Review

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Review

Advances in the Synthesis and Biological Applications of Enoxacin Based Compounds

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Abstract: A comprehensive review of advances in the synthesis and biological applications of enoxacin (ENX) based compounds is presented. ENX, a second-generation fluoroquinolone (FQ) is a prominent 1,8-naphthyridine containing compounds studied in medicinal chemistry. Quinolones, a class of synthetic antibiotics, are crucial building blocks for designing multi-biological libraries due to their inhibitory properties against DNA replication. Chemical modifications at positions 3 and 7 of the quinolone structure can transform antibacterial FQs into anticancer analogs. ENX and its derivatives have been examined for various therapeutic applications, including anticancer, antiviral, and potential treatment against COVID-19. Several synthetic methodologies have been devised for the efficient and versatile synthesis of ENX and its derivatives. This review emphasizes all-inclusive developments in the synthesis of ENX derivatives, focusing on modifications at the C3 (carboxylic acid, Part A), C7 (piperazinyl, Part B), and other positions (Part C). The reactions considered were chosen based on their reproducibility, ease of execution, accessibility, and availability of the methodology reported in the literature. The review provides valuable insights into the medicinal properties of these compounds, highlighting their potential as therapeutic agents in various fields.

Keywords: antibacterial; biological activity; anticancer; enoxacin; fluoroquinolone; naphthyridine; synthesis; quinolone

1. Introduction

Quinolones, a class of synthetic antibiotics, are widely recognized as crucial building blocks for designing multi-biological libraries [1,2]. Their inhibitory properties against DNA replication make them effective against various pathogens, including mycoplasma, bacteria, and protozoa [3–5]. These synthetic antibacterial drugs belong to the broader class of fluoroquinolones (FQs) and act by targeting DNA gyrase, topoisomerase enzymes, and topoisomerase IV involved in DNA replication and repair processes in bacteria [6–13].

The discovery of nalidixic acid in 1962 marked the beginning of quinolone derivatives' use as antibacterial agents worldwide [13,14]. The subsequent development of FQs in the 1970s and the 1980s significantly expanded their coverage [15,16]. FQs exhibit diverse biological activities, including anti-infectious diseases like malaria, parasitic, bacterial, and fungal [3,17–19] as well as viral infections like hepatitis, human immunodeficiency virus (HIV), and herpes [20]. They are highly effective against Gram-negative Pseudomonas infections and have been employed in treating pneumonia and intra-abdominal infections [21]. Additionally, they show promise in treating autoimmune diseases, organ transplantation, and rheumatoid arthritis with low toxicity [2,22–24]. FQs can impede tumor growth by inducing damage to type II human DNA topoisomerases, similar to specific chemotherapy drugs like etoposide [25,26] , making them noteworthy agents in infectious disease management and potential adjuncts in certain cancer treatment strategies.

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The critical structural attributes of quinolones have been identified, with 4-oxo-quinolone-3-carboxylic acid being a significant substructure in numerous quinolone derivatives with outstanding biological activities [27,28]. Chemical modifications at position 7 transform antibacterial FQs into anticancer analogs, while the carboxylic group at position 3 plays a vital role in enzyme binding and functional group transformation, enhancing anticancer potential [27,29,30]. FQs like levofloxacin and moxifloxacin are designated by the WHO as second-line drugs for treating tuberculosis due to their broad and potent spectrum of activities as well as oral administration [31–33]. The versatility of quinolones and FQs makes them valuable tools in medicinal research and therapeutic applications across different disciplines.

FQs with a 1,8-naphthyridine core are a specific subset of the fluoroquinolone class, where the quinolone nucleus is replaced by a naphthyridine structure. In the case of FQs with a 1,8-naphthyridine core, the compounds primarily differ at two key positions: N1 and C7, with modifications often occurring at C3 and C7. Figure 1 depicts the 1,8-naphthyridine core, clearly labeling N1 through N8 to emphasize these distinctions within the structure. To illustrate, enoxacin (ENX) is known for having a piperazinyl group at C7 and an ethyl group at N1. In contrast, gemifloxacin, while also featuring the 1,8-naphthyridine core, has an aminopyrrolidinyl group at C7 and a cyclopropyl group at N1. Other FQs with this core typically have a different group at C7 as well as N1 positions as illustrated in Figure 2.

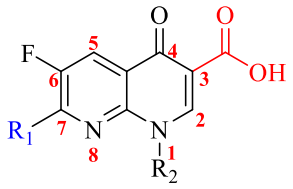

Figure 1. Labeled structural representation of FQs containing 1,8-naphthyridine core. There are two important distinct positions, C7 and N1 (R_1 and R_2) with diverse substituents.

In 1980, ENX, a 1,8-naphthyridine derivative of nalidixic acid was discovered [34]. Although six distinct isomeric forms of naphthyridine exist, 1,8-naphthyridine derivatives have been extensively researched [35–37]. This unique skeleton has led to various bioactive compounds derived from natural sources, demonstrating significant biological applications [38–40]. ENX, a fluorinated antibacterial drug, and voreloxin, a non-fluorinated potential anticancer agent, are prominent 1,8-naphthyridines studied in medicinal chemistry [26,41]. Other important 1,8-naphthyridine containing molecules with demonstrated biological activity include nalidixic acid, trovafloxacin, tosufloxacin, voreloxin, and gemifloxacin (Figure 2).

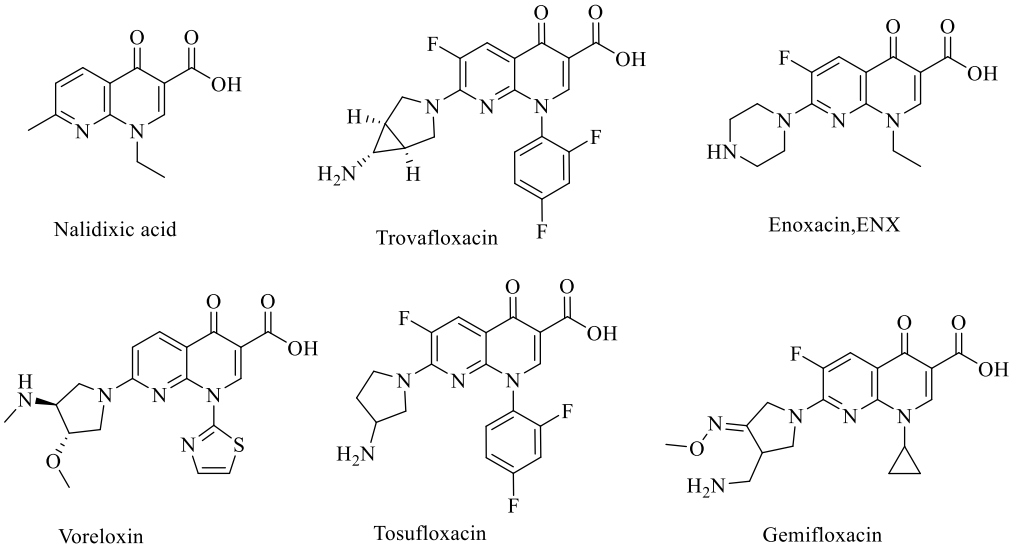

Figure 2. Fluorinated & non-fluorinated 1,8-naphthyridine containing molecules.

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ENX, a second-generation fluoroquinolone, is known for its wide-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria. [42–44]. Structurally, ENX comprises of two fused six-membered rings with 1,8-naphthyridine core as the parental structure (Figure 3) [45,46]. This drug is often well tolerated and has a low frequency of side effects. It is typically delivered orally in the form of tablets. However, due to the development of resistance by many strains of bacteria, including *Escherichia coli (E. coli)* and *Pseudomonas aeruginosa (P. aeruginosa)*, it is no longer considered a first-line treatment for bacterial infections [47]. Over the past few decades, scientists have examined the potential usage of ENX and its derivatives for several therapeutic applications [48–50]. *In vitro* tests have revealed that ENX exerts significant cytotoxicity in human cancer cells [48,51]. Moreover, it has also been reported to enhance the anticancer effects of other chemotherapeutic medications, including paclitaxel [51–53]. In addition, ENX possesses antiviral properties, making it effective against many different infections including HIV and hepatitis C virus (HCV) [48,52].

