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Enhancing Anti-Infective Activity through Structural Adaptability and Synthesis of Quinolone Analogues: Comprehensive Review

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ABSTRACT
Fluoroquinolones (FQs) are a widely used class of antibacterial agents, renowned for their excellent physicochemical and pharmacokinetic properties. Their flexibility in synthesis and ease of modification have led to the development of therapeutically beneficial analogues with improved antibacterial activities. Interestingly, recent studies have shown that certain derivatives of ciprofloxacin and norfloxacin exhibit enhanced anticancer properties in different kinds of cancer cells. This project goal is to investigate the structure-activity relationship of fluoroquinolone derivatives, focusing on their antimicrobial and anticancer potential. In order to combat urinary tract infections (UTIs), the project will investigate the creation of new FQ derivatives with enhanced antibacterial properties. prevalent and debilitating condition. Additionally, the anticancer properties of these derivatives will be evaluated, with the ultimate goal of identifying promising leads for the treatment of UTIs and cancer. The results of this study might help create more focused and efficient treatments, tackling the rising issues of cancer therapy and antibiotic resistance.

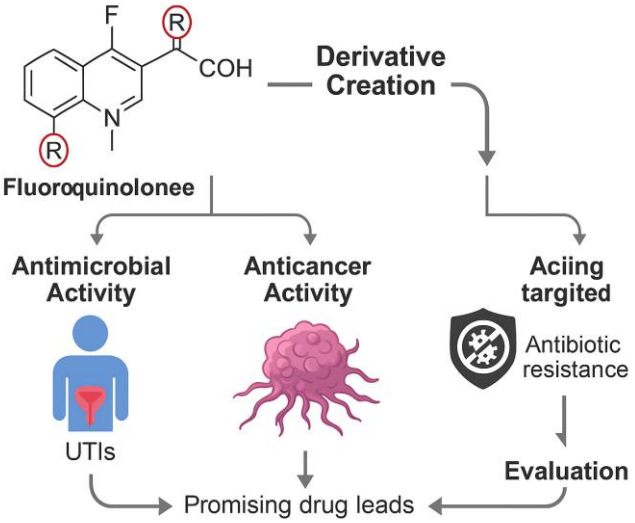
Keywords: Fluoroquinolones (FQs), Antibacterial agents, Anticancer activity, Urinary tract infections (UTIs), Antimicrobial agents, Antioxidant

1. INTRODUCTION

The fluoroquinolones (FQs) are one of the most often utilised classes of antibacterial medicines in the world due to their excellent physicochemical and pharmacokinetic characteristics. Following oral administration, late-generation drugs have good half-lives (levofloxacin: 13 hours) and exceptional bioavailability (levofloxacin: 99%) [1–3]. Due to their high synthesis flexibility and ease of usage with a range of methods and building blocks, quinolone derivatives make it easier to construct and test a wide range of flexible chemical structures [4,6,7]. Research on the fluoroquinolone structure activity relationship (SAR) led to the development of therapeutically beneficial analogues with improved antibacterial qualities [3,8]. Recent research has shown that some derivatives of ciprofloxacin (CIP) and norfloxacin (NOR) have more anticancer activity than their parent medications in a range of cancer cell lines [3,5,9]. Antibiotic therapy is necessary for urinary tract infections (UTIs), one of the most prevalent bacterial illnesses with a high percentage of morbidity in the general population [10]. Because fluoroquinolones (FQs) have a range of action that includes enteric Gram-negative bacilli, they have been widely utilised as an empirical therapy for UTI [11], that is, before the aetiology and antibiogram have been verified [12]. As soon as the bacteria causing the diseases and their antibiogram are identified [12], they are recommended as guided treatment [11] due to their several advantageous pharmacokinetic characteristics. Additionally, complex UTIs can be treated with FQs in conjunction with shorter antibiotic regimens [11,13,14]. Complex fluoroquinolone resistance can be caused by changes in enzymes, target-protection proteins, increased efflux pump production, or mutations in one or more target-site genes [15]. When the main binding is changed, the secondary target becomes a target, and fluoroquinolones will bind to it notwithstanding their preference [16]. They will go after either Both Gram-positive and Gram-negative bacteria use DNA

gyrase or topoisomerase IV. It is the Mycobacterium tuberculosis (mtb) that causes the infectious illness tuberculosis (TB). Prior to COVID-19, TB was acknowledged as the most prevalent infectious illness caused by a single agent worldwide [17]. Globally, TB-related causes claimed 1.5 million lives in 2020. The number of deaths from TB in the same year is almost twice as large as the number from HIV/AIDS (0.68 million) [18]. Years of advancement in the worldwide control of tuberculosis have been erased by The epidemic of COVID-19 Regarding the rise of TB that is both extensively and multi-drug-resistant (MDR and XDR).[17]. Together, these factors have increased the frequency of TB-related fatalities. Notably, the total number of TB deaths in 2020 was higher than in 2018, a 5.6% rise over the number of TB-related deaths in 2005 [19]. Antimicrobial resistance is becoming a global concern. Because they can form antibiotic-tolerant biofilms and/or show multidrug resistance against common antibiotics, the most dangerous ESKAPE pathogens are Klebsiella pneumoniae, Staphylococcus aureus, Enterococcus fecium, Pseudomonas aeruginosa, and Acinetobacter baumannii. This fact highlights the necessity for academia and the pharmaceutical industry to increase and better coordinate their research efforts in the fight against antibiotic resistance [20–28]. Often referred to as FQs, fluoroquinolones are antibacterial drugs that can Effective against urinary tract infections, acute pyelonephritis, chronic prostatitis, and community-acquired pneumonia to a moderate extent [29–32]. Four generations of quinolones, including 4-quinolone (Fig. 1), are a family of medicines that share a bicyclic core structure.

Graphical abstract:



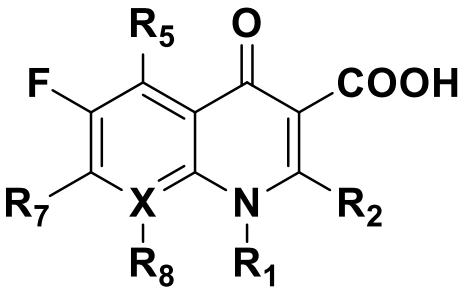
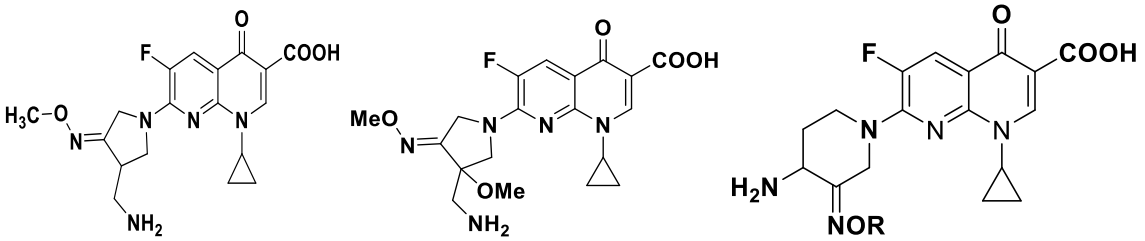


Figure 1: General structure of Fluoroquinolone

The potential biological and pharmacological ramifications of quinolone heterocyclic chemistry have garnered significant attention despite recent advancements. As a scaffold, this system has served organic and medicinal chemists well Conversely, quinolone derivatives have been extensively studied as bioactive compounds [33]. Distillations of quinolone are utilised extensively these days. Research into compounds with improved antibacterial and broad-spectrum action is desperately needed since germs continue to represent a severe danger to human health. Three chemical organics and medicines. Their antimalarial [34,35], anticancer [36,37], antifungal [40,41], therapeutic antibacterial [38,39], antidiabetic [42], antiviral [43], antioxidant [44], anti-allergic [45], anti-proliferative [46], and anti-tubercular [47] qualities have all been demonstrated. Quinolone, which has the chemical formula C9H7N, The molecule is a rare hetero-aromatic. The structure has ten electrons in it. The bicyclic heterocyclic compound quinolone structure composed comprising a six-membered benzene ring and

