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Synthesis, characterization and biological activities of 2-aryl-3-substituted-4-thiazolidinones carrying benzothiazole moiety

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ABSTRACT

A new series of 3-substituted-2-aryl-4-thiazolidinones carrying benzothiazole (5a-l) have been synthesized starting from 6-amino benzothiazole. The structures of these newly synthesized compounds were elucidated by elemental analysis, 1H NMR and mass spectral data. Also these compounds were evaluated for their antibacterial activity against bacteria Pseudomonas, Staphylcoccus aureus, Enterococcus, Eschericia coli and antifungal activity against Candida albicans and antioxidant activity by DPPH radical scavenging assay method.

Keywords: thiazolidinone, benzothiazole, DPPH scavenging, antimicrobial

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INTRODUCTION

During recent years there has been considerable interest in the development of novel compounds with anticonvulsant, antidepressant, analgesic, anti-inflammatory, antiallergic, antipsychotic, antimicrobial, antimycobecterial, antitumour, antiviral, antitubercular activities, etc. Most of the Benzoheterocycles such as benzothiazoles, benzimidazoles, benzoxazoles, etc are the important scaffolds for drug design as most of the molecules with these moieties are reported with excellent pharmacological activities. Among these benzoheterocycles, the benzothiazoles have attracted wide attention due to their multiple applications. Recently, a large number of therapeutic agents are developed with the help of benzothiazole core. These molecules have significant uses in the field of medicinal chemistry due to their diverse pharmacological potentialities such as anticancer[1], anti-inflammatory[2], anti-oxidant, antimicrobial[3, 4], anti-convulsant[5, 6], anthelmintic activity[7] etc.

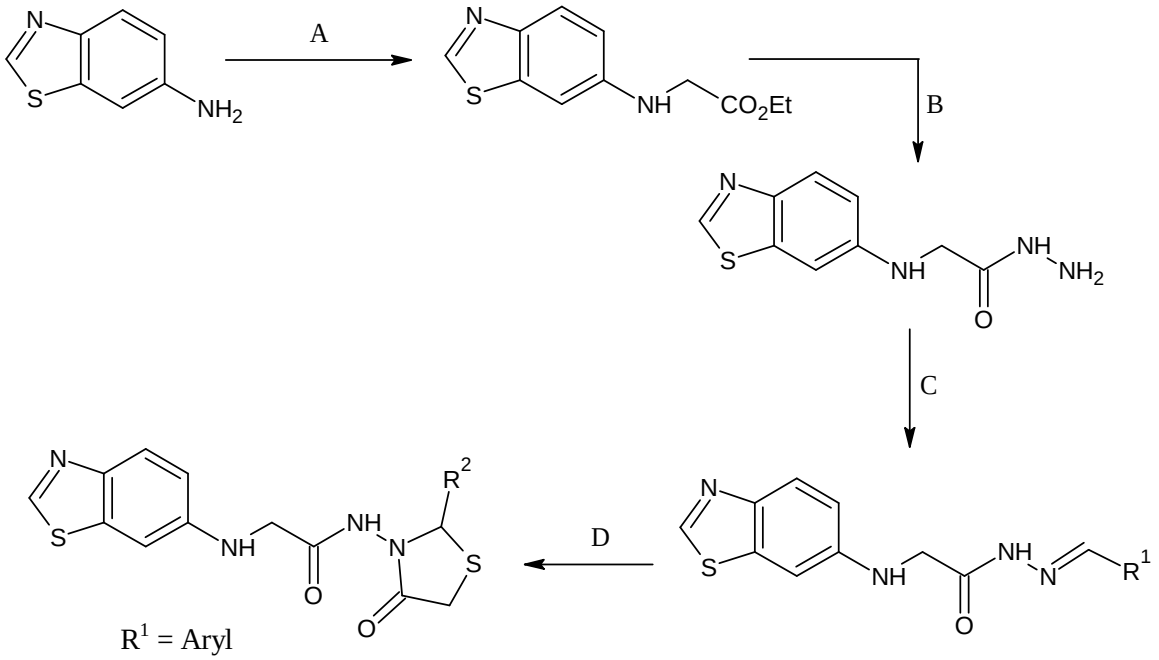
Thiazolidinones and their derivatives are an important class of heterocyclic compounds containing Sulphur and Nitrogen in a five membered ring. The 4-Thiazolidinone ring system also a core structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities such as, anti-cancer[8], anti-HIV[9], anti-microbial[10-13], antioxidant[13], analgesic[14], local anesthetic, anti-inflammatory activities[15, 16], anti-tubercular[17], anthelmintic activity[11] etc.

