

Efficient One-pot microwave-assisted Synthesis and Spectroscopic Characterization of Novel Antitumor and Antimicrobial Hydroxypyrrolidin-2-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 stimulation 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 agents¹, antitumours², HIV-1 integrase inhibitors³, anti-microbial⁴, antibacterial⁵ and anti-inflammatory⁶

In view of the importance of substituted pyrrolidinones, various synthetic methods have been reported⁷⁻¹⁵.

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-thienylmethylene)-4-arylbutanamides and (2E, 3Z)-4-hydroxy-4-aryl-2-(5-substituted thien-2-ylmethylene)but-3-enohydrazide derivatives¹⁶, which showed pronounced antimicrobial and in vitro cytotoxic activity (IC₅₀) against human breast carcinoma cell line (using fluoracile as a reference drug). The method used is that reported by Skehan¹⁷.

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.
- 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**)^{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 furanone 1, 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

Comp.	Compound name	Crystals Color, m p °C/solvent of crystallization	Yield %	
			Conventional heating	Microwave irradiation
4	(3E)-5-Hydroxy-1-methyl-5-phenyl-3-(2-thienylmethylene)pyrrolidin-2-one	Black, 128-130 (a)	77.19	98.94
5	(3E)-5-Hydroxy-5-phenyl-1-propyl-3-(2-thienylmethylene)pyrrolidin-2-one	Yellow, 128-130 (a)	71.24	95.20
6	(3E)-5-Hydroxy-1-isopropyl-5-phenyl-3-(2-thienylmethylene)pyrrolidin-2-one	Pale brown, 156-158 (a)	76.67	98.87
7	(4E)-2-Hydroxy-5-oxo-2-phenyl-4-(2-thienylmethylene)pyrrolidine-1-carboxamide	Orange, 268-270 (a)	73.24	96.17
8	(4E)-2-Hydroxy-5-oxo-2-phenyl-4-(2-thienylmethylene)pyrrolidine-1-carbothioamide	Deep brown, 254-256 (a)	72.72	95.45
9	(3E)-5-Hydroxy-1-methyl-5-(4-methylphenyl)-3-(2-thienylmethylene)pyrrolidin-2-one	Yellow, 136-138 (a)	48.82	95.31
10	(3E)-5-Hydroxy-5-(4-methylphenyl)-1-propyl-3-(2-thienylmethylene)pyrrolidin-2-one	Brown, 135-137 (a)	28.74	91.13

Comp.	Compound name	Crystals Color, m p °C/solvent of crystallization	Yield %	
			Conventional heating	Microwave irradiation
11	(3E)-5-Hydroxy-1-isopropyl-5-(4-methylphenyl)-3-(2-thienylmethylene)pyrrolidin-2-one	Yellow, 142-144 (a)	40.97	94.18
12	(4E)-2-Hydroxy-2-(4-methylphenyl)-5-oxo-4-(2-thienylmethylene)pyrrolidine-1-carboxamide	Brown, 284-286 (a)	33.84*	92.68
13	(4E)-2-Hydroxy-2-(4-methylphenyl)-5-oxo-4-(2-thienylmethylene)pyrrolidine-1-carbothioamide	Black, 182-184 (a)	30.81*	91.86
14	(3E)-5-Hydroxy-1-methyl-3-[(5-methyl-2-thienyl)methylene]-5-phenylpyrrolidin-2-one	Deep brown, 125-127 (a)	77.92	99.66
15	(3E)-5-Hydroxy-3-[(5-methyl-2-thienyl)methylene]-5-phenyl-1-propylpyrrolidin-2-one	Yellow, 155-157 (a)	72.47	96.02
16	(3E)-5-Hydroxy-1-isopropyl-3-[(5-methyl-2-thienyl)methylene]-5-phenylpyrrolidin-2-one	Brown, 165-167 (a)	76.75	99.38
17	(4E)-2-Hydroxy-4-[(5-methyl-2-thienyl)methylene]-5-oxo-2-phenylpyrrolidine-1-carboxamide	Deep green, 182-184 (a)	-	97.25
18	(4E)-2-Hydroxy-4-[(5-methyl-2-thienyl)methylene]-5-oxo-2-phenylpyrrolidine-1-carbothioamide	Black, 160-162 (a)	-	96.51

(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), mp 128-130 °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), mp 128-130 °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%, C₁₈H₁₉NO₂S), 285 (1.53, C₁₆H₁₅NO₂S), 284 (0.73, C₁₆H₁₄NO₂S), 269 (0.99, C₁₆H₁₅NOS), 257 (3.08, C₁₅H₁₅NOS), 252 (1, C₁₅H₁₀NOS), 236 (1.86, C₁₂H₁₄NO₂S), 218 (1.80, C₁₂H₁₂NOS), 166 (1.63, C₁₂H₈N), 148 (5.11, C₈H₆NS), 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), 7.144-7.085 (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).

