RESEARCH ARTICLE

Synthesis, Characterization and Antibacterial Studies of New Crown Ether Prodrugs

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ABSTRACT

New three esters (E1, E2 and E3) from crown ethers and drugs were prepared by Stiglich esterification. These procedures began with the reaction of certain quinolones (levofloxacin, ciprofloxacin, and nalidixic acid) with thionyl chloride to produce a considerably more potent acylating agent. Next, for the production of ester prodrugs, 2-hydroxymethyl-15-crown-5 ether (a lariat crown ether) was esterified using an acid chloride in the presence of pyridine. These molecules were synthesized as carrier-mediated prodrugs in order to solve different pharmacokinetic and pharmacological difficulties, enhance physicochemical features, and augment the antibacterial efficacy of the parent drugs by structural modifications while avoiding bacterial resistance. The compounds` structures were verified by FTIR, UV, H^1 & ^{13}C-NMR spectroscopy and certain physiochemical qualities. In a concentration-dependent manner, all of the synthesized prodrugs' biological studies revealed improved activity against certain bacterial species.

Keywords: Crown ether, Levofloxacin, Ciprofloxacin, Nalidixic acid, Antibacterial activity.

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INTRODUCTION

All traditional crown ethers that have 3 to 20 oxygen atoms divided by two carbon atoms or more are macrocyclic polyethers. All crown ethers have a hydrophilic cavity in the core, which can hold a metal ion that is bonded to oxygen (in the ring system), while the outside shell is lipophilic. Stability and solvation were improved by interactions of oxygen lone pairs` cation and electrons on the crown framework. They are extremely flexible in their ability to selectively bind a variety of metal ions as well as ionic and neutral organic species. Crown ethers play a crucial role in several synthetic system designs with distinctive and controllable activities. They are also essential in the fields of chemistry, biology, separation, transport, catalysis, material sciences, and encapsulation.

In general, crown compounds can be classified according to the type of donor atom in the crown ring as single or multi-donor crown compounds. Examples of single donor crown compounds include crown ethers, which contain oxygen (Compound 1, Figure 1); a nitrogen atom (Compound 2, Figure 1); crown thia compounds, which involve a sulfur atom in the general structures (Compound 3, Figure 1). Furthermore, the multi-donor crown compounds may involve oxygen, nitrogen and sulfur atom as a combination of two or all of them (Compound 4, Figure 1); aza-crown ethers (Compound 5 & 6, Figure 1); and crown thia amine compounds (Compound 7, Figure 1); Aza-thia-crown ethers are crown compounds containing three donor atoms in their structures (Compound 8, Figure 1).

According to their structures, Vogel and Weber postulated a path of greater ligand preorganization, starting with flexible podands and moving on to macrocyclic coronands and macro bicyclic cryptands. These receptors may be tuned for features in between, allowing binding of induced fit based on their strict or flexible preorganization.[1] Weber and Vogel found that linking a pod with a ligand will give acyclic receptors "podand" as an example of high-affinity guests-host interaction in the supramolecular host's systematic nomenclature.[2] Many podand receptors serve a variety of purposes, such as detecting prostate cancer and using water and other natural resources. Figure 2 shows the chemical structures of some podands. Figure 3 shows lariat ether describes a combination of the extra stability and flexibility of podand and the higher stiffness crown ether, giving the structure more 3D binding characteristics and enhancing the capacity of complexation with metal cation.[3,4] These polyether compounds are macrocyclic molecules of one sidearm or more having donor-group[5] which attached to C-atom[6] or N-atom.[7]

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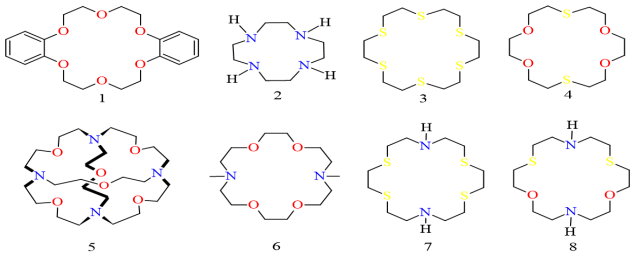


Figure (1): Chemical structures of different crown compounds.

The new synthetic cation host molecules equivalent to 3D bicyclic and polycyclic crown ethers are cryptands that normally involve heteroatoms, sulfur, oxygen and nitrogen donors to produce hydrophobic complexes.[8] Cryptands are amphiphiles play a pivotal role in transportation as a carrier for various charged molecules, in chromatography (as stationary phase), active redox systems, as structure-directing agents, for sol-gel materials doping. Figure 4 shows the chemical structures of some cryptans.

