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Original Research Article

Synthesis of some quinoline-pyrazoline-based naphthalenyl thiazole derivatives and their evaluation as potential antimicrobial agents

Mohd Imran[1]*, Mohammed Afroz Bakht[2], Abdul Samad[2] and Abida[1]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Rafha, 91911, PO Box 840, Saudi Arabia, [2]Department of Pharmaceutical Chemistry, College of Pharmacy, Prince Sattam Bin Abdulaziz University, PO Box 173, Al-Kharj 11942, Saudi Arabia

For correspondence:* ***Email:* *imran_inderlok@yahoo.co.in;* ***Tel:*** *+966599577945*

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Abstract

Purpose: *To prepare and evaluate some quinoline-pyrazoline-based naphthalenyl thiazole derivatives as antimicrobial agents.*

Methods: *Some quinoline-pyrazoline-based naphthalenyl thiazoles (**5a-5e** and **6a-6e**) were prepared by reacting 5-(2-chloroquinolin-3-yl)-3-substitutedphenyl-4,5-dihydro-1H-pyrazole-1-carbothiamides (4a-4e) with 2-bromo-1-(1-naphthyl)ethanone and 2-bromo-1-(2-naphthyl)ethanone, respectively. Fourier transform infra-red (FTIR), ^{13}C-Nuclear magnetic resonance (^{13}C-NMR), ^{1}H-Nuclear magnetic resonance (^{1}H-NMR), elemental analysis, and mass spectrometry were used to elucidate and confirm the chemical structures of the target compounds. Serial plate dilution technique was used to evaluate the antimicrobial activity of the title compounds using ketoconazole and ofloxacin as standards, and their minimum inhibitory concentrations (MIC) were determined.*

Results: *A total of ten compounds, (**5a-5e**) & (**6a-6e**) were prepared. Compound **6d** (R = 4-F, naphthalen-2-yl derivative) exhibited antimicrobial activities that were higher than those of the standard drug (ofloxacin) against S. aureus (MIC = 25 µg/mL, $p < 0.05$), S. epidermidis (MIC = 25 µg/mL, $p < 0.0001$), K. pneumonia (MIC = 25 µg/mL, $p < 0.0001$), P. vulgaris (MIC = 25 µg/mL, $p < 0.0001$) and P. citrinum (MIC = 25 µg/mL, $p < 0.0001$). Compound **5d** (R = 4-F, naphthalen-1-yl derivative) displayed higher antifungal activity than ketoconazole against C. albicans (MIC = 25 µg/mL, $p < 0.0001$).*

Conclusion: *The naphthalen-2-yl derivatives (**6a-6e**) are superior antimicrobial agents as compared to the naphthalen-1-yl derivatives (**5a-5e**) and the presence of 4-F substituent in 6d and 5d is essential for stronger antimicrobial activity. The compound **6d** needs further investigations related to its safety and efficacy.*

Keywords: *Quinoline, Pyrazoline, Thiazole, Antibacterial, Antifungal, Structure-activity relationship*

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INTRODUCTION

Antimicrobial resistance (AMR), a current global concern for human health, is mostly related to the irrational use of antibiotics [1,2]. This has caused the emergence of multidrug-resistant (MDR) pathogens and has also made treatment of many bacterial infections difficult. It is reported that the infections caused by the antibiotic resistant bacteria kill about twenty thousand patients annually in the USA and also leads to economic loss [3]. The cases of AMR bacterial infections are also increasing in the Kingdom of Saudi Arabia due to irrational use of antibiotics as well as due to the socio-economic and

demographic characteristics of Saudi, non-Saudi and pilgrim population [4-7]. Another factor contributing to the development of AMR is failure to discover new antimicrobial agents [8-10]. Accordingly, there is a need to take remedial actions with respect to the issues related to the antimicrobial resistance.

Thiazolyl heterocycles, quinolinyl heterocycles, and pyrazolinyl heterocycles have an important place in medicinal chemistry. Recently, review articles mentioning the usefulness of thiazolyl heterocycles [11,12], quinolinyl heterocycles [13,14], and pyrazolinyl heterocycles [15,16] as analgesic, anti-inflammatory, antibacterial, antifungal, antiviral, antiparasitic, anticoagulant, anti-Parkinson's Disease, anticancer, antioxidants, antidiabetic, CNS depressant, and antimalarial have been published. Recently, thiazolyl pyrazoline derivatives (I) and quinolinyl-pyrazoline-based thiazole derivatives (II) have been postulated as templates for the development of new antimicrobial agents [17,18] (Figure 1).

On the basis of these findings and our continued search for novel heterocyclic antimicrobial agents [19-21], some quinoline-pyrazoline-based naphthalenyl thiazoles (**5a-5e** and **6a-6e**) were synthesized and evaluated as antimicrobial agents.

