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Synthesis, Characterization and Anti-Inflammatory and Antipyreticevaluationof Novel Indole Derivatives

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Abstract: Indole, the bicyclic ring system consists of pyrrole ring fused with benzene ring. Although indole moiety is very small but is fascinated by scientists because of the diverse biological activities by not only indole but its various substituted derivatives as well. In the present study some novel indole derivatives like 6-Chloro-3-[(N,N-diethylamino)(oxo)acetyl]-1-benzyl-N-aryl-1H-indole-5-carboxamide derivatives (IC-1 to IC-10) were synthesized according to the scheme. The synthesized novel indole derivatives have been characterized by using elemental analysis, FT-IR, ^{1}HNMR, ^{13}C NMR spectroscopy and further supported by Mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and HPLC technique. All the synthesized compounds were evaluated for anti-inflammatory and antipyreticactivities. All the compounds exhibited moderate to significant anti-inflammatory and antipyreticactivities.

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INTRODUCTION:

Heterocyclic compound is one which possesses a cyclic structure with at least one hetero atom in the ring. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways. The chemistry and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. A number of heterocyclic derivatives containing nitrogen atom serve as a unique and versatile scaffolds for experimental drug design. Indole is a heterocyclic compound, is made from pyrrole ring fused with benzene ring, having various biological activities and still of great scientific interest now a days. Indole compounds and their derivatives were found to numerous pharmacological activities like antitumor (S. Murali Krishna *et al*, 2013), anticonvulsant (Rohini R M *et al*, 2012), antimicrobial (Gollapalli Naga Raju*et al*, 2015), anthelmintic (Mondal P*et al*, 2012), antileishmanial (Delorenzi et al, 2001), antitubercular (Prabhaker Walmik and Saundane A. R, 2014), antioxidant (Monica S. Estevao *et al*, 2010), antifungal (P. Ashok GajapathiRaju *et al*, 2013), anti-inflammatory (A.S.H. da Silva Guerra *et al*, 2011), antipsychotic (Mahadevan *et al*, 2013), antidepressant (Patil, P.O., Bari, S.B, 2013), antimycobacterial (Avinash Rangaraju *et al*, 2013), cardiovascular activity (Singh *et al*, 2013), analgesic (H. Mandour *et al* 2010), and antibacterial (S. Jain., B. N. Reddy, and K. S. Rao, 2012) activities. The present research work focuses on the efficient synthesis of novel indole derivatives and their biological evaluation foranti-inflammatory and antipyreticactivities.

EXPERIMENTAL:

Material and Methods:

All the chemicals used were of laboratory grade and procured from E.Merck, Germany; Qualigens, Mumbai; Sigma Aldrich, USA and S.D. Fine Chemicals, Mumbai. Melting points were determined in digital melting point apparatus and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. All compounds were purified by recrystallization with suitable organic solvents. All the microwave experiments were performed using RAGA's microwave synthesizer. IR spectra were recorded on BROOKER-ALPHA FT-IR instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR was determined in $CDCl_3$ solution on a BRUKER Ac 400 MHz spectrometer. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Purity of the synthesized compounds was checked by HPLC AGILENT. The results are in agreements with the structures assigned. All chemicals were reagent grade and

used without further purification, and all solvents were freshly distilled before use.

Preparation of Methyl 1-benzyl-6-chloro-1*H*-indole-5-carboxylate: To a stirred suspension of CS_2CO_3 (2.72 gm, 0.02 mol) and methyl 6-chloro-1*H*indole-5-carboxylate (2.09 gm, 0.01 mol) in dry DMF (10 ml), after 5.0 minute benzylchloride (1.14 ml, 0.01 mol) was added drop wise. The resultant solution was stirred for 5hour at room temperature, and poured onto crushed ice; the product was isolated andwashed with water and hexane to give pure product. Yield: 94 %, M.P 70-72 ^{0}C.

