Efficient One-pot microwave-assisted Synthesis and Spectroscopic Characterization of Novel Antitumor and Antimicrobial Hydroxypyrrolidin2-ones

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Abstract

A microwave-assisted, chemoselective synthesis of the novel antitumor and antimicrobial \((3E)-5\)-hydroxy-1-isopropyl-3-\{5-methyl-2-thienyl\}methylene\(-5\)-phenylpyrrolidin-2-one has been achieved via assisted microwave solvent-free one-pot reaction of \((3E)-3\)-\{5-methyl-2-thienyl\}methylene\(-5\)-phenylfuran-2(3H)-one with amines, urea and thiourea. The products are obtained in significant purity, yield, and eco-friendly reaction conditions. The structural formula of the products is confirmed by their spectroscopic characterizations. A mechanism is proposed in which an intramolecular nucleophilic attack takes place on the carbonyl carbon by the lone pair of electrons on the nitrogen atom, leading to ring closure with proton transfer to oxygen forming the hydroxyl group.

Keywords: microwave, antitumor, antimicrobial, pyrrolidin-2-one, furan-2(3H)-one, urea, thiourea.

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Introduction

Heterocyclic motif is an important scaffold that has both industrial and medicinal applications. Pyrrolidinones are heterocyclic compounds that possess significant biological and pharmacological activities, including anticonvulsant and respiratory simulation activities. 2-Pyrrolidinone moiety is very important in medicinal chemistry as many derivatives have shown significant pharmacological and biological activities, as, e.g., anti-cancer agents\textsuperscript{1}, antitumours\textsuperscript{2}, HIV-1 integrase inhibitors\textsuperscript{3}, antimicrobial\textsuperscript{4}, antibacterial\textsuperscript{5} and anti-inflammatory\textsuperscript{6}

In view of the importance of substituted pyrrolidinones, various synthetic methods have been reported\textsuperscript{7-15}.

Microwave-assisted organic synthesis is used as a modern and eco-friendly technique to accelerate organic synthesis. The use of microwave to accelerate reactions has proven to be a useful tool green chemistry which is an efficient technology that minimizes or preferably eliminates the formation of waste, avoids the use of toxic
solvents and reagents. Microwave may also support cleaner reactions by improving yields and stereoselectivity. In our previous work we synthesized (2E)-2-(5-substituted 2-thienylmethylene)-4-arylbutanamides and (2E, 3Z)-4-hydroxy-4-aryl-2-(5-substituted thien-2-ylmethylene)but-3-enohydrazide derivatives, which showed pronounced antimicrobial and in vitro cytotoxic activity (IC50) against human breast carcinoma cell line (using fluoraciele as a reference drug). The method used is that reported by Skehan.

The aim of the present work is to synthesize novel antitumor and antimicrobial hydroxypyrrrolidin-2-one derivatives which are expected to possess potent antitumor and biologically active properties.

**General Remarks**
Spectral measurements were carried out at Micro Analytical Centre, Ain shams University, using:
- Microwave irradiation was carried out in a Galanz Microwave Oven, WP1000AP30-2, Chemistry Department, Faculty of Women for Arts, Science and Education, Ain Shams University.
- IR Spectra were carried out at Micro Analytical Centre, Ain shams University, using: FTIR: PERKIN-ELMER-1430.
- MS Spectra were carried out at Micro Analytical Centre, Al-Azhar University, using: GCMS QP 1000 EX Shimaedzy.
- 1H-NMR spectra. were carried out at the main chemical warfare laboratories, chemical warfare department, Ministry of defense, using: Varian Gemmi (300 MHz);
- Antimicrobial Screening was measured at the Botany Department, Al-Azhar University.
- Cytotoxic measurements were carried out at the Botany Department, Al-Azhar University.

**Experimental**

**Solvent-free one-pot Microwave-assisted Synthesis**

**General Procedure**

In a microwave oven (1000 watt, 30-80% of its total power) a grind mixture from 1 mole furanone (1-3) and 2 moles amine (a-e) with or without dimethyl formamide (DMF) was irradiated in an open vessel for 3-20 minutes. The time and power of each reaction was adjusted according to the reactivity, melting point, or boiling point of the starting materials. Completion of reaction was followed up by (TLC). The reaction mixture was then cooled down to the room temperature and the product obtained was dissolved in diethyl ether, chloroform, or methylene chloride, followed by washing the organic layer several times with dilute
hydrochloric acid to remove the unreacted excess amine. Thoroughly wash of the organic layer with water followed by its dryness over anhydrous sodium sulfate then evaporation, gave the corresponding products (4-18).

**Conventional Thermal Condensation Technique**

**General Procedure**

A mixture from furanone (1-3) with amine (a-e) (1:2, 1:5 or 1:10 moles) in the appropriate organic solvent was refluxed for 2-15 hours. Completion of reaction was followed up by (TLC). The reaction solvent was then distilled to give a product which was dissolved in chloroform and worked up in a similar way to that reported in the microwave irradiation reaction. All trials to react furanone (3) with amines (d and e) in different molar ratios 1:2, 1:5 or 1:10 under reflux for up to 72 hours were unsuccessful.