Quinolones are broad-spectrum synthetic bactericidal agents with antibacterial activity toward both bacterial subtypes (gram -ve & gram +ve) through the bacterial topoisomerase enzyme inhibition (DNA gyrase plays a pivotal role in the inhibition of DNA synthesis by negative supercoils introduction into DNA's circular duplex). Three generations of quinolones: the 1'st generation naphthyridines (cinoxacin & nalidixic acid); 2'nd generation fluoroquinolones (ofloxacin, ciprofloxacin, lomefloxacin & norfloxacin) and levofloxacin which is the 3'rd generation fluoroquinolone as shown in Figure 5.

Quinolones present a variety of pharmaceutical-pharmacokinetic profile problems. Gene mutation is one of the most common quinolone resistance forms that encode enzymes that prevent fluoroquinolone from binding to DNA gyrase or topoisomerase IV, or because changes in the cell's permeability prevent fluoroquinolones from entering and accessing the target enzyme. Additionally, some bacterial cell membranes includes MDR efflux pumps, which may provide resistance to fluoroquinolone. Ciprofloxacin [class IV (↓ solubility, ↓ GI permeability)],[9] levofloxacin [class I (↑

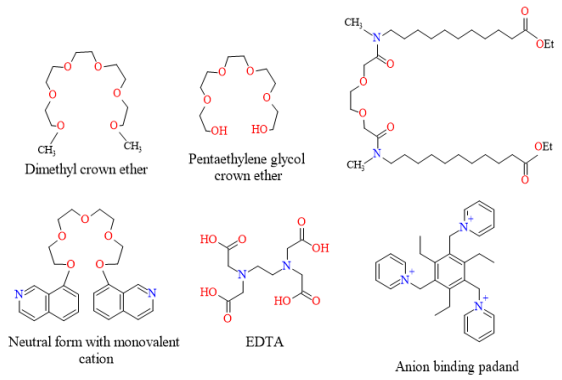


Figure (2): Chemical structures of podands [1].

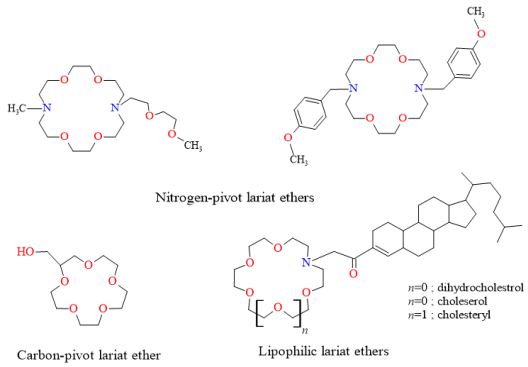


Figure (3): Chemical structures of lariat ethers [3]'[4].

solubility, ↑ GI permeability)][10] & nalidixic acid [class II (↓ solubility, ↓ absorption & ↓ bioavailability)] according to the BCS (Biopharmaceutical Classification System).[11-15]

A reaction known as "esterification" occurs when an organic or inorganic acid reacts with phenolic or alcoholic compounds (hydroxyl component in excess amount), containing a catalytic amount of a mineral acid. Esters (R–COO–R′) are chemical molecules and German chemist Leopold Gmelin first described them in the first half of the 19th century.

MATERIALS SAND METHODS

Chemicals

2-Hydroxy methyl-15-crown-5 ether (China, Hyper chemical), ciprofloxacin HCl monohydrate (China, Hyper chemical), levofloxacin HCl monohydrate (China, Hyper chemical), nalidixic acid (China, Hyper chemical), absolute methanol & absolute ethanol (96%) & anhydrous dichloromethane & ammonium hydroxide & thionyl chloride & sodium bicarbonate (Germany, Sigma–Aldrich), acetone (England, Atom), chloroform (England, BDH), pyridine (India, HIMEDIA), triethylamine (India, CDH), dimethyl sulfoxide (USA, Santacruz Biotechnology), anhydrous tetrahydrofuran (China, Hyper chemical), TLC Silica gel F_{254} plates (Width = 20 cm; Length = 20 cm & Thickness = 2 mm) (Germany, Merck) and Mueller-Hinton agar (India, CDH).

