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An Ecofriendly Systhesis of 4-Thiazolidinone Derivative Using Tributylammonium Bromide Under Microwave Irradiation

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Abstract. A series of new compounds 5-benzylidene-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone were synthesized by adopting environment friendly microwave irradiation methodology, their structures and *in vitro* antibacterial and antifungal activities are reported.The synthesized compounds exhibited different levels of antibacterial activities. Three compounds showed broad spectrum antibacterial activity.

Keywords: microwave irradiation, tributylammonium bromide, 4-thiazolidinone, environment friendly, antibacterial compounds .

Introduction

Thiazolidinone is a useful precursor for a variety of heterocyclic products including drugs, dyes, herbicides, sulfur drugs, chemical reaction accelerators, flavouring substances and is associated with broad spectrum of biological activities including antibacterial, antifungal, tuberculostatic, anthelmentic, antitumor, anticonvulsant, diuretic, insecticidal and pesticidal properties (Singh *et al.*, 1981).

The derivatives of 4-thiazolidinone moiety have been synthesized by condensation of aromatic aldehyde and pipradinium benzoate in refluxing toluene (Kasmi-Mir *et al*., 2006). Such methods involve long reaction time, require large quantities of organic solvents and generally yield unsatisfactorily. Microwave radiation has been employed for the formation of different products under simple operational conditions (Algul *et al*., 2008).

Phase transfer catalysts (PTC) are environmentally benign and are used for reactions in which tetraalkylammonium cations are preferred in heterogeneous two-phase system.

Solvents like carbon tetrachloride, pryridine, dimethyl sulphoxide, dimethyl sulphate, toluene, 1,4-dioxane are commonly used as reaction media and for purification purposes. The common adverse effects of these solvents may include redness, itching and rashes on skin, swelling of face, troubled breathing, shortness of breath, nasal congestion, headache, vomiting, severe upper abdominal pain, back pain, and possible allergic reaction to material if inhaled, ingested or even contacted. Particularly adverse effects like loss of appetite, insomnia, fatigue, depression, delirium, fever, frequent urination, and loss of coordination or judgment are caused by pyridine, while confusion, drowsiness, diarrhoea are due to carbon tetrachloride (Ballell *et al*., 2004; Rao *et al*., 2004; Merck Index, 1996).

In the present investigations, reaction of 3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone with different aromatic aldehyde in the presence of tributylammonium bromide (TBAB) as phase transfer catalyst in an aqueous medium was carried out under microwave irradiation and *in vitro* activity of the newly synthesized compounds was evaluated focusing on qualitative as well as quantitative analysis. This reaction requires only 6-8 min, is environmentally benign with low energy consumption and easy workup.

Materials and Methods

Melting points determined on digital melting point apparatus (Gallenkamp, England) were uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400 instrument as KBr discs and only noteworthy absorption levels (cm^{-1}) were listed. ^{1}H-NMR spectra were recorded on a Bruker AC-300 MHz using TMS as the internal standard and represented in chemical shift as ä ppm downfield from TMS. Elemental analysis was carried out using a Perkin Elmer CHNS analyzer and mass spectra were recorded on a Juel D-300 spectrometer. Zone of inhibition was calculated on digital automatic zone reader (AZ-II, SUPICO, Korea). All solvents and reagents were purchased from Fluka, Merck, Sigma-Aldrich and used without purification.

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The reaction mixture was irradiated with microwave of low power (200 W). The temperature of the reaction mixture was monitored by temperature reader. Temperature of the reaction mixture continuously increased and the reaction was completed in 6-8 min using microwave oven (Model No.MV 32/8-O, SUPICO, Korea). The reactions were monitored by TLC using *n*-hexane: ethylacetate (3:7, v/v) as developing solvent, and target compounds were isolated in high yield. This novel energy-saving procedure was found to be useful for the efficient preparation of several compounds. The crude product was purified by column chromatography on silica gel to ensure purity.

