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Preparation and antimicrobial activity evaluation of some quinoline derivatives containing an azole nucleus

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Quinoline-2-carbohydrazide (**2**) obtained from quinaldic acid (**1**) was converted to the corresponding carbothioamide **3** and carboxamide **6** by treatment with benzyliso(thio)cyanate. The basic treatment of **3** and **6** yielded the corresponding 1,2,4-triazole derivatives **4** and **7**. The synthesis of 5-(quinolin-2-yl)-1,3,4-oxadiazol-2-thiol (**9**) was performed from the reaction of **1** with CS_2 in basic media. The Mannich reaction of compounds **4, 7**, and **9** resulted in the formation of aminoalkylated derivatives **5a-c, 8**, and **10a,b**. The condensation of **1** with thiosemicarbazide, carbohydrazide, or thiocarbohydrazide gave the corresponding 1,2,4-triazole derivatives (**11-13**). The treatment of 4-amino-5-(quinolin-2-yl)-4*H*-1,2,4-triazole-3-thiol (**13**) with 4-chlorophenacyl bromide caused the formation of fused triazolothiadiazine **14**. The condensation of **13** with 4-methoxybenzaldehyde generated the corresponding Schiff base **15**.

The newly synthesized compounds were characterized by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra. The antimicrobial activity study revealed that some of the newly synthesized compounds showed good to moderate activity against a variety of microorganisms.

Key Words: Quinoline, 1,3,4-thiadiazole, 1,2,4-triazole, Mannich base, antimicrobial activity

Introduction

The steadily increasing bacterial resistance to first-line antibiotic agents has become a serious problem in antibacterial therapy and required continuing research into new classes of compounds possessing antimicrobial activities.

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Infections caused by these resistant microorganisms fail to respond to treatment, resulting in prolonged illness and greater risk of death. The growing number of reports of antibiotic resistance worldwide has led to fears that some lethal human pathogens, such as *Mycobacterium tuberculosis*, will soon become untreatable.[1–6]

These trends have emphasized the urgent need for new, more effective, and safe antibacterial agents and which in turn has opened up a new area of research for medicinal chemists. Besides the development of completely new agents possessing chemical characteristics that clearly differ from those of existing ones, there is another approach involving the combination of 2 or more biologically active heterocyclic systems in a single molecular scaffold.[7–12]

Among the pharmacologically important heterocyclic compounds, quinoline and its derivatives have been shown to possess antimalarial,[13–15] antibiotic,[16,17] anticancer,[18] anti-inflammatory,[19] antihypertensive,[20] tyrosine kinase PDGF-RTK inhibition,[21] and anti-HIV[22,23] properties. Chloroquine, primaquine, mefloquine, and quinine constitute notable examples of the drugs containing the quinoline scaffold that are used for the treatment of malaria (Chart).[24,25] Floroquinolones, which are closely related to the quinoline ring, constitute another important class of antimicrobial agents used for the treatment of the infectious caused by especially gram-negative bacteria.

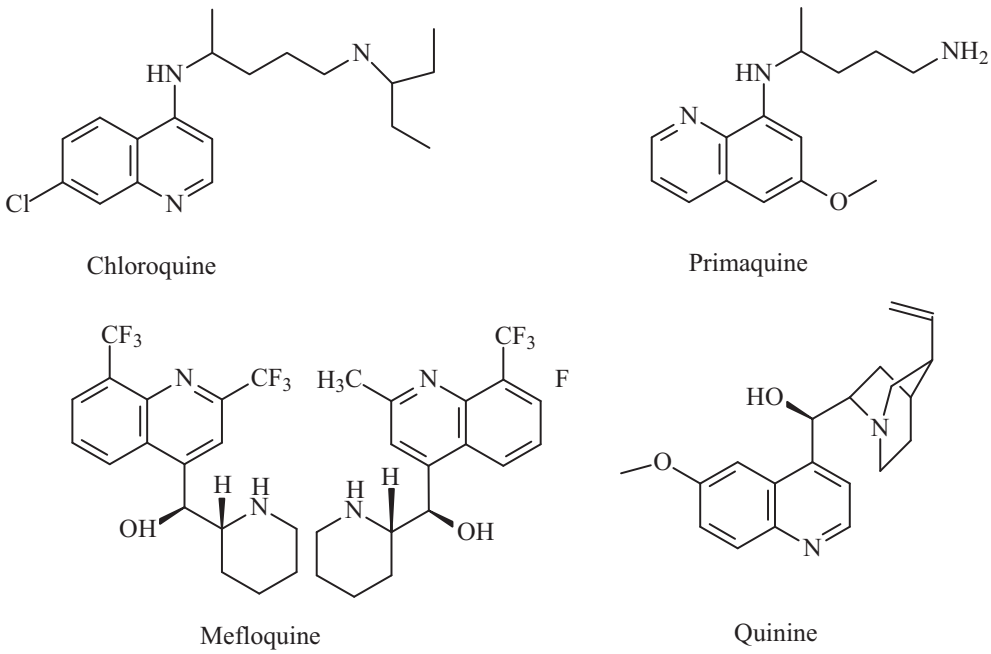


Chart.

In addition, compounds incorporating a 1,2,4-triazole nucleus have been reported to possess a wide-range spectrum of chemotherapeutic activities including anti-inflammatory,[26] anticancer,[27–29] antidepressant,[30] antibacterial,[31–35] antifungal,[36] and anticonvulsant activities.[37] In recent years, some studies have been reported incorporating the synthesis and antimicrobial activities of compounds containing the quinoline and triazole nucleus in a single structure.[1,17,38–42] However, an extensive literature survey reveals that sufficient efforts have not been made to combine these heterocycles in the same molecular scaffold and to investigate their antimicrobial activity.

Multicomponent reactions have been considered a major part of synthetic organic chemistry with advantages ranging from lower reaction times and temperatures to higher yields. The amino alkylation of aromatic compounds by Mannich reaction has been reported to have considerable importance for designing efficient bioactive molecules.[43] As a part of our continuing study on the synthesis of biologically active compounds and on the basis of the fact that more efficacious antibacterial compounds can be designed by joining 2 or more biologically active heterocyclic systems together in a single molecular framework,[44] this paper presents the synthesis of new quinoline derivatives carrying different pharmacophores as hybrid molecules possessing antimicrobial activity.

Experimental

All the chemicals were purchased from Fluka Chemie AG Buchs (Switzerland). Melting points of the synthesized compounds were determined in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 aluminum sheets. The mobile phase was ethyl acetate and detection was conducted using UV light. IR spectra were recorded as potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance II 400 MHz NMR Spectrometer (chemical shift in ppm downfield from TMS as an internal reference). The elemental analysis was performed on a Costech Elemental Combustion System CHNS-O elemental analyzer. The mass spectra were obtained on a Quattro LC-MS (70 eV) Instrument.

