Synthesis of some medicinal and biological active (E)-2-arylidine-4-oxo-4-(4-(N-arylsulfamoyl)phenylamino)butanoic acids and (E)-4-(3-arylidene)-2,5-dioxopyrrolidin-1-yl)-N-arylbenzenesulfonamides

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Abstract: Microwave irradiation of anhydride (E)-3-(3,4-dimethoxybenzylidene)dihydrofuran-2,5-dione **1** gives with N-aryl-4-aminobenzenesulfonamides (a and d) separable mixtures of (E)-2-(3,4-dimethoxybenzylidene)-4-oxo-4-(4-(N-arylsulfamoyl)phenylamino)butanoic acids **3** and **6**, and (E)-4-(3-(3,4-dimethoxybenzylidene)-2,5-dioxopyrrolidin-1-yl)-N-arylbenzenesulfonamides **10** and **13**, respectively**.** Also anhydride (E)-3-(benzo[d][1,3]dioxol-5-ylmethylene)dihydrofuran-2,5-dione **2** gives with amines (a, b, d, and g), separable mixtures of (E)-2-(benzo[d][1,3]dioxol-5-ylmethylene)- 4-oxo-4-(4-(N-arylsulfamoyl) phenylamino) butanoic acids **16**, **17**, **19** and **22**, and (E)-4-(3- (benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-aryl-benzenesulfonamides **23**, **24**, **26**, and **28**, respectively. On the other hand, reaction of **1** with amines (b, c, e, and g) gives benzenesulfonamides **11**, **12**, **14**, and **15**, whereas compound **2** gives with amines (c and e) the corresponding benzenesulfonamides **25** and **27,** as only products. Compounds **1** and **2** give, either in presence or absence of solvent DMF, with amine (f) the corresponding butanoic acids **8** and **21**, respectively. Microwave irradiation of (g) with **1** gives benzenesulfonamide **15** as an only product, whereas with **2**, it gives a separable mixture of **22** and **28**, whereas in DMF, it gives compound **28** as an only product. Reaction of **1** and **2** with (a-g) using the conventional thermal heating technique, gives the corresponding butanoic acid derivatives **3-7**, **9** and **16-20**, **22**, respectively.
Trials to react **1** and **2** with (f) were unsuccessful. The structural formulas of the products obtained **3-28** were assigned by their spectral analysis. Cytotoxic and antimicrobial activities of some prepared compounds have been studied and reported.
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1. Introduction

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[1, 2]. It proved to accomplish the reactions with excellent yields, high purity, assist cyclization, regioselectivity, and convenient working out[3-12] than the conventional thermal heating technique. Moreover it proves to be more economically and environmentally safe (green chemistry) than thermal heating technique. Sulfonamides represent an important class of medicinally important compounds which are extensively used as antibacterial agents[10-14]. The synthesis of 1-aryl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-sulfonamides under microwave irradiation showed that the presence of sulfonamide group deepen the structure activity, where it is capable to inhibit the enzymes[13].

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, offered by microwave technique; short time with high yield and purity, and also to study the factors affecting the reactions such as structure of reactants, basicity of amines, and effect of solvent.

2. 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[15] and reacted with different sulfonamides (a-g); N-phenyl-, N-(4-methylphenyl)-, N-(4-methoxyphenyl)-, N-(4-chlorophenyl)-, N-(4-nitrophenyl)-, N-(1-naphthyl)-, and N-benzyl-4-aminobenzenesulfonamides (1:1) using microwave irradiation and conventional thermal heating

techniques. The factors affecting the reaction such as structure of reactants, basicity of amines, effect of solvent, and technique, were also studied. The results obtained are given in Table 1.

General remarks

Microwave irradiation was carried out in a Galanz Microwave Oven, WP1000AP30-2, Chemistry Department, 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.

Biological activity: Antimicrobial screenings were measured in the Botany Department, College of Women for Arts, Science, and Education, Ain Shams University, Cairo, Egypt.

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

Solvent-free microwave irradiation technique

General procedure

In a microwave oven (1000 watt, 30-80% of its total power) a grind equimolecular mixture of (E)-3-(3,4-dimethoxybenzylidene)dihydrofuran-2,5-dione **1** or (E)-3-(benzo[d] [1,3] dioxol-5-ylmethylene)dihydrofuran-2,5-dione **2** and sulfonamide (a-g) was dry-irradiated in an open vessel for 2-20 minutes. The reaction progress was monitored by thin layer chromatography (TLC) until no more unreacting starting materials were observed. The reaction mixture was then cooled down to the room temperature and the product obtained was dissolved in chloroform followed by washing the organic layer several times with ice-cold dilute hydrochloric acid to remove the unreacted amine. Treatment of the organic layer with 10% ice-cold sodium carbonate solution followed by acidification of the aqueous layer with ice-cold concentrated hydrochloric acid precipitated the produced (E)-2-(3,4-dimethoxybenzylidene)-4-oxo-4-(4-(N-arylsulfamoyl)phenylamino)butanoic acids **3**,**6**,and **8** or (E)-2-(benzo[d] [1,3] dioxol-5-ylmethylene) -4-oxo-4-(4-(N-arylsulfamoyl)phenylamino)butanoic acids **16**,**17**,**19**, **21**, and **22**. Thoroughly washing of the organic layer with water followed by its dryness over anhydrous sodium sulfate and evaporation, gave (E)-4-(3-(3,4-dimethoxybenzylidene)-2,5-dioxopyrrolidin-1-yl)-N-(4-aryl)benzenesulfonamides **10**-**15** or (E)-4-(benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-(4-aryl)benzenesulfonamides **23**-**28,** respectively. The products obtained were crystallized from the appropriate solvent and their structures were confirmed by their spectral data; IR, ^{1}HNMR and MS**.** Yields of products are given in Table 1.

Conventional thermal heating technique

General procedure

A homogenous equimolecular mixture of **1** or **2**, and different sulfonamides (a-g) in ethanol was refluxed for 4-10 hrs. The reaction progress was monitored by TLC. The reaction mixture was then concentrated and the precipitate formed was filtered off to give the corresponding butanoic acid derivatives **3**-**7** and **9**, or **16**-**20** and **22**, respectively. The products were dissolved in chloroform then worked out in the same way as that given in the solvent-free microwave irradiation technique. Yields of products are given in Table 1.

Biological activity: Antimicrobial screening

The antimicrobial screening of compounds; **4**, **5**, **7**, **14**, **17**, **18**, **20**, **25**, and **27**, 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 results obtained are given in Table 2.

Medicinal application: Cytotoxic activity

Cytotoxic activity of compounds **8**, **10**, **12**, **21**, and **25** was tested by using Flouraciele as a reference drug, against human breast carcinoma cell line using the method reported by Skehan *et al.*[16]. The results obtained are given in Table 2.

