Synthesis of some new (E)-2-arylidine-4-oxo-4-arylaminobutanoic acids and (E)-3-arylidine-1-arylpyrrolidine-2,5-diones of possible medicinal applications and biological activities

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Abstract: Synthesis of compounds **3-32** of possible medicinal and biological activities have been carried out by reaction of (E)-3-(3,4-dimethoxybenzylidene)dihydrofuran-2,5-dione (**1**) and (E)-3-(benzo[d] [1,3] dioxol-5-ylmethylene)dihydrofuran-2,5-dione (**2**) with aromatic amines (**a-h**) using microwave and conventional thermal heating to study the structural effect of reactants and techniques used. The microwave irradiation of compound **1** gave (E)-2-(3,4-dimethoxybenzylidine)-4-oxo-4-arylaminobutanoic acid**s 3-5** and (E)-3-(3,4-dimethoxybenzylidene)-1-arylpyrrolidine-2,5-diones **11-17.** Also compound **2** gave (E)-2-(benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-arylaminobutanoic acids **18-23**, and (E)-3-(benzo[d][1,3]dioxol-5-ylmethylene)-1-arylpyrrolidine-2,5-diones **26-32.** In all reactions, microwave irradiation technique, showed enhancement in yields, selectivity, cleaner reactions with reduction in reaction time, and easier working up than in the conventional thermal heating technique. On the other hand, reaction of compounds **1** or **2** with amines **a-h** using the conventional thermal heating technique yielded only the corresponding (E)-2-arylidine-4-oxo-4-arylaminobutanoic acid derivatives **3-10**, or **18-25**, respectively. The structural formulas of the products obtained were assigned by their spectral data. Some prepared compounds were found to have cytotoxic and antimicrobial activities.

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Introduction

Microwave-assisted organic synthesis is rapidly becoming recognized[1]. Coupling of microwave irradiation with solvent-free technique allows enhancement in yields, selectivity, cleaner reactions with reduction in reaction time, and easier working up[2-8].

The synthesis of some butenamides and pyrrolidine-2,5-diones by microwave irradiation of some α,β-unsaturated anhydrides with some aliphatic or aromatic amines, was found to be more convenient and efficient, comparable to the conventional thermal heating technique. Some of the products obtained showed biological and cytotoxic (antiproliferative) activities[9-11]. The conventional thermal condensation of γ-phenylitaconic anhydrides with hydrazine hydrate, aromatic or aliphatic amines gave the corresponding biological active γ-aryl itaconic hydrazides, γ-aryl itaconamic acids and γ-aryl itaconimides, respectively[12].

The aim of the present work is to synthesize some new 2-substituted methylene-4-oxo-4-arylaminobutanoic acid and pyrrolidine-2,5-dione derivatives as antimicrobial and cytotoxic compounds in an efficient procedure, short time, high yield and purity, and also to study the factors affecting the reaction.

Experimental

(E)-3-(3,4-dimethoxybenzylidene)dihydrofuran-2,5-dione **1** and (E)-3-(benzo[d] [1,3] dioxol-5-ylmethylene) dihydrofuran-2,5-dione **2** were prepared and purified[13]. Microwave irradiation of compounds **1** or **2** with different aromatic amines; aniline (**a**), 2-aminoaniline (**b**), 2-mercaptoaniline (**c**), 2-hydroxyaniline (**d**), 2-methoxyaniline (**e**), 2-methylaniline (**f**), 2-aminopyridine (**g**), or 2-aminothiazole (**h**), have been carried out in absence of solvents. The factors affecting this reaction, such as structures of reactants, basicity of amines, and solvent effect were studied. Some microwave irradiation reactions were carried out in presence of dimethyl formamide as an aprotic solvent, in order to study the effect of solvation on the reaction. The biological activities; cytotoxic and antimicrobial were screened. The results obtained from the microwave irradiation reactions were compared with the corresponding conventional thermal reactions.

General remarks

Microwave irradiation was carried out in a Galanz Microwave Oven, WP1000AP30-2, Chemistry Department, University College of Women for Arts, Science and Education, Ain Shams

University. 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.

(d) Biological activity: Antimicrobial Screening was measured in the Botany Department, University College of Women for Arts, Science, and Education, Ain Shams University, Asma Fahmy Street, Heliopolis, Cairo, Egypt

(e) Cytotoxic measurements were carried out in the National Institute of Cancer, Cairo University, Cairo, Egypt.

Microwave irradiation technique

In an open vessel a homogenous grinded mixture of compounds **1** or **2** with different aromatic amines (**a**-**h**) was dry irradiated for 2-5 minutes in a microwave oven (1000 watt, 100% power). The reaction progress was monitored by thin layer chromatography (TLC) until no more unreacted materials were observed. The reaction mixture was then cooled down to room temperature and dissolved in chloroform. The chloroform layer was washed with dilute HCl to get rid of unreacted amine, followed by its extraction with 10% ice-cold sodium carbonate solution. Acidification of the aqueous layer with ice-cold concentrated hydrochloric acid, precipitated the corresponding (E)-2-(3,4-dimethoxybenzylidine)-4-oxo-4-(arylamino)butanoic acids **3**-**5** or (E)-2-(benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(arylamino)butanoic acids **18**-**23**. On the other hand the organic layer was thoroughly washed with water, dried over anhydrous sodium sulfate and distilled to give the corresponding (E)-3-(3,4-dimethoxybenzylidene)-1-arylpyrrolidine-2,5-diones **11**-**17**, or (E)-3-(benzo[d] [1,3] dioxol-5-ylmethylene)-1-arylpyrrolidine-2,5-diones **26**-**32**.

Reaction of compounds **1** and **2** with amine **b** in presence of DMF as a solvent gave the arylpyrrolidine-2,5-diones **12** and **27**, respectively.

The products obtained **3**-**32** were crystallized from the appropriate solvent and their structures were confirmed by their spectral analysis data; IR, ^{1}H-NMR and MS.

Conventional thermal heating technique

A homogenous mixture of **1** or **2**, with different aromatic amines (**a**-**h**) (1:2) was heated under reflux for at least 4 hrs in benzene. The reaction progress was monitored by TLC. The reaction mixture was then concentrated and the precipitate formed was filtered and dissolved in chloroform then worked up in the same way given in the solvent-free microwave irradiation technique. Structures of products were confirmed by their melting and mixed melting points, spectral measurements, FTIR, ^{1}H-NMR, and MS.

