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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization, and biological evaluation of novel thiazole and pyrazole derivatives of quinoline-4-carboxylic acid as potential antimicrobial agents

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Abstract A series of quinoline-based heterocycles prepared and bioevaluated for their possible antimicrobial activity against a panel of gram-positive bacteria [*Staphylococcus aureus* (ATCC-9144) and *Bacillus subtilis* (ATCC-6633)] and gram-negative bacteria [*Pseudomonas aeruginosa* (ATCC-25615), and *Escherichia coli* (MTCC-739)], and fungal strains [C*andida albicans* (ATCC-24433), *Aspergillus niger* (MTCC-872), and *Aspergillus fumigatus* (MTCC-343)] by the known methods. All the prepared quinoline derivatives have shown significant antimicrobial activities. Few compounds, viz. **4b**, **4c** and **4a**, **4c** proved to be active at low concentrations against Sa and Ca, respectively, while compounds **4a**, **6d**, and **6b** showed milder inhibitory effects against other microbes. The structures of newly synthesized compounds were characterized by elemental analysis, Infrared (IR), ^{1}HNMR, ^{13}C-NMR and Mass-spectroscopy.

Keywords Quinoline-4-carboxylic acid · Acetophenone · Thiosemicarbazide · Polyphosphoric acid · Antimicrobial activity

Introduction

The increasing incidence of bacterial resistance to antibiotics and antimicrobial agents poses a tremendous threat to the human race, and a continued search for new chemotherapeutic agents is vital to combat this threat. Recently, a significant amount of attention has been directed toward the development of novel classes of biocides. To this end, one of the best ways to design new biocidal agents is to synthesize hybrid molecules by combining two or more bioactive moieties in a single molecular scaffold.

Among pharmacologically active compounds, nitrogen-containing heterocyclic molecules are significant target owing to their wide range of applications as pharmaceutically active molecules. Quinoline derivatives have been known to possess varied biological properties and medicinal uses, such as antitumor (Yamato *et al*., 1990, 1989; Fujimoto, 2007), antibacterial (Parekh *et al*., 2011; Eswaran *et al*. 2010a, b), antifungal (Robert *et al*., 2006; Ryu *et al*., 2009), antihypertensive (Conklin and Hollifield, 1970; Jandhyala *et al*., 1967), antileishmanial (Tempone *et al*., 2005; Palit *et al*., 2009) and antidepressant (Kumar *et al*., 2011; Alhaider, 1986) agents. An important role played by quinoline compounds was that of providing the first photographic film sensitizer such as the cyanine dye and ethyl red. Several quinoline derivatives as antimalarial agents are in clinical use, since a long time (Charris *et al*., 2007; Hans *et al*., 2010). In addition, thiosemicarbazides can easily be cyclized to various heterocyclic ring systems and therefore used as key intermediates in the preparation of numerous synthetic compounds with significant biological activities. It is known that, thiazole derivatives exhibit various biological activities such as antitubercular (Andreani *et al*., 2001; Kolavi *et al*., 2006), antimicrobial (Bondock *et al*., 2007; Vijesh *et al*., 2010; Mullican *et al*., 1993; Song *et al*., 1999), anti-inflammatory (Labanauskas *et al*., 2001), antiviral (El-Sabbagh *et al*.; 2009, Stawinska *et al*., 2009), anticonvulsant (Bachir *et al*., 1990; Kaminski and Obniska, 2008), antihypertensive (Adhikary *et al*.,

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1976; Bakr *et al*., 2008), and hypoglycemic (Sohda *et al*., 1992) activities among others (Messaoudi *et al*., 2004). Besides, pyrazole derivatives have occupied a unique place in the field of medicinal chemistry and have been reported in the literature as potential biologically active pharmacophores (Bondock *et al*., 2010; Veronique *et al*., 1998; Fleming *et al*., 2010; Ozdemir *et al*., 2007). Giving attention to the biological significance of these classes of compounds and in continuation of our research program on the synthesis of antimicrobial agents (Bishnoi *et al*., 2009, 2010, 2011), we planned to synthesize a combined molecular framework, consisting of these well-established pharmacologically active nuclei in them.

Results and discussion

Chemistry

Two novel series of thiazole **4(a–f)** and pyrazole **6(a–f)** derivatives were synthesized by the application of various cyclization reactions (Scheme 1).The compound **1** required for the synthesis of title compounds was prepared according to the procedure described in the literature (Holla *et al*., 2005). 4-carboxy-1-(2-oxo-2-phenylethyl)-2-(4-substituted phenyl quinolinium iodide **2(a–c)** were obtained by the reaction of 2-(4-substituted phenyl) quinoline-4-carboxylic acid **1(a–c)** with acetophenone in the presence of iodine.The IR spectra of **2** revealed one additional C=O stretching vibration at 1688–1680 cm^{-1} region, along with C=O stretching vibration of COOH at 1714–1700 cm^{-1}. The ^{1}HNMR of the compound showed signal corresponding to CH_2 attached to quinoline nitrogen at δ 2.2–2.4 ppm. Reaction of **2(a–c)** with thiosemicarbazide in glacial acetic acid afforded the thiosemicarbazones **3(a–c)**. The IR spectra of the products revealed the disappearance of the C=O absorption band at 1680–1688 cm^{-1} and showed symmetric and asymmetric stretching bands at 3253–3358 cm^{-1} for NH_2 along with C=N stretching vibration band at 1589–1643 cm^{-1} and C=S stretching vibration at 1186–1198 cm^{-1}. A further reaction of **3(a–c)** with substituted acetophenones in glacial acetic acid in the presence of iodine led to corresponding 4-carboxy-1-(2-phenyl-2-(4-substituted phenyl thiazol-2(5H)-ylidene)hydrazono)ethyl-2-(p-substituted phenyl) quinolinium iodide **4(a–f)** derivatives, utilizing Hantzsch synthesis. IR, ^{1}HNMR, and ^{13}CNMR spectra of these compounds were well in agreement with the structure assigned.The conversion of **3** to **4** involves the cyclization of thiosemicarbazones into an azine. In the ^{1}HNMR spectra of **3(a–c)**, the proton signals at 8.11–8.26 ppm appeared for NH_2 protons integrating for two proton and the signal at 11.08–11.28 ppm for NH. On the other hand, compound **1(a–c)** were heated with benzoin in the presence of PPA to afford the corresponding 5-(4-substituted phenyl)-3, 4-diphenyl -1H-pyrano[4,3-c] quinolin-1-one **5(a–c)**. The IR spectra of **5** showed the shifting of C=O stretching band from 1678 cm^{-1} to 1685 cm^{-1} and the absence of OH stretching band region revealing the fusion between **1** and benzoin. In ^{1}HNMR, the signals observed were at the expected chemical shifts with appropriate integrals. Compound **5(a–c)** on reaction with thiosemi/semicarbazides in refluxing ethanol furnished 7-(4-substituted phenyl)-5,6-diphenyl benzo[*h*][1, 2, 4] triazole[3,4-*a*][2, 6]-naphthyridine-3-(2*H*)-thione/one **6(a–f)**. The structures of these compounds were well supported by their spectral data. The IR spectra of **6** showed disappearance of absorption band due to C=O stretching vibration, and appearance of a band at 1659–1629 cm^{-1} attributable to C=N vibrations and bands at 1186–1200 and 1754–1762 cm^{-1}attributable to C=S and C=O, respectively, providing a strong evidence for the formation of the titled compounds. The ^{1}HNMR spectra of the **6(a–f)** showed the NH proton as singlet at 12.95–13.85 ppm region which disappeared upon deuteration.