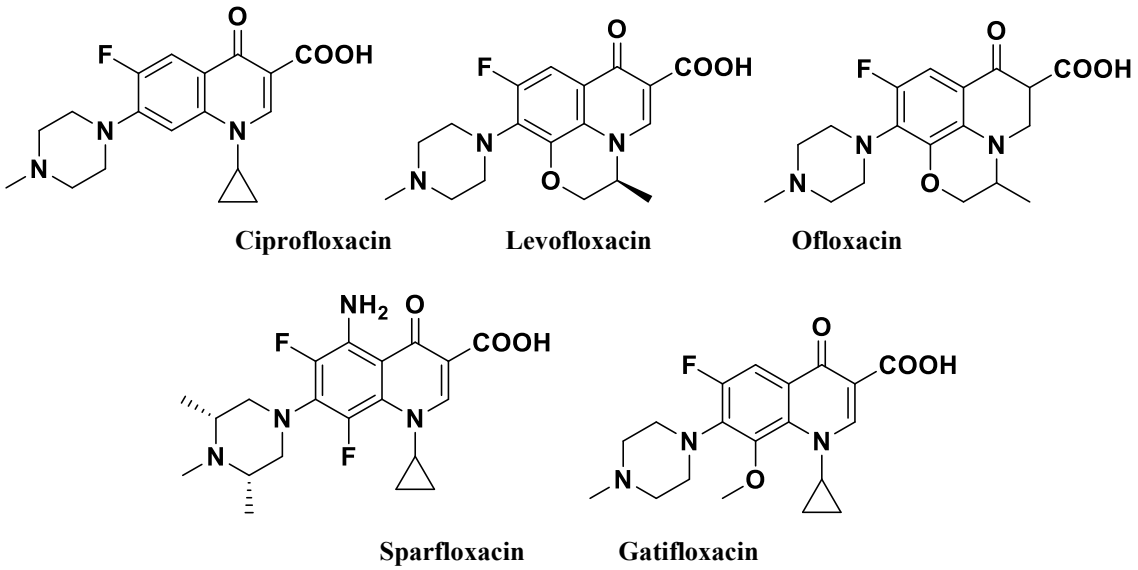
pyridine [48]. Bacteria are unicellular organisms that vary widely in size and shape, between 0.5 and 5 μm. Numerous bacteria may be found in the skin, reproductive systems, digestive tracts, mouths, respiratory tracts, together with additional bodily areas of both people as well as animals. [49, 50]. Methicillin-intolerant Increasingly prevalent clinically relevant pathogenic bacteria include Methicillin-resistant Staphylococcus aureus (MRSA) and Staphylococcus epidermidis (MRSE). Therefore, in recent years, there has been a greater focus on finding more powerful antibacterial drugs that have a wide range of action and efficacy opposition to Gram-positive infections, particularly resistant pathogens [51,52]. We have focused on incorporating new groups with functions into piperidine ring [54–57]. A methyl group added to the third position of the pyrrolidine ring may increase its capacity to inhibit Gram-positive bacteria, per previous studies on pyrrolidine analogues. After being chemically altered to DZH (Fig. 2), DW 286 (Fig. 2) is an example of a Gemifloxacin (GMFX) analogue that has demonstrated strong in vitro ability to combat MRSA, Pseudomonas aeruginosa, and other Gram-positive and Gram-negative bacteria [53].



Gemifloxacin **DW286** **DZH**

Figure 2: Structures of quinolone compounds

The most recent guidelines state that the four-drug combination of Ethambutol (EMB), rifampicin (RMP), isoniazid (INH), and pyrazinamide (PZA) constitutes the intense phase of therapy for drug-sensitive tuberculosis (DS-TB) [58]. A two-part phase of continuation consisting of INH and RMP comes next. The primary cause of mortality for children globally and the fourth leading cause of death for adults, acute respiratory infections (ARIs) claim the lives of millions of people each year [59–62]. A number of other fluoroquinolones, such as ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, and Gemifloxacin, have also been synthesised and evaluated (Fig. 3). They work against a wide range of harmful bacteria that are resistant to cephalosporins, penicillin's, aminoglycosides, tetracycline, and other antibiotics. When compared to current bactericidal medications, this family of chemicals exhibits better pharmacokinetic characteristics and broad-spectrum activity against bacteria, mycobacteria, and parasites, including resistant strains [63, 64].



Ciprofloxacin **Levofloxacin** **Ofloxacin**

Sparfloxacin **Gatifloxacin**

Figure 3:Structures of quinolone compounds

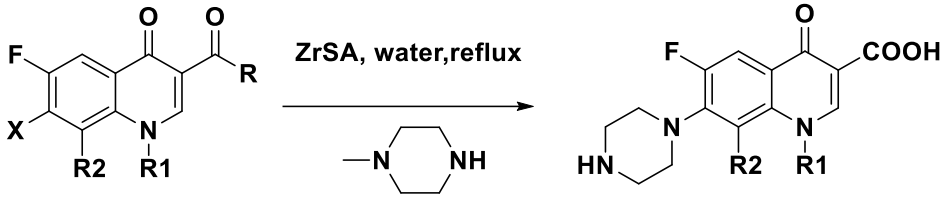
2. CHEMISTRY

Synthesis of fluoroquinolone

Current developments in the anti-infective area of fluoroquinolone derivative green synthesis

Scheme – 1

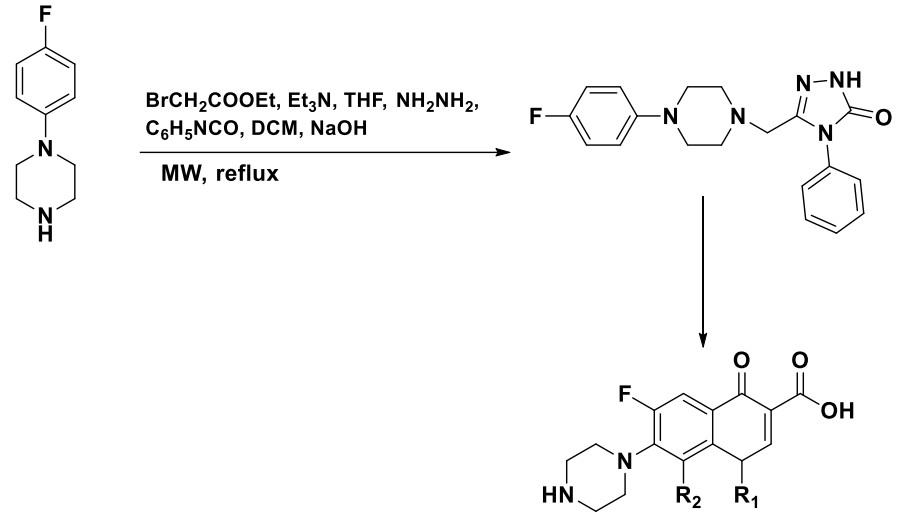
Utilising Zirconia Sulphuric Acid (ZrSA) catalysts in the form of nanoparticles under reflux conditions with either dinary or magnetised water, Nakhaei et al. (2018) reported a number of novel Antibacterial fluoroquinolone analogues are produced by directly aminating 7-halo-6-fluoroquinolone-3-carboXylic acids with various piperazine derivatives and (4aR, 7aR)-octahydro-1H-pyrrolo[3,4-b] pyridine. The findings showed that ZrSA had strong Production of derivatives of fluoroquinolones via catalysis in two different kinds of water [65].



Scheme 1

Scheme – 2

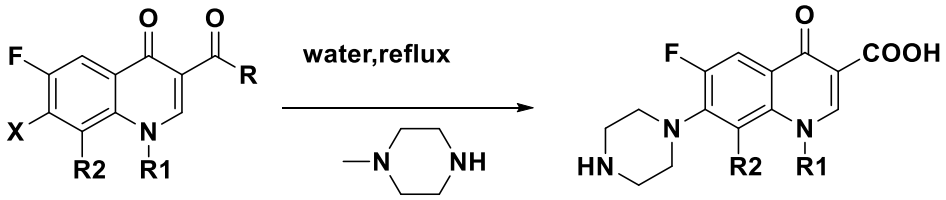
1,2,4-triazole based on piperazine, azole, and fluoroquinolone compounds were synthesised under the influence of microwave radiation from Ozdemir et al. (2018). 1-(4-fluoropenyl) piperazine was the starting point for the process, which then went on to The appropriate amines, include fluoroquinolone, DCM, NaOH, HCHO, DMF, $BrCH_2COOEt$, Et_3N, THF, NH_2NH_2, and C_6H_5NCO [66].



Scheme 2

Scheme – 3

New fluoroquinolone compounds were synthesised by Nakhaei et al. (2018) as a magnetic catalyst, Nano Fe_3O_4 ZrO_2-SO_3H (n-FZSA). derivatives of piperazine and (4aR,7aR)-Octa Hydro3-carboXylic acids and 7-halo-6-fluoroquinolone pyridine using [3,4-b] -1H-pyrrolo were combined directly in water to create them [67].