By reviewing the above literatures we planned to synthesize a series of 2- aryl, 3-substituted 4-Thiazolidinones from Schiff bases carrying benzothiazole moiety **(4a-l)** as outlined in scheme-1. The title compounds 3-substituted-2-aryl-1,3-thiazolidin-4-one **(5a-l)** were obtained by the attack of Sulphur nucleophile on imine carbon followed by intramolecular cyclization with elimination of water.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker AMX-400 (400 MHz) spectrometer using DMSO-d6 as solvent and TMS as an internal standard. All chemical shifts values are reported in δ scale downfield from TMS. Mass spectra of these compounds were recorded Agilent mass spectrometer operating at 20 eV and C, H, N analysis was carried out on a Vario-EL (Elementar-III) model. Homogenecity of the compounds was checked by TLC on silica gel plates. Characterization data of these compounds were tabulated in Table-1

Scheme-1: Synthetic route for thiazolidinone:



Reaction conditions: A-Et_3N/Ethylchloroacetate/THF/65°C; B- $NH_2NH_2.H_2O$/ Ethanol/ 80°C; C-Aromatic aldehyde/ Ethanol/ H_2SO_4/ 80°C; D-Thioglycolic acid/ Toluene/ PTSA/110°C.

Synthesis of *Ethyl 2-(benzo[d]thiazol-6-ylamino)acetate* (2):
A mixture of 6-aminobenzothiazole **(1)** (0.07 mol), Ethylchloroacetate (0.08 mol) and triethylamine (0.14 mol) in presence of tetrahydrofuran was heated under reflux with stirring for ~ 15 h. The reaction mixture was diluted with water at room temperature and then extracted with ethylacetate. The ethylacetate layer was distilled off under reduced pressure, and then recrystallized from methyl tert butyl ether. (Yield: 85%). **^{1}H-NMR: (400 MHz, DMSO-d6):** δ 8.932 (s, 1H, ArH), δ 7.76-7.782 (d, 1H, ArH, J-8.8 Hz), δ 7.095-7.101 (d, 1H, ArH, J-2.4 Hz), δ 6.879-6.907 (dd, 1H, ArH, J-2.4 Hz, 8.8 Hz), δ 6.339-6.370 (t, 1H,-NH-, 6.2 Hz), δ 4.107-4.160 (q, 2H, -CH_2-) δ 3.971-3.987 (d, 2H, -CH_2-, 6.4 Hz), δ 1.188-1.223 (t, 3H, -CH_3, 7.0 Hz).

Synthesis of *2-(benzo[d]thiazol-6-ylamino)acetohydrazide* (3)
A mixture of ethyl 2-(benzo[d]thiazol-6-ylamino)acetate **(2)** (0.055 mol), hydrazine hydrate (0.066 mol), in presence of ethanol was heated under reflux with stirring for ~ 15 h. The reaction mixture was cooled and filtered, washed the product with ethanol, dried. (Yield: 82%) **^{1}H-NMR: (400 MHz, DMSO-d_6)**: δ 9.130 (s, 1H, -CONH-), δ 8.924 (s, 1H, ArH), δ 7.753-7.775 (d, 1H, ArH, J-8.8 Hz), δ 7.05-7.056 (d, 1H, ArH, J-2.4 Hz), δ 6.865-6.897 (dd, 1H, ArH, J-2.4 Hz, 8.8 Hz), δ 6.237-6.267 (t, 1H,-NH-), δ 4.253 (s, 2H, -NH_2), δ 3.694-3.709 (d, 2H, -CH_2-).

***General procedure for the synthesis of Schiff base* (4a-l):**
A mixture of 2-(benzo[*d*]thiazol-6-ylamino)acetohydrazide **(2)** (0.01 mol) and Aromatic aldehyde (0.01 mol) stirred with ethanol in presence of 2-3 drops of sulphuric acid at 65-70˚C for 2-6 hrs. The solid formed was filtered and purified with ethanol. (Yield-70-90%).

