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SYNTHESIS AND ANTIMICROBIAL POTENTIAL OF THIAZOLIDIN-4-ONE DERIVATIVES

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ABSTRACT

A series of thiazolidin-4-one derivatives (TH1-T15) was synthesized and evaluated for their antimicrobial potential. Antimicrobial Activity was performed by Minimum Inhibitory Concentration (MIC) and zone of inhibition methods against Gram negative *E. Coli*, Gram positive bacteria: *B. Subtilis*, *S. aureus*, and fungal strains: A. *niger* and *C. albicans*. Among the synthesized derivatives**,** compounds 2, 10 and 14 was found to be most active against bacterial strains and compounds 6 and 12 was found to be most active against the fungal strains. In case of zone of inhibition, compounds 4, 5, 9 and 11 showed the good results against the tested strains. All the titled compounds (TH1-T16) were characterized by ^{1}H NMR and IR spectral data.

KEYWORDS: 4-Thiazolidinone, Hydrazone, Antimicrobial activity.

INTRODUCTION

The emergence of multi-drug resistant strains of microorganisms is a problem of ever increasing significance. The therapeutic problem has achieved increasing importance in hospitalized patients, in immunosuppressed patients with AIDS or undergoing anticancer therapy and organ transplants. Consequently, the development of new antimicrobial agents will remain an important challenging task for medicinal chemists.[1]

So, there is an urgent need for identification of novel lead structure for the designing of new, potent and less toxic agents, which ideally shorten the duration of therapy and are effective against resistant strain.[2]

4-Thiazolidinone scaffold and its derivatives have attracted considerable attention of medicinal chemists and have become an important class of heterocyclic compounds because of their diverse biological activities such as antimicrobial,[3-5] anticancer,[6-7] antimycobacterial,[8-9] analgesic and anti-inflammatory,[10-11] antioxidant activities.[12] These works prompted us to synthesize the novel derivatives of 2-(aryl)-5-(arylidene)-4-thiazolidinone and evaluation their antimicrobial activity.

Experimental

Starting materials were obtained from commercial sources and were used without further purification. Reaction progress was observed by thin layer chromatography making use of commercial silica gel plates (Merck). Melting points were determined in open capillary tubes on a Sonar melting point apparatus and are uncorrected. ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were determined by Bruker Avance II 400 NMR spectrometer in appropriate deuterated solvents and are expressed in parts per million (δ, ppm) downfield from tetramethylsilane (internal standard). NMR data are given as multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) and number of protons. Infrared (IR) spectra were recorded on a Perkin Elmer FTIR spectrometer. All the synthesized titled derivatives have been evaluated for their antimicrobial potential.

Chemistry

A series of novel 4-thiazolidinone have been synthesized. The reaction between *p*-Nitro acetophenone, thiourea and iodine yielded the corresponding 4-(4-nitrophenyl)thiazol-2-amine (2) which on reaction with required aromatic aldehydes afforded the corresponding hydrazone of 4-(4-nitrophenyl)-thiazol-2-amine (3) in appreciable yield. Further the hydrazone were condensed with required amount of thioglycolic acid to yield 2-substituted 4hiazolidinones (4). In the next step 2-disubstituted-4-thiazolidinone was reacted with aromatic aldehydes (0.01 M) and anhydrous sodium acetate in glacial acetic acid yielded title compounds (TH1-TH15) (5).

General procedure of 4-thiazolidinone derivatives

Synthesis of 4-(4-nitrophenyl)thiazol-2-amine

p-Nitro acetophenone, (0.01m), thiourea (0.02m) and iodine (0.01 m) were dissolved in appropriate amount of ethanol and refluxed for 8 hours on a heating mantle. The reaction mixture was then cooled and poured on to the crushed ice and NaOH solution (10%) was added. The solid thus acquired was filtered, washed with water, and the product was recrystallized from rectified spirit. The purity of the sample was tested by TLC using the solvent system petroleum ether and ethyl acetate 8:2.[12]

Synthesis of hydrazone of 4-(4-nitrophenyl)-thiazol-2-amine

A mixture of (0.025 M) 4-(4-nitrophenyl)thiazol-2-amine was refluxed for about 2 hours with required amount of aldehydes (0.025 M) and methanol in the presence of a catalytic amount of glacial acetic acid. The solid thus acquired was filtered, washed with water, and the product was recrystallized from rectified spirit to give the corresponding hydrazones.

