Synthesis, Biological Screening and Antioxidant Activities of Some Novel 5-Arylidene-4-Thiazolidinone Derivatives

N. J. SIDDIQUI[1], MOHAMMAD IDREES[1] , B. R. ABHARE[2]

[1]Department of Chemistry, Government Institute of Science, Nagpur (M.S.), INDIA
[2]Department of Chemistry, Government Science College, Gadchiroli (M.S.), INDIA
Corresponding author e-mail: naquiphd.2010@gmail.com, Mob: 09422153242

Abstract

*Condensation of 1-(5-chloro-3-methylbenzofuran-2-yl)ethanone **(1)** with 4-phenyl thiosemicarbazide **(2)** afforded 1-(1-(5-chloro-3-methylbenzofuran-2-yl)ethylidene)-4-phenylthiosemicarbazide **(3).** On its treatment with ethyl bromoacetate, sulfur atom of 4-phenylthiosemicarbazide **(3)**, underwent nucleophilic attack at C_2 of the ethyl bromoacetate followed by cyclocondensation reaction between the nitrogen containing hydrogen and the ester moiety to furnish the desired thiazolidinones **(4),** which was subsequently reacted with different aryl aldehydes **(a-e)** yielded corresponding 5-Arylidene-4-thiazolidinone derivatives **(5a-e).**The structures of the novel compounds were characterized by CHN&S analysis and various spectroscopic techniques including IR, ^{1}H NMR, and Mass spectra. Synthesized compounds were screened for antimicrobial activity against E. coli, S. aureus, B. thurengienesis and E. aerogenes. The zone of inhibition was determined and compared with Chloramphenicol as a reference drug. Simultaneously these compounds were also studied for their antioxidant activities. Some of the newly synthesized compounds showed promising antimicrobial and antioxidant activity.*

Keywords: 4-thiazolidinone, 5-arylidene-4-thiazolidinone, antibacterial, antioxidant

Introduction

4-Thiazolidinones belong to an important group of heterocyclic compounds which are extensively explored for their applications in the field of medicine. Numerous reports appear in the literatures that highlights its chemistry and use. Several protocols are available in literature that allows the synthesis of 4-thiazolidinone which involves conventional one pot[1], two pot synthesis and microwave[2] as well as syntheses of 2-imino, amino, thione or 2-disubstituted 4-thiazolidinones derivatives[3-7]. Recently, some researchers[8-14] has used new methodology for thiazolidinone synthesis. Similarly, thiazolidinones have shown interesting biological activity profiles hence have emerged as an important class of compound of therapeutic importance. 4-Thiazolidinones, substituted at 2 and 3 position are reported to exhibit a wide variety of biological activities such as antiviral agents acting as NNRTIs with minimal cytotoxicity[15-16] antibacterial[17], antitubercular[18], anticancer[19], insecticidal[20], antifungal[21], cardiovascular[22], mosquito repellent[23], antiviral[24], antimicrobial[25-27], antiamalarial[28], anticonvulsant[29], antiinflammatory[30] , antithyroid and amoebicidal[31] antioxidant[32] activities. Recently, 4-thiazolidinone derivatives have reported as novel class of HIV-integrase inhibitors[33] as well as CFTR inhibitor[34-35] in rodents. More recently thiazolidinone library are found as agonists of the follicle stimulating hormone receptor[36]. Bearing in mind, the biological implication of this class of compounds, it provoked us to synthesize the target compounds and view for their spectral characterization. The reaction series of 4-thiazolidones with different aromatic aldehydes for synthesizing 5-arylidene 4-thiazolidones derivatives was found to be appealing. Thus, in

this communication we report the synthesis of some novel 5-arylidine 4-thiazolidone derivatives and simultaneously carry out the biological screening and antioxidant activities of the synthesized compounds.

Experimental Work

^{1}H NMR spectra were recorded using tetramethylsilane as internal standard and chemical shifts being reported in parts per million (δ) relative to TMS. Chemical Shifts are given in parts per million (ppm). FT-IR spectra were recorded with ν max in inverse centimeters. The reactions were monitored by E. Merck TLC aluminum sheet silica gel 60 F254 and visualizing the spot in UV Cabinet and iodine chamber. The compounds were analyzed for carbon, hydrogen and nitrogen and the results obtained were in ± 0.04% of the calculated values.

