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ANTIMICROBIAL EVALUATION OF IMINES AND THIAZOLIDINONES DERIVED FROM 3-PHENYLPROPANE HYDRAZIDE

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Abstract: Methyl 3-phenylpropanoate **(1),** after hydrazination into 3-phenylpropanehydrazide **(2),** was converted into N-arylidene-3-phenylpropane hydrazides **(3a-e),** which on cyclization with thioglycolic acid yielded N-(4-oxo-2-arylthiazolidin-3-yl)-3-phenylpropanamides **(4a-e)**. All the proposed structures of newly synthesized compounds were in full agreement with the spectral data. Due to *para* substitution, compound **3a, 4a** and **4b** were found to be the most potent when evaluated for antibacterial and antifungal activities.

Keywords: methylphenylpropanoate, propane hydrazide, imines, thiazolidinones, thioglycolic acid

It is an established fact that thiazolidinones, imines and propionates show potent antitubercular (1), antimicrobial (2), anticancer (3), antiviral (4), antifungal (4), antibacterial (4) and CCR4 antagonist (5) activities. On the other hand, it is known that imines can be synthesized from ester moieties (6-8), which are precursors for thiazolidinones (9-10). Due to the activities associated with imines and thiazolidinones, an attempt was made to generate novel potent antimicrobial imines (**3a-e)** and N-(4-oxo-2-arylthiazolidin-3-yl)-3-phenylpropanamides **(4a-e)** from ester moiety **(1)** *via* synthesis of hydrazide (**2)** as an intermediate. All the newly synthesized compounds were further characterized and evaluated for antimicrobial activities.

EXPERIMENTAL

All the necessary solvents and chemicals used in the present work were procured from Merck India Pvt. Ltd. (India). The melting points of newly synthesized compounds were determined in open capillary tubes. The IR spectra were recorded (in KBr) on Bruker PCIR instrument, ^{1}H-NMR on Bruker DPX 300 spectrometer, mass spectra on MASPEC (MSW/9629) apparatus and elemental analysis was done on CHN analyzer 240 (Perkin Elmer). Purity of synthesized compounds was checked by TLC on aluminium sheets with silica gel 60 F_{254} (0.2 mm).

Synthesis of 3-phenylpropane hydrazide (2)

A mixture of compound **1** (0.01 mol) and hydrazine hydrate (0.01 mol) was refluxed for 6 h using ethanol as a solvent. The formed product was isolated and recrystallized from methanol to yield white needle like crystals of pure compound **2**. Physical data and R_f values found using chloroform and methanol in the ratio of 9:1 (v/v) as a mobile phase are given in Table 1.

IR (KBr, cm^{-1}): 3256 (NH), 3210, 3205 (NH_2), 2921 (CH_2); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.57 (2H, t, J = 6.9 Hz, -CH_2-CO-), 2.80 (2H, t, J = 6.9 Hz, Ar-CH_2), 5.62 (2H, brs, NH_2), 7.09-7.22 (5H, m, Ar-H 2, 3, 4, 5 & 6), 9.50 (1H, s, NH); MS (m/z): 164 (M^+), 148, 105, 91, 65; Elemental analysis: (calculated) found: C (65.83) 65.81, H (7.37) 7.34, N (17.06) 17.05 %.

General procedure for synthesis of N-(substituted benzylidene)-3-phenylpropane hydrazides (3a-e):

A mixture of compound **2** (0.01 mol) and aromatic aldehyde (0.01 mol) in the presence of few drops of sulfuric acid (0.001 mol) was refluxed for 6 h. The formed product was isolated and recrystallized

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from methanol to yield compounds **3a-e.** Physical data and R_f values found using chloroform and methanol in the ratio of 9:1 (v/v) are given in Table 1).

