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Synthesis of New Substituted Thiazolidin-4-One Analogues with Anticancer and Antimicrobial Activity

Shelke RN, Pansare DN*, Dake SA, Pawar RP and Bembalkar SR

Department of Chemistry, Deogiri College, Station Road, Aurangabad 431 005, MS, India

***Corresponding author:** Dattatraya N Pansare, Department of Chemistry, Deogiri College, Station Road, Aurangabad 431 005, MS, India, E-Mail: dbsdattatraya10@rediffmail.com

Abstract

The anticancer and antimicrobial activity associated with the thiazolidinone framework, several new (Z)-5-(substituted)-2-(methylthio) thiazol-4(5H)-one analogues 3a-l and 5a-l. All synthesized compounds were evaluated for anticancer and antimicrobial activity in vitro. Amongst these, the compounds 3c, 3f, 3h, 3j and 5a, 5c, 5d, 5e, 5f, 5h, 5j showed highest antibacterial and antifungal activity among the series. The compounds 3c and 5e exhibited significant antibacterial activity against E. coli, whereas compound 5f displayed significant antifungal activity against fungal strains i.e. A. oryzae. The in vitro anticancer studies revealed that 3i, 3k and 5b, 5k are the most active compounds against MCF-7 and BT-474 human breast cancer cell lines.

Keywords: ***Knoevenagel reaction; 2-thioxothiazolidin-4-one; Aldehyde; Anticancer; Antimicrobial***

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Introduction

Thiazolidinone core and its derivatives have become among the most extensively investigated compounds last decade. They constitute a very important group of heterocyclic compounds, having valuable biological activities in the areas of medicine as well as agriculture. The rhodanine scaffold is a central part of biologically active compounds with various applications and uses [1-3], such as antimicrobial [4,5], antimalarial [6], anti-HIV agents [7-10], anti-inflammatory [11-13], antifungal [14,15], anticancer [16], antidiabetic [17], anti-tubercular [18,19] and antioxidant [20]. Cancer is a common disease that poses a serious threat to human health [21]. Thousands of people die of cancer every year in worldwide. Despite the availability of a variety of anticancer agents, such as cisplatin, but no currently available agents can entirely eradicate cancer cells without also having toxic effects on patients' noncancerous, healthy tissues. Therefore, the development of new anticancer agents that enable more selective treatment strategies is very important.

With this in mind, we initiated a program to synthesized thiazolidinone derivatives are good example of a anticancer and antimicrobial compound by preparing hybrid molecules having the similar features of reported potent antimicrobial agents [22,23] (**FIG. 1**). In continuation of our work [24], we have developed the new protocol for the synthesis of (Z)-5-benzylidene-2-thioxothiazolidin-4-one (**3a**) (Scheme 1) condensation between 2-thioxothiazolidin-4-one (**1**) and benzaldehyde (**2a**). The compound (**3a**) was then subjected to a Knoevenagel condensation with the appropriate rhodanine, which was synthesized using the reported procedure [25].