Preparation of Methyl 1-benzyl-6-chloro-3-[(*N*,*N*-diethylamino)(oxo)acetyl]-1*H*-indole-5-carboxylate: To a stirred cooled (ice bath) solution of methyl 1-benzyl-6-chloro-1*H*-indole-5-carboxylate (0.5 gm, 1.67 mmol) in dry DCM (12 ml), oxalyl chloride (0.71 ml, 8.35 mmol)was added drop wise in solution. The obtained solution was stirred at 0 oC for 30.0 minutes and then at 25-30 ^{0}C for 1 hour. Dark yellow colored was formed. The solvent was removed *in vacuo*, the residue was dissolved in dry DCM (12 ml) then add Diethylamine (5.01 mmol) was added drop wise. The reaction mixture was stirred at 0^{0}C for 30.0 minute and then 25-30 ^{0}C for another 30.0 minute (monitored by TLC). Thesolvent was removed *in vacuo*. The product was dissolved in water and extracted with ethylacetate (25 ml × 3). The combined organic layers were washed with water followedby brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the solid was triturated with hexane and resulting precipitate was filtered, washed withhexane and dried to give analytical pure product.

Preparation of 1-Benzyl-6-chloro-3-[(N,N-diethylamino)(oxo)acetyl]-1*H*-indole-5-carboxylic acid: To a stirred solution of methyl 1-benzyl-6-chloro-3-(N,N-diethylamino)(oxo)acetyl]-1*H*-indole-5-carboxylate (0.5 gm, 1.17 mmol) in methanol (10 ml), 40% NaOH (1ml) solution was added. The reaction mixture was refluxed for 4 hour and the solvent was removed *in vacuo*. The viscous oil obtained was neutralized with an aqueous solution of HCl. The product was extracted with ethylacetate (25 ml × 3), and the combined organiclayers were washed with water followed by brine and dried over anhydrous Na_2SO_4. Thesolvent was removed *in vacuo*, and the solid product was obtained. Yield: 80%, M.P 160-161 ^{0}C.

General procedure for the preparation of 6-Chloro-3-[(diethylamino)(oxo)acetyl]-1-benzyl-*N*-aryl-1*H*-indole-5-carboxamides: To a stirred cooled (ice bath) solution of 1-benzyl-6-chloro-3-[(diethylamino)(oxo)acetyl]-1*H*-indole-5-carboxylic acid (0.4 gm, 0.93 mmol) in dry DCM(10 ml), *N*-hydroxybenzotrizole (0.18 gm, 1.40 mmol) and *N*,*N'*-dicyclohexylcarbodiimide (0.28 gm, 1.40 mmol) was added in solution at 0 ^{0}C. Theobtained solution was stirred for 15.0 minutes at 0 ^{0}C. To this solution arylamine in dryDCM (5 ml) was added drop wise, then after 2.0 minute triethylamine (0.26 ml, 1.87 mmol) was added. The reaction mixture was stirred for 10 hour at room temperature (monitored byTLC). The solvent was removed *in* vacuo. The product was extracted with ethylacetate (20 ml × 3), and the combined organic layer was washed with water followed by brineand dried over anhydrous Na_2SO_4. The solvent was evaporated under *vacuo* and the residue was purified by column chromatography on silica gel (eluent: 5:5 = E.A.:Hexane) to obtain pure product. The physical constants of the product are recorder in Table 1.

1-Benzyl-6-chloro-3-[(diethylamino)(oxo)acetyl]-N-(4-methoxyphenyl)-1H-indole-5-carboxamide (IC-1):M.P 89-91 ^{0}C; IR (KBr): 3359, 3023, 2952, 2865, 1717, 1638, 1532, 1462, 1258, 767 cm^{-1}; MS: *m/z* = 518 $[M]^+$; Anal. Calcd for $C_{29}H_{28}ClN_3O_4$: C, 67.24; H, 5.45; N, 8.11. Found: C, 66.95; H, 5.40; N, 7.98%.