General procedure for the synthesis of 3-substituted-2-aryl-1,3-thiazolidin-4-one (5a-l):
A mixture of Schiff base **(5a-l)** (0.01 mol) and Thioglycolic acid (0.02 mol) stirred with Toluene in presence of catalytic amount of p-Toluene sulphonic acid at 110-115˚C for 15-20 hrs. The reaction mass was concentrated under reduced pressure, the concentrated mass was stirred with ethanol. The resulting solid was filtered, washed solid with ethanol, dried. (Yield-55-75%)

2-(benzo[d]thiazol-6-ylamino)-N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)acetamide (5a) (Yield: 75%). **^{1}H-NMR: (400 MHz, DMSO-d_6)**, δ 10.253 (s, 1H, -CONH-), δ 8.934 (s, 1H, -ArH), δ 7.705-7.727 (d, 1H, -ArH, J- 8.8 Hz), δ 7.456-7.478 (d, 2H, -ArH, J- 8.8 Hz), δ 7.149-7.171 (d, 2H, -ArH, J- 8.8 Hz), δ 6.892-6.898 (d, 1H, -ArH, J-2.4 Hz), δ 6.763-6.791 (dd, 1H, -ArH, J-2.4 Hz, 8.8 Hz), δ 6.272-6.3 (t, 1H, -NH-), δ 5.789 (s, 1H, -CH-), δ 3.86-3.904 (q, 1H, Ha of cyclic -CH_2-), δ 3.705-3.744 (t, 3H, -CH_2-, Hb of cyclic -CH_2-)

2-(benzo[d]thiazol-6-ylamino)-N-(2-(3-bromophenyl)-4-oxothiazolidin-3-yl)acetamide (5b) (Yield: 68%), **1H-NMR: (400 MHz, DMSO-d_6)**, δ 10.345 (s, 1H, -CONH-), δ 8.928 (s, 1H, -ArH), δ 7.652-7.73 (m, 2H, -ArH), δ 7.523-7.55 (m, 1H, -ArH), δ 7.275-7.406 (m, 2H, -ArH), δ 6.94-6.945 (d, 1H, -ArH, J-2.0 Hz), δ 6.773-6.801 (dd, 1H, -ArH, J-2.4 Hz, 8.8 Hz), δ 6.28-6.31 (t, 1H, -NH-), δ 5.781-5.784 (d, 1H, -CH-), δ 3.903-3.947 (q, 1H, Ha of cyclic -CH_2-) δ 3.701-3.764 (q, 3H, -CH_2-, Hb of cyclic -CH_2-)

2-(benzo[d]thiazol-6-ylamino)-N-(2-(3-fluorophenyl)-4-oxothiazolidin-3-yl)acetamide (5c) (Yield: 70%), **1H-NMR: (400 MHz, DMSO-d_6)**, δ 10.363 (s, 1H, -CONH-), δ 8.935 (s, 1H, -ArH), δ 7.699-7.721 (d, 1H, -ArH, J- 8.8 Hz), δ 7.15-7.411 (m, 4H, -ArH), δ 6.91-6.915 (d, 1H, -ArH, J-2.0 Hz), δ 6.769-6.797 (dd, 1H, -ArH, J-2.4 Hz, 8.8 Hz), δ 6.329-6.359 (t, 1H, -NH-), δ 5.806 (s, 1H, -CH-), δ 3.904-3.948 (q, 1H, Ha of cyclic -CH_2-), δ 3.703-3.761 (q, 3H, -CH_2-, Hb of cyclic -CH_2-)