Table 1: Biological activities of some butanoic acids

Product	Antimicrobial Activity Inhibition zone (mm/mg sample)				Cytotoxic activity IC50 µg/ml
	Bacillus subtilis (G^+)	*E. Coli* (G^-)	*Pseudomonas aeruginosa* (G^-)	*Staphylococcus Aureus* (G^+)	
5	30	---	15	03	---
6	15	---	---	20	---
7	22	15	20	21	---
9	15	20	21	17	---
10	---	16	17	---	---
13	---	---	---	---	7.5
16	---	---	---	---	7.7
17	---	---	---	---	9
20	30	---	---	30	---
21	23	16	15	22	---
22	15	17	22	16	---
24	15	16	19	15	---
25	15	---	20	15	---
28	---	---	---	---	16
31	---	---	---	---	6.45
32	---	---	---	---	13.7
Doxorubicin	---	---	---	---	3.73

Biological activity: Antimicrobial screening

The antimicrobial screening of carboxylic compounds; **5**-**7**, **9**, **10**, **20**-**22**, **24**, and **25**, was carried out using the disk diffusion method, inhibition zone diameter (mm/mg sample) in DMSO as solvent. It showed 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 most pronounced antibacterial activities were obtained with compounds **5** and **20**, where (G^+) is 30 (mm/mg), whereas the other compound showed (G^-) and/or (G^+) in the range 15-23 (mm/mg). The results obtained are given in Table 1. The high activity of compounds **5** and **20** could be attributed to the presence of mercapto (-SH) group.

Medicinal application: Cytotoxic activity

Cytotoxic activity of compounds **13**, **16**, **17**, **28**, **31**, and **32** was tested by using HEPG2-DOX as a reference drug, against human liver carcinoma cell line using the method that reported by **Skehan *et al.***[14]. The results obtained showed that compounds **28**, **32** and **17**, have low activity (16.0, 13.7, 9.0; IC50 µg/ml, respectively), whereas compounds **13**, **16** show moderate activity, (7.5, 7.7; IC50 µg/ml, respectively), and compound **31** is the most active one (6.45; IC50 µg/ml), compared to the reference drug (3.73; IC50 µg/ml). IC50 is defined as the concentration that results in a 50% decrease in cell number as compared with that of the control structures in the absence of an inhibitor.

(E)-2-(3,4-Dimethoxybenzylidine)-4-oxo-4-phenylaminobutanoic acid (3): White crystals from ethanol, mp 190 ºC**,** 5% yield in microwave and 99% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3345 (NH, amide) 3400-2400 (OH, acid), 1703 (CO, acid) and 1665 (CO, amide). MS: m/z = 341 (M^+, 3.5%, $C_{19}H_{19}NO_5$), 323 (1.5, $C_{19}H_{17}NO_4$), 248 (38, $C_{13}H_{12}O_5$), 176 (100, $C_{11}H_{12}O_2$), 161 (47, $C_{10}H_9O_2$), 147 (2.5, $C_8H_5NO_2$), 119 (7, C_7H_5NO), 115 (20, $C_4H_5NO_3$), 93 (36, C_6H_7N) and 92 (14, C_6H_6N).

(E)-2-(3,4-Dimethoxybenzylidine)-4-oxo-4-(2-aminophenylamino)butanoic acid (4): White crystals from ethanol, mp 249-250 ºC, 97% yield in microwave and 95% yield in thermal. FTIR (KBR): υ (cm^{-1}) = 3300-3272 ($^+NH_3$, anilinium and NH, amide), 1679 (CO, amide), and 1516-1448 (2CO, carboxylate). MS: m/z = 356 (M^+, 2%, $C_{19}H_{20}N_2O_5$), 339 (5, $C_{19}H_{19}N_2O_4$), 338 (24, $C_{19}H_{18}N_2O_4$), 321 (1, $C_{19}H_{15}NO_4$), 310 (1.5, $C_{18}H_{18}N_2O_3$), 293 (30, $C_{17}H_{13}N_2O_3$), 248 (6, $C_{13}H_{12}O_5$), 247 (6, $C_{13}H_{13}NO_4$), 217 (3, $C_{12}H_{11}NO_3$), 134 (3, $C_7H_6N_2O$), 133 (9, $C_7H_5N_2O$), and 132 (100, $C_7H_4N_2O$).
^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.68 (3H, s, H-1), 3.76 (3H, s, H-2), 3.63 (2H, s, H-7), 6.98-7.01 (1H, dd, H-10), 7.10-7.13 [3H, m, (H-3), (H-11), and (H-12)], 7.18-7.20 (1H, dd, H-4), 7.46-7.49 [3H, m, (H-5), (H-6), and (H-13)], 7.49 (1H, s, H-8), and 7.82 (3H, s, H-9).

(E)-2-(3,4-Dimethoxybenzylidine)-4-oxo-4-(2-mercaptophenylamino)butanoic acid (5): White crystals from acetone, mp 168-170 ºC, 93% yield in microwave and 88% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-2400 (OH, acid), 3100-3050 (NH, amide), 2614 (SH), and 1657 (CO, acid and CO, amide). MS: m/z = 373 (M^+, 0.01%, $C_{19}H_{19}NO_5S$), 356 (14, $C_{19}H_{18}NO_4S$), 355 (59, $C_{19}H_{17}NO_4S$), 328 (0.02, $C_{18}H_{18}NO_3S$), 248 (3, $C_{13}H_{12}O_5$), 247 (2, $C_{13}H_{13}NO_4$), 151 (6.6, C_7H_5NOS), 150 (10.5, C_7H_4NOS), and 149 (100, C_7H_3NOS). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.40 (2H, imp, H-7), 3.75 (3H, s, H-1), 3.77 (3H, s, H-2), 4.33 (1H, s, H-9), 6.99-7.03 (1H, dd, H-4), 7.17-7.19 (1H, d, H-3), 7.35-7.44 [2H, m, (H-5) and (H-12)], 7.46-7.52 (1H, m, H-11), 7.86 (1H, s, H-6), 7.92-7.95 (1H, dd, H-10), 8.02-8.05(1H, dd, H-13), and 12.80 (1H, br., H-14).

(E)-2-(3,4-Dimethoxybenzylidine)-4-oxo-4-(2-hydroxyphenylamino)butanoic acid (6): Pale brown crystals from benzene, mp 193-194 ºC, 0% yield in microwave and 96% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-2400 (OH, acid), 3318 (OH, phenol), 3173 (NH, amide), and 1662 (CO, acid and CO, amide). MS: m/z =357 (M^+, 14%, $C_{19}H_{19}NO_6$), 340 (1, $C_{19}H_{18}NO_5$), 339 (6, $C_{19}H_{17}NO_5$), 248 (96, $C_{13}H_{12}O_5$), 220 (6, $C_{11}H_9NO_4$), 176 (99, $C_{11}H_{12}O_2$), 161 (56, $C_{10}H_9O_2$), 136 (5, $C_7H_6NO_2$), and 109 (100, C_6H_7NO). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.62 (2H, s, H-7), 3.76 (3H, s, H-1), 3.78 (3H, s, H-2), 6.73-6.79 [(1H, d, H-3) and (1H, dd, H-10)], 6.84-6.94 [2H, m, (H-11) and (H-12)], 7.01-7.16 (1H, dd, H-4), 7.25-7.26 (1H, d, H-5), 7.77 (1H, s, H-6), 7.87-7.90 (1H, dd, H-13), 9.33 (1H, s, H-9), 9.84 (1H, s, H-8), and 12.56 (1H, br., H-14).

