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Synthesis and Pharmacological Activities of 2,3,4,10-Tetrahydro-3,10-dioxo-2-(substituted phenyl)-[1,2,4]triazino[4,3-a]indoles

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In this study, for developing potent analgesic and antiinflammatory compounds, some new 3-substituted 1,2,4-triazino-indole derivatives have been synthesized and performed preliminary screening of their *in vivo* analgesic and antiinflammatory activities at a single dose of 100 mg/kg in mice by acetic acid induced writhing test and a carrageenan induced hind paw edema model, respectively. Compounds **4b, 4d** and **4g** exhibited good analgesic activity and compounds **4a** and **4g** showed very good antiinflammatory activity.

Key Words: Isatin, 1,2,4-Triazines, Analgesic, Antiinflammatory activity.

INTRODUCTION

Non-steroidal antiinflammatory drugs (NSAIDs) show the same side effects to a certain extent, including gastrointestinal, renal and hematological toxicities. Therefore, the development of new compounds in which their analgesic and antiinflammatory activites are separated from the above side effects has been a challenge for many years. Early studies demonstrated that isatin derivatives exhibit a variety of pharmacological effects, including analgesic[1,2] and antiinflammatory activity[3]. In addition 1,2,4-trazines are associated with diverse biological activities[4–7]. Therefore, it was envisioned that a new series of isatin fused 1,2,4-triazines would possess high analgesic, antiinflammatory acitivty. The chemical structures of the synthesized compounds were confirmed by means of their ^{1}H-NMR, IR spectral data and elemental analysis.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on Shimadzu FTIR-800. ^{1}H NMR spectra were recorded on Bruker 300 MHz spectrophotometer using TMS as an internal standard. The purity of synthesized compounds was routinely checked by TLC.

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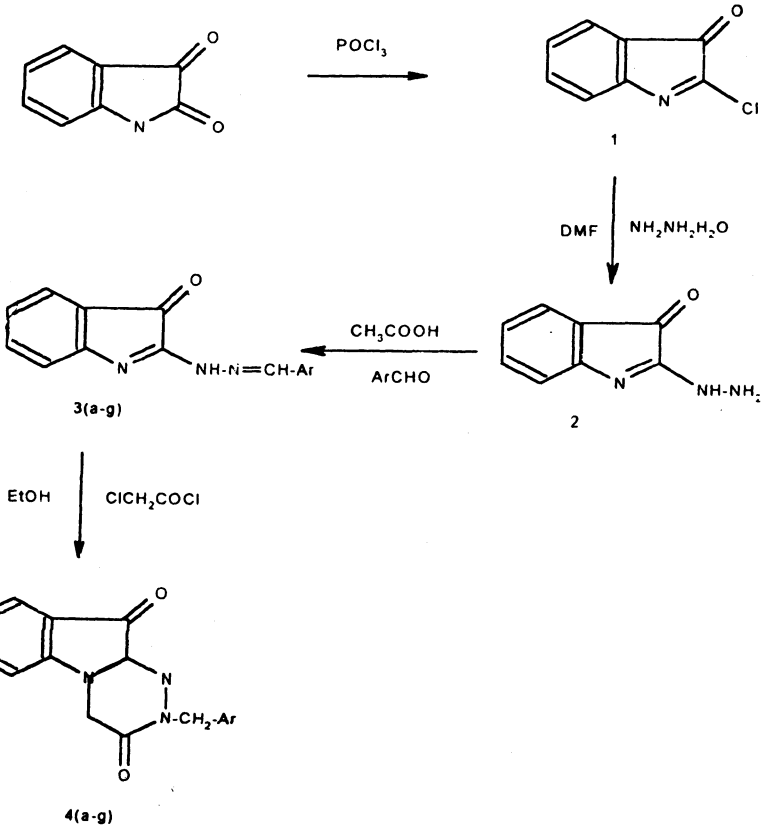
Synthesis of 2-chloroindol-3-one (1): Istain and phosphorus oxychloride (20 mL) were heated under reflux for 1 h, cooled and the resultant oil poured into ice and filtered. The solid obtained was recrystallized from ethanol to give Compound **1**. The purity was established by single spot on silica gel coated TLC plates. The solvent used was chloroform : methanol (95 : 5); m.p. 75.5°C, yield 63%.



Scheme

Synthesis of 2-hydrazino-indole-3-one (2): A solution of **1** (0.01 mol) in DMF (20 mL) was treated with hydrazine hydrate (0.01 mol) and the reaction mixture was refluxed for 1 h and cooled, diluted with cold water, the solid thus obtained was filtered and recrystallized with ethanol to give **2**. The purity was established by single spot on silica gel coated TLC plates. The solvent used was chloroform : methanol (95 : 5); m.p. 80°C, yield 69%.

Synthesis of 2-(substituted-benzylidene-hydrazine)indole-3-one 3(a–g): Compound **2** (0.01 mol) and equimolar proportion of different aldehydes, anhydrous sodium acetate (0.82 g) were added with 75 mL of glacial acetic acid in 250 mL round-bottomed flask. It was refluxed for 4 h using double surface condenser with a calcium chloride guard tube. The reaction mixture was kept for overnight. The mixture was poured into water, the solid thus obtained was filtered

and recrystallized from ethanol to give **3**. The purity was established by single spot on TLC plates. The solvent used was chloroform : methanol (95 : 5).

Preparation of 2,3,4,10-tetrahydro-3,10-dioxo-2-hydroxy-benzyl)[1,2,4]-triazino[4,3-a]indole (4a): A mixture of Compound **3(a)** (0.01 mol) in ethanol (100 mL) and chloroacetyl chloride was heated under reflux for 2 h, cooled and treated with aqueous sodium chloride. The solid thus obtained was filtered and recrystallized from ethanol to give the final Compound **4a.** The purity was established by single spot on TLC plates. The solvent used was chloroform : methanol (95 : 5).

