AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Microwave Accelerated Synthesis of Novel Thiazolidin-4-Ones as Potent Antimicrobial Agents

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ABSTRACT

Thiazolidinone is considered as biologically significant compound that possesses almost all types of biological activities. Some new 1,3-thiazolidin-4-ones have been synthesized from ketimines by microwave irradiation method. Microwave mediated organic reactions take place more rapidly, safely, with high yields and ecofriendly too. All the synthesized products were tested for their antibacterial and antifungal activities. The results of the tests showed that some of the synthesized compounds are effective antibacterial as well as antifungal agents.

Keywords: Thiazolidinones, Ketimines, Antimicrobial, Microwave irradiation method.

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Received 25 March 2015, Accepted 31 March 2015

Please cite this article as: Borgaonkar VV *et al*., Microwave Accelerated Synthesis of Novel Thiazolidin-4-Ones as Potent Antimicrobial Agents. American Journal of PharmTech Research 2015.

INTRODUCTION

The structural and therapeutic diversity of nitrogen and sulphur containing heterocyclic compounds has attracted organic and medicinal chemists. 4-Thiazolidinones cover various remarkable activity profiles as bactericidal[1], antifungal[2], anticonvulsant[3], antituberculotic[4]. 4-Thiazolidinones has been reported to possess activities namely COX-1 inhibitors[5]. They have been reported as novel inhibitors of the bacterial enzyme Mur B which is precursor acting during the biosynthesis of peptidoglycan[6], as non-nucleoside inhibitors of HIV-RT[7], anti-histaminic agents[8], anticancer[9], antitumor[10], diuretics[11], nematicidal[12] and anti-viral[13]. Microwave technologies offer several advantages. Certain organic transformations which require several hours or even days to complete are effectively completed in minutes. Microwave assisted conditions provide advantages such as shorter reaction time, enhanced yields of products and eco friendly one[14,15]. In view of these findings large number of thiazolidinones have been widely investigated from the aldimine source however significant attention have not given when precursors are ketimines. These reports prompted us to synthesize some novel 4- thiazolidinones from ketimines by using microwave accelerated method as an ecofriendly synthetic rout and to assess their bio potential.

Experimental

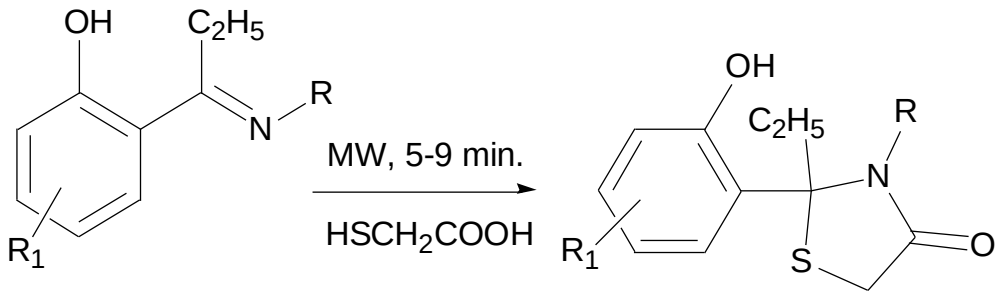
Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a FTIR perkin-Elmer spectrometer. ^{1}HNMR spectra were recorded on Avance 300 MHz spectrometer in $CDCl_3$ solvent. Mass spectra were taken on Agilent 5973 N GC-MS. Nutrient agar was used as culture for antibacterial activity and potato dextrose agar was used as culture for antifungal activity and DMSO was used to dissolve compounds.

General procedure for synthesis of thiazolidinones

Ketimines (0.01mole) dissolved in DMF, Freshly distilled mercaptoacetic acid (0.01mole) was added slowly to it. The mixture stirred for 5 min. and then irradiated in a Q Pro-M modified microwave oven for about 7 min. After completion of reaction monitored by TLC, It was diluted with ice cold water. The residue thus formed was washed with 5% sodium bicarbonate (3x10 ml) followed by water (2x25 ml). The solid was filtered, dried and recrystallised from ethanol to obtain pure crystals of desired compounds 3(a-k). Newly synthesized compounds were tested for their antibacterial activity employing the agar cup method[16]. The antifungal activity was evaluated by poison plate method[17].

