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Synthesis and antibacterial activity of *N*-[2-(5-bromothiophen-2-yl)-2-oxoethyl] and *N*-[(2-5-bromothiophen-2-yl)-2-oximinoethyl] derivatives of piperazinyl quinolones

Alireza Foroumadi,[a,c] Saeed Emami,[b] Massood Mehni,[c] Mohammad Hassan Moshafi[c] and Abbas Shafiee[a,*]

[a]*Department of Medicinal Chemistry and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14174, Iran*
[b]*Department of Medicinal Chemistry, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari 48175, Iran*
[c]*Faculty of Pharmacy, Kerman University of Medical Sciences, Kerman 76351, Iran*

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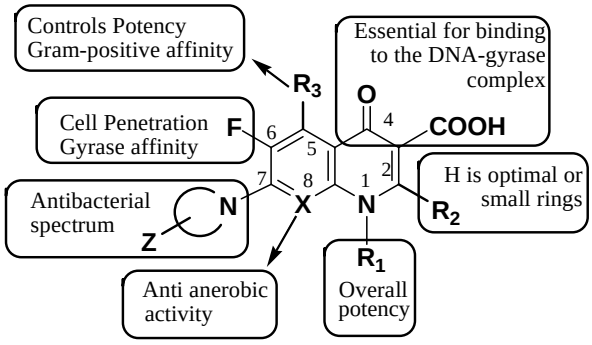
Abstract—A series of *N*-[2-(5-bromothiophen-2-yl)-2-oxoethyl] and *N*-[2-(5-bromothiophen-2-yl)-2-oximinoethyl]derivatives of piperazinyl quinolones were synthesized and evaluated for antimicrobial activity against Gram-positive and Gram-negative microorganisms. Some of these derivatives exhibit comparable or better activity against Gram-positive bacteria, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Bacillus subtilis*, than ciprofloxacin, norfloxacin and enoxacine as reference drugs.

Increasingly multidrug-resistant pathogens have become a serious problem particularly during the last decade.[1] The design of new agents active against resistant organisms is of critical importance. In the field of quinolones antibacterial agents, the new generation of quinolones achieved significant improvement in terms of potency, spectrum and pharmacokinetic properties, but these agents faced a rapid increase of resistance from Gram-positive organisms.[2,3] Therefore, enhancing the potency of quinolones, especially against Gram-positive organisms, has become increasingly urgent.

Quinolones consist of a bicyclic ring structure (Fig. 1) in which there is a substitution at position N-1, with various moieties. Most of the current agents have a carboxyl group at position 3, a keto group at position 4, a fluorine atom at position 6 and a nitrogen heterocycle moiety at the C-7 position.[4] The quinolones exert their antibacterial action by interfering with the function of two bacterial type-II topoisomerase enzymes, DNA gyrase and topoisomerase IV.[5] Structure–activity relationship (SAR) studies and the known drug target



R_1= Et, cyclopropyl, halo substituted aromatic ring , etc.
R_2= H, -SMe, or R_1& R_2 may join to form a ring.
R_3= H, -NH_2 ,-OMe
X= N, CH, CF, C-OMe, or X & R_1 may join to form a ring.
Z= attached group to cycloalkylamine ring.

Figure 1. Structural features and common pharmacophor of quinolone antibacterials.

Keywords: Bromothiophene; Quinolone; Oxime derivative; Antibacterial activity.
* Corresponding author. Tel.: +98 21 66406757; fax: +98 21 66461178; e-mail: ashafiee@ams.ac.ir

