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Article

Synthesis, Characterization, and Pharmacological Evaluation of some Newly Synthesized Alkoxy Derivatives of 4-Methyl Benzimidozolyl Thiazolidinones

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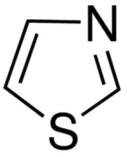
ABSTRACT

In this study, synthesis and pharmacological screening of various derivatives of 3-[4-(1H-4 methyl benzamidazol-2-yl) 2-hydroxy phenyl] -1-N-ethoxy phthalimido -5 (arylidene)-2-phenyl- 1,3-thiazolidin-4-one (5a-5d) were reported. These compounds (5a-5d) were synthesized by reaction of corresponding arylidene derivatives (4a-4d) with phthalimidoxy ethyl bromide in presence of C_2H_5OH/pyridine, while these compounds (4a-4d) have been synthesized by treating 3-[4-(1H-4methyl benzimidazol-2-yl)-2-hydroxy phenyl] 2-phenyl-1,3 – thiazolidin-4one with substituted aromatic aldehydes. The structure of newly synthesized compounds was characterized by IR, ^{1}H NMR, mass spectroscopy, and elemental analysis. These compounds were screened for their pharmacological activity, namely, anti-inflammatory activity and antibacterial activity.

Key words: Benzimidazole thiazolidiones, Schiff base, Pharmacological activity viz anti-inflammatory activity and antibacterial activity.

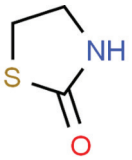
1. INTRODUCTION

Small ring heterocycles containing nitrogen and sulfur have been under investigation for a long time because of their important medicinal properties. Among the wide range of heterocycles explored to develop pharmaceutically important molecules, thiazoles have played an important role in medicinal chemistry.



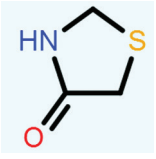
Thiazole

Thiazolidinones, which are derivatives of thiazolidine, belong to an important class of heterocyclic compounds. They have molecular formula C_3H_5NOS and a molecular weight 269.40. Thiazolidinones having a carbonyl group at positions 2, 4, or 5 have been an interest in extensive study among researchers. A comprehensive review of 4-thiazolidinone came in 1961 [1]. Later on, various researchers published articles on thiazolidinone derivatives as medicinal agents and intermediates in organic syntheses.



Thiazolidinone

4-Thiazolidinone scaffold is not only synthetically important but also possesses diverse pharmacological properties [2] and also have antitumor [3], anti-Parkinsonian [4], anti-arthritic [5], analgesic [6], and anti-inflammatory [7,8] activities.



4-Thioazolidinones

The literature survey reveals that among these type of molecules, 4-thiazolidinones have also shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, antituberculostatic, anti-HIV, antihistaminic, anticancer, anticonvulsant, anti-inflammatory, and analgesic properties [9-16].

Recently, a study reported the synthesis, chemical, and wide rang biological properties of a series of 4-thiazolidinone molecules [17-22]. Some of these compounds showed moderate-to-good biological properties. The observed interesting biological properties of this class of compounds impelled us to synthesize new examples with possible improved biological properties with applicative possibilities.

Benzimidazole nucleus is a useful structure for further molecular exploration and for development of new pharmaceutical compounds [23-26]. Synthesis of benzimidazole has received much attention due to varied biological activity exhibited by numer of

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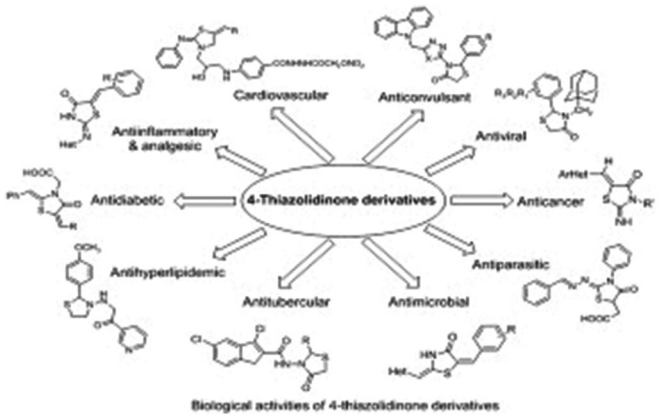


Biological activities of 4-thiazolidinone derivatives

its derivatives. Several derivatives of alkoxy phthalimide [27-30] have been synthesize and reported to demonstrate a wide range of pharmacological activity, that is, anticancer, antimalarial, and antidiuretic.