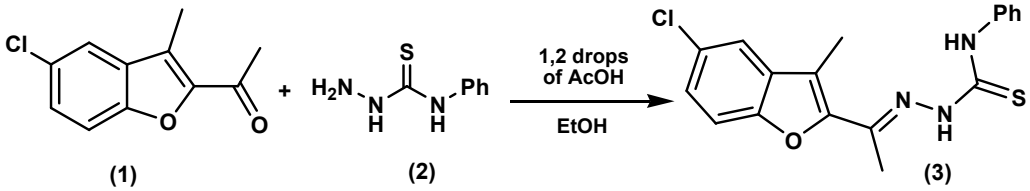
Material and Methods

Chemicals used for the synthesis were of AR grade of Merck, S.D.Fine and Aldrich. Purification of compounds was done by recrystallization method by using suitable solvent. The melting points were recorded in open capillary in paraffin bath and are uncorrected. IR spectra were recorded on a Shimadzu IR Spectrophotometer (KBr, ν max in cm^{-1}). ^{1}H NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO-d_6 as solvent. Positive-ion Electro Spray Ionization (ESI) mass spectra were obtained with a Waters Micromass Q–TOF Micro, Mass Spectrophotometer. Elemental (CHN) analysis was done using Thermo Scientific (Flash-2000).

Preparing of starting material: The method required for the preparation of starting material such as 1-(5-chloro-3-methylbenzofuran-2-yl)ethanone **(1)** and 4-phenylthiosemicarbazide **(2)** were taken from the published literature.

Synthesis of 1-(1-(5-chloro-3-methylbenzofuran-2-yl)ethylidene)-4-phenyl thiosemicarbazide (3): A mixture of 1-(5-chloro-3-methylbenzofuran-2-yl)ethanone (**1**) **(**10 mmol) and 4-phenyl thiosemicarbazide **(2)** (10 mmol) in ethanol (30 mL) and acetic acid (1 mL) was refluxed for 2h. The separated solid was filtered off and recrystallized from acetic acid to give compounds **3.** The structure of synthesized **3** was characterized by physicochemical analysis: m.pt 210°C, Yield-78%, Solubility- 1,4-Dioxane and Recrystallization solvent-acetic acid.

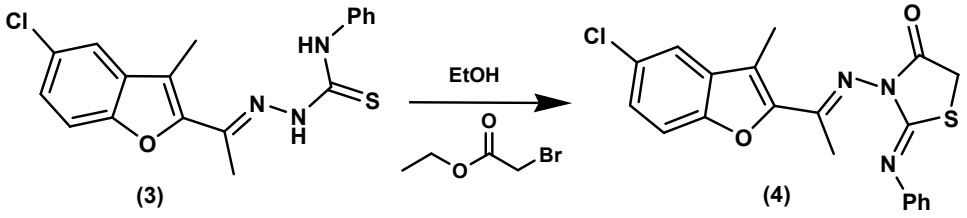
Reaction Scheme : 1



(1) (2) (3)

Synthesis of 3-(-1-(5-chloro-3-methylbenzofuran-2-yl)ethylideneamino)-2-(phenylimino) thiazolidin-4-one (4):A mixture of **3 (**10 mmol), ethyl bromoacetate (10 mmol) and fused sodium acetate (20 mmol) in ethanol (20 mL) was refluxed for 2h, the obtained product was collected by filtration, washed with water and recrystallized from glacial acetic acid to give compound **4.**

