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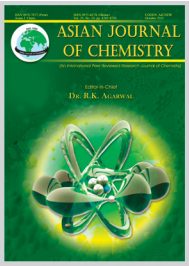

Analgesic and Antiinflammatory Activity of Derivatives of 2-Aminobenzothiazole

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A series of 5-(4-substituted benzylidene-2-(substituted benzo[d]thiazol-2-ylimino)thiazolidin-4-one (**5a-r**) have been synthesized from 2-aminobenzothiazole as starting material. Condensation of thiazolidin-4-one with different substituted aromatic benzaldehyde occurred at reactive methylene group present at C-5 position of thiazolidin-4-one ring and resulted in the formation of compounds (**5a-r**). These were characterized using physical and spectral methods. The compounds (**5a-r**) were evaluated for analgesic and antiinflammatory activity using *in vivo* models.

Key Words: 2-Aminobenzothiazole, Benzaldehyde, Thiazolidin-4-one antiinflammatory, Analgesic, Ulcerogenicity.

INTRODUCTION

A repertoire of popularly used NSAIDs is available including selective COX-2 inhibitors such as celecoxib developed to reduce risk of GI erosion and bleeding, a common side effect of NSAIDs[1]. Several NSAIDs have been linked to adverse renal effects, again because of the antiprostaglandin effects. The COX-1 and COX-2 inhibitors may also contribute to renal toxicity, because the COX-2 enzyme is present in renal tissue and may be important in maintaining renal perfusion[2]. Thus, there is a need to search for newer targets and newer molecules for the treatment of pain and inflammation. Benzothiazole is an important heterocyclic compound that enjoys the interest of medicinal chemists because of the wide range of biological activities displayed by it[3].

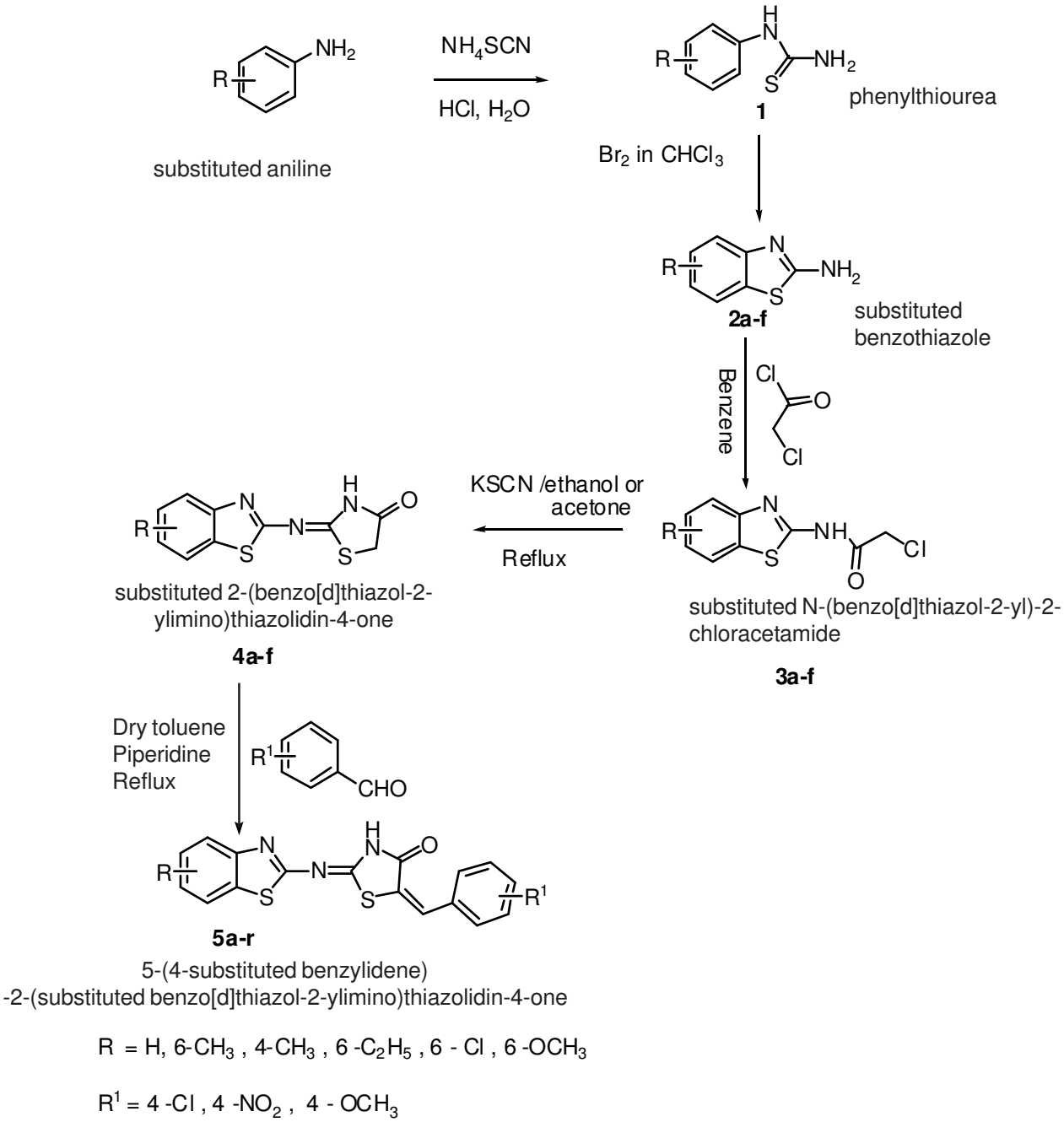
There are several reports indicating that this moiety can be exploited in designing newer analgesic and antiinflammatory agents[4-6]. Similarly, thiazolidinone, another heterocyclic compound containing sulphur and nitrogen has been found to display antiinflammatory activity[7]. In continuation of our work in the field of analgesic, antiinflammatory compounds containing heterocyclics[8], we contemplated to combine benzothiazole and thiazolidinone ring containing a benzylidene substituent into our target compounds. Similar compounds, but with an unsubstituted benzothiazole ring have been recently reported to possess antimicrobial activity[9]. Thus, a series of 5-(4-substituted benzylidene-2-(substituted benzo[d]thiazol-2-ylimino)thiazolidin-4-one (**5a-r**) were synthesized and evaluated for *in vivo* analgesic and inflammatory activity using standard animal models. The structures were confirmed by physical and spectral data (IR, NMR and mass).