Quinoline-2-carbohydrazide (2). A solution of quinaldic acid (0.035 mol) in absolute ethanol was stirred under reflux in the presence of 2-3 drops of sulfuric acid for 10 h. After the solvent was evaporated under reduced pressure, a solid was obtained. This crude product was solved in 1-butanol, hydrazine hydrate (0.0875 mol) was added into it, and the mixture was refluxed for 6 h (the progress of the reaction was monitored by TLC). On cooling the reaction content, a solid appeared. This was recrystallized from ethanol to give pure compound. (Yield: 6.33 g, 97%); mp 136 °C; IR (KBr, ν, cm^{-1}): 3294 and 3201 (NH_2+NH), 1663 (C=O), 1620 (C=N), 1498 (aromatic C=C); ^{1}H-NMR (DMSO-d_6) δ (ppm): 4.69 (brs, 2H, NH_2), 7.58-7.81 (m, 2H, ar-H), 7.96-8.05 (m, 3H, ar-H), 8.44-8.48 (d, 1H, ar-H, J= 8.2 Hz), 10.01 (brs, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm): ar-C:[124.05 (C), 133.32 (C), 133.45 (C), 134.04 (C), 134.61 (C), 135.82 (C), 143.11 (C), 151.45 (C), 155.43 (C)], 168.30 (C=O); MS (ESI): m/z (%) 266.03 (19), 228.99 (16), 227.99 ([M+2+K]$^+$, 100), 188.00 ([M+1]$^+$, 24).

***N*-Benzyl-2-(quinolin-2-ylcarbonyl)hydrazincarbothioamide (3).** Benzyl isothiocyanate (26 mmol) was added to a solution of compound **2** (26 mmol) in absolute ethanol and the reaction mixture was allowed to reflux for 1 h protecting from moisture. On cooling it to room temperature, a solid was obtained. This was recrystallized from ethanol to afford the desired compound. (Yield: 8.14 g, 93%); mp 202-203 °C (lit. 42, 180-182); IR (KBr, ν, cm^{-1}): 3286 and 3152 (NH), 2978 (CH_2), 1692 (C=O), 1555 (C=N), 1476 (aromatic C=C), 1228 (C=S); ^{1}H-NMR (DMSO-d_6) δ (ppm): 4.69-4.72 (d, 2H, CH_2, J= 5.6 Hz), 7.20-7.29 (m, 5H, ar-H, phenyl), 7.66-7.89 (m, 3H, quinoline-C5-H, C6-H and C7-H), 8.04-8.15 (m, 2H, quinoline-C3-H and C8-H), 8.53-8.57 (d, 1H, quinoline C4-H, J= 8.2 Hz), 8.67 (brs, 1H, NH), 9.58 (s, 1H, NH), 10.83 (s,1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 47.26 (CH_2), ar-C:[119.74, 127.27, 127,73, 128.71, 128.78, 129.06, 129.54, 129.97, 131.31, 138.36, 139.95, 146.59, 150.06], 167 (C=O), 182 (C=S); MS (ESI): m/z (%) 383.12 (100), 374.86 ([M+K]$^+$, 80), 358.91 ([M+Na]$^+$, 67), 338.02 ([M+2]$^+$, 16), 336.90 ([M+1]$^+$, 76), 251.71 (62), 249.77 (57),

229.75 (21), 209.67 (14), 187.72 (93), 162.82 (12), 134.68 (42), 127.67 (37).

4-Benzyl-5-(quinolin-2-yl)-4*H*-1,2,4-triazol-3-thiol (4). A solution of carbothioamide **3** (10 mmol) in ethanol-water (1:1) was refluxed in the presence of 2 N NaOH for 3 h; then the resulting solution was cooled to room temperature and neutralized with 37% HCl. The precipitate formed was filtered off, washed with water, and recrystallized from dimethyl sulfoxide/water (1:1) to afford the desired compound. (Yield: 3.10 g, 96%); mp 256-257 °C (lit. 42, 284-286); IR (KBr, ν, cm^{-1}): 3061 (NH), 2911 (CH_2), 2762 (SH), 1541 (C=N), 1508 (aromatic C=C); ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.99 (s, 2H, CH_2), 7.13-7.25 (m, 5H, ar-H, phenyl), 7.60-8.05 (m, 5H, quinoline-C3-H, C5-H, C6-H, C7-H and C8-H), 8.37-8.41 (d, 1H, quinoline C4-H, J = 8.6 Hz), 14.44 (s, 1H, SH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 48.61 (CH_2), ar-C:[120.02, 127.60, 127.76, 128.22, 128.68, 128.90, 129.57, 131.29, 137.65, 138.29, 146.06, 146.86], 148.96 (triazole C-5), 170.13 (triazole C-3); MS (ESI): m/z (%) 357.04 ($[M+K]^+$, 100), 341.09 ($[M+Na]^+$, 16), 320.07 ($[M+2]^+$, 11), 319.01 ($[M+1]^+$, 44), 154.94 (19), 129.86 (22), 120.79 (17).

General method for the synthesis of compounds 5a-c, 8, and 10a,b. Morpholine (for **5a** and **8**), methylpiperazine (for **5b**), 2-(morpholin-4-yl)ethanamin (for **5c**), phenyl piperazine (for **10a**), or methyl piperidine-4-carboxylate (for **10b**) (10 mmol) was added to a solution of compound **4** (for **5a-c**), compound **7** (for **8**), or compound **9** (for **10a,b**) (10 mmol) in dry tetrahydrofuran and the mixture was stirred at room temperature in the presence of formaldehyde (40%, 1.5 mL) for 3 h. Then the resulting solution was kept overnight in cold conditions. The separated solid was collected by filtration and recrystallized from dimethyl sulfoxide-water (1:1) (for **5a** and **5b**) or ethanol (for **5c, 8,** and **10a,b**) to yield the target compounds.

4-Benzyl-2-(morpholin-4-ylmethyl)-5-(quinolin-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-thione (5a). (Yield: 0.76 g, 89%); mp 204-205 °C; IR (KBr, ν, cm^{-1}): 2855 (CH_2), 1602 (C=N), 1411 (aromatic C=C), 1115 (C=S); Anal. Calcd. (%) for $C_{23}H_{23}N_5OS$: C, 66.16; N, 16.77; H, 5.55; S, 7.68. Found C, 66.29; N, 16.43; H, 5.22; S, 7.78. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.78 (brs, 4H, $2CH_2$), 3.58 (brs, 4H, $2CH_2$), 5.24 (brs, 2H, CH_2), 6.05 (brs, 2H, CH_2), 7.16-7.26 (m, 5H, ar-H, phenyl), 7.63-7.66 (m, 1H, quinoline-C6-H), 7.79-7.83 (m, 2H, quinoline-C5-H and C7-H), 7.96-8.04 (m, 2H, quinoline-C3-H and C8-H), 8.40-8.44 (m, 1H, quinoline-C4-H); MS (ESI): m/z (%) 419.16 ($[M+1]^+$, 12), 340.91 (12), 418.09 ($[M]^+$, 40), 384.17 (20), 383.17 (100), 356.90 (18), 326.99 (14), 318.97 (16).

