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Synthesis and Antibacterial Activity of *N*-[2-(2-naphthyl)ethyl]piperazinyl Quinolones

A. Shafiee[a,b,*], S. Emami[c], S. Ghodsi[d], S. Najjari[a], M. Sorkhi[a], N. Samadi[e], M.A. Faramarzi[e] and A. Foroumadi[a,b]

[a]*Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14174, Iran*

[b]*Drug Design & Development Research Center, Tehran University of Medical Sciences, Tehran 14174, Iran*

[c]*Department of Medicinal Chemistry and Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran*

[d]*Department of Chemistry, Faculty of Sciences, Islamic Azad University, Karaj-Branch, Karaj, Iran*

[e]*Department of Pharmaceutical Biotechnology, Tehran University of Medical Sciences, Tehran 14174, Iran*

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A series of *N*-[2-(2-naphthyl)ethyl]piperazinyl quinolones containing a carbonyl related functional groups (oxo- or oxyimino-) on the ethyl spacer was synthesized and evaluated for antibacterial activity. The synthesis of *N*-[2-(2-naphthyl)ethyl]piperazinyl quinolones was achieved through the versatile and efficient synthetic route that involved reaction of piperazinyl quinolones with appropriate α-bromoketone or α-bromooxime derivatives. The structures of new compounds were confirmed by elemental analysis, IR and NMR spectra. Antibacterial data indicated that some of the new *N*-[2-(2-naphthyl)ethyl]piperazinyl quinolones showed good antibacterial activity and modification of the position 8 and N-1 substituent on quinolone ring, and ethyl spacer functionality produced significant changes in activity against Gram-positive and Gram-negative bacteria.

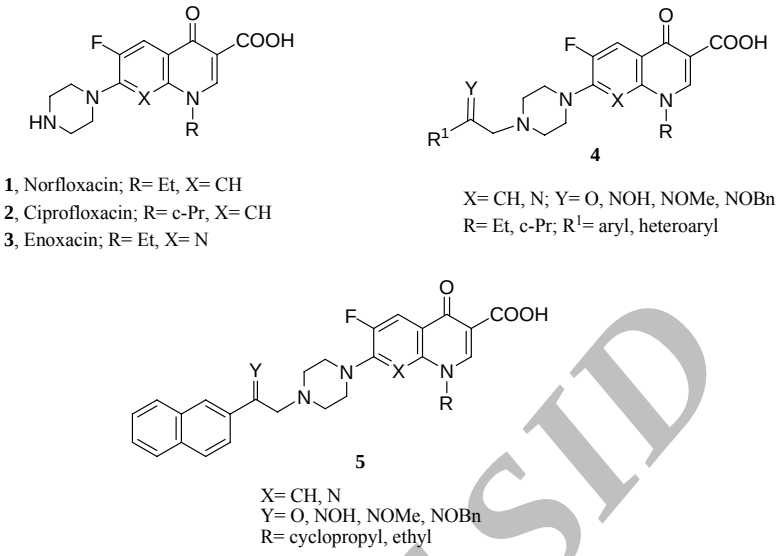
Keywords: Fluoroquinolones, Piperazinyl quinolones, Antibacterial activity, Structure-activity relationships

INTRODUCTION

Increasing multidrug-resistant pathogens have become a serious problem particularly during the last decade. A more controlled usage of these drugs may be a way to partially counterbalance this challenge. However, the design of new agents active against resistant organism remains of critical importance [1].

The fluoroquinolone class of antibacterials is widely used in the treatment of Gram-positive and Gram-negative bacterial infections [2]. Since the development of norfloxacin, many fluoroquinolone antibacterials have been synthesized to improve their antimicrobial activities against various infectious organisms. After the discovery of prototypic norfloxacin, most of the research concerning quinolone antibacterials has been focused on the basic group at the C-7 position, which plays a key role in the improvement of potency, spectrum and pharmacokinetic profile of quinolone antibacterials [3]. As a results, ciprofloxacin, ofloxacin, lomefloxacin, fleroxacin and sparfloxacin have been successfully introduced into the market, all of which contain a piperazine derivative at the C-7 position [4,5]. Whereas, the great majority of the new quinolones under development or in clinical use is incorporated with piperazine, bearing small substitution (*e.g.*, methyl); however, a few of quinolones are substituted at C-7 with bulky substituent on cyclic amine [3].

*Corresponding author. E-mail: ashafiee@ams.ac.ir



1, Norfloxacin; R= Et, X= CH
2, Ciprofloxacin; R= c-Pr, X= CH
3, Enoxacin; R= Et, X= N

X= CH, N; Y= O, NOH, NOMe, NOBn
R= Et, c-Pr; R^1= aryl, heteroaryl

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

Fig. 1.