Physical measurements

SMP 30 equipment [Electro-Thermal Stuart (U. K.)] was used to measure compounds` melting point (M.P). Using a UV-visible 7200 spectrophotometer [CECILL (U. K)], the electronic spectra of each prodrug are analyzed by dissolving it in dimethyl sulfoxide at (10^{-3} M) concentration. Using

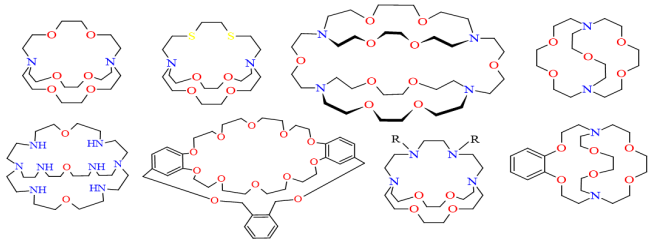


Figure (4): Chemical structures of some cryptands.

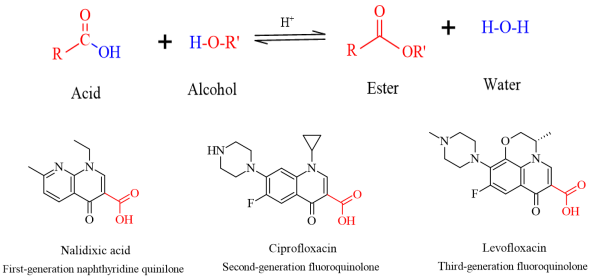


Figure (5): Chemical structures of parent materials with pharmaceutical and pharmacokinetic profile problems.

a Shimadzu-8400S spectrophotometer (Germany), the preparation of KBr discs produced FTIR (Fourier Transform Infrared Spectra) in the range of (200–4000 cm^{-1}). H^1 and C^{13} nuclear magnetic resonance spectra were obtained using 500 MHz NMR spectrometer [Bruker Inova/Varian (USA)].

Synthesis of CAC (1-cyclo propyl-6 fluoro-4 oxo-7 [piperazine-1-yl] - 1,4-dihydro quinoline 3-Carbonyl Chloride)

About 1 g of ciprofloxacin (equivalent to 3 mmol) was dissolved in 20 mL dry THF in a flask (250 mL, two-neck & rounded bottom) with a stirrer (2 mL, equivalent to 27.6 mmol) of $SOCl_2$ was added as drop by drop over 40 minutes time period, chilling & stirring in a cooled bath. The refluxed combination with stirring for 4 hours and hydrochloric gas evolution was observed. This, when placed on top of the flask, causes litmus paper to become red in coloration. After being redissolved in 20 mL of dry THF, the precipitate (look deep yellow in appearance) was filtered several times to remove any thionyl chloride (i.e., the remaining excess amount).[16] The powder of CAC (ciprofloxacin acid chloride), which looks deep yellow in appearance [yield (0.87 g, 83%); melting point (297–299°C)] was collected and utilized immediately in the following coupling step with 2-hydroxymethyl-15-crown-5 ether (Table 1).

Synthesis of Compound E1 (Ethyl [1,4,7,10,13 -penta oxa cyclo pentadecane 2-yl],1-cyclopropyl-6 fluoro-4 oxo-7 [piperazine-1-yl]-1,4 dihydroquinolin-3 Carboxylate)

A combination of (1.77 g, 7 mmol) 2-HM-15-C-5 ether, dry methylene dichloride, & (1-mL) of pyridine, in a flask dissolve an acid chloride (1.79 gram, 5.13 mmol) (20 mL). TLC (Retardation factor value = 0.78; in Ethanol:Chloroform: NH_4OH 4.3: 4.3: 1.4) confirmed the finishing reaction when stirring at 25°C after 24 hours. Following the evaporation of the solvent, the residue was stirred for half an hour using a 10 mL solution of 5% sodium carbonate, and it was extracted three times using 20 mL chloroform. To make a pale yellow powder, the chloroform extracts were mixed, dried, and washed multiple times with 20 mL parts of acetone[17] (Table 2).

Spectral data [Prodrug E1]. Faint-yellow powder; yield (81%); melting point. (251–253°C); (KBr) (FTIR cm^{-1}) (Table 3): 3045.60 ν (C-H) $_{Aromatic}$ Stretching, 2868.15 and 2849.57ν (C-H) $_{Aliphatic}$ Stretching, (C=O) Stretching 1727.16 ν, 1489.05 ν (C=C) $_{Aromatic}$ Stretching, 1379.10 ν (C-H) $_{Aliphatic}$ bending, 1180.44 and 1145.72 ν (C-O-C) Stretching, 1026.13 ν (C-O) Stretching. In 500 MHz & ppm [^{1}H-NMR data, DMSO-d*6*, δH]: δ of 6.04 to 6.18 (HC=N); In 75 MHz & ppm [^{13}C-NMR data, DMSO-d*6*]: δ = 179, 169, 155, 151, 149, 140, 133, 119, 114, 107, 73, 69, 64, 47, 43 and 37.