N-(4-(dimethylamino)benzylidene)-3-phenylpropane hydrazide (3a)

IR (KBr, cm^{-1}): 3252 (NH of CONH), 1643 (CO of CONH); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.52 (2H, t, *J* = 6.6 Hz, -CH_2-CO-), 2.80 (2H, t, *J* = 6.9 Hz, Ar-CH_2), 2.87 (6H, s, -N(CH_3)$_2$), 6.58 (2H, d, *J* = 7.5 Hz, Ar'-H3' & 5'), 7.05-7.18 (5H, m, Ar-H 2, 3, 4, 5 & 6), 7.44 (2H, d, *J* = 7.8 Hz, Ar'-H2' & 6'), 8.1 (1H, s, N=CH), 9.50 (1H, s, NH); MS (m/z): 295 (M^+), 190 (base peak), 162, 147, 148, 120, 105, 91, 65; Elemental analysis: (calculated) found: C (73.19) 73.16, H (7.17) 7.15, N (14.23) 14.21%.

N-(4-chlorobenzylidene)-3-phenylpropane hydrazide (3b)

IR (KBr, cm^{-1}): 3259 (NH of CONH), 1646 (CO of CONH); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.55 (2H, t, *J* = 6.6 Hz, -CH_2-CO-), 2.80 (2H, t, *J* = 6.9 Hz, Ar-CH_2), 7.08-7.21 (5H, m, Ar-H 2, 3, 4, 5 & 6), 7.38 (2H, d, *J* = 7.2 Hz, Ar'-H3' & 5'), 7.65 (2H, d, *J* = 7.5 Hz, Ar'-H2' & 6'), 8.56 (1H, s, N=CH), 9.65 (1H, s, NH); MS (m/z): 286 (M^+), 181 (base peak), 153, 148, 138, 111, 105, 91, 65; Elemental analysis: (calculated) found: C (67.02) 67.00, H (5.27) 5.24, N (9.77) 9.74%.

N-(2,4-dihydroxybenzylidene)-3-phenylpropane hydrazide (3c)

IR (KBr, cm^{-1}): 3511 (OH on phenyl ring), 3310 (NH of CONH), 1642 (CO of CONH); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.59 (2H, t, *J* = 6.9 Hz, -CH_2-CO-), 2.85 (2H, t, *J* = 6.9 Hz, Ar-CH_2), 5.16 (1H, s, 4-OH), 5.24 (1H, s, 2-OH), 6.26 (1H, d, *J* = 2.9 Hz, Ar'-H3'), 6.38 (1H, dd, *J* = 2.8, 7.2 Hz, Ar'-H5'), 7.02-7.15 (5H, m, Ar-H2, 3, 4, 5 & 6), 7.39 (1H, d, *J* = 7.5 Hz, Ar'-H6'), 8.59 (1H, s, N=CH), 9.42 (1H, s, NH); MS (m/z): 284 (M^+), 148 (base peak), 179, 151, 136, 109, 105, 91, 65; Elemental analysis: (calculated) found: C (67.59) 67.57, H (5.67) 5.64, N (9.85) 9.83%.

Table 1. Physical data of compounds **2**, **3**(**a-e**) and 4(**a-e**)