EXPERIMENTAL

Chemistry

Open capillary tube method was used to determine the melting points of the synthesized compounds which are uncorrected. The FTIR spectra in KBr were generated using a 5PC FT-IR spectrophotometer (Nicolet, Browser Morner, USA). The ^{1}H-NMR and ^{13}C-NMR spectra were generated using a DRX-300 FT NMR (Germany, Bruker) spectrophotometer. Mass spectra were generated on a mass spectrometer (70 eV, Jeol-JMS-D-300, Japan). The C, H and N were analysed satisfactorily for the titled compounds within the range of ±0.4 % of theoretical value. Completion of reaction was monitored by checking on pre-coated commercial thin layer chromatography plates, by using ultra-violet cabinet for visualization purpose. The solvent system to run these plates consisted of a mixture of toluene, ethyl acetate and formic acid (5:4:1). Only analytical grade reagents were used for the present work. Ofloxacin was procured from Sun Pharmaceuticals, India, as a gift sample. Ketoconazole was procured from Cipla, India, as a gift sample. Figure 2 provides the route of synthesis of the desired compounds (**5a-5e**) & (**6a-6e**).

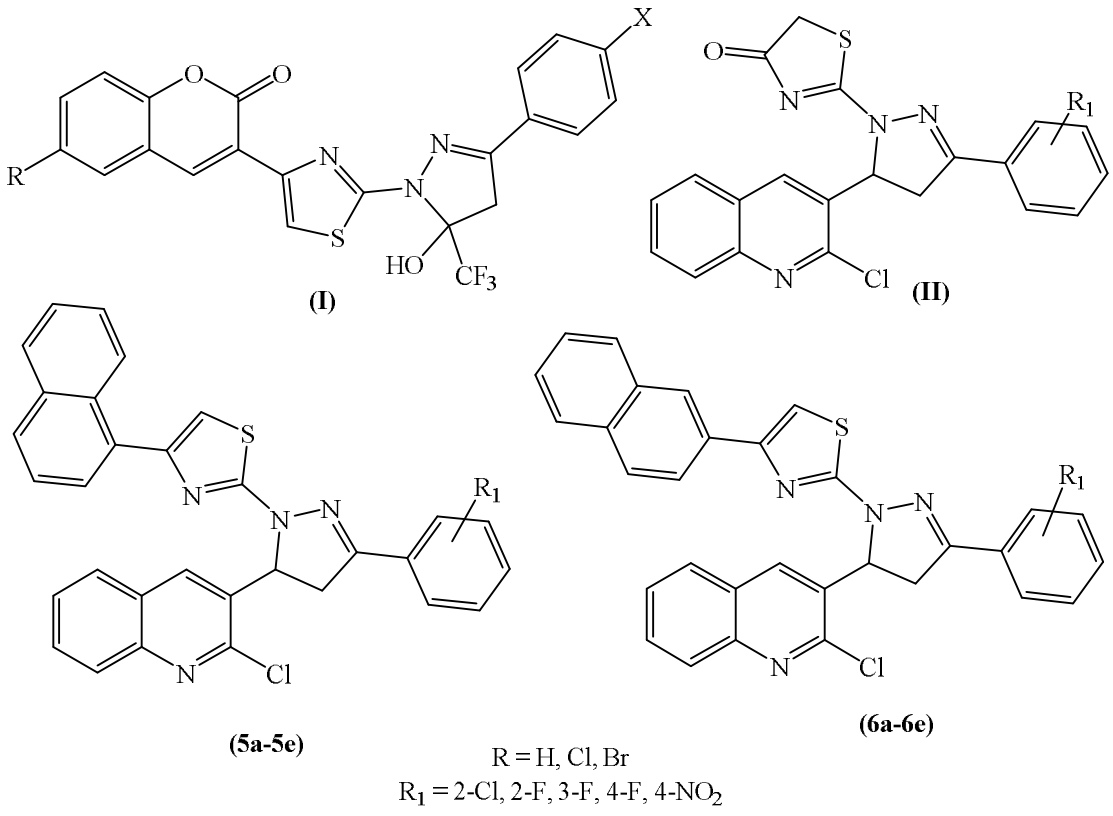

Figure 1: Structures of the postulated antimicrobial lead compounds (I and II), and proposed ones to be synthesized (5a-5e and 6a-6e)