EXPERIMENTAL

All the chemicals used in the synthesis were of laboratory grade. Melting points were determined in open capillary on Veego (model: VMP-D) electronic apparatus and are uncorrected. The IR spectra of the synthesized compounds were recorded on Shimadzu 8400-S FT-IR Spectrophotometer using potassium bromide. The ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO using NMR Varian-Mercury 300 and 400 MHz spectrometer and chemical shifts are given in units as parts per million, downfield from tetra methyl silane (TMS) as an internal standard. The mass spectra were recorded on a Shimadzu GCMS Q5-2010. To monitor the reactions, as well as, to establish the identity and purity of reactants and products, thin layer chromatography was performed on precoated aluminium sheets (silica gel 60 F_{254}, 6 cm × 2.5 cm) using appropriate solvent systems. The spots were visualized under ultra-violet light or by exposure to iodine vapours.

2-Chloro-N-(4 or 6-substituted benzo[d]thiazol-2-yl)acetamide (3a-f)

General procedure: Substituted 2-aminobenzothiazole (**2a-f**) (0.01 mol) was dissolved in 100 mL of dry benzene containing about 2-3 drops of pyridine. The solution was kept in ice bath and stirred for 0.5 h at 0-5 ºC. To this 1.6 mL (0.02 mol) of chloroacetyl chloride was added dropwise and stirring continued for another 2 h. Solvent was then distilled off and the residue added to 5 % sodium bicarbonate solution, stirred for 15 min and filtered. The solid thus obtained was washed well with water, dried and recrystallized from ethanol (Table-1).



Scheme-I

2-(4 or-6-Substitute dbenzo[d]thiazol-2-ylimino)thiazolidin-4-one (4a-f)

General procedure: A mixture of substituted N-(benzo[d]-thiazol-2-yl)-2-chloroacetamide **3a-f** (0.01 mol) and potassium thiocyanate (1.94 g, 0.02 mol) in 100 mL 95 % ethanol was heated under reflux for 4 h and then left undisturbed overnight at room temperature. The precipitated solid was filtered and recrystallized from ethanol. The physical and spectral characteristics of **4a-f** are given in Table-2.

5-(4-Substituted benzylidene-2-(substituted benzo[d]thiazol-2-ylimino)thiazolidin-4-one (5a-r)

General procedure: 2-(4 or-6- substituted benzo[d]thiazol-2-ylimino)thiazolidin-4-one **4a-f** (0.01 mol) and appropriately substituted benzaldehyde (0.01 mol) were suspended in 50 mL of dry toluene containing 2-3 drops of piperidine. The mixture was refluxed for 2 h and then kept at room temperature leading to precipitation of the product. The compound was filtered and washed with dry toluene followed by ethanol. Recrystallization from acetic acid gave a pure compound.

