Synthesis of 5,6-Dichloroindan-1-Acids and their Tetrazolyl Derivatives as Analgesic and Anti-inflammatory Agents

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Abstract: Indan derivatives, namely, 5-(5',6'-dichloroindan-1'-yl)-tetrazole (**12a**) and 5-(5',6'-dichloroindan-1'-yl)-methyltetrazole (**12b**), were synthesized conveniently from 5,6-dichloroindan-1-carboxylic acid (**9a**) and 5,6-dichloroindan-1-acetic acid (**9b**), respectively, as potential analgesic and anti-inflammatory agents. The analgesic and anti-inflammatory properties of **9a**, **9b**, **12a** and **12b** were evaluated by the acetic acid induced writhing in *Swiss albino* mice and the carrageenan-induced rat paw edema models, respectively. Compounds **9a** and **12a** exhibited significant analgesic activity with the doses of 50 and 100 mg/kg body weight, comparable to that of the positive controls, phenylbutazone, indomethacin and aminopyrine. The anti-inflammatory potencies of **9a** and **12a** were also comparable to that of the positive control, phenylbutazone. Compounds **9b** and **12b** showed analgesic and anti-inflammatory activities, but were weaker than that of compounds **9a** and **12a**.

Keywords: Indan acids, Indanyl tetrazoles, 5,6-dichloroindan-1-carboxylic acid, 5,6-dichloroindan-1-acetic Acid, 5-(5',6'-dichloroindan-1'-yl)-tetrazole, 5-(5',6'-dichloroindan-1'-yl)-methyltetrazole, Carrageenan, Analgesic activity, Anti-inflammatory activity.

INTRODUCTION

Indan ring system is regarded as an ideal chemical feature associated with various biological activities [1]. Among indan derivatives, 1*H*-indene-3-acetic acid-5-fluoro-2-methyl-1-[4-(methylsulfinyl)-phenyl]methylene (sulindac) and indan-1,3-dione are well known anti-inflammatory agent [2] and anticoagulant [3], respectively. Several indan derivatives, particularly indan acid derivatives, have been synthesized and their potential analgesic and anti-inflammatory properties have also been reported to date [4-14].

Tetrazole, an aromatic azapyrrole, exists in a tautomeric form. Although tetrazole itself does not exhibit any pharmacological activity, many of its derivatives possess interesting biological properties [15, 16]. The combined inductive effect of three tertiary nitrogen atoms gives tetrazole an acidic strength similar to that of aliphatic carboxylic acids. The metabolic stability of the tetrazole function, which is similar to that of carboxylic group, has inspired the syntheses of various potential therapeutic agents [17-19]. The replacement of carboxylic group by tetrazol-5-yl to a series of 1-substituted 3-(tetrazole-5-yl-methyl)-indole as analogues of indomethacin were synthesized [20]. Among them, the most active candidate was 1-(4-chlorobenzoyl)-3-(tetrazole-5-yl methyl)-indole. Similarly, a series of 5-(2-anilinophenyl)-tetrazoles were synthesized as analogs of flufenamic acid, which showed activity comparable to that of their corresponding acids. The most active anti-inflammatory tetrazoles were 5-[2-(3-trifluoromethylanilino)-phenyl]-tetrazoles and 5-[2-(2,6-dichloro-3-methylanilino)-phenyl]-tetrazoles. A series of arryltetrazolylalkanoic acids were prepared, and the maximum anti-inflammatory activity was observed with the compounds containing *meta*-halogenated aromatic substituents and a propionic acid residue at position 2 of the tetrazole ring [16].

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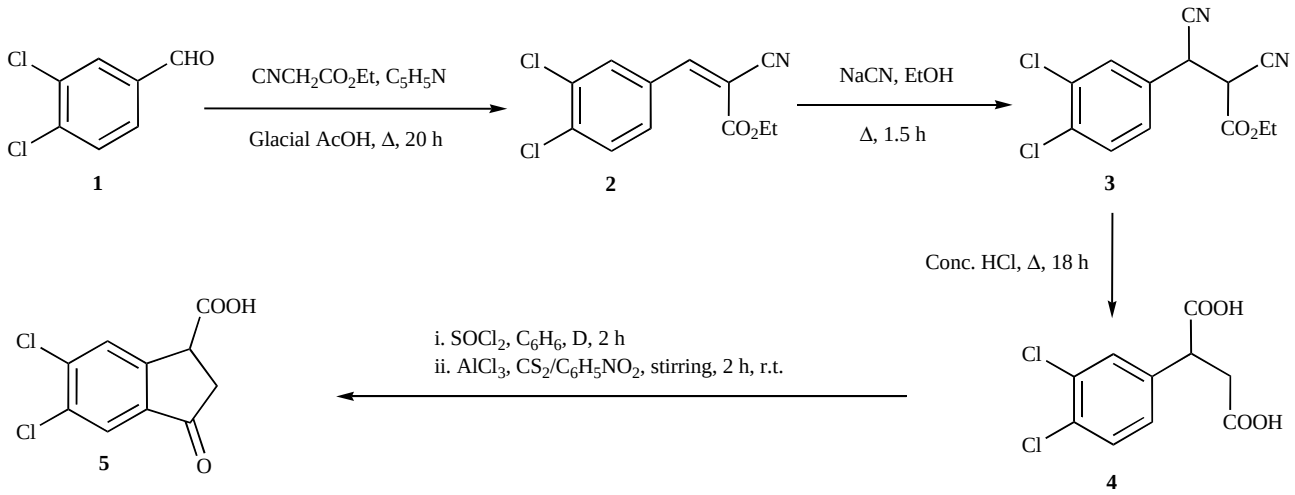
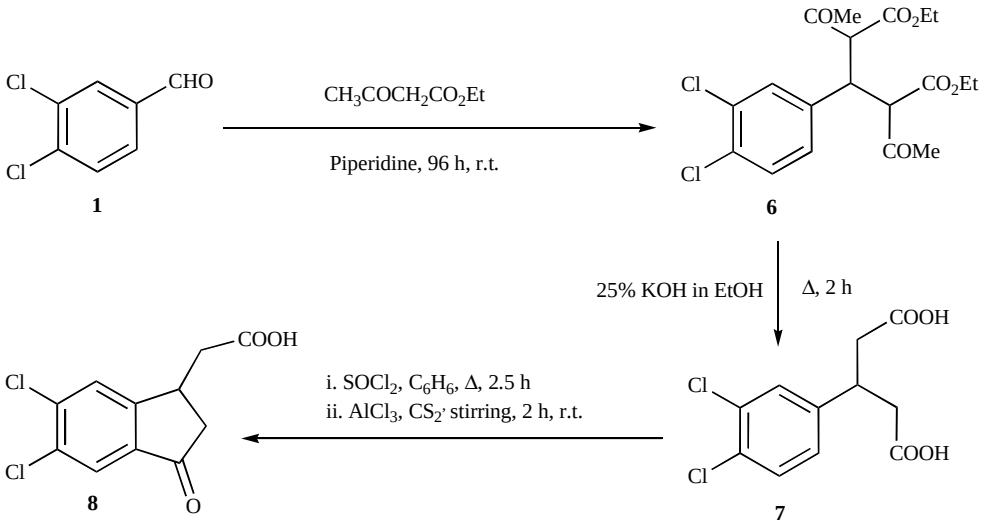


