Synthesis of Some Medicinal and Biological Active (2E)-2-(5-Substituted 2-thienylmethylene)-4-oxo-4-arylbutanamides and (2E,3Z)-4-hydroxy-4-aryl-2-(5-substituted thien-2-ylmethylene)but-3-enohydrazides

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Abstract: Solvent-free microwave irradiation of (3E)-5-phenyl-3-(2-thienylmethylene)furan-2(3H)-one **1**, (3E)-5-(4-methylphenyl)-3-(2-thienylmethylene)furan-2(3H)-one **2**, and (3E)-3-[(5-methyl-2-thienyl)methylene]-5-phenylfuran-2(3H)-one **3** with aromatic and aliphatic amines (a-g and i) gave the corresponding (2E)-2-(5-substituted 2-thienylmethylene)-4-oxo-4-arylbutanamides **4-10**, **12**, **13-19**, **21**, **22-28**, and **30**. However, reaction of furanones **1-3** with hydrazine hydrate (h) gave (2E,3Z)-4-hydroxy-4-phenyl-2-(thien-2-ylmethylene)but-3-enohydrazide **11**, (2E,3Z)-4-hydroxy-4-(4-methylphenyl)-2-(thien-2-ylmethylene)but-3-enohydrazide **20**, and (2E,3Z)-4-hydroxy-2-[(5-methylthien-2-yl)methylene]-4-phenylbut-3-enohydrazide **29**, respectively. Comparison between microwave-assisted and thermal heating synthesis of compounds **4-30** showed that microwave irradiation significantly reduces the reaction time with the enhancement of yields and purity. Structural formulas of synthesized compounds were assigned by their spectral data. Mechanisms of reactions are proposed. Some synthesized products showed antibacterial and cytotoxic activity.

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1. Introduction

Furanones are widely distributed in nature and found in about 10% of all natural compounds. They display a broad biological profile including strong antibiotic, antihelmetic, antifungal, antitumor, antiviral, anti-inflammatory and cytostatic properties, which make them interesting to be synthesized.[1-3] El-Abbady et al.,[4] prepared 2-(1-acetyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-N-benzyl-4-oxo-4-arylbuntanamides and (2E)-2-(1-acetyl-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-4-oxo-4-arylbutanehydrazides, from the reflux of (3E)-1-acetyl-3-(5-aryl-2-oxofuran-3(2H)-ylidene)-1,3-dihydro-2H-indol-2-ones with benzyl amine and hydrazine hydrate in ethanol. Guirguis et al[5]., synthesized (3E)-5-phenyl-3-(2-thienylmethylene)furan-2(3H)-one **1**, (3E)-5-(4-methylphenyl)-3-(2-thienylmethylene)furan-2(3H)-one **2**, and (3E)-3-[(5-methyl-2-thienyl)methylene]-5-phenylfuran-2(3H)-one[6] **3** from the reaction of 4-substituted β-benzoylpropionic acid with 5-methyl-2-furancarboxyaldehyde, 5-methylthiophene-2-carboxyaldehyde, or thiophen-2-carboxyaldehyde under Perkin's conditions. Hashem et al.,[7] found that reflux of 2(3H)-furanones with hydrazine hydrate in ethanol, led to ring opening with the formation of the E-isomers of α-aracyl-β-(2-furyl) acrylic acid hydrazides as the only products. There was no detectable amount of the corresponding Z-isomers according to the ^{1}HNMR spectra. However ring closure of the acrylic acid hydrazides obtained using a mixture from acetic acid and hydrochloric acid gave the corresponding pyridazinones.[8] Also it was reported that the conversion of furanone derivatives into (E)-2-aroylmethyl-3-arylacrylohydrazides took place by their reaction with hydrazine in ethanol at room temperature for 2 days under stirring.[9]

Microwave technology has become very important in many areas of preparative science and particularly in the area of synthetic chemistry. Microwave methods have become reliable, safe and relatively inexpensive.[10,11] It proved to accomplish the reactions with excellent yields, high purity, assist cyclization, regioselectivity, and convenient working out[12-17] than the conventional thermal heating technique. Moreover it proves to be more economically and environmentally safe (green chemistry) than thermal heating technique.

The aim of the present work is to extend and compare between furanones and anhydrides[18-20], as α,β-unsaturated carbonyl compounds, on their reaction with different aliphatic and aromatic amines and phenylhydrazine, using microwave irradiation and thermal heating techniques.

General Remarks

Spectral measurements were carried out at Micro Analytical Centre, Faculty of Science, Cairo University, using:

(a) FTIR: PERKIN-ELMER-1430; Infrared Spectrophotometer.

(b) GCMS QP 1000 EX Shimaedzy; MS spectra.
(c) Varian Gemmi (300 MHz); ^{1}H-NMR spectra.

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.

Antimicrobial Screening was measured at the Botany Department, Faculty of Women for Arts, Science, and Education, Ain Shams University.

Cytotoxic measurements were carried out at the National Institute of Cancer, Cairo University.

2. Experimental

(3E)-5-phenyl-3-(2-thienylmethylene)furan-2(3H)-one[5] **1**, (3E)-5-(4-methylphenyl)-3-(2-thienylmethylene)furan-2(3H)-one[5] **2** and (3E)-3-[(5-methyl-2-thienyl)methylene)-5-phenylfuran-2(3H)-one[6] **3** were prepared and their structures confirmed.

Solvent-free Microwave Irradiation of Furanones 1-3 with Amines

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 with or without dimethyl formamide (DMF) was dry irradiated in an open vessel for 3-20 minutes. The time and power of each reaction were 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 (2E)-2-(5-substituted 2-thienylmethylene)-4-oxo-4-aryl butanamide derivatives **4-10, 12, 13-19, 21, 22-28, 30,** (2E,3Z)-4-hydroxy-4-phenyl-2-(thien-2-ylmethylene)but-3-enohydrazide **11**, (2E,3Z)-4-hydroxy-4-(4-methylphenyl)-2-(thien-2-ylmethylene)but-3-enohydrazide **20**, and (2E,3Z)-4-hydroxy-2-[(5-methylthien-2-yl)methylene]-4-phenylbut-3-enohydrazide **29**, respectively. The products obtained were crystallized from the appropriate solvent. Melting points, solvents of crystallization, yield, and crystals shapes are given in Table 1.

Conventional Thermal Heating of Furanones 1-3 with Amines

General Procedure

A mixture from furanone **1-3** with amines (a-i) (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 used in the microwave irradiation reaction. Reflux of furanones **1** and **3** with amines (a-i) in molar ratio 1:2 for 2 hours gave butanamides **4-10**, **12, 22-28** and **30** or butenohydrazides **11**, **29**, respectively. However reflux of furanone **2** with amines (c, e-i) for 2 hours gave butanamides **15**, **17-19**, **21**, or butenohydrazide **20**, respectively. On the other hand, all trials to react furanone **2** with amines (a, b, or d), in molar ratios 1:2 or 1:5 under reflux up to 15 hours were unsuccessful, except with molar ration 1:10 their reflux for 15 hours yielded compounds **13**, **14**, and **16**, respectively. All trials to condense furanones **1-3** with aromatic and aliphatic amines under conventional thermal heating technique in non polar solvents; p-xylene and benzene were unsuccessful. The products obtained **4-30** were crystallized from the appropriate solvent. Melting points, solvents of crystallization, yield, and crystals shapes are given in Table 1. Their chemical structures were confirmed by spectral data; IR, ^{1}H-NMR, and MS.

Table (1): Melting points and solvents of crystallization of Compounds 4-30

Comp. No.	Compound name	Color and shape of crystals	m p °C/ (solvent of crystallization)	Yield %	
				Conventional heating	Microwave irradiation
4	(E)-4-Oxo-N,4-diphenyl-2-((thiophen-2-yl)methylene)butanamide	Brown crystals	131-132 (b)	28.53	83.00
5	(E)-4-Oxo-4-phenyl-2-((thiophen-2-yl)methylene)-N-p-tolylbutanamide	yellow crystals	164-166 (a)	44.32	85.00
6	(E)-N-(4-Methoxyphenyl)-4-oxo-4-phenyl-2-((thiophen-2-yl)methylene)butanamide	Green crystals	186-188 (a)	47.75	87.00
7	(E)-N-(4-Chlorophenyl)-4-oxo-4-phenyl-2-((thiophen-2-yl)methylene)butanamide	Green crystals	187-189 (a)	55.11	73.50
8	(E)-N-Ethyl-4-oxo-4-phenyl-2-((thiophen-2-yl)methylene)butanamide	Brown crystals	122-124 (b)	69.00	96.00
9	(E)-N-Butyl-4-oxo-4-phenyl-2-((thiophen-2-yl)methylene)butanamide	Brown crystals	164-166 (a)	65.72	94.00

