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Synthesis and Biological Evaluation of Thiazolidin-4-ones

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A new series of 2-(1,3-benzothiazol-2-ylimino)-5-arylidene-1,3-thiazolidine-4-ones (**4**) were synthesized and evaluated for their antiinflammatory and analgesic activity. The 2-(1,3-benzothiazol-2-ylimino)-5-arylidene-1,3-thiazolidine-4-one (**4**) were synthesized from 2-(1,3-benzothiazol-2-ylimino)-1,3-thiazolidin-4-one (**3**) upon treating with different substituted aryl aldehydes. The 2-(1,3-benzothiazol-2-ylimino)-1,3-thiazolidin-4-one (**3**) was prepared by treating 2-chloroacetamido benzothiazole (**2**) with potassium thiocyanate, where as the compound **2** was prepared by treating 2-aminobenzothiazole with chloroacetyl chloride in benzene medium. The synthesized 2-(1,3-benzothiazol-2-ylimino)-5-aryl-1,3-thiazolidine-4-one (**4a$_1$-a$_{10}$**) were screened for anti-inflammatory and analgesic activity. The tested compounds exhibited good antiinflammatory and analgesic activity as compared to standard drug.

Key Words: Synthesis, Benzothiazole, Chloroacetyl chloride, Thiazolidinone, Antiinflammatory and Analgesic activity.

INTRODUCTION

A number of thiazolidin-4-ones have been associated with significant biological activities like antibacterial[1], antifungal[2], antitubercular[3], anticonvulsant[4,5], anticancer[6], antiinflammatory[7], *etc*., like wise benzothiazoles were also known to posses antibacterial[8-10], antiinflammatory, analgesic, antitumor activities[11-14], *etc*. Recently it has been reported[15] that the benzothiazolyl thiazolidinones were shown good antimicrobial property against bacteria, yeast and moulds.

The synthetic protocol of thiazolidin-4-ones is outlined in the **Scheme-I**, the formation of the compound **3** is in accordance with the recently reported paper[15], where as the expected compound **5** which was reported earlier by Ameya *et al.*[9] and Hui-Ling Liu *et al.*[16] was not correlated with the spectral data. The mechanism for the formation of compound **3** was well supported by the ^{1}H NMR spectral data.

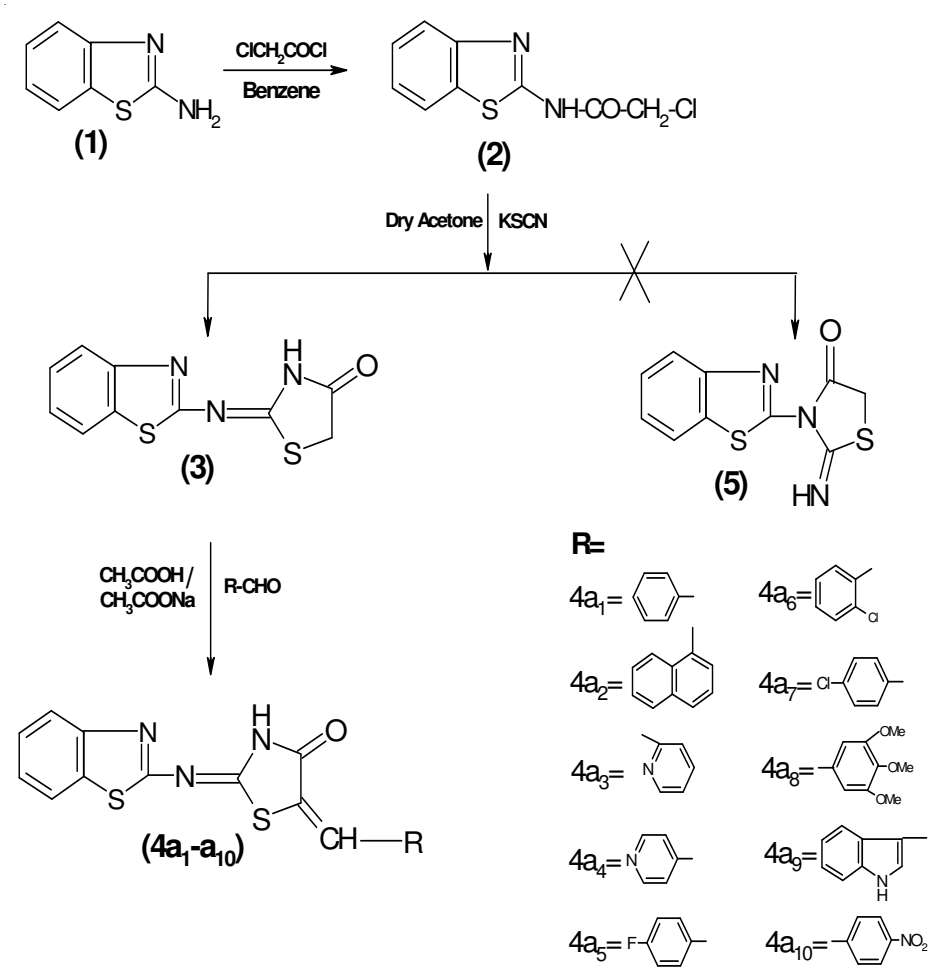
The signal for NH proton was reported by Ameya *et al.*[9] was in between 4.6 to 4.8 δ ppm, where as ^{1}H NMR spectra of present synthesized compounds does not shows any signal in the region of 4.0 to 5.0 δ ppm, which clearly indicates the formation of compound **3** and compound **4** in which the proton of NH was observed in the region of 12.0 to 13.0 δ ppm which clearly supports the compound structure **3** and **4**.