(E)-2-(3,4-Dimethoxybenzylidine)-4-oxo-4-(2-methoxyphenylamino)butanoic acid (7): White crystals from ethanol, mp 196 ºC, 0% yield in microwave and 93% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-2400 (OH, acid), 3323 (NH, amide), 1679 (CO, acid) and 1653 (CO, amide). MS: m/z = 371 (M^+, 47%, $C_{20}H_{21}NO_6$), 354 (0.6, $C_{20}H_{20}NO_5$), 353 (3, $C_{20}H_{19}NO_5$), 326 (1, $C_{19}H_{20}NO_4$), 248 (39, $C_{13}H_{12}O_4$), 177 (13, $C_9H_7NO_3$), 176 (48, $C_{11}H_{12}O_2$), 161 (27, $C_{10}H_9O_2$), 150 (5, $C_8H_8NO_2$), 149 (4, $C_8H_7NO_2$), and 123 (100, C_7H_9NO). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.62 (2H, s, H-7), 3.76 (3H, s, H-1), 3.78 (3H, s, H-2), 3.84 (3H, s, H-9), 6.65-6.95 [2H, m, (H-3), and (H-10)], 7.01-7.04 (1H, m, H-12), 7.01-7.17 (1H, dd, H-4), 7.20-7.28 (1H, m, H-11), 7.36 (1H, d, H-5), 7.76 (1H, s, H-6), 8.02-8.05 (1H, dd, H-13), and 9.33 (1H, s, H-8).

(E)-2-(3,4-Dimethoxybenzylidine)-4-oxo-4-(2-methylphenylamino)butanoic acid (8): White crystals from ethanol, mp 212-213 ºC, 0% yield in microwave and 91% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3305 (NH, amide), 3400-2400 (OH, acid), 1684 (CO, acid) and 1661.5 (CO, amide). MS: m/z = 355 (M^+, 92%, $C_{20}H_{21}NO_5$), 354 (3, $C_{20}H_{20}NO_5$), 338

(2, $C_{20}H_{20}NO_4$), 337 (6, $C_{20}H_{19}NO_4$), 310 (7, $C_{19}H_{20}NO_3$), 248 (37, $C_{13}H_{12}O_5$), 176 (62, $C_{11}H_{12}O_2$), 175 (55.5, $C_{10}H_9NO_2$), 161 (41, $C_{10}H_9O_2$ or $C_9H_7NO_2$), 132 (10, C_8H_6NO), 107 (100, C_7H_9N), 91 (87, C_7H_7) and 89 (19, C_7H_5).

(E)-2-(3,4-Dimethoxybenzylidine)-4-oxo-4-(pyridin-2-ylamino)butanoic acid (9): White crystals from ethanol, mp 198-200 ºC, 0% yield in microwave and 99% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-2400 (OH, acid), 3246 (NH, amide), and 1685 (CO, acid and CO, amide). MS: m/z = 342 (M^+, 19%, $C_{18}H_{18}N_2O_5$), 325 (5, $C_{18}H_{17}N_2O_4$), 324 (23, $C_{18}H_{16}N_2O_4$), 297 (2, $C_{17}H_{17}N_2O_3$), 248 (48, $C_{13}H_{12}O_5$), 176 (52, $C_{11}H_{12}O_2$), 134 (4, $C_7H_6N_2O$), 121 (100, $C_6H_5N_2O$), and 78 (64, C_5H_4N).

(E)-2-(3,4-Dimethoxybenzylidine)-4-oxo-4-(thiazol-2-ylamino)butanoic acid (10): White crystals from ethanol, mp 226-228 ºC, 0% yield in microwave and 99% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-2400 (OH, acid), 2966 (NH, amide), and 1675 (CO, acid and CO, amide). MS: m/z = 348 (M^+, 4%, $C_{16}H_{16}N_2O_5S$), 331 (7, $C_{16}H_{15}N_2O_4S$), 330 (36, $C_{16}H_{14}N_2O_4S$), 302 (1, $C_{15}H_{14}N_2O_3S$), 248 (46, $C_{13}H_{12}O_5$), 176 (100, $C_{11}H_{12}O_2$), 161 (40.5, $C_{10}H_9O_2$), 126 (2, $C_4H_2N_2OS$), 115 (20, $C_4H_5NO_3$), 100 (63, $C_3H_4N_2S$), and 98 (1.2, $C_4H_4NO_2$).

(E)-3-(3,4-Dimethoxybenzylidene)-1-phenylpyrrolidine-2,5-dione (11): Pale yellow crystals from benzene , mp 211-212 ºC, 95% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1770 and 1706 (2CO, imide). MS: m/z = 323 (M^+, 74%, $C_{19}H_{19}NO_5$), 176 (100, $C_{11}H_{12}O_2$), 175 (9, $C_{11}H_{11}O_2$), 162 (6, $C_{10}H_{10}O_2$), 161 (46, $C_{10}H_9O_2$ or $C_9H_7NO_2$), 145 (6, $C_{10}H_9O$), 119 (17, C_7H_5NO), 107 (11, C_7H_7O) and 91 (25, C_6H_5N).

(E)-3-(3,4-Dimethoxybenzylidene)-1-(2-aminophenyl)pyrrolidine-2,5-dione (12): Pale brown crystals from benzene, mp 224-226 ºC, 95% yield in microwave (only in the presence of DMF) and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3426-3348 (NH_2) and 1758-1635 (2CO, imide). MS: m/z = 338 (M^+, 57%, $C_{19}H_{18}N_2O_4$), 322 (4, $C_{19}H_{16}NO_4$), 321 (28, $C_{19}H_{15}NO_4$), 247 (15, $C_{13}H_{12}NO_4$), 246 (8, $C_{13}H_{12}NO_4$), 176 (49, $C_{11}H_{12}O_2$), 162 (9.5, $C_8H_6N_2O_2$), and 134 (56, $C_7H_6N_2O$).

