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A convenient synthesis and preparation of the derivatives of ethyl-6-(8-hydroxyquinolin-5-yl)-3-methylpyridazine-4-carboxylate as antimicrobial agents

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ABSTRACT

Synthesis of ethyl 6-(8-hydroxyquinolin-5-yl)-3-methylpyridazin-4-carboxylate (4) *via* one-pot three component reaction of ethyl acetoacetate with (8-hydroxyquinolin-5-yl)(oxo) acetaldehyde (2) in the presence of hydrazine hydrate at room temperature in water was described. A new series of heterocyclic moieties such as oxadiazoles, triazoles, pyrazoles and Schiff bases were prepared and characterized. The structures of the newly synthesized compounds were established by elemental and spectral data. The antimicrobial activity of some of the synthesized compounds was examined against two Gram-positive bacteria, two Gram-negative bacteria and four fungi. The results showed that the tested compounds exhibited significant to moderate antimicrobial.

1. Introduction

Various pyridazine-annulated heterocycles have been attracted considerable interest because their derivatives exhibit a wide range of pharmacological activities [1-4]. A substantial number of pyridazines have been reported to possess and are often employed as potent analgesic [5], antimicrobial [6,7], anti-inflammatory [8], antioxidant [9], antiplatelet [10], anticancer [11], anticonvulsant [12], antifeedant [13], antihypertensive [14], and antidiabetic [15]. Moreover, pyridazines are useful intermediates in the construction of several other heterocycles [16,17]. With all the above facts in mind and as a part of our program directed towards the synthesis of polyfunctionalized substituted 5-heterocyclo-8-hydroxyquinolines of potential biologically interest [18-22], we have devoted some efforts to the construction of a novel ethyl 6-(8-hydroxy quinolin-5-yl)-3-methylpyridazin-4-carboxylate (**4**) as a conveniently accessible precursor for the synthesis of some hitherto unreported substituted 8-quinolinolinyl-5-pyridazines and their related derivatives in one-pot three component environ-mental friendly method [23].

2. Experimental

2.1. Instrumentation

Melting points were determined on a Kofler melting point apparatus. IR spectra were recorded on a Pye Unicam SP3-100 spectrophotometer using the KBr wafer technique. The ^{1}H NMR spectra were recorded on a Bruker ARX 200 spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C) at the Faculty of Science, University of King Saud, Saudi Arabia, Riyadh and on a Jeol a 400 MHz (400 MHz for ^{1}H and 100 MHz for the ^{13}C) at Assiut University using $CDCl_3$ and DMSO-d_6 as solvents. Mass spectra were taken on a JEOL JMS600 spectrometer at an ionizing potential of 70 eV (EI) at Assiut University. Elemental analyses were recorded on Gmbh VarioEL V2.3 Micro analyzer at Assiut University and they were found to be within ±0.4% of the theoretical values.

2.2. Synthesis

2.2.1. Synthesis of (8-hydroxyquinolin-5-yl)(oxo) acetaldehyde (2)

The starting compound 5-acetyl-8-hydroxyquinoline (**1**) was prepared following reported procedures [24].

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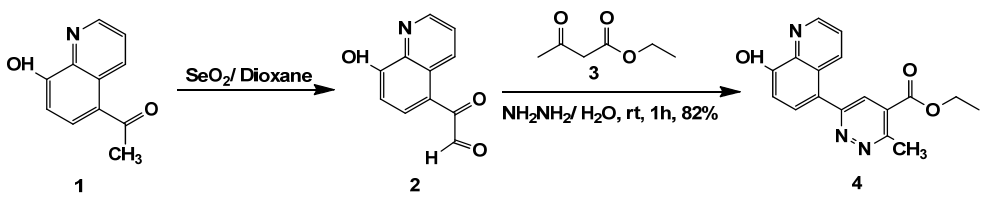


Scheme 1

5-Acetyl-8-hydroxyquinoline (**1**) (2.21 g, 10 mmol) and SeO_2 (5.55 g, 50 mmol) were dissolved in a mixture of dioxane (80 mL) and water (5 mL) and refluxed for 8 h. After filtration of the black selenium powder, the clear filtrate as concentrated nearly to dryness. Toluene (40 mL) was added, the reaction mixture was refluxed for 2 h, decanted from the remaining residue and the solvents were evaporated to leave yellow needles after cooling. The crystals were filtered off, washed with small amount of ethanol, dried and crystallized from ethanol to give compound **2** (Scheme 1). Color: Yellow. Yield: 62%. M.p.: 139-141 °C. FT-IR (KBr, ν, cm^{-1}): 1676, (C=O), 1665 (HC=O). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 7.03-8.81 (m, 6H, 5 Ar-H, OH), 10.12 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 201.1, 189.6, 155.7, 154.3, 150.3, 148.7, 144.4, 129.9, 128.8, 125.4, 115.3. MS (EI, *m/z* (%)): 201.23 ($M^{+\cdot}$, 75). Anal. calcd. for $C_{11}H_7NO_3$: C, 65.67; H, 3.51; N, 6.96. Found: C, 65.96; H, 3.76; N, 7.24%.

2.2.2. Synthesis of ethyl 6-(8-hydroxyquinolin-5-yl)-3-methyl pyridazin-4-carboxylate (4)

To a mixture of compound **2** (4.02 g, 20 mmol) and ethyl acetoacetate (2.6 g, 20 mmol) in water (60 mL), was gradually added hydrazine hydrate (10 mmol) at room temperature; the resultant mixture was stirred for 1 h. During which time, a precipitate was formed, and then it was filtered off and washed with water. The crude product was purified by recrystallization from ethanol to give compound **4** (Scheme 1). Color: Yellow. Yield: 82%. M.p.: 177-179 °C. FT-IR (KBr, ν, cm^{-1}): 2980, 2885 (CH- aliphatic), 1732 (C=O), 1620 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 1.35 (t, J = 7.4 Hz, 3H, CH_3), 3.15 (s, 3H, CH_3), 4.25 (q, J = 7.4 Hz, 2H, CH_2), 7.25-8.80 (m, 7H, 5 Ar-H, CH-pyridazine, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 169.2, 155.3, 152.2, 150.4, 148.4, 140.8, 139.6, 129.3, 127.2, 125.5, 124.3, 122.9, 115.8, 112.3, 62.7, 22.4, 14.6. MS (EI, *m/z* (%)): 309.09 ($M^{+\cdot}$, 74). Anal. calcd. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 66.47; H, 5.16; N, 13.95%.

2.2.3. Synthesis of 6-(8-hydroxyquinolin-5-yl)-3-methyl pyridazine-4-carbohydrazide (8)

To a suspension of compound **4** (3.09 g, 10 mmol) in ethanol (30 mL), hydrazine hydrate (20 mmol) was added and the mixture was heated under reflux for 4 h. The precipitate was collected by filtration and recrystallized from ethanol to give compound **8** (Scheme 2). Color: Yellow. Yield: 80%. M.p.: 303-305 °C. FT-IR (KBr, ν, cm^{-1}): 3400, 3350, 3200 (NH_2, NH), 2995 (CH-aliphatic), 1665 (C=O), 1620 (C=N). ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 2.95 (s, 3H, CH_3), 4.42 (s, 2H, NH_2), 7.30-8.89 (m, 7H, 5 Ar-H, CH-pyridazine, OH), 10.14 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6 δ, ppm): 166.6, 159.2, 156.1, 146.4, 146.1, 140.2, 138.3, 129.0, 128.9, 125.1, 123.6, 120.5, 118.2, 111.9, 18.2. MS (EI, *m/z* (%)): 295.18 ($M^{+\cdot}$, 62). Anal. calcd. for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 61.44; H, 4.81; N, 23.98%.