Scheme 1. Synthesis of 5,6-dichloro-3-oxo-indan-1-carboxylic Acid (**5**).



Scheme 2. Synthesis of 5,6-dichloro-3-oxo-indan-1-acetic acid (**8**).

It was, therefore, hypothesized that a combination of various substituted indanyl groups which was substituted at position 5 of the tetrazole moiety would possibly have better anti-inflammatory property. Working on this hypothesis, Lahiri and his co-workers [21-24] synthesized several simple 6-methoxy and 5,6-dimethoxy substituted indanyl tetrazoles and indanyl methyl tetrazoles with significant non-steroidal anti-inflammatory effect with low ulcerogenicity. Later, 6-chloro(indan-1'-yl)-tetrazole, 6-bromo(indan-1'-yl)-tetrazole, 6-chloro(indan-1'-yl)-methyltetrazole and 6-bromo(indan-1'-yl)-methyltetrazole were synthesized with promising analgesic activity in the acetic acid induce writhing model [6].

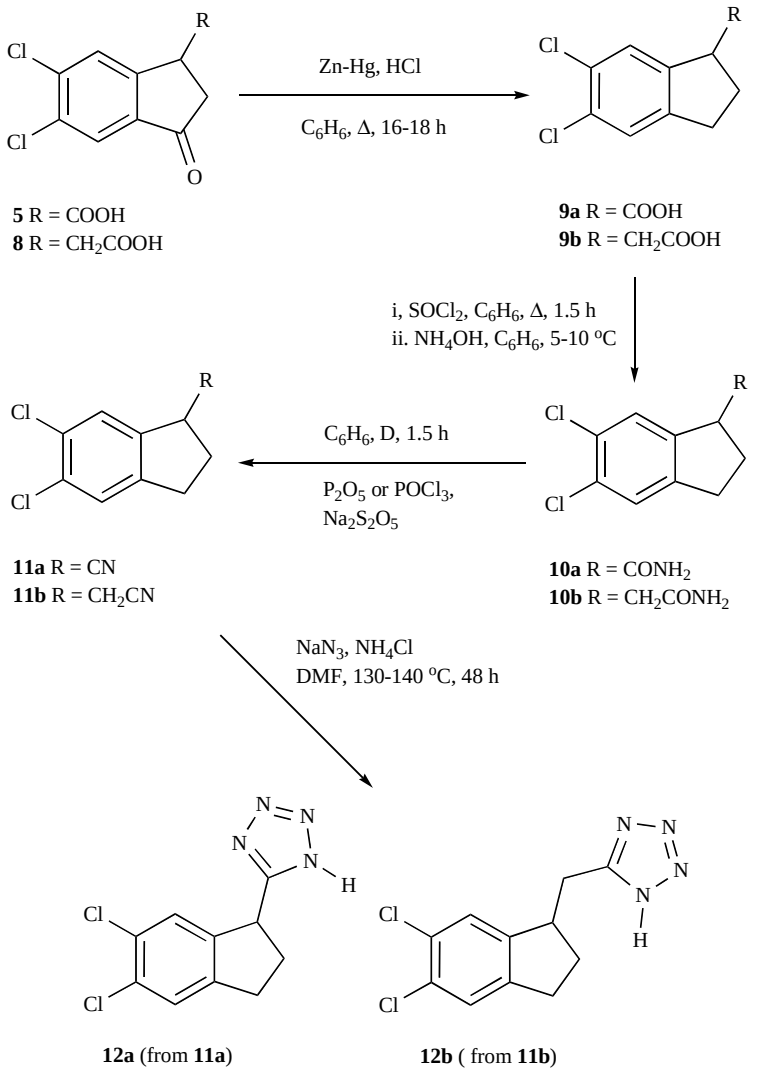
Since aromatic halogen substitution has been shown to be a reasonable means of increasing the analgesic and anti-inflammatory activity and widening the margin of safety [6, 13, 14], the objective of the current study was to synthesize 5,6-dichloroindan-1-carboxylic acid (**9a**), 5,6-dichloroindan-1-acetic acid (**9b**), 5-(5',6'-dichloroindan-1'-yl)-tetrazole (**12a**) and 5-(5',6'-dichloroindan-1'-yl)-methyl-tetrazole (**12b**), and to evaluate their analgesic and anti-inflammatory potentials in animal models.

CHEMISTRY AND ANALGESIC AND ANTI-INFLAMMTORY ACTIVITIES

Synthesis of 5,6-dichloroindan-1-carboxylic acid (9a), 5,6-dichloroindan-1-acetic acid (9b), 5-(5',6'-dichloroindan-1'-yl)-tetrazole (12a) and 5-(5',6'- dichloroindan-1'-yl)-methyltetrazole (12b)

The protocols for the synthesis of 5,6-dichloroindan-1-carboxylic acid (**9a**), 5,6-dichloroindan-1-acetic acid (**9b**), 5-(5',6'-dichloroindan-1'-yl)-tetrazole (**12a**) and 5-(5',6'-dichloroindan-1'-yl)-methyl-tetrazole (**12b**) are represented in Schemes **1**-**3**.