Experimental section

Methods and materials

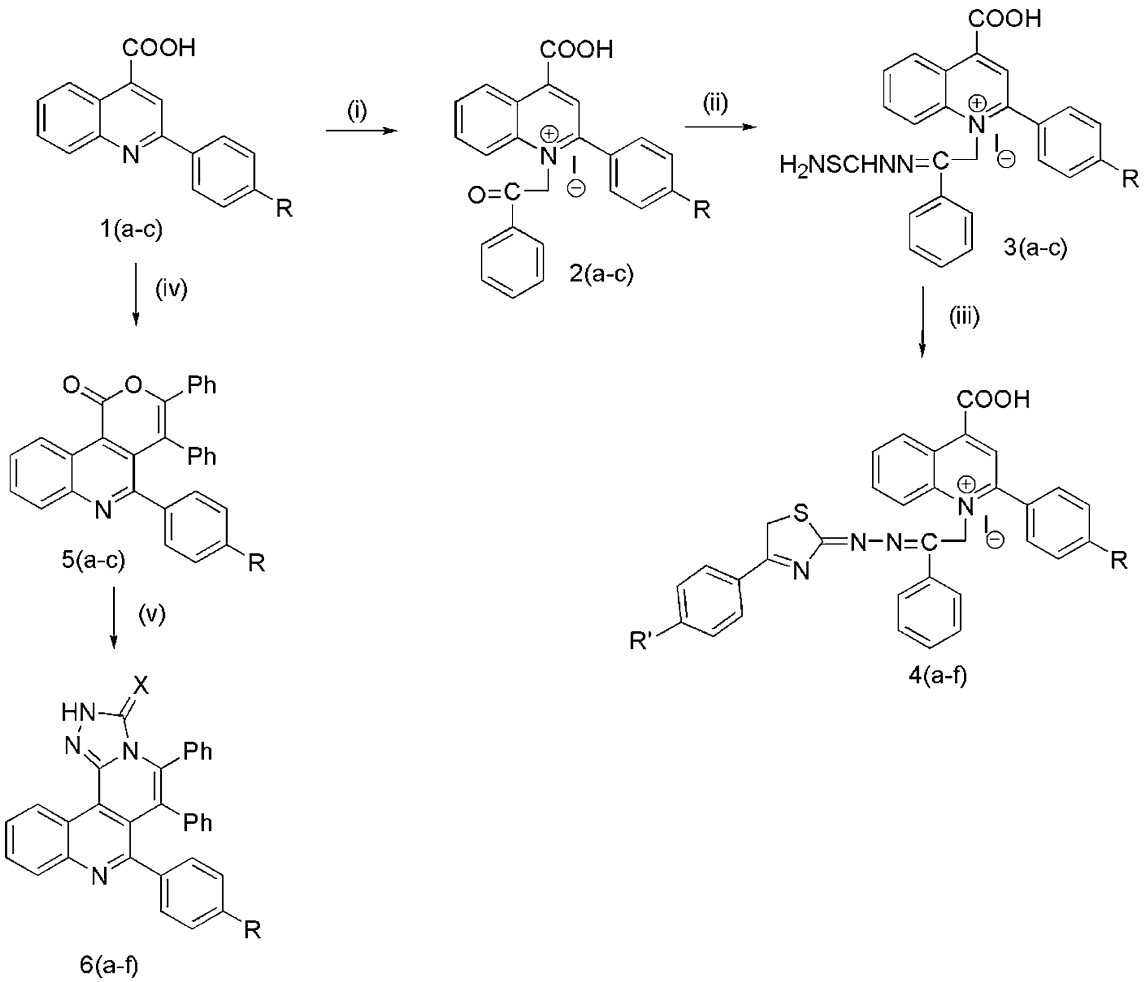
All chemicals were purchased from Alfa Aesar, Sigma-Aldrich, Merck, Sdfine, Qualigens, and Spectrochem. Solvents and reagents were used without further purification, unless otherwise specified. IR Spectra (potassium bromide) were recorded on Perkin-Elmer FTIR spectrophotometer (ν_{max} in cm^{-1}); ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker 300 MHz instruments using $CDCl_3$/DMSO-d_6 as solvents. Chemical shifts (δ) are reported in p.p.m. using TMS as internal standard. EI mass spectra were recorded on a Va 70–70H mass spectrometer at 70 eV. Elemental Analysis was performed on a Perkin-Elmer 2400 series II elemental CHNS analyzer. Melting points were determined in an open capillary tube and are uncorrected. The TLCs were visualized in an iodine chamber.

*General procedure for the preparation of 2-substituted phenylquinoline-4-carboxylic acid **1(a–c)***

Compounds **1** (**a**–**c**) were prepared by known method reported in the literature (Holla *et al*., 2005).