(E)-2-(3,4-Dimethoxybenzylidene)-4-oxo-4-(4-(N-phenylsulfamoyl)phenylamino)butanoic acid (3); White crystals from ethanol, mp 142-143 ºC**,** 10% yield in microwave and 65% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3460-3300 (2NH), 3500-2500 (OH, acid), 1728 (CO, acid) and 1669 (CO, amide), 1267 (SO_2, asy.), and 1187 (SO_2, sym.). MS: m/z = 497 (M^+, 1%, $C_{25}H_{24}N_2O_7S$), 294 (5, $C_{18}H_{16}NO_3$), 248 (3, $C_{13}H_{12}O_5$ or $C_{12}H_{12}N_2O_2S$), 233 (0.65, $C_{12}H_{11}NO_2S$), 176 (25, $C_{11}H_{12}O_2$), 161 (15, $C_{10}H_9O_2$), 139 (1, C_6H_5NOS), 133 (29, $C_8H_5O_2$), 131 (32, $C_9H_7O_2$), 119 (12, C_7H_5NO), 115 (47, $C_4H_5NO_3$), 102 (61, C_8H_6) and 62 (100, NOS). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.7879 (3H, s, H-1), 3.8048 (3H, s, H-2), 3.8307 (2H, s, H-7), 6.99 (1H, d, H-5), 7.0053-7.0466 (1H, q, H-4), 7.0894-7.1047 (1H, d, H-3), 7.202-7.262 (5H, m, H-12), 7.3309 (1H, s, H-6), 7.499 (1H, s, H-8), 7.5326-7.551 (2H, d, H-9),7.8567-7.8735 (2H, d, H-10), and 10.3985 (1H, s, H-11).

Table 1: Comparison between yields of products resulted from the microwave irradiation and conventional thermal heating techniques

	Anhydride **1**				Anhydride **2**			
	Microwave irradiation		Conventional thermal heating		Microwave irradiation		Conventional thermal heating	
	Butanoic acid	Benzene sulfonamide	Butanoic acid	Benzene sulfonamide	Butanoic acid	Benzene sulfonamide	Butanoic acid	Benzene sulfonamide
N-phenyl-4-aminobenzenesulfonamide (a)	**3**, 10%	**10**, 83%	**3**, 65%	-	**16**, 33%	**23**, 50%	**16**, 55%	-
N-(4-methylphenyl)-4-aminobenzenesulfonamide (b)	-	**11**, 92%	**4**, 75%	-	**17**, 30%	**24**, 60%	**17**, 67%	-
N-(4-methoxyphenyl)-4-aminobenzenesulfonamide (c)	-	**12**, 93%	**5**, 82%	-	-	**25**, 89%	**18**, 74%	-
N-(4-clorophenyl)-4-aminobenzenesulfonamide (d)	**6**, 13%	**13**, 65%	**6**, 45%	-	**19**, 37%	**26**, 40%	**19**, 45%	-
N-(4-nitroyphenyl)-4-aminobenzenesulfonamide (e)	-	**14**, 93%	**7**, 40%	-	-	**27**, 92%	**20**, 36%	-
N-(1-naphthyl)-4-aminobenzenesulfonamide (f)	**8**, 75% **8**, 83%*	-	-	-	**21**, 69% **21**, 85%*	-	-	-
N-benzyl-4-aminobenzenesulfonamide (g)	-	**15**, 82%	**9**, 55%	-	**22**, 35%	**28**, 52% **28**, 90%*	**22**, 50%	-

* (in presence of DMF)

(E)-2-(3,4-Dimethoxybenzylidene)-4-oxo-4-(4-(N-(4-methylphenyl)sulfamoyl)-phenylamino)butanoic acid (4); White crystals from ethanol, mp 105-107 ºC**,** 0% yield in microwave and 75% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3500-3200 (2NH), 3500-2800 (OH, acid), 1700 (CO, acid) and 1687 (CO, amide), 1263(SO_2, asy.), and 1156 (SO_2, sym.). MS: m/z = 510 (M^+, 2%, $C_{26}H_{26}N_2O_7S$), 492 (2, $C_{26}H_{24}N_2O_6S$), 464 (1, $C_{25}H_{24}N_2O_5S$), 403 (2, $C_{19}H_{17}NO_7S$), 288 (2, $C_{14}H_{12}N_2O_3S$), 262 (46.5, $C_{13}H_{14}N_2O_2S$), 107 (100, C_7H_9N), 106 (74, C_7H_8N), and 92 (61, C_7H_8).

(E)-2-(3,4-Dimethoxybenzylidene)-4-oxo-4-(4-(N-(4-methoxyphenyl)sulfamoyl)- phenylamino) butanoic acid (5); White crystals from ethanol, mp 212-214 ºC**,** 0% yield in microwave and 82% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3444-3263 (2NH), 3600-2800 (OH, acid), 1727 (CO, acid) and 1646 (CO, amide), 1233 (SO_2, asy.), and 1155 (SO_2, sym.). MS: m/z = 526 (M^+, 0.04%, $C_{26}H_{26}N_2O_8S$), 508 (0.03, $C_{26}H_{24}N_2O_7S$), 480 (1, $C_{25}H_{24}N_2O_6S$), 323 (1, $C_{19}H_{17}NO_4$), 319 (0.05, $C_{15}H_{15}N_2O_4S$), 278 (17.5, $C_{13}H_{14}N_2O_3S$), 249 (8.5, $C_{13}H_{13}O_5$), 248 (60, $C_{13}H_{12}O_5$ or $C_{12}H_{12}N_2O_2S$), 247 (2, $C_{13}H_{13}NO_4$), 122 (100, C_7H_8NO), 115 (11, $C_4H_5NO_3$), 92 (13, C_6H_6N), and 63 (22.5, HNOS).

(E)-2-(3,4-Dimethoxybenzylidene)-4-oxo-4-(4-(N-(4-chlorophenyl)sulfamoyl)- phenylamino) butanoic acid (6); Yellow crystals from ethanol, mp 144-146 ºC**,** 13% yield in microwave and 45% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3446 and 3373 (2NH), 3200-2500 (OH, acid), 1729 (CO, acid) and 1669 (CO, amide), 1268 (SO_2, asy.), and 1187 (SO_2, sym.). MS: m/z = 530.9 (M^+, 0.12%, $C_{25}H_{23}ClN_2O_7S$), 294 (2.3, $C_{18}H_{16}NO_3$), 282 (0.14, $C_{12}H_{11}ClN_2O_2S$), 248 (3, $C_{13}H_{12}O_5$), 247 (0.5, $C_{13}H_{13}NO4$), 176 (5.5, $C_{11}H_{12}O_2$), 161 (2.5, $C_{10}H_9O_2$ or $C_9H_7NO_2$), 126 (35, C_6H_5NCl), 115 (12, $C_4H_5NO_3$), 101 (38, C_8H_5), and 62 (100, NOS).

