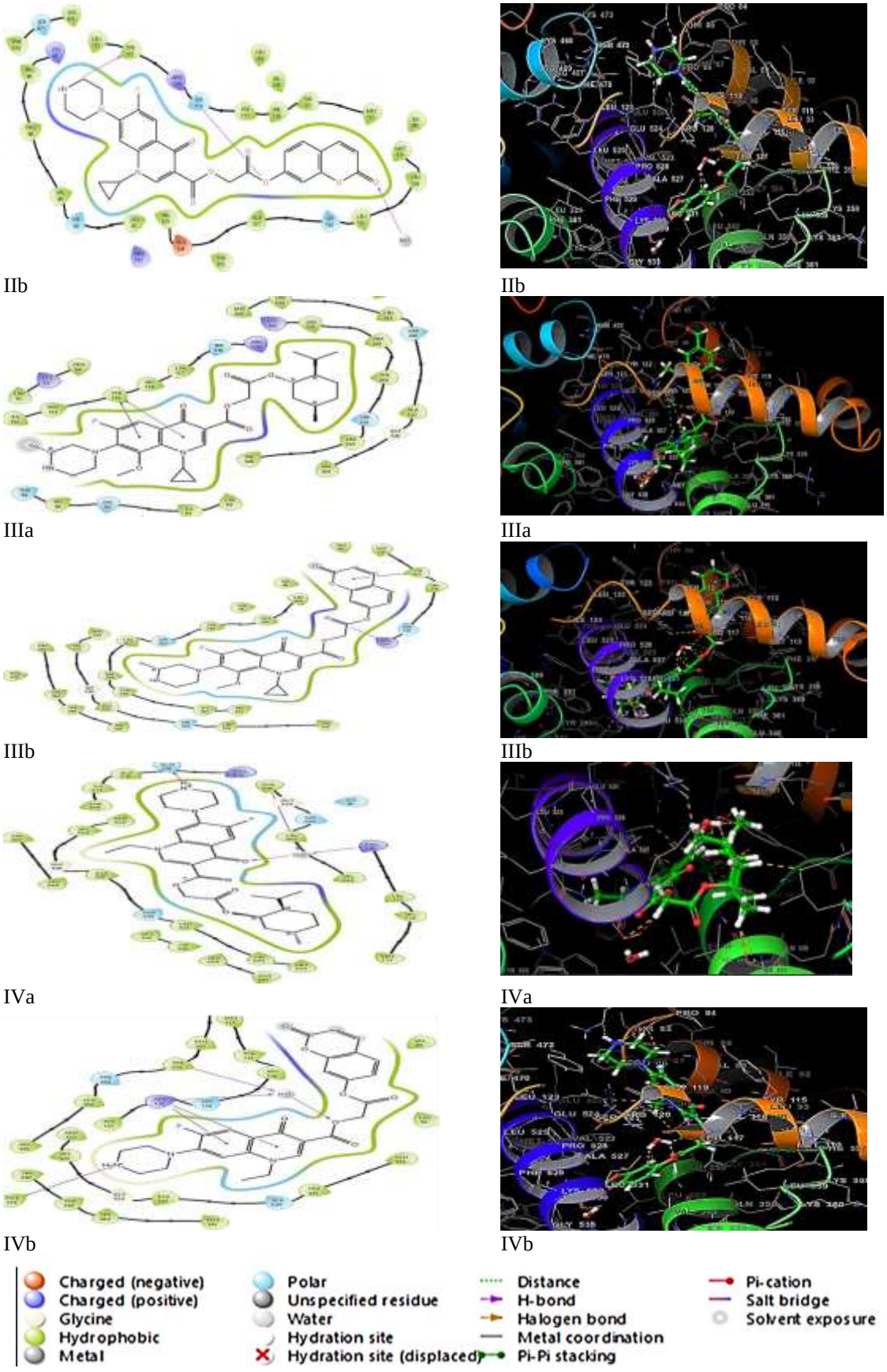


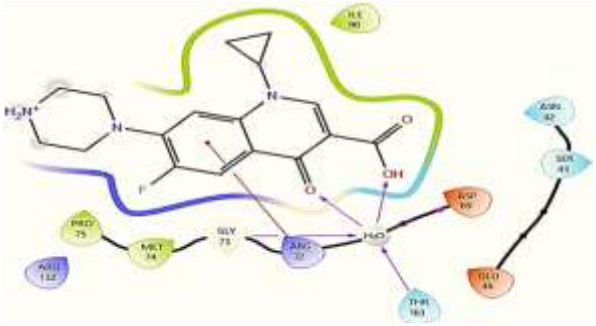
Figure 1. Anti-inflammatory docking/ 2D and 3D structure for compounds.

Table 3. Anti-bacterial docking scores: protein/ E. *coli* Topoisomerase IV co-complexed with inhibitor (PDB code 3FV5)[56], ciprofloxacin as reference.