(3E)-5-Hydroxy-1-isopropyl-5-phenyl-3-(2-thienylmethylene)pyrrolidin-2-one (6): Pale brown crystals from benzene-petroleum ether (40-60), mp 156-158 °C, 95.20% yield in microwave and 71.24% yield in thermal. FTIR (KBr): ν (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, C₁₅H₁₂NO₂S), 269 (1.49, C₁₆H₁₅NOS), 242 (1.46, C₁₄H₁₂NOS), 202 (7.60, C₁₁H₈NOS), 139 (100, C₇H₉NS), 136 (3.56, C₇H₆NS). 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, 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).

(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): ν (cm⁻¹) = 3384 (OH, hydroxy), 3167 (NH₂, 1st 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, C₁₄H₁₀NO₂S), 252 (11.67, C₁₅H₁₀NOS), 237 (4.26, C₁₀H₉N₂O₃S), 231 (0.89, C₁₂H₁₁N₂O₃), 225 (100, C₁₄H₁₁NS), 224 (49.70, C₁₄H₁₀NS), 219 (10.46, C₁₀H₇N₂O₂S), 203 (2.54, C₁₁H₁₁N₂O₂). 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)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): ν (cm⁻¹) = 3368 (OH, hydroxy), 3106 (NH₂, 1st amine), 1691 (CO, lactam). MS: m/z = 330 (M⁺, 1.89%, C₁₆H₁₄N₂O₂S₂), 314 (1.10, C₁₆H₁₂NO₂S₂), 286 (2.46, C₁₅H₁₄N₂O₂S), 271 (5.14, C₁₅H₁₃NO₂S), 268 (2.49, C₁₅H₁₀NS₂), 253 (8.76, C₁₀H₉N₂O₂S₂), 247 (0.78, C₁₂H₁₁N₂O₂S), 229 (12.43, C₁₂H₉N₂OS), 207 (4.51, C₉H₇N₂S₂), 163 (17.87, C₈H₇N₂S), 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%, C₁₇H₁₇NO₂S), 285 (5.87, C₁₆H₁₅NO₂S), 284 (5.63, C₁₆H₁₄NO₂S), 243 (3.44, C₁₄H₁₃NOS), 239 (12.2, C₁₅H₁₃NS), 226 (0.86, C₁₄H₁₂NS), 208 (7.20, C₁₀H₁₀NO₂S), 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, C₁₅H₁₉NO₂), 243 (29.86, C₁₅H₁₇NO₂), 236 (10.32, C₁₂H₁₄NO₂S), 173 (5.13, C₁₁H₁₁NO), 158 (100, C₁₁H₁₂N), 146 (16.01, C₉H₈NO). ¹HNMR (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, C₁₈H₂₀NS), 281 (1.24, C₁₈H₁₉NS), 268 (2.91, C₁₇H₁₈NS), 266 (0.93, C₁₆H₁₂NOS), 226 (1.14, C₁₄H₁₂NS), 212 (1.79, C₁₃H₁₀NS), 43 (100, CHNO). ¹HNMR (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, 1st amine), 1690 (CO, lactam), 1616 (CO, urea). MS: m/z = 328 (M⁺, 11.49%, C₁₇H₁₆N₂O₃S), 271 (2.07, C₁₄H₁₁N₂O₂S), 245 (0.95, C₁₃H₁₃N₂O₃), 243 (0.73, C₁₃H₁₁N₂OS), 238 (5.66, C₁₀H₁₀N₂O₃S), 224 (19.06, C₉H₈N₂O₃S), 219 (2.46, C₁₀H₇N₂O₂S), 217 (4.09, C₁₂H₁₃N₂O₂), 189 (19.56, C₁₁H₁₃N₂O), 157 (1.95, C₁₀H₉N₂), 85 (100, C₂H₂N₂O₂). ¹HNMR (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, 1st amine), 1646 (CO, lactam). MS: m/z = 344 (M⁺, 2.08%, C₁₇H₁₆N₂O₂S₂), 326 (1.28, C₁₇H₁₄N₂OS₂), 302 (2.84, C₁₅H₁₄N₂OS₂), 285 (8.72, C₁₅H₁₃N₂S₂),