*General procedure for the preparation of 4-carboxy-2-substituted phenyl-1-(2-oxo-2-phenylethyl)-2-phenyl quinolinium iodide **2(a–c)***

2-substituted quinoline-4-carboxylic acid **1**(**a**–**c**) (0.01 mol) were refluxed with acetophenone (0.01 mol) and iodine



Scheme 1 Synthesis of compounds **1–6**. The substituent R in compounds **1**, **2**, **3** & **5** are as follows: **a** R=H **b** R=Cl; **c** R=CH_3. The nature of substituents R and R' in compound **4** are **a** R=H; R'=NH_2; **b** R=Cl; R'=NH_2; **c** R=CH_3; R'=NH_2; **d** R=H; R'=H; **e** R=Cl; R'=H; **f** R=CH_3; R'=H. The nature of R and X in compounds **6** are **a** R=H, X=O; **b** R=Cl, X=O; **c** R=CH_3, X=O; **d** R=H, X=S; **e** R=Cl, X=S; **f** R=CH_3, X=S. (*i*) $PhCOCH_3/I_2$; (*ii*) $H_2NNHCSNH_2$/gla.AcOH; (*iii*) $R'C_6H_5COCH_3$, I_2/gla. AcOH; (*iv*) Benzoin/PPA (*v*) $H_2NNHCXNH_2$/EtOH

(0.5gm) in a RB flask at 100 °C for 2 h under anhydrous reaction conditions. The crystalline mass which separated on cooling the reaction mixture was filtered, washed repeatedly with water, and recrystallised from ethanol. The TLCs were checked using Benzene: Acetone (8.5:1.5 v/v) as mobile phase.

*4-Carboxy-1-(2-oxo-2-phenylethyl)-2-phenyl quinolinium iodide (**2a**)* Yield 72 %., brown crystals, mp 198–200 °C, Rf value, 0.62. IR (KBr) cm^{-1}: 3390 (OH), 1700 (C=O), 1643 (C=N), 1580 (C=C), 1682(C=O). ^{1}HNMR (DMSO-d_6) δ: 7.24–8.72 (m, 15H, Ar–H) 2.2 (s, 2H, CH_2), 12.02 (s, 1H, COOH). ^{13}CNMR (DMSO-d_6) δ: 70.0 (N–CH_2–CO), 118.6–139.7 (quinoline and phenyl), 167.4 (COOH), 196.2 (COPh). EI-MS (m/z): M^+ 367, 351, 323, 291, 263, 249, 119, 105. Anal.calcd. for $C_{24}H_{18}NO_3$: C, 78.26; H, 4.89; N, 3.80. Found: C, 0.47; H, 4.63; N, 3.80 %.

*4-Carboxy-2-(4-chloro phenyl)-1-(2-oxo-2-pheny ethyl) quinolinium iodide (**2b**)* Yield 81 %., light brown crystals, mp 160–161 °C, Rf value, 0.70. IR (KBr) cm^{-1} : 3396 (OH), 1705 (C=O), 1618 (C=N), 1586 (C=C), 732 (C–Cl), 1688 (C=O). ^{1}HNMR (DMSO-d_6) δ: 7.03–8.88 (m, 14H, Ar–H), 2.4 (s, 2H, CH2), 12.86 (s, 1H, COOH). ^{13}CNMR (DMSO-d_6) δ: 69.8 (N–CH_2–CO), 115.8–147.1 (quinoline and phenyl), 167.7 (COOH), 196.5 (COPh). EI-MS (m/z): M^+ 402, 404, 385, 357, 325, 297, 291, 283, 119, 111, 77. Anal.calcd. for $C_{24}H_{17}ClNO_3$: C, 71.64; H, 4.22; N, 3.48. Found: C, 71.73; H, 3.98; N, 3.46 %.

*4-Carboxy-1-(2-oxo-2-phenylethyl)-2-p-tolyl quinalinium iodide (**2c**)* Yield; 74 %., greenish crystals, mp 178–180 °C, Rf value, 0.36. IR (KBr) cm^{-1}: 3416 (OH), 1712(C=O), 1622 (C=N), 1580 (C=C), 1686 (C=O). ^{1}HNMR (DMSO-d_6) δ: 7.09–8.90 (m, 14H, Ar–H), 2.3 (s, 2H, CH2),

2.1(s, 3H, CH_3), 12.42(s, 1H, COOH). ^{13}CNMR (DMSO-d_6) δ: 21.3 (CH_3 of tolyl), 70.8 (N–CH_2–CO), 119.4–140.9 (quinoline and phenyl), 169.0 (COOH), 195.9 (COPh). EI-MS (m/z): M^+; 381, 365, 337, 291, 277, 263, 172, 105, 71. Anal.calcd. for $C_{25}H_{20}NO_3$: C, 78.50; H, 5.23; N, 3.66. Found: C, 78.32; H, 5.22; N, 3.65 %.

*General procedure for the preparation of 1-(2-(-carbamothioylhydrazono)-2-phenylethyl)-4-carboxy-2-(4-substituted phenyl)-quinolinium iodide **3(a–c)***

A mixture of **2(a–c)** (0.01 mol) and thiosemicarbazide (0.01 mol) was dissolved in glacial acetic acid (50 ml) by warming gently on a water bath and was heated under reflux for 2 h. Acetic acid was distilled off under reduced pressure, and the residual solid mass thus obtained was washed with water The crude products were dried in vacuum and recrystallized from methanol. The TLCs were checked using Benzene: Acetone (in various ratios v/v) as mobile phase.

*1-(2-(-Carbamothioylhydrazono)-2-phenylethyl)-4-carboxy-2-phenyl quinolinium iodide (**3a**)* Yield 72 %., yellow crystals, mp 158–164 °C, Rf value, 0.68 (8.5:1.5, Benzene: Acetone). IR (KBr) cm^{-1}: 3401 (O–H), 1705 (C=O), 1630 (C=N), 1578 (C=C), 3310 (N–H), 1186(C=S). ^{1}HNMR (DMSO-d_6) δ: 7.12-8.59 (m, 15H, Ar–H), 1.4 (s, 2H, CH_2), 8.11 (s, 2H, NH_2), 11.08 (s, 1H, NH), 12.08 (s, 1H, COOH). ^{13}CNMR (DMSO-d_6) δ: 50.1 (–N–CH_2–CNNH–), 119.6–139.7 (quinoline and phenyl), 154.2 (C=N), 165.3 (COOH), 180.4 (C=S). EI-MS (m/z): M^+ 440, 424, 396, 381, 364, 350, 263, 249, 190, 171, 103, 77. Anal.calcd. for $C_{25}H_{21}N_4O_2S$: C, 68.02; H, 4.76; N, 12.69. Found: C, 68.00; H, 4.77; N, 12.72 %.