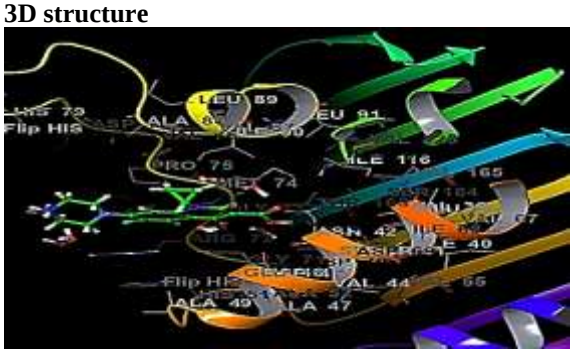
ID	ΔG (Kcal/mol)
Ciprofloxacin (reference)	-5.500
IIa*	-5.180
IIb	-4.409
IIIa	-3.418
IIIb*	-5.238
IVa*	-5.190
IVb	-3.527

Final synthesized compounds: IIa, IIIb, and IVa give moderate activity.

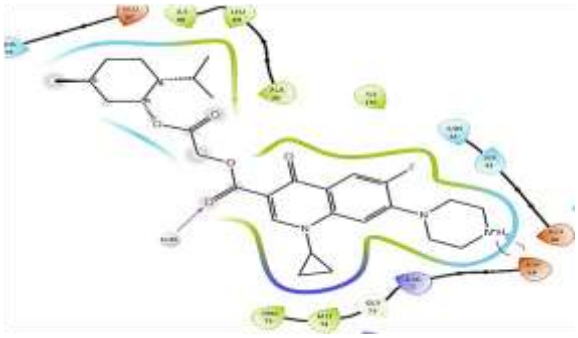
2D structure **3D structure**



Ciprofloxacin

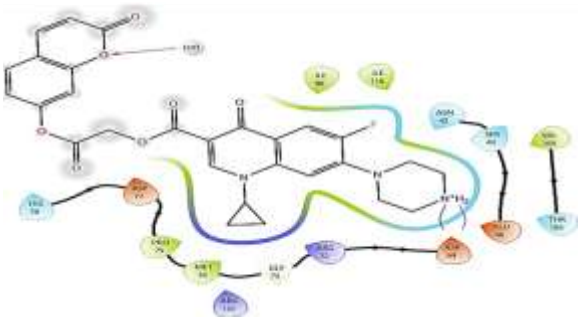


Ciprofloxacin

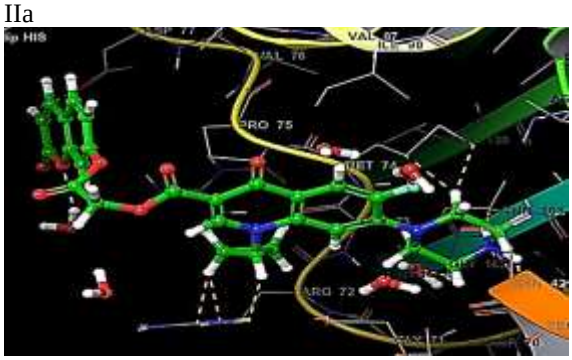


IIa

IIa

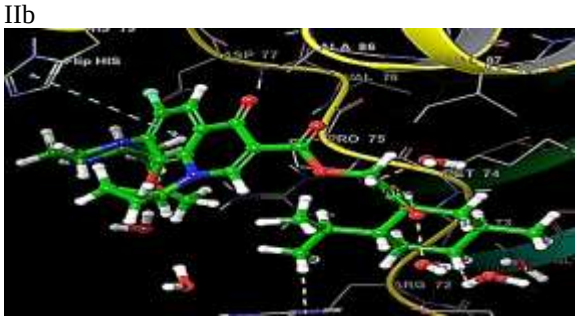


IIb



IIb

IIIa



IIIa

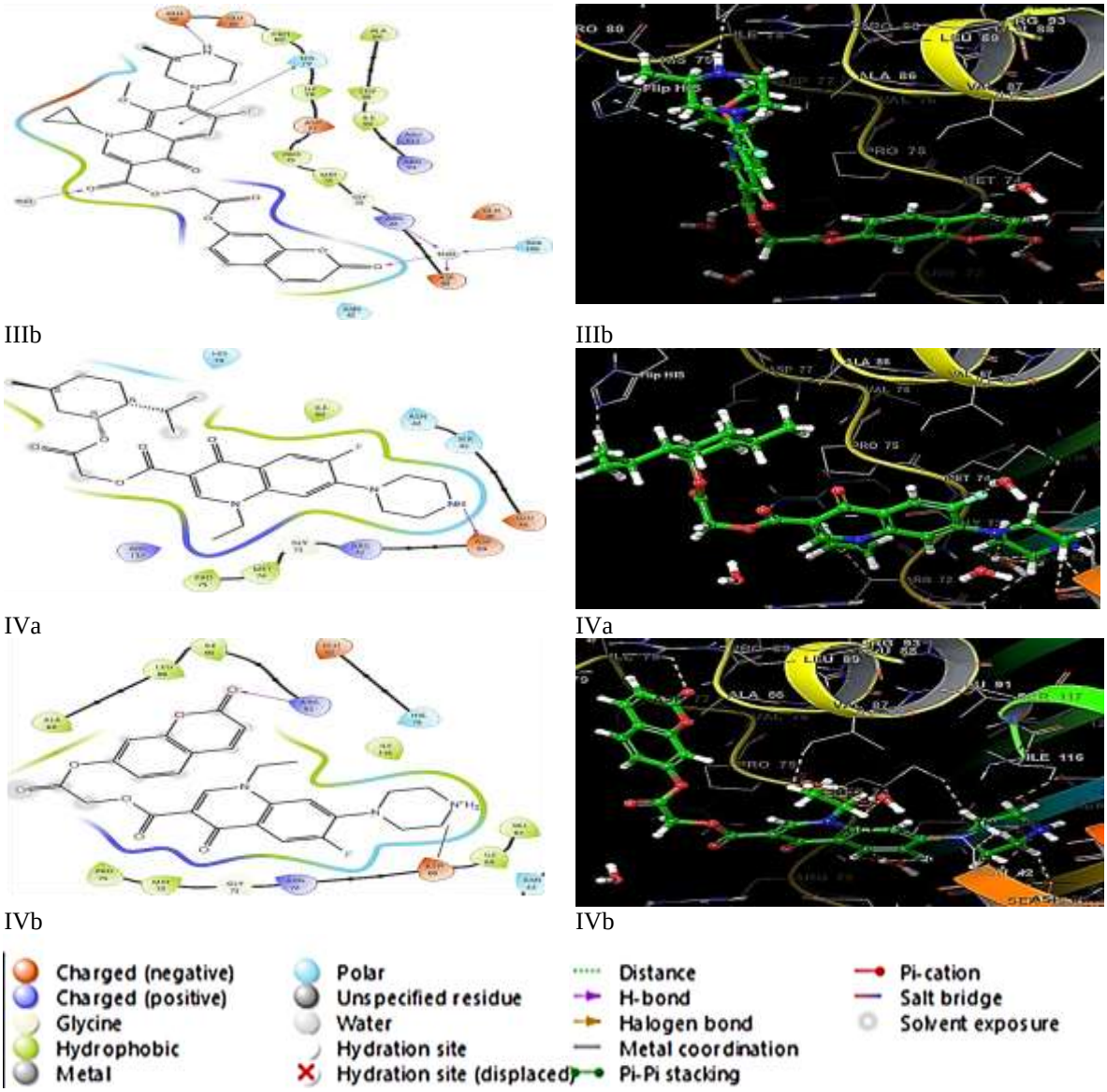


Figure 2. Anti-bacterial docking / 2D and 3D structure for compounds.

ADME Studies [55-57]

The ADME (Absorption, Distribution, Metabolism, and Excretion) properties for the final compounds (IIa-IVb) were predicted in silico using various pharmacokinetic parameters. The molecular weight of these compounds ranged from 515 to 577. The polar surface area (PSA) was observed to have an inverse relationship with cell wall permeability and the percentage of human intestinal absorption.The number of hydrogen bond donors, which refers to the number of hydrogen atoms in the solute that can form hydrogen bonds with water molecules, gives 1. The number of hydrogen bonds that the solute can accept from water molecules ranges from 9 to 12. The QPlogPo/w value was used to estimate the lipophilicity (octanol-water partition coefficient) of the compounds. Lipophilicity is a critical physical property that enhances absorption and molecular permeability through passive diffusion.Generally, high lipophilicity values pose a significant risk of toxicity due to poor metabolic clearance, while low renal clearance may be associated with high lipophilicity levels. The compounds exhibited favorable QPlogPo/w values. Several potential metabolic reactions of the substances were observed, ranging from 1 to 2. All final compounds complied with Lipinski's rule of five, with values ranging from 0 to 2, indicating good oral bioavailability, which ranged from 42% to 100%.Overall, the in silico ADME screening results for the majority of the compounds fell within the recommended ranges. These findings support the continued development of these compounds as potential drug candidates, as detailed in Table 4.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 show good QPlogPo/w values. Several possible metabolic reactions of the substances show in the range of 1-2. It is evident that every final

compound complies with Lipinski's five rules in the range of 1-2. The excellent oral bioavailability shown with these final compounds is 42-75%. Therefore, the majority of the compounds' *insilico* ADMET screening findings fall within the advised ranges.We believe that *in silico* ADME prediction results could support the ongoing development of the medication candidates; as shown below in Table 4.