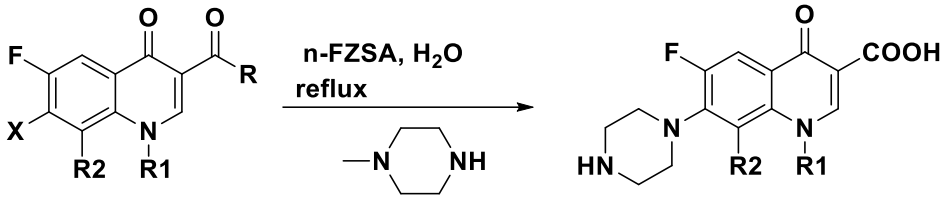


Scheme 3

Scheme – 4

Using piperazine derivatives and 6-fluoroquinolone-3-carbo, 7-halo Xylic acids as a starting point, Miraie et al. (2017) synthesised a variety of possible antibacterial fluoroquinolone derivatives (4aR, 7aR)- 1-H-octahydropyrrolo[3,4-b].

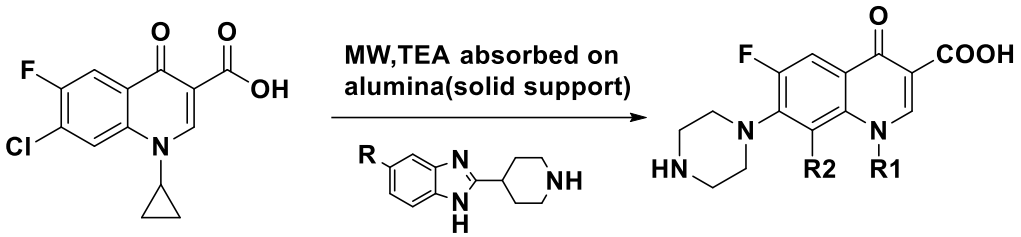
Molybdites, New fluoroquinolone compounds were synthesised by Nakhaei et al. (2018) employing a magnetic catalyst called Nano Fe_3O_4 ZrO_2-SO_3H (n-FZSA). derivatives of piperazine and (4aR,7aR)-Octa Hydro3-carboXylic acids and 7-halo-6-fluoroquinolone pyridine with -1H-pyrrolo[3,4-b] when pyridine is used [68].



Scheme 4

Scheme – 5

With the use of a microwave irradiation technology and triethylamine adsorbed in a catalytic amount on a solid alumina substrate present, Guruswamy et al. (2012) produced a number of novel ciprofloxacin derivatives using an environmentally friendly and green methodology. Remarkably high product yields (72–90%) were achieved with this microwave-assisted technique [69].



Scheme 5

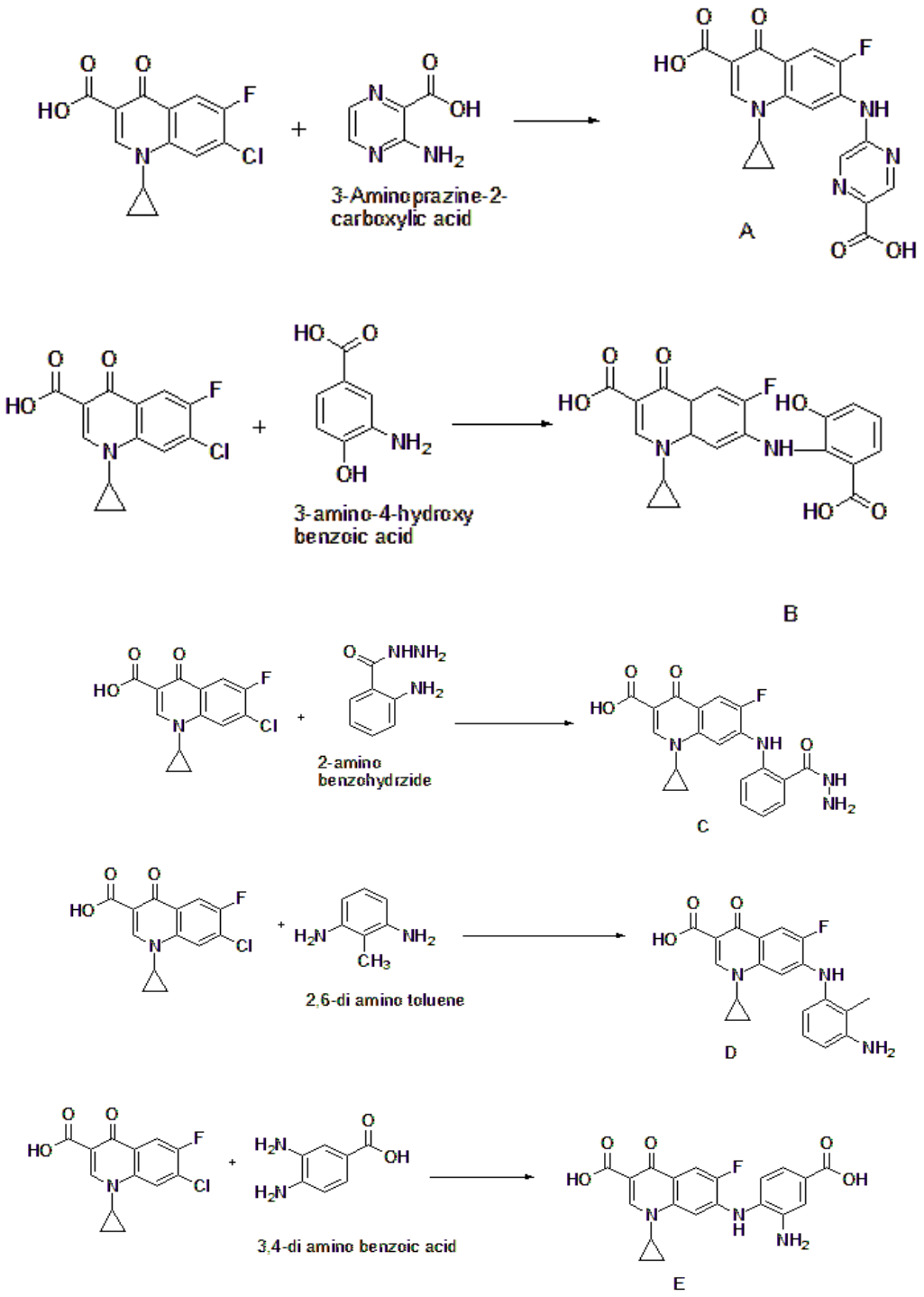
Production of derivatives of quinolone

displays the synthesis derivatives, which were verified using FTIR, 1H, and 13C (NMR) spectroscopy. Five derivatives were synthesised. The distinct functional groups found in the pure products were described using FTIR spectroscopy. Every chemical utilised in this study was as pure as possible and came straight from the manufacturer, requiring no further processing. Thin layer chromatography (7:3 tetrahydrofuran, cyclohexane) was used to track the reaction's progress and produced the best results in all derivatives using the same eluent. Results from in vitro tests of the compounds' antibacterial activities indicate that bacterial growth is suppressed (Scheme - 6). [70]. Table 1 also provides an overview of these findings.

Table 1 Displays, in millimetres, the synthetic compounds A–E's inhibition zone against two bacteria that are Gram-positive and two that are Gram-negative in relation to the widely used antibiotic ciprofloxacin.[70]

Organism	Ciprofloxacin (Control)	A (250 µg)	A (500 µg)	B (250 µg)	B (500 µg)	C (250 µg)	C (500 µg)	D (250 µg)	D (500 µg)	E (250 µg)	E (500 µg)
E. coli	10	5	10	30	33	3	9	29	30	27	
S. aureus	44	45	45	47	43	44	41	43	42	44	40
K. pneumonia	20	21	29	30	26	27	31	35	23	24	28
S. pyogenes	45	47	42	43	40	43	35	38	38	39	44

