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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activity of some novel quinoline-pyrazoline-based coumarinyl thiazole derivatives

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Abstract A series of novel 3-(2-(5-(2-chloroquinolin-3-yl)-3-substituted phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4-yl)-6-H/halo-2*H*-chromen-2-ones (**9a–9y**) was prepared as antimicrobial agents by the condensation of 3-(2-bromoacetyl)-6-H/halo-2*H*-chromen-2-ones (**4a–4e**) and 5-(2-chloroquinolin-3-yl)-3-substituted phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothiamide (**8a–8e**) in ethanol. The structures of these compounds were confirmed on the basis of their infrared, ^{1}H-nuclear magnetic resonance, ^{13}C-nuclear magnetic resonance, mass and elemental analysis data. The antimicrobial activity of these compounds was determined by the serial plate dilution method. The compounds with fluoro-substituted coumarin ring along with the fluoro-substituted phenyl ring, **9q**, **9r**, and **9s**, produced better and potent antimicrobial activity than their corresponding H/chloro/iodo/bromo-substituted analogs with statistically significant results ($p < 0.05$). The compounds **9q** and **9r** also produced higher antifungal activity than standard drug ketoconazole against *Penicillium citrinum*. However, these compounds required higher concentration than standard drugs, ofloxacin, and ketoconazole, to produce these effects. The structural modification of these compounds may enhance their potency as antimicrobial agents, but this requires further studies.

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Introduction

Antimicrobial resistance was first reported in the 1940s. It is the resistance developed by a microorganism for an antimicrobial agent against, which it was originally sensitive. Infection caused by a resistant microorganism often fails to respond to conventional treatment, resulting in prolonged illness, higher risk of death and greater costs (Jindal et al. 2015). Today antimicrobial resistance has become a global concern because in the modern era of travel and trade, resistant organisms rapidly cross the man-made boundaries through humans or the food chain (Jindal et al. 2015; Bhatia 2013). Studies have revealed that the cause of antibiotic resistance includes the irrational use of antibiotics and failure to discover new antimicrobial agents since the second half of 1980s. Accordingly, development of new antimicrobial agents is the need of today to combat antimicrobial resistance (Jindal et al. 2015; Bhatia 2013; Brandt et al. 2014).

Coumarinyl heterocycles, thiazolyl heterocycles, quinolinyl heterocycles, and pyrazolinyl heterocycles have an important place in medicinal chemistry. Recently, review articles mentioning the usefulness of coumarinyl heterocyles (Jayashree et al. 2014; Xin-Mei et al. 2013; Venugopala et al. 2013), thiazolyl heterocycles (Kashyap et al. 2012; Mishra et al. 2015; Leoni et al. 2014a; Leoni et al. 2014b), quinolinyl heterocycles (Kumar et al. 2009; Marella et al. 2013b; Kaur et al. 2010), and pyrazolinyl heterocycles (Alex and Kumar 2014; Marella et al. 2013a) as analgesic, anti-inflammatory, antibacterial, antifungal, antiviral, antiparasitic, anticoagulant, anti-Alzheimer's disease, anti-Parkinson's Disease,

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anticancer, antioxidants, antidiabetic, Central Nervous System depressant, and antimalarial have been published. Among these, coumarinyl thiazoles have also been reported to possess different biological activities like antimicrobial (Shaaban et al. 2012; Vijesh et al. 2010; Bondock et al. 2013; Chimenti et al. 2011; Arshad et al. 2011; Abd El-Wahab et al. 2014; Venugopala and Jayashree 2008; Rao et al. 2008; Venugopala et al. 2008), anticancer (Gali et al. 2015), antioxidant (Thota et al. 2015), anticonvulsant (Siddiqui et al. 2009; Amin et al. 2008), anti-tubercular (Karalı et al. 2002; Gursoy and Karali 2003), anti-inflammatory (Kalkhambkar et al. 2007; Aggarwal et al. 2013; Venugopala et al. 2004; Jayashree et al. 2005), analgesic (Venugopala and Jayashree 2003), and anticholinesterase activities (Kurt et al. 2015).

Recently, coumarinyl thiazole moiety attached with pyrazoline ring (I) and quinoline-pyrazoline-based thiazoles (II) have been postulated as templates and lead compounds for the development of new antimicrobial agents (Aggarwal et al. 2013; Desai et al. 2013a) (Fig. 1).

Encouraged by these observations and in continuation of our search for potent heterocyclic biological agents (Imran and Khan 2004b; Khan et al. 2005; Alam et al. 2005a; Alam et al. 2005b; Gupta et al. 2005; Alam et al. 2010; Gilani and Khan 2013; Kaushik et al. 2012; Gilani et al. 2010) including coumarinyl heterocycles (Imran and Khan 2004a) and thiazolyl heterocycles (Imran et al. 2009), we decided to prepare some novel quinoline-pyrazoline-based coumarinyl thiazoles (**9a–9y**), herein after the targeted compounds (**9a–9y**), as potent antimicrobial agents.

Material and methods

General

Melting points were measured in open capillary tubes and are uncorrected. Infrared (IR) (KBr) spectra were recorded on a Nicolet, 5PC FT-IR spectrometer (Browser Morner, USA). ^{1}H-nuclear magnetic resonance (NMR) and ^{13}C-NMR spectra were recorded on a Bruker DRX-300 FT NMR (Bruker, Germany) spectrophotometer using Tetramethylsilane as internal reference (chemical shift in δ ppm). Mass spectra were recorded on a Jeol-JMS-D-300 mass spectrometer (70 eV) (Jeol, Japan). Satisfactory analysis for C, H, and N was obtained for the compounds within $\pm$ 0.4% of the theoretical values. The Purity of the compounds was checked on silica gel G plates using iodine vapors as visualizing agent. The R_f value of the compounds was determined by using a mixture of toluene, ethyl acetate and formic acid (5:4:1). All reagents used in the present work were of analytical grade.

Synthesis of the targeted compounds (9a–9y)

*General procedure for the synthesis of 3-acetyl-6-H/halo-2H-chromen-2-one (**3a–3e**)*

An equimolar mixture of appropriate salicyldehyde (**1a–1e**) and ethyl acetoacetate (**2**) was stirred in 20 mL of ethanol in the presence of piperidine (0.2 mL) for about 1 to 2 h.

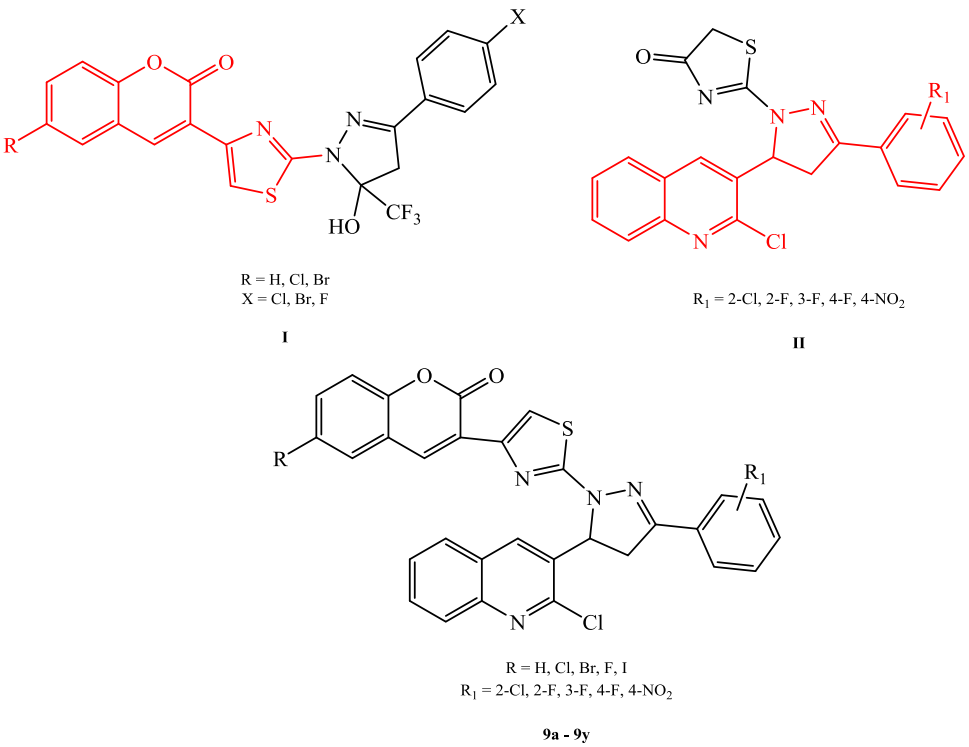


Fig. 1 Structures of postulated antimicrobial lead compounds, **I** and **II**, and synthesized compounds (**9a–9y**)

The mixture was cooled, the solid was separated and recrystallized from ethanol.

The detailed characterization data of (**3a–3d**) is provided in the literature (Gali et al. 2015; Siddiqui et al. 2009; Gursoy and Karali 2003; Aggarwal et al. 2013; Jayashree et al. 2005; Venugopala and Jayashree 2003; Chopra et al. 2006; Kumar et al. 2011; Abdel-Sattar 2008).

3-Acetyl-6-iodo-2H-chromen-2-one (**3e**) It was obtained from the reaction of 5-iodosalicyldehyde (**1e**) and ethyl acetoacetate (**2**) as yellowish brown crystals (EtOH). Yield 80%; m.p. 202–205 °C; IR (KBr) ν_{max} 1725 and 1710 (C=O), 1608 (C=C), 1230 (C–O–C), 560 (C–I); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 2.55$ (s, 3H, –CO$\underline{CH_3}$), 7.30–7.90 (m, 3H, Ar–H), 8.24 (s, 1H, C_4–H); Mass (*m/z*) 314 (M^+); Anal. Calcd for $C_{11}H_7IO_3$: C, 42.07; H, 2.25; N, 0.0. Found: C, 42.03; H, 2.24; N, 0.0.

*General procedure for the synthesis of 3-(2-bromoacetyl)-6-H/halo-2H-chromen-2-one (**4a–4e**)*

To a mixture of appropriate compound (**3a–3e**) (0.25 moles) in 200 mL of alcohol free chloroform, bromine (0.30 moles) in 25 mL of chloroform was added drop wise with stirring. The reaction mixture was first stirred for 1 h at room temperature and then it was refluxed for about 30 min. The reaction mixture was cooled, solid mass was separated, washed with diethyl ether and recrystallized from acetic acid.

The detailed characterization data of (**4a–4d**) is provided in the literature (Gali et al. 2015; Siddiqui et al. 2009; Gursoy and Karali 2003; Aggarwal et al. 2013; Jayashree et al. 2005; Venugopala and Jayashree 2003; Chopra et al. 2006; Desai et al. 2013b).

