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Microwave assisted synthesis of (*E*)-2-(4-(3-(aryl) acryloyl) phenyl) isoindoline-1, 3-diones and their antibacterial activity

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ABSTRACT

A series of (E)-2-(4-(3-(Aryl) acryloyl) phenyl) isoindoline-1,3-diones synthesized from 2-(4-acetylphenyl)isoindoline-1,3-dione and aromatic aldehydes using conventional and microwave irradiation method. The newly synthesized compounds were characterized by spectral data such as IR, [1]H-NMR, mass spectrometry and elemental analysis. The titled compounds were evaluated for their antibacterial activity against gram positive and negative strains, the compounds showed good activity against all the microorganisms.

Keywords: Isobenzofuran-1, 3-dione, 1-(4-aminophenyl) ethanone, microwave irradiation antibacterial activity.

INTRODUCTION

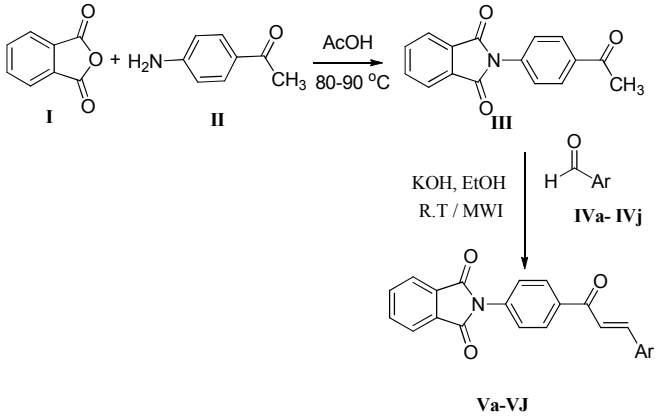
Chalcones are of interest for various studies because of their vital role as precursor in the biosynthesis of flavanoids and other pharmacological important compounds. The chalcones explored as a new class of non-azo dyes [1] and they have displayed a broad spectrum of biological and pharmacological activities, among which antioxidant [2-4], antibacterial [5-7], antifungal [8-10], anticancer, anti-inflammatory [11-13] and antidepressant [14,15] activities. In addition, some photo physical properties of these substances such as non-linear optical properties [16,17] and their use as fluorescent probe [18]. On the other hand, the different traditional methods used for synthesizing chalcones such as base catalyzed (NaOH, KOH, $Ba(OH)_2$ and acid catalyzed (including Lewis acids) condensation processes in the presence of suitable solvent and the recent literature revealed the so many new eco-friendly methods like adopted such as ultrasonic radiations [19], microwave assisted [20], solvent free synthesis by grinding [21] etc. In these the microwave radiation has gained the attention of chemists due to its unique advantages, such as shorter reaction times, cleaner reaction products, higher yields and better selectivities, being a valuable alternative to accomplish more efficient syntheses of a variety of organic compounds with a considerable simplicity of operation and milder reaction conditions, when combined with the solvent-free approach. Keeping in view of these findings, herein we synthesize a series of (*E*)-2-(4-(3-(Aryl) acryloyl) phenyl) isoindoline-1,3-diones under microwave irradiation method and tested their antibacterial activities.

MATERIALS AND METHODS

Melting points (mp) were determined using Boetieus micro heating apparatus and are uncorrected. Purity of compounds was monitored by TLC on silica gel plates 60 F254 (Merck). IR (KBr, cm^{-1}) spectra were obtained on Perkin-Elmer FT-IR spectrum BX. ^{1}H-NMR spectra were recorded on Bruker AMX-400 (400 MHz) spectrometer

using TMS as an internal reference (Chemical shifts in δ, ppm). Mass spectra were recorded on Quatro Lc micromas (Waters Manchester.UK) (70 eV) and elemental analysis was carried out by a Thermo Finnigan CHNS analyzer.

Scheme: Preparation of (*E*)-2-(4-(3-(Aryl)acryloyl)phenyl)isoindoline-1,3-diones (Va-Vj)



I **II** **III** **IVa- IVj** **Va-VJ**

Va) *Ar= phenyl;* ***Vb)*** *Ar= methyl phenyl;* ***Vc)*** *Ar= methoxy phenyl;* ***Vd)*** *Ar= 4-fluoro phenyl;* ***Ve)*** *Ar=4-chloro phenyl;* ***Vf)*** *Ar= 2,4-dichloro phenyl;* ***Vg)*** *Ar= 2,4-dichloro phenyl;* ***Vh)*** *Ar= 4-bromo phenyl;* ***Vi)*** *Ar= 4-nitro phenyl;* ***Vj)*** *Ar= theinyl.*