(E)-3-(3,4-Dimethoxybenzylidene)-1-(2-hydroxyphenyl)pyrrolidine-2,5-dione (13): Brown crystals from benzene, mp 223-224 ºC, 96% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3374 (OH, phenol), 1766 -1643 (2CO, imide).MS: m/z = 339 (M^+, 100%, $C_{19}H_{17}NO_5$), 338 (2,$C_{19}H_{16}NO_5$), 322 (2, $C_{19}H_{16}NO_4$), 311 (1, $C_{18}H_{17}NO_4$), 297 (2, $C_{17}H_{15}NO_4$), 294 (30.5, $C_{18}H_{16}NO_3$), 246 (0.3, $C_{13}H_{12}NO_4$), 189 (3, $C_{10}H_7NO_3$),176 (44, $C_{11}H_{12}O_2$), and 135 (12, $C_7H_5NO_2$). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.75 (2H, s, H-7), 3.83 (3H, s, H-1), 3.85 (3H, s, H-2), 6.87-6.92 [2H, m, (H-3) and (H-9)], 6.95-6.98 (1H, dd, H-4), 7.06-7.11 [2H, m, (H-10) and (H-11)], 7.13 (1H, d, H-5), 7.26-7.31 (1H, dd, H-12), 7.51 (1H, s, H-6), and 9.75 (1H, s, H-8).

(E)-3-(3,4-Dimethoxybenzylidene)-1-(2-methoxyphenyl)pyrrolidine-2,5-dione (14): Grey crystals from benzene, mp 186 ºC, 93% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1769-1647 (2CO, imide). MS: m/z = 353 (M^+, 93%, $C_{20}H_{19}NO_5$), 339 (3, $C_{19}H_{17}NO_5$), 322 (3, $C_{19}H_{16}NO_4$), 294 (3, $C_{18}H_{16}NO_4$), 280 (7, $C_{17}H_{14}NO_3$), 203 (4, $C_{11}H_{19}NO_3$), 177 (14.5, $C_9H_7NO_3$), 161 (31, $C_{10}H_9O_2$), 150 (11, $C_8H_8NO_2$), 149 (57, $C_8H_7NO_2$), and 57 (100, C_2H_3NO). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.75 (2H, s, H-7), 3.80 (3H, s, H-1), 3.81 (3H, s, H-2), 3.83 (3H, s, H-8), 7.02-7.04 (1H, m, H-9), 7.06-7.09 (1H, d, H-3), 7.18-7.21 (1H, dd, H-4), 7.23-7.28 [2H, m, (H-10) and (H-11)], 7.30 (1H, d, H-5), 7.44-7.49 (1H, dd, H-12), and 7.52 (1H, s, H-6).

(E)-3-(3,4-Dimethoxybenzylidene)-1-(2-methylphenyl)pyrrolidine-2,5-dione (15): White crystals from benzene, mp 186-188 ºC, 90% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1766-1647 (2CO, imide). MS: m/z = 337 (M^+, 100%, $C_{20}H_{19}NO_4$), 336 (15, $C_{20}H_{18}NO_4$), 322 (4, $C_{19}H_{16}NO_4$), 306 (8, $C_{19}H_{17}NO_3$), 292 (12, $C_{18}H_{15}NO_3$), 176 (77, $C_{11}H_{12}O_2$), 175 (13, $C_{10}H_9NO_2$), 161 (39, $C_{10}H_9O_2$ or $C_9H_7NO_2$), 132 (3, C_8H_6NO), and 91 (13.5, C_7H_7).

(E)-3-(3,4-Dimethoxybenzylidene)-1-(pyridin-2-yl)pyrrolidine-2,5-dione (16): Yellow crystals from benzene, mp 214-215 ºC, 98% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1769-1709 (2CO, imide). MS: m/z = 324 (M^+, 100%, $C_{18}H_{16}N_2O_4$), 296 (1.5, $C_{17}H_{16}N_2O_3$), 264 (1, $C_{16}H_{12}N_2O_2$), 187 (2, $C_{10}H_7N_2O_2$), 176 (56, $C_{11}H_{12}O_2$), 175 (6, $C_9H_7N_2O_2$), 161 (35, $C_{10}H_9O_2$), 120 (11, $C_6H_4N_2O$), and 78 (50, C_5H_4N).

(E)-3-(3,4-Dimethoxybenzylidene)-1-(thiazol-2-yl)pyrrolidine-2,5-dione (17): Pale brown crystals from benzene, mp 236-238 ºC, 99% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1768-1647 (2CO, imide). MS: m/z = 330 (M^+, 67%, $C_{16}H_{14}N_2O_4S$), 302 (1, $C_{15}H_{14}N_2O_3S$), 288 (1, $C_{14}H_{12}N_2O_3S$), 193 (1, $C_8H_5N_2O_2S$), 176 (100, $C_{11}H_{12}O_2$), 161 (40, $C_{10}H_9O_2$), 126 (5, $C_4H_2N_2OS$), and 84 (1, C_3H_2NS).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-phenylaminobutanoic acid (18): White crystals from ethanol, mp 190 ºC, 20% yield in microwave and 98% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3284 (NH, amide), 3400-2400 (OH, acid), 1700-1640 (CO, acid) and (CO, amide). MS: m/z = 325 (M^+, 3%, $C_{18}H_{13}NO_4$), 307 (2, $C_{18}H_{13}NO_4$), 206