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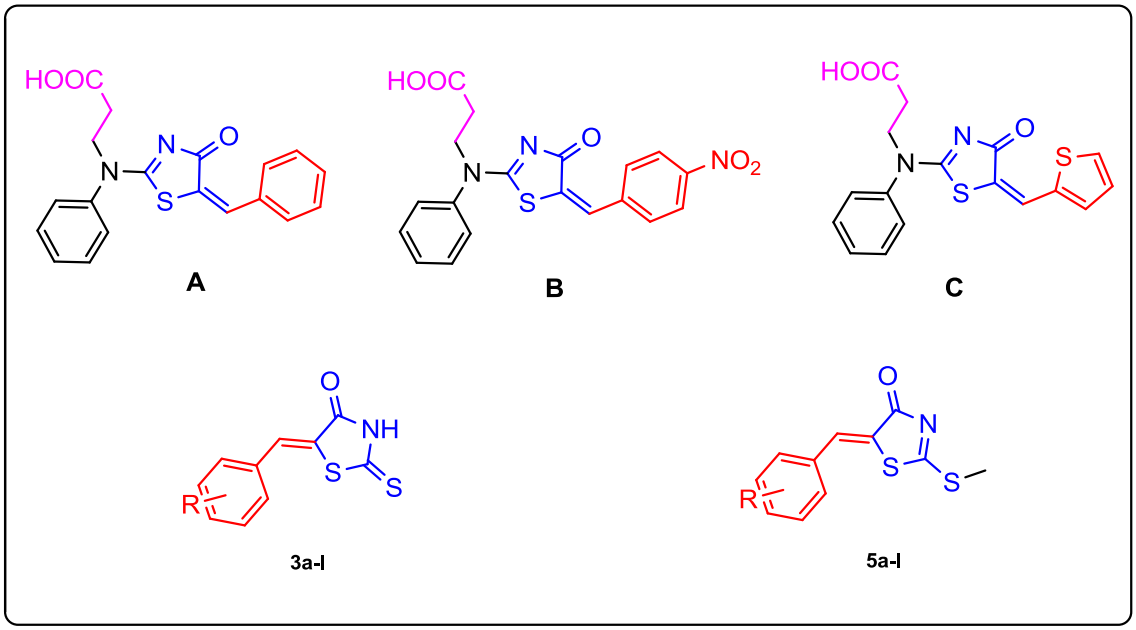
Here, we wish to mention the development and implementation of a methodology allowing for the synthesis of some new (*Z*)-5-(substituted)-2-thioxothiazolidin-4-one **3a-l** and (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one **5a-l** derivatives. The reported reaction under microwave irradiation as well as by conventional method, preceed in short reaction time and give good to excellent yield. The structures of compounds **3a-l** and **5a-l** were substantiated by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis.

FIG.1. **Previously reported antimicrobial agents and synthesized compounds.**



Experimental

The 2-thioxothiazolidin-4-one (Rhodanine), aromatic aldehydes, anhydrous sodium acetate, triethylamine, iodomethane, dichloromethane and various solvents were commercially available. The major chemicals were purchased from Sigma Aldrich and Avra labs. Microwave reactions were carried out in MicroSYNTH Lab station of Ethusi Milestone. Reaction courses were monitored by TLC on silica gel precoated F254 Merck plates. Developed plates were examined with UV lamps (254 nm). IR spectra were recorded on a FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus and these are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz Bruker spectrometer. Chemical shifts are reported as δ_{ppm} units. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

General procedure for the synthesis of compounds (3a-l)

In a 50 ml round bottom flask, equimolar amounts of 2-thioxothiazolidin-4-one **1** (1 m mol), anhydrous sodium acetate (1 m mol), glacial acetic acid (1 mL) and then aromatic aldehydes **2a-l** (1 m mol) were added to the reaction mixture. The mixture was stirred under reflux condition for 4-8 h. The progress of reaction was monitored by TLC (20% ethyl acetate: *n*-hexane). After completion of the reaction, the reaction mixture was poured into the ice-cold water. The precipitate was filtered off and washed with water (3×15 mL), dried, and purified by recrystallization in ethanol as solvent to give 92-98% yield.

General procedure for the synthesis of compounds (5a-l)

In a 50 ml round bottom flask, the compound **3a-l** (1 m mol), triethylamine (1.2 m mol), dichloromethane (1 mL), with iodomethane (1.2 m mol) was added and stirred for 1-2 h at room temperature. The progress of the reaction was monitored by TLC (10% chloroform: methanol). After completion of reaction the reaction mixture was concentrated *in vacuo*. The residue was washed with water (3×15 mL) to afford the crude product. The crude product was recrystallized using ethanol as solvent to give yield in the range 92-96%.

