



N-substituted piperazinyl sarafloxacin derivatives: synthesis and *in vitro* antibacterial evaluation

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Abstract

Background Fluoroquinolones (FQs) are compounds of major interest with broad antimicrobial activities against community and hospital-acquired infections such as respiratory tract infections (nosocomial pneumonia, chronic bronchitis and tuberculosis), skin and soft tissue infections, bone and joint infections, intra-abdominal infections and sexually transmitted diseases. This broad range of activities along with favorable pharmacokinetic and low toxicity introduced this class of compounds as important antimicrobial chemotherapy agents. The rapid increase in prevalence of FQs resistant microbes in environment motivated medicinal chemists to discover new quinolone-based compounds with potent activities against Gram-positive bacteria.

Methods The designed compounds were prepared through the two-component reaction between aromatic α -haloketones or α -halooximes and sarafloxacin in the presence of NaHCO₃ in DMF, affording the corresponding N-[2-(aryl-3-yl) ethyl] piperazinyl quinolone derivatives in good yields. All synthesized compounds were evaluated for antibacterial activities against Gram-positive [*Staphylococcus aureus* ATCC 6538p, *Micrococcus luteus*, ATCC 1110, *Staphylococcus epidermidis* ATCC 12228 and *Bacillus subtilis* ATCC 6633] and Gram-negative [*Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 10031 *Pseudomonas aeruginosa* ATCC 9027 and *Serratia marcescens* PTCC 1111] bacteria.

Results The antibacterial activities of 24 new compounds were reported as MIC values in comparison to sarafloxacin. The most active compound, **4 g**, exhibited similar inhibitory activity against Gram-positive bacteria including *S. aureus*, *S. epidermidis* and *B. subtilis* compared to positive control. Furthermore, benzyloxime incorporated derivatives (**4 s–4 x**) showed poor activity against all tested strains, except **4 x**.

Conclusion The obtained results indicated that the synthesized compounds containing substituted piperazine moiety at the C-7 position displayed same or weak inhibitory activities compared to sarafloxacin.

Keywords Antibacterial activity · Quinolones · Synthesis · Gram-positive bacteria

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Introduction

The fatal infections caused by multiresistant pathogens have become the worldwide concern. In addition, the inappropriate prescription and misuse of antibiotics which led to the increased rate of hospitalization, illness and death in patients have driven infectious disease to global health catastrophic threat. Therefore, the development of efficient, potent and new compounds would be a highly desirable task [1–4].

The wide spectrum of activities and compelling chemistry of quinolones have made this bicyclic core attractive for researchers. The introduction of fluoroquinolones (FQs) as antibacterial agents in 1960s eradicated the infections caused by Gram-negative pathogens. Furthermore, the

capability of new members to fight against Gram-positive bacteria resulted in successfully introduction of the popular class of antibiotics into the market [5–8]. DNA gyrase, topoisomerase IV and bacterial topoisomerase II enzymes are considered as targets of quinolone derivatives [9–13]. FQs consist of a 4-quinolone/naphthyridone-3-carboxylic acid heterocyclic core, a fluorine atom and a secondary amine group attached to the C-6 and -7 positions, respectively. The ongoing researches on quinolone and its analogues inaugurated nearly 10,000 analogues with promising antibacterial activities, opening up new horizons in the field of antibacterial chemotherapy [14, 15]. The C-7 position was subjected to various changes with hopes to find more potent and effective agents. Based on the previous extensive research in this field, the basic character of this position is significantly related to the observed activity against DNA gyrase [16]. The lipophilicity of fluoroquinolones plays an important role in the penetration of these compounds into bacterial cells, indicating that increasing the lipophilic character at C-7 position may increase their activity. In this regard, the presence of a bulky group at the N-4 position of piperazine is permitted. Therefore, different derivatives containing 2-oxoethyl or 2-oximinoethyl derivative attached to the piperazine ring at C-7 position were synthesized [13]. In addition, the attachment of thiophene [17, 18], furan [19], substituted phenyl [20] and coumarin [21, 22] to piperazine ring was also investigated by our research team. In continuation of our expertise in this field [23–25], we report some novel analogues of sarafloxacin **3**, possessing α -haloketones- (**1a-f**), hydroxyimino- (**2 g-l**), methoxyimino- (**2 m-r**) and benzyloxyimino (**2 s-x**)-functionalized piperazine as C-7 substituents and evaluate their antibacterial activity against Gram-positive and Gram-negative bacteria.

Methods

Materials

All chemicals and solvents were obtained from Merck and Aldrich and used without further purification. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Shimadzu 470 spectrophotometer (potassium bromide disks) was used to record the IR spectra. ^1H - and ^{13}C -NMR spectra were recorded on Bruker FT-500 (Germany), using TMS as an internal standard. Elemental analyses were measured by CHN-O-rapid elemental analyzer (GmbH-Germany).

General procedure for the synthesis of compounds 4a-x A mixture of compounds (**1a-f**) or (**2 g-x**) (0.55 mmol), sarafloxacin (**3**) (0.5 mmol) and NaHCO_3 (0.5 mmol) in DMF (5 mL) was stirred at room temperature for 3–7 days.

After consumption of sarafloxacin (**3**), monitored by TLC, water (20 mL) was added and the precipitate was filtered, washed with water. For further purification, the products were recrystallized from $\text{CH}_3\text{OH}/\text{CHCl}_3$ to afford target compounds **4a-x**.

6-Fluoro-1-(4-fluorophenyl)-4-oxo-7-(4-(2-oxo-2-phenylethyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (**4a**)

Off-white powder, ^1H -NMR (500 MHz, $\text{DMSO}-d_6$) δ (ppm): 2.65 (bs, 4H, piperazine), 3.07 (bs, 4H, piperazine), 3.37 (s, 2H), 6.39 (d, $^4J_{\text{H-F}} = 7.5$ Hz, 1H, aromatic), 7.30–7.33 (m, 3H, aromatic), 7.52–7.58 (m, 3H, aromatic), 7.78–7.79 (m, 3H, aromatic), 7.98 (d, $^3J_{\text{H-F}} = 13$ Hz, 1H, aromatic), 8.64 (s, 1H, aromatic), 11.35 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3580$ –3300 (OH), 1722, 1672, 1622 (C=O). Anal. Calcd. For $\text{C}_{28}\text{H}_{23}\text{F}_2\text{N}_3\text{O}_4$: C: 66.79; H: 4.60; N: 8.35; Found: C: 66.50; H: 4.82; N: 8.15.