N,1-Dibenzyl-6-chloro--3-[(diethylamino)(oxo)acetyl]-1H-indole-5-carboxamide (IC-2):M.P 120-122 ^{0}C; Purity by HPLC: 94 %; IR (KBr): 3394 (N-H str), 3032 (Ar, C-H str), 2929 (C-H str), 2856 (C-H str), 1708 (ketone, C=O str), 1627 (amide, C=O str), 1519 (Ar, C=C str), 1456 (Ar, C=C str), 1300 (N-H ban), 1244 (C-H ban), 794 (C-Clstr) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.05-1.16 (m, 3H, CH_3), 1.16-1.23 (m, 3H, CH_3), 3.24-3.34 (m, 2H, CH_2), 3.34-3.43 (m, 2H, CH_2), 4.46 (s, 2H, CH_2), 5.61 (s, 2H, CH_2), 7.26-7.35 (m, 10H, ArH), 7.83 (s, 1H, ArH), 8.13 (s, 1H, ArH), 8.45 (s, 1H, ArH), 8.98 (s, 1H, NH). MS: *m/z* = 504 $[M+2]^+$; Anal. Calcd for $C_{29}H_{28}ClN_3O_3$: C, 69.38; H, 5.62; N, 8.37. Found: C, 68.99; H, 5.53; N, 8.23%.

1-Benzyl-6-chloro-3-[(diethylamino)(oxo)acetyl]-N-(3-methylphenyl)-1H-indole-5-carboxamide (IC-3). M.P 97-99 ^{0}C; IR (KBr): 3354, 3014, 2977, 1730, 1637, 1523, 1446, 1230, 777 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.05-1.08 (t, J=7.2 Hz, 3H, CH3), 1.16-1.19 (t, J=7.2 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.23-3.28 (q, J=7.2 Hz, 2H, CH_2), 3.42-3.47 (q, J=7.2 Hz, 2H, CH_2), 5.64 (s, 2H, CH_2), 6.91-6.93 (d, J=7.2 Hz, 1H, ArH), 7.20-7.22 (m, 1H, ArH), 7.24-7.29 (m, 2H, ArH), 7.31-7.38 (m, 3H, ArH), 7.46-7.48 (d, J=8.0 Hz, 1H, ArH), 7.57 (s, 1H, ArH), 7.88 (s, 1H, ArH), 8.21 (s, 1H, ArH), 8.50 (s, 1H, ArH), 10.40 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 13.15, 14.58, 21.69, 38.67, 42.14, 50.28, 113.07, 113.38, 117.22, 120.49, 121.58, 124.33, 124.90, 126.02,

127.60, 128.41, 129.07, 129.28, 132.56, 136.90, 137.12, 138.40, 139.43, 141.72, 165.74, 166.84, 186.65; MS: *m/z* = 501 [M-1] $^{+}$; Anal. Calcd for $C_{29}H_{28}ClN_3O_3$: C, 69.38; H, 5.62; N, 8.37. Found: C, 69.05; H, 5.54; N, 8.25%.

1-Benzyl-6-chloro-3-[(diethylamino)(oxo)acetyl]-N-(4-methylphenyl)-1H-indole-5-carboxamide (IC-4).M.P 115-116 ^{0}C; IR (KBr): 3355, 3078, 2941, 2912, 1705, 1646, 1520, 1468, 1260, 738 cm^{-1}; MS: *m/z* = 501 [M-1] $^{+}$; Anal. Calcd for $C_{29}H_{28}ClN_3O_3$: C, 69.38; H, 5.62; N, 8.37. Found: C, 69.01; H, 5.50; N, 8.20%.

1-Benzyl-6-chloro-3-[(diethylamino)(oxo)acetyl]-N-(2-fluorophenyl)-1H-indole-5-carboxamide (IC-5). M.P 170-172 ^{0}C; IR (KBr): 3356, 3070, 2911, 2831, 1728, 1626, 1528, 1432, 1268, 740 cm^{-1}; MS: *m/z* = 506 [M+1] $^{+}$; Anal. Calcd for $C_{28}H_{25}ClFN_3O_3$: C, 66.47; H, 4.98; N, 8.30. Found: C, 66.12; H, 4.88; N, 8.12%.

1-Benzyl-6-chloro-3-[(diethylamino)(oxo)acetyl]-N-(4-fluorophenyl)-1H-indole-5-carboxamide (IC-6).M.P 165-167 ^{0}C; IR (KBr): 3344, 3084, 2981, 2901, 1726, 1633, 1520, 1447, 1246, 786 cm^{-1}; MS: *m/z* = 506 [M+1] $^{+}$; Anal. Calcd for $C_{28}H_{25}ClFN_3O_3$: C, 66.47; H, 4.98; N, 8.30. Found: C, 66.15; H, 4.90; N, 8.21%.