General procedure: Synthesis of (*E*)-2-(4-(3-(Aryl)acryloyl)phenyl)isoindoline-1,3-diones:

a) Conventional stirring method:

To a solution of 2-(4-Acetylphenyl)-isoindole-1,3-dione **(III)** (1 mmol), aromatic aldehydes **(IVa-IVj)** (1 mmol) and 20% sodium hydroxide in methanol were stirred for 5-7 hr at room temperature. The reaction progress was monitored by TLC. After completion of the reaction the reaction mixture was poured into ice cold water and neutralized with dil. HCl, the resulting solid was filtered, dried and purified by column chromatography using EtOAc: Pet Ether (1:2) to obtain the titled compounds **(Va-Vj).**

b) Microwave irradiation method:

To a mixture of 2-(4-Acetylphenyl)-isoindole-1,3-dione **(III)** (1 mmol), aromatic aldehydes **(IVa-IVj)** (1 mmol) and 20% sodium hydroxide in methanol were irradiated under microwave at 180 watt for 6-8 min. with 30 sec intervals. The reaction progress was checked by TLC. After completion of the reaction the reaction mixture poured into ice cold water and neutralized with dil. HCl the resulting solid was filtered, dried and purified by column chromatography using EtOAc: Pet Ether (1:2) to obtain the titled compounds **(Va-Vj).**

Table-1: Physical data of (*E*)-2-(4-(3-(Aryl)acryloyl)phenyl)isoindoline-1,3-diones (Va-Vj)

Compounds	M.P. (°C)	Reaction Time		% Yield	
		Conventional (hr)	MWI (min)	Conventional	MWI
Va	164	5.0	7.0	75	88
Vb	246	5.0	6.0	79	90
Vc	188	4.0	6.0	77	92
Vd	174	7.0	8.0	65	80
Ve	156	5.0	6.0	72	86
Vf	271	6.0	8.0	69	78
Vg	282	6.0	8.0	65	76
Vh	167	5.0	6.0	70	85
Vi	181	7.0	8.0	63	72
Vj	139	5.0	7.0	67	82

Antibacterial activity:

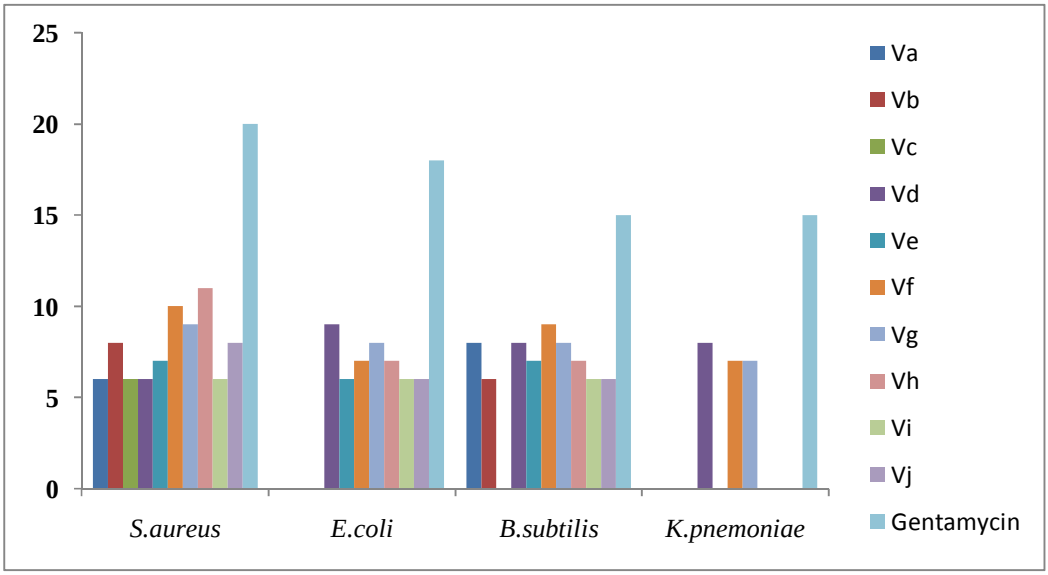
A new series of thiazole derivatives were screened for their antibacterial activity against Gram positive bacteria *viz. Staphylococcus aureus* and *Bacillus subtilis* and Gram negative bacteria *viz. Escherichia coli*, *Klebsiella pnemoniae* at concentration 50µg/ml using disc diffusion method using Gentamycin as a standard. The test organism was a two hour culture of *Escherichia coli, Klebsiella pnemoniae, Staphylococcus aureus* and *Bacillus subtilis* incubated and grown in peptone-water medium (temp-37°C). DMF was used as solvent control which did not show any zone of inhibition. Muller-Hilton agar medium was used as culture medium. The culture plates were incubated at 37°C for

24 hrs. The growth inhibition zones around the discs were observed that indicating that the examined compound inhibits the growth of microorganism. Each assay in this experiment was repeated three times.