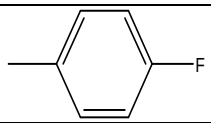
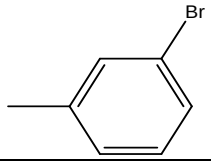
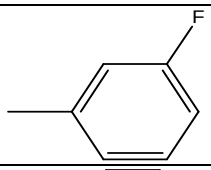
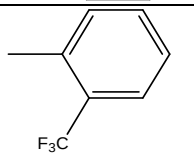
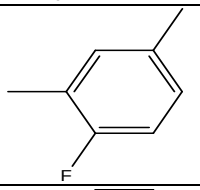
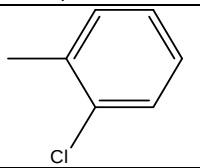
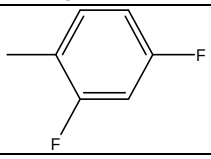
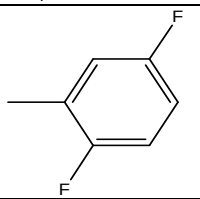
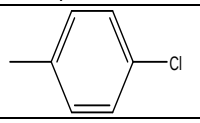
2-(benzo[d]thiazol-6-ylamino)-N-(2-(2-fluoro-5-methylphenyl)-4-oxothiazolidin-3-yl) acetamide (5e) (Yield: 72%), **1H-NMR: (400 MHz, DMSO-d_6)**, δ 10.459 (s, 1H, -CONH-), δ 8.933 (s, 1H, -ArH), δ 7.691-7.72 (d, 1H, -ArH, J- 8.7 Hz), δ 7.303-7.334 (dd, 1H, -ArH, J- 2.1 Hz, 7.2 Hz), δ 7.036-7.202 (m, 2H, -ArH), δ 6.925-6.932 (d, 1H, -ArH, J-2.1 Hz), δ 6.773-6.81 (d, 1H, -ArH, J- 2.3 Hz, 8.9 Hz), δ 6.338-6.378 (t, 1H, -NH-), δ 5.995-5.96 (d, 1H, -CH-), δ 3.719-3.914 (m, 4H, -CH_2-,Ha and Hb of cyclic -CH_2-), δ 2.251 (s, 3H, -CH_3)

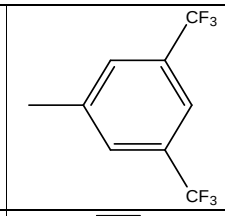
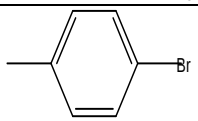
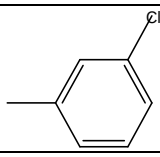
2-(benzo[d]thiazol-6-ylamino)-N-(2-(2,4-difluorophenyl)-4-oxothiazolidin-3-yl)acetamide (5g) (Yield: 66%), **1H-NMR: (300 MHz, DMSO-d_6),** δ 10.409 (s, 1H, -CONH-), δ 8.938 (s, 1H, -ArH), δ 7.7-7.729 (d, 1H, -ArH, J- 8.7 Hz), δ 7.54-7.62 (m, 1H, -ArH), δ 7.037-7.253 (m, 2H, -ArH), δ 6.892-6.9 (d, 1H, -ArH, J-2.4 Hz), δ 6.76-6.797 (dd, 1H, -ArH, J- 2.4 Hz, 8.7 Hz), δ 6.338-6.379 (t, 1H, -NH-), δ 5.954-5.958 (d, 1H, -CH-), δ 3.72-3.912 (m, 4H, -CH_2-, Ha and Hb of -CH_2-)

2-(benzo[d]thiazol-6-ylamino)-N-(2-(2,5-difluorophenyl)-4-oxothiazolidin-3-yl)acetamide (5h) (Yield: 68%), **1H-NMR: (400 MHz, DMSO-d_6)**, δ 10.460 (s, 1H, -CONH-), δ 8.94 (s, 1H, -ArH), δ 7.705-7.727 (d, 1H, -ArH, J- 8.8 Hz), δ 7.39-7.426 (dd, 1H, -ArH, J- 5.8 Hz, 8.9 Hz), δ 7.223-7.263 (m, 2H, -ArH), δ 6.939-6.944 (d, 1H, -ArH, J-2.0 Hz), δ 6.783-6.811 (dd, 1H, -ArH, J- 2.4 Hz, 8.8 Hz), δ 6.353-6.385 (t, 1H, -NH-), δ 5.966 (s, 1H, -CH-), δ 3.914-3.958 (q, 1H, Ha of cyclic -CH_2-) δ 3.729-3.797 (m, 3H, -CH_2- and Hb of -CH_2-)