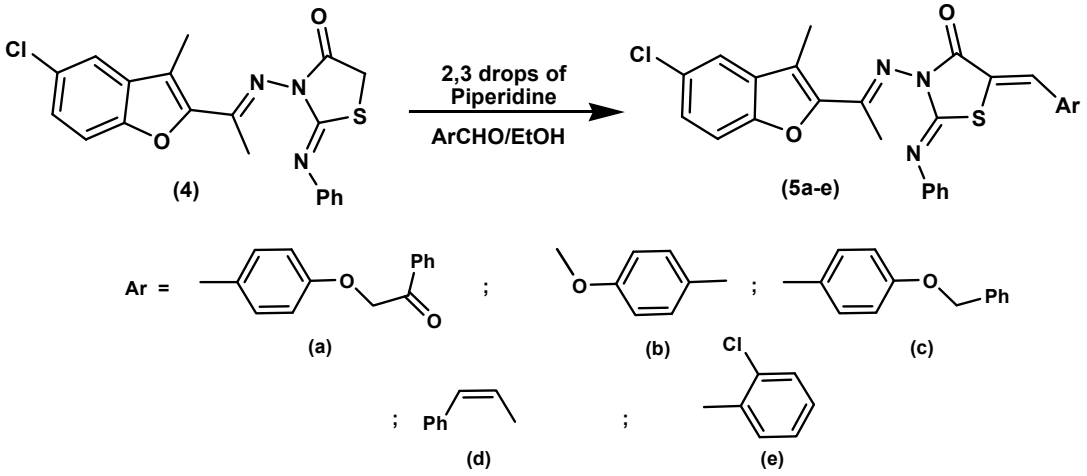
Reaction Scheme : 2



Compound 4: Physical, Spectral and analytical data: Molecular formula $C_{20}H_{16}ClN_3O_2S$, Fluffy pale yellow solid ,Yield 81.2 %, Melting point 239°C , Solubility 1,4-Dioxane, Recrystallization solvent : Acetic acid. Spectral Analysis: IR (cm^{-1}): 3061, 3014 (Ar-H str.), 2921, 2969, 2950, 2848 (CH_3, CH_2 str.), 1721 (C=O str.), 1590 (C=N str.), 1548,1498 (C=C str.), 1242 (C-O-C sym.str.), 1031 (C-O-C asym. str.), 696,660 (C-S-C), 1130,1096 (C-N str.); ^{1}H NMR (DMSO-d_6) δ: 2.23 (s, 3H, $\underline{CH_3}$), 2.54 (s, 3H, CH_3), 4.11 (s, 2H, -CH_2), 7.33-7.72 (m, 8H, Ar-H).

General procedure for synthesis of 5-(4-(2-oxo-2-phenylethoxy)benzylidene)-3-(1-(5-chloro-3-methylbenzofuran-2-yl)ethylideneamino)-2-(phenylimino)thiazolidin-4-one (5a): A mixture of **4** (10 mmol) and 4-(2-oxo-2-phenylethoxy)benzaldehyde (10 mmol) in acetic acid (20mL) in the presence of catalytic amount of piperidine (1mL) was refluxed for 6h , the resulting solid was collected by filtration and recrystallized from 1,4-dioxane to give compound (**5a).**

Reaction Scheme : 3

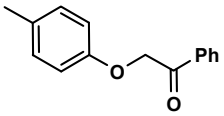
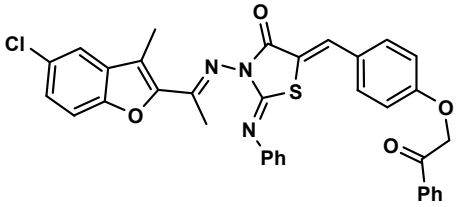
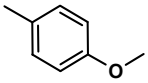
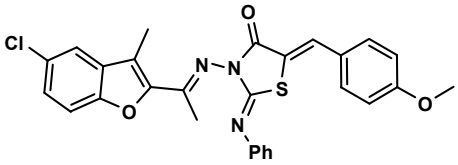
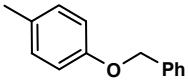
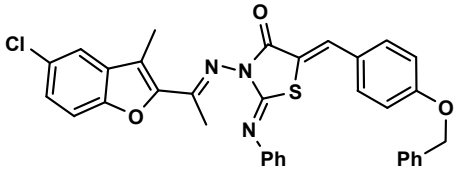
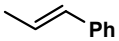
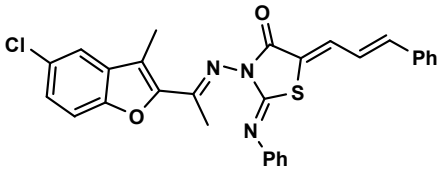
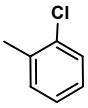
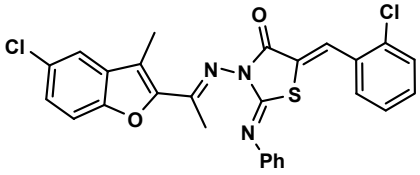


Similarly, (**5b-e)** were synthesised from 4-anisaldehyde **(b)**, 4-benzyloxybenzaldehyde **(c)**, cinnamaldehyde **(d)**, 2–chlorobenzaldehyde **(e)** with **4** by adopting the same procedure as for **5a.**