3-(2-bromoacetyl)-6-iodo-2H-chromen-2-one (**4e**) It was obtained by the reaction of the compound (**3e**) with bromine as faint yellowish needles (CH_3COOH).Yield 60%; m.p. 188–192 °C;°C; IR (KBr) ν_{max} 1722 and 1690 (C=O), 1604 (C=C), 1232 (C–O–C), 685 (C–Br), 560 (C–I); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 4.55$ (s, 2H, –CO$\underline{CH_2}$Br), 7.30–8.04 (m, 3H, Ar–H), 8.28 (s, 1H, C_4–H); Mass (*m/z*): 392 (M^+); Anal. Calcd for $C_{11}H_6BrIO_3$: C, 33.62; H, 1.54; N, 0.0. Found: C, 33.60; H, 1.51; N, 0.0.

*General procedure for the synthesis of 5-(2-chloroquinolin-3-yl)-3-substituted phenyl-4,5-dihydro-1H-pyrazole-1-carbothiamide (**8a–8e**)*

The starting materials for the preparation of the compounds (**8a–8e**) namely, 2-Chloroquinoline-3-carbaldehyde of formula **5** (Desai et al. 2013a; Kumar et al. 2010) and 3-(2-chloroquinolin-3-yl)-1-substituted phenylprop-2-en-1-ones of formula (**7a–7e**) (Desai et al. 2013a; Abdel-Sattar 2008) were prepared by the method described in the literature. The 5-(2-chloroquinolin-3-yl)-3-substituted phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothiamides of formula (**8a–8e**) were also prepared according to the method provided in the literature (Desai et al. 2013a).

The detailed characterization data of the compounds (**8a–8e**) is also provided in the literature (Desai et al. 2013a).

*3-(2-Chlorophenyl)-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**8a**)*

It was obtained by the reaction of the compound (**7a**) with thiosemicarbazide as faint gray crystals (EtOH).Yield 75%; m.p. 174–176 °C; IR (KBr) ν_{max} 3455 (N–H), 1570 (C=N), 1520 (C=C), 1330 (C=S); Anal. Calcd for $C_{19}H_{14}Cl_2N_4S$: C, 56.87; H, 3.52; N, 13.96. Found: C, 56.85; H, 3.48; N, 13.90.

*5-(2-Chloroquinolin-3-yl)-3-(2-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**8b**)*

It was obtained by the reaction of the compound (**7b**) with thiosemicarbazide as faint brown crystals (EtOH). Yield 70%; m.p. 179–181 °C; IR (KBr) ν_{max} 3458 (N–H), 1583 (C=N), 1521 (C=C), 1333 (C=S); Anal. Calcd for $C_{19}H_{14}ClFN_4S$: C, 59.30; H, 3.67; N, 14.51. Found: C, 59.25; H, 3.66; N, 14.51.

*5-(2-Chloroquinolin-3-yl)-3-(3-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**8c**)*

It was obtained by the reaction of the compound (**7c**) with thiosemicarbazide as faint pink crystals (EtOH). Yield 75%; m.p. 167–169 °C; IR (KBr) ν_{max} 3465 (N-H), 1578 (C=N), 1522 (C=C), 1330 (C=S); Anal. Calcd for $C_{19}H_{14}ClFN_4S$: C, 59.30; H, 3.67; N, 14.56. Found: C, 59.24; H, 3.63; N, 14.50.

*5-(2-Chloroquinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**8d**)*

It was obtained by the reaction of the compound (**7d**) with thiosemicarbazide as faint reddish-brown crystals (EtOH). Yield 76%; m.p. 208–210 °C; IR (KBr) ν_{max} 3470 (N–H), 1585 (C=N), 1523 (C=C), 1336 (C=S); Anal. Calcd for $C_{19}H_{14}ClFN_4S$: C, 59.30; H, 3.67; N, 14.56. Found: C, 59.22; H, 3.64; N, 14.53.

*5-(2-Chloroquinolin-3-yl)-3-(4-nirophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**8e**)*

It was obtained by the reaction of the compound (**7e**) with thiosemicarbazide as orange crystals (EtOH). Yield 70%; m.p. 223–225 °C; IR (KBr) ν_{max} 3470 (N–H), 1584 (C=N), 1515 (C=C), 1328 (C=S); Anal. Calcd for $C_{19}H_{14}ClN_5O_2S$: C, 55.41; H, 3.43; N, 17.00. Found: C, 55.35; H, 3.40; N, 16.94.

*General procedure for the synthesis of 3-(2-(5-(2-chloroquinolin-3-yl)-3-substituted phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-H/halo-2H-chromen-2-ones (**9a–9y**)*

To a mixture of the appropriate compound (**8a–8e**) (0.01 mole) in ethanol (99.9%), respective compound (**4a–4e**) (0.01 mole) was added and the resulting mixture was heated to reflux for about 1 to 3 h. The mixture was cooled, the solid was separated and washed with 10% ethanol. The products were recrystallized from ethanol.

3-(2-(3-(2-Chlorophenyl)-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9a**) It was obtained by the reaction of the compound (**4a**) with the compound (**8a**) as yellowish-brown crystals (EtOH). Yield 75%; m.p. 238–240 °C; R_f value 0.58; IR (KBr) ν_{max} 1715 (C=O), 1578 (C=N), 1535 (C=C), 1255 (C–O–C), 1108 (C–S); ^{1}HNMR (DMSO-d_6, 400 MHz):$\delta =$ 3.58 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.83 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.75 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.35–8.05 (m, 13H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.54 (s, 1H, C_4–H coumarin); ^{13}CNMR (DMSO-d_6, 100 MHz):$\delta = 40.0$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 117.1 (Ar–C), 121.9 (Ar–C), 126.4 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.9 (Ar–C), 129.3 (Ar–C), 129.8 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.1 (Ar–C), 131.3 (Ar–C), 131.6 (Ar–C), 131.9 (Ar–C), 133.4 (Ar–C), 137.2 (Ar–C), 138.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 154.0, 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*) 568 (M^+); Anal. Calcd for $C_{30}H_{18}Cl_2N_4O_2S$: C, 63.28; H, 3.19; N, 9.84. Found: C, 63.20; H, 3.15; N, 9.79.

3-(2-(5-(2-chloroquinolin-3-yl)-3-(2-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9b**) It was obtained by the reaction of the compound (**4a**) with the compound (**8b**) as reddish-yellow crystals (EtOH). Yield 60%; m.p. 220–222 °C; R_f value 0.64; IR (KBr) ν_{max} 1718 (C=O), 1578 (C=N), 1533 (C=C), 1266 (C–O–C), 1111 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.57$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.86 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.78 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.33–8.07 (m, 13H, Ar–H), 8.20 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 116.6 (Ar–C), 117.1 (Ar–C), 119.2 (Ar–C), 121.9 (Ar–C), 125.4 (Ar–C), 126.4 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.9 (Ar–C), 129.3 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.8 (Ar–C), 131.9 (Ar–C), 133.6 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 154.0 (Ar–C), 157.6 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 552 (M^+); Anal. Calcd for $C_{30}H_{18}ClFN_4O_2S$: C, 65.16; H, 3.28; N, 10.13. Found: C, 65.10; H, 3.25; N, 10.10.

3-(2-(5-(2-chloroquinolin-3-yl)-3-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9c**) It was obtained by the reaction of the compound (**4a**) with the compound (**8c**) as faint yellow crystals (EtOH). Yield 78%; m.p. 210–212 °C; R_f value 0.66; IR (KBr) ν_{max} 1721 (C=O), 1580 (C=N), 1535 (C=C), 1261 (C–O–C), 1112 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.59$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.87 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.75 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.31–8.05 (m, 13H, Ar–H), 8.19 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 115.0 (Ar–C), 117.1 (Ar–C), 118.8 (Ar–C), 121.9 (Ar–C), 124.8 (Ar–C), 126.4 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.9 (Ar–C), 129.3 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.4 (Ar–C), 131.9 (Ar–C), 136.6 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 154.0 (Ar–C), 162.9 (C=O carbon of coumarin ring), 164.0 (Ar–C), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 552 (M^+); Anal. Calcd for $C_{30}H_{18}ClFN_4O_2S$: C, 65.16; H, 3.28; N, 10.13. Found: C, 65.12; H, 3.27; N, 10.11.

3-(2-(5-(2-chloroquinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9d**) It was obtained by the reaction of the compound (**4a**) with the compound (**8d**) as yellow crystals (EtOH). Yield 75%; m.p. 226–228 °C; R_f value 0.69; IR (KBr) ν_{max} 1713 (C=O), 1586 (C=N), 1530 (C=C), 1255 (C–O–C), 1114 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.59$ (d, $J =$ 17 Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.30–8.01 (m, 13H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the

pyrazoline ring), 114.5 (Ar–C), 116.6 (2C, Ar–C), 117.1 (Ar–C), 121.9 (Ar–C), 126.4 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.9 (Ar–C), 129.3 (Ar–C), 130.4 (Ar–C), 130.5 (2C, Ar–C), 130.9 (Ar–C), 131.9 (Ar–C), 133.0 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 154.0 (Ar–C), 162.9 (C=O carbon of coumarin ring), 166.2 (Ar–C), 168.3 (C_5 carbon of the thiazole ring); Mass (*m*/*z*): 552 (M^+); Anal. Calcd for $C_{30}H_{18}ClFN_4O_2S$: C, 65.16; H, 3.28; N, 10.13. Found: C, 65.11; H, 3.22; N, 10.12.

3-(2-(5-(2-chloroquinolin-3-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9e**) It was obtained by the reaction of the compound (**4a**) with the compound (**8e**) as reddish-brown crystals (EtOH). Yield 78%; m.p. 238–240 °C; R_f value 0.71; IR (KBr) ν_{max} 1717 (C=O), 1579 (C=N), 1534(C=C), 1258 (C–O–C), 1105 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.61$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.30–8.05 (m, 13H, Ar–H), 8.20 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 117.1 (Ar–C), 121.9 (Ar–C), 126.4 (Ar–C), 127.6 (Ar–C), 128.0 (3C, Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.7 (2C, Ar–C), 128.9 (Ar–C), 129.3 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.9 (Ar–C), 137.2 (Ar–C), 143.5 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 151.2 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 154.0 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m*/*z*): 579 (M^+); Anal. Calcd for $C_{30}H_{18}ClN_5O_4S$: C, 62.12; H, 3.13; N, 12.07. Found: C, 62.10; H, 3.10; N, 12.00.