284 (3.87, C₁₅H₁₂N₂S₂ = C₁₆H₁₄NO₂S), 267 (69.19, C₁₆H₁₃NOS), 266 (3.37, C₁₆H₁₂NOS), 252 (11.81, C₁₅H₁₀NOS), 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): ν (cm⁻¹) = 3402 (OH, hydroxy), 1688 (CO, lactam). MS: m/z = 299 (M⁺, 0.91%, C₁₇H₁₇NO₂S), 284 (17.41, C₁₆H₁₄NO₂S), 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, C₂H₂N).

(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): ν (cm⁻¹) = 3429 (OH, hydroxy), 1687 (CO, lactam). MS: m/z = 327 (M⁺, 7.30%, C₁₉H₂₁NO₂S), 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, C₈H₈NOS). 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).

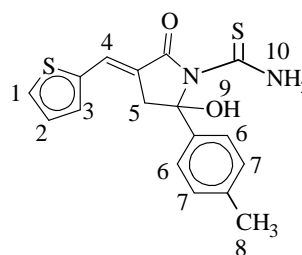
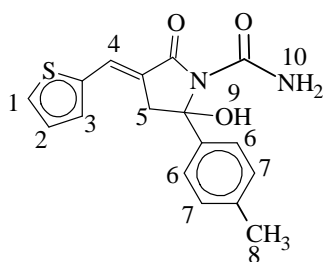
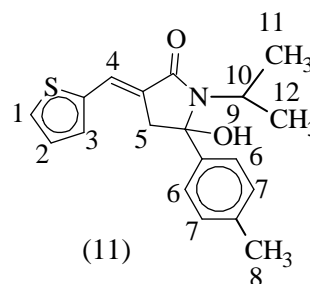
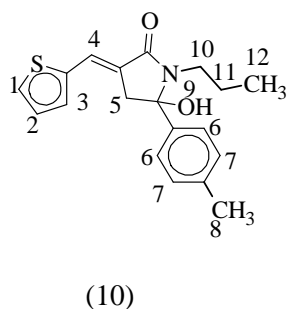
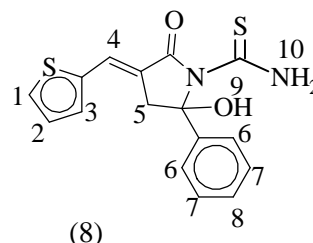
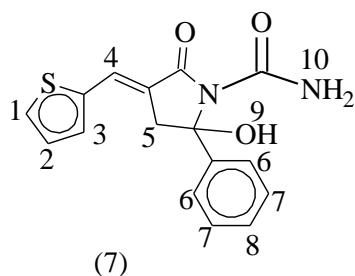
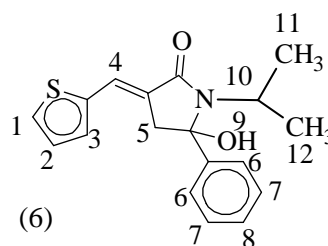
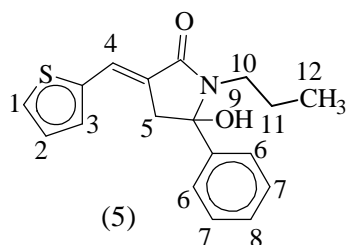
(3E)-5-Hydroxy-1-isopropyl-3-[(5-methyl-2-thienyl)methylene]-5-phenylpyrrolidin-2-one (16): Brown crystals from benzene-petroleum ether (40-60), mp 165-167 °C, 96.02% yield in microwave and 72.47% in thermal. FTIR (KBr): ν (cm⁻¹) = 3345 (OH, hydroxy), 1671 (CO, lactam). MS: m/z = 327 (M⁺, 9.11%, C₁₉H₂₁NO₂S), 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, C₁₇H₁₈NOS), 250 (2.89, C₁₃H₁₆NO₂S), 232 (11.46, C₁₃H₁₄NOS), 60 (100, C₂H₆NO). ¹HNMR (DMSO-d₆): δ (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).