2.2.4. Synthesis of 5-[6-(8-hydroxyquinolin-5-yl)-3-methyl pyridazin-4-yl]-1,3,4-oxadiazole-2(3H)-thione (9)

A mixture of acid hydrazide (**8**) (2.95 g, 10 mmol), potassium hydroxide (0.56 g, 10 mmol), carbon disulfide (1.29 g, 17 mmol), and ethanol (70 mL) was heated under reflux with stirring until the evolution of hydrogen sulfide ceased (9 h). Ethanol was distilled off under reduced pressure and the residue was dissolved in water and then acidified with dilute hydrochloric acid (10%). The resulting precipitate was filtered, washed with water, dried, and recrystallized from ethanol to give compound **9** (Scheme 2). Color: Yellow. Yield: 69%. M.p.: 216-218 °C. FT-IR (KBr, ν, cm^{-1}): 3250 (NH), 2990 (CH-aliphatic), 1365 (C=S), 1620 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.05 (s, 3H, CH_3), 7.25-8.85 (m, 7H, 5 Ar-H, CH-pyridazine, OH), 10.14 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 162.7, 155.3, 152.1, 147.7, 138.3, 130.1, 126.3, 125.4, 123.8, 120.4, 120.1, 116.3, 115.3, 112.5, 113.4, 18.4. MS (EI, *m/z* (%): 337.28 ($M^{+\cdot}$, 47). Anal. calcd. for C_{16} $H_{11}N_5O_2S$: C, 56.96; H, 3.29; N, 20.76. Found: C, 57.31; H, 3.64; N, 20.99%.

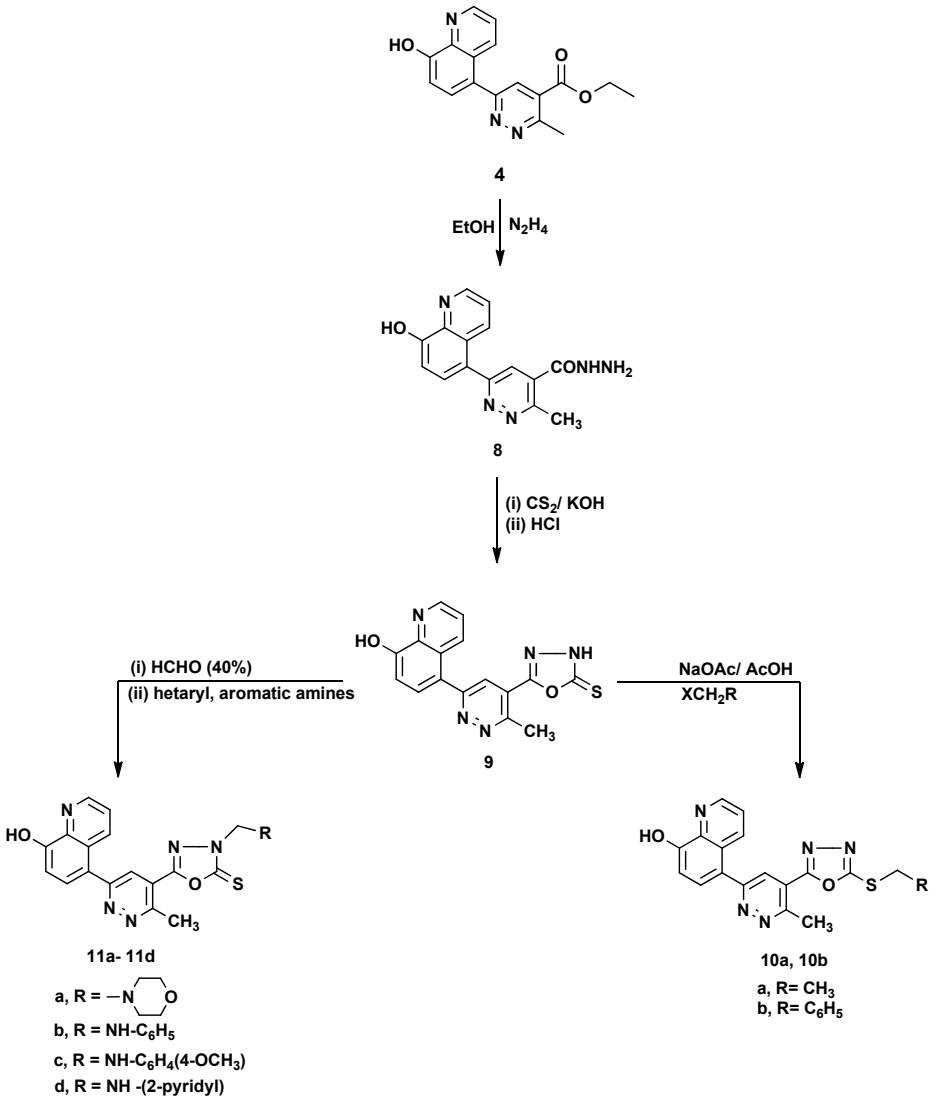
2.2.5. General procedure for the synthesis of compounds (10a,b) and (14a,b)

A mixture of compound **9** or **13** (5 mmol), ethyl iodide and/or benzyl bromide (5 mmol) in ethanol (30 mL) was refluxed in the presence of anhydrous sodium acetate (5 mmol) for 4 h. The solid product separated from the hot mixture was filtered off, washed with water and recrystallized from ethanol to afford compounds **10a**,**b** (Scheme 2) and **14a-d** (Scheme 3), respectively.

5-(5-(5-(Ethylthio)-1,3,4-oxadiazol-2-yl)-6-methylpyridazin-3-yl)quinolin-8-ol (**10a**): Color: Yellow. Yield: 72%. M.p.: 132-134 °C. FT-IR (KBr, ν, cm^{-1}): 2980 (CH- aliphatic), 1625 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 1.20 (t, J = 7.4 Hz, 3H, CH_3), 2.99 (s, 3H, CH_3), 3.65 (q, J = 7.4 Hz, 2H, CH_2), 7.18-8.75 (m, 7H, 5 Ar-H, CH-pyridazine, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 162.3, 154.4, 151.2, 146.2, 138.0, 130.4, 127.8, 125.5, 124.4, 123.2, 120.0, 115.7, 113.7, 112.3, 111.19, 28.6, 18.4, 15.9. Anal. calcd. for C_{18} $H_{15}N_5O_2S$: C, 59.16; H, 4.14; N, 19.17. Found: C, 59.49; H, 3.51; N, 19.49%.

5-{5-[5-(Benzyl sulfanyl)-1,3,4-oxadiazol-2-yl]-6-methylpyridazin-3-yl}quinolin-8-ol (**10b**): Color: Yellow. Yield: 65%. M.p.: 147-149 °C. FT-IR (KBr, ν, cm^{-1}): 2980 (CH- aliphatic), 1625 (C=N). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 3.03 (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 6.99-8.88 (m, 12H, 10 Ar-H, CH-pyridazine, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161.7, 155.0, 150.5, 148.8, 137.5, 129.1, 128.3, 127.5, 126.2, 125.3, 124.6, 123.7, 122.1, 120.2, 120.0, 119.6, 118.4, 116.7, 115.6, 115.3, 113.4, 36.7, 18.2. Anal. calcd. for C_{23} $H_{17}N_5O_2S$: C, 64.62; H, 4.01; N, 16.38. Found: C, 64.83; H, 4.35; N, 16.66%.