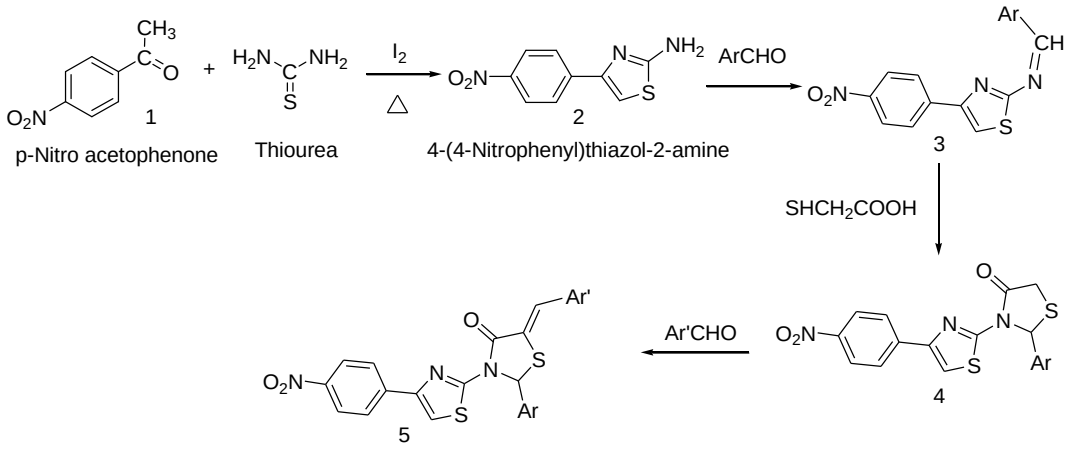
Synthesis of 2-disubstituted-4-thiazolidinone

A mixture of (0.015 M) hydrazone of 4-(4-nitrophenyl)-thiazol-2-amine and required amount of thioglycolic acid (0.015 M) in DMF was refluxed for about 6 h, containing a pinch of anhydrous $ZnCl_2$. The reaction mixture was cooled and poured on to crushed ice. The solid thus acquired was filtered, washed with water, and the product was recrystallized from rectified spirit to obtained the titled derivatives.[4]

Synthesis of 2,5-disubstituted-4-thiazolidinone

A mixture of (0.01 M) 2-substituted-4-thiazolidinone required aromatic aldehydes (0.01 M) and anhydrous sodium acetate in glacial acetic acid (20 ml) and refluxed for 5–7 h. After cooling, the solution was poured on crushed ice to precipitate the product. The product was recrystallized from rectified spirit [4].

Synthetic pathway for preparation of title 4-thiazolidinone derivatives is shown in Scheme 1. Physical and analytical data of synthesized derivatives are presented in Table 1.



Scheme 1

Table 1: Physical data of title compounds (TH1-TH15).