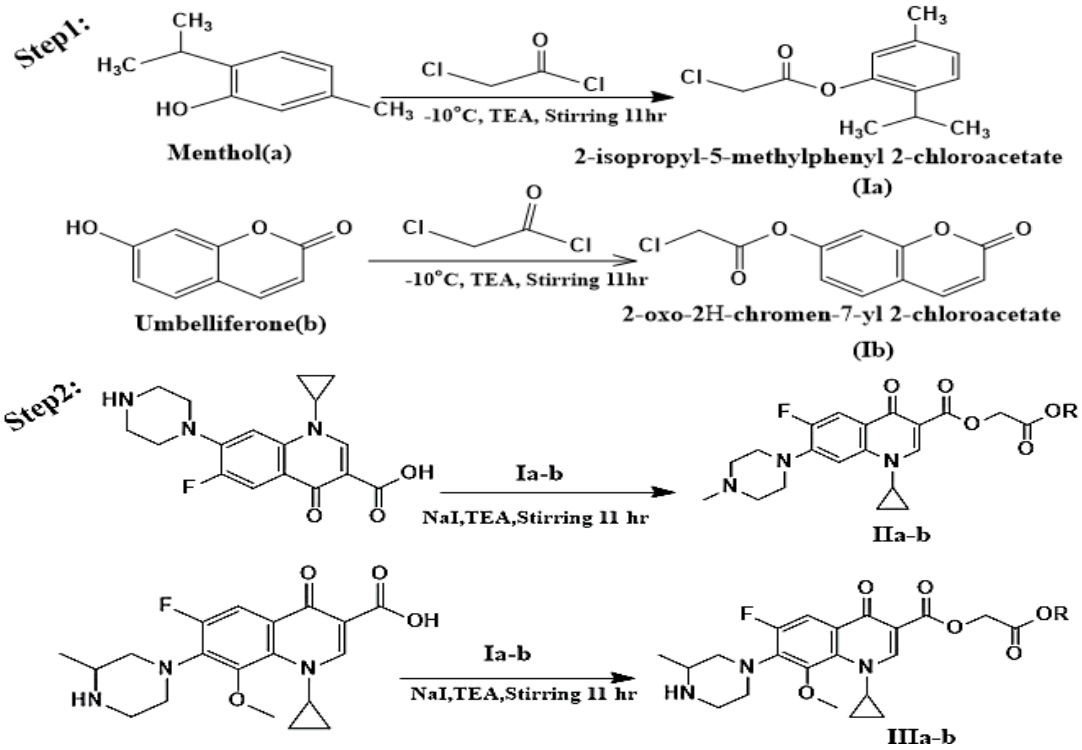
Table 4. *In silico* ADME prediction results of the final compounds.

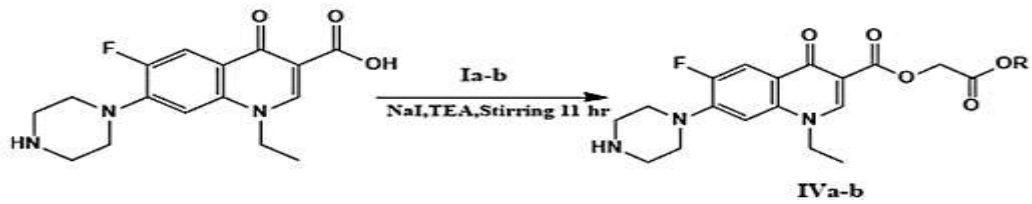
Compounds	Mol.wt	PSA Å²	Donor HB	Accept HB	QPlogP o/w	#metab	Rule of Five	%Human oral absorption
IIa	527.635	117.379	1	9	4.631	1	1	75.354
IIb	533.512	161.483	1	12	2.325	1	1	48.405
IIIa	571.688	115.595	1	9.75	5.191	2	2	69.1
IIIb	577.565	161.254	1	12.75	2.722	2	2	42.451
IVa	515.624	116.629	1	9	4.508	2	1	75.792
IVb	521.501	161.855	1	12	2.052	2	1	45.303
Recommended values	130-725	7-200Å²	0-6	2-20	-2-6.5	1-8	Max4	>80% is high <25% is poor

Mol.Wt: Molecular weight of the molecule.-**PSA:** Computed Vander Waals surface area of polar nitrogen and oxygen atoms. - **Donor HB:** Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution. - **Accept HB:** 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.Related to what is mentioned in Table 4, according to:PSA:-**IVb** (161.855), **IIb** (161.483) and **IIIb** (161.254) give high results.**IIa-IVb** form hydrogen bond donor; as hydrogen bond acceptor **IIIb** (12.75), **IIb** (12) and **IVb** (12) give the highest results.QPlogP o/w:-**IIIa** (5.191), **IIa** (4.631), and **IVa** (4.508) give the highest results.#metab:-all the synthesized compounds give good results.Rule of Five: - All the compounds within the acceptable value with Lipinski's rule of five.%Human oral absorption: - **IVa** (75.792), **IIa** (75.354), and **IIIa** (69.1) give good oral absorption while **IIb** (48.405), **IVb** (45.303) and **IIIb** (42.451) give moderate oral absorption.

Chemical synthesis

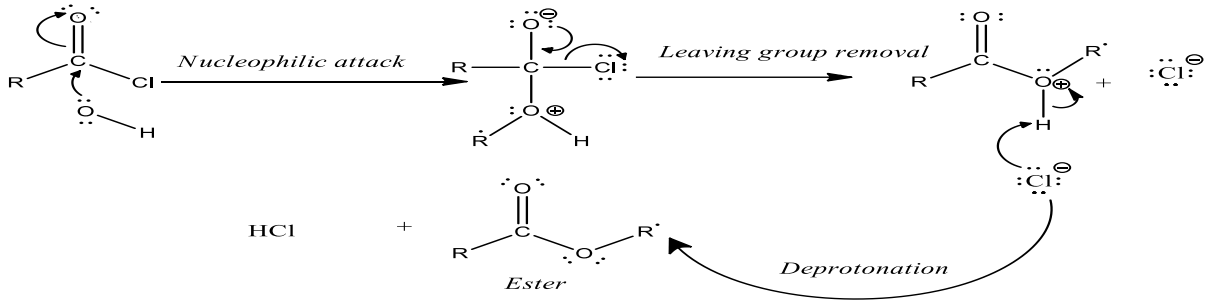
The synthesized compounds IIa-IVb was obtained successively ; the overall process for synthesizing the intermediates and targeted compounds were depicted in Scheme 1.