3,4-Dicholorobenzaldehyde (**1**) was treated with ethyl-cyanoacetate in dry benzene (C_6H_6) in the presence of pyridine (C_5H_5N) and glacial acetic acid (AcOH) to obtain 3,4-dichlorophenyl cyanoacrylic ester (**2**), which was further treated with NaCN to yield 3,4-dichlorophenyl α,β-dicyanoethyl propionate (**3**) (Scheme **1**). Compound **3** was acid hydrolyzed to afford 3,4-dichlorophenyl succinic acid (**4**), which on cyclization through the Freidel-Crafts acylation reaction produced 5,6-dichloro-3-oxo-indan-1-carboxylic acid (**5**) with good yield. 5,6-Dichloro-3-oxo-



Scheme 3. Synthesis of 5-(5',6'-dichloroindan-1'-yl)-tetrazole (**12a**) and 5-(5',6'-dichloroindan-1'-yl)-methyl-tetrazole (**12b**).

indan-1-acetic acid (**8**) was obtained in good yield by condensation of 3,4-dichlorobenzaldehyde (**1**) and ethylacetoacetate in presence of piperidine using the Knoevenagel reaction followed by hydrolysis and cyclization (Scheme **2**).

The 3-oxo-derivatives (**5** and **8**) were reduced to compounds **9a** and **9b**, respectively (Scheme **3**), which were further treated with thionyl chloride ($SOCl_2$) to obtain acid chlorides. Immediate addition of ammonia solution to the acid chlorides at 1-5°C afforded respective amides **10a** and **10b** in excellent yields. The amides (**10a** and **10b**) were dehydrated with P_2O_5 in dry C_6H_6 or in a mixture of $POCl_3$ and NaS_2O_5 (10:1 ratio) by refluxing for 2-4 h. After decomposing the reaction mixtures and working up, the respective nitriles **11a** and **11b** were obtained. Subsequently, the nitriles were allowed to react with activated NaN_3 in presence of NH_4Cl in DMF at 130-140°C for 48 h to afford the target compounds 5-(5',6'-dichloroindan-1'-yl)-tetrazole (**12a**) and 5-(5',6'-dichloroindan-1'-yl)-methyltetrazole (**12b**) as crystalline solid (Scheme **3**). The structures of compounds were confirmed by various spectral analyses as outlined in the experimental section.

Analgesic activity of 5,6-dichloroindan-1-carboxylic acid (9a), 5,6-dichloroindan-1-acetic acid (9b), 5-(5',6'-dichloroindan-1'-yl)-tetrazole (12a) and 5-(5',6'-dichloroindan-1'-yl)-methyltetrazole (12b)

The acetic acid induced writhing response is a sensitive procedure for the evaluation of peripherally acting analgesics. The analgesic activity of **9a**, **9b**, **12a** and **12b** (Table **1**) was measured by the acetic acid-induced writhing in *Swiss albino* mice. The significant ($p < 0.001$) analgesic activity, exhibited by the compounds **9a** and **12a** with the doses of 50 and 100 mg/kg body weight, was better than that of the reference compounds, phenylbutazone, indomethacin and aminopyrine, with the doses of 100, 50 and 30 mg/kg body weight, respectively. With the dose of 25 mg/kg body weight, **9b** exhibited almost similar potency ($p < 0.001$) to that of indomethacin. Compound **9b** ($p < 0.001$) and **12b** ($p < 0.001$) at 50 and 100 mg/kg weight, respectively, also showed good therapeutic activity, but was less than that of **9a** and **12a**. This investigation revealed that all compounds (**9a**, **9b**, **12a** and **12b**) displayed good peripheral analgesic activity with the doses of 50 and 100 mg/kg body weight. The writhing response observed after the treatment with syn-

Table 1. Analgesic Activity of 5,6-dichloroindan-1-caroxylic Acid (9a), 5,6-dichloroindan-1-acetic acid (9b), 5-(5′,6′-dichloroindan-1′-yl)-tetrazole (12a), 5-(5′,6′-dichloroindan-1′-yl)-methyltetrazole (12b) in the Acetic Acid Induced Writhing on *Albino* Mice

Test Samples	Dose (mg/kg Body Weight)	Writhing (Mean±SE); n=5	% Inhibition
9a	25	18.67 ± 1.56	44.55 [a]
	50	6.17 ± 1.07	81.68 [a]
	100	2.33 ± 0.56	93.08 [a]
9b	25	23.83 ± 1.38	29.22 [b]
	50	10.50 ± 1.07	68.88 [a]
	100	8.11± 0.86	75.91 [a]
12a	25	22.33± 1.64	33.68 [b]
	50	10.33± 1.33	69.32 [a]
	100	3.17± 0.64	90.58 [a]
12b	25	30.33± 1.56	09.11 [ns]
	50	12.83± 1.50	61.89 [a]
	100	10.33± 0.99	69.32 [a]
Phenylbutazone	100	16.67 ±1.61	50.49 [a]
Indometacin	50	19.50 ± 1.52	42.08 [a]
Aminopyrine	30	13.67± 0.90	59.40[a]
Control	-----	33.67± 1.91	-------

Probability values (calculated as compared to control using student's t-test): a < 0.001, b<0.01, ns < not significant.

thesized compounds was assumed to be mediated through peritoneal mast cell [25], acid sensing ion channels [26] and the prostaglandin pathways [27].

