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SYNTHESIS AND EVALUATION OF NEW 3- SUBSTITUTED-[3, 4-DIHYDRO PYRIMIDINONES]-INDOLIN-2-ONES FOR ANTI INFLAMMATORY ACTIVITY

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ABSTRACT

New 3-substituted [3, 4-dihydropyrimidinones]-Indolin-2-ones have been synthesized and tested for Anti-inflammatory activity by caragenen induced rat paw method. Among them compounds AJ_{16}, AJ_{15}, AJ_{14}, AJ_{13} and AJ_{12} exhibited higher anti inflammatory activity. However, these anti-inflammatory activities are lower than standard Diclofenac Sodium.

KEY WORDS

Dihydropyrimidinones, Indole-2-ones, Anti-inflammatory activity

INTRODUCTION

Heterocyclic systems possessing an indole moiety exhibit a number of interesting biological activities such as antiviral, antibacterial, anti-fungal, anti-inflammatory, analgesic, diuretic and anticonvulsant activities [1-6]. A lot of work have been carried out on indole derivatives and no work has been carried on 3- substituted [3,4-dihydro pyrimidinones]-Indolin-2-ones. It is also evident from the literature that dihydro pyrimidinones are equally important in terms of pharmacological activities such as Calcium channel blockers, antifungal, and antihypertensive agents [7-9]. Therefore, it seems promising to synthesize some new 3-substituted [3,4-dihydro pyrimidinones]-Indolin-2-ones using the multi component one pot condensation of biginelli's synthesis using Isatin semicarbazone, ethylacetoacetate and aromatic aldehyde[10]. We present here our results on the design of New 3- substituted [3,4-dihydro pyrimidinones]-Indolin-2-ones emphasizing in particular the presence of aromatic nucleus at the 5-postion of 3,4-dihydropyrimidine ring [benzaldehyde, 4-chlorobenzaldehyde, 4-hydroxybenzaldehyde, 4-methoxybenzaldehyde and 2-Nitrobenzaldehyde] in one skeleton (B_1 to B_9, AJ_1 to AJ_{45}), Scheme-1).

MATERIALS AND METHODS

ANTI-INFLAMMATORY:

Animals:

All the experiments were carried out using male, Wistar rats (150-200 gm) were obtained from animal house, UCPSc, Kakatiya University, Warangal, India. On arrival the animals were placed at random and allocated to treatment groups in polypropylene cages with paddy husk as bedding. Animals were housed at a temperature of 24 ± 2°C and relative humidity of 30 – 70 %. 12:12 light: day cycle was followed. All animals were allowed to free access to water and fed with standard commercial rat chaw pallets. All the experimental procedures and protocols used in this study were reviewed by the Institutional Animal Ethics Committee, Kakatiya University, and Warangal, India.

Drugs and Chemicals

The drugs and fine chemicals were purchased from Sigma-Aldrich, India. All other chemicals and solvents were obtained from local firms (India) and were of highest pure and analytical grade. Test compounds and Diclofenac Sodium were suspended in 0.5% w/v carboxyl methylcellulose sodium (CMC) and administered orally to animals. Carragenen, diluted separately in normal saline and injected.

Acute Anti-inflammatory Studies

Carrageenan, induced paw oedema models were used for evaluating potential of Test compounds on inflammation. For each model, rats were divided in to five groups (n = 6). 10 mg /kg of test compound and Diclofenac Sodium (10 mg/kg) were administered orally one hour before the sub plantar injection of edematogenic agent. The control groups of animals were received vehicle (1 ml/kg) orally. A vernier caliper used for measuring paw thickness (mm) of rats[11]. Edema (T) was

calculated as follows: .T = Tt – T0 Where Tt is the right hind paw thickness (mm) at time't', T0 is hind paw thickness (mm) before subplantar injection.

Synthesis of the compounds

The reaction sequence used in the synthesis of the target compounds AJ_{1-45} is depicted in the scheme-I. Isatin semicarbazone B_{1-9} were obtained from appropriate isatin in alcohol with addition of semicarbazide hydrochloride and sodium acetate in water and refluxed on waterbath for about 1 hour[12]. Compounds AJ_{1-45} were synthesized by refluxing B_{1-9} with ethylacetoacetate and an appropriate aromatic aldehydes (Benzaldehyde, 4-chlorobenzaldehyde,4 hydroxybenzaldehyde,4-methoxybenzaldehyde and 2-nitro benzaldehyde by multicomponent one pot condensation using named Bigineli's reaction in presence of catalytic amount of concentrated hydrochloric acid for 10-12 hours[13]. All the newly synthesized compounds were characterized by physical, spectral (IR, Mass, NMR) and Elemental analysis.