Comp. no.	Ar	Ar'	Molecular Formula	Molecular Weight	Melting Points (°C)	%Yields	R_f
TH1	2-$NO_2C_6H_4$	4-FC_6H_4	$C_{25}H_{15}FN_4O_5S_2$	534.54	169-171	81.77	0.65
TH2	2-$NO_2C_6H_4$	3-$OCH_3C_6H_4$	$C_{26}H_{18}N_4O_6S_2$	546.57	235–237	67.28	0.45
TH3	2-$NO_2C_6H_4$	2-ClC_6H_4	$C_{25}H_{15}ClN_4O_5S_2$	550.99	216–218	85.01	0.66
TH4	2-$NO_2C_6H_4$	4-$OCH_3C_6H_4$	$C_{26}H_{18}N_4O_6S_2$	546.57	221-223	88.02	0.54
TH5	2-$NO_2C_6H_4$	3-$NO_2C_6H_4$	$C_{25}H_{15}N_5O_7S_2$	561.55	241-243	77.01	0.59
TH6	2-ClC_6H_4	C_6H_5-	$C_{25}H_{16}ClN_3O_3S_2$	506.00	173-175	67.01	0.61
TH7	2-ClC_6H_4	2-$NO_2C_6H_4$	$C_{25}H_{15}ClN_4O_5S_2$	550.99	245-247	78.91	0.66
TH8	2-ClC_6H_4	4-ClC_6H_4	$C_{25}H_{15}C_{l2}N_3O_3S_2$	540.44	211-213	72.11	0.58
TH9	2-ClC_6H_4	4-OHC_6H_4	$C_{25}H_{16}ClN_3O_4S_2$	522.00	261-263	87.12	0.69
TH10	2-ClC_6H_4	3-BrC_6H_4	$C_{25}H_{15}BrClN_3O_3S_2$	584.89	222-224	71.14	0.75
TH11	2-ClC_6H_4	4-FC_6H_4	$C_{25}H_{15}ClFN_3O_3S_2$	523.99	172-174	71.21	0.64
TH12	2-ClC_6H_4	3-$OCH_3C_6H_4$	$C_{26}H_{18}ClN_3O_4S_2$	536.02	237–239	68.21	0.65
TH13	2-ClC_6H_4	2-ClC_6H_4	$C_{25}H_{15}Cl_2N_3O_3S_2$	540.44	249–251	80.21	0.60
TH14	2-ClC_6H_4	4-$OCH_3C_6H_4$	$C_{26}H_{18}ClN_3O_4S_2$	536.02	225-227	73.12	0.56
TH15	2-ClC_6H_4	3-$NO_2C_6H_4$	$C_{25}H_{15}ClN_4O_5S_2$	550.99	211-213	71.98	0.58

Solvent system chloroform: benzene: glacial acetic acid (3:1:1).

Spectral Data

Chlorofo(Z)-5-(4-fluorobenzylidene)-2-(2-nitrophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (1): IR (KBr, cm^{-1}): 3060 (C-H Ar), 1700 (C=O), 1599 (C=N), 1525 (NO_2), 1417 (C-N), 1143(C-F), 695(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 8.62-7.00 (m, 12H, ArH), 7.28 (s, 1H, CH), 6.96 (s, 1H, CH, thiazole), 6.79 (s, 1H, CH, thiazolidinone).

(Z)-5-(3-methoxybenzylidene)-2-(2-nitrophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (2): IR (KBr, cm^{-1}): 3077 (C-H Ar), 1688 (C=O), 1636(C=C Ar), 1602 (C=N), 1549(NO_2), 1411 (C-N), 1281 (C–O–C str), 693(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 8.69-7.00 (m, 12H, ArH), 7.23 (s, 1H, CH), 6.55 (s, 1H, CH, thiazole), 6.50 (s, 1H, CH, thiazolidinone), 3.81 (s, 3H, -OCH_3).

(Z)-5-(2-chlorobenzylidene)-2-(2-nitrophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (3): IR (KBr, cm^{-1}): 3036 (C-H Ar), 1673 (C=O), 1637(C=C Ar), 1539 (NO_2), 1413 (C-N), 758(Cl), 695(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 9.41-7.02 (m, 12H, ArH), 7.28 (s, 1H, CH), 7.02 (s, 1H, CH, thiazole), 6.91 (s, 1H, CH, thiazolidinone).