A recent study on repositioning FQs demonstrated the potential of repurposing ENX for its use as a potential treatment against COVID-19 (SARS-CoV-2) [54–56]. Although there are many motives for reviewing the chemical synthesis of ENX and its derivatives, some of the critical reasons are selectivity [57], repositionability [51], oral bioavailability [58], better safety profile, prooxidative activity, and regulation of microRNA biogenesis [59]. ENX 's unique microRNA-interfering activity sets it apart from other FQs and topoisomerase II drugs [45].

Several synthetic methodologies have been devised and implemented and are known for their efficiency, versatility, and convenience [1,60,61]. However, no exhaustive review has exclusively presented the synthesis of ENX and its derivatives based on current literature and understanding [62]. In this review, we highlight key developments in the synthesis of 4-quinolone-3-carboxylic acid derivatives with a 1,8-naphthyridine core, specifically focusing on ENX, and discuss its medicinal properties where relevant. Recent publications have discussed the expanded therapeutic potential of diverse heterocyclic molecules beyond their conventional applications [63–66].

The present analysis is structured into three distinct segments: part A focuses on the modification of the carboxylic acid at the C3 position, part B addresses the modification of the piperazinyl group at the C7 position, and part C explores combined modifications involving both parts A and B. The reactions considered in this review were chosen based on their capacity for reproducibility, relative ease of execution, accessibility, and availability of the methodology, as reported in the literature. Below is the structural representation of ENX with labeled atom positions comprising the C3-carboxylic part, C7-piperazinyl part and the fluoroquinolone core (Figure 1).

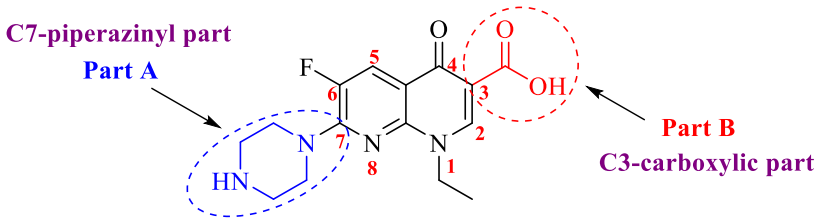

Figure 3. Main sites for structural modification of ENX. .

2. Modifications of ENX Based Compounds

2.1. C3 Modification of ENX (Part A)

In 2009, You and colleagues [67] designed and synthesized a novel series of quinolone and naphthyridine derivatives as potential topoisomerase I inhibitors by modifying the scaffold in three steps. The first step involved condensation of ENX with **2** in polyphosphoric acid (PPA) at 170-250 °C to obtain **3a-c** or **4** (Table 1). In the subsequent step, intermediate **3a-c** was nitrated in a mixture of concentrated sulfuric acid (H_2SO_4) and nitric acid (HNO_3) in an approximately equal ratio at 5 °C, followed by heating at 40-45 °C for 1-2 h, yielding **5a-c**. In the final step, the nitro-containing compound **5c** was subjected to hydrogenation over Pd/C in 1N hydrochloric acid (HCl) solution to produce **6** (Scheme 1). All derivatives containing three kinds of heterocycles, benzoxazole,

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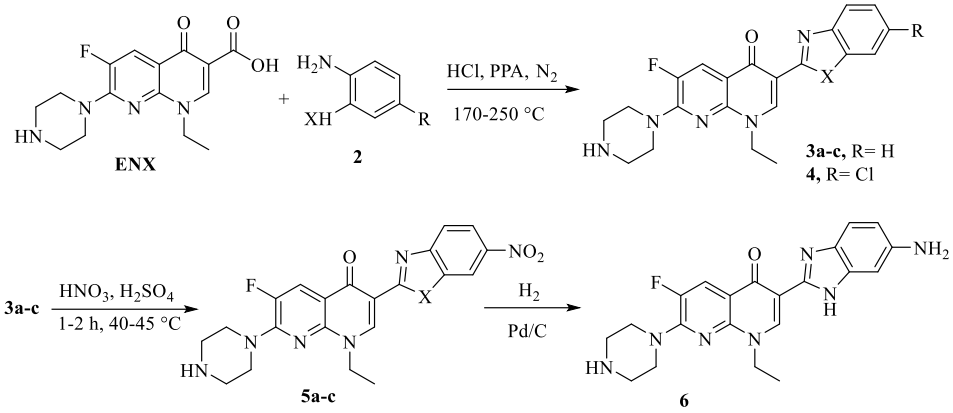
benzimidazole, and benzothiazole, at the C3 position were screened *in vitro* for their antiproliferative effects against oral epidermal carcinoma (KB), ovarian carcinoma (A270), and hepatocellular carcinoma cells (Bel-7402) using a 1-*N*-methyl-5-thiotetrazole (MTT)-based assay (Table 1). In summary, the 3-benzothiazolenaphthyridine skeleton **3c** showed the highest antiproliferative activity (IC_{50}= 2.4-2.7 μM) against three tumor cell lines. Conversely, nitro-containing 3-benzoxazolenaphthyridine scaffold **5b** displayed even better cytotoxic activity (IC_{50}=31.8-3.0 μM). Surprisingly, reducing the nitro group in **5a** to **6** resulted in significantly diminished cytotoxicity. This reinforces the hypothesis that an electron-withdrawing group is essential for cytotoxic activity.



Scheme 1. Synthesis of 1,8-naphthyridin-3-yl-1*H*-benzo derivatives **3a-c, 4, 5a-c,** and **6**.

Table 1. *In vitro* antiproliferative activity of compounds **3a-c, 4, 5a-c,** and **6.**

Compound	R	X	Antiproliferative activity (IC_{50}, μM)		
			KB	A2780	Bel7402
3a	H	NH	2.0	4.8	4.1
3b	H	O	11.7	15.3	16.8
3c	H	S	2.4	2.7	2.4
4	Cl	NH	10.3	6.3	21.5
5a	NO_2	NH	22.4	12.4	10.8
5b	NO_2	O	1.8	ND	3.0
5c	NO_2	S	179.3	200.2	24.6
6	-	-	30.1	42.3	93.3

ND: not determined.

Few years later, Yang and coworkers [68] synthesized 1,8-naphthyridin-3-yl-1*H*-benzo-6-carbonitrile derivatives of ENX by replacing the carboxyl group at C3 with a 2,3-dihydro-1*H*-benzimidazole-5-carbonitrile system in a single step employing same procedure as described in Scheme 1 [67]. The target compound was realized by condensing ENX with **7** at 170-250 °C in PPA to yield product **8**. Their studies were primarily centered around investigating the potential molecular mechanism by which it exhibits its antitumor activity against non-small cell lung cancer (NSCLC). The results revealed that compound **8** exhibited significantly stronger inhibitory effects against NSCLC compared to its leading compound ENX, both in cultured cells and in a xenograft mice model. It also increases Reactive Oxygen Species (ROS) generation and DNA Damage Response (DDR) dose-dependently. The ROS scavenger *N*-acetyl-cysteine (NAC) reduced DDR and apoptosis triggered by **8**, confirming its antitumor actions are due to oxidative stress. Thus, **8** promotes oxidative stress and cell death by activating the mitochondrial and endoplasmic reticulum (ER) stress pathways [68].