Scheme 6: synthesis or quinolone derivatives



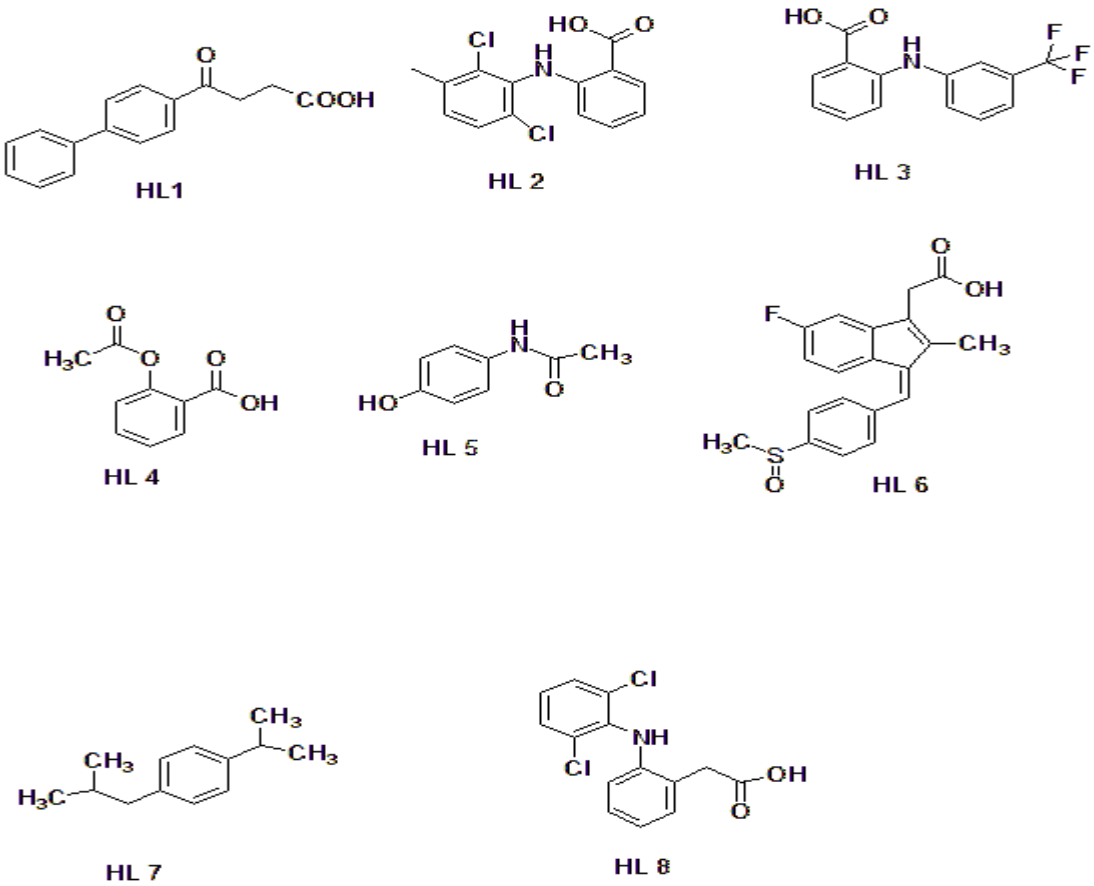
Scheme 6

Formation of derivatives of 4-oxo-1,4-dihydroquinoline

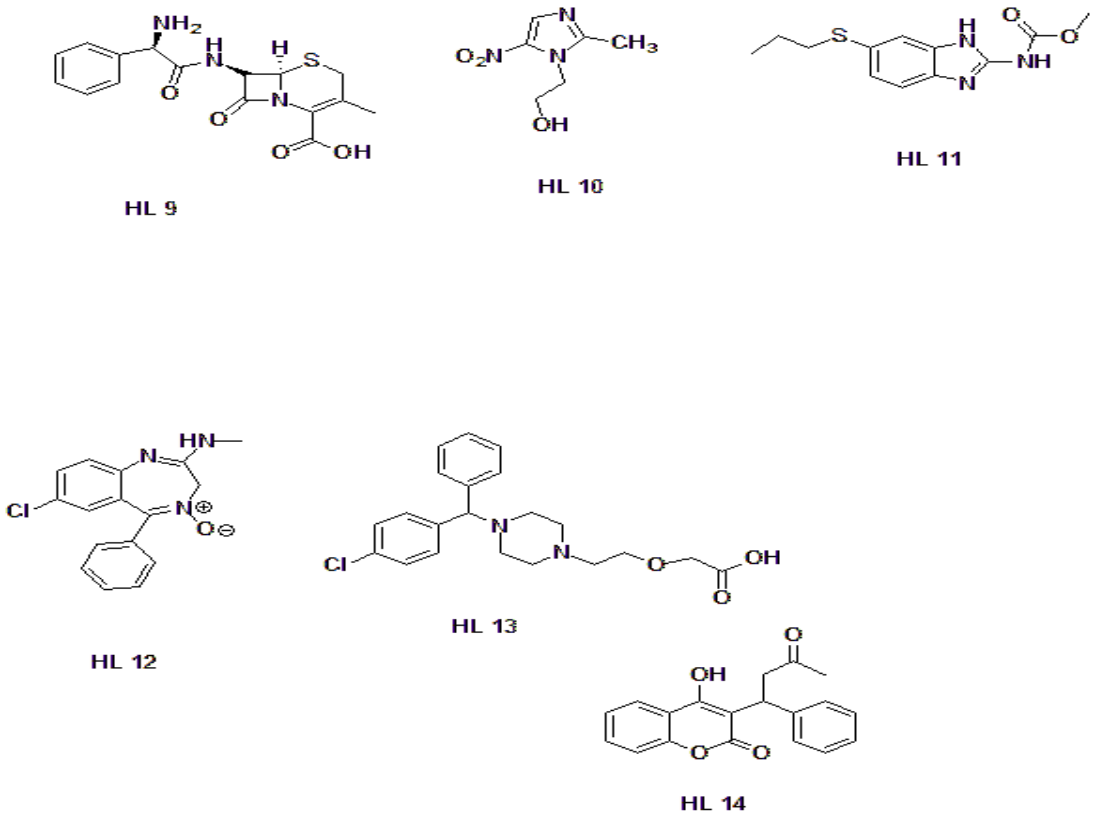
The class of synthetic antibacterial drugs known as "quinolones" is named after its the 4-oxo-1,4-dihydroquinoline molecule structure. These substances are sometimes referred to as 4-quinolones or quinolone carboxylic acids (Scheme 7) [71,72]. Nalidixic acid (Scheme 7) was the first commercial antimicrobial quinolone with anti-gram-negative antibacterial properties. The spectrum of action is greatly increased by a piperazine ring at number seven and a fluorine (F) at number six. according to modifications of nalidixic acid based on the structure–activity relationship (SAR) [71]. As a result, The quinolones of the second generation, such as ciprofloxacin, ofloxacin, and levofloxacin, and norfloxacin, was discovered. and the quinolones of the third generation, such as sparfloxacin, gatifloxacin, and moxifloxacin [71,72]. It has been demonstrated that fluoroquinolones are the most commercially and clinically effective of all the fully synthetic antibacterial medicines. This is due to its wide range of antimicrobial properties, capacity to generate resistance at comparatively manageable levels, ease of

synthesis, therapeutically relevant amounts of bacterial death, and an interesting mechanism of action [72]. Fluoroquinolones are also very beneficial in treating respiratory infections, urinary tract infections (UTI), typhoid fever, sinusitis, acute bronchitis, community-acquired pneumonia, soft tissue infections, and bone-joint infections, among others [71]. Two fluoroquinolones, sparfloxacin (Scheme) and ciprofloxacin (Scheme 9), have drawn a lot of attention from researchers [71]. The synthetic fluoroquinolone antibiotic ciprofloxacin has a wide variety of antibacterial activity invitro. Organotin (IV) complexes of NSAID drugs include fenbufen (a clinically used NSAID as an analgesic, anti-inflammatory, and antipyretic drug) (HL1), its synthesis, solid and solution phase spectroscopic characterisation, single crystal x-ray structural analysis, and in vitro antimycobacterial and/or anti-tumour activity, particularly di- and trialkyltin (Scheme 8). When tested against the selected cancer cell lines, Invitro anticancer activity was higher for the complexes n-Bu2SnL1 (1) and Ph3SnL1 (2) than for cis-platin. In particular, Me2Sn (IV) and Ph3Sn (IV), NSAID derivatives (Complex 5 and 6), belong to the fen mate family. Osteoarthritis and rheumatoid arthritis are treated with the medication meclofenamic acid (HL2) (Scheme 8). The triphenyl Tin (IV) ester of flufenamic acid (HL3), another NSAID fen mate (Complex 7–8) that is often utilised in clinical Organotin (IV) therapy, was reported by Kaur et al. [73]. Complexes 9–14 consist of two drugs, aspirin (HL4) and paracetamol (HL5), which have analgesic and antipyretic effects. (Scheme 8)

Scheme 7: The most important antibacterial quinolones and their fundamental skeleton architecture