4-Benzyl-2-[(4-methylpiperazin-1-yl)methyl]-5-(quinolin-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-thione (5b). Yield: 0.71 g, 81%. mp 201-203 °C; IR (KBr, ν, cm^{-1}): 2929 and 2793 (aliphatic CH), 1599 (C=N), 1413 (aromatic C=C), 1169 (C=S); Anal. Calcd. (%) for $C_{24}H_{26}N_6S$: C, 66.95; N, 19.52; H, 6.09; S, 7.45. Found C, 67.22; N, 19.43; H, 5.87; S, 7.21. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.11 (s, 3H, CH_3), 2.32 (s, 4H, $2CH_2$), 2.79 (s, 4H, $2CH_2$), 5.25 (s, 2H, CH_2), 6.04 (s, 2H, CH_2), 7.10-7.29 (m, 5H, ar-H, phenyl), 7.58-7.66 (m, 1H, quinoline-C6-H), 7.75-7.82 (m, 1H, quinoline-C7-H), 7.93-8.05 (m, 3H, quinoline-C3-H, C4-H and C8-H), 8.36-8.42 (m, 1H, ar-H); MS (ESI): m/z (%) 453.14 ($[M+Na]^+$, 10), 432.32 ($[M+1]^+$, 29), 431.26 ($[M]^+$, 100), 383.30 (11), 319.09 (21), 262.16 (14), 229.00 (11), 212.82 (24), 196.83 (27).

4-Benzyl-2-({[2-(morpholin-4-yl)ethyl]amino}methyl)-5-(quinolin-2-yl)-2,4-dihidro-3*H*-1,2,4-triazol-3-thione (5c). Yield: 0.64 g, 76%; mp 217-218 °C; IR (KBr, ν, cm^{-1}): 3435 (NH), 3060 (aromatic CH), 2952, 2852 and 2807 (aliphatic CH), 1599 (C=N), 1419 (aromatic C=C); Anal. Calcd. (%) for $C_{25}H_{28}N_6OS$: C, 65.19; N, 18.25; H, 6.13; S, 6.96. Found C, 65.36; N, 18.04; H, 6.11; S, 6.67. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.49 (brs, 4H, $2CH_2$), 3.37 (brs, 8H, $4CH_2$), 5.68 (s, 2H, CH_2), 5.94 (s, 2H, CH_2),

6.03 (brs, 1H, NH), 7.08-7.24 (m, 5H, ar-H, phenyl), 7.62-7.99 (m, 5H, quinoline-C3-H, C5-H, C6-H, C7-H and C8-H), 8.33-8.37 (m, 1H, quinoline-C4-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): CH_2: 47.98, 48.62, 49.54, 54.14, 56.72, 57.25, 66.78, 68.19, ar-C:[120.09, 127.57, 127.84, 128.18, 128.27, 128.63, 128.75, 128.87, 129.61, 131.34, 131.49, 137.64, 138.37, 146.90, 147.74], 145.60 (triazole C-5), 169.80 (C=S); MS (ESI): m/z (%) 475.41 (94), 473.29 (100), 461.33 ([M]$^+$, 10), 453.39 (19).

4-Benzyl-2-(morpholin-4-ylmethyl)-5-(quinolin-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (8). Yield: 0.86 g, 84%. mp 122-125 °C; IR (KBr, ν, cm^{-1}): 2928 and 2854 (aliphatic CH), 1686 (C=O), 1602 (C=N); Anal. Calcd. (%) for $C_{23}H_{23}N_5O_2$: C, 68.81; N, 17.44; H, 5.77. Found C, 69.03; N, 17.28; H, 5.81. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.64 (s, 4H, 2CH_2), 3.57 (s, 4H, 2CH_2), 4.74 (s, 2H, CH_2), 5.62 (s, 2H, CH_2), 7.15-7.33 (m, 5H, ar-H, phenyl), 7.60-8.17 (m, 5H, quinoline-C3-H, C5-H, C6-H, C7-H and C8-H), 8.38-8.57 (m, 1H, quinoline-C4-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): CH_2: 48.10, 51.30, 55.39, 71,47, 71.75, ar-C:[124.04, 131.70, 132.34, 132.42, 132.47, 132.65, 132.89, 133.20, 133.52, 133.83, 134.24, 135.97, 142.77, 143.12, 147.75], 151.69 (C=O), 160.38 (CH=N); MS (ESI): m/z (%) 475.46 (100), 453.52 (13), 424.30 ([M+Na]$^+$, 44), 403.36 (11), 402.29 ([M+1]$^+$, 40), 359.16 (12), 344.17 (17), 343.17 (75), 325.17 (25), 321.16 (19).

3-[(4-Phenylpiperazin-1-yl)methyl]-5-(quinolin-2-yl)-1,3,4-oxadiazol-2(3*H*)-thione (10a). Yield: 1.25 g, 79%. mp 162-163 °C; IR (KBr, ν, cm^{-1}): 3064 (aromatic CH), 2821 (aliphatic CH), 1599 (C=N), 1501 (aromatic C=C), 1236 (C=S); Anal. Calcd. (%) for $C_{22}H_{21}N_5O_2$: C, 65.49; N, 17.36; H, 5.25. Found C, 65.62; N, 17.21; H, 5.18. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.93 (s, 4H, 2CH_2), 3.10 (s, 4H, 2CH_2), 5.15 (s, 2H, CH_2), 6.69-6.89 (m, 3H, phenyl-C2-H, C4-H and C6-H), 7.11-7.19 (m, 2H, phenyl-C3-H and C5-H), 7.67-7.90 (m, 2H, quinoline-C6-H and C7-H), 8.04-8.16 (m, 3H, quinoline-C3-H, C4-H and C5-H), 8.54-8.58 (d, 1H, ar-H, quinoline-C8-H, J= 7.8 Hz); ^{13}C-NMR (DMSO-d_6) δ (ppm): CH_2: 48.98, 50.20, 70.68, ar-C: [116.33, 116.72, 119.55, 119.70, 128.87, 129.18, 129.56, 129.80, 129.96, 131.65, 138.66, 147.74], 151.64 (oxadiazole C-5), 167.20 (oxadiazole C2); MS (ESI): m/z (%) 414.39 (28), 413.39 (100), 411.38 (20), 402.25 ([M-1]$^+$, 10), 393.36 (17), 392.30 (27), 346.12 (23), 339.30 (13).

