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.

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., anticancer agents\textsuperscript{1}, antitumours\textsuperscript{2}, HIV-1 integrase inhibitors\textsuperscript{3}, anti-microbial\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.

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In our previous work we synthesized (2E)-2-(5-substituted 2-thienyl)methylene)-4-arylbutanamides and (2E, 3Z)-4-hydroxy-4-aryl-2-(5-substituted thien-2-ylmethylene)but-3-enohydrazide derivatives\textsuperscript{16}, which showed pronounced antimicrobial and in vitro cytotoxic activity (IC50) against human breast carcinoma cell line (using flouraciele as a reference drug). The method used is that reported by Skehan\textsuperscript{17}.

The aim of the present work is to synthesize novel antitumor and antimicrobial hydroxypyrrolidin-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.
- \textsuperscript{1}H 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)\textsuperscript{18,19} 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, 1HNMR, 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>
</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>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>7</td>
<td>(4E)-2-Hydroxy-5-oxo-2-phenyl-4-(2-thienylmethylene)pyrrolidin-1-carboxamide</td>
<td>Orange, 268-270 (a)</td>
<td>73.24</td>
</tr>
<tr>
<td>8</td>
<td>(4E)-2-Hydroxy-5-oxo-2-phenyl-4-(2-thienylmethylene)pyrrolidin-1-carbothioamide</td>
<td>Deep brown, 254-256 (a)</td>
<td>72.72</td>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Comp.</td>
<td>Compound name</td>
<td>Crystals Color, m p °C/solvent of crystallization</td>
<td>Yield %</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>-------------------------------------------------</td>
<td>---------</td>
</tr>
<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>
</tr>
<tr>
<td>12</td>
<td>(4E)-2-Hydroxy-2-(4-methylphenyl)-5-oxo-4-(2-thienylmethylene)pyrrolidin-1-carboxamide</td>
<td>Brown, 284-286 (a)</td>
<td>33.84*</td>
</tr>
<tr>
<td>13</td>
<td>(4E)-2-Hydroxy-2-(4-methylphenyl)-5-oxo-4-(2-thienylmethylene)pyrrolidin-1-carbothioamide</td>
<td>Black, 182-184 (a)</td>
<td>30.81*</td>
</tr>
<tr>
<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>
</tr>
<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>
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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>
</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>
</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>
</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): υ (cm⁻¹) = 3392 (OH, hydroxy), 1678 (CO, lactam). MS: m/z =285 (M⁺, 1.35%, C₁₆H₁₅NO₂S), 266 (1.12, C₁₀H₁₂NOS), 254 (2.29, C₁₃H₁₂NOS), 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): v (cm⁻¹) = 3401 (OH, hydroxy), 1681 (CO, lactam). MS: m/z =313 (M⁺, 1%, C18H19NO2S), 285 (1.53, C16H15NO2S), 284 (0.73, C16H14NO2S), 269 (0.99, C16H13NOS), 257 (3.08, C15H12NOS), 252 (1, C13H10NOS), 236 (1.86, C13H14NO2S), 218 (1.80, C12H12NOS), 166 (1.63, C12H9N), 148 (5.11, C12H8NS), 69 (100, C3H3NO). ¹HNMR (DMSO-d₆): δ (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), 7.144-7.105 (1H, d, H-2), 6.995-6.967 (1H, t, H-8), 3.644-3.607 (2H, t, H-5), 1.977-1.741 (2H, q, H-10), 1.486-1.411 (2H, sext, H-11) and 0.994-0.962 (3H, t, H-12).

(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): v (cm⁻¹) = 3401 (OH, hydroxy), 1678 (CO, lactam). MS: m/z =313 (M⁺, 3.01, C18H19NO2S), 297 (1.12, C17H15NO2S), 293 (1.37, C18H15NOS), 285 (2.27, C17H19NOS), 270 (1.10, C15H12NOS), 269 (1.49, C15H12NOS), 242 (1.46, C14H12NOS), 202 (7.60, C11H8NOS), 139 (100, C7H8NS), 136 (3.56, C6H7NS). ¹HNMR (DMSO-d₆): δ (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, sepet, 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).

(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): v (cm⁻¹) = 3384 (OH, hydroxy), 3167 (NH₂, 1¹ amine), 1691 (CO, lactam), 1616 (CO, urea). MS: m/z =314 (M⁺, 2.26%, C16H14N2O3S), 297 (1.32, C16H13N2O2S), 296 (0.74, C16H12N2O2S), 256 (3.94, C14H10NO3S), 252 (11.67, C15H10NOS), 237 (4.26, C10H9N2O3S), 231 (0.89, C12H11N2O3), 225 (100, C14H11NS), 224 (49.70, C14H10NS), 219 (10.46, C10H9N2O3S), 203 (2.54, C10H11N2O), ¹HNMR (DMSO-d₆): δ (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).