1-Benzyl-6-chloro-3-[(diethylamino)(oxo)acetyl]-N-(3-chlorophenyl)-1H-indole-5-carboxamide (IC-7):M.P 145-147 ^{0}C; IR (KBr): 3378, 3043, 2934, 2876, 1721, 1651, 1526, 1446, 1265, 768 cm^{-1}; MS: *m/z* = 523 [M+1] $^{+}$; Anal. Calcd for $C_{28}H_{25}Cl_2N_3O_3$: C, 64.37; H, 4.82; N, 8.04. Found: C, 63.98; H, 4.69; N, 7.89%.

1-Benzyl-6-chloro-3-[(diethylamino)(oxo)acetyl]-N-(4-chlorophenyl)-1H-indole-5-carboxamide (IC-8): M.P 137-138 ^{0}C; IR (KBr): 3338, 3019, 2942, 2836, 1716, 1646, 1545, 1435, 1248, 757 cm^{-1}; MS: *m/z* = 524 [M+2] $^{+}$; Anal. Calcd for $C_{28}H_{25}Cl_2N_3O_3$: C, 64.37; H, 4.82; N, 8.04. Found: C, 64.02; H, 4.75; N, 7.91%.

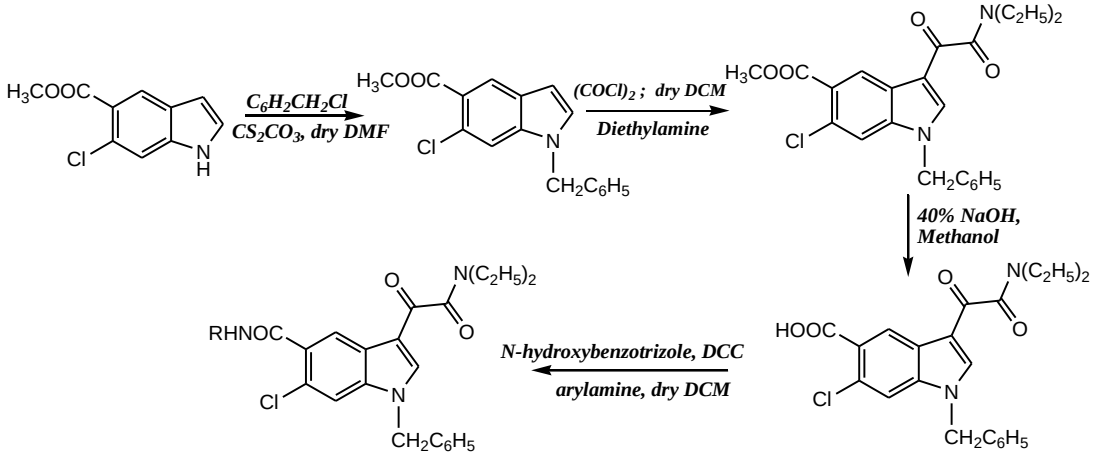
N-(4-Acetylphenyl)-1-benzyl-6-chloro--3-[(diethylamino)(oxo)acetyl]-1H-indole-5-carboxamide (IC-9): M.P 85-86 ^{0}C; IR (KBr): 3368, 3040, 2935, 2840, 1708, 1630, 1562, 1451, 1216, 791 cm^{-1}; MS: *m/z* = 529 [M-1] $^{+}$; Anal. Calcd for $C_{30}H_{28}ClN_3O_4$: C, 67.98; H, 5.32; N, 7.93. Found: C, 67.61; H, 5.23; N, 7.77%.

1-Benzyl-6-chloro-3-[(diethylamino)(oxo)acetyl]-N-phenyl-1H-indole-5-carboxamide (IC-10): M.P 104-106 ^{0}C; IR (KBr): 3350, 3015, 2919, 2860, 1710, 1633, 1548, 1460, 1232, 762 cm^{-1}; MS: *m/z* = 487 [M]$^{+}$; Anal. Calcd for $C_{28}H_{26}ClN_3O_3$: C, 68.92; H, 5.37; N, 8.61. Found: C, 68.55; H, 5.30; N, 8.48%.