*1-(2-(-carbamothioylhydrazono)-2-phenylethyl)-4-carboxy-2-(4-chlorophenyl)-quinoliniumiodide (**3b**)* Yield 72 %., orange crystals, mp 182–184 °C, Rf value, 0.39 (8.0:1.0, Benzene: Acetone). IR (KBr) cm^{-1}: 3405 (OH), 1708 (C=O), 1643 (C=N), 1569 (C=C), 3327 (NH), 1198 (C=S), 729 (C–Cl). ^{1}HNMR (DMSO-d_6) δ: 698–8.13(m, 14H, Ar–H), 1.2 (s, 2H CH_2), 8.26 (s, 2H, NH_2), 11.21 (s, 1H, NH), 12.41 (s, 1H, COOH). ^{13}CNMR (DMSO-d_6) δ: 50.8 (–N–CH_2–CNNH–), 118.9–147.1 (quinoline and phenyl), 155.6 (C=N), 167.7 (COOH), 181.0 (C=S). EI-MS (m/z): M^+ 474, 476, 459, 458, 430, 415, 400, 398, 386, 297, 283, 192, 178, 111, 103. Anal.calcd. for $C_{25}H_{20}Cl$ N_4O_2S: C, 63.15; H, 4.21; N, 11.78. Found: C, 63.27; H, 4.18; N, 11.81 %.

*1-(2-(-Carbamothioylhydrazono)-2-phenylethyl)-4-carboxy-2-p-tolylquinolinium iodide (**3c**)* Yield 68 %., yellow crystals, mp.190–195 °C, Rf value, 0.67 (8.5:1.5, Benzene: Acetone). IR (KBr) cm^{-1}: 3414 (OH), 1710 (C=O), 1640 (C=N), 1582 (C=C), 3312 (NH), 1192 (C=S). ^{1}HNMR (DMSO-d_6) δ: 7.08–8.62 (m, 14H, Ar–H), 1.6 (s, 2H, CH_2), 2.21 (s, 3H, CH_3), 8.21 (s, 2H, NH_2), 11.28 (s, 1H, NH), 12.91 (s, 1H, COOH). ^{13}CNMR (DMSO-d_6) δ: 22.4 (CH_3 of tolyl), 50.5 (–N–CH_2–CNNH–), 118.7–141.5 (quinoline and phenyl), 154.9 (C=N), 166.0 (COOH), 180.8 (C=S). EI-MS (m/z): M^+ 454, 277, 263, 192, 186, 103, 91. Anal.calcd. for $C_{26}H_{23}$ N_4O_2S: C, 68.54; H, 5.05; N, 12.30; Found: C, 68.72; H, 5.06; N, 12.33 %.

*General procedure for the preparation of **4(a–f)***

A mixture of **3**(**a**–**c**) (0.01 mol), acetophenone/substituted acetophenone (0.01 mol) and iodine(1.3 g) in glacial acetic acid (50 ml) was refluxed for 8–10 h. The reaction mixture was cooled ,and the solid, which separated out, was filtered, washed with water and dried in vacuum. The crude compounds were recrystallized from a mixture of methanol and chloroform (1:2). The TLCs were checked using Benzene: Acetone (in various ratios v/v) as mobile phase.

*(4-(4-Aminophenyl)thiazol-2(5H)-ylidene)hydrazono)-2-phenylethyl)-4-carboxy-2-phenylquinolinium iodide (**4a**)* Yield 82 %., brown crystals, mp 132–133 °C, Rf value, 0.61 (8.5:1.5, Benzene: Acetone). IR (KBr) cm^{-1}:3404 (OH), 1708 (C=O), 1604 (C=N), 1638 (C=N), 1578 (C=C), 3217 (NH). ^{1}HNMR (DMSO-d6) δ: 6.30–7.94 (m, 19H, Ar–H), 1.6 (s, 2H, CH_2), 2.8 (s, 2H, CH_2 of thiazole), 5.26 (s, 2H, NH_2), 12.78 (s, 1H, COOH). ^{13}CNMR (DMSO-d_6): 124.2–151.1 (quinoline, phenyl and aniline), 165.2 (C=O), 28.9 (C–S of thiazole), 164.1 (C=N of thiazole), 161.9 (C=N). EI-MS (m/z): M^+ 555, 540, 539, 511, 479, 464, 380, 366, 352, 307, 249, 204, 176, 103, 97. Anal.calcd. for $C_{33}H_{26}$ N_5O_2S: C, 71.19; H, 4.67; N, 12.58. Found: C, 71.35; H, 4.68; N, 12.61 %.

*(2-(4-(4-Aminophenyl)thiazol-2(5H)-ylidene)hydrazono)-2-phenylethyl)-4-carboxy-2-(4-chlorophenyl) quinolinium iodide (**4b**)* Yield 84 %., yellow crystals, mp 160–161 °C, Rf value, 0.54 (9.0:1.0, Benzene: Acetone). IR (KBr) cm^{-1}: 3402 (OH), 1708 (C=O), 1626 (C=N), 1640 (C=N), 1582 (C=C), 3226 (NH), 729 (C–Cl). ^{1}HNMR (DMSO-d6)δ: 6.42–8.91 (m,18H,Ar–H), 1.8(s, 2H, CH_2), 2.4 (s, 2H,CH_2, of thiazole), 5.29 (s, 2H, NH_2), 12.17 (s, 1H, COOH). ^{13}CNMR (DMSO-d_6) δ: 118.4–151.7 (quinoline, phenyl and aniline), 166.1 (C=O), 29.1 (C–S of thiazole), 161.7 (C=N of thiazole), 163.7 (C=N). EI-MS(m/z): M^+, 589, 591, 574, 573, 545, 498, 479, 414, 400, 386, 307, 297, 293, 283, 190, 176, 111, 103, 97, 92. Anal.calcd. for $C_{33}H_{25}ClN_5O_2S$: C, 67.10; H, 4.23; N, 11.86. Found: C, 67.23; H, 4.25; N, 11.88 %.