5-(4-Chlorobenzylidene)-2-(benzo[d]thiazol-2-ylimino)thiazolidin-4-one (5a): Yield 80 %, m.p. 260-262 ºC, IR (KBr, ν_{max}, cm^{-1}): 3059 (NH), 2804 (Ar.C-H), 1732 (C=O), 1581 (C=N), 1550 (C=C), 1298 (C-N), 752 (C-Cl). ^{1}H NMR (DMSO, δ ppm): 12.981(s, 1H, NH), 7.778 (s, 1H, CH), 7.35-8.022 (m, 4H, ArH).

5-(4-Nitrobenzylidene)-2-(benzo[d]thiazol-2-ylimino)-thiazolidin-4-one (5b): Yield 75 %, m.p. 296-298 ºC, IR (KBr, ν_{max}, cm^{-1}): 3086 (NH), 2810 (Ar.C-H), 1716 (C=O), 1589 (C=N), 1555 (C=C), 1342 (N=O), 1292 (C-N). ^{1}H NMR

(DMSO, δ ppm): 12.88 (s, 1H, NH), 7.78 (s, 1H, CH), 7.33-8.38 (m, 8H, ArH).

5-(4-Methoxybenzylidene)-2-(benzo[d]thiazol-2-ylimino)thiazolidin-4-one (5c): Yield 75 %, m.p. 236-238 ºC, IR (KBr, ν_{max}, cm^{-1}): 3053 (NH), 2802 (Ar.CH), 1697 (C=O), 1593 (C=N), 1570 (C=C), 1263 (C-N). ^{1}H NMR (DMSO, δ ppm): 12.9 (s, 1H, NH), 7.738 (s, 1H, CH), 7.13-8.00 (m, 8H, ArH), 3.8 (s, 3H, OCH_3). D_2O exchange: 7.738 (s, 1H, CH), 7.13-8.009 (m, 8H, ArH), 3.8 (s, 3H, OCH_3).

5-(4-Chlorobenzylidene)-2-(6-methylbenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5d): Yield 70 %, m.p. 274-276 ºC, IR (KBr, ν_{max}, cm^{-1}): 3055 (NH), 2781 (Ar.CH), 1722 (C=O), 1647 (C=N), 1608 (C=C), 1278 (C-N), 815 (C-Cl). ^{1}H NMR (DMSO, δ ppm): 12.93 (s, 1H, NH), 7.77 (s, 1H, CH), 7.31-7.82 (m, 8H, ArH), 2.43 (s, 3H, CH_3).

5-(4-Nitrobenzylidene)-2-(6-methylbenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5e): Yield 65 %, m.p. 286-288 ºC, IR (KBr, ν_{max}, cm^{-1}): 3072 (NH), 2812 (Ar.CH), 1716 (C=O), 1589 (C=N), 1540 (C=C), 1338 (N=O) 1290 (C-N). ^{1}H NMR (DMSO, δ ppm): 12.90 (s, 1H, NH), 7.6 (s, 1H, CH), 7.25-8.37(m, 7H, ArH), 2.62 (s, 3H, CH_3).

5-(4-Methoxybenzylidene)-2-(6-methylbenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5f): Yield 69 %, m.p. 228-230 ºC, IR (KBr, ν_{max}, cm^{-1}): 3059 (NH), 2806 (Ar.CH), 1716 (C=O), 1591 (C=N), 1570 (C=C), 1292 (C-N). ^{1}H NMR (DMSO, δ ppm): 12.9 (s, 1H, NH), 7.73 (s, 1H, CH), 7.14-7.8 (m, 7H, ArH), 3.85 (s, 3H, OCH_3) 2.24 (s, 3H, CH_3).

5-(4-Chlorobenzylidene)-2-(4-methylbenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5g): Yield 65 %, m.p. 302-305 ºC, IR (KBr, ν_{max}, cm^{-1}): 3064 (NH), 2810 (Ar.CH), 1728 (C=O), 1600 (C=N), 1491 (C=C), 1298 (C-N), 742 (C-Cl). ^{1}H NMR (DMSO, δ ppm): 12.96 (s, 1H, NH), 7.65 (s, 1H, CH), 7.25-7.72 (m, 7H, ArH), 2.66 (s, 3H, CH_3).

5-(4-Nitrobenzylidene)-2-(4-methylbenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5h): Yield 65 %, m.p. 300-302 ºC, IR (KBr, ν_{max}, cm^{-1}): 3057 (NH), 2810 (Ar.CH), 1716 (C=O), 1689 (C=N), 1595 (C=C), 1338 (N=O) 1292 (C-N). ^{1}H NMR (DMSO, δ ppm): 12.83 (s, 1H, NH), 7.647 (s, 1H, CH), 7.2-8.3 (m, 7H, ArH), 2.75 (s, 3H, CH_3).