Physical, Spectral and analytical data: 5-(4-methoxybenzylidene)-3-(-1-(5-chloro-3-methylbenzofuran-2-yl)ethylideneamino)-2-(phenylimino) thiazolidin-4-one **(5b):** Molecular formula $C_{28}H_{22}ClN_3O_3S$, Yellow crystalline solid ,Yield 83.5 %, Melting point 286°C, Solubility Hot DMF, Recrystallization solvent : 1,4-Dioxane, IR (cm^{-1}): 3063,3039 (Ar-H str.), 2959,2919,2840 (CH_3 str.), 1583 (C=N str.), 1536,1511,1452 (C=C str.), 1262,1236 (C-O-C sym. str.),1019,1067 (C-O-C asym. str.), for thiazolidine

ring, 1702 (C=O str.), 1164,1019 (C-N), 687,668 (C-S-C),1374,1362,1315,1300 (Arylidene,=CH i.p.),857,820 (Arylidene, =CH o.o.p.); ^{1}H NMR (DMSO-d_6) δ: 2.50 (s, 3H, $\underline{CH_3}$), 3.38 (s, 3H, -CH_3), 3.58 (s, 3H, -OCH_3), 6.86-7.87 (m, 13H, ArH + Other H); MS : 516 $[M]^+$, 517 $[(M+H)^+]$, 518 [M+2], 539 $[(M + Na)^+]$; Calculated: C, 65.16; H, 4.26; N, 8.15; S, 6.21% Found: C, 65.18; H, 4.30; N, 8.10; S, 6.24%.

Table 1: Physical Data of 5-Arylidene-4-Thiazolidinone Derivatives (5a-e)

Entry	-Ar	Product 5-arylidene 2-(phenylimino) thiazolidin-4-one derivatives	Physical Data		
5a			**M.F**	**:**	**$C_{35}H_{26}ClN_3O_4S$**
			Colour	:	Yellow solid
			Yield	:	84.33%
			M.Pt	:	270°C
			Recys.S	:	1,4-Dioxane
			Solubility	:	Hot DMF
5b			**M.F**	**:**	**$C_{28}H_{22}ClN_3O_3S$**
			Colour	:	Yellow solid
			Yield	:	83.5 %
			M.Pt	:	286°C
			Recys.S	:	Hot DMF
			Solubility	:	1,4-Dioxane
5c			**M.F**	**:**	**$C_{34}H_{26}ClN_3O_3S$**
			Colour	:	Yellow solid
			Yield	:	81.5 %,
			M.Pt	:	292°C
			Recys.S	:	Hot DMF
			Solubility	:	1,4-Dioxane
5d			**M.F**	**:**	**$C_{29}H_{22}ClN_3O_2S$**
			Colour	:	Yellow solid
			Yield	:	79.23 %,
			M.Pt	:	286°C
			Recys.S	:	Hot DMF
			Solubility	:	1,4-Dioxane
5e			M.F	:	**$C_{27}H_{19}Cl_2N_3O_2S$**
			Colour	:	Yellow solid
			Yield	:	76.88 %,
			M.Pt	:	276°C °C
			Recys.S	:	Hot DMF
			Solubility	:	1,4-Dioxane

Antibacterial Activity: The novel synthesized heterocyclic compounds were screened for their *in vitro* antimicrobial activity using disc-diffusion method against two Gram positive bacterial strains, *B. thurengienesis* and *S. aureus* and two Gram negative strains, *E. coli* and *E. aerogenes*. Chloramphenicol was used as standard drugs for bacteria.

Procedure for the determination of Zone of Inhibition by Agar disc-diffusion method: Test solutions were prepared with known weight of compound in dimethyl sulphoxide (DMSO) and diluted suitably to give the resultant concentration of 31, 62, 125, 250, 500 and 1000µg/mL. Whatmann no. 1 sterile filter paper discs (6 mm) were impregnated with solution and allowed to dry at room temperature. *In vitro* antibacterial activity was determined by using Mueller Hinton Agar obtained from Himedia Ltd., Mumbai. Twenty-four hours old culture of selected bacterial strain was mixed with physiological saline and the turbidity was corrected by adding sterile physiological saline and sub cultured on Sabouraud Dextrose and suspended in sterile distilled water to an absorbance of 0.6 at 450 nm. Petri plates were prepared by pouring 10 mL of Mueller Hinton Agar for bacteria containing microbial culture was allowed to solidify. The discs were then applied and the plates were incubated at 37°C for 24h (bacteria) and the inhibition zone was measured as diameter in four directions and expressed as mean. The results were compared using Chloramphenicol as a standard antibacterial agent. The results of antibacterial activity (i.e. Zone of inhibition in mm) of the synthesized compounds are given in the Table **2-3.**