Results and Discussion

Chemistry

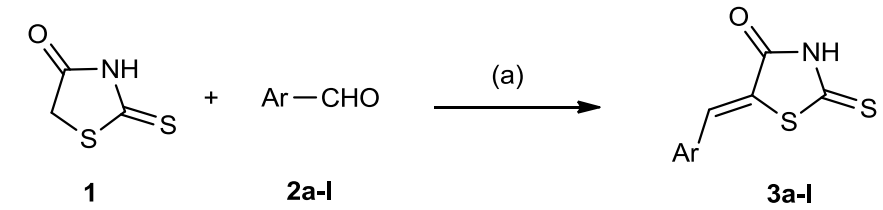
The compounds **2a-l** were then subjected to a Knoevenagel condensation with the appropriate rhodanines, which were synthesized using the reported procedure [26], to provide new series of target compounds **3a-l**. Thiazolidinone based compounds were synthesized by conventional heating with sodium acetate and glacial acetic acid. We synthesized the new (*Z*)-5-(substituted)-2-thioxothiazolidin-4-one **3a-l** (Scheme 1, TABLE 1) derivatives and (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one **5a-l** (Scheme 2, TABLE 2) derivatives under conventional method. However, the reaction provided cleaner reaction, short reaction time, and the products were only required to be washed with ice-cold water. The yields were good to excellent. The IR spectrum of representative compound (*Z*)-5-(benzylidene)-2-thioxothiazolidin-4-one **3a**, shows a strong absorption band at 1693 cm^{-1} which is due to a carbonyl group thiazolidinone moiety. The mass spectrum revealed a molecular ion peak at m/z = 221.05 corresponding to a molecular formula $C_{10}H_7NOS_2$. ^1H NMR spectra of compounds **3a** show only one signal for the methyne proton in the range δ 7.72 ppm, at lower field values than those expected for the *E*-isomers. This strongly indicates that the compounds have the *Z*-configuration. The compounds **5a-l** were synthesized from compound **3a-l** and IR spectrum of representative compound (Z)-5-(benzylidene)-2-(methylthio)thiazol-4(5H)-one **5a**, showed a strong absorption band at 1694 cm^{-1} due to a carbonyl group. The mass spectrum revealed a molecular ion peak at m/z = 235.00 corresponding to a molecular formula $C_{11}H_9NOS_2$.

TABLE 1**. Synthesis of (Z)-5-(substituted)-2-thioxothiazolidin-4-one (3a-l).**

Entry	Ar	Product	Time	Yield b (%)	M.P. (ºC)
1	benzyl	3g	4	98	204-206
2	2,4-dichlorobenzyl	3b	6	98	230-232
3	4-methoxybenzyl	3c	6	95	247-249
4	4-chlorobenzyl	3d	7	95	131-133
5	4-fluorobenzyl	3e	7	94	226-228
6	4-hydroxybenzyl	3f	6	95	265-267
7	2-chlorobenzyl	3a	5	98	180-182
8	4-nitrobenzyl	3h	4	95	255-257
9	2-Thiophenyl	3i	5	94	231-233

10	2,4-dimethoxybenzyl	3j	5	94	271-273
11	3-fluorobenzyl	3k	7	95	198-200
12	4-Methylbenzyl	3l	8	92	219-221
[a]Reaction condition (3a-l): Acetic acid, Sodium acetate, reflux 4-8 h. [b] Isolated yields.					

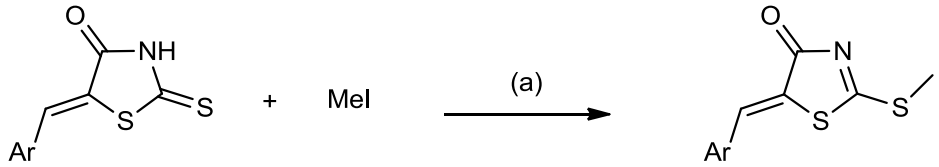
SCHEME 1. **Synthesis of (*Z*)-5-(substituted)-2-thioxothiazolidin-4-one (3a-l) ([a] [a]Reaction condition (3a-l). (a) Compound 1 (1m mol), 2a-l (1m mol), sodium acetate (1m mol), 1 mL acetic acid, reflux 2-4 h).**



1 **2a-l** **3a-l**

Ar = 3a = benzyl
3b = 2,4-dichlorobenzyl
3c = 4-methoxybenzyl
3d = 4-chlorobenzyl
3e = 4-fluorobenzyl
3f = 4-hydroxybenzyl
3g = 2-chlorobenzyl
3h = 4-nitrobenzyl
3i = 2-Thiophenyl
3j = 2,4-dimethoxybenzyl
3k= 3-fluorobenzyl
3l = 4-Methylbenzyl

SCHEME 2**. Synthesis of (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one (5a-l)[a] ([a]Reaction condition (5a-l). (a) Compounds 3a-l (1 m mol), 4 (1 m mol), triethylamine (1.2 m mol), 1 mL ethanol, stirring room temperature, 1-2 h)**