5-(4-Methoxybenzylidene)-2-(4-methylbenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5i): Yield 70 %, m.p. 274-276 ºC, IR (KBr, ν_{max}, cm^{-1}): 3034 (NH), 2798 (Ar.CH), 1701 (C=O), 1570 (C=N), 1539 (C=C), 1300 (C-N). ^{1}H NMR (DMSO, δ ppm): 12.83 (s, 1H, NH), 7.74 (s, 1H, CH), 7.13-7.82 (m, 7H, ArH), 3.85 (s, 3H, OCH_3), 2.69 (s, 3H, CH_3).

5-(4-Chlorobenzylidene)-2-(6-ethylbenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5j): Yield 70 %, m.p. 259-261 ºC, IR (KBr, ν_{max}, cm^{-1}): 3068 (NH), 2804 (Ar.CH), 1714 (C=O), 1585 (C=N), 1647 (C=C), 1296 (C-N), 771 (C-Cl). ^{1}H NMR (DMSO, δ ppm): 12.94 (s, 1H, NH), 7.77 (s, 1H, CH), 7.35-7.84 (m, 7H, ArH), 2.69-2.76 (m, 2H, CH_2), 1.23 (t, 3H, CH_3).

5-(4-Nitrobenzylidene)-2-(6-ethylbenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5k): Yield 65 %, m.p. 265-267 ºC, IR (KBr, ν_{max}, cm^{-1}): 3082 (NH), 2804 (Ar.CH), 1716 (C=O), 1587 (C=N), 1647 (C=C), 1338 (N=O) 1290 (C-N). ^{1}H NMR (DMSO, δ ppm): 12.87(s, 1H, NH), 7.65 (s, 1H, CH), 7.3-8.3 (m, 7H, ArH), 2.7-2.8 (m, 2H, CH_2), 1.29 (t, 3H, CH_3).

5-(4-Methoxybenzylidene)-2-(6-ethylbenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5l): Yield 70 %, m.p. 209-211 ºC, IR (KBr, ν_{max}, cm^{-1}): 3049 (NH), 2808 (Ar.CH), 1712 (C=O), 1581 (C=N), 1635 (C=C), 1261 (C-N). ^{1}H NMR (DMSO, δ ppm): 12.82 (s, 1H, NH), 7.73 (s, 1H, CH), 7.14-7.85 (m, 7H, ArH), 3.85 (s, 3H, OCH_3), 2.69-2.76 (m, 2H, CH_2), 1.23 (t, 3H, CH_3).

5-(4-Chlorobenzylidene)-2-(6-chlorobenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5m): Yield 72 %, m.p. 300-302 ºC, IR (KBr, ν_{max}, cm^{-1}): 3036 (NH), 2804 (Ar.CH), 1708 (C=O), 1600 (C=N), 1593 (C=C), 1274 (C-N), 823 (C-Cl). ^{1}H NMR (DMSO, δ ppm): 13.04 (s, 1H, NH), 7.78 (s, 1H, CH), 7.5-8.16 (m, 7H, ArH).

5-(4-Nitrobenzylidene)-2-(6-chlorobenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5n): Yield 70 %, m.p. 305-307 ºC, IR (KBr, ν_{max}, cm^{-1}): 3072 (NH), 2814 (Ar.CH), 1712 (C=O), 1598 (C=N), 1521 (C=C), 1338 (N=O), 1292 (C-N), 754 (C-Cl). ^{1}H NMR (DMSO, δ ppm): 13.01 (s, 1H, NH), 7.84 (s, 1H, CH), 7.5-8.37 (m, 7H, ArH).

5-(4-Methoxybenzylidene)-2-(6-chlorobenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5o): Yield 69 %, m.p. 244-246 ºC, IR (KBr, ν_{max}, cm^{-1}): 3064 (NH), 2798 (Ar.CH), 1716 (C=O), 1593 (C=N), 1554 (C=C), 1296 (C-N), 823 (C-Cl). ^{1}H NMR (DMSO, δ ppm): 12.98 (s, 1H, NH), 7.74 (s, 1H, CH), 7.13-8.15 (m, 7H, ArH), 3.84 (s, 3H, OCH_3).