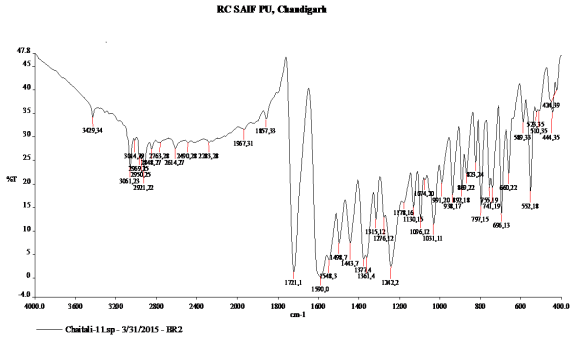
Antioxidant Activity: The reducing power in-vitro model was used to evaluate antioxidant activity according to the method of Oyaizu[37]. This method is based on the principle of increase in the absorbance of the reaction mixture, indicates increase in the antioxidant activity hence increasing reducing power of the samples. In this method antioxidant compound gives a colored complex with potassium ferricyanide, trichloroacetic acid and ferric chloride, which is measured at 700 nm.

Procedure: The standard drug and test compounds were dissolved in dimethyl formamide so as to get different concentrations (20µg/mL to 100µg/mL). This was mixed with 2.5mL of (pH 6.6) 0.2 mol phosphate buffer and 2.5mL of 1 % potassium ferricyanide. The mixture was incubated at 50°C for 20 minutes. 2.5mL of 10 % trichloroacetic acid was added to the mixture, which was then centrifuged for 10 minutes at 1000 rpm. 2.5mL upper layer of solution was mixed with 2.5mL of distilled water and 0.5mL of 0.1% ferric chloride. The absorbance was measured at 700nm. The absorbance of the blank was also measured in similar manner. The results were compared with ascorbic acid, which was used as a reference standard antioxidant. Antioxidant activities of some representative compounds are given in Table **4**.

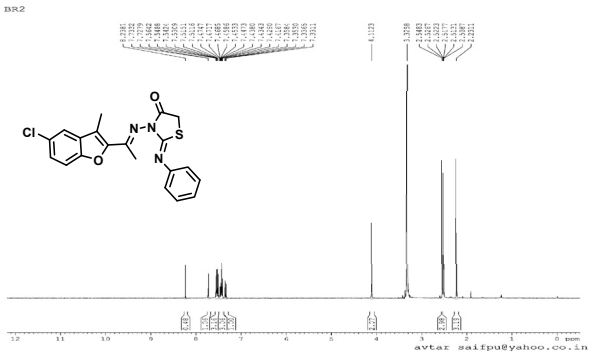
Result and Discussions

The common synthetic route for the synthesis of final products **3**, **4** and **5a-e** are summarized in reaction schemes **1-3**. The reactions completion and purity of all the synthesised compounds were monitored by TLC. The identities of the newly synthesized compounds have been identified on the basis of their elemental analysis and spectral data[38] such as IR, ^{1}H NMR and Mass spectral studies. The required 4-phenylthiosemicarbazide **(3)** was synthesized by refluxing mixture of 1-(5-chloro-3-methylbenzofuran-2-yl)ethanone **(1)** with 4-phenyl thiosemicarbazide **(2)** in presence of acetic acid in ethanol. This 1-(1-(5-chloro-3-methylbenzofuran-2-yl)ethylidene)-4-phenylthiosemicarbazide **(3)** underwent cyclization or ring closure on treatment with one equivalent ethyl bromoacetate giving the 3-(-1-(5-chloro-3-methylbenzofuran-2-yl)ethylideneamino)-2-(phenylimino)thiazolidin-4-one **(4)**, this reaction is assumed

to progress via imine formation in the first step followed by attack of sulphur nucleophile on the imine carbon and finally intramolecular cyclization with the elimination of water. The IR spectra of **4** showed stretching bands at 1721 cm^{-1} due to the appearance of –CO group in 4-thiazolidinone ring which is in the accordance with the literature, similarly, the ^{1}H NMR spectrum showed a singlet at δ 4.11 ppm for $–CH_2$ protons and multiplet in the range of δ 7.33 to 7.72 ppm due to eight aromatic protons confirms the formation of **4** (Scheme **2)**.