(6, $C_{11}H_{10}O_4$), 161 (13, $C_{10}H_9O_2$), 160 (100, $C_{10}H_8O_2$), 159 (21, $C_{10}H_7O_2$), 147 (3, $C_8H_5NO_2$), 119 (3, C_7H_5NO), 115 (2, $C_4H_5NO_3$), 98 (3, $C_4H_2O_3$) and 93 (92, C_6H_7N).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(2-aminophenylamino)butanoic acid (19): White crystals from ethanol**,** mp 258-260 ºC, 93% yield in microwave and 88% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3354-3270 ($^+NH_3$, anilinium and NH, amide), 1667 (CO, amide), and 1498-1443 (2CO, carboxylate).MS: m/z = 340 (M^+, 1%, $C_{18}H_{16}N_2O_5$), 323 (2, $C_{18}H_{15}N_2O_5$), 322 (9, $C_{18}H_{14}N_2O_4$), 296 (0.6, $C_{17}H_{16}N_2O_3$), 233 (5, $C_{12}H_9O_5$), 232 (27, $C_{12}H_8O_5$), 231 (2, $C_{12}H_9NO_4$), 206 (2.5, $C_{10}H_{10}N_2O_3$), 160 (100, $C_{10}H_8O_2$), 135 (9, $C_7H_7N_2O$), 134 (8, $C_7H_6N_2O$), 108 (47, $C_6H_8N_2$), and 107 (18, $C_6H_7N_2$).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(2-mercaptophenylamino)butanoic acid (20): White crystals from acetone, mp 178-180 ºC, 90% yield in microwave and 86% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-2400 (OH, acid), 3400-3055 (NH, amide), 2511 (SH), and 1665 (CO, acid and CO, amide). MS: m/z = 357 (M^+, 0.02%, $C_{18}H_{15}NO_5S$), 340 (12, $C_{18}H_{14}NO_4S$), 339 (55, $C_{18}H_{13}NO_4S$), 313 (0.1, $C_{17}H_{15}NO_3S$), 248 (2, $C_{12}H_{10}NO_5$), 233 (2, $C_{12}H_{19}O_5$), 223 (3, $C_{10}H_9NO_3S$), 151 (5, C_7H_5NOS), 150 (10.6, C_7H_4NOS), and 149 (100, C_7H_3NOS).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(2-hydroxphenylamino)butanoic acid (21): White crystals from benzene, mp 194-196 ºC, 6% yield in microwave and 95% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-2400 (OH, acid), 3300 (OH, phenol), 3178 (NH, amide), 1664-1616 (CO, acid and CO, amide). MS: m/z = 341 (M^+, 15%, $C_{18}H_{15}NO_6$), 324 (6, $C_{18}H_{14}NO_5$), 323 (30, $C_{18}H_{13}NO_5$), 297 (8, $C_{17}H_{18}NO_4$), 232 (52, $C_{12}H_9NO_4$), 160 (100, $C_{10}H_8O_2$), 135 (5, $C_7H_5NO_2$), 109 (83, C_6H_7NO), and 108 (13, C_6H_6NO). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.58 (2H, s, H-6), 6.06 (2H, s, H-1), 6.37-6.40 (1H, dd, H-9), 6.49-6.54 (1H, m, H-11), 6.61-6.63 (1H, m, H-2), 6.73-6.94 (1H, m, H-10), 6.98-7.11 (1H, dd, H-3), 7.22 (1H, d, H-4), 7.73 (1H, s, H-5), 7.86-7.89 (1H, dd, H-12), 9.31 (1H, s, H-8), and 9.84 (1H, s, H-7).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(2-methoxyphenylamino)butanoic acid (22): White crystals from ethanol, mp 204 ºC, 8% yield in microwave and 91% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-2400 (OH, acid), 3318 (NH, amide), 1680-1630 (CO, acid and CO, amide). MS: m/z= 355 (M^+, 8%, $C_{19}H_{17}NO_6$), 338 (2, $C_{19}H_{15}NO_5$), 337 (2, $C_{19}H_{15}NO_5$), 232 (53, $C_{12}H_8O_5$), 231 (3, $C_{12}H_9NO_4$), 206 (10, $C_{11}H_{10}O_4$), 177 (2, $C_9H_7NO_3$), 160 (91, $C_{10}H_8O_2$), 159 (18, $C_{10}H_7O_2$), 146 (5, $C_9H_6O_2$), 123 (100, C_7H_9NO), 119 (2, C_7H_5NO), 115 (2, $C_4H_3NO_3$), 108 (67.5, C_7H_8O), 102 (66, C_8H_6) and 98 (3, $C_4H_2O_3$). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.58 (2H, s, H-6), 3.79 (3H, s, H-8), 6.07 (2H, s, H-1), 6.87-6.93 (1H, dd, H-9), 6.98-7.01 (1H, d, H-2), 6.98-7.11 [3H, m, (H-11), (H-10), and (H-3)], 7.22 (1H, d, H-4), 7.73 (1H, s, H-5), 7.99-8.02 (1H, dd, H-12), 9.30 (1H, s, H-7), and 12.63 (1H, br., H-13).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(2-methylphenylamino)butanoic acid (23): White crystals from ethanol, mp 217-218 ºC, 10% yield in microwave and 90% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3292 (NH, amide), 3400-2400 (OH, acid), 1683 (CO, acid), and 1656 (CO, amide) MS: m/z = 339 (M^+, 31%, $C_{19}H_{17}NO_5$), 338 (1,$C_{19}H_{16}NO_5$), 322 (1, $C_{19}H_{16}NO_4$), 321 (2.5, $C_{19}H_{15}NO_4$), 294 (1, $C_{18}H_{16}NO_3$), 206 (20, $C_{11}H_{10}O_4$), 175 (18.5, $C_{10}H_9NO_2$), 161 (8, $C_{10}H_9O_2$ or $C_9H_7NO_2$), 160 (44, $C_9H_6NO_2$), 107 (100, C_7H_9N), 91 (13, C_7H_7), and 89 (11.5,C_7H_5).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(pyridin-2-ylamino)butanoic acid (24): White crystals from ethanol, mp 223-224 ºC, 0% yield in microwave and 99% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-2400 (OH, acid), 3245 (NH, amide), and 1683 (CO, acid and CO, amide). MS: m/z = 326 (M^+, 19%, $C_{17}H_{12}N_2O_5$), 309 (2, $C_{17}H_{13}N_2O_4$), 308 (9, $C_{17}H_{12}N_2O_4$), 281 (2, $C_{16}H_{13}N_2O_3$), 232 (27, $C_{12}H_8O_5$), 231 (1, $C_{12}H_9NO_4$), 204 (19, $C_{11}H_{10}NO_3$), 161 (6, $C_9H_9N_2O$), 160 (51, $C_{10}H_8O_2$), 135 (3.5, $C_7H_7N_2O$), 121 (91, $C_6H_5N_2O$), and 102 (100, C_8H_6). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.59 (2H, s, H-6), 6.05 (2H, s, H-1), 6.99 (1H, d, H-2), 7.07-7.11 [3H, m, (H-3),(H-4), and (H-9)], 7.72 (1H, s, H-5), 7.74-7.80 (1H, m, H-10), 8.04-8.07 (1H, m, H-11), 8.30-8.32 (1H, dd, H-8), and 10.64 (1H, s, H-7).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(thiazol-2-ylamino)butanoic acid (25): White crystals from ethanol, mp 213-215 ºC**,** 0% yield in microwave and 99% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3400-2400 (OH, acid), 3176 (NH, amide), and 1679 (CO, acid and amide). MS: m/z = 332 (M^+, 3%, $C_{15}H_{12}N_2O_5S$), 315 (1, $C_{15}H_{11}N_2O_4S$), 314 (7, $C_{15}H_{10}N_2O_4S$), 232 (33, $C_{12}H_8O_5$), 231 (1, $C_{12}H_9NO_4$), 188 (2, $C_{14}H_{12}N_2O_3S$), 160 (74, $C_{10}H_8O_2$), and 127 (15.5, $C_4H_3N_2OS$).