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

The synthesis of the intermediate as antioxidant-chloroacetyl chloride- (Ia-b) were synthesized from two types of antioxidants (a-menthol and b-umbelliferone) with chloroacetylchloride .The conversion of chloroacetyl chloride into ester, will occur through nucleophilic acyl substitution reactions which involve tetrahedral intermediate according to the following mechanism[58,59]:-



Scheme 2. Mechanism Synthesis of antioxidant-chloroacetyl chloride (Ia-b)

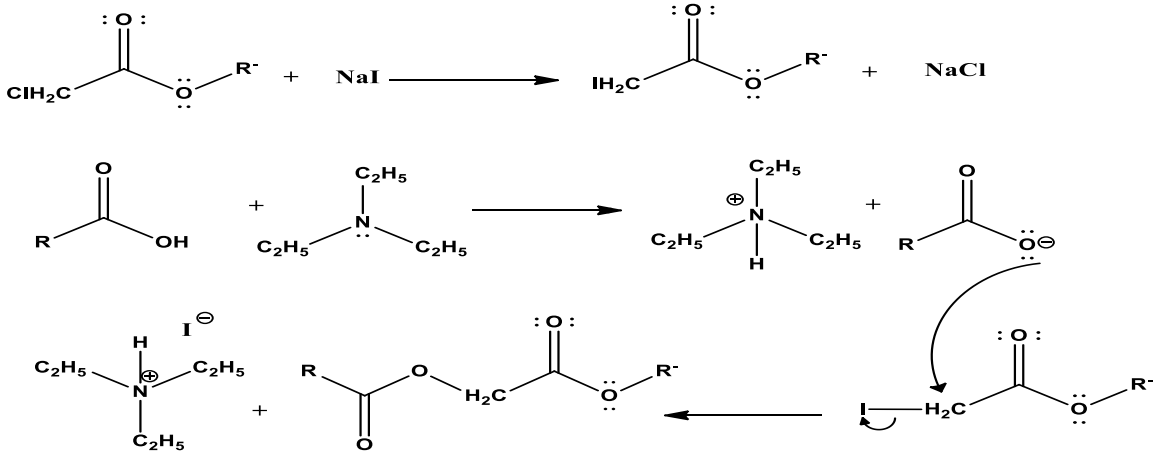
Nucleophilic substitution occurs selectively at the acyl carbon atom in α-chloroacetyl chloride because of the greater reactivity of nucleophiles toward acid chlorides compared to alkyl chlorides. The reasons for this selectivity are attributed to the differences in the electrophilicity of the two carbon 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 IR spectrum of the intermediates Ia and Ib indicated to the disappearance of broad bands at (3352.28, 3325.28) cm^{-1} and (3350.40, 3210.11) cm^{-1} respectively and the revealed bands at (1755.22, 1735.93) cm^{-1} and (1766.80 and 1728.22) cm^{-1} respectively which attributed ester(C=O) str.

Synthesis of Target Compounds (IIa-IVb)

The target compounds were synthesized according to the following steps:

1- Finkelstein reaction, halo-de-halogenation takes place by the 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 the presence of TEA in DMF[60].



R=Quinoline residue; R-=Antioxidant residue

Scheme 3. Synthesis of fluoroquinolones and Antioxidant compounds (IIa-IVb)

The IR spectrum of compound IIa - IVb indicated the disappearance of broadband of OH group of Ciprofloxacin (3255.84-3209.55) cm^{-1}, Gatifloxacin (3371.57-3216.58) cm^{-1}, and Norfloxacin (3332.10 -3276.58) cm^{-1} and the appearance of band attributed to (C=O) str. vib. of ester group for IIa-IVb respectively :{(1735.39, 1701.22), (1755.22 and 1728.22), (1735.93), (1770.65 and 1732.08), (1739.79) and (1762.94, 1724.36 and1697.36)} cm^{-1} .The interpretation of the ^{1}HNMR spectrum for compounds IIa-IVb revealed a singlet peak due to the (CH_2 α to ester group) at δ= (ppm): 7.43, 5.71, 4.75, 5.96, 5.26 and 4.99 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.

Table 5. Anti-inflammatory activity of control, standard and quinolone derivatives on egg-white induced paw edema in rat; propylene glycol as control and Diclofenac as standard compound.