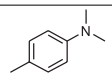
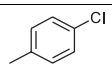
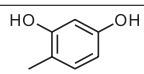
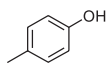
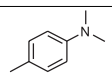
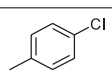
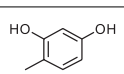
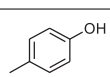
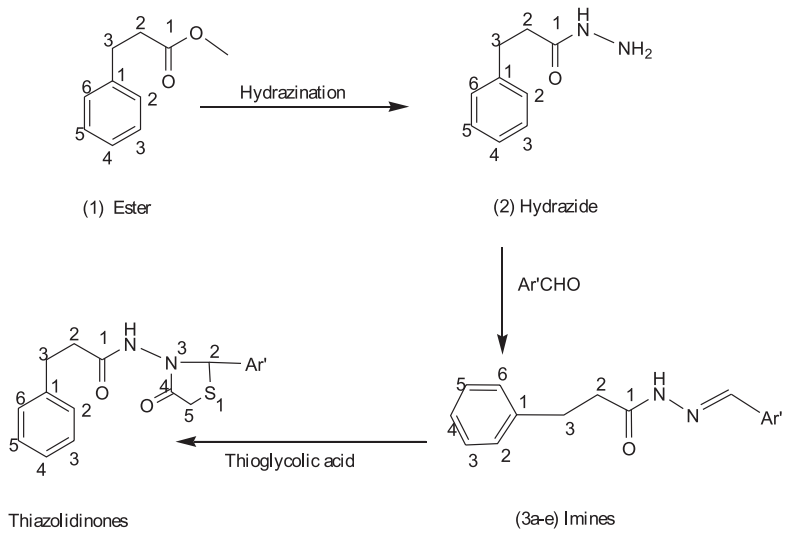
Compd. no.	Ar'	Physical characteristics	Yield (%)	Molecular formula	Mol. wt.	M.p. (^oC)	R_f value
2	-	White crystals	85	$C_9H_{12}N_2O$	164.2	134-135	0.57
3a		White needle like crystals	69.26	$C_{18}H_{21}N_3O$	295.38	210-211	0.59
3b		White needle like crystals	65.32	$C_{16}H_{15}N_2OCl$	286.76	198-199	0.52
3c		White needle like crystals	62.25	$C_{16}H_{16}N_2O_3$	284.31	206-207	0.55
3d		White needle like crystals	69.84	$C_{16}H_{16}N_2O$	252.31	194-195	0.49
3e		White needle like crystals	68.56	$C_{16}H_{16}N_2O_2$	268.31	202-203	0.53
4a		Light brown crystals	61.25	$C_{20}H_{23}N_3O_2S$	369.48	222-223	0.61
4b		White crystals	59.68	$C_{18}H_{17}N_2O_2SCl$	360.86	210-211	0.58
4c		Yellowish crystals	66.52	$C_{18}H_{18}N_2O_4S$	358.41	221-222	0.62
4d		White crystals	57.26	$C_{18}H_{18}N_2O_2S$	326.41	205-206	0.56
4e		Orange crystals	64.45	$C_{18}H_{18}N_2O_3S$	342.41	212-213	0.63

Table 2. Antimicrobial activity-sensitivity testing of compounds **3a-e** and **4a-e**

Compd. no.	Zone of inhibition in mm					
	Antibacterial activity			Antifungal activity		
	S. aureus	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. flavus*	*A. fumigatus*
3a	23	24	23	13	12	10
3b	24	22	23	12	10	11
3c	21	18	18	12	9	10
3d	23	12	17	11	10	12
3e	18	17	22	10	11	9
4a	21	24	23	16	14	15
4b	24	25	24	15	15	14
4c	18	17	17	14	12	15
4d	24	22	23	16	15	14
4e	17	16	18	12	11	13
Ampicillin	25	24	24	-	-	-
Fluconazole	-	-	-	17	16	17



where Ar' = 4-dimethylaminophenyl, 4-chlorophenyl, 2,4-dihydroxyphenyl, phenyl and 4-hydroxyphenyl group

Scheme 1.

N-benzylidene-3-phenylpropane hydrazide (3d)

IR (KBr, cm^{-1}): 3250 (NH of CONH), 1644 (CO of CONH); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.50 (2H, t, J = 6.9 Hz, -CH_2-CO-), 2.78 (2H, t, *J* = 6.9 Hz, Ar-CH_2), 7.06-7.19 (5H, m, Ar-H 2, 3, 4, 5 & 6), 7.31 (3H, m, Ar'-H3', 4' & 5'), 7.61 (2H, d, *J* = 7.5 Hz, Ar'-H2' & 6'), 8.52 (1H, s, N=CH), 9.61 (1H, s, NH); MS (m/z): 252 (M^+), 147 (base peak), 148, 119, 105, 104, , 65, 77; Elemental analysis: (calculated) found: C (76.16) 76.14, H (6.39) 6.38, N (11.10) 11.00%.

