SYNTHESIS OF NEW 4(3H)-QUINAZOLINONE
DERIVATIVES OF POTENTIAL ANTIMICROBIAL
ACTIVITY

Awwad A. Radwan\textsuperscript{1*} and Salah G. Ali\textsuperscript{2}

\textsuperscript{1}Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Assiut University, Assiut-71527, Egypt
\textsuperscript{2}Department of Botany and Microbiology, Faculty of Science, Al-Azhar University, 71524 Assiut, Egypt

A new series of quinazoline-4(3H)-one derivatives containing hydrazone, thiosemicarbazide, pyrazole moiety and 1,2,4-
triazolo[4,3-a]quinazolin-5-(4H)-one derivatives, were prepared in order to study the effect of such combinations on the expected antimicrobial activity. Synthesis of target compounds (3-8) has been achieved through an interaction of the starting $2\text{a}$ or $2\text{b}$ with different alkyl or aryl isothiocyanate. Condensation of $2\text{a}$ or $2\text{b}$ with various aromatic aldehydes or ketones afforded the corresponding hydrazones $9$-$12$. 1-(4-Pyridinyl)-1,2-dihydro-4-
phenyl(allyl)-1,2,4-triazolo[4,3-a]quinazolin-5-(4H)-one derivatives

Received in 6/10/2007, Received in revised form in 25/12/2007 & Accepted in 27/12/2007

*Correspondence author e-mail address: dhna_2001@hotmail.com
tives 13, 14 have been synthesized through reflux of compound 9 or 10 in glacial acetic acid. On the other hand, 1-(3-substituted-3,4-dihydro-4-quinazolinon-2-yl)-3-(4-chlorophenyl) pyrazole-4-carbaldehyde 15 or 16 has also been synthesized through interaction of compounds 11 or 12 with Vilsmeier-Haack reagent.

The structures of the new compounds were assigned by spectral and elemental methods of analyses. The synthesized compounds were tested for their in vitro antibacterial and antifungal activities. The tested compounds showed moderate antibacterial activity and weak or no antifungal activity.

INTRODUCTION

Quinazolinone derivatives are important compounds in chemistry and pharmacology. They have drawn much attention due to their broad range of pharmacological properties, which include anticancer, anti-inflammatory, anticonvulsant and diuretic activities. Meanwhile, the quinazoline nucleus, as isostere for naphthalene, offers a convenient starting point in the search for new therapeutic agents, since several of its derivatives have been reported to possess antifungal activity as selective DHF-reductase inhibitors.

The scientific literature also states that the antiviral and antibacterial activities of thiourea derivatives are due to the presence of the \(-\text{NH-C(=S)-NH}\) function in the molecule and the changes in this activity depend on the nature of its substituents. These observations prompted us to synthesize some new thiosemicarbazides, hydrazones and triazoloquinazolinones derived from 2-hydrazino-3-phenyl-4(3H)-quinazolinone 2a and 2-hydrazino-3-allyl-4(3H)-quinazolinone 2b to investigate their antibacterial and antifungal activities.

EXPERIMENTAL

Materials and equipments

Melting points were uncorrected and determined on an electrothermal melting point apparatus [Stuart Scientific, UK]. Precoated silica gel plates (kiesel gel 0.25 mm, 60G F254, Merck) were used for thin layer chromatography. Developing solvent system of chloroform/methanol (10:3) was used and the spots were detected by ultraviolet light. IR spectra (KBr disc) were recorded on IR-470 Shimadzu spectrometer, Japan. \(^1\)H-NMR Spectra were scanned on a Varian EM-360 L NMR spectrometer (60 MHz) USA at Faculty of Pharmacy Assiut University. Chemical shifts are expressed in \(\delta\)-values (ppm) relative to TMS as an internal standard, using either CDCl\(_3\) or DMSO-d\(_6\) as a solvent. Elemental analyses were performed at the Department of Chemistry, Faculty of Science, Assiut.
University, Assiut, and at micro analytical center, Faculty of Science, Cairo University, Cairo, Egypt. Antimicrobial activity was performed at Department of Botany and Microbiology, Faculty of Science, Al-Azhar University, Assiut, Egypt.