**Results and Discussion**

Comparison of the reaction of amines (a-c), urea (d), and thiourea (e) with furanones (1-3) has been carried out using free-solvent microwave irradiation technique and conventional thermal heating technique in which different solvents are used. Reaction of amines (a-c) gave with furanone 1 gave (4-6), furanone 2 gave (9-11), furanone 3 gave (14-16), whereas urea (d) gave with furanon1, compound 7, with furanone 2 it gave 12 and with furanone 3 it gave (17). Reaction of thiourea (e) furanone 1 gave 8, with furanone 2 it gave 13, whereas with furanone 3 it gave 18. The comparison showed that microwave technique outweighs the conventional thermal technique where products obtained through microwave irradiation were significantly purity, in excellent yield, and reaction conditions were eco-friendly.

The products obtained were crystallized from the appropriate solvent (cf. Table 1). The chemical structures of products (4-18) were confirmed by their spectral data; IR, $^1$HNMR, and MS.

### Table (1): Melting Points and Solvents of Crystallization of Compounds 4-30

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Compound name</th>
<th>Crystals Color, m.p °C/solvent of crystallization</th>
<th>Yield %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>(3E)-5-Hydroxy-1-methyl-5-phenyl-3-(2-thienylmethylene)pyrrolidin-2-one</td>
<td>Black, 128-130 (a)</td>
<td>77.19</td>
<td>98.94</td>
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<tr>
<td>5</td>
<td>(3E)-5-Hydroxy-5-phenyl-1-propyl-3-(2-thienylmethylene)pyrrolidin-2-one</td>
<td>Yellow, 128-130 (a)</td>
<td>71.24</td>
<td>95.20</td>
<td></td>
</tr>
<tr>
<td>Comp.</td>
<td>Compound name</td>
<td>Crystals Color, m p °C/solvent of crystallization</td>
<td>Yield %</td>
<td></td>
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<td>6</td>
<td>(3E)-5-Hydroxy-1-isopropyl-5-phenyl-3-(2-thienylmethylene)pyrrolidin-2-one</td>
<td>Pale brown, 156-158 (a)</td>
<td>76.67</td>
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<tr>
<td>7</td>
<td>(4E)-2-Hydroxy-5-oxo-2-phenyl-4-(2-thienylmethylene)pyrrolidine-1-carboxamide</td>
<td>Orange, 268-270 (a)</td>
<td>73.24</td>
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<td>8</td>
<td>(4E)-2-Hydroxy-5-oxo-2-phenyl-4-(2-thienylmethylene)pyrrolidine-1-carbothioamide</td>
<td>Deep brown, 254-256 (a)</td>
<td>72.72</td>
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<td>9</td>
<td>(3E)-5-Hydroxy-1-methyl-5-(4-methylphenyl)-3-(2-thienylmethylene)pyrrolidin-2-one</td>
<td>Yellow, 136-138 (a)</td>
<td>48.82</td>
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<td>10</td>
<td>(3E)-5-Hydroxy-5-(4-methylphenyl)-1-propyl-3-(2-thienylmethylene)pyrrolidin-2-one</td>
<td>Brown, 135-137 (a)</td>
<td>28.74</td>
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<tr>
<td>11</td>
<td>(3E)-5-Hydroxy-1-isopropyl-5-(4-methylphenyl)-3-(2-thienylmethylene)pyrrolidin-2-one</td>
<td>Yellow, 142-144 (a)</td>
<td>40.97</td>
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<td>12</td>
<td>(4E)-2-Hydroxy-2-(4-methylphenyl)-5-oxo-4-(2-thienylmethylene)pyrrolidine-1-carboxamide</td>
<td>Brown, 284-286 (a)</td>
<td>33.84*</td>
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<td>13</td>
<td>(4E)-2-Hydroxy-2-(4-methylphenyl)-5-oxo-4-(2-thienylmethylene)pyrrolidine-1-carbothioamide</td>
<td>Black, 182-184 (a)</td>
<td>30.81*</td>
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<tr>
<td>Comp.</td>
<td>Compound name</td>
<td>Crystals Color, m.p °C/solvent of crystallization</td>
<td>Yield %</td>
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<td>Conventional heating</td>
<td>Microwave irradiation</td>
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<td>14</td>
<td>(3E)-5-Hydroxy-1-methyl-3-[(5-methyl-2-thienyl)methylene]-5-phenylpyrrolidin-2-one</td>
<td>Deep brown, 125-127 (a)</td>
<td>77.92</td>
<td>99.66</td>
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<tr>
<td>15</td>
<td>(3E)-5-Hydroxy-3-[(5-methyl-2-thienyl)methylene]-5-phenyl-1-propylpyrrolidin-2-one</td>
<td>Yellow, 155-157 (a)</td>
<td>72.47</td>
<td>96.02</td>
<td></td>
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<tr>
<td>16</td>
<td>(3E)-5-Hydroxy-1-isopropyl-3-[(5-methyl-2-thienyl)methylene]-5-phenylpyrrolidin-2-one</td>
<td>Brown, 165-167 (a)</td>
<td>76.75</td>
<td>99.38</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>(4E)-2-Hydroxy-4-[(5-methyl-2-thienyl)methylene]-5-oxo-2-phenylpyrrolidine-1-carboxamide</td>
<td>Deep green, 182-184 (a)</td>
<td>-</td>
<td>97.25</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>(4E)-2-Hydroxy-4-[(5-methyl-2-thienyl)methylene]-5-oxo-2-phenylpyrrolidine-1-carbothioamide</td>
<td>Black, 160-162 (a)</td>
<td>-</td>
<td>96.51</td>
<td></td>
</tr>
</tbody>
</table>

(a) Benzene-petroleum ether (40-60), *Molar ratio up to (1:10), 15 to 72 hours reflux in ethanol or xylene or t-butyl alcohol.