5-(4-Chlorobenzylidene)-2-(6-methoxybenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5p): Yield 65 %, m.p. 277-279 ºC, IR (KBr, ν_{max}, cm^{-1}): 3089 (NH), 2835 (Ar.CH), 1712 (C=O), 1604 (C=N), 1589 (C=C), 1263 (C-N), 740 (C-Cl). ^{1}H NMR (DMSO, δ ppm): 12.89 (s, 1H, NH), 7.75 (s, 1H, CH), 7.08-7.8 (m, 7H, ArH), 3.82 (s, 3H, OCH_3).

5-(4-Nitrobenzylidene)-2-(6-methoxybenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5q): Yield 65 %, m.p. 286-288 ºC, IR (KBr, ν_{max}, cm^{-1}): 3078 (NH), 2839 (Ar.CH), 1716 (C=O), 1597 (C=N), 1521 (C=C), 1338 (N=O) 1263 (C-N). ^{1}H NMR (DMSO, δ ppm): 12.79 (s, 1H, NH), 7.31 (s, 1H, CH), 7.04-8.37 (m, 7H, ArH), 3.88 (s, 3H, OCH_3).

5-(4-Methoxyenzylidene)-2-(6-methoxybenzo[d]thiazol-2-ylimino)thiazolidin-4-one (5r): Yield 65 %, m.p. 241-243 ºC, IR (KBr, ν_{max}, cm^{-1}): 3039 (NH), 2833 (Ar.CH), 1720 (C=O), 1593 (C=N), 1554 (C=C), 1296 (C-N). ^{1}H NMR (DMSO, δ ppm): 12.98 (s, 1H, NH), 7.72 (s, 1H, CH), 7.07-7.84 (m, 7H, ArH), 3.82-3.84 (d, 6H, OCH_3).

Evaluation of antiinflammatory activity: Antiinflammatory activity was evaluated by carrageenin induced rat paw edema method of Winter *et al.*[10]. The suspensions of test compounds were prepared in sterile 0.9 % NaCl solution. In all cases control received the same quantity of sterile 0.9 % NaCl solution as vehicle. Sprague Dawley rats of either sex weighing between 150-250 g were randomly distributed in control and experimental group of six animals each. At 0 h target compounds (**5a-r**) (15 mg/kg) and Indomethacin (20 mg/kg) were administered orally. After 1 h 0.1 mL of 1 % (w/v) suspension of carrageenin in distilled water was injected into the planter tissue of right paw of rat by using 27 gauge needles. The paw was marked with ink at the level of the tibia-tarsal junction and the initial volume of paw was measured by plathysmometer within 30 s of injection. The relative increase in paw volume was found by measuring the paw volume again after 3 h of carrageenin injection. The percentage inhibition of edema was calculated and the results are presented in Table-3.

Evaluation of analgesic activity

Acetic acid induced writhing in mice: Analgesic activity was tested by acetic acid induced writhing in mice as described by Koster *et al.*[11]. Analgesic activity was determined *in vivo* by calculating total number of writhings following intraperitonial (I.P.) administration of 0.6 % acetic acid in mice. Albino mice of either sex (25-30 g) were used. Target compounds (**5a-r**) were administered orally (15 mg/kg) as a suspension in sterile 0.9 % NaCl solution. Diclofenac sodium (20 mg/kg) was used as standard under same conditions. Acetic acid solution was administered I.P. 0.5 h after the administration of the compounds. 10 min after intraperitonial injection of the acetic acid solution, the number of writhings per animal were recorded for 20 min. Control animals received an equal volume of vehicle. Analgesic activity was expressed as percentage of inhibition of number of writhings, when compared with the vehicle control group. Results of percentage analgesic activity of compounds were calculated and are presented in Table-3.

Formalin induced licking and biting in mice: Analgesic activity was tested by formalin induced licking and biting in mice as described by Leal *et al.*[12]. The analgesic activity was determined by calculating total number of licking and biting in mice, following administration of 0.1 % (0.1 mL/10 g) formalin into the subplanter area of right hind paw of mice. Albino mice of either sex (25-30 g) were used. Target compounds (**5a-r**) (15 mg/kg) were administered I.P. as a suspension in sterile 0.9 % NaCl solution. Diclofenac sodium (20 mg/kg) was used as standard under same conditions. Thirty min after the administration of the compounds, number of paw licking, an index of noniception, was measured at 0-5 min (first phase, which indicates central analgesic activity) and 15-25 min (second phase, which indicates peripheral analgesic activity) after formalin administration. Control animals received an equal volume of vehicle. Analgesic activity was expressed as percentage of inhibition of frequency of paw licking, when compared with the vehicle control group and the results are presented in Table-3.