N-(4-hydroxybenzylidene)-3-phenylpropane hydrazide (3e)

IR (KBr, cm^{-1}): 3506 (OH), 3310 (NH of CONH), 1640 (CO of CONH); ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.53 (2H, t, *J* = 6.6 Hz, -CH_2-CO-), 2.81 (2H, t, *J* = 6.6 Hz, Ar-CH_2), 5.22 (1H, s, 4-OH), 6.84 (2H,

d, *J* = 7.2 Hz, Ar'-H3' & 5'), 7.08-7.22 (5H, m, Ar-H 2, 3, 4, 5 & 6), 7.45 (2H, d, *J* = 7.5 Hz, Ar'-H2' & 6'), 8.62 (1H, s, N=CH), 9.54 (1H, s, NH); MS (m/z): 268 (M^+), 163 (base peak), 148, 105, 135, 120, 93, 91, 65; Elemental analysis: (calculated) found: C (71.62) 71.61, H (6.01) 6.00, N (10.44) 10.42%.

General procedure for synthesis of N-(4-oxo-2-arylthiazolidin-3-yl)-3-phenylpropanamides (4a-e)

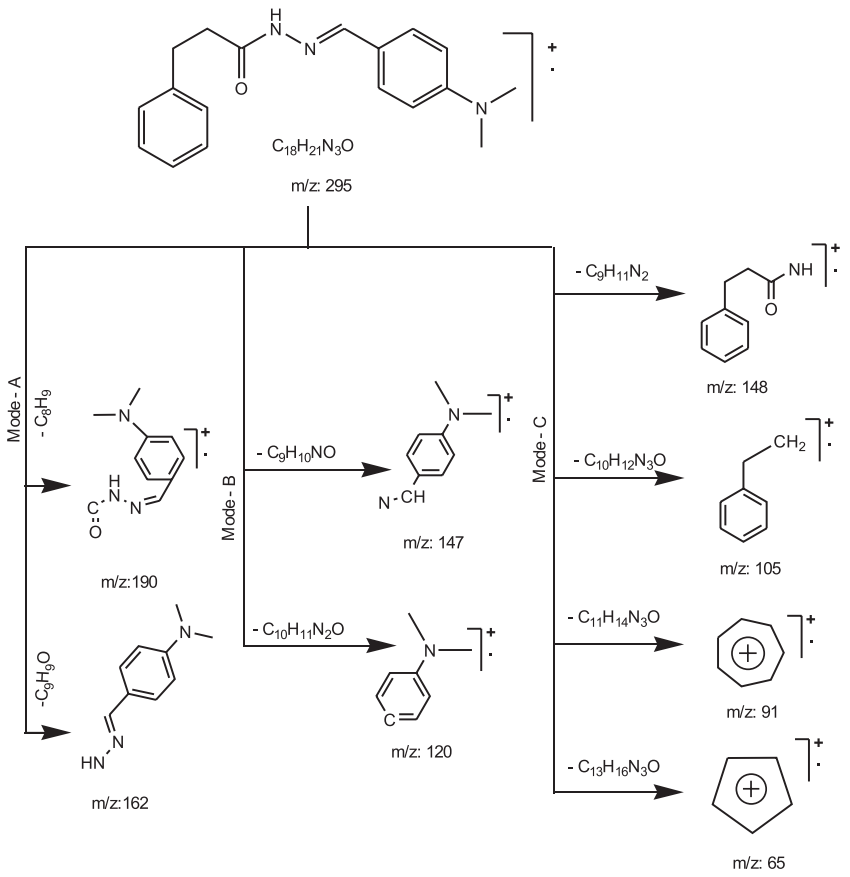
A mixture of compound **3a-e** (0.01 mol) and thioglycolic acid (0.02 mol) in the presence of zinc chloride (0.001 mol) was refluxed for 12 h. The formed product was isolated and recrystallized from methanol to yield compounds **4a-e.** Physical data and R_f values found using chloroform and methanol in the ratio of 8:2 (v/v) are given in Table 1.