5-(5-(5-(Ethylthio)-4-phenyl-4H-1,2,4-triazol-3-yl)-6-methyl pyridazin-3-yl)quinolin-8-ol (**14a**): Color: Yellow. Yield: 79%. M.p.: 170-172 °C. FT-IR (KBr, ν, cm^{-1}): 2900 (CH-aliphatic), 1625 (C=N), 1360 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.31 (t, J = 7.4 Hz, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.85 (q, J = 7.4 Hz, 2H, CH_2), 6.85-8.60 (m, 12H, 10 Ar-H, CH-pyridazine, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 157.6, 156.2, 153.4, 149.0, 148.4, 140.6, 138.1, 136.6, 130.9, 130.1, 129.5, 128.3, 127.0, 126.7, 126.1, 125.9, 123.5, 120.2, 116.7, 113.3, 112.7 , 30.3, 18.2, 15.2. Anal. calcd. for $C_{24}H_{20}N_6OS$: C, 65.44; H, 4.58; N, 19.08. Found: C, 65.74; H, 4.93; N, 19.35%.



Scheme 2

5-(5-(5-(Benzylthio)-4-phenyl-4H-1,2,4-triazol-3-yl)-6-methylpyridazin-3-yl)quinolin-8-ol (**14b**): Color: Yellow. Yield: 61%. M.p.: 188-190 °C. FT-IR (KBr, ν, cm^{-1}): 2950 (CH-aliphatic), 1625 (C=N), 1420 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.10 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 7.01-8.85 (m, 17H, 15 Ar-H, CH-pyridazine, OH). Anal. calcd. for $C_{29}H_{22}N_6OS$: C, 69.30; H, 4.41; N, 16.72. Found: C, 69.56; H, 4.73; N, 16.97%.

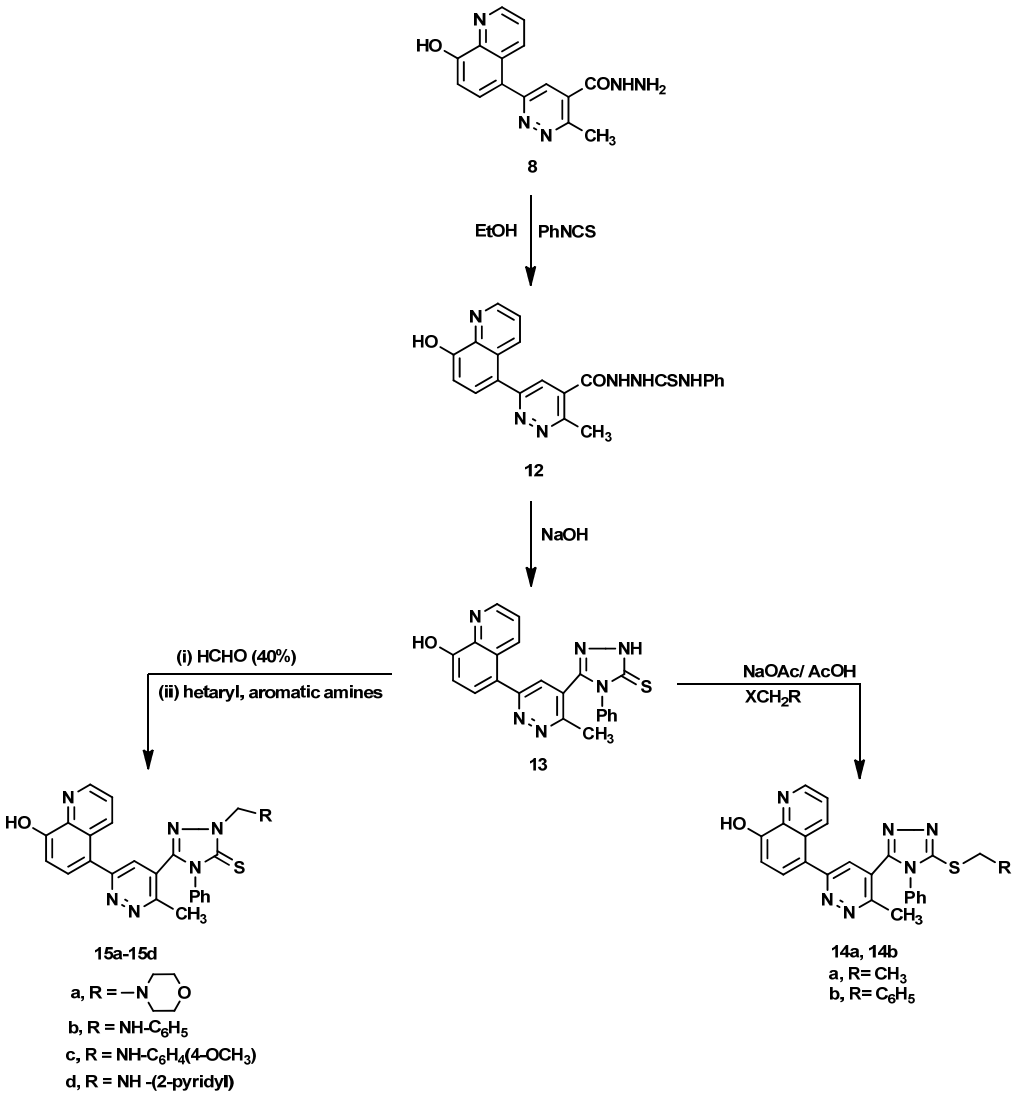
2.2.6. General procedure for the synthesis of compounds (11a-d) and (15a-d)

Formalin 40% (1.5 mL, 20 mmol) was added to a stirred solution of compound **9** or **13** (20 mmol) in absolute ethanol (40 mL). An ethanolic solution (10 mL) of the appropriate amine (20 mmol) was added portion wise to the reaction mixture, stirred for 3 h at room temperature, and left overnight in a refrigerator. The precipitate formed was filtered, washed with cold ethanol, dried, and crystallized from ethanol to afford compounds **11a-d** (Scheme 2) and **15a-d** (Scheme 3), respectively.

5-[6-(8-Hydroxyquinolin-5-yl)-3-methylpyridazin-4-yl]-3-[(morpholino)methyl]-1,3,4-oxadiazole-2(3H)-thione (**11a**): Color: Yellow. Yield: 60%. M.p.: 187-189 °C. FT-IR (KBr, ν, cm^{-1}): 2990 (CH-aliphatic), 1625 (C=N), 1350 (C=S). ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 2.99 (s, 3H, CH_3), 3.15 (t, J = 7.4 Hz, 4H, $2CH_2$), 3.65 (t, J = 7.4 Hz, 4H, $2CH_2$), 5.12 (s, 2H, CH_2), 7.25-8.78 (m, 7H, 5 Ar-H, CH-pyridazine, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 178.8, 158.7, 155.6, 150.9, 146.3, 139.5, 130.3, 127.6, 126.3, 125.2, 124.7, 122.3, 116.4, 114.8, 112.9, 70.1, 66.4, 53.6, 18.1. Anal. calcd. for $C_{21}H_{20}N_6O_3S$: C, 57.79; H, 4.62; N, 19.25. Found: C, 58.11; H, 4.99; N, 19.60%.