In view of these findings, it was contemplated to design and synthesize some imidazole derivatives bearing thiazolidinone and azetidinone moieties and evaluate their pharmacological activity such as antibacterial and anti-inflammatory activity.

2. SCHEME OF WORK

3. EXPERIMENTAL SECTION

3.1. Materials

Solvents are carried of S.D Fine Chemical and E. Merck grade and were purified and dried by conventional method [31]. All other chemicals of S.D. Fine Chemical and E. Merck grade have checked for their purity before use.

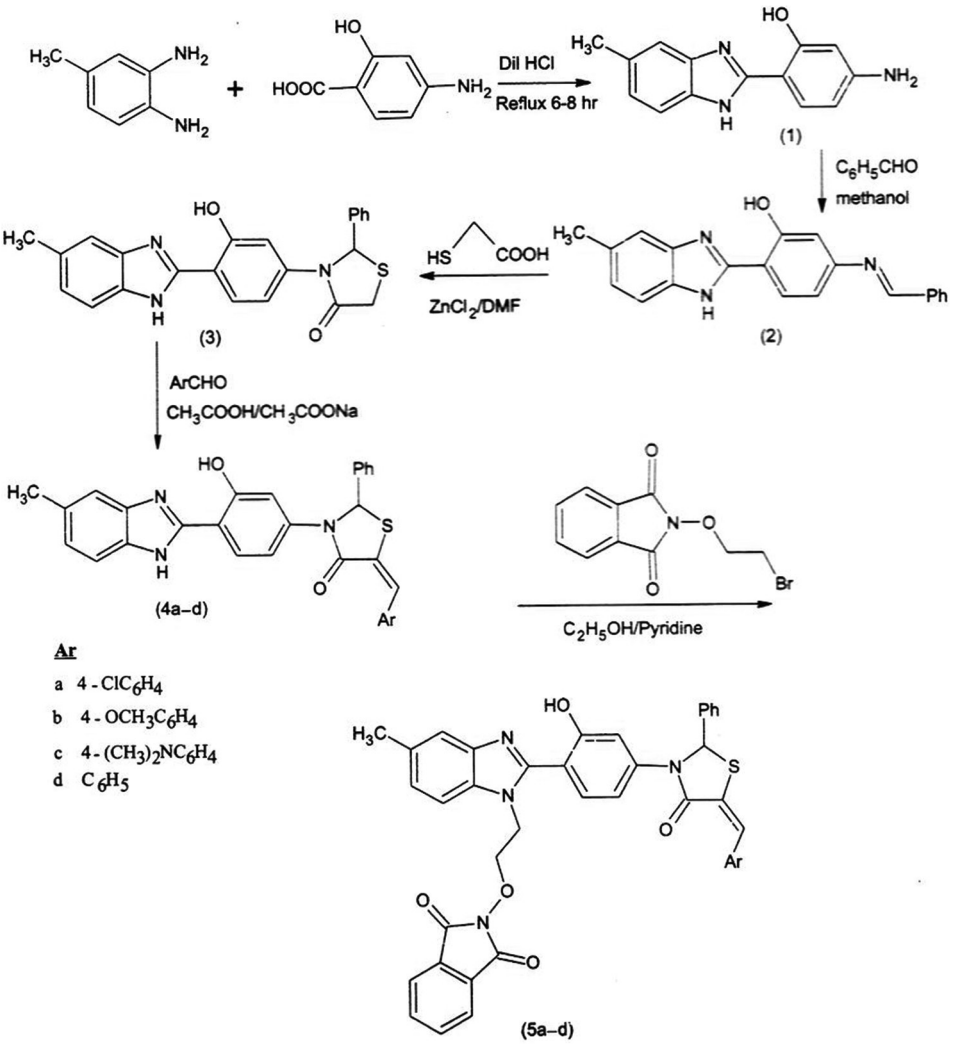
The homogeneity and purity of the compounds were checked over thin layer chromatography coated with silica Gel – G (thickness 0.5 mm) developing solvent acetone/DMF (3:1) non-saturated chamber at room temperature (20 ± 1°c).

The melting points of the synthesized compounds were determined by capillary method and were uncorrected. The IR spectra (in KBr) were recorded on JASCO FI-IR spectrophotometer. ^{1}NMR spectra (dimethylsulfoxide [DMSO]/$CDCl_3$) were taken on VRO–300 MHZ spectrophotometer and chemical shift expressed as ppm and TMS was used as internal standard. ε- bromoalkoxy phthalimides have been prepared by reported methods [32].