Comp. No.	Compound name	Color and shape of crystals	m p °C/ (solvent of crystallization)	Yield %	
				Conventional heating	Microwave irradiation
10	(E)-N-Benzyl-4-oxo-4-phenyl-2-((thiophen-2-yl)methylene)butanamide	White crystals	199-200 (a)	59.53	89.00
11	(2*E*,3*Z*)-4-Hydroxy-4-phenyl-2-(thien-2-ylmethylene)but-3-enohydrazide	Orange crystals	166-168 (a)	34.27	64.48
12	(E)-4-Oxo-N`,4-diphenyl-2-((thiophen-2-yl)methylene)butanehydrazide	Brown crystals	196-198 (b)	45.00	86.00
13	(E)-4-Oxo-N-phenyl-2-((thiophen-2-yl)methylene)-4-p-tolylbutanamide	Yellow crystals	121-123 (a)	72.02*	86.00
14	(E)-4-Oxo-2-((thiophen-2-yl)methylene)-N,4-dip-tolylbutanamide	Yellow crystals	164-166 (a)	77.33*	88.00
15	(E)-N-(4-Methoxyphenyl)-4-oxo-2-((thiophen-2-yl)methylene)-4-p-tolylbutanamide	Gray crystals	130-132 (a)	53.70	90.00
16	(E)-N-(4-Chlorophenyl)-4-oxo-2-((thiophen-2-yl)methylene)-4-p-tolylbutanamide	Brown crystals	136-139 (b)	60.75*	81.00
17	(E)-N-Ethyl-4-oxo-2-((thiophen-2-yl)methylene)-4-p-tolylbutanamide	yellow crystals	136-138 (b)	71.00	97.00
18	(E)-N-Butyl-4-oxo-2-((thiophen-2-yl)methylene)-4-p-tolylbutanamide	Brown crystals	159-160 (a)	67.44	95.00
19	(E)-N-Benzyl-4-oxo-2-((thiophen-2-yl)methylene)-4-p-tolylbutanamide	Yellow crystals	159-160 (a)	69.33	91.00
20	(2*E*,3*Z*)-4-Hydroxy-4-(4-methylphenyl)-2-(thien-2-ylmethylene)but-3-enohydrazide	Pink crystals	202-204 (a)	36.00	66.33
21	(E)-4-Oxo-N`-phenyl-2-((thiophen-2-yl)methylene)-4-p-tolylbutanhydrazide	Orange crystals	197-199 (b)	28.72	89.00
22	(E)-2-((5-Methylthiophen-2-yl)methylene)-4-oxo-N,4-diphenylbutanamide	Yellow crystals	118-120 (b)	60.94	90.00
23	(E)-2-((5-Methylthiophen-2-yl)methylene)-4-oxo-4-phenyl-N-p-tolylbutanamide	Brown crystals	175-177 (b)	64.00	91.00
24	(E)-N-(4-Mmethoxyphenyl)-2-((5-methylthiophen-2-yl)methylene)-4-oxo-4-phenylbutanamide	Brown crystals	124-126 (b)	71.61	93.00
25	(E)-N-(4-Chlorophenyl)-2-((5-methylthiophen-2-yl)methylene)-4-oxo-4-phenylbutanamide	brown crystals	162-164 (b)	68.35	83.54
26	(E)-N-Ethyl-2-((5-methylthiophen-2-yl)methylene)-4-oxo-4-phenylbutanamide	Gray crystals	162-164 (b)	77.00	99.00
27	(E)-N-Butyl-2-((5-methylthiophen-2-yl)methylene)4-oxo-4-phenylbutanamide	Yellow crystals	126-128 (a)	73.31	96.00
28	(E)-N-Benzyl-2-((5-methylthiophen-2-yl)methylene)-4-oxo-4-phenylbutanamide	Yellow crystals	180-181 (a)	74.66	93.00
29	(2*E*, 3*Z*)-4-Hydroxy-2-[(5-methylthien-2-yl)methylene]-4-phenylbut-3-enohydrazide	Orange crystals	160-162 (a)	46.66	80.00
30	(E)-2-((5-Methylthiophen-2-yl)methylene)-4-oxo-N`,4diphenylbutanhydrazide	Brick red crystals	126-128 (b)	66.00	92.00

(a) Benzene (b) Benzene-petroleum ether 40-60 *Molar ratio (1:10), 15 hours reflux

(2E)-4-Oxo-N,4-diphenyl-2-(2-thienylmethylene)butanamide (4): Brown crystals from benzene-petroleum ether 40-60, mp131-132 °C, 83.00% yield in microwave and 28.53% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3383 (NH, amide), 1680, and 1641 (2CO, conjugated ketone and amide). MS: m/z =347 (M^+, 5.3%, $C_{21}H_{17}NO_2S$), 331(31.8, $C_{21}H_{17}NOS$), 330 (100, $C_{21}H_{16}NOS$), 270 (2.4,

$C_{15}H_{12}NO_2S$), 269 (6.8, $C_{15}H_{11}NO_2S$), 254 (4, $C_{15}H_{12}NOS$), 242 (2, $C_{14}H_{12}NOS$), 241 (3.3, $C_{14}H_{11}NOS$), 226 (2.2, $C_{14}H_{12}NS$), 121 (6.7, C_7H_5S), and 120 (2, C_7H_6NO).

(2E)-N-(4-Methylphenyl)-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide (5): Yellow crystals from benzene, mp 164-166 °C, 85.00% yield in microwave and 44.32% yield in thermal. FTIR (KBr): υ (cm^{-1}) =3264 (NH, amide), 1680 and 1622 (2CO, conjugated ketone and amide). MS: m/z =361 (M^+, 8%, $C_{22}H_{19}NO_2S$), 347 (0.3, $C_{21}H_{17}NO_2S$), 345 (4.7, $C_{22}H_{19}NOS$), 344 (14.6, $C_{22}H_{18}NOS$), 343 (53.2, $C_{22}H_{17}NOS$), 270 (1.3, $C_{15}H_{12}NO_2S$), 256 (9.4, $C_{15}H_{14}NOS$), 254 (33, $C_{15}H_{10}O_2S$), 242 (3, $C_{14}H_{12}NOS$), 228 (3, $C_{13}H_{10}NOS$), 227 (13.4, $C_{14}H_{11}OS$), 134 (2, C_8H_8NO), and 105 (100, C_7H_5O).^{1}HNMR (DMSO-d_6): δ (ppm) = 8.05-7.94 (1H, q, H-1), 7.87-7.85 (2H, d, H-9), 7.82-7.78 (2H, m, H-6), 7.74-7.69 (1H, q, H-3), 7.60 (1H, s, H-8), 7.49-7.46 (2H, d, H-10), 7.50-7.44 (3H, m, H-7), 7.31(1H, s, H-4), 7.27-7.23 (1H, m, H-2), 3.49-3.2 (2H, imp, H-5), and 1.2 (3H, s, H-11).

(2E)-*N*-(4-Methoxyphenyl)-4-oxo-4-phenyl-2-thienylmethylene)butanamide (6): Green crystals from benzene, mp 186-188 °C, 87.00% yield in microwave and 47.75% yield in thermal. FTIR (KBr): υ (cm^{-1}) =3350 (NH, amide), 1673 and 1638 (2 CO, conjugated ketone and amide). MS: m/z =377 (M^+ , 1%, $C_{22}H_{19}NO_3S$), 361 (10, $C_{22}H_{19}NO_2S$), 360 (21, $C_{22}H_{18}NO_2S$), 359 (79.4, $C_{22}H_{17}NO_2S$), 346 (3.1, $C_{21}H_{16}NO_2S$), 300 (5.8, $C_{16}H_{14}NO_3S$), 282 (2, $C_{16}H_{12}NO_2S$), 270 (2.4, $C_{15}H_{12}NO_2S$), 258 (4, $C_{14}H_{12}NO_2S$), 253 (6, $C_{15}H_{11}NOS$), 150 (3.2, $C_8H_8NO_2$), 136 (5, $C_7H_6NO_2$), and 105(100, C_7H_5O). ^{1}HNMR (DMSO-d_6): δ (ppm)= 7.76-7.74 (1H, dd, H-1), 7.65 (1H, s, H-9), 7.51-7.49 (2H, m, H-6), 7.41-7.37(2H, d, H-10), 7.39-7.38 (1H, imp, H-3), 7.27-7.22 (2H, m, H-8), 7.20 (1H, s, H-4), 7.17-7.14 (2H, d, H-11), 7.19-7.14 (3H, m, H-7), 6.76-6.72 (1H, dd, H-2), 3.6 (3H, s, H-12), and 3.25 (2H, s, H-5).

(2E)-*N*-(4-Chlorophenyl)-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide (7): Green crystals from benzene, mp 187-189 °C, 73.50% yield in microwave and 55.11% yield in thermal. FTIR (KBr): υ (cm^{-1}) =3261 (NH, amide), 1664 and 1620 (2CO, conjugated ketone and amide). MS: m/z =381(M^+, 0.7%, $C_{21}H_{16}NO_2SCl$), 365 (0.6, $C_{21}H_{16}NOSCl$), 298 (3.3, $C_{17}H_{13}NO_2Cl$), 287 (0.7, $C_{15}H_{10}NOSCl$), 280 (2, $C_{17}H_{11}NOCl$), 270 (3, $C_{15}H_{12}NO_2S$), 262 (2.7, $C_{13}H_9NOSCl$), 259(1.1, $C_{14}H_{10}NSCl$), 242 (4, $C_{14}H_{12}NOS$), 224 (2.4, $C_{14}H_{10}NS$), 154 (3, C_7H_5NOCl), 153 (5.3, C_7H_4NOCl), and 105 (100, C_7H_5O). ^{1}HNMR (DMSO-d_6): δ (ppm)= 7.77-7.79 (1H, dd, H-1), 7.71-7.68 (2H, m, H-6), 7.54-7.51 (1H, m, H-3), 7.41(1H, s, H-8), 7.41-7.39 (3H, m, H-7), 7.38-7.36 (2H, d, H-9), 7.33 (1H, s, H-4), 7.28-7.25 (2H, d, H-10), 7.2-7.17 (1H, q, H-2), and 7.17-7.16 (2H, d, H-5).