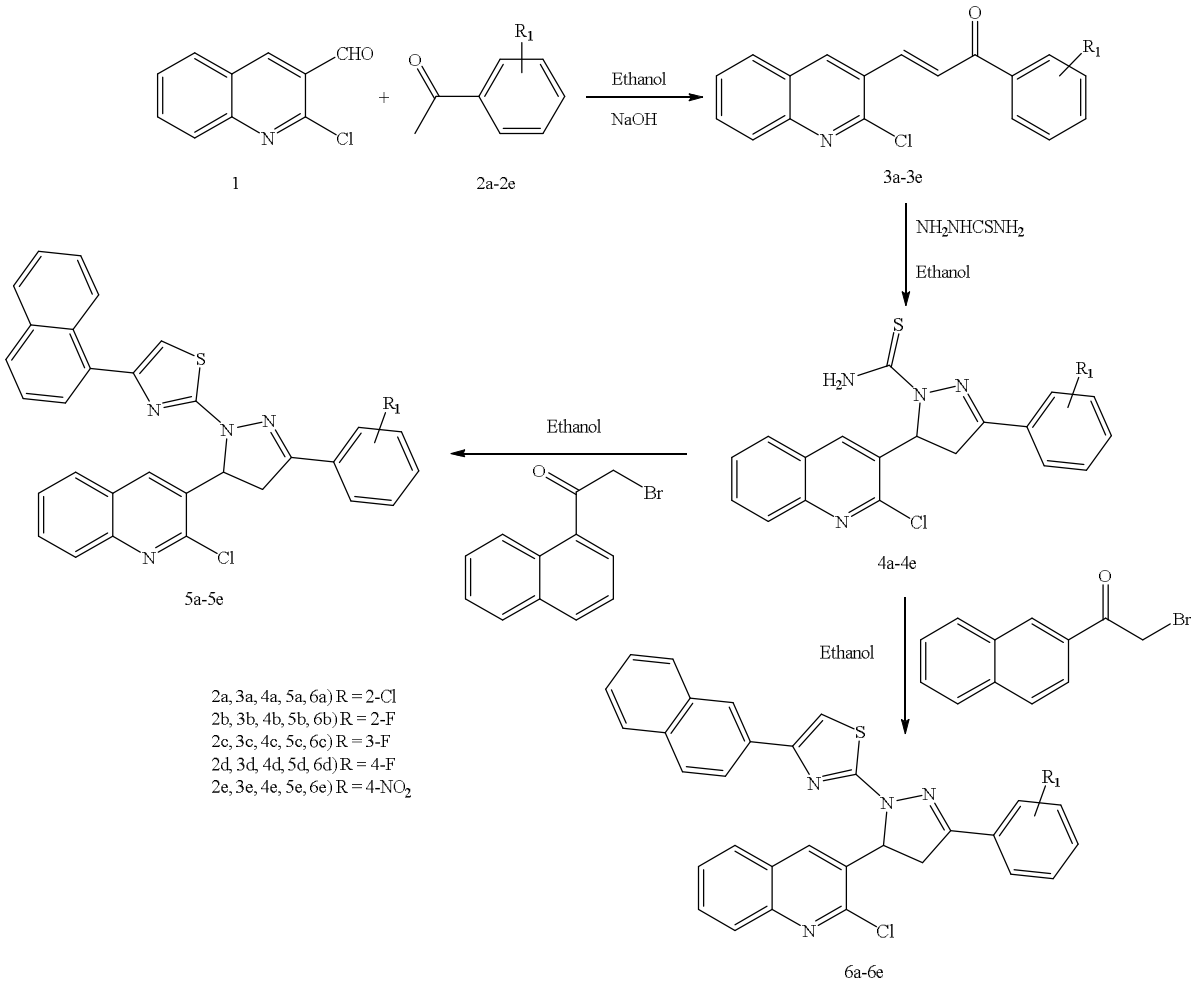

Figure 2: General procedure for the synthesis of compounds 5a-5e & 6a-6e

The compounds (**4a-4e**) were prepared according to the method provided in the literature [18]. The compounds 2-bromo-1-(1-naphthyl) ethanone and 2-bromo-1-(2-naphthyl)ethanone were prepared according to the method provided in our earlier report [22].

Preparation of 2-(3-substitutedphenyl-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(naphthalen-1-yl) thiazole (5a-5e)

A mixture of the appropriate compound (**4a-4e**) (0.01 mole), 2-bromo-1-(1-naphthyl)ethanone (0.01 mole) in 30 ml of ethanol (99.9%) was reflux for about 4 to 6 h. The mixture was cooled, the solid was separated, washed with 10% ethanol, and recrystallized from ethanol.

Preparation of 2-(3-substitutedphenyl-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)-4-(naphthalen-2-yl)thiazole (6a-6e)

A mixture of the appropriate compound (**4a-4e**) (0.01 mole), 2-bromo-1-(2-naphthyl)ethanone (0.01 mole) in 30 ml of ethanol (99.9 %) was reflux for about 4 to 6 h. The mixture was cooled, the solid was separated, washed with 10 % ethanol, and recrystallized from ethanol.

Antimicrobial activity

The compounds (**5a-5e**) & (**6a-6e**) were screened for their antimicrobial activity using the serial plate dilution technique [23-24] against five Gram-positive bacteria; five Gram-negative bacteria; and five fungi. The procedure provided in our earlier reports [19-21] was followed and the minimum inhibitory concentrations (MICs) values were also determined with respect to ketoconazole and ofloxacin.

Statistical analysis

The data presented in Table 1, Table 2 and Table 3 (n = 6) were analyzed using one-way analysis of variance along with Dunnett's comparison test in comparison to control group and standard group using GraphPad Prism version 5.00 for Windows (GraphPad Software (www.graphpad.com). The results were considered significantly different at $p < 0.05$.