Synthesis of LAC (3-Methyl-9 fluoro-7 oxo-10 [4-methylpiperazin-1-yl] 2,3-dihydro-7H (1,4) oxazine 2,3,4 quinoline-6 Carbonyl Chloride)

About 1.45 g of levofloxacin (equivalent to 4 mmol) was dissolved in 10 mL dry DCM in a flask (250 mL, two-neck & rounded-bottom) with a stirrer. (1.5 mL, equivalent to 20.67 mmol) of $SOCl_2$ was added as drop by drop over 40-minute time period, chilling & stirring in a cooled bath. The refluxed combination with stirring for 4 hours and hydrochloric gas evolution was observed (This, when placed on top of the flask, causes litmus paper to become red in coloration). After being redissolved in 20 mL of dry DCM, the precipitate (looks deep orange to deep red in appearance) was filtered several times to remove any thionyl chloride (i.e., the remaining excess amount).[16] The powder of LAC (levofloxacin acid chloride), which look deep orange to deep red in appearance [yield (1.27 g, 84%); melting point (229°C)] was collected and utilized immediately in the following coupling step with 2-hydroxymethyl-15-crown-5 ether.

Synthesis of Compound E2 (Ethyl [1,4,7,10,13 -penta oxa-cyclo pentadecane 2-yl],3-methyl-9 fluoro-7 oxo-10 [4-methylpiperazine-1-yl]-2,3 dihydro-7H (1,4) oxazine 2,3,4 quinolin-6 Carboxylate)

A combination of (0.75 g, 3 mmol) 2-HM-15-C-5 ether, dry DCM, & (1 mL) of pyridine, in a flask, dissolve an acid chloride (1.137 g, 3 mmol) (10 mL). TLC (Retardation factor value = 0.69; in Methanol: Chloroform: NH_4OH 3: 6: 1) confirmed finishing reaction when stirring at 25°C after 24 hours. Following the evaporation of the solvent, the residue was stirred for half an hour using a 10 mL solution of 5% sodium carbonate, and it was extracted three times using 20 mL chloroform. To make a dark coffee like oily, the acetone extracts were mixed, dried, and washed multiple times with 20 mL parts of acetone[17] (Table 1).

Spectral data [Prodrug E2]. Oily brown like-coffee; yield (83%); melting point. (Viscous); (KBr) (FTIR cm^{-1}) (Table 3): 3022.43 ν (C-H) $_{Aromatic}$ Stretching, 2939.52, 2846.93 and 2802.57 ν (C-H) $_{Aliphatic}$ Stretching, 1724.36 ν (C=O) Stretching, 1544.98 and 1396.46 ν (C=C) $_{Aromatic}$ Stretching, 1357.89 ν (C-H $_{Aliphatic}$ bending), 1118.71 ν (C-O-C) Stretching, 1089.78 ν (C-O) Stretching. In 500 MHz & ppm [^{1}H-NMR data, DMSO-d*6*, δH]: δ = 7.15–7.17 (HC=N); In 75 MHz & ppm [^{13}C-NMR data, DMSO-d*6*]: δ = 183, 171, 147, 105, 72, 70, 69, 61, 57, 55, 51, 46 and 18.

Synthesis of NAC (1-ethyl-7 methyl-4 oxo-1,4 dihydro-1,8 naphthyridin-3 Carbonyl Chloride)

1.16 g of nalidixic acid (equivalent to 5 mmol) was dissolved in 10 mL dry in a flask (250 mL, two-neck & rounded-bottom) with a stirrer. (1.5 mL, equivalent to 27.6 mmol) of $SOCl_2$ was

added as drop by drop over 40 minutes time period, chilling & stirring in a cooled bath. The refluxed combination with stirring for 4 hours and hydrochloric gas evolution was observed (This, when placed on top of the flask, causes litmus paper to become red in coloration). After being redissolved in 20 mL of dry DCM, the precipitate (look dark green to dark navy in appearance) was filtered several times to remove any thionyl chloride (i.e. the remaining excess amount).[16] The powder of NAC (nalidixic acid chloride), which look dark navy to ink in appearance [yield (0.83 g, 66%); melting point (229°C)] was collected and utilized immediately in the following coupling step with 2-hydroxymethyl-15-crown-5 ether.

