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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization and biological evaluation of some novel fluoroquinolones

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Abstract Different derivatives of fluoroquinolones were synthesized by combining it with different thiadiazoles. The synthesized compounds were characterized by infrared spectroscopy, proton nuclear magnetic resonance and mass spectral data. The compounds were screened for their antibacterial and antifungal activity. Ciprofloxacin derivatives with thiadiazoles **7c** showed good antibacterial as well as antifungal activities, whereas **13c** and **13e** showed antibacterial and antifungal activity respectively. Sparfloxacin derivative **8c** showed both antibacterial and antifungal activity. Sparfloxacin derivatives **14b** and **14e** showed antibacterial and antifungal activity respectively.

Keywords Floroquinolones · Antimicrobial · Ciprofloxacin · Sparfloxacin · Antifungal

Introduction

Fluoroquinolones are important broad-spectrum antibacterial agents. They are active against species such as *Enterobacter, Proteus mirabilis, Morganella morganii and Staphylococcus epidermis.* Furthermore, most of them are active against *Hemophilus influenza, Providencia rettgeri, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus, Enterococcus fecalis, Mycoplasma pneumoniae, Chlamydia pneumoniae and Neisseria gonorrheae.* Thiadiazole is a five-membered heterocyclic compound which acts as "hydrogen-binding domain" and "two-electron donor system"(Kempegowda *et al*., 2011). 1,3,4-Thiadiazole derivatives possess interesting biological activity probably conferred to them due to strong aromaticity of the ring system which leads to great in vivo stability and, generally, a lack of toxicity for higher vertebrates, including humans, when diverse functional groups that interact with biological receptor are attached to thiadiazole ring. The reported studies showed broad-spectrum antimicrobial (Marquez *et al*., 2014; Al-Zoubi *et al*., 2014; Chen *et al*., 2007; Swamy *et al*., 2006; Qandil *et al*., 2006), antihypertensive (Samel and Pai, 2010), anticonvulsant (Sharma *et al*., 2013), hypoglycemic (Datar and Deokule, 2014), anthelmentic (Sukla *et al*., 1983), anticancer (Noolvi *et al*., 2011), antiulcerogenic (Tweit, 1973) activities of thiadiazole.

As triazoles (Huang *et al.,* 2010), oxadiazoles (Kumar *et al.,* 2011), piperidines (Yunchai *et al.,* 2010), nitro aryl thiadiazoles (Senthilkumar *et al.,* 2009) coupled with fluoroquinolones showed good antimicrobial activity. So, it was thought worthwhile to synthesize some newer derivatives of thiadiazole, coupled them with fluoroquinolones and evaluate them for their antimicrobial activity. Here known compound ciprofloxacin and sparfloxacin were coupled with different derivatives of thiadiazoles with keeping aim to show promising antimicrobial activity and least toxicity (Figs. 1, 2).

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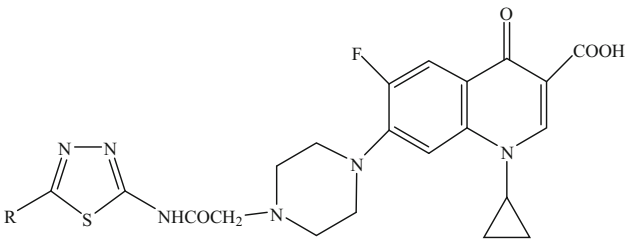


Fig. 1 Ciprofloxacin derivatives

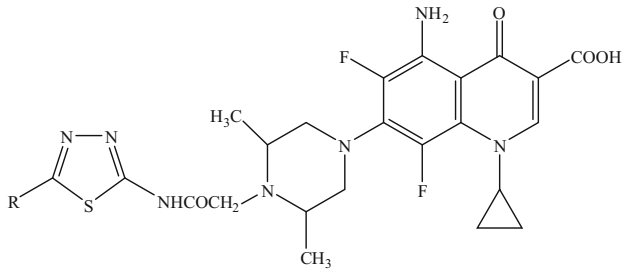


Fig. 2 Sparfloxacin derivatives

Materials and methods

Chemistry

Melting points of the newly synthesized compounds were determined by open capillary method and were uncorrected. IR spectra were recorded on Shimadzu IR Affinity-1 FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker DPX-300 MHz NMR spectrophotometer with $CDCl_3$ as solvent. Chemical shifts (δ) were reported in parts per million (ppm) relative to internal TMS. Splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). The mass spectra were recorded on a Bruker Daltonics micro TOF-Q II by using (ESI) method. Reagents and solvents were purchased from common commercial suppliers and were used without further purification unless stated otherwise.

General procedure for the synthesis of 7a–d and 8a–d

A well-stirred mixture of fatty acids **4a**–**d** (0.1 mol), concentrated sulfuric acid (25 mL) and thiosemicarbazide (3)(0.1 mol, 9.1 g) was slowly heated to 80–90 °C and maintained at that temperature for 7 h. After cooling, it was poured on crushed ice with constant stirring and then made alkaline with ammonia. The crude product thus precipitated was filtered, washed with ice-cold water and recrystallised from aqueous ethanol (70 %v/v) to give compounds **5a**–**d**.

The compounds **5a**–**d** (0.05 mol) were taken in a two-necked round-bottomed flask fitted containing 100 mL of dioxane with reflux condenser, and dropping funnel contained chloro acetyl chloride (0.05 mol, 5.64 mL) in 10 mL of dioxane. The round-bottom flask was heated with the help of heating mantel. The whole assembly was housed in fume cupboard, and while refluxing the contents of flask, the chloro acetyl chloride solution was slowly added to it. The refluxing was continued for half an hour, after the complete addition of chloroacetyl chloride. The content was cooled and poured on crushed ice. The crude product thus precipitated was filtered, washed with ice-cold water and recrystallized from ethanol (95 %v/v) to give the compounds **6a**–**d**.