RESULTS AND DISCUSSION

4-Thiazolidinones were synthesized from different ketimines (Scheme 1). Both analytical and spectroscopic data of all the synthesized compounds are in agreement with the proposed structures. Assignments of chosen characteristic of IR band positions provided significant sign for the formation of the thiazolidinones. Synthesized thiazolidinones shows absorption at 1682-1740 cm^{-1} for C=O confirms formation of thiazolidinone, which was supported by the absence of absorption band at 1600–1631 cm^{-1} for C=N. Compound shows band near 675 cm^{-1}due to C-S-C and at 1460 cm^{-1}due to C-N. The band near 1510-1585 cm^{-1} is for C=C aromatic stretch, absorption at 3400-3490 cm^{-1} is due to (-OH) hydroxyl group. In addition confirmation for the formation of thiazolidinones was obtained from the ^{1}H NMR spectra, which provide indicative tools for the positional elucidation of the protons. Singlet appears at δ 3.6-4.45 due to S-CH_2 conforming cyclization. Triplet at δ 1.20-1.30 for -CH_2-$\underline{CH_3}$ and quartet at δ 2.80-3.00 for -$\underline{CH_2}$-CH_3 is observed in all compounds. Common signal appearing at δ 13.00-16.10 is due to -OH group in all the compounds. The mass spectra of the synthesized compounds show the molecular ion peak confirming the molecular weight of the compounds. All synthesized compounds were screened for antibacterial activity against *E. coli, P. auregenosa, S. Aureus* and *B. subtilis* as well as antifungal activity against *A.niger, P. chrysogenum, F. moneliforme* and *A. flavus,* the results of the antibacterial and antifungal activity are shown in Table 1. Result showed that compounds 3i and 3j are having significant antibacterial and antifungal activity. The compounds 3b, 3c, 3e, 3h showed good antifungal activity.



1 **2** **3a-k**

Scheme 1:- Synthesis of 4-thiazolidinone from ketimines

3a:	R_1 = H,	R = C_6H_5	**3b:**	R_1 = 5-Cl,	R = C_6H_5
3c:	R_1 = 5-Cl,	R = *n*-C_4H_9	**3d:**	R_1 = 5-CH_3,	R = *n*-C_4H_9
3e:	R_1 = 5-CH_3,	R = C_6H_4-OCH_3	**3f:**	R_1 = 4-CH_3,	R = C_6H_4-CH_3
3g:	R_1 = 3-I, 5-CH_3,	R = *n*-C_3H_7	**3h:**	R_1 = 3-I, 5-CH_3,	R = *n*-C_4H_9
3i:	R_1 = 3-I, 5-Cl,	R = *iso*-C_3H_7	**3j:**	R_1 = 3-I, 5-Cl,	R = C_6H_5
3k:	R_1 = 3-CH_3, 5-I,	R =C_6H_4-CH_3			

2-Ethyl-2-(2-hydroxy-phenyl)-3-phenyl-thiazolidin-4-one (3a) :- Yield – 73%; M.P.- 150^{o}C; **IR (KBr):** 3490(OH), 1682(C=O), 1550(C=C), 690(C-S) cm^{-1}; **^{1}HNMR ($CDCl_3$)** :- δ 1.30(t, 3H, *J* = 6.0 Hz), 3.00 (q, 2H), 3.65 (s, 2H, S- CH_2), 7.10-7.70 (m, 9H), 13.00 (s,-OH) ppm; **M.S.-** *m/z* -299 $M^{+\cdot}$, Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.27; N, 4.68. Found: C, 68.80; H, 5.05; N, 4.10.