Scheme: 1

Schematic diagram of 3- substituted-[3,4-dihydro pyrimidinones]-Indolin-2-ones

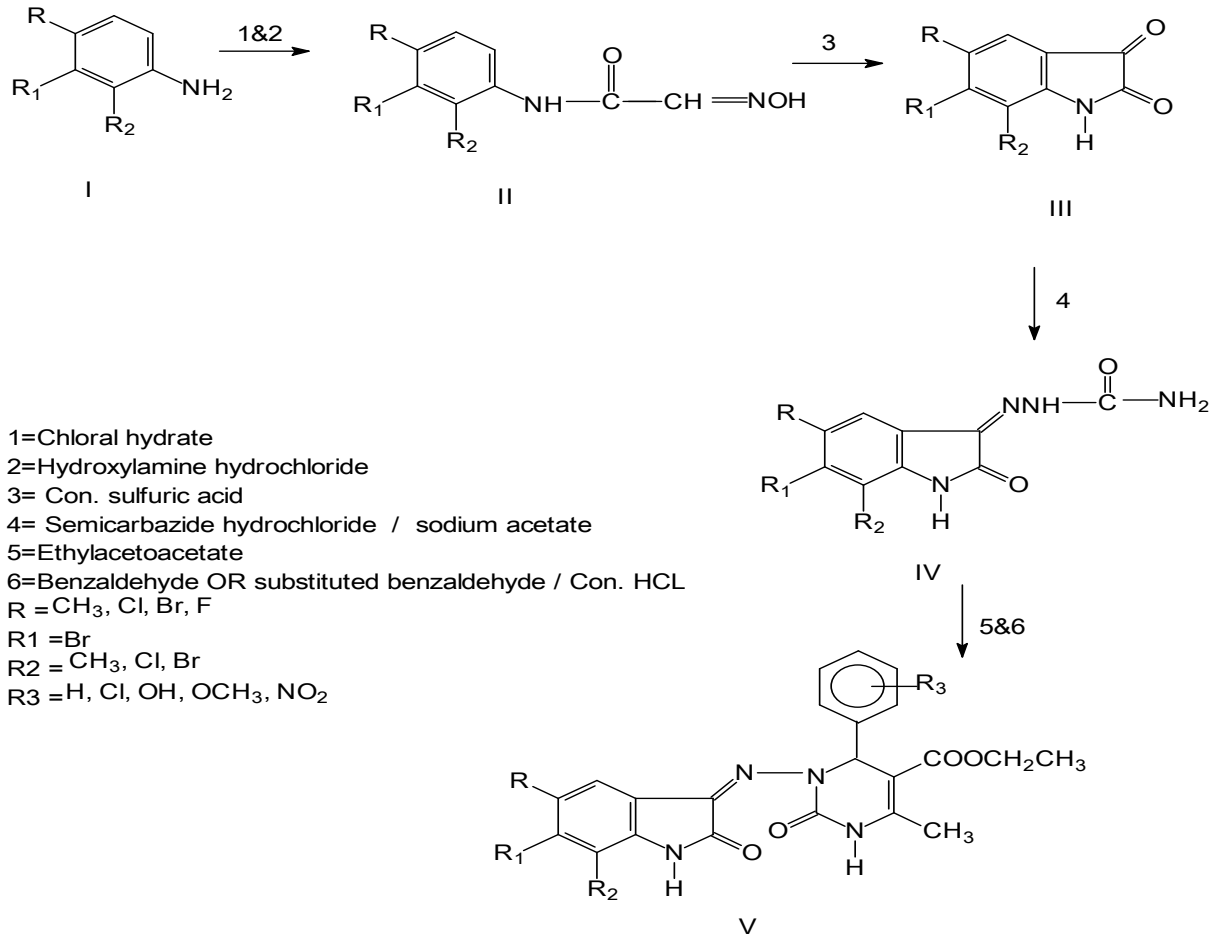

Table-1

Synthesis and characterization of 3- [(4-phenyl / substituted phenyl - 5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)Indolin-2-ones]