(E)-2-(3,4-Dimethoxybenzylidene)-4-oxo-4-(4-(N-(4-nitrophenyl)sulfamoyl)phenylamino)-butanoic acid (7); Brown crystals from ethanol, mp 188-190 ºC**,** 0% yield in microwave and 40% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3441 and 3300 (2NH), 3500-2400 (OH, acid), 1732 (CO, acid) and 1660 (CO, amide), 1267 (SO_2, asy.), and 1156 (SO_2, sym.). MS: m/z = 541 (M^+, 1%, $C_{25}H_{23}N_3O_9S$), 294 (2.5, $C_{18}H_{16}NO_3$), 293 (0.5, $C_{12}H_{11}N_3O_4S$), 248 (2, $C_{13}H_{12}O_5$), 176 (4, $C_{11}H_{12}O_2$), 175 (2, $C_{11}H_{11}O_2$), 161 (1.5, $C_{10}H_9O_2$), 138 (1, $C_6H_6N_2O_2$), 115 (7, $C_4H_5NO_3$), 102 (29, C_8H_6), and 62 (100, NSO).

(E)-2-(3,4-Dimethoxybenzylidene)-4-oxo-4-(4-(N-(1-naphthyl)sulfamoyl)phenylamino)-butanoic acid (8); Pale violet crystals from ethanol, mp 130-132 ºC**,** 75% yield in microwave, 83% in microwave with DMF, and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3475-3250 (2NH), 3500-2800 (OH, acid), 1674 (CO, acid) and 1627 (CO, amide), 1261 (SO_2, asy.), and 1154 (SO_2, sym.). MS: m/z = 546 (M^+, 0.37%, $C_{29}H_{26}N_2O_7S$), 248 (0.48, $C_{13}H_{12}O_5$ or $C_{12}H_{12}N_2O_2S$), 161 (2, $C_{10}H_9O_2$ or $C_7H_6N_2O_2S$ or $C_9H_7NO_2$), 156 (2, $C_6H_6NO_2S$), 142 (4, $C_{10}H_8N$), 128 (0.54, $C_{10}H_8$), 115 (100, $C_4H_5NO_3$), 102 (2, C_8H_6), 65 (47, HSO_2), and 62 (72, NOS).

(E)-2-(3,4-Dimethoxybenzylidene)-4-oxo-4-(4-(N-benzylsulfamoyl)phenylamino)-butanoic acid (9); White crystals from ethanol, mp 219-222 ºC**,** 0% yield in microwave and 55% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3443 and 3300 (2NH), 3500-2800 (OH, acid), 1731 (CO, acid) and 1660 (CO, amide), 1264 (SO_2, asy.), and 1160 (SO_2, sym.). MS: m/z = 510 (M^+, 0%, $C_{26}H_{26}N_2O_7S$), 466 (0.01, $C_{25}H_{26}N_2O_5S$), 464 (0.01, $C_{25}H_{24}N_2O_5S$), 356 (0.12, $C_{18}H_{16}N_2O_4S$), 295 (100, $C_{18}H_{17}NO_3$), 294 (99.5, $C_{18}H_{16}NO_3$), 290 (1, $C_{14}H_{14}N_2O_3S$), 250 (27, $C_{10}H_6N_2O_4S$), 249 (87, $C_{10}H_5N_2O_2$), 247 (80, $C_{13}H_{13}NO_4$), and 176 (100, $C_{11}H_{12}O_2$). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.831 (3H, s, H-1), 3.85 (3H, s, H-2), 3.901 (2H, s, H-7), 4.035-4.056 (2H, d, H-12), 7.070-7.098 (1H, d, H-5), 7.277 (5H, s, H-13), 7.566 [(1H, d, H-3) & (1H, q, H-4)], 7.592-7.620 [(2H, d, H-9) & (1H, imp, H-6)], 7.932-7.960 [(2H, d, H-10) & (1H, imp, H-8)], and 8.246 (1H, t, H-12).

(E)-4-(3-(3,4-Dimethoxybenzylidene)-2,5-dioxopyrrolidin-1-yl)-N-(4-phenyl)benzene-sulfonamides (10); Yellow crystals from benzene, mp 138-140 ºC**,** 83% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3248 (NH), 1766 and 1710 (2CO, imide), 1266 (SO_2, asy.), and 1160 (SO_2, sym.). MS: m/z = 478 (M^+, 18%, $C_{25}H_{22}N_2O_6S$), 463 (6, $C_{25}H_{22}N_2O_5S$), 401 (8, $C_{19}H_{17}N_2O_6S$), 400 (6, $C_{19}H_{16}N_2O_6S$), 328 (8, $C_{16}H_{12}N_2O_4S$), 294 (16, $C_{18}H_{16}NO_3$), 247 (28, $C_{13}H_{12}NO_4$), 176 (19, $C_{11}H_{12}O_2$), 161 (8, $C_{10}H_9O_2$ or $C_9H_7NO_2$), and 149 (100, $C_9H_9O_2$).

(E)-4-(3-(3,4-Dimethoxybenzylidene)-2,5-dioxopyrrolidin-1-yl)-N-(4-methylphenyl)-benzenesulfonamide (11); Brown crystals from benzene, mp over 300 ºC**,** 92% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3247 (NH), 1765 and 1707 (2CO, imide), 1277 (SO_2, asy.), and 1158 (SO_2, sym.). MS: m/z = 492 (M^+, 32%, $C_{26}H_{24}N_2O_6S$), 491 (46, $C_{26}H_{25}N_2O_6S$), 322 (41, $C_{19}H_{16}NO_4$), 288 (42, $C_{14}H_{12}N_2O_3S$), 176 (39, $C_{11}H_{12}O_2$), 156 (44, C_7H_7NOS), and 107 (100, C_7H_9N). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.203 (3H, s; H-13), 3.8 (2H, s., H-7), 3.852 [6H, s, (H-1) & (H-2)], 6.48-6.52 (1H,d, H-5), 6.9-7.2 (2H, d, H-12), 7.564-7.9 [(2H, d, H-9), (2H, d, H-8), (1H, q, H-4), (1H, d, H-3), and (1H, d, H-11)], and 10.3 (1H, s, H-10).

(E)-4-(3-(3,4-Dimethoxybenzylidene)-2,5-dioxopyrrolidin-1-yl)-N-(4-methoxyphenyl)-benzenesulfonamide (12); Grey crystals from ethanol, mp 193-195 ºC**,** 93% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3244 (NH), 1750 and 1707 (2CO, imide), 1388 (SO_2, asy.), and 1161 (SO_2, sym.). MS: m/z = 508 (M^+, 13%, $C_{26}H_{24}N_2O_7S$), 480 (4, $C_{25}H_{24}N_2O_6S$), 479 (5, $C_{25}H_{23}N_2O_6S$), 322 (9.5, $C_{19}H_{16}NO_4$), 306 (3, $C_{14}H_{14}N_2O_4$), 252 (4, $C_{10}H_8N_2O_4S$), 176 (8, $C_{11}H_{12}O_2$), 122 (100, C_7H_8NO), 108 (13, C_7H_8O), and 97 (10.5, C_4H_3 NO_2). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.671 (2H, s, H-7), 3.776-3.886 [9H, s, (H-1), (H-2), and (H-13)], 6.917-6.961 [(2H, d, H-12) and (1H,d, H-5)] 7.046-7.141 [(1H, q, H-4), (1H, d, H-3), and (1H, imp, H-6)], 7.549-7.593 [(2H, d, H-8) and (2H, d, H-11)], 7.875-7.897 (2H, d, H-9), and 10.044 (1H, s, H-10).