6-Chloro-3-(2-(3-(2-chlorophenyl)-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9f**) It was obtained by the reaction of the compound (**4b**) with the compound (**8a**) as yellowish crystals (EtOH). Yield 75%; m.p. 254–256 °C; R_f value 0.71; IR (KBr) ν_{max} 1722 (C=O), 1580 (C=N), 1538 (C=C), 1260 (C–O–C), 1118 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.58$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.31–8.09 (m, 12H, Ar–H), 8.17 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.0$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 119.0 (Ar–C), 124.6 (Ar–C), 127.6 (Ar–C), 127.8 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 129.8 (Ar–C), 130.4 (Ar–C), 130.5 (Ar–C), 130.9 (Ar–C), 131.1 (Ar–C), 131.3 (Ar–C), 131.6 (Ar–C), 131.9 (Ar–C), 132.0 (Ar–C), 133.4 (Ar–C), 137.2 (Ar–C), 138.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m*/*z*): 602 (M^+); Anal. Calcd For $C_{30}H_{17}Cl_3N_4O_2S$: C, 59.67; H, 2.84; N, 9.28. Found: C, 59.65; H, 2.79; N, 9.25.

6-Chloro-3-(2-(5-(2-chloroquinolin-3-yl)-3-(2-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9g**) It was obtained by the reaction of the compound (**4b**) with the compound (**8b**) as creamy yellow crystals (EtOH). Yield 80%; m.p. 240–242 °C; R_f value 0.66; IR (KBr) ν_{max} 1723 (C=O), 1582 (C=N), 1533 (C=C), 1255 (C–O–C), 1108 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.59$ (d, $J = 17$ Hz, 1H, C_4-H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.76 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.32–8.08 (m, 12H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 116.6 (Ar–C), 119.0 (Ar–C), 119.2 (Ar–C), 124.6 (Ar–C), 125.4 (Ar–C), 127.6 (Ar–C), 127.8 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.5 (Ar–C), 130.9 (Ar–C), 131.8 (Ar–C), 131.9 (Ar–C), 132.0 (Ar–C), 133.6 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 160.6 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m*/*z*): 586 (M^+); Anal. Calcd for $C_{30}H_{17}Cl_2FN_4O_2S$): C, 61.34; H, 2.92; N, 9.54. Found: C, 61.30; H, 2.90; N, 9.51.

6-Chloro-3-(2-(5-(2-chloroquinolin-3-yl)-3-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9h**) It was obtained by the reaction of the compound (**4b**) with the compound (**8c**) as faint yellow crystals (EtOH). Yield 70%; m.p. 250–252 °C; R_f value 0.64; IR (KBr) ν_{max} 1719 (C=O), 1578 (C=N), 1533 (C=C), 1258 (C–O–C), 1110 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.59$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.76 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.30–8.04 (m, 12H, Ar–H), 8.19 (s, 1H, C_5–H thiazole), 8.54 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 115.0 (Ar–C), 118.8 (Ar–C), 119.0 (Ar–C), 124.6 (Ar–C), 124.8 (Ar–C), 127.6 (Ar–C), 127.8 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.5 (Ar–C), 130.9 (Ar–C), 131.4 (Ar–C), 131.9 (Ar–C), 132.0 (Ar–C), 136.6 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 162.9 (C=O carbon of coumarin ring), 164.0 (Ar–C), 168.3 (C_5 carbon of the thiazole ring); Mass (*m*/*z*): 586 (M^+); Anal. Calcd for $C_{30}H_{17}Cl_2FN_4O_2S$: C, 61.34; H, 2.92; N, 9.54. Found: C, 61.32; H, 2.91; N, 9.50.

6-Chloro-3-(2-(5-(2-chloroquinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9i**) It was obtained by the reaction of the compound (**4b**) with the compound (**8d**) as orange crystals (EtOH). Yield 75%; m.p. 235–237 °C; R_f value 0.69; IR (KBr) ν_{max} 1720 (C=O), 1585 (C=N), 1533 (C=C), 1260 (C–O–C), 1112 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.55$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.85 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.75 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.35–8.05 (m, 12H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 116.6 (2C, Ar–C), 119.0 (Ar–C), 124.6 (Ar–C), 127.6 (Ar–C), 127.8 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.5 (3C, Ar–C), 130.9 (Ar–C), 131.9 (Ar–C), 132.0 (Ar–C), 133.0 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 162.9 (C=O carbon of coumarin ring), 166.2 (Ar–C), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 586 (M^+); Anal. Calcd for $C_{30}H_{17}Cl_2FN_4O_2S$: C, 61.34; H, 2.92; N, 9.54. Found: C, 61.30; H, 2.88; N, 9.49.

6-Chloro-3-(2-(5-(2-chloroquinolin-3-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9j**) It was obtained by the reaction of the compound (**4b**) with the compound (**8e**) as brownish-yellow crystals (EtOH). Yield 65%; m.p. 230–232 °C; R_f value 0.71; IR (KBr) ν_{max} 1722 (C=O), 1577 (C=N), 1534 (C=C), 1259 (C–O–C), 1116 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.58$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.30–8.02 (m, 12H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 117.0 (Ar–C), 124.6 (Ar–C), 127.6 (Ar–C), 127.8 (Ar–C), 128.0 (3C, Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.7 (2C, Ar–C), 130.4 (Ar–C), 130.5 (Ar–C), 130.9 (Ar–C), 131.9 (Ar–C), 132.0 (Ar–C), 137.2 (Ar–C), 143.5 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 151.2 (Ar–C), 152.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 613 (M^+); Anal. Calcd for $C_{30}H_{17}Cl_2N_5O_4S$: C, 58.64; H, 2.79; N, 11.40. Found: C, 58.59; H, 2.75; N, 11.38.

6-Bromo-3-(2-(3-(2-chlorophenyl)-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9k**) It was obtained by the reaction of the compound (**4c**) with the compound (**8a**) as brownish-yellow crystals (EtOH). Yield 75%; m.p. 255–257 °C; R_f value 0.73; IR (KBr) ν_{max} 1715 (C=O), 1588 (C=N), 1534 (C=C), 1263 (C–O–C), 1114 (C–S) ; ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.58$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.30–8.05 (m, 12H, Ar–H), 8.20 (s, 1H, C_5–H thiazole), 8.54 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.0$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 119.2 (Ar–C), 120.8 (Ar–C), 125.4 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 129.8 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.1 (Ar–C), 131.3 (2C, Ar–C), 131.6 (Ar–C), 131.9 (Ar–C), 133.4 (Ar–C), 135.2 (Ar–C), 137.2 (Ar–C), 138.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 153.0 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 646 (M^+); Anal. Calcd for $C_{30}H_{17}BrCl_2N_4O_2S$: C, 55.58; H, 2.64; N, 8.64. Found: C, 55.55; H, 2.60; N, 8.61.

6-Bromo-3-(2-(5-(2-chloroquinolin-3-yl)-3-(2-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9l**) It was obtained by the reaction of the compound (**4c**) with the compound (**8b**) as dark yellow crystals (EtOH). Yield 70%; m.p. 245–247 °C; R_f value 0.72; IR (KBr) ν_{max} 1714 (C=O), 1576 (C=N), 1532 (C=C), 1266 (C–O–C), 1110 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.56$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.85 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.32–8.01 (m, 12H, Ar–H), 8.19 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 116.6 (Ar–C), 119.2 (2C, Ar–C), 120.8 (Ar–C), 125.4 (2C, Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.3 (Ar–C), 131.8 (Ar–C), 131.9 (Ar–C), 133.6 (Ar–C), 135.2 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 153.0 (Ar–C), 160.6 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 630 (M^+); Anal. Calcd for $C_{30}H_{17}BrClFN_4O_2S$: C, 57.02; H, 2.71; N, 8.87. Found: C, 56.99; H, 2.67; N, 8.85.

6-Bromo-3-(2-(5-(2-chloroquinolin-3-yl)-3-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9m**) It was obtained by the reaction of the compound (**4c**) with the compound (**8c**) as light-yellow brown crystals (EtOH). Yield 65%; m.p. 230–232 °C; R_f value 0.65; IR (KBr) ν_{max} 1718 (C=O), 1574 (C=N), 1534 (C=C), 1258 (C–O–C), 1115 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.58$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.87 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.75 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.33–8.05 (m, 12H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.54 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline

ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 115.0 (Ar–C), 118.8 (Ar–C), 119.2 (Ar–C), 120.8 (Ar–C), 124.8 (Ar–C), 125.4 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.3 (Ar–C), 131.4 (Ar–C), 131.9 (Ar–C), 135.2 (Ar–C), 136.6 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 153.0 (Ar–C), 162.9 (C=O carbon of coumarin ring), 164.0 (Ar–C), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 630 (M^+); Anal. Calcd for $C_{30}H_{17}BrClFN_4O_2S$: C, 57.02; H, 2.71; N, 8.87. Found: C, 57.00; H, 2.68; N, 8.84.

6-Bromo-3-(2-(5-(2-chloroquinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9n**) It was obtained by the reaction of the compound (**4c**) with the compound (**8d**) as light-brown crystals (EtOH). Yield 68%; m.p. 245–247 °C; R_f value 0.71; IR (KBr) ν_{max} 1719 (C=O), 1578 (C=N), 1534 (C=C), 1258 (C–O–C), 1110 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.56$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.85 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.30–8.05 (m, 12H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 116.6 (2C, Ar–C), 119.2 (Ar–C), 120.8 (Ar–C), 125.4 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.5 (2C, Ar–C), 130.9 (Ar–C), 131.3 (Ar–C), 131.9 (Ar–C), 133.0 (Ar–C), 135.2 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 153.0 (Ar–C), 162.9 (C=O carbon of coumarin ring), 166.2 (Ar–C), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 630 (M^+); Anal. Calcd for $C_{30}H_{17}BrClFN_4O_2S$: C, 57.02; H, 2.71; N, 8.87. Found: C, 57.00; H, 2.69; N, 8.85.

6-Bromo-3-(2-(5-(2-chloroquinolin-3-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**9o**) It was obtained by the reaction of the compound (**4c**) with the compound (**8e**) as light reddish-brown yellow crystals (EtOH). Yield 65%; m.p. 255–257 °C; R_f value 0.69; IR (KBr) ν_{max} 1715 (C=O), 1578 (C=N), 1531 (C=C), 1259 (C–O–C), 1109 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.57$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.75 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.33–8.03 (m, 12H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 119.2 (Ar–C), 120.8 (Ar–C), 125.4 (Ar–C), 127.6 (Ar–C), 128.0 (3C, Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.7 (2C, Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.3 (Ar–C), 131.9 (Ar–C), 135.2 (Ar–C), 137.2 (Ar–C), 143.5 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 151.2 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 153.0 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 657 (M^+); Anal. Calcd for $C_{30}H_{17}BrClN_5O_4S$: C, 54.69; H, 2.60; N, 10.63. Found: C, 54.63; H, 2.55; N, 10.63.