Synthesis of Compound E3 (Ethyl [1,4,7,10,13 -penta oxa-cyclopentadecane 2-yl],1-Ethyl-7 Methyl 4-oxo 1,4-dihydro- 1,8 naphthyridine-3 Carboxylate)

A combination of (1 g, 4 mmol) 2-HM-15-C-5 ether, dry chloroform, & (1-mL) of pyridine, in flask dissolve an Acid Chloride (1 gram, 4 mmol) (10 mL). TLC (Retardation factor value = 0.43, in (TEA: DCM 1:10) confirmed the finishing reaction when stirring at 25°C after 24 hours. Following the evaporation of the solvent, the residue was stirred for half an hour using a 10 mL solution of 5% sodium carbonate, and it was extracted three times using 20 mL chloroform. To make dark ink to black, the chloroform extracts were mixed, dried, and washed multiple times with 20 mL parts of acetone[17] (Table 1).

Spectral data [Prodrug E3]. Oily dark ink to black; yield (85%); melting point. (Viscous); (KBr) (FTIR cm^{-1}) (Table 3): 3045.60 ν (C-H) $_{Aromatic}$ Stretching, 2899.01 and 2872.01 ν (C-H) $_{Aliphatic}$ Stretching, 1720.50 ν (C=O) Stretching, 1543.05 and 1442.75 ν (C=C) $_{Aromatic}$ Stretching, 1355.96 ν (C-H $_{Aliphatic}$ bending), 1120.64 ν (C-O-C) Stretching, 1045.42 ν (C-O) Stretching. In 500 MHz & ppm [^{1}H-NMR data, DMSO-d*6*, δH]: δ = 7.15–7.17 (HC=N); In 75 MHz & ppm [^{13}C-NMR data, DMSO-d*6*]: δ = 180, 169, 166, 149, 150, 140, 133, 120, 112, 81, 72, 69, 65, 46, 24 and 14.

Antibacterial Activity

The final compounds' initial antibacterial activity test was carried out at the University of Basra's Department of Microbiology, College of Pharmacy. In compliance with the National Committee for Clinical Laboratory Standards (NCCLS), the Agar well diffusion technique was applied.[17,18] The antibacterial activity was studied against (*E. coli; P. aeruginosa*, *K. pneumoniae* & *S. aureus*) every bacterial culture that was going to be examined was kept at 4° on nutrient agar slants and sub-cultured by spreading them out over nutrient broth for a whole day. Each strain of bacteria was suspended in 0.9% NaCl to achieve a concentration of about 1.5 x 10^{8} CFU/mL. By comparing the turbidity of the bacterial suspension to the McFarland criteria of 0.5, an acceptable concentration was determined. Seven concentrations of each produced ester prodrug and one concentration of each standard component of certain quinolones. In order to create each chemical, it was first dissolved in DMSO at a stock concentration of 1000 ppm, and then it was diluted twice to 250 and 500 ppm. The bacteria were inoculated by swabbing bacterial suspension over the whole Mueller-Hinton agar plate surface. Next, 5 mm diameter wells were used to puncture the agar medium. 100 µL of the tested chemical at the intended concentration was injected into each well. Following a 24-hour incubation period at 37°C, the perpendicular diameter of the inhibitory zone in each well was measured. The obtained results are mentioned in (Table 3).

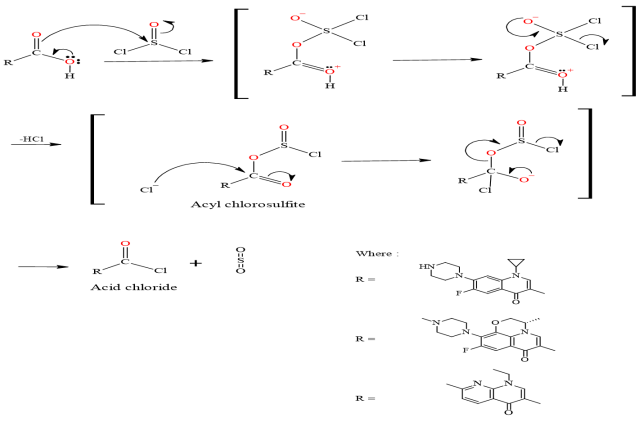
RESULTS AND DISCUSSION

Synthesis of Prodrugs E1, E2 and E3 by Direct Ester Coupling

Numerous techniques are employed in the esterification process. The Stiglich esterification reaction is one of them. This technique has previously been used for 2-HM-15-C-5 ether esterification. However, in our study, the quinolones, (i.e., the carboxyl component) were combined with thionyl chloride to create a substantially more efficient acylating agent. Next, in the presence of pyridine, 2-hydroxymethyl-15-crown-5 ether (i.e., the alcoholic component) was esterified using an acid chloride. This process yields a decent yield and is characterized by being easy to use, effective, low in toxicity, and free of gaseous byproducts that contaminate the final product.