6-Fluoro-1-(4-fluorophenyl)-7-(4-(2-(4-fluorophenyl)-2-oxoethyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4b**)

Off-white powder, ^1H -NMR (500 MHz, $\text{DMSO}-d_6$) δ (ppm): 2.63–2.67 (m, 4H, piperazine), 3.05–3.10 (m, 4H, piperazine), 3.86 (s, 2H), 6.39 (d, $^3J_{\text{H-F}} = 7.5$ Hz, 1H, aromatic), 7.32 (t, $J = 9$ Hz, 2H, aromatic), 7.52 (t, $J = 8.5$ Hz, 2H, aromatic), 7.76–7.79 (m, 2H, aromatic), 7.97 (d, $J = 13$ Hz, 1H, aromatic), 8.05–8.08 (m, 2H, aromatic), 8.62 (s, 1H, aromatic), 11.21 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3580$ –3300 (OH), 1716, 1661, 1618 (C=O). ^{13}C -NMR (125 MHz, $\text{DMSO}-d_6$) δ (ppm): 49.0, 52.0 (CH_2 piperazine), 63.4 (CH_2), 106.4, 107.2, 111.0 (d, $^3J_{\text{C-F}} = 23.75$ Hz), 115.5 (d, $^3J_{\text{C-F}} = 21.25$ Hz), 117.2 (d, $^3J_{\text{C-F}} = 22.5$ Hz), 119.0, 121.3, 129.8 (d, $^1J_{\text{C-F}} = 7.5$ Hz), 131.2 (d, $^1J_{\text{C-F}} = 8.75$ Hz), 132.4, 136.1, 139.1, 145.2, 148.6, 152.0, 154.0, 165.7 (COOH), 176.6 (C=O), 195.4. Anal. Calcd. For $\text{C}_{28}\text{H}_{22}\text{F}_3\text{N}_3\text{O}_4$: C: 64.49; H: 4.25; N: 8.06; C: 64.72; H: 4.47; N: 7.85.

7-(4-(2-(4-Chlorophenyl)-2-oxoethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4c**)

Off-white powder, ^1H -NMR (500 MHz, $\text{DMSO}-d_6$) δ (ppm): 2.63–2.68 (m, 4H, piperazine), 3.06–3.12 (m, 4H, piperazine), 3.86 (s, 2H), 6.39 (d, $^4J_{\text{H-F}} = 7.5$ Hz, 1H, aromatic), 7.52 (t, $J = 8$ Hz, 2H, aromatic), 7.57 (d, $J = 8.5$ Hz, 2H, aromatic), 7.76–7.79 (m, 2H, aromatic), 7.96–8.02 (m, 3H, aromatic), 8.62 (s, 1H, aromatic), 10.20 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3590$ –3300 (OH), 1725, 1679, 1619 (C=O). ^{13}C -NMR (125 MHz, $\text{DMSO}-d_6$) δ (ppm): 48.9, 51.9 (CH_2 piperazine), 63.3 (CH_2), 106.3, 107.0, 111.0 (d, $^3J_{\text{C-F}} = 22.5$ Hz), 117.1 (d, $^3J_{\text{C-F}} = 22.5$ Hz), 119.0, 128.5, 129.7, 129.9 (d, $^1J_{\text{C-F}}$

$F = 7.5$ Hz), 130.0, 134.1, 136.1, 138.0, 139.1, 145.2, 149.3, 153.7, 165.6 (COOH), 178.1 (C=O), 196.6. Anal. Calcd. For $C_{28}H_{22}ClF_2N_3O_4$: C: 62.52; H: 4.12; N: 7.81; C: 62.80; H: 4.39; N: 7.59.

7-(4-(2-(4-Bromophenyl)-2-oxoethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4d)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.30–2.35 (m, 4H, piperazine), 3.01–3.07 (m, 4H, piperazine), 3.30 (s, 2H), 6.39 (d, $^4J_{H-F} = 6$ Hz, 1H, aromatic), 7.53–7.54 (m, 2H, aromatic), 7.74–7.79 (m, 3H, aromatic), 7.83 (s, 1H, aromatic), 7.88–7.93 (m, 2H, aromatic), 8.01–8.03 (m, 1H, aromatic), 8.64 (s, 1H, aromatic), 10.66 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3580$ – 3300 (OH), 1722, 1666, 1621 (C=O). ^{13}C -NMR (125 MHz, DMSO- d_6) δ (ppm): 49.1, 52.0 (CH₂ piperazine), 63.0 (CH₂), 106.5, 107.3, 111.0 (d, $^1J_{C-F} = 23.75$ Hz), 117.2 (d, $^3J_{C-F} = 22.5$ Hz), 119.0, 128.0, 128.6, 129.5, 129.8 (d, $^1J_{C-F} = 7.5$ Hz), 133.4, 136.4, 139.4, 146.2, 148.8, 152.5, 154.0, 165.8 (COOH), 176.8 (C=O), 197.3. Anal. Calcd. For $C_{28}H_{22}BrF_2N_3O_4$: C: 57.74; H: 3.81; N: 7.22; C: 58.00; H: 3.54; N: 7.59.

6-Fluoro-1-(4-fluorophenyl)-4-oxo-7-(4-(2-oxo-2-(p-tolyl)ethyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (4e)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.39 (s, 3H, CH₃), 2.64 (bs, 4H, piperazine), 3.01 (bs, 4H, piperazine), 3.84 (s, 2H), 6.39 (d, $^4J_{H-F} = 7$ Hz, 1H, aromatic), 7.30 (d, $J = 8$ Hz, 2H, aromatic), 7.50–7.53 (m, 2H, aromatic), 7.76 (d, $J = 7.5$ Hz, 2H, aromatic), 7.87 (t, $J = 6.5$ Hz, 2H, aromatic), 7.96 (d, $^3J_{H-F} = 12.5$ Hz, 1H, aromatic), 8.61 (s, 1H, aromatic), 11.77 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3580$ – 3300 (OH), 1716, 1661, 1618 (C=O). Anal. Calcd. For $C_{29}H_{25}F_2N_3O_4$: C: 67.30; H: 4.87; N: 8.12; C: 67.55; H: 7.51; N: 8.39.