3.2. Experimental Method

3.2.1. Synthesis of 2-(2-hydroxy-4-aminophenyl) -1H- 4- methyl benzimidazole compound (1)

A mixture of 3,4 diamino toluene (1.22 g, 0.01mole) and 2-Hydroxy benzoin acid (1.53 g, 0.01 mole) in 4N Hcl (40 ml) was refluxed for about 6–8 h on steam bath. After cooling, the contents were neutralized



with aqueous NaOH. The colorless solid mass is obtained, which is filtered, dried, and washed with hot water and recrystallize the products from ethanol.

Yield: 64%, M.P. = 307°C, Color: Colorless solid shining crystals
Molecular Formula: $C_{14}H_{13}N_3O$, Molecular weight = 239
Elemental analysis (Calculated %) C = 70.20 (70.29), H = 5.32 (5.43), N = 17.50 (7.57)
IR (KBr) (in Cm^{-1}): 3415, 3350 (NH str), 3025 (C-H str, Ar-H), 1590 (C=N str), 3430 (OH)
^{1}H-NMR ($CDCl_3$) (δ-ppm): 11.30 (s, 1H, NH), 7.0-6.0 (m, 7H, Ar-H), 4.90 (s, 2H, NH2), 5.78 (s, 1H, OH), 2.4 (3H, S, CH_3).

3.2.2. Synthesis of 2-(2-hydroxy-4-N-phenyl methylene amino phenyl) -1H- 4- methyl benzimidazole compound (2)
Compound (1) [2.39 g, 0.01 mole], benzaldehyde [1 ml, 0.01 mole] in C_2H_5OH [20 ml] was refluxed for 6–7 h on steam bath. After removing the excess solvent under reduced pressure gives solid compound on cooling, which was filtered, dried, and washed with water. The product was recrystallized from methanol.

Yield: 50%, M.P. 121°C, Colour: Colourless needle like crystals
Molecular Formula: $C_{21}H_{17}N_3O$, Molecular weight = 327
Elemental analysis (Calculated %) C = 76.95 (77.06), H = 5.10 (5.19), N = 12.75 (12.84)
IR (KBr) (in Cm^{-1}): 3370 (NH str), 3025 (C-H str, Ar-H), 1600 (C=N str), 2913 (C-H, CH_3)
^{1}H-NMR ($CDCl_3$) (δ-ppm): 10.3 (s, 1H, NH), 8.0–7.0 (m, 11H, Ar-H), 7.10 (s, 1H, N=CH), 2.4 (3H, s, CH_3), 5.4 (1H, s, OH)

3.2.3. Synthesis of 3-[4-(1H-4-methyl benzimidazol-2-yl)-2-hydroxy phenyl] -2-phenyl- 1,3-thiazolidin-4-one (Compound 3)
A mixture of compound (2) and mercapto acetic acid in equimolar ratio in equivalent amount in 200ml DMF with a pinch of anhydrous ZnCl2 was refluxed for 12–14 h on steam bath. After concentration and on cooling, a solid compound was obtained, which was filtered, dried, and washed with water. The product was recrystallized from methanol.

Yield: 45%, M.P. 102°C, Color: Colorless crystals
Molecular Formula: $C_{23}H_{19}N_3O_2S$, Molecular weight = 401
Elemental analysis (Calculated %) C = 68.75(68.82), H = 4.67 (4.73), N = 10.40(10.47)
IR (KBr) (in Cm^{-1}) 3380 (NH str), 3020 (C-H str, Ar-H), 1730 (C=O str), 1596 (C=N, str), 767 (C-S-C, str).
^{1}H-NMR ($CDCl_3$) (δ-ppm): 10.53 (s, 1H, NH), 7.98–6.34 (m, 11H, Ar-H), 4.2 (s, 2H, CH_2), 2.4 (3H, s, CH_3), 5.7 (1H, s, OH).

3.2.4.Synthesisof3-[4-(1H-4-methylbenzimidazol-2-yl)-2-hydroxy phenyl] -5(4-chlorobenzylidene) 2--phenyl- 1,3-thiazolidin-4-one (Compound 4a-4d)
A mixture of compound (3) (94.01 g, 0.01 mole) and sodium acetate (0.02 mole) in 10 ml glacial acetic acid has been added substituted benzaldehyde (4-chlorobenzaldehyde) (1.16 g, 0.01 mole) and the contents were refluxed for 14–16 h continuously on steam bath. After completion of reaction, the contents were poured into ice cold water. A solid mass is obtained, which was filtered, dried, and washed with hot water. The product is recrystallized from ethyl alcohol.