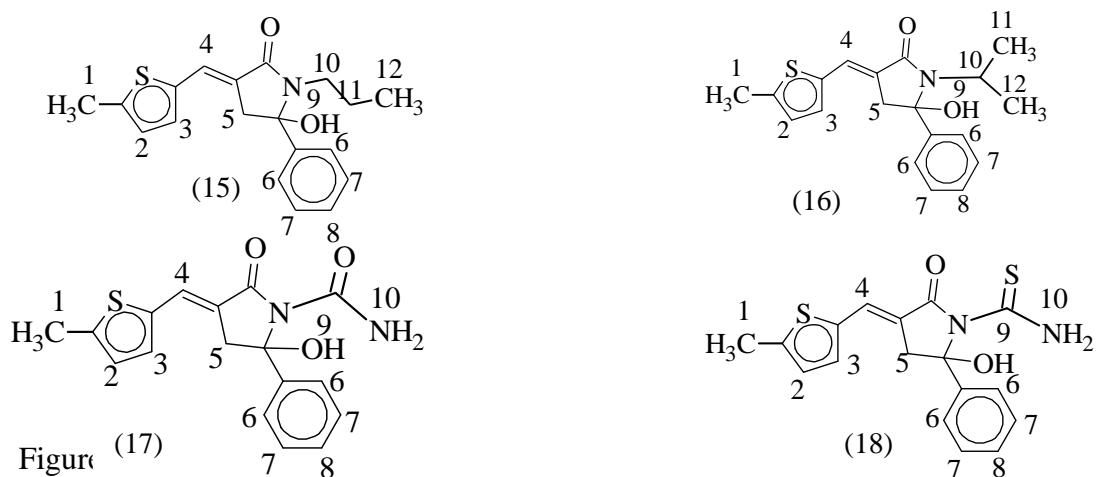
(4E)-2-Hydroxy-4-[(5-methyl-2-thienyl)methylene]-5-oxo-2-phenylpyrrolidine-1-carboxamide (17): Deep green crystals from benzene-petroleum ether (40-60), mp 182-184 °C, 97.25% yield in microwave and -ve in thermal. FTIR (KBr): ν (cm⁻¹) = 3423 (OH, hydroxy), 3205 (NH₂, 1st amine), 1688 (CO, lactam), 1616 (CO, urea). MS: m/z = 328 (M⁺, 2.38%, C₁₇H₁₆N₂O₃S), 327 (7.26, C₁₇H₁₅N₂O₃S), 310 (5.65, C₁₇H₁₄N₂O₂S), 300 (3.42, C₁₆H₁₆N₂O₂S), 299 (44.77, C₁₆H₁₅N₂O₂S), 283 (3.33, C₁₆H₁₅N₂OS), 271 (2.49, C₁₅H₁₅N₂OS), 253 (2.18, C₁₅H₁₃N₂S), 232 (8.73, C₁₂H₁₂N₂O₃), 181 (4.49, C₈H₉N₂OS), 134 (100, C₈H₁₀N₂). 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): ν (cm⁻¹) = 3391 (OH, hydroxy), 3182 (NH₂, 1st amine), 1688 (CO, lactam). MS: m/z = 344 (M⁺, 7.08%, C₁₇H₁₆N₂O₂S₂), 329 (6.40, C₁₆H₁₃N₂O₂S₂), 311 (4.22, C₁₆H₁₁N₂OS₂), 300 (4.21, C₁₆H₁₄NOS₂), 298 (6.82, C₁₆H₁₄N₂S₂), 286 (2.35, C₁₅H₁₂NOS₂), 284 (12.37, C₁₆H₁₄NO₂S), 282 (11.05, C₁₆H₁₄N₂OS), 219 (17, C₁₁H₁₁N₂OS), 175 (12.05, C₁₀H₁₁N₂O), 84 (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).