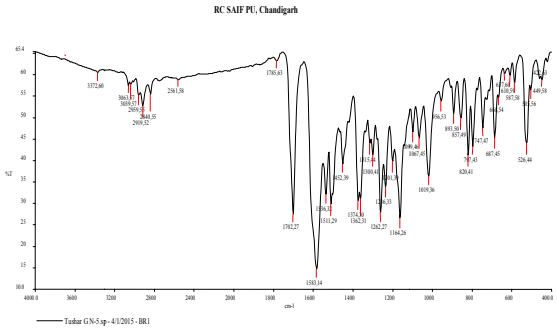
IR Spectra of 4



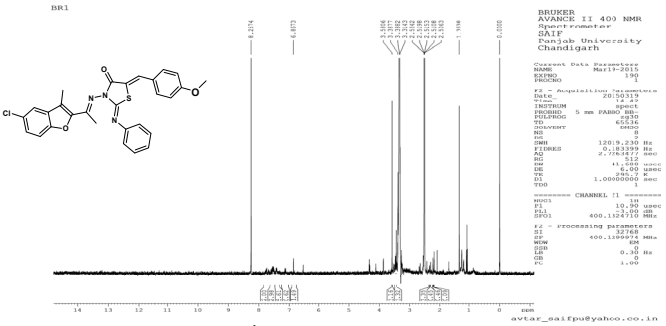
^{1}H NMR Spectra of 4

A series of some novel 5-arylidine 4-thiazolidinone derivatives **(5a-e)** were synthesized by refluxing 3-(-1-(5-chloro-3-methylbenzofuran-2-yl)ethylideneamino)-2-(phenylimino) thiazolidin-4-one **(4)** with various aromatic aldehydes **(a-e)** in presence of piperidine as base in ethanol. The IR spectrum of **5b** indicated the appearance of characteristic absorption bands at 1720 cm^{-1} for C=O group, at 687,668 cm^{-1} due C-S-C stretch and at 1164,1019 cm^{-1} for C-N stretch in 4-thiazolidinone ring and also showed C-O-C stretching bands at 1123, 1140 and 1095 cm^{-1}. Furthermore, the IR spectrum of **5b** also exhibited expected various absorption bands due to aliphatic, aromatic and other region as given in its experimental section. Further support for the formation of **5b** came from ^{1}H NMR spectra, indicated that the signal associated with $–CH_2$ protons as singlet at δ 4.11 ppm for compound **4** has been completely disappeared besides, appearance of singlet at δ 6.86 ppm for –CH and other signals associated with aromatic protons appeared to match the expected signals (see experimental section), therefore ^{1}H NMR spectra of **5b** showed that condensation of **4** with anisaldehyde has taken place to form **5b** (Scheme **3**). Structure of **5b** having molecular weight 516, was further confirmed by mass spectrum which showed a molecular ion peak at 516 $[M]^+$ and 539 $[(M+Na)^+]$, the percentage of elements i.e. C, H and N, found corresponded with the calculated values for **5b**. The physical data of synthesized compounds **5a-e** is shown in the Table No. **1**

Antimicrobial activity: All five synthesized 5-arylidine-4-thiazolidinone derivatives **(5a-e)** were screened for antimicrobial activity. Table **1**, shows the inhibition zone determined for **5a-e** at different concentrations from 62.5-500 µg/mL using as Chloramphenicol as the standard drug. Data obtained revealed that the test compounds **5a, 5d** showed moderate to high activity against *S. aureus* whereas **5b** showed antibacterial activity against *B. thurengienesis* and compounds **5b, 5d** and **5e** showed moderate to high activity against *E. coli* while compounds **5b** and **5c** showed moderate to high activity at different concentrations against *E. aerogenes* compared with standard drug. The obtained data of activity of these tested compounds is shown in Table **2-3.**



IR Spectra of 5b



^{1}H NMR Spectra of 5b

Antioxidant activity: All the synthesized compounds (**3, 4** and **5a-e**) were assessed for their *in-vitro* antioxidant activities using the free radical reducing power at various concentrations. Ascorbic acid (AA) was used as reference standard. The antioxidant activity of tested compounds **5a, 5b** and **5c** and showed significant activity at the concentration 20-100 µg/mL, the results reveal that **5d** and **5e** possess moderate activity and **4** gives mild antioxidant activity at the given concentrations. The obtained data of activity of these tested compounds is shown in Table **4**.