3-(2-(3-(2-Chlorophenyl)-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-fluoro-2H-chromen-2-one (**9p**) It was obtained by the reaction of the compound (**4d**) with the compound (**8a**) as yellow crystals (EtOH). Yield 70%; m.p. 225–227 °C; R_f value 0.73; IR (KBr) ν_{max} 1720 (C=O), 1580 (C=N), 1533 (C=C), 1266 (C–O–C), 1110 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.58$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.84 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.31–8.04 (m, 12H, Ar–H), 8.19 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.0$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 115.6 (Ar–C), 116.1 (Ar–C), 124.8 (Ar–C), 126.1 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 129.8 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.1 (Ar–C), 131.3 (Ar–C), 131.6 (Ar–C), 131.9 (Ar–C), 133.4 (Ar–C), 137.2 (Ar–C), 138.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 147.6 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 160.6 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 586 (M^+); Anal. Calcd for $C_{30}H_{17}Cl_2FN_4O_2S$: C, 61.34; H, 2.92; N, 9.54. Found: C, 61.30; H, 2.89; N, 9.51.

3-(2-(5-(2-Chloroquinolin-3-yl)-3-(2-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-fluoro-2H-chromen-2-one (**9q**) It was obtained by the reaction of the compound (**4d**) with the compound (**8b**) as faint brownish-yellow crystals (EtOH). Yield 72%; m.p. 215–217 °C; R_f value 0.70; IR (KBr) ν_{max} 1719 (C=O), 1578 (C=N), 1532 (C=C), 1259 (C–O–C), 1114 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.55$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.89 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.33–8.05 (m, 12H, Ar–H), 8.20 (s, 1H, C_5–H thiazole), 8.53 (s, 1H, C_4–H coumarin), ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 115.6 (Ar–C), 116.1 (Ar–C), 116.6 (Ar–C), 117.2 (Ar–C), 124.8 (Ar–C), 125.4 (Ar–C), 126.1 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.8 (Ar–C), 131.9 (Ar–C), 133.6 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 149.6 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 160.6 (2C, Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 570 (M^+); Anal. Calcd for

$C_{30}H_{17}ClF_2N_4O_2S$: C, 63.11; H, 3.00; N, 9.81. Found: C, 63.08; H, 2.97; N, 9.77.

3-(2-(5-(2-Chloroquinolin-3-yl)-3-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-fluoro-2H-chromen-2-one (**9r**) It was obtained by the reaction of the compound (**4d**) with the compound (**8c**) as light-yellow crystals (EtOH).Yield 77%; m.p. 233–235 °C; R_f value 0.74; IR (KBr) ν_{max} 1717 (C=O), 1577 (C=N), 1533 (C=C), 1257 (C–O–C), 1109 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.57$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.76 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.33–8.05 (m, 12H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.56 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 115.0 (Ar–C), 115.6 (Ar–C), 116.1 (Ar–C), 118.8 (Ar–C), 124.8 (2C, Ar–C), 126.1 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.4 (Ar–C), 131.9 (Ar–C), 136.6 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 149.6 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 160.6 (Ar–C), 162.9 (C=O carbon of coumarin ring), 164.0 (Ar–C), 168.3 (C_5 carbon of the thiazole ring); Mass (*m*/*z*): 570 (M^+); Anal. Calcd for $C_{30}H_{17}ClF_2N_4O_2S$: C, 63.11; H, 3.00; N, 9.81. Found: C, 63.09; H, 2.99; N, 9.76.

3-(2-(5-(2-Chloroquinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-fluoro-2H-chromen-2-one (**9s**) It was obtained by the reaction of the compound (**4d**) with the compound (**8d**) as brownish-yellow crystals (EtOH). Yield 68%; m.p. 240–241 °C; R_f value 0.72; IR (KBr) ν_{max} 1716 (C=O), 1577 (C=N), 1533 (C=C), 1263 (C–O–C), 1111 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.58$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.34–8.02 (m, 12H, Ar–H), 8.19 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 115.6 (Ar–C), 116.1 (Ar–C), 116.6 (2C, Ar–C), 124.8 (Ar–C), 126.1 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.5 (2C, Ar–C), 130.9 (Ar–C), 131.9 (Ar–C), 133.0 (Ar–C), 137.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 149.6 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 160.6 (Ar–C), 162.9 (C=O carbon of coumarin ring), 166.2 (Ar–C), 168.3 (C_5 carbon of the thiazole ring); Mass (*m*/*z*): 570 (M^+); Anal. Calcd for $C_{30}H_{17}ClF_2N_4O_2S$: C, 63.11; H, 3.00; N, 9.81. Found: C, 63.06; H, 2.95; N, 9.78.

3-(2-(5-(2-Chloroquinolin-3-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-fluoro-2H-chromen-2-one (**9t**) It was obtained by the reaction of the compound (**4d**) with the compound (**8e**) as reddish-yellow crystals (EtOH). Yield 75%; m.p. 255–257 °C; R_f value 0.66; IR (KBr) ν_{max} 1716 (C=O), 1577 (C=N), 1535 (C=C), 1259 (C–O–C), 1108 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.56$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.75 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.31–8.05 (m, 12H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 114.5 (Ar–C), 115.6 (Ar–C), 116.1 (Ar–C), 124.8 (Ar–C), 126.1 (Ar–C), 127.6 (Ar–C), 128.0 (3C, Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.7 (2C, Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.9 (Ar–C), 137.2 (Ar–C), 143.5 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 149.6 (Ar–C), 151.2 (Ar–C), 152.7 (Ar–C), 152.9 (Ar–C), 160.6 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m*/*z*): 597 (M^+); Anal. Calcd for $C_{30}H_{17}ClFN_5O_4S$: C, 60.26; H, 2.87; N, 11.71. Found: C, 60.22; H, 2.85; N, 11.66.

3-(2-(3-(2-Chlorophenyl)-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-iodo-2H-chromen-2-one (**9u**) It was obtained by the reaction of the compound (**4e**) with the compound (**8a**) as light-orange crystals (EtOH).Yield 80%; m.p. 233–235 °C; R_f value 0.69; IR (KBr) ν_{max} 1717 (C=O), 1583 (C=N), 1533 (C=C), 1262 (C–O–C), 1113 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.57$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.85 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.75 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.33–8.04 (m, 12H, Ar–H), 8.19 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.0$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 93.8 (Ar–C), 114.5 (Ar–C), 121.4 (Ar–C), 124.8 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 129.8 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.1 (Ar–C), 131.3 (Ar–C), 131.6 (Ar–C), 131.9 (Ar–C), 133.4 (Ar–C), 135.2 (Ar–C), 137.2 (Ar–C), 138.2 (2C, Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (2C, Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m*/*z*): 694 (M^+); Anal. Calcd for $C_{30}H_{17}Cl_2IN_4O_2S$: C, 51.82; H, 2.46; N, 8.06. Found: C, 51.80; H, 2.41; N, 8.05.

3-(2-(5-(2-Chloroquinolin-3-yl)-3-(2-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-iodo-2H-chromen-2-one (**9v**) It was obtained by the reaction of the compound (**4e**) with the compound (**8b**) as faint brownish-yellow crystals (EtOH). Yield 75%; m.p. 241–243 °C; R_f value 0.61; IR (KBr) ν_{max} 1716 (C=O), 1578 (C=N), 1533 (C=C), 1257 (C–O–C), 1105 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.58$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$

Hz, 1H, C_5–H pyrazoline), 7.31–8.05 (m, 12H, Ar–H), 8.18 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 93.8 (Ar–C), 114.5 (Ar–C), 116.6 (Ar–C), 119.2 (Ar–C), 121.4 (Ar–C), 124.8 (Ar–C), 125.4 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.8 (Ar–C), 131.9 (Ar–C), 133.6 (Ar–C), 135.2 (Ar–C), 137.2 (Ar–C), 138.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (2C, Ar–C), 160.6 (Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Anal. Calcd for $C_{30}H_{17}ClFIN_4O_2S$: C, 53.08; H, 2.52; N, 8.25. Found: C, 53.02; H, 2.48; N, 8.23.

3-(2-(5-(2-Chloroquinolin-3-yl)-3-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-iodo-2H-chromen-2-one (**9w**) It was obtained by the reaction of the compound (**4e**) with the compound (**8c**) as yellow crystals (EtOH). Yield 70%; m.p. 215–217 °C; R_f value 0.74; IR (KBr) ν_{max} 1719 (C=O), 1575 (C=N), 1534 (C=C), 1260 (C–O–C), 1110 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.55$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.86 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.30–8.04 (m, 12H, Ar–H), 8.20 (s, 1H, C_5–H thiazole), 8.54 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 93.8 (Ar–C), 114.5 (Ar–C), 115.0 (Ar–C), 118.8 (Ar–C), 121.4 (Ar–C), 124.8 (2C, Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.4 (Ar–C), 131.9 (Ar–C), 135.2 (Ar–C), 136.6 (Ar–C), 137.2 (Ar–C), 138.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (2C, Ar–C), 162.9 (C=O carbon of coumarin ring), 164.0 (Ar–C), 168.3 (C_5 carbon of the thiazole ring); Anal. Calcd for $C_{30}H_{17}ClFIN_4O_2S$: C, 53.08; H, 2.52; N, 8.25. Found: C, 53.01; H, 2.49; N, 8.22.

3-(2-(5-(2-Chloroquinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-iodo-2H-chromen-2-one (**9x**) It was obtained by the reaction of the compound (**4e**) with the compound (**8d**) as orange crystals (EtOH). Yield 77%; m.p. 236–238 °C; R_f value 0.66; IR (KBr) ν_{max} 1717 (C=O), 1581 (C=N), 1534 (C=C), 1255 (C–O–C), 1114 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.55$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.85 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.30–8.05 (m, 12H, Ar–H), 8.19 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 93.8 (Ar–C), 114.5 (Ar–C), 116.6 (2C, Ar–C), 121.4 (Ar–C), 124.8 (Ar–C), 127.6 (Ar–C), 128.0 (Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 130.4 (Ar–C), 130.5 (2C, Ar–C), 130.9 (Ar–C), 131.9 (Ar–C), 133.0 (Ar–C), 135.2 (Ar–C), 137.2 (Ar–C), 138.2 (Ar–C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 152.7 (Ar–C), 152.9 (2C, Ar–C), 162.9 (C=O carbon of coumarin ring), 166.2 (Ar–C), 168.3 (C_5 carbon of the thiazole ring); Anal. Calcd for $C_{30}H_{17}ClFIN_4O_2S$: C, 53.08; H, 2.52; N, 8.25. Found: C, 53.00; H, 2.51; N, 8.23.