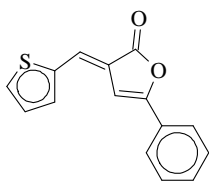
Protons Numbering of ¹H-NMR Spectra



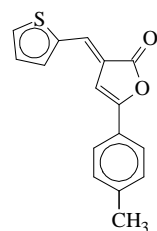


Protons Numbering of ^1H -NMR Spectra

Names of furanones (1-3)

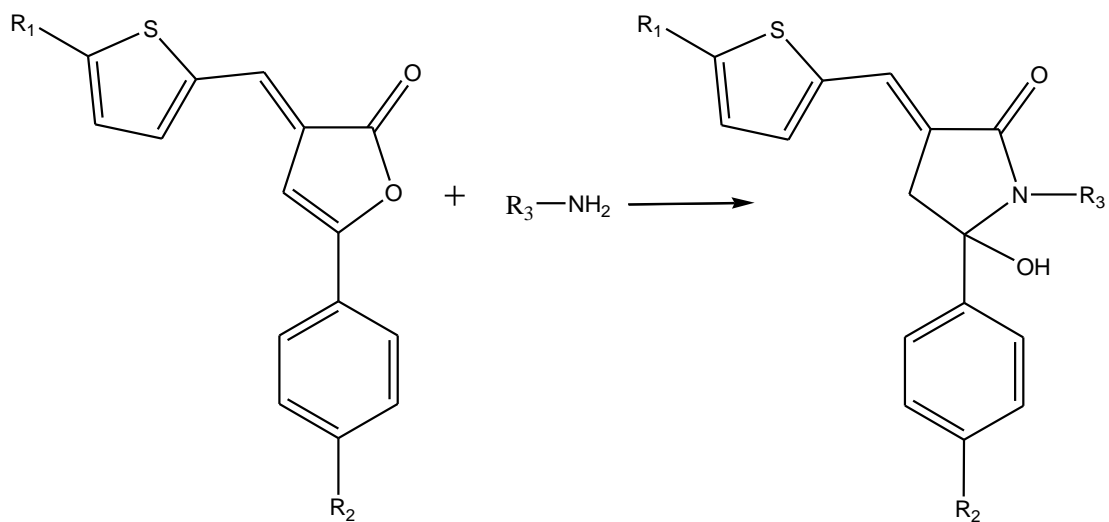


(3E)-5-phenyl-3-(2-thienylmethylene)furan-2(3H)-one



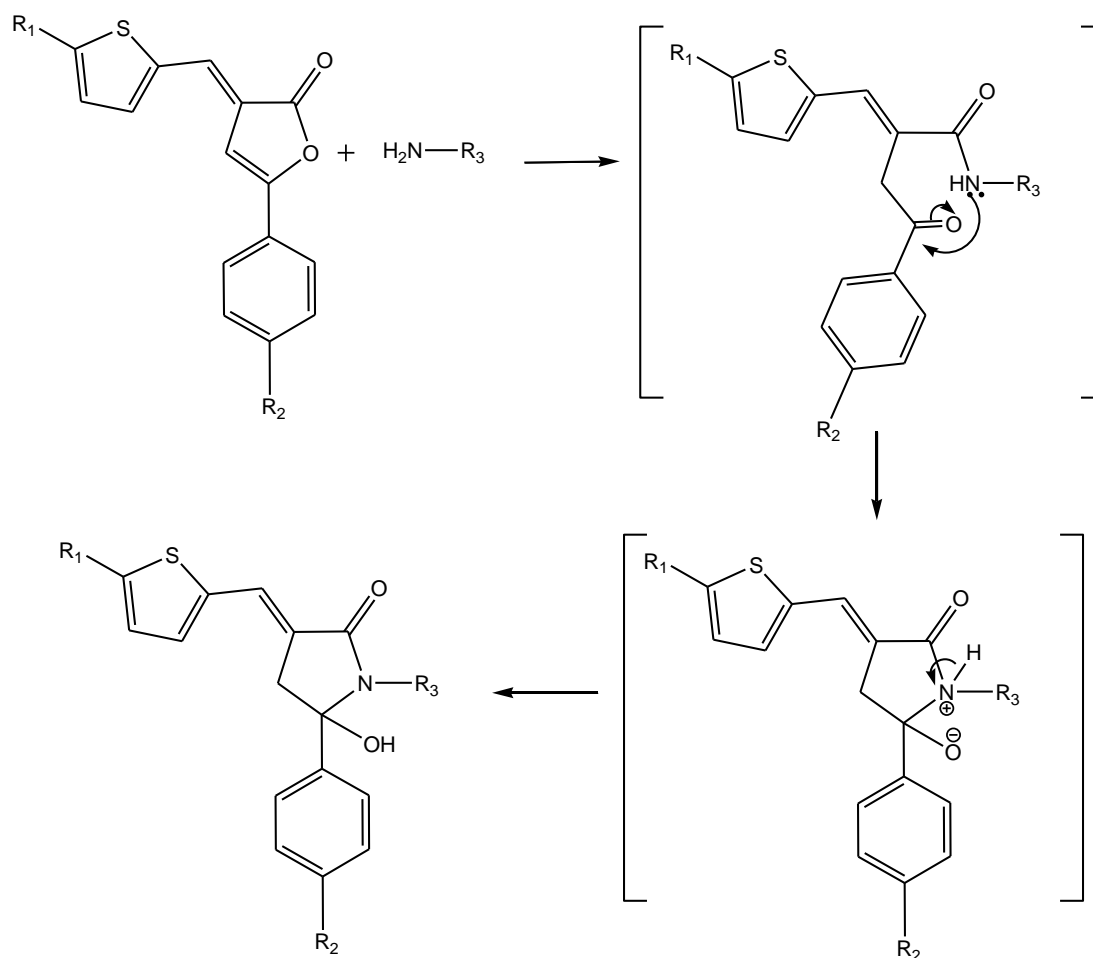
(2)