Table 1: Antibacterial activity of compounds **5a-5e** and **6a-6e** against Gram-positive bacteria

Compound	Activity (%) with respect to standard drug (ofloxacin)				
	S. aureus	***E. faecalis***	***S. epidermidis***	***B. subtilis***	***B. cereus***
5a	67.38[a]	47.22[a]	63.39[a]	55.88[a]	54.79[a]
5b	60.05[a]	61.41[a]	53.35[a]	59.22[a]	63.34[a]
5c	73.84[a]	62.89[a]	66.98[a]	74.54[a]	89.91[a]
5d	85.97[a]	79.18[a]	94.09[a]	91.23[a]	99.10[a]
5e	62.38[c]	47.51[a]	45.98[c]	50.21[a]	57.71[a]
6a	72.79[a]	65.61[a]	69.65[a]	57.50[a]	67.42[a]
6b	58.83[a]	50.50[a]	60.51[a]	59.31[a]	74.22[a]
6c	82.73[c]	82.49[a]	90.44[a]	80.57[a]	89.91[a]
6d	100.60[c]	92.01[a]	101.37[a]	91.85[a]	99.46[a]
6e	62.99[a]	44.50[b]	39.18[a]	46.50[a]	53.86[a]
Ofloxacin	100.00%[a]	100.00%[a]	100.00[a]	100.00[a]	100.00[a]
Control	0	0	0	0	0

a = p <0.0001 with respect to the control and/or the standard; b = p <0.0001 with respect to the control and p <0.001 as compared to the standard; c = p <0.0001 with respect to the control and p <0.05 with respect to the standard; d = p <0.0001 with respect to the control and p > 0.05 as compared to the standard

Table 2: Antibacterial activity of compounds **5a-5e** and **6a-6e** against Gram-negative bacteria

Compound	Activity (%) with respect to the standard drug (ofloxacin)				
	E. coli	***P. aeruginosa***	***K. pneumonia***	***B. bronchiseptica***	***P. vulgaris***
5a	75.65[a]	72.27[a]	87.14[a]	68.15[a]	76.24[a]
5b	70.59[a]	69.69[a]	74.89[a]	74.17[a]	79.09[a]
5c	92.73[a]	84.33[a]	93.29[a]	86.57[a]	90.30[a]
5d	96.57[a]	99.75[a]	99.16[a]	94.33[a]	99.69[a]
5e	76.44[b]	72.48[a]	89.98[a]	68.53[a]	70.06[a]
6a	68.62[a]	70.47[a]	69.58[a]	79.42[a]	67.19[a]
6b	78.09[a]	77.76[a]	72.11[a]	65.43[b]	77.34[c]
6c	82.95[a]	87.36[b]	87.57[a]	88.34[a]	90.85[a]
6d	98.44[a]	98.70[a]	100.30[a]	97.34[a]	103.45[a]
6e	64.67[c]	67.98[a]	81.70[a]	81.61[b]	85.70[d]
Ofloxacin	100.00[a]	100.00[a]	100.00[a]	100.00[a]	100.00[a]
Control	0	0	0	0	0

a = p <0.0001 with respect to the control and/or the standard; b = p <0.0001 with respect to the control and p <0.001 with respect to the standard; c = p <0.0001 with respect to the control and p <0.05 with respect to the standard; d = p <0.0001 with respect to the control and p > 0.05 with respect to the standard

Table 3: Antifungal activity data of compounds **5a-5e** and **6a-6e** against fungi

Compound	Activity (%) with respect to standard drug (ketoconazole)				
	C. albicans	***A. niger***	***A. flavus***	***M. purpureous***	***P. citrinum***
5a	68.21[a]	85.80[a]	82.97[a]	72.80[a]	79.08[a]
5b	79.76[a]	80.71[a]	84.22[c]	77.71[a]	85.65[a]
5c	93.92[a]	89.49[a]	91.26[c]	86.18[a]	89.05[a]
5d	106.16[a]	96.50[a]	96.33[a]	96.07[a]	96.69[a]
5e	82.40[a]	83.85[a]	80.88[b]	78.51[a]	84.72[a]
6a	71.57[a]	76.25[a]	65.37[d]	74.71[a]	91.09[a]
6b	87.48[a]	93.52[b]	89.14[b]	89.71[a]	93.72[a]
6c	91.99[a]	94.48[a]	93.96[b]	92.06[a]	94.02[a]
6d	99.93[a]	96.50[a]	96.04[a]	95.48[a]	103.80[a]
6e	85.46[a]	86.76[a]	92.32[a]	84.75[b]	87.25[a]
Ketoconazole	100.00[a]	100.00[a]	100.00[a]	100.00[a]	100.00[a]
Control	0	0	0	0	0

a = p <0.0001 with respect to the control and/or the standard; b = p <0.0001 with respect to the control and p <0.001 with respect to the standard; c = p <0.0001 with respect to the control and p <0.05 with respect to the standard; d = p <0.0001 with respect to the control and p > 0.05 with respect to the standard

RESULTS

Chemistry

The synthetic route for the preparation of the compounds (**5a-5e**) & (**6a-6e**) is depicted in Scheme 1. The compounds (**4a-4e**) were synthesized according to the method described in the literature [18]. The compounds (**5a-5e**) were prepared by reacting compounds (**4a-4e**) with 2-bromo-1-(1-naphthyl)ethanone using ethanol as solvent. Similarly, the compounds (**6a-6e**) were prepared by reacting compounds (**4a-4e**) with 2-bromo-1-(2-naphthyl)ethanone using ethanol as solvent.