(2E)-*N*-Ethyl-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide (8): Brown crystals from benzene-petroleum ether 40-60, mp 122-124 °C, 96.00% yield in microwave and 69.00% yield in thermal. FTIR (KBr): υ (cm^{-1}) =3383 (NH, amide), 1671, and 1639 (2 CO, conjugated ketone and amide). MS: m/z =299 (M^+, 14%, $C_{17}H_{17}NO_2S$), 283 (10, $C_{17}H_{17}NOS$), 282 (27, $C_{17}H_{16}NOS$), 281 (100, $C_{17}H_{15}NOS$), 270 (1.5, $C_{15}H_{10}NO_2S$), 266 (21.2, $C_{16}H_{12}NOS$), 253 (5.5, $C_{15}H_{11}NOS$), 252 (6, $C_{15}H_{10}NOS$), 204 (4.1, $C_{11}H_{10}NOS$), 194 (1.6, $C_{10}H_{12}NOS$), and 180 (2.4, $C_9H_{10}NOS$).

(2E)-N-n-Butyl-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide (9): Brown crystals from benzene, mp 164-166 °C, 94.00% yield in microwave and 65.72% yield in thermal. FTIR (KBr): υ (cm^{-1}) =3265 (NH, amide), 1673 and 1637 (2 CO, conjugated ketone and amide). MS: m/z =327 (M^+, 5%, $C_{19}H_{21}NO_2S$), 311 (1.3, $C_{19}H_{21}NOS$), 310 (3.1, $C_{19}H_{20}NOS$), 309 (8.6, $C_{19}H_{19}NOS$), 298 (5.5, $C_{17}H_{16}NO_2S$), 271 (6.2, $C_{15}H_{13}NO_2S$), 254 (6.5, $C_{15}H_{10}O_2S$), 250 (5.3, $C_{13}H_{16}NO_2S$), 232 (6.8, $C_{13}H_{14}NOS$), 226 (3, $C_{15}H_{16}NO$), 105 (23.5, C_7H_5O), 100 (8.7, C5H10NO), 77 (100, C6H5), and 74 (5, C4H12N). 1HNMR (DMSO-d6): δ (ppm) = 7.72-7.70 (1H, d, H-1), 7.51-7.49 (1H, t, H-8), 7.44-7.33 (2H, m, H-6), 7.36 (1H, s, H-3), 7.35-7.32 (1H, m, H-4), 7.31-7.26 (3H, m, H-7), 7.16-7.13 (1H, m, H-2), 3.2 (2H, s, H-5), 1.4-1.3 (2H, q, H-9), 1.26-1.18 (2H, quintet, H-10), 1.14-1.06 (2H, sextet, H-11), and 0.74-0.69 (3H, t, H-12).

(2E)-N-Benzyl-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide (10): White crystals from benzene, mp 199-200 °C, 89.00% yield in microwave and 59.53% yield in thermal. FTIR (KBr): υ (cm^{-1}) =3244 (NH, amide), 1670 and 1634 (2 CO, conjugated ketone and amide). MS: m/z =361 (M^+, 2%, $C_{22}H_{19}NO_2S$), 360 (2.4, $C_{22}H_{18}NO_2S$), 345 (44.7, $C_{22}H_{19}NOS$), 344 (34.4, $C_{22}H_{18}NOS$), 284 (2, $C_{16}H_{14}NO_2S$), 266 (7, $C_{16}H_{12}NOS$), 256 (13.4, $C_{15}H_{14}NOS$), 252 (34, $C_{15}H_{10}NOS$), 227 (9, $C_{14}H_{11}OS$), 134 (2.3, C_8H_8NO), and 91 (100, C_7H_7). ^{1}HNMR (DMSO-d_6): δ (ppm) = 7.77-7.73 (1H, dd, H-1), 7.6-7.57 (1H, t, H-9), 7.49-7.47 (1H, m, H-6), 7.36 (1H, s, H-4), 7.35-7.33 (1H, dd, H-3), 7.29-7.26 (1H, m, H-8), 7.20-7.15 (2H, m, H-7), 7.14 (5H, s, H-11), 6.84 (1H, d, H-2), 4.35-4.30 (2H, d, H-10), and 3.32 (2H, imp, H-5).

(2E,3Z)-4-Hydroxy-4-phenyl-2-(thien-2-ylmethylene)but-3-enohydrazide (11): Orange crystals from benzene, mp 166-168 °C, 64.48% yield in microwave and 34.27% yield in thermal. FTIR (KBr): υ (cm^{-1}) =3300-3000 (hydrogen bonded OH, NH and NH_2), and 1654 (CO, amide). MS: m/z =286

(M^+, 0%, $C_{15}H_{14}N_2O_2S$), 270 (6.5, $C_{15}H_{12}NO_2S$) = (6.5, $C_{15}H_{14}N_2OS$), 269 (20.3, $C_{15}H_{13}N_2OS$) = (20.3, $C_{15}H_{11}NO_2S$), 268 (100, $C_{15}H_{12}N_2OS$), 267 (12.4, $C_{15}H_{11}N_2OS$), 209 (5.1, $C_9H_9N_2O_2S$), 207 (3.1, $C_9H_7N_2O_2S$), 191 (3, $C_9H_7N_2OS$), 167 (1.7, $C_7H_7N_2OS$), and 165 (11.2, $C_7H_5N_2OS$). ^{1}HNMR (DMSO-d_6): δ (ppm) = 13.2 (1H, s, H-8), 7.89 (1H, s, H-9), 7.78-7.74 (2H, m, H-6) = (1H, dd, H-1), 7.48-7.46 (1H, dd, H-3), 7.45-7.38 (3H, m, H-7), 7.35-7.32(1H, d, H-4), 6.98-6.96 (1H, d, H-5), 6.95-6.92 (1H, q, H-2), and 4.03 (2H, s, H-10).

(2E)-4-Oxo-N′,4-diphenyl-2-(2-thienylmethylene)butanehydrazide (12): Brown crystals from benzene-petroleum ether 40-60, mp 196-198 °C, 86.00% yield in microwave and 45.00% yield in thermal. FTIR (KBr): υ (cm^{-1}) =3348-3031 (2-NH), 1681 and 1643 (2CO, conjugated ketone and amide). MS: m/z =362 (M^+, 4.6%, $C_{21}H_{18}N_2O_2S$), 346 (4.4, $C_{21}H_{18}N_2OS$), 345 (27.5, $C_{21}H_{17}N_2OS$), 344 (82, $C_{21}H_{16}N_2OS$), 271 (2.5, $C_{15}H_{13}NO_2S$), 270 (2.4, $C_{15}H_{12}NO_2S$), 257 (1.6, $C_{14}H_{13}N_2OS$), 252 (86.3, $C_{15}H_{10}NOS$), 243 (3.5, $C_{13}H_{11}N_2OS$), 235 (18.5, $C_{15}H_{11}N_2O$), 135 (1.3, $C_7H_7N_2O$), 105 (40.1, C_7H_5O), and 77 (100, C_6H_5).

(2E)-4-(4-Methylphenyl)-4-oxo-N-phenyl-2-(2-thienylmethylene)butanamide (13): Yellow crystals from benzene, mp 121-123 °C, 86.00% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3279 (NH, amide), 1682 and 1640 (2CO, conjugated ketone and amide). MS: m/z =361 (M^+, 0.5%, $C_{22}H_{19}NO_2S$), 360 (2, $C_{22}H_{18}NO_2S$), 346 (1.2, $C_{21}H_{16}NO_2S$), 345 (5, $C_{22}H_{19}NOS$), 344 (6.6, $C_{22}H_{18}NOS$), 343 (13.1, $C_{22}H_{17}NOS$), 278 (3.1, $C_{18}H_{16}NO_2$), 271 (1, $C_{15}H_{13}NO_2S$), 266 (0.4, $C_{16}H_{13}NOS$), 238 (0.1, $C_{15}H_{12}NS$), 228 (4.5, $C_{13}H_{10}NOS$), 120 (27, C_7H_6NO), 119 (90, C_7H_5NO), and 93 (100, C_6H_7N).