3a-l **4** **5a-l**

Ar = 5a = benzyl
5b = 2,4-dichlorobenzyl
5c = 4-methoxybenzyl
5d = 4-chlorobenzyl
5e = 4-fluorobenzyl
5f = 4-hydroxybenzyl
5g = 2-chlorobenzyl
5h = 4-nitrobenzyl
5i = 2-Thiophenyl
5j = 2,4-dimethoxybenzyl
5k= 3-fluorobenzyl
5l = 4-Methylbenzyl

TABLE 2**. Synthesis of (Z)-5-(substituted)-2-(methylthio) thiazol-4(5H)-one (5a-l)[a].**

Entry	Ar	Product	Time	Yieldb (%)	M.P. (ºC)
1	benzyl	5a	1	96	145-147
2	2,4-dichlorobenzyl	5b	1	92	165-167
3	4-methoxybenzyl	5c	1	92	162-164
4	4-chlorobenzyl	5d	1	92	160-162

5	4-fluorobenzyl	5e	1	92	143-145
6	4-hydroxybenzyl	5f	2	90	222-224
7	2-chlorobenzyl	5g	2	92	170-172
8	4-nitrobenzyl	5h	1	94	160-162
9	2-Thiophenyl	5i	2	94	150-152
10	2,4-dimethoxybenzyl	5j	1	92	172-174
11	3-fluorobenzyl	5k	1	94	160-162
12	4-Methylbenzyl	5l	2	92	175-177
[a]Reaction condition (5a-l). Compounds 3a-l (1 mmol), 4 (1.2 mmol), triethylamine (1.2 mmol), 1 mL dichloromethane, stirring room temperature, 1-2 h.					

Antimicrobial activity

All the synthesized compounds (**3a-l** and **5a-l**) were screened for their *in-vitro* antimicrobial activity against six bacteria; *Bacillus subtilis (NCIM-2063), Staphylococcus aureus (NCIM-2901), Escherichia coli (NCIM-2256), Enterococcus faecalis (NCIM-5443), Pseudomonas aeruginosa (NCIM-2037), Salmonella typhimurium (NCIM-2501)* and six fungal strains; *Aspergillus oryzae* (NCIM-570), *Penicillium chrysogenum* (NCIM-707), *Fusarium oxysporum* (NCIM-1282), *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539) and *Aspergillus Niger* (NCIM-1196). The antimicrobial activity of compounds was monitored by observing their Minimum Inhibitory Concentration (MIC, µg/ml) as previously mentioned [27] by broth dilution methods with Ciprofloxacin and Ampicillin as control drugs. While the antifungal study was carried by the standard agar dilution method were Fluconazole and Miconazole used as control drugs. Ethanol was used as a solvent control for both antibacterial and antifungal testing. All the synthesized compounds were also tested for their general cytotoxicity on mammalian cell lines MCF-7 and BT-474 human breast cancer cell line. This test is performed as previously mentioned MTT colorimetric assay [28]. Cytotoxicity of the compounds was determined by calculating their IC_{50} values, concentration of compound required to inhibit 50% of cell growth compared to untreated control cells. The IC_{50} values were presented in micro molar per milliliter (µM/ml). Adriamycin was used as positive control for the comparison of cytotoxicity of synthesized compounds. Therefore, our current work is highlighted synthesis, structure activity. Relationship (SAR) and biological evaluation of thiazolidinone and its derivatives for their anticancer, antibacterial and antifungal activity.

TABLE 3**. Antibacterial activity of the synthesized compounds 3a-l and 5a-l (MIC Values (µg/mL).**

Compounds	**MIC Values (µg/mL)**					
	B.s.	***S.a.***	***E.c.***	***E.f.***	***P.a.***	***S.t.***
3a	48.70	39.57	60.37	44.70	55.90	45.95
3b	48.13	67.15	44.40	46.14	36.76	36.75
3c	51.70	41.50	12.30	39.13	75.30	33.90
3d	55.13	55.17	49.40	65.12	52.73	81.75
3e	46.14	56.12	47.17	44.16	23.35	28.35