EXPERIMENTAL

2-Aminobenzothiazole compound was purchased from Sigma Aldrich Company. All the melting points were determined by Toshniwal apparatus in open capillaries and are uncorrected. The purity of the compounds was determined by using TLC on Silica gel G plates using *n*-butanol:ethyl acetate (1:3) solvent system and UV lamp was used as a visualizing agent.

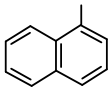
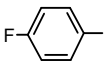
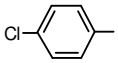
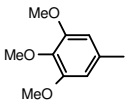
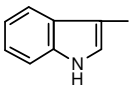
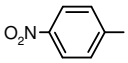
^{1}H NMR spectra were recorded on a avance 300 MHz spectrophotometer using DMSO-d_6 as solvent and TMS as internal standard (chemical shifts are expressed in δ ppm). Mass spectra were recorded on LCMS Shimadzu spectrophotometer.

All the compounds were synthesized according to **Scheme-I**. The physical data of all synthesized compounds **4a$_1$-4a$_{10}$** were represented in Table-1.



Scheme-I

TABLE-1
PHYSICAL DATA OF COMPOUNDS **$4a_1$-a_{10}**

Product code	R	m.f.	m.w.	m.p. (ºC)	Yield (%)
$4a_1$		$C_{17}H_{11}N_3OS_2$	337	280-282	57 [a]
$4a_2$		$C_{21}H_{13}N_3OS_2$	387	212-214	51 [b]
$4a_3$		$C_{16}H_{10}N_4OS_2$	338	254-256	60 [b]
$4a_4$		$C_{16}H_{10}N_4OS_2$	338	296-300	68 [a]
$4a_5$		$C_{17}H_{10}N_3OS_2F$	355	168-172	76 [c]
$4a_6$		$C_{17}H_{10}N_3OS_2Cl$	372	218-220	70 [c]
$4a_7$		$C_{17}H_{10}N_3OS_2Cl$	372	242-246	67 [c]
$4a_8$		$C_{20}H_{17}N_3O_4S_2$	427	198-202	61 [c]
$4a_9$		$C_{19}H_{12}N_4OS_2$	376	172-176	45 [b]
$4a_{10}$		$C_{17}H_{10}N_4O_3S_2$	382	104-108	48 [c]

Crystallization solvents: a = DMF; b = Acetone; c = Toluene

Preparation of 2-chloroacetamido benzothiazole (2): To a solution of 2-amino benzothiazole (20 g) (**1**) in dry benzene (200 mL), a solution of chloroacetyl chloride (10 mL) in dry benzene (50 mL) was added gradually. The reaction mixture was then refluxed at 70 ºC on a water bath for 1.5 h. The benzene was distilled off and the residue was washed with a sodium bicarbonate solution and water and then dried. The product was crystallized from alcohol to get 2-chloroacetamido benzothiazole (**2**) having melting point 162-164 °C. ^{1}H NMR (DMSO-d_6, δ ppm): 4.3 to 4.5 (2H, s, CH_2 of -$COCH_2$-), 7.2 to 8.0 (4H, m, Ar-H), 12.6 to 12.8 (1H, s, NH of -CONH-).