(2E)-N,4-bis(4-Methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide (14): Yellow crystals from benzene, mp 164-166 °C, 88.00% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3267 (NH, amide), 1666 and 1624 (2CO, conjugated ketone and amide). MS: m/z =375 (M^+, 0.8%, $C_{23}H_{21}NO_2S$), 360 (1.4, $C_{22}H_{18}NO_2S$), 359 (7.7, $C_{23}H_{21}NOS$), 358 (25.4, $C_{23}H_{20}NOS$), 357 (89, $C_{23}H_{19}NOS$), 284 (0.7, $C_{16}H_{14}NO_2S$), 274 (1, $C_{19}H_{16}NO$), 242 (1.5, $C_{14}H_{12}NOS$), 241 (4, $C_{15}H_{13}OS$), 222 (6.7, $C_{15}H_{10}S$), 208 (100, $C_{14}H_8S$),134 (1.3, C_8H_8NO), and 91 (20.1, C_7H_7). ^{1}HNMR (DMSO-d_6): δ (ppm)= 8-7.93 (1H, m, H-1), 7.73 (1H, s, H-9), 7.67-7.61 (2H, d, H-6), 7.49-7.40 (2H, d, H-7), 7.38-7.34 (2H, d, H-10), 7.34-7.31(1H, d, H-3), 7.24 (1H, s, H-4), 7.16-7.12 (2H, d, H-11), 7.06-6.95 (1H, q, H-2), 3.79 (2H, imp, H-5), 2.18 (3H, s, H-8), and 2.14 (3H, s, H-12).

(2E)-N-(4-Methoxyphenyl)-4-(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide (15): Gray crystals from benzene, mp 130-132 °C, 90.00% yield in microwave and 53.70% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3388 (NH, amide), 1675 and 1636 (2CO, conjugated ketone and amide). MS: m/z =391(M^+, 5%, $C_{23}H_{21}NO_3S$), 377 (7.6, $C_{22}H_{19}NO_3S$), 308 (40, $C_{19}H_{18}NO_3$), 300 (12.2, $C_{16}H_{14}NO_3S$), 287 (24, $C_{15}H_{13}NO_3S$), 285(15, $C_{16}H_{15}NO_2S$), 284 (5.1, $C_{16}H_{14}NO_2S$), 270 (18, $C_{15}H_{12}NO_2S$), 267(11, $C_{16}H_{11}O_2S$), 150 (21.5, $C_8H_8NO_2$), 119 (100, C_8H_7O). ^{1}HNMR (DMSO-d_6): δ (ppm)= 7.89-7.82 (1H, dd, H-1), 7.77-7.74 (2H, d, H-6), 7.64 (1H, s, H-9), 7.51-7.48 (2H, d, H-7), 7.27-7.23 (2H, d, H-10), 7.19-7.11(1H, m, H-3), 7.14 (1H, s, H-4), 7.07-6.99 (1H, m, H-2), 6.77-6.73 (2H, d, H-11), 3.75-3.7 (2H, m, H-5), 3.6 (3H, s, H-12), and 2.19 (3H, s, H-8).

(2E)-N-(4-Chlorophenyl)-4-(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide (16): Brown crystals from benzene-petroleum ether 40-60, mp 136-139 °C, 81.00% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3252(NH, amide), 1659 and1632 (2CO, conjugated ketone and amide). MS: m/z =395(M^+, 0.05, $C_{22}H_{18}NO_2SCl$), 379 (1, $C_{22}H_{18}NOSCl$), 378 (0.5, $C_{22}H_{17}NOSCl$), 377 (2, $C_{22}H_{16}NOSCl$), 286 (0.2, $C_{15}H_9NOSCl$), 269 (100, $C_{16}H_{13}O_2S$ or $C_{16}H_{15}NOS$), 267 (39.3, $C_{16}H_{13}NOS$), 266 (2.5, $C_{16}H_{12}NOS$), 262 (0.5, $C_{13}H_9NOSCl$), and 240 (12, $C_{15}H_{14}NS$).

(2E)-N-Ethyl-4-(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide (17): Yellow crystals from benzene-petroleum ether 40-60, mp 136-138 °C, 97.00% yield in microwave and 71.00% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3399.9 (NH, amide), 1682 and1640 (2CO, conjugated ketone and amide). MS: m/z =313 (M^+, 1%, $C_{18}H_{19}NO_2S$), 312 (2.2, $C_{18}H_{18}NO_2S$), 297 (0.1, $C_{18}H_{19}NOS$), 296 (1.1, $C_{18}H_{18}NOS$), 295 (3.3, $C_{18}H_{17}NOS$), 284 (5, $C_{17}H_{18}NOS$ or $C_{16}H_{14}NO_2S$), 267 (0.8, $C_{17}H_{17}NS$), 266 (1, $C_{16}H_{12}NOS$), 228 (3, $C_{13}H_{10}NOS$), 204 (1, $C_{11}H_{10}NOS$), 119 (100, C_8H_7O), and 72 (7, C_3H_6NO).

(2E)-N-n-Butyl-4-(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide (18): Brown crystals from benzene, mp 159-160 °C, 95.00% yield in microwave and 67.44% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3250 (NH, amide), 1667 and 1636 (2CO, conjugated ketone and amide). MS: m/z =341(M^+, 0.4%, $C_{20}H_{23}NO_2S$), 325 (17, $C_{20}H_{23}NOS$), 324 (55.2, $C_{20}H_{22}NOS$), 323 (100, $C_{20}H_{21}NOS$), 267 (61, $C_{16}H_{13}NOS$), 266 (23.1, $C_{16}H_{12}NOS$), 252 (58.2, $C_{15}H_{10}NOS$), 250 (7, $C_{13}H_{16}NO_2S$), 232 (3, $C_{13}H_{14}NOS$), 222 (24.2, $C_{12}H_{16}NOS$), and 208 (61, $C_{11}H_{14}NOS$). ^{1}HNMR (DMSO-d_6): δ (ppm) = 7.71-7.69 (1H, dd, H-1), 7.48-7.44 (1H, t, H-9), 7.42-7.39 (1H, dd, H-3), 7.22-7.19 (2H, d, H-6), 7.16-7.12 (2H, d, H-7) or (1H, imp, H-4), 6.72-6.66 (1H, dd, H-2),

3.53 (2H, s, H-5), 2.25 (3H, s, H-8), 1.4-1.3 (2H, q, H-10), 1.29-1.2 (2H, quintet, H-11), 0.75-0.69 (3H, t, H-13), and 1.12-1.07 (2H, sextet, H-12).

(2E)-N-Benzyl-4-(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide (19): Yellow crystals from benzene, mp 159-160 °C, 91.00% yield in microwave and 69.33% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3274 (NH, amide), 1670 and 1635 (2CO, conjugated ketone and amide). MS: m/z =375 (M^+, 4.1%, $C_{23}H_{21}NO_2S$), 359 (2.5, $C_{23}H_{21}NOS$), 358 (7.6, $C_{23}H_{20}NOS$), 357 (26.3, $C_{23}H_{19}NOS$), 284 (0.2, $C_{16}H_{14}NO_2S$), 266 (7, $C_{16}H_{12}NOS$), 256 (2, $C_{15}H_{14}NOS$), 252 (1.3, $C_{15}H_{10}NOS$), 242 (0.7, $C_{14}H_{12}NOS$), 214 (0.8, $C_{13}H_{12}NS$), 134 (0.5, C_8H_8NO), 119 (15.4, C_8H_7O), and 78 (100, C_6H_6). ^{1}HNMR (DMSO-d_6): δ (ppm) =7.73-7.71 (1H, dd, H-1), 7.54-7.52 (1H, t, H-9), 7.45-7.42 (2H, m, H-6), 7.32 (1H, s, H-4), 7.21-7.12 (1H, dd, H-3), 7.16-7.12 (2H, d, H-7), 7.1 (5H, s, H-11), 7.09-7.06 (1H, d, H-2), 4.31-4.28 (2H, d, H-10), 3.53 (2H, imp, H-5), and 2.22 (3H, s, H-8).

(2E,3Z)-4-Hydroxy-4-(4-methylphenyl)-2-(thien-2-ylmethylene)but-3-enohydrazide (20): Pink crystals from benzene, mp 202-204 °C, 66.33% yield in microwave and 36.00% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3350-3000 (hydrogen bonded OH, NH and NH_2), 1651 (CO, amide). MS: m/z =300 (M^+, 0.03%, $C_{16}H_{16}N_2O_2S$), 285 (2.3, $C_{15}H_{13}N_2O_2S$), 284 (14.2, $C_{16}H_{14}NO_2S$) = (14.2, $C_{16}H_{16}N_2OS$), 283 (38, $C_{16}H_{15}N_2OS$), 282 (100, $C_{16}H_{14}N_2OS$), 266 (2.5, $C_{16}H_{12}NOS$), 209 (28.5, $C_9H_9N_2O_2S$), 191 (32.4, $C_9H_7N_2OS$), 167 (6.5, $C_7H_7N_2OS$), 165 (57.2, $C_7H_5N_2OS$), and 119 (4.4, C_8H_7O). ^{1}HNMR (DMSO-d_6): δ (ppm) = 13.13 (1H, s, H-9), 7.86 (1H, s, H-10), 7.68-7.64 (2H, d, H-6) or (1H, d, H-1), 7.35-7.32 (1H, d, H-4 or 1H, d, H-3), 7.28-7.24 (2H, d, H-7), 6.94-6.92 (1H, q, H-2), 4.02 (2H, s, H-11), 3.38-3.34 (2H, imp, H-5), and 2.33(3H, s, H-8).