Recently, we identified a series of *N*-substituted piperazinyl quinolones **4** (Fig. 1) in which the N-4 hydrogen of piperazinyl group of norfloxacin **1**, ciprofloxacin **2**, and enoxacin **3** is replaced with various 2-oxoethyl or 2-oxyiminoethyl moieties and displayed *in vitro* antibacterial activity comparable or higher than respective parent quinolones [6-11]. Therefore our strategy to achieve a better antimicrobial profile has focused on introducing new functionality on the piperazine ring [12]. In the current study, structure **4** was used as starting point for chemical manipulation. Therefore, twelve new analogs **5a-l** (Fig. 1), were prepared by replacing aryl with naphthyl ring on 2-oxoethyl or 2-oxyiminoethyl moieties and evaluated for antibacterial activity against Gram-negative and Gram-positive bacteria.

EXPERIMENTAL

Chemistry

Chemical reagents and all solvents used in this study were purchased from Merck AG and Aldrich Chemicals. 2-Bromo-1-(naphthalen-2-yl)ethanone (**7**) was prepared according to the literature method [13]. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained on a Shimadzu 470 spectrophotometer (potassium bromide disc). NMR spectra were recorded on a Bruker 500 spectrometer and chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. Elemental analyses were carried out on a CHN-O rapid elemental analyzer (GmbH-Germany) for C, H and N, and the results were within ± 0.4% of the theoretical values. Merck silica gel 60 F_{254} plates were used for analytical TLC.

General procedure for the synthesis of 7-[4-[2-(naphthalen-2-yl)-2-oxoethyl] piperazinylquinolones (5a-c). A mixture of 2-bromo-1-(naphthalen-2-yl)ethanone **7** (0.55 mmol), quinolone **1-3** (0.5 mmol) and $NaHCO_3$ (0.5 mmol) in DMF (5 ml), was stirred at room temperature for 72 h. After consumption of quinolone, water (20 ml) was added and the precipitate was filtered, washed with water and crystallized from methanol-chloroform (9:1) to give compounds **5a-c**.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-oxoethyl]piperazin-1-yl]-4-oxo-3-quinoline carboxylic acid (5a). Yield: 60%; m.p.: 175-177 ºC; IR (KBr, cm^{-1}) υ_{max}: 1629, 1680 and 1721 (C=O), 3441 (OH); ^{1}H NMR (DMSO-d_6) δ: 1.01-1.31 (m, 4H, cyclopropyl), 2.75-2.89 (m, 4H, piperazine), 3.25-3.38 (m, 4H, piperazine), 3.75-3.86 (m, 1H, cyclopropyl), 4.11 (s, 2H, $COCH_2$), 7.55-7.72 (m, 3H, H-8 quinolone, H-6 and H-7 naphthyl), 7.90 (d, 1H, *J* = 13.32 Hz, H-5 quinolone), 7.94-8.07 (m, 3H, H-4, H-5 and H-8 naphthyl), 8.12 (d, 1H, *J* = 8.05 Hz, H-3 naphthyl), 8.65 (s, 1H, H-1 naphthyl), 8.72 (s, 1H, H-2 quinolone), 15.20

(s, 1H, COOH).

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-oxoethyl]piperazin-1-yl]-4-oxo-3-quinoline carboxylic acid (5b). Yield: 65%; m.p.: 193-194 ºC; IR (KBr, cm^{-1}) υ_{max}: 1623, 1675 and 1741 (C=O), 3450 (OH); ^{1}H NMR (DMSO-d_6) δ: 1.40 (t, 3H, CH_3), 2.62-2.97 (m, 4H, piperazine), 3.34-3.58 (m, 4H, piperazine), 4.10 (s, 2H, $COCH_2$), 4.58 (q, 2H, CH_2-CH_3), 7.09-7.32 (m, 1H, H-8 quinolone), 7.55-7.72 (m, 2H, H-6 and H-7 naphthyl), 7.90 (d, 1H, *J* = 13.11 Hz, H-5 quinolone), 7.94-8.23 (m, 4H, H-3, H-4, H-5 and H-8 naphthyl), 8.72 (s, 1H, H-1 naphthyl), 8.93 (s, 1H, H-2 quinolone), 15.32 (s, 1H, COOH).

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-oxoethyl]piperazin-1-yl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (5c). Yield: 63%; m.p.: 170-172 ºC; IR (KBr, cm^{-1}) υ_{max}: 1623, 1685 and 1726 (C=O), 3420 (OH); ^{1}H NMR (DMSO-d_6) δ: 1.38 (t, 3H, CH_3), 2.75-2.91 (m, 4H, piperazine), 3.74-4.00 (m, 4H, piperazine), 4.10 (s, 2H, $COCH_2$), 4.48 (q, 2H, CH_2-CH_3), 7.53-7.75 (m, 2H, H-6 and H-7 naphthyl), 7.87-8.23 (m, 5H, H-3, H-4, H-5 and H-8 naphtyl, H-5 naphthyridine), 8.71 (s, 1H, H-1 naphthyl), 8.96 (s, 1H, H-2 naphthyridine), 15.23 (s, 1H, COOH).