3f	64.55	48.56	64.53	43.54	37.16	9.18
3g	67.10	73.10	38.40	48.10	42.13	52.15
3h	16.20	28.30	65..40	63.10	42.20	51.90
3i	45.70	53.57	56.37	33.70	33.90	45.85
3j	7.14	68.16	48.40	17.10	48.76	59.85
3k	33.70	33.50	32.39	35.10	25.30	57.90
3l	48.15	37.10	47.40	37.10	58.60	42.70
5a	8.50	9.75	30.10	34.10	28.50	27.30
5b	32.10	39.10	48.50	48.50	32.70	53.10
5c	8.45	9.78	45.40	48.10	55.13	42.15
5d	16.20	50.30	59..40	60.10	55.20	56.90
5e	38.70	38.57	18.37	38.70	32.90	46.95
5f	54.13	53.15	35.40	58.10	37.76	12.70
5g	33.70	43.50	33.39	35.10	26.30	36.90
5h	47.10	48.15	47.47	48.10	8.60	32.70
5i	39.50	48.10	30.10	34.10	28.50	27.30
5j	15.10	34.10	7.50	15.50	35.70	15.10
5k	47.10	38.50	38.40	38.10	46.13	53.15
5l	53.20	45.30	64..40	62.10	56.20	56.90
Ciprofloxacin	10.70	10.50	10.50	12.68	12.50	13.50
Ampicillin	5.51	5.30	5.30	5.30	5.80	5.40
	[a]Values are the average of three readings.					
B.s.- Bacillus subtilis (NCIM-2063), *S.a.-Staphylococcus aureus* (NCIM-2901), *E.c.- Escherichia coli* (NCIM-2256), *E.f. Enterococcus faecalis* (NCIM-5443), *P.a.- Pseudomonas aeruginosa* (NCIM-2037), *S.t.- Salmonella typhimurium* (NCIM-2501)						

TABLE 4. Antifungal activity of the synthesized compounds **3a-l** and **5a-l** (MIC Values (µg/mL).

Compounds	***A.o.***	***P.c.***	***F.o.***	***C.a.***	***A.f.***	***A.n.***
3a	31.50	51.39	33.50	32.50	16.30	10.30
3b	52.10	52.10	64.12	64.10	32.20	72.33
3c	37.00	37.20	33.20	33.20	33.20	30.00
3d	32.20	42.60	71.10	32.30	31.88	31.00
3e	5.50	5.39	35.50	33.50	11.30	17.30
3f	46.10	46.10	62.12	32.10	33.20	41.33
3g	34.00	34.20	34.20	32.60	32.60	34.60
3h	48.20	48.50	47.10	66.38	33.88	46.00

3i	33.50	16.39	16.50	17.50	33.30	38.30
3j	48.40	32.40	34.32	33.30	84.30	85.33
3k	42.30	55.40	32.30	57.50	68.50	39.50
3l	42.30	52.20	84.10	52.00	72.30	51.50
5a	36.30	13.80	51.20	31.25	44.25	30.55
5b	36.80	34.70	65.18	60.18	30.64	45.69
5c	34.00	34.20	34.20	55.20	34.70	31.00
5d	43.20	44.60	49.10	65.35	35.88	48.00
5e	6.55	5.36	39.50	18.50	16.30	36.30
5f	10.10	48.10	32.11	35.10	32.22	32.23
5g	32.00	38.50	34.40	68.40	58.10	34.40
5h	51.34	50.25	84.15	72.05	33.30	54.50
5i	46.35	55.80	43.26	31.26	74.26	35.58
5j	52.80	35.78	62.38	62.38	42.84	49.29
5k	45.40	34.24	54.26	38.66	34.26	38.07
5l	50.25	40.65	40.15	62.48	33.89	58.08
Fluconazole	4.60	2.68	25.65	8.70	8.42	2.28
Miconazole	42.25	6.30	7.16	2.34	40.20	146.30

[a]Values are the average of three readings.

A.o.- Aspergillus oryzae (NCIM-570), *P.c.- Penicillium chrysogenum* (NCIM-707), *F.o.- Fusarium oxysporum* (NCIM-1282), *C.a.- Candida albicans* (NCIM-3471), *A.f.- Aspergillus flavus* (NCIM-539) and *A.n.- Aspergillus Niger* (NCIM-1196).