Methyl 1-{[5-(quinolin-2-yl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl]methyl}piperidin -4-carboxylate (10b). Yield: 1.75 g, 83%. mp 134-137 °C; IR (KBr, ν, cm^{-1}): 2948 and 2829 (aliphatic CH), 1730 (C=O), 1600 (C=N), 1439 (C=C), 1317 (C=S); Anal. Calcd. (%) for $C_{19}H_{20}N_4O_3S$: C, 59.36; N, 14.57; H, 5.24; S, 8.34. Found C, 59.39; N, 14.34; H, 5.18; S, 8.37. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.49-1.84 (m, 4H, 2CH_2), 2.15-2.35 (m, 1H, O=C-CH), 2.49-2.61 (m, 2H, N-CH_2), 3.02-3.07 (m, 2H, N-CH_2), 3.54 (s, 3H, OCH_3), 5.01 (s, 2H, CH_2), 7.66-8.15 (m, 5H, quinoline-C3-H, C4-H, C5-H, C6-H and C7-H), 8.53-8.58 (d, 1H, quinoline-C8-H, J= 8.6 Hz); ^{13}C-NMR (DMSO-d_6) δ (ppm): CH_2: 28.60, 49.90, 71.31, CH_3: 52.11, CH: 119.55, ar-C:[128.88, 128.96, 129.16, 129.97, 131.67, 138.70, 142.47], 147.76 (oxadiazole C-5), 175.37 (C=O), 179.03 (oxadiazole C-2); MS (ESI): m/z (%) 414.39 (23), 413.39 (100), 385.29 ([M]$^+$, 10), 373.22 (23).

Synthesis of *N*-benzyl-2-(quinolin-2-yl-carbonyl)hydrazincarboxamide (6). Benzyl isocyanate (26 mmol) was added to a solution of compound **2** in absolute ethanol and the reaction mixture was allowed to reflux for 4 h protecting from moisture. Then the reaction content was cooled overnight and a solid obtained. This crude product was recrystallized from ethanol to afford the desired compound. Yield: 3.14 g, 92%. mp 205-206 °C; IR (KBr, ν, cm^{-1}): 3380 and 3315 (3NH), 1716 and 1643 (C=O), 1573 (C=N), 1489 (aromatic C=C); Anal. Calcd. (%) for $C_{18}H_{16}N_4O_2$: C, 67.49; N, 17.49; H, 5.03. Found C, 67.68; N, 17.23; H, 5.27. ^{1}H-NMR (DMSO-d_6) δ (ppm): 4.24-4.27 (d, 2H, CH_2, J= 6.0 Hz), 7.11 (s, 1H, NH), 7.20-7.31 (brs, 5H, phenyl),

7.68-7.91 (m, 2H, quinoline-C6-H, C7-H), 8.06-8.16 (m, 4H, quinoline-C3-H, C5-H + 2NH), 8.54-8.58 (d, 2H, quinoline-C4-H, C8-H, $J=$ 8.2 Hz), 10.48 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm): CH_2: 43.21, ar-C:[119.57, 127.27, 127.65, 128.77, 128.83, 129.02, 129.54, 129.99, 131.31, 138.46, 141.06, 146.64, 150.11], 158.94 (C=O), 164.87 (C=O); MS (ESI): m/z (%) 359.10 ($[M+K]^+$, 37), 343.03 ($[M+Na]^+$, 12), 321.13 ($[M+1]^+$, 14), 224.00 (13), 223.00 (19), 187.91 (34), 184.90 (13), 156.82 (100), 148.81 (16), 113.91 (11), 108.84 (19),

Synthesis of 4-benzyl-5-(quinolin-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (7). A solution of carboxamide **6** (10 mmol) in ethanol/water (1:1) was refluxed in the presence of 2 N NaOH for 3 h. Then the resulting solution was cooled to room temperature and acidified to pH 5.5 with 37% HCl. The precipitate formed was filtered off, washed with water, and recrystallized from dimethyl sulfoxide/water (1:1) to afford the desired compound. Yield: 1.57 g, 98%. mp 245-247 °C; IR (KBr, ν, cm^{-1}): 3314 (NH), 2923 (CH_2), 1697 (C=O), 1642 (aromatic C=C); Anal. Calcd. (%) for $C_{18}H_{14}N_4O$: C, 71.51; N, 18.53; H, 4.67. Found C, 71.79; N, 18.74; H, 5.01. ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.60 (s, 2H, CH_2), 7.29-7.64 (m, 5H, phenyl), 7.81-8.02 (m, 5H, quinoline-C3-H, C4-H, C5-H, C6-H and C7-H), 8.41 (m, 1H, quinoline-C8-H), 12.47 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm): CH_2: 45.10, ar-C:[118.40, 126.35, 126.89, 127.29, 127.53, 127.95, 128.21, 128.68, 129.14, 130.36, 137.14, 137.56, 137.90, 143.57, 146.70], 146.10 (triazole C-5), 155.56 (C=O); MS (ESI): m/z (%) 359.02 (46), 343.00 ($[M+2+K]^+$, 57), 325.98 ($[M+1+Na]^+$, 11), 325.04 ($[M+Na]^+$, 32), 321.04 (26), 304.08 (12), 302.95 ($[M+1]^+$, 40), 235.81 (23), 187.75 (21), 148.70 (21), 135.75 (12), 134.75 (100), 115.97 (14), 108.46 (28), 107.96 (39).

Synthesis of 5-(quinolin-2-yl)-1,3,4-oxadiazol-2-thiol (9). Compound **2** (10 mmol) and CS_2 (10 mmol) were added to the solution of KOH (10 mmol) in 50 mL of H_2O and 50 mL of ethanol and the reaction content was allowed to reflux for 6 h (the progress of the reaction was monitored by TLC). Then the ethanol was removed under reduced pressure and the resulting solution was acidified with concentrated HCl. The formed precipitate was filtered off, washed with water, and recrystallized from dimethyl sulfoxide-water (1:1) to give the target compound. Yield: 3.14 g, 87%. mp 234-238 °C. IR (KBr, ν, cm^{-1}): 3054 (aromatic CH), 2917 (aliphatic CH), 2596 (SH), 1587 and 1529 (2C=N), 1459 and 1375 (aromatic C=C); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.33-8.14 (m, 5H, quinoline-C3-H, C4-H, C5-H, C6-H and C7-H), 8.53-8.58 (m, 1H, quinoline-C8-H), 14.95 (brs, 1H, SH); ^{13}C-NMR (DMSO-d_6) δ (ppm): ar-C: [119.47, 128.88, 129.01, 129.83, 129.99, 131.69, 138.73, 142.45, 147.68], 147.79 (oxadiazole C-5), 182.12 (oxadiazole C-2); MS (ESI): m/z (%) 267.79 ($[M+K]^+$, 10), 230.80 ($[M+1]^+$, 14), 229.80 ($[M]^+$, 100), 175.67 (13), 154.77 (16), 128.74 (81), 127.74 (77), 101.77 (17).