Table 2: Biological Activity of 5-Arylidene-4-Thiazolidinone Derivatives (5a-e)

Zone of Inhibition (in mm) for Gm +ve Pathogenic Bacteria								
	S. aureus				*B. thurengienesis*			
Conc.→	500	250	125	62.5	500	250	125	62.5
Compd. ↓	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL
5a	27	30	24	19	17	16	15	13
5b	25	22	14	18	23	27	21	16
5c	20	24	10	17	19	17	19	18
5d	15	21	22	25	12	14	16	13
5e	24	16	20	17	15	19	12	20
Std.	30	27	21	20	20	21	16	16

Table 3: Biological Activity of 5-Arylidene-4-Thiazolidinone Derivatives (5a-e)

Zone of Inhibition (in mm) for Gm -ve Pathogenic Bacteria								
	S. aureus				*B. thurengienesis*			
Conc.→	500	250	125	62.5	500	250	125	62.5
Compd. ↓	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL
5a	13	17	14	10	14	16	13	12
5b	22	19	22	09	15	20	21	12
5c	18	13	17	16	19	22	17	12
5d	17	21	11	23	13	12	12	14
5e	10	18	12	9	7	15	10	11
Std.	20	18	17	11	16	17	16	15

Table 4 : Antioxidant Activity of 3, 4 and 4-Thiazolidinone Derivatives (5a-e)

Compound Code	Absorbance					%Increase in Absorbance				
	20 µg/mL	**40** µg/mL	**60** µg/mL	**80** µg/mL	**100** µg/mL	**20** µg/mL	**40** µg/mL	**60** µg/mL	**80** µg/mL	**100** µg/mL
Control			0.100					--		
(Std: AA)	0.148	0.157	0.162	0.176	0.183	48	57	62	76	83
3	0.132	0.145	0.152	0.159	0.178	32	45	52	59	78
4	0.145	0.150	0.160	0.167	0.159	45	50	60	67	59
5a	0.142	0.160	0.173	0.181	0.183	42	60	73	81	83
5b	0.143	0.158	0.164	0.179	0.182	43	58	64	79	82
5c	0.153	0.157	0.170	0.175	0.179	53	57	70	75	79
5d	0.152	0.155	0.160	0.170	0.189	52	55	60	70	89
5e	0.135	0.147	0.158	0.175	0.181	35	47	58	75	81

Conclusion

We have reported here in synthesis of some new heterocyclic 5-arylidine 4-thiozolidinone **(5a-e)** from 4-thiazolidinone **(4)** and different aryl aldehydes via condensation in ethanol and catalytic amount of piperidine in good yield. Antimicrobial screening of the synthesized compounds were done and found to possess moderate to high activity against selected strains of bacteria. Antioxidant activity of the synthesized compounds also showed moderate to good activity.

References

[1] T. Srivastava, W. Haq, S. B. Katti, *Tetrahedron*, 2002, 58, 7619–7624. (b) R. M. Shaker. *Phosphorus Sulfur Silicon Relat Elem*. 1999, 149, 7–14. (c) W. Cunico, et al., *Tetrahedron Letters,* 2007, 48, 6217-6220.

[2] V. Gududuru, V. Nguyen, J. T. Dalton, D. D. Miller, *Synlett.* 2004, 2357–2358. (b) A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, E. Novellino, V. Barone, *Org. Biomol. Chem.*, 2004, 2, 2809–2813.

[3] K. A. Kandeel, *Arkivoc*, 2006, 1-6,

[4] M. D'hooge, N. De Kimpe, *Tetrahedron*, 2006, 62, 513-535.

[5] P. Vicini, A. Gerenikaki, K. Anastasia, M. Incertia, F. Zania, *Bioorg. Med. Chem*, 2006, 14, 3859-3864.

[6] Z. Jieping, J. Blanchet, *Tetrahedron Letters,* 2004, 45, 4449–4452.

[7] D. R. St. Laurent, Q. G. DedongWu, H. Serrano-Wu, *Tetrahedron Letters*, 2004, 45, 1907-1910.

[8] R. P. Umesh, V. J. Dhanaji, R. B. Manisha, A. M. Ramrao, *Tetrahedron Letters*, 2012, 52, 1689–1691.

[9] R. K. Rawal, T. Srivastava, W. Haq, S. B. Katti, *J. Chem. Res.,* 2004, 5, 368–369.

[10] (a) A. K. Yadav, M. Kumar, T. Yadav, R. Jain, *Tetrahedron Letters,* 2009, 50, 5031–5034, (b) X. Zhang, X. Li, D. Li, G. Qu, J.Wang, P. M. Loiseau, X. Fan, *Bioorg. Med. Chem. Lett.,* 2009, 19, 6280–6283.