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



R ₃	Furanone 1 R ₁ , R ₂ = H	Furanone 2 R ₁ = H, R ₂ = CH ₃	Furanone 3 R ₁ = CH ₃ , R ₂ = H
Methyl	4	9	14
n-Propyl	5	10	15
Isopropyl	6	11	16
H ₂ NCO	7	12	17
H ₂ NCS	8	13	18

Mechanism:



Molecular Structural Assignment

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

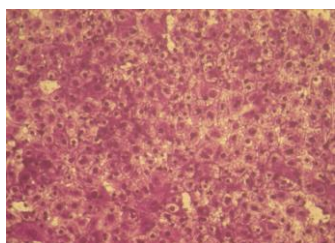
Cytotoxic Activity

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 Siplatin as a reference drug, similar to the method that reported by Skehan⁸, 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.

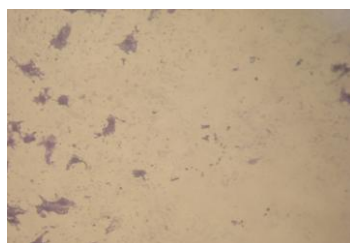


Anti-tumor Activity

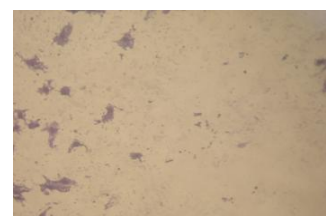
In vitro antiproliferative activity (IC₅₀) of compounds **5**, **12**, **13** and **16** against a human breast carcinoma cell line and a human colon carcinoma cells using Doxorubsin or Sisplatin as a reference drug, similar to the method that reported by *Skehan P.* and *Storeng R., (1990)*, where IC₅₀ 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.