Compounds (4b-4d) were synthesized by the same manner with minor change in reaction conditions of refluxing time.

4a: Yield: 55%, M.P. 302°C, Colour: White crystals
Molecular Formula: $C_{30}H_{22}N_3O_2SCl$, Molecular weight = 523.5
Elemental analysis (Calculated %) C = 68.68 (68.76), H = 4.12 (4.20), N = 7.89 (8.02)
IR (KBr) (in Cm^{-1}) 3375 (NH str), 3025 (C-H str, Ar-H), 1685 (C=O str), 1590 (C=N, str), 760 (C-S-C, str), 675 (C-Cl str), 3470 (-OH free); 2930 (CH_3)

^{1}H-NMR ($CDCl_3$) (δ-ppm): 10.40 (s, 1H, NH), 7.4–6.4 (m, 15H, Ar-H), 6.16 (s, 1H, C=CH-Ar), 2.4 (3H, s, CH_3), 5.7 (1H, s, OH).

4b: Yield: 55%, M.P. 302°C, Color: White crystals
Molecular Formula: $C_{30}H_{22}N_3O_2SCl$, Molecular weight = 523.5
Elemental analysis (Calculated %) C = 68.68 (68.76), H = 4.12 (4.20), N = 7.89 (8.02)
IR (KBr) (in Cm^{-1}) 3370 (NH str), 3020 (C-H str, Ar-H), 1735 (C=O str), 1600 (C=N, str), 745 (C-S-C, str), 675 (C-Cl str), 3470 (-OH free); 2935 (CH_3)

^{1}H-NMR ($CDCl_3$) (δ-ppm): 10.32 (s, 1H, NH), 6.0–7.0 (m, 15H, Ar-H), 6.24 (s, 1H, C=CH-Ar), 3.36 (3H, s, OCH_3), 2.34 (3H, s, CH_3), 5.6 (1H, s, OH).

4c: Yield: 56%, M.P. 195°C, Color: light yellow crystals
Molecular Formula: $C_{32}H_{28}N_4O_2S$, Molecular weight = 532
Elemental analysis (Calculated %) C = 72.10 (72.18), H = 5.20 (5.26), N = 10.45 (10.52)
IR (KBr) (in Cm^{-1}) 3380 (NH str), 3025 (C-H str, Ar-H), 1682 (C=O str), 1585 (C=N, str), 1080 (C-O str), 740 (C-S-C, str), 3458 (-OH free); 2936 (CH_3)

^{1}H-NMR ($CDCl_3$) (δ-ppm): 10.4 (s, 1H, NH), 6.0–7.0 (m, 15H, Ar-H), 6.22 (s, 1H, C=CH-Ar), 2.92 (s, 6H, $N(CH_3)_2$), 2.32 (3H, s, CH_3), 5.5 (1H, s, OH).

4d: Yield: 40%, M.P. 177°C, Color: white crystals
Molecular Formula: $C_{30}H_{23}N_3O_2S$, Molecular weight = 489
Elemental analysis (Calculated %) C = 73.52 (73.62), H = 4.62 (4.70), N = 8.50 (8.58)
IR (KBr) (in Cm^{-1}) 3338 (NH str), 3026 (C-H str, Ar-H), 1700 (C=O str), 1580 (C=N, str), 730 (C-S-C, str), 3460 (-OH free); 2932 (CH_3)

^{1}H-NMR ($CDCl_3$) (δ-ppm): 10.42 (s, 1H, NH), 6.1–7.2 (m, 15H, Ar-H), 6.2 (s, 1H, C=CH-Ar), 2.4 (3H, s, CH_3), 5.6 (1H, s, OH).

3.2.5. Synthesis of 3-[4-(1H-4-methyl benzimidazol-2-yl)-2-hydroxy phenyl]-1-N-ethoxy phtyalimido-5- (4-chlorobenzylidene) 2--phenyl- 1,3-thiazolidin-4-one Compound (5a)
To a mixture containing compound 4a (5.08 g, 0.01 mole) and phthalimidoxy ethyl bromide (2.70 g., 0.01 mole) in 20 ml absolute ethyl alcohol; pyridine was added as a base, the whole contents were refluxed for 17–18 h on steam bath to complete the reaction. After removing the excess of solvent contents cooled to yield the colorless product, which was filtered, washed, and dried and after that recrystallized from ethanol.