These compounds were characterized by their different melting points with respect to their respective starting materials, different R_f values in a particular solvent system, spectral data (IR, ^{13}C-NMR and ^{1}H-NMR) and elemental analysis. The IR spectra of the compounds (**5a-5e**) & (**6a-6e**) showed IR peaks for C=N group ranging from 1575 cm^{-1} to 1580 cm^{-1}; and for C=C group ranging from 1535 cm^{-1} to 1540 cm^{-1}. It also displayed characteristic IR peak of C-S group of thiazole moiety ranging from 1106 cm^{-1} to 1112 cm^{-1}. The ^{1}H-NMR spectra of the compounds (**5a-5e**) & (**6a-6e**) 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 3.59-3.65) and another proton also appeared as doublet (δ 3.87- 3.91).

The C_5-H proton of the pyrazoline ring appeared as doublet at δ 5.16 - 5.21. The ^{1}H-NMR spectra also showed characteristic signals as multiplets at δ 7.10-8.15 for aromatic protons. The ^{13}C-NMR spectra also supported the assigned number of carbon atoms. It showed characteristic signal at δ 37.0 – 37.5 due to the methylene carbon (C_4) of the pyrazoline ring and at δ 53.4 due to the methine carbon (C_5) of the pyrazoline ring. The signals at about δ 166.3 – 166.6 arose due to the C_2 carbon of the thiazole ring. The mass spectra and the elemental analysis data for the compounds (**5a-5e**) & (**6a-6e**) were also in accordance with the assigned chemical structures.

The spectral data for the compounds (**5a-5e**) and (**6a-6e**) are provided below.

2-(3-(o-chlorophenyl)-5-(2-chloroquinolin-3-yl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-1-yl) thiazole (5a)

Yield: 55 %; m.p.: 192 ^{o}C; R_f value: 0.71; IR (KBr): 1575, 1536, 1109; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 3.61 (d, J=17Hz, 1H), 3.89 (d, J=17Hz, 1H), 5.17 (d, J=18Hz, 1H), 7.15-8.10 (m, 17H, Ar-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ ppm: 37.0 (C_4 of the pyrazoline ring), 53.4 (C_5 of the pyrazoline ring), 105.0 (C_5 of the thiazole ring), 121.1, 123.4, 124.3 (2C), 124.6, 125.0, 125.3, 125.5, 126.3 (3C), 126.8, 127.9, 128.1, 128.3, 128.6, 128.9, 130.4, 130.7, 132.2 (2C), 135.2, 138.6, 143.4, 145.8, 149.7 (C_3 of the pyrazoline ring), 149.9 (C_5 carbon of the quinoline ring), 166.5 (C_2 carbon of the thiazole ring); Mass (m/z): 550 (M^+, 100%), 551 (M^++1), 276, 184, 138, 111, 92; Elemental Analysis ($C_{31}H_{20}C_{l2}N_4S$): Calcd.: C, 67.51; H, 3.65; N, 10.15; Found: C, 67.51; H, 3.64; N, 10.16.

2-(5-(2-chloroquinolin-3-yl)-3-(o-fluorophenyl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-1-yl)thiazole (5b)

Yield: 60 %; m.p.: 210 ^{o}C; R_f value: 0.77; IR (KBr): 1578, 1539, 1111; ^{1}H-NMR: 3.60 (d, J=17Hz, 1H), 3.90 (d, J=17Hz, 1H), 5.19 (d, J=18Hz, 1H), 7.13-8.11 (m, 17H, Ar-H); ^{13}C-NMR: 37.5 (C_4 of the pyrazoline ring), 53.4 (C_5 of the pyrazoline ring), 105.0 (C_5 of the thiazole ring), 113.6, 116.2, 121.1, 122.4, 123.4, 124.3 (2C), 124.6, 125.0, 125.3, 125.5, 126.3 (3C), 127.9, 128.8 (2C), 130.6, 130.7, 132.2, 134.2, 138.6, 143.4, 145.8, 149.7 (C_3 of the pyrazoline ring), 149.9 (C_5 carbon of the quinoline ring), 157.6 (Ar-C), 166.4 (C_2 carbon of the thiazole ring); Mass (m/z): 534 (M^+, 100%), 535 (M^++1), 268, 179, 134, 107, 90; Elemental Analysis ($C_{31}H_{20}ClFN_4S$): Calcd.: C, 69.59; H, 3.76; N, 10.46; Found: C, 69.56; H, 3.75; N, 10.45.