N-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)-3-phenylpropanamide (4a)

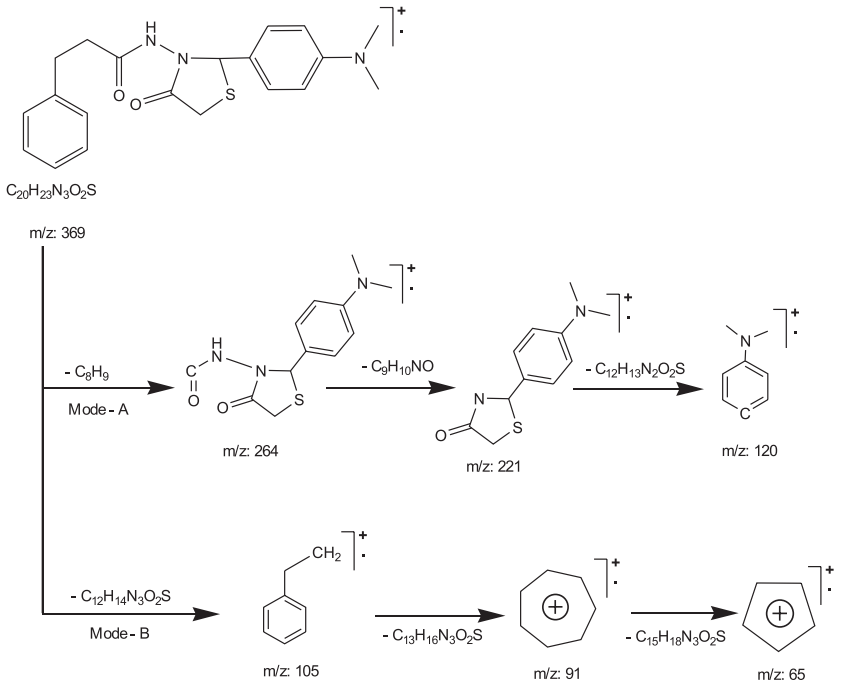
IR (KBr, cm^{-1}): 3256 (NH of CONH), 2921 (C-H of CH_2), 1770 (CO of thiazolidinone), 1652 (CO of CONH), 691 (C-S of thiazolidinone); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.52 (2H, t, *J* = 6.8 Hz, -CH_2-CO-), 2.86 (2H, t, *J* = 6.9 Hz, Ar-CH_2), 2.92 (6H, s, -N(CH_3)$_2$), 3.38 (2H, s, -CH_2-S-), 5.92 (1H, s, -N-CH-S-), 6.49 (2H, d, *J* = 8.2 Hz, Ar'-H3' & 5'), 6.88 (2H, d, *J* = 8.0 Hz, Ar'-H2' & 6'), 7.1-7.23 (5H, m, Ar-H2, 3, 4, 5 & 6), 8.54 (1H, s, -NH-); MS (m/z): 369 (M^+), 221 (base peak), 120, 105, 91, 65; Elemental analysis: (calculated) found: C (65.01) 65.00, H (6.27) 6.25, N (11.37) 11.34%.

N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-3-phenylpropanamide (4b)

IR (KBr, cm^{-1}): 3250 (NH of CONH), 2922 (C-H of CH_2), 1765 (CO of thiazolidinone), 1650 (CO of CONH), 697 (C-S of thiazolidinone); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.59 (2H, t, *J* = 6.7 Hz, -CH_2-CO-), 2.89 (2H, t, *J* = 6.6 Hz, Ar-CH_2), 3.48 (2H, s, -CH_2-S-), 5.97 (1H, s, -N-CH-S-), 7.00 (2H, d, *J* = 8.2 Hz, Ar'-H2' & 6'), 7.15 (2H, d, *J* = 8.3 Hz, Ar'-H3' & 5'), 7.20 (5H, m, Ar-H2, 3, 4, 5 & 6), 8.61 (1H, s, -NH-); MS (m/z): 360 (M^+), 105 (base peak),



Scheme 2. Fragmentation pattern of imine (**3a**)



Scheme 3. Fragmentation pattern of thiazolidinone (**4a**)

212, 111, 105, 91, 65; Elemental analysis: (calculated) found: C (59.91) 59.90, H (4.75) 4.73, N (7.76) 7.74%.