Preparation of 2-(1,3-benzothiazol-2-ylimino)-1,3-thiazolidin-4-one (3): A mixture of 2-chloro-acetamido benzothiazole (0.03 mol) (**2**), potassium thiocyanate (0.06 mol) and dry acetone (100 mL) were refluxed for 3 h. Excess of acetone was removed *in vacuo* and the residue was stirred with water (50 mL). The solid product thus separated was filtered, washed with water and dried. The obtained product was crystallized from acetone to get 2-(1,3-benzothiazol-2-ylimino)-1,3-thiazolidin-4-one (**3**) having melting point 192-196 ºC. ^{1}H NMR (DMSO-d_6, δ ppm): 3.9 to 4.1 (2H, s, CH_2 of thiazolidinone), 7.2 to 8.1 (4H, m, of Ar-H), 12.1 to 12.4 (1H, s, NH of thiazolidinone).

Preparation of 2-(1,3-benzothiazol-2ylimino)-5-arylidene-1,3-thiazolidine-4-one ($4a_1$-a_{10}): A mixture of 2-(1,3-benzothiazol-2-ylimino)-1,3-thiazolidin-4-one (0.01 mol) (**3**) and substituted benzaldehyde (0.02 mol) was added to a solution of anhydrous sodium acetate (0.02 mol) in acetic acid (30 mL). The mixture was refluxed for 5-6 h at 120 ºC and cooled to room temperature. The solid product thus separated was filtered, washed with water, dried and crystallized from suitable solvent to yield compounds **$4a_1$-a_{10}** and the data is represented in Table-1.

Compound $4a_1$: ^{1}H NMR (DMSO-d_6, δ ppm): 7.3 to 7.7 and 7.9 to 8.1 (9H, m, of Ar-H), 7.7 to 7.8 (1H, s, of CH of =CH), 12.8 to 13.0 (1H, s, NH of thiazolidinone).

Compound $4a_2$: ^{1}H NMR (DMSO-d_6, δ ppm): 7.3 to 8.2 (11H, m, of Ar-H), 8.4 to 8.5 (1H, s, of CH of =CH), 12.8 to 13.1 (1H, s, NH of thiazolidinone). MS (LCMS) m/e: 386 (m-1).

Compound $4a_6$: ^{1}H NMR (DMSO-d_6, δ ppm): 7.2 to 7.9 (8H, m, of Ar-H), 7.9 to 8.0 (1H, s, of CH of =CH), 12.7 to 12.9 (1H, s, NH of thiazolidinone).

Compound $4a_9$: ^{1}H NMR (DMSO-d_6, δ ppm): 7.1 to 8.1 (9H, m, of Ar-H), 8.2 to 8.3 (1H, s, CH of =CH), 9.8 to 10.0 (1H, s, NH of indole), 12.1 to 12.2 (1H, s, NH of thiazolidinone). MS (LCMS) m/e: 375 (m-1).

Antiinflammatory activity: The synthesized compounds **$4a_1$-a_{10}** were assessed for antiinflammatory activity at a concentration of 200 mg/kg oral dose by acute carrageenan-induced oedema in rat hind paw by following the reported technique[17,18]. The activity was performed on albino rats of either sex weighing 150-200 g were selected in group of 6 each; the oedema volume of injected paws were measured plethysmographically by mercury displacement method. The activity was compared with standard diclofenac sodium and the data is represented in the Table-2.

Analgesic activity: The analgesic activity of the synthesized compounds **$4a_1$-a_{10}** was carried out by Eddy's hot plate method[19] on albino mice of either sex each group comprising of 6 animals, weighing between 20-36 g. Pentazocin was used as standard drug to compare the analgesic activity and the data is represented in Table-3.

RESULTS AND DISCUSSION

All the synthesized compounds were screened for antiinflammatory activity. Results are presented in the Table-2. Compounds **$4a_1$**, **$4a_2$**, **$4a_3$**, **$4a_4$**, **$4a_5$**, **$4a_6$**, **$4a_7$**, **$4a_8$**, **$4a_9$** and **$4a_{10}$** exhibited maximum inhibition of 73.94, 75.53, 77.81, 80.97, 79.01,

TABLE-2
ANTIINFLAMMATORY ACTIVITY OF THE SYNTHESIZED COMPOUNDS **4a$_1$-a$_{10}$**
Animals: Albino rat; Route: P.O