2-(5-(2-chloroquinolin-3-yl)-3-(m-fluorophenyl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-1-yl)thiazole (5c)

Yield: 60 %; m.p.: 222 ^{o}C; R_f value: 0.71; IR (KBr): 1580, 1540, 1106; ^{1}H-NMR: 3.64 (d, J=17Hz, 1H), 3.88 (d, J=17Hz, 1H), 5.21 (d, J=18Hz, 1H), 7.16-8.13 (m, 17H, Ar-H); ^{13}C-NMR: 37.4 (C_4 of the pyrazoline ring), 53.4 (C_5 of the pyrazoline ring), 105.0 (C_5 of the thiazole ring), 113.0, 115.8, 121.1, 121.8, 123.4, 124.3 (2C), 124.6, 125.0, 125.3, 125.5, 126.3 (3C), 127.9, 128.4, 128.9, 130.7, 132.2, 133.6, 134.2, 138.6, 143.4, 145.8, 149.7 (C_3 of the pyrazoline ring), 149.9 (C_5 carbon of the quinoline ring), 161.0 (Ar-C), 166.5 (C_2 carbon of the thiazole ring); Mass (m/z): 534 (M^+, 100 %), 535 (M^++1), 268, 179, 134, 107, 90; Elemental Analysis ($C_{31}H_{20}ClFN_4S$): Calcd.: C, 69.59; H, 3.76; N, 10.46; Found: C: C, 69.51; H, 3.73; N, 10.43.

2-(5-(2-chloroquinolin-3-yl)-3-(p-fluorophenyl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-1-yl)thiazole (5d)

Yield: 65 %; m.p.: 205 ^{o}C; R_f value: 0.74; IR (KBr): 1579, 1538, 1109; ^{1}H-NMR: 3.59 (d, J=17Hz, 1H), 3.89 (d, J=17Hz, 1H), 5.19 (d, J=18Hz, 1H), 7.11-8.11 (m, 17H, Ar-H); ^{13}C-NMR: 37.5 (C_4 of the pyrazoline ring), 53.4 (C_5 of the pyrazoline ring), 105.2 (C_5 of the thiazole ring), 113.6 (2C), 121.1, 123.4, 124.3 (3C), 125.0, 125.3, 125.5, 126.3 (3C), 127.5 (2C), 127.9, 128.9, 130.0, 130.7, 132.2, 134.2, 138.6, 143.4, 145.8, 149.7 (C_3 of the pyrazoline ring), 149.9 (C_5 carbon of the quinoline ring), 163.2, 166.3 (C_2 carbon of the thiazole ring); Mass (m/z): 534 (M^+, 100%), 535 (M^++1), 268, 179, 134, 107, 90; Elemental Analysis ($C_{31}H_{20}ClFN_4S$): Calcd.: C, 69.59; H, 3.76; N, 10.46; Found: C, 69.56; H, 3.76; N, 10.44.

2-(5-(2-chloroquinolin-3-yl)-3-(p-nitrophenyl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-1-yl)thiazole (5e)

Yield: 50 %; m.p.: 210 ^{o}C; R_f value: 0.68; IR (KBr): 1579, 1535, 1111; ^{1}H-NMR: 3.60 (d, J=17Hz, 1H), 3.87 (d, J=17Hz, 1H), 5.18 (d, J=18 Hz, 1H), 7.14-8.12 (m, 17H, Ar-H); ^{13}C-NMR: 37.5 (C_4 of the pyrazoline ring), 53.4 (C_5 of the pyrazoline ring), 105.2 (C_5 of the thiazole ring), 121.1, 123.4, 124.3 (2C), 124.6, 125.0 (3C), 125.3, 125.5, 125.7 (2C), 126.3 (3C), 127.9, 128.9, 130.7, 132.2, 134.2, 138.6, 140.5, 143.4, 145.8, 148.2, 149.7 (C_3 of the pyrazoline ring), 149.9 (C_5 carbon of the quinoline ring), 166.5 (C_2 carbon of the thiazole ring); mass (m/z): 561 (M^+, 100%), 562 (M^++1), 281, 188, 141, 113, 94; Elemental Analysis ($C_{31}H_{20}ClN_5O_2S$): Calcd.: C, 66.24; H, 3.58; N, 12.45; Found: C, 66.23; H, 3.55; N, 12.45.

2-(3-(o-chlorophenyl)-5-(2-chloroquinolin-3-yl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-2-yl)thiazole (6a)

Yield: 55 %; m.p.: 189 ^{o}C; R_f value: 0.73; IR (KBr): 1580, 1538, 1112; ^{1}H-NMR: 3.63 (d, J=17Hz, 1H), 3.90 (d, J=17Hz, 1H), 5.16 (d, J=18Hz, 1H), 7.10-8.12 (m, 17H, Ar-H); ^{13}C-NMR: 37.0 (C_4 of the pyrazoline ring), 53.4 (C_5 of the pyrazoline ring), 105.1 (C_5 of the thiazole ring), 124.2 (3C), 124.6, 125.0, 125.3 (3C), 125.5, 125.6, 126.1 (2C), 126.8, 127.9, 128.1, 128.3, 128.6, 128.9, 130.4 (2C), 131.8, 134.2, 135.2, 143.4, 148.2, 149.7 (C_3 of the pyrazoline ring), 149.9 (C_5 carbon of the quinoline ring), 166.4 (C_2 carbon of the thiazole ring); mass (m/z): 550 (M^+, 100%), 551 (M^++1), 276, 184, 138, 111, 92; Elemental Analysis ($C_{31}H_{20}Cl_2N_4S$): Calcd.: C, 67.51; H, 3.65; N, 10.15; Found: C, 67.50; H, 3.67; N, 10.13.