General procedure for the synthesis of 7-[4-[2-(naphthalen-2-yl)-2-hydroxyimino ethyl]piperazinyl-quinolones (5d-f). A solution of 2-bromo-1-(naphthalen-2-yl)ethanone **7** (249 mg, 1.0 mmol) and hydroxylamine hydrochloride (209 mg, 3.0 mmol) in methanol (5 ml) was stirred at room temperature for 24 h. Water (25 ml) was added and the precipitate was filtered and washed with water to give 2-bromo-1-(naphthalen-2-yl)ethanone oxime (**8a**) which was used without further purification for next step. Yield: 80%; m.p.: 164-165 ºC; IR (KBr, cm^{-1}) υ_{max}: 1615 (C=N), 3250 (OH). A mixture of compound **8a** (0.55 mmol), quinolone **1-3** (0.5 mmol) and $NaHCO_3$ (0.5 mmol) in DMF (5 ml) was stirred at room temperature for 72 h. After consumption of quinolone, water (20 ml) was added and the precipitate was filtered, washed with water and crystallized from methanol-chloroform (9:1) to give compounds **5d-f**.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-hydroxyimino ethyl]piperazin-1-yl]-4-oxo-3-quinoline carboxylic acid (5d). Mixture of *E*- and *Z*-isomers, *E/Z*: 55/45; Yield: 80%; m.p.: 227-228 ºC; IR (KBr, cm^{-1}) υ_{max}: 1628, 1724 (C=O), 3230 (OH); ^{1}H NMR (DMSO-d_6) δ: 1.02-1.32 (m, 4H, cyclopropyl), 2.60-2.74 (m, 4H, piperazine), 3.20-3.37 (m, 4H, piperazine), 3.54 (s, N=C-CH_2, *E*-isomer), 3.85 (s, N=C-CH_2, *Z*-isomer), 3.65-3.81 (m, 1H, cyclopropyl), 7.42-7.58 (m, 3H, H-6 and H-7 naphthyl, H-8 quinolone), 7.70-7.98 (m, 5H, H-3, H-4, H-5 and H-8 naphthyl, H-5 quinolone), 8.18 (s, H-1 naphthyl, *E*-isomer), 8.29 (s, H-1 naphthyl, *Z*-isomer), 8.62 (s, 1H, H-2 quinolone), 11.08 (s, NOH, *E*-isomer), 11.58 (s, NOH, *Z*-isomer), 15.17 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 8.00, 35.79, 49.35, 49.47, 49.84, 52.22, 52.56, 61.36, 95.42, 106.42, 110.75, 110.94, 118.62, 123.87, 125.94, 126.14, 126.27, 126.43, 126.60, 126.91, 127.45, 127.65, 128.33, 128.43, 131.06, 132.43, 132.63, 132.73, 132.94, 133.45, 139.08, 145.19, 147.89, 152.01, 152.22, 152.95, 153.99, 165.97, 176.23.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-hydroxyiminoethyl] piperazin-1-yl]-4-oxo-3-quinoline carboxylic acid (5e). *Z*-isomer; Yield: 81%; m.p.: 224-226 ºC; IR (KBr, cm^{-1}) υ_{max}: 1629, 1726 (C=O), 3331 (OH); ^{1}H NMR (DMSO-d_6) δ: 1.35 (t, *J* = 7.02 Hz, 3H, CH_3), 2.65-2.78 (m, 4H, piperazine), 3.15-3.29 (m, 4H, piperazine), 3.86 (s, 2H, N=C-CH_2), 4.53 (q, *J* = 7.02 Hz, 2H, CH_2-CH_3), 7.13 (d, 1H, *J* = 7.02 Hz, H-8 quinolone), 7.46-7.58 (m, 2H, H-6 and H-7 naphthyl), 7.83-8.03 (m, 5H, H-3, H-4, H-5 and H-8 naphthyl, H-5 quinolone), 8.29 (s, 1H, H-1 naphthyl), 8.91 (s, 1H, H-2 quinolone), 11.58 (s, 1H, NOH), 15.34 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.30, 48.98, 49.51, 49.54, 49.86, 52.54, 105.92, 107.02, 110.92, 111.10, 119.18, 119.24, 123.89, 125.93, 126.22, 126.38, 127.37, 127.44, 128.39, 132.71, 132.91, 133.43, 137.06, 145.44, 145.52, 148.35, 151.88, 153.03, 153.85, 166.10, 176.08.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-hydroxyiminoethyl] piperazin-1-yl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (5f). Mixture of *E*- and *Z*-isomers, *E/Z*: 82/18; Yield: 83%; m.p.: 223-225 ºC; IR (KBr, cm^{-1}) υ_{max}: 1634, 1726 (C=O), 3405 (OH); ^{1}H NMR (DMSO-d_6) δ: 1.33 (t, *J* = 6.93 Hz, 3H, CH_3), 2.54-2.70 (m, 4H, piperazine), 3.68-3.75 (m, 4H, piperazine), 3.51 (s, N=C-CH_2, *E*-isomer), 3.82 (s, N=C-CH_2, *Z*-isomer), 4.41 (q, *J* = 6.93 Hz, 2H, CH_2-CH_3), 7.47-7.58 (m, 2H, H-6 and H-7 naphthyl), 7.83-7.97 (m, 4H, H-3, H-4, H-5 and H-8 naphthyl), 8.02 (d, 1H, *J* = 13.57 Hz, H-5 naphthyridine), 8.16 (s, H-1 naphthyl, *E*-isomer), 8.29 (s, H-1 naphthyl, *Z*-isomer), 8.93 (s, 1H, H-2