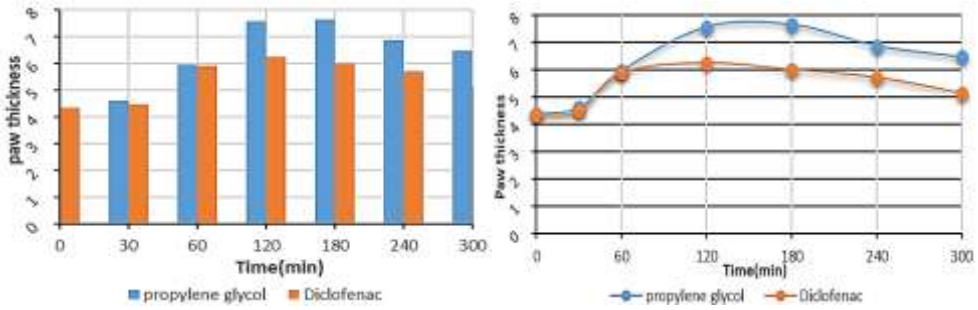
Paw Thickness (mm±SD)							
Time (hrs.)	**0 hr.**	**0.5 hr.**	**1 hr.**	**2 hr.**	**3hr.**	**4hr.**	**5h hr.**
control	4.38±0.03	4.61±0.02	5.95±0.03	7.56±0.5	7.65±0.03	6.87±0.02	6.46±0.11
Standard	4.33±0.02	4.47±0.02	5.89±0.04	6.24±0.02^{*a}	6.00±0.01^{*a}	5.72±0.01^{*a}	5.14±0.02^{*a}
IIa	4.38±0.02	4.61±0.02	5.96±0.04	6.19±0.01^{*a}	5.93±0.03^{*a}	5.72±0.02^{*a}	5.15±0.04^{*a}
IIIa	4.55±0.01	4.62±0.01	5.91±0.01	6.60±0.04^{*b}	6.36±0.4^{*b}	6.35±0.01^{*b}	5.77±0.01^{*b}
IVa	4.49±0.03	4.61±0.02	5.94±0.03	6.94±0.02^{*c}	6.82±0.01^{*c}	6.62±0.02^{*c}	6.19±0.02^{*c}
IIb	4.44±0.01	4.59±0.02	5.91±0.04	6.10±0.01^{*a}	5.89±0.03^{*a}	5.70±0.02^{*a}	5.09±0.01^{*a}
IIIb	4.46±0.02	4.59±0.02	5.89±0.03	6.55±0.01^{*b}	6.40±0.01^{*b}	6.20±0.03^{*b}	5.70±0.01^{*b}
IVb	4.42±0.01	4.61±0.01	5.93±0.03	6.93±0.04^{*c}	6.85±0.01^{*c}	6.67±0.02^{*c}	6.14±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 min is time of injection of egg-white (induced of paw edema) , *significantly different with control ($p \leq 0.05$).

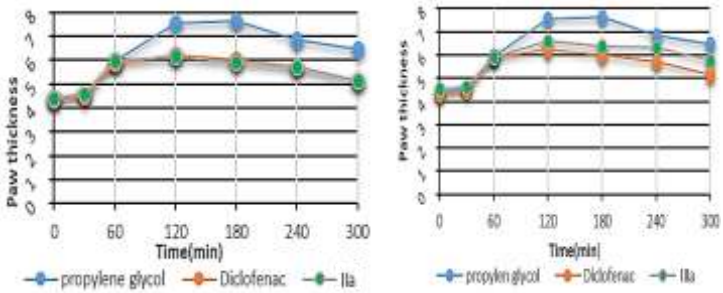
All tested compounds and standard drug showed significant activity in comparison to control at 2hrs time.

- (IIa & IIb) compounds showed comparable activity to standard drugs.
- (IIIa & IIIb) compounds showed lower activity than standard drugs.
- Finally; (IVa & IVb) compounds showed lower activity than standard drugs.