Anti-inflammatory activity of 5,6-dichloroindan-1-carboxylic acid (9a), 5,6-dichloroindan-1-acetic acid (9b), 5-(5',6'-dichloroindan-1'-yl)-tetrazole (12a) and 5-(5',6'-dichloroindan-1'-yl)-methyltetrazole (12b)

The anti-inflammatory activity of **9a**, **9b**, **12a** and **12b** was observed in the carrageenan induced rat paw edema model with the doses of 25 and 50 mg/kg body weight (Table **2**). The significant ($p < 0.001$) anti-inflammatory activity, exhibited by the compound **9a** and **12a** with the dose of 50 mg/kg body weight, was comparable to that of reference standard phenylbutazone (dose of 100 mg/kg body weight) after 3 h of carrageenan administration. Compounds **9b** ($p < 0.001$) and **12b** ($p < 0.001$) with the doses of 25 and 50 mg/kg body weight also displayed good anti-inflammatory activity. Compound **12b** exhibited almost similar effect as that of phenylbutazone in 1, 2 and 3 h after carrageenan administration. The inflammation in rat paw induced by carrageenan is believed to be biphasic [28]. The first phase of the inflammation is due to the release of histamine or serotonin, and the second phase is caused by the release of bradykinin, protease, prostaglandin and lysosome [29, 30]. Therefore, it could be assumed that the significant ($p < 0.001$) anti-inflammatory activity of **9a** and **12a** might be owing to the inhibition of the enzyme cyclooxygenase leading to inhibition of prostaglandin biosynthesis.

Indan derivatives, namely, 5-(5',6'-dicholoroindan-1'-yl)-tetrazole (**12a**) and 5-(5',6'-dicholoroindan-1'-yl)-methyl-tetrazole (**12b**), were synthesized conveniently from 5,6-dichloroindan-1-carboxylic acid (**9a**) and 5,6-dichloroindan-1-acetic acid (**9b**), respectively. The observed significant analgesic and anti-inflammatory activity of these newly synthesized indan acids and indanyl tetrazoles, particularly of **9a** and **12a**, could be a useful indicator for further development of indan-based effective analgesic and anti-inflammatory agents.

EXPERIMENTAL SECTION

General

The chemicals and solvents used in various reaction procedures were obtained from Merck Co. (Germany); BDH **(**India) and SD Fine Chemicals (India). The starting material 3,4-dichloro-benzaldehyde 98% (25 g) was purchased from Acros Organics, New Jersey, USA and used without purification. The melting points were determined by using an Adco Melting Point Apparatus and were uncorrected. Thin-layer chromatography was performed on Kieselgel 60 F_{254} pre-coated plates (Merck). The absorption maxima (λ_{max} in nm) were determined in absolute methanol by using a Genesis-2 UV-Vis spectrophotometer. By using an 8010M FTIR spectrometer, the characteristic IR absorption bands (ν_{max} in

Table 2. Anti-inflammatory Activity of 5, 6-dichloroindan-1-carboxylic acid (9a), 5, 6-dichloroindan-1-acetic acid (9b), 5-(5′, 6′-dichloroindan-1′-yl)-tetrazole (12a) and 5-(5′, 6′-dichloroindan-1′-yl)-methyltetrazole (12b) in the Carrageenan-induced Rat Paw Edema Model

Test Samples	Dose mg/kg	Percent Change in Paw Edema (x ± SE)				
		1 h	2 h	3 h	4 h	24 h
9a	25	70.0 ± 3.01 [b] (19.35)[*]	73.4 ± 2.80 [a] (26.45)	90.3 ± 2.88 [a] (30.11)	87.6 ± 3.36 [a] (27.84)	78.0±3.47[e] (13.04)
	50	63.3 ± 2.39 [a] (27.07)	64.1 ± 2.32[a] (35.77)	71.7 ± 2.63[a] (44.51)	71.3 ± 2.93 [a] (41.27)	78.5 ± 1.89[d] (12.48)
9b	25	72.8 ± 4.04 [d] (16.13)	76.7 ± 5.36 [c] (23.15)	93.2 ± 4.06[a] (27.86)	91.4 ± 2.79 [a] (24.71)	79.8 ± 3.31[e] (11.03)
	50	71.5 ± 1.28 [a] (17.62)	72.8 ± 1.43 [a] (27.05)	84.1 ± 1.40[a] (34.91)	91.2 ± 1.95 [a] (24.87)	86.1 ± 2.01[ns] (4.01)
12a	25	72.2 ± 1.92 [a] (16.82)	77.4 ± 1.77[a] (22.44)	95.4 ± 2.18 [a] (26.16)	96.6 ± 2.96 [a] (20.42)	79.1± 2.82 [e] (11.82)
	50	61.8 ± 2.10[a] (28.80)	66.6 ± 1.69 [a] (33.17)	74.4 ± 2.28 [a] (42.41)	72.6 ± 1.84 [a] (40.19)	70.8±1.08[a] (21.07)
12b	25	72.4 ± 2.30 [b] (16.58)	79.8 ± 2.51[b] (20.04)	96.6 ± 3.01 [a] (25.23)	94.6 ± 2.88 [a] (22.07)	78.8± 2.7 [e] (12.15)
	50	65.2 ± 2.75 [a] (24.88)	67.8 ± 2.77 [a] (32.06)	78.8 ± 2.42 [a] (39.01)	82.6 ± 2.68 [a] (31.96)	74.5 ± 2.24 [c] (16.94)
Phenylbutazone	100	67.2 ± 2.16 [a] (22.58)	68.4 ± 1.14 [a] (31.46)	77.6 ± 3.0 [a] (39.93)	76.2 ± 2.46 [a] (37.23)	73.6 ± 1.65 [b] (17.94)
Control	----	86.8 ± 2.19	99.8 ± 3.54	129.2 ± 2.79	121.4 ± 2.10	89.7 ± 2.75

* Figures in parentheses indicate percent inhibition of paw edema.
[a-c] Probability values (calculated as compared to control using student's t-test):
a < 0.001, b < 0.002, c < 0.01, d < 0.02, e < 0.05; ns < not significant All values are means of five rats.

cm^{-1}) were recorded on KBr disk. The ^1H NMR and ^{13}C NMR spectra of the synthesized compounds were recorded on a Varian VXR-500 spectrometer and JEOL 500 spectrometer (500 MHz) as solutions in deuterodimethyl sulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) were expressed in ppm units downfield from TMS, and the coupling constant *J* in Hz. MS analyses were performed on a Finnigan MAT95 spectrometer. The studies involving mice and rats were approved by the Ethical Review Committee (approval number: SCB090111) Biological Science, University of Dhaka, Bangladesh, and the experiments were carried out strictly in accordance with the guidelines provided by the World Health Organization.