3-(2-(5-(2-Chloroquinolin-3-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)-6-iodo-2H-chromen-2-one (**9y**) It was obtained by the reaction of the compound (**4e**) with the compound (**8e**) as light reddish-yellow crystals (EtOH). Yield 68%; m.p. 251–253 °C; R_f value 0.73; IR (KBr) ν_{max} 1722 (C=O), 1585 (C=N), 1533 (C=C), 1266 (C–O–C), 1115 (C–S); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 3.55$ (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 3.88 (d, $J = 17$ Hz, 1H, C_4–H pyrazoline), 5.77 (d, $J = 18$ Hz, 1H, C_5–H pyrazoline), 7.30–8.05 (m, 12H, Ar–H), 8.19 (s, 1H, C_5–H thiazole), 8.55 (s, 1H, C_4–H coumarin); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 40.5$ (C_4 of the pyrazoline ring), 56.4 (C_5 of the pyrazoline ring), 93.8 (Ar–C), 114.5 (Ar–C), 121.4 (Ar–C), 124.8 (Ar–C), 127.6 (Ar–C), 128.0 (3C, Ar–C), 128.3 (Ar–C), 128.5 (Ar–C), 128.7 (2C, Ar–C), 130.4 (Ar–C), 130.9 (Ar–C), 131.2 (Ar–C), 131.9 (Ar–C), 137.2 (Ar–C), 138.2 (Ar–C), 143.5 (A–-C), 145.9 (Ar–C), 146.4 (Ar–C), 147.1 (Ar–C), 151.2 (Ar–C), 152.7 (Ar–C), 152.9 (2C, Ar–C), 162.9 (C=O carbon of coumarin ring), 168.3 (C_5 carbon of the thiazole ring); Mass (*m/z*): 705 (M^+); Anal. Calcd for $C_{30}H_{17}ClIN_5O_4S$: C, 51.04; H, 2.43; N, 9.92. Found: C, 51.01; H, 2.39; N, 9.92.

Antimicrobial activity

The targeted compounds (**9a–9y**) were tested for their in vitro antimicrobial activity by the serial plate dilution method (Cruickshank et al. 1975; Arthington-Skaggs et al. 2000) against five Gram-positive bacteria, namely, *Staphylococcus aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212), *Staphylococcus epidermidis* (ATCC 12228), *Bacillus subtilis* (ATCC 6633), and *Bacillus cereus* (ATCC 9946); five Gram-negative bacteria, namely, *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumoniae* (ATCC 700603), *Bordetella bronchiseptica* (ATCC 4617) and *Proteus vulgaris* (ATCC 9920); and five fungi, namely, *Candida albicans* (ATCC 2091), Aspergillus *niger* (MTCC 281), Aspergillus *flavus* (MTCC 277), *Monascus purpureous* (MTCC 369), and Penicillium *citrinum* (NCIM 768). The microorganisms were available at the Department of Microbiology, Majeedia Hospital, New Delhi, India. The Department of Microbiology of Majeedia Hospital obtained some of these microorganisms from the Institute of Genomics and Integrative Biology, New Delhi, India. Nutrient agar medium and Sabouraud dextrose medium were used

for antibacterial activity and antifungal activity, respectively. The compounds were tested at concentrations of 200, 150, 100, 75, 50, 25, and 12.5 µg/mL. The reference or standard antibiotics, ofloxacin, and ketoconazole were used at 50, 25, and 12.5 µg/mL concentrations for antibacterial activity and antifungal activity, respectively. Sterile dimethyl sulfoxide (DMSO) was used for the preparation of desired concentrations of the synthesized compounds and standard antibiotics. Sterile DMSO without the synthesized compounds and standard antibiotics served as a control group. The minimum inhibitory concentrations (MICs) values of the synthesized compounds, ofloxacin, and ketoconazole were also determined. The MIC (MIC) has been defined as the lowest concentration of a compound that inhibited visible growth of microorganisms on the plate.

Statistical analysis

All data ($n = 6$) are presented as mean ± standard error mean (SEM). The data were analyzed by one-way analysis of variance (ANOVA) with Dunnett's Multiple Comparison Test with respect to control group and standard group using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com. The results were considered significantly different at $p < 0.05$ as compared with control group as well as standard drug groups.

Results and discussion

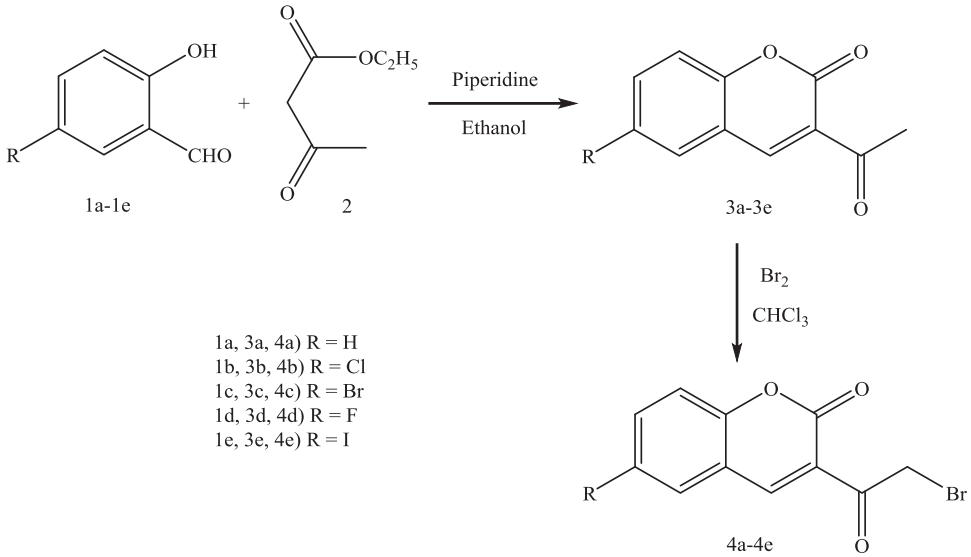
Chemistry

The targeted compounds (**9a–9y**) were prepared according to the methods as depicted in Schemes 1–3.

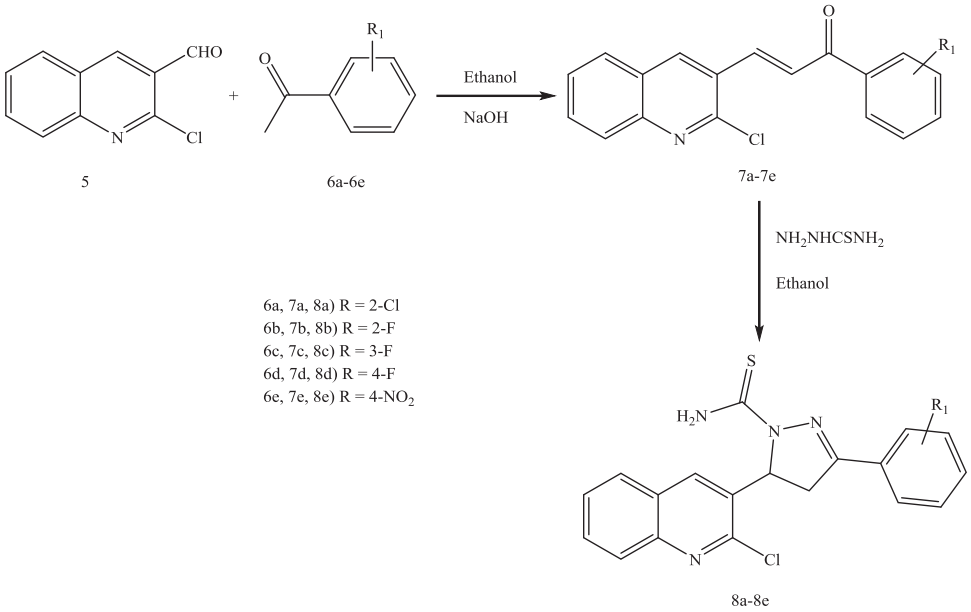
The compounds (**4a–4e**) (Scheme 1) (Gali et al. 2015; Siddiqui et al. 2009; Gursoy and Karali 2003; Aggarwal et al. 2013; Jayashree et al. 2005; Venugopala and Jayashree 2003; Chopra et al. 2006; Desai et al. 2013b), the compound 5 (Scheme 2) (Desai et al. 2013a; Kumar et al. 2010), the compounds **7a–7e** (Scheme 2) (Desai et al. 2013a; Kumar et al. 2010), and the compounds (**8a–8e**) (Scheme 2) (Desai et al. 2013a) were prepared according to the methods provided in the literature. The appropriate compounds (**4a–4e**) and compounds (**8a–8e**) were reacted in ethanol to provide the targeted compounds (**9a–9y**) (Scheme 3). These targeted compounds were characterized by their different melting points with respect to their respective starting materials, different R_f values in a particular solvent system, elemental analysis, and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, and Mass).

The IR spectra of the targeted compounds (**9a–9y**) showed characteristic IR peaks for C=O and C–O–C groups of coumarin ring at 1713–1723 and 1005–1118 cm^{-1}, respectively. It also displayed characteristic IR peak of C–S group of the thiazole ring at 1255–1266 cm^{-1}. The ^{1}H-NMR spectra of the targeted compounds (**9a–9y**) exhibited characteristic signals for the methylene protons (C_4–H protons) of pyrazoline ring. One proton of the methylene group of pyrazoline ring appeared as doublet at δ 3.55–3.61 and other proton appeared as doublet at δ 3.83–3.89. The C_5–H proton of the pyrazoline ring appeared as doublet at δ 5.75–5.78. The ^{1}H-NMR spectra also showed characteristic signals as multiplets at δ 7.30–8.09 for aromatic protons; as singlet at δ 8.17–8.20 for C_5–H proton of the thiazole ring and as singlet at δ 8.53–8.56 for the C_4–H proton of the coumarin ring. The ^{13}C-NMR spectra also supported the assigned number of carbon atoms. It showed characteristic signal at δ 40–40.5 due to the methylene carbon (C_4) of the pyrazoline ring and at δ 56.4 due to the methine carbon (C_5)