(E)-3-(Benzo[d][1,3]dioxol-5-ylmethylene)-1-phenylpyrrolidine-2,5-dione (26): White crystals from benzene, mp 219-220 ºC, 80% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1766 and 1706 (2CO, imide). MS: m/z = 307 ($M^{\cdot+}$, 57%, $C_{18}H_{13}NO_4$), 278 (1, $C_{17}H_{12}NO_3$), 173 (1, $C_{10}H_7O_2$), 161 (12, $C_{10}H_9O_2$), 160 (100, $C_{10}H_8O_2$), 159 (16, $C_{10}H_7O_2$), 147 (0.3, $C_9H_7O_2$), 146 (0.5,

$C_9H_6O_2$), 119 (7, C_7H_5NO), 102 (46, C_8H_6), 77 (11, C_6H_5), 75 (16, C_6H_3) and 51 (89, C_4H_3).

(E)-3-(Benzo[d][1,3]dioxol-5-ylmethylene)-1-(2-aminophenyl)pyrrolidine-2,5-dione (27): Brown crystals from benzene, mp 240-241 ºC, 90% yield in microwave (only in the presence of DMF) and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3437 (NH_2) and 1729-1646 (2CO, imide). MS: m/z = 338 (M^+, 57%, $C_{19}H_{18}N_2O_4$), 322 (4, $C_{19}H_{16}NO_4$), 321 (28, $C_{19}H_{15}NO_4$), 247 (15, $C_{13}H_{12}NO_4$), 246 (8, $C_{13}H_{12}NO_4$), 176 (49, $C_{11}H_{12}O_2$), 162 (9.5, $C_8H_6N_2O_2$), and 134 (56, $C_7H_6N_2O$).

(E)-3-(Benzo[d][1,3]dioxol-5-ylmethylene)-1-(2-hydroxyphenyl)pyrrolidine-2,5-dione (28): Brown crystals from benzene, mp 226-228 ºC, 93% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3235 (OH, phenol), 1769-1647 (2CO, imide).MS: m/z = 323 (M^+, 100%, $C_{18}H_{13}NO_5$), 306 (4,$C_{18}H_{12}NO_4$), 295 (2, $C_{17}H_{13}NO_4$), 294 (4, $C_{17}H_{12}NO_4$), 281 (3, $C_{16}H_{11}NO_4$), 279 (24, $C_{17}H_{13}NO_3$),187 (9, $C_{11}H_9NO_2$), 163 (1, $C_8H_5NO_3$), 135 (14, $C_7H_5NO_2$), and 134 (6.5, $C_7H_4NO_2$). ^{1}H-NMR ($CDCl_3$-d): δ (ppm) = 3.77 (2H, s, H-6), 6.08 (2H, s, H-1), 6.91-6.94 [2H, m, (H-2) and (H-8)], 7.01 (1H, s, H-7), 7.07-7.10 [3H, m, (H-3), (H-10), and (H-9)], 7.27 (1H, s, H-5), 7.30-7.33 (1H, dd, H-11), and 7.67 (1H, d, H-4).

(E)-3-(Benzo[d][1,3]dioxol-5-ylmethylene)-1-(2-methoxyphenyl)pyrrolidine-2,5-dione (29): Pale grey crystals from benzene, mp 188-192 ºC, 89% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1766-1649 (2CO, imide). MS: m/z = 337 (M^+, 11%, $C_{19}H_{15}NO_5$), 309 (0.16, $C_{18}H_{15}NO_4$), 293 (10, $C_{18}H_{15}NO_3$), 160 (100, $C_{10}H_8O_2$), 149 (0.32, $C_8H_7NO_2$), 119 (15.5, C_7H_5NO), and 108 (4, C_7H_8O).

(E)-3-(Benzo[d][1,3]dioxol-5-ylmethylene)-1-(2-methylphenyl)pyrrolidine-2,5-dione (30): White crystals from benzene, mp162-163 ºC, 85% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1766-1652 (2CO, imide). MS: m/z = 321 (M^+, 67%, $C_{19}H_{15}NO_4$), 320 (2.6, $C_{19}H_{14}NO_4$), 306 (1, $C_{18}H_{12}NO_4$), 292 (1, $C_{18}H_4NO_3$), 279 (1, $C_{17}H_{13}NO_3$), 276 (2, $C_{18}H_{14}NO_2$), 200 (1.5, $C_{12}H_{10}NO_2$), 174 (1, $C_{10}H_8NO_2$), 161 (14, $C_9H_7NO_2$), 160 (100, $C_9H_6NO_2$), 133 (2, C_8H_7NO), 91 (8, C_7H_7), and 89 (7.5, C_7H_5).

(E)-3-(Benzo[d][1,3]dioxol-5-ylmethylene)-1-(pyridin-2-yl)pyrrolidine-2,5-dione (31): Yellow crystals from benzene, mp 216-218 ºC, 95% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1763-1646 (2CO, imide). MS: m/z = 308 (M^+, 77%, $C_{17}H_{12}N_2O_4$), 280 (3.5, $C_{16}H_{12}N_2O_3$), 279 (10, $C_{16}H_{11}N_2O_3$), 187 (3, $C_{10}H_7N_2O_2$), 175 (1, $C_9H_7N_2O_2$), 161 (9, $C_8H_5N_2O_2$), 160 (73, $C_{10}H_8O_2$), 134 (2.6, $C_7H_7N_2O$), 120 (8, $C_6H_4N_2O$), and 102 (100, C_8H_6).

(E)-3-(Benzo[d][1,3]dioxol-5-ylmethylene)-1-(thiazol-2-yl)pyrrolidine-2,5-dione (32): Pale yellow crystals from benzene, mp 204-206 ºC, 97% yield in microwave and 0`% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 1768-1647 (2CO, imide). MS: m/z = 314 (M^+, 49%, $C_{15}H_{10}N_2O_4S$), 269 (0.4, $C_{19}H_{10}N_2O_2S$), 286 (1.3, $C_{14}H_{10}N_2O_3$), 231 (2.3, $C_{12}H_9NO_4$), 230 (0.4, $C_{12}H_8NO_4$), 187 (4, $C_{11}H_9NO_2$), 160 (100, $C_{10}H_8O_2$), 140 (0.3, $C_5H_4N_2OS$), 127 (45, $C_4H_3N_2OS$), and 126 (4, $C_4H_2N_2OS$).