Synthesis of Compounds

Preparation of 3,4-dichlorophenyl Cyanoacrylate (2)

3,4-Dicholorobenzaldehyde (**1**, 10.5 g, 0.06 mole) was treated with ethylcyanoacetate (6.78 g, 0.06 mole) in dry C_6H_6 in presence of C_5H_5N (2 mL) and glacial AcOH (2 mL). The reaction mixture was refluxed for 20 h in an oil bath. The mixture was then evaporated to dryness under reduced pressure. The solid residue was filtered, washed with water, HCl (5%) and again with cold water, dried and crystallized in aqueous ethanol (aq. EtOH, 25%) to obtain 3,4-dichlorophenyl cyanoacrylic ester (**2**, 91.36% yield).

Crystalline solid, mp. 126-128ºC. FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 212 and $[M+H]^+$ 214 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 212.0032 calcd. 212.0034 for $C_{10}H_8Cl_2N$.

Preparation of 3,4-dicholorophenyl Succinic Acid (4)

The 3,4-dichlorophenyl cyanoacrylic ester (**2**, 13.15 g, 0.05 mole) was treated with sodium cyanide (NaCN, 2.45 g, 0.05 mole) dissolving it in 10 mL of water. The reaction mixture was refluxed in presence of 50% aq. EtOH (100 mL) for 1.5 h. The reaction mixture was cooled and poured in 300 mL of water. Conc. HCl (150 mL) was added to it and kept for overnight. The mixture was then extracted with chloroform ($CHCl_3$, 50 mL) for three times. The pooled extract was washed with water, dried over baked sodium sulfate (Na_2SO_4) and evaporated. The product 3,4-dichlorophenyl α,β-dicyanoethyl propionate (**3**, 89.78%, m.p. 104-106ºC) thus formed was hydrolyzed by refluxing with conc. HCl (150 mL) to obtain the target compound **4**, separated as a white solid upon cooling. The white solid (**4**) was then filtered from the reaction mixture, washed with cool water, dried and re-crystallized from hot water with a yield of 67.8%.

Crystalline solid, mp. 196-198ºC. UV, (MeOH) λ_{max} in nm: 226. IR, (KBr) ν_{max} in cm^{-1}: 1695, 660. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.53 (dd, 1H, *J* = 8.0, 1.7, H-6), 7.38 (d, 1H, *J* = 8.0 Hz, H-5), 7.33 (d, 1H, *J* = 1.7 Hz, H-2), 3.78 (dd, 1H, *J* = 7.0, 4.0, H-β), 2.84 (m, 2H, H-α). FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 263 and $[M+H]^+$ 265 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 262.9876 calcd. 262.9877 for $C_{10}H_9Cl_2O_4$.

Preparation of 3,4-dichlorobenzylidine-bis-acetoacetate (6)

Compound **1** (25 g; 0.143 mole) was condensed with ethyl acetoacetate (37.22 g; 0.286 mole) in 1:2 molar ratio in presence of piperidine (2.5 mL) and allowed the reaction mixture to stay in anhydrous condition for 96 h at r. t. following the Hey and Kohn method [31]. After completion of the reaction, a yellow solid mass was obtained. It was then crushed in a mortar and pestle and washed with ether to remove piperidine. The white crystalline powder was recrystallized from acetone-water to obtain 3,4-dichlorobenzylidine-*bis*-acetoacetate (**6**, 49 g, 86.25% yield).

White crystalline solid, mp. 158-160°C. FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 301 and $[M+H]^+$ 303 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 301.0760, calcd. 301.0762 for $C_{10}H_8Cl_2N$.

Preparation of 3,4-dichlorophenyl Glutaric Acid (7)

Compound **6** (0.117 mole) was hydrolyzed in presence of 100 mL alcoholic solution of KOH (25%) by refluxing for 2.5 h. The alcohol was then distilled off under reduced pressure, diluted with water, washed with $CHCl_3$ and neutralized by conc. HCl in cold condition with continuous stirring. The precipitation thus formed was filtered and re-crystallized from aq. EtOH to obtain target compound (**7**) as crystalline solid in 81.3% yield.

Crystalline solid, mp. 168-170ºC. UV (MeOH) λ_{max} in nm: 222. IR (KBr) ν_{max} in cm^{-1}: 1700, 640. ^1H NMR (500 MHz, DMSO-d_6) δ: 11.88 (bs, 1H, COOH), 11.80 (bs, 1H, COOH), 7.44 (dd, 1H, *J* = 8.0, 1.6, H-6), 7.40 (d, 1H, *J* = 8.0 Hz, H-5), 7.35 (d, 1H, *J* = 1.6 Hz, H-2), 2.53 (dd, 1H, *J* = 5.0, 4.5, H-β), 2.44 (m, 4H, H-α and H-γ); FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 277 and $[M+H]^+$ 279 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 277.0034 calcd. 277.0034 for $C_{11}H_{11}Cl_2O_4$.

Preparation of 5,6-dichloro-3-oxo-indan-1-acid (5 and 8)

The diacids (**4** and **7**) (0.028 mole each) were separately converted to respective diacylchlorides by refluxing with $SOCl_2$ (sp. gr. 1.631; 6.60 g; 0.056 mole) for 1.5 h in dry C_6H_6 (40 mL). Benzene and excess $SOCl_2$ were removed *in vaccuo* to obtain diacylchlorides as liquid. Immediately, anhydrous aluminum chloride ($AlCl_3$, 0.084 moles) was poured into the reaction mixture in portion-wise in well stirred condition using carbon disulfide (CS_2, 40 mL) as a solvent. The mixture was stirred for 2 h at r. t. Then it was decomposed in ice water mixture (300 mL). The solvent CS_2 was evaporated on hot water bath. The precipitates formed after cooling of the mixture were filtered, washed thoroughly with water, dried and re-crystallized from aq. EtOH (25%) to obtain target compounds **5** (4.60 g, 67.05% yield) and **8** (4.85 g, 66.85% yield) separately.