2-(benzo[d]thiazol-6-ylamino)-N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)acetamide (5i) (Yield: 70%), **1H-NMR: (400 MHz, DMSO-d_6)**, δ 10.341 (s, 1H, -CONH-), δ 8.938 (s, 1H, -ArH), δ 7.699-7.721 (d, 2H, -ArH, J- 8.8 Hz), δ 7.37-7.476 (m, 4H, -ArH), δ 6.88-6.885 (d, 1H, -ArH, J-2.0 Hz), δ 6.754-6.782 (dd, 1H, -ArH, J-2.2 Hz, 8.9 Hz), δ 6.335-6.364 (t, 1H, -NH-), δ 5.779 (s, 1H, -CH-), δ 3.87-3.914 (q, 1H, Ha of cyclic -CH_2-) δ 3.707-3.746 (q, 3H, -CH_2- and Hb of cyclic -CH_2-)

Table-I: Characterization data of (5a-l)

Comp. No	R_1	Mol. formula & Mol. wt	m/z value	MP (°C)	Elemental analysis % Found (Calculated)
5a		$C_{18}H_{15}FN_4O_2S_2$ 402.47	403.1	205-210	C: 53.65 (53.72) H: 3.78 (3.76) N: 13.97 (13.92)
5b		$C_{18}H_{15}BrN_4O_2S_2$ 463.37	463.0	225-230	C: 46.69 (46.66) H: 3.27 (3.26) N: 12.13 (12.09)
5c		$C_{18}H_{15}FN_4O_2S_2$ 402.47	403.1	235-240	C: 53.70 (53.72) H: 3.79 (3.76) N: 13.9 (13.92)
5d		$C_{19}H_{15}F_3N_4O_2S_2$ 452.47	453.1	230-235	C: 50.4 (50.43) H: 3.35 (3.34) N: 12.4 (12.38)
5e		$C_{19}H_{17}FN_4O_2S_2$ 416.49	417.1	215-219	C: 54.85 (54.79) H: 4.09 (4.11) N: 13.44 (13.45)
5f		$C_{18}H_{15}ClN_4O_2S_2$ 418.92	420.0	215-220	C: 51.65 (51.61) H: 3.63 (3.61) N: 13.41 (13.37)
5g		$C_{18}H_{14}F_2N_4O_2S_2$ 420.46	421.1	175-180	C: 51.44 (51.42) H: 3.37 (3.36) N: 13.3 (13.33)
5h		$C_{18}H_{14}F_2N_4O_2S_2$ 420.46	421.1	215-220	C: 51.47 (51.42) H: 3.40 (3.36) N: 13.28 (13.33)
5i		$C_{18}H_{15}ClN_4O_2S_2$ 418.92	419.3	201-206	C: 51.55 (51.61) H: 3.66 (3.61) N: 13.4 (13.37)

5j		$C_{20}H_{14}F_6N_4O_2S_2$ 520.47	521.0	252-257	C: 46.22 (46.15) H: 2.79 (2.71) N: 10.7 (10.76)
5k		$C_{18}H_{15}BrN_4O_2S_2$ 463.37	463.0	195-200	C: 46.56 (46.66) H: 3.35 (3.26) N: 12.17 (12.09)
5l		$C_{18}H_{15}ClN_4O_2S_2$ 418.92	419.3	231-236	C: 51.65 (51.61) H: 3.69 (3.61) N: 13.45 (13.37)

Biological activity:

Antimicrobial activity:

The newly synthesized compounds were screened for their antibacterial activity against four bacterial strains, namely *Pseudomonas*, *Eschericia coli (*Gram negative bacilli), *Enterococcus*, *Staphylococcus aureus (*Gram positive cocci) by Agarwell diffusion method by dissolving compounds in DMSO (Dimethyl sulfoxide). Ciprofloxacin was used as the standard. Also the compounds were screened for antifungal studies against fungus *Candida albicans* using Flucanazol as standard drug. The antibacterial and antifungal activities were evaluated by measuring zone of inhibition surrounding the compounds. The results of antibacterial and antifungal activities are summarized in Table-II.

Table-II: Antimicrobial activities of compounds 5a-l

Comp. No	Antibacterial				Antifungal
	Pseudomonas	**S. *aureus***	**Enterococcus**	**E *coli***	**C *albicans***
5a	13mm	13mm	9mm	10mm	-
5b	11mm	-	8mm	-	-
5e	12mm	13mm	10mm	10mm	-
5f	10mm	-	-	-	-
5g	8mm	11mm	-	-	8mm
5h	9mm	12mm	-	-	10mm
5i	-	-	-	-	11mm
Ciprofloxacin (Std)	24mm	24mm	23mm	23mm	-
Flucanazol (Std)	-	-	-	-	22mm
Solvent control	-	-	-	-	-