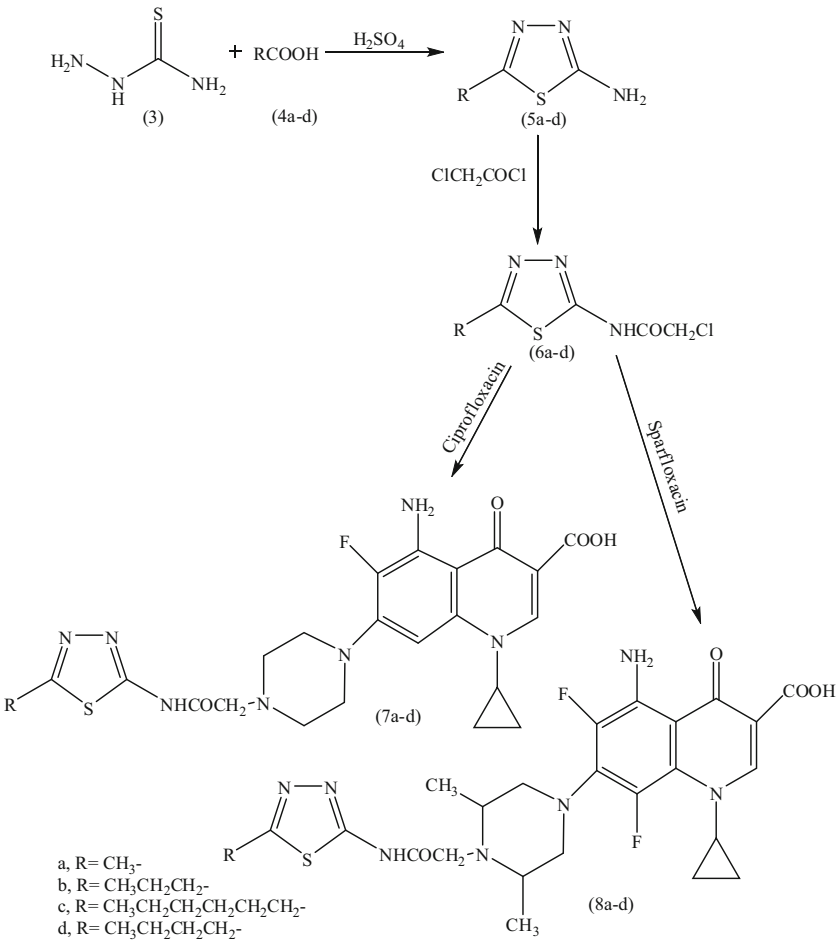
The compounds **6a**–**d** (0.012 mol) and sodium bicarbonate (0.012 mol, 1.00 g) in dimethylformamide (30 mL) were heated under reflux at 90 °C for 6 h with ciprofloxacin (0.012 mol, 3.96 g) and sparfloxacin (0.012 mol, 4.68 g) to give **7a**–**d** and **8a**–**d** (Scheme 1), respectively. The solvent was removed under reduced pressure. Water was added to the residue; solid was filtered, washed with water and recrystallized with DMF–water.

*2-[Amino acetyl 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic acid]-5-methyl thiadiazole (**7a**)* White crystals; yield: 54.5 %; m.p.: 308°–313°; IR (KBr, cm^{-1}): 3111.18 (N–H str), 3062.96 (Ar C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1456.20 (–CH_2 bend), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str); ^{1}H NMR ($CDCl_3$, δ, ppm): δ = 7.981 (s, 1H; Ar–H), 10.927 (s, 1H; –COOH), 7.094 (s, 1H; Ar–H), 3.369–3.450 (t, 4H; 2-CH_2), 2.496–2.592 (t, 4H; 2CH_2), 3.245 (s, 2H; –CH_2), 7.993 (s, 1H; –NH), 2.359 (s, 3H; –CH_3), 5.921 (s, 1H; Ar–H), 1.294–1.356 (t, 2H; –CH_2), 0.491–0.529 (m, 2H; [–CH]$_2$), 0.263–0.279 (m, 2H; [–CH]$_2$); Mass (ESI, *m/z*): M^+ = 486.527.

*2-[Amino acetyl 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic acid]-5-propyl thiadiazole (**7b**)* Light yellow crystals; yield: 63.9 %; mp.: 320°–323°; IR (KBr, cm^{-1}): 3111.18 (N–H str), 3062.96 (Ar C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1456.20 (–CH_2 bend), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str); ^{1}H NMR ($CDCl_3$, δ, ppm): δ = 7.962 (s, 1H; Ar–H), 11.013 (s, 1H; –COOH), 7.125 (s, 1H; Ar–H), 3.224–3.420 (t, 4H; 2-CH_2), 2.540–2.597 (t, 4H; 2-CH_2), 3.356 (s, 2H; –CH_2), 8.470 (s, 2H; –NH), 2.464–2.492 (t, 2H; –CH_2), 1.591–1.620 (t, 3H; –CH_3), 1.311–1.337 (t, 2H; –CH_2), 0.939–0.957 (t, 3H; –CH_3), 5.931 (s, −1H; Ar–H), 1.359 (t, 2H; –CH_2), 0.491–0.529 (m, 2H; [–CH]$_2$), 0.263–0.279 (m, 2H; [CH]$_2$); Mass (ESI, *m/z*): M^+ = 514.185.