(Z)-5-(4-methoxybenzylidene)-2-(2-nitrophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (4): IR (KBr, cm^{-1}): 3200 (C-H Ar), 1699 (C=O), 1628(C=C Ar), 1583 (C=N), 1504 (NO_2), 1441 (C-N), 1294 (C–O–C str), 695(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 8.22-7.14 (m, 12H, ArH), 7.14 (s, 1H, CH), 7.10 (s, 1H, CH, thiazole), 5.64 (s, 1H, CH, thiazolidinone), 3.39 (s, 3H, -OCH_3).

(Z)-5-(3-nitrobenzylidene)-2-(2-nitrophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (5): IR (KBr, cm^{-1}): 3032 (C-H Ar), 1739 (C=O), 1664(C=C Ar), 1609 (C=N), 1513 (NO_2), 1419 (C-N), 623(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 9.07-7.72 (m, 12H, ArH), 7.98 (s, 1H, CH), 7.55 (s, 1H, CH, thiazole), 7.54 (s, 1H, CH, thiazolidinone).

(Z)-5-benzylidene-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (6): IR (KBr, cm^{-1}): 3079 (C-H Ar), 1701 (C=O), 1639(C=C Ar), 1602 (C=N), 1519 (NO_2), 1400 (C-N), 711(Cl), 668(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 7.72-6.38 (m, 13H, ArH), 7.29 (s, 1H, CH), 6.17 (s, 1H, CH, thiazole), 5.58 (s, 1H, CH, thiazolidinone).

(Z)-5-(2-nitrobenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (7): IR (KBr, cm^{-1}): 2990 (C-H Ar), 1688 (C=O), 1607 (C=N), 1492 (NO_2), 1436 (C-N), 754(Cl), 651(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 8.09-7.27 (m, 12H, ArH), 7.47 (s, 1H, CH), 6.97 (s, 1H, CH, thiazole), 6.68 (s, 1H, CH, thiazolidinone).

(Z)-5-(4-chlorobenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (8): IR (KBr, cm^{-1}): 2966 (C-H Ar), 1713 (C=O), 1681(C=C Ar), 1649 (C=N), 1520(NO_2), 1455 (C-N), 731(Cl), 689(C-S);); ^{1}H NMR (DMSO-*d*6, 400 MHz): 9.08-7.54 (m, 12H, ArH), 7.74 (s, 1H, CH), 7.52 (s, 1H, CH, thiazole), 7.28 (s, 1H, CH, thiazolidinone).

(Z)-5-(4-hydroxybenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (9): IR (KBr, cm^{-1}): 3412 (OH), 2960 (C-H Ar), 1592 (C=N), 1529 (NO_2), 1416 (C-N), 719(Cl), 637(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 7.39-7.24 (m, 12H, ArH), 7.31 (s, 1H, CH), 6.98 (s, 1H, CH, thiazole), 6.95 (s, 1H, CH, thiazolidinone), 4.73 (s, 1H, -OH).

(Z)-5-(3-bromobenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (10): IR (KBr, cm^{-1}): 3012 (C-H Ar), 1739 (C=O), 1692(C=C Ar), 1649 (C=N), 1539 (NO_2), 1416 (C-N), 723(Cl), 666(C-S) 631(Br); ^{1}H NMR (DMSO-*d*6, 400 MHz): 7.62-7.35 (m, 12H, ArH), 7.50 (s, 1H, CH), 7.10 (s, 1H, CH, thiazole), 7.07 (s, 1H, CH, thiazolidinone).

(Z)-5-(4-fluorobenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (11): IR (KBr, cm^{-1}): 3032 (C-H Ar), 1711 (C=O), 1659(C=C Ar), 1559 (NO_2), 1401 (C-N), 1161(C-F), 715(Cl), 681(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 8.11-7.55 (m, 12H, ArH), 7.53 (s, 1H, CH), 7.50 (s, 1H, CH, thiazole), 7.28 (s, 1H, CH, thiazolidinone).