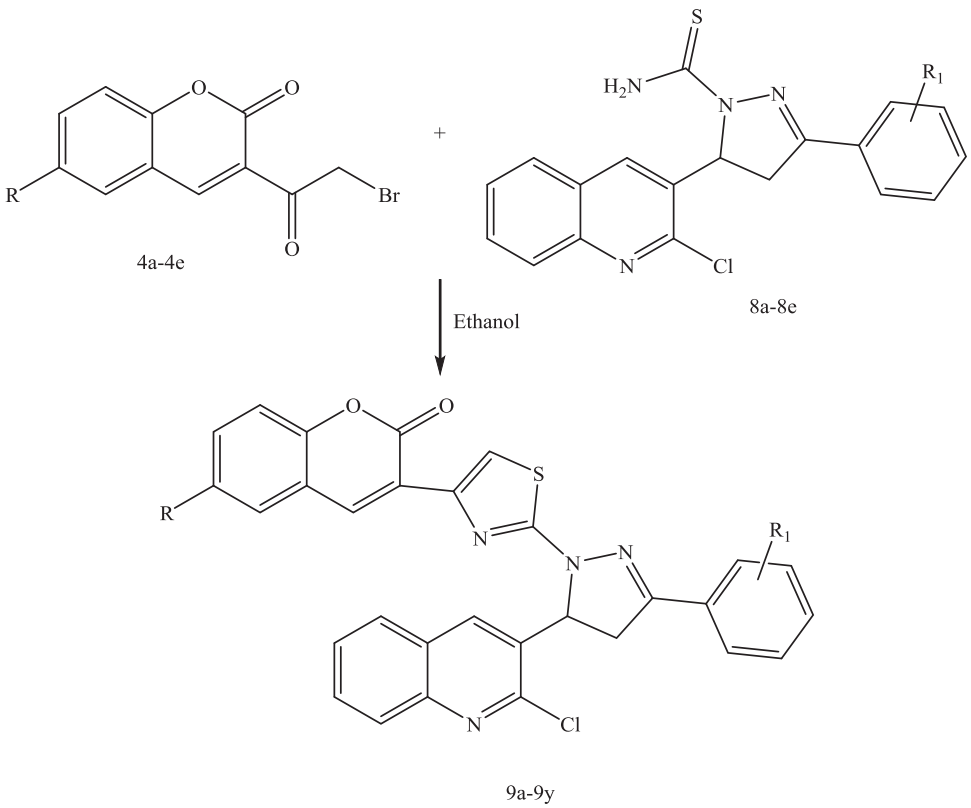
Scheme 1 General procedure for the synthesis of compounds **4a–4e**



Scheme 2 General procedure for the synthesis of compounds **8a–8e**



Scheme 3 General procedure for the synthesis of compounds **9a–9e**



9a) R= H, R_1 = 2-Cl; 9b) R = H, R_1 = 2-F; 9c) R = H, R_1 = 3-F; 9d) R = H, R_1 = 4-F; 9e) R = H, R_1 = 4-NO_2; 9f) R= Cl, R_1 = 2-Cl; 9g) R = Cl, R_1 = 2-F; 9h) R = Cl, R_1 = 3-F; 9i) R = Cl, R_1 = 4-F; 9j) R = Cl, R_1 = 4-NO_2; 9k) R= Br, R_1 = 2-Cl; 9l) R = Br, R_1 = 2-F; 9m) R = Br, R_1 = 3-F; 9n) R = Br, R_1 = 4-F; 9o) R = Br, R_1 = 4-NO_2; 9p) R= F, R_1 = 2-Cl; 9q) R = F, R_1 = 2-F; 9r) R = F, R_1 = 3-F; 9s) R = F, R_1 = 4-F; 9t) R = F, R_1 = 4-NO_2; 9u) R= I, R_1 = 2-Cl; 9v) R = I, R_1 = 2-F; 9w) R = I, R_1 = 3-F; 9x) R = I, R_1 = 4-F; 9y) R = I, R_1 = 4-NO_2

of the pyrazoline ring. The signals at about δ 168 and at about δ 162.9 also confirmed the C_5 carbon of the thiazole ring and C=O carbon of coumarin ring, respectively. The molecular ion peak of the mass spectrum as well as the elemental analysis of the targeted compounds (**9a–9y**) were also in accordance with the assigned chemical structures. These spectral data of the targeted compounds (**9a–9y**) were also in accordance with the reported literature (Vijesh et al. 2010; Gali et al. 2015; Aggarwal et al. 2013; Desai et al. 2013a).

Antimicrobial activity

The antimicrobial activity data of the targeted compounds (**9a–9y**) at different concentrations against Gram-positive bacteria, Gram-negative bacteria, and fungi obtained by the serial plate dilution method is provided in Tables 1, 2, and Table 3, respectively.

In the following discussion, the zone of inhibition produced by the MIC of standard drugs, ofloxacin and ketoconazole, has been considered as 100% for comparing the antibacterial activity and antifungal activity of the targeted compounds (**9a–9y**), respectively.

The antibacterial activity of the targeted compounds (**9a–9y**) against Gram-positive bacteria revealed that the standard drug ofloxacin had MIC values of 25 µg/mL against *S. aureus*, *E. faecalis*, and *S. epidermidis*. It also had a MIC value of 12.5 µg/mL against *B. subtilis*, and *B. cereus*. The compound **9s** (R=F, R_1 = 4-F), exhibited the

Table 1 Antibacterial activity data of the targeted compounds (**9a–9y**) against Gram-positive bacteria

Compounds	Zone of inhibition in mm and MIC (minimum inhibitory concentration) in µg/mL				
	S. aureus	*E. faecalis*	*S. epidermidis*	*B. subtilis*	*B. cereus*
9a	11.48 ± 0.25^{a} (75)	13.23 ± 0.37^{a} (75)	13.17 ± 0.51^{a} (50)	11.55 ± 0.33^{a} (50)	15.50 ± 0.31^{a} (75)
9b	16.62 ± 0.50^{a} (50)	17.73 ± 0.29^{a} (75)	18.33 ± 0.28^{a} (75)	16.80 ± 0.39^{a} (50)	21.25 ± 045^{a} (75)
9c	19.47 ± 0.48^{a} (50)	19.03 ± 0.17^{a} (50)	20.93 ± 0.34^{a} (50)	18.44 ± 0.44^{a} (75)	22.90 ± 0.13^{a} (50)
9d	18.21 ± 0.34^{a} (75)	18.88 ± 0.30^{a} (50)	20.33 ± 0.38^{a} (50)	18.44 ± 0.32^{a} (50)	22.22 ± 0.36^{a} (75)
9e	10.40 ± 0.46^{a} (75)	12.74 ± 0.40^{a} (75)	12.68 ± 0.56^{a} (50)	9.32 ± 0.45^{a} (75)	15.48 ± 0.26^{a} (50)
9f	13.14 ± 0.29^{a} (50)	14.52 ± 0.51^{a} (50)	16.48 ± 0.41^{a} (75)	13.28 ± 0.40^{a} (50)	18.80 ± 0.23^{a} (75)
9g	21.63 ± 0.27^{a} (75)	20.34 ± 0.44^{a} (75)	22.92 ± 0.29^{a} (75)	19.15 ± 0.38^{a} (50)	25.49 ± 0.24^{a} (75)
9h	23.13 ± 0.44^{a} (75)	22.32 ± 0.31^{a} (75)	26.18 ± 0.28^{a} (50)	23.03 ± 0.44^{a} (50)	26.16 ± 0.45^{a} (25)
9i	11.85 ± 0.35^{a} (75)	13.62 ± 0.29^{a} (50)	15.29 ± 0.34^{a} (50)	13.23 ± 0.33^{b} (50)	18.65 ± 0.35^{a} (75)
9j	14.20 ± 0.30^{b} (50)	14.61 ± 0.36^{a} (75)	16.53 ± 0.28^{b} (50)	13.89 ± 0.29^{a} (75)	19.80 ± 0.33^{a} (50)
9k	16.02 ± 0.39^{a} (50)	16.23 ± 0.18^{a} (75)	18.04 ± 0.32^{a} (75)	16.55 ± 0.26^{a} (75)	20.89 ± 0.13^{a} (50)
9l	17.95 ± 0.18^{a} (50)	18.49 ± 0.28^{a} (50)	20.22 ± 0.41^{a} (50)	18.07 ± 0.31^{a} (75)	22.11 ± 0.30^{a} (50)
9m	17.19 ± 0.38^{a} (75)	17.99 ± 0.41^{a} (75)	18.83 ± 0.22^{a} (50)	16.91 ± 0.40^{a} (50)	21.89 ± 0.13^{c} (75)
9n	23.40 ± 0.46^{b} (75)	22.82 ± 0.39^{a} (50)	26.21 ± 0.31^{a} (75)	23.15 ± 0.34^{a} (75)	26.94 ± 0.34^{a} (50)
9o	15.83 ± 0.45^{a} (50)	15.53 ± 0.33^{a} (50)	17.57 ± 0.39^{a} (75)	16.33 ± 0.31^{a} (75)	20.83 ± 0.26^{a} (75)
9p	22.06 ± 0.35^{a} (75)	22.01 ± 0.34^{a} (75)	23.57 ± 0.42^{c} (50)	21.96 ± 0.36^{a} (75)	25.80 ± 0.37^{a} (75)
9q	25.89 ± 0.32^{b} (50)	23.25 ± 0.41^{a} (50)	26.25 ± 0.28^{a} (50)	23.60 ± 0.34^{a} (50)	27.50 ± 0.35^{a} (50)
9r	26.11 ± 0.38^{a} (50)	25.07 ± 0.40^{a} (50)	27.34 ± 0.38^{a} (50)	24.25 ± 0.32^{a} (50)	28.47 ± 0.33^{a} (50)
9s	27.52 ± 0.38^{b} (50)	25.94 ± 0.42^{a} (50)	29.43 ± 0.28^{a} (50)	27.69 ± 0.49^{a} (50)	29.33 ± 0.39^{a} (50)
9t	20.27 ± 0.30^{a} (75)	19.22 ± 0.33^{a} (75)	21.04 ± 0.41^{a} (50)	18.72 ± 0.46^{a} (50)	23.47 ± 0.44^{a} (75)
9u	5.64 ± 0.28^{a} (75)	12.02 ± 0.18^{c} (75)	10.03 ± 0.25^{a} (75)	5.09 ± 0.43^{a} (75)	10.24 ± 0.43^{a} (75)
9v	8.96 ± 0.44^{a} (75)	12.55 ± 0.30^{a} (75)	10.12 ± 0.44^{a} (75)	9.20 ± 0.26^{a} (50)	14.03 ± 0.31^{a} (50)
9w	15.02 ± 0.32^{a} (75)	15.14 ± 0.17^{a} (75)	17.48 ± 0.37^{c} (50)	16.08 ± 0.46^{a} (25)	20.28 ± 0.27^{a} (75)
9x	21.61 ± 0.37^{a} (75)	19.98 ± 0.27^{a} (75)	21.49 ± 0.36^{a} (75)	18.83 ± 0.28^{a} (50)	23.73 ± 0.43^{a} (75)
9y	14.58 ± 0.60^{a} (50)	15.09 ± 0.29^{a} (50)	17.02 ± 0.44^{c} (75)	15.80 ± 0.48^{a} (50)	20.20 ± 0.39^{a} (75)
Ofloxacin	27.81 ± 0.46^{a} (25)	31.03 ± 0.46^{a} (25)	30.03 ± 0.45^{a} (25)	34.73 ± 0.45^{a} (12.5)	32.08 ± 0.30^{a} (12.5)
Control	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