5-[6-(8-Hydroxyquinolin-5-yl)-3-methylpyridazin-4-yl]-3-[(phenylamino)methyl]-1,3,4-oxadiazole-2(3H)-thione (**11b**): Color: Pale yellow. Yield: 59%. M.p.: 208-210 °C. FT-IR (KBr, ν, cm^{-1}): 3235 (NH), 2990 (CH-aliphatic), 1635 (C=N), 1360 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.85 (s, 3H, CH_3), 5.18 (s, 1H, NH), 5.45 (d, J = 7.4 Hz, 2H, CH_2), 6.95-8.75 (m, 12H, 10 Ar-H, CH-pyridazine, OH). Anal. calcd. for $C_{23}H_{18}N_6O_2S$: C, 62.43; H, 4.10; N, 18.99. Found: C, 62.75; H, 4.38; N, 19.36%.

5-[6-(8-Hydroxyquinolin-5-yl)-3-methylpyridazin-4-yl]-3-[(4-methoxyphenylamino)methyl]-1,3,4-oxadiazole-2(3H)-thione (**11c**): Color: Yellow. Yield: 64%. M.p.: 172-174 °C. FT-IR (KBr, ν, cm^{-1}): 3330 (NH), 2990 (CH-aliphatic), 1630 (C=N), 1377 (C=S), 1236 (C-O).



Scheme 3

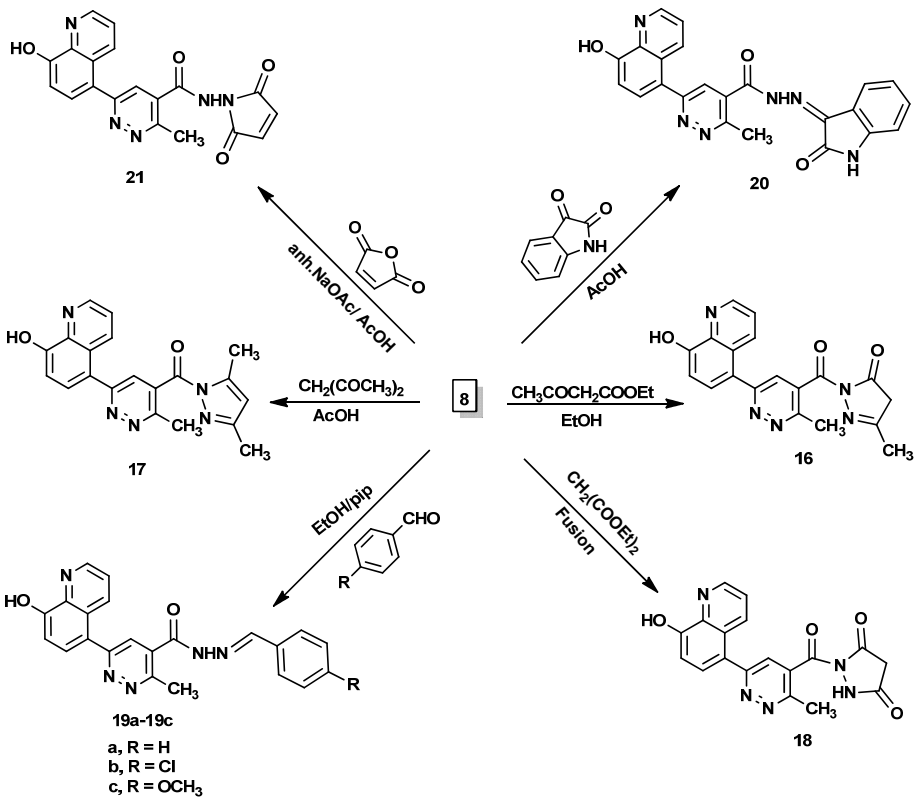
^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.95 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.30 (d, J = 7.4 Hz, 2H, CH_2), 5.85 (s, 1H, NH), 6.85-8.80 (m, 11H, 9 Ar-H, CH-pyridazine, OH). Anal. calcd. for C_{24} $H_{20}N_6O_3S$: C, 61.01; H, 4.27; N, 17.79. Found: C, 61.45; H, 4.63; N, 18.09%.

5-(6-(8-Hydroxyquinolin-5-yl)-3-methylpyridazin-4-yl)-3-((pyridin-2-ylamino)methyl)-1,3,4-oxadiazole-2(3H)-thione (**11d**): Color: Yellow. Yield: 81%. M.p.: 159-161 °C. FT-IR (KBr, ν, cm^{-1}): 3245 (NH), 2880 (CH-aliphatic), 1630 (C=N), 1360 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.05 (s, 3H, CH_3), 5.30 (s, 1H, NH), 5.55 (d, J = 7.4 Hz, 2H, CH_2), 6.95-8.90 (m, 11H, 9 Ar-H, CH-pyridazine, OH). Anal. calcd. for $C_{22}H_{17}N_7O_2S$: C, 59.58; H, 3.86; N, 22.11. Found: C, 59.92; H, 3.83; N, 22.45%.

3-(6-(8-Hydroxyquinolin-5-yl)-3-methylpyridazin-4-yl)-1-(morpholinomethyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (**15a**): Color: Yellow. Yield: 62%. M.p.: 197-199 °C. FT-IR (KBr, ν, cm^{-1}): 2995, 2890 (CH-aliphatic), 1620 C=N), 1340 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.78 (s, 3H, CH_3), 3.65 (t, J = 7.4 Hz, 4H, 2CH_2), 3.70 (t, J = 7.4 Hz, 4H, 2CH_2), 5.20 (s, 2H, CH_2), 7.05-8.85 (m, 12H, 10 Ar-H, CH-pyridazine, OH). Anal. calcd. for C_{27} $H_{25}N_7O_2S$: C, 63.39; H, 4.93; N, 19.16. Found: C, 63.59; H, 5.02; N, 19.44%.

3-(6-(8-Hydroxyquinolin-5-yl)-3-methylpyridazin-4-yl)-4-phenyl-1-((phenylamino)methyl)-1H-1,2,4-triazole-5(4H)-thione (**15b**): Color: Yellow. Yield: 55%. M.p.: 275-277 °C. FT-IR (KBr, ν, cm^{-1}): 3320 (NH), 2990, 2895 (CH-aliphatic), 1620 (C=N), 1330 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.80 (s, 3H, CH_3), 5.20 (s, 1H, NH), 5.60 (d, J = 7.4 Hz, 2H, CH_2), 6.90-8.80 (m, 17H, 15 Ar-H, CH-pyridazine, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 165.5, 159.4, 158.8, 157.2, 155.5, 154.3, 150.6, 148.1, 146.4, 144.7, 140.8, 139.5, 138.7, 136.4, 130.3, 128.2, 127.3, 126.5, 125.4, 124.8, 122.3, 117.5, 116.7, 114.8, 113.3, 112.1, -111.5, 71.6, 18.6. Anal. calcd. for C_{29} $H_{23}N_7OS$: C, 67.29; H, 4.48; N, 18.94. Found: C, 67.45; H, 4.81; N, 19.19%.