N-(2-(2,4-dihydroxyphenyl)-4-oxothiazolidin-3-yl)-3-phenylpropanamide (4c)

IR (KBr, cm^{-1}): 3524 (OH), 3249 (NH of CONH), 2920 (C-H of CH_2), 1764 (CO of thiazolidinone), 1656 (CO of CONH), 690 (C-S of thiazolidinone); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.56 (2H, t, J = 6.7 Hz, -CH_2-CO-), 2.91 (2H, t, J = 6.9 Hz, Ar-CH_2), 3.42 (2H, s, -CH_2-S-), 5.29 (1H, s, 4-OH), 5.31 (1H, s, 2-OH), 5.98 (1H, s, -N-CH-S-), 6.08 (1H, d, J = 2.9 Hz, Ar'-H3'), 6.20 (1H, dd, J = 2.8, 8.1 Hz, Ar'-H5'), 6.74 (1H, d, J = 7.9 Hz, Ar'-H6'), 7.09-7.22 (5H, m, Ar-H2, 3, 4, 5 & 6), 8.57 (1H, s, -NH-); MS (m/z): 358 (M^+), 210 (base peak), 109, 148, 105, 91, 65; Elemental analysis: (calculated) found: C (60.32) 60.30, H (5.06) 5.02, N (7.82) 7.80%.

N-(4-oxo-2-phenylthiazolidin-3-yl)-3-phenylpropanamide (4d)

IR (KBr, cm^{-1}): 3256 (NH of CONH), 2921 (C-H of CH_2), 1770 (CO of thiazolidinone), 1652 (CO of CONH), 691 (C-S of thiazolidinone); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.51 (2H, t, J = 6.9 Hz, -CH_2-CO-), 2.84 (2H, t, J = 6.8 Hz, Ar-CH_2), 3.48 (2H, s, -CH_2-S-), 5.97 (1H, s, -N-CH-S-), 7.04-7.17 (10H, m, Ar-H2, 3, 4, 5, 6 & Ar'-H'2', 3', 4', 5', 6'), 8.53 (1H, s, -NH-); MS (m/z): 326 (M^+), 148 (base peak), 178, 77, 51, 105, 91, 65; Elemental analysis: (calculated) found: C (66.23) 66.21, H (5.56) 5.52, N (8.58) 8.57%.

N-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-3-phenylpropanamide (4e)

IR (KBr, cm^{-1}): 3518 (OH), 3253 (NH of CONH), 2924 (C-H of CH_2), 1759 (CO of thiazolidinone), 1649 (CO of CONH), 686 (C-S of thiazolidinone); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.54 (2H, t, J = 6.9 Hz, -CH_2-CO-), 2.89 (2H, t, J = 6.8 Hz, Ar-CH_2), 3.39 (2H, s, -CH_2-S-), 5.28 (1H, s, 4-OH), 5.94 (1H, s, -N-CH-S-), 6.61 (2H, d, J = 8.2 Hz, Ar'-H3' & 5'), 6.89 (2H, d, J = 8.0 Hz, Ar'-H2' & 6'), 7.11-7.24 (5H, m, Ar-H2, 3, 4, 5 & 6), 8.59 (1H, s, -NH-); MS (m/z): 342 (M^+), 148 (base peak), 194, 93, 105, 91, 65; Elemental analysis: (calculated) found: C (63.14) 63.11, H (5.30) 5.30, N (8.18) 8.14%.

Biological activity

The newly synthesized compounds **3a-e** and **4a-e** were screened for antibacterial (*Staphylococcus aureus, Escherichia coli, Pseudoonas aeruginosa* at 37°C) and antifungal (*Candida albicans,*

Asperigillus flavus, Asperigillus fumigatus at 25°C) activities, using nutrient agar and Sabouraud's agar media, respectively, by disk diffusion method at a concentration of 2 mg per mL using DMF as a solvent. The results were recorded in duplicate using ampicillin 1 mg/mL and fluconazole 2.5 mg/mL as standards (6, 11) and are given in Table 2.