(2-(4-(4-Aminophenyl)thiazol-2(5H)-ylidene)hydrazono)-2-phenylethyl)-4-carboxy-2-p-tolyl quinolinium iodide ***(4c)*** Yield 76 %., orange crystals, mp 210–212 °C, Rf value, 0.57 (8.5:1.5, Benzene: Acetone). IR (KBr) cm^{-1}: 3418 (OH), 1714 (C=O), 1632 (C=N), 1644 (C=N), 1510 (C=C), 3237 (NH). ^{1}HNMR (DMSO-d6)δ: 6.38–8.78 (m, 18H, Ar–H), 2.24(s, 3H, CH_3), 1.5 (s, 2H, CH2), 2.6 (s, 2H, CH_2 of thiazole), 5.22 (s, 2H, NH_2), 12.98 (s, 1H, COOH). ^{13}CNMR (DMSO-d_6) δ: 114.2–148.9 (quinoline, phenyl and aniline), 164.8 (C=O), 18.6 (CH_3 of toluene), 28.8 (C–S of thiazole), 160.0 (C=N of thiazole), 162.6 (C=N). EI-MS (m/z): M^+; 569, 554, 553, 525, 479, 478, 394, 380, 307, 293, 277, 263, 190, 176, 103. Anal.calcd. for $C_{34}H_{28}N_5O_2$ S: C, 71.55; H, 4.91; N, 12.27. Found: C, 71.83; H, 4.92; N, 12.32 %.

4-Carboxy-2-phenyl-1-(2-phenyl-2-(4-phenylthiazol-2(5H)-ylidene)hydrazono) quinoliniumiodide ***(4d)*** Yield 82 %., light brown crystals, mp 120–121 °C, Rf value, 0.66 (9.5:0.5 Benzene: Acetone). IR (KBr) cm^{-1}: 3410 (OH), 1710 (C=O), 1628 (C=N), 1635 (C=N), 1588 (C=C). ^{1}HNMR (DMSO-d_6) δ: 6.23–8.42 (m, 20H Ar–H), 1.2 (s, 2H, CH_2), 2.7 (s, 2H, CH_2 of thiazole), 12.62 (s, 1H, COOH). ^{13}CNMR (DMSO-d_6): 114.2–152.1 (quinoline and phenyl), 162.6 (C=O), 28.8 (C–S of thiazole), 166.3 (C=N of thiazole), 162.4 (C=N). EI-MS (m/z): M^+; 540, 496, 464, 380, 366, 352, 278, 263, 249, 189, 186, 175. Anal. calcd. for C_{33} H_{25} N_4 O_2 S: C, 73.17; H, 4.61; N, 10.34. Found: C, 73.06; H, 4.60; N, 10.33 %.

4-Carboxy-2-(4-chlorophenyl-1-(2-phenyl-2-(4-phenylthiazol-2(5H)-ylidene)hydrazono)ethyl quinolinium iodide ***(4e)*** Yield 78 %., dark brown crystals, mp 148–151 °C, Rf value, 0.58 (9.0:1.0 Benzene: Acetone). IR (KBr) cm^{-1}: 3406 (OH), 1708 (C=O), 1630 (C=N), 1635 (C=N), 1589 (C=C), 725 (C–Cl). ^{1}HNMR (DMSO-d_6) δ: 6.75–8.96 (m, 19H Ar–H), 1.4 (s, 2H, CH_2), 2.6 (s, 2H, CH_2 of thiazole), 12.71 (s, 1H, COOH). ^{13}CNMR (DMSO-d_6) δ: 122–150.7 (quinoline and phenyl), 164.7 (C=O), 29.7 (C–S of thiazole), 163.5 (C=N of thiazole), 163.1 (C=N). EI-MS (m/z): M^+, 574, 576, 558, 530, 498, 414, 400, 386, 292, 283,189, 186, 175,111. Anal.calcd. for $C_{33}H_{24}$ ClN_4 O_2 S: C, 68.85; H, 4.34; N, 9.73; Found: C, 68.98; H, 4.35; N, 9.75 %.

4-Carboxy-2-phenyl-2-(4-phenyl thiqzol-2(5H)-ylidene) hydrazono) ethyl)-2-p-tolylquinolinium iodide ***(4f)*** Yield 87 %., purple crystals, mp 181–184 °C, Rf value, 0.62, (9.0:1.0 Benzene: Acetone). IR (KBr) cm^{-1}: 3422 (OH), 1712 (C=O), 1622 (C=N), 1638 (C=N), 1584 (C=C). ^{1}HNMR (DMSO-d_6) δ: 7.08–8.29 (m, 19H Ar–H), 2.14 (s, 3H, CH_3), 1.8 (s, 2H, CH_2), 2.4 (s, 2H, CH_2 of thiazole), 12.08 (s, 1H, COOH). ^{13}CNMR (DMSOd_6)δ: 112–146.8 (quinoline and phenyl), 162.8 (C=O), 19.6 (CH_3 of toluene), 27.2 (C–S of thiazole), 159.8(C=N of thiazole), 160.9 (C=N). EI-MS (m/z): $M^{+,}$ 554, 538, 510, 478, 464, 394, 380, 292, 278,277, 263, 186,175, 103, 97, 91, 77. Anal.calcd for C_{34} H_{27} N_4 O_2 S: C, 73.48; H, 4.86; N, 10.08. Found: C, 73.77; H, 4.88; N, 10.12 %.

General procedure for the preparation of ***5(a–c)***

A mixture of 2-substituted quinoline-4-carboxylic acid of **1(a–c)** (0.05 mol), Benzoin (0.05 mol), and PPA (100 ml) was heated in an oil bath for 4 h at 130 °C, and the reaction mixture was poured into ice-cold water and stirred vigorously for 0.5 h. The solid mass thus obtained was treated with 5 % sodium bicarbonate solution (50 ml) to remove any unreacted acid. The products obtained were recrystallized from methanol. The TLCs were checked using Benzene: Acetone (9.5: 0.5 v/v) as mobile phase.