Preparation of 3-substituted-2-substituted-thiocarbamoylhydrazino-3,4-dihydro-4-quinazolinones 3-8

A hot solution of 2a or 2b (0.01 mol) in abs. ethanol (25 mL) was treated with the equimolar amount of substituted isothiocyanate (0.01 mol). The clear solution was allowed to cool to room temperature while stirring. The product started to deposit after 30 min. Stirring was continued for 3 hrs and the separated product were filtered, washed with ethanol, dried and crystallized from methanol; IR, ν cm⁻¹ (KBr): 3450-3230 (NH), 1683-1645 (C=O), 1646-1615 (C=N), 1600-1593 (C=C), 1531-1522, 1339-1329, 1077-1062, 896-812 (NCS I, mixed vibration bands); elemental analysis data are listed in Table 1 while ¹H-NMR data are presented in Table 2.

Table 1: Physicochemical data of the newly synthesized derivatives 3-8.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>R'</th>
<th>Yield</th>
<th>Formula</th>
<th>M.p. °C</th>
<th>Elemental analysis (Calc/found)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>C₂H₅</td>
<td>90</td>
<td>C₁₃H₂₁N₄O₅</td>
<td>136-8</td>
<td>60.16</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>H₂C==C—CH₂</td>
<td>85</td>
<td>C₁₃H₂₁N₄O₅</td>
<td>144-6</td>
<td>61.52</td>
</tr>
<tr>
<td>5</td>
<td>allyl</td>
<td>H₂C==C—CH₂</td>
<td>70</td>
<td>C₁₃H₁₉N₄O₅</td>
<td>150-2</td>
<td>57.12</td>
</tr>
<tr>
<td>6</td>
<td>allyl</td>
<td>C₆H₅</td>
<td>82</td>
<td>C₁₃H₂₁N₄O₅</td>
<td>164-6</td>
<td>61.52</td>
</tr>
<tr>
<td>7</td>
<td>allyl</td>
<td>p-CH₃-C₆H₅</td>
<td>80</td>
<td>C₁₃H₂₁N₄O₅</td>
<td>156-8</td>
<td>62.44</td>
</tr>
<tr>
<td>8</td>
<td>allyl</td>
<td>m-CH₃-C₆H₅</td>
<td>74</td>
<td>C₁₃H₂₁N₄O₅</td>
<td>150-2</td>
<td>62.44</td>
</tr>
</tbody>
</table>
Table 2: $^1$H NMR data (CDCl$_3$) (60 MHz) of 3-substituted-2-substituted-thiocarbamoylhydrazino-3,4-dihydro-4-quinazolinone 3-8.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>$R'$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Ph</td>
<td>$C_2H_5$</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>$H_2C\equiv C\equiv CH_2$</td>
</tr>
<tr>
<td>5</td>
<td>allyl</td>
<td>$H_2C\equiv C\equiv CH_2$</td>
</tr>
<tr>
<td>6</td>
<td>allyl</td>
<td>$C_6H_5$</td>
</tr>
<tr>
<td>7</td>
<td>allyl</td>
<td>$p-CH_3-C_6H_5$</td>
</tr>
<tr>
<td>8</td>
<td>allyl</td>
<td>$m-CH_3-C_6H_5$</td>
</tr>
</tbody>
</table>

Table continued...
Synthesis of the hydrazones 9-12

A solution of compound 2a or 2b (0.01 mol) and concentrated acetic acid (1 mL) in absolute ethanol (25 mL) was treated with the equimolar amount of the appropriate aldehyde or acetophenone and heated under reflux for 2 h. The separated product was filtered, washed with ethanol, dried and crystallized from dioxane-water; IR, ν cm⁻¹ (KBr): 3202-3118 (NH), 1673-1677 (C=O), 1602-1609 (hydrazone C=N), 1548-1554 (pyrimidine C=N); MS: m/z (rel. abund. %): for compound 9 M⁺ at 341 (30.6), 262 (96.3), 235 (29.2), 220 (13.1), 119 (28.0), 76 (100). MS: m/z (rel. abund. %): for compound 11 M⁺ at 388 (13.4), M⁺+2 at 390 (4.0), 373 (20.8), 276 (10.1), 235 (16.1), 138 (14.6), 118 (13.4), 102 (45.3), 77 (83.1), 76 (100). Elemental analysis data are listed in Table 3 while ¹H-NMR data in Table 4.