3-(6-(8-Hydroxyquinolin-5-yl)-3-methylpyridazin-4-yl)-1-(((4-methoxyphenyl)amino)methyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (**15c**): Color: Yellow. Yield: 71%. M.p.: 231-233 °C. FT-IR (KBr, ν, cm^{-1}): 3330 (NH), 2990, 2895 (CH-aliphatic), 1630 (C=N), 1330 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.90 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.95 (s, 1H, NH), 5.65 (d, J = 7.4 Hz, 2H, CH_2), 6.95-8.85 (m, 16H, 14 Ar-H, CH-pyridazine, OH). Anal. calcd. for C_{30} $H_{25}N_7O_2S$: C, 65.80; H, 4.60; N, 17.90. Found: C, 65.95; H, 4.71; N, 18.12%.



Scheme 4

3-(6-(8-Hydroxyquinolin-5-yl)-3-methylpyridazin-4-yl)-4-phenyl-1-((pyridin-2-ylamino)methyl)-1H-1,2,4-triazole-5(4H)-thione (**15d**): Color: Yellow. Yield: 78%. M.p.: 280-282 °C. FT-IR (KBr, ν, cm^{-1}): 3280 (NH), 2990, 3000 (CH-aliphatic), 1625 (C=N), 1345 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.85 (s, 3H, CH_3), 5.75 (s, 2H, CH_2), 6.80-8.80 (m, 16H, 14 Ar-H, CH-pyridazine, OH), 9.90 (s, 1H, NH). Anal. calcd. for $C_{28}H_{22}N_8OS$: C, 64.85; H, 4.28; N, 21.61. Found: C, 65.11; H, 4.43; N, 21.88%.

2.2.7. Synthesis of 2-(6-(8-hydroxyquinolin-5-yl)-3-methyl pyridazine-4-carbonyl)-N-phenylhydrazinecarbothioamide (12)

A mixture of hydrazide (**8**) (1.48 g, 5 mmol) and phenyl isothiocyanate (0.65 g, 5 mmol) in 30 mL of absolute ethanol were refluxed on a steam bath for 1 h. The resulting solid was filtered and recrystallized from the methanol to give compound **12** (Scheme 3). Color: Pale yellow. Yield: 72%. M.p.: 221-223 °C. FT-IR (KBr, ν, cm^{-1}): 3315, 3270, 3190 (3NH), 2987 (CH-aliphatic), 1674 (C=O), 1325 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.88 (s, 3H, CH_3), 6.85-8.80 (m, 12H, 10 Ar-H, CH-pyridazine, OH), 9.25 (S, 1H, NH), 9.85 (s, 1H, NH), 10.35 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 187.2, 166.1, 159.3, 153.3, 149.2, 148.7, 145.2, 138.7, 130.1, 129.1, 126.6, 125.6, 125.0, 124.9, 123.8, 120.3, 118.5, 115.3, 113.2, 112.4, 112.9, 18.5. Anal. calcd. for $C_{22}H_{18}N_6O_2S$: C, 61.38; H, 4.21; N, 19.52. Found: C, 61.70; H, 4.58; N, 19.88%.

2.2.8. Synthesis of 5-[6-(8-hydroxyquinolin-5-yl)-3-methyl pyridazin-4-yl]-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (13)

A suspension of thiosemicarbazide (**12**) (1.3 g, 3 mmol) in sodium hydroxide solution (5%, 25 mL) was heated under reflux for 1 h. The reaction mixture was allowed to cool and then adjusted to pH 6 with 10% hydrochloric acid. The precipitate formed was filtered, washed with water, dried, and recrystallized from methanol to give compound **13** (Scheme 3). Color: White. Yield: 66%. M.p.: 165-167 °C. FT-IR (KBr, ν, cm^{-1}): 3170 (NH), 1625 (C=N), 1395 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.69 (s, 3H, CH_3), 6.85-8.85 (m, 12H, 10 Ar-H, CH-pyridazine, OH), 13.67 (S, 1H, NH). Anal. calcd. for $C_{22}H_{16}N_6OS$: C, 64.06; H, 3.91; N, 20.38. Found: C, 64.38; H, 4.22; N, 20.70%.

2.2.9. Synthesis of 2-{[6-(8-hydroxyquinolin-5-yl)-3-methyl pyridazin-4-yl]carbonyl}-5-methyl-2,4-dihydro-3H-pyrazol-3-one (16)

Ethyl acetoacetate (0.39 g, 3 mmol) was added to a solution of the acid hydrazide (**8**) (0.59 g, 2 mmol) in absolute ethanol (15 mL), and the reaction mixture was heated under reflux for 10 h. Solvent was removed under reduced pressure and the remaining residue was recrystallized from aqueous ethanol to give compound **16** (Scheme 4).

2.2.10. Synthesis of (3,5-dimethyl-1H-pyrazol-1-yl)[6-(8-hydroxyquinolin-5-yl)3-methylpyridazin-4-yl]methanone (17)

To a solution of compound **8** (0.59 g, 2 mmol) in glacial acetic acid (15 mL), was added acetylacetone (0.2 g, 2 mmol). The reaction mixture was heated under reflux for 8 h, and then allowed to cool to room temperature. The solid product thus formed was filtered, thoroughly washed with cold ethanol, dried and recrystallized from ethanol to give compound **17** (Scheme 4). Color: Pale light. Yield: 70%. M.p.: 260-262 °C. FT-IR (KBr, ν, cm^{-1}): 2990 (CH-aliphatic), 1700 (C=O), 1635 (C=N). ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 2.35 (s, 3H, CH_3), 2.40 (s, 3H,

CH_3), 2.75 (s, 3H, CH_3), 6.15 (s, 1H, CH-pyrazole), 7.05-8.80 (m, 7H, 5 Ar-H, CH-pyridazine, OH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.2, 159.2, 150.7, 148.3, 140.5, 137.6, 134.8, 130.5, 129.0, 128.4, 125.1, 124.3, 123.6, 122.9, 115.8, 113.7, 112.5, 102.9, 18.2, 17.8, 11.7. Anal. calcd. for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49. Found: C, 67.01; H, 5.10; N, 19.73%.

2.2.11. Synthesis of 1-(6-(8-hydroxyquinolin-5-yl)-3-methyl pyridazine-4-carbonyl)pyrazolidine-3,5-dione (18)

A mixture of the starting compound **8** (0.59 g, 2 mmol) and diethyl malonate (0.48 g, 3 mmol) was heated at 200 °C in an oil bath for 2 h. After being cooled to room temperature, the solidified product was treated with cold diethyl ether, filtered, washed with diethyl ether, dried and recrystallized from aqueous ethanol to give compound **18** (Scheme 4). Color: Pale light. Yield: 48%. M.p.: 241-243 °C. FT-IR (KBr, ν, cm^{-1}): 3250 (NH), 1720 (C=O), 1700 (C=O), 1675 (C=O), 1620 (C=N). ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 2.79 (s, 3H, CH_3), 3.50 (s, 2H, CH_2), 7.05-8.80 (m, 7H, 5 Ar-H, CH- pyridazine, OH), 10.35 (s, 1H, NH). Anal. calcd. for $C_{18}H_{13}N_5O_4$: C, 59.50; H, 3.61; N, 19.28. Found: C, 59.82; H, 3.85; N, 19.43%.

2.2.12. General procedure for the synthesis of compounds (19a-c)

A mixture of compound **8** (10 mmol) and the appropriate aromatic aldehyde (10 mmol) was stirred under reflux in ethanol (30 mL) in the presence of a few drops of piperidine for 5 h. The reaction mixture was allowed to cool to room temperature, poured into water, whereby a solid formed that was filtered off and crystallized from an appropriate solvent (Scheme 4).