Schematic presentation of magnetron is given in Fig. 1.

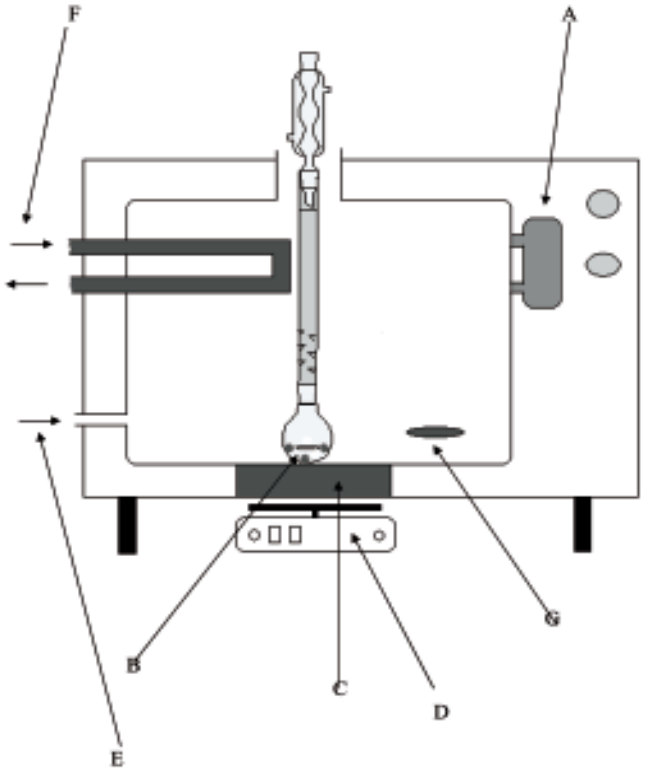


Fig. 1. Schematic diagram of magnetron.

A. Magnetron
B. Reaction mixture with the EDL and a magnetic stir bar
C. Aluminum plate
D. Magnetic stirrer
E. Pyrometer
F. Circulating water in a glass tube
G. Dummy load inside the oven cavity

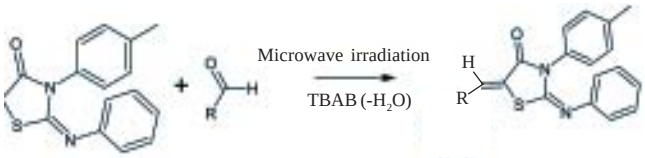
Series (1a-j). ***Synthesis of 5-benzylidene-3-(4-methylphenyl)-2-(phenyli-mino)-4-thiazolidinone.*** Equimolar (5 mmol) quantity of compound 3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone (1.4118 g) was treated with different aromatic aldehydes in the presence of phase transfer catalyst (1.6 mmol tetrabutylammonium bromide) and 20 ml water. The mixture was irradiated in microwave oven at 200 watts at 110 °C for 6-8 min and then cooled to room temperature. The prepared compounds were recrystallized from ethanol to get target compounds.

Antimicrobial activity test. The test was performed according to the disk diffusion method (United States Pharmacopoeia, 2004). All compounds were screened for their antimicrobial activity against a variety of bacterial strains, such as *Escherichia coli, Bacillus subtilis, Staphylococcus aureus* and *Aspergillus niger* at 20 µg/ml concentration. Apparatus were sterilized by using autoclave for 15 min at 121 ºC (Fazzini, Model F-31, Italy). Agar plates were surface inoculated uniformly using the broth culture of the tested microorganisms. The potency of synthesized compound was inserted in a hole made by the porcelain cylinders under laminar flow hood. The impregnated disks were placed on the medium suitably spaced apart and then transferred to an incubator at 37 ºC for 72 h for bacteria, and at 28 ºC for fungi (Naeem *et al.*, 2008). Inhibition zones caused by various compounds on the microorganisms were examined. The results of the preliminary screening are listed in Table 3.