7-(4-(2-(2,4-Dichlorophenyl)-2-oxoethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4f)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.62 (bs, 4H, piperazine), 3.02 (bs, 4H, piperazine), 3.76 (s, 2H), 6.38 (d, $^4J_{H-F} = 7$ Hz, 1H, aromatic), 7.54–7.58 (m, 3H, aromatic), 7.72–7.84 (m, 3H, aromatic), 7.96 (d, $^3J_{H-F} = 13$ Hz, 1H, aromatic), 8.00 (t, $J = 7.5$ Hz, 1H, aromatic), 8.63 (s, 1H, aromatic), 12.10 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3585$ – 3300 (OH), 1720, 1680, 1620 (C=O). ^{13}C -NMR (125 MHz, DMSO- d_6) δ (ppm): 48.9, 51.8 (CH₂ piperazine), 65.8 (CH₂), 104.3, 106.6, 107.8, 111.0 (d, $^3J_{C-F}$

$F = 22.5$ Hz), 117.2 (d, $^3J_{C-F} = 22.5$ Hz), 119.0, 127.4, 129.8 (d, $^1J_{C-F} = 7.5$ Hz), 130.7, 131.0, 136.1, 139.1, 139.8, 146.0, 148.7, 154.0, 161.2, 162.2, 165.8 (COOH), 177.3 (C=O), 196.6. Anal. Calcd. For $C_{28}H_{21}Cl_2F_2N_3O_4$: C: 58.75; H: 3.70; N: 7.34; C: 59.00; H: 3.47; N: 7.64.

6-Fluoro-1-(4-fluorophenyl)-7-(4-(2-(hydroxyimino)-2-phenylethyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4 g)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.98 (bs, 8H, piperazine), 3.65 (s, 2H), 6.37 (s, 1H, aromatic), 7.34–7.40 (m, 3H, aromatic), 7.51–7.58 (m, 3H, aromatic), 7.75–7.80 (m, 3H, aromatic), 7.95 (d, $^3J_{H-F} = 13$ Hz, 1H, aromatic), 8.62 (s, 1H, aromatic), 10.96 (s, 1H, NOH), 11.44 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3580$ – 3300 (OH), 1718, 1618 (C=O). ^{13}C -NMR (125 MHz, DMSO- d_6) δ (ppm): 49.8, 52.0 (CH₂ piperazine), 61.2 (CH₂), 106.5, 107.4, 110.9 (d, $^3J_{C-F} = 23.75$ Hz), 117.2 (d, $^3J_{C-F} = 23.75$ Hz), 119.0, 126.1, 127.7, 128.4 (d, $^1J_{C-F} = 7.5$ Hz), 129.8, 133.5, 136.1, 139.1, 145.1, 148.6, 152.6, 155.0, 161.5 (C=N), 165.7 (COOH), 176.6 (C=O). Anal. Calcd. For $C_{28}H_{24}F_2N_4O_4$: C: 64.86; H: 4.67; N: 10.81; C: 65.09; H: 4.40; N: 11.03.

6-Fluoro-1-(4-fluorophenyl)-7-(4-(2-(4-fluorophenyl)-2-(hydroxyimino)ethyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4 h)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.97–3.04 (m, 4H, piperazine), 3.17–3.21 (m, 4H, piperazine), 3.65 (s, 2H), 6.36 (s, 1H, aromatic), 7.41 (t, $^3J_{H-F} = 13$ Hz, 1H, aromatic), 7.51–7.53 (m, 3H, aromatic), 7.64 (d, $J = 7.5$ Hz, 1H, aromatic), 7.76 (s, 3H, aromatic), 7.95 (d, $J = 12$ Hz, 1H, aromatic), 8.62 (s, 1H, aromatic), 11.14 (s, 1H, NOH), 11.57 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3585$ – 3300 (OH), 1720, 1620 (C=O). Anal. Calcd. For $C_{28}H_{23}F_3N_4O_4$: C: 62.68; H: 4.32; N: 10.44; C: 62.40; H: 4.05; N: 10.63.

7-(4-(2-(4-Chlorophenyl)-2-(hydroxyimino)ethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4i)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.70–2.79 (m, 4H, piperazine), 3.06–3.11 (m, 4H, piperazine), 3.87 (s, 2H), 6.42 (d, $^4J_{H-F} = 7$ Hz, 1H, aromatic), 7.53 (t, $J = 8$ Hz, 2H, aromatic), 7.57 (d, $J = 8.5$ Hz, 1H, aromatic), 7.68 (d, $J = 8.5$ Hz, 1H, aromatic), 7.73–7.80 (m, 2H, aromatic), 7.92 (d, $^3J_{H-F} = 13$ Hz, 1H, aromatic), 7.97–8.02 (m, 2H, aromatic), 8.63 (s, 1H, aromatic), 11.14 (s, 1H, NOH), 11.57 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3600$ – 3300 (OH), 1719, 1620 (C=O). ^{13}C -NMR (125 MHz, DMSO- d_6) δ (ppm): 49.7, 51.9 (CH₂ piperazine), 61.0 (CH₂), 106.5, 107.3, 111.0 (d, $^3J_{C-F} =$

23.75 Hz), 117.2 (d, $^3J_{C-F}$ = 22.5 Hz), 127.7, 128.0, 129.8 (d, $^1J_{C-F}$ = 10 Hz), 130.4, 133.1, 134.7, 136.1, 139.1, 145.1, 148.6, 151.9, 155.0, 161.6 (C=N), 165.7 (COOH), 176.6 (C=O). Anal. Calcd. For $C_{28}H_{23}ClF_2N_4O_4$: C: 60.82; H: 4.19; N: 10.13; Cl: 60.63; F: 3.89; O: 10.40.

7-(4-(2-(4-Bromophenyl)-2-(hydroxyimino)ethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4j)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.98–3.05 (m, 4H, piperazine), 3.17–3.22 (m, 4H, piperazine), 3.69 (s, 2H), 6.36 (d, $^4J_{H-F}$ = 7 Hz, 1H, aromatic), 7.55–7.56 (m, 2H, aromatic), 7.96–7.74 (m, 3H, aromatic), 7.58 (s, 1H, aromatic), 7.90–7.95 (m, 2H, aromatic), 8.03 (t, J = 7 Hz, 1H, aromatic), 8.63 (s, 1H, aromatic), 11.19 (s, 1H, NOH), 11.60 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu}$ = 3590–3300 (OH), 1725, 1619 (C=O). ^{13}C -NMR (125 MHz, DMSO- d_6) δ (ppm): 49.0, 52.2 (CH₂ piperazine), 61.0 (CH₂), 106.5, 107.3, 111.0, 117.2 (d, $^3J_{C-F}$ = 22.5 Hz), 119.0, 122.0, 128.2, 129.8 (d, $^1J_{C-F}$ = 7.5 Hz), 130.6, 131.0, 136.1, 139.1, 145.1, 148.6, 152.0, 155.1, 161.2 (C=N), 165.7 (COOH), 176.6 (C=O). Anal. Calcd. For $C_{28}H_{23}BrF_2N_4O_4$: C: 56.29; H: 3.88; N: 9.38; Br: 56.03; F: 3.59; O: 9.54.