(2E)-4-(4-Methylphenyl)-4-oxo-N'-phenyl-2-(2-thienylmethylene)butanehydrazide (21): Orange crystals from benzene-petroleum ether 40-60, mp 197-199 °C, 89.00% yield in microwave and 28.72% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-3306 (2NH), 1697 and 1640 (2CO, conjugated ketone and amide). MS: m/z =376 (M^+, 0%, $C_{22}H_{20}N_2O_2S$), 375 (60, $C_{22}H_{19}N_2O_2S$), 374 (51.4, $C_{22}H_{18}N_2O_2S$), 362 (26, $C_{21}H_{18}N_2O_2S$), 334 (16.3, $C_{20}H_{18}N_2OS$), 306 (20.3, $C_{19}H_{18}N_2S$), 300 (46,$C_{16}H_{16}N_2O_2S$), 297 (22, $C_{16}H_{13}N_2O_2S$), 285 (12.6, $C_{16}H_{15}NO_2S$), 284 (80.4, $C_{16}H_{14}NO_2S$), 257 (36, $C_{14}H_{13}N_2OS$), 229 (73.4, $C_{13}H_{13}N_2S$), 135 (50.6, $C_7H_7N_2O$), and 101 (100, C_8H_5).

(2E)-2-[(5-Methyl-2-thienyl)methylene]-4-oxo-N,4-diphenylbutanamide (22): Yellow crystals from benzene-petroleum ether 40-60, mp 118-120 °C, 90.00% yield in microwave and 60.94% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3308 (NH, amide), 1677 and 1640 (2CO, conjugated ketone and amide). MS: m/z =361 (M^+, 3.3%, $C_{22}H_{19}NO_2S$), 360 (10.4, $C_{22}H_{18}NO_2S$), 345 (7.1, $C_{22}H_{19}NOS$), 344 (18, $C_{22}H_{18}NOS$), 343 (57.3, $C_{22}H_{17}NOS$), 315 (4.4, $C_{21}H_{17}NS$), 284 (15.5, $C_{16}H_{14}NO_2S$), 267 (7.5, $C_{16}H_{13}NOS$), 243 (9.5, $C_{14}H_{13}NOS$), 151 (100, C_8H_7OS), 121 (57, C_7H_7NO), and 97 (7, C_5H_5S).

(2E)-N-(4-Methylphenyl)-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide (23): Brown crystals from benzene-petroleum ether 40-60, mp 175-177 °C, 91.00% yield in microwave and 64.00% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3386 (NH, amide), 1690 and 1640 (2CO, conjugated ketone and amide). MS: m/z =375 (M^+, 1.1%, $C_{23}H_{21}NO_2S$), 359 (8.5, $C_{23}H_{21}NOS$), 358 (26.6, $C_{23}H_{20}NOS$), 357 (100, $C_{23}H_{19}NOS$), 329 (4.7, $C_{22}H_{19}NS$), 315 (2.3, $C_{21}H_{17}NS$), 268 (6, $C_{16}H_{12}O_2S$), 256 (1.6, $C_{15}H_{14}NOS$), 238 (1.4, $C_{15}H_{12}NS$), 214 (2, $C_{13}H_{12}NS$), 134 (3.3, C_8H_8NO), and 91 (31.4, C_7H_7). ^{1}HNMR (DMSO-d_6): δ (ppm) = 7.54 (1H, s, H-8), 7.38-7.35 (1H, d, H-3), 7.33 (1H, s, H-4), 7.31-7.28 (2H, m, H-6), 7.26-7.22 (3H, m, H-7), 7.17-7.14 (2H, d, H-9), 6.99-6.96 (2H, d, H-10), 6.89-6.87 (1H, d, H-2), 3.5 (2H, imp, H-5), 2.3 (3H, s, H-1), and 2.15 (3H, s, H-11).

(2E)-N-(4-Methoxyphenyl)-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide (24): Brown crystals from benzene-petroleum ether 40-60, mp 124-126 °C, 93.00% yield in microwave and 71.61% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3229 (NH, amide), 1670 and 1632 (2CO, conjugated ketone and amide). MS: m/z =391 (M^+, 3.3%, $C_{23}H_{21}NO_3S$), 375 (7.5, $C_{23}H_{21}NO_2S$), 374 (29, $C_{23}H_{20}NO_2S$), 373 (100, $C_{23}H_{19}NO_2S$), 345 (2.1, $C_{22}H_{19}NOS$), 314 (3.7, $C_{17}H_{16}NO_3S$), 300 (2.3, $C_{16}H_{14}NO_3S$), 272(1, $C_{15}H_{14}NO_2S$), 269 (6.7, $C_{16}H_{13}O_2S$), 268 (23.2, $C_{16}H_{14}NOS$), 258 (3.1, $C_{15}H_{16}NOS$), and 149 (17.4, $C_8H_7NO_2$). ^{1}HNMR (DMSO-d_6): δ (ppm) = 7.83 (1H, s, H-8), 7.67-7.6 (1H, d, H-3), 7.6-7.4 (2H, m, H-6), 7.47 (2H, d, H-9), 7.38-7.05 (3H, m, H-7), 7.24 (1H, s, H-4), 7.02-6.92 (2H, d, H-10), 6.91-6.81 (1H, d, H-2), 3.71 (3H, s, H-11), 3.5-3.12 (2H, imp, H-5), and 2.54 (3H, s, H-1).

(2E)-N-(4-Chlorophenyl)-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide (25): Brown crystals from benzene-petroleum ether 40-60, mp 162-164 °C, 83.54% yield in microwave and 68.35% yield in thermal. FTIR (KBr): υ (cm^{-1}) =3397 (NH, amide), 1671 and 1633 (2CO, conjugated ketone and amide). MS: m/z =395 (M^+, 3%, $C_{22}H_{18}NO_2SCl$), 379 (9.2, $C_{22}H_{18}NOSCl$), 378 (6, $C_{22}H_{17}NOSCl$), 377 (18.1, $C_{22}H_{16}NOSCl$), 349 (0.7, $C_{21}H_{16}NSCl$), 342 (0.7, $C_{22}H_{16}NOS$), 318 (2, $C_{16}H_{13}NO_2SCl$), 290 (1.5, $C_{15}H_{13}NOSCl$), 276 (2,

$C_{14}H_{11}NOSCl$), 153 (5.5, C_7H_4NOCl), 111 (2, C_6H_4Cl), and 105 (100, C_7H_5O).

(2E)-N-Ethyl-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide (26): Gray crystals from benzene-petroleum ether 40-60, mp 162-164 °C, 99.00% yield in microwave and 77.00% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3402 (NH, amide), 1676 and 1640 (2CO, conjugated ketone and amide). MS: m/z =313 (M^+, 1%, $C_{18}H_{19}NO_2S$), 299 (1.5, $C_{17}H_{17}NO_2S$), 297 (1.3, $C_{18}H_{19}NOS$), 296 (1.3, $C_{18}H_{18}NOS$), 295 (2.5, $C_{18}H_{17}NOS$), 285 (2, $C_{16}H_{15}NO_2S$), 266 (1.1, $C_{16}H_{12}NOS$), 194(3, $C_{10}H_{12}NOS$), 185 (6.2, $C_{12}H_{11}NO$), 157 (42, $C_{10}H_7NO$), 98 (7, C_5H_8NO), 72 (7, C_3H_6NO), 71 (94, C_3H_5NO), and 57 (100, C_2H_3NO).

(2E)-N-n-Butyl-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide (27): Yellow crystals from benzene, mp 126-128 °C, 96.00% yield in microwave and 73.31% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3395 (NH, amide), 1675 and 1640 (2CO, conjugated ketone and amide). MS: m/z =341 (M^+, 3%, $C_{20}H_{23}NO_2S$), 326 (9.4, $C_{19}H_{20}NO_2S$), 324 (4, $C_{20}H_{22}NOS$), 323 (9.4, $C_{20}H_{21}NOS$), 298 (3.3, $C_{17}H_{16}NO_2S$), 280 (3.2, $C_{17}H_{14}NOS$), 268 (8, $C_{16}H_{12}O_2S$), 267 (7.1, $C_{16}H_{13}NOS$), 246 (2, $C_{14}H_{16}NOS$), 222 (4, $C_{12}H_{16}NOS$), 125 (70, $C_7H_{11}NO$), 105 (100, C_7H_5O), and 99 (15, C_5H_9NO). ^{1}HNMR (DMSO-d_6): δ (ppm) = 7.94-7.9 (1H, t, H-8), 7.84-7.74 (1H, m, H-6), 7.5-7.48 (1H, d, H-3), 7.44-7.26 (3H, m, H-7), 7.34 (1H, s, H-4), 7.1-7 (1H, m, H-2), 3.5 (2H, imp, H-5), 2.05 (3H, s, H-1), 1.6-1.5 (2H, q, H-9), 1.4-1.3 (2H, quintet, H-10), 1.2-1.1 (2H, sextet, H-11), and 0.9-0.74 (3H, t, H-12).