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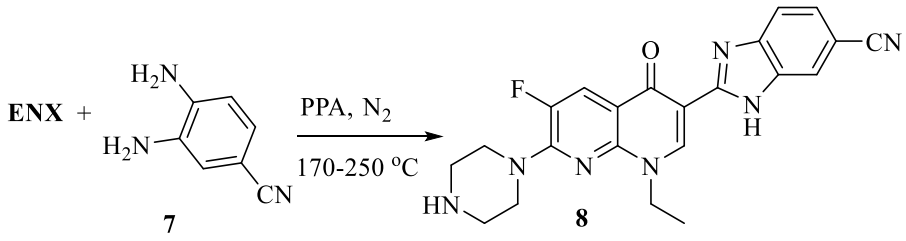
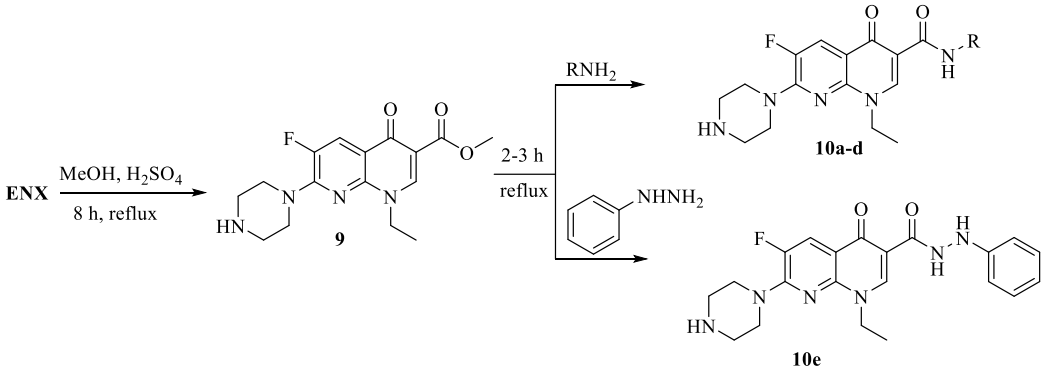


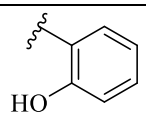
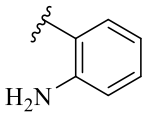
Scheme 2. Synthesis of 1,8-naphthyridin-3-yl-1H-benzo[d]imidazole-6-carbonitrile **8**.

In a study conducted by Arayne *et al.* [69], the synthesis of various ENX carboxamide and carbohydrazide derivatives as antibacterial agents was reported. This synthesis involved the amidation of 3-carboxylic acid group of ENX using aromatic amines and phenyl hydrazine. Initially, ENX ester, **9** was prepared via Fischer esterification, in methanol with a catalytic amount of H_2SO_4 at reflux for 7-8 h. The resulting ester was further reacted with different aromatic amines under reflux for 2-3 h to yield the desired carboxamides **10a-d** and carbohydrazide **10e** with moderate to good yields (Scheme 3). Compounds **10a-e** were tested against various bacteria, revealing remarkably improved antimicrobial effectiveness against Gram-negative strains. Furthermore, their potential to influence the immune response was assessed in a separate study [70]. To evaluate their immunomodulatory activity, the impact on the oxidative burst activity of phagocytes in whole blood, as well as macrophages and neutrophils, was investigated. Among the synthesized derivatives, compounds **10c** and **10d** exhibited the highest level of inhibition in whole blood (IC_{50}= 2.6 and 1.4 µg/mL), macrophages (IC_{50}= 3.2 and 1.4 µg/mL), and isolated neutrophils (IC_{50}= 0.8 and 1.4 µg/mL), respectively (Table 2).



Scheme 3. Synthesis of aryl substituted ENX carboxamides **10a-d** and carbohydrazide **10e.**

Table 2. Immunomodulatory effect of ENX carboxamides **10a-d** and carbohydrazide **10e** (Comparable effects of **10a-d** and **10e** on the oxidative burst activity of whole blood phagocytes, neutrophils and macrophages).

		Oxidative burst effects (IC_{50}, µg/mL)			
Compound	**R**	**Oxidative burst of whole blood using**	**Oxidative burst of PMNs using**		**Oxidative burst of Macrophages using**
		Luminol	**Luminol**	**Lucigenin**	**Luminol**
10a		8.5	7.6	17.5	8.7
10b		2.6	0.8	1.0	3.2

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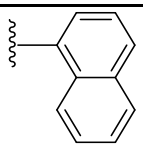
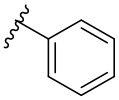
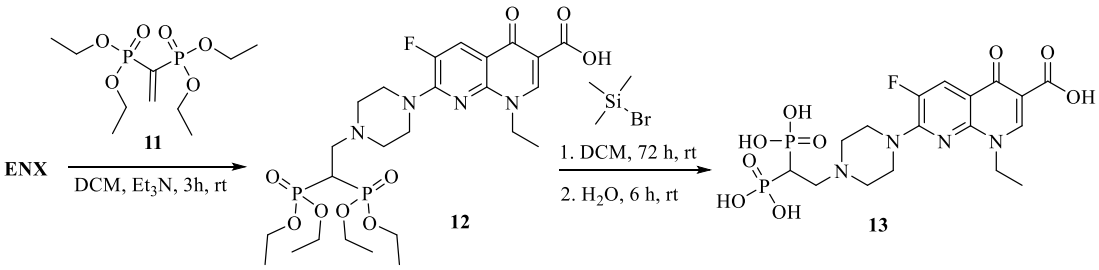
10c		13.3	9.1	22.3	9.5
10d		>25	>25	>25	>25
10e	-	1.4	1.4	2.6	1.4
ENX	-	>25	>25	>25	>25

PMNs: Polymorphoneutrophils.

2.2. C7 Modification of ENX (Part B)

According to the literature, C7 piperazinyl quinolone modifications are effective not only against Gram-positive and Gram-negative pathogens [71] but also have numerous biological applications against cancer [72,73], inflammation [74], osteoclasts [75], viral infections [76], and other diseases [77,78]. As prospective osteo-adsorptive drugs, Herczegh and coworkers [79] developed a series of bisphosphonate FQ derivatives. The piperazinyl group of ENX was transformed with tetraethyl ethene-1,1-diylbis(phosphonate) **11.** In the first step, ENX was combined with **11** in the presence of triethylamine (Et_3N) in dichloromethane (DCM), under stirring at room temperature (rt), for 3 h. Afterwards, an aqueous work-up and recrystallization from toluene produced the bis-(diethoxy-phosphoryl)-ethyl ester **12**. The ester was then hydrolyzed with bromotrimethylsilane $(CH_3)_3SiBr$ in DCM at rt for 72 h, yielding **13** as hydrobromide salt. Treatment of the salt with water (H_2O) at rt for 6 h, followed by agitation in DCM and subsequent ether washing resulted in an average yield of the desired compound, bis-phosphonic-ENX derivative **13** (Scheme 4).

In another study, Vracar and colleagues [80] discovered that ENX and bis-phosphonic -ENX, **13** have been found to induce the release of extracellular vesicles from 4T1 murine breast cancer cells, which possess inhibitory effects on osteoclastogenesis. Surprisingly, adding a bisphosphonate moiety boosted bone binding affinity. Moreover, bis-phosphonic-ENX, similar to ENX, displayed inhibitory effects on the binding of V-ATPase to microfilaments, as well as on bone resorption *in vitro*. In summary, bis-phosphonic-ENX, offers multiple benefits beyond preventing bone mineral loss. It does not only modify the composition of bone glycoproteins, making them more resistant to fractures but also completely suppresses osteoclast differentiation. Both ENX and bis-phosphonic-ENX demonstrate similar potency, with IC_{50} values around 10 μM, indicating their strong inhibitory effects on osteoclasts.



Scheme 4. Synthesis of bis-phosphonic-ENX **13**.

Darekhordi and colleagues [81] established a one-pot approach for the synthesis of antibacterial *N*-aryl-2,2,2-trifluoroacetimidoyl piperazinylquinolone **15** under moderate conditions. *N*-aryl trifluoroacetimidoyl chloride **14** was nucleophilically substituted by ENX using potassium carbonate (K_2CO_3) in dimethylformamide (DMF) at reflux for 24 h to give **15** in moderate to good yields (Scheme 5). In addition, the synthesized conjugate was tested *via* the agar diffusion method and exhibited a concentration-dependent improved antibacterial activity against *E. coli*, *Klebsiella pneumoniae (K. pneumoniae)* and *Staphylococcus aureus (S. aureus)*.