(E)-4-(3-(3,4-Dimethoxybenzylidene)-2,5-dioxopyrrolidin-1-yl)-N-(4-chlorophenyl) benzenesulfonamide (13); Yellow crystals from benzene, mp 115-118 ºC**,** 65% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3241 (NH), 1766 and 1707 (2CO, imide), 1270 (SO_2, asy.), and 1157 (SO_2, sym.). MS: m/z = 512 (M^+, 20%, $C_{25}H_{21}ClN_2O_6S$), 484 (11.6, $C_{24}H_{21}ClN_2O_5S$), 478 (11, $C_{25}H_{22}N_2O_6S$), 360 (14, $C_{16}H_{19}ClN_2O_4S$), 360 (14, $C_{16}H_9ClN_2O_4S$), 322 (60, $C_{19}H_{16}NO_4$), 176 (83, $C_{11}H_{12}O_2$), 175 (20, $C_{11}H_{11}O_2$), 161 (68, $C_{10}H_9O_2$), 156 (80, $C_6H_6NO_2S$), 126 (46, C_6H_5NCl), 111 (21, C_6H_4NCl), 102 (24, C_8H_6), 92 (100, C_6H_6N), and 63 (54, HNOS).

(E)-4-(3-(3,4-Dimethoxybenzylidene)-2,5-dioxopyrrolidin-1-yl)-N-(4-nitrophenyl) benzenesulfonamide (14); Brown crystals from ethanol, mp 178-180 ºC**,** 93% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3240 (NH), 1764 and 1711 (2CO, imide), 1277 (SO_2, asy.), and 1159 (SO_2, sym.). MS: m/z = 523 (M^+, 0%, $C_{25}H_{21}N_3O_8S$), 477 (5, $C_{25}H_{21}N_2O_6S$), 361 (5, $C_{15}H_{11}N_3O_6S$), 320 (5, $C_{13}H_{10}N_3O_5S$), 175 (7, $C_{11}H_{11}O_2$), 149 (100, $C_9H_9O_2$), 138 (14, $C_6H_6N_2O_2$), and 63 (21, HNOS).

(E)-4-(3-(3,4-Dimethoxybenzylidene)-2,5-dioxopyrrolidin-1-yl)-N-benzylbenzene sulfonamide (15); White crystals from benzene, mp 212-214 ºC**,** 82% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3280 (NH), 1761 and 1709 (2CO, imide), 1330 (SO_2, asy.), and 1155 (SO_2, sym.). MS: m/z = 492 (M^+, 61%, $C_{26}H_{24}N_2O_6S$), 461 (2, $C_{25}H_{21}N_2O_5S$), 356 (3, $C_{18}H_{16}N_2O_4S$), 322 (8, $C_{19}H_{16}NO_4$), 290 (2, $C_{14}H_{14}N_2O_3S$), 251 (4,

$C_{10}H_7N_2O_4S$), 176 (44, $C_{11}H_{12}O_2$), and 106 (100, C_7H_8N). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.518 (2H, s, H-7), 3.771 (3H, s, H-1), 3.801 (3H, s, H-2), 4.092-4.126 (2H, d, H-11), 7.48-6.52 (1H, d, H-5), 7.001-7.182 (5H, s, H-12), 7.04-7.059 (1H, q, H-4), 7.059-7.088 [(1H, d, H-3) and 1H, imp, H-6)], 7.252 (2H, d, H-8), 7.874 (2H, d, H-9), and 8.516-8.545 (1H, t, H-10).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(4-(N-phenylsulfamoyl)phenylamino)- butanoic acids (16); White crystals from ethanol, mp 196-198 ºC**,** 33% yield in microwave and 55% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3282 (2NH), 3600-2500 (OH, acid), 1663 (2CO, acid and amide), 1243 (SO_2, asy.), and 1161 (SO_2, sym.). MS: m/z = 480.5 (M^+, 0%, $C_{24}H_{20}N_2O_7S$), 462 (2, $C_{24}H_{18}N_2O_6S$), 248 (32, $C_{12}H_{12}N_2O_2S$), 232 (37, $C_{12}H_8O_5$), 160 (41, $C_{10}H_8O_2$), 159 (14, $C_{10}H_7O_2$), 156 (60, $C_6H_6NO_2S$), 130 (14, C_9H_6O), 115 (2, $C_4H_5NO_3$), 102 (52, C_8H_6), 92 (94, C_6H_6N), 65 (100, HSO_2), and 62 (100, NOS).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(4-(N-(4-methylphenyl)sulfamoyl) phenylamino)butanoic acid (17); White crystals from ethanol, mp 192 ºC**,** 30% yield in microwave and 67% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3266 and 3110 (2NH), 3600-2200 (OH, acid), 1690 (CO, acid) 1666 (CO, amide), 1242 (SO_2, asy.), and 1155 (SO_2, sym.). MS: m/z = 494.5 (M^+, 0.2%, $C_{25}H_{22}N_2O_7S$), 248 (0.2, $C_{12}H_{12}N_2O_2S$), 247 (0.2, $C_{13}H_{13}NO_5S$), 160 (0.54, $C_{10}H_8O_2$), 106 (45, C_7H_8N), 102 (32, C_8H_6), 91 (16, C_7H_7), 77 (63, C_6H_5), 65 (27.5, HSO_2), and 62 (100, NOS). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.174 (3H, s, H-13), 3.65 (2H, s, H-6), 6.048 (2H, s, H-1), 6.405-6.45 (1H, d, H-2), 6.998 (1H, d, H-12), 7.389-7.399 (2H, d, H-8), 7.405-7.602 [3H, m, (H-3), (H-4) & (H-5)], 8.010-8.048 (2H, d, H-11), 8.389-8.402 (2H, d, H-9), 10.01 (1H, s, H-7), 10.6 (1H, s, H-10), and 12.4 (1H, broad, H-14).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(4-(N-(4-methoxyphenyl)sulfamoyl) phenylamino)butanoic acid (18); Pale grey crystals from ethanol, mp over 300 ºC**,** 0% yield in microwave and 74% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3436 (2NH), 3400-2600 (OH, acid), 1711 (CO, acid), 1636 (CO, amide), 1248 (SO_2, asy.), and 1138 (SO_2, sym.). MS: m/z = 510 (M^+, 0%, $C_{25}H_{22}N_2O_8S$), 278 (23, $C_{13}H_{14}N_2O_3S$), 232 (4, $C_{12}H_8O_5$ or $C_{12}H_{10}NO_2S$), 175 (18, $C_{10}H_7O_3$), 160 (9, $C_{10}H_8O_2$), 122 (2, C_7H_8NO), and 93 (2, C_6H_5O).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(4-(N-(4-chlorophenyl)sulfamoyl) phenylamino)butanoic acid (19); White crystals from ethanol, mp 134-136 ºC**,** 37% yield in microwave and 45% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3450 (2NH), 3600-2500 (OH, acid), 1731 (CO, acid), 1662 (CO, amide), 1251 (SO_2, asy.), and 1167 (SO_2, sym.). MS: 514 (M^+, 1%, $C_{24}H_{19}ClN_2O_7S$), 232 (5, $C_{12}H_8O_5$ or $C_{12}H_{10}NO_2S$), 175 (2, $C_{10}H_7O_3$), 160 (1, $C_{10}H_8O_2$), 157 (0.82, $C_6H_7NO_2S$), 127 (1, C_6H_6NCl), 92 (2, C_6H_6N), 65 (6, HSO_2), and 62 (100, NOS).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(4-(N-(4-nitrophenyl)sulfamoyl)- phenylamino)butanoic acid (20); Brown crystals from ethanol, mp 140-141 ºC**,** 0% yield in microwave and 36% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3386 (2NH), 3400-2500 (OH, acid), 1731 (CO, acid), 1662 (CO, amide), 1252 (SO_2, asy.), and 1166 (SO_2, sym.). MS: m/z = 525.5 (M^+, 0%, $C_{24}H_{19}N_3O_9S$), 293 (3, $C_{12}H_{11}N_3O_4S$), 278 (70, $C_{12}H_{10}N_2O_4S$), 277 (100, $C_{12}H_9$ N_2O_4S), 232 (95.5, $C_{12}H_8O_5$ or $C_{12}H_{10}NO_2S$), 175 (67, $C_{10}H_7O_3$), 160 (40, $C_{10}H_8O_2$), and 93 (0.2, C_6H_5O).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(4-(N-(1-naphthyl)sulfamoyl)- phenylamino)butanoic acid (21); Pale violet crystals from ethanol, mp 130-132 ºC**,** 69% yield in microwave, 75% yield in microwave with DMF, and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3302 and 3227 (2NH), 3300-2800 (OH, acid), 1715 (CO, acid), 1666 (CO, amide), 1256 (SO_2, asy.), and 1150 (SO_2, sym.). MS: m/z = 530.5 (M^+, 0%, $C_{28}H_{22}N_2O_7S$), 159 (0.37, $C_{10}H_7O_2$), 156(2, $C_6H_6NO_2S$) 142 (5.4, $C_{10}H_8N$), 128 (0.32, $C_{10}H_8$), 115 (100, $C_4H_5NO_3$ or C_9H_7), 102 (0.85, C_8H_6), 65 (42, HSO_2), and 63 (29, HNOS).