*2-[Amino acetyl 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic acid]-5-hexyl thiadiazole (**7c**)* Brown needle-shaped crystals; yield: 77.4 %, m.p.:

Scheme 1 Synthesis of compounds **7a–d** and **8a–d**



289°–292°; IR (KBr, cm^{-1}): 3111.18 (N–H str), 3062.96 (Ar C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar C=O str), 1456.20 ($–CH_2$ bend), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str), 745.56 ($[–CH_2]_6$); ^{1}H NMR ($CDCl_3$, δ, ppm): $\delta = 7.96$ (s, 1H; Ar–H), 11.013 (s, 1H; –COOH), 7.127 (s, 1H; Ar–H), 3.374–3.458 (t, 4H; 2-CH_2), 2.571–2.596 (t, 4H; 2-CH_2), 3.252 (s, 2H; $–CH_2$), 8.012 (s, 1H; –NH), 2.490–2.569 (t, 2H;$–CH_2$), 1.598–1.624 (t, 2H; $–CH_2$), 1.216–1.291 (t, 6H; 3-CH_2), 1.318–1.336 (t, 2H; $–CH_2$), 0.939–0.957 (t, 3H; $–CH_3$), 5.931 (s, 1H; –CH), 1.349–1.359 (t, 1H; CH), 0.491–0.529 (m, 2H; $[–CH]_2$), 0.263–0.279 (m, 2H; $[–CH]_2$); Mass (ESI, *m/z*): $M^+ = 556.605$.

*2-[Amino acetyl 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic acid]-5-butyl thiadiazole (**7d**)* Pale-yellow needle-shaped crystals; yield: 81.0 %; m.p.: 268°–271°; IR (KBr, cm^{-1}): 3111.18 (N–H str), 3062.96 (Ar C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1456.20 ($–CH_2$ bend), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str), 745.56 ($[–CH_2]_4$); ^{1}H NMR ($CDCl_3$, δ, ppm): $\delta = 7.964$ (s, 1H; Ar–H), 10.927 (s, 1H; –COOH), 7.120 (s, 1H; Ar–H), 3.413–3.457 (t, 2H; $–CH_2$), 2.561–2.595 (t, 2H; $–CH_2$), 3.256 (s, 2H; $–CH_2$), 7.982 (s, 1H; –NH), 2.517–2.551 (t, 2H; $–CH_2$), 1.596–1.628 (t, 2H; $–CH_2$), 1.230–1.291 (t, 2H; $–CH_2$), 1.304–1.332 (t, 2H; $–CH_2$), 0.947–0.968 (t, 3H; $–CH_3$), 5.931 (s, 1H; Ar–H), 1.344–1.351 (t, 1H; –CH); Mass (ESI, *m/z*): $M^+ = 528.634$.

*[5-amino-1-cyclopropyl-7-[(3R,5S)3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-quinoline-3-carboxylicacid]-5-methyl thiadiazole (**8a**)* Yellow needle-shaped crystals; yield: 62.4 %; m.p.: 256°–259°; IR (KBr, cm^{-1}): 3412 & 3189 ($–NH_2$ bend), 3111.18 (N–H str), 3062.96 (Ar C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1456.20 ($–CH_2$ bend), 1389.53 ($–CH_3$ bend), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str); ^{1}H NMR ($CDCl_3$, δ, ppm): $\delta = 7.967$ (s, 1H; Ar–H), 11.015 (s, 1H; –COOH), 3.992 (s, 2H; $–NH_2$), 3.530–3.546 (d, 2H; $[–CH]_2$), 3.273–3.298 (d, 2H; $[CH]_2$), 2.983–3.039 (m, H; –CH), 1.086–1.103 (d, 6H; $[–CH_3]_2$), 3.255 (s, 2H; $–CH_2$), 8.012 (s, 1H; –NH), 2.358 (s, 3H; $–CH_3$), 1.347–1.352 (t, 1H; –CH), 0.263–0.279 (m, 2H; $[–CH]_2$), 0.491–0.529 (m, 2H; $[–CH]_2$); Mass (ESI, *m/z*): $M^+ = 547.062$.

*[5-amino-1-cyclopropyl-7-[(3R,5S)3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-quinoline-3-carboxylicacid]-5-propyl thiadiazole (**8b**)* Yellow needle-shaped crystals; yield: 62.4 %; m.p.: 279°–283°; IR (KBr, cm^{-1}): 3412 & 3189 (–NH_2 bend), 3111.18 (N–H str), 3062.96 (Ar C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1456.20 (–CH_2 bend), 1389.53 (–CH_3 bend), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str); ^{1}H NMR ($CDCl_3$, δ, ppm): $\delta = 7.967$ (s, 1H; Ar–H), 11.015 (s, 1H; –COOH), 4.097 (s, 2H; –NH_2), 3.521–3.542 (d, 1H; –CH), 3.268–3.291 (d, 1H; –CH), 2.957–3.035 (m, 1H; –CH), 1.063–1.108 (d, 6H; [–CH_3]$_2$), 3.252 (s, 2H; –CH_2), 8.012 (s, 1H; –NH), 2.497–2.556 (t, 2H; –CH_2), 1.607–1.624 (t, 2H; –CH_2), 1.311–1.330 (t, 2H; –CH_2), 0.917–0.968 (t, 3H; –CH_3), 1.343–1.356 (t, 1H; –CH), 0.263–0.279 (m, 2H; [–CH]$_2$), 0.491–0.529 (m, 2H; [–CH]$_2$); Mass (ESI, *m/z*): $M^+ = 575.208$.

*[5-amino-1-cyclopropyl-7-[(3R,5S)3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-quinoline-3-carboxylicacid]-5-hexylthiadiazole (**8c**)* Yellow needle-shaped crystals; yield: 82.6 %; m.p.: 346°–348°; IR (KBr, cm^{-1}): 3412 &3189 (–NH_2 bend), 3111.18 (N–H str), 3062.96 (Ar C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1456.20 (–CH_2 bend), 1389.53 (–CH_3 bend), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str), 745.56 ([–CH_2]$_6$); NMR ($CDCl_3$, δ, ppm): $\delta = 7.967$ (s, 1H; Ar–H), 11.467 (s, 1H; –COOH), 4.097 (s, 1H; –NH_2), 3.521–3.542 (d, 1H; –CH), 3.268–3.291 (d, 1H; –CH), 2.957–3.035 (m, 1H; –CH), 1.062–1.108 (d, 6H; [–CH_3]$_2$), 3.252 (s, 2H; –CH_2), 8.012 (s, 1H; –NH), 2.497–2.556 (t, 2H; –CH_2), 1.578–1.624 (t, 2H; –CH_2), 1.263–1.290 (t, 6H; [–CH_2]$_3$), 1.309–1.330 (t, 2H; –CH_2), 0.917–0.968 (t, 3H; –CH_3), 1.343–1.356 (t, 1H; –CH), 0.264–0.279 (m, 2H; [–CH]$_2$), 0.491–0.529 (m, 2H; [–CH]$_2$); Mass (ESI, *m/z*): $M^+ = 617.707$.