AC synthesis

The carboxyl component compounds were activated to an acid chloride because acyl halides are more reactive with nucleophiles than their corresponding carboxylic acids. Acid chloride is extremely electron-deficient because its carbon core is linked to two electronegative groups: the carbonyl and the chloride. Furthermore, chloride is an excellent leaving group. Compare this to carboxylic acid, where the hydroxide leaving group makes the carbon center less reactive to additional nucleophiles. The process begins with a nucleophilic assault on thionyl chloride, resulting in a highly electrophilic chlorosulfite formation and the expulsion of a chloride anion. After adding chloride to the carbonyl carbon, HCl and SO2 are released, forming acyl chloride (AC). This action cannot be reversed due to sulfur dioxide (Scheme 1) & (Table 1).



Scheme (1): The general mechanism of the synthesis of an acid chloride.

Synthesis of Ester Compounds by Acid Chloride Direct Coupling

An alcoholic component functions as a nucleophile that attacks in the nucleophilic acyl substitution process, which produces the ester molecule. An alkoxide anion is created from the hydroxyl and an AC is present in the presence of pyridine (an equimolar quantity), which acts as a base to neutralize hydrogen chloride that develops during the reaction. Through an addition step, the nucleophile targets the acid chloride's carbonyl group, creating an unstable tetrahedral intermediate. Methylene dichloride was employed to speed up the process of generating carbon-oxygen double bonds, which led to the ejection of the chloride anion in an elimination step. It does this by dissolving both nucleophiles and electrophiles and having a rapid rate of evaporation (Scheme 2). The various characteristics of new compounds are shown in (Table 1).

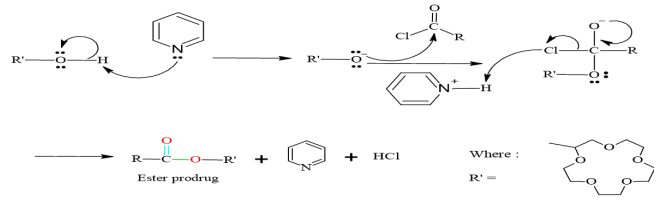
Electronic Spectra

With their parent compounds at equimolar concentration, all novel ester prodrugs were scanned by a UV spectrophotometer; Table 2 shows the maximum difference, proving this approach important for the study. The electronic transitions for levofloxacin, nalidixic acid & ciprofloxacin, respectively, reveal a maximum absorbance that was consistent with documented references at wavelengths of 293, 340 & 278 nm in solution, which is acidic in nature.

Every ester prodrug exhibits distinct UV spectra, with λ max values that deviate from the original materials. The fluoroquinolone ring absorption is directly responsible for the greater absorption bands observed in the produced prodrugs. Similar transitions take place in related molecules, including carboxylic and ketone groups, as well as unsaturated hydrocarbons that have an oxygen atom linked to them. Prodrugs E1, E2, and E3 showed a maximum absorption band at 290, 320, and 355.5 nm, respectively, in their UV spectra. This bathochromic alteration from the original materials is caused by the vital role of two charged centers, NH2+ and COO-, in raising the stabilizing energy through electronic delocalization. Ester prodrugs have lower excitation energy when the zwitterionic character of the starting ingredients is eliminated. As a result, prodrugs with max values that have longer wavelengths are created, as the energy required for electrons to go from HOMO (highest occupied molecular orbital) to LUMO (lowest unoccupied molecular orbital) is significantly reduced.

FTIR Spectra

All ester prodrugs' FTIR data conform to the ester "Rule of Three," as indicated in Table 3. The stretching vibration of (C=O) is overlaid with a high peak spanning from 1700 to 1730 cm^{-1}. The stretching (CCO) vibration lies in an area of 1310 & 1250 cm^{-1} and is the second medium-intensity peak. The last and less powerful peak is the (C-O-C) stretching vibration, which lies between 1150 and 1100 cm^{-1}. Additionally, the effective synthesis of the esterification process was confirmed by the elimination of the (O-H) stretch within the range 3500 to 3200 cm^{-1} (Table 3).



Scheme (2): The general mechanism of the synthesis of ester prodrug.