Results and Discussion

A series of ten compounds **1(a-j)**, 5-benzylidene-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone were synthesized using phase transfer catalyst (TBAB) under microwave irradiation (synthetic scheme).

Synthetic scheme



Compounds	R	Compounds	R
1a	$-C_6H_5$	**1f**	$4\text{-}CH_3C_6H_4$
1b	$4\text{-}ClC_6H_4$	**1g**	$2\text{-}ClC_6H_4$
1c	$4\text{-}N(CH_3)_2C_6H_4$	**1h**	$4\text{-}NH_3C_6H_4$
1d	$4\text{-}OCH_3H_4$	**1i**	$3\text{-}OH\text{-}5\text{-}OHC_6H_3$
1e	$3\text{-}OCH_3\text{-}4\text{-}OHC_6$	**1j**	$4\text{-}OHC_6H_4$

Structures of synthesized compounds were elucidated by spectral data mentioned in Table 1 and Table 2. Previously, under microwave irradiation, a reaction of 3-phenyl, 4-thiazolidinone with aromatic aldehyde was conducted without TBAB using water as solvent, for 8 min but target compounds were not obtained, because 3-phenyl,4-thiazolidinone with

Table 1. Characterization of synthesized compounds by FTIR, NMR, and MS spectrometer

Compounds	Yield % physical state	M.p. °C	IR (KBr, cm^{-1})	^{1}H-NMR ($CDCl_3$) ä	Mass Molecular ion peak *m/z*
1a [5-benzylidene-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone]	88, off white powder, reaction time 6 min	208	3460 (–N= thiazolidinone), 3040-3010 (Ar-C-), 1724 (C=O, thiazolidinone)	8.01 (s, 1H, CH=C_5) 7.58-7.24 (m, 15H, *J*=8.4 Hz, aromatic proton), 3.20 (t, 3H of CH_3)	370.467, Calc. 370.202
1b [5-(4-chlorobenzylidene)-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone]	96, yellow crystalline powder, reaction time 6 min	224	3440 (–N= thiazolidinone), 3044-3010 (Ar-C-), 1716 (C=O, thiazolidinone), 660 (-Cl)	8.36 (s, 1H, CH=C_5) 7.48-7.30 (m, 10H aromatic proton), 7.18 (d, 2H, *J*=7 Hz), 7.10 (d, 2H, *J*=6.4 Hz), 3.16 (t, 3H of CH_3)	404.912 Calc. 404.891
1c [5-[4-(dimethylamino)pheny)]-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone]	86, yellow powder, reaction time 8 min	210	3414 (–N= thiazolidinone), 3040-3010 (Ar-C-), 1740 (C=O, thiazolidinone)	8.35 (s, 1H, CH=C_5) 7.45-7.34 (m, 10H aromatic proton), 7.22 (d, 2H,), 7.10 (d, 2H), 3.28 (s, 6H, $(CH_3)_2$), 2.46 (t, 3H of CH_3)	413.535 Calc. 413.52
1d [5-(4-methoxybenzylidene)-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone]	73, light yellow powder reaction time 8 min	206	3430 (–N= thiazolidinone), 3024-3002 (Ar-C-), 1740 (C=O, thiazolidinone).	8.24 (s, 1H, CH=C_5) 7.46-7.30 (m, 10H aromatic proton), 7.18 (d, 2H,), 7.06 (d, 2H), 3.48 (s, 3H, CH_3O), 3.02 (t, 3H of CH_3	400.493, Calc. 400.48
1e [5-(4-hydroxy-3-methoxybenzylidene)-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone]	77, off white powder, reaction time 8 min	236	3380 (–N= thiazolidinone), 3200(-OH), 3030-3010 (Ar-C-), 1738 (C=O, thiazolidinone).	10.05 (s, 1H, OH) , 8.14 (s, 1H, CH=C_5) 7.54-7.28 (m, 10H aromatic proton), 7.12 (d, 2H, aromatic), 6.98 (s, 1H, aromatic), 3.68 (s, 3H, CH_3O), 2.88 (t, 3H of CH_3)	416.492 Calc. 416.48