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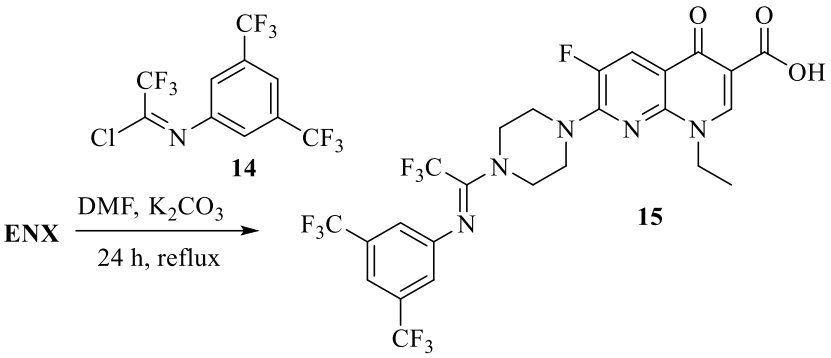
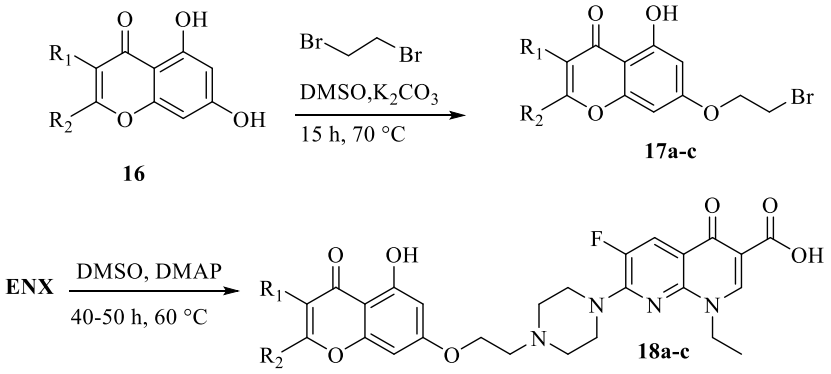


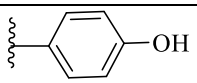
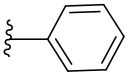
Scheme 5. Synthesis of *N*-aryl-2,2,2-trifluoroacetimidoyl piperazinylquinolone **15**.

In their study, Xiao *et al.* [82] described the synthesis of FQ-flavonoid hybrids using a well-designed pharmacophore system, aiming to develop a multi-target bacterial topoisomerase inhibitor with potential as efflux pump inhibitors. The synthesis involved the reaction of FQs with different flavonoids, such as apigenin and naringenin, while including an ethylene linker in the process (Scheme 6). In the initial step, the flavonoids **16** was *o*-selectively alkylated with 1,2-dibromoethane in the presence of K_2CO_3 in DMSO at 70 °C for 15 h yielding compound **17a-c**. Treating the intermediates **17a-c** with ENX in DMSO using DMAP as base at 60 °C for 40-50 h produced new antibacterial hybrids **18a-c** in moderate yields (55–75%). The antibacterial efficacy of FQ-flavonoid hybrids was tested against different microorganisms including Tetracycline-resistant *Bacillus subtilis* ATCC 6633 *(B. subtilis)*, amphotericin B-resistant *Candida albicans (C. albicans)*, multiple drug-resistant *E. coli* ATCC 35218, and methicillin-resistant *S. aureus* ATCC 25923. Some of these compounds displayed impressive antibacterial properties, particularly against drug-resistant strains. Remarkably, derivative **18a** exhibited outstanding activity against *B. subtilis and C. albicans* with minimum inhibitory concentration (MIC) of 0.45 μg/mL and 2.60 μg/mL in comparison to the standard drug ciprofloxacin (CPX), with MIC values of 2.70 μg/mL and 32.4 μg/mL for the respective microorganisms (Table 3).



Scheme 6. Synthesis of ENX flavonoids-based analogs **18a-c**.

Table 3. *In vitro* antibacterial activity of **18a-c** against selected microbes.

			Antibacterial activity (MIC, μg/mL)			
Compound	**R1**	**R2**	***E. Coli***	***B. subtilis***	***S. aureus***	***C. albicans***
18a	H	H	46.3	0.45	21.5	2.60
18b	H		>50	16.1	33.6	17.5
18c		H	>50	>50	>50	>50
CPX	-	-	5.65	2.70	6.82	32.4

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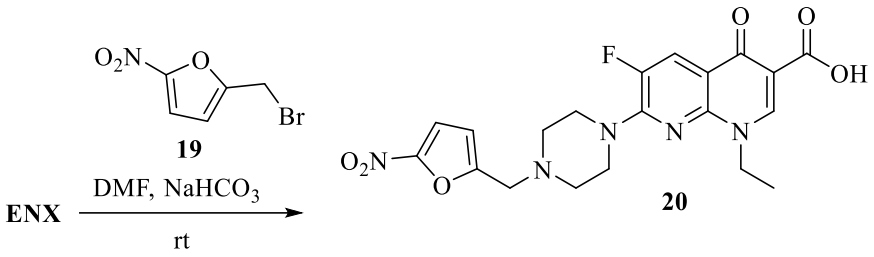
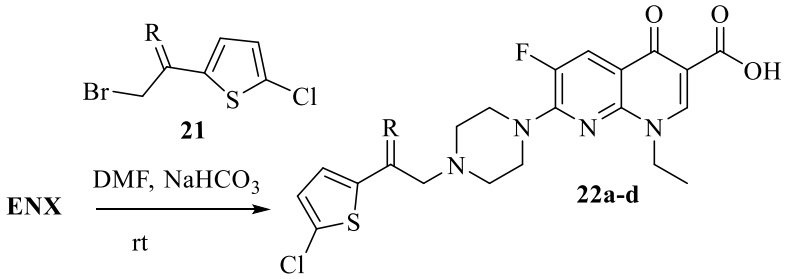
A methylene-bridged nitrofuran *N*-substituted piperazinylquinolone was designed and synthesized by Emami and colleagues [83]. ENX mixed with 2-(bromomethyl)-5-nitrofuran **19** in DMF in the presence of sodium hydrogen carbonate ($NaHCO_3$) as a base at rt for 120 h resulting in the formation of the desired compound **20** (Scheme 7), in good yield (81%). The antibacterial assessment demonstrated that the efficacy of 7-piperazinylquinolones with (5-nitrofuran-2-yl) derivative against diverse bacterial strains is contingent upon the nature of the substituents located at the N1 and C7 sites. Overall, the compound displayed noteworthy antibacterial efficacy against *Staphylococci* in a manner that was dependent on their concentration. **20** showed the best inhibitory activity against *S. aureus* with MIC of 0.39 μg/mL.



Scheme 7. Methylene-bridged nitrofuran *N*-substituted quinolone synthesis **20**.

In another report [84], four novel ENX derivatives were synthesized by introducing 2-(5-chlorothiophen-2-yl)ethyl into the piperazine ring. The synthesis was performed by reacting ENX with either *α*-bromoketone or *α*-bromooxime **21** in DMF at rt, in the presence of $NaHCO_3$ yielding **22a-d** in 62-73% yields (Scheme 8). The introduction of 2-(5-chlorothiophen-2-yl)ethyl into the piperazine ring of ENX resulted in an enhanced cytotoxicity against various cancer cell lines compared to the unmodified ENX [85]. **22** exhibit varying modifications to the ethyl spacer structures. Regarding their cytotoxicity against cancer cell lines, including melanoma (SKMEL-3), breast (MCF-7), epidermoid (A431), bladder (EJ), colon (SW480) and KB cell line. Compounds **22b** and **22c** demonstrated the most significant impact. Specifically, **22b** displayed an IC_{50} range of 3 to 10 μM, while **22c** showed an IC_{50} range of 3 to 20 μM (Table 4). On the other hand, **22d** exhibited IC_{50} values of 2 to 14 μM for melanoma, epidermoid, cervical, and bladder cell lines, respectively. In summary, incorporating the 2-(5-chlorothio-phen-2-yl)ethyl group into the piperazinyl portion of ENX enhanced its cytotoxic properties compared to the parent ENX. Though the extent of improvement depended on the structure of the spacer. By introducing an additional functionality, the antitumor effectiveness rose considerably (Table 4).



Scheme 8. Synthesis of chlorothiophene ENX derivatives **22a-d**.

Table 4. *In vitro* cytotoxic evaluation of compounds **22a-d** against a panel of cell lines.