2-(5-Chloro-2-hydroxy-phenyl)-2-ethyl-3-phenyl-thiazolidin-4-one (3b):- Yield – 70%; M.P.- 157^{o}C; **IR (KBr) :** 3410(OH), 1725(C=O), 1550(C=C), 680(C-S) cm^{-1} ; **^{1}HNMR ($CDCl_3$)** :- δ 1.21 (t, 3H, *J* = 6.0 Hz), 3.00 (q, 2H), 3.75(s, 2H, S-CH_2), 6.50-7.18 (m, 5H), 7.28 (d, 1H, *J* = 8.0 Hz, C-3H), 7.48 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.2 Hz, C-4H), 7.70 (d, 1H, *J* = 2.2 Hz, C-6H), 15.15 (s, -OH) ppm; **M.S.-** *m/z* -333 $M^{+\cdot}$, Anal. Calcd for $C_{17}H_{16}ClNO_2S$: C, 61.16; H, 4.83; N, 4.20. Found: C, 61.75; H, 5.08; N, 4.90.

3-Butyl-2-(5-chloro-2-hydroxy-phenyl)-2-ethyl-thiazolidin-4-one(3c):- Yield–73%; M.P.- 128^{o}C; **IR (KBr) :** 3450(OH), 1730(C=O), 1575(C=C), 710(C-S) cm^{-1} ; **^{1}HNMR ($CDCl_3$)** :- δ 0.90 (t, 3H, *J* = 7.5 Hz, H-4"), 1.30 (m, 2H, H-3"), 2.40 (m, 2H,H-2"), 3.40(t,2H, H-1'), 1.24 (t, 3H, *J* = 6.0 Hz), 2.90 (q, 2H), 3.90 (s, 2H, S- CH_2), 7.30 (d, 1H, *J* = 8.0 Hz, C-3H), 7.43 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.2 Hz, C-4H), 7.64 (d, 1H, *J* = 2.2 Hz, C-6H), 15.50 (s,-OH) ppm; **M.S.-** *m/z* -313 $M^{+\cdot}$, Anal. Calcd for $C_{15}H_{20}ClNO_2S$: C, 57.40; H, 6.42; N, 4.46. Found: C, 56.87; H, 6.98; N, 5.09.

3-Butyl-2-ethyl-2-(2-hydroxy-5-methyl-phenyl)-thiazolidin-4-one (3d):- Yield–73%; M.P.- 131^{o}C; **IR (KBr) :** 3440(OH), 1720(C=O), 1525(C=C), 690(C-S) cm^{-1} ; **^{1}HNMR ($CDCl_3$)** :- δ 0.95 (t, 3H, *J* = 7.5 Hz, H-4"), 1.80 (m, 2H, H-3"), 2.45 (m, 2H, H-2"), 3.50 (t, 2H, H-1'), 1.20 (t, 3H, *J* = 6.4 Hz), 3.00 (q, 2H), 2.35 (s, 3H, Ar-CH_3), 3.60 (s, 2H, S- CH_2), 6.60-6.80 (m,3H), 14.25 (s,-OH) ppm; **M.S.-** *m/z* -293 $M^{+\cdot}$, Anal. Calcd for $C_{16}H_{23}NO_2S$: C, 65.49; H, 7.90; N, 4.77. Found: C, 65.98; H, 7.24; N, 4.31.

2-Ethyl-2-(2-hydroxy-5-methyl-phenyl)-3-(4-methoxy-phenyl)-thiazolidin-4-one (3e):- Yield– 70%, M.P.- 169^{o}C; **IR (KBr) :** 3420(OH), 1720(C=O), 1530(C=C), 665(C-S) cm^{-1} ; **^{1}HNMR ($CDCl_3$)** :- δ 1.24 (t, 3H, *J* = 6.2 Hz), 2.85 (q, 2H), 2.30 (s, 3H, Ar-CH_3), 3.65 (s, 2H, S-CH_2), 3.75 (s, 3H, OCH_3), 6.60-6.85 (m, 7H), 13.65 (s, -OH) ppm; **M.S.-** *m/z* -343 $M^{+\cdot}$, Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.16; H, 6.59; N, 4.62.