(3E)-5-Hydroxy-1-methyl-5-phenyl-3-(2-thienylmethylene)pyrrolidin-2-one (4): Black crystals from benzene-petroleum ether (40-60), mp128-130 °C, 98.94% yield in microwave and 77.19% yield in thermal. FTIR (KBr): ν (cm⁻¹) = 3392 (OH, hydroxy), 1678 (CO, lactam). MS: m/z =285 (M⁺, 1.35%, C₁₆H₁₅NO₂S), 266 (1.12, C₁₆H₁₂NOS), 254 (2.29, C₁₅H₁₂NOS), 242 (2.56, C₁₄H₁₂NOS), 240 (8.00, C₁₄H₁₀NOS), 208 (1.57, C₁₀H₁₀NO₂S), 202 (1.38, C₁₂H₁₂NO₂), 194 (8.01, C₉H₈NO₂S), 180 (3.09, C₉H₁₀NOS), 138 (4.13, C₇H₈NS), 43 (100, CHNO).

(3E)-5-Hydroxy-5-phenyl-1-propyl-3-(2-thienylmethylene)pyrrolidin-2-one (5): Yellow crystals from benzene-petroleum ether (40-60), mp128-130 °C, 98.87% yield in microwave and 76.67% yield in thermal. FTIR (KBr): ν (cm⁻¹) = 3401 (OH, hydroxy), 1681 (CO, lactam). MS: m/z =313 (M⁺, 1%, C₁₃H₁₉NO₂S), 285 (1.53, C₁₆H₁₅NO₂S), 284 (0.73, C₁₆H₁₄NO₂S), 269 (0.99, C₁₆H₁₅NOS), 257 (3.08, C₁₅H₁₅NOS), 252 (1, C₁₃H₁₀NOS), 236 (1.86, C₁₂H₁₄NO₂S), 218 (1.80, C₁₂H₁₂NOS), 208 (1.48, C₁₁H₁₀NOS), 138 (4.13, C₇H₈NS), 43 (100, CHNO).
166 (1.63, C_{12}H_{8}N), 148 (5.11, C_{9}H_{8}NS), 69 (100, C_{3}H_{3}NO). \textsuperscript{1}HNMR (DMSO-d_{6}): \delta (ppm) = 9.951 (1H, s, H-9), 8.097-8.077 (1H, d, H-1), 7.624-7.540 (2H, m, H-6), 7.489-7.464 (1H, d, H-3), 7.411-7.278 (2H, m, H-7), 7.258 (1H, s, H-4), 7.144-7.085 (1H, t, H-2), 6.995-6.967 (1H, t, H-8), 3.644-3.607 (2H, t, H-5), 1.797-1.741 (2H, q, H-10), 1.486-1.411 (2H, sextet, H-11) and 0.994-0.962 (3H, t, H-12).

\textbf{(3E)-5-Hydroxy-1-isopropyl-5-phenyl-3-(2-thienylmethylene)pyrrolidin-2-one (6):} Pale brown crystals from benzene-petroleum ether (40-60), mp156-158 °C, 95.20% yield in microwave and 71.24% yield in thermal. FTIR (KBr): \upsilon (cm\textsuperscript{-1}) = 3401 (OH, hydroxy), 1678 (CO, lactam). MS: m/z =313 (M\textsuperscript{+}, 3.01, C_{18}H_{19}NO_{2}S), 292 (1.12, C_{17}H_{12}NO_{2}S), 293 (1.37, C_{18}H_{15}NOS), 285 (2.27, C_{17}H_{16}NOS), 270 (1.10, C_{15}H_{12}NO_{2}S), 269 (1.49, C_{16}H_{15}NOS), 242 (1.46, C_{14}H_{12}NOS), 202 (7.60, C_{13}H_{10}NOS), 194 (100, C_{7}H_{6}NO), 136 (3.56, C_{4}H_{4}NS). \textsuperscript{1}HNMR (DMSO-d_{6}): \delta (ppm) = 7.623 (1H, s, H-9), 7.525-7.522 (1H, d, H-1), 7.411-7.399 (2H, d, H-6), 7.387-7.367 (1H, d, H-3), 7.351-7.314 (2H, t, H-7), 7.258 (1H, s, H-4), 7.230-7.222 (1H, d, H-8), 7.093-7.071 (1H, t, H-2), 3.435-3.181 (1H, septet, H-10), 3.023 (2H, s, H-5), 1.434-1.417 (3H, d, H-11) and 1.267-1.250 (3H, d, H-12).