Synthesis of compounds 11-13. In a round bottom flask attached to an air condenser, the mixture of compound **1** (10 mmol) and thiocarbohydrazide (for **11**), carbohydrazide (for **12**), or thiocarbonohydrazide (for **13**) (10 mmol) was heated at melting temperature (about 156-160 °C) for 2 h. On cooling the reaction content to room temperature, a solid was obtained. This product was washed with hot $NaHCO_3$ solution and recrystallized from ethanol (for **11** and **12**) or dimethyl sulfoxide (for **13**) to give the desired product.

5-(Quinolin-2-yl)-1,3,4-thiadiazol-2(*H*)-imine (11). Yield: 0.69 g, 30%. mp > 300 °C. Anal. Calcd. (%) for $C_{11}H_8N_4S$: C, 57.88; N, 24.54; H, 3.53; S, 14.05. Found C, 57.82; N, 24.43; H, 3.62; S, 14.11. IR (KBr, ν, cm^{-1}): 3106 (2NH), 1577 and 1560 (2C=N), 1495 (aromatic C=C); ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.52-7.78 (m, 2H, quinoline-C6-H and C7-H), 7.90-8.03 (m, 3H, quinoline-C3-H, C5-H, C8-H), 8.38-8.42 (d, 1H, quinoline-C4-H, $J=$ 8.6 Hz), 13.89 (s, 1H, NH), 14.08 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 118.66, 128.34, 128.58, 128.74, 129.56, 131.19, 138.30, 145.14, 147.48, 151.15 (thiadiazole C-5), 168.53

(thiadiazole C-2); MS (ESI): m/z (%) 267.02 ($[M+K]^+$, 10), 250.98 ($[M+1+Na]^+$, 11), 229.03 ($[M+1]^+$, 100), 196.89 (15), 180.79 (15), 154.94 (24), 148.90 (31), 127.89 (25), 118.84 (71).

4-Amino-5-(quinolin-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (12). Yield: 1.24 g, 55%. mp > 300 °C. Anal. Calcd. (%) for $C_{11}H_9N_5O$: C, 58.14; N, 30.82; H, 3.99. Found C, 58.35; N, 30.56; H, 4.13. IR (KBr, ν, cm^{-1}): 3266 and 3145 (NH+ NH_2), 1654 (C=O); ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.06 (s, 2H, NH_2), 7.71-7.77 (m, 1H, quinoline-C6-H), 7.87-7.94 (m, 1H, quinoline-C7-H), 8.08-8.22 (m, 4H, quinoline-C3-H + C5-H + C8-H + NH), 8.54-8.62 (m, 1H, quinoline-C4-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 122.88, 126.42, 126.92, 129.47, 131.14, 133.69, 134.75, 137.13, 143.11, 145.56 (triazole C3), 155.12 (triazole C5); MS (ESI): m/z (%) 279.15 (18), 278.15 (10), 234.00 (16), 232.99 (91), 164.00 (43), 151.98 (25), 106.89 (82).

4-Amino-5-(quinolin-2-yl)-4*H*-1,2,4-triazole-3-thiol (13). Yield: 1.36 g, 56%. mp 213 °C. IR (KBr, ν, cm^{-1}): 3258 and 3077 (NH_2 + aromatic CH), 2918 (aliphatic CH), 2763 (SH), 1595 and 1545 (2C=N), 1493 (aromatic C=C), 1212 (C=S); Anal. Calcd. (%) for $C_{12}H_{10}N_4S$: C, 59.48; N, 23.12; H, 4.16. Found C, 59.65; N, 23.16; H, 4.12. ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.69 (s, 2H, NH_2), 7.69-7.85 (m, 2H, quinoline-C6-H, C7-H), 8.03-8.17 (m, 3H, quinoline-C3-H, C5-H, C8-H), 8.53-8.57 (d, 1H, quinoline-C4-H, J= 8.6 Hz), 14.20 (brs, 1H, SH); due to the slight solubility in any NMR solvent, a satisfactory ^{13}C-NMR spectrum could not be obtained; MS (ESI): m/z (%) 284.20 (19), 282.06 ($[M+K]^+$, 81), 265.96 ($[M+Na]^+$, 44), 262.00 (11), 248.04 (20), 244.02 ($[M+1]^+$, 60), 228.92 (16), 225.90 (34), 224.90 (22), 203.70 (11), 193.89 (11), 168.80 (18), 156.91 (37), 152.89 (57), 148.93 (11), 134.84 (39), 105.85 (26), 100.88 (100).

2-[6-(4-Chlorophenyl)-8*H*-[1,2,4]triazolo[4,3-d][1,3,4]thiadiazin-3-yl]quinoline (14). The mixture of compound **13** (10 mmol) and 4-chlorophenacylbromide (10 mmol) in absolute ethanol was allowed to reflux in the presence of dried sodium acetate (20 mmol) for 12 h. Then the mixture was allowed to reach to room temperature and the solid formed was filtered off, washed with water several times, and recrystallized from ethyl acetate to afford the desired compound. Yield, 2.43 g, 68%. mp 204-206 °C. Anal. Calcd. (%) for $C_{19}H_{12}ClN_5S$: C, 60.40; N, 18.53; H, 3.20; S, 8.49. Found C, 60.57; N, 18.45; H, 3.22; S, 8.56. IR (KBr, ν, cm^{-1}): 3087 (ar-CH), 1693, 1645 and 1587 (HC=N); ^{1}H-NMR (DMSO-d_6) δ (ppm): 4.49 (s, 2H, CH_2), 7.63-7.74 (m, 4H, ar-H), 7.74-7.86 (m, 1H, ar-H), 8.04-8.10 (m, 4H, ar-H), 8.56-8.61 (m, 1H, ar-H), ^{13}C-NMR (DMSO-d_6) δ (ppm): 23.29 (CH_2), ar C: [128.82 (2CH), 129.97 (2CH), 130.16 (2CH), 131.34 (2CH), 137.92 (2CH), 145.20 (C), 145.62 (C), 149.23 (C), 154.04 (C), 155.10 (ar-C + triazole C5), 145.05 (ar-C + triazole C3)]. 108.17 (90.62), 115.80 (48.12), 132.82 (30.00), 148.84 (26.25), 180.87 (26.25), 196.83 (48.75), 199.52 (40.62), 212.03 (35.00), 214.85 (23.12), 246.14 (24.37), 271.16 (20.00), 318.22 (49.37), 334.23 (54.30), 336.30 (34.37), MS (ESI): m/z (%) 457.37 (30), 416.20 ([M-1+K], 23.12), 399.24 (32.5), 383.29 (48.12), 378.16 ([M^+], 100).