Compound	R	Anticancer activity (IC_{50}, μM)					
		SKMEL-3	MCF-7	A431	EJ	SW480	KB
22a	O	106	106	131	66	100	117
22b	NOH	10.3	3.6	5.6	5.0	3.2	4.8
22c	NOMe	13	19	2.9	5.9	6.7	4.7

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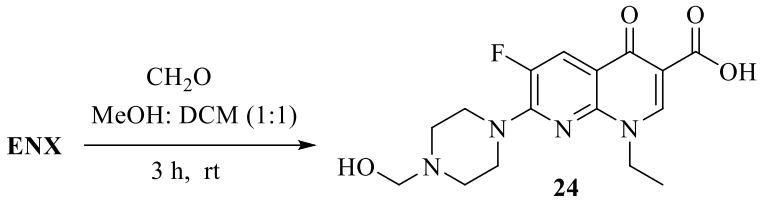
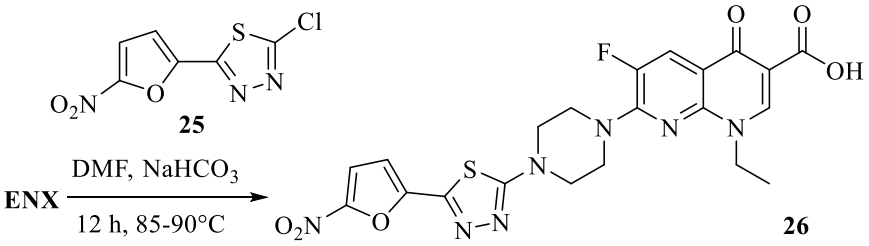
22d	NOBn	13.6	125	2.2	8.0	42	12
ENX	-	196	193	175	178	159	137

Chadha and Agarwal [86] conducted synthesis and preformulation studies on a prodrug of ENX , resulting in the synthesis of *N*-hydroxymethylenoxacin **25**. The synthesis involved condensing ENX with formaldehyde (CH_2O) as solution in a mixture of methanol and dichloromethane (1:1) at rt for 3h. The resulting compound was obtained in 89% yield (Scheme 9). The antimicrobial effectiveness of the prodrug was evaluated in comparison to ENX using the agar diffusion method, specifically targeting *E. coli, P. aureginosa* and *S. aureus*. The most noteworthy outcome was observed against *E. coli*, where the MIC was determined to be 0.2 µg/mL.



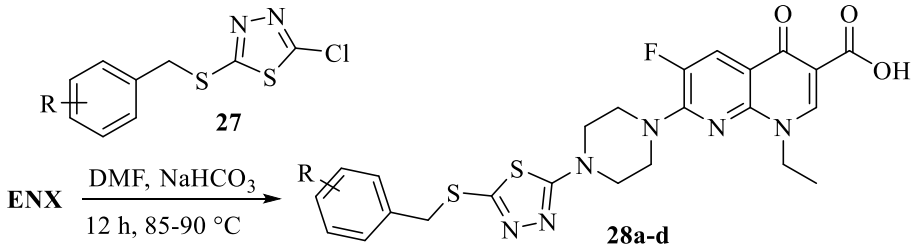
Scheme 9. Synthesis of *N*-hydroxymethylenoxacin **24.**

N-substituted piperazinyl quinolone **26** was synthesized and examined for *in vitro* antibacterial activity against various strains of bacteria [87,88]. Through the reaction of ENX with **25** and $NaHCO_3$ in DMF at 85-90 °C for 12 h, **26** was obtained in satisfactory yield (Scheme 10). The antibacterial evaluation demonstrated that **26** exhibited potent and superior activity against the tested Gram-positive bacteria compared to reference FQs like ENX. Compound **26** exhibited the highest activity against *B. subtilis*, with a MIC value of 0.008 µg/mL, surpassing the ENX value of 0.125 µg/mL.



Scheme 10. Synthesis of *N*-substituted piperazinyl quinolone **26.**

Foroumadi *et al.* [89] reported a series of *N*-substituted piperazinyl quinolones via nucleophilic substitution reaction using thiadiazole derivatives **27** with ENX and $NaHCO_3$ in DMF at 85-90 °C for 12 h (Scheme 11). This method successfully synthesized bioactive derivatives of *N*-[5-(chlorobenzylthio)-1,3,4-thiadiazol-2-yl] piperazinyl quinolones **28a-d** in moderate yields (62-67%). To evaluate the efficacy of the synthesized compounds, the agar dilution method was employed against a panel of bacteria including *S. aureus, Staphylococcus epidermidis (S. epidermidis), B. subtilis, E. coli, K. pneumoniae,* and *P. aeruginosa.* The results indicate that the obtained derivatives exhibited moderate antibacterial activity against the tested microorganisms (Table 5).



Scheme 11. Synthesis of *N*-[5-(chlorobenzylthio)-1,3,4-thiadiazol-2-yl] quinolones **28a-d**.

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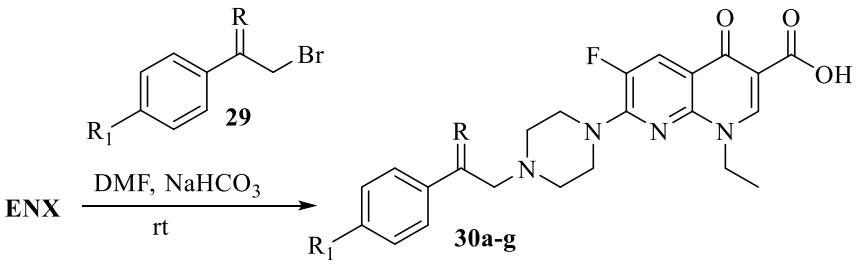
Table 5. *In vitro* antibacterial activity of **28a-d** against different bacterial strain.

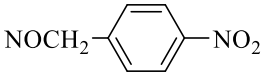
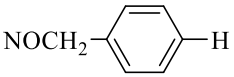
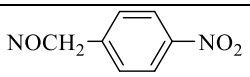
Compound	R	Antibacterial activity (MIC, µg/mL)					
		S. aureus	*S. epidermidis*	*B. subtilis*	*E. coli*	K. *pneumoniae*	*P. aeruginosa*
28a	2-Cl	1	2	4	>4	>4	>4
28b	3-Cl	>4	>4	>4	>4	>4	>4
28c	4-Cl	>4	>4	>4	>4	>4	>4
28d	2,4-diCl	4	4	>4	>4	>4	>4
ENX	-	1	0.5	0.125	0.25	0.25	4

In a similar study, a variety of *N*-substituted piperazinyl quinolones **30a-g** were synthesized and tested for antibacterial activity *in vitro* combining the ENX with α-bromo ketones or oximes **29** as precursors [90]. Zahoor and their colleagues recently reported the synthesis of these compounds [62]. The target derivatives were obtained through the condensation of ENX with properly substituted precursors **29** in the presence of $NaHCO_3$ in DMF as an appropriate solvent in good yields (76-79%) (Scheme 12). The *in vitro* antibacterial activity of **30a-g** against various bacterial strains revealed that compounds **30a-c**, and **30g** demonstrate antibacterial activity similar to ENX against certain bacterial strains, particularly Gram-positive bacteria like Staphylococci and Gram-negative bacteria like *E. coli* and *Enterobacter cloacae (E. cloacae)*. However, none of the derivatives consistently outperformed ENX across all the tested strains (Table 6).



Scheme 12. Synthesis of ENX substituted ketone or oxime derivatives **30a-g.**

Table 6. *In vitro* antibacterial activity of **30a-g** against various bacterial strains.