\textbf{(4E)-2-Hydroxy-5-oxo-2-phenyl-4-(2-thienylmethylene)pyrrolidine-1-carboxamide (7):} Orange crystals from benzene-petroleum ether (40-60), mp 268-270 °C, 96.17% yield in microwave and 73.24% yield in thermal. FTIR (KBr): \upsilon (cm\textsuperscript{-1}) = 3384 (OH, hydroxy), 3167 (NH\textsubscript{2} \textsuperscript{15} amine), 1691 (CO, lactam), 1616 (CO, urea). MS: m/z =314 (M\textsuperscript{+}, 2.26%, C_{16}H_{11}N_{2}O_{5}S), 297 (1.32, C_{16}H_{11}N_{2}O_{5}S), 296 (0.74, C_{16}H_{12}N_{2}O_{2}S), 256 (3.94, C_{14}H_{10}NO_{2}S), 252 (11.67, C_{15}H_{10}NOS), 237 (4.26, C_{16}H_{9}N_{2}O_{2}S), 231 (0.89, C_{12}H_{11}N_{2}O_{3}), 225 (100, C_{14}H_{11}NS), 224 (49.70, C_{14}H_{10}NS), 219 (10.46, C_{12}H_{10}N_{2}O_{3}), 203 (2.54, C_{11}H_{11}N_{2}O_{2}). \textsuperscript{1}HNMR (DMSO-d_{6}): \delta (ppm) = 9.446 (1H, s, H-9), 7.919-7.909 (1H, d, H-1), 7.878-7.852 (2H, d, H-6), 7.791-7.752 (1H, t, H-2), 7.597-7.587 (1H, d, H-3), 7.524 (1H, s, H-4), 7.499-7.392 (2H, m, H-7), 7.223-7.160 (1H, t, H-8), 6.696 (2H, s, H-10) and 2.808 (2H, s, H-5).

\textbf{(4E)-2-Hydroxy-5-oxo-2-phenyl-4-(2-thienylmethylene)pyrrolidine-1-carbothioamide (8):} Deep brown crystals from benzene-petroleum ether (40-60), mp 254-256 °C, 95.45% yield in microwave and 72.72% yield in thermal. FTIR (KBr): \upsilon (cm\textsuperscript{-1}) = 3368 (OH, hydroxy), 3106 (NH\textsubscript{2} \textsuperscript{15} amine), 1691 (CO, lactam). MS: m/z =330 (M\textsuperscript{+}, 1.89%, C_{16}H_{11}N_{2}O_{2}S), 314 (1.10, C_{16}H_{12}NO_{2}S), 286 (2.46, C_{15}H_{14}N_{2}O_{2}S), 271 (5.14, C_{15}H_{13}NO_{2}S), 268 (2.49, C_{15}H_{10}N_{2}S), 253 (8.76, C_{10}H_{9}N_{2}O_{2}S), 247 (0.78, C_{12}H_{11}N_{2}O_{2}S), 229 (12.43, C_{12}H_{10}NO_{2}S), 207 (4.51, C_{9}H_{7}N_{2}S), 163 (17.87, C_{8}H_{5}NS), 57 (100, CHN\textsubscript{2}O). \textsuperscript{1}HNMR (DMSO-d_{6}): \delta (ppm) = 9.452 (1H, s, H-9), 7.882-7.860 (1H, d, H-1), 7.765-7.752 (2H, d, H-6), 7.596-7.587 (1H, d, H-3), 7.531-7.484 (1H, t, H-2), 7.469-7.416 (2H, t, H-7), 7.402 (1H, s, H-4), 7.223-7.201 (1H, t, H-8), 2.857 (2H, s, H-5) and 2.046 (2H, s, H-10).

\textbf{(3E)-5-Hydroxy-1-methyl-5-(4-methylphenyl)-3-(2-thienylmethylene)pyrrolidin-2-one (9):} Yellow crystals from benzene-petroleum ether (40-60), mp 136-138 °C, 95.31% yield in microwave and 48.82% yield in thermal. FTIR (KBr): \upsilon (cm\textsuperscript{-1}) =
3235 (OH, hydroxy), 1672 (CO, lactam). MS: m/z = 299 (M\(^+\), 6.61%, C\(_{17}\)H\(_{17}\)N\(_2\)O\(_2\)S), 285 (5.87, C\(_{16}\)H\(_{14}\)NO\(_2\)S), 284 (5.63, C\(_{16}\)H\(_{14}\)NO\(_2\)S), 243 (3.44, C\(_{16}\)H\(_{17}\)NOS), 239 (12.2, C\(_{15}\)H\(_{13}\)NS), 226 (0.86, C\(_{14}\)H\(_{12}\)NS), 208 (7.20, C\(_{10}\)H\(_{10}\)NO\(_2\)S), 190 (6.20, C\(_{10}\)H\(_8\)NOS), 188 (4.56, C\(_{12}\)H\(_{14}\)NO), 141 (100, C\(_{10}\)H\(_4\)N).