(2E)-N-Benzyl-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide (28): Yellow crystals from benzene, mp 180-181 °C, 93.00% yield in microwave and 74.66% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3248 (NH, amide), 1674 and 1632 (2CO, conjugated ketone and amide). MS: m/z =375 (M^+, 69%, $C_{23}H_{21}NO_2S$), 359 (6.6, $C_{23}H_{21}NOS$), 358 (25.1, $C_{23}H_{20}NOS$), 357 (85.1, $C_{23}H_{19}NOS$), 284 (2.5, $C_{16}H_{14}NO_2S$), 270 (30.3, $C_{16}H_{16}NOS$), 270 (30.3, $C_{16}H_{14}O_2S$), 268 (12.3, $C_{16}H_{12}O_2S$), 266 (33.5, $C_{16}H_{12}NOS$), 256 (5, $C_{15}H_{14}NOS$), 136 (100, C_8H_8S), 134 (9.4, C_8H_8NO), and133 (1.2, C_8H_7NO). ^{1}HNMR (DMSO-d_6): δ (ppm) = 7.46-7.42 (1H, t, H-8), 7.33 (1H, s, H-4), 7.3-7.24 (2H, m, H-6), 7.23-7.22 (1H, d, H-3), 7.16-7.09 (3H, m, H-7), 7.12 (5H, s, H-10), 6.86-6.82 (1H, m, H-2), 4.32-4.26 (2H, d, H-9), 3.31 (2H, imp, H-5), and 2.46 (3H, s, H-1).

(2E, 3Z)-4-Hydroxy-2-[(5-methylthien-2-yl)methylene]-4-phenylbut-3-enohydrazide (29): Orange crystals from benzene, mp 160-162 °C, 80.00% yield in microwave and 46.66% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3300-3000 (hydrogen bonded OH, NH and NH_2), 1654 (CO, amide). MS: m/z =300 (M^+, 0.04%, $C_{16}H_{16}N_2O_2S$), 284 (21, $C_{16}H_{16}N_2OS$), 283 (65.2, $C_{16}H_{15}N_2OS$), 282 (100, $C_{16}H_{14}N_2OS$), 268 (9.3, $C_{16}H_{12}O_2S$), 267 (47, $C_{16}H_{13}NOS$), 266 (8.1, $C_{16}H_{12}NOS$), 254 (4, $C_{15}H_{14}N_2S$), 238 (11, $C_{15}H_{12}NS$), 205 (7.2, $C_{10}H_9N_2OS$), 195 (3.6, $C_9H_{11}N_2OS$), 181 (3, $C_8H_9N_2OS$), and 59 (2.5, CH_3N_2O). ^{1}HNMR (DMSO-d_6): δ (ppm) = 13.19 (1H, s, H-8), 7.86 (2H, s, H-9), 7.78-7.74 (1H, d, H-3), 7.47-7.38 (2H, m, H-6) or (1H, d, H-4), 7.33-7.28 (3H, m, H-7), 6.73-6.70 (1H, d, H-2), 6.6-6.57 (1H, d, H-5), 3.93 (2H, s, H-10), and 2.32 (3H, s, H-1).

(2E)-2-[(5-Methyl-2-thienyl)methylene]-4-oxo-N',4-diphenylbutanehydrazide (30): Brick red crystals from benzene-petroleum ether 40-60, mp 126-128 °C, 92.00% yield in Microwave and 66% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3430-3268 (2NH), 1690 and 1640 (2CO, conjugated ketone and amide). MS: m/z =376 (M^+, 0.22%, $C_{22}H_{20}N_2O_2S$), 359 (2, $C_{22}H_{19}N_2OS$), 358 (4, $C_{22}H_{18}N_2OS$), 330 (0.4, $C_{21}H_{18}N_2S$), 281 (1.1, $C_{16}H_{13}N_2OS$), 279 (24.3, $C_{17}H_{15}N_2O_2$), 267 (2, $C_{15}H_{11}N_2OS$), 266 (2.1, $C_{16}H_{12}NOS$), 251 (5.5, $C_{16}H_{11}OS$), 149 (100, $C_8H_9N_2O$), 135 (2, $C_7H_7N_2O$), 134 (1, $C_7H_6N_2O$), and 105 (4.2, C_7H_5O).

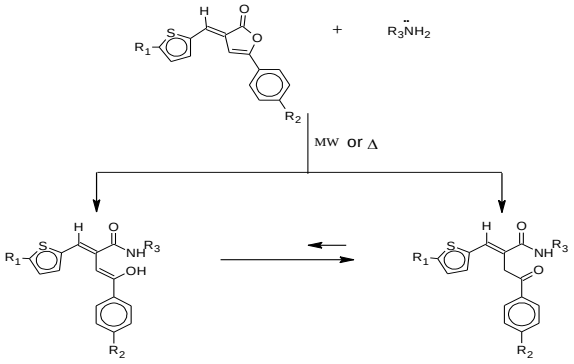
2. Results and Discussion

Solvent-free microwave irradiation reactions were carried out in a one-pot reaction in order to synthesize compounds that expected to have bioactivity **4-30** in an environmentally-safe technique (green chemistry), appreciable high yields and purity. Such requirements are essential for synthesis of bioactive compounds.

The solvent-free microwave irradiation reactions of the studied furanones; (3E)-5-phenyl-3-(2-thienylmethylene)furan-2(3H)-one **1**, (3E)-5-(4-methylphenyl)-3-(2-thienylmethylene)furan-2(3H)-one **2**, and (3E)-3-[(5-methyl-2-thienyl)methylene]-5-phenylfuran-2(3H)-one **3**, with aromatic, aliphatic amines, and phenylhydrazine gave the corresponding (2E) 2-(substituted 2-thienylmethylene)-4-oxo-4-aryl butanamide derivatives **4-10, 12, 13-19, 21, 22-28, 30,** as only products. However in our previous work using □□□-unsaturated anhydrides, the corresponding butanoic acid derivatives, or/and pyrrolidine-2,5-diones.[18-20] were produced. On the other hand, reaction of furanones **1-3** with hydrazine hydrate gave (2E,3Z)-4-hydroxy-4-phenyl-2-(thien-2-ylmethylene)but-3-enohydrazide **11**, (2E,3Z)-4-hydroxy-4-(4-methylphenyl)-2-(thien-2-ylmethylene)but-3-enohydrazide **20**, and (2E,3Z)-4-hydroxy-2-[(5-methylthien-2-yl)methylene]-4-

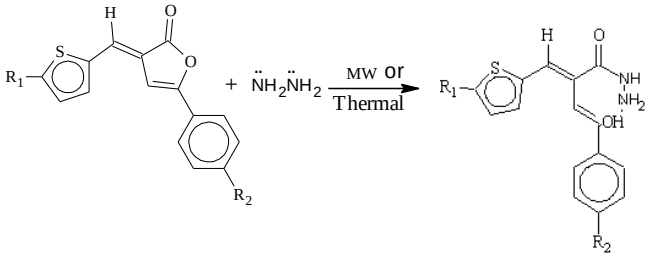
phenylbut-3-enohydrazide **29**, respectively, whereas anhydrides formed the hydrazide derivatives.[18-20]

Solvent-free microwave irradiation of furanones **1-3**, with aniline (a) ($K_b=4.2\times10^{-10}$) as an unsubstituted amine, gave (2E)-4-oxo-N,4-diphenyl-2-(2-thienylmethylene)butanamide **4** (83%), (2E)-4-(4-Methylphenyl)-4-oxo-N-phenyl-2-(2-thienylmethylene)butanamide **13** (86%), and (2E)-2-[(5-methyl-2-thienyl)methylene]-4-oxo-N,4-diphenylbutanamide **22** (90%), respectively. This was attributed to the low basicity of the amine. However with 4-methylaniline (b) ($K_b=14.8\times10^{-10}$), furanones **1-3** formed the corresponding (2E)-N-(4-methylphenyl)-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide **5** (85%), (2E)-N,4-bis(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide **14** (88%), and (2E)-N-(4-methylphenyl)-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide **23** (91%), respectively. Also with 4-methoxyaniline (c) ($K_b=15\times10^{-10}$), furanones **1-3** yielded (2E)-N-(4-methoxyphenyl)-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide **6** (87%), (2E)-N-(4-Methoxyphenyl)-4-(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide **15** (90%), and (2E)-N-(4-methoxyphenyl)-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide **24** (93%), respectively. The higher yield can be attributed to the presence of the electron donating, methyl and methoxyl groups in amines (b) and (c). The enhancement in yields formed with 4-methoxyaniline can be assigned to the higher basicity results from the mesomeric effect exerted by the methoxyl group.



R3	Compound Number: Furanone 1 R_1=H, R_2=H	Furanone 2 R_1 = H, R_2 = CH_3	Furanone 3 R_1=CH_3, R_2=H
C_6H_5	4	13	22
$CH_3C_6H_4$	5	14	23
$CH_3OC_6H_4$	6	15	24
ClC_6H_4	7	16	25
CH_3CH_2	8	17	26
n-Bu	9	18	27
$C_6H_5CH_2$	10	19	28
C_6H_5NH	12	21	30

Scheme (1)



Comp.	R_1	R_2
11	H	H
20	H	CH_3
29	CH_3	H

Scheme (2)

On the other hand, with 4-chloroaniline (d) ($K_b=1\times10^{-10}$), furanones **1-3** formed (2E)-N-(4-chlorophenyl)-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide **7** (73.5%), (2E)-N-(4-chlorophenyl)-4-(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide **16** (81%), and (2E)-N-(4-chlorophenyl)-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide **25** (83.5%), respectively. The decrease in yield could be assigned to the presence of the electron attracting chlorine atom which decreases the amine basicity.