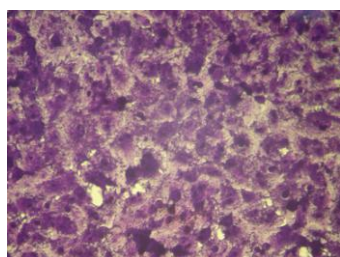
MCF-7 cells not treated



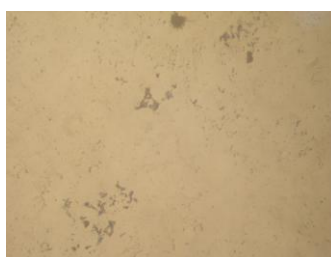
sample 16



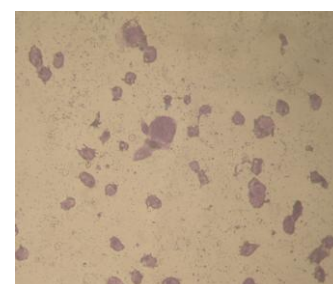
sample 5



HCT cells not treated



sample 16



sample 5

Table(2): Antimicrobial and Cytotoxic Activities of the some compounds

Compound No.	FUNGI		Gram positive Bacteria		Gram negative Bacteria		Anti-tumor activity IC50 $\mu\text{g/ml}$	
	Aspergillus fumigates (RCMB 02568)	Candida albicans (RCMB 05036)	Streptococcus pneumonia (RCMB 010010)	Staphylococcus aureus (RCMB 010028)	Escherichia coli (RCMB 010052)	Pseudomonas aeruginosa (RCMB 010043)	MCF-7	HCT-116
1	14.3 \pm 1.2	12.3 \pm 1.5	13.6 \pm 0.63	16.3 \pm 0.58	11.4 \pm 1.2	NA	-	-
5	NA	NA	NA	NA	NA	NA	-	-
6	NA	NA	NA	NA	NA	NA	-	-
7	18.3 \pm 0.58	17.3 \pm 1.2	18.2 \pm 1.5	20.1 \pm 1.2	15.3 \pm 0.58	NA	-	-
8	21.3 \pm 0.36	19.8 \pm 0.35	20.1 \pm 0.55	23.1 \pm 0.52	16.9 \pm 0.58	NA	-	-
2	12.3 \pm 1.2	10.3 \pm 0.58	12.4 \pm 1.5	13.2 \pm 0.63	11.4 \pm 1.5	NA	-	-
10	NA	NA	NA	NA	NA	NA	-	-
11	15.2 \pm 0.53	14.3 \pm 0.44	14.3 \pm 0.53	13.2 \pm 0.44	12.3 \pm 0.23	NA	-	-
12	17.3 \pm 0.63	15.2 \pm 0.36	16.3 \pm 0.67	17.6 \pm 0.56	15.2 \pm 0.72	NA	95.4	61.1
13	22.3 \pm 0.58	20.6 \pm 0.63	21.5 \pm 1.2	23.3 \pm 1.5	19.4 \pm 1.2	NA	152	46.3
3	10.3 \pm 1.2	9.2 \pm 0.58	10.1 \pm 1.2	10.9 \pm 0.63	9.1 \pm 0.72	NA	-	-
15	20.4 \pm 1.2	19.6 \pm 0.63	20.3 \pm 0.58	22.3 \pm 0.72	20.2 \pm 0.63	NA	-	-
16	23.2 \pm 1.2	21.3 \pm 0.63	22.6 \pm 0.58	25.3 \pm 1.5	23.1 \pm 0.63	NA	-	-
17	21.6 \pm 0.63	20.5 \pm 1.2	21.3 \pm 0.72	23.4 \pm 0.58	21.1 \pm 1.2	NA	14.4	35.8
18	21.1 \pm 1.2	19.8 \pm 0.58	20.7 \pm 0.63	22.8 \pm 1.2	20.4 \pm 0.58	NA	11.5	8.88
Reference drug	Amphotericin B 23.7 \pm 1.2	Amphotericin B 25.4 \pm 0.58	Ampicillin 23.8 \pm 1.2	Ampicillin 27.4 \pm 0.72	Genyamycine 23.4 \pm 0.63	Genyamycine 20.6 \pm 1.2	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.

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المخلص باللغة العربية

تحضير مركبات الهيدروكسي بيرليدونات -2- اون جديدة ذات النشاط ضد السرطان والميكروبات با استخدام كفاءة الميكروويف

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عفاف محمد الطوخي¹ ، أحمد فرغلي معبد²

1- قسم الكيمياء العضوية- كلية النبات

2- باحث بمعمل حيود الأشعة السينية بالمركز القومي للبحوث

تحضير مركبات لها نشاط لعلاج الخلايا السرطانية والبكتريا والفطريات من خلال تفاعل الفيورانونات (3-1) مع الإمينات واليوريا والثيوبيوريا وقد تم الحصول على مركبات من 4-18 وتم التأكيد على تركيبها البنائي لها من خلال الأطياف تحت الحمراء و وقد اجريت التجارب باستخدام الميكروويف فى غياب اى مذيبات عضوية وبالتسخين الحرارى التقليدى فى وجود مذيبات عضوية او غيابها وقد لاحظ ان استخدام الميكروويف يفوق لكثيرا استخدام التسخين الحرارى التقليدى من حيث كمية ونقاوة النواتج وقصر الزمن فى الحصول عليها والحفاظ على البيئة لعدم استخدام مذيبات عضوية ضارة بها .

وقد افترض ميكانيكية للتفاعل من خلال تكوين وسيط تم فيه مهاجمة من الكنتونات الموجودة على ذرة النيتروجين فى الايميد على ذرة كربون الموجودة فى مجموعة الكربونيل مما ادى الى تكوين وسيط حلقي حدث بالتزامن مع تكوين انتقال للبروتون الموجود مع النيتروجين للايميد لتكوين مشتقات الهيدروكسي بيرليدونات ذات النشاط الطبى والبيولوجي.