*[5-amino-1-cyclopropyl-7-[(3R,5S)3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-quinoline-3-carboxylicacid]-5-butyl thiadiazole (**8d**)* Yellow needle-shaped crystals; yield: 74.6 %; m.p.: 309°–312°; IR (KBr, cm^{-1}): 3412 & 3189 (–NH_2 bend), 3111.18 (N–H str), 3062.96 (Ar C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1389.53 (–CH_3 bend), 1456.26 for ring (Ar–C=O str), 1456.20 (–CH_2 bend), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str), 745.56 ([–CH_2]$_4$); NMR ($CDCl_3$, δ, ppm): $\delta = 7.967$ (s, 1H; Ar–H), 11.467 (s, 1H;COOH), 4.097 (s, 2H; NH_2), 3.521–3.542 (d, 1H; –CH), 3.268–3.291 (d, 1H; –CH), 2.961–3.035 (m, 1H; –CH), 1.062–1.108 (d, 6H; [–CH_3]$_2$), 3.252 (s, 2H; –CH_2), 8.012 (s, 1H; –NH), 2.497–3.556 (t, 2H; –CH_2), 1.578–1.624 (t, 2H; –CH_2), 1.263–1.290 (t, 2H; –CH_2), 1.309 = 1.330 (t, 2H; –CH_2), 0.917–0.968 (t, 3H; –CH_3), 1.356–1.343 (t, H; –CH), 0.263–0.279 (m, 2H; [–CH]$_2$), 0.491–0.529 (m, 2H; [–CH]$_2$); Mass (ESI, *m/z*): $M^+ = 589.663$.

General procedure for the synthesis of 7a–d and 8a–d

Aromatic aldehyde (0.1 mol) (**9a**–**e**) in warm alcohol (300 mL) and a solution of thiosemicarbazide (0.1 mol) in 300 mL of hot water were mixed slowly with continuous stirring. The product which separated after cooling was filtered off and recrystallized from appropriate solvents to give **10a**–**e**.

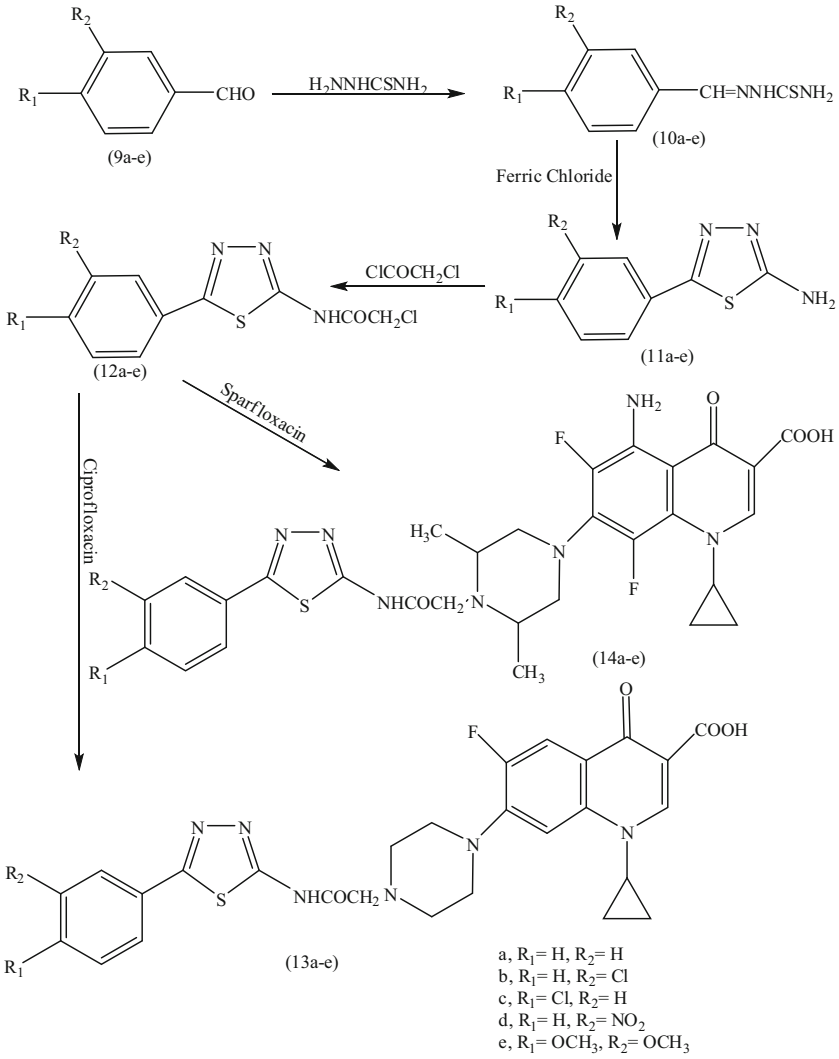
10a–**e** (0.05 mol, g) was suspended in 300 mL distilled water, and a solution of ferric chloride (0.15 mol, 24.33 g) in 300 mL of distilled water was added to it. This was heated to 80–90 °C and maintained for 3 h. Then, solution was filtered and cooled. A mixture of citric acid (0.11 mol, 21.1 g) and sodium citrate (0.05 mol, 12.9 g) was dissolved in minimum amount of distilled water and added to filtered mixture and stirred. After cooling, the whole solution was divided into four parts, and then, neutralization was affected by 10 % ammonia. The precipitate so obtained was filtered and washed with distilled water and allowed to dry to give **11a**–**e**. Crystallization was done using appropriate solvent.