(Z)-5-(3-methoxybenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (12): IR (KBr, cm^{-1}): 3026 (C-H Ar), 1685 (C=O), 1633(C=C Ar), 1604 (C=N), 1549 (NO_2), 1413 (C-N), 1259 (C–O–C str), 755(Cl), 692(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 7.32-7.18 (m, 12H, ArH), 7.22 (s, 1H, CH), 7.06 (s, 1H, CH, thiazole), 7.03 (s, 1H, CH, thiazolidinone), 3.60 (s, 3H, -OCH_3).

(Z)-5-(2-chlorobenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (13): IR (KBr, cm^{-1}): 3051 (C-H Ar), 1681 (C=O), 1632(C=C Ar), 1603 (C=N), 1583 (NO_2), 1449 (C-N), 747(Cl), 695(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): ^{1}H NMR (DMSO-*d*6, 400 MHz): 9.34-7.11 (m, 12H, ArH), 7.20 (s, 1H, CH), 6.92 (s, 1H, CH, thiazole), 6.72 (s, 1H, CH, thiazolidinone).

(Z)-5-(4-methoxybenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (14): IR (KBr, cm^{-1}): 3030 (C-H Ar), 1602 (C=N), 1506 (NO_2), 1457 (C-N), 744(Cl), 627(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): 9.36-7.20 (m, 12H, ArH), 7.16 (s, 1H, CH), 6.92 (s, 1H, CH, thiazole), 6.72 (s, 1H, CH, thiazolidinone), 3.47 (s, 3H, -OCH_3).

(Z)-5-(3-nitrobenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (15): IR (KBr, cm^{-1}): 3079 (C-H Ar), 1641(C=C Ar), 1578 (C=N), 1501 (NO_2), 1413 (C-N), 714(Cl), 672(C-S); ^{1}H NMR (DMSO-*d*6, 400 MHz): ^{1}H NMR (DMSO-*d*6, 400 MHz): 7.96-7.26 (m, 12H, ArH), 7.38 (s, 1H, CH), 6.61 (s, 1H, CH, thiazole), 6.58 (s, 1H, CH, thiazolidinone).

Biological Evaluations

Evaluation of antimicrobial activity

Determination of Minimum Inhibitory Concentration

The antimicrobial potential of titled compounds thiazolidin-4-one was performed against Gram-negative bacterium: *E. coli*, Gram-positive bacteria: *B. sublitis*, *S. aureus*, and fungal strains: *A. niger* and *C. albicans* by tube dilution method. Dilutions of test (titled compounds) and standard compounds [ciprofloxacin (antibacterial) and Clotrimazole (antifungal)] was prepared in double strength nutrient broth – I.P. (bacteria) and Sabouraud dextrose broth I.P. (fungi) (Indian Pharmacopoeia 2007). The samples was incubated at 37 °C for 24 h (bacteria), at 25 °C for 7 d (*A. niger*) and at 37 °C for 48 h (*C. albicans*), respectively, and the results will be recorded in terms of Minimum inhibitory concentration (MIC).[13] Results of antimicrobial potential are shown in Table-2

Table 2: *In Vitro* Antimicrobial Activity of the Title Compounds (T1-T15).

Compound	Minimum inhibitory concentration (µg ml^{-1})				
	Bacterial Strains			Fungal Strains	
	E. coli	*S. aureus*	*B. subtilis*	*C. albicans*	A. *Niger*
TH1	25	25	25	25	12.5
TH2	25	3.12	1.56	25	25
TH13	25	12.5	25	12.5	25
TH4	25	25	12.5	6.25	25
TH5	12.5	25	12.5	12.5	25
TH6	12.5	12.5	25	1.56	1.56
TH7	12.5	25	50	12.5	12.5
TH8	12.5	12.5	6.25	12.5	25
TH9	12.5	25	12.5	50	12.5
TH10	1.56	12.5	1.56	25	25
TH11	25	12.5	25	50	25
TH12	25	25	3.12	1.56	3.12
TH13	12.5	12.5	6.25	25	25
TH14	1.56	1.56	3.12	50	25
TH15	6.25	25	12.5	25	25
Ciprofloxacin (standard drug)	0.01	0.15	0.12	---	--
Clotrimazole (standard drug)	--	--	--	0.10	0.30

Antimicrobial evaluation by Zone of inhibition.