Microwave irradiation of furanones **1-3** with ethylamine (e) ($K_b=5.2\times10^{-4}$), gave (2E)-N-ethyl-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide **8** (96%), (2E)-N-ethyl-4-(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide **17** (97%), and (2E)-N-ethyl-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide **26** (99%), respectively. However, with n-butylamine (f) ($K_b= 4.8\times10^{-4}$), furanones **1-3** produced (2E)-N-butyl-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide **9** (94%), (2E)-N-butyl-4-(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide **18** (95%), and (2E)-N-butyl-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide **27** (96%), respectively. The relative lower yields of the products **9**, **18**, and **27**, than **8**, **17**, and **26**, could be assigned to both the steric factor exerted by the n-butyl group in (f) comparable to the ethyl group in (e), and the higher basicity of (e). With benzylamine (g) ($K_b=0.24\times10^{-4}$), the results obtained showed that furanones **1-3** gave (2E)-N-benzyl-4-oxo-4-phenyl-2-(2-thienylmethylene)butanamide **10** (89%), (2E)-N-benzyl-4-(4-methylphenyl)-4-oxo-2-(2-thienylmethylene)butanamide **19** (91%), and 2E)-N-benzyl-2-[(5-methyl-2-thienyl)methylene]-4-oxo-4-phenylbutanamide **28** (93%). The results obtained ascertained that the basicity of amines outweighs the steric factor. Also with the low basic phenyl hydrazine (h) ($K_b=1.62\times10^{-9}$), furanones **1-3** produced (2E)-4-oxo-N',4-diphenyl-2-(2-thienylmethylene)butanehydrazide **12** (86%), (2E)-4-(4-methylphenyl)-4-oxo-N'-phenyl-2-(2-thienylmethylene)butanehydrazide **21** (89%), and (2E)-2-[(5-methyl-2-thienyl)methylene]-4-oxo-N',4-diphenylbutanehydrazide **30** (92%), respectively.

The results obtained led us to propose a mechanism in which a nucleophilic attack by the lone pair of amino nitrogen takes place on the carbonyl carbon of the furanone to form the unstable enol form, which undergoes tautumerization to give the more stable keto compounds. (Scheme 1)

However, the results obtained from solvent-free microwave irradiation of furanones **1-3**. with hydrazine hydrate (i) ($K_b=8.5\times10^{-7}$), to give (2E,3Z)-4-hydroxy-4-phenyl-2-(thien-2-ylmethylene)but-3-enohydrazide **11** (64.5%), (2E,3Z)-4-hydroxy-4-(4-methylphenyl)-2-(thien-2-ylmethylene)but-3-enohydrazide **20** (66.3%), and (2E,3Z)-4-hydroxy-2-[(5-methylthien-2-yl)methylene]-4-phenylbut-3-enohydrazide **29** (80%), respectively, led us to propose a mechanism in which the enol form is stabilized by the formation of a hydrogen bond between the amino nitrogen and the OH group (Scheme 2). This mechanism was confirmed by the ^{1}H-NMR of the products (**11**, **20**, and **29**) where they showed signals at δ (ppm) = 13.2 (1H, s, H-8), 13.13 (1H, s, H-9), and 13.19 (1H, s, H-8), respectively corresponding to the OH of the enol form. Also their FTIR (KBr) showed bands at υ (cm^{-1}) in the range 3350-3000 characteristic for hydrogen bonded OH, NH and NH_2, and 1651-1654, for C=O amide. This was also confirmed by the results obtained from microwave irradiation of furanones **1-3** with phenylhydrazine where stable keto compounds (2E)-4-oxo-N',4-diphenyl-2-(2-thienylmethylene)butanehydrazide **12**, (2E)-4-(4-methylphenyl)-4-oxo-N'-phenyl-2-(2-thienylmethylene)butanehydrazide **21**, and (2E)-2-[(5-methyl-2-thienyl)methylene]-4-oxo-N',4-diphenylbutanehydrazide **30** respectively, were produced.

Structural Effect of Furanones 1-3 on their Reaction with Amines and Hydrazines (a-i)

It was of great interest to study the structural effect of furanones **1-3** on their solvent-free microwave irradiation reactions with amines (a-g), and phenylhydrazine (i), to give the corresponding (2E)-N-substituted -2-(5-substituted-2-thienylmethylene)-4-oxo-4-aryl butanamide derivatives **4-10, 12, 13-19, 21, 22-28,** and **30,** whereas with hydrazine hydrate, they gave (2E,3Z)-4-hydroxy-4-aryl-2-(5-substituted thienylmethylene)but-3-enohydrazide **11**, **20**, and **29**, respectively. With all amines, the results obtained showed that the yields produced from furanones **1-3** fall in the order: **3**>**2**>**1**. These results led us to propose a mechanism in which intermediate (II) is formed, that containing charge separation, so that the presence of electron releasing methyl (CH_3) group in the thinly ring stabilizes and activates it toward product formation. The presence of the (CH_3) group in the phenyl ring in furanone **2**, stabilizes intermediate II, leading to enhancement in the yield than furanone **1.**

Furanones versus Anhydrides

Comparison between the results obtained from solvent-free microwave irradiation of furanones **1-3,** as α,β-unsaturated carbonyl compounds, with those obtained from α,β-unsaturated anhydrides, showed

that furanones formed the corresponding butanamides as only products, whereas α,β-unsaturated anhydrides produced butanoic acid derivatives or/and pyrrolidine-2,5-diones.[18-20] This can be attributed to the low susceptibility of the carbonyl carbon of the aroyl group in the butanamides towards further intramolecular nucleophilic attack by the amido nitrogen to form the cyclic product. Moreover, with hydrazine hydrate, furanones **1-3** produced the corresponding enolhydrazines (**11**, **20**, and **29**), respectively, whereas α,β-unsaturated anhydrides gave the corresponding hydrazides.[10-12] These results led us to propose a mechanism in which intermediate II is formed through the reaction of furanones, whereas intermediate I is formed with anhydrides. In intermediate I the presence of partial positive charge on carbonyl carbon increase its susceptibility towards intramolecular nucleophilic attack by the amido nitrogen to form the cyclic products. Many trials for cyclizing the produced butenamides in presence of different cyclizing agents were unsuccessful.

Although both intermediates I and II contain charge separation, but the amido nitrogen in intermediate II is involved in the continuous conjugated system until the thienyl ring, whereas in intermediate I it is separated by the methylene group. Therefore, the presence of the electron-releasing methyl group in the thienyl ring would stabilize intermediate II, through the decrease of the positive charge on the amido nitrogen, resulting in the enhancement of the yield produced from furanone **3**. (Fig. 1)

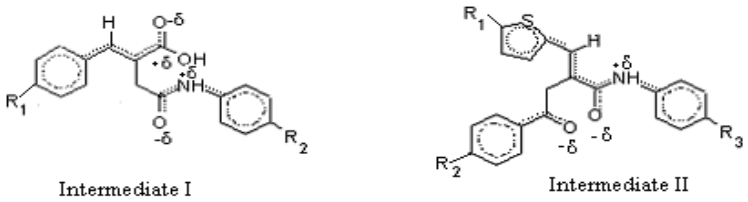


Figure 1

Conventional Thermal Heating of Furanones 1-3 with Amines and Hydrazines (a-i)

Conventional thermal heating reactions of furanones **1-3** with amines (a-i) gave the corresponding butanamides and hydrazides **4-30** as only products, in lower yields comparable to the products obtained from the microwave irradiation reactions. However, reaction of furanone **2** with the aromatic amines; aniline (a), 4-methylaniline (b), and 4-chloroaniline (d), to give butanamides **13**, **14**, and **16**, respectively, required more drastic conditions (reflux for 15 hours, molar ratio 1:10), instead of 3 hours and molar ratio 1:2, used with 4-methoxyaniline (c). These results can be explained on the basis of the weak basicity of amines (a, b, and d) relative to the basicity of amine (c), due to mesomeric effect exerted by the electron releasing methoxyl group. It can also be attributed to the steric effect exerted by the sp^3 hybridized CH_3 carbon in furanone **2**, attached to the phenyl group in the reacting moiety.

However, under microwave irradiation technique, the unexpected formation of the corresponding butanamides **13**, **14** and **16** from furanone **2** with amines (a, b, and d), irrespective to their low basicity, can be attributed to the acceleration results from material-wave interactions, leading to thermal effects (dielectric heating), or/and specific non-purely thermal effects. The combination of these two contributions can be responsible for the observed results.

Molecular Structural Assignment

Molecular structural assignment of compounds **4-30** were assigned by their spectral analyses; FTIR, MS, and ^{1}H-NMR. The protons numbering of ^{1}H-NMR spectra of some compounds are given in Figure 2.

Antimicrobial Activity

The antimicrobial screening of compounds; **4**, **6**, **9-13**, **15**, **18-22**, and **24-30**, 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; *Bacillus subtilis* (G^+), *Staphylococcus aureus* (G^+), *Escherichia coli* (G^-), and *Pseudomonas aeruginosa* (G^-). The screened compounds showed pronounced antibacterial activity. The results obtained are given in Table 2.