Synthesis of 1-(4-pyridinyl)-1,2-dihydro-4-substituted-[1,2,4]triazolo[4,3-a]quinazolin-5-(4H)-one (13, 14)

A solution of compound 9 or 10 (0.01 mol) in gl. acetic acid (6 ml) was heated under reflux for 8 hr. The reaction mixture was allowed to cool to room temperature, and poured onto ice-cold water. The separated product was filtered, washed with water, dried and crystallized from DMF-water. Yield 85% (4.7 g) of 13 or 80% (4.17 g) of 14.

1-(4-pyridinyl)-1,2-dihydro-4-phenyl[1,2,4]triazolo[4,3-a]quinazolin-5-(4H)-one (13)

Yellowish crystals, m.p. 328-30°. IR, ν cm⁻¹ (KBr): 1696 (C=O), 1616 (C=N), 1595 (C=C); ¹H-NMR (DMSO-d₆): δ 7.6-8.5 (m, 11H, NH, N-Ph-Hs, Ar-Hs at C-1, C-6, C-7, C-8, C-9), 8.7 (d, 2H, pyridine C-3-H and C-5-H), 9.1 (d, 2H, pyridine C-2-H and C-6-H). MS: m/z (rel. abund. %): M⁺ at 341 (2.6), 338 (100), 76 (75.1). Anal. Calc. for C₂₀H₁₅N₃O (M.Wt 341.37): C, 70.37; H, 4.43; N, 21.25.

1-(4-pyridinyl)-1,2-dihydro-4-Allyl-[1,2,4]triazolo[4,3-a]quinazolin-5-(4H)-one 14

Orange crystals, m.p. 126-8°. IR, ν cm⁻¹ (KBr): 1681 (C=O), 1602 (C=N), 1538 (C=C); ¹H-NMR (DMSO-d₆): δ 4.5 (d, 2H, -CH₂-CH=CH₂), 5.2 (d, 2H, -CH=CH₂), 5.4-5.9 (m, 1H, -CH=CH₂), 7.3-8.4 (m, 6H, NH, Ar-Hvs at C-1, C-6, C-7, C-8, C-9), 8.4-8.8 (d, 2H, pyridine C-3-H and C-5-H), 9.2-9.7 (d, 2H, pyridine C-2-H and C-6-H). MS: m/z (rel. abund. %): M⁺ at 305 (0.8), 290 (1.6), 232 (41.0), 190 (12.1), 161 (11.9), 144 (44.9), 118 (16.6), 106 (100), 90 (71.2), 76 (37.4). Anal. Calc. for C₁₇H₁₅N₃O (M.Wt 305.33): C, 66.87; H, 4.95; N, 22.94. Found: C, 67.11; H, 4.80; N, 22.98.
Table 3: Physicochemical data of the newly synthesized derivatives 9-12.

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Yield %</th>
<th>Formula</th>
<th>M.p. °C</th>
<th>Elemental analysis (Calc/found)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>H</td>
<td>4'-pyridinyl</td>
<td>85</td>
<td>C₂H₂N₂O (341.37)</td>
<td>70.37</td>
<td>4.43</td>
</tr>
<tr>
<td>10</td>
<td>Allyl</td>
<td>H</td>
<td>4'-pyridinyl</td>
<td>81</td>
<td>C₁H₂N₂O (305.33)</td>
<td>66.87</td>
<td>4.95</td>
</tr>
<tr>
<td>11</td>
<td>Ph</td>
<td>CH₃</td>
<td>4'-Cl-phenyl</td>
<td>80</td>
<td>C₂H₁₁ClN₂O (388.85)</td>
<td>67.95</td>
<td>4.41</td>
</tr>
<tr>
<td>12</td>
<td>Allyl</td>
<td>CH₃</td>
<td>4'-Cl-phenyl</td>
<td>76</td>
<td>C₁₀H₁₁ClN₂O (352.82)</td>
<td>64.68</td>
<td>4.86</td>
</tr>
</tbody>
</table>