6-(8-Hydroxyquinolin-5-yl)-N'-[phenylmethylidene]-3-methyl pyridazine-4-carbohydrazide (**19a**): Color: Pale white from acetic acid. Yield: 66%. M.p.: 255-257 °C. FT-IR (KBr, ν, cm^{-1}): 3425 (NH), 1675 (C=O), 1625 (C=N). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.85 (s, 3H, CH_3), 6.90-8.70 (m, 12H, 10 Ar-H, CH-pyridazine, OH), 8.95 (s, 1H, CH-azomethine), 11.10 (s, 1H, NH D_2O-exchangeable). Anal. calcd. for $C_{22}H_{17}N_5O_2$: C, 68.92; H, 4.47; N, 18.27. Found: C, 69.16; H, 4.63; N, 18.41%.

6-(8-Hydroxyquinolin-5-yl)-N'-[4-chlorophenylmethylidene]-3-methylpyridazine-4-carbohydrazide (**19b**): Color: Pale light yellow from dioxane. Yield: 60%. M.p.: 266-268 °C. FT-IR (KBr, ν, cm^{-1}): 3320 (NH), 1685 (C=O), 1640 (C=N). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.77 (s, 3H, CH_3), 6.95-8.65 (m, 11H, 9 Ar-H, CH-pyridazine, OH), 9.15 (s, 1H, CH azomethene), 11.25 (s, 1H, NH D_2O-exchangeable). MS (EI, *m/z* (%)): 417.84 ($M^{+\cdot}$, 61). Anal. calcd. for $C_{22}H_{16}ClN_5O_2$: C, 63.24; H, 3.86; N, 16.76. Found: C, 63.58; H, 4.09; N, 18.98%.

6-(8-Hydroxyquinolin-5-yl)-N'-[4-methoxyphenyl methylide ne]-3-methyl pyridazine-4-carbohydrazide (**19c**): Color: Pale white from dioxane. Yield: 59%. M.p.: 310-312 °C. FT-IR (KBr, ν, cm^{-1}): 3330 (NH), 1690 (C=O), 1630 (C=N), 1230 (C-O). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.82 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 7.01-8.77 (m, 11H, 9 Ar-H, CH-pyridazine, OH), 9.44 (s, 1H, CH-azomethene), 10.65 (s, 1H, NH D_2O-exchangeable). Anal. calcd. for $C_{23}H_{19}N_5O_3$: C, 66.82; H, 4.63; N, 16.94. Found: C, 67.03; H, 4.99; N, 17.11%.

2.2.13. Synthesis of 6-(8-hydroxyquinolin-5-yl)-3-methyl-N'-[2-oxo-1,2-dihydro-3H-indol-3-ylidene]pyridazine-4-carbo hydrazide (20)

A solution of the acid hydrazide (**8**) (0.59 g, 2 mmol) and isatin (0.29 g, 2 mmol) in glacial acetic acid (10 mL) was heated under reflux for 2 h, during which a deep yellow solid was partially crystallized out. The solid separated upon cooling was filtered, washed with cold ethanol and recrystallized from ethanol to give compound **20** (Scheme 4). Color: Yellow. Yield: 68%. M.p.: 320-322 °C. FT-IR (KBr, ν, cm^{-1}): 3310, 3225 (2NH), 1675 (CO), 1660 (CO), 1630 (C=N). ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 2.65 (s, 3H, CH_3), 6.85-8.80 (m, 11H, 9 Ar-H, CH-pyridazine, OH), 9.15 (s, 1H, NH), 9.33 (s, 1H, NH). Anal. calcd. for $C_{23}H_{16}N_6O_3$: C, 65.09; H, 3.80; N, 19.80. Found:C, 65.26; H, 4.07; N, 19.95%.

2.2.14. Synthesis of N-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-6-(8-hydroxyquinolin-5-yl)-3-methylpyridazine-4-carboxamide (21)

A mixture of the acid hydrazide (**8**) (0.59 g, 2 mmol), maleic anhydride (0.2 g, 2 mmol) and anhydrous sodium acetate (0.16 g, 2.5 mmol) in glacial acetic acid (15 mL) was heated under reflux for 10 h. The reaction mixture was concentrated in vacuum to half its volume and allowed to cool. The precipitated solid product was filtered, washed with cold ethanol, dried and recrystallized from acetic acid to give compound **21** (Scheme 4). Color: Yellow. Yield: 55%. M.p.: 173-175 °C. FT-IR (KBr, ν, cm^{-1}): 3330 (NH), 1705, 1680, 1665 (3C=O), 1620 (C=N). ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 2.70 (s, 3H, CH_3), 6.40-6.48 (m, 2H, olefinic-CH), 7.15-8.80 (m, 7H, 5 Ar-H, CH-pyridazine, OH), 9.05 (s, 1H, NH). Anal. calcd. for $C_{19}H_{13}N_5O_4$: C, 60.80; H, 3.49; N, 18.66. Found: C, 61.11; H, 3.87; N, 18.91%.

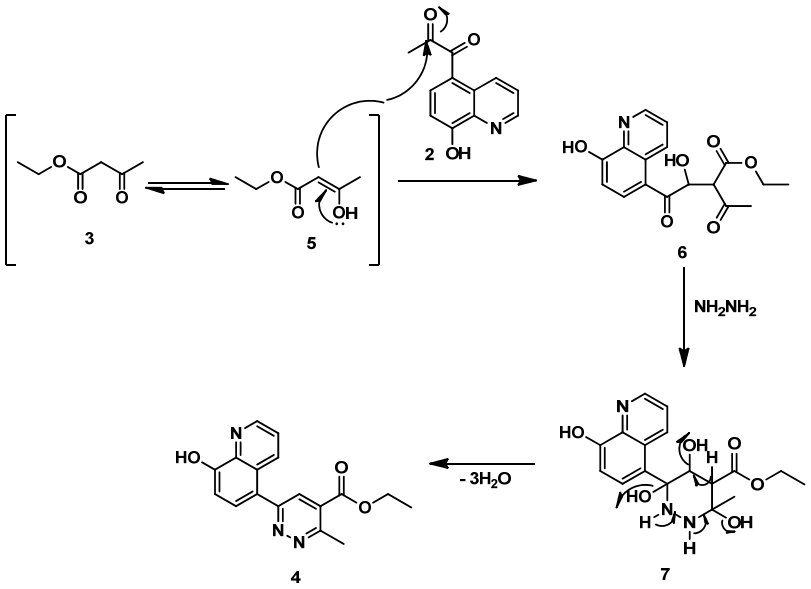
2.3. Antimicrobial assay

The antimicrobial activity of 13 selected compounds was evaluated against four bacterial and four fungal strains. All microbial strains were kindly provided by the Assiut University Mycological Centre (AUMC). These strains are common contaminants of the environment in Egypt and some of which are involved human and animal diseases (*Trichophyton rubrum*, *Candida albicans*, *Geotrichum candidum*, *Scopulariopsis brevicaulis*, *Aspergillus flavus*), plant diseases (*Fusarium oxysporum*) or frequently reported from contaminated soil, water and food substances (*Escherichia coli*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Micrococcus luteus*) To prepare inocula for bioassay, bacterial strains were individually cultured for 48 h in 100 mL conical flasks containing 30 mL nutrient broth medium. Fungi were grown for 7 days in 100 mL conicals containing 30 mL Sabouraud's dextrose broth. Bioassay was done in 10 cm sterile plastic Petri plates in which microbial suspension (1 mL/plate) and 15 mL of appropriate agar medium (15 mL/plate) were poured. Nutrient agar and Sabouraud's dextrose agar were respectively used for bacteria and fungi. After solidification of the media, 5 mm diameter cavities were cut in the solidified agar (4 cavities/plate) using sterile cork borer. The tested compounds were dissolved in dimethyl sulfuxide (DMSO) at 2%*w:v* (20 mg/mL), pipetted and poured in the cavities (20 µL/cavity). Cultures were then incubated at 28 °C for 48 h in case of bacteria and up to 7 days in case of fungi. Results were read as the diameter (in mm) of inhibition zone around cavities. To determine the minimum inhibitory concentrations (MICs), several concentrations in DMSO of the compounds under testing that gave positive results, have been prepared in descending manner down to a concentration of 0.08 mg/mL. The solutions of different compounds were similarly assayed as mentioned before and the least concentration (below which no activity was observed) was recorded as the MIC.