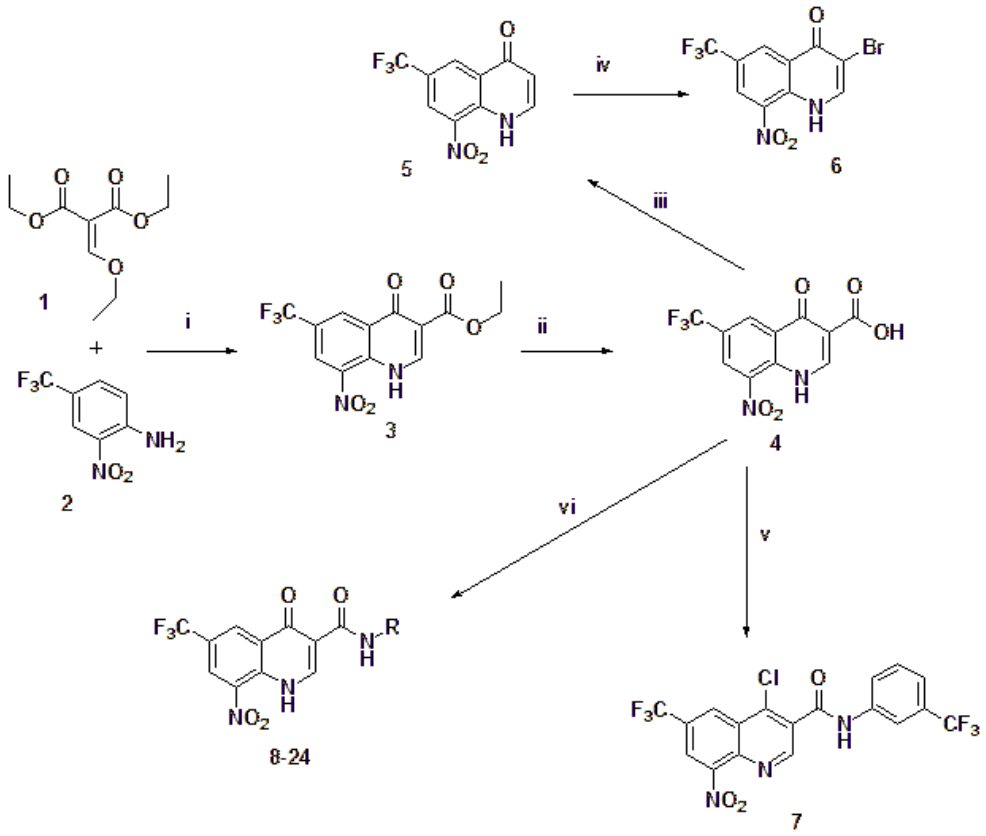
Scheme 8: The reported NSAID complexes' structures.



Scheme 9: Organotin complexes with recognized antibiotics, anticonvulsants, antihistamines, anthelminthics, antiprotozoal, antiviral, bronchodilators, and hypnotic medication.

2.4 Synthesis of target compounds

Our target compounds were produced using the four-step synthetic procedure depicted in Scheme 10. Following diethyl ethoxymethylenemalonate's first condensation with the line (5) of 3-nitro-4-(trifluoromethyl) ani, compound 3 was produced in 80% yields via intramolecular cyclisation between 245 and 250 C. Following compound 3's saponification, compound 4 was produced in 70%. Three more chemical changes were made to compound four. Decarboxylation at 245–250 ◦ C was the initial transition to produce chemical 5. Compound 6 produced 60% yields when N-bromosuccinamide was used as the bromine source.in the subsequent bromination phase. By refluxing $SOCl_2$ and employing amidation and chlorination at the same time, the second reaction yielded chemical 7. Third, At ambient temperature, amide coupling with HATU as a coupling reagent produced 50–70% yields of target compounds 8–24. To characterise the synthesised quinolones, The techniques used were NMR, High-resolution mass spectrometry (HRMS) with 1 H NMR. Proton signals were confirmed using the multiplicities, coupling constants, and chemical shifts of the 1 13 C H NMR spectra. The singlet signal of The quinolone ring's amine proton (-NH) at N-1 was seen at around 12 ppm. At around 9.5–10.5 ppm, the amide proton at C-3 manifested as a triplet, with a coupling constant of about 6. The amide signal was not present in compounds 3, 4, 5, and 6 because the amide moiety was absent at C-3. It is the ketone carbon (C=O) at C-4 that causes the peaks at ca 177–178 in 13 C NMR spectra. Between 159 and 163 ppm, the amide carbon (CONH) arrived at C-3. The anticipated molecular ion for every chemical was validated by HRMS experiments. Conditions and agents: (iv) diphenyl ether, 260 ◦ C, 15 min; (iv) N-bromo succinimide, DMF, (iv) amine, HATU (2eq), TEA (3eq), DMF, rt, 80 ◦ C, 3–5 hours; (v) thionyl chloride, chloroform, reflux, 24 hours; (ii) LiOH, THF: H_2O (2:1), reflux, 24 hours and 72h [74].



Scheme 10: Synthesis of target compounds

Table 2 Synthesis of target compounds

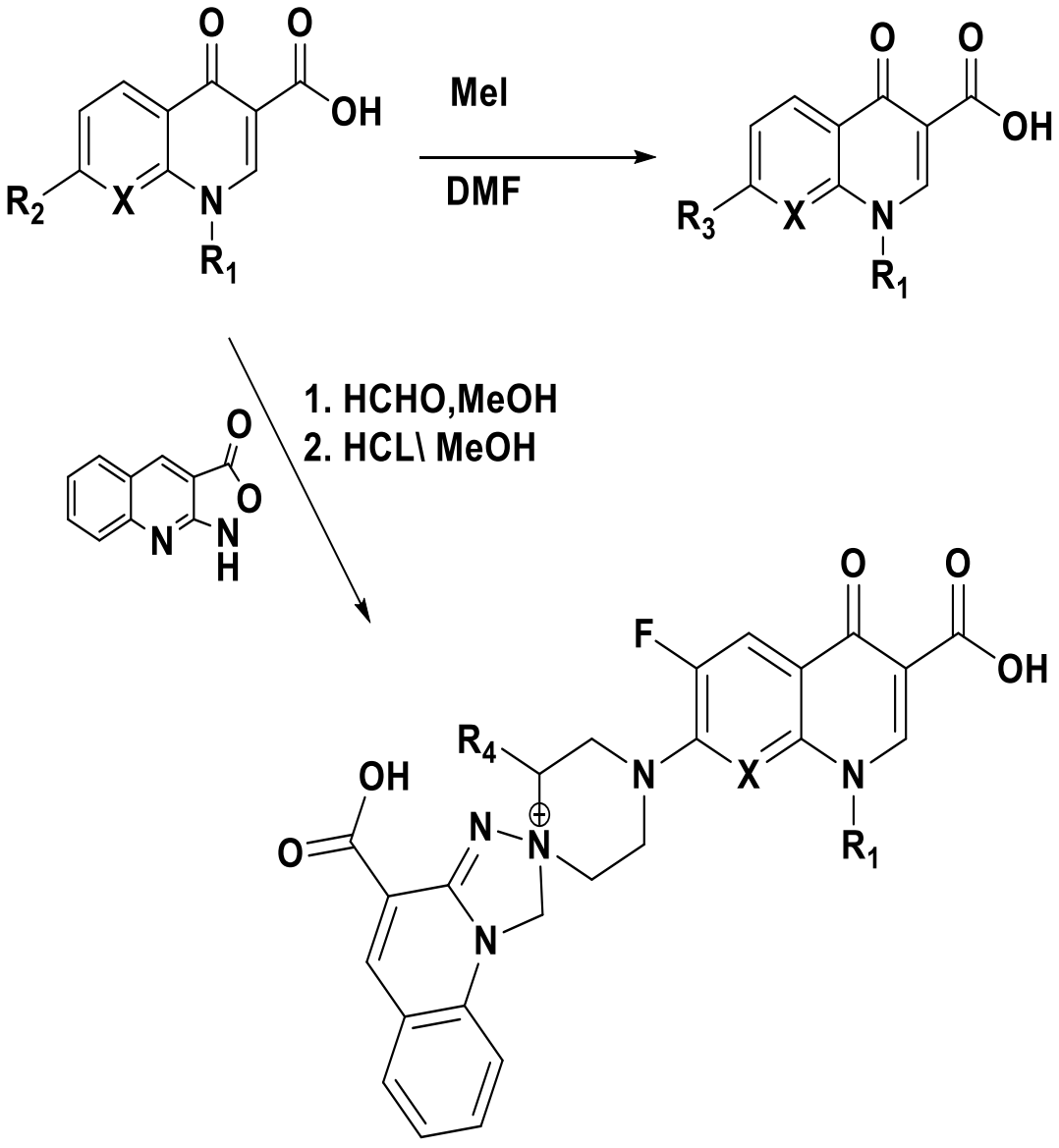
8	**R**	**NH_2**	**17**	**R**	**3-F-benzyl**
9	R	2-Cl-phenyl	18	R	4-F-benzyl
10	R	3-Cl-phenyl	19	R	3,4-di F-benzyl
11	R	3-CF_3-phenyl	20	R	3-methylbenzyl
12	R	3-F-phenyl	21	R	1-F-4-ethylphenyl
13	R	3,4-diethylphenyl	22	R	1-CF_3-4-ethylphenyl
14	R	2-Cl-benzyl	23	R	1-Cl-4-ethylphenyl
15	R	3-Cl-benzyl	24	R	1-Ch_3-4-ethylphenyl
16	R	4-Cl-benzyl			