The titled compounds thiazolidin-4-one derivatives were also screened for their antimicrobial potential against these strains by zone of inhibition. The experiment performed by disc-diffusion method.[14] A standard inoculum (1-2 x 10^7 c.f.u./ml 0.5 McFarland standards) was introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculum. The disc measuring 6.25 mm in diameter were prepared from Whatman no. 1 filter paper and sterilized by dry heat at 140 °C for 1 h. The sterile discs previously soaked with the titled compounds (test compound) solution in DMSO of specific concentration 100 µg/disc were carefully placed on the agar culture plates. The plates were inverted and incubated for 24 h at 37 °C. Ciprofloxacin was used as a standard drug for antibacterial activity and clotrimazole was used as a standard drug for antifungal activity. The results of antimicrobial zones of inhibition are presented in table 3.

Table 3: Antimicrobial screening results of the tested compounds.

Comp.	Concentration (µg/ml)	Zone of inhibition (in mm)				
		Gram positive bacteria		Gram negative Bacteria		Fungal strain
		B.subtilis	*S. aureus*	*E. coli*	*C. albicans*	*A. niger*
TH1	100	20	21	19	19	11
TH 2	100	17	18	15	13	14
TH 3	100	19	17	19	14	17
TH 4	100	15	28	20	17	15
TH 5	100	19	19	22	20	15
TH 6	100	19	20	22	11	17
TH 7	100	22	15	22	15	12
TH 8	100	15	19	22	19	13
TH 9	100	24	15	29	17	15
TH 10	100	22	26	19	13	13
TH11	100	19	20	28	15	14
TH12	100	22	15	20	15	19
TH13	100	22	19	22	15	15
TH14	100	19	11	22	19	13
TH15	100	13	14	22	16	11
Ciprofloxacin	100	25	30	30	-	-
Clotrimazole	100	-	-	-	20	19

RESULT AND DISCUSSION

All the synthesized thiazolidin-4-one derivatives were evaluated for their antimicrobial potential against Gram negative *E. Coli*, Gram positive bacteria: *B. Subtilis, S. aureus*, and fungal strains: A. *niger. and C. albicans.* Ciprofloxacin and Clotriamazole were taken as standard drug for antibacterial and antifungal activity respectively. The newly synthesized compounds were characterized by IR and ^{1}H NMR analyses. The results revealed that all synthesized compounds have a significant biological activity against the tested microorganisms.

All the synthesized derivatives were subjected to antimicrobial screening against Gram negative *E. Coli*, Gram positive bacteria: *B. Subtilis, S. aureus*, and fungal strains: A. *niger. and C. albicans.* by zone of inhibition method. Ciprofloxacin and Clotriamazole were taken as reference drugs for antibacterial and antifungal activity. Among the synthesized derivatives**,** compounds 2, 10 and 14 was found to be most active against bacterial strains and compounds 6 and 12 was found to be most active against the fungal strains. In case of zone of inhibition, compounds 4,5,9 and 11 showed the good results against the tested strains. Results are presented in table 3.

CONCLUSION

In conclusion, a series of thiazolidin-4-one derivatives (TH1-T15) was synthesized and evaluated for their antimicrobial potential. Antimicrobial Activity was performed by Minimum Inhibitory Concentration (MIC) and zone of inhibition methods against Gram negative *E. Coli*, Gram positive bacteria: *B. Subtilis, S. aureus*, and fungal strains: A. *niger* and *C. albicans.* Data obtained was found to be in good agreement with the calculated values of the proposed structure. Most of the synthesized compounds exhibited moderate to significant antimicrobial activity.

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