S.No.	Compound	R	R1	R2	R3	Molecular formula	M.P (°C)	Yield (%)
1	AJ1	H	H	H		$C_{22}H_{20}N_4O_4$	243	68
2	AJ2	CH3	H	H		$C_{23}H_{22}N_4O_4$	246	65
3	AJ3	F	H	H		$C_{22}H_{19}N_4O_4F$	248	70
4	AJ4	Cl	H	H		$C_{22}H_{19}N_4O_4C1$	251	72
5	AJ5	Br	H	H		$C_{22}H_{19}N_4O_4Br$	252	68
6	AJ6	H	Br	H		$C_{22}H_{19}N_4O_4Br$	253	65
7	AJ7	Br	H	Br		$C_{22}H_{18}N_4O_4Br_2$	255	72
8	AJ8	H	H	CH3		$C_{23}H_{22}N_4O_4$	244	65
9	AJ9	H	H	Cl		$C_{22}H_{19}N_4O_4C1$	245	67
10	AJ10	H	H	H		$C_{22}H_{19}N_4O_4C1$	244	67
11	AJ11	CH_3	H	H		$C_{23}H_{20}N_4O_4C1$	246	66
12	AJ12	F	H	H		$C_{22}H_{18}N_4O_4C1F$	248	65
13	AJ13	Cl	H	H		$C_{22}H_{18}N_{4254}O_4C1_2$	254	66
14	AJ14	Br	H	H		$C_{22}H_{18}N_4O_4C1Br$	256	67
15	AJ15	H	Br	H		$C_{22}H_{18}N_4O_4C1Br$	257	66
16	AJ16	Br	H	Br		$C_{21}H_{17}N_4O_4C1Br_2$	259	67
17	AJ17	H	H	CH_3		$C_{23}H_{20}N_4O_4C1$	246	65
18	AJ18	H	H	Cl		$C_{22}H_{18}N_4O_4C1_2$	255	65
19	AJ19	H	H	H		$C_{22}H_{19}N_4O_5$	258	68
20	AJ20	CH_3	H	H		$C_{23}H_{21}N_4O_5$	259	67
21	AJ21	F	H	H		$C_{22}H_{18}N_4O_5F$	261	66
22	AJ22	Cl	H	H		$C_{22}H_{18}N_4O_5C1$	263	67
23	AJ23	Br	H	H		$C_{22}H_{18}N_4O_5Br$	266	68
24	AJ24	H	Br	H		$C_{22}H_{18}N_4O_5Br$	267	66
25	AJ25	Br	H	Br		$C_{22}H_{17}N_4O_5Br_2$	270	68
26	AJ26	H	H	CH_3		$C_{23}H_{21}N_4O_5$	258	65
27	AJ27	H	H	Cl		$C_{23}H_{22}N_4O_5$	263	66
28	AJ28	H	H	H		$C_{23}H_{22}N_4O_5$	245	64
29	AJ29	CH_3	H	H		$C_{24}H_{23}N_4O_5$	246	63
30	AJ30	F	H	H		$C_{23}H_{21}N_4O_5F$	248	64
31	AJ31	Cl	H	H		$C_{23}H_{21}N_4O_5C1$	250	64
32	AJ32	Br	H	H		$C_{23}H_{21}N_4O_5Br$	252	65
33	AJ33	H	Br	H		$C_{23}H_{21}N_4O_5Br$	251	63
34	AJ34	Br	H	Br		$C_{23}H_{20}N_4O_5Br_2$	254	64
35	AJ35	H	H	CH_3		$C_{24}H_{23}N_4O_5$	246	62
36	AJ36	H	H	Cl		$C_{23}H_{21}N_4O_5C1$	251	63
37	AJ37	H	H	H		$C_{22}H_{19}N_5O_6$	270	64
38	AJ38	CH_3	H	H		$C_{23}H_{22}N_5O_6$	272	63
39	AJ39	F	H	H		$C_{22}H_{18}N_5O_6F$	274	64
40	AJ40	Cl	H	H		$C_{22}H_{18}N_5O_6Cl$	276	65
41	AJ41	Br	H	H		$C_{22}H_{18}N_5O_6Br$	278	64
42	AJ42	H	Br	H		$C_{22}H_{18}N_5O_6Br$	275	63
43	AJ43	Br	H	Br		$C_{22}H_{17}N_5O_6Br_2$	281	64
44	AJ44	H	H	CH_3		$C_{23}H_{22}N_5O_6$	271	62
45	AJ45	H	H	Cl		$C_{22}H_{18}N_5O_6Cl$	277	63