Design and Synthesis

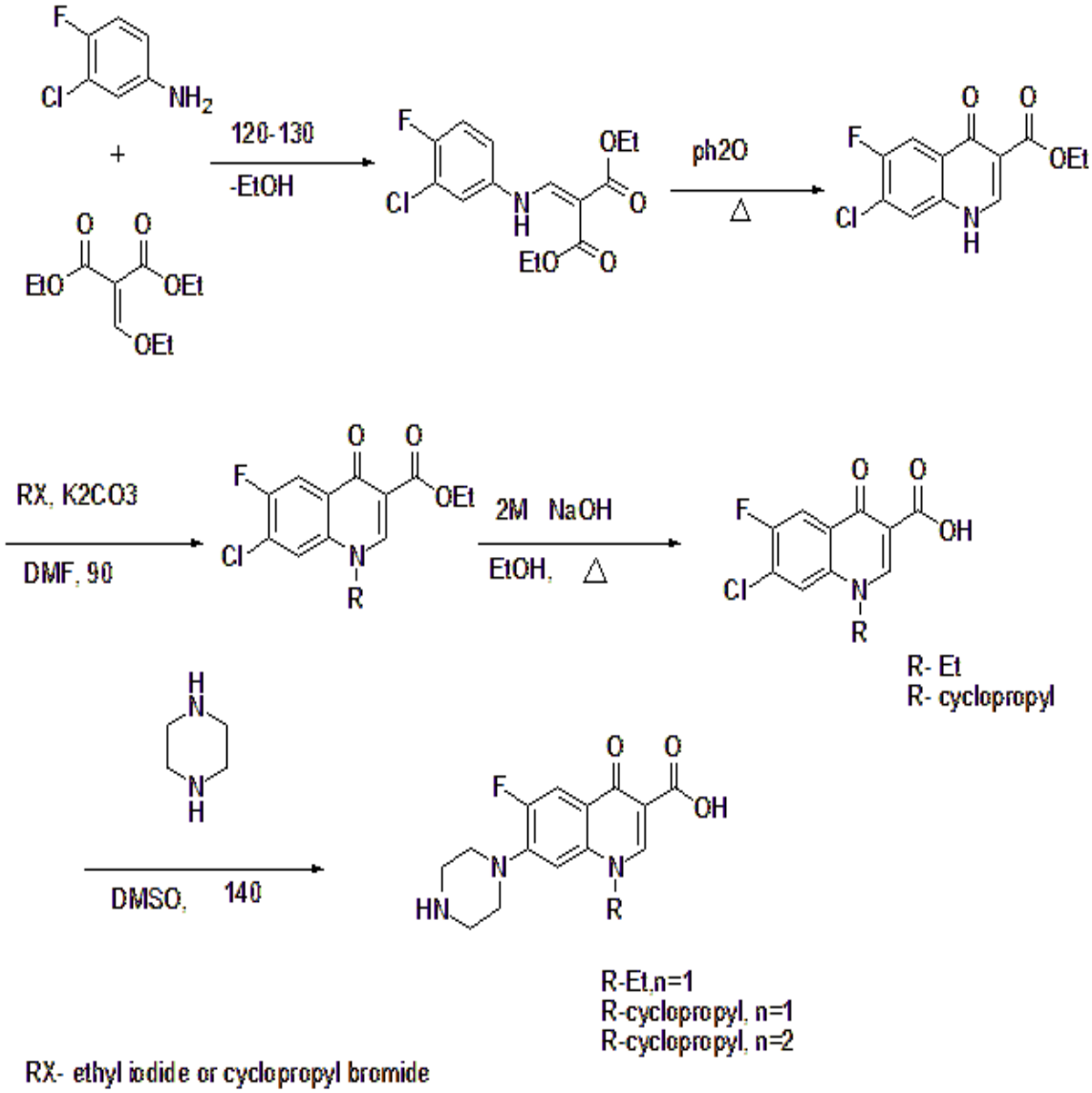
synthesis of N- quaternate quinolones and intermediates

The fused bicyclic structure of a FQ typically contains a cyclic amine at the C7 position, for instance, piperazine has a 6-membered ring. The novel Compounds 1a–h of dimethyl quaternary ammonium (Scheme 11) were created by alkylating the last aliphatic nitrogen atom with a C7 heterocyclic substituent. To investigate the antibacterial capabilities of the dual-acting molecules (FQ-Safirinium hybrids), four hybrid compounds 2a-d were added to the test set (Scheme 11). that had previously been assessed [75]. Following the protocol described in the literature, The intermediates of FQ-core were created using 3-chloro-4-fluoroaniline's multi-step technique (Scheme 12) [76,77]. Simply put, crude malonate 3 was created via the reaction

of diethyl 2-(ethoxy methylene) malonate and 3-chloro-4-fluoroaniline. This was later With the presence of anhydrous potassium carbonate, the latter molecule underwent N-alkylation reactions with alkyl halides, yielding 7-chloro-6-fluor o-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester 4 and 1-alkyl-1,4-dihydro-4-oxoquinoline esters 5a-b. The carboxylic acids 6a and 6b were produced by hydrolysing the esters with sodium hydroxide. When these acids reacted with piperazine or Hom piperazine, they yielded the respective 7-amino compounds, c (norfloxacin), e (ciprofloxacin), and g. Pipemidic acid (a), enoxacin (b), lomefloxacin (d), gatifloxacin (f), and moxifloxacin (h) were the additional (fluoro)quinolones that were purchased commercially. The proposed dimethyl quaternary ammonium compounds 1a–h (Scheme 12) were created by extensively commercially available FQ antibiotics and the produced intermediates 7a–c by alkylating them with methyl iodide. Mannich-electrophilic amination procedures of Isoxazole profluorophoric [3,4-b] quinolin-3(1H)-one and FQs were performed in tandem to produce the hybrid FQs 2a-d. With formaldehyde present, these hybrid FQs were further converted into hydrochlorides (Scheme 11).[78]