11a–**e** (0.025 mol, g) was taken in a two-necked round-bottom flask containing 100 mL dry benzene, fitted with reflux condenser and a dropping funnel containing chloroacetyl chloride (0.025 mol, 2.82 mL). Chloroacetyl chloride was added dropwise with stirring. After the total addition, contents were refluxed for 3 h. The solvent was distilled off, and the product so obtained was taken out of the round-bottom flask with aid of appropriate solvent and poured on crushed ice. The product was filtered off and washed several times with cold distilled water to free it from chloride to give **12a**–**e**. Crystallization was done using appropriate solvent.

12a–**e** (0.025 mol) and ciprofloxacin (0.03 mol, 9.94 g) or sparfloxacin (0.015 mol, 5.85 g) were taken in round-bottom flask containing dry benzene 100 mL and dry pyridine (0.025 mol, 0.94 mL) to give **13a**–**e** or **14a**–**e** (Scheme 2), respectively. The content was refluxed for 48 h on an electrically heated water bath. The solvent was distilled off and product dried under reduced pressure in a rotary vacuum evaporator. The dried product so obtained was taken out of flask with the aid of appropriate solvent and poured on crushed ice. The product was filtered off and washed several times with cold distilled water to free it from chloride. The crystallization was done using appropriate solvent.

2-[Amino acetyl 1-cyclopropyl-6-fluoro-4-oxo- 7-piperazin-1-yl-quinoline-3-carboxylic acid]-(5-phenyl)-1,3,4-

Scheme 2 Synthesis of compounds **13a–e** and **14a–e**



*thiadiazole (**13a**)* Light-green crystals; yield: 62.1 %; m.p.: 326°–329°; IR (KBr, cm^{-1}): 3111.18 (N–H str), 3062.96 (Ar C–H str), 3056.82 (=C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1489.20 ($–CH_2$ bend), 1498 (C=C str), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str); NMR ($CDCl_3$, δ, ppm): $\delta = 7.967$ (S, 1H; Ar–H), 10.980 (s, 1H; –COOH), 7.126 (s, 2H; $–NH_2$), 3.402–3.489 (t, 2H; $–CH_2$), 2.562–2.681 (t, 2H; $–CH_2$), 3.252 (s, 2H; CH_2), 8.102 (s, 1H; –NH), 7.401–7.485 (d, 2H; $[Ar–H]_2$), 7.313–7.329 (d, 2H; $[Ar–H]_2$), 7.214–7.228 (d, 1H; Ar–H), 5.930 (s, 1H; Ar–H), 1.318–1.357 (t, 1H; Ar–H), 0.263–0.279 (q, 2H; $[CH_2]$), 0.491–0.529 (q, 2H; $[CH]_2$); Mass (ESI, *m/z*): $M^+ = 548.632$.

*2-[Amino acetyl 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic acid]-5-(3-chlorophenyl)-1,3,4-thiadiazole (**13b**)* White crystals; yield: 69.3 %; m.p.: 308°–309°; IR (KBr, cm^{-1}): 3111.18 (N–H str), 3062.96 (Ar C–H str), 3056.82 (=C–H stre), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1456.20 ($–CH_2$ bend), 1498 (C=C str), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str), 864.79 (ortho-substitution), 510.84 (C–Cl); NMR ($CDCl_3$, δ, ppm): $\delta = 7.967$ (S, 1H; Ar–H), 10.980 (s, 1H; –COOH), 7.126 (s, 2H; $–NH_2$), 3.402–3.489 (t, 2H; $–CH_2$), 2.562–2.681 (t, 2H; $–CH_2$), 3.252 (s, 2H; CH_2), 8.102 (s, 1H; –NH), 7.485 (s, 1H; CH), 7.228–7.237 (d, H; –CH), 7.237–7.263 (t, H; –CH), 7.351–7.366 (d, H; CH), 5.930 (s, 1H; Ar–H), 1.318–1.357 (t, 1H; Ar–H), 0.263–0.279 (q, 2H; $[CH_2]$), 0.491–0.529 (q, 2H; $[CH]_2$); Mass (ESI, *m/z*): $M^+ = 582.135$.

*2-[Amino acetyl 1-cyclopropyl-6-fluoro-4-oxo- 7-piperazin-1-yl-quinoline-3-carboxylic acid]-5-(4-chlorophenyl)l-1,3,4-thiadiazole (**13c**)* White crystals; yield: 64.6 %; m.p.: 330°–333°; IR (KBr, cm^{-1}): 3111.18 (N–H str), 3062.96 (Ar C–H str), 3056.82 (=C–H str), 2234.38 (C–S

str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1412.20 (–CH_2 bend), 1498 (C=C str), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str), 746.79 (meta-substitution), 510.84 (C–Cl); NMR ($CDCl_3$, δ, ppm): $\delta = 7.967$ (S, 1H; Ar–H), 10.980 (s, 1H; –COOH), 7.126 (s, 1H; Ar–H), 3.402–3.489 (t, 2H; –CH_2), 2.562–2.681 (t, 2H; –CH_2), 3.252 (s, 2H; –CH_2), 8.102 (s, 1H; –NH), 7.329 (s, H; CH), 7.413–7.420 (s, 4H; 2-CH_2), 5.930 (s, 1H; Ar–H), 1.318–1.357 (s, 1H. –CH), 0.263–0.279 (q, 2H; [CH_2]), 0.491–0.529 (q, 2H; [$CH]_2$); Mass (ESI, *m/z*): $M^+ = 582.133$.