Table 1: Physical constants of novel indole derivatives (IC-1 to IC-10)

Compd	R	M.F	M.W	Yield (%)	M.P (^{0}C)	R_f
IC-1	4-Methoxy phenyl	$C_{29}H_{28}ClN_3O_4$	518.00	76	89-91	0.58
IC-2	Benzyl	$C_{29}H_{28}ClN_3O_3$	502.00	72	120-122	0.54
IC-3	3-Methyl phenyl	$C_{29}H_{28}ClN_3O_3$	502.00	78	97-99	0.55
IC-4	4-Methyl phenyl	$C_{29}H_{28}ClN_3O_3$	502.00	73	115-117	0.56
IC-5	2-Fluorophenyl	$C_{28}H_{25}ClFN_3O_3$	505.96	74	170-172	0.60
IC-6	4-Fluorophenyl	$C_{28}H_{25}ClFN_3O_3$	505.96	68	165-167	0.61
IC-7	3-Chloro phenyl	$C_{28}H_{25}Cl_2N_3O_3$	522.42	69	145-147	0.54
IC-8	4-Chloro phenyl	$C_{28}H_{25}Cl_2N_3O_3$	522.42	70	137-139	0.53
IC-9	4-Acetylphenyl	$C_{30}H_{28}ClN_3O_4$	530.01	72	85-87	0.55
IC-10	Phenyl	$C_{28}H_{26}ClN_3O_3$	487.97	73	104-106	0.52

Scheme 1: Synthesis of novel indole derivatives (IC-1 to IC-10)



Novel indole derivatives (IC-1 to IC-10)

Table 2: Effect of novel indole derivatives on carrageenan induced paw edema in rats

Compd	Dose mg/kg	Edema Volume (Mean ± SEM)		Percentage Inhibition	
		1st hr	3rd hr	1st hr	3rd hr
IC-1	50	0.510±0.004**	0.600±0.004**	10.6%	34.8%
	100	0.490±0.005**	0.610±0.010**	14.1%	33.7%
IC-2	50	0.467±0.006**	0.595±0.005**	19.3%	35.9%
	100	0.417±0.002**	0.675±0.002**	28.1%	27.2%
IC-3	50	0.445±0.002**	0.595±0.002**	22.9%	35.9%
	100	0.400±0.004**	0.615±0.002**	29.9%	33.7%
IC-4	50	0.410±0.007**	0.505±0.008**	28.1%	45.7%
	100	0.372±0.004**	0.400±0.006**	35.1%	56.6%
IC-5	50	0.487±0.006**	0.560±0.008**	15.8%	39.2%
	100	0.420±0.004**	0.472±0.011**	26.4%	49.0%
IC-6	50	0.397±0.006**	0.497±0.014**	31.6%	46.8%
	100	0.480±0.002**	0.412±0.007**	15.8%	55.5%
IC-7	50	0.520±0.007**	0.642±0.006**	08.8%	30.5%
	100	0.590±0.008	0.722±0.006**	0.0%	21.8%
IC-8	50	0.445±0.011**	0.527±0.007**	22.9%	43.5%
	100	0.300±0.002**	0.39±0.0190**	47.4%	57.7%
IC-9	50	0.452±0.061**	0.459±0.110**	23.1%	31.4%
	100	0.439±0.190**	0.346±0.130**	25.4%	28.5%
IC-10	50	0.436±0.041**	0.439±0.030**	26.2%	29.8%
	100	0.403±0.160**	0.385±0.130**	21.6%	24.8%
Control (CMC)	0.5%	0.570±0.010	0.925±0.002	00.0%	00.0%
Nimesulide	50	0.190±0.010**	0.275±0.002**	67.0%	70.7%

n = 6 in each group. P<0.01 (**) Significant

BIOLOGICAL EVALUATION

Animals used: The anti-inflammatory and analgesic activities were carried out using Wistar rats of either sex weighing 150-200gm and 20-25gm respectively. Six rats and six mice were used for each experiment and for each test compound. The animals were housed in polypropylene cages with free access to standard pellet diet and water *ad libitum*. The study has been approved by the Institutional Animal Ethical Committee of chalapathi Institute of Pharmaceutical Sciences.