Crystalline solid [5,6-dichloro-3-oxo-indan-1-carboxylic acid (**5**)], mp. 182-184ºC. UV (MeOH) λ_{max} in nm: 254. IR (KBr) ν_{max} in cm^{-1}: 1695, 1600, 640. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.80 (s, 1H, H-4), 7.76 (s, 1H, H-7), 4.20 (t, 1H, *J* = 7.5 Hz, H-1), 2.94 (dd, 1H, *J* =14.0, 4.5, H-2a), 2.68 (dd, 1H, *J* = 14.0, 7.5, H-2b). FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 245 and $[M+H]^+$ 247 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 244.9770, calcd. 244.9772 for $C_{10}H_7Cl_2O_3$.

Crystalline solied [5,6-dichloro-3-oxo-indan-1-acetic acid (**8**)], mp. 140-142ºC. UV (MeOH) λ_{max} in nm: 255. IR (KBr) ν_{max} in cm^{-1}: 1695, 1600, 640. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.84 (s, 1H, H-4), 7.78 (s, 1H, H-7); 4.46 (m, 1H, H-1), 3.82 (dd, 1H, *J* = 13.5, 5.5, H-α), 3.65 (dd, 1H, *J* = 14.0, 2.5, H-2a), 3.44 (dd, 1H, *J* = 13.5, 7.5, H-α'), 2.82 (dd, 1H, *J* = 14.0, 3.5, H-2b); FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 259 and $[M+H]^+$ 261 (intensity ratio: 3:1, respectively); HR-FABMS *m/z*: $[M+H]^+$ 258.9927 calcd. 258.9929 for $C_{11}H_9Cl_2O_3$.

Preparation of 5,6-dichloroindan-1-acids (9a and 9b)

Compounds **5** and **8** (0.018 mole each) were separately treated with amalgamated zinc (20 g), water (15 mL), conc. HCl (20 mL) and C_6H_6 (30 mL) as a solvent and refluxed following the Clemmensen reduction process in a water-bath for 16-18 h until the reaction mixtures gave no positive result in the test for a keto functionality. The C_6H_6 layer was separated and the aqueous layer was extracted with C_6H_6 (20 x 3 = 60 mL) and combined together. The combined C_6H_6 layers were washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the yellowish white solid thus formed was dried and re-crystallized from aq. EtOH (25%) to obtain separately the target compounds, 5,6-dichloroindan-1-carboxylic acid (**9a**, 3.36 g, 80.96% yield) and 5,6-dichloroindan-1-acitic acid (**9b**, 3.67 g, 83.38% yield).

White crystalline solid [5,6-dichloroindan-1-carboxylic acid **(9a)**], mp. 118-120ºC. UV (MeOH) λ_{max} in nm: 280. IR (KBr) ν_{max} in cm^{-1}: 1690, 1600, 640. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.50 (s, 2H, H-4 and H-7), 4.00 (t, 1H, *J* = 8.0 Hz, H-1), 2.90 (ddd, 1H, *J* = 16.0, 8.5, 6.0, H-3a), 2.80 (ddd, 1H, *J* = 16.0, 8.0, 7.5, H-3b), 2.20 (m, 2H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 173.8 (1-COOH), 145.0 (C-6), 142.3 (C-5), 129.6 (C-7), 128.5 (C-4), 126.5 (C-8), 126.3 (C-9), 49.0 (C-1), 30.6 (C-3), 28.7 (C-2). FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 231 and $[M+H]^+$ 233 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 230.9981 calcd. 230.9980 for $C_{10}H_9Cl_2O_2$.

Yellowish white crystalline solid [5,6-dichloroindan-1-acitic acid **(9b)**], mp. 48-49ºC. UV (MeOH) λ_{max} in nm: 280. IR (KBr) ν_{max} in cm^{-1}: 1690, 1600, 640. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.45 (s, 1H, H-7), 7.43 (s, 1H, H-4), 3.40 (t, 1H, *J* = 8.0 Hz, H-1), 2.80 (ddd, 1H, *J* = 12.5, 8.5, 4.0, H-3a), 2.70 (dd, 1H, *J* = 16.0, 7.0, H-10a), 2.30 (dd, 1H, *J* = 16.0, 8.0, H-10b), 2.20 (ddd, 1H, *J* = 12.5, 7.5, 4.5, H-3b), 1.60 (m, 2H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 173.3 (10-COOH), 147.1 (C-6), 144.8 (C-5), 128.8 (C-7), 128.5 (C-4), 126.1 (C-8), 125.5 (C-8), 49.4 (C-1), 38.7 (C-10), 32.1 (C-3), 30.2 (C-2). FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 245 and $[M+H]^+$ 247 (intensity ratio: 3:1, respectively). HR-

FABMS *m/z*: $[M+H]^+$ 245.0134 calcd. 245.0136 for $C_{11}H_{11}Cl_2O_2$.

Preparation of 5,6-dichloroindan-1-amides (10a and 10b)

5,6-Dichloroindan-1-acids (**9a** and **9b**) (1 mole each) were treated individually with $SOCl_2$ (1.5 mole) in dry C_6H_6 and refluxed for 1.5 h. The acid chlorides thus formed were made free from excess $SOCl_2$ *in vacuo* and immediately dissolved in dry C_6H_6. The solutions were added drop wise to an excess solution of NH_4OH (50 mL) at 1-5°C. The reaction mixtures were saturated with NaCl and then extracted with C_6H_6. The C_6H_6 layer of respective compound was then vigorously shaken with saturated sodium bicarbonate solution and washed with distilled water, dried over anhydrous Na_2SO_4. The combined C_6H_6 layers were then distilled off under reduced pressure and the solid masses thus obtained were re-crystallized from aq. EtOH (25%) to obtain the target compounds 5,6-dichloroindan-1-carboxamide (**10a**, 1.72 g, 86.25%) and 5,6-dichloroindan-1-acetamide (**10b**, 2.2 g, 88.0%).