propylene glycol and diclofenac



IIa ,IIIa , and IVa



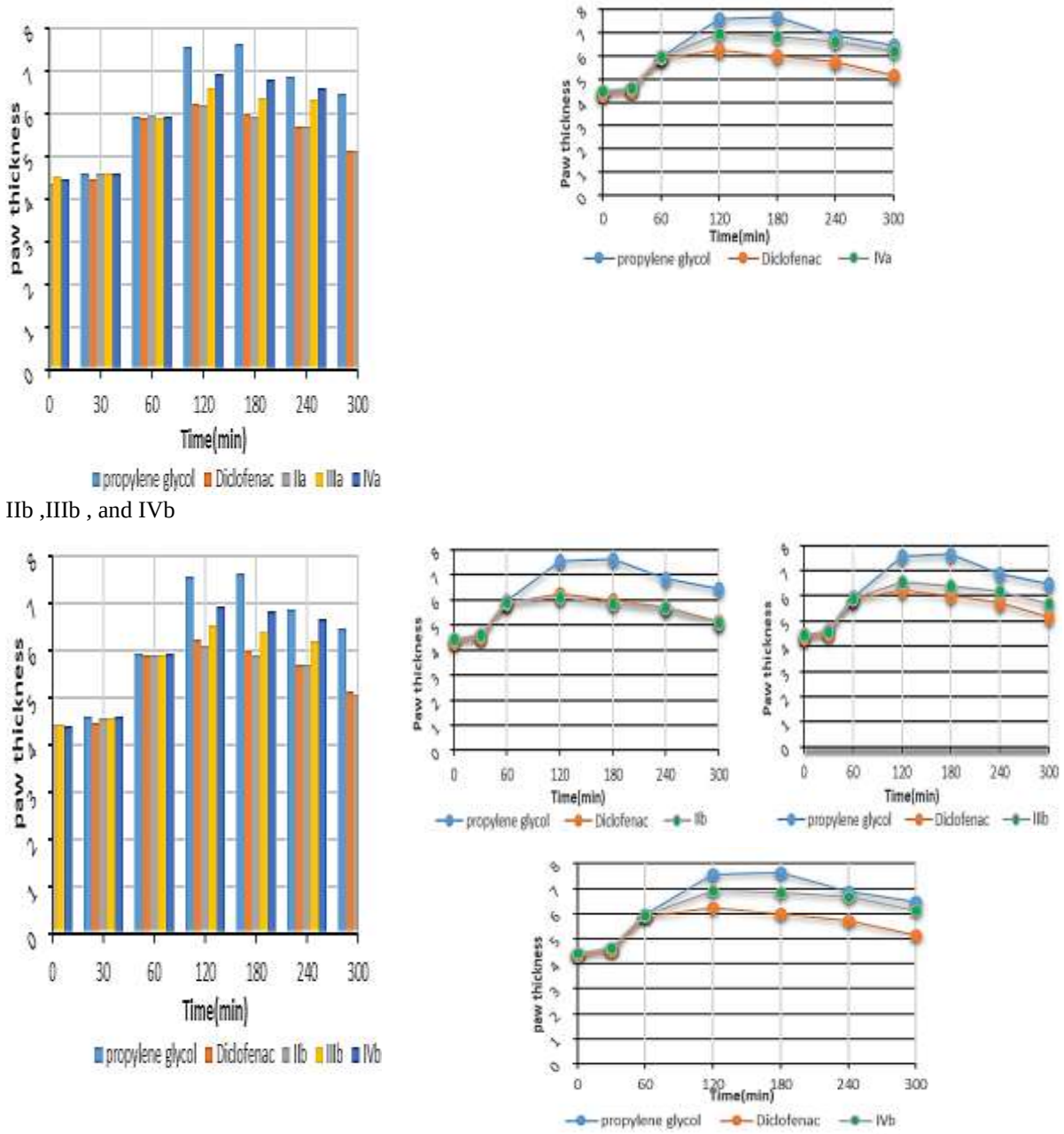


Figure 3. Curves illustrates anti-inflammatory activities of final compounds in comparison with control and standard.

Antimicrobial biological study (63-65)

The final compounds that were synthesized (Ia–IVb) were tested using the well diffusion method to determine their antimicrobial activity against gram positive, gram negative, and gram negative bacteria and fungi. The standard compounds used as antifungal agent was fluconazole, while the antibacterial agent was ciprofloxacin. The solvent and control used was DMSO. A higher degree of compound molecule diffusion in the solvent, which results in an increase in inhibitory activity at lower concentrations than at absolute concentrations.The results were expressed in MIC as showed in the tables **6** and **7**.

Table 6. Antimicrobial activity as of final compounds as Inhibition zone

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**
Ciprofloxacin	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*	40*	40*	35*	23*	45*	35*	32*	0	13	10	0
IIb	30*	40*	36*	27*	22*	35*	30*	26*	0	0	0	0
IIIa	30*	29*	14	14	20*	30*	25*	15	0	0	0	0
IIIb	30*	29*	25*	19*	25*	27*	25*	18*	0	0	0	0
IVa	30*	28*	15	29*	30*	23*	28*	21*	0	12	10	0
IVb	20*	15	12	0	15	26*	18*	0	15	12	12	0

***When the inhibitory zones of the chemical under test measure more than 15 mm, they are classified as highly active; when they measure between 10 and 15 mm, they are classified as moderately active; when they measure between 5 and 10 mm, they are classified as little active; and beyond 5 mm, they are classified as inactive** [66,67].

As shown in Table 6, the final synthesized derivatives **IIa-IVb** demonstrated superior antibacterial activity against gram-negative bacteria (*Escherichia coli*) compared to the reference drug ciprofloxacin : (**IIa-IVb**) at 100 mg/l; (**IIa-IVa**) at 50 mg/l; (**IIa, IIb &IIIb**) at 25 mg/l; and (**IIa, IIb, IIIb &IVa**) at 12.5 mg/l concentrations give high activity; (**IVb**) at 50 mg/l; (**IIIa, IVa, & IVb**) at 25 mg/l; and (**IIIa**) at 12.5 mg/l give moderate activity; (**IVb**) at 12.5 mg/l concentrations are considered inactive. For gram-positive bacteria (*Staphylococcus aureus*): (**IIa-IVa**) at 100 mg/l; (**IIa-IVb**) at 50 mg/l; (**IIa-IVb**) at 25 mg/l; and (**IIa, IIb, IIIb & IVa**) at 12.5 mg/l concentrations give high activity; (**IVb**) at 100 mg/l; and (**IIIa**) at 12.5 mg/l moderately active; while (**IVb**) at 12.5 mg/l is classified as inactive. According to antifungal activity against *Candida albicans*, when compared with the drug Fluconazole, the final compounds (**IVb**) at 100 mg/l, (**IIa, IVa & IVb**) at 50 mg/l, and at 25 mg/l showed moderate activity; the other final compounds are classified as inactive.