(E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(4-(N-(4-benzylsulfamoyl)- phenylamino)butanoic acid (22); White crystals from ethanol, mp 222-223 ºC**,** 35% yield in microwave and 50% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3297 and 3200 (2NH), 3500-2200 (OH, acid), 1695 (CO, acid), 1664 (CO, amide), 1243 (SO_2, asy.), and 1161 (SO_2, sym.). MS: m/z = 494.5 (M^+, 0.54%, $C_{25}H_{22}N_2O_7S$), 262 (31, $C_{13}H_{14}N_2O_2S$), 232 (94, $C_{12}H_8O_5$), 160 (87, $C_{10}H_8O_2$), 159 (24, $C_{10}H_7O_2$), 106 (67, C_7H_8N), 102 (77, C_8H_6), 91 (53, C_7H_7), 65 (69, HSO_2), and 63 (33, HNOS). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.856 (2H, s, H-6), 4.041-4.062 (2H, d, H-11), 6.126 (2H, s, H-1), 7.042-7.069 (1H, d, H-2), 7.235-7.290 [8H, m, (H-3), (H-4), (H-5) & (H-12)], 7.541 (1H, s, H-7), 7.585-7.614 (2H, d, H-8), 7.930-7.959 (2H, d, H-9), and 8.224-8.265 (1H, t, H-10).

(E)-4-(3-(Benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-(4-phenyl)benzenesulfonamides (23); Yellow crystals from benzene, mp 226-227 ºC**,** 50% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3255 (NH), 1762 and 1704 (2CO, imide), 1246 (SO_2, asy.), and 1163 (SO_2, sym.). MS: m/z = 462 (M^+, 70%, $C_{24}H_{18}N_2O_6S$), 370 (5, $C_{18}H_{12}NO_6S$), 306 (90, $C_{18}H_{12}NO_4$), 232 (69, $C_{12}H_8O_5$), 231 (7,

$C_{12}H_9NO_4$), 160 (100, $C_{10}H_8O_2$), 159 (47, $C_{10}H_7O_2$), 102 (98, C_8H_6), 92 (71, C_6H_6N), 65 (67, HSO_2), and 63 (40, HNOS).

(E)-4-(3-(Benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-(4-methylphenyl)benzenesulfonamide (24); Yellow crystals from benzene, mp 190-194 ºC**,** 60% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3267 (NH), 1770 and 1706 (2CO, imide), 1245 (SO_2, asy.), and 1163 (SO_2, sym.). MS: m/z = 476 (M^+, 20%, $C_{25}H_{20}N_2O_6S$), 160 (22, $C_{10}H_8O_2$), 134 (25, $C_8H_6O_2$), 122 (36, C_6H_4NS), 106 (23, C_7H_8N), 102 (33, C_8H_6), 97 (37, $C_4H_3NO_2$), 91 (21.5, C_7H_7), 62 (32, NOS), and 57 (100, C_2H_3NO).

(E)-4-(3-(Benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-(4-methoxyphenyl)benzenesulfonamide (25); Grey crystals from ethanol, mp 210-211 ºC**,** 89% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3261 (NH), 1769 and 1704 (2CO, imide), 1250 (SO_2, asy.), and 1166 (SO_2, sym.). MS: m/z = 492 (M^+, 10%, $C_{25}H_{20}N_2O_7S$), 463 (3, $C_{24}H_{19}N_2O_6S$), 232 (2, $C_{12}H_{10}NO_2S$), 231 (1.5, $C_{12}H_9O_4$), 175 (2, $C_{10}H_7O_3$), 160 (13, $C_{10}H_8O_2$), 122 (100, C_7H_8NO), 102 (8, C_8H_6), 92 (9.5, C_6H_6N), and 65 (14, HSO_2). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.67 (2H, s, H-6), 3.834 (3H, s, H-12), 6.123 (2H, s, H-1), 6.791-6.801 (1H, d, H-2), 7.031-7.194 [4H, m, (H-3), (H-4) & (H-11)], 7.238-7.355 (2H, d, H-7), 7.645 (1H, imp, H-5), 7.765 (2H, d, H-10), 7.875-7.897 (2H, d, H-8), and 10.094 (1H, s, H-9).

(E)-4-(3-(Benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-(4-chlorophenyl)benzenesulfonamide (26); Yellow crystals from benzene, mp 122-124 ºC**,** 40% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3244 (NH), 1760 and 1711 (2CO, imide), 1257 (SO_2, asy.), and 1167 (SO_2, sym.). MS: m/z = 498 (M+1, 7%, $C_{24}H_{18}ClN_2O_6S$), 306 (7, $C_{18}H_{12}NO_4$), 232 (100, $C_{12}H_8O_5$ or $C_{12}H_{10}NO_2S$), 175 (20, $C_{10}H_7O_3$), 160 (37, $C_{10}H_8O_2$), 159 (37, $C_{10}H_7O_2$), 127 (14, C_6H_6NCl), 102 (85, C_8H_6), 92 (24, C_6H_6N), 65 (31.5, HSO_2), and 63 (64, HNOS).