(4E)-2-Hydroxy-5-oxo-2-phenyl-4-(2-thienylmethylene)pyrrolidin-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): v (cm⁻¹) = 3368 (OH, hydroxy), 3106 (NH₂, 1¹ amine), 1691 (CO, lactam). MS: m/z =330 (M⁺, 1.89%, C16H14N2O2S), 314 (1.10, C10H12N2O2S), 286 (2.46, C15H14N2O2S), 271 (5.14, C13H13NO3S), 268 (2.49, C15H10NS2), 253 (8.76, C10H9N2O2S2), 247 (0.78, C12H11N2O2S2), 229 (12.43, C12H9N2OS), 207 (4.51, C9H7N2S2), 163 (17.87, C2H7N2S), 57 (100, CHN₂O). ¹HNMR (DMSO-d₆): δ (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).
(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): ν (cm⁻¹) = 3235 (OH, hydroxy), 1672 (CO, lactam). MS: m/z = 299 (M⁺, 6.61%, C₁₇H₁₂NO₂S), 285 (5.87, C₁₆H₁₃NO₂S), 284 (5.63, C₁₆H₁₄NO₂S), 243 (3.44, C₁₄H₉NOS), 239 (12.2, C₁₅H₁₃NS), 226 (0.86, C₁₄H₁₁NS), 208 (7.20, C₁₉H₁₈NO₂S), 190 (6.20, C₁₀H₈NOS), 188 (4.56, C₁₂H₁₄NO), 141 (100, C₁₀H₇N).

(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): ν (cm⁻¹) = 3362 (OH, hydroxy), 1687 (CO, lactam). MS: m/z = 327 (M⁺, 14.74%, C₁₉H₂₁NO₂S), 323 (0.86, C₁₉H₁₇NO₂S), 306 (0.77, C₁₉H₁₆NOS), 245 (3.59, C₁₅H₉NO₂), 243 (29.86, C₁₃H₇NO₂), 236 (10.32, C₁₃H₁₄NO₂S), 173 (5.13, C₁₅H₁₃NO), 158 (100, C₁₁H₁₄N), 146 (16.01, C₉H₈NO). ¹H NMR (DMSO-d6): δ (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): ν (cm⁻¹) = 3339 (OH, hydroxy), 1681 (CO, lactam). MS: m/z = 327 (M⁺, 0.92%, C₁₉H₂₁NO₂S), 310 (2.96, C₁₉H₂₀NOS), 309 (3.73, C₁₉H₁₉NOS), 284 (0.82, C₁₆H₁₄NO₂S), 282 (0.95, C₁₅H₂₀NS), 281 (1.24, C₁₉H₁₈NS), 268 (2.91, C₁₇H₁₈NS), 266 (0.93, C₁₆H₁₂NOS), 226 (1.14, C₁₄H₁₁NS), 212 (1.79, C₁₃H₁₀NS), 43 (100, CHNO). ¹H NMR (DMSO-d6): δ (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): ν (cm⁻¹) = 3468 (OH, hydroxy), 3205 (NH₂, 1° amine), 1690 (CO, lactam), 1616 (CO, urea). MS: m/z = 328 (M⁺, 11.49%, C₁₇H₁₆N₂O₅S), 271 (2.07, C₁₄H₁₁N₂O₂S), 245 (0.95, C₁₃H₁₃N₂O₃), 243 (0.73, C₁₃H₁₁N₂OS), 238 (5.66, C₁₀H₁₀N₂O₂S), 224 (19.06, C₉H₈N₂O₃S), 219 (2.46, C₁₀H₇N₂O₂S), 217 (4.09, C₁₂H₁₃N₂O₂), 189 (19.56, C₁₁H₁₃N₂O), 157 (1.95, C₁₀H₈N₂), 85 (100, C₂HN₂O₂). ¹H NMR (DMSO-d6): δ (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): ν (cm⁻¹) = 3340 (OH, hydroxy), 3167 (NH₂, 1° amine), 1646 (CO, lactam). MS: m/z = 344 (M⁺, 2.08%, C₁₇H₁₆N₂O₂S₂), 326 (1.28, C₁₇H₁₄N₂O₂S₂), 302 (2.84, C₁₅H₁₄N₂OS₂), 285 (8.72, C₁₅H₁₃N₂S₂), 208
284 (3.87, C_{15}H_{12}N_{2}S_{2} = C_{16}H_{14}NO_{2}S), 267 (69.19, C_{16}H_{13}NOS), 266 (3.37, C_{16}H_{12}NOS), 252 (11.81, C_{15}H_{16}NOS), 199 (2.21, C_{15}H_{11}N_{2}O), 43 (100, CHNO). \(^1\)HNMR (DMSO-d_{6}): \(\delta (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): \(\nu (cm^{-1}) = 3402\) (OH, hydroxy), 1688 (CO, lactam). MS: \(m/z = 299\) (M\(^+\), 0.91%, C_{17}H_{17}NO_{2}S), 284 (17.41, C_{16}H_{14}NO_{2}S), 282 (2.01, C_{17}H_{16}NOS), 281 (6.09, C_{17}H_{15}NOS), 253 (0.89, C_{16}H_{13}NS), 240 (2.10, C_{15}H_{14}NS), 239 (1.87, C_{15}H_{13}NS), 225 (2.58, C_{14}H_{11}NS), 212 (2.20, C_{13}H_{10}NS), 148 (3.01, C_{8}H_{8}NS), 40 (100, C_{2}H_{2}N)

