Synthesis and antibacterial activity of 1,3-dione derivatives of 1-cyclopropyl-7-[4-(2,6-dimethyl/ dimethoxypyrimidin-2-yl-diazenyl)-piperzin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-carboxylic acid

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In the present study, a series of 1-cyclopropyl-7-[4-(2,6-dimethylpyrimidin-2-yl-diazenyl)-piperzin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-carboxylic acid, 1-cyclopropyl-7-[4-(2,6-dimethoxypyrimidin-2-yl-diazenyl)-piperzin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-carboxylic acid and their dione derivatives have been synthesized in moderate yield. The newly synthesized compounds 5a-j have been characterized by IR, 1H NMR and elemental analysis. These compounds have been evaluated for their in vitro antibacterial activity against some gram-positive and gram-negative bacteria using conventional agar-dilution method. The antibacterial data of the newly synthesized compounds indicate that some of them showed better antibacterial activity as compared to their reference drug ciprofloxacin.

Keywords: Dimethylpyrimidine, dimethoxypyrimidine, 1,3-dione derivatives, ciprofloxacin, antibacterial activity

Quinolone antibacterial are compounds of profound interest because of their broad antibacterial spectrum both towards gram-positive and gram-negative bacteria and their in vitro chemotherapeutic efficacy1,2. Many quinolone antibacterial agents have been introduced into clinical use and significant improvements in antibacterial spectrum and activity have been achieved3-5. The most intensive structural variation has been carried out at the 7-position, partially due to the ease of their introduction through a nucleophilic aromatic-substitution reaction on the corresponding halide6,7. Piperazine, aminopyrrolidine and their substituted derivatives have been the most successfully employed side chains, as evidenced by the compounds currently on the market6,7. Originally, the newer fluoroquinolones arose with the development of 7-piperazinyl quinolones, such as norfloxacin 1 and ciprofloxacin 2 (Figure 1), which combined structural features of flumequine (C-6 fluorine atom) and pipemidic acid (C-7 piperazine side chain)8-11.

According to the inhibition mechanisms of the quinolones, proposed by Shen et al.12,14, the site near the C-7 substituent is regarded as drug–enzyme interaction domain. The piperazine moiety of 7-piperazinyl quinolones possesses enough structural flexibility to allow product optimization. In addition, the C-7 substituent interacts with the target and both the activity spectrum and kinetic profile can be controlled at C-715,16. Quinolones act by converting their targets, gyrase and topoisomerase IV, into toxic enzymes that fragment the bacterial chromosome17. Quinolone antibacterials represent one of medicine’s most important classes of anti-infective agents18.

4-Quinolones which are exemplified by fluoroquinolones are the second largest chemotherapy agents used in clinical practice for the treatment of various bacterial infections19.

As part of our ongoing program to find potent and broad-spectrum antibacterial agents that display strong gram-positive activity20,21, in this paper we have focused our attention on modification of

![Figure 1](image-url)

**Figure 1**

Norfloxacin (1) R₁ = ethyl, R₅ = H, R₆ = piperazin-1-yl, X = CH

Ciprofloxacin (2) R₁ = cyclopropyl, R₅ = H, R₆ = piperazin-1-yl, X = CH

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the C-7 basic group and C-3 acidic group of the quinolone22,23.

Results and Discussion

A series of 1-cyclopropyl-7-[4-(2,6-dimethyl-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-carboxylic acid 3a and 1-cyclopropyl-7-[4-(2,6-dimethoxy-pyrimidin-2-yl-diazenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-carboxylic acid 3b and their dione derivatives were synthesized in moderate yields using the synthetic route outlined in Scheme I. Structures of the synthesized compounds were established on the basis of IR, 1H NMR spectral data and elemental analysis. Ciprofloxacin was treated with diazonium chloride derivative of 4,6-dimethylpyrimidine-2-yl-amine /4,6-dimethoxypyrimidine-2-yl-amine in presence of base to give piperazine substituted ciprofloxacin derivatives 3a-b. The acid part of these derivatives was converted to acid chloride using thionyl chloride, which further condensed with various diketone 4a-e to obtain 5a-j.

Table I summarizes the in vitro antibacterial data of the newly synthesized compounds 5a-j against three gram-positive bacteria (Staphylococcus aureus ATCC 6538p, Staphylococcus epidermidis ATCC 12228 and Bacillus subtilis PTCC 1023) and three gram-negative organisms (Escherichia coli ATCC 8739, Klebsiella pneumoniae ATCC 10031 and Enterobacter cloacae PTCC 1003). The data of ciprofloxacin are included for comparison.