1f [5-(4-methylbenzylidene)-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone]	69, yellow powder, reaction time 8 min	245	3450 (–N= thiazolidinone), 3040-3010 (Ar-C-), 1730 (C=O, thiazolidinone).	8.34 (s, 1H, CH=C_5) 7.44-7.26 (m, 10H aromatic proton), 7.22 (d, 2H, aromatic), 7.14 (d, 2H, aromatic), 3.32 (s, 3H, CH_3), 2.68 (t, 3H of CH_3)	384.493, Calc. 384.47
1g [5-(2-chlorobenzylidene)-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone]	78, white crystalline powder, reaction time 6 min	218	3440 (–N= thiazolidinone), 3024 (Ar-C-), 1728 (C=O, thiazolidinone)	8.58 (s, 1H, CH=C_5), 7.48-7.34 (m, 10H aromatic proton), 7.24 (m, 4H, aromatic), 3.18 (t, 3H of CH_3)	393.04, Calc. 393.89
1h [5-(4-aminobenzylidene)-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone]	92, off white crystalline powder, reaction time 6 min	225	3445 (–N= thiazolidinone), 3020 (Ar-C-), 1730 (C=O, thiazolidinone)	9.78 (d, 2H, NH_2), 8.46 (s, 1H, CH=C_5), 7.38-7.22 (m, 10H aromatic proton), 7.10 (d, 2H, aromatic), 6.90 (d, 2H, aromatic), 3.21 (t, 3H of CH_3)	385.481, Calc. 385.458
1i [5-(3,5-dihydroxybenzylidene)-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone]	44, white crystalline powder, reaction time 8 min	240	445 (–N= thiazolidinone), 3025 (Ar-C-), 1715 (C=O, thiazolidinone)	10.02 (s, 1H, OH) , 9.094 (s, 1H, OH), 8.20 (s, 1H, CH=C_5), 7.54-7.32 (m, 10H aromatic proton), 7.24 (d, 2H, aromatic), 7.16 (s, 1H, aromatic), 3.22 (t, 3H of CH_3)	402.466, Calc. 402.391
1j [5-(4-hydroxybenzylidene)-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone]	90, white crystalline powder, reaction time 8 min	216	3440 (–N= thiazolidinone), 3015 (Ar-C-), 1720 (C=O, thiazolidinone)	9.94 (s, 1H, OH) , 8.22 (s, 1H, CH=C_5), 7.66-7.34 (m, 10H aromatic proton), 7.28 (d, 2H, 7.22 (s, 1H, aromatic), 3.18 (t, 3H of CH_3)	386.466 Calc. 385.886

Table 2. Elemental analysis data of synthesized compounds (CHNS analyzer)

Compounds	Chemical formula	Elemental analysis %							
		Calc. value	Analysis value	Calc. value	Analysis value	Calc. value	Analysis value	Calc. value	Analysis value
		C	C	H	H	N	N	S	S
1a	$C_{23}H_{18}N_2OS$	74.55	74.57	4.92	4.90	7.55	7.56	8.68	8.66
1b	$C_{23}H_{17}ClN_2OS$	68.16	68.22	4.26	4.23	6.94	6.92	7.90	7.92
1c	$C_{25}H_{23}N_3OS$	72.60	72.61	5.60	5.61	10.17	10.16	7.77	7.75
1d	$C_{24}H_{20}N_2O_2S$	71.99	71.98	5.12	5.03	6.98	6.99	8.00	8.01
1e	$C_{24}H_{20}N_2O_3S$	69.20	69.21	4.49	4.48	6.71	6.73	7.68	7.70
1f	$C_{24}H_{20}N_2OS$	74.96	74.97	5.22	5.24	7.28	7.29	8.33	8.34
1g	$C_{23}H_{17}ClN_2OS$	68.20	68.22	4.25	4.23	6.95	6.92	7.91	7.92
1h	$C_{23}H_{19}N_3OS$	71.67	71.66	4.96	4.97	10.88	10.90	8.33	8.32
1i	$C_{23}H_{18}N_2O_3S$	68.66	68.64	4.50	4.51	6.96	6.96	7.96	7.97
1j	$C_{23}H_{18}N_2O_2S$	71.50	71.48	4.70	4.69	7.24	7.25	8.29	8.30