The values in brackets represent the MIC in µg/mL of the corresponding compounds

[a] $p < 0.0001$ as compared to control and/or standard

[b] $p < 0.0001$ as compared to control and $p < 0.05$ as compared to standard

[c] $p < 0.0001$ as compared to control and $p < 0.001$ as compared to standard

[d] $p < 0.0001$ as compared to control and $p > 0.05$ as compared to standard

Table 2 Antibacterial activity data of the targeted compounds (**9a–9y**) against Gram-negative bacteria

Compounds	Zone of inhibition in mm and MIC (minimum inhibitory concentration) in μg/mL				
	E. coli	*P. aeruginosa*	*K. pneumonia*	*B. bronchiseptica*	*P. vulgaris*
9a	8.30 ± 0.45^{a} (75)	10.70 ± 0.41^{a} (75)	12.26 ± 0.41^{b} (75)	19.73 ± 0.41^{c} (75)	14.80 ± 0.27^{a} (75)
9b	18.26 ± 0.50^{b} (50)	22.51 ± 0.34^{b} (75)	30.16 ± 0.27^{b} (50)	27.56 ± 0.32^{b} (50)	15.57 ± 0.27^{b} (50)
9c	18.23 ± 0.47^{b} (75)	22.13 ± 0.38^{b} (75)	13.51 ± 0.45^{b} (50)	15.07 ± 0.37^{b} (75)	23.41 ± 0.38^{b} (50)
9d	18.33 ± 0.38^{b} (75)	23.25 ± 0.29^{b} (50)	22.32 ± 0.32^{b} (50)	20.13 ± 0.13^{b} (75)	23.61 ± 0.39^{b} (50)
9e	18.22 ± 0.33^{b} (50)	21.70 ± 0.27^{b} (75)	23.69 ± 0.47^{b} (75)	25.68 ± 0.42^{b} (50)	13.67 ± 0.29^{b} (75)
9f	13.65 ± 0.44^{b} (75)	15.29 ± 0.46^{b} (50)	22.09 ± 0.31^{b} (50)	13.05 ± 0.41^{b} (50)	27.01 ± 0.27^{b} (50)
9g	23.83 ± 0.39^{b} (75)	26.60 ± 0.41^{b} (50)	28.78 ± 0.42^{b} (50)	20.01 ± 0.34^{b} (75)	23.83 ± 0.35^{b} (75)
9h	18.00 ± 0.40^{b} (50)	21.04 ± 0.40^{b} (50)	18.49 ± 0.51^{b} (50)	21.73 ± 0.28^{b} (50)	26.11 ± 0.36^{b} (50)
9i	25.25 ± 0.47^{b} (50)	27.25 ± 0.34^{b} (50)	23.41 ± 0.32^{b} (50)	26.03 ± 0.40^{b} (50)	20.42 ± 0.35^{b} (50)
9j	17.70 ± 0.51^{c} (75)	20.16 ± 0.44^{b} (75)	24.66 ± 0.42^{b} (50)	13.44 ± 0.55^{b} (50)	13.73 ± 0.36^{b} (75)
9k	10.77 ± 0.27^{a} (50)	13.11 ± 0.35^{b} (75)	21.18 ± 0.45^{b} (50)	18.58 ± 0.42^{b} (50)	9.39 ± 0.41^{b} (75)
9l	22.33 ± 0.38^{b} (50)	23.79 ± 0.42^{b} (75)	18.51 ± 0.31^{b} (50)	26.84 ± 0.18^{b} (75)	12.68 ± 0.33^{c} (75)
9m	15.35 ± 0.28^{b} (50)	16.80 ± 0.38^{b} (75)	12.72 ± 0.38^{b} (75)	19.95 ± 0.37^{b} (50)	13.41 ± 0.35^{b} (75)
9n	23.59 ± 0.33^{b} (50)	26.18 ± 0.27^{c} (50)	22.44 ± 0.26^{b} (50)	22.15 ± 0.42^{c} (50)	21.43 ± 0.39^{b} (50)
9o	15.21 ± 0.43^{a} (75)	16.19 ± 0.30^{b} (50)	21.47 ± 0.28^{b} (50)	18.00 ± 0.31^{b} (50)	15.05 ± 0.29^{b} (50)
9p	14.49 ± 0.31^{b} (50)	15.98 ± 0.38^{b} (50)	9.23 ± 0.41^{b} (75)	16.99 ± 0.31^{b} (75)	15.03 ± 0.41^{a} (75)
9q	27.50 ± 0.33^{b} (50)	30.19 ± 0.32^{b} (50)	23.62 ± 0.36^{b} (75)	25.08 ± 0.29^{b} (50)	24.93 ± 0.44^{b} (75)
9r	26.67 ± 0.31^{b} (50)	29.0 ± 0.41^{b} (50)	31.30 ± 0.32^{b} (50)	26.26 ± 0.46^{b} (50)	24.55 ± 0.38^{b} (75)
9s	28.71 ± 0.30^{b} (50)	30.28 ± 0.41^{b} (50)	25.29 ± 0.38^{a} (50)	25.97 ± 0.32^{b} (50)	29.74 ± 0.28^{b} (50)
9t	16.23 ± 0.31^{a} (75)	18.44 ± 0.37^{b} (75)	11.45 ± 0.33^{b} (50)	12.50 ± 0.33^{b} (75)	23.70 ± 0.43^{b} (50)
9u	10.05 ± 0.25^{a} (75)	12.76 ± 0.49^{b} (50)	14.44 ± 0.41^{b} (75)	21.69 ± 0.42^{c} (50)	18.59 ± 0.48^{d} (75)
9v	20.49 ± 0.33^{b} (50)	23.67 ± 0.30^{b} (50)	22.07 ± 0.41^{b} (50)	29.84 ± 0.31^{b} (50)	25.95 ± 0.41^{c} (50)
9w	15.91 ± 0.31^{a} (50)	18.20 ± 0.29^{c} (50)	10.77 ± 0.25^{b} (75)	12.76 ± 0.50^{b} (50)	22.33 ± 0.39^{b} (50)
9x	21.00 ± 0.47^{b} (50)	23.76 ± 0.43^{b} (75)	18.51 ± 0.35^{b} (50)	12.22 ± 0.44^{a} (50)	17.09 ± 0.40^{b} (75)
9y	15.73 ± 0.18^{b} (75)	16.91 ± 0.34^{a} (75)	18.05 ± 0.41^{b} (75)	26.33 ± 0.29^{b} (50)	18.13 ± 0.30^{b} (75)
Ofloxacin	31.61 ± 0.41^{b} (12.5)	34.23 ± 0.14^{b} (12.5)	31.55 ± 01.9^{b} (12.5)	34.80 ± 0.24^{b} (25)	32.08 ± 0.31^{b} (12.5)
Control	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

The values in brackets represent the MIC in μg/mL of the corresponding compounds

[a] $p < 0.0001$ as compared to control and $p < 0.05$ as compared to standard

[b] $p < 0.0001$ as compared to control and/or standard

[c] $p < 0.0001$ as compared to control and $p < 0.001$ as compared to standard

[d] $p < 0.0001$ as compared to control and $p > 0.05$ as compared to standard

highest activity of 98.95% (MIC = 50 μg/mL; $p < 0.05$), 83.59% (MIC = 50 μg/mL; $p < 0.0001$), 98% (MIC = 50 μg/mL; $p < 0.0001$), 79.72% (MIC = 50 μg/mL; $p < 0.0001$), and 91.42% (MIC = 50 μg/mL; $p < 0.0001$); the compound **9r** (R=F, R_1 = 3-F) showed activity of 93.88% (MIC = 50 μg/mL; $p < 0.0001$), 80.79% (MIC = 50 μg/mL; $p < 0.0001$), 91.04% (MIC = 50 μg/mL; $p < 0.0001$), 69.82% (MIC = 50 μg/mL; $p < 0.0001$), and 88.74% (MIC = 50 μg/mL; $p < 0.0001$); **9q** (R=F, R_1 = 2-F) displayed activity of 93.09% (MIC = 50 μg/mL; $p < 0.05$), 74.92% (MIC = 50 μg/mL; $p < 0.0001$), 87.41% (MIC = 50 μg/mL; $p < 0.0001$), 67.95% (MIC = 50 μg/mL; $p < 0.0001$), and 85.72% (MIC = 50 μg/mL; $p < 0.0001$) with respect to standard drug ofloxacin against *S. aureus*, *E. faecalis*, *S. epidermidis*, *B. subtilis*, and *B. cereus*, respectively.

The antibacterial activity of the targeted compounds (**9a–9y**) against Gram-negative bacteria revealed that the standard drug ofloxacin had MIC values of 12.5 μg/mL against *E. Coli*, *P. aeruginosa*, *K. pneumonia*, and *P. vulgaris*. It also had a MIC value of 25 μg/mL against *B. bronchiseptica.* The compound **9s** (R=F, R_1 = 4-F) showed higher activity of 90.82% (MIC = 50 μg/mL; $p < 0.0001$), 88.46% (MIC = 50 μg/mL; $p < 0.0001$), and 92.70% (MIC = 50 μg/mL; $p < 0.0001$) against *E. coli*, *P. aeruginosa*, and *P. vulgaris*, respectively; and the compound **9r** (R=F, R_1 = 3-F) displayed highest activity of 99.20% (MIC = 50 μg/mL;

Table 3 Antifungal activity data of the targeted compounds (**9a–9y**) against fungi