2-Ethyl-2-(2-hydroxy-4-methyl-phenyl)-3-p-tolyl-thiazolidin-4-one (3f):- Yield–71%; M.P.- 175^{o}C; **IR (KBr) :** 3490(OH), 1720(C=O), 1510(C=C), 670(C-S) cm^{-1} ; **^{1}HNMR ($CDCl_3$)** :- δ 1.21 (t, 3H, *J* = 6.2 Hz), 2.80 (q, 2H), 2.85 (s, 3H, Ar-CH_3), 3.68 (s, 2H, S- CH_2), 2.30 (s, 3H, p-tolyl CH_3), 6.50-6.80 (m, 7H), 13.50 (s, -OH) ppm; **M.S.-** *m/z* -327 $M^{+\cdot}$, Anal. Calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28. Found: C, 69.34; H, 6.80; N, 4.74.

2-Ethyl-2-(2-hydroxy-3-iodo-5-methyl-phenyl)-3-propyl-thiazolidin-4-one (3g):- Yield–75%; M.P.- 133^{o}C; **IR (KBr) :** 3445(OH), 1730(C=O), 1545(C=C), 780(C-S) cm^{-1} ; **^{1}HNMR (CDCl$_3$)** :- δ1.05 (t, 3H, *J* = 7.5 Hz, H-3"), 1.80 (m, 2H, H-2"), 3.10(t, 2H, H-1'), 1.24 (t, 3H, *J* = 6.5 Hz), 2.91 (q, 2H), 2.30 (s, 3H, Ar-CH_3), 4.10 (s, 2H, S-CH_2), 7.38 (d, 1H, *J* = 2.3 Hz, C-4H), 7.18 (d, 1H, *J* = 2.3 Hz, C-6H), 15.80 (s, -OH) ppm; **M.S.-** *m/z* - 405 $M^{+\cdot}$, Anal. Calcd for $C_{15}H_{20}INO_2S$: C, 44.45; H, 4.97; N, 3.46. Found: C, 44.20; H, 4.61; N, 3.88.

3-Butyl-2-ethyl-2-(2-hydroxy-3-iodo-5-methyl-phenyl)-thiazolidin-4-one (3h):- Yield–73%; M.P.- 145^{o}C; **IR (KBr) :** 3440(OH), 1730(C=O), 1540(C=C), 775(C-S) cm^{-1}; **^{1}HNMR (CDCl$_3$)** :- δ 0.94 (t, 3H, *J* = 7.5 Hz, H-4"), 1.35 (m, 2H, H-3"), 1.65 (m, 2H, H-2"), 3.68 (t, 2H, H-1'), 1.23 (t, 3H, *J* = 6.3 Hz), 2.88 (q, 2H), 2.35 (s, 3H, Ar-CH_3), 4.10 (s, 2H, S- CH_2), 7.35 (d, 1H, *J* = 2.3 Hz, C-4H), 7.20 (d, 1H, *J* = 2.3 Hz, C-6H), 15.05 (s,-OH) ppm; **M.S.-** *m/z* -419 $M^{+\cdot}$, Anal. Calcd for $C_{16}H_{22}INO_2S$: C, 45.83; H, 5.29; N, 3.34. Found: C, 45.33; H, 5.73; N, 3.84.

2-(5-Chloro-2-hydroxy-3-iodo-phenyl)-2-ethyl-3-isopropyl-thiazolidin-4-one (3i):- Yield–71%; M.P.- 140^{o}C; **IR (KBr) :** 3450(OH), 1740(C=O), 1572(C=C), 790(C-S) cm^{-1}; **^{1}HNMR (CDCl$_3$)** :- δ 1.25 (d, 6H, *J* = 7.2 Hz), 3.45 (m, 1H), 1.20 (t, 3H, *J* = 6.2 Hz), 3.00 (q, 2H), 4.45 (s, 2H, S-CH_2), 7.47 (d, 1H, *J* = 2.3 Hz, C-4H), 7.29 (d, 1H, *J* = 2.3 Hz, C-6H), 16.10 (s, -OH) ppm; **M.S.-** *m/z* -425 $M^{+\cdot}$, Anal. Calcd for $C_{14}H_{17}ClINO_2S$: C, 39.50; H, 4.03; N, 3.29. Found: C, 39.11; H, 4.61; N, 3.92.