(E)-4-(3-(Benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-(4-nitrophenyl)benzenesulfonamide (27); Brown crystals from benzene, mp 178-180 ºC**,** 92% yield in microwave and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3251 (2NH), 1768 and 1711 (2CO, imide), 1244 (SO_2, asy.), and 1164 (SO_2, sym.). MS: m/z = 507.5 (M^+, 3%, $C_{24}H_{17}N_3O_8S$), 370 (3, $C_{18}H_{12}NO_6S$), 278 (3, $C_{12}H_{10}N_2O_4S$), 232 (17, $C_{12}H_{10}NO_2S$), 175 (3, $C_{10}H_7O_3$), 160 (100, $C_{10}H_8O_2$), 102 (72.5, C_8H_6), 92 (15, C_6H_6N), 65 (20, C_5H_5), and 63 (32.5, HNOS).

(E)-4-(3-(Benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-benzylbenzenesulfonamide (28); Yellow crystals from benzene, mp 212-214 ºC**,** 52% yield in microwave , 90% yield in microwave with DMF, and 0% yield in thermal. FTIR (KBr): υ (cm^{-1}) = 3219 (NH), 1757 and 1697 (2CO, imide), 1261 (SO_2, asy.), and 1170 (SO_2, sym.). MS: m/z = 476.5 (M^+, 4%, $C_{25}H_{20}N_2O_6S$), 371 (2.5, $C_{18}H_{13}NO_6S$), 307 (4, $C_{18}H_{12}NO_4$), 289 (2.5, $C_{14}H_{12}N_2O_3S$), 231 (3, $C_{12}H_9N$), 160 (19.5, $C_{10}H_8O_2$), 106 (100, C_7H_8N), 102 (16, C_8H_6), 91 (45, C_7H_7), 65 (36.5, HSO_2), and 63 (14, HNOS). ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.65 (2H, imp, H-6), 4.048-4.104 (2H, d, H-10), 6.134 (2H, s, H-1), 7.077-7.099 (1H, d, H-2), 7.283-7.295 (5H, s, H-11), 7.593-7.601 [5H, m, (H-3), (H-4), (H-5) & (H-7)], 7.895-7.947 (2H, d, H-8), and 8.314 (1H, t, H-9).

3. Results and Discussion

Microwave irradiation of anhydride (E)-3-(3,4-dimethoxybenzylidene)dihydrofuran-2,5-dione **1** or (E)-3-(benzo[d][1,3]dioxol-5-ylmethylene)dihydrofuran-2,5-dione **2** with N-phenyl-4-aminobenzenesulfonamide (a) as an unsubstituted amine gave separable mixtures, **3** (10%), **10** (83%), and **16** (33%), **23** (50%), respectively. This can be attributed to the low basicity of the reacted amine. Also with N-(4-chlorophenyl)-4-aminobenzenesulfonamide (d) that containing the electron attracting chlorine atom, both anhydrides **1** and **2** formed separable mixtures from **6** (13%), **13** (65%) and **19** (37%), **26** (40%), respectively. These results can be ascribed to the low nucleophilicity of the nitrogen atom in the amido group, due to the presence of the electron withdrawing chlorine atom, which causes incomplete transformation of the resulted butenamide to the cyclic compound.

However, microwave irradiation of anhydride **1** or **2**, with N-4-methoxyphenyl-4-aminobenzenesulfonamide (c) gave the corresponding (E)-4-(3-(3,4-dimethoxybenzylidene)-2,5-dioxopyrrolidin-1-yl)-N-(4-methoxyphenyl)benzenesulfonamide **12** (93%) or (E)-4-(3-(benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-(4-methoxyphenyl) benzenesulfonamide **25** (89%) as only products. This can be attributed to the high basicity of the electron releasing methoxyl group in amine (c) which facilitates the intramolecular nucleophilic attack of the amido nitrogen on the carbonyl carbon.

On the other hand in spite of the low basicity of N-4-nitrophenyl-4-aminobenzenesulfonamide (e) due to the presence of the electron attracting nitro group, both of anhydrides **1** and **2** gave the corresponding (E)-4-(3-(3,4-dimethoxybenzylidene)-2,5-dioxopyrroliden-1-yl)-N-(4-nitrophenyl)benzenesulfonamide **14** (93%) and (E)-4-

(3-(benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-(4-nitrophenyl) benzenesulfonamide **27** (92%), as only products. This could be ascribed to the microwave effects on the dipolar nitro group in amine (e) where microwave thermal and specific non-purely thermal effects, resulted from material-wave interactions[17] led to further intramolecular nuchleophilic attack by the amido nitrogen on the carbonyl carbon. The greater the polarity of a molecule, the more pronounced microwave effects to enhance the formation of the cyclic product. The combination of these two contributions can be responsible for regiospecific selectivity and the formation of the cyclic compounds.

Reaction of N-(4-methylphenyl)-4-aminobenzenesulfonamide (b) with anhydride **1** gave (E)-4-(3-(3,4-dimethoxybenzylidene)-2,5-dioxopyrrolidin-1-yl)-N-(4-methylphenyl)-benzenesulfonamide **11** (92%) as an only product, whereas with anhydride **2** it gave a separable mixture from (E)-2-(benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(4-(N-(4-methylphenyl) sulfamoyl) phenylamino)butanoic acid **17** (30%), and (E)-4-(3-(benzo[d][1,3]dioxol-5-ylmethylene)-2,5-dioxopyrrolidin-1-yl)-N-(4-methylphenyl) benzenesulfonamide **24** (60%). These results can be explained on the basis of the anhydrides structure where in anhydride **2** the distortion exerted by the 2-benzo[d][1,3]dioxol moiety, could decrease the complete coplanarity, that is necessary for ring closure, to form the corresponding pyrrolidine-2,5-dione, to be an only product.

On the other hand with N-(1-naphthyl)- 4-aminobenzenesulfonamide (f), anhydrides **1** and **2**, produced (E)-2-(3,4-dimethoxybenzylidene)-4-oxo-4-(4-(N-(1-naphthyl)sulfamoyl)-phenylamino) butanoic acid **8** (75%) and (E)-2-(benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(4-(N-(1-naphthyl)sulfamoyl)phenylamino)butanoic acid **21** (69%), respectively, as only products. This result can be ascribed to the low nucleophilicity of the amido nitrogen towards further attack on the carbonyl carbon.