2-(5-(2-chloroquinolin-3-yl)-3-(o-fluorophenyl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-2-yl)thiazole (6b)

Yield: 60 %; m.p.: 214 ^{o}C; R_f value: 0.63; IR (KBr): 1576, 1537, 1110; ^{1}H-NMR: 3.62 (d, J=17Hz, 1H), 3.88 (d, J=17Hz, 1H), 5.19 (d, J=18Hz, 1H), 7.14-8.13 (m, 17H, Ar-H); ^{13}C-NMR: 37.5 (C_4 of the pyrazoline ring), 53.4 (C_5 of the pyrazoline ring), 105.1 (C_5 of the thiazole ring), 113.3, 116.2, 122.4, 124.2 (3C), 124.6, 125.0, 125.3 (3C), 125.5 (2C), 126.1 (2C), 127.9, 128.8 (2C), 130.5 (2C), 131.8, 134.2, 143.4, 148.2, 149.7 (C_3 of the pyrazoline ring), 149.9 (C_5 carbon of the quinoline ring), 157.6, 166.6 (C_2 carbon of the thiazole ring); Mass (m/z): 534 (M^+, 100%), 535 (M^++1), 268, 179, 134, 107, 90; Elemental Analysis ($C_{31}H_{20}ClFN_4S$): Calcd.: C, 69.58; H, 3.76; N, 10.46; Found: C: C, 69.55; H, 3.75; N, 10.45.

2-(5-(2-chloroquinolin-3-yl)-3-(m-fluorophenyl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-2-yl)thiazole (6c)

Yield: 50 %; m.p.: 178 ^{o}C; R_f value: 0.72; IR (KBr): 1580, 1540, 1108; ^{1}H-NMR: 3.65 (d, J=17Hz, 1H), 3.91 (d, J=17Hz, 1H), 5.20 (d, J=18Hz, 1H), 7.10-8.15 (m, 17H, Ar-H); ^{13}C-NMR: 37.5 (C_4 of the pyrazoline ring), 53.4 (C_5 of the pyrazoline ring), 105.1 (C_5 of the thiazole ring), 113.0, 115.8, 121.8, 124.2 (3C), 124.6, 125.0, 125.3 (3C), 125.5, 125.6, 126.1 (2C), 127.9, 128.4, 128.9, 130.5, 131.8, 133.6, 134.2, 143.4, 148.2, 149.7 (C_3 of the pyrazoline ring), 149.9 (C_5 carbon of the quinoline ring), 161.0, 166.4 (C_2 carbon of the thiazole ring); Mass (m/z): 534 (M^+, 100%), 535 (M^++1), 268, 179, 134, 107, 90; Elemental Analysis ($C_{31}H_{20}ClFN_4S$): Calcd.: C, 69.58; H, 3.76; N, 10.46; Found: C: C, 69.61; H, 3.75; N, 10.46.

2-(5-(2-chloroquinolin-3-yl)-3-(p-fluorophenyl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-2-yl)thiazole (6d)

Yield: 65 %; m.p.: 188 ^{o}C; R_f value: 0.70; IR (KBr): 1577, 1538, 1108; ^{1}H-NMR: 3.62 (d, J=17Hz, 1H), 3.89 (d, J=17Hz, 1H), 5.18 (d, J=18Hz, 1H), 7.11-8.13 (m, 17H, Ar-H); ^{13}C-NMR: 37.5 (C_4 of the pyrazoline ring), 53.4 (C_5 of the pyrazoline ring), 105.2 (C_5 of the thiazole ring), 114.6 (2C), 124.2 (3C), 124.6, 125.0, 125.3 (3C), 125.5 (2C), 126.1 (2C), 127.5 (2C), 127.9, 128.9, 130.0, 130.5, 131.8, 134.2, 143.4, 148.2, 149.7 (C_3 of the pyrazoline ring), 149.9 (C_5 carbon of the quinoline ring), 163.2, 166.5 (C_2

carbon of the thiazole ring); Mass (m/z): 534 (M^+, 100%), 535 (M^++1), 268, 179, 134, 107, 90; Elemental Analysis ($C_{31}H_{20}ClFN_4S$): Calcd.: C, 69.58; H, 3.76; N, 10.46; Found: C: C, 69.57; H, 3.75; N, 10.46.