6-Fluoro-1-(4-fluorophenyl)-7-(4-(2-(hydroxyimino)-2-(p-tolyl)ethyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4 k)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.23 (s, 3H), 2.92–3.09 (m, 8H, piperazine), 3.61 (s, 2H), 6.36 (d, $^4J_{H-F}$ = 7.5 Hz, 1H, aromatic), 7.32 (d, J = 8 Hz, 2H, aromatic), 7.53–7.65 (m, 2H, aromatic), 7.78 (d, J = 7.5 Hz, 2H, aromatic), 7.89 (t, J = 7.5 Hz, 2H, aromatic), 7.96 (d, $^3J_{H-F}$ = 13 Hz, 1H, aromatic), 8.64 (s, 1H, aromatic), 11.12 (s, 1H, NOH), 11.40 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu}$ = 3590–3300 (OH), 1719, 1618 (C=O). ^{13}C -NMR (125 MHz, DMSO- d_6) δ (ppm): 20.8 (CH₃), 47.0, 49.0 (CH₂ piperazine), 52.4 (CH₂), 106.5, 107.4, 111.0 (d, $^3J_{C-F}$ = 23.75 Hz), 117.3 (d, $^3J_{C-F}$ = 22.5 Hz), 119.1, 126.1, 128.8, 129.9 (d, $^1J_{C-F}$ = 7.5 Hz), 131.5, 133.5, 136.1, 139.1, 143.1, 148.8, 150.0, 154.5, 161.6 (C=N), 165.7 (COOH), 176.7 (C=O). Anal. Calcd. For $C_{29}H_{26}F_2N_4O_4$: C: 65.41; H: 4.92; N: 10.52; F: 65.18; O: 5.19; N: 10.82.

7-(4-(2-(2,4-Dichlorophenyl)-2-(hydroxyimino)ethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4 l)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.98–3.19 (m, 8H, piperazine), 3.65 (s, 2H), 6.37 (s, 1H, aromatic), 7.26 (m, 1H, aromatic), 7.43–7.48 (m, 1H, aromatic), 7.52 (t, J = 5.5 Hz, 2H, aromatic), 7.63 (s,

1H, aromatic), 7.70–7.77 (m, 2H, aromatic), 7.96 (d, $^3J_{H-F}$ = 13 Hz, 1H, aromatic), 8.63 (s, 1H, aromatic), 11.15 (s, 1H, NOH), 11.48 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu}$ = 3580–3300 (OH), 1716, 1618 (C=O). ^{13}C -NMR (125 MHz, DMSO- d_6) δ (ppm): 49.0, 52.1 (CH₂ piperazine), 61.0 (CH₂), 106.5, 107.3, 111.4 (d, $^3J_{C-F}$ = 22.5 Hz), 117.3 (d, $^3J_{C-F}$ = 22.5 Hz), 119.0, 127.1, 128.6, 128.2, 129.8 (d, $^1J_{C-F}$ = 7.5 Hz), 131.2, 133.4, 136.1, 139.1 (2C), 146.1, 148.7, 152.0, 154.0, 161.5 (C=N), 165.7 (COOH), 176.6 (C=O). Anal. Calcd. For $C_{28}H_{22}Cl_2F_2N_4O_4$: C: 57.25; H: 3.78; N: 9.54; Cl: 57.00; F: 3.98; O: 9.21.

6-Fluoro-1-(4-fluorophenyl)-7-(4-(2-(methoxyimino)-2-phenylethyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4 m)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.90–3.00 (m, 8H, piperazine), 3.64 (s, 2H), 3.90 (s, 3H, NOCH₃), 6.35 (d, $^4J_{H-F}$ = 7 Hz, 1H, aromatic), 7.36–7.39 (s, 3H, aromatic), 7.50 (t, J = 8.5 Hz, 2H, aromatic), 7.73–7.75 (m, 4H, aromatic), 7.96 (d, $^3J_{H-F}$ = 13.5 Hz, 1H, aromatic), 8.62 (s, 1H, aromatic), 15.14 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu}$ = 3625–3250 (OH), 1724, 1623 (C=O). ^{13}C -NMR (125 MHz, DMSO- d_6) δ (ppm): 49.0, 50.4 (CH₂ piperazine), 52.2 (CH₂), 61.7 (OCH₃), 106.2, 107.1, 111.1 (d, $^3J_{C-F}$ = 23.75 Hz), 117.2 (d, $^3J_{C-F}$ = 23.75 Hz), 118.0, 126.5, 128.1, 129.0, 129.8 (d, $^1J_{C-F}$ = 8.75 Hz), 134.8, 136.1, 139.1, 146.0, 146.8, 152.0, 153.9, 163.7 (C=N), 165.8 (COOH), 176.8 (C=O). Anal. Calcd. For $C_{29}H_{26}Cl_2F_2N_4O_4$: C: 65.41; H: 4.92; N: 10.52; Cl: 65.19; F: 5.11; O: 10.80.

6-Fluoro-1-(4-fluorophenyl)-7-(4-(2-(4-fluorophenyl)-2-(methoxyimino)ethyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4n)

Off-white powder, 1H -NMR (500 MHz, DMSO- d_6) δ (ppm): 2.90–2.99 (m, 8H, piperazine), 3.63 (s, 2H), 3.90 (s, 3H, NOCH₃), 6.35 (d, $^4J_{H-F}$ = 6.5 Hz, 1H, aromatic), 7.19–7.21 (m, 2H, aromatic), 7.51–7.53 (m, 2H, aromatic), 7.77–7.79 (m, 4H, aromatic), 7.96 (d, $^3J_{H-F}$ = 12.5 Hz, 1H, aromatic), 8.62 (s, 1H, aromatic), 15.10 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu}$ = 3600–3250 (OH), 1713, 1619 (C=O). ^{13}C -NMR (125 MHz, DMSO- d_6) δ (ppm): 49.0, 50.4 (CH₂ piperazine), 52.1 (CH₂), 61.8 (OCH₃), 106.7, 107.7, 111.1 (d, $^3J_{C-F}$ = 23.75 Hz), 115.0 (d, $^3J_{C-F}$ = 23.75 Hz), 117.2 (d, $^3J_{C-F}$ = 23.75 Hz), 122.1, 128.8 (d, $^1J_{C-F}$ = 8.75 Hz), 129.8 (d, $^1J_{C-F}$ = 8.75 Hz), 131.2, 136.2, 139.4 (2C), 146.0, 148.6, 153.0, 158.2, 161.8 (C=N), 176.4 (COOH), 179.6 (C=O). Anal. Calcd. For $C_{29}H_{25}F_3N_4O_4$: C: 63.27; H: 4.58; N: 10.18; Cl: 63.01; F: 4.84; O: 9.94.