Table-2: Antibacterial studies of (*E*)-2-(4-(3-(Aryl)acryloyl)phenyl)isoindoline-1,3-diones (Va-Vj)

Compounds	Antibacterial activity zone of inhibition(mm)			
	S. aureus	*E.coli*	*B. subtilis*	*K. pnemoniae*
Va	06	-	08	-
Vb	08	-	06	-
Vc	06	-	-	-
Vd	06	09	08	08
Ve	07	06	07	-
Vf	10	07	09	07
Vg	09	08	08	07
Vh	11	09	07	-
Vi	06	06	06	-
Vj	08	07	06	-
Gentamycine	20	18	15	15

Fig-1: Graphical representation of Antibacterial activity of (*E*)-2-(4-(3-(Aryl)acryloyl) phenyl)isoindoline-1,3-diones (Va-Vj)



RESULTS AND DISCUSSION

All the compounds **(Va-Vj)** were in solid state, yellowish in colour, stable to moisture and temperature. The structures were established by Mass spectrometry, IR, ^{1}H-NMR and Elemental analysis.

Spectral data:

Compound Va. IR spectrum, ν, cm–1: 1659 (C=O); 1709 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.47-7.48 (m, Ar-H, 3H); 7.59-7.67 (m, Ar-H, 3H); 7.72-7.76 (d, *J* =16 Hz, H_α, 1H); 7.88-7.91 (m, Ar-H, 5H); 7.95-7.99 (d, *J* =16 Hz, H_β, 1H); 8.18-8.20 (d, Ar-H, 2H). Found, %: C, 78.19; H, 4.29; N, 3.97. $C_{23}H_{15}NO_3$ calculated, %: C, 78.17; H, 4.28; N, 3.96. *M* 354 $[M+H]^+$.

Compound Vb. IR spectrum, ν, cm–1: 1659 (C=O); 1702 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.51 (s, -CH_3, 3H); 7.47-7.49 (m, Ar-H, 2H); 7.69-7.71 (m, Ar-H, 2H); 7.78-7.82 (d, 16 Hz, H_α, 1H); 7.92-7.95 (m, Ar-H, 4H); 7.99-8.03 (m, H_β & Ar-H, 3H); 8.31-8.33 (m, Ar-H, 2H). Found, %: C, 78.48; H, 4.67; N, 3.82. $C_{24}H_{17}NO_3$ calculated, %: C, 78.46; H, 4.66; N, 3.81. *M* 368 $[M+H]^+$.

Compound Vc. IR spectrum, ν, cm–1: 1662 (C=O); 1710 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.83 (s, -OCH_3, 3H); 7.02-7.04 (m, Ar-H, 2H), 7.58-7.62 (m, Ar-H, 2H), 7.66-7.68 (m, Ar-H, 2H), 7.69-7.73 (d, *J* =16 Hz, H_α, 1H), 7.82-

7.92 (m, Ar-H & H_β, 5H), 8.16-8.18 (m, Ar-H, 2H). Found, %: C, 75.21; H, 4.48; N, 3.66. $C_{24}H_{17}NO_4$ calculated, %: C, 75.19; H, 4.47; N, 3.65. *M* 384 $[M+H]^+$.

Compound Vd. IR spectrum, ν, cm–1: 1645 (C=O); 1697 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.52-7.55 (m, Ar-H, 2H); 7.57-7.62 (m, Ar-H, 2H); 7.67-7.68 (m, Ar-H, 1H); 7.70-7.74 (d, 15.2 Hz, H_α, 1H); 7.87-7.95 (m, Ar-H, 2H); 7.98-8.01 (d, 15.2 Hz, H_β, 1H); 8.18-8.20 (m, Ar-H, 2H). Found, %: C, 74.41; H, 3.81; N, 3.78. $C_{23}H_{14}FNO_3$ calculated, %: C, 74.39; H, 3.80; N, 3.77. *M* 372 $[M+H]^+$.