White crystalline solid [5,6-dichloroindan-1-carboxamide (**10a**)], mp. 180-182ºC. UV (MeOH) λ_{max} in nm: 280. IR (KBr) ν_{max} in cm^{-1}: 3335, 1662. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.40 (s, 1H, H-7), 7.30 (s, 1H, H-4), 5.60 (s, 1H, NH), 5.60 (s, 1H, NH'), 3.80 (t, 1H, *J* = 7.5, H-1), 3.00 (m, 1H, H-3a), 2.80 (m, 1H, H-3b), 2.40 (m, 1H, H-2a), 2.30 (m, 1H, H-2b). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 175.0 (1-$CONH_2$), 144.7 (C-6), 141.4 (C-5), 131.7 (C-7), 130.6 (C-4), 126.6 (C-8), 126.3 (C-9), 51.2 (C-1), 31.3 (C-3), 30.7 (C-2). FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 230 and $[M+H]^+$ 232 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 230.0139 calcd. 230.0139 for $C_{10}H_{10}Cl_2NO$.

White crystalline solid [5,6-dichloroindan-1-acetamide (**10b**)], mp. 138-1409ºC. UV (MeOH) λ_{max} in nm: 280. IR (KBr) ν_{max} in cm^{-1}: 3339, 1659. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.20 (s, 2H, H-4 and H-7), 5.50 (s, 1H, NH), 5.40 (s, 1H, NH'), 3.60 (m, 1H, H-1), 2.80 (m, 2H, H-3), 2.53 (dd, 1H, *J* = 15.0, 7.0, H-10a), 2.44 (m, 1H, H-2a), 2.30 (dd, 1H, *J* = 15.0, 7.0, H-10b), 1.71 (m, 1H, H-2b). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 173.3 (10-$CONH_2$), 146.2 (C-6), 144.0 (C-5), 130.5 (C-7), 130.0 (C-4), 126.3 (C-8), 125.4 (C-9), 41.0 (C-1), 40.9 (C-10), 32.9 (C-3), 30.7 (C-2). FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 244 and $[M+H]^+$ 246 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 244.0296 calcd. 244.0296 for $C_{11}H_{12}Cl_2NO$.

Preparation of 5,6-dichloroindan-1-nitriles (11a and 11b)

5,6-Dichloroindan-1-amides (**10a** and **10b**) (1 mole each) was mixed separately with P_2O_5 (5 moles) and was refluxed for 1.5 h using dry C_6H_6 following the method described previously. The reaction mixture was cooled and decomposed by addition of ice-water. After complete decomposition, the mixture was extracted with C_6H_6. The C_6H_6 layer was washed successively with 10% $NaHCO_3$ solution and distilled water and dried over anhydrous Na_2SO_4.

Alternatively, the nitriles could be prepared by dehydrating the amides. Compounds **10**a and **10b** (1 mole each) was mixed individually with $POCl_3$ (10 moles) and $Na_2S_2O_5$ (1 mole) in a round bottom flask. When the reaction began, the mixture was warmed to 70°C on a water bath. The temperature was slowly raised to 95°C where it was maintained for 2 h. After quenching the reaction with ice, the nitriles (**11a** and **11b**) were extracted with ether and dried over anhydrous Na_2SO_4. The dried ether layer was distilled off under reduced pressure. The residues obtained as crystalline solid for 5,6-dichloroindan-1-carbonitrile (**11a**, 1.36 g, 95% yield) and 5,6-dichloeoindan-1-acetonitrile (**11b**, 1.33 g, 88.7% yield) were re-crystallized from aq. EtOH (25%).

Yellowish white crystalline solid [5,6-dichloroindan-1-carbonitrile (**11a**)], mp. 94-96ºC. UV (MeOH) λ_{max} in nm: 280. IR (KBr) ν_{max} cm^{-1}: 2241. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.50 (s, 1H, H-7), 7.40 (s, 1H, H-4), 4.00 (t, 1H, *J* = 7.5, H-1), 3.00 (m, 1H, H-3a), 2.90 (m, 1H, H-3b), 2.60 (m, 1H, H-2a), 2.40 (m, 1H, H-2b). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 142.9 (C-6), 140.2 (C-5), 132.8 (C-7), 131.4 (C-4), 126.8 (C-8), 126.1 (C-9), 119.9 (CN), 34.1 (C-1), 31.5 (C-3), 30.9 (C-2). FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 212 and $[M+H]^+$ 214 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 212.0035 calcd. 212.0034 for $C_{10}H_8Cl_2N$.

White crystalline solid [5,6-dichloeoindan-1-acetonitrile (**11b**)], mp. 56-58°C. UV, (MeOH) λ_{max} in nm: 280. IR (KBr) ν_{max} cm^{-1}: 2247. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.30 (s, 2H, H-4 and H-7), 3.66 (m, 1H, H-1), 3.04 (bd, 2H, *J* = 7.6 Hz, H-10), 2.81 (m, 2H, H-3), 2.43 (m, 1H, H-2a), 1.75 (m, 1H, H-2b). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 143.9 (C-6), 143.4 (C-5), 131.0 (C-7), 130.6 (C-4), 126.7 (C-8), 125.3 (C-9), 118.1 (CN), 40.9 (C-10), 40.8 (C-1), 31.9 (C-3), 30.5 (C-2). FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 226 and $[M+H]^+$ 228 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 226.0188 calcd. 226.0190 for $C_{11}H_{10}Cl_2N$.

Preparation of 5-(5',6'-dichloroindan-1'-yl)-tetrazole (12a) and 5-(5',6'-dichloroindan-1'-yl)-methyltetrazole (12b)

Activated sodium azide (NaN_3) was prepared by taking NaN_3 (10 g) in a glass mortar, adding 5-8 drops of hydrazine hydrate to it, triturating the mixture and keeping it over night. The mixture was taken into a beaker and dissolved in 8-10 mL of water. Acetone (500-600 mL) was added to it until precipitation occurred. It was kept undisturbed for 2 h. Then the crystals were collected by filtration and dried.