7-(4-(2-(4-Chlorophenyl)-2-(methoxyimino)ethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4o)

Off-white powder, $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ (ppm): 2.87–2.95 (m, 8H, piperazine), 3.60 (s, 2H), 3.90 (s, 3H, NOCH_3), 6.22 (d, $^4J_{\text{H-F}} = 6.5$ Hz, 1H, aromatic), 7.36–7.37 (m, 1H, aromatic), 7.41–7.42 (m, 1H, aromatic), 7.46–7.49 (m, 1H, aromatic), 7.62–7.64 (m, 3H, aromatic), 7.73–7.78 (m, 3H, aromatic), 8.08 (s, 1H, aromatic), 15.15 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3585\text{--}3300$ (OH), 1720, 1620 (C=O). Anal. Calcd. For $\text{C}_{29}\text{H}_{25}\text{ClF}_2\text{N}_4\text{O}_4$: C: 61.43; H: 4.44; N: 9.88; Cl: 61.68; F: 4.21; O: 10.09.

7-(4-(2-(4-Bromophenyl)-2-(methoxyimino)ethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4p)

Off-white powder, $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ (ppm): 2.83–2.90 (m, 8H, piperazine), 3.63 (s, 2H), 3.95 (s, 3H, NOCH_3), 6.24 (d, $^4J_{\text{H-F}} = 6.5$ Hz, 1H, aromatic), 7.38–7.39 (m, 2H, aromatic), 7.49–7.55 (m, 3H, aromatic), 7.65 (s, 1H, aromatic), 7.71–7.75 (m, 2H, aromatic), 7.83 (t, $J = 6.5$ Hz, 1H, aromatic), 8.60 (s, 1H, aromatic), 15.18 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3580\text{--}3300$ (OH), 1716, 1618 (C=O). Anal. Calcd. For $\text{C}_{29}\text{H}_{25}\text{BrF}_2\text{N}_4\text{O}_4$: C: 56.97; H: 4.12; N: 9.16; Br: 57.10; F: 3.95; O: 8.99.

6-Fluoro-1-(4-fluorophenyl)-7-(4-(2-(methoxyimino)-2-(p-tolyl)ethyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4q)

Off-white powder, $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ (ppm): 2.44 (s, 3H, CH_3), 2.86–2.94 (m, 8H, piperazine), 3.60 (s, 2H), 3.91 (s, 3H, NOCH_3), 6.31 (d, $^4J_{\text{H-F}} = 6.5$ Hz, 1H, aromatic), 7.34 (d, $J = 7.5$ Hz, 2H, aromatic), 7.52–7.57 (m, 2H, aromatic), 7.78 (d, $J = 7$ Hz, 2H, aromatic), 7.89 (t, $J = 6$ Hz, 2H, aromatic), 7.94 (d, $^3J_{\text{H-F}} = 12.5$ Hz, 1H, aromatic), 8.65 (s, 1H, aromatic), 15.25 (1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3580\text{--}3300$ (OH), 1722, 1622 (C=O). Anal. Calcd. For $\text{C}_{30}\text{H}_{28}\text{F}_2\text{N}_4\text{O}_4$: C: 65.92; H: 5.16; N: 10.25; F: 66.11; O: 5.01; O: 10.51.

7-(4-(2-(2,4-Dichlorophenyl)-2-(methoxyimino)ethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4r)

Off-white powder, $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ (ppm): 2.85–2.91 (m, 8H, piperazine), 3.61 (s, 2H), 3.94 (s, 3H, NOCH_3), 6.30 (d, $^4J_{\text{H-F}} = 6.5$ Hz, 1H, aromatic), 7.42–7.46 (m, 2H, aromatic), 7.52 (t, $J = 8$ Hz, 2H, aromatic), 7.63 (s, 1H, aromatic), 7.73–7.75 (m, 2H, aromatic), 7.94 (d, $^3J_{\text{H-F}} = 12.5$ Hz, 1H, aromatic), 8.61 (s, 1H,

aromatic), 15.11 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3590\text{--}3300$ (OH), 1725, 1619 (C=O). $^{13}\text{C-NMR}$ (125 MHz, $\text{DMSO-}d_6$) δ (ppm): 48.8, 52.4 (CH_2 piperazine), 53.4 (CH_2), 61.9 (OCH_3), 106.4, 107.3, 111.4 (d, $^3J_{\text{C-F}} = 23.75$ Hz), 117.3 (d, $^3J_{\text{C-F}} = 23.75$ Hz), 123.0, 126.9, 128.7, 129.8 (d, $^1J_{\text{C-F}} = 8.75$ Hz), 132.2, 133.3 (2C), 133.7, 136.0, 139.0, 146.0, 148.5, 151.0, 155.8, 163.2 (C=N), 166.1 (COOH), 176.43 (C=O). Anal. Calcd. For $\text{C}_{29}\text{H}_{24}\text{Cl}_2\text{F}_2\text{N}_4\text{O}_4$: C: 57.91; H: 4.02; N: 9.32; Cl: 57.78; F: 3.88; O: 9.60.