Experimental Section

All the reagents and chemical were procured from commercial sources (Merck, India, Aldrich USA) and used without any further purification. Microanalysis for C, H, and N was performed using Perkin-Elmer 2400 analyzer. Infra red (IR) spectra were recorded using KBr disk on a Nicolet-Magna FT-IR spectrometer. Melting points were determined using

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<td>4</td>
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Scheme I — Synthesis of 1,3-dione derivatives 5a-j
open capillary tube method and are uncorrected. 1H NMR spectra were recorded on model DRX-300 at 300.13 MHz, using TMS as an internal standard. Homogeneity of the compounds was tested by E. Merck 60 F254 precoated silica gel TLC plates.

**General method of preparation of compounds 3a-b**

A mixture of ciprofloxacin (2, 1.65 g, 5.0 mmol) and sodium bicarbonate (1.0 g, excess) in acetonitrile (10 mL) was stirred at 50°C for 2 h. Reaction mixture was cooled to 0°C and diazonium chloride salt of 4,6-dimethylpyrimidine-2-yl-amine (5.0 mmol) was added. The mixture was stirred at 0-5°C for 5 h. Volatiles were removed under reduced pressure and the residue was partitioned between chloroform/ water. The organic layer was separated, washed with water, dried over anhyd. MgSO4, concentrated under reduced pressure and purified by column chromatography and recrystallised from 95% ethanol to give compounds 3a-b.

1-Cyclopropyl-7-[4-(2,6-dimethylpyrimidin-2-yl-diazetyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-carboxylic acid, 3a: Light yellow crystals in 48% yield. m.p.174°C. IR (KBr): 3510, 3100, 2942, 2830, 1710, 1625, 1595, 1252, 1039 cm⁻¹; 1H NMR (300 MHz, DMSO-d₆): δ 1.73 (m, 4H, CH₂-CH₂), 2.15 (s, 6H, CH₃), 3.5-3.8 (m, 9H, piperazine ring, CH-cyclopropyl), 5.93 (s, 1H, CH), 7.03 (d, 1H, C₆-H), 7.2 (d, 1H, C₆-H), 7.5 (s, 1H, C₂-H), 15.07 (s, 1H, COOH). Anal. Calcd for C₂₈H₂₈N₆O₄: C, 62.3; H, 5.12; N, 17.90%. Found: C, 62.24; H, 5.15; N, 17.90%.

**General method of preparation of 1-cyclopropyl-7-[4-(2,6-dimethylpyrimidin-2-yl-diazetyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-carboxylic acid derivatives, 5a-e**

A solution of 3a in SOCl₂ was refluxed for 10 h. The solvent was removed in vacuo to obtain acid chloride derivative of 3a as dark foam. Thereafter, sodium salt of β-diketone (prepared by using NaOMe and β-diketone 4a-e in dry methanol) was added and stirred at RT for 4 h. The solvent was removed and the residue was dissolved in 20 mL 95% ethanol. After concentration of the reaction mixture under reduced pressure, the residue was purified by recrystallisation from 95% ethanol to give compounds 5a-e.

3-[1-Cyclopropyl-7-[4-(2,6-dimethylpyrimidin-2-yl-diazetyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-yl]-pentane-2,4-dione, 5a: Yellowish red crystals in 47% yield. m.p.165°C. IR (KBr): 3100, 2950, 2838, 1715, 1620, 1589, 1250, 1039 cm⁻¹; 1H NMR (300 MHz, DMSO-d₆): δ 1.75 (m, 4H, CH₂-CH₂), 2.09 (s, 6H, COCH₃), 2.18 (s, 6H, CH₃), 3.5-3.7 (m, 9H, piperazine ring, CH-cyclopropyl), 4.2 (s, 1H, CH-COCH₃), 6.01 (s, 1H, CH), 7.04 (d, 1H, C₀-H), 7.3 (d, 1H, C₀-H), 7.48 (s, 1H, C₂-H). Anal. Calcd for C₂₉H₂₇FN₃O₄: C, 61.42; H, 5.52; N, 17.91. Found: C, 61.40; H, 5.50; N, 17.90%.

2-Benzoyl-1- {1-cyclopropyl-7-[4-(2,6-dimethylpyrimidin-2-yl-diazetyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-yl}-butane-1,3-dione, 5b: Yellowish crystals in 45% yield. m.p.160°C. IR (KBr): 3090, 2970, 2840, 1718, 1619, 1591, 1251, 1037 cm⁻¹; 1H NMR (300 MHz, DMSO-d₆): δ 1.73 (m, 4H, CH₂-CH₂), 2.08 (s, 3H, COCH₃), 2.18 (s, 6H, CH₃), 3.6-3.7 (m, 9H, piperazine ring, CH-cyclopropyl), 4.4 (s, 1H, CH-COCH₃), 6.3 (s, 1H, CH), 7.04 (d, 1H, C₀-H), 7.3 (d, 1H, C₀-H), 7.48 (s, 1H, C₂-H), 7.6-7.7 (m, 5H, C₆-H). Anal. Calcd for C₃₃H₃₂FN₄O₄: C, 65.01; H, 5.29; N, 16.08. Found: C, 65.00; H, 5.25; N, 16.05%.