*2-[Amino acetyl 1-cyclopropyl-6-fluoro-4-oxo- 7-piperazin-1-yl-quinoline-3-carboxylic acid]-5-(3-nitrophenyl)-1,3,4-thiadiazole (**13d**)* Pale-yellow needle-shaped crystals; yield: 69.8 %; m.p.: 289°–292°; IR (KBr, cm^{-1}): 3111.18 (N–H str), 3062.96 (Ar C–H str), 3056.82 (=C–H stre), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1522.61 and 1385.17 (–NO_2)1456.26 for ring (Ar–C=O str), 1456.20 (–CH_2 bend), 1498 (C=C str), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str), 864.7 9 (ortho-substitution); NMR ($CDCl_3$, δ, ppm): $\delta = 7.967$ (S, 1H; Ar–H), 10.980 (s, 1H; –COOH), 7.126 (s, 1H, Ar–H), 3.402–3.489 (t, 2H; –CH_2), 2.562–2.681 (t, 2H; –CH_2), 3.252 (s, 2H; –CH_2), 8.410 (s, 1H; –NH), 8.152 (s, 2H; –CH_2), 8.124–8.152 (d, 2H; –CH_2), 7.557–7.589 (t, 2H; CH_2), 7.843–7.876 (d, 2H; –CH_2), 5.907 (s, 1H; Ar–H), 1.318–1.357 (s, 1H. –CH), 0.263–0.279 (q, 2H; [CH_2]), 0.491–0.529 (q, 2H; [$CH]_2$); Mass (ESI, *m/z*): $M^+ = 593.153$.

*2-[Amino acetyl 1-cyclopropyl-6-fluoro-4-oxo- 7-piperazin-1-yl-quinoline-3-carboxylic acid]-5-(3,4-dimethoxy)phenyl-1,3,4-thiadiazole (**13e**)* Light-green crystals; yield: 72.5 %; m.p.: 296°–298°; IR (KBr, cm^{-1}): 3111.18 (N–H str), 3062.96 (Ar C–H str), 3056.82 (=C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1456.20 (–CH_2 bend), 1498 (C=C str), 1336.37 (C–F str), 1230.74 and 1067.93 (Ar–OCH_3) 1275.25 (Aliph C–N str), 927.56 (N–N str); NMR ($CDCl_3$, δ, ppm): $\delta = 7.967$ (S, 1H; Ar–H), 10.980 (s, 1H; –COOH), 7.126 (s, 2H; –NH_2), 3.402–3.489 (t, 2H; –CH_2), 2.562–2.681 (t, 2H; –CH_2), 3.252 (s, 2H; –CH_2), 8.002 (s, 1H; –NH), 6.889 (s, 1H; Ar–H), 3.735 (s, 6H; 2-OCH_3), 6.178 -6.721 (d, 1H; Ar–H), 6.942 (s, 1H; Ar–H), 5.937 (s, 1H; Ar–H), 1.318–1.357 (s, 1H; –CH), 0.263–0.279 (q, 2H; [CH_2]), 0.491–0.529 (q, 2H; [$CH]_2$); Mass (ESI, *m/z*): $M^+ = 608.194$.

*[5-amino-1-cyclopropyl-7-[(3R,5S)3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-quinoline-3-carboxylic acid]-5-(phenyl)-1,3,4 thiadiazole (**14a**)* Pale-yellow needle-shaped crystals; yield: 47.3 %; m.p.: 330°–336°; IR (KBr, cm^{-1}): 3412 & 3189 (–NH_2 bend), 3111.18 (N–H str), 3062.96 (Ar C–H str), 3056.82 (=C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1389.53 (–CH_3 bend), 1456.26 for ring (Ar–C=O str), 1456.20 (–CH_2 bend), 1498 (C=C str), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str); NMR ($CDCl_3$, δ, ppm): $\delta = 7.96$ (s, 1H; Ar–H), 10.980 (s, 1H; COOH), 3.992 (s, 2H; NH_2), 3.530–3.546 (d, 1H; –CH), 3.273–3.298 (d, 1H; –CH), 2.911–3.039 (m, 1H; –CH), 1.086–1.103 (d, 6H; [–CH_3]$_2$), 3.255 (s, 2H; CH_2), 8.612 (s, 1H; –NH), 7.485–7.489 (d, 2H; [–CH]$_2$), 7.313–7.330 (d, 2H; [–CH]$_2$), 7.202–7.228 (t, 1H; –CH), 1.318–1.357 (t, 1H; –CH), 0.263–0.279 (q, 2H; [CH_2]), 0.491–0.529 (q, 2H; [$CH]_2$); Mass (ESI, *m/z*): $M^+ = 609.621$.

*[5-amino-1-cyclopropyl-7-[(3R,5S)3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-quinoline-3-carboxylic acid]-5-(3-chlorophenyl)-1,3,4 thiadiazole (**14b**)* Pale-yellow needle-shaped crystals; yield: 60.9 %; m.p.: 289°–293°; IR (KBr, cm^{-1}): 3412 & 3189 (–NH_2 bend), 3111.18 (N–H str), 3062.96 (Ar C–H str), 3056.82 (=C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1389.53 (–CH_3 bend), 1456.26 for ring (Ar–C=O str), 1456.20 (–CH_2 bend), 1498 (C=C str), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str), 864.79 (ortho-substitution), 510.84 (C–Cl); NMR ($CDCl_3$, δ, ppm): $\delta = 7.96$ (s, 1H; Ar–H), 10.980 (s, 1H; COOH), 3.992 (s, 2H; NH_2), 3.530–3.546 (d, 1H; –CH), 3.273–3.298 (d, 1H; –CH), 2.911–3.039 (m, 1H; –CH), 1.086–1.103 (d, 6H; [–CH_3]$_2$), 3.255 (s, 2H; CH_2), 8.005 (s, 1H; –NH), 7.492 (s, 1H; –CH), 7.235–7.239 (d, 1H; –CH), 7.261–7.263 (t, 1H; –CH), 7.362–7.369 (d, 1H; –CH), 1.318–1.357 (t, 1H; –CH), 0.263–0.279 (q, 2H; [CH_2]), 0.491–0.529 (q, 2H; [$CH]_2$); Mass (ESI, *m/z*): $M^+ = 643.903$.