naphthyridine), 11.06 (s, NOH, *E*-isomer), 11.57 (s, NOH, *Z*-isomer), 15.32 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.67, 46.57, 46.63, 47.17, 52.30, 52.38, 61.30, 108.02, 112.58, 119.30, 119.47, 123.83, 126.12, 126.39, 126.58, 126.92, 127.44, 127.59, 128.31, 128.44, 131.08, 132.43, 132.62, 144.80, 145.80, 147.69, 147.86, 149.82, 149.89, 152.17, 165.87, 176.32.

General procedure for the synthesis of 7-[4-[2-(naphthalen-2-yl)-2-methoxyimino ethyl]piperazinyl-quinolones (5g-i). To a stirred solution of 2-bromo-1-(naphthalen-2-yl)ethanone **7** (498 mg, 2.0 mmol) in methanol (8 ml) at room temperature, was added 25% solution of *O*-methylhydroxylammonium chloride in diluted HCl (1002 mg, 3.0 mmol). After 3 days stirring at room temperature, water (25 ml) was added and the precipitated solid was filtered, washed with water and dried to give 2-bromo-1-(naphthalen-2-yl)ethanone *O*-methyl oxime (**8b**) which was used without further purification for next step. Yield: 46%; m.p.: 45-46 ºC; IR (KBr, cm^{-1}) υ_{max}: 1616 (C=N). A mixture of compound **8b** (0.55 mmol), quinolone **1-3** (0.5 mmol) and $NaHCO_3$ (0.5 mmol) in DMF (5 ml), was stirred at room temperature for 72 h. After consumption of quinolone, water (20 ml) was added and the precipitate was filtered, washed with water and crystallized from methanol-chloroform (9:1) to give compounds **5g-i**.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-methoxyimino ethyl]piperazin-1-yl]-4-oxo-3-quinoline carboxylic acid (5g). *Z*-isomer; Yield: 43%; m.p.: 220-221 ºC; IR (KBr, cm^{-1}) υ_{max}: 1634, 1731 (C=O), 3452 (OH); ^{1}H NMR ($CDCl_3$) δ: 1.11-1.19 (m, 2H, cyclopropyl), 1.30-1.35 (m, 2H, cyclopropyl), 2.74-2.82 (m, 4H, piperazine), 3.25-3.32 (m, 4H, piperazine), 3.45-3.50 (m, 1H, cyclopropyl), 3.86 (s, 2H, N=C-CH_2), 4.05 (s, 3H, $NOCH_3$), 7.28 (d, 1H, *J* = 7.00 Hz, H-8 quinolone), 7.47-7.51 (m, 2H, H-6 and H-7 naphthyl), 7.80-7.90 (m, 3H, H-4, H-5 and H-8 naphthyl), 7.97 (dd, 1H, *J* = 8.50 and 1.5 Hz, H-3 naphthyl), 7.98 (d, 1H, *J* = 13.00 Hz, H-5 quinolone), 8.27 (d, 1H, *J* = 1.4 Hz, H-1 naphthyl), 8.73 (s, 1H, H-2 quinolone), 15.18 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 8.00, 36.30, 49.86, 50.90, 52.93, 62.44, 107.00, 107.14, 111.23, 111.42, 119.04, 119.10, 124.43, 126.86, 126.93, 127.21, 127.96, 128.00, 128.99, 132.74, 133.08, 133.62, 139.58, 145.67, 148.43, 152.50, 154.63, 166.42, 176.81.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-methoxyiminoethyl] piperazin-1-yl]-4-oxo-3-quinoline carboxylic acid (5h). *Z*-isomer; Yield: 48%; m.p.: 190-192 ºC; IR (KBr, cm^{-1}) υ_{max}: 1623, 1736 (C=O), 3420 (OH); ^{1}H NMR (DMSO-d_6) δ: 1.34 (t, 3H, CH_3), 2.59-2.76 (m, 4H, piperazine), 3.17-3.27 (m, 4H, piperazine), 3.84 (s, 2H, N=C-CH_2), 3.97 (s, 3H, $NOCH_3$), 4.54 (q, 2H, CH_2-CH_3), 7.12 (d, 1H, H-8 quinolone), 7.42-7.61 (m, 2H, H-6 and H-7 naphthyl), 7.76-8.08 (m, 5H, H-3, H-4, H-5 and H-8 naphthyl, H-5 quinolone), 8.31 (s, 1H, H-1 naphthyl), 8.90 (s, 1H, H-2 quinolone), 15.31 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.34, 49.01, 49.54, 52.36, 52.50, 61.97, 95.44, 106.02, 107.07, 110.99, 111.17, 119.28, 119.34, 123.76, 124.01, 126.37, 126.49, 126.72, 126.93, 127.50, 128.19, 128.52, 129.62, 129.90, 132.14, 132.29, 132.63, 133.17, 137.11, 145.52, 148.46, 151.93, 153.92, 154.24, 166.12, 176.15.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-[2(naphthalen-2-yl)-2-methoxyiminoethyl] piperazin-1-yl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (5i). *Z*-isomer; Yield: 51%; m.p.: 170-172 ºC; IR (KBr, cm^{-1}) υ_{max}: 1629, 1726 (C=O); ^{1}H NMR (DMSO-d_6) δ: 1.33 (t, 3H, CH_3), 2.63 (br s, 4H, piperazine), 3.73 (br s, 4H, piperazine), 3.81 (s, 2H, N=C-CH_2), 3.96 (s, 3H, $NOCH_3$), 4.46 (q, 2H, CH_2-CH_3), 7.47-7.58 (m, 2H, H-6 and H-7 naphthyl), 7.83-8.01 (m, 4H, H-3, H-4, H-5 and H-8 naphthyl), 8.04 (d, 1H, *J* = 13.50 Hz, H-5 naphthyridine), 8.32 (s, 1H, H-1 naphthyl), 8.94 (s, 1H, H-2 naphthyridine), 15.29 (s, 1H, COOH).