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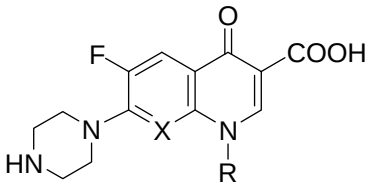
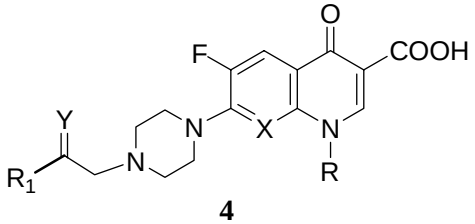
have facilitated the development of new more potent quinolones with broader spectrum activity, better pharmacokinetics and good tolerability. The SARs of quinolones have been the subject of extensive review.[6–8] In general, β-keto carboxylic acid moiety is required for hydrogen bonding interactions with DNA bases in the single-stranded regions of double helix of DNA created by the action of the enzyme, and therefore it is essential (Fig. 1). The substituent at N-1 and C-8 positions should be relatively small and lipophilic to enhance self-association.[9,10] Groups at C-5 and C-6 have also been optimized in which an amino and fluoro substituent, respectively, at C-5 and C-6 appear to be the best. The nature of substituent at C-7 position has a great impact on potency, spectrum, solubility and pharmacokinetics. Almost all quinolones have nitrogen heterocycles linked to the C-7 position of quinolone ring through the heterocyclic nitrogen.[9,10] Extensively investigated substituent at C-7 are piperazin-1-yl and its 4-substituted derivatives. Ciprofloxacin **1**, norfloxacin **2** and enoxacin **3** are characterized by having a piperazine moiety at C-7, which represents a site amenable to significant modification (Fig. 2). In addition, a position on the 7-piperazinyl quinolone molecule, where substitutions of bulky groups are permitted, is at the N-4 of piperazine ring.[11] Accordingly, a number of quinolones **4** with a 2-oxoethyl or 2-oximinoethyl derivative attached to the piperazine ring at C-7 position were synthesized and evaluated for antibacterial activity by us and others.[12–19]



1, Ciprofloxacin; R= cyclopropyl, X= CH
2, Norfloxacin; R= ethyl, X= CH
3, Enoxacin; R= ethyl, X= N



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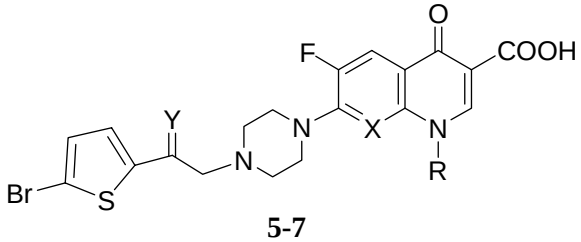
X= CH, N; Y= O, NOH, $NOCH_2Ar$
R= cyclopropyl, ethyl; R_1= aryl, heteroaryl



5-7

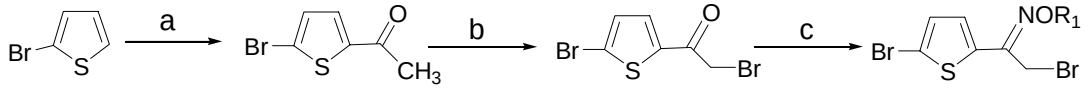
X= CH, N
Y= O, NOH, NOBn
R= cyclopropyl, ethyl

Figure 2.

In continuation of our efforts to complete the SARs of *N*-piperazinyl quinolones and to achieve a better antimicrobial profile at lower concentrations against Gram-positive bacteria, herein, we report the synthesis and antibacterial activity of a new series of *N*-piperazinyl quinolones (**5**, **6** and **7**) containing 2-(5-bromothiophen-2-yl)-2-oxoethyl or 2-(5-bromothiophen-2-yl)-2-oximinoethyl groups (Fig. 2).

Our synthetic pathway to intermediates **10** and **11**, and target compounds **5**–**7** is presented in Schemes 1 and 2. 1-(5-Bromothiophen-2-yl)ethanone **9** was obtained from 2-bromothiophene **8** according to the method reported in the literature.[20] Ketone **9** was brominated with Br_2 in $CHCl_3$ to give corresponding α-bromoketone **10**.[21] Compound **10** was converted to oxime derivative **11a** by stirring with 3 equiv of hydroxylamine hydrochloride in methanol at room temperature. Similarly, the *O*-benzyloxime ethers **11b** were synthesized by reaction of compound **10** with *O*-benzylhydroxylamine hydrochloride.[12–16] Reaction of quinolones (**1**, **2** or **3**) with α-bromoketone **10** or α-bromooxime derivatives **11a**,**b** in DMF, in the presence of $NaHCO_3$ at room temperature afforded corresponding ketones **5** and oxime derivatives **6** and **7**, respectively.[12–16]