Group	Treatment	Dose (mg/kg)	Paw oedema volume							
			After 1 h		After 2 h		After 3 h		After 4 h	
			Mean	ROV (%)	Mean	ROV (%)	Mean	ROV (%)	Mean	ROV (%)
1	Control	1.5 mL	1.190	-	2.290	-	3.050	-	4.290	-
2	Standard	50	0.171	55.91	0.167	66.95	0.179	72.35	0.150	87.69
3	**4a$_1$**	200	0.510	45.58	1.080	54.62	1.080	63.16	1.100	73.94
4	**4a$_2$**	200	0.690	39.62	1.100	55.22	1.050	66.02	1.030	75.53
5	**4a$_3$**	200	0.750	38.01	1.060	57.42	0.910	68.63	0.930	77.81
6	**4a$_4$**	200	0.670	44.95	0.950	61.84	0.930	71.88	0.800	80.97
7	**4a$_5$**	200	0.590	45.91	1.020	55.91	1.100	68.21	0.890	79.01
8	**4a$_6$**	200	0.720	43.05	1.010	57.91	0.910	67.92	0.900	77.91
9	**4a$_7$**	200	0.760	37.19	0.910	59.64	1.160	64.02	1.110	75.99
10	**4a$_8$**	200	0.670	44.95	1.050	57.83	0.890	71.51	0.910	82.56
11	**4a$_9$**	200	0.760	37.19	1.120	51.41	1.060	65.80	1.150	76.58
12	**4a$_{10}$**	200	0.900	25.61	0.980	60.64	0.930	66.38	0.960	79.02

Standard = Diclofenac; ROV = Reduction in paw oedema volume.

TABLE-3
ANALGESIC ACTIVITY OF THE SYNTHESIZED COMPOUNDS **4a$_1$-a$_{10}$**

Group	Treatment	No. of animals	Average wt. of animals (g)	Average dose (mg/mL)	Basal reaction time (s) after				
					0 min	15 min	30 min	60 min	90 min
I	Control gum acacia	6	34.00	-	5.00 ± 0.70	4.00 ± 0.81	4.75 ± 0.94	5.25 ± 0.47	7.00 ± 0.40
II	Pentazocin	6	28.00	30	5.50 ± 0.64	10.50 ± 0.64	11.75 ± 0.47	12.25 ± 0.25	12.50 ± 0.28
III	4a$_1$	6	28.00	25	4.14 ± 0.08	5.58 ± 0.56	6.66 ± 1.13	7.78 ± 1.02	12.22 ± 1.30
IV	4a$_2$	6	35.00	20	5.84 ± 0.39	7.73 ± 0.47	8.36 ± 0.28	8.90 ± 0.19	11.78 ± 1.60
V	4a$_3$	6	32.00	20	3.64 ± 0.22	7.54 ± 0.05	8.22 ± 0.15	9.32 ± 0.13	12.01 ± 0.88
VI	4a$_4$	6	26.00	15	5.03 ± 0.43	6.34 ± 0.17	7.22 ± 0.25	11.61 ± 1.10	12.24 ± 0.71
VII	4a$_5$	6	26.00	15	4.35 ± 0.19	6.25 ± 0.39	6.80 ± 0.29	8.27 ± 0.16	9.10 ± 0.35
VIII	4a$_6$	6	25.67	15	4.29 ± 0.10	5.65 ± 0.35	7.20 ± 0.99	11.20 ± 1.86	12.10 ± 1.87
IX	4a$_7$	6	27.00	20	4.84 ± 0.10	5.91 ± 0.57	7.10 ± 1.31	8.21 ± 1.07	12.09 ± 1.12
X	4a$_8$	6	29.00	15	6.02 ± 0.18	7.90 ± 0.91	8.21 ± 1.35	9.35 ± 1.17	12.03 ± 1.32
XI	4a$_9$	6	28.05	20	5.34 ± 0.41	7.35 ± 0.52	8.35 ± 0.31	8.50 ± 0.21	12.34 ± 1.80
XII	4a$_{10}$	6	31.15	25	6.34 ± 0.21	8.10 ± 0.92	9.35 ± 1.37	10.05 ± 1.21	11.70 ± 1.49

77.91, 75.99, 82.56, 76.58 and 79.02 %, respectively where as standard diclofenac sodium showed reduction in oedema volume by 87.69 % in carrageenan induced rat hind paw oedema model. Among the tested compounds, **4a$_4$**, **4a$_5$**, **4a$_8$** and **4a$_{10}$** showed good antiinflammatory activity.

The synthesized compounds have shown a significant analgesic activity. The compound **4a$_1$**, **4a$_2$**, **4a$_3$**, **4a$_4$**, **4a$_5$**, **4a$_6$**, **4a$_7$**, **4a$_8$**, **4a$_9$** and **4a$_{10}$** has shown good to equipotent analgesic activity when compared to standard (pentazocin). Results are presented in Table-3.

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