**(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): \(\nu (cm^{-1}) = 3429\) (OH, hydroxy), 1687 (CO, lactam). MS: \(m/z = 327\) (M\(^+\), 7.30%, C_{19}H_{21}NO_{2}S), 326 (15.88, C_{19}H_{20}NO_{2}S), 325 (62.16, C_{19}H_{19}NO_{2}S), 309 (100, C_{18}H_{19}NOS), 299 (5.60, C_{18}H_{21}NOS), 297 (16.60, C_{18}H_{18}NOS), 296 (69.85, C_{18}H_{18}NOS), 266 (2.52, C_{16}H_{12}NOS), 264 (5.60, C_{17}H_{14}NS), 236 (3.68, C_{12}H_{14}NO_{2}S), 166 (4.87, C_{8}H_{8}NO). \(^1\)HNMR (DMSO-d_{6}): \(\delta (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-phenylpyrrolidin-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): \(\nu (cm^{-1}) = 3345\) (OH, hydroxy), 1671 (CO, lactam). MS: \(m/z = 327\) (M\(^+\), 9.11%, C_{19}H_{21}NO_{2}S), 326 (17.47, C_{19}H_{20}NO_{2}S), 325 (8.91, C_{19}H_{19}NO_{2}S), 313 (14.74, C_{19}H_{19}NOS), 312 (10.56, C_{18}H_{19}NO_{2}S), 308 (5.35, C_{19}H_{18}NOS), 307 (3.70, C_{19}H_{17}NOS), 284 (5.45, C_{17}H_{17}NOS), 250 (2.89, C_{13}H_{16}NO_{2}S), 232 (11.46, C_{13}H_{14}OS), 60 (100, C_{2}H_{6}NO). \(^1\)HNMR (DMSO-d_{6}): \(\delta (ppm) = 9.110 (1H, s, H-9), 7.826-7.818 (2H, d, H-6), 7.488-7.477 (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): \(\nu (cm^{-1}) = 3423\) (OH, hydroxy), 3205 (NH_{2}, 1\(^\circ\) amine), 1688 (CO, lactam), 1616 (CO, urea). MS: \(m/z = 328\) (M\(^+\), 2.38%, C_{17}H_{16}N_{2}O_{3}S), 327 (7. 26, C_{17}H_{15}N_{2}O_{3}S), 310 (5.65, C_{17}H_{14}N_{2}O_{2}S), 300 (3.42, C_{16}H_{16}N_{2}O_{2}S), 299 (44.77, C_{15}H_{15}N_{2}O_{3}S), 283 (3.33, C_{15}H_{15}N_{2}OS), 271 (2.49, C_{15}H_{15}N_{2}OS), 253 (2.18, C_{15}H_{13}N_{2}S), 232 (8.73, C_{15}H_{12}N_{2}O_{3}), 181 (4.49, C_{8}H_{8}N_{2}O_{3}), 134 (100, C_{8}H_{10}N_{2}). \(^1\)HNMR (DMSO-d_{6}): \(\delta (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): \( \nu (\text{cm}^{-1}) = 3391 \) (OH, hydroxy), 3182 (NH\(_2\), primary amine), 1688 (CO, lactam). MS: \( m/z = 344 \) (M\(^+\), 7.08%, C\(_{17}\)H\(_{16}\)N\(_2\)O\(_2\)S\(_2\)), 329 (6.40, C\(_{16}\)H\(_{13}\)N\(_2\)O\(_2\)S), 311 (4.22, C\(_{16}\)H\(_{14}\)N\(_2\)S\(_2\)), 300 (4.21, C\(_{16}\)H\(_{14}\)NO\(_2\)S), 298 (6.82, C\(_{16}\)H\(_{14}\)N\(_2\)S\(_2\)), 286 (2.35, C\(_{15}\)H\(_{12}\)N\(_2\)S\(_2\)), 284 (12.37, C\(_{16}\)H\(_{14}\)NO\(_2\)S), 282 (11.05, C\(_{16}\)H\(_{14}\)N\(_2\)S), 219 (17, C\(_{11}\)H\(_{11}\)N\(_2\)O), 175 (12.05, C\(_{10}\)H\(_{11}\)N\(_2\)), 84 (100, C\(_4\)H\(_4\)S).