NMR Spectra

As listed previously, the compounds` NMR were obtained using an internal standard tetramethyl saline (TMS) & solvent deuterated dimethyl sulfoxide (DMSO-d6).

Antibacterial Study

When compared to levofloxacin, ciprofloxacin exhibited equivalent efficacy against *Escherichia coli* and less powerful bactericidal action against *Staphylococcus aureus*. It also

Table (1): The physicochemical parameters of the target compounds and their intermediates.

Compound	Molecular Formula	Molecular Weight (g/mol)	Appearance	Yield (%)	Melting Point (°C)	R_f value	Eluent system
2-HM-15-C-5	$C_{11}H_{22}O_6$	250.29	Colorless to faint yellow	_	Viscous	_	_
Ciprofloxacin	$C_{17}H_{18}FN_3O_3$	331.34	Faint to light yellow crystalline powder	_	255-257	0.68	$CHCl_3$ / EtOH / NH_4OH 4.3:4.3:1.4
Levofloxacin	$C_{18}H_{20}FN_3O_4$	361.4	White smoke to light grey greasy powder	_	225-226	0.78	$CHCl_3$ / MeOH / NH_4OH 6:3:1
Nalidixic acid	$C_{12}H_{12}N_2O_3$	232.23	Cream-colored to pale yellow powder	_	229-230	0.15 0.96	DCM / TEA 10:1 $CHCl_3$ / EtOH 8:2
CAC	$C_{17}H_{17}ClFN_3O_2$	349.7871	Deep-yellowish powder	83	297-299	_	_
Prodrug E1	$C_{28}H_{38}FN_3O_8$	563.6150	Faint-yellow powder	81	251-253	0.78	$CHCl_3$ / EtOH / NH_4OH 4.3: 4.3: 1.4
LAC	$C_{18}H_{19}ClFN_3O_3$	379.8131	Deep orange-reddish powder	84	229	_	_
Prodrug E2	$C_{29}H_{40}FN_3O_9$	593.6410	Oily brown like-coffee	83	Viscous	0.69	$CHCl_3$ / MeOH / NH_4OH 6:3:1
NAC	$C_{12}H_{11}ClN_2O_2$	250.6809	Dark navy to ink powder	66	229	_	_
Prodrug E3	$C_{23}H_{32}N_2O_8$	464.5087	Oily dark ink to black	85	Viscous	0.43 0.2	DCM / TEA 10:1 $CHCl_3$ / EtOH 8:2

Table (2): The λ_{max} values of some starting materials and prodrugs.

Compound	λ_{max} values (nm)	Assignment
Ciprofloxacin	278	pi → p* of the aromatic system
Levofloxacin	293	pi → p* of the aromatic ring
Nalidixic acid	340	p → p* of the system
Prodrug E1	290	pi → p* of the aromatic system
Prodrug E2	320	pi → p* of the aromatic system
Prodrug E3	355.5	pi → p* of the aromatic system

Table (3): The data and vibrational mode description of FTIR spectra of ester prodrugs

Compounds	Vibrational mode (cm^{-1})										
	O-H Stretching	C-H Stretching (Aromatic)	C-H Stretching (Aliphatic)	C=O Stretching	C=N Stretching	C=C Stretching (Aromatic)	C-H bending (Aliphatic)	C-O-C Stretching	C-O Stretching	C-H bending (Out plane) (Aromatic)	C-O-H bending (Out plane)
Prodrug E1	_	3045.60	2868.15 2849.57	1727.16	_	1489.05 1396.46	1379.10	1180.44 1145.72	1026.13	943.19 731.02	623.01
Prodrug E2	_	3022.43	2939.52 2846.93	1724.36	_	1544.98 1396.46	1357.89	1118.71	1089.78	931.62 802.39	667.37
Prodrug E3	_	3045.60	2899.01 2872.01	1720.50	_	1543.05 1442.75	1355.96	1120.64	1045.42	952.84	