TABLE 5**. *In vitro* cytotoxicity of compounds towards the MCF-7 and BT-474 cells, after 24 h.**

Compounds	**(IC_{50})[a] µMolar[b]**	
	MCF-7[c]	**BT-474[d]**
3a	48.6	52.2
3b	56.8	23.6
3c	46.9	44.2
3d	48.2	60.1
3e	58.3	52.5
3f	80.4	46.3
3g	78.5	46.6
3h	86.4	58.8
3i	1.2	0.7
3j	72.2	74.1

3k	1.3	1.2
3l	78.7	64.5
5a	10.3	11
5b	1.6	1.4
5c	38.6	53.4
5d	34.8	25
5e	43.9	43.4
5f	48.2	62.2
5g	46.3	56.6
5h	72.4	48.6
5i	66.5	48.6
5j	72.4	56.8
5k	1.6	0.7
5l	74.2	67.1
Adriamycin[e]	0.8	0.6

[a]GI_{50}(Growth inhibition of 50) : Concentration of drug that decreases the growth of the cells by 50compared to non-treated control cell.

[b]Values are the average of three readings

[c]MCF-7: Human Breast cancer cell line

[d]BT-474: Human Breast cancer cell line

[e]Adriamycin: Positive control compound.

The antimicrobial activities of the synthesized compounds against selected Gram-positive and Gram-negative bacteria and multidrug-resistant bacteria are illustrated in TABLES 3 and 4. The synthesized compounds of present new series shows a variety of antibacterial activity, specific molecule active against the majority of bacterial strains tested to the narrow spectrum compounds. From the antibacterial data it is clearly observed that many of the synthesized compounds were shows prominent antibacterial and antifungal activity. The antibacterial and antifungal activity data indicate that among the twenty four synthesized compounds of present series many shows promising good to moderate level of antibacterial and antifungal activity. Some compounds were shows narrow spectrum, active against specific fungal and bacterial strain while some of them were found to be broad spectrum molecules, active against bacterial strains. Among these the compounds **3c**, **3f, 3h, 3j, 5a, 5c, 5d, 5e, 5f, 5h** and **5j,** was found to be the best activity as they specifically active against the bacterium *B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa* and *S. typhimurium*. The compounds (**3f**), (**3j**), (**5a**), (**5c**) and (**5h**) were found to be the good activity as they were specifically active against the bacterium *E. coli*, *S. aureus*, *P. aeruginosa* and *S. typhimurium*. They are also most active molecules among the series, more potent than standard antibacterial drugs Ciprofloxacin and Ampicillin, with a MIC of 7.14 to MIC of 17.10. These compound (**3c**) MIC of 12.30, (**3f**) MIC of 9.18, and (**3h**) MIC of 16.20. On the

other hand, the compounds (**3j**) MIC of 7.14, active against the bacterium *B. subtilis*, MIC of 17.10, active against the bacterium *E. faecalis*, the compounds (**5c**) MIC of 8.45, MIC of 9.78, The compound (**5f**) was found active against the testing strains in the present studies**,** bacteria *S. typhimurium* MIC of 12.70, The compound (**5j**) was found active against the *B. subtilis* MIC of 15.10, *E. coli* MIC of 7.50, *E. faecalis* MIC of 15.50 and *S. typhimurium* MIC of 15.10. The synthesized thiazolidinone derivatives mainly depend on type of substitution on thiazolidinone nucleus. Among these the compounds **3a**, **3e, 3i, 5e** and **5f** were found to be the best fungal activity as they active against the fungal strain *A. oryzae*, *P. chrysogenum*, *F. oxysporum*, *C. albicans*, *A. flavus and A. nigar*. The compound (**5f**) was found to be the good activity as they were specifically active against *A. oryzae*. They are also comparatively active molecules among the series, more potent than standard antifungal drugs Fluconazole and Miconazole with a MIC of 5.36 to MIC of 18.50. These compound (**3a**) MIC of 16.30, 10.30, (**3e**) MIC of 5.50, 5.39, 11.30, 17.30 and (**3i**) MIC of 16.39, 16.50, 17.50. The compound (**5e**), MIC of 6.55 and 5.36 active against *A. oryzae* and *P. chrysogenum*, respectively.