2-Benzoyl-1- {1-cyclopropyl-7-[4-(2,6-dimethylpyrimidin-2-yl-diazetyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-yl}-3-phenyl-propane-1,3-dione, 5c: Light reddish crystals in 40% yield. m.p.163°C. IR (KBr): 3095, 2976, 2835, 1720, 1615, 1589, 1259, 1036 cm⁻¹; 1H NMR (300 MHz, DMSO-d₆): δ 1.75 (m, 4H, CH₂-CH₂), 2.20 (s, 6H, CH₃), 3.5-3.7 (m, 9H, piperazine ring, CH-cyclopropyl), 5.30 (s, 1H, CH-CO), 6.8 (s, 1H, CH) 7.05 (d, 1H, C₀-H), 7.25 (d, 1H, C₀-H), 7.49 (s, 1H, C₀-H), 7.6-7.7 (m, 10H, C₆-H). Anal. Calcd for C₃₈H₃₄FN₄O₄: C, 67.95; H, 5.10; N, 14.60. Found: C, 67.93; H, 5.12; N, 14.55%.

2-[1-Cyclopropyl-7-[4-(2,6-dimethylpyrimidin-2-yl-diazetyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-yl]-3-oxobutyric acid ethyl...
ester, 5d: Reddish brown crystals in 56% yield.

General method of preparation of 1-(cyclopropyl-7-[4-(4,6-dimethylpyrimidin-2-yl-diazeyn)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolene-3-yl)-malonic acid diethyl ester, 5e: Light pink crystals in 60% yield.

General method of preparation of 1-[cyclopropyl-7-[4-(4,6-dimethylpyrimidin-2-yl-diazeyn)]-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolene-3-yl]-carboxylic acid derivatives, 5f-j

A solution of 3b in SOCl₂ was refluxed for 10 h. The solvent was removed in vacuo to obtain acid chloride derivative of 3b as dark foam. Thereafter, sodium salt of β-diketone (prepared by using NaOMe and β-diketone 4a-e in dry methanol) was added and stirred at RT for 5 h. The solvent was removed and the residue was dissolved in 20 mL 95% ethanol. After concentration of the reaction mixture under reduced pressure, the residue was purified by recrystallization from 95% ethanol to give compounds 5f-j.

3-[1-Cyclopropyl-7-[4-(4,6-dimethylpyrimidin-2-yl-diazeyn)]-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolene-3-yl]-pentane-2,4-dione, 5f:

Reddish crystals in 52% yield.

2-Benzoyl-1-[1-cyclopropyl-7-[4-(4,6-dimethylpyrimidin-2-yl-diazeyn)]-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolene-3-yl]-butane-1,3-dione, 5g:

Pink crystals in 53% yield.

2-Benzyol-1-[1-cyclopropyl-7-[4-(4,6-dimethylpyrimidin-2-yl-diazeyn)]-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolene-3-yl]-3 phenyl-propane-1,3-dione, 5h:

Yellowish crystals in 53% yield.

2-[1-Cyclopropyl-7-[4-(4,6-dimethylpyrimidin-2-yl-diazeyn)]-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolene-3-yl]-3-oxo-butric acid ethyl ester, 5i:

Yellow red crystals in 49% yield.

2-[1-Cyclopropyl-7-[4-(4,6-dimethylpyrimidin-2-yl-diazeyn)]-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolene-3-yl]-malonic acid diethyl ester, 5j:

Red crystals in 53% yield.
Antibacterial activity
Compounds 5a-j were evaluated for their antibacterial activity against gram-positive (S. aureus ATCC 6538p, S. epidermidis ATCC 12228 and B. subtilis PTCC 1023) and gram-negative (E. coli ATCC 8739, K. pneumoniae ATCC 10031 and E. cloaca ATCC 1003) bacteria using conventional agar-dilution method. The minimum inhibitory concentration (MIC) values were determined in comparison to ciprofloxacin as reference drugs.

As noted in Table I, the MIC values of the tested compounds indicated that some compounds exhibited high activity against gram-positive bacteria and mild activity against gram-negative bacteria.

Conclusion
In conclusion, 1-cyclopropyl-7-[4-(2,6-dimethylpyrimidin-2-yl-diazanyl)piperizin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-carboxylic acid, 1-cyclopropyl-7-[4-(2,6-dimethoxy pyrimidin-2-yl-diazanyl)piperizin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinolone-3-carboxylic acid and their dione derivatives were synthesized, characterized and evaluated for antibacterial activity. The newly synthesized compounds exhibited moderate antibacterial activity against gram-positive (S. aureus, S. epidermidis and B. subtilis) and gram-negative (E. coli, K. pneumoniae and E. cloaca) bacteria. Compounds 5a, 5e and 5f showed good activity against gram-positive bacteria (S. aureus, S. epidermidis and B. subtilis).

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References