Compound	R	R1	Antibacterial activity (MIC, µg/mL)					
			S. aureus	*S. epidermis*	*E. coli*	*K. pneumoniae*	*E. cloacae*	*P. aeruginosa*
30a	-	H	2	2	0-25	0-5	0-5	4
30b	-	F	4	2	0-5	2	1	8
30c	OH	H	0-5	0-5	16	0-5	16	>64
30d	OH	F	1	0-5	16	0-25	16	>64
30e		H	16	16	4	16	16	>64
30f		F	64	64	16	64	16	>64
30g		F	0-5	0-5	8	0-5	8	>64
ENX	-	-	1	0.5	0.13	0.5	0.13	4

Foroumadi et al. [91] synthesized novel ENX analogs from diverse α- chloro methyl oxime precursors **31**. By reacting **31** with ENX using $NaHCO_3$ in DMF at rt, they successfully generated ENX analogs **32a-d** in 45-72% yields (Scheme 13). The synthesized derivatives were evaluated against a

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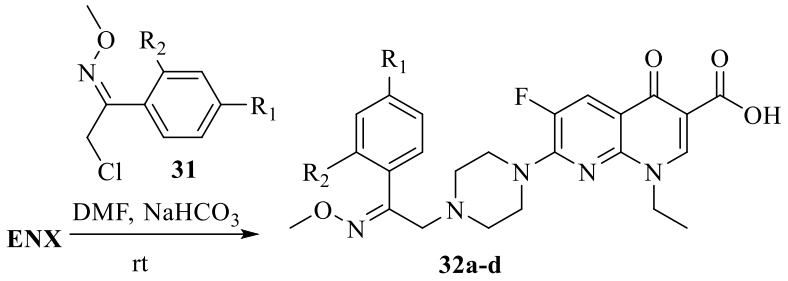
variety of bacterial strains. All the tested derivatives show appreciable antibacterial activity against *B. subtilis* with inhibitory concentration ranging from 1.56 to 6.25 µg/mL. Although **32b** has consistently shown moderate activity across the tested strains, none of the compounds **32a-d** demonstrated potent antibacterial effects that were comparable to the reference drug ENX (Table 7).

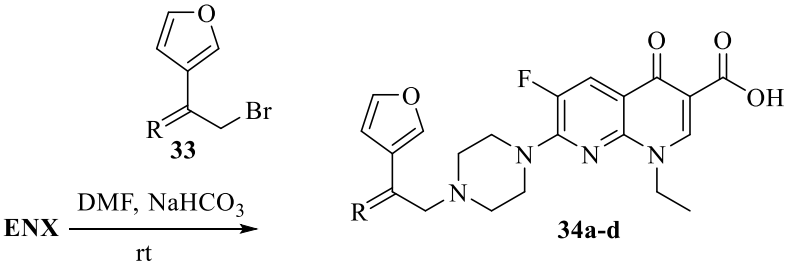


Scheme 13. Synthesis of ENX derivatives **32a-d** from α- chloro methyl oxime precursors.

Table 7. *In vitro* antibacterial activity of **32a-d** against various bacterial strains.

Compound	R1	R2	Antibacterial activity (MIC, µg/mL)					
			S. aureus	*S. epidermis*	*B. Subtilis*	*E. coli*	*K. pneumoniae*	*P. aeruginosa*
32a	H	H	25	25	6.25	12.5	12.5	>100
32b	F	H	12.5	6.25	6.25	6.25	1.56	100
32c	H	F	25	25	1.56	50	25	>100
32d	Cl	Cl	25	25	3.13	12.5	6.25	50
ENX	-	-	15.6	0.78	0.098	0.098	0.098	6.25

The same group [92] synthesized novel antibacterial ENX derivatives via nucleophilic substitution of furan-based α-bromoketone or oximes **33**. *N*-[2-(furan-3-yl)-2-oxoethyl] or *N*-[2-(furan-3-yl)-2-oxyiminoethyl] **34a-d** were produced by treating ENX with α-bromoketone or α-bromooxime **33** in the presence of $NaHCO_3$ at rt in moderate yields (41-59%) (Scheme 14). Evaluation of **34** against various bacterial strains revealed that **34a-c** exhibit comparable antibacterial activity to ciprofloxacin (CPX) against *S. aureus*, methicillin-resistant *S. aureus* (MRSA I and II), *S. epidermidis*, and *B. subtilis*. Specifically, compound **34a** has an MIC range of 0.39 to 0.78 µg/mL against these strains, which is similar to the MIC range of 0.19 to 0.39 µg/mL observed for CPX. Compound **34b** demonstrates a potency of 0.39 µM against *S. aureus*, MRSA, and *S. epidermidis*, closely matching the efficacy of CPX. Likewise, compound **34c** shows an MIC of 0.78 µg/mL against the same strains, again aligning with the antibacterial potency of CPX (Table 8).



Scheme 14. Synthesis of ENX derivatives **34a-d** from α-bromo ketone or oximes.

Table 8. *In vitro* antibacterial activity results of compounds **34a-d**.

Compound	R	Antibacterial activity (MIC, µg/mL)							
		S. aureus	MRSA I	MRSA II	*S. epidermis*	*B. Subtilis*	*E. coli*	*K. pneumoniae*	*P. aeruginosa*
34a	O	0.78	0.78	0.78	0.78	0.39	0.39	0.19	12.5
34b	NOH	0.39	0.39	0.39	0.39	1.56	1.56	0.39	50

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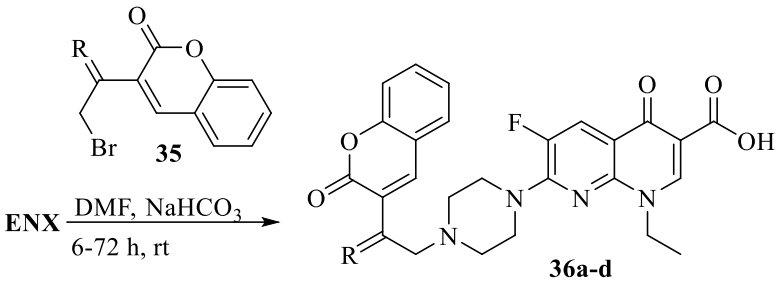
34c	NOMe	0.78	0.78	0.78	0.78	1.56	156	0.78	>100
34d	NOBn	25	12.5	12.5	12.5	3.13	3.13	1.56	>100
NOR	-	0.39	0.78	0.78	0.39	0.025	0.049	0.025	3.13
CPX	-	0.19	0.39	0.39	0.19	0.012	0.012	0.012	0.39

Emami et al. [93] synthesized ENX-coumarin structural hybrids **36a-d** with strong antibacterial activities. The synthesis of the analogs required the reaction of piperazinyl quinolones with a coumarin-based oximes **35** through nucleophilic substitution reaction (Scheme 15). This reaction took place in DMF in the presence of $NaHCO_3$ at rt for 6-72 h, resulting in the desired compounds **36a-d** in good yields (88-91%). The antimicrobial efficacy of the synthesized derivatives was assessed using the agar diffusion method. Compound **36a**, exhibits the most potent antibacterial activity across all tested bacteria, including *S. aureus*, MRSA I, MRSA II, *S. epidermidis, B. subtilis, E. coli,* and *K. pneumoniae*, with MIC values ranging from 0.049 to 3.13 μg/mL. Notably, **36a** shows comparable or superior activity to the reference compound ENX against *S. aureus*, MRSA I, MRSA II, *S. epidermidis, B. subtilis,* and *E. coli.* Compound **36b**, also demonstrates significant antibacterial activity, with MIC values between 0.39 μg/mL and 12.5 μg/mL. However, **36b** is generally less potent compared to ENX. On the other hand, compounds **36c** and **36d** exhibit weaker antibacterial potency compared to both **36a** and **36b**, with MIC values that are generally higher than those of ENX (Table 9).



Scheme 15. Synthesis of enoxacin-coumarin hybrid **36a-d.**

Table 9. *In vitro* antibacterial activity of **36a-d** against various bacterial strains.