7-(4-(2-((Benzyloxy)imino)-2-phenylethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4 s)

Off-white powder, $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ (ppm): 2.93–3.05 (m, 8H, piperazine), 3.67 (s, 2H), 5.18 (s, 2H, NOCH_2), 6.34 (d, $^4J_{\text{H-F}} = 7$ Hz, 1H, aromatic), 7.19 (t, $J = 8.5$ Hz, 2H, aromatic), 7.31 (d, $J = 7$ Hz, 1H, aromatic), 7.35–7.40 (m, 5H, aromatic), 7.51 (t, $J = 5.5$ Hz, 2H, aromatic), 7.76–7.78 (m, 4H, aromatic), 7.96 (d, $^3J_{\text{H-F}} = 13$ Hz, 1H, aromatic), 8.62 (s, 1H, aromatic), 10.11 (s, 1H, COOH). IR (KBr cm^{-1}), ν : 3590–3300 (OH), 1719, 1618 (C=O). $^{13}\text{C-NMR}$ (125 MHz, $\text{DMSO-}d_6$) δ (ppm): 48.9, 50.3 (CH_2 piperazine), 52.1 (CH_2), 75.8 (OCH_2), 106.4, 107.3, 111.0 (d, $^3J_{\text{C-F}} = 23.5$ Hz), 117.2 (d, $^3J_{\text{C-F}} = 23.75$ Hz), 118.0, 122.5, 127.8, 128.1, 128.3, 128.6, 129.1, 129.8 (d, $^1J_{\text{C-F}} = 7.5$ Hz), 131.1, 133.9, 136.1, 137.4, 139.1, 146.0, 148.8, 153.6, 163.0 (C=N), 165.6 (COOH), 177.1 (C=O). Anal. Calcd. For $\text{C}_{35}\text{H}_{30}\text{F}_2\text{N}_4\text{O}_4$: C: 69.07; H: 4.97; N: 9.21; F: 69.30; O: 5.11; O: 9.50.

7-(4-(2-((Benzyloxy)imino)-2-(4-fluorophenyl)ethyl)piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4 t)

Off-white powder, $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ (ppm): 2.93–2.99 (m, 8H, piperazine), 3.68 (s, 2H), 5.19 (s, 2H), 5.19 (s, 2H, NOCH_2), 6.33 (d, $^4J_{\text{H-F}} = 7$ Hz, 1H, aromatic), 7.30–7.39 (m, 5H, aromatic), 7.50 (t, $J = 8$ Hz, 2H, aromatic), 7.71–7.75 (m, 4H, aromatic), 7.94 (d, $^3J_{\text{H-F}} = 13$ Hz, 1H, aromatic), 8.62 (s, 1H, aromatic), 11.22 (s, 1H, COOH) IR (KBr cm^{-1}), $\tilde{\nu} = 3580\text{--}3300$ (OH), 1718, 1619 (C=O). $^{13}\text{C-NMR}$ (125 MHz, $\text{DMSO-}d_6$) δ (ppm): 48.9, 50.5 (CH_2 piperazine), 52.2 (CH_2), 75.7 (OCH_2), 106.5, 111.5 (d, $^3J_{\text{C-F}} = 21.25$ Hz), 115.0 (d, $^3J_{\text{C-F}} = 21.25$ Hz), 117.2 (d, $^3J_{\text{C-F}} = 23.75$ Hz), 118.0, 127.8, 128.1, 128.7 (d, $^1J_{\text{C-F}} = 7.5$ Hz), 131.2 (d, $^1J_{\text{C-F}} = 6.5$ Hz), 131.5, 132.3, 135.0, 136.1, 137.5, 139.5, 145.4, 148.7, 153.5, 154.0, 159.3, 163.9 (C=N), 166.5 (COOH), 177.1 (C=O). Anal. Calcd. For $\text{C}_{35}\text{H}_{29}\text{F}_3\text{N}_4\text{O}_4$: C: 67.09; H: 4.66; N: 8.94; F: 67.25; O: 4.80; O: 9.11.

7-(4-(2-((Benzyloxy)imino)-2-(4-chlorophenyl)ethyl) piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4u)

Off-white powder, $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ (ppm): 2.84–2.90 (m, 4H, piperazine), 2.92–3.00 (m, 4H, piperazine), 3.68 (s, 2H), 5.23 (s, 2H, NOCH_2), 6.33 (d, $^4J_{\text{H-F}} = 7$ Hz, 1H, aromatic), 7.31 (d, $J = 8$ Hz, 2H, aromatic), 7.36–7.42 (m, 4H, aromatic), 7.47–4.53 (m, 2H, aromatic), 7.62 (d, $J = 7.5$ Hz, 2H, aromatic), 7.73–7.79 (m, 2H, aromatic), 7.96 (d, $^3J_{\text{H-F}} = 12.5$ Hz, 1H, aromatic), 8.08 (s, 1H, aromatic), 8.62 (s, 1H, aromatic), 15.12 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3580$ –3300 (OH), 1718, 161 (C=O). Anal. Calcd. For $\text{C}_{35}\text{H}_{29}\text{ClF}_2\text{N}_4\text{O}_4$: C: 65.37; H: 4.55; N: 8.71; Cl: 65.10; F: 4.41; N: 8.94.

7-(4-(2-((Benzyloxy)imino)-2-(4-bromophenyl)ethyl) piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4v)

Off-white powder, $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ (ppm): 2.92–3.09 (m, 8H, piperazine), 3.67 (bs, 2H), 5.19 (s, 1H, NOCH_2), 6.33 (s, 1H, aromatic), 7.36–7.42 (m, 4H, aromatic), 7.51–7.55 (m, 4H, aromatic), 7.67 (d, $J = 8$ Hz, 2H, aromatic), 7.76–7.79 (m, 2H, aromatic), 7.94 (d, $^3J_{\text{H-F}} = 12$ Hz, 1H, aromatic), 8.09–8.11 (m, 2H, aromatic), 8.62 (s, 1H, aromatic), 15.10 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3580$ –3300 (OH), 1712, 1620 (C=O). $^{13}\text{C-NMR}$ (125 MHz, $\text{DMSO-}d_6$) δ (ppm): 48.9, 50.3 (CH_2 piperazine), 52.1 (CH_2), 75.8 (OCH_2), 106.4, 107.3, 111.0 (d, $^3J_{\text{C-F}} = 23.5$ Hz), 117.2 (d, $^3J_{\text{C-F}} = 23.75$ Hz), 118.0, 122.5, 127.8, 128.1, 128.3, 128.6, 129.1, 129.8 (d, $^1J_{\text{C-F}} = 7.5$ Hz), 131.1, 133.9, 136.1, 137.4, 139.1, 146.0, 148.8, 153.6, 163.0 (C=N), 165.6 (COOH), 177.1 (C=O). Anal. Calcd. For $\text{C}_{35}\text{H}_{29}\text{BrF}_2\text{N}_4\text{O}_4$: C: 61.14; H: 4.25; N: 8.15; Br: 61.33; F: 4.01; N: 8.32.