3,4,5-Triphenyl-1H-Pyrano[4,3-c]quinolin-1-one ***(5a)*** Yield 79 %., Chrome yellow crystals, mp 140 °C, Rf value, 0.58 (9.5:0.5 Benzene: Acetone). IR (KBr) cm^{-1}: 1678 (C=O), 1650 (C=N), 1592 (C=C). ^{1}HNMR ($CDCl_3$)δ: 6.86–7.95 (m, 19H, Ar–H). ^{13}CNMR ($DMSOd_6$)δ: 110.6–146.3 (quinoline and phenyl), 150.5 (C=O). Anal. calcd for $C_{30}H_{19}$ NO_2: C, 84.71; H, 4.47; N, 3.29; Found: C, 85.52; H, 4.52; N, 3.41 %.

5-(4-Chlorophenyl)-3,4-diphenyl-1H-Pyrana[4,3-c] quinolin-1-one ***(5b)*** Yield 73 %., dirty white crystals, mp 109 °C, Rf value, 0.39 (9.5:0.5 Benzene: Acetone). IR (KBr) cm^{-1}: 1680 (C=O), 1648(C=N), 1588(C=C), 725 (C–Cl). ^{1}HNMR ($CDCl_3$) δ: 6.5–7.88 (m, 18H, Ar–H). ^{13}CNMR (DMSO-d_6) δ: 129–130.2 (quinoline and phenyl), 155.4 (C=O). EI-MS (m/z): M^+ 459, 178, 126, 111, 91. Anal. calcd. For $C_{30}H_{18}$ NO_2Cl: C, 78.35; H, 3.92; N, 3.05; Found: C, 76.73; H, 4.16; N, 2.86 %.

3,4-Diphenyl-5-p-tolyl-1H-pyrano[4,3-c]quinolin-1-one ***(5c)*** Yield 68 %., pale yellow crystals, mp 181 °C, Rf value, 0.41 (9.5: 0.5, Benzene: Acetone). IR (KBr) cm^{-1}: 1685 (C=O), 1652 (C=N), 1590 (C=C). ^{1}HNMR ($CDCl_3$) δ: 2.34 (s, 3H,–CH_3), 6.37–7.92 (m, 18H, Ar–H). ^{13}CNMR (DMSO-d_6) δ: 21.3 (–CH_3), 127–148.7 (quinoline and phenyl), 150.4 (C=O). Anal. calcd. For $C_{31}H_{21}$ NO_2: C, 84.74; H, 4.78; N, 3.19; Found: C, 85.69; H, 5.03; N, 2.93 %.

General procedure for the preparation of ***6(a–f)***

A mixture of **5(a–c)** (0.01 mol) and semicarbazide/thiosemicarbazide (0.12 mol) in ethanol (30 ml) was heated under reflux for 8–12 h. Ethanol was distilled off, and the residual solid mass was washed with water. Crude products

were dried in vacuum and recrystallized from methanol. The TLCs were checked using Benzene: Acetone (in various ratios v/v) as mobile phase.

*4,5,6-Triphenylbenzo[h][1, 2, 4]triazolo[3,4a][2, 6]naphthyridin-3(2H)-one (**6a**)* Yield 75 %., yellow crystals, mp 172–174 °C, Rf value, 0.53 (8.5:1.5 Benzene: Acetone). IR (KBr) cm^{-1}: 1759 (C=O), 1569 (C=C), 1641 (C=N), 1589 (C=C). ^{1}HNMR ($CDCl_3$) δ: 6.74–8.69 (m, 19H,–Ar–H), 12.95 (s, 1H,–NH). ^{13}CNMR ($DMSOd_6$)δ: 122.4–147.0 (quinoline and phenyl), 155 (N–C=N), 159.2 (C=O). Anal.calcd. for $C_{31}H_{21}N_4O$: C, 80.17; H, 4.31; N, 12.07; Found: C, 79.89; H, 4.26; N, 12.31 %.

*7-(4-Chlorophenyl)-5,6-diphenylbenzo[h][1, 2, 4]triazolo [3,4-a][2, 6]napthyridin-3(2H)-one (**6b**)* Yield 75 %., grey crystals, mp 194–195 °C, Rf value, 0.48 (8.0:2.0 Benzene: Acetone). IR (KBr) cm^{-1}: 1754(C=O), 1633 (C=N), 1565 (C=C), 713 (C–Cl). ^{1}HNMR ($CDCl_3$) δ: 7.11–8.92 (m, 18H, Ar–H), 13.83 (s, 1H,–NH). ^{13}CNMR ($DMSOd_6$)δ: 123–150.5 (quinoline and phenyl), 154.7 (N–C=N), 159.8 (C=O). EI-MS (m/z): M^+, 500, 502, 417, 419, 180, 111, 99. Anal. calcd. for $C_{31}H_{20}N_4O$: C, 74.62; H, 3.81; N, 11.23. Found: C, 75.32; H, 4.02; N, 10.95 %.

*5,6-Diphenyl-7-p-tolylbenzo[h][1, 2, 4]triazolo[3,4-a] [2, 6]naphthyridin-3(2H)-one (**6c**)* Yield 76 %., grayish white crystals, mp 203–205 °C, Rf value, 0.61 (8.5:1.5 Benzene: Acetone). IR (KBr) cm^{-1}: 1762 (C=O), 1629 (C=N), 1573 (C=C). ^{1}HNMR ($CDCl_3$) δ: 2.17 (s, 3H, CH3), 7.02–8.84 (m, 18H, ArH), 13.45 (s, 1H, NH). ^{13}CNMR ($DMSOd_6$)δ: 20.8 (–CH_3), 121–148.9 (quinoline and phenyl), 155.6 (N–C=N), 158.9 (C=O). EI-MS (m/z): $M^{+\cdot}$ 480, 180, 126, 91, 83. Anal.calcd. for $C_{32}H_{23}N_4O$: C, 80.33; H, 4.60; N, 11.72; Found: C, 80.65; H, 4.74; N, 11.867 %.