Table 4: ¹H NMR data (CDCl₃ / DMSO-d₆) (60 MHz) hydrazone derivatives 9-12.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9*</td>
<td>Ph</td>
<td>H</td>
<td>4'-pyridinyl</td>
<td>7.1-8.9 (m, 12H, quinazolinone Ar-Hs, N=CH pyridinyl C-3 and C-5-Hs), 9.3 (d, 2H, pyridinyl C-2 and C-6-Hs), 11.6 (br.s., 1H, NH).</td>
</tr>
<tr>
<td>10</td>
<td>Allyl</td>
<td>H</td>
<td>4'-pyridinyl</td>
<td>5.2 (d, 2H, -CH₂-CH=CH₂), 5.7 (d, 2H, -CH₂-CH=CH₂), 6.1-6.8 (m, 1H, -CH₂=CH=CH₂), 7.5-8.4 (m, 4H, quinazolinone Ar-Hs), 8.8 (d, 2H, pyridine C-3-H and C-5-H), 9.0 (s, 1H, -N=CH), 9.3 (d, 2H, pyridine C-2-H and C-6-H), 10 (br.s., 1H, NH).</td>
</tr>
<tr>
<td>11</td>
<td>Ph</td>
<td>CH₃</td>
<td>4'-Cl-phenyl</td>
<td>2.3 (s, 3H, CH₃), 7.5-8.9 (m, 13H, Ar-Hs), 10.1 (br.s., 1H, NH)</td>
</tr>
<tr>
<td>12</td>
<td>Allyl</td>
<td>CH₃</td>
<td>4'-Cl-phenyl</td>
<td>2.7 (s, 3H, CH₃), 5.2 (d, 2H, -CH₂-CH=CH₂), 5.6 (d, 2H, -CH₂-CH=CH₂), 6.1-7.0 (m, 1H, -CH₂-CH=CH₂), 7.4-8.9 (m, 8H, Ar-Hs), 9.8 (br.s., 1H, NH)</td>
</tr>
</tbody>
</table>

* Deuterated solvent is DMSO-d₆
Vilsmeier-Haack reaction

Dimethylformamide (2.56 g, 0.035 mol) and POCl₃ (5.35 g 0.035 mol) were separately cooled at 0 °C before being mixed and stirred at such temperature. A solution of compounds 11 or 12 (0.0116 mol) in DMF (3 mL) was added drop wise to the reaction mixture, which was warmed at room temperature then heated at 70-80°C for 5 h. After cooling at room temperature, the mixture was basified with a cold saturated K₂CO₃ solution. The precipitate was filtered, strongly washed with water and crystallized from ethanol, yielding 95% (4.7 g) of 15 or 92% (4.17 g) of 16.

1-(3-Phenyl-3,4-dihydro-4-quinazolin-2-yl)-3-(4-chlorophenyl) pyrazole-4-carbaldehyde 15

Yellow crystals, m.p. 230-23°. IR, ν cm⁻¹ (KBr): 1709 (aldehyde C=O), 1666 (quinazoline C=O), 1645 and 1597 (C=N). ¹H-NMR (DMSO-d₆) δ 7.7-9.0 (m, 14H, Ar-Hs and pyrazole-C₅-H), 10.3 (s, 1H, CHO). Anal. Calc. for C₂₄H₁₅ClN₄O₂ (M.Wt 426.85): C, 67.53; H, 3.54; N, 13.13. Found: C, 67.50; H, 3.41; N, 13.37.

1-(3-Allyl-3,4-dihydro-4-quinazolin-2-yl)-3-(4-chlorophenyl) pyrazole-4-carbaldehyde 16

Yellow needles, m.p. 146-148°. ¹H-NMR (DMSO-d₆) δ 5.2 (d, 2H, -CH=CH₂, CH=CH₂), 5.7 (d, 2H, -CH=CH₂), 6.1-6.6 (m, 1H, -CH=CH₂), 7.5-8.8 (m, 9H, aromatic Hs and pyrazole-C₅-H), 10.5 (s, 1H, CHO). Anal. Calc. for C₂₁H₁₅ClN₄O₂ (M.Wt 390.82): C, 64.54; H, 3.87; N, 14.34. Found: C, 64.80; H, 3.89; N, 14.53.

Antimicrobial screening

Bacterial and Fungal cultures were obtained from Department of Botany and Microbiology, Faculty of science, Al-Azhar University, Assiut, Egypt

Antibacterial activity

Organisms and culture conditions

Four bacterial species represent both Gram-positive and Gram-negative strains were used to test the antibacterial activities of the target compounds: *Staphylococcus aureus*, and *Bacillus subtilis* as representatives for the Gram-positive strains, while the Gram-negative strains were represented by *Klebsiella pneumoniae*, and *Escherichia coli*.