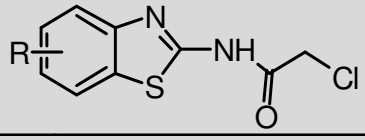
RESULTS AND DISCUSSION

The target compounds (**5a-r**) were prepared involving a three step procedure. Substituted anilines were converted to the corresponding 2-aminobenzothiazoles **2a-f** as per the reported procedure[13]. These amines were then reacted with chlorocetylchloride in benzene to yield the chloroacetamides **3a-f**. Refluxing these in ethanol with ammonium thiocyanate yielded compounds **4a-f** in excellent yields. These when condensed with commercially available substituted benzaldehydes in presence of piperidine as catalyst and dry toluene as solvent gave the target compounds **5a-r** (yield 65-70 %).

All 2-chloro-N-(4 or 6-substitutedbenzo[d]thiazol-2-yl)-acetamides (**3a-f**) obtained were solids melting at around the range of 162-218 ºC (Table-1). These were found to be freely soluble in acetone and DMSO. The solid state IR (KBr, ν_{max}, cm^{-1}) spectra of these compounds (Table-1) reveal a characteristic aromatic stretch between 3100-2900 cm^{-1}. The C=N group present in the benzothiazole ring revealed peaks at 1597 and 1590 cm^{-1}, secondary amide peak showed at 1647 cm^{-1} and C=C group of benzothiazole ring showed stretching vibrations at around 1554 cm^{-1}. The stretching vibrations for secondary amide are seen at 3450-3508 cm^{-1} and for C=O, at 1697-1715 cm^{-1}. The free amino peak visible in the spectra of **2a-f** was absent in these spectra, confirming formation of an amide bond.

The ^{1}H NMR spectra were recorded in DMSO. A peak by secondary amide proton was displayed at 12.73 ppm and that of methylene proton at 4.47 ppm. The aromatic protons showed

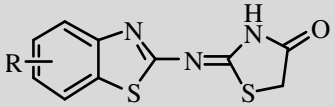
TABLE-1
SPECTRAL DATA OF 2-CHLORO-N-(4 OR 6-SUBSTITUTED BENZO[d]THIAZOL-2-YL)ACETAMIDES (**3a-f**)



Comp.	R	*R_f	m.p. (ºC)	Yield (%)	IR (KBr, ν_{max}, cm^{-1})	^{1}H NMR (δ ppm)
3a	H	0.48	162-164	95	3508(NH), 2983 (ArCH), 1697.41(C=O), 1647 (NH), 1597 (C=N), 1550 (C=C), 1442 (CH_2, bend), 1271(C-N), 777 (C-Cl).	12.73 (s, 1H, NH), 7.33-8.02 (m, 4H, ArH), 4.47 (s, 2H, CH_2).
3b	6-CH_3	0.52	198-200	92	3455 (NH), 2980 (Ar.CH), 1690 (C=O), 1645 (NH), 1590.25 (C=N), 1555 (C=C), 1278 (C-N), 1380 (CH_3, bend), 780 (C-Cl).	12.75 (s, 1H, NH), 7.35-8.05 (m, 3H, ArH), 4.46 (s, 2H, CH_2), 2.44 (s, 3H, CH_3).
3c	4-CH_3	0.55	204-206	90	3490 (NH), 2970 (Ar.CH), 1695 (C=O), 1635 (NH), 1595 (C=N), 1550 (C=C), 1273 (C-N), 1390 (CH_3, bend), 770 (C-Cl).	12.78 (s, 1H, NH), 7.35-8.05 (m, 3H, ArH), 4.46 (s, 2H, CH_2), 2.45 (s, 3H, CH_3).
3d	6-C_2H_5	0.53	174-176	95	3380 (NH), 2945 (Ar.CH), 1705 (C=O), 1640 (NH), 1585 (C=N), 1554 (C=C), 1275, (C-N), 1385 (CH_3, bend), 780 (C-Cl).	12.77 (s, 1H, NH), 7.38-8.04 (m, 3H, ArH), 4.49 (s, 2H, CH_2), 2.7-2.9 (m, 2H, CH_2), 1.28 (t, 3H, CH_3).
3e	6-Cl	0.5	216-218	94	3980 (NH), 2933 (Ar.CH), 1710 (C=O), 1650 (NH), 1581 (C=N), 1545 (C=C), 1278 (C-N), 1385 (CH_2, bend), 781(C-Cl).	12.78 (s, 1H, NH), 7.35-8.05 (m, 3H, ArH), 4.46 (s, 2H, CH_2).
3f	6-OCH_3	0.55	178-180	90	3857 (NH), 2893 (Ar, CH), 1695 (C=O), 1654 (NH), 1571 (C=N), 1555 (C=C), 1288 (C-N), 1385 (CH_2, bend), 771 (C-Cl).	12.8 (s, 1H, NH), 7.4-8.1 (m, 3H, ArH), 4.6 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3).