3. Results and discussion

3.1. Chemistry

The starting compound (8-hydroxyquinolin-5-yl)(oxo) acetaldehyde (**2**) was prepared from the well-known 5-acetyl-8-hydroxyquinoline (**1**) *via* oxidation with selenium dioxide in a mixture of dioxane and water according to the reported procedure for the synthesis of aryglyoxal [25].



Scheme 5

Multi-compo-nent reaction of compound **2**, ethyl acetoacetate **3** and an excess amount of hydrazine hydrate in water at room temperature afforded ethyl 6-(8-hydroxy quinolin-5-yl)-3-methyl pyridazin-4-carboxylate (**4**) (Scheme 1). The structure of synthesized compound **4** was established by ^{1}H NMR, ^{13}C NMR, IR, MS spectroscopes in combination with elemental analyses. In the ^{1}H NMR spectrum of compound **4**, the CH-pyridazine ring is much deshielded and resonating at low field and appear at δ = 8.3 ppm. The mass spectrum of compound **4** showed its correct parent ion peak at *m/z* 309.11 (M^+, 67%) (Scheme 1).

The suggested mechanism involves the attack of enolate structure **5** onto the glyoxal **2**, then *in situ* generated ethyl 2-acetyl-3-hydroxy-4-(8-hydroxyquinolin-5-yl)-4-oxobutanoate (**6**), in the presence of NH_2NH_2, converts to compound **7** which then loses three H_2O molecules to afford the target product **4** (Scheme 5).

Treatment of compound **4** with hydrazine hydrate leads to the formation of the corresponding carbohydrazide **8**. Because of the broad utility of heterocyclization carbohydrazides as intermediates for the synthesis of several systems containing oxadiazole and triazole nuclei [26], 6-(8-hydroxyquinolin-5-yl)-3-methylpyridazine-4-carbohydrazide (**8**) was used in prepa-ring a new series of heterocyclic compounds. The reaction of compound **8** with carbon disulphide in the presence of ethanol solution of potassium hydroxide gave the mercaptooxadiazole derivative **9**. The later was easily converted into the corres-ponding s-alkylated products **10a** and **10b** upon treatment with ethyl iodide and/or benzyl bromide, respectively. The interaction of compound **9** with formaldehyde and some different primary and secondary amines afforded the corres-ponding Mannich bases **11a-d**. The IR spectrum of compound **9** revealed the characteristic band at 1437 cm^{-1} corresponding to the thione (C=S) function. The ^{1}H NMR spectrum of compound **11a** (R = Morpholine) displayed a singlet signal due to CH_2 protons at 5.12 ppm. Whereas, compounds **11b-d** (R = Primary aromatic and heterocyclic amine) displayed a doublet signals ranged at 5.45-5.55 ppm corresponding to CH_2 protons (Scheme 2).

On the other hand, compound **8** when allowed to react with phenyl isothiocyanate in ethanol, it gave the thiosemicarbazide derivative (**12**). Heating of compound **12** in an aqueous sodium hydroxide solution (5%) yielded 5-[6-(8-hydroxyquinolin-5-yl)-3-methylpyridazin-4-yl]-4-phenyl-2,4-dihydro-3H-1,2,4-tri azole-3-thione (**13**). The later was converted into the corres-ponding s-alkylated triazolo products **14a** and **14b** upon treatment with ethyl iodide and /or benzyl bromide in ethanol in the presence of anhydrous sodium acetate. Mannich bases (**15a-d**) were obtained from compound **13** using the former procedure for producing compounds **11a-d** (Scheme 3).

The synthesis of the target compounds **16-21** is depicted in Scheme 4, in which the starting compound 6-(8-hydroxy-quinolin-5-yl)-3-methylpyridazine-4-carbohydrazide (**8**) was allowed to react with ethyl acetoacetate in ethanol to produce the pyrazolinone derivative (**16**). Condensing of compound **8** with acetyl acetone in glacial acetic acid gave rise to the corresponding (3,5-dimethyl-1*H*-pyrazol-1-yl)[6-(8-hydroxy quinolin-5-yl)3-methylpyridazin-4-yl]methanone (**17**).

Whereas, heating the same acid hydrazide **8** with diethyl malonate at 200 °C afforded the targeted 1-(6-(8-hydroxy quinolin-5-yl)-3-methylpyridazine-4-carbonyl) pyrazolidine-3,5-dione (**18**). The azomethine derivatives **19a-19c** and **20** were obtained upon treatment of compound **8** with aromatic aldehydes in refluxing ethanol in presence of catalytic amount of piperidine and/or condensing of the acid hydrazide **5** with isatin in glacial acetic acid, respectively. On the other hand, (8-hydroxyquinolin-5-yl)pyridazine scaffold was allowed to link to a nitrogenous heterocyclic ring system through a carboxamide functionality. Thus, compound **8** when reacted with maleic anhydride in glacial acetic acid in the presence of anhydrous sodium acetate, it produced *N*-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-6-(8-hydroxyquinolin-5-yl)-3-methylpyridazine-4-carboxamide (**21**) (Scheme 4).

3.2. Biological studies

3.2.1. In vitro antibacterial activity

Using agar well-diffusion method [27], thirteen selected derivatives (**4**, **8**, **9**, **10a**, **11b**, **11c**, **12**, **13**, **14a**, **14b**, **15b**, **15c** and **19b**) were screened against *Staphylococcus aureus* (AUMC B.54) and *Bacillus cereus* (AUMC B.52) as Gram positive bacteria and *Escherichia coli* (AUMC B.53) and *Pseudomonas aeruginosa* (AUMC B.73) as Gram negative bacteria using Chloramphenicol as control (in a concentration of 20 mg/mL) (Table 1).

Table 1. Antibacterial activity of some 5-pyridazinyl-8-quinolinol derivatives (20 mg/mL).

Compound	Diameter of growth of inhibition zone (mm) *			
	Staphylococcus aureus AUMC.B-54	*Bacillus cereus* AUMC.B-52	*Escherichia coli* AUMC.B-53	*Pseudomonas aeruginosa* AUMC.B-73
4	-	6	8	-
8	20	24	25	-
9	-	-	-	-
10a	16	30	33	-
11b	-	5	-	-
11c	-	-	26	30
12	-	-	-	-
13	24	34	-	-
14a	-	-	7	-
14b	26	25	33	23
15b	18	29	26	23
15c	22	32	-	-
19b	-	5	-	7
Chloramphenicol	18	23	21	19

* The amount added in each pore is 50 µL, AUMC = Assiut University Mycological Center.