Antioxidant activity

The free radical-scavenging activity of the synthesized molecules was measured in terms of hydrogen donating or radical scavenging ability using the stable radical DPPH. The reduction capacity of DPPH radicals was determined by the decrease in its absorbance at 517nm, which is induced by antioxidants. This was expressed as the inhibition percentage, and butylated hydroxyanisole (BHA) as standard. All tests were performed in triplicate and the results were expressed as mean values ± standard deviations. The DMSO sample of compounds at 100 µg/mL was diluted to 3mL using Ethanol, this was mixed with the ethanolic 2,2-diphenyl-1-picrylhydrazyl (DPPH) solution (1 mL, 0.5 mM). The mixed solution was incubated at room temperature for 30 min, and then absorbance was measured immediately at 517 nm by using UV-visible spectrophotometer. The percentage of scavenging has been calculated by using the following formula and the results are shown in Table III.

$$\% \text{ Inhibition} = \left(\frac{(Ac - As)}{Ac} \times 100 \right)$$

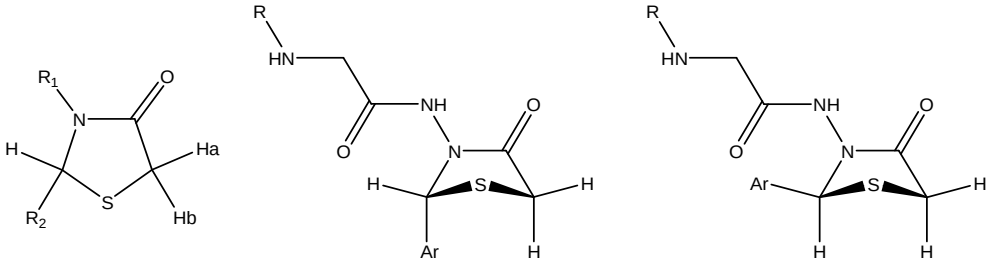
Where Ac is the absorbance of the control (blank, without test sample) and As is the absorbance of the test samples

Table-III: Percentage inhibition of compounds (5a-l) on DPPH radical

Comp. No	Percentage inhibition
5a	18.09±0.15
5b	17.91±0.20
5c	13.04±0.12
5d	21.13±0.28
5e	17.73±0.18
5f	21.94±0.29
5g	3.56±0.62
5h	5.75±0.11
5i	24.37±0.05
5j	34.78±0.22
5k	45.92±0.15
5l	32.93±0.11
BHA	25.02±0.03

RESULTS AND DISCUSSION

The formation of 3-substituted-2-aryl-1,3-thiazolidin-4-one **(5a-l)** were confirmed by the spectral and analytical data. Theoretically, in the case of 2- aryl, 3-substituted 4-thiazolidinones two diastereoisomers (Fig-**I** and **II**) are possible, and preferred configuration **(I)** is that in which the C2 proton and one of the methylene proton at C5 are in cis 1,3-diequitorial relationship[18], due to the fact that the phenyl groups prefers the axial orientation to avoid the steric crowding with N3 substituents, however this also depends on the nature of substituents at N3 position. In the 1H NMR spectrum the proton at C2 appeared as a singlet in the range of 5.7-6 ppm, and in few cases (5b,e,f,g) this proton appeared as doublet with 1.2 Hz. Ha and Hb at C5 appears as separate doublets/ doublet of doublet in the range of 3.7-4 ppm. The mass spectrum of compound is consistent with that of molecular formula of the compound.



I **II**

Compounds 5a and 5e showed moderate to good inhibitory activity against all the four bacteria, 5b showed moderate to good inhibitory activity against Pseudomonas and Enterococcus, 5g and 5h showed moderate to good inhibitory activity against Pseudomonas and S *aureus* and compound 5f showed moderate inhibitory activity against Pseudomonas. And 5g, 5h, 5i showed moderate inhibitory activity against fungus C *albicans.* Also many of them displayed significant antioxidant property comparable with that of standard BHA.

CONCLUSION

The data of these antimicrobial and antioxidant studies indicate the possibility of obtaining good molecules of 4-Thiazolidinones carrying benzothiazole by varying the substitution at C2 position. And derivatives of 4-Thiazolidinone **(5)** appear to be suitable moiety in the field of medicine.

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