2-(5-Chloro-2-hydroxy-3-iodo-phenyl)-2-ethyl-3-phenyl-thiazolidin-4-one (3j):- Yield–70%; M.P.- 155^{o}C; **IR (KBr) :** 3400(OH), 1725(C=O), 1534(C=C), 690(C-S) cm^{-1}; **^{1}HNMR (CDCl$_3$)** :- δ 1.25 (t, 3H, *J* = 6.0 Hz), 2.80 (q, 2H), 4.00 (s, 2H, S-CH_2), 6.80-7.22 (m,5H), 7.46 (d, 1H, *J* = 2.3 Hz, C-4H), 7.24 (d, 1H, *J* = 2.3 Hz, C-6H), 16.00s (s,-OH) ppm; **M.S.-** *m/z* -460 $M^{+\cdot}$, Anal. Calcd for $C_{17}H_{15}ClINO_2S$: C, 44.41; H, 3.29; N, 3.05. Found: C, 44.76; H, 3.78; N, 2.75.

2-Ethyl-2-(2-hydroxy-5-iodo-3-methyl-phenyl)-3-p-tolyl-thiazolidin-4-one (3k):- Yield–68%; M.P.- 205^{o}C; **IR (KBr) :** 3425(OH), 1730(C=O), 1585(C=C), 760(C-S) cm^{-1}; **^{1}HNMR (CDCl$_3$)** :- δ 1.23 (t, 3H, *J* = 6.0 Hz), 3.00 (q, 2H), 2.90 (s, 3H, Ar-CH_3), 4.40 (s, 2H, S- CH_2), 2.35 (s, 3H, p-tolyl CH_3), 6.60-7.05 (m, 4H), 7.28 (d, 1H, *J* = 2.3 Hz, C-4H), 7.83 (d, 1H, *J* = 2.3 Hz, C-6H), 15.20 (s, -OH) ppm; **M.S.-** *m/z* -453 $M^{+\cdot}$, Anal. Calcd for $C_{19}H_{20}INO_2S$: C, 50.34; H, 4.45; N, 3.09. Found: C, 50.95; H, 4.03; N, 3.87.

Table 1: Antimicrobial activity of thiazolidinones

Sr. No.	Comp.	Antibacterial activity Zone of Inhibition (mm)				Antifungal activity			
		S.Aureus	*B.subtilis*	*E.coli*	*P.auregenosa*	*A.niger*	*P.chrysogenum*	*F.moneliforme*	*A.flavus*
1	3a	10	10	00	10	+ ve	+ve	RG	RG
2	3b	10	12	02	10	RG	-ve	-ve	-ve
3	3c	10	08	00	08	-ve	RG	RG	-ve
4	3d	00	08	00	08	RG	+ve	+ve	RG
5	3e	08	10	08	10	RG	RG	-ve	-ve
6	3f	00	08	08	08	-ve	-ve	RG	+ve
7	3g	10	08	00	08	-ve	RG	RG	+ve
8	3h	10	10	02	10	RG	RG	-ve	-ve
9	3i	12	12	00	10	-ve	-ve	-ve	-ve
10	3j	12	14	00	12	-ve	-ve	-ve	RG
11	3k	08	00	00	08	RG	RG	RG	RG
Std.	Penicillin	30	19	14	33	---	---	---	---
	Griseofulvin	---	---	---	---	-ve	-ve	-ve	-ve

+ve – Growth (Antifungal activity absent)

-ve – No Growth (Antifungal activity present)

RG – Reduced Growth (More than 50% reduction in growth)

CONCLUSION

Novel thiazolidinones were synthesized from ketimines using microwave accelerated conditions which provides advantages such as shorter reaction time, enhanced yields of products and eco friendly one. All synthesized compounds were screened for antibacterial activity against *E. coli, P. auregenosa, S. Aureus* and *B. subtilis* as well as antifungal activity against *A. niger*, *P. chrysogenum*, *F. moneliforme* and *A. flavus.* It is observed that compound 3i and 3j are having significant antibacterial and antifungal activity. The compounds 3b, 3c, 3e, 3h showed good antifungal activity. Remaining compounds showed moderate properties. In summary synthesized thiazolidinone compounds have significant antifungal properties than antibacterial properties.

ACKNOWLEDGMENTS

The authors are thankful to IICT, Hyderabad for providing spectral data of synthesized compounds.

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