General procedure for the synthesis of 7-[4-[2-(naphthalen-2-yl)-2-(phenyl methoxyimino)ethyl] piperazinylquinolones (5j-l). A solution of 2-bromo-1-(naphthalen-2-yl)ethanone **7** (249 mg, 1.0 mmol) and *O*-benzylhydroxylamine hydrochloride (479 mg, 3.0 mmol) in methanol (5 ml) was stirred at room temperature for 48 h. Water (20 ml) was added and the resulting suspension was cooled (0-4 °C) and the precipitated solid was filtered off, washed with water and dried to give 2-bromo-1-(naphthalen-2-yl)ethanone *O*-benzyl oxime (**8c**) which was used without further purification for next step. Yield: 85%; m.p.: 52-53 ºC; IR (KBr, cm^{-1}) υ_{max}: 1620 (C=N). A mixture of compound **8c** (0.55 mmol), quinolone **1-3** (0.5 mmol) and $NaHCO_3$ (0.5 mmol) in DMF (5 ml), was stirred at room temperature for 72 h. After consumption of quinolone, water (20 ml) was added

and the precipitate was filtered, washed with water and crystallized from methanol-chloroform (9:1) to give compound **5j-l**.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-(phenyl methoxyimino)ethyl] piperazin-1-yl]-4-oxo-3-quinoline carboxylic acid (5j). *Z*-isomer; Yield: 81%; m.p.:204-206 ºC; IR (KBr, cm^{-1}) υ_{max}: 1623, 1731 (C=O), 3430 (OH); ^{1}H NMR (DMSO-d_6) δ: 1.03-1.32 (m, 4H, cyclopropyl), 2.59-2.75 (m, 4H, piperazine), 3.10-3.24 (m, 4H, piperazine), 3.68-3.86 (m, 2H, cyclopropyl), 3.89 (s, 2H, N=C-CH_2), 5.27 (s, 2H, NO-CH_2), 7.28-7.60 (m, 8H, phenyl, H-8 quinolone, H-6 and H-7 naphthyl), 7.82-7.99 (m, 5H, H-5 quinolone, H-3, H-4, H-5 and H-8 naphthyl), 8.32 (s, 1H, H-1 naphthyl), 8.62 (s, 1H, H-2 quinolone), 15.21 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 7.35, 35.81, 49.41, 50.57, 52.47, 75.84, 95.40, 106.50, 110.76, 110.95, 123.93, 126.40, 126.56, 126.77, 127.51, 127.56, 127.85, 127.96, 128.19, 128.38, 128.53, 132.27, 132.60, 133.18, 137.66, 139.09, 147.93, 154.28, 154.61, 165.94, 176.32.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-(phenylmethoxyimino) ethyl]piperazin-1-yl]-4-oxo-3-quinoline carboxylic acid (5k). Mixture of *E* and *Z* isomers, *E*/*Z*: 65/35; Yield: 79%; m.p.: 136-138 ºC; IR (KBr, cm^{-1}) υ_{max}: 1629, 1721 (C=O), 3400 (OH); ^{1}H NMR (DMSO-d_6) δ: 1.34 (t, *J* = 7.10 Hz, 3H, CH_3), 2.57-2.70 (m, 4H, piperazine), 3.15-3.24 (m, 4H, piperazine), 3.89 (s, 2H, N=C-CH_2), 4.51 (q, *J* = 7.10 Hz, 2H, CH_2-CH_3), 5.24 and 5.27 (2s, 2H, NO-CH_2, *E*- and *Z*-isomers, respectively), 7.09 (d, 1H, *J* = 7.22 Hz, H-8 quinolone), 7.27-7.48 (m, 5H, phenyl), 7.50-7.56 (m, 2H, H-6 and H-7 naphthyl), 7.83-8.00 (m, 5H, H-5 quinolone, H-3, H-4, H-5 and H-8 naphthyl), 8.15 and 8.31 (2s, 1H, H-1 naphthyl, *E*- and *Z*-isomers, respectively), 8.90 (s, 1H, H-2 quinolone), 15.34 (s, 1H, COOH).