*5,6,7-Triphenylbenzo[h][1, 2, 4]triazolo[3,4-a][2, 6]naphthyridin-3(2H)-thione (**6d**)* Yield 77 %., pale white crystals, mp 169 °C, Rf value, 0.56 (9.0:1.0 Benzene: Acetone). IR (KBr) cm^{-1}: 1649(C=N), 1569(C=C), 1200 (C=S). ^{1}HNMR (CDCl3) δ: 6.82–8.45 (m, 19H, Ar–H), 13.31 (s, 1H, NH). ^{13}CNMR (DMSO-d_6) δ: 111–146.8 (quinoline and phenyl), 148.6 (C=S), 154.8 (N–C=N). Anal. calcd for $C_{31}H_{21}N_4S$: C, 77.5; H, 4.17; N, 11.6. Found: C, 77.2; H, 4.29; N, 11.5 %.

*7-(4-Chlorophenyl)-5,6-diphenylbenzo[h][1, 2, 4]triazolo [3,4-a][2, 6]naphthyridin-3(2H)-thione (**6e**)* Yield 76 %., light yellow crystals, mp 185 °C, Rf value, 0.65 (9.0:1.0 Benzene: Acetone). IR (KBr) cm^{-1}: 1652 (C=N), 1571 (C=C), 1186 (C=S), 719 (C–Cl). ^{1}HNMR ($CDCl_3$)δ: 6.95–8.58 (m, 18H, Ar–H), 13.56 (s, 1H,–NH). ^{13}CNMR (DMSO-d_6)δ: 109.6–148 (quinoline and phenyl), 149.5(C=S), 155 (N–C=N). EI-MS (m/z): $M^{+\cdot}$ 516, 518, 419, 417, 180, 126, 111, 91. Anal.calcd for $C_{31}H_{20}N_4$ SCl: C, 72.3; H, 3.69; N, 10.88 Found: C, 71.86; H, 3.75; N, 11.29 %.

*5,6-Diphenyl-7-p-tolylbenzo[h][1, 2, 4]triazolo[3,4-a][2, 6] naphthyridin-3(2H)-thione (**6f**)* Yield 69 %., yellow crystals, mp 256 °C, Rf value, 0.59 (9.0:1.0 Benzene: Acetone). IR (KBr) cm^{-1}: 1659 (C=N), 1579 (C=C), 1194 (C=S). ^{1}HNMR ($CDCl_3$) δ: 1.99 (s, 3H,–CH_3), 6.93–8.52 (m, 18H, Ar–H), 13.39 (s, 1H, –NH). ^{13}CNMR ($DMSOd_6$)δ: 110.5–150.3 (quinoline and phenyl), 150.6 (C=S), 155.2(N–C=N). EI-MS (m/z): $M^{+\cdot}$ 496, 397, 180, 126, 99, 91. Anal. calcd. for $C_{32}H_{23}N_4S$; C, 77.73; H, 4.45; N, 11.34. Found: C, 78.07; H, 4.52; N, 10.98 %.

Biological assay

In vitro antibacterial activity

The invitro antibacterial activities of compounds (**4a–f** and **6a–f**) and standard drug (Gentamicin) were carried out against gram-positive and gram- negative bacterial strains, viz. *Staphylococcus aureus(Sa)* (ATCC-9144), *Bacillus subtilis (Bs)* (ATCC-6633), *Pseudomonas aeruginosa(Pa)* (ATCC-25615), and *Escherichia coli(Ec)* (MTCC-739) using Disc-diffusion Method (Karaman *et al*., 2003) by standard micro broth dilution as per NCCLS protocol. Some of the compounds have shown significant activity against the various strains. The compounds **4a, 4b, 4c, 6d**, and **6e** were the most active antibacterial agents. Among these, **4a** and **4c** have shown an MIC value of 3.12 μg/mL against *Sa* which exceeds that of the reference drug (MIC = 6.25 μg/mL). Compound **6e** has also shown good activity with an MIC value of 12.5 μg/mL. Compound **6d** needs to have a special mention here, as it is the only active compound among the whole series which has shown excellent activity against *Ba* with an MIC of 12.5 μg/mL. The zone of inhibition of this compound (21 mm) is quite comparable to Gentamicin (22 mm). Compounds **6a** and **6e** have shown considerable activity against the multiresistant bacterial strain; *Pa* and their structure can be further modified to increase the antibacterial activity.

In vitro antifungal activity

Compounds **4a–f** and **6a–f** were also evaluated for their antifungal activities against a variety of fungal strains viz. *Candida albicans (Ca)* (ATCC-24433), *Aspergillus niger (An)* (MTCC-872), and *Aspergillus fumigatus(Af)* (MTCC-343) using Disc-diffusion Method (Sahm and Washington 1991) by standard micro broth dilution as per NCCLS

protocol with a view to develop therapeutic agents having broad spectrum of antifungal activity. As far as the antifungal activity is concerned, many compounds of both the series were found to be active, some of them with par excellence (**4a** and **4b**). The compounds which have shown moderate-to-excellent antifungal activity are, **4a, 4b, 4c, 4d, 4e**, and **6b**. The substituted phenyl quinolinium iodides (**4a, 4b, 4d, 4e**) were found to be more active against the fungi than the benzotriazolo-naphthyridin-one/thione derivatives (**6b**). The compounds also showed more activity against the single celled *Ca* than the filamentous strains of *Af* and *An*. Compounds **4a** and **4c** showed outstanding activity against *Ca* with an MIC of 3.12 μg/mL exceeding that of the standard drug (6.25 μg/mL). These were followed by compounds **4e** and **6b** with an MIC of 12.5 μg/mL and moderate activities of **4f** and **6e** (MIC = 25 μg/mL). Compound **4d** proved to be the most active against the filamentous fungi with an MIC value of 12.5 μg/mL against *An* followed by **4d** and **6a** with MIC = 25 μg/mL against *Af*.

The results of preliminary in vitro antimicrobial testing are displayed graphically in Figure 1 and in tabular form in Table 1.