Anti-inflammatory activity:

This activity was studied using acute and chronic models by carrageenan induced paw edema test. All the test compounds namely IC-1 to IC-10 were administered dose 50mg/kg and 100mg/kg body weight based upon their acute toxicity studies and nimesulide 50mg/kg b.w. was used as standard. The test compounds were administered orally to the rats suspended in 0.5% carboxymethyl cellulose (CMC). The control animals received 0.5% CMC. Thirty minutes after drug administration, 0.1ml of 1% carrageenan (Himedia) in normal saline solution was injected into the sub plantar region of one of the hind paws. The paw edema volume was recorded using a plethysmo meter at different time intervals.

Anti-inflammatory activity was also checked by xylol induced mouse ear edema test. The test compounds, standard and vehicle as mentioned above were administered orally to the mice. 30 minutes afteradministration, inflammation was induced by a topical application of 2% xylol (20µl) to the right ear of each mouse. The left ear was kept as control. The positive control group received only 0.5ml of 1% CMC. After 30 minutes of xylol application, the animals were killed by cervical dislocation. A 6 mm section of ear disc was obtained by punching the ear and then weighed. The inflammation induced by xylol was assessed by the change in the weight of ear punch of treated groups over control and this is called the edema index.

Anti-inflammatory activity was further confirmed by cotton pellet-induced granuloma in rats. Two sterilized cotton pellets, each weighing 10 mg were implanted subcutaneously into axilla in anaesthetized rats. After treatment with test compounds, standard and vehicle for 10 days the rats were sacrificed. They were dissected to take out granuloma tissue and dried at 60^0C overnight to determine the dry weight. Results were expressed as mg/100g. Data recorded in Table 2&3.

Antipyretic activity:

Yeast induced pyrexia was used to evaluate the antipyretic activity of the test compounds. The body temperature of each rat was recorded by measuring the rectal temperature at predetermined time intervals. Fever was induced by injecting 15% suspension of Brewer's yeast (*Saccharomyces cerevisiae*) following a standard method. The rats were allowed to remain quiet in the cage for some time. A thermister probe was inserted 3-4 cm deep into the rectum after fastening the tail to record the basal rectal temperature.

Table 3: Effect of novel indole derivatives on cotton pellet induced granuloma studies in rats

Compd	Dose mg/kg	Dry granuloma tissue weight in mg (mean ± SEM)	Percentage Inhibition
IC-1	50	30.71±1.476**	32.9%
	100	27.12±1.910**	40.7%
IC-2	50	30.40±1.103**	33.5%
	100	26.10±2.150**	42.9%
IC-3	50	28.74±2.733**	37.2%
	100	27.76±1.286**	39.3%
IC-4	50	31.31±1.473**	31.5%
	100	27.44±1.929**	40.0%
IC-5	50	28.85±2.237**	36.9%
	100	26.04±0.8571**	43.1%
IC-6	50	29.35±2.652**	35.8%
	100	28.24±1.199**	38.3%
IC-7	50	30.40±2.477**	33.5%
	100	26.90±0.9203**	41.2%
IC-8	50	32.12±0.9870**	29.8%
	100	27.70±1.655**	39.4%
IC-9	50	42.49±1.458**	28.1%
	100	40.34±1.456**	29.2%
IC-10	50	41.93±1.445**	30.4%
	100	31.31±1.473**	31.5%
Control (CMC)	0.5%	45.70±1.133	00%
Nimesulide	50	25.82±1.398**	43.6%