showed lesser activity against *Klebsiella pneumoniae*. Only *K. pneumoniae* is susceptible to the extremely little action of nalidixic acid, which has no effect on other G+ve and G-ve aerobic pathogens. The study's findings show that, at 400 ppm, ciprofloxacin has much better activity ($p < 0.05$) against *S. aureus* than the prodrug E1. Additionally, at 400 ppm, ciprofloxacin has stronger activity against *E. coli* & *K. pneumoniae*, but this difference is not statistically significant. However, prodrug E1 is produced when the carboxyl group of ciprofloxacin is esterified, and this leads to concentration-dependent antibacterial action against the bacterial species previously listed without any anti-pseudomonal activity as shown in Figure 6. Levofloxacin at 400 ppm showed noticeably greater bactericidal activity against *E. coli* and *K. pneumoniae* than prodrug E2 at the same concentration ($p < 0.05$) (Figures 7 and 8). However, as Figure 9 illustrates, prodrug E2 has somewhat greater effectiveness against *S. aureus* ($p > 0.05$). Additionally, prodrug E2, which exhibits concentration-dependent antibacterial activity against the previously listed bacteria, was produced by modifying LEV through introducing COOH group of an ester as detailed in Figure 7. When compared to the same concentration of its equivalent prodrug, NA had significantly better bactericidal effectiveness against K. pneumoniae, with the exception of 400 ppm, all four species of the studied bacteria displayed resistance to nalidixic acid. In addition, prodrug E3 has significant bactericidal action against *K. pneumoniae* at 1000 ppm in contrast to 600 ppm of the same chemical. At the doses under investigation, *P. aeruginosa* was not susceptible to any antibacterial activity from the

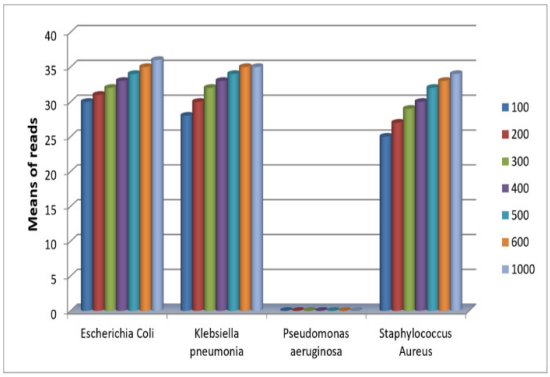


Figure 6: Mean values of prodrug E1

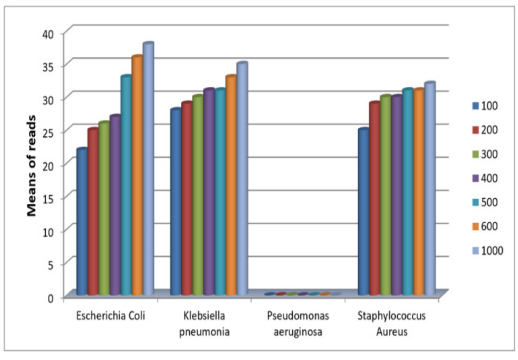


Figure 7: Mean values of prodrug E2

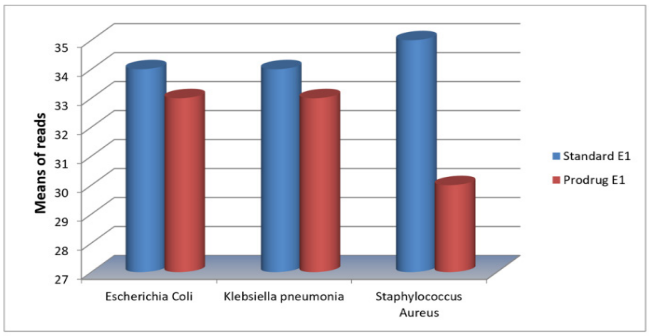


Figure 8: Mean values of ciprofloxacin & prodrug E1 at 400 ppm

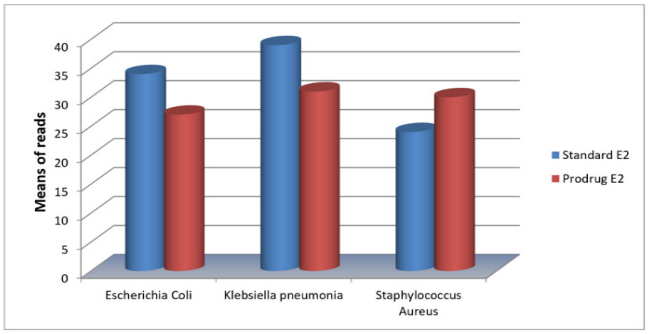


Figure 9: Mean values of levofloxacin & prodrug E2 at 400 ppm

starting ingredients or their ester prodrugs. According to earlier research, all quinolones can kill *P. aeruginosa* bacteria Nonetheless, the current study's findings run counter to those of the earlier research. The isolated species that were studied in the current studies may provide an explanation for this. Furthermore, the outcomes showed that the solvent (DMSO) employed in this investigation had no action against any kind of aerobic pathogen.

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