Compound	R	Antibacterial activity (MIC, μg/mL)							
		S. aureus	**MRSA I**	**MRSA II**	***S. epidermis***	***B. Subtilis***	***E. coli***	***K. pneumoniae***	***P. aeruginosa***
36a	O	0.78	0.78	0.78	0.39	0.39	0.049	0.049	3.13
36b	NO	3.13	3.13	3.13	1.56	0.78	0.78	0.39	12.5
36c	NOMe	3.13	3.13	3.13	6.25	0.78	6.25	1.56	>100
36d	NOBn	50	>100	>100	100	100	100	12.5	>100
ENX	-	0.39	0.78	0.78	0.098	0.19	0.098	0.049	1.56

Shafiee et al. [94] documented the synthesis and antibacterial activity of *N*-[2-(2-naphthyl)ethyl]piperazinyl quinolones. The desired compounds **38a-d** were successfully synthesized using a versatile and efficient synthetic pathway (Scheme 16). This approach involved reacting ENX with suitable *α*-bromooxime or *α*-bromo ketone derivatives **37** in the presence of $NaHCO_3$ in DMF at rt for 72 h. The resulting products were obtained in good to excellent yields (51-83%). The antibacterial evaluation of these derivatives demonstrated promising activity for certain *N*-[2-(2-naphthyl)ethyl]piperazinyl quinolones. Compound **38a** displays comparable or superior antibacterial activity to ENX across all tested strains, with IC_{50} values ranging from 0.049 to 0.780 μg/mL. Similarly, **38b** shows superior activity compared to ENX, particularly against *B. subtilis* and *E. coli*, with IC_{50} values of 0.190 and 0.390 μg/mL, respectively. In contrast, compounds **38c** and **38d** generally exhibit weaker antibacterial activity compared to **38a** and **38b**, as well as the reference compound ENX (Table 10).

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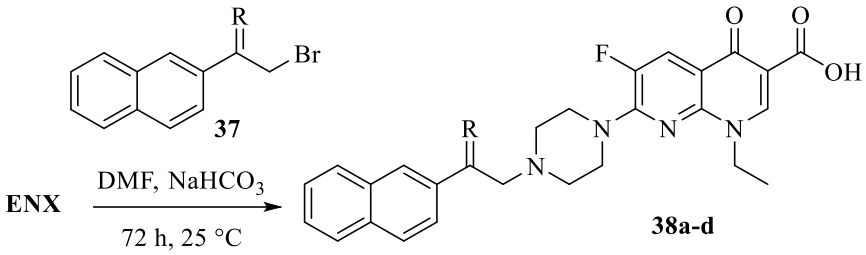
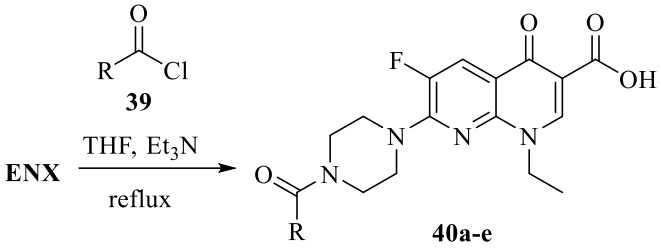


Scheme 16. Synthesis of *N*-[2-(2-naphthyl) ethyl] piperazinyl quinolones **38a-d.**

Table 10. *In vitro* antibacterial activity of **38a-d** against a panel of bacteria.

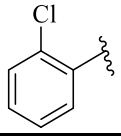
Compound	R	Antibacterial activity (MIC, µg/mL)							
		S. aureus	MRSA I	MRSA II	*S. epidermis*	*B. Subtilis*	*E. coli*	*K. pneumoniae*	*P. aeruginosa*
38a	O	0.780	0.780	0.780	0.780	0.390	0.098	0.049	0.780
38b	NOH	0.780	0.780	0.780	0.780	0.190	3.130	0.390	>100
38c	NOMe	3.130	3.130	3.130	3.130	0.780	1.560	0.780	100
38d	NOBn	>100	>100	>100	100	100	100	25	>100
ENX	-	0.78	0.78	0.78	1.26	0.78	0.098	0.098	1.56

Ahmed and colleagues [95] conducted a groundbreaking study where they skillfully synthesized and screened new alternative molecules of ENX derivatives as potential antibacterial as well as antibiofilm agents (Scheme 17). ENX was acylated with acid chlorides **39** using Et_3N as base in refluxing tetrahydrofuran (THF). The desired products **40a-e** were obtained with a moderate yield (49-64%). Evaluation of the antimicrobial potential of **40** against a panel of pathogens via micro broth dilution method revealed that all the synthesized derivatives were found to be active at low concentrations against MRSA, *K. pneumoniae, and Proteus mirabilis (P. mirabilis)* with MIC in the range of 12.5 to 25 µg/mL compared to the parent molecule, ENX. Specifically, compounds **40b**, **40c**, and **40e** inhibited the growth of MRSA at a 1 µg/mL concentration better than the parent drug ENX. The antibiofilm inhibitory properties of the synthesized derivatives revealed that **40b**, **40c**, and **40e** inhibited MRSA biofilm formation in the range of 0.5 to 1 µg/mL concentration (Table 11).



Scheme 17. Synthesis of acyl substituted ENX derivatives **40a-e.**

Table 11. *In vitro* antimicrobial/antibiofilm activity evaluation of **40a-e.**

Compound	R	Antimicrobial/antibiofilm activity (µg/mL)								
		K. pneumoniae			*Proteus mirabilis*			MRSA		
		MIC	MBC	MBIC	MIC	MBC	MBIC	MIC	MBC	MBIC
40a		25	25	6.25	12.5	50.0	25.0	6.4	12.1	4.0
40b	Cl 	8.0	16.0	8.0	32.5	65.0	16.0	1.0	2.0	0.5

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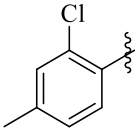
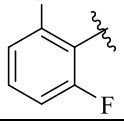
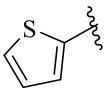
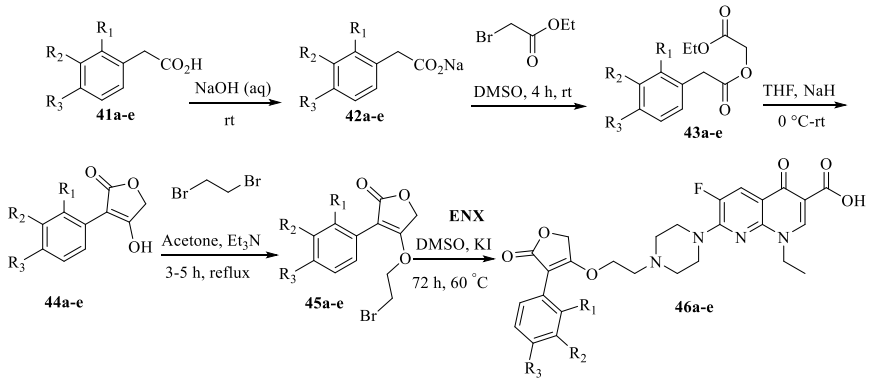
40c		25.0	50.0	6.25	25.0	50.0	25.0	1.0	2.0	1.0
40d		12.5	25.0	6.25	12.5	50.0	25.0	12.5	30.0	2.0
40e		12.5	25	6.25	25.0	50.0	12.5	1.0	2.5	0.5

MBC: minimum bactericidal concentration; MBIC: minimum biofilm inhibitory concentration; MIC: minimum inhibitory concentration.

Wang and coworkers [96] generated a library of 3-arylfuran-2(*5H*)-one-fluoroquinolone hybrids **46a-e**. Initially, substituted phenylacetic acids **41a-e** were converted to sodium phenylacetates **42a-e** in dilute NaOH solution. Subsequent treatment of the intermediate salt with ethyl bromoacetate in DMSO at rt for 4 h resulted in the formation of phenylacetic acid ethyl esters **43a-e** in excellent yields (90–95%). Cyclization of **43a-e** were accomplished using sodium hydride (NaH) in THF at 0 °C to rt, leading to the formation of 4-hydroxy-3-phenylfuran-2(*5H*)-ones **44a-e.** Introduction of an ethyl linker was achieved by dissolving **44a-e** in acetone and adding 1,2-dibromoethane and Et_3N, followed by refluxing the mixture for 3-5 h, resulting in the formation of compounds **45a-e** in good yields. Finally, the target products **46a-e** were realized in moderate yields by combining ENX with **45a-e** in the presence of KI, and DMAP in DMSO at 60 °C for 72 h (Scheme 18). The conjugated compounds were evaluated against a range of bacteria including tetracycline-resistant *B. subtilis, E. coli,* and *S. aureus*. Many of these analogs displayed antibacterial activity that was akin to the reference drug, CPX. Specifically, **46b** exhibited superior antibacterial efficacy across all the tested bacteria, with MIC_{50} values ranging from 1.6 to 2.6 μg/mL, significantly better than CPX, with MIC_{50} values between 2.7 and 6.82 μg/mL (Table 12).