n = 6 in each group. P<0.01 (**) Significant

Table 4: Effect of novel indole derivatives on yeast induced pyrexia in rats

Compd	Dose mg/kg	Yeast Induced Pyrexia (^{0}C) (Mean ± SEM)			
		0 hr	½ hr	1 hr	3 hr
IC-1	50	37.52±0.10	37.16±0.06	36.88±0.08*	36.76±0.06
	100	37.24±0.14	36.86±0.08**	36.34±0.06**	35.62±0.11**
IC-2	50	37.80±0.11	37.42±0.11	37.04±0.05	36.66±0.07
	100	37.50±0.19	36.96±0.08*	36.68±0.06**	35.86±0.15**
IC-3	50	37.86±0.06	36.80±0.10**	36.58±0.04**	36.00±0.14**
	100	37.18±0.15	36.84±0.08**	36.44±0.09**	35.24±0.09**
IC-4	50	37.84±0.10	37.34±0.08	36.70±0.06**	36.32±0.03
	100	37.10±0.08	36.84±0.10**	36.42±0.08**	35.78±0.03**
IC-5	50	37.88±0.10	36.88±0.08**	36.52±0.03**	35.84±0.15**
	100	37.12±0.13	36.80±0.13**	36.60±0.08**	35.88±0.10**
IC-6	50	37.64±0.08	37.10±0.13	36.64±0.08**	35.96±0.08**
	100	37.04±0.10	36.74±0.09**	36.46±0.08**	35.64±0.09**
IC-7	50	37.58±0.03	36.90±0.03**	36.60±0.06**	36.58±0.05
	100	36.90±0.15	36.66±0.12**	36.40±0.20**	35.58±0.22**
IC-8	50	37.60±0.10	37.10±0.08	36.66±0.07**	36.28±0.09
	100	37.12±0.13	36.78±0.08**	36.40±0.03**	35.52±0.10**
IC-9	50	37.76±0.15	37.42±0.11	37.04±0.05	36.66±0.07
	100	37.50±0.19	36.96±0.08	36.68±0.06*	35.86±0.15**
IC-10	50	37.26±0.16	36.90±0.14*	36.60±0.20**	36.32±0.12
	100	36.96±0.08	36.66±0.06**	36.22±0.06**	35.64±0.05**
Control (CMC)	0.5%	37.66±0.26	37.48±0.22	37.24±0.15	36.66±0.18
Nimesulide	50	37.46±0.12	36.94±0.06*	36.66±0.07**	35.44±0.11**

n = 5 in each group. P<0.01 (**) Significant

The animals were then given a subcutaneous injection of 10ml/kg of 15% w/v Brewer's yeast suspended in 0.5% w/v CMC solution and the animals were returned to their housing cages. 19 hr after yeast injection, the rats were again restrained in individual cage to record their rectal temperature. Immediately the test compounds and standard were administered orally at their respective doses. Rectal temperature of all the rats was recorded at 19 hr immediately before the administration of test compounds, vehicle and paracetamol (50 mg/kg b.w.) and again at 1hr intervals up to 3 hr after the administration**.**

RESULTS AND DISCUSSION:

In the present research work methyl 6-chloro-1*H*indole-5-carboxylate was treated with CS_2CO_3in dry DMF after that benzyl chloride was added to get methyl 1-benzyl-6-chloro-1*H*-indole-5-carboxylate. Then it is treated with oxalyl chloride in dry DCM yields methyl 1-benzyl-6-chloro-3-[(N,N-diethylamino)(oxo)acetyl]-1H-indole-5-carboxylate. Then it is treated with 40% NaOH to get 1-benzyl-6-chloro-3-[(N,N-diethylamino) (oxo) acetyl]-1H-indole-5-carboxylic acid. Then the solution of this compound in dry DCM, *N*-hydroxybenzotrizole, DCC and triethylamine was added to yield 6-Chloro-3-[(N,N-diethylamino) (oxo)acetyl]-1-benzyl-N-aryl-1H-indole-5-carboxamide derivatives.

All the ten synthesized compounds IC-1 to IC-10 showed significant inhibition of edema at both the doses tested 50 mg/kg and 100 mg/kg in a dose dependent manner. The maximum inhibition was observed at 3rd hr. There was significant reduction of granuloma dry weight by all test compounds. The maximum inhibition of edema and reduction in dry weight was shown by compounds IC-1 (40.7%, 27.12 ± 1.910), IC-2 (42.9%, 26.10 ± 2.150), IC-4 (40.0%, 27.41 ± 1.929), IC-5 (43.1%, 26.04 ± 0.857), and IC-7 (41.2%, 26.90 ± 0.920), as compared to standard nimesulide (43.6%, 25.82 ± 1.398). All the test compounds also showed significant inhibition of edema in xylol induced mouse ear edema, however, it was less as compared to standard nimesulide. In yeast induced pyrexia test compounds IC-1, IC-3, IC-4, IC-6, IC-7, IC-8 andIC-10 showed significant inhibition of pyrexia at higher dose of 100 mg/kg as compared to IC-2, IC-5 and IC-9.