However, microwave irradiation of N-benzyl-4-aminobenzenesulfonamide (g), as a relatively high basic aliphatic amine, with compound **1** gave benzenesulfonamide derivative **15** (82%) as an only product, whereas with compound **2**, it gave a separable mixture from **22** (35%) and **28** (52%). In presence of the aprotic solvent DMF, compound **2** gave with amine (g), **28** (90%) as an only product. The presence of the aprotic solvent (DMF), caused the super heating effect in the microwave irradiation, where the energy transferred from large excess solvent molecules to the reaction mixture. The presence of solvent also slightly enhanced the yield of the products where microwave irradiation reactions of compound **1** or **2** with amine (f), in DMF gave the corresponding butanoic acids in slightly better yields **8** (83%), **21** (75%) instead of (75%) and (69%), respectively. This result indicated that in such a case, no more agitation or molecules reorientation could take place by microwave irradiation, to allow further intramolecular nucleophilic attack by the nitrogen atom of amido group on the carbonyl carbon to form the cyclic compound (Schemes 1 and 2).

Thermal conventional heating technique

Conventional thermal condensation of anhydrides **1** or **2** with N-substituted aryl-4-aminobenzenesulfonamides (a-e, and g) gave the corresponding (E)-2-(3,4-dimethoxybenzylidene)-4-oxo-4-(4-(N-arylsulfamoyl)- phenylamino)butanoic acids **3-7** and **9**, and (E)-2-(benzo[d][1,3]dioxol-5-ylmethylene)-4-oxo-4-(4-(N-arylsulfamoyl)-phenylamino) butanoic acids **16-20**, and **22**, respectively.

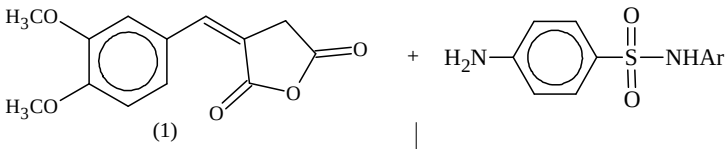
However, with amine (f), all trials carried out for its reaction with **1** or **2**, under reflux or fusion, were unsuccessful. These results were attributed to the low basicity of amine (f).

In general, the results indicated that microwave irradiation effects enhance the susceptibility of amido nitrogen towards further intramolecular nucleophilic attack to form the cyclic product, more than the conventional thermal heat technique (Scheme 3).

Molecular structures of compounds **3-28** were assigned by their spectral analyses; IR, MS, and ^{1}H-NMR. Protons numbering of ^{1}H-NMR spectra of some compounds are given in Figure 1.

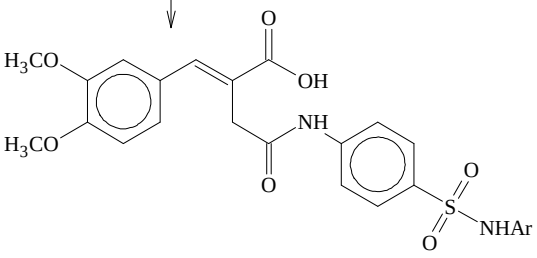
The most pronounced antibacterial activities with compounds **5**, **14**, **17**, **20** and **27** could be attributed to the presence of carboxyl (COOH), methoxyl (OCH_3), and nitro (NO_2) groups.

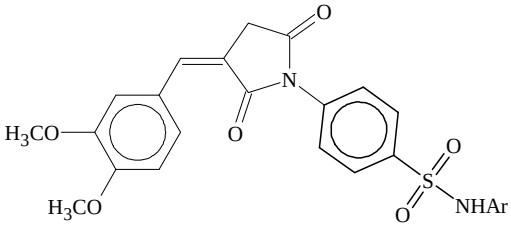
The results of cytotoxic activity of screened compounds showed low activity (Table 2).



(1)

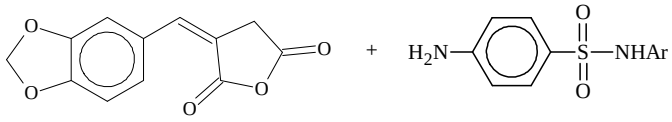
Microwave





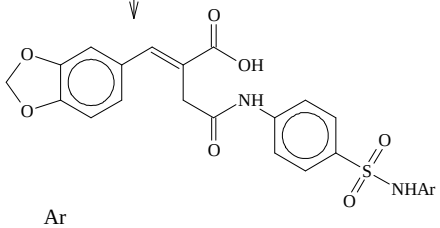
Ar	Ar
3 C_6H_5	10 C_6H_5
6 4-ClC_6H_4	11 4-$CH_3C_6H_4$
8 1-Naphthyl	12 4-$OCH_3C_6H_4$
	13 4-ClC_6H_4
	14 4-$NO_2C_6H_4$
	15 Benzyl

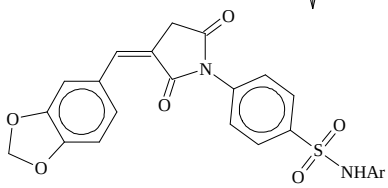
Scheme 1



(2)

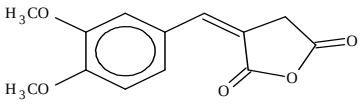
Microwave



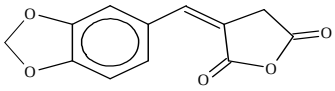


Ar	Ar
16 C_6H_5	23 C_6H_5
17 4-$CH_3C_6H_4$	24 4-$CH_3C_6H_4$
19 4-ClC_6H_4	25 4-$OCH_3C_6H_4$
21 1-Naphthyl	26 4-ClC_6H_4
22 Benzyl	27 4-$NO_2C_6H_4$
	28 Benzyl

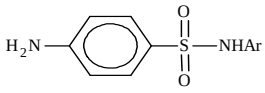
Scheme 2



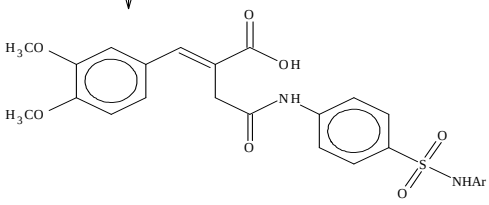
(1)

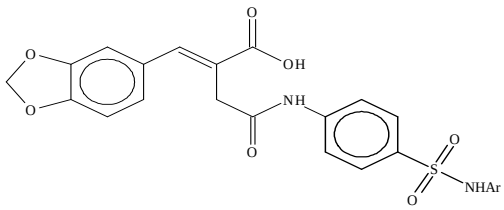


(2)



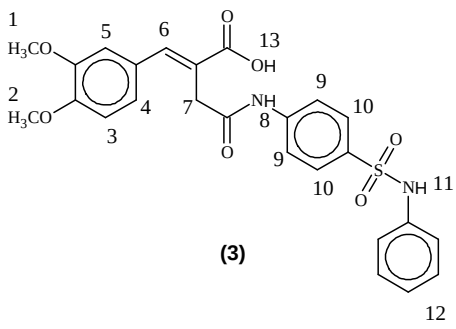
Thermal heating



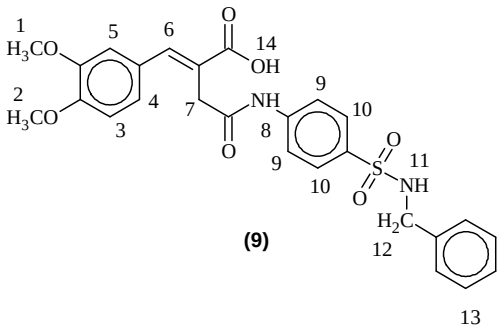


Ar	Ar
3 C_6H_5	16 C_6H_5
4 $4\text{-}CH_3C_6H_4$	17 $4\text{-}CH_3C_6H_4$
5 $4\text{-}OCH_3C_6H_4$	18 $4\text{-}OCH_3C_6H_4$
6 $4\text{-}ClC_6H_4$	19 $4\text{-}ClC_6H_4$
7 $4\text{-}NO_2C_6H_4$	20 $4\text{-}NO_2C_6H_4$
9 Benzyl	22 Benzyl