Cytotoxic Activity

In vitro cytotoxic activity (IC50) of compounds **4**, **13**, **22**, **6**, **15**, **24**, **10**, **19** and **28** against a human breast carcinoma cell line using flouraciele as a reference drug, using the method that reported by Skehan[21], 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.

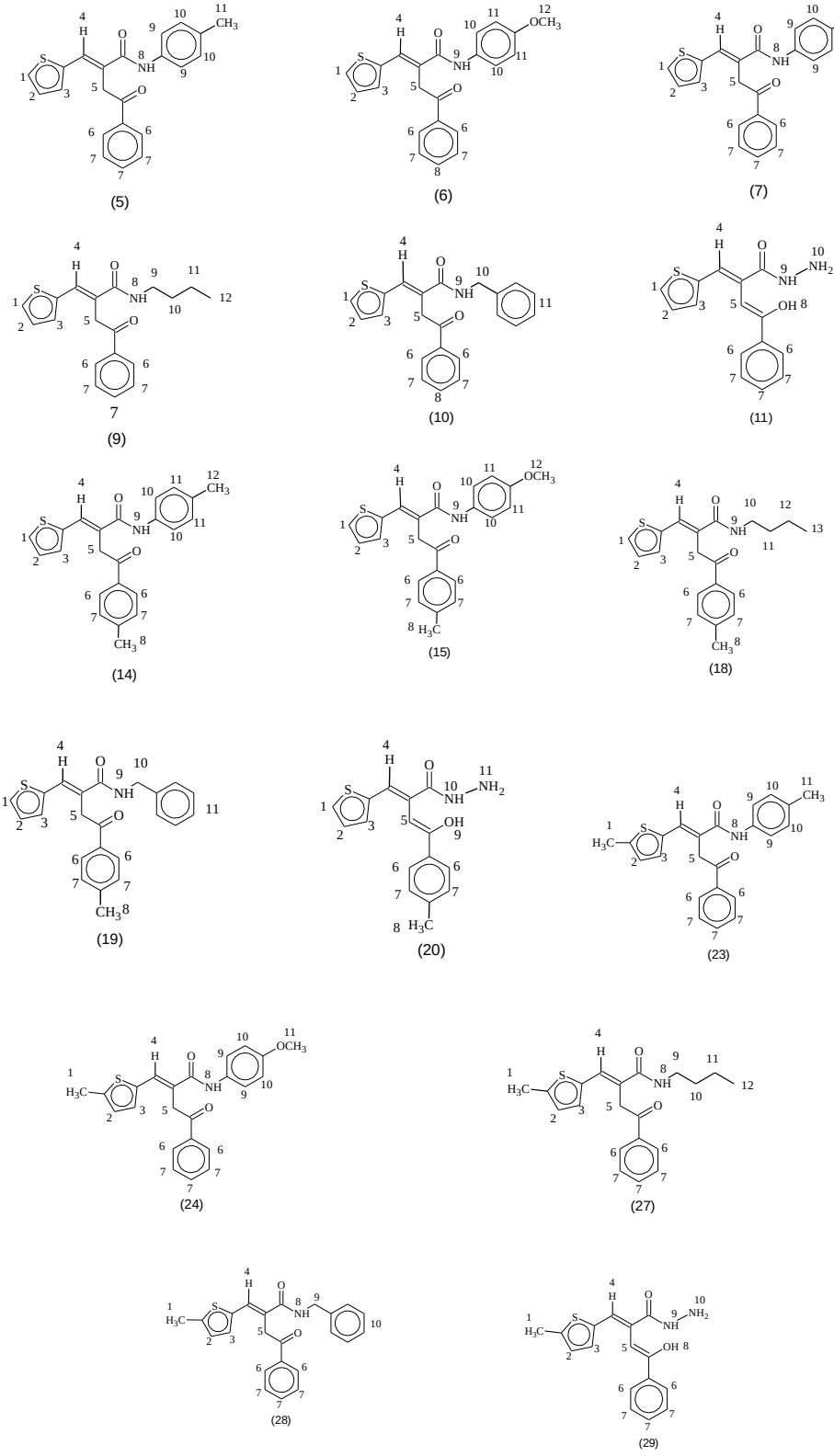


Figure 2

Table (2): Antimicrobial and Cytotoxic Activities of the Some Compounds

Compd. No.	Inhibition zone (mm)				Cytotoxic activity IC50 µg/ml
	Staphylococcus aureus	*Escherichia coli*	*Bacillus subtilis*	*Pseudomonas aeroginosa*	
4	No growth	No growth	18 ++	No growth	10.7
6	No growth	No growth	-ve	No growth	11.4
9	No growth	No growth	19 ++	No growth	---
10	No growth	No growth	-ve	No growth	17.6
11	No growth	No growth	-ve	No growth	---
12	No growth	No growth	15 ++	No growth	---
13	No growth	No growth	10 +	No growth	16.8
15	No growth	No growth	-ve	No growth	13.1
18	No growth	No growth	-ve	No growth	---
19	No growth	No growth	-ve	No growth	11
20	No growth	No growth	-ve	No growth	---
21	No growth	No growth	-ve	No growth	---
22	No growth	No growth	-ve	No growth	11
24	No growth	No growth	-ve	No growth	11.1
27	No growth	No growth	-ve	No growth	---
28	No growth	No growth	10	No growth	12.8
29	No growth	No growth	-ve	No growth	---
30	No growth	No growth	10 +	No growth	---
Standard antibacterial agent is Durecif	No growth	No growth	No growth	33 +++	Reference drug is Flouraciele

4. Conclusion

- The one-pot solvent-free microwave irradiation reactions were carried out in to synthesize compounds expected to have bioactivity **4-30** in environmentally-safe technique (green chemistry), appreciable high yields and purity. Such requirements are essential for synthesis of bioactive compounds.
- Furanones reactivity **1-3** falls in the order: **3**>**2**>**1**. These results are attributed to the presence of electron releasing methyl (CH_3) group in the thinly ring which stabilizes and activates it toward product formation.
- The formation of the corresponding butanamides as only products with furanones, comparable to the formation of butanoic acid derivatives or/and pyrrolidine-2,5-diones with α,β-unsaturated anhydrides, is attributed to the low susceptibility of the carbonyl carbon of the aroyl group in the butanamides towards further intramolecular nucleophilic attack by the amido nitrogen to form the cyclic product.

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References

1. Negishi, E.-I.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707-6738.
2. Collins, I. *J. Chem. Soc., Perkin Trans.* **1999**, 1377-1395.
3. Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285-292.
4. El-Abbady, A. M.; Omera, M. A.; Kandil, N. G. *Rev. Roum. Chim.* **1974**, *19*, 79.
5. Guirguis, N. R.; Awad, B. M.; Saad, H. A. Liebigs. *Ann. Chem.* **1986**, *6*, 1003-11.
6. Guirguis, N. R.; Awad, B. M.; Saad, H. A. *J. Prackt. Chem.* **1990**, *332*, 414
7. Hashem, A. I.; Shaban, M. E. *J. Prakt. Chem.* **1981**, *323*, 164.
8. Hashem, A. I.; Hamad, A. S. S. *Molecules* **2000**, *5*, 895-907.
9. Hashem, A. I.; Hamad, A. S. S.; Derbala, H. A.; El-Sayed, W. A. *Acta. Chem. Sol.* **2001**, 417-425.
10. Gedye, R. N.; Smith, F.; Westaway, K.; Ali, H.;Baldisera, L.; Laberge, L.; Rousell, J. Tetrahedron Letters **1986**, *27*, 279-282.
11. Caddick, S.; Fizmaurice, R. *Tetrahedron Letters* **2009**, *65*, 3325-3355.
12. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Taquault, P.; Mathe, D. *Synthesis* **1998**, 1213-1234.
13. Loupy, A., *C. R. Chim.* **2004**, *7*, 103-112.
14. Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565-3585.
15. Marquez, H.; Loupy, A.; Calderon, O.; Perez, E. R. *Tetrahedron* **2006**, *62*, 2616-2621.
16. Gardre, J. N.; Vardhan, D. K.; Late R. N.; Mohit M.; Chaitanya, V. *Research J. Chem. Enviro.* **2004**, *8* (1), 13-15.
17. Strubing, D.; Neumann, H.; Jacobi von Wangelin, A.; Klaus, S.; Hubnre, S. Beller, M. *Tetrahedron* **2006**, *62*, 10962-10967.
18. Abdallah, Sh. M; Hefny, H. A. *Turkish Journal of Chemistry* **2012**, *35*, 463- 474
19. Awad, B. M.; Abdallah, Sh. M; Hefny, H. A. Abdou, M.; Abdelmonem, F.; Abdelmonem, N. *Journal of American Science* **2012**, *8*(2), 87-95.
20. Awad, B. M.; Abdallah, Sh. M; Hefny, H. A. Abdou, M.; Abdelmonem, F.; Abdelmonem, N. *Life Science Journal* **2012**, *9* (4), 567-577.
21. Skehan, P.; Storeng, R. *J. Nat. Cancer Inst*. **1990**, *82*, 1107-1112.

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