Compound Ve. IR spectrum, ν, cm–1: 1652 (C=O); 1696 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.53-7.55 (m, Ar-H, 2H); 7.58-7.62 (m, Ar-H, 2H); 7.67-7.69 (m, Ar-H, 2H); 7.71-7.75 (d, 15.8 Hz, H_α, 1H); 7.87-7.96 (m, Ar-H, 4H); 7.98- 8.02 (d, 15.8 Hz, H_β, 1H); 8.18-8.20 (d, Ar-H, 2H). Found, %: C, 71.25; H, 3.65; N, 3.62. $C_{23}H_{14}ClNO_3$ calculated, %: C, 71.23; H, 3.64; N, 3.61. *M* 388 $[M+H]^+$.

Compound Vf. IR spectrum, ν, cm–1: 1653 (C=O); 1695 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.58-7.61 (m, Ar-H, 3H); 7.67-7.69 (m, Ar-H, 1H); 7.77-7.78 (dd, Ar-H, 1H); 7.88-7.98 (m, Ar-H & H_α, 4H); 8.05-8.09 (d, H_β, 1H, 16 Hz); 8.20-8.22 (m, Ar-H, 2H); 8.27-8.29 (m, Ar-H, 1H). Found, %: C, 65.43; H, 3.11; N, 3.33. $C_{23}H_{13}Cl_2NO_3$ calculated, %: C, 65.42; H, 3. 10; N, 3.32; *M* 422 $[M+H]^+$.

Compound Vg. IR spectrum, ν, cm–1: 1656 (C=O); 1699 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.57- 7.60 (m, Ar-H, 3H); 7.68-7.69 (m, Ar- H, 1H); 7.73-7.77 (m, Ar-H, 1H); 7.88-7.92 (m, Ar-H, 2H); 7.94-7.98 (d, 15.6Hz, H_α, 1H); 8.05-8.09 (d, 15.6 Hz, 1H, H_β); 8.20-8.22 (m, Ar-H, 3H); 8.27- 8.29 (m, Ar-H, 1H). Found, %: C, 65.43; H, 3.11; N, 3.33. $C_{23}H_{13}Cl_2NO_3$ calculated, %: C, 65.42; H, 3. 10; N, 3.32. *M* 422 $[M+H]^+$.

Compound Vh. IR spectrum, ν, cm–1: 1651 (C=O); 1692 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.52-7.54 (m, Ar-H, 2H); 7.57- 7.62 (m, Ar- H, 2H); 7.66- 7.68 (m, Ar-H, 1H); 7.70-7.74 (d, 15.2 Hz, 1H, H_α); 7.87-7.95 (m, Ar-H, 2H); 7.97-8.01 (d, 15.2 Hz, 1H, H_β); 8.18-8.20 (m, Ar-H, 2H). Found, %: C, 63.92; H, 3.26; N, 3.25. $C_{23}H_{14}BrNO_3$ calculated, %: C, 63.91; H, 3.26; N, 3.24 *M* 432 $[M+H]^+$.

Compound Vi. IR spectrum, ν, cm–1: 1644 (C=O); 1694 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.58-7.60 (m, Ar-H, 3H); 7.63-7.71 (m, Ar-H & H_α, 2H); 7.80-7.93 (m, Ar-H, 5H); 8.16-8.32 (m, Ar-H & H_β, 4H). Found, %: C, 69.35; H, 3.55; N, 7.04. $C_{23}H_{14}N_2O_5$ calculated, %: C, 69.34; H, 3.54; N, 7.03. *M* 399 $[M+H]^+$.

Compound Vj. IR spectrum, ν, cm–1: 1648 (C=O); 1706 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.20-7.21 (dd, Th-H, 1H); 7.57-7.69 (m, Ar-H & H_α, 6H); 7.78-7.80 (m, Ar-H, 1H); 7.87-7.93 (m, Ar-H & H_β, 4H); 8.11-8.13 (m, Ar-H, 2H). Found, %: C, 70.20; H, 3.66; N, 3.91; S, 8.93. $C_{21}H_{13}NO_3S$ calculated, %: C, 70.18; H, 3.65; N, 3.90; S, 8.92. *M* 360 $[M+H]^+$.

CONCLUSION

The title compounds were synthesized by conventional method and microwave irradiation method. Among these, microwave irradiation method is an easy, high yielding, convenient and green method. The process proved to be a simple and environmentally friendly technique with high rate of acceleration was achieved in performing the reaction. Synthesized compounds were tested for their antimicrobial activity. The compounds **Vf, Vg** and **Vh** were showed good activity against gram-positive bacteria *viz. Staphylococcus aureus* & *Bacillus subtilis* and gram negative bacteria *viz. Escherichia coli* & *Klebsiella pnemoniae*.

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