Materials and method

Cell suspension of bacterial strains was prepared from 48 h old cultures, grown on Nutrient Agar (NA) in sterilized water. The nutrient agar plates (15 cm in diameter) were seeded using 0.1 mL of diluted organism. Cylindrical plugs were removed from the agar using a sterile cork bore. 100 µL of the tested compounds 3-16 (100 µmol/mL in DMSO) and the blank solvent were added to each well in triplicate. The seeded plates were incubated at 35±2°C for 24 h. After 24 h incubation the average diameter of inhibition zones was measured in millimeters, Table 5. A solution of chloramphenicol (100 µg/mL in DMSO) was used as the standard antibacterial agent.
Table 5: Antimicrobial activity of the tested compounds (expressed as the diameter of the inhibition zone\(^a\)).

<table>
<thead>
<tr>
<th>No.</th>
<th>Rhizopus nigricans</th>
<th>Aspergillus flavus</th>
<th>Aspergillus parasiticus</th>
<th>Penicillum italicum</th>
<th>Staphylococcus aureus</th>
<th>Bacillus subtilis</th>
<th>Escherichia coli</th>
<th>Klebsiella pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>13</td>
<td>11</td>
<td>15</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>18</td>
<td>18</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>-</td>
<td>20</td>
<td>11</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>8</td>
<td>-</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13</td>
<td>10</td>
<td>16</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>21</td>
<td>15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>-</td>
<td>19</td>
<td>15</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22</td>
<td>14</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td>13</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14</td>
<td>11</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chlor</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>32</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Mycost</td>
<td>23</td>
<td>22</td>
<td>20</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\)Average of three observations.
Inhibition zone in mm.
“-” no inhibition zone.

Antifungal activity
Organisms and culture conditions
Four fungal species were used in the present study: *Rhizopus nigricans*, *Aspergillus flavus*, *Aspergillus parasiticus*, and *Penicillum italicum*.

Materials and method\(^{10}\)
Spore suspension in sterile malt extract broth media was prepared from 2-5 days old culture of the test fungi growing on malt extract agar (MEB). The final spore concentration was \(5 \times 10^4\) spores/mL. About 15 mL of growth medium was introduced on sterilized Petri dishes of 9 cm diameter and inoculated with 1 mL spore suspension. Plates were shaken gently to homogenize the inoculum. Antifungal activity of the tested compounds 3-16 was performed by the standard agar cup diffusion method as follow: Cylindrical plugs were removed from the agar using a sterile cork bore. 100 \(\mu\)L of the tested
compounds (100 µmol/mL in DMSO) and the blank solvent were added to each well in triplicate. The seeded plates were incubated at 28±2°C for 3-7 days. After the specified time for incubation the average diameter of inhibition zones was measured in millimeters, Table 5. In addition to a solution of mycostatin (100 µmol/mL in DMSO) was used as standard antifungal agent.

RESULTS AND DISCUSSION

Chemistry

In this study we have prepared new 4(3H)-quinazolinone derivatives from 2-hydrazino-3-allyl(phenyl)-4(3H)-quinazolinone 2a or 2b as shown in the following scheme. The initial step in the synthetic method involved the synthesis of 2-mercapto-3-allyl(phenyl)-4(3H)-quinazolinone 1a or 1b through a reported method13. In the second step, 1a or 1b was refluxed with hydrazine hydrate to give 2-hydrazino-3-allyl(phenyl)-4(3H)-quinazolinone 2a or 2b which was reacted with equimolar amount of substituted isothiocyanate, isonicotinaldehyde and p-chloroaceto phenone to give the required new compounds 3-8, 3-substituted-2-substituted-thiocarbamoylhydrazino-3,4-dihydro-4-quinazolinone 3-8, 3-substituted-2-(4-pyridinyl)methylidenehydrazino-3,4-dihydro-4-quinazolinone 9, 10, 3-substituted-2-[1-(4-chlorophenyl)]ethylidenehydrazino-3,4-dihydro-4-quinazolinone 11, 12, respectively. 1-(3-Substituted-3,4-dihydro-4-quinazolinone-2-yl)-3-(4-chloro phenyl)pyrazole-4-carbaldehyde (15, 16) were prepared by the reaction of compounds 11 or 12 with Vilsmeier-Haack reagent. While heating compounds 9 or 10 in acetic acid under reflux gave the corresponding derivatives 1-(4-pyridinyl)-1,2-dihydro-4-substituted-[1,2,4]triazolo[4,3-a]quinazolin-4-(3H)-one 13 or 14.