4-{[(4-Methoxyphenyl)methylidene]amino}-5-(quinolin-2-yl)-4*H*-1,2,4-triazole-3-thiol (15). In a round bottom flask attached to an air condenser, the mixture of compound **13** (10 mmol) and 4-methoxybenzaldehyde (10 mmol) was heated at 120 °C for 2 h. On cooling the reaction content to room temperature, a solid was obtained. This crude product was recrystallized from dimethyl sulfoxide to give the desired product. Yield, 2.26 g, 62%. mp 253 °C. Anal. Calcd. (%) for $C_{19}H_{15}N_5OS$: C, 63.14; N, 19.38; H, 4.18; S, 8.87. Found C, 63.38; N, 19.21; H, 4.24; S, 8.71. IR (KBr, ν, cm^{-1}): 2829 (SH), 3060 (ar-CH), 1607, 1567 and 1504 (C=N), 1258 (C-O); ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.86 (s, 3H, CH_3), 7.06-7.09 (m, 2H, phenyl-C3-H, C5-H), 7.68-8.09 (m, 7H, phenyl-C2-H + C6-H + quinoline), 8.50-8.51 (m, 1H, quinoline-C4-H),

9.30 (s, 1H, HC=N), 14.32 (s, 1H, SH); due to the slight solubility in any NMR solvent, a satisfactory ^{13}C-NMR spectrum could not be obtained. MS (ESI): m/z (%) 413.39 (100), 384.24 ([M+Na]$^+$, 13), 363.20 (21), 362.20 ([M+1]$^+$, 86), 301.13 (10), 230.05 (12), 228.99 (80), 154.91 (16), 148.78 (16), 118.81 (33).

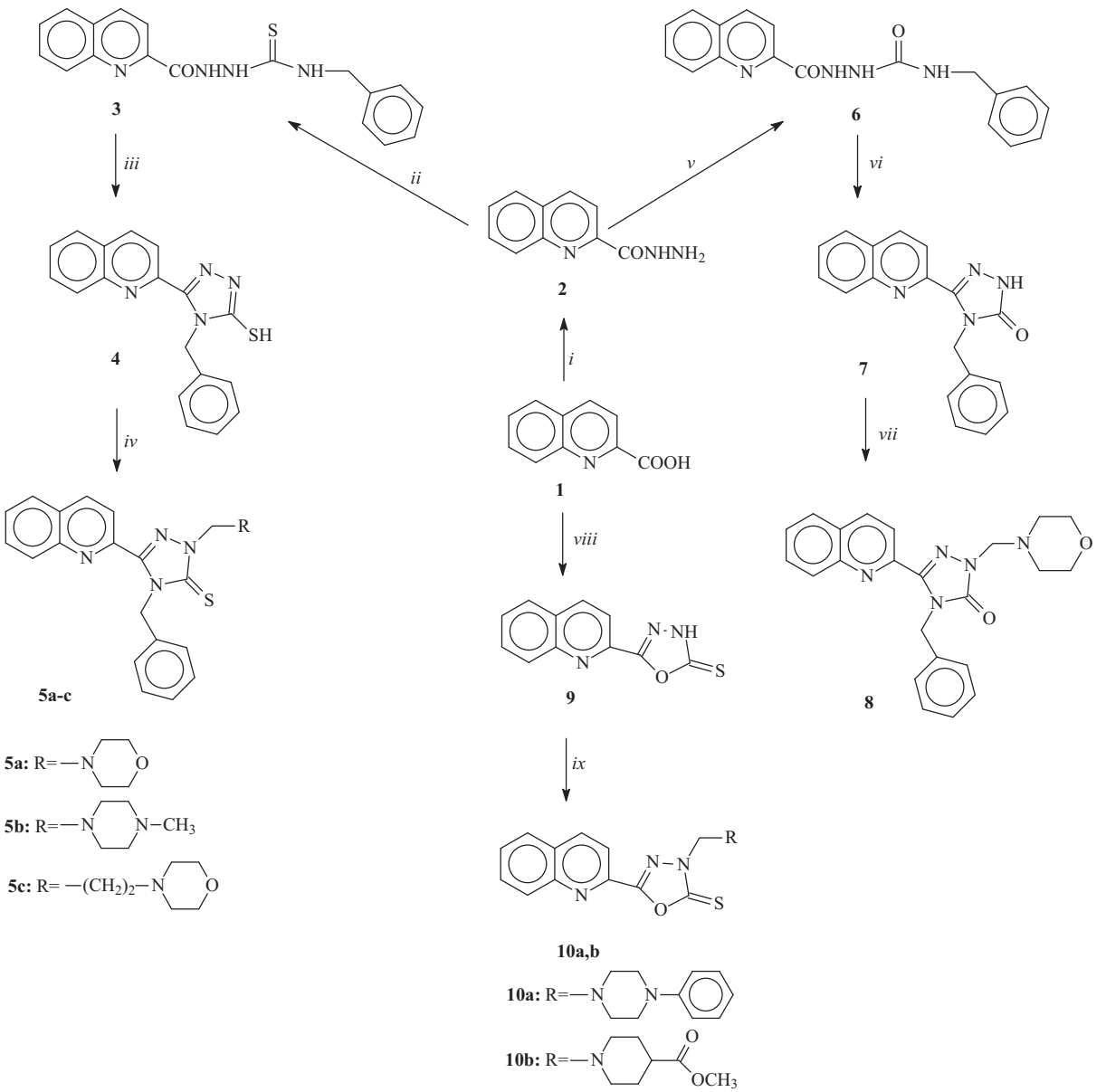
Antimicrobial activity assessment

All test microorganisms were obtained from the Refik Saydam Hygiene Institute (Ankara, Turkey) and were as follows: *E. coli* ATCC35218, *E. aerogenes* ATCC13048, *Y. pseudotuberculosis* ATCC911, *P. aeruginosa* ATCC43288, *S. aureus* ATCC25923, *E. faecalis* ATCC29212, *B. cereus* 709 Roma, *M. smegmatis* ATCC607, *C. albicans* ATCC60193, *C. tropicalis* ATCC 13803, *A. niger* RSKK 4017, and *S. cerevisiae* RSKK 251. All the newly synthesized compounds were weighed and dissolved in dimethyl sulfoxide to prepare extract stock solution of 5.000 mg/mL. Agar-well diffusion method screening test using agar-well diffusion[45] as adapted earlier[46] was used for all newly synthesized compounds. Each microorganism was suspended in Mueller Hinton (MH) (Difco Detroit, MI, USA) broth and diluted approximately to 10^6 colony forming units (cfu)/mL. They were flood-inoculated onto the surface of the MH agar and Sabouraud Dextrose Agar (SDA) (Difco, Detriot, MI, USA) and then dried. For *C. albicans* and *C. tropicalis*, SDA was used. Five millimeter diameter wells were cut from the agar using a sterile cork-borer, and 50 mL of the extract substances was delivered into the wells. The plates were incubated for 18 h at 35 °C. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organism. Ampicillin (10 mg), Streptomycin (10 mg), and Fluconazole (5 mg) were the standard drugs. Dimethyl sulfoxide and ethanol were used as solvent controls.