7-(4-(2-((Benzyloxy)imino)-2-(p-tolyl)ethyl) piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4w)

Off-white powder, $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ (ppm): 2.23 (s, 3H, CH_3), 2.99–3.11 (m, 4H, piperazine), 2.84–2.89 (m, 4H, piperazine), 3.64 (s, 2H), 5.35 (s, 2H, NOCH_2), 6.20 (d, $^4J_{\text{H-F}} = 7$ Hz, 1H, aromatic), 7.08 (d, $J = 8$ Hz, 1H, aromatic), 7.15 (d, $J = 7$ Hz, 1H, aromatic), 7.28–7.35 (m, 4H, aromatic), 7.38 (t, $^3J_{\text{H-F}} = 7$ Hz, 2H, aromatic), 7.47–7.50 (m, 3H, aromatic), 7.59–7.63 (m, 2H, aromatic), 7.77 (d, $^3J_{\text{H-F}} = 13$ Hz, 1H, aromatic), 8.04 (s, 1H, aromatic), 11.02 (s, 1H, COOH). IR (KBr cm^{-1}); ν 3580–3300 (COOH), 1726, 1620 (C=O). $^{13}\text{C-NMR}$ (125 MHz, $\text{DMSO-}d_6$) δ (ppm): 20.7 (CH_3), 49.0, 50.4 (CH_2 piperazine), 52.3 (CH_2), 75.7 (OCH_2), 106.3, 108.8, 111.8 (d, $^3J_{\text{C-F}} = 23.75$ Hz), 117.9 (d, $^3J_{\text{C-F}} = 23.75$ Hz), 121.5, 126.4, 127.8, 128.1, 128.2, 128.7,

129.8 (d, $^1J_{\text{C-F}} = 8.75$ Hz), 132.2, 136.3, 137.8, 138.6, 140.5, 145.5, 148.9, 151.2, 154.9, 163.0 (COOH), 169.0 (C=N), 173.0 (C=O). Anal. Calcd. For $\text{C}_{36}\text{H}_{32}\text{F}_2\text{N}_4\text{O}_4$: C: 69.44; H: 5.18; N: 9.00; F: 69.62; H: 5.41; N: 9.22.

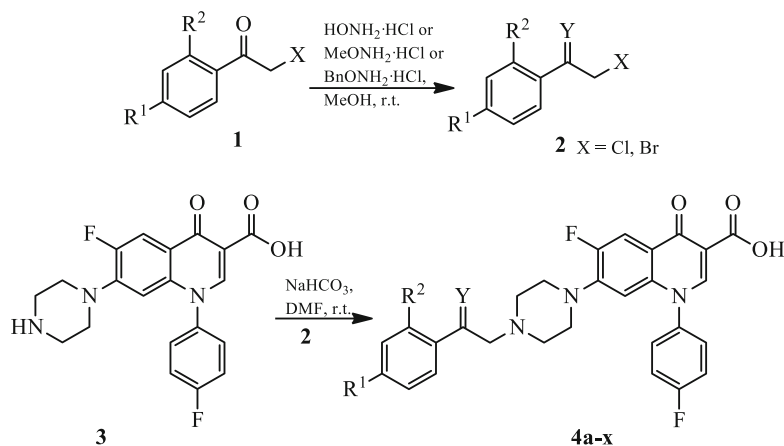
7-(4-(2-((Benzyloxy)imino)-2-(2,4-dichlorophenyl)ethyl) piperazin-1-yl)-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4x)

Off-white powder, $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ (ppm): 2.62 (bs, 4H, piperazine), 3.02–3.08 (m, 4H, piperazine), 3.58 (s, 2H), 5.16 (s, 2H, NOCH_2), 6.44 (d, $^4J_{\text{H-F}} = 7$ Hz, 1H, aromatic), 7.37 (d, $J = 7$ Hz, 1H, aromatic), 7.53 (t, $^3J_{\text{H-F}} = 6.5$ Hz, 2H, aromatic), 7.63 (d, $J = 9$ Hz, 1H, aromatic), 7.72–7.78 (m, 5H, aromatic), 7.96–8.01 (m, 3H, aromatic), 8.01 (s, 1H, aromatic), 8.63 (s, 1H, aromatic), 12.85 (s, 1H, COOH). IR (KBr cm^{-1}), $\tilde{\nu} = 3580$ –3300 (OH), 1715, 1619 (C=O). $^{13}\text{C-NMR}$ (125 MHz, $\text{DMSO-}d_6$) δ (ppm): 45.0, 49.0 (CH_2 piperazine), 51.7 (CH_2), 76.0 (OCH_2), 106.8, 111.1 (d, $^3J_{\text{C-F}} = 22.5$ Hz), 117.9 (d, $^3J_{\text{C-F}} = 22.5$ Hz), 119.0, 128.3, 130.6, 129.8 (d, $^1J_{\text{C-F}} = 8.75$ Hz), 132.2, 132.2, 136.3, 137.8, 138.6, 146.0, 148.9, 151.2, 154.9, 166.1 (COOH), 172.0 (C=N), 176.43 (C=O). Anal. Calcd. For $\text{C}_{35}\text{H}_{28}\text{Cl}_2\text{F}_2\text{N}_4\text{O}_4$: C: 62.05; H: 4.17; N: 8.27; Cl: 62.32; F: 4.36; N: 8.55.

Pharmacology

Conventional agar-dilution method was used to determine the minimum inhibitory concentrations (MIC) of the synthesized compounds (**4a-x**), according to previously reported method [26]. The results of antibacterial testing of *N*-[2-(aryl-3-yl)ethyl] piperazinyl quinolones **4** and their oxime derivatives (**4 g-x**) against a panel of selected Gram-positive [*Staphylococcus aureus* ATCC 6538p, *Micrococcus luteus*, ATCC 1110, *Staphylococcus epidermidis* ATCC 12228, *Bacillus subtilis* ATCC 6633], and Gram-negative [*Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 10031 and *Pseudomonas aeruginosa* ATCC 9027, *Serratia marcescens* PTCC 1111] bacteria are reported in Table 2, compared to the reference drug sarafloxacin.

Two-fold dilution of compounds **4a-x** and positive control were done by dissolving 6.4 mg in dimethylsulfoxide (DMSO; 1 mL), which were diluted with water (9 mL) and added to molten Mueller-Hinton (MH) agar to give a final concentration of 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.13, 0.06, 0.03, 0.015, 0.0075 and 0.00375 $\mu\text{g/mL}^{-1}$. Petri dishes were incubated with $1\text{--}5 \times 10^4$ colony forming units (cfu) at 35–37 °C and examined after 18 h. The lowest concentration of the agent, which completely led to the visible growth inhibition on the Petri dish of the microorganisms was determined as the minimum inhibitory concentration (MIC).