Structures of the synthesized compounds were verified on the bases of microanalysis, IR, 1H NMR and MS spectral data. The IR of the quinazolinone derivatives 3-8 showed 3442-3192 (NH), 1690-1645 (C=O), 1646-1615 (C=N), 1550-1520, 1340-1310, 1073-1050, and 870-830 cm⁻¹ (NCS I, mixed vibration bands).

Tables 1 and 3 show the physicochemical constants of compounds 3-8 and 9-12 respectively. The spectral data of compounds 3-8 and 9-12 are shown in Tables 2 and 4 respectively. All spectral data are in accordance with the expected structures.

Antimicrobial activity

The synthesized compounds 3-16 were tested for their antifungal activity in vitro against (Rhizopus nigrecans, Aspergillus flavus, Aspergillus parasiticus, and Penicillum italicum) fungi using agar cup diffusion method11 and mycostatin12 as standard. The same compounds were tested, in vitro for their antibacterial activity against Staphylococcus aureus, Bacillus subtilis, Klepsilla pneumoniae, and
Awwad A. Radwan, et al.

Scheme

\[
\begin{align*}
& \text{O} \quad \text{O} \\
& \text{N} \quad \text{N} \\
& \text{NO}_2 \\
& \text{NH}_2 \\
& \text{AcOH gl.} \\
& \text{(9,10)} \\
& \text{(13, 14)} \\
& \text{N} \quad \text{N} \\
& \text{SH} \\
& \text{R-NCS} \\
& \text{(1a,b)} \\
& \text{R} = \text{Ph, allyl} \\
& \text{R}' = \text{C}_2\text{H}_5, \text{CH}_2=\text{CH}-\text{CH}_2, \text{C}_6\text{H}_5, \text{p-CH}_3-\text{C}_6\text{H}_4, \text{m-CH}_3-\text{C}_6\text{H}_4 \\
& \text{NH}_2\text{NH}_2 \\
& \text{(2a,b)} \\
& \text{O} \quad \text{Cl} \\
& \text{O} \quad \text{Cl} \\
& \text{V.R.} \\
& \text{(11,12)} \\
& \text{(15, 16)}
\end{align*}
\]

R= Ph, allyl; R’= C₂H₅, CH₂=CH-CH₂, C₆H₅, p-CH₃-C₆H₄, m-CH₃-C₆H₄
**Escherichia coli** using chloramphenicol as standard.\textsuperscript{12} Table 5.

The antimicrobial study explored variable activities for variation at position 2 and 3 of 4(3H)-quinazolinone nucleus. Results clearly indicate that 4(3H)-quinazolinone nucleus has good antibacterial activity while showed weak antifungal activity against *Aspergillus parasiticus*, and *Penicillium italicum* and no antifungal activity against *Rhizopus nigricans*, *Aspergillus flavus*.

Against *Staphylococcus aureus*, all the tested 4(3H)-quinazolinone compounds 3-16 showed good antibacterial activity.

While against *Bacillus subtilis*, *Klepsilla pneumoniae*, and *Escherichia coli* good antibacterial results obtained with thiosemicarbazide and hydrazone compounds 3-12 and no antibacterial activity found for the 1-(4-pyridinyl)-1,2-dihydro-4-substituted-[1,2,4]triazolo-[4,3-a]quinazolin-4-(3H)-one 13 or 14 and 1-(3-Substituted-3,4-dihydro-4-quinazolinon-2-yl)-3-(4-chlorophenyl)pyrazole-4-carbaldehyde 15, 16. In other words cyclization of the hydrazones into pyrazolecarbaldehyde or into triazole ring abolished the antibacterial activity of the compounds.

**Conclusions**

In this work a series of quinazoline-4(3H)-one derivatives was synthesized and tested for antimicrobial activity. The study showed that these compounds have antibacterial activity and have weak or no antifungal activity. The thiosemicarbazide, hydrazone derivatives of quinazoline-4(3H)-one showed antibacterial activity against all the tested bacterial organisms. However, 4-quinazolinon-2-yl pyrazole-4-carbaldehyde derivatives and [1,2,4]triazolo[4,3-a]quinazolin-4-(3H)-one derivatives showed antibacterial activity only against *Staphylococcus aureus*.

**REFERENCES**