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-(phenylmethoxyimino) ethyl]piperazin-1-yl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (5l). *Z*-isomer; Yield: 80%; m.p.: 179-181 ºC; IR (KBr, cm^{-1}) υ_{max}: 1623, 1726 (C=O), 3440 (OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 (t, *J* = 7.10 Hz, 3H, CH_3), 2.60-2.65 (m, 4H, piperazine), 3.70-3.75 (m, 4H, piperazine), 3.86 (s, 2H, N=C-CH_2), 4.45 (q, *J* = 7.10 Hz, 2H, CH_2-CH_3), 5.26 (s, 2H, NO-CH_2), 7.28-7.48 (m, 5H, phenyl), 7.51-7.57 (m, 2H, H-6 and H-7 naphthyl), 7.78-7.99 (m, 4H, H-3, H-4, H-5 and H-8 naphthyl), 8.08 (d, 1H, *J* = 13.5 Hz, H-5 naphthyridine), 8.32 (s, 1H, H-1 naphthyl), 8.97 (s, 1H, H-2 naphthyridine), 15.30 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.52, 46.66, 47.33, 50.95, 52.48, 108.77, 113.24, 119.58, 119.76, 123.57, 125.84, 126.20, 126.25, 127.23, 127.28, 127.38, 127.57, 128.04, 128.09, 128.14, 132.25, 132.59, 133.25, 137.13, 144.58, 145.89, 147.93, 149.92, 149.98, 153.71, 166.60, 176.59.

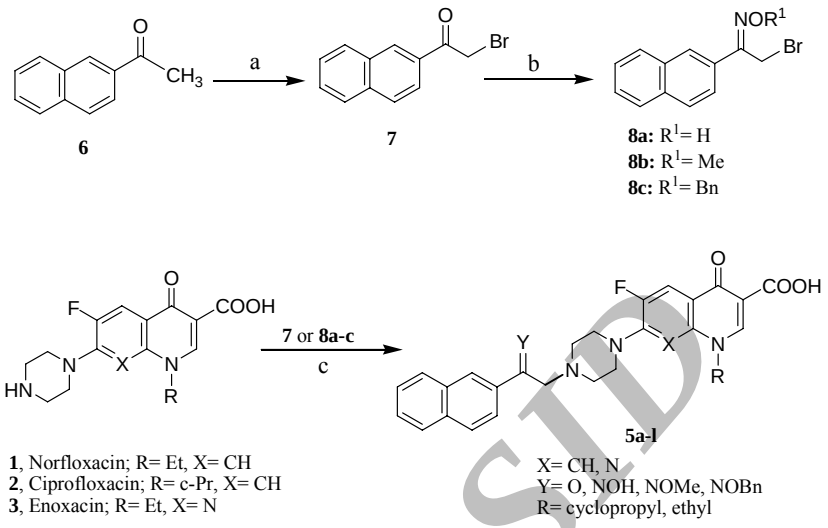
Antibacterial Activity

Agar-dilution method for determination of MIC. Compounds **5a-l** were evaluated for their antibacterial activity using agar-dilution method [14]. Twofold serial dilutions of the compounds and reference drugs **1-3** were prepared in Mueller-Hinton agar. Drugs (10.0 mg) were dissolved in DMSO (1 ml) and the solution was diluted with water (9 ml). Further progressive double dilution with melted Mueller-Hinton agar was performed to obtain the required concentrations of 100, 50, 25, 12.5, 6.25, 3.13, 1.56, 0.78, 0.39, 0.19, 0.098, 0.049, 0.025, 0.013, 0.006, 0.003 and 0.0015 μg ml^{-1}. The bacteria inocula were prepared by suspending overnight colonies from Mueller-Hinton agar media in 0.85% saline. The inocula were adjusted photometrically at 600 nm to a cell density equivalent to approximately 0.5 McFarland standard (1.5 $\times 10^8$ CFU/ml). The suspensions were then diluted in 0.85% saline to give 10^7 CFU/ml. Petri dishes were spot-inoculated with 1 μl of each prepared bacterial suspension (10^4 CFU/spot) and incubated at 35-37 ºC for 18 h. The minimum inhibitory concentration (MIC) was the lowest concentration of the test compound, which resulted in no visible growth on the plate. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment.