Scheme 11: production of N-quaternate quinolones



Scheme 12: synthesis of intermediates

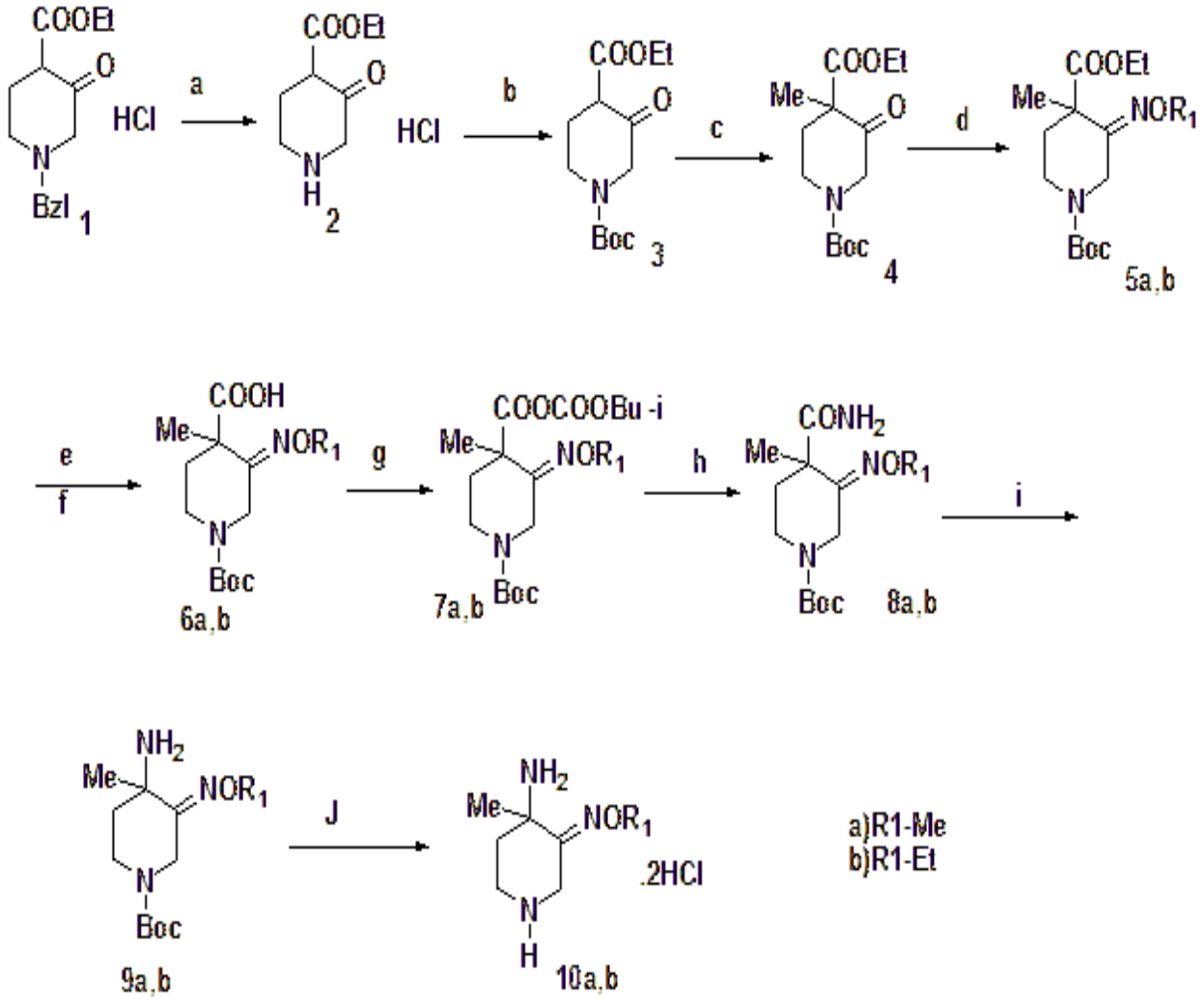
Synthesis of new piperidine derivatives

The novel fluoroquinolones 12–25 and 10a and b, the novel piperidine derivatives shown here were synthesised as indicated in Scheme 13 (reaction optimization in table 3), respectively. A secondary amine 2 was produced by catalytically hydrogenating ethyl N-benzyl-3-oxopiperidine-4-carboxylate hydrochloride 1. Amine 2 was treated with di-tert-butyl decarbonate (Boc_2O) in ethanol to provide Boc-safe molecule 3. Methyl ketone 4 was then produced by adding methyl iodide to the molecule while anhydrous potassium carbonate was present. The acids 6a, b was created by saponifying and acidifying the oximes 5a, b that were created when 4 reacted at 60 C with alkoxyl amines. After reacting with isobutyl chloroformate, the acids 6a, b produced the activated esters 7a, b.

They were then ammonolysis to produce amides 8a, b by pumping ammonia gas in methylene chloride. Hoffmann degradation of the Amines 9a, b was the outcome of combining freshly made sodium hypobromite with amides 8a, b. Through the use of dry hydrogen chloride The Boc protective group on amines 9a, b, and gas in methylene chloride was deprotected, forming new piperidine derivative dihydro chlorides 10a, b. Following the methods described in the literature, Ultimately, the target compounds 12–25 [79] were created by combining the new piperidine derivatives 10a, b with other compounds that included a quinolone or naphthyridine core.

For quinolones 12–21, condensation of 10a, b with 11a–f was carried out in the presence of triethylamine. However, boric chelates 11g, h were employed to increase reactivity for 22–25. The cytotoxicity and structures of the new fluoroquinolones 12–25 is displayed in Table 1. All oxime target compounds' geometries (12–25) must be determined because there are two possible configurations for the oxime group: E and Z. Unfortunately, we were unable to create individual compound crystals

Twelve through 25 that were suitable for X-rays. A methyl or amino group that is next to the oxime group did not correlate in NOE spectra 12–25. Therefore, the E configuration is most likely the oxime group's form. X-ray data for compound 8a was finally obtained [80].

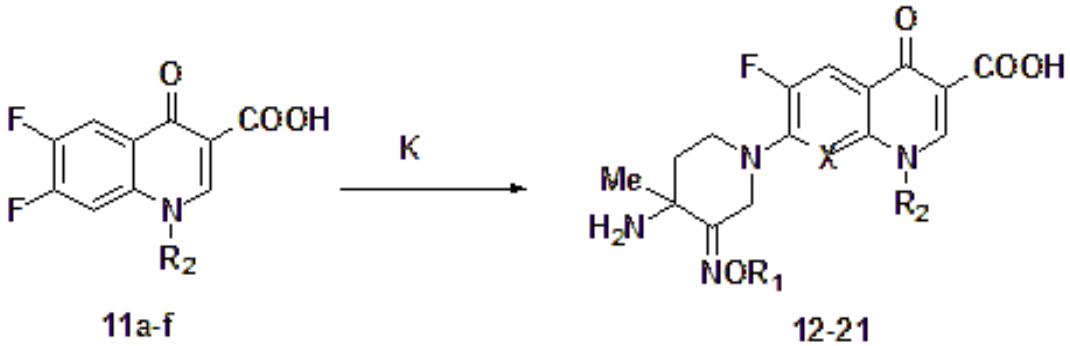


Scheme 13: Creation of Novel Piperidine Compounds 10a,b

Table 3

Step	Reaction Description	Reagents/Conditions
(a)	Hydrogenation of starting material	EtOH, rt, 4 hours, Pd/C 5%, and H_2 0.5 MPa
(b)	Boc protection of amine	EtOH 50%, rt, 1 hour, $NaHCO_3$, and Boc_2O
(c)	Methylation of Boc-protected amine	Mei, Me_2CO, K_2CO_3, 50 °C, 1.5 h
(d)	Coupling with amine derivative	80%, 60 °C, 2 hours, R_1ONH_2·HCl, Et_3N, EtOH
(e)	Deprotection of Boc group	EtOH, Aq. NaOH, rt, 5 h
(f)	Acetic acid treatment	0.5 hours, HOAc, H_2O, rt
(g)	Formation of ester with acid chloride	CH_2Cl_2, Et_3N, ClCOOBu-i, 15 °C, 2 h
(h)	Ammonolysis of ester	CH_2Cl_2, NH_3, 0 °C, 2 hours

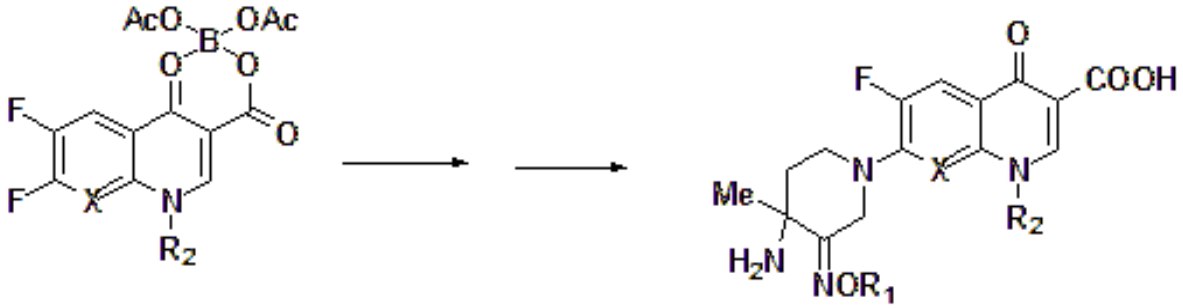
(i)	Oxidation using sodium bromide	MeCN, Aq. NaBrO, 5 °C, 10 h
(j)	Hydrochloric acid gas treatment	CH_2Cl_2, rt, 1 h, HCl gas



11a-f

12-21

11a: X=N, R2=c-Pr
11b: X=N, R2=2,4-difluorophenyl
11c: X=CF, R2=Et
11d: X=CF, R2=2-fluoroethyl
11e: X=CF, R2=C-Pr
11f: X=COCHf2, R2=C-Pr



11g,h

22-25

11g: COMe, R2=c-pr

11h: X, R2=

Scheme 14: Production of new fluoroquinolones 12e25

Step (k): Combine 10a, 10b, Et3N, and MeCN at room temperature for 3 to 10 hours.

Step (l): Add aqueous NaOH at room temperature for 1 to 4 hours.

Step (m): Treat with aqueous HCl at room temperature**.**

Formation of copper (II) complexes with 3-(4-chloro-3-nitrophenyl) thiourea.

Complexes 1–8 were produced using the previously reported method of reacting copper (II) chloride with 3-(4-chloro-3-nitrophenyl) thiourea ligands [81]. Fig. 4 shows the chemical structures of the compounds. Complexes of halogenated copper

(II) include: One of the two and one of the three bromophenyls3-(4-chloro-3) Nitrophenyl, Thiourea (2), 1-(4-bromophenyl) (1), -3-(4-chloro-3) Thiourea (1) 3-(4-chloro-3-nitro phenyl) thiourea, 3-chloro-4-fluorophenyl The substances 1-(2-fluorophenyl), 3-(4-chloro-3-nitrophenyl)thiourea (4), 3-(4-chloro-3-nitro phenyl)thiourea (5), and 3-(3,4-dichlorophenyl)thiourea (6)1-(4-iodophenyl)-3-(4-chloro-3-nitrophenyl)thiourea (8) and -3-(4-chloro-3-nitrophenyl)thiourea (7). The large number of substituents available for phenyl rings allows the investigation of the effects of substitution isomerism and electron-withdrawing functionalities on the antitubercular capabilities of metal-organic compounds. [82]