The IR (KBr, cm^{-1}) **4a** 1627 ν(C=O), 3393 ν(CH, Ar), 3680 ν(phenolic OH), 1458 ν(C=N, Ar), ^1H NMR ($CDCl_3$), 1.6–1.78 (s, 2H, CH_2 of benzyl protons), 2.5–2.8 (CH_2 of triazine), 7.5–7.9 (m, 4H, benzo-H), 9.24–9.34 (s, 1H, NH of indole exchangeable with D_2O).

Similarly, other members of **4(a–g)** were preapred and their physical and analytical data are presented in Table-1.

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF THE SYNTHESISED COMPOUNDS **4(a–g)**

Compd.	R	m.f.	m.w.	m.p. (°C)	Yield (%)	% Analysis : Found (calcd.) C	H	N
4a	2-Hydroxyphenyl	$C_{17}H_{13}N_3O_3$	307	70	66	66.60 (66.44)	4.10 (4.23)	13.54 (13.68)
4b	2-Chlorophenyl	$C_{17}H_{12}N_3O_2Cl$	325	72	64	62.68 (62.76)	3.58 (3.69)	13.88 (12.92)
4c	4-Chlorophenyl	$C_{17}H_{12}N_3O_2Cl$	290	74	66	62.84 (62.76)	3.74 (3.69)	13.04 (12.92)
4d	2-Nitrophenyl	$C_{17}H_{12}N_4O_4$	336	79	62	60.62 (60.71)	3.49 (3.57)	16.60 (16.66)
4e	4-Nitrophenyl	$C_{17}H_{12}N_4O_4$	336	75	65	60.68 (60.71)	3.62 (3.57)	16.72 (16.66)
4f	4-Methoxyphenyl	$C_{18}H_{16}N_3O_4$	320	72	62	67.66 (67.50)	4.40 (4.37)	13.22 (13.12)
4g	4-Methylphenyl	$C_{18}H_{16}N_3O_3$	304	78	68	71.16 (71.05)	4.76 (4.60)	13.88 (13.81)

In this first screening study, all the compounds were tested for their analgesic and antiinflammatory activities at a single dose of 100 mg/kg in mice by acetic acid induced writhing test and carrageenan-induced hind paw edema model respectively. For comparison, the active references aspirin and indomethacin were included in the analgesic and anti-inflammatory activity tests. Indomethacin was used at a dose of 100 mg/kg according to a published report[8].

RESULTS AND DISCUSSION

The synthesized compounds were evaluated for analgesic, antiinflammatory activities. Student t-test was performed for all the activities to ascertain the significance of the exhibited activities. Compounds **4b, 4d** and **4g** showed very good analgesic activity when compared to the standard to the standard aspirin.

Compounds **4a** and **4g** showed very good antiinflammatory activity when compared to that of the standard indomethacin. Analgesic and antiinflammatory activities were tablulated in Tables 2 and 3 respectively.

TABLE-2
ANALGESIC ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Compound	Number of writhing ± SEM	Activity (%)
4a	19.20 ± 0.79	51.8***
4b	10.05 ± 1.06	73.6***
4c	17.00 ± 0.97	57.3***
4d	11.50 ± 0.92	71.1***
4e	17.30 ± 2.04	56.5***
4f	16.70 ± 2.14	58.0***
4g	11.80 ± 0.60	70.4***
Control	38.76 ± 3.25	—
Aspirin	18.20 ± 1.57	53.86***

Analgesic activity of the compounds and aspirin were tested at 100 mg/kg doses.
*P < 0.05; **P < 0.01; ***P < 0.001.

TABLE-3
ANTIINFLAMMATORY ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Compound	Swelling thickness ($\times 10^{-2}$ mm) ± SEM (% inhibition)			
	90 min	180 min	270 min	360 min
4a	40.20 ± 4.13 (6.5)	46.00 ± 4.20 (8.9)	49.20 ± 4.26 (9.4)	53.50 ± 4.23 (15.1)
4b	32.00 ± 3.09 (25.6)	38.00 ± 2.88 (42.8)	36.70 ± 2.64 (32.4)	39.30 ± 1.94 (37.6)
4c	36.70 ± 4.86 (14.7)	43.20 ± 4.69 (14.5)	47.70 ± 4.29) (12.2)	52.80 ± 3.98 (16.2)
4d	38.30 ± 4.46 (10.9)	44.00 ± 4.28 (12.9)	47.00 ± 3.69 (13.3)	50.70 ± 3.31 (19.5)
4e	39.20 ± 4.22 (8.8)	45.30 ± 3.68 (10.3)	50.00 ± 3.48 (12.5)	54.30 ± 3.40 (17.1)
4f	40.00 ± 4.17 (6.9)	44.20 ± 4.49 (12.5)	47.50 ± 4.54 (12.5)	52.20 ± 4.32 (17.1)
4g	36.50 ± 4.78 (15.1)	40.30 ± 4.86 (20.2)	39.50 ± 3.14 (27.3)	43.50 ± 3.18 (30.9)
Control	43.00 ± 3.15	50.50 ± 3.49	54.30 ± 4.15	63.00 ± 3.06
Indomethacin (10 mg/kg)	26.3 ± 3.11 (38.8)	31.20 ± 3.44 (38.2)	29.50 ± 2.05 (45.7)	31.80 ± 2.68 (49.5)

Antiinflammatory activities of the compounds were tested at 100 mg/kg doses.
*P < 0.05; **P < 0.01; ***P < 0.001.

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