*R_f determined in CH_3Cl:CH_3OH-9:1.

TABLE-2
SPECTRAL DATA OF 2-(4 OR-6-SUBSTITUTED BENZO[D]THIAZOL-2-YLIMINO)THIAZOLIDIN-4-ONE (**4a-f**)



Comp.	R	*R_f	m.p. (ºC)	Yield (%)	IR (KBr, ν_{max}, cm^{-1})	^{1}H NMR (δ ppm)
4a	H	0.5	213-215	80	3010 (NH), 2970 (Ar.CH), 1714 (C=O), 1635 (NHCO),1570 (C=N), 1554 (C=C), 1456 (CH_2, bend), 1265 (C-N).	12.30 (s, 1H, NH), 7.3-7.9 (m, 4H, ArH), 4.05 (s, 2H, CH_2).
4b	6-CH_3	0.55	252-253	85	3110 (NH), 2923 (Ar.CH), 1715 (C=O), 1655 (NHCO), 1575 (C=N), 1552 (C=C), 1270 (C-N), 1458 (CH_2, bend).	12.30 (s, 1H, NH), 7.35-7.89 (m, 3H, ArH), 4.02 (s, 2H, CH_2), 2.46 (s, 3H, CH_3).
4c	4-CH_3	0.56	224-226	80	3120 (NH), 2900 (Ar.CH), 1712 (C=O), 1650 (NHCO), 1578 (C=N), 1554 (C=C), 1278 (C-N), 1467 (CH_2, bend).	12.35 (s, 1H, NH), 7.3-7.71 (m, 3H, ArH), 4.02 (s, 2H, CH_2), 2.45 (s, 3H, CH_3).
4d	6-C_2H_5	0.50	252-254	78	3115 (NH), 2920 (Ar.CH), 1705 (C=O), 1650 (NHCO), 1571 (C=N), 1549 (C=C), 1275 (C-N), 1460 (CH_2, bend).	12.35 (s, 1H, NH), 7.3-7.71 (m, 3H, ArH), 4.02 (s, 2H, CH_2), 2.75-2.98 (m, 2H, CH_2), 1.3 (t, 3H, CH_3).
4e	6-Cl	0.54	256-258	85	3098 (NH), 2902 (Ar.CH), 1725 (C=O), 1650 (NHCO), 1565 (C=N), 1542 (C=C), 1273 (C-N), 1460 (CH_2, bend), 780 (C-Cl).	12.36 (s, 1H, NH), 7.4-7.76 (m, 3H, ArH), 4.02 (s, 2H, CH_2).
4f	6-OCH_3	0.53	247-249	80	3095 (NH), 2906 (Ar.CH), 1708 (C=O), 1652 (NHCO), 1565 (C=N), 1549 (C=C), 1268 (C-N), 1459 (CH_2, bend).	12.38 (s, 1H, NH), 7.5-7.85 (m, 3H, ArH), 4.1 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3).

*R_f determined in Pet. ether:Ethyl acetate- 8:2.

peaks at 7.33-8.02 ppm as multiplet. Absence of singlet by amino protons confirmed the formation of chloroacetamides. The 2-(4 or -6-substitutedbenzo[d]thiazol-2-ylimino)thiazolidin-4-ones (**4a-f**) were obtained as solids melting at around the range of 213-258 ºC (Table-2) and were found to be freely soluble in acetone and DMSO.