Compounds	Zone of inhibition in mm and MIC (minimum inhibitory concentration) in μg/mL				
	C. albicans	*A. niger*	*A. flavus*	*M. purpureous*	*P. citrinum*
9a	13.03 ± 0.06^{a} (150)	15.26 ± 0.27^{b} (75)	15.45 ± 0.30^{c} (50)	16.28 ± 0.28^{c} (75)	17.36 ± 0.31^{c} (75)
9b	26.10 ± 0.48^{c} (75)	28.16 ± 0.42^{c} (75)	27.57 ± 0.32^{c} (75)	26.67 ± 0.39^{c} (100)	26.75 ± 0.36^{b} (100)
9c	20.01 ± 0.35^{c} (75)	21.16 ± 0.46^{c} (75)	19.41 ± 0.10^{c} (150)	20.69 ± 0.35^{c} (75)	21.86 ± 0.37^{c} (75)
9d	26.80 ± 0.39^{c} (75)	28.92 ± 0.29^{a} (100)	27.97 ± 0.36^{c} (75)	29.34 ± 0.31^{c} (100)	27.36 ± 0.66^{a} (100)
9e	21.91 ± 0.55^{c} (75)	21.70 ± 0.43^{c} (100)	19.83 ± 0.36^{c} (100)	21.49 ± 0.46^{c} (75)	22.41 ± 0.45^{c} (100)
9f	20.53 ± 0.47^{c} (75)	21.52 ± 0.31^{b} (75)	19.68 ± 0.41^{c} (75)	21.36 ± 0.46^{c} (75)	22.35 ± 0.49^{c} (100)
9g	25.62 ± 0.39^{c} (75)	25.95 ± 0.43^{c} (75)	26.16 ± 0.31^{a} (100)	26.35 ± 0.48^{c} (75)	25.67 ± 0.42^{c} (100)
9h	19.37 ± 0.36^{c} (100)	21.01 ± 0.38^{c} (75)	18.93 ± 0.38^{b} (75)	20.09 ± 0.38^{c} (75)	21.28 ± 0.29^{c} (75)
9i	25.97 ± 0.36^{c} (75)	26.13 ± 0.43^{c} (75)	26.84 ± 0.49^{a} (100)	26.41 ± 0.27^{c} (75)	26.20 ± 0.30^{c} (100)
9j	14.08 ± 0.51^{a} (100)	15.51 ± 0.36^{c} (75)	15.99 ± 0.25^{c} (75)	16.40 ± 0.41^{a} (75)	18.34 ± 0.45^{c} (75)
9k	24.14 ± 0.41^{c} (100)	24.32 ± 0.45^{c} (75)	25.0 ± 0.37^{c} (100)	24.01 ± 0.45^{c} (100)	25.26 ± 0.26^{c} (75)
9l	14.98 ± 0.30^{c} (150)	18.10 ± 0.59^{d} (100)	16.12 ± 0.38^{c} (100)	18.40 ± 0.38^{c} (75)	19.38 ± 0.46^{c} (75)
9m	24.57 ± 0.36^{c} (75)	24.77 ± 0.32^{c} (75)	25.88 ± 0.27^{b} (75)	24.42 ± 0.45^{c} (75)	25.39 ± 0.49^{c} (100)
9n	18.28 ± 0.40^{c} (100)	20.12 ± 0.53^{c} (75)	18.80 ± 0.44^{c} (75)	19.91 ± 0.41^{c} (75)	21.21 ± 0.37^{c} (75)
9o	12.89 ± 0.23^{c} (50)	13.80 ± 0.45^{c} (50)	10.33 ± 0.11^{d} (100)	15.34 ± 0.41^{c} (150)	17.33 ± 0.43^{c} (100)
9p	8.10 ± 0.22^{c} (150)	11.61 ± 0.30^{b} (100)	9.60 ± 0.41^{a} (150)	13.29 ± 0.17^{c} (75)	12.42 ± 0.40^{c} (100)
9q	27.90 ± 0.38^{c} (50)	29.19 ± 0.27^{b} (50)	28.75 ± 0.46^{b} (50)	30.19 ± 0.17^{c} (50)	30.94 ± 0.32^{c} (50)
9r	27.14 ± 0.34^{c} (50)	28.97 ± 0.28^{a} (50)	28.30 ± 0.29^{a} (50)	29.54 ± 0.47^{c} (50)	29.90 ± 0.31^{a} (50)
9s	29.45 ± 0.47^{c} (50)	29.42 ± 0.21^{c} (50)	29.05 ± 0.37^{b} (50)	30.33 ± 0.35^{c} (50)	30.99 ± 0.30^{c} (50)
9t	23.17 ± 0.37^{c} (100)	23.49 ± 0.42^{c} (75)	22.09 ± 0.54^{c} (75)	22.62 ± 0.39^{c} (75)	23.76 ± 0.35^{c} (75)
9u	22.50 ± 0.29^{c} (75)	23.12 ± 0.30^{c} (75)	21.0 ± 0.37^{c} (100)	22.13 ± 0.38^{c} (75)	23.68 ± 0.52^{c} (75)
9v	23.53 ± 0.37^{c} (75)	23.77 ± 0.37^{c} (75)	22.17 ± 0.47^{c} (75)	23.18 ± 0.38^{c} (75)	24.04 ± 0.55^{c} (75)
9w	17.65 ± 0.42^{c} (50)	19.08 ± 0.49^{c} (100)	18.71 ± 0.43^{b} (100)	18.51 ± 0.35^{b} (100)	21.10 ± 0.44^{c} (75)
9x	23.93 ± 0.34^{c} (100)	24.11 ± 0.38^{c} (75)	22.86 ± 0.37^{c} (75)	23.32 ± 0.37^{c} (75)	24.34 ± 0.35^{c} (100)
9y	17.23 ± 0.20^{c} (100)	18.66 ± 0.34^{c} (75)	18.68 ± 0.25^{c} (100)	18.50 ± 0.52^{c} (75)	19.91 ± 0.43^{c} (50)
Ketoconazole	34.24 ± 0.31^{c} (12.5)	30.71 ± 0.41^{c} (12.5)	29.93 ± 0.56^{c} (25)	34.45 ± 0.36^{c} (12.5)	28.68 ± 0.31^{c} (25)
Control	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

The values in brackets represent the MIC in μg/mL of the corresponding compounds

[a] $p < 0.0001$ as compared to control and $p < 0.05$ as compared to standard

[b] $p < 0.0001$ as compared to control and $p < 0.001$ as compared to standard

[c] $p < 0.0001$ as compared to control and/or standard

[d] $p < 0.0001$ as compared to control and $p > 0.05$ as compared to standard

$p < 0.0001$) against *K. pneumonia*; and compound **9v** (R = I; R_1 = 2-F) exhibited highest activity of 85.74% (MIC = 50 μg/mL; $p < 0.0001$) against *B. bronchiseptica*. Further, the compound **9q** (R=F, R_1 = 2-F) and **9r** (R=F, R_1 = 3-F) displayed activity of 86.99% (MIC = 50 μg/mL; $p < 0.05$) and 84.37% (MIC = 50 μg/mL; $p < 0.0001$) against *E. coli*, respectively. These compounds also exhibited activity of 88.19% (MIC = 50 μg/mL; $p < 0.0001$) and 84.72% (MIC = 50 μg/mL; $p < 0.0001$) against *P. aeruginosa*, respectively. The compound **9b** (R = H, R_1 = 2-F) and **9g** (R = Cl, R_1 = 2-F) showed activity of 95.59% (MIC = 50 μg/mL; $p < 0.0001$) and 91.22% (MIC = 50 μg/mL; $p < 0.0001$) against *K. pneumonia*, respectively. The compound **9b** (R = H, R_1 = 2-F) and **9l** (R = Br, R_1 = 2-F) showed activity of 79.19% (MIC = 50 μg/mL; $p < 0.0001$) and 77.12% (MIC = 75 μg/mL; $p < 0.0001$) against *B. bronchiseptica*, respectively. The compound **9f** (R = Cl, R_1 = 2-Cl) and **9h** (R = Cl, R_1 = 3-F) showed activity of 84.19% (MIC = 50 μg/mL; $p < 0.0001$) and 81.39% (MIC = 50 μg/mL; $p < 0.0001$) against *P. vulgaris*, respectively.

The antifungal activity of the targeted compounds (**9a–9y**) against fungi revealed that the standard drug ketoconazole had MIC values of 12.5 μg/mL against *C. albicans*, *A. niger*, and *M. purpureous*. It also had MIC value of 25 μg/mL against *A. flavus* and *P. citrinum*. The compound **9s** (R=F, R_1 = 4-F), exhibited the highest activity of 98.95% (MIC = 50 μg/mL; $p < 0.0001$), 83.59% (MIC = 50 μg/mL; $p < 0.0001$), 98% (MIC = 50 μg/mL;

$p < 0.001$), 79.72% (MIC = 50 μg/mL; $p < 0.0001$), and 91.42% (MIC = 50 μg/mL; $p < 0.0001$); the compound **9r** (R=F, R_1 = 3-F) showed activity of 79.26% (MIC = 50 μg/mL; $p < 0.0001$), 94.33% (MIC = 50 μg/mL; $p < 0.05$), 94.55% (MIC = 50 μg/mL; $p < 0.05$), 85.74% (MIC = 50 μg/mL; $p < 0.0001$), and 104.25% (MIC = 50 μg/mL; $p < 0.05$); and the compound **9q** (R=F, R_1 = 2-F) displayed activity of 81.48% (MIC = 50 μg/mL; $p < 0.0001$), 95.05% (MIC = 50 μg/mL; $p < 0.001$), 96.05% (MIC = 50 μg/mL; $p < 0.001$), 87.63% (MIC = 50 μg/mL; $p < 0.0001$), and 107.88% (MIC = 50 μg/mL; $p < 0.0001$) with respect to standard drug ketoconazole against *C. albicans*, *A. niger*, *A. flavus*, *M. purpureous*, and *P. citrinum*, respectively.

Structure activity relationship

The structure activity relationship of the targeted compounds revealed that the compounds with fluoro-substituted coumarin ring along with the fluoro-substituted phenyl ring (**9q**, **9r**, **9s**) produced better and potent antimicrobial activity than their corresponding H/chloro/iodo/bromo-substituted analogs. Antimicrobial activity against Gram-positive bacteria and fungi revealed that the 4-fluoropheyl derivative **9s** produce better and potent antimicrobial activity that was followed by 2-fluoropheyl derivative **9q** and 3-fluoropheyl derivative **9r**. The 2-fluorophenyl and 3-fluorophenyl derivatives with fluoro-substituted coumarin ring produced higher antifungal activity against *P. citrinum* than the standard drug ketoconazole. Antimicrobial activity against Gram-negative bacteria revealed that these fluoro-substituted compounds were active with little change in the potency and activity.

Conclusion

It is evident from the antimicrobial activity data of the targeted compounds (**9a–9y**) that the compounds **9q**, **9r**, and **9s** with fluoro-substituted coumarin ring along with the fluoro-substituted phenyl ring produced better and potent antimicrobial activity than their corresponding H/chloro/iodo/bromo-substituted analogs. However, the compounds **9q**, **9r**, and **9s** produced these results in higher concentrations (more MIC) than the standard drugs. The compounds **9q**, **9r**, and **9s**, have been considered as the lead compounds for further development to prepare derivatives having better and potent antimicrobial activities. Accordingly, further studies to acquire more information about structure activity relationships are in progress in our laboratories.

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Conflict of interest The authors declare that they have no competing interests.

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