aromatic aldehyde were non-miscible mixture of oil and water. Then phase transfer catalysts [tetraethylammonium bromide (TBAB), trethylbenzyl-ammonium chloride (TEBAC), polyethyleneglycol (PEG)] were tried (Shi *et al.*, 2005) and found that TBAB was best in molar ratio 1.5: 5: 5 (TBAB, 3-phenyl, 4-thiazolidinone and aromatic aldehyde), respectively. Increase in the quantity of TBAB had no effect on yield and time. The compounds **1b**, **1h**, and **1j** gave better yields of 92%, 90% and 93%, respectively.

Tetraalkylammonium cations are preferred in heterogeneous two-phase system, one phase containing reacting base used to generate organic anions and the second phase containing organic reactant. (Alexander *et al.*, 2004; Anjaiah *et al.*, 2004; Appleby *et al.*, 1986). The $(C_2H_5)_4N^+Br^-$ serves both as a phase-transfer catalyst and a base because the reactants would exist as a non-miscible mixture of oil and water in the absence of $(C_2H_5)_4N^+Br^-$ and 3-CH_2 of 4-thiazolidinone cannot remove the alkali effect. The enolate ions would not be formed in the reaction that explains the reaction does not take place in the presence of polyethylene glycol, or in the absence of TBAB. Microwave irradiation was used to accelerate the rates of the reactions (Chiappe and Pieraccini, 2005).

The synthesized compounds were subjected to bacterial analysis that was presented in Table 3, which exhibited different activities depending on the nature and position of the substituent on thiazolidinone ring. The compounds **1c**, **1e** and **1h** showed the best activity against *E. coli*, *B. subtilis*, *S. aureus*, compounds **1d** and **1i** were observed slightly active against *E. coli*, *B. subtilis*, *S. aureus* and compounds **1b** and **1g** were active against *Proteus vulgaris* and *Aspergillus niger.* Ciprofloxacin and Gentamycin were used as reference antibacterial compounds and results were shown in Table 3.

Table 3. Results of antimicrobial activity of the compounds **1a-j**

Compounds	Zones of inhibition (mm)				
	Antibacterial activity			Antifungal activity	
	E. coli	*B. subtilis*	*S. aureus*	*P. vulgaris*	*A. niger*
1a	+	+	+	-	-
1b	+	-	+	++	++
1c	+++	++++	++++	-	-
1d	++	++	++	-	-
1e	+++	++++	++++	+	++
1f	+	+	+	+	-
1g	+	+	+	++	++
1h	+++	++++	++++	-	-
1i	+	+	+	-	-
1j	-	+	+	+	+
Ciprofloxacin	+++	++++	++++	-	-
Gentamycin	+++	++++	++++	-	-

Highly active = ++++ (inhibition zone > 20 mm); highly active = +++ (inhibition zone 15-20 mm); active = ++ (inhibition zone 10-15 mm); slightly active = + (inhibition zone 5-10 mm); inactive = - (inhibition zone < 5mm)

The data given in Table 3, revealed compounds **1c**, **1e** and **1h** to be highly active against *B. subtilis*, *S. aureus* and compounds **1a**, **1f**, **1g** and **1i** were observed to be slightly active against *B. subtilis*, *S. aureus* and *E. coli*. Compound **1d** was active against *P. vulgaris* and **1e**, **1j** were active to fungi *A. niger***.**