Results and discussion

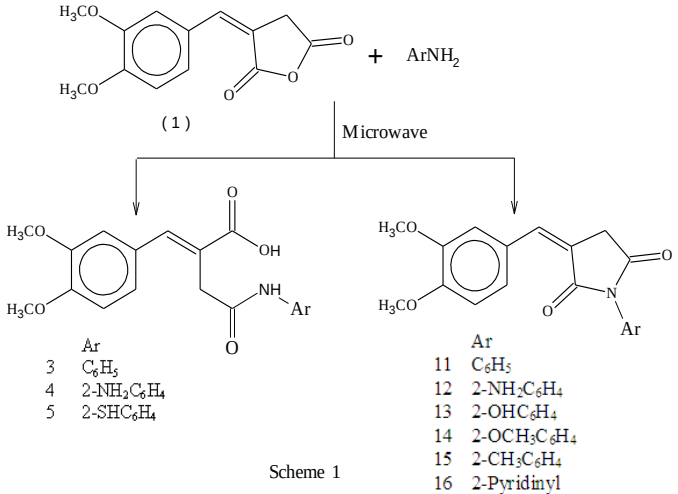
Microwave irradiation reaction

Microwave irradiation of compounds **1** or **2**, with the unsubstituted amine (**a**) ($K_b = 4.2 \times 10^{-10}$) gave the corresponding separable mixtures of pyrrolidiene-2,5-diones as major products (**11**, 95% and **26**, 80%), and butanoic acids as minor products (**3**, 5% and **18**, 20%). However with the amines that containing electron repelling groups; hydroxyl, methoxyl and methyl groups (**d-f**), compound **1** formed the corresponding pyrrolidine-2,5-diones **13-15**, as only products, whereas compound **2** gave separable mixtures from butanoic acids **21-23** as minor products (6, 8, 10%, respectively), and pyrrolidine-2,5-dinoes **28-30** as major products (93, 89, 85%, respectively). The formation of butanoic acid derivatives as minor products is ascribed to the slight distortion resulted from the presence of the 2-benzo[d][1,3]dioxol moiety, which could prevent the complete coplanarity necessary for ring closure. The formation of the separable mixtures can be attributed to the presence of the electron donating, hydroxyl, methoxyl, and methyl groups which increases the susceptibility of amido nitrogen atom towards nucleophilic attack on the carbonyl carbon. This means that with amines (**a**, **d-f**) the basicity factor outweighs the distortion effect exerted by the 2-benzo[d][1,3]dioxol moiety.

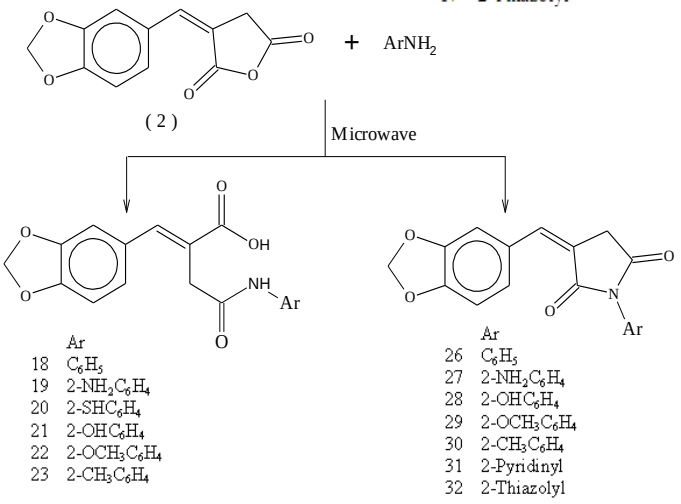
The basicity factor has been confirmed by the reaction of compound **1** with amines (**g** and **h)**, where the corresponding pyrrolidine-2,5-diones **16** (98%) and **17** (99%), are formed as the only products. Similarly compound **2** gave with amines (**g** and **h**) pyrrolidine-2,5-diones **31** (95%) and **32** (97%), respectively as only products.

These results can be attributed to the presence of the lone pair of electrons on the heterocyclic nitrogen atom, results in increasing the nucleophilicity of the amido nitrogen towards further intramolecular attack on the carbonyl carbon to give the cyclic products. The unexpected formation of the corresponding butanoic acids **4** and **19** as only products, from the reaction of amine (**b**) with

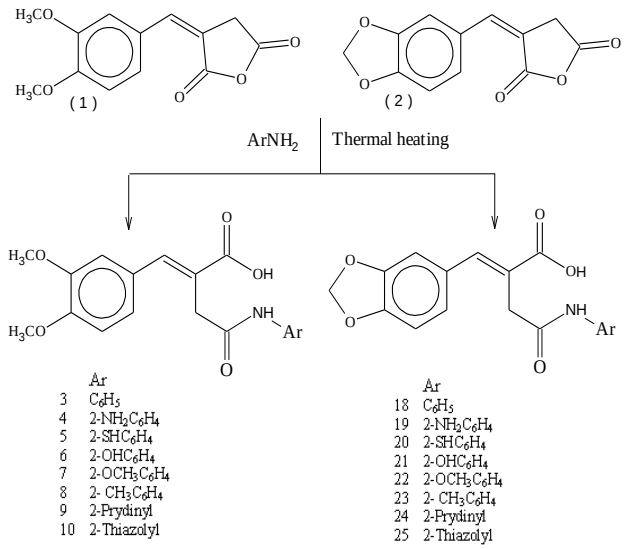
compounds **1** or **2**, respectively, irrespective to their structure or the basicity of amine (**b**) (K_b= 3×10^{-10}), led us to propose a mechanism in which a proton transfer takes place from the carboxyl group to the amino group, forming the anilinium $^{+}NH_3$ ion. These results were ascertained by the IR measurements of **4** and **19**, where υ (cm^{-1}) appeared at 3300-3272, and 3354-3270, characteristic for ($^{+}NH_3$, anilinium and NH, amide), 1679 (CO, amide), 1516-1448 and 1498-1443 (2CO, carboxylate), respectively. Also the ^{1}H-NMR data of compound **4**, showed signals at δ =7.82 (3H, s, H-9) representing ($^{+}NH_3$). The presence of such anilinium ion could decrease the susceptibility of the amido nitrogen atom towards further intramolecular nucleophilic attack on the carbonyl carbon to form the cyclic products. However, by repeating the same reactions with compounds **1** and **2**, in presence of DMF, as aprotic solvent, the corresponding pyrrolidine-2,5-diones **12** and **27** were formed as the only products. These results were confirmed by the IR spectrum where two bands appeared at 3426-3348 and 3437-3300 cm^{-1} characteristic for NH_2 in compounds **12** and **27**, respectively.