RESULTS

N-(substituted benzylidene)-3-phenylpropanehydrazides **(3a-e)**, a key intermediate of methyl 3-phenyl propanoate **1**, on cyclization with thioglycolic acid yield potent antibacterial and antifungal N-(4-oxo-2-arylthiazolidin-3-yl)-3-phenylpropanamides **(4a-e)**. The method of chemical conversion of compound **1** to **2**, **3a-e** and **4a-e** is illustrated in Scheme 1. The physical data of compounds **2**, **3a-e** and **4a-e** are presented in Table 1. The investigation for purity of all newly synthesized compounds was done by TLC (Rf values given in Table 1) and elemental analysis. The molecular formulae, structure, also anomeric configuration of the newly synthesized compounds **3a-e** and **4a-e** were further confirmed and supported by mass, ^{1}H NMR and IR spectral data, based on occurrence of molecular ion peak of the assigned structures, downfield shifting of protons and different stretching of bands of the compounds. To further support the molecular structure of newly synthesized compounds **3a-e** and **4a-e,** the general fragmentation patterns of compounds **3a** and **4a** are given in Schemes 2 and 3**.** From antimicrobial evaluation of all the newly synthesized compounds it was seen that each of **3a-e** and **4a-e** compounds possesses significant antibacterial and antifungal activity.

DISCUSSION AND CONCLUSSION

The structural elucidation of the newly synthesized compounds **2**, **3a-e** and **4a-e** was done on the basis of spectral and analytical data. The appearance of IR spectral values for newly synthesized compounds near 3250, 3511, 2921, 1650, 1765 and 690 cm^{-1} revealed the presence of NH, OH, CH_2, CO (CONH), CO (thiazolidinone) and C-S groups, respectively. The appearance of ^{1}H-NMR signals for newly synthesized compounds near 2.5, 2.8, 3.4, 5.9, 6.0-7.6, 8.5 and 8.6 ppm were corresponding to the protons of -CH_2-CO-, Ar-CH_2-, -CH_2-S-, -N-CH-S-, aromatic, N=CH and NH groups, respectively. The appearance of m/z peaks at 295 (M^+), 190 (base peak), 162, 148, 147, 120, 105, 91 and 65 in the mass spectra for compound **3a** were corresponding to loss of one electron and -C_8H_9, -C_9H_9O, -$C_9H_{11}N_2$, -$C_9H_{10}NO$, -$C_{10}H_{12}N_3O$, -$C_{11}H_{14}N_3O$ and -$C_{13}H_{16}N_3O$ fragments, respectively. The appearance of m/z peaks at 369 (M^+), 221 (base peak), 264, 120, 105, 91 and 65 in the mass spectra for compound **4a** were corresponding to loss of one electron, and -$C_9H_{10}NO$, -C_8H_9, -$C_{12}H_{13}N_2O_2S$, -$C_{12}H_{14}N_3O_2S$, -$C_{13}H_{16}N_3O_2S$ and -$C_{15}H_{18}N_3O_2S$ fragments, respectively. In the same manner, fragmentation pattern of compounds **3b-e** and **4b-e** further support the structural elucidation. The results of elemental analysis were also in full agreement, being within ± 0.4% of the theoretical values. The analytical and spectral data (IR, ^{1}H-NMR, MS) of all the newly synthesized compounds were in full agreement with the proposed structures. The antimicrobial studies of all the newly synthesized compounds **3a-e** and **4a-e** against freshly cultured strains of *S. aureus, E. coli, P. aeruginosa*, using sterile Nutrient agar media *and C. albicans, A. flavus, A. fumigatus* using sterile Sabouraud's agar media, revealed that all the compounds possess antibacterial and antifungal activities to certain extent. Among the newly synthesized derivatives, compound **4b** was found to be more potent than ampicillin when tested against the strains of *E. coli*. Compounds **3a**, **4a** and **4b** were found to be equipotent to ampicillin when tested on the organisms like *E. coli,* and *P. aeruginosa*. Whereas some of the tested compounds **3b, 4a, 4b** and **4d** have shown good antibacterial and antifungal activity, the remaining compounds have shown moderate activities on tested organisms presented in Table 2. After comparing the antimicrobial results of compounds **3a-e** and **4a-e**, it was concluded that the incorporation of thiazolidinone moiety in the imine derivatives of methyl phenylpropanoate enhances their antimicrobial activity and also *para* substitution in Ar' group of thiazolidinones enhances the potency especially in compounds **3a, 4a,** and **4b**. Further studies to acquire more information about structure activity relationships are in progress in our laboratory.

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