CONCLUSION:

In the present research work 6-Chloro-3-[(N,N-diethylamino)(oxo)acetyl]-1-benzyl-N-aryl-1H-indole-5-carboxamide derivatives were synthesized according to the scheme 1.All the ten synthesized compounds were evaluated for their anti-inflammatory and analgesic activities. Compounds IC-1, IC-2, IC-4, IC-5 and IC-7showed significant anti-inflammatory activity.Compounds IC-1, IC-3, IC-4, IC-6, IC-7, IC-8 andIC-10 showed significant inhibition of pyrexia at higher dose of 100 mg/kg as compared to IC-2, IC-5 and IC-9.

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REFERENCES:

A.S.H. da Silva Guerra et al, Anti-inflammatory and antinociceptive activities of indole – imidazolidine derivatives; International Immunopharmacology, 2011; 11: 1816–1822.

AvinashRangaraju et al, Synthesis of Novel 1H-Indole-2, 3-Dione Derivatives as potent Antimycobacterial Agents; IJAPBC – Oct-Dec, 2013; 2(4).

Delorenzi et al, Antileishmanial Activity of an Indole Alkaloid from Peschieraaustralis; Antimicrobial Agents and Chemotherapy, May 2001; 45(5): 1349–1354.

Gollapalli Naga Raju et al, Synthesis, characterization and biological activity of some 1,3,4-oxadiazole derivatives with indole moiety; Der Pharmacia Lettre, 2015; 7(5): 153-159.

H. Mandour et al.: Synthesis, anti-inflammatory, analgesic and anticonvulsant activities of 1,8-dihydro-1-aryl-8-alkyl pyrazolo-(3,4-b)indoles; Acta Pharm., 2010; 60: 73–88.

Mahadevan et al, Synthesis and Docking Study of 3-(N-Alkyl/Aryl Piperidyl) Indoles with Serotonin-5HT, H1 and CCR2 Antagonist Receptors; Int J Pharm PharmSci, 6(4): 475-482. 2013.

Mondal P, Jana S, Balaji A, Ramakrishna R, Kanthal LK. Synthesis of some new isoxazoline derivatives of chalcon is edindoline 2-one as a potential analgesic, antibacterial and anthelmimtic agents; J Young Pharmacists, 2012; 4: 38-41.

Monica S. Estevao et al, Antioxidant activity of unexplored indole derivatives: Synthesis and screening; European Journal of Medicinal Chemistry, November 2010; 45(11): 4869–4878.

P. Ashok Gajapathi Raju et al, Synthesis and biological activity of some new indole derivatives containing pyrazole moiety; J. Chem. Pharm. Res., 2013; 5(10): 21-27.

Patil, P.O., Bari, S.B. Synthesis, characterization and screening for antidepressant and anticonvulsant activity of 4,5-dihydropyrazole bearing indole derivatives; Arabian Journal of Chemistry, 2013; 1-8.

Prabhaker Walmik and Saundane A. R, Synthesis of novel indolyl-azetidinone and thiazolidinone derivatives as a potent antioxidant, antimicrobial and antitubercular agents; Der Pharma Chemica, 2014; 6(4): 70-79.

Rohini R M et al, Synthesis and anti-convulsant activity of triazothiole/thiazolylthiazolidinone derivatives of indole; Der Pharma Chemica, 2012; 4(6): 2438-2441.

S. Jain., B. N. Reddy, and K. S. Rao, Synthesis of Biheterocycles Containing Indole Nucleus and Their Antibacterial Activity; J. Sci. Res., 2012; 4(1): 273-278.

S. Muralikrishna et al, Synthesis Characterization and antitumor activity of thiazole derivatives containing indole moiety bearing-tetrazole; Der Pharma Chemica, 2013; 5(6): 87-93.

Singh et al, Synthesis and Evaluation of Some Substituted Indole Derivatives for Cardiovascular Activity; International Journal of Pharmaceutical Sciences and Drug Research, 2013; 5(1): 14-17.