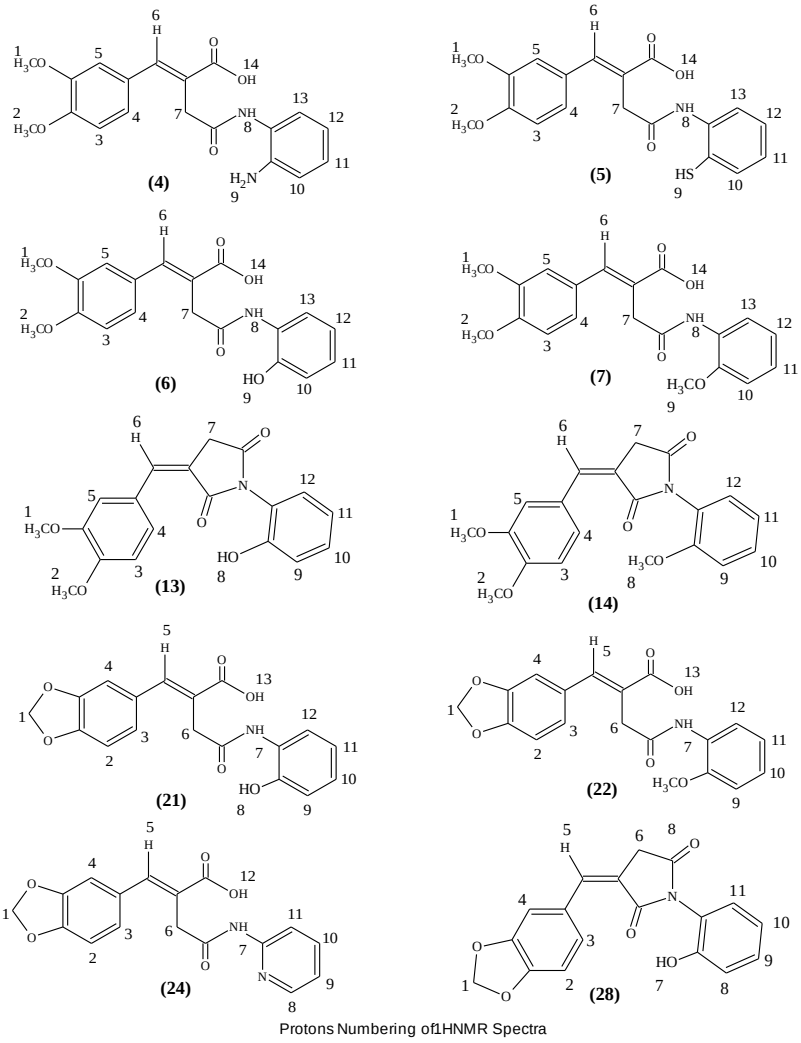
Scheme 1



Scheme 2



Scheme 3



Protons Numbering of1HNMR Spectra

Table 2: Comparison between yields of products resulted from the microwave irradiation and conventional thermal heating technique.

Amine	Product (Yield %)							
	Compound **1**				Compound **2**			
	Microwave irradiation		Conventional thermal heating		Microwave irradiation		Conventional thermal heating	
	Butanoic acid	Pyrrolidine-2,5-dione	Butanoic acid	Pyrrolidine-2,5-dione	Butanoic acid	Pyrrolidine-2,5-dione	Butanoic acid	Pyrrolidine-2,5-dione
Aniline	3; 5%	11; 95%	3; 99%	-	18; 20%	26; 80%	18; 98%	-
2-Aminoaniline	4; 97%	12*; 95%	4; 95%	-	19; 93%	27*; 90%	19; 88%	-
2-Mercaptoaniline	5; 93%	-	5; 88%	-	20; 90%	-	20; 96%	-
2-Hydroxyaniline	-	13; 96%	6; 96%	-	21; 6%	28; 93%	21; 95%	-
2-Methoxyaniline	-	14; 93%	7; 93%	-	22; 8%	29; 89%	22; 91%	-
2-Methylaniline	-	15; 90%	8; 91%	-	23; 10%	30; 85%	23; 90%	-
Pyridine	-	16; 98%	9; 99%	-	-	31; 95%	24; 99%	-
Thiazole	-	17; 99%	10; 99%	-	-	32; 97%	25; 99%	-

* (in presence of DMF)

These results can be ascribed to the solvent effect in microwave irradiation technique, where interaction takes place between microwave and polar molecules of the solvent. Such an interaction results

in energy transfer through solvent molecules to the reaction mixture so that it enhances the intramolecular nucleophilic attack by the lone pair electrons the of amido nitrogen atom on the carbonyl carbon to form the pyrrolidine-2,5-diones **12** and **27**.

Microwave irradiation reactions of compounds **1** and **2** in absence of solvent with amine (**c**) gave the substituted butanoic acids **5** and **20**, respectively as only products. These results can be attributed to the presence of the electron deficient d-orbital in the mercapto (-SH) group which decreases the nucleophilicity of the nitrogen in the amido group to form the corresponding pyrrolidine-2,5-diones. However, in the presence of the aprotic solvent DMF, no cyclization took place. Such results indicate that the effect resulted from the presence of mercapto (-SH) group, outweighs the effect due to the microwave-solvent interaction (Schemes 1 and 2).

Conventional thermal heating of compounds 1 and 2 with amines (a-h)

Conventional thermal heating reactions of compounds **1** or **2** with amines (**a-h**) gave the corresponding butanoic acids **3-10** and **18-25**, respectively, as only products irrespective to the structure of compounds **1**, **2** or amines (Scheme 3). The comparison between results obtained from microwave irradiation reactions and conventional thermal condensation, can be attributed to the acceleration of reactions exerted by microwave thermal effects and specific non-purely thermal effects, resulted from material-wave interactions[15]. The combination of these two contributions can be responsible for regiospecific property and the formation of the cyclic compounds (Table 2).

Compounds **5-7**, **9**, **10**, **20-22**, **24**, and **25** showed biological activities, and compounds **13**, **16**, **17**, **28**, **31**, and **32** showed cytotoxic activity.

Conclusion

The present work shows that microwave irradiation effects assist the cyclization and regiospecific property of the reaction. It accomplishes the reactions in excellent yields, purity and shorter time, in addition to be environmental friendly, more than the conventional thermal heating technique. These requirements are important for the industrial synthesis of compounds having medicinal applications (cytotoxic) and biological activities such as methylene-4-oxo-4-arylaminobutanoic acids and pyrrolidine-2,5-diones. Also the reactions showed that the presence of aprotic solvent DMF in the microwave irradiation technique enhances the cyclization process. With compound **2** the presence of the 2-benzo[d][1,3]dioxol moiety, could prevent the complete coplanarity that is necessary for ring closure to form the corresponding pyrrolidine-2,5-diones as only products.

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