RESULTS AND DISCUSSION

Chemistry

The efficient synthetic rout to obtain *N*-[2-(2-naphthyl)ethyl]piperazinyl quinolones **5a-l** is outlined in Scheme 1. The starting compound 2-acetylnaphthalene **6** was converted to 2-(bromoacetyl)naphthalene **7** by treating with Br_2 in $CHCl_3$. Compound **7** was converted to oxime **8a** by



Scheme 1. Synthesis of *N*-[2-(2-naphthyl)ethyl] piperazinyl quinolones **5a-l**. Reagents and conditions: (a) Br_2, $CHCl_3$, r.t. (b) appropriate hydroxylamine hydrochloride derivative, MeOH, r.t.; (c) DMF, $NaHCO_3$, r.t.

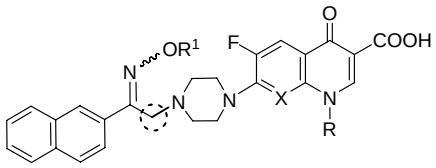
stirring with 3 equiv of hydroxylamine hydrochloride in methanol at room temperature. Similarly, the oxime ethers **8b,c** were prepared by reaction of compound **7** with methoxylamine hydrochloride or *O*-benzylhydroxylamine hydrochloride. Reaction of quinolones (**1**, **2** or **3**) with α-bromoketone **7** or α-bromooxime derivatives **8a-c** in DMF, in the presence of $NaHCO_3$ at room temperature afforded corresponding ketones **5a-c** and oxime derivatives **5d-l**, respectively. In the reaction of piperazinyl quinolones **1-3** with α-bromooxime derivatives **8a-c**, compounds **5e**, **5g-j** and **5l** were isolated as pure *Z*-isomer while compounds **5d**, **5f** and **5k** were obtained as a mixture of *E*- and *Z*-isomers, predominantly in the *E*-configuration. The stereochemical assignment of the oxime derivatives **5d-l** was elucidated by ^1H and ^{13}C NMR spectroscopy. It is known from the literature that the assignment of geometry in α-substituted ethanone oximes is possible on the basis of the chemical shifts of the methylene attached to the imino-group [15-18]. The selected ^1H and ^{13}C NMR spectroscopic data of *Z* and *E*-isomers are presented in Table 1. In *Z*-isomers, the methylene protons are deshielded by the presence of the proximal oxygen of oxime function and appeared lower field at δ 3.81-3.89 ppm compare to the corresponding *E*-isomers (δ 3.51-3.54 ppm). These results is in accordance to previous experiences in oximes and oxime ethers suggesting that proximity to the oxygen of the oxime in the α-*syn* configuration will deshield the proton and cause a downfield shift in the signals of related protons. In contrast, the ^{13}C signals of the α-*syn* carbon (methylene connected to C=N) of oxime derivatives akin to the *Z*-isomers have a significant upfield shift (δ 52.38-52.93 ppm) relative to the α-*anti*-counterparts of the *E*-isomers (δ 61.30-61.39 ppm). This is based upon steric compression (called the γ effect) causing an upfield shift of the ^{13}C nuclei in close proximity to the oxygen of oxime moiety [19-21].

Antibacterial Activity

The compounds **5a-l** were tested against a panel of microorganisms including *Staphylococcus aureus* ATCC 6538p, methicillin-resistant *Staphylococcus aureus* (MRSA I and MRSA II, clinical isolates), *Staphylococcus epidermidis* ATCC 12228, *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 10031 and *Pseudomonas aeruginosa* ATCC 9027. The minimum inhibitory concentration (MIC) values were determined using agar-dilution method [22]. The MICs (μg ml^{-1}) obtained for compounds **5a-l** in comparison with norfloxacin, ciprofloxacin and enoxacin are presented in Table 2.

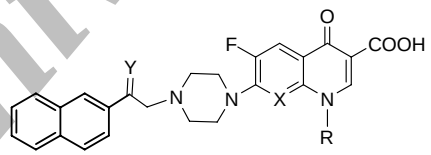
Generally, the MICs of the test compounds indicate that ketones **5a-c** and oximes **5d-f** exhibit good activity against Gram-positive and Gram-negative bacteria.

Table 1. Selected ^{1}H and ^{13}C NMR Spectroscopic Data Related to Methylene Group Attached to C=N of *Z*- and *E*-Oxime Derivatives **5d-l**



Compd	X	R	R^1	δ_H (ppm)		δ_C (ppm)	
				Z-isomer	*E*-isomer	*Z*-isomer	*E*-isomer
5d	CH	c-Pr	H	3.85	3.54	52.56	61.39
5e	CH	Et	H	3.86	-	52.54	-
5f	N	Et	H	3.82	3.51	52.38	61.30
5g	CH	c-Pr	Me	3.86	-	52.93	-
5h	CH	Et	Me	3.84	-	52.50	-
5i	N	Et	Me	3.81	-	-	-
5j	CH	c-Pr	Bn	3.89	-	52.47	-
5k	CH	Et	Bn	3.89	Obscured	-	-
5l	N	Et	Bn	3.86	-	52.48	-

Table 2. *In vitro* Antibacterial Activities of Compounds **5a-l** Against Selected Strains (MICs in μg ml^{-1})