[11] F. Naser, E. Sattar, *Chinese Chem. Lett.,* 2013, 24, 389-391.

[12] R. M. Jyotirling, R. P. Umesh, D. N. Prashant, A. M. Ramrao *Tetrahedron Letters,* 2009, 50, 5025-5027.

[13] H. Pang, Y. Hui, K. Fan, X. Xing, Y. Wu, J. Yang, W. Shi, Z. Xie, *Chinese Chemical Lett.* 2016, 27(3), 335-339
[14] S. A. Jadhav, M. G. Shioorkar, O. S. Chavan, D. B. Shinde, R. K. Pardeshi, *Heterocyclic Lett.* 2015, 5(3), 375-382.
[15] P. Monforte, et al., *Bioorg. Med. Chem. Letters.*2001, 11, 1793–1796.
[16] A. Rao, et al., *IL Farmaco,* 2004, 59, 33-39.
[17] T. J. Shah, V. A. Desai, *Arkivoc,* 2007, (xiv), 218-228.
[18] A. Solankee and K. Kapadia, *Orient J. Chem.,* 1994, 10(1), 70-78 *Chem. Abstr.* 1995,122, 55939f.
[19] O. Devinyak, D. Havrylyuk, B. Zimenkovsky and R. Lesyk, *Mol. Inf.,* 2014,33, 216–229.
[20] P. Schauen, A. Krbarae,, M. Tisler and M. Likar, *Experimental,*1996, 22, 304 *Chem. Abstr*., 1966,65, 4440h.
[21] A. Saeed, S. Zaman, M. Jamil, B. Mirza, *Turk. J. Chem*., 2008, 32, 585.
[22] S. P. Singh, S. K. Anyoung, S. S. Parmar, *J. Pharm. Sci.,* 1974, 63, 960.
[23] W. A. Skinner, H. H. C. Tong, G. Bordy and T. E. Edward, *Chem. Abstr.,* 1975, 83, 189351t.
[24] T. Takematsu, K. Yokohama, K. Deda, Y. Hayashi and E. Taniyamal, *Jpn. Patent,*1975,7 51, 21, 431, *Chem. Abstr.,* 1976, 84, 26880w.
[25] A. Upadhyay, S.K. Srivastava, S.D. Srivastava, *Eur. J. Med. Chem.,* 2010, 45, 3541.
[26] R. Yadav, V. Jain, S.D. Srivastava, S. Srivastava, S. K. Srivastava, *J. Indian Chem. Soc.,* 2009, 86, 537.
[27] S. K. Sonwane, S.D. Srivastava, S.K. Srivastava, *J. Indian. Council Chem.,* 2008, 25, 115.
[28] M. J. Rout, *Sci. Ind. Research* (India).1956, 15B, 422, *Chem. Abstr.,* 1957, 51, 4358.
[29] A.C. Tripathi, et al. *European Journal of Medicinal Chemistry*, 2014, 72, 52-77.
[30] R. Yadav, S.D. Srivastava, S. Srivastava, *Indian J. Chem.,* 2005, 44(B), 1262.
[31] I. Mohammad, A. G. Doshi, *Asian J. of Chem*., 2002, 14(1), 181-184.
[32] M. H. Shih, F. Y. Ke, *Bioorg. Med. Chem.,* 2004, 12(17), 4633-4643.
[33] R. Dayam, T. Sanchez, O. Clement, R. Shoemaker, S. Sei, N. Neamati, *J. Med. Chem.,* 2005, 48(1), 111-120.
[34] N. D. Sonawane, C. Muanprasat, R. Jr. Nagatani, Y. Song, A. S. Verkman, *J. Pharm. Sci.,* 2004, 94(1), 134-143.
[35] D. Reigada, C. H. Mitchell, *Am. J. Physiol Cell Physiol.,* 2005, 288(1), 132-140.
[36] D. Maclean, F. Holden, A. M. Davis, R. A. Scheuerman, S. Yanofsky, *J. Comb. Chem*. 2004, 6(2), 196-206.
[37] P. Jayanthi and P. Lalitha, *International Journal of Pharmacy and Pharmaceutical Sciences*, 2011, 3, 126-128.
[38] R. M.Silverstein, F. X. Webster, *Spectrometric Identification of Organic Compounds,* 6th Ed., John Wiley & Sons, New Delhi, 2010.