Conclusion

One pot synthesis carried out using nontoxic solvent, phase transfer catalyst under microwave irradiation was a simple, time saving, economically feasible, environment friendly and efficient method for the preparation of 5-benzylidene-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinonecompounds. The synthesized compounds yielded very promising results

when compared with Ciprofloxacin and Gentamycin as reference antibiotic (fourth generation). The compounds **1c**, 5-[4-(dimethylamino)pheny)]-3-(4-methylphenyl)-2-(phenylimino)-4-thiazolidinone. 1e, 5-(4-hydroxy-3-methoxybenzylidene)-3-(4-methylphenyl)-2-(phenylimino)-4-thiazoli-dinone and **1h** [5-(4-aminobenzylidene)-3-(4-methylphenyl)-2-(Phenylimino)-4-thiazolidinone] can be used as broad spectrum antibiotics after carrying out toxicological studies; since bacteria are developing resistance against the existing antibiotics, there is always need for developing new antibacterial compounds.

References

Alexander, M.V., Khandekar, A.C., Samant, S.D. 2004. Sulfonylation reactions of aromatics using $FeCl_3$ based ionic liquids. *Journal of Molecular Catalysis* **223:** 1-2.

Algul, O., Kaessler, A., Apcin, Y., Yilmaz, A., Jose, J. 2008. Comparative studies on conventional and microwave synthesis of some benzimidazole, benzothiazole and indole derivatives and testing on inhibition of hyaluronidase. *Molecules* **13:** 736-748.

Anjaiah, S., Chandrasekhar, S., Gree, R. 2004. Synthesis and preliminary use of novel acrylic ester-derived task-specific ionic liquids. *Tetrahedron Letters* **45:** 569-574.

Appleby, D., Hussey, C.L., Seddon, K.R., Turp, J.E. 1986. Room-temperature ionic liquids as solvents for electronic absorption spectroscopy of halide complexes. *Nature* **323:** 614-614.

Ballell, L., Joosten, J.A.F., Maate, F.A., Liskamp, R.M., Pieters, R.J. 2004. Microwave assisted, tin-mediated, regioselective 3-*O*-alkylation of galactosides. *Tetrahedron Letters* **45:** 6685-6688.

Chiappe, C., Pieraccini, D. 2005. Ionic liquids: solvent properties and organic reactivity. *Journal of Physical Organic Chemistry* **18:** 275-278.

Kasmi-Mir, S., Djafri, A., Paquin, L., Hamelin, J., Rahmouni, M. 2006. One-pot synthesis of 5-arylidene-2-imino-4-thiazolidinones under microwave irradiation. *Molecules* **11:** 597-602.

Merck Index, 1996. *Drug Guides*, 12th edition, Merck and Company, Germany.

Naeem, M., Chauhdhry, M.N., Baloch, I.H., Rehman, S. 2008. An environmental friendly procedure for the synthesis of potentially biologically active compounds containing 4-thiazolidinone. *Journal of The Chemical Society of Pakistan* **30:** 23-28.

Rao, A., Chimirri, A., Ferro, S., Monforte, A.M., Monforte, P. 2004. Microwave -thiazolidinones derivatives as HIV-1 RT inhibitors. *ARKIVOC* 147-155.

Shi, F., Tu, S.J., Fang, F., Li, T.J. 2005. One-pot synthesis of 2-amino-3-cyanopyridine derivatives under microwave irradiation without solvent. *ARKIVOC* 137-142.

Singh, S.P., Parmer, K.S., Raman, K., Stenberg, V.I. 1981. Chemistry and biological activity of thiazolidinones. *Chemical Reviews* **81:** 175-203.

United States Pharmacopoeia (USP), 2004. *Bioassay*, USP 27-NF 22, **3:** 2163-2167.