Anticancer activity

All the synthesized compounds were tested for their general cytotoxicity on mammalian cell lines MCF-7, human breast cancer cell line (TABLE 5). This test is performed as previously mentioned MTT colorimetric assay. The cytotoxicity of the compounds was determined by calculating their IC_{50} values, concentration of compound required to inhibit 50% of cell growth compared to untreated control cells. IC_{50} values were presented in micro molar per milliliter (µM/ml). Adriamycin was used as positive control for the comparison of cytotoxicity of synthesized compounds. Assays were performed in triplicate on three independent experiments and they mean is taken as a final reading. The synthesized 24 compounds were screened for their in vitro growth inhibitory activities against two human barest cancer cells line MCF-7 and BT-474, 100 µM/ml by MTT assays method. The results are shown as percentage cytotoxicity after 24 h. The compounds found active in preliminary screening were further studied for their cytotoxic effect on human barest cancer cell line MCF-7 and BT-474 cell lines and the results are expressed as IC_{50}. Among the 24 newly synthesized thiazolidinone screened for their cytotoxic effect on MCF-7 and BT-474 cells, three compounds showed percentage cell death greater against cell lines used. Among the most active four compounds exhibited cell death greater than 50% against both cell lines. The synthesized compounds (**3i**), (**3k**), (**5b**) and (**5k**), showed maximum percentage cell death. The cytotoxicity studies of compound (**3i**), (**3k**), (**5b**) and (**5k**), against MFC-7 and BT-474 cell lines exhibited IC_{50} values are 1.2, 0.7, 1.3, 1.2, 1.6, 1.4, 1.6 and 0.7 µM/ml respectively. The IC_{50} of reference drug Adriamycin against MFC-7 and BT-474 cells was found to be 0.8 and 0.6 µM/ml respectively. The cytotoxicity of all synthesized thiazolidinone mainly depends on type of substitution on thiazolidinone moiety. The compounds with specific groups substituted on aromatic ring attached to thiazolidinone ring showed the highest percentage of cell death.

Structure activity relationship (SAR)

The results of the antimicrobial screening demonstrated some definite and interesting facts about the structural-activity relationship (SAR) of a synthesized Thiazolidinone moiety. In the majority of cases, dependence of the activity profile on structural modifications of the molecule is clear and fascinating. Due to the different types of substitution on aromatic ring

and variation in the activity profile of molecules are also directly attributed to the structural variations. The important highlights of structure-activity relationship are as follows.

Effect of chlorine group: In the present study it is clear that the activity profile of molecule is strongly affected by the branching pattern and chlorine group on aromatic ring. Attachment of a chlorine group at *ortho* and *para* position on aromatic ring. The compounds (**3b**), (**3d**) and (**3g**) inactive against bacterial and fungal strains may be due to its size and electron donating effects of chlorine group.

Effect of hydroxyl group: The compounds (**3f** and **5f**), containing hydroxyl group on aromatic ring at *para* position. The molecule selective active against gram positive bacteria *S. typhimurium* and fungal strain *A. oryzae.* The increase activity of the molecules may be due to the electron donating effect of hydroxyl group.

Effect of phenyl ring: Unsubstituted phenyl ring compound (**3a**) at the Thiazolidinone moiety gives the inactive molecule towards all tested bacterial strains. But the compound (**5a**) shows better activity towards tested bacterial strains like *B. subtilis and S. aureus.* While compound (**3a**) make the molecule active towards fungal strains *A. flavus* and *A. niger*. But the compound (**5a**) shows inactive molecule towards all tested fungal strains. This observation clearly shows that unsubstituted phenyl ring gives the active molecule and towards specific strains.

Highlight of synthesis (Z)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one 5a-l derivatives: (i) Evasion of cumbersome workup procedures. (ii) Excellent yields in shorter reaction time making the process economically lucrative for industrial application, (iii) Opening the horizon for the synthesis of series new **3a-l** and **5a-l** with promising antibacterial, antifungal and anticancer activity which are yet to be explored and exploring them for other biological applications.

Conclusion

In conclusion, we have successfully developed an easy access to a new series of (*Z*)-5-(substituted)-2-(methylthio)thiazol-4(5H)-one **5a-l** derivatives. The mild reaction conditions, good to excellent yields, easy workup, and easily available substrates make the reactions attractive for the preparation of compounds **3a-l** and **5a-l**. *In vitro* anticancer studies revealed that the compounds **3i**, **3k** and **5b**, **5k** are the most active compounds against MCF-7 and BT-474 human breast cancer cell lines. Amongst these, the compounds **3c**, **3f**, **3h**, **3j** and **5a**, **5c**, **5d**, **5e**, **5f**, **5h**, **5j** showed highest antibacterial and antifungal activity among the series. The compounds **3c** and **5e** exhibited significant antibacterial activity against *E. coli*, whereas compound **5f** displayed significant antifungal activity against fungal strains i.e. *A. oryzae*.

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