Other compounds (5b-5d) were synthesized by the same manner with a minute change in the refluxation time and crystallization solvent etc.

Physical Properties of Compounds (5a-5d)

Compounds	Yield (%)	Rf	MP(°C)	Mol. Formula	Mol. Wt.
5a	62%	0.715	267	$C_{40}H_{29}ClN_4O_5S$	712.50
5b	65%	0.692	215	$C_{41}H_{32}N_4O_6S$	708
5c	60%	0.678	151	$C_{42}H_{35}N_5O_5S$	721
5d	54%	0.682	135	$C_{40}H_{30}N_4O_5S$	678

3.3. Spectral Data of Compounds (5a-5d)

5a: IR (KBr) (in Cm^{-1}): 3020 (C-H str, Ar-H), 2945 (C-H str, CH_2), 1735 (C=O str), 1595 (C=N, str), 1370 (N-O str), 670 (C-Cl str), 3465 (-OH free); 2930 (CH_3)

^{1}H-NMR ($CDCl_3$) (δ-ppm): 7.12–7.50 (m, 19H, Ar-H), 6.24 (s, 1H, C=CH-Ar), 4.4 (t, 2H, OCH_2), 3.7 (t, 2H, NCH_2), 2.4 (s, 3H, CH_3).

S. No.	Substituted (R) Benzaldehyde	% yield	M.P.(°C)	Colour	Found (Calc)%		
					C	H	N
5a	4-Cl	62	267	White	67.30 (67.36)	3.94 (4.07)	7.78 (7.85)
5b	4-OCH_3	65	215	White shining	69.40 (69.49)	4.42 (4.51)	7.80 (7.90)
5c	4-$(CH_3)_2N$	60	151	Yellowish white	69.80 (69.90)	4.79 (4.85)	9.60 (9.70)
5d	H	54	135	Dull white	70.70 (70.79)	4.36 (4.42)	8.17 (8.25)

MS (m/z): 713, 615, 566, 509, 482, 344, 254, 220, 168, 124.

5b: IR (KBr) (in Cm^{-1}): 3020 (C-H str, Ar-H), 2935 (C-H str, CH_2), 1748 (C=O str), 1565 (C=N str), 1350 (N-O str), 3470 (-OH free); 2940 (CH_3)

^{1}H-NMR ($CDCl_3$) (δ-ppm): 5.8–6.2 (m, 19H, Ar-H), 6.16 (s, 1H, C=CH-Ar), 4.6 (t, 2H, OCH_2), 3.58 (t, 2H, NCH_2), 3.74 (s, 3H, OCH_3), 2.4 (3H, s, CH_3), 5.6 (1H, s, OH)

MS (m/z): 708, 610, 566, 482, 477, 339, 249, 215, 163, 119.

5c: IR (KBr) (in Cm^{-1}): 3018 (C-H str, Ar-H), 2956 (C-H str, CH_2), 1770 (C=O str), 1590 (C=N, str), 1365 (N-O str), 3475 (-OH free); 2935 (CH_3)

^{1}H-NMR ($CDCl_3$) (δ-ppm): 5.75–6.0 (m, 19H, Ar-H), 6.18 (s, 1H, C=CH-Ar), 4.52 (t, 2H, OCH_2), 3.65 (t, 2H, NCH_2), 2.80 (s, 6H, $N(CH_3)_2$), 2.35 (3H, s, CH_3), 5.5 (1H, s, OH)

MS (m/z): 921, 588, 516, 439, 412, 336, 272, 220, 168, 124.

5d: IR (KBr) (in Cm^{-1}): 3035 (C-H str, Ar-H), 2950 (C-H str, CH_2), 1770 (C=O str), 1585 (C=N, str), 1385 (N-O str), 3470 (-OH free); 2935 (CH_3)

^{1}H-NMR ($CDCl_3$) (δ- ppm): 7.13–6.02 (m, 20H, Ar-H), 6.22 (s, 1H, C=CH-Ar), 4.65 (t, 2H, OCH_2), 3.56 (t, 2H, NCH_2), 2.34 (3H, s, CH_3), 5.4 (1H, s, OH)

MS (m/z): 678, 585, 528, 451, 412, 361, 323, 220, 168, 124.