(3E)-5-Hydroxy-5-(4-methylphenyl)-1-propyl-3-(2-thienylmethylene)pyrrolidin-2-one (10): Brown crystals from benzene-petroleum ether (40-60), mp 135-137 °C, 94.18% yield in microwave and 40.97% yield in thermal. FTIR (KBr): \(\nu\) (cm\(^{-1}\)) = 3362 (OH, hydroxy), 1687 (CO, lactam). MS: m/z =327 (M\(^+\), 14.74%, C\(_{19}\)H\(_{21}\)NO\(_2\)S), 323 (0.86, C\(_{19}\)H\(_{17}\)NO\(_2\)S), 306 (0.77, C\(_{19}\)H\(_{16}\)NOS), 245 (3.59, C\(_{13}\)H\(_{19}\)NO\(_2\)S), 243 (29.86, C\(_{13}\)H\(_{17}\)NO\(_2\)S), 236 (10.32, C\(_{12}\)H\(_{14}\)NO\(_2\)S), 173 (5.13, C\(_{11}\)H\(_{11}\)NO), 158 (100, C\(_{11}\)H\(_{12}\)N), 146 (16.01, C\(_{9}\)H\(_8\)NO). \(^1^H\)NMR (DMSO-d\(_6\)): \(\delta\) (ppm) = 9.952 (1H, s, H-9), 8.025-7.960 (1H, d, H-1), 7.578-7.559 (2H, d, H-6), 7.480-7.467 (1H, d, H-3), 7.393-7.356 (2H, d, H-7), 7.258 (1H, s, H-4), 7.114-7.035 (1H, dd, H-2), 3.637-3.601 (2H, d, H-5), 2.421 (3H, s, H-8), 2.389-2.311 (2H, q, H-10), 1.766-1.590 (2H, sextet, H-11) and 0.985-0.968 (3H, t, H-12).

(3E)-5-Hydroxy-1-isopropyl-5-(4-methylphenyl)-3-(2-thienylmethylene)pyrrolidin-2-one (11): Yellow crystals from benzene-petroleum ether (40-60), mp 142-144 °C, 91.13% yield in microwave and 28.74% yield in thermal. FTIR (KBr): \(\nu\) (cm\(^{-1}\)) = 3339 (OH, hydroxy), 1681 (CO, lactam). MS: m/z =327 (M\(^+\), 0.92%, C\(_{15}\)H\(_{21}\)NO\(_2\)S), 310 (2.96, C\(_{19}\)H\(_{20}\)NOS), 309 (3.73, C\(_{19}\)H\(_{19}\)NOS), 284 (0.82, C\(_{16}\)H\(_{14}\)NO\(_2\)S), 282 (0.95, C\(_{18}\)H\(_{20}\)NS), 281 (1.24, C\(_{18}\)H\(_{19}\)NS), 268 (2.91, C\(_{17}\)H\(_{18}\)NS), 266 (0.93, C\(_{16}\)H\(_{17}\)NOS), 226 (1.14, C\(_{16}\)H\(_{12}\)NS), 212 (1.79, C\(_{13}\)H\(_{13}\)NOS), 43 (100, CHNO). \(^1^H\)NMR (DMSO-d\(_6\)): \(\delta\) (ppm) = 9.953 (1H, s, H-9),8.001-7.963 (1H, d, H-1), 7.525-7.475 (2H, d, H-6), 7.459-7.363 (1H, d, H-3), 7.335-7.302 (2H, d, H-7), 7.222 (1H, s, H-4), 7.156-6.986 (1H, dd, H-2), 4.015-3.981 (2H, m, H-5), 2.421 (3H, s, H-8), 2.388-2.308 (1H, septet, H-10), 1.568-1.524 (3H, d, H-11) and 1.467-1.458 (3H, d, H-12).

(4E)-2-Hydroxy-2-(4-methylphenyl)-5-oxo-4-(2-thienylmethylene)pyrrolidine-1-carboxamide (12): Brown crystals from benzene-petroleum ether (40-60), mp 282-284 °C, 92.68% yield in microwave and 33.84% in fusion, -ve in thermal. FTIR (KBr): \(\nu\) (cm\(^{-1}\)) = 3468 (OH, hydroxy), 3205 (NH\(_2\), \(^1^H\) amine), 1690 (CO, lactam), 1616 (CO, urea). MS: m/z = 328 (M\(^+\), 11.49%, C\(_{17}\)H\(_{16}\)N\(_2\)O\(_2\)), 271 (2.07, C\(_{14}\)H\(_{11}\)N\(_2\)O\(_2\)S), 245 (0.95, C\(_{13}\)H\(_{13}\)N\(_2\)O\(_3\)S), 243 (0.73, C\(_{13}\)H\(_{13}\)N\(_2\)OS), 238 (5.66, C\(_{10}\)H\(_{10}\)N\(_2\)O\(_3\)S), 224 (19.06, C\(_{9}\)H\(_8\)N\(_2\)O\(_3\)S), 219 (2.46, C\(_{10}\)H\(_7\)N\(_2\)O\(_2\)S), 217 (4.09, C\(_{13}\)H\(_{13}\)N\(_2\)O), 189 (19.56, C\(_{11}\)H\(_{13}\)N\(_2\)O), 157 (1.95, C\(_{10}\)H\(_9\)N\(_2\)), 85 (100, C\(_{9}\)H\(_8\)N\(_2\)). \(^1^H\)NMR (DMSO-d\(_6\)): \(\delta\) (ppm) = 8.015 (1H, s, H-9), 7.802-7.776 (1H, d, H-1), 7.532-7.518 (2H, d, H-6), 7.479-7.459 (1H, d, H-3), 7.425-7.384 (1H, t, H-2), 7.258 (1H, s, H-4), 7.144-7.111 (2H, d, H-7), 6.514 (2H, s, H-10), 3.747-3.695 (2H, dd, H-5) and 2.408 (3H, s, H-8).