*[5-amino-1-cyclopropyl-7-[(3R,5S)3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-quinoline-3-carboxylic acid]-5-(4-chlorophenyl)-1,3,4 thiadiazole (**14c**)* Pale-yellow needle-shaped crystals; yield: 49.3 %; m.p.: 292°–295°; IR (KBr, cm^{-1}): 3412 & 3189 (–NH_2 bend), 3111.18 (N–H str), 3062.96 (Ar C–H str), 3056.82 (=C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1389.53 (–CH_3 bend), 1456.26 for ring (Ar–C=O str), 1456.20 (–CH_2 bend), 1498 (C=C str), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str), 864.79 (ortho-substitution), 510.84 (C–Cl); NMR ($CDCl_3$, δ, ppm): $\delta = 7.96$ (s, 1H; Ar–H), 10.980 (s, 1H; COOH), 3.992 (s, 2H; NH_2), 3.530–3.546 (d, 1H; –CH), 3.273–3.298 (d, 1H; –CH), 2.911–3.039 (m, 1H; –CH), 1.086–1.103 (d, 6H; [–CH_3]$_2$), 3.255 (s, 2H; CH_2), 8.005 (s, 1H; –NH), 7.417–7.462 (s, 2H; [–CH]$_2$), 7.330 (s, 2H; [–CH]$_2$), 1.318–1.357 (t, 1H; –CH), 0.263–0.279 (q, 2H; [CH_2]), 0.491–0.529 (q, 2H; [$CH]_2$); Mass (ESI, *m/z*): M^+=643.903.

[5-amino-1-cyclopropyl-7-[(3R,5S)3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-quinoline-3-carboxylic acid]-5-

Table 1 Antibacterial activity of synthesized compounds (100 μg/mL concentration)

Compound	Zone of inhibition in mm ± SD[a]			
	B. subtillis	*S. aureus*	*E. coli*	*K. pneumoniae*
Control	–	–	–	–
Ciprofloxacin	20.0 ± 0.89	21.0 ± 0.87	27.0 ± 0.45	26.0 ± 0.57
Sparfloxacin	23.0 ± 0.67	20.0 ± 0.55	29.0 ± 0.29	27.0 ± 0.21
7a	8.0 ± 0.05	7.0 ± 0.69	8.0 ± 0.35	6.0 ± 0.50
7b	12.0 ± 0.57	7.0 ± 0.76	8.0 ± 0.50	7.0 ± 0.50
7c	11.0 ± 0.50	8.00 ± 0.95	9.0 ± 0.32	8.0 ± 1.00
7d	10.0 ± 0.05	7.0 ± 1.10	7.0 ± 0.76	6.0 ± 0.76
8a	11.0 ± 0.50	8.00 ± 0.98	14.0 ± 0.94	10.0 ± 0.73
8b	14.0 ± 0.32	9.0 ± 0.56	17.0 ± 0.76	10.0 ± 0.65
8c	16.0 ± 0.76	10.0 ± 0.98	19.0 ± 0.99	11.0 ± 0.76
8d	13.0 ± 0.92	10.0 ± 0.94	16.0 ± 0.86	10.0 ± 0.96
13a	10.0 ± 0.45	9.0 ± 0.94	10.0 ± 0.97	13.0 ± 0.97
13b	8.0 ± 0.55	6.0 ± 0.18	8.0 ± 0.98	7.0 ± 0.99
13c	12.0 ± 0.45	9.0 ± 0.65	13.0 ± 0.77	14.0 ± 0.94
13d	11.0 ± 0.23	12.0 ± 0.38	10.0 ± 0.59	9.0 ± 0.32
13e	10.0 ± 0.89	10.0 ± 0.31	11.0 ± 0.90	11.0 ± 0.21
14a	8.0 ± 0.99	9.0 ± 0.67	10.0 ± 0.98	9.0 ± 0.59
14b	10.0 ± 0.56	11.0 ± 0.99	24.0 ± 0.44	9.0 ± 0.74
14c	9.0 ± 0.78	12.0 ± 0.34	12.0 ± 0.76	11.0 ± 0.66
14d	10.0 ± 0.87	9.0 ± 0.54	11.0 ± 0.78	13.0 ± 0.38
14e	12.0 ± 0.44	11.0 ± 0.69	11.0 ± 0.45	12.0 ± 0.24

[a] Mean of three readings

(3-nitrophenyl)-1,3,4 thiadiazole ***(14d)*** Pale-yellow needle-shaped crystals; yield: 52.7 %; m.p.: 325°–327°; IR (KBr, cm^{-1}): 3412 & 3189 ($–NH_2$ bend), 3111.18 (N–H str), 3062.96 (Ar C–H str), 3056.82 (=C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1522.61 and 1385.17 ($–NO_2$), 1456.26 for ring (Ar–C=O str), 1412.20 ($–CH_2$ bend), 1498 (C=C str), 1336.37 (C–F str), 1275.25 (Aliph C–N str), 927.56 (N–N str), 864.79 (ortho-substitution); NMR ($CDCl_3$, δ, ppm): $\delta = 7.96$ (s, 1H; Ar–H), 10.980 (s, 1H; COOH), 3.992 (s, 2H; NH_2), 3.530–3.546 (d, 1H; –CH), 3.273–3.298 (d, 1H; –CH), 2.911–3.039 (m, 1H; –CH), 1.086–1.103 (d, 6H; $[–CH_3]_2$), 3.255 (s, 2H; CH_2), 8.014 (s, 1H; –NH), 8.457 (s, 1H; –CH), 8.158–8.169 (d, 1H; –CH), 7.542–7.584 (t, 1H; –CH), 7.856–7.871 (d, 1H; –CH), 1.318–1.357 (t, 1H; –CH), 0.263–0.279 (q, 2H; $[CH_2]$), 0.491–0.529 (q, 2H; $[CH]_2$); Mass (ESI, *m/z*): $M^+ = 654.159$.