Results and discussion

The synthesis of the target compounds was carried out as outlined in Schemes 1 and 2.

Compounds **1**-**4** and **9** are commercially available. The synthesis of compounds **3** and **6** was performed by the reaction of **2** with benzylisothiocyanate (for **3**) or benzylisocyanate (for **6**). The products **3** and **6** were characterized by their physical, analytical, and spectral data. IR spectra of these compounds showed NH stretching bands between 3380 and 3152 cm^{-1}. The absorption bands associated with other functional groups appeared in the expected regions. In the ^{1}H-NMR spectra of the target carbo(thio)amides, the NH protons appeared between 8.67 and 10.48 ppm as D_2O exchangeable singlets. The intramolecular cyclization of **3** and **6** was performed by basic treatment of these intermediates under reflux conditions. It is well known that **4** type of compounds exist as their thion-mercapto tautomeric forms, and the SH signal due to thiol form is a more downfield singlet than the NH signal derived from thione form.[7,30–33] In the ^{1}H-NMR spectrum of **4**, the appearance of one signal observed at 14.44 ppm integrating one proton indicated that the dominant form for compound **4** is the mercapto form. The other protons appeared at the expected chemical shifts and integral values as D_2O nonexchangeable signals. In the IR spectrum of **7**, the presence of a stretching band representing NH and C=O functionalities at 3314 and 1692 cm^{-1} and the absence of any signals due to a OH group demonstrated that the dominant tautomeric form of compound **7** is keto form. Moreover, no signal originating from a OH group was recorded in the ^{1}H-NMR spectrum of 7, while the NH group of compound 7 resonated at 12.47 ppm integrating one proton. The endocyclic C=O (triazole C-3) was observed at 155.56 ppm in the ^{13}C-NMR spectrum of **7**. These observations are consistent with the literature.[7,29,32–36]

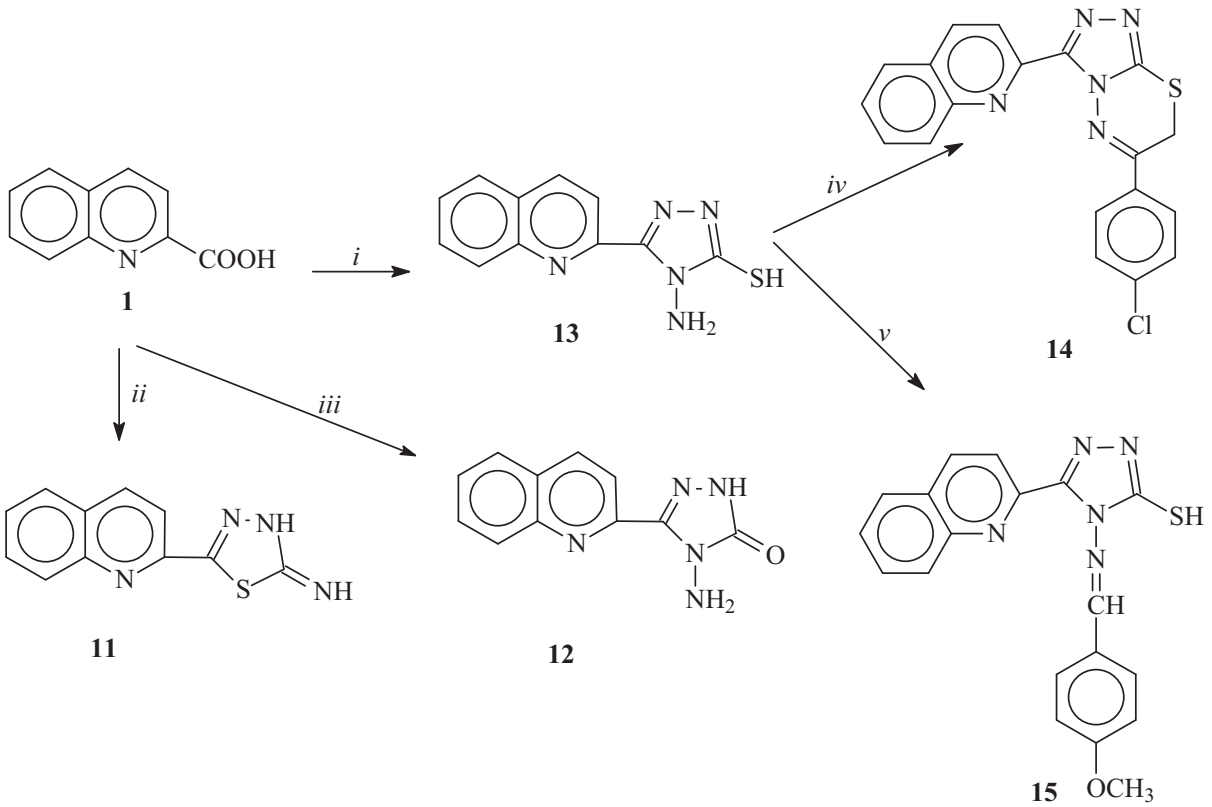


Scheme 1. Reaction and conditions: *i*) H_2NNH_2, *ii*) benzylisothiocyanate, *iii*) NaOH, *iv*) CH_2O and morpholine (for **5a**), methyl piperazine (for **5b**) or 2-(morpholin-4-yl)ethylamine (for **5c**), *v*) benzylisothiocyanate, *vi*) NaOH, *vii*) CH_2O and morpholine, *viii*) CS_2, *ix*) CH_2O and phenyl piperazine (for **10a**) or methyl piperidine-4-carboxylate (for **10b**).

The base catalyzed cyclocondensation of hydrazide (**2**) with carbondisulfide generated 1,3,4-oxadiazole derivative (**9**) in good yield under reflux conditions. This compound (**9**) exhibited spectral data consistent with its structure.