**1HNMR (DMSO-d\(_6\)):** \( \delta \) (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 \(^1\)H-NMR Spectra**

![Protons Numbering of \(^1\)H-NMR Spectra](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
Mechanism:
Molecular Structural Assignment

Molecular structural assignment of compounds 4-18 were assigned by their spectral analyses; FTIR, Ms, and 1H NMR. The protons numbering of 1H NMR 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, 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.

MCF-7 cells not treated  sample 16  sample 5

HCT cells not treated  sample 16  sample 5
Table (2): Antimicrobial and Cytotoxic Activities of the 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>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MCF- 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HCT- 116</td>
</tr>
<tr>
<td>1</td>
<td>14.3±1.2</td>
<td>12.3±1.5</td>
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</tr>
<tr>
<td>5</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>7</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>8</td>
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<td>19.8±0.35</td>
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<tr>
<td>2</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>15.2±0.53</td>
<td>14.3±0.44</td>
<td>14.3±0.53</td>
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<tr>
<td>12</td>
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<td>21.5±1.2</td>
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</tr>
<tr>
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<tr>
<td>15</td>
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<tr>
<td>16</td>
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<tr>
<td>17</td>
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<tr>
<td>18</td>
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<td>19.8±0.58</td>
<td>20.7±0.63</td>
<td>22.8±1.2</td>
</tr>
<tr>
<td>Reference drug</td>
<td>Amphotericin B</td>
<td>23.7±1.2</td>
<td>Amphotericin B</td>
<td>25.4±0.58</td>
</tr>
</tbody>
</table>

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:


Zhu, Q.; Jiang, H.; Li, J.; Liu, Sh.; Xia Ch. and Zhang, M. J. Comb. Chem., 2009, 11, 685–696
الملخص باللغة العربية

تحضير مركباث الهيدروكسي بيرليدونات -2-أون جديدة ذات النشاط ضد السرطان والмиكروبات باستعمال كفاءة الميكروويف

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1 - قسم الكيمياء العضوية، كلية البنات
2 - بحث بعمل حيوي الاحتراق بالبيئة المركزي القومي للبحوث

تحضير مركبات لها نشاط لعلاج الخلايا السرطانية والبكتريا والفطريات من خلال تفاعل الفيروانات (1-3) مع الأمينات واليوريا والأثيوبريا وقد تم الحصول على مركبات من4-18 وتم التأكيد على تركيبها البنائي لها من خلال الأطياف تحت الحمراء وقد أجريت التجارب باستخدام الميكروويف في غياب أي مذيبات عضوية وبالتسخين الحراري التقليدي في وجود مذيبات عضوية أو غيابها وقد لاحظ أن استخدام الميكروويف يفوق لدئبوا استخدام التسخين الحراري التقليدي من حيث كمية ونقاوة النواتج وقصر الزمن في الحصول عليها والحفاظ على البيئة لعدم استخدام مذيبات عضوية ضارة بها.

وقد افترض ميكانيكية للتفاعل من خلال تكوين وسيط تم فيه مهاجمة من الكيتونات الموجودة على ذرة النيتروجين في الإيميد على ذرة كربون الموجودة في مجموعة الكربونيل مما أدى إلى تكوين وسيط حليم حديث بالتزامن مع تكوين انتقال للبروتون الموجود مع النيتروجين للإيميد لتكوين مشتقات الهيدروكسي بيرليدونات ذات النشاط الطبي والبيولوجي.