(4E)-2-Hydroxy-2-(4-methylphenyl)-5-oxo-4-(2-thienylmethylene)pyrrolidine-1-carbothioamide (13): Black crystals from benzene-petroleum ether (40-60), mp 182-184 °C, 91.86% yield in microwave and 30.81% in thermal. FTIR (KBr): \(\nu\) (cm\(^{-1}\))
= 3340 (OH, hydroxy), 3167 (NH₂, 1⁹ amine), 1646 (CO, lactam). MS: m/z = 344 (M⁺, 2.08%), C₁₇H₁₆N₂O₂S₂, 326 (1.28, C₁₇H₁₄N₂O₂S), 302 (2.84, C₁₅H₁₄N₂O₂S), 285 (8.72, C₁₅H₁₃N₂S), 284 (3.87, C₁₅H₁₂N₂S₂ = C₁₆H₁₄NO₂S), 267 (69.19, C₁₆H₁₃NOS), 266 (3.37, C₁₆H₁₃NOS), 252 (11.81, C₁₅H₁₆NOS), 199 (2.21, C₁₂H₁₁N₂O), 43 (100, CHNO).¹HNMR (DMSO-d₆): δ (ppm) = 9.464 (1H, s, H-9), 7.767-7.732 (1H, t, H-1), 7.571-7.553 (2H, d, H-6), 7.387 (1H, s, H-4), 7.301-7.280 (1H, d, H-3), 7.211-7.153 (1H, t, H-2), 7.153-7.055 (2H, d, H-7), 3.580-3.563 (2H, dd, H-5), 2.385 (3H, s, H-8) and 2.041 (2H, s, H-10).

(3E)-5-Hydroxy-1-methyl-3-[(5-methyl-2-thienyl)methylene]-5-phenylpyrrolidin-2-one (14): Deep brown crystals from benzene-petroleum ether (40-60), mp 125-127° C, 99.66% yield in microwave and 77.92% in thermal. FTIR (KBr): v (cm⁻¹) = 3402 (OH, hydroxy), 1688 (CO, lactam). MS: m/z = 299 (M⁺, 0.91%), C₁₇H₁₇NO₂S, 284 (17.41, C₁₆H₁₆NO₂S), 282 (2.01, C₁₇H₁₆NOS), 281 (6.09, C₁₇H₁₅NOS), 253 (0.89, C₁₆H₁₅NS), 240 (2.10, C₁₅H₁₄NS), 239 (1.87, C₁₅H₁₃NS), 225 (2.58, C₁₄H₁₁NS), 212 (2.20, C₁₃H₁₀NS), 148 (3.01, C₈H₆NS), 40 (100, C₂H₅N).

(3E)-5-Hydroxy-3-[(5-methyl-2-thienyl)methylene]-5-phenyl-1-propylpyrrolidin-2-one (15): Yellow crystals from benzene-petroleum ether (40-60), mp 155-157° C, 99.38% yield in microwave and 76.75% in thermal. FTIR (KBr): v (cm⁻¹) = 3429 (OH, hydroxy), 1687 (CO, lactam). MS: m/z = 327 (M⁺, 7.30%), C₁₈H₂₁N₂O₂S, 326 (15.88, C₁₉H₂₀NO₂S), 325 (62.16, C₁₉H₁₉NO₂S), 309 (100, C₁₉H₁₉NOS), 299 (5.60, C₁₈H₂₁NOS), 297 (16.60, C₁₈H₁₉NOS), 296 (69.85, C₁₈H₁₈NOS), 266 (2.52, C₁₆H₁₂NOS), 264 (5.60, C₁₇H₁₄NS), 236 (3.68, C₁₂H₁₄NO₂S), 166 (4.87, C₆H₈NOS).

¹HNMR (DMSO-d₆): δ (ppm) = 8.220 (1H, s, H-9), 7.516-7.477 (2H, d, H-6), 7.387-7.365 (1H, d, H-3), 7.365-7.327 (2H, t, H-7), 7.258 (1H, s, H-4), 7.236-7.217 (1H, d, H-2), 7.112-7.104 (1H, t, H-8), 3.637-3.601 (2H, imp., H-5), 2.549 (3H, s, H-1), 1.785-1.748 (2H, q, H-10), 1.252-1.223 (2H, sextet, H-11) and 0.992-0.956 (3H, t, H-12).