5-amino-1-cyclopropyl-7-[(3R,5S)3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-quinoline-3-carboxylicacid]5 (3,4dimethoxyphenyl)thiadiazole ***(14e)*** Pale-yellow needle-shaped crystals; yield: 74.6; m.p.: 340°–342°; IR (KBr, cm^{-1}): 3111.18 (N–H str), 3062.96 (Ar C–H str), 3056.82 (=C–H str), 2234.38 (C–S str), 1796.38 (C=O str), 1635.64 for C=O, 1456.26 for ring (Ar–C=O str), 1456.20 ($–CH_2$ bend), 1498 (C=C str), 1336.37 (C–F str), 1230.74 and 1067.93 (Ar–OCH_3) 1275.25 (Aliph C–N str), 927.56 (N–N str); NMR ($CDCl_3$, δ, ppm): $\delta = 7.96$ (s, 1H; Ar–H), 10.980 (s, 1H; COOH), 3.992 (s, 2H; NH_2), 3.530–3.546 (d, 1H; –CH), 3.273–3.298 (d, 1H; –CH), 2.911–3.039 (m, 1H; –CH), 1.086–1.103 (d, 6H; $[–CH_3]_2$), 3.255 (s, 2H; CH_2), 8.014 (s, 1H; –NH), 6.885 (s, 1H; –CH), 3.730–3.734 (d, 6H; -$[CH_3]_2$), 6.700–6.723 (d, 1H; –CH), 6.934 (s, 1H; –CH), 1.318–1.357 (t, 1H; –CH), 0.263–0.279 (q, 2H; $[CH_2]$), 0.491–0.529 (q, 2H; $[CH]_2$); Mass (ESI, *m/z*): $M^+ = 669.172$.

Antimicrobial activity

All novel synthesized compounds were screened for their in vitro antibacterial activity against two gram-positive (*Bacillus subtilis* [MTCC 121], *Staphylococcus aureus* [MTCC 7443]), two gram-negative (*Escherichia coli* [MTCC 118], *Klebsiella pneumonia* [MTCC 7028]) and antifungal activity against *Candida albicans* [MTCC 1637] and *Aspergillus tubingensis* [MTCC 2479] by paper disk diffusion method (Aneja 2007). The paper disks which were previously sterilized by dry heat and impregnated

Table 2 Antifungal activity of synthesized compounds (100 μg/mL)

Compound	Zone of inhibition in mm ± SD[a]	
	C. albicans	*A. tubingensis*
Control	–	–
Clotrimazole	18.0 ± 0.57	19.0 ± 0.76
7a	6 ± 0.29	6 ± 0.26
7b	8 ± 0.32	7 ± 0.37
7c	10 ± 0.53	9 ± 0.89
7d	9 ± 0.59	8 ± 0.57
8a	7 ± 0.07	7 ± 0.23
8b	9 ± 0.24	8 ± 0.35
8c	11 ± 0.68	10 ± 0.96
8d	10 ± 0.31	9 ± 0.16
13a	8 ± 0.38	8 ± 0.84
13b	10 ± 0.57	11 ± 0.11
13c	11 ± 0.43	10 ± 0.66
13d	12 ± 0.96	11 ± 0.24
13e	13 ± 0.53	12 ± 0.37
14a	12 ± 0.20	10 ± 0.85
14b	11 ± 0.36	13 ± 0.27
14c	12 ± 0.95	11 ± 0.64
14d	13 ± 0.36	13 ± 0.39
14e	16 ± 0.85	15 ± 0.15

[a] Mean of three readings

with the test compounds (100 μg/mL, Dimethyl formamide as solvent) were placed on the solidified medium. The plates were incubated at 37 °C for 24 h. After incubation, the growth inhibition zones around the disks were observed, indicating that the examined compound inhibits the growth of microorganism. Ciprofloxacin and sparfloxacin in concentration of 100 μg/mL were used as standard drugs for antibacterial activity, and clotrimazole in concentration of 100 μg/mL was used as a standard drug for antifungal activity. Results were interpreted in terms of the diameter of the zone of inhibition and are given in Tables 1 and 2.

Results and discussion

Both the nucleus thiadiazoles and fluoroquinolones are well established in the literature as biologically active heterocyclic pharmacophore. Here thiadiazole derivatives fused with ciprofloxacin and sparfloxacin by the molecular conjugation with expectation of highly potent more specific and less toxic antimicrobial fluoroquinolones.

Thiadiazoles were synthesized from fatty acids and aromatic aldehydes. In first series, the starting material thiosemicarbazide reacted with fatty acid in the presence of concentrated sulfuric acid, and then, the reacting mixture was neutralized with liquor ammonia to get cyclized product, thiadiazole.

In second series, different aldehydes reacted with thiosemicarbazide to yield thiosemicarbazones. It was cyclized in the presence of ferric chloride to yield thiadiazole. Different derivatives of 2-chloro acetyl amino-5-alkylthiadiazole were simultaneously fused with ciprofloxacin and sparfloxacin in the presence of dimethylformamide and sodium bicarbonate. The compounds were characterized by spectral data (IR, ^{1}H NMR and Mass) and evaluated for antimicrobial activity.

All synthesized compounds and standard drugs are taken in the concentration of 100 μg/mL in DMF and screened for antimicrobial activity. Some of the compounds showed good activity against gram-positive, gram-negative bacteria and fungi. The data of antimicrobial studies showed that compounds **7c** and **8c** have comparable good antibacterial activity which may be due to six carbon chains attached to thiadiazole which may be increasing its lipophilicity among ciprofloxacin and sparfloxacin derivatives. Compounds **13c** and **14b** are having good activity and it may be due to aromatic ring fused with thiadiazole having halogen substituent.

The data of antifungal activity showed that compounds **7c** and **8c** have good activity among ciprofloxacin and sparfloxacin derivatives, respectively, which may be also due to higher lipophilicity among all. Compounds **13e** and **14e** have better activity that may be due to aromatic ring substitution. So from this study, we can conclude that if the further clinical studies will be performed and such molecule will be explored, it may lead to give better antimicrobial agent where the dose of fluoroquinolones can be reduced without compromising with the activity of the parent drug.

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