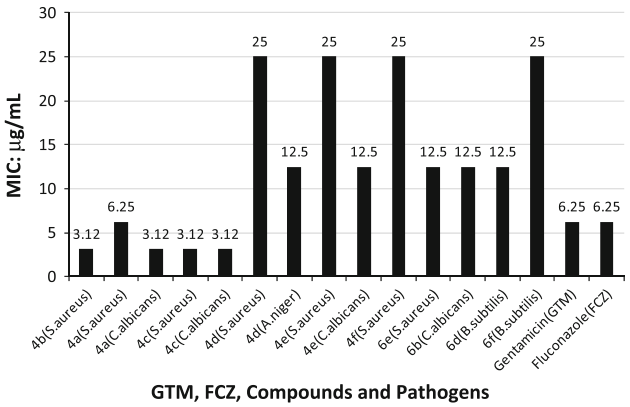


Fig. 1 Comparative antibacterial and antifungal study plot with Gentamicin, Flucanozole, compounds and pathogens

Results and discussion

The derivatives **4a–f** and **6a–f** were screened for their antimicrobial activities against different bacterial and fungal strains. Among all the assayed compounds, the substituted phenyl quinolinium iodides have shown more potent and universal activity as compared to the benzotriazolo–naphthyridin–one/thione derivatives. The compounds **4a, b**, and **c** showed remarkably high order of activities against the microbes. It is very interesting to observe here that substituent **R'** plays a greater role in conferring antimicrobial activity than the substituent **R**. Thus, compounds **4a, b**, and **c** containing R'=NH_2 were found to be the most active against two strains, viz. *Sa* and *Ca*, with an MIC of 3.12 μg/mL, better than that of the reference drugs (Gentamicin and Fluconazole), while other compounds either showed moderate activities or unable to provoke any measurable degree of activity.

Table 1 Antibacterial and Antifungal activities of newly synthesized compounds (**4a–f** and **6a–f**) (MIC values (μg/mL) of different strains) by twofold serial dilution technique and diameter of zone of inhibition (mm) of bacterial (gram +ve and gram −ve) and fungal strains by disc-diffusion assay

Compounds	*S. aureus*	*B. subtilis*	*E. coli*	*P.aeruginosa*	*C. albicans*	*A. fumigatus*	*A. niger*
4a	6.25 (24)	>100 (09‹)[a]	>100 (08)[a]	>100 (09)[a]	**3.12 (36)[c]**	>100 (06)[a]	>100 (07)[a]
4b	**3.12 (34)[b]**	>100 (07)[a]	>100 (07)[a]	>100 (08)[a]	>100 (07)[a]	>100 (09)[a]	>100 (06)[a]
4c	**3.12 (40)[b]**	>100 (06)[a]	>100 (06)[a]	>100 (06)[a]	**3.12 (40)[c]**	>50 (10)	>100 (08)[a]
4d	25 (18)	>100 (10)[a]	>100 (09)[a]	>100 (09)[a]	>50 (10)	25 (12)	12.5 (14)
4e	25 (15)	>100 (06)[a]	>100 (06)a	>100 (06)[a]	12.5 (19)	>100 (06)[a]	>100 (06)[a]
4f	25 (14)	>100 (09)[a]	>100 (11)[a]	>100 (08)[a]	25 (17)	>100 (08)[a]	>100 (07)[a]
6a	>100 (08)[a]	>100 (08)[a]	25 (21)	50 (12)	>100 (06)[a]	25 (12)	>100 (06)[a]
6b	>100 (09)[a]	>100 (11)[a]	>100 (06)[a]	>100 (06)[a]	12.5 (24)	>100 (06)[a]	>100 (08)[a]
6c	50 (11)	50 (18)	>100 (06)[a]	>100 (09)[a]	50 (14)	>100 (09)[a]	>100 (06)[a]
6d	>100 (08)[a]	12.5 (21)	50 (18)	>100 (08)[a]	>100 (08)[a]	>100 (07)[a]	>100 (06)[a]
6e	12.5 (20)	>100 (08)[a]	>100 (07)[a]	50 (13)	25 (18)	>100 (06)[a]	>100 (06)[a]
6f	>100 (06)[a]	25 (19)	>100 (06)[a]	>100 (06)[a]	>100 (06)[a]	>100 (06)[a]	>100 (07)[a]
Gentamicin	6.25 (22)	– (22)	25.0 (20)	– (23)	–	–	– (18)
Fluconazole	–	–	–	–	6.25 (21)	– (–)	–

[a] No activity observed

[b] Entries in bold font indicate better activity than reference drugs Gentamicin (Bauer *et al*., 1966)

[c] Entries in bold font indicate better activity than reference drugs Fluconazole

This clearly suggests that the nature of substituent attached to the aromatic ring of thiazole nucleus has larger role than the nature of substituents in the aromatic ring attached to Cinchophen nuclei or alternatively an electron-releasing amino group, when present, compound may diffuse from the blood to the site of fungal multiplication in the skin, more easily. It is here inferred that, in order to develop potentially more powerful Cinchophen derivatives, synthesis of compounds bearing electron-releasing groups should be encouraged.

The other class of compounds **6a–f** showed random activity against different strains of microorganisms. Some of the compounds bear an electron-withdrawing group, and others, an electron-releasing one in their structure. Therefore, no correlation can be drawn between the structure and activity.

Conclusions and future directions

In order to obtain new compounds with improved antimicrobial activity, a novel series of 4-carboxy-1-(2-phenyl-2-(4-substituted phenyl thiazol-(5H)-ylidene)hydrazono) ethyl-2-p-substituted phenyl quinolinium iodide **4a–f** and 7-(4-substituted phenyl)-5,6-diphenyl benzo(h) [1, 2, 4] triazolo [3,4-*a*] [2, 6] naphthyridine-3-(2*H*)-thione/one **6(a–f)** was synthesized and characterized by their spectral data and elemental analysis. The derivatives **4a–f** and **6a–f** have been evaluated for their antibacterial and antifungal activities against various microbial strains. The antifungal profiles of **4a–f** and **6a–f** indicated that compounds **4a**, **4c,** and **6b** have potent antifungal activity. Among the most promising compounds, **4a** and **4c** exhibited better antifungal activities than clinically prevalent antifungal drug, Fluconazole, against *Candida albicans* (ATCC-24433). Compounds **4b** and **4c** exhibited promising antibacterial activity against *Staphylococcus aureus* (ATCC-9144). Compounds **4a**, **4b,** and **4c** are the lead drug candidates, and further study is being carried out at Central Drug Research Institute, Lucknow, India concerning their toxicological evaluation. Efforts are paving ways to synthesize more potent biologically active quinoline derivatives, utilizing the structure–activity relationships.

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