(3E)-5-Hydroxy-1-isopropyl-3-[(5-methyl-2-thienyl)methylene]-5-phenylpyrroloidin-2-one (16): Brown crystals from benzene-petroleum ether (40-60), mp 165-167° C, 96.02% yield in microwave and 72.47% in thermal. FTIR (KBr): v (cm⁻¹) = 3345 (OH, hydroxy), 1671 (CO, lactam). MS: m/z = 327 (M⁺, 9.11%), C₁₉H₂₁N₂O₂S, 326 (17.47, C₁₉H₂₀NO₂S), 325 (8.91, C₁₉H₁₉NO₂S), 313 (14.74, C₁₈H₁₉NO₂S), 312 (10.56, C₁₈H₁₈NO₂S), 308 (5.35, C₁₉H₁₈NOS), 307 (3.70, C₁₉H₁₇NOS), 284 (5.45, C₁₇H₁₅NOS), 250 (2.89, C₁₅H₁₄NOS), 232 (11.46, C₁₄H₁₄NOS), 60 (100, C₂H₆NO).¹HNMR (DMSO-d₆): δ (ppm) = 9.110 (1H, s, H-9), 7.826-7.818 (2H, d, H-6), 7.486-7.477 (1H, d, H-3), 7.378-7.338 (2H, t, H-7), 7.258 (1H, s, H-4), 7.204-7.112 (1H, t, H-8), 6.899-6.891 (1H, d, H-2), 3.728-3.641 (2H, m, H-5), 2.552 (3H, s, H-1), 2.493-2.298 (1H, septet, H-10), 1.548-1.301 (3H, d, H-11) and 1.301-1.007 (3H, d, H-12).

(4E)-2-Hydroxy-4-[(5-methyl-2-thienyl)methylene]-5-oxo-2-phenylpyrrolidine-1-carboxamide (17): Deep green crystals from benzene-
petroleum ether (40-60), mp 182-184 °C, 97.25% yield in microwave and −ve in thermal. FTIR (KBr): v (cm⁻¹) = 3423 (OH, hydroxy), 3205 (NH₂, 1⁹ amine), 1688 (CO, lactam), 1616 (CO, urea). MS: m/z = 328 (M⁺, 2.38%, C₁₇H₁₆N₂O₂S), 327 (7.26, C₁₇H₁₅N₂O₂S), 310 (5.65, C₁₇H₁₄N₂O₂S), 300 (4.42, C₁₆H₁₄N₂O₂S), 299 (44.77, C₁₆H₁₃N₂O₂S), 283 (3.33, C₁₅H₁₃N₂OS), 271 (2.49, C₁₅H₁₃N₂OS), 253 (2.18, C₁₃H₁₃N₂S), 232 (8.73, C₁₂H₁₂N₂O₃), 181 (4.49, C₈H₉N₂OS), 134 (100, C₃H₁₀N₂).

¹HNMR (DMSO-d₆): δ (ppm) = 7.670 (1H, s, H-9), 7.562-7.544 (2H, d, H-6), 7.478-7.449 (1H, d, H-3), 7.430-7.359 (2H, m, H-7), 7.258 (1H, s, H-4), 7.218-7.209 (1H, d, H-2), 7.000-6.995 (1H, d, H-8), 6.529 (2H, s, H-10), 3.747-3.695 (2H, dd, H-5) and 2.572 (3H, s, H-1).

(4E)-2-Hydroxy-4-[(5-methyl-2-thienyl)methylene]-5-oxo-2-phenylpyrrolidine-1-carbothioamide (18): Black crystals from benzene-petroleum ether (40-60), mp 160-162 °C, 96.51% yield in microwave and −ve in thermal. FTIR (KBr): v (cm⁻¹) = 3391 (OH, hydroxy), 3182 (NH₂, 1⁹ amine), 1688 (CO, lactam). MS: m/z = 344 (M⁺, 7.08%, C₁₇H₁₆N₂O₂S), 329 (6.40, C₁₆H₁₃N₂O₂S), 311 (4.22, C₁₆H₁₁N₂OS), 300 (4.21, C₁₆H₁₄N₂SO₂), 298 (6.82, C₁₆H₁₄N₂OS₂), 286 (2.35, C₁₆H₁₂NOS₂), 284 (12.37, C₁₅H₁₄N₂OS), 282 (11.05, C₁₅H₁₃N₂OS), 219 (17, C₁₃H₁₁N₂OS), 175 (12.05, C₁₀H₁₁N₂O), 161 (100, C₄H₄S).¹HNMR (DMSO-d₆): δ (ppm) = 8.273 (1H, s, H-9), 7.701-7.692 (2H, d, H-6), 7.580-7.564 (1H, d, H-3), 7.523-7.505 (2H, imp., H-7), 7.258 (1H, s, H-4), 7.208-7.199 (1H, d, H-2), 7.181-7.060 (1H, t, H-8), 3.745-3.692 (2H, dd, H-5), 2.446 (3H, s, H-1) and 2.353 (2H, s, H-10).

Protons Numbering of ¹H-NMR Spectra

![Diagram](image_url)
Names of furanones (1-3)

(3E)-5-phenyl-3-(2-thienylmethylene)furan-2(3H)-one

(3E)-5-(4-methylphenyl)-3-(2-thienylmethylene)furan-2(3H)-one

(3E)-3-[(5-methyl-2-thienyl)methylene]-5-phenylfuran-2(3H)-one
Mechanism:
Molecular Structural Assignment

Molecular structural assignment of compounds 4-18 were assigned by their spectral analyses; FTIR, Ms, and $^1$HNMR. The protons numbering of $^1$HNMR spectra of some compounds are given in figure 1.