The **11a** and **11b** (1 mole each) were added separately to activated sodium azide (2 moles) and ammonium chloride (2 moles), and refluxed at 130-140°C for 48 h using dimethylformamide (DMF) as the solvent following the method of Finnegan *et al.* [32]. Subsequently, the DMF was distilled off under reduced pressure and the solid mass obtained was taken up in warm 5% aq. KOH solution. The cooled alkaline solution was filtered, extracted with ether, and the ether extract was made acidic (pH~2) with conc. HCl to obtain the precipitates of 5-(6'-haloindan-1'-yl)-tetrazoles (**12a**, 1.0 g, 50.01% yield) and 5-(6'-haloindan-1'-yl)-methyltetrazoles (**12b**, 0.98 g, 49% yield) separately. The precipitates were washed with water and re-crystallized from hot water.

White crystalline solid [5-(5',6'-dichloroindan-1'-yl)-tetrazole (**12a**)], mp. 158-160°C. UV (MeOH) λ_{max} in nm: 280 nm. IR (KBr) ν_{max} in cm^{-1}: 271 (bending, C-N=N-N), 1578 (C-N, cyclic). ^1H NMR (500 MHz, DMSO-d_6) δ: 7.30 (s, 1H, H-7), 7.20 (s, 1H, H-4), 4.70 (t, 1H, *J* = 7.5, H-1), 3.10 (m, 1H, H-3a), 3.00 (m, 1H, H-3b), 2.70 (m, 1H, H-2a),

2.40 (m, 1H, H-2b). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 144.0 (C-6), 141.9 (C-5), 131.9 (C-7), 130.7 (C-4), 126.6 (C-8), 126.4 (C-9), 98.1 (C-10), 40.1 (C-1), 32.6 (C-3), 31.1 (C-2). FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 255 and $[M+H]^+$ 257 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 255.0201 calcd. 255.0204 for $C_{10}H_9Cl_2N_4$.

White crystalline solid [5-(5',6'-dichloroindan-1'-yl)-methyltetrazole (**12b**)], mp. 166-168°C. UV (MeOH) λ_{max} in nm 280. IR (KBr) ν_{max} in cm^{-1}: 269 (bending, C-N=N-N), 1556 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.30 (s, 2H, H-7), 7.20 (s, 2H, H-4), 3.65 (m, 1H, H-1), 3.30 (dd, 1H, *J* = 15.0, 6.0 Hz, H-10a), 3.00 (dd, 1H, *J* = 15.0, 9.0 Hz, H-10b), 2.90 (m, 2H, H-3a), 2.80 (m, 1H, H-2b), 2.30 (m, 1H, H-2a), 1.82 (m, 1H, H-2b); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 151.1 (C-6), 145.7 (C-5), 132.9 (C-7), 131.8 (C-4), 127.4 (C-8), 126.5 (C-9), 99.8 (C-11, C≡N), 44.2 (C-10), 32.9 (C-1), 31.2 (C-3), 29.2 (C-2). FABMS (+ve ion mode) *m/z*: $[M+H]^+$ 269 and $[M+H]^+$ 271 (intensity ratio: 3:1, respectively). HR-FABMS *m/z*: $[M+H]^+$ 269.0360 calcd. 269.0361 for $C_{11}H_{11}Cl_2N_4$.

Evaluation of Analgesic and Anti-inflammatory Activity

Animals

Young *Swiss albino* mice aged 4-5 weeks weighed 20-25 g of either sex were used for the assessment of analgesic activity, and adult Wister rats of either sex weighing 150±10 g were used for the assessment of anti-inflammatory activity. They were collected from the animal house of the International Center for Diarrheal Diseases and Research, Bangladesh (ICDDR,B), Mohakhali, Dhaka. The ICDDR, B formulated food pellets were supplied to the animals and water *at libitum*. They were kept in polyvinyl cages under controlled room temperature (25±2°C) in the laboratory environment under 12 h dark and 12 h light cycle for seven days; were fasted overnight and weighed before the experiment. The study involving rats was approved by the Ethical Review Committee Biological Science, University of Dhaka, Bangladesh, and the experiments were carried out strictly in accordance with the guidelines provided by the World Health Organization.

Evaluation of Analgesic Activity

Adult *Swiss albino* mice were used to study the analgesic activity by the acetic acid-induced writhing test as described by Vogel and Vogel [27] with slight modifications. Animals were divided into different groups consisted of five in each. Test drugs were given orally to the respective groups of animals at dose levels of 25 and 50 mg/kg body weight and the standard drugs phenylbutazone and indomethacin were given at doses of 100 and 50 mg/kg body weight, respectively. Control mice were treated with normal saline only. After 45 min of drug administration, acetic acid solution (0.7%, 0.10 mL/10g) was administered intraperitoneally (i.p.) to the each group of animals. After an interval of ten minutes, numbers of writhing were counted for another 10 min. The percent inhibition of writhing was measured using the following formula.

$$\text{Percent inhibition} = \frac{W_c - W_t}{W_c} \times 100$$

Where W_C represents the average writhing produced by the control group and W_t represents the average writhing produced by the test group, respectively.

Evaluation of Anti-inflammatory Activity

Adult Wister rats were used in this study. The anti-inflammatory activity was studied by the method described by Winter *et al*. [33]. The animals were randomly divided into different groups consisted of five rats in each group. The test compounds at doses of 25 and 50 mg/kg of body weight were administered by gavage. Phenylbutazone was given *per oral* at a dose of 100 mg/kg body weight as a standard anti-inflammatory drug. One group of rats given only saline solution was served as control (Table **2**). After 1 h of drug administration, 0.1 mL of 1% (W/V) carrageenan in sterile saline solution was injected into the subplanter surface of the right hind paw for the production of acute inflammation. Paw volumes were measured up to a fixed mark plethysmometrically (Ugo Basile, Italy) after 1, 2, 3, 4 and 24 h of carrageenan injection. The percent inhibition of paw volume was measured using the following formula.

$$\text{Percent inhibition} = \frac{Vc - Vt}{Vc} \times 100$$

Where V_C represents the average paw volume of the control group and V_t represents the average paw volume of the test group, respectively.

Statistical Analyses

Statistical analysis was performed using the SPSS-11.5 statistical Software for Windows. Experimental values were expressed as mean ±SEM. Independent Sample t-test was carried out for statistical comparison.

CONFLICTS OF INTEREST

There is no conflict of interest associated with work presented in this paper.

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