Scheme 18. Synthesis of 3-arylfuran-2(5*H*)-one-ENX hybrids **46a-e.**

Table 12. *In vitro* antibacterial activity of compounds **46a-e.**

Compound	R_1	R_2	R_3	Antibacterial activity (MIC (μg/mL)		
				E. coli	*S. aureus*	[a]*B. subtilis*
46a	H	H	H	5.6	6.8	12.6
46b	F	H	H	2.6	2.6	1.6
46c	H	Cl	H	2.9	8.7	15.3
46d	H	H	Cl	9.6	24.9	13.2
46e	H	Br	H	12.2	13.1	4.7
CPX	-	-	-	5.65	6.82	2.70

[a]*B. subtilis*: tetracycline-resistant *Bacillus subtilis*.

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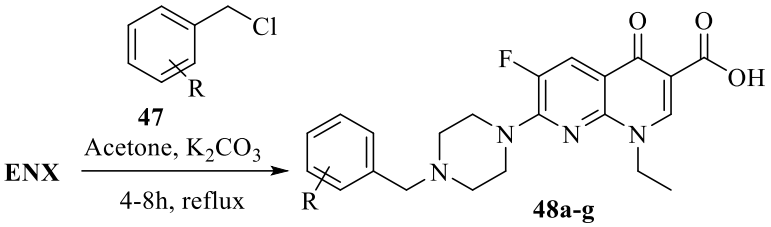
Shaheen et al. [97] developed and produced a series of novel FQs that exhibit strong inhibitory effects on α-glucosidase (Scheme 19). The analogs were prepared by subjecting ENX to reflux conditions with various substituted benzyl chlorides **47a-g** in anhydrous acetone, in the presence of K_2CO_3, for 4-8 h. This process resulted in the desired monosubstituted compounds **48a-g** with satisfactory yields. The synthesized derivatives were then subjected to *in vitro* screening for α-glucosidase inhibition, along with in silico docking studies. The analogs **48a-g** demonstrated strong α-glucosidase inhibitory activity ranging from 48.7 to 74.5 μM, in comparison to the IC_{50} value of 425.6 μM observed for the reference α-glucosidase standard inhibitor drug, 1-deoxynojirimycin (Table 13). Docking studies of **48a-g** reveal that the molecular interactions of mono benzylated derivatives align well with their inhibitory activity. These compounds were observed to form polar contacts with the active site of proteins, mainly involving residues such as Glu771, Asp392, Trp391 and Arg428.



Scheme 19. Synthesis of piperazinyl mono benzylated ENX derivatives **48a-g**.

Table 13. *In vitro* α-glucosidase inhibitory activity of compounds **48a-g**.

Compound	R	α-glucosidase inhibitory effect (GIC, μM)
48a	-	57.8
48b	4-Me	69.8
48c	4-Cl	74.5
48d	2,4-diCl	63.8
48e	3,4-diCl	52.7
48f	2,6-diCl	74.2
48g	2,6-diF	48.7
DNJ	-	425.6

DNJ: 1-deoxynojirimycin (standard inhibitor α- glucosidase); GIC: α-glucosidase inhibitory concentration.

2.3. Other Modifications (Part C)

This category encompasses modifications performed on both the **C3 and C7** sites of the 1,8-naphthyridine core of ENX derivatives.

In the same report, Shaheen and colleagues [97] developed and produced a novel di substituted benzyl FQ derivatives with an excellent α-glucosidase inhibitory effect (Scheme 20). The analogs were prepared as demonstrated in scheme 19. However, in this case the ENX was refluxed with various substituted benzyl bromide **49a-c** in the presence of K_2CO_3, for 4-8 h resulting in the formation of disubstituted derivatives **50a-c**. The *in vitro* α-glucosidase inhibition screening showed that compound **50a** had the highest potency among all tested analogs, with an IC_{50} value of 45.8 μM. Other analogs in this series, **50b** and **50c**, also exhibited notable inhibitory activity, with IC_{50} values of 67.8 μM and 59.8 μM, respectively. These values are significantly lower than the IC_{50} of 425.6 μM for the reference α-glucosidase inhibitor. Interestingly, **50a** is not only more potent than the reference drug but also surpasses the parent compound, ENX, which has an IC_{50} of 58.9 μM. Specifically, **50a** is about 9.3-fold more potent than the reference drug, stressing its strong potential as a lead candidate for further development. Docking studies of compounds **50a-c** indicate that their molecular interactions are consistent with their observed inhibitory activity. These studies show that the di-benzylated

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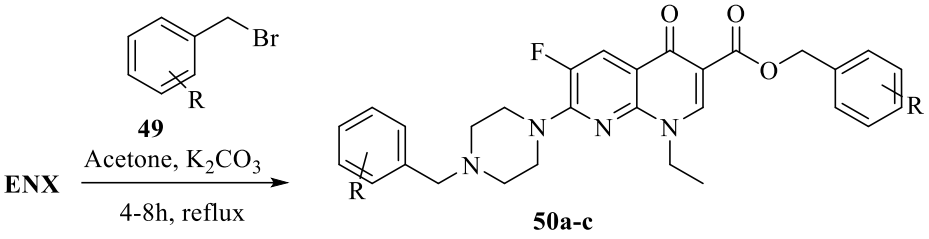
derivatives form polar contacts with the active site of the enzyme, primarily interacting with residues such as Gly566, Glu771, Trp391, Asp508, Arg428 and Asp392 (Table 14).



Scheme 20. Synthesis of piperazinyl di- benzylated ENX derivatives **50a-c.**

Table 14. *In vitro* α-glucosidase inhibitory activity of compounds **50a-c**.

Compound	R	α-glucosidase inhibitory effect (GIC, μM)
50a	2-Br	45.8
50b	2-Cl,4-F	67.8
50c	4-NO_2	59.8
ENX	-	58.9
DNJ	-	425.6

3. Future Perspectives

The recent developments discussed in this review shed light on the synthesis of 4-quinolone-3-carboxylic acid derivatives, with a particular focus on scaffolds containing a 1,8-naphthyridine core reminiscent of ENX. These advancements pave the way for future exploration and innovation in this field. One promising avenue for future research is the further exploration of C3 modifications, as they have shown potential for generating diverse analogs with improved medicinal properties. By employing strategic modifications at the C3 position, researchers can fine-tune the pharmacological profile of these compounds, enhancing their efficacy and reducing potential side effects. Additionally, the C7 modification segment warrants further investigation, as it offers opportunities to optimize the physicochemical properties and biological activities of 4-quinolone-3-carboxylic acid derivatives. By carefully manipulating the C7 position, researchers can potentially enhance the bioavailability, target specificity, and overall therapeutic potential of these compounds. Lastly, the approach that combines modifications from both A and B presents a promising direction for the design and synthesis of novel enoxacin derivatives with diverse pharmacological applications. Within this framework, researchers can explore a wide range of structural modifications in order to produce analogs with specialized features and unique biological activities. Overall, these prospects for the future emphasize the intriguing possibility for further breakthroughs in the synthesis and research of 4-quinolone-3-carboxylic acid derivatives.

4. Conclusions

In conclusion, this review provides a comprehensive analysis of developments in the synthesis of 4-quinolone-3-carboxylic acid derivatives, focusing on scaffolds containing a 1,8-naphthyridine core akin to ENX. The reviewed literature showcases various modifications at the C3 and C7, and combination of C3 and C7 positions, demonstrating their impact on the structural diversity, medicinal properties, and potential pharmacological applications of these compounds. The chosen reactions were selected based on their reproducibility, ease of execution, and the accessibility of the described methodologies. Researchers seeking to design and synthesize novel ENX derivatives with diverse pharmacological activities will find the insights presented in this review both valuable and insightful. This comprehensive analysis sets the stage for future investigations, where researchers can explore the untapped potential of 4-quinolone-3-carboxylic acid specifically ENX derivatives, thereby opening new avenues for drug discovery and therapeutic interventions.

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