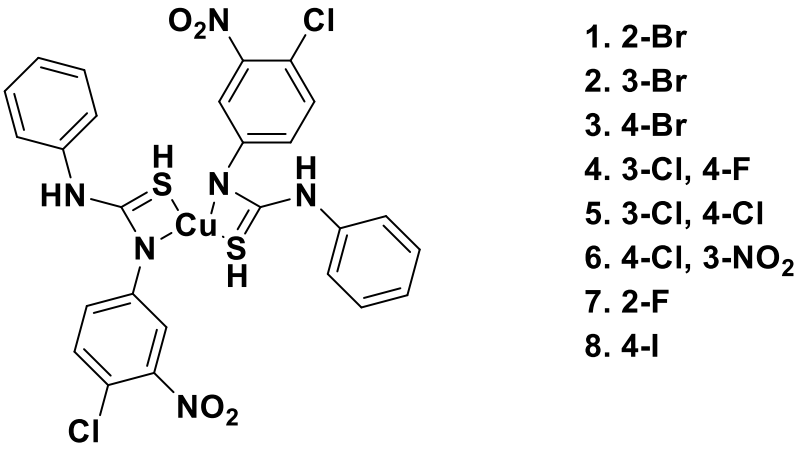


Figure 4: Thiourea complexes of 3-(4-chloro-3-nitrophenyl)

3. FUTURE PERSPECTIVES

Evaluation of Fluoroquinolone Resistance in Gram-Negative Bacteria

Even though there is a large body of research on fluoroquinolone resistance, knowledge on the molecular causes of resistance has stalled. Most of the research reaffirms earlier conclusions on mutational landscapes, susceptibility tests, and the frequency of resistance mechanisms. Nevertheless, little is known about the molecular processes that underlie fluoroquinolone resistance. Future studies should concentrate on clarifying how varying degrees of DNA supercoiling affect a species' vulnerability to fluoroquinolones. Developing future generations of fluoroquinolones that can target certain amounts of supercoiling requires this understanding. [83,84] The present study on quinolones primarily focusses on two aspects: direct targeted action that results in lesions and indirect buildup of poisons and cell death. This was discovered by analysing the link of quinolones with drug resistance and SOS response. The approaches primarily concentrate on three components of drug resistance formation: mutations that target the carrying plasmid, antibiotic efflux, or enzyme sites. Numerous genes are involved in the control of the SOS response, and research has demonstrated a tight relationship between quinolone antibiotics and this mechanism. Even while we are increasingly gaining a better knowledge of quinolone antibiotics, there are still some difficulties that must be considered. For example, quinolone antibiotics' reversible binding to the target does not imply that their sterilisation is only dependent on the buildup of toxins during treatment; other sites of action may be possible. However, the quinolone-related toxin is a result of ROS production. The concerns of whether other significant toxins are involved, how the repair-related proteinuria F controls and eliminates bacteria via the cytotoxic mechanism, and how the body balances toxin expression are still unresolved. Quinolones are also frequently used to treat infectious diseases because of their strong bactericidal action. To lower the danger of drug misuse, measures must be taken when using them. [85]

Antibacterial activity

The microbiological investigations that were conducted yielded information on the antibacterial characteristics of the compounds that were synthesised. Positive Gramme Gram-negative bacteria and Staphylococcus aureus Aeruginosa pseudomonas, two bacterial species that form biofilms and infect people, were tested against the compounds. Ciprofloxacin hydrochloride served as the standard substance. The compounds were first tested at a 50 µ M concentration. Derivatives that showed more than 80% growth inhibition in the screening tests were given values for the MIC, or minimum inhibitory concentration. A listing of the active compounds' determined data is provided. Compounds 2a–c has already been shown to have antibacterial properties [66]. The most potent chemicals against both tested bacteria were found to be 1e and 1g, Having MIC values that fall within the low micromolar range. Compound 1.f had preferential action against the S. aureus strain (MIC of 6.25 µ M), even though hybrid 2d had a slightly greater concentration of activity against both bacteria (MIC of 25 µ M).[78]

Cytotoxicity studies

The bright ATP-based Cell Titer-Glo® cell viability assay was used to investigate In mouse embryonic fibroblasts

(BALB/3T3 clone A31), the cytotoxicity of the strongest compounds 1e–g and 2d was evaluated. at 50 and 200 µ M. Up to 50 µ M, none of the chemicals that were examined were determined to be hazardous. Compounds 1f, g, and ciprofloxacin reduced cell viability by around 30, 20, and 15% at 200 µ M, respectively, However, hybridisation 2d showed less than 2% viable cells and was highly cytotoxic. Nevertheless, The second compound had a computed 50% cytotoxicity concentration (CC 50) of over 160, that is much greater than the 25 µm MIC value, and a there was 6.4 for the selectivity index (SI). The safety of the other active compounds was indicated by SI values greater than 32 in animals. [78]

Bioactivity of Compounds

Table also provides an overview of these findings. One The findings unequivocally demonstrated that nearly every chemical was effective against two Gram-positive and two Gram-negative bacteria. The zone of inhibition was found to be between 20 and 47 mm; at 250 and 500 µg ml, it was 30 and 33 mm respectively, with the exception of Escherichia coli, which shows a pattern of resistance to all drugs. [70]

4. CONCLUSION

Fluoroquinolones (FQs) are still an important family of antibacterial medicines because of their good pharmacokinetic characteristics, which include lengthy half-lives and excellent bioavailability. Recent developments in synthetic chemistry have produced a number of quinolone derivatives that exhibit encouraging anticancer qualities in addition to improved antibacterial performance. The development of resistance presents serious difficulties even while FQs are empirically successful therapies for ailments including acute respiratory infections and urinary tract infections (UTIs). Resistance mechanisms including target gene mutations and enzyme changes highlight how urgently further research on FQ derivatives and other treatments is needed. Novel antimicrobial approaches are crucial given the worldwide burden of illnesses like TB, which has been made worse by the COVID-19 pandemic. Effectively combating antibiotic resistance requires cooperation between the pharmaceutical and academic sectors due to the multidrug-resistant strains of microorganisms. In order to address the urgent medical issues related to resistant infections, more research into the bicyclic core structure of quinolones may produce molecules with enhanced broad-spectrum antibacterial action. All things considered, the creation of novel FQ derivatives and their possible uses in a range of therapeutic domains underscore the necessity of more study and creativity in this crucial area. Collaborative research activities aimed at creating novel compounds with enhanced broad-spectrum antibacterial action are desperately needed to counter the issue of resistance. Quinolones' bicyclic core structure offers a flexible framework for medicinal chemistry, enabling the creation of analogues that might improve therapeutic results and circumvent existing resistance mechanisms. All things considered, even while FQs are still very important in the treatment of bacterial illnesses, further study into their derivatives and creative therapeutic approaches is necessary to guarantee their sustained effectiveness.

Studydesign: Literature Search Strategy

A thorough literature search was conducted using major scientific databases including PubMed, Scopus, Web of Science, and Google Scholar. Keywords and Boolean operators used in the search included:*"quinolone analogues," "quinolone synthesis," "structural modification," "antimicrobial activity," "anti-infective agents," "SAR of quinolones," "quinolone resistance"*.
The search was limited to peer-reviewed articles published in English language.

Data were compiled into comparative tables and discussed thematically to identify trends, gaps, and promising directions for future research.

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ABBREVIATIONS

FQs – Fluoroquinolones

SAR – Structure-Activity Relationship

UTIs – Urinary Tract Infections

TB – Tuberculosis

MDR – Multi-Drug Resistant

XDR – Extensively Drug-Resistant

MRSA – Methicillin-Resistant *Staphylococcus aureus*

MRSE – Methicillin-Resistant *Staphylococcus epidermidis*

EMB – Ethambutol

RMP – Rifampicin

INH – Isoniazid

PZA – Pyrazinamide

MIC – Minimum Inhibitory Concentration

CC50 – 50% Cytotoxic Concentration

SI – Selectivity Index

n-FZSA – Nano Fe_3O_4 ZrO_2-SO_3H

ATP – Adenosine Triphosphate

HRMS – High-Resolution Mass Spectrometry

NMR – Nuclear Magnetic Resonance

FTIR – Fourier Transform Infrared Spectroscopy

DMF – Dimethylformamide

THF – Tetrahydrofuran

DCM – Dichloromethane

NSAID – Non-Steroidal Anti-Inflammatory Drug

ROS – Reactive Oxygen Species

ARIs – Acute Respiratory Infections

ESKAPE – Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows:

Study conception and design: Sachin, A. Rajendiran ; **Data collection:** Sachin, Surendra Kumar, Aniket Yadav, Avdhesh Pal, Jayati Dwivedi, Himanshi Bhaduria; **Analysis and interpretation of results:** Sachin, Surendra Kumar, Aniket Yadav; **Draft manuscript:** Jayati Dwivedi. All authors reviewed the results and approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors affirm they have no known financial or personal conflicts and interests.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this paper.

ETHICS APPROVAL

Not applicable.

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