3.4. Biological Activity of Newly Synthesized Compounds

3.4.1. Antibacterial evaluation

The synthesized compounds were subjected to antibacterial evaluation by well-diffusion method [33]. The zone of inhibition (mm) was measured in comparison with cephalexin. These compounds were subjected against four types of bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacillus cereus*, *Staphylococcus aureus*). The antibacterial activity was performed in nutrient agar medium containing *E. coli*, *P. aeruginosa* and *B. cereus*, *S. aureus* and the compounds used at concentrations (250 µg/well). The activity was determined after incubation for 24 h at 37°C by the comparison of inhibition of growth of bacteria by (cephalexin) using DMSO as the solvent.

3.4.2. Anti-inflammatory activity

Anti-inflammatory activity [34] of all newly synthesized derivatives (5a-5d) was determined by the carrageenan-induced rat paw edema model. Albino rats (100–200 g) were divided into three groups as control, test, and standard (six animals per group). Overnight fasted animals were used and during that period, only tap water was given. In general, indomethacin was used as standard drug. Both test and standard drugs were suspended in 1% carboxymethyl cellulose (CMC) and administered orally through gastric gavage needle. About 1% of CMC was administered in control group. After 1 h of administrating the compound, we induced the carrageenan (1%) by the sub planner surface of the right hind paws of animals. The initial paw volume and also the paw volume after 3 and 6 h of administrating carrageenan were measured. Percent paw edema inhibition was calculated.

4. RESULTS AND DISCUSSION

Final products (5a-5d) was obtained by the same manner as given in Scheme 1 and they were characterized by IR, NMR, and mass spectroscopy.

4.1. Antibacterial Activity

A novel series of substituted alkoxy phthalimide derivatives of 4-methyl-benzimidozolyl thiazolidin-4-one have been synthesized successfully in appreciable yields and screened for their antibacterial activity using well diffusion method against bacterial strains (*E. coli*, *P. aeruginosa* and *B. cereus*, *S. aureus*) [Table 1].

The antibacterial evaluation revealed that the newly synthesized Compounds 5a-d showed reasonable antibacterial activities against G (-) bacteria, such as *P. aeruginosa and* G (+) bacteria, such as *B. cereus* in comparison with cephalexin, which has no activity against these type of microbes.

Compound 5a showed significant activity against *P. aeruginosa* and reduction in antibacterial activities against *S. aureus* and *E. coli* as compared with cephalexin. Compound 5b showed significant activity against *P. aeruginosa* and *B. cereus*, as compared with cephalexin.

However, Compound 5c showed significant activity against *P. aeruginosa* and moderate antibacterial activities against *E. coli*, *S. aureus,* and *B. cereus* as compared with cephalexin.

Compound 5d showed very significant activity against *E. coli*, *P. aeruginosa,* and *B. cereus* and slight activity toward *S. aureus*. This result indicates that Compound 3d has a broader spectrum of antibacterial activities, that is, against both G (+) and G (-) bacteria.

It is concluded that the newly synthesized derivatives possess good antibacterial activities. Furthermore, the new derivative (Compound 5d) has significant activity against *P. auroginosa* and *B. cereus*.

4.2. Anti-inflammatory Study

4.2.1. Anti-inflammatory activities of compounds (5a-5d)

Columns	Dose Mg/Kg	Inhibition of paw edema after 3 h (%) 1	Inhibition of paw edema after 6 h (%) 2
5a	30	3.28±0.28	58.24
5b	30	2.48±0.23	56.48
5c	30	3.46±0.22	51.16
5d	30	1.62±0.27	70.98
Control	_	0 0.36±0.28	_
Indomethacin	40	1.78±0.340	66.44

1: Dose for 1–7: 30 mg/kg b.wt, 2: Dose for indomethacin 40 mg/Kg b.wt, mean±SEM, *n*+6

It is concluded that the newly synthesized derivatives possess good anti-inflammatory activities. Furthermore, the new derivative (compound 5d) has significant activity while other show moderate anti-inflammatory activity.

Table 1: Antibacterial activity of the new derivatives of thiazolidine (diameter of the zone of inhibition [mm]) at 250 µg/mL.

Compound	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillus cereus*
DMSO	–	–	–	–
Cephalexin	11	–	12	–
5a	9	12	8	–
5b	10	14	9	1
5c	10	15	10	11
5d	12	16	7	17

Key to symbols: (-) = no inhibition

5. CONCLUSION

IR, ^{1}H NMR, mass spectroscopy, and elemental analyses were used to characterize the structure of 4-Methyl Benzimidozolyl Thiazolidinones. These chemicals were sucessfully tested for pharmacological action, specifically anti-inflammatory and antibacterial activity.

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