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	50	1000
IIb	100	100	-
IIIa	100	100	-
IIIb	100	100	-
IVa	100	50	1000
IVb	1000	1000	1000

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. The 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, as illustrated in Table 5 and Figure 3, all synthesized derivatives (**IIa-IVb**) showed significant activity compared to the control from 2-5 hrs. Additionally, the synthesized compounds exhibited considerable antibacterial activity. *In vivo* study, as depicted in Table 6, the final synthesized derivatives **IIa-IVb** demonstrated superior antibacterial activity, exhibiting significant antibacterial activity against gram-negative bacteria (*Escherichia coli*) compared

to the reference drug (ciprofloxacin) [27,38,64,68]: (**IIa-IVb**) at 100 mg/l; (**IIa-IVa**) at 50 mg/l; (**IIa, IIb &IIIb**) at 25 mg/l; and (**IIa, IIb, IIIb &IVa**) at 12.5 mg/l concentrations give high activity; (**IVb**) at 50 mg/l; (**IIIa, IVa, & IVb**) at 25 mg/l; and (**IIIa**) at 12.5 mg/l give moderate activity; (**IVb**) at 12.5 mg/l concentrations are considered inactive. For gram-positive bacteria (*Staphylococcus aureus*): (**IIa-IVa**) at 100 mg/l; (**IIa-IVb**) at 50 mg/l; (**IIa-IVb**) at 25 mg/l; and (**IIa, IIb, IIIb &IVa**) at 12.5 mg/l concentrations give high activity; (**IVb**) at 100 mg/l; and (**IIIa**) at 12.5 mg/l moderately active; while (**IVb**) at 12.5 mg/l is classified as inactive. According to antifungal activity against *Candida albicans*, when compared with the drug Fluconazole, the final compounds (**IVb**) at 100 mg/l, (**IIa, IVa & IVb**) at 50 mg/l, and at 25 mg/l showed moderate activity; the other final compounds are classified as inactive. The six designed derivatives were successfully synthesized with acceptable yields, and their ^{1}H-NMR 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.

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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.

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دراسات داخل السيليكو وتوليف وتقييم بيولوجي أولي لمركبات هجينة جديدة من الفلوروكينولونات ومضادات الأكسدة

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الخلاصة

الفلوروكينولونات هي واحدة من أكثر أنواع مضادات البكتيريا الواعدة التي تستخدم لعلاج أنواع شديدة من العدوى بسبب نطاق نشاطها الواسع. تم تصميم هذا البحث بطريقة تركز على تعديل البنية الأساسية للفلوروكينولونات من خلال إدخال مجموعة إستر وظيفية جديدة في موضع أل3Cعبر رابط الجليكول. تم فحص المركبات المحضرة وتشخيصها باستخدام التقنيات الطيفية الرنين النووي المغناطيسي والاشعة تحت الحمراء. بالإضافة إلى ذلك، تم فحص أنشطتها الدوائية. في الجسم الحي، تم تقدير التأثير المضاد للالتهابات لمركبات (IIa-IVb) باستخدام نموذج وذمة مخلب الفئران، مما يدل على نشاط كبير للمركبات النهائية IIa-IVb من ٢-٥ ساعات. عند مقارنتها بـ ثنائي مثيل السلفوكسيد (المذيب والتحكم). تم اختبار المشتقات الهجينة الجديدة بشكل إضافي لنشاطها المضاد للميكروبات ضد كل من البكتيريا إيجابية الجرام وسالبة الجرام باستخدام طريقة الانتشار الجيد وفقًا لمنطقة التثبيط للمركبات النهائية الستة المحضرة، والتي أظهرت النتائج التالية: مع البكتيريا سالبة الجرام(IIa-IVb) : (IIa-IVb) بتركيز ١٠٠ ملغ/لتر؛ (IIa-IVa) بتركيز ٥٠ ملغ/لتر؛ (IIa, IIb &IIIb) بتركيز ٢٥ ملغ/لتر؛ و(IIa, IIb, IIIb &IVa) بتركيز ١٢,٥ ملغ/لتر تعطي نشاطًا عاليًا؛ (IVb) بتركيز ٥٠ ملغ/لتر؛ (IIIa, IVa, & IVb) بتركيز ٢٥ ملغ/لتر؛ و(IIIa) بتركيز ١٢,٥ ملغ/لتر تعطي نشاطًا متوسطًا؛ (IVb) بتركيز ١٢,٥ ملغ/لتر تعتبر غير نشطة. بالنسبة للبكتيريا إيجابية الجرام (المكورات العنقودية الذهبية): (IIa-IVa) بتركيز ١٠٠ ملغ/لتر؛ (IIa-IVb) بتركيز ٥٠ ملغ/لتر؛ (IIa-IVb) بتركيز ٢٥ ملغ/لتر؛ و(IIa, IIb, IIIb &IVa) بتركيز ١٢,٥ ملغ/لتر تعطي نشاطًا عاليًا؛ (IVb) بتركيز ١٠٠ ملغ/لتر؛ و(IIIa) بتركيز ١٢,٥ ملغ/لتر نشط بشكل معتدل؛ بينما (IVb) بتركيز ١٢,٥ ملغ/لتر يصنف على أنه غير نشط. ووفقًا للنشاط المضاد للفطريات ضد المبيضات البيضاء، عند مقارنته بدواء الفلوكونازول، أظهرت المركبات النهائية (IVb) بتركيز ١٠٠ ملغ/لتر، و(IIa، IVa & IVb) بتركيز ٥٠ ملغ/لتر، و٢٥ ملغ/لتر نشاطًا معتدلًا؛ وتصنف المركبات النهائية الأخرى على أنها غير نشطة.

الكلمات المفتاحية: ADME، مضاد للبكتيريا، المنثول، الرسو الجزيئي، مشتقات الفلوروكينولونات ، الأومبيليفيرون.