Compd.	X	Y	R	Gram-positive organisms					Gram-negative organisms		
				S. a. [a]	MRSA I	MRSA II	*S. e.*	*B. s.*	*E. c.*	*K. p*	*P. a.*
5a	CH	O	c-Pr	0.190	0.190	0.190	0.390	0.098	0.006	0.003	0.390
5b	CH	O	Et	0.780	1.560	1.560	1.560	0.780	0.049	0.024	1.560
5c	N	O	Et	0.780	0.780	0.780	0.780	0.390	0.098	0.049	0.780
5d	CH	NOH	c-Pr	0.098	0.098	0.098	0.098	0.049	0.098	0.098	6.250
5e	CH	NOH	Et	0.39	0.098	0.098	0.390	0.049	0.098	0.049	3.130
5f	N	NOH	Et	0.780	0.780	0.780	0.780	0.190	3.130	0.390	>100
5g	CH	NOMe	c-Pr	0.780	0.780	0.780	0.390	0.190	0.780	0.190	50
5h	CH	NOMe	Et	1.560	3.130	3.130	1.560	0.780	0.390	0.190	12.5
5i	N	NOMe	Et	3.130	3.130	3.130	3.130	0.780	1.560	0.780	100
5j	CH	NOBn	c-Pr	>100	>100	>100	100	50	12.5	6.250	>100
5k	CH	NOBn	Et	>100	>100	>100	>100	>100	50	1.560	>100

Table 2. Continued

5l	N	NOBn	Et	>100	>100	>100	100	100	100	25	>100
Norfloxacin				0.39	0.78	0.78	0.78	0.39	0.049	0.025	0.78
Ciprofloxacin				0.19	0.39	0.39	0.39	0.19	0.013	0.003	0.39
Enoxacin				0.78	0.78	0.78	1.56	0.78	0.098	0.098	1.56

[a]*S. a.*: *Staphylococcus aureus* ATCC 6538p, MRSA I and II: methicillin-resistant *Staphylococcus aureus* (clinical isolates I and II), *S. e.*: *Staphylococcus epidermidis* ATCC 12228, *B. s.*: *Bacillus subtilis* ATCC 6633, *E. c.*: *Escherichia coli* ATCC 8739, *K. p.*: *Klebsiella pneumoniae* ATCC 10031, *P. a.*: *Pseudomonas aeruginosa* ATCC 9027.

Antibacterial data of compounds **5a-l** against staphylococci reveals that compound **5d** exhibits the most potent antibacterial activity against staphylococci including methicillin-resistant *S. aureus*. Its activity (MIC = 0.098 μg ml^{-1}) was better than that of reference drugs (MICs = 0.19-1.56 μg ml^{-1}). Moreover, the activities of compounds **5c** and **5e-g** against staphylococci were comparable to standard quinolones (MIC ≤ 0.78 μg ml^{-1}). Compounds **5a-i** had significant in vitro activity against *B. subtilis* (MICs = 0.049-0.78 μg ml^{-1}). Among them, compounds **5d** and **5e** exhibited the most potent antibacterial activity against *B. subtilis*, being more active than the reference drugs. All compounds did not show any improvement of activity against Gram-negative bacteria in comparison to parent quinolones. However, the ketones **5a-c** showed comparable activity against Gram-negative bacteria, with respect to the reference drugs.

The MIC values of the ketones **5a-c**, oximes **5d-f** and *O*-methyl oximes **5g-i** indicate that the most active compounds in each series were ciprofloxacin derivatives (R = cyclopropyl, X = CH). These results reveal the impact of cyclopropyl substituent at N-1 position in all derivatives.

Generally, in the case of Gram-positives, better results are obtained with cyclopropyl at N-1 and oxime on the spacer of naphthyl and piperazine. In contrast, against Gram-negatives, ciprofloxacin derivative bearing carbonyl functionality on the ethyl spacer showed better activity. Thus, the type of functionality on ethyl spacer seemed to have different influence on the antibacterial activity against Gram-negative and Gram-positive strains. On the other hand, the introduction of methyl pendent on oxime group decreased activity against both Gram-positive and negative bacteria. Furthermore, the substitution of bulky *O*-benzyl group on oxime moiety led to very week or inactive compounds (compounds **5j-l**).

The size and lipophilicity of the substitution on the piperazine moiety of piperazinyl quinolones were considered to be key factors in determining antibacterial activity. Thus, the introduction of bulky and lipophilic naphthyl ring was expected to allow modulation of the biological activity and physical properties of the corresponding quinolones. Moreover, the functionality on spacer between naphthyl and piperazine rings may also influence the steric characteristics and the hydrophilic-hydrophobic balance of the molecules.

In conclusion, some of the new *N*-[2-(2-naphthyl)ethyl]piperazinyl quinolones containing a carbonyl related functional groups (oxo- or oxyimino-) on the ethyl spacer showed good antibacterial activity and modification of the position 8 and N-1 substituent on quinolone ring, and ethyl spacer functionality produced significant changes in activity against Gram-positive and Gram-negative bacteria.

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