The solid state IR (KBr, ν_{max}, cm^{-1}) spectra of **4a-f** (Table-2) reveal a characteristic aromatic stretch between 2950-2800 cm^{-1}. The C=N group present in the benzothiazole ring revealed peaks at 1575-1565 cm^{-1} while the secondary amide peak showed at 1655-1635 cm^{-1}. The C=C group of benzothiazole ring showed stretching vibrations at around 1554-1549 cm^{-1}. The stretching vibrations for NH group as multiple bands were seen at 3120-3010 cm^{-1} and a strong band of the C=O group at 1725-1708 cm^{-1}. In the ^{1}H NMR spectra a NH proton appears at 12.30 ppm (disappearance in D_2O exchange), accounting for lactum proton confirming the cyclization of chloracetamides to the thiazolidinones. The aromatic protons showed peaks at 7.3-7.9 ppm as multiplet. The shifting of singlet of methylene proton from 4.77 ppm (in **3a-f**) to 4.05 ppm due to increased shielding in the cyclized product can also be considered to be a strong confirmation for ring closure. The target compounds 5-(4-substituted benzylidene-2-(substituted benzo[d]thiazol-2-ylimino) thiazolidin-4-ones **5a-r** obtained were solids melting at around the range of 209-307 ºC and were slightly soluble in acetone and freely soluble in DMSO. The solid state IR (KBr, ν_{max}, cm^{-1}) spectra of **5a-r** revealed a characteristic aromatic stretch between 3000-2800 cm^{-1} and a multiple band near 3100-3038 cm^{-1} for NH. The characteristic stretch for α,β-unsaturated carbonyl group at around at 1732-1697 cm^{-1} and stretching vibrations of C=C around 1635-1540 cm^{-1} are indicative of incorporation of this group into the ring. The ^{1}H NMR spectra of **5a-r** were recorded in DMSO. The lactum NH revealed peak at 12.98 ppm. The aromatic protons showed peaks at 7.1-8.00 ppm. Singlet by methylene protons at 4.05 ppm seen in the spectra of **4a-f** but it's absent in the spectra of **5a-r** confirmed that the intermediates **4a-f** have been successfully condensed with aromatic aldehydes. This is further confirmed by appearance of peak by olefinic proton at around 7.6-7.8 ppm.

All compounds (**5a-r**) were evaluated for their analgesic and antiinflammatory activity. The analgesic activity was evaluated by two models namely: (**a**) acetic acid induced writhing in mice[11] and (**b**) Formalin induced licking and biting in mice[12]. All showed a significant decrease in number of writhings (Table-3) with compound (**5r**) found to be the most potent among the series. In the formalin induced licking and biting model in mice most of the compounds (**5a-r**) failed to show central analgesic activity in first phase, but have shown significant peripheral analgesic activity. In this model also (**5r**) was found to be most potent.

Antiinflammatory activity was evaluated by carrageenin induced hind-paw edema in rats. All compounds except (**5g**) caused a significant decrease in inflammation (Table-3). Compound (**5j**) was found to be the most potent among the series showing a 62 % decrease in inflammation when compared with control. Thus it can be concluded that this series of 5-(4-substituted benzylidene-2-(substituted benzo[d]thiazol-2-ylimino)thiazolidin-4-ones hold potential for further optimization.

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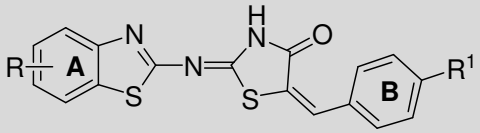
TABLE-3
RESULTS OF ANALGESIC AND ANTIINFLAMMATORY ACTIVITY



Compounds (15 mg/kg)	R	R^1	Antiinflammatory activity (inhibition %)	Analgesic activity (protection %) (diclofenac sodium, 20 mg/kg, test comp. 15 mg/kg)	
				Acetic acid induced writhing response in mice	Formalin induced licking and biting response in mice (peripheral activity)
Indomethacin (20 mg/kg)	–	–	75.40***	–	–
Diclofenac sodium (20 mg/kg)	–	–	–	84.34***	77.73***
5a	H	4-Cl	44.45*	52.15*	41.04*
5b	H	4-NO_2	34.22*	63.27**	64.74**
5c	H	4-OCH_3	27.86^{ns}	67.09**	49.04*
5d	6-CH_3	4-Cl	37.70*	47.79*	44.62*
5e	6-CH_3	4-NO_2	50.81**	58.29**	65.32**
5f	6-CH_3	4-OCH_3	39*	55.02*	52.89*
5g	4-CH_3	4-Cl	6.55^{ns}	56.33*	41.07*
5h	4-CH_3	4-NO_2	34.22*	53.60*	38.87^{ns}
5i	4-CH_3	4-OCH_3	40.98*	51.55*	40.66*
5j	6-C_2H_5	4-Cl	62.29**	50.04*	68.09**
5k	6-C_2H_5	4-NO_2	26.22^{ns}	61.05**	47.93*
5l	6-C_2H_5	4-OCH_3	27.86^{ns}	68.00**	19.58^{ns}
5m	6-Cl	4-Cl	54.09**	69.39**	70.79***
5n	6-Cl	4-NO_2	36.06*	60.00**	51.10*
5o	6-Cl	4-OCH_3	34.42*	61.57**	54.54*
5p	6-OCH_3	4-Cl	60.65**	63.27**	56.49*
5q	6-OCH_3	4-NO_2	39*	64.45**	56.99*
5r	6-OCH_3	4-OCH_3	59.01**	73.44***	71.73***

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, ^{ns}: non significant, compared with control (saline) group. Data expressed as mean ± SEM. Data was analyzed by one way ANNOVA followed by Dunnett's test.

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