Antimicrobial Activity

The antimicrobial screening of compounds; 5-8, 10-13 and 15-18 using the disk diffusion method, inhibition zone diameter (mm/mg sample) in DMSO as solvent, show that all derivatives examined have antimicrobial activity ranging from high to moderate values against; Streptococcus pneumonia (G+), Staphylococcus aureus (G+), Escherichia coli (G-), Pseudomonas aeruginosa (G-), Aspergillus fumigates and Candida albicans. The screened compounds showed pronounced antibacterial activity using Ampicillin, Genyamycine and Amphotericin B respectively as a reference. (Table 2)

Cytotoxic Activity

In vitro cytotoxic activity (IC50) of compounds 12, 13, 17, and 18 against a human breast carcinoma cell line and human colon carcinoma cell line using Doxorubsin or Sisplatin as a reference drug, similar to the method that reported by Skehan$^8$, where IC50 is defined as the concentration results in a 50% decrease in cell
number as compared with that of the control structures in the absence of an inhibitor. The results obtained are given in Table 2.

**Anti-tumor Activity**

In vitro antiproliferative activity (IC50) of compounds 5, 12, 13 and 16 against a human breast carcinoma cell line and a human colon carcinoma cells using Doxorubsin or Sisplatin as a reference drug, similar to the method that reported by Skehan P. and Storeng R., *(1990)*, where IC50 is defined as the concentration results in a 50% decrease in cell number as compared with that of the control structures in the absence of an inhibitor. The results obtained are given in Table 2.
### Table (2): Antimicrobial and Cytotoxic Activities of some Compounds

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>FUNGI</th>
<th>Gram positive Bacteria</th>
<th>Gram negative Bacteria</th>
<th>Anti-tumor activity IC50 µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Aspergillus fumigates (RCMB 02568)</td>
<td>Candida albicans (RCMB 05036)</td>
<td>Streptococcus pneumonia (RCMB 010010)</td>
</tr>
<tr>
<td>1</td>
<td>14.3±1.2</td>
<td>12.3±1.5</td>
<td>13.6±0.63</td>
<td>16.3±0.58</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>18.3±0.58</td>
<td>17.3±1.2</td>
<td>18.2±1.5</td>
<td>20.1±1.2</td>
</tr>
<tr>
<td>7</td>
<td>21.3±0.36</td>
<td>19.8±0.35</td>
<td>20.1±0.55</td>
<td>23.1±0.52</td>
</tr>
<tr>
<td>8</td>
<td>12.3±1.2</td>
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<td>12.4±1.5</td>
<td>13.2±0.63</td>
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<tr>
<td>11</td>
<td>15.2±0.53</td>
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<td>14.3±0.53</td>
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<tr>
<td>12</td>
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<td>16.3±0.67</td>
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<tr>
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<td>10.1±1.2</td>
<td>10.9±0.63</td>
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<tr>
<td>15</td>
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<td>20.3±0.58</td>
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</tr>
<tr>
<td>16</td>
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<td>22.6±0.58</td>
<td>25.3±1.5</td>
</tr>
<tr>
<td>17</td>
<td>21.6±0.63</td>
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<td>21.3±0.72</td>
<td>23.4±0.58</td>
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<tr>
<td>18</td>
<td>21.1±1.2</td>
<td>19.8±0.58</td>
<td>20.7±0.63</td>
<td>22.8±1.2</td>
</tr>
</tbody>
</table>

**Reference drug**
- Amphotericin B
- Ampicillin
- Genymycin
- Doxorubsin or Sisplatin

### Conclusion
Microwave-assisted technique proved to accomplish the reactions with excellent yields, high purity, assist cyclization, regioselectivity and convenient working out than conventional thermal heating technique. Moreover it proves to be more economically and environmentally safe (green chemistry) than thermal heating technique.
References:

تحضير مركبات الهيدروكسي بيرليدونات (2-اون) جديدة ذات النشاط ضد السرطان والميكروبات باستخدام كفاءة الميكروويف

اسم الباحث: إيمان عزمي محمد عزمي

المشرفين

أ/ د. شريف محمد عوض
أ/ د. حنفي علي حنفي
د/ محمد عبد المومن
د/ راشد جلال
د/ أحمد فرجلي معيهد

تحضير مركبات لها نشاط لعلاج الخلايا السرطانية والبكتيريا والفطريات من خلال تفاعل الفيروسات (1-3) مع الإيميد والأيوريا والثيوبريا وقد تم الحصول على مركبات من 4-18 وتم التأكيد على تركيبها البنائي لها من خلال الأطيف تحت الحمراء وقد أجريت التجارب باستخدام الميكروويف في غبال أي مذيبات عضوية وبالتسنمن الحراري التقليدي في وجود مذيبات عضوية أو غيابها وقد لاحظ ان استخدام الميكروويف يفوق أحيانا استخدام التسخين الحراري التقليدي من حيث كمية ونقاوة النواتج وقصر الزمان في الحصول عليها واحتفاظ بالبيئة لعدم استخدام مذيبات عضوية ضارة بها.

وقد افترض ميكانيكية للتفاعل من خلال تكوين وسيط تساهمية من الكترونات الموجودة على ذرة البيتروجين في الإيميد على ذرة كربون الموجودة في مجموعة الكربنيل مما أدى إلى تكوين وسيط حقل حديث بالنظام مع تكوين انتقال للبروتون الموجود مع البيتروجين للإيميد لتكون مشتقات الهيدروكسي بيرليدونات ذات النشاط الطبي والبيولوجي.