The attempts for aminoalkylations of triazole and oxadiazole derivatives (**4, 7,** and **9**) by Mannich reaction allowed the isolation of the corresponding products (**5a-c, 8,** and **10a,b**) in good yields, after 3 h

at room temperature. Different from **4, 7,** and **9**, the NMR spectra of the obtained Mannich bases (**5a-c, 8,** and **10a,b)** displayed additional signals derived from the amine moiety and -CH_2- linkage at the related shift and integral values as D_2O nonexchangable signals, while the SH(NH) signals disappeared. Due to the lower solubility in any NMR solvent, no satisfactory ^{13}C-NMR spectrum could be obtained for **5a,b**. These compounds displayed elemental analysis data consistent with their structures.



Scheme 2. Synthesis of compounds **11-15**. *i*) thiocarbohydrazide, *ii*) thiosemicarbazide, *iii*) carbohydrazide, *iv*) 4-chlorophenacylbromide, *v*) 4-methoxybenzaldehyde.

The heating in the solvent free media of quinaldic acid (**1**) with thiocarbohydrazide to melting temperature led to the formation of 4-amino-5-(quinolin-2-yl)-4*H*-1,2,4-triazole-3-thiol (**13**); while the treatment of the same precursor with carbohydrazide yielded 4-amino-5-(quinolin-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**12**) in the same reaction conditions. On the other hand, the cyclocondensation of **1** with thiosemicarbazide afforded 5-(qinolin-2-yl)-1,3,4-thiadiazol-2(*H*)-imine (**11**). The IR and NMR spectra of compounds **11-13** displayed additional signals derived from NH_2, NH, and/or SH functionalities as D_2O exchangeable signals. The reaction of **13** with 4-chlorophenacyl bromide caused fusion between the NH_2 and SH groups and acyl nucleus; thus, 2-[6-(4-chlorophenyl)-8*H*-[1,2,4]triazolo[4,3-*d*][1,3,4]thiadiazin-3-yl]quinoline (**14**) formed. In the IR spectra of compound **14**, the absence of any absorption bands originating from –SH and $–NH_2$ stretching frequencies clearly indicated fusion between compound **13** and 4-chlorophenacyl bromide. Furthermore, additional signals in the aromatic region were observed due to the 4-chlorophenyl nucleus.

The condensation of **13** with 4-methoxybenzaldehyde at melting temperature in the solvent-free media afforded the corresponding Schiff base, 4-{[(4-methoxyphenyl)methylidene]amino}-5-(quinolin-2-yl)-4*H*-1,2,4-triazole-3-thiol (**15**). The IR and ^{1}H-NMR spectra of compound **15** exhibited no signal belonging to a NH_2 group, while additional signals originating from the 4-methoxyphenyl nucleus were recorded in the related chemical shift values.

Additional support for the formation of the targeted compounds was obtained by the appearance of $[M]^+$, $[M+1]^+$, $[M+Na]^+$, and/ or $[M+K]^+$ ion peaks at corresponding m/z values confirming their molecular masses.

Antimicrobial activity

All the newly synthesized compounds were tested for their antimicrobial activities and the results obtained are presented in the Table. Among the synthesized compounds, compounds **5a-c** displayed no activity against the test microorganisms. The highest activity was observed for compound **11**, which contains a 1,3,4-thiadiazole

Table. Screening for antimicrobial activity of the new compounds (mm).

Comp. no	Microorganisms and inhibition zone (mm)									
	Ec	Ea	Yp	Pa	Sa	Ef	Bc	Ms	Ca	Sc
5a	-	-	-	-	-	-	-	-	-	-
5b	-	-	-	-	-	-	-	-	-	-
5c	-	-	-	-	-	-	-	-		
6	8	6	6	-	-	-	-	-	-	-
7	10	10	10	8	-	-	-	10	-	-
8	10	10	10	-	-	-	-	10	-	-
10a	8	6	8	8	10	10	10	10	-	-
10b	8	6	-	-	-	-	-	10	-	-
11	10	10	16	16	8	6	8	8	-	-
12	10	8	8	8	10	10	10	6	-	-
13	6	6	8	8	-	-	-	-	-	-
14	8	6	6	8	-	-	-	-	-	-
15	10	10	8	8	6	6	-	-	-	-
Amp.	10	10	18	18	35	10	15			
Strep.								35		
Flu									25	> 25

Ec*: Escherichia coli* ATCC 25922, Ea: *Enterobacter aerogenes* ATCC 13048 Yp: *Yersinia pseudotuberculosis* ATCC 911, Pa: *Pseudomonas aeruginosa* ATCC 43288, Sa: *Staphylococcus aureus* ATCC 25923, Ef: *Enterococcus faecalis* ATCC 29212, Bc: *Bacillus cereus* 702 Roma, Ms: *Mycobacterium smegmatis* ATCC607, Ca: *Candida albicans* ATCC 60193, Sc: *Saccharomyces cerevisiae* RSKK 251, Amp.: Ampicillin, Strep.: Streptomycin, Flu.: Fluconazole.

skeleton and an imine functionality in its structure. When compared to the standard drug ampicillin, compounds **7, 8,** and **11** were found to have equal activity against enteric bacteria, *Escherichia coli* (*Ec*) and *Enterobacter aerogenes* (*Ea*). Very good activity was observed for compound **11** on *Yersinia pseudotuberculosis* (Yp) and *Pseudomonas aeruginosa* (Pa), while promising activities were observed for 7 and 8 towards Yp. In fact, compound **7**, a 1,2,4-triazol-3-one derivative, and its Mannich base (**8**) incorporating morpholine moiety exhibited similar activities against *Escherichia coli* (*Ec*), *Enterobacter aerogenes* (*Ea*), *Yersinia pseudotuberculosis* (Yp), and a nonpigmented rapidly growing mycobacterium, *Mycobacterium smegmatis* (Ms), activity. This result showed that the introduction of morpholine moiety into the structure did not contribute to the activity of compound 7. In fact, for compound **8,** this structural modification caused loss of activity towards *Staphylococcus aureus* (*Sa*), which is a gram-positive coccus.

Among the Mannich base derivatives (**10a,b**) of compound **9**, **10a** displayed good-moderate activity towards the test microorganisms except Ca and Sc, which are yeast-like fungi, while compound **10b** showed activity against only Ec, Ea, and Ms. The activity of **10a** on *Enterococcus faecalis* (*Ef*) was equal to the activity of ampicillin. When compared to ampicillin, the 4-amino-1,2,4-triazol-3-one compound **(12)** exhibited equal activity on *Ec* and *Ef*, which are gram-positive cocci, and promising activity on *Bacillus cereus* (*Bc*), which is a gram-positive spore bacillus, while moderate-slight activities were observed against the other test microorganisms except Ca and Sc.

Compounds **13-15** were found to be active against some of the test microorganisms. The activity of **15** towards Ec and Ea was equal to that of ampicillin. None of the newly synthesized compounds demonstrated activity on yeast-like fungi, Ca and Sc.

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