2-(5-(2-chloroquinolin-3-yl)-3-(p-nitrophenyl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-2-yl)thiazole (6e)

Yield: 55 %; m.p.: 196 ^oC; R_f value: 0.69; IR (KBr): 1578, 1538, 1109; ^1H-NMR: 3.61 (d, J=17Hz, 1H), 3.9 1(d, J=17Hz, 1H), 5.20 (d, J=18Hz, 1H), 7.14-8.13 (m, 17H, Ar-H); ^{13}C-NMR: 37.5 (C_4 of the pyrazoline ring), 53.4 (C_5 of the pyrazoline ring), 105.1 (C_5 of the thiazole ring), 124.2 (3C), 124.6, 125.0 (3C), 125.3 (3C), 125.5 (2C), 125.7 (2C), 126.1 (2C), 127.9, 128.9, 130.5, 131.8, 134.2, 140.5, 143.4, 148.2 (2C), 149.7 (C_3 of the pyrazoline ring), 149.9 (C_5 carbon of the quinoline ring), 165.5 (C_2 carbon of the thiazole ring); Mass (m/z): 561 (M^+, 100 %), 562 (M^++1), 281, 188, 141, 113, 94; Elemental Analysis ($C_{31}H_{20}ClN_5O_2S$): Calcd.: C, 66.24; H, 3.58; N, 12.45; Found: C, 66.27; H, 3.55; N, 12.45.

Antimicrobial activity

The data of the antimicrobial activity of the compounds (**5a-5e** and **6a-6e**) obtained by serial plate dilution technique are listed in Table 1, Table 2 and Table 3, respectively.

Compound **6d** (R = 4-F, naphthalen-2-yl derivative) exhibited MIC of 25 µg/mL and the highest activity of 100.60, 92.01, 101.37, 91.85, and 99.46 % against *S. aureus, E.faecalis, S. epidermidis, B. subtilis* and *B. cereus,* respectively, in regard to the standard drug. Additionally, compound **6d** exhibited the highest activity of 98.44, 100.30, 97.34, and 103.45 % against *E.coli, K. pneumonia, B. bronchiseptica*, and *P. vulgaris* respectively, in comparison to the standard drug. Compound **5d** (R = 4-F, naphthalen-1-yl derivative) exhibited the highest activity of 99.75 % with MIC of 25 µg/mL against *P. aeruginosa* with respect to the standard drug. The compound **5d** (R = 4-F, naphthalen-1-yl derivative) displayed MIC value of 25 µg/mL and highest antifungal activity of 106.16, 96.50, 96.33, and 96.07 % against *Candida albicans*, *A. niger, A. flavus* and *M. purpureous, respectively,* in comparison to standard drug. The compound **6d** (R = 4-F, naphthalen-2-yl derivative) exhibited the highest activity of 96.50 and 103.80 % against *A. niger and P. citrinum,* respectively.

DISCUSSION

The spectral data and elemental analysis of the titled compounds (**5a-5e** and **6a-6e**) were in accordance with the assigned chemical structures. The disappearance of the characteristic IR peaks at about 3370 cm^{-1} to about 3442 cm^{-1} due to the N-H group, and the peaks at about 1330 cm^{-1} to about 1340 cm^{-1} due to the C=S groups present in the compounds (**4a-4e**) [23], supported the formation of the compounds (**5a-5e** and **6a-6e**). The disappearance of signal of two amino protons of the compounds (**4a-4e**) at δ 8.44 to 8.68 [23] also supported the formation of the compounds (**5a-5e** and **6a-6e**).

It is also expected that these compounds might be exhibiting their antimicrobial effect by the same mechanism as has been reported for similar type of compounds. It has also been observed that the naphthalen-2-yl derivatives (**6a-6e**) produced better antimicrobial activity than the naphthalen-1-yl derivatives (**5a-5e**). The compounds (**5a-5e** and **6a-6e**) were also found to be better antibacterial agents against Gram negative bacteria. This effect may be because of the presence of more aromatic groups that impart lipophilic character to the compounds. The structure activity relationship of the compounds (**5a-5e** and **6a-6e**) revealed that the presence of 4-F substituent in naphthalen-2-yl derivative (**6d**) and in naphthalen-1-yl derivative (**5d**) is required for superior antimicrobial activity against the gram positive bacteria, gram negative bacteria as well as fungi. The replacement of 4-F substituent with 4-NO_2 substituent (**6e**) or with 2-F substituent (**6b**) or with 2-Cl substituent (**6a**) provide compounds with lower antibacterial and antifungal potencies.

CONCLUSION

The findings for the synthesized compounds (**5a-5e** and **6a-6e**) indicate that the naphthalen-2-yl derivative (**6d**) with 4-F substituent in the phenyl ring yields more potent antimicrobial activity against *S. aureus, S. epidermidis, K. pneumonia*, *P. vulgaris* and *P. citrinum*. Compound **6d** is a potential lead compound for further development, and therefore, needs to be tested against other microbial strains to confirm its broad spectrum antimicrobial activity.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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