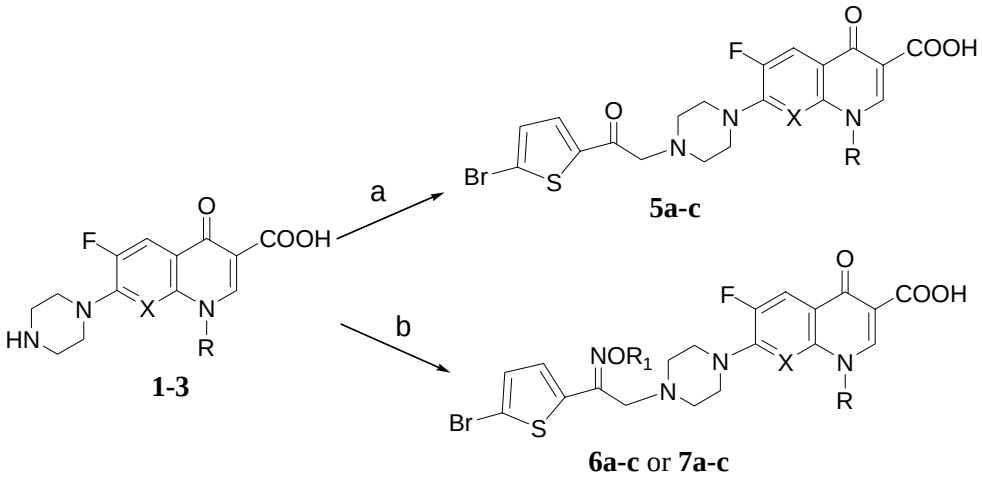
Compounds **5**–**7** (**a**–**c**) were evaluated for their antibacterial activity against Gram-positive (*Staphylococcus aureus* ATCC 6538p, *Staphylococcus epidermidis* ATCC 12228 and *Bacillus subtilis* PTCC 1023) and Gram-negative (*Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 10031, *Pseudomonas aeruginosa*



8 **9** **10**

11a;R_1= H
11b;R_1= Bn

Scheme 1. Synthesis of intermediates α-bromoketone **10** and α-bromooxime **11a**,**b**. Reagents and conditions: (a) acetyl chloride, $AlCl_3$, CS_2, rt; (b) Br_2, $CHCl_3$, rt; (c) hydroxylamine hydrochloride or *O*-benzyl hydroxylamine hydrochloride, MeOH, rt.



Scheme 2. Synthesis of compounds **5**–**7**. Reagents and conditions: (a) α-bromoketone **10**, $NaHCO_3$, DMF, rt; (b) α-bromooxime **11a**,**b**, $NaHCO_3$, DMF, rt.

ATCC 9027 and *Enterobacter cloacae* PTCC 1003) bacteria using conventional agar-dilution method.[22] The minimum inhibitory concentration (MIC) values were determined in comparison to ciprofloxacin **1**, norfloxacin **2** and enoxacin **3** as reference drugs.

As noted in Table 1, the MIC values of the tested compounds indicated that most compounds exhibited high activity against Gram-positive bacteria and mild activity against Gram-negative bacteria, except *P. aeruginosa*.

The MIC values of ketones **5** and oximes **6** against *Staphylococcus* strains indicate that most compounds possessed a comparable or better activity (MIC = 0.03–1 μg/mL) in comparison to the reference drugs (MIC = 0.25–1 μg/mL). Compound **6a** was the most active compound against *S. aureus*; its activity was found to be 16 to 32 times better than reference drugs. Derivatives **5a**,**b** and **6a** were the most active against *S. epidermidis*, showing MIC values of 0.06 μg/mL; their activities were four- to eight fold more than reference drugs.

Most compounds showed significant activity against *B. subtilis*. In fact, the most active compound was **6a** (MIC = 0.03 μg/mL) being fourfold more active than enoxacin and almost equipotent to ciprofloxacin and norfloxacin.

Generally, most compounds showed moderate to significant activity (MIC = 0.25–16 μg/mL) against Gram-negative bacteria, with the exception for antibacterial activity against *P. aeruginosa*. Nearly, all compounds except **5a**, showed poor or no activity against *P. aeruginosa*. Compound **5a** showed good activity comparable to the reference drugs against this microorganism. In fact, compound **5a** was the most potent against all Gram-negative bacteria, with MIC value of 0.25–4 μg/mL. Its activity was found to be comparable to reference drugs.

In terms of SAR, ketones **5** and oximes **6** showed better antibacterial activity than *O*-benzyl oximes **7** against both Gram-positive and Gram-negative bacteria. Comparison between MIC values of ketones **5** and oximes **6** revealed that oximation of ketones seemed to have different influence on the antibacterial activity against various bacteria strains. The results of MIC tests against both Gram-positive and Gram-negative bacteria revealed that ciprofloxacin derivatives (R = cyclopropyl, X = CH) were usually more active than norfloxacine and enoxacine derivatives (R = ethyl, X = CH or N, respectively).