Table 1 Synthetic pathway and physical data of target compounds **4a-x**

Compd.	R ¹	R ²	Y	mp (°C)	Yield (%) ^a	Reaction time (days)
4a	H	H	O	190-192	31	4
4b	F	H	O	197-199	48	3
4c	Cl	H	O	199-200	36	3
4d	Br	H	O	193-194	46	3
4e	CH ₃	H	O	200-201	35	3
4f	Cl	Cl	O	195-197	41	3
4g	H	H	NOH	205-208	52	4
4h	F	H	NOH	217-220	60	3
4i	Cl	H	NOH	211-213	58	3
4j	Br	H	NOH	210-212	58	3
4k	CH ₃	H	NOH	233-235	50	3
4l	Cl	Cl	NOH	224-226	53	3
4m	H	H	NOCH ₃	207-209	63	5
4n	F	H	NOCH ₃	198-200	67	4
4o	Cl	H	NOCH ₃	206-208	70	4
4p	Br	H	NOCH ₃	202-204	66	4
4q	CH ₃	H	NOCH ₃	235-237	62	5
4r	Cl	Cl	NOCH ₃	219-221	68	5
4s	H	H	NOBn	162-164	67	7
4t	F	H	NOBn	165-166	75	5
4u	Cl	H	NOBn	172-175	76	5
4v	Br	H	NOBn	169-170	72	5
4w	CH ₃	H	NOBn	185-187	61	7
4x	Cl	Cl	NOBn	179-181	70	6

^a Isolated yields

Results and discussion

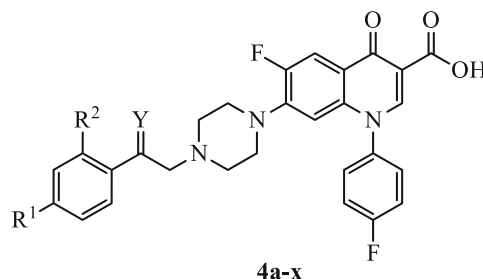
Chemistry

The synthetic pathways for the synthesis of intermediates (**2 g-r**), the target compounds (**4a-x**) and their physical data are shown in Table 1. Compounds (**2 g-r**) were prepared by stirring the ketone analogues with excess amounts of hydroxylamine, *O*-methylhydroxylamine and *O*-benzylhydroxylamine hydrochloride salts in methanol at room temperature [20–22].

Then, the reaction of **3** with compounds (**1a-f**) and (**2 g-r**) in DMF in the presence of NaHCO₃ at 25 °C afforded corresponding *N*-[2-(aryl-3-yl) ethyl] piperazinyl quinolones (**4a-x**) which was purified by recrystallization from methanol-chloroform.

Antibacterial activity

The activity of synthesized compounds (**4a-x**) were evaluated against Gram-positive [*Staphylococcus aureus* ATCC 6538p, *Micrococcus luteus*, ATCC 1110, *Staphylococcus*

Table 2 *In vitro* antibacterial activities of compounds **4a–x** in Comparison to sarafloxacin (MICs in $\mu\text{g}/\text{mL}$)

Compd.	<i>E. coli</i>	<i>Klebsiella</i>	<i>Serratia</i>	<i>Pseudomona</i>	<i>S. aureus</i>	<i>S. epidermidis</i>	<i>M. luteus</i>	<i>B. subtilis</i>
4a	0.5	4	2	0.5	0.5	0.5	8	0.5
4b	8	8	8	1	16	1	16	1
4c	0.5	1	1	1	0.5	1	0.5	0.5
4d	1	8	8	8	2	1	16	2
4e	4	4	16	1	0.5	1	16	0.5
4f	0.5	1	1	0.5	2	16	16	2
4g	0.5	4	4	4	<0.125	<0.125	2	<0.125
4h	2	8	8	4	0.25	0.25	1	0.25
4i	8	16	8	8	32	16	32	16
4j	8	8	16	4	0.5	1	16	0.5
4k	0.2	2	16	1	1	1	16	1
4l	4	32	32	8	1	2	0.5	0.5
4m	>64	>64	>64	>64	>64	>64	>64	>64
4n	1	4	2	1	1	1	8	1
4o	>64	>64	>64	32	16	64	>64	16
4p	64	64	>64	16	16	64	64	64
4q	>64	>64	>64	>64	>64	>64	>64	>64
4r	8	8	4	4	4	4	8	4
4s	>64	>64	>64	>64	32	32	>64	8
4t	>64	>64	>64	>64	>64	>64	>64	>64
4u	32	>64	>64	64	32	>64	>64	32
4v	>64	>64	>64	>64	>64	>64	>64	>64
4w	>64	>64	>64	>64	>64	>64	>64	>64
4x	0.25	4	8	2	1	0.5	8	0.5
Sarafloxacin	<0.125	<0.125	<0.125	<0.125	<0.125	<0.125	<0.125	<0.125

epidermidis ATCC 12228 and *Bacillus subtilis* ATCC 6633] and Gram-negative [*Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 10031 and *Pseudomonas aeruginosa* ATCC 9027 and *Serratia marcescens* PTCC 1111] using conventional agar-dilution method.

The MIC (minimum inhibitory concentration) values were determined against the eight strains and summarized in Table 2. As indicated in this table, it was concluded that compound **4 g** exhibited comparable results with sarafloxacin against *S. aureus*, *S. epidermidis* and *B. subtilis*, while other synthesized compounds showed moderate to poor activity against these bacteria. The obtained data suggested that the good activities were obtained in case of Gram-positive microorganism, *Bacillus subtilis*. In accordance with antibacterial

results, among ketones, *O*-methyloximes and *O*-benzyloximes derivatives of target compounds, lower susceptibilities (higher MICs) were observed in *O*-methyloxime and *O*-benzyloxime-incorporated derivatives. Thus, *O*-methyloxime and *O*-benzyloxime moiety diminished the activity against both Gram-positive and Gram-negative bacteria. The most potent compound against Gram-positive (compound **4 g**) belongs to the oxime series.

Conclusions

In conclusion, a series of FQ derivatives are synthesized and evaluated for their biological activity. Compound **4 g** showed

good activity against *S. aureus*, *S. epidermidis* and *B. subtilis*. It was concluded that the introduction of bulky moieties on piperazine ring at C-7 position of fluoroquinolones reduced the antibacterial activities against both Gram-negative and Gram-positive bacteria. In addition, the antibacterial activity of target compounds could not be improved by *O*-methylation or *O*-benzylation of oxime derivatives.

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