Table 2. Antibacterial activity data.

Compound	Diameter of growth of inhibition zone (mm)* MIC (mg/mL)			
	Staphylococcus aureus AUMC.B-54	*Bacillus cereus* AUMC.B-52	*Escherichia coli* AUMC.B-53	*Pseudomonas aeruginosa AUMC.B-73*
8	18 (2.5)	18 (2.5)	12 (1.25)	-
10a	10 (5)	16 (5)	10 (0.15)	-
11c	-	-	10(1.25)	9 (0.3)
13	9 (0.3)	11(2.5)	-	-
14b	13 (0.3)	8 (1.25)	11 (1.25)	9 (0.6)
15b	8(0.25)	10 (0.3)	8 (2.5)	10 (0.3)
15c	13 (5)	10 (0.3)	-	-
Chloramphenicol	10 (0.08)	12 (1.25)	10 (0.07)	12 (0.3)

The results were recorded for each tested compound as average diameter of zone of inhibition of bacterial growth in millimeters. Minimum inhibitory concentration (MIC) measurements were performed using agar well diffusion method (Table 2). MIC of those compounds was determined which were showing activity in primary screening. The results of preliminary antibacterial testing of selected compounds are shown in Table 1 revealed that only seven compounds **8**, **10a**, **11c**, **13**, **14b**, **15b** and **15c** possessed moderate to excellent antibacterial activity against both Gram-positive and Gram-negative bacteria. It was found that conversion of 4-ethoxy group in compound **4** with carbohydrazide one compound **8**, contribute to a good potency towards Gram-positive bacteria *Staphylococcus aureus*, *Bacillus cereus* and against Gram-negative bacteria *Escherichia coli* only (zones of inhibition range from 20 to 25 mm) and with minimum inhibitory concentrations (MIC) range between 2.5 and 1.25 mg/mL. Construction of an thiooxadiazole ring compound **9**, did not display any antibacterial activity. Whereas, the ethyl thiooxadiazole derivative compound **10a**, exhibited a remarkable antibacterial activity against both Gram-positive and Gram-negative bacteria except towards *Pseudomonas aeruginosa* with 0.15 mg/mL of MIC against *Escherichia coli*. However, the substituted-3-aminooxadiazole derivative with an electron donating methoxy group (**11c**) was more potent against Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) zones of inhibition range from 26 to 30 mm, while the non-substituted one compound **11b** was inactive. Construction of an thiotriazole ring compound **13** displayed a remarkable activity against Gram-positive bacteria *Staphylococcus aureus*, *Bacillus cereus* only. The ethyl triazolethiol derivative (**14a**) did not show any activity. Whereas, the benzyl one (**14b**) is more potent against both Gram-positive and Gram-negative bacteria with 0.3 mg/mL of MIC against *Staphylococcus aureus*. Among the Mannich bases **15b** and **15c**, compound **15b** with non-substituted phenyl group showed highest activity against both Gram-positive and Gram-negative bacteria with minimum inhibitory concentrations (MIC) range between 0.25 and 2.5 mg/mL. Whereas, the derivative **15c** with an electron withdrawing group exhibited only a good activity against Gram-positive bacteria *Staphylococcus aureus*, *Bacillus cereus* only. It should be noted that Schiff bases with an electron withdrawing chlorine atom compound **19b** did not exihibit any antibacterial activity towards the tested bacteria (Table 2).

3.2.2. In vitro antifungal activity

The same thirteen selected derivatives compounds (**4**, **8**, **9**, **10a**, **11b**, **11c**, **12**, **13**, **14a**, **14b**, **15b**, **15c** and **19b**) were screened for their antifungal activities against four fungal strains; *Candida albicans* (AUMC No.418), *Trichophyton rubrum* (AUMC No. 1804), *Aspergillus flavus* (AUMC No. 1276) and *Fusarium oxysporum* (AUMC No. 5119) using Clotrimazole as control (in a concentration of 20 mg/mL). The results are listed in Table 3. It has been revealed that mainly five compounds **8**, **9**, **11c**, **14b** and **15c** showed considerable antifungal activity against the tested fungi species. However, the 4-carbo hydrazide derivative (**8**), 5-[6-(8-hydroxyquinolin-5-yl)-3-methyl pyridazin-4-yl]-3-[(4-methoxyphenylamino) methyl]-1,3,4-oxadiazole-2(3*H*)-thione derivative **11c** and its thio-triazole analogue **14b** exhibited good activity against *Candida albicans*, *Aspergillus flavus* and *Fusarium oxysporum* only in comparison with the standard drug and did not exhibit antifungal activity against *Trichophyton rubrum* and gave a promising MIC, 0.08 mg/mL against *Fusarium oxysporum*. Also, the thiooxadiazole derivative **9** showed a moderate activity against all the tested fungi species except for *Aspergillus flavus* (MIC, 0.08 mg/mL) against *F. oxysporum* (Table 3). Finally, the thio triazolo derivative **15c** gave potent activity against *Aspergillus flavus* and *Fusarium oxysporum* only and did not show activity against *Candida albicans* and *Trichophyton rubrum* (MIC, 0.15 mg/mL) against *Aspergillus flavus.*

4. Conclusion

In summary, we developed an efficient synthesis of ethyl 6-(8-hydroxyquinolin-5-yl)-3-methylpyridazin-4-carboxylate (**4**) *via* one-pot three component reaction of (8-hydroxyquinolin-5-yl)(oxo)acetaldehyde (**2**), ethyl acetoacetate and hydrazine hydrate in aqueous media.

Table 3. Antifungal activity of some 5-pyridazinyl-8-quinolinol derivatives (20 mg/mL).

Compound	Diameter of growth of inhibition zone (mm)*			
	Candida albicans AUMC.418	*Trichophyton rubrum AUMC.1804*	*Aspergillus flavus AUMC.1276*	*Fusarium oxysporum AUMC.5119*
4	-	-	6	-
8	31	-	33	18
9	29	39	-	16
10a	-	-	-	-
11b	-	-	-	-
11c	22	-	37	16
12	-	-	-	-
13	-	-	-	-
14a	-	-	-	-
14b	19	-	31	20
15b	-	-	-	-
15c	-	-	33	26
19b	-	-	-	8
Clotrimazole	24	36	45	22

* The amount added in each pore is 50 µL, AUMC = Assiut University Mycological Center.

Table 4. Antifungal activity data *.

Compound	Diameter of growth of inhibition zone (mm), (MICs (mg/L))			
	Candida albicans AUMC.418	*Trichophyton rubrum AUMC.1804*	*Aspergillus flavus AUMC.1276*	*Fusarium oxysporum AUMC.5119*
8	10 (0.3)	-	8 (0.3)	9 (1.25)
9	11(1.25)	18(5)	-	8(0.08)
11c	10 (1.25)	-	9 (0.6)	8(0.08)
14b	12 (2.5)	-	11 (0.6)	9(0.08)
15c	-	-	11 (0.15)	10 (2.5)
Clotrimazole	12 (0.08)	25 (0.08)	15 (0.15)	14 (0.15)

* AUMC = Assiut University Mycological Center.

Moreover, novel heterocycles such as oxadiazoles, triazoles, Schiff bases, pyrazoles and fused pyridazine were synthesized, characterized and evaluated as antimicrobial agents. The results prompted us for further studies to exploit the synthetic potential as well as the biological activities of these compounds and other related in progress.

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