In the 5-bromothiophene series **5**–**7**, comparison with the corresponding non-bromo substituted thiophene derivatives[16] brought to the fore that this pharmaco-

Table 1. Antibacterial activities of compounds **5**–**7** against selected strains (MICs in μg/mL)

Compound	X	Y	R	*S. aureus*	*S. epidermidis*	*B. subtilis*	*K. pneumoniae*	*E. coli*	*P. aeruginosa*	*E. cloacae*
5a	CH	O	Cyclopropyl	0.125	0.06	0.06	0.5	0.25	4	0.5
5b	CH	O	Ethyl	2	0.06	0.125	2	16	>64	8
5c	N	O	Ethyl	1	0.5	0.5	4	4	32	4
6a	CH	NOH	Cyclopropyl	0.03	0.06	0.03	8	1	>64	1
6b	CH	NOH	Ethyl	0.5	0.125	0.125	8	4	>64	4
6c	N	NOH	Ethyl	2	0.25	0.125	32	8	>64	4
7a	CH	NOBn	Cyclopropyl	32	8	0.25	32	64	>64	64
7b	CH	NOBn	Ethyl	64	32	0.5	64	>64	>64	>64
7c	N	NOBn	Ethyl	64	32	1	>64	>64	>64	>64
1 (Ciprofloxacin)				0.5	0.25	0.015	0.03	0.125	1	0.06
2 (Norfloxacin)				1	0.5	0.06	0.125	0.25	4	0.125
3 (Enoxacin)				1	0.5	0.125	0.25	0.25	4	0.25

modulation in many cases exerted a positive effect: for example, compounds **5a** and **6a** were more active than non-bromo substituted analogues against all of the tested Gram-positive strains. Compound **6a** was the most potent antibacterial against Gram-positive among the studied 5-bromo- and non-bromo-substituted thiophene derivatives and other previously described *N*-substituted piperazinyl quinolone series **4**.[12–16] Nevertheless, the effect of bromo-substitution was dependent on the other substituents.

These results demonstrated that the introduction of thiophen-2-yl or 5-bromothiophen-2-yl group instead of phenyl, substituted phenyl and furan-2-yl group at 2 position of 2-oxoethyl or 2-oximinoethyl moiety attached to the piperazine ring in 7-piperazinyl quinolones improved the overall antibacterial activity against Gram-positive bacteria.

Differences in the moiety present at N-1 position or at C-7 position markedly influence both microbiological and pharmacokinetic properties.[23] Generally, the 7-piperazinyl quinolones (ciprofloxacin, norfloxacin and enoxacin) have better Gram-negative than Gram-positive antimicrobial potency. In contrast, from our biological results, it is evident that *N*-[2-(5-bromothiophen-2-yl)-2-oxoethyl] derivatives of piperazinyl quinolones **5**–**7** exhibited more potent antibacterial activity against Gram-positive rather than Gram-negative bacteria. This change of antibacterial profile may be due to the change of selectivity to target enzyme. Recently it was investigated that the mode of action of quinolones involves interaction with both DNA gyrase, the originally recognized drug target and topoisomerase IV, a related type II topoisomerase.[5] In a bacterial cell, these two enzymes often differ in their relative sensitivities to many quinolones, and commonly DNA gyrase is more sensitive in Gram-negative bacteria and topoisomerase IV more sensitive in Gram-positive bacteria. It seems that topoisomerase IV is the primary target of the quinolones (**5**–**7**) with bulky functional group at N-4 position of piperazine ring. Thus, the improvement of overall antibacterial activity of these compounds against Gram-positive bacteria might be a result of better interaction with topoisomerase IV rather than with DNA gyrase.

In conclusion, we have described a convenient synthesis of *N*-[2-(5-bromothiophen-2-yl)-2-oxoethyl] and *N*-[2-(5-bromothiophen-2-yl)-2-oximinoethyl] derivatives of piperazinyl quinolones **5**–**7** and biological studies have shown that many of these derivatives were highly potent as antibacterial agents especially against Gram-positive bacteria. First approach in the series of new *N*-[2-(5-bromothiophen-2-yl)-2-oxoethyl] derivatives of piperazinyl quinolones bearing different structural features on the quinolone ring and piperazine moiety points out that compound **6a** exerts significant in vitro antibacterial activity against Gram-positive bacteria and it was more potent than the reference drugs against *S. aureus*, *S. epidermidis* and *B. subtilis*. These data demonstrated the importance of the attached moiety to piperazine ring to obtain potent antibacterial agents.

Acknowledgments

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