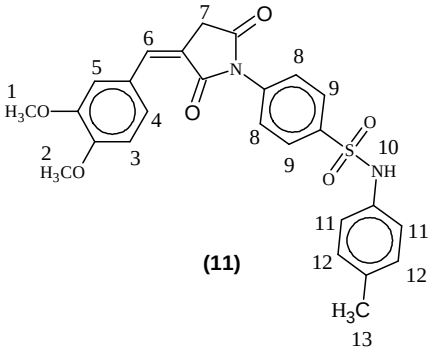
Scheme 3



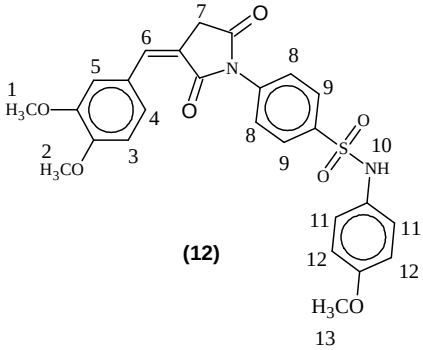
(3)



(9)



(11)



(12)

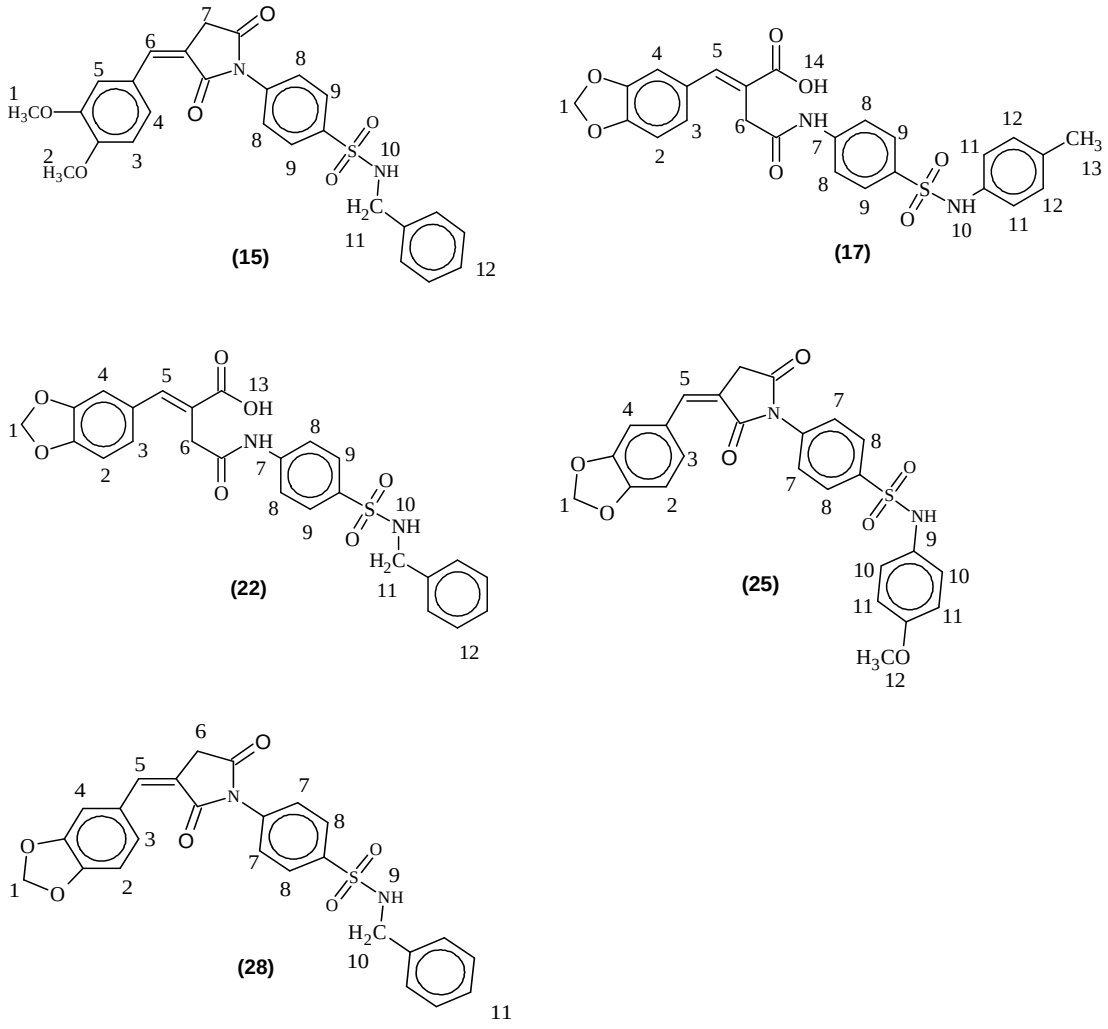


Figure 1: Protons Numbering of ^{1}H-NMR Spectra

Table 2: Biological activities of some compounds

Compound	Antimicrobial ActivityInhibition zone (mm/mg sample)				Cytotoxic activity IC50 µg/ml
	Bacillus subtilis (G^+)	*E. Coli* (G^-)	*Pseudomonas aeruginosa* (G^-)	*Staphylococcus Aureus* (G^+)	
4	13	---	---	13	
5	14	15	15	16	
7	13	13	---	---	
8					20.7
10					20.7
12					16.7
14	13	13	14	13	
17	16	12	---	20	
18	18	13	---	15	
20	16	14	---	14	
21					18.9
25	12	---	---	---	19.7
27	15	15	15	14	
Flouraciele					2.97

Conclusion

Microwave irradiation effects enhance the yield, purity, regioselectivity, and cyclization, more than the conventional thermal heat effect. The distortion exerted by the 2-benzo[d][1,3]dioxol moiety, could decrease the probability of molecular coplanarity that is necessary for ring closure to form the corresponding cyclic products. Aprotic solvent (DMF), assists the super heating effect in the microwave irradiation where the energy transfers from large excess solvent molecules to the reaction mixture so that it facilitates the formation of the cyclic products and enhances the yields. Compounds containing carboxyl (COOH), methoxyl (OCH_3), and nitro (NO_2) groups showed high activity towards antimicrobial activities. Compounds that screened for cytotoxic activity IC50µg/ml showed low reactivity towards it.

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