Experimental

All reagents used were purchased from Sd Fine Chemical Company, Mumbai, India. Melting points were determined in an open capilries on a gallen camp apparatus (Sanyo gallen camp, lough, borough, UK), and were un corrected. IR spectra (KBR, cm^{-1}) were recorded on perkin elmer spectrophotometer (577 model). H1 NMR spectra were recorded on a brukar WM-400 spectrophotometry (in δppm)

Isatin semicarbazone (B_1 to B_9):

To a stirred solution of an appropriate isatin(A_1 to A_9) 2gm in 20ml of alcohol at room temperature, semicarbazide hydrochloride, sodium acetate dissolved in water is added to the above solution and refluxed on a water bath for about 1hour, the resultant yellow crystalline solid was filtered ,washed repeatedly with small portions of cold water and finally with small portions of cold methanol and recrystllized with methanol to give pure products (B_1 to B_9). The data of the compounds produced was compared data available in the literature.

3- Substituted-[3,4-dihydro pyrimidinones]-Indolin-2-ones (AJ $_{1\ to\ 45}$):

Compounds B_1 to B_9 (2.04gm, 0.01mol), ethylacetoacetate and aromatic aldehyde (0.01 mol), in drymethanol and a few drops of concentrated hydrochloric acid as a catalyst was condensed by multicomponent one pot condensation by named Biginelli's reaction for 10 to 12 hours on a water bath. The solvent was evaporated, the precipitated solid was poured on to crushed ice, filtered, dried and recrystallized from methanol to give pure products (AJ_1 to AJ_{45}). The compounds obtained were characterized by physical and spectral data .for eg, the yield of the compound C_2[R_1=H, R_2=H, R_3=benzaldehyde] was 2g[65]M.P246andspectraldata (KBr): 159[NH,indole],3330[NH,pyramidine],1720[NH-CO],1688[C=O,indole],1621[C=N,13601280[C N,13001000[CO].PMRspectra[inDMSOD6,ppm]12.03[S,1H,NHindole],11.73[S,1H,NHpyrimidin e] 6.0- .7.0[m,8H,2Ar-H], 0.9[t-CH_3] 4.0[q,2H,O CH_2] 2.20[S,3H,CH_3].compoundsAJ_{1-45}were prepared similarly.

RESULTS

Compounds AJ_1 to AJ_{45}, consisting of five series, 3[(4-phenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)indolin-2-ones] (X), 3[(4-chlorophenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)indolin-2-ones] (Y), 3[(4-hydroxyphenyl-5carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]2one)indolin-2-ones](Z),3[(4-methoxyphenyl-5- carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]2one)indolin-2-ones] (X_1) and 3[(2-nitrophenyl-5carboethoxy-6methyl3,4dihydropyrimidin[1H]-2-one)indolin-2-ones] (Y_1). All the results are depicted in table – 2 to 6.

Tables-2

Anti-inflammatory activity of 3[(4-phenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)Indolin-2-ones] (X)

Initial *Mean ±SD (1.65 ± 0.1)*	*1hr*		*2hr*		*3hr*		*4hr*	
	Mean ±SD	*% red*	*Mean ±SD*	*% red*	*Mean ±SD*	*% red*	*Mean ±SD*	*% red*
Control	*3.42 ± 0.16*	NA	*3.57 ± 0.16*	NA	*3.63 ± 0.1*	NA	*3.47 ± 0.10*	NA
Standard	2.38 ± 0.13	30.40*	2.13 ± 0.12	40.33*	1.93 ± 0.12	46.83*	1.72 ± 0.13	50.43*
AJ 1	3.25 ± 0.16	4.97	3.10 ± 0.12	13.16	2.98 ± 0.11	17.90	2.82 ± 0.07	18.73
AJ 2	3.15 ± 0.16	7.89	3.03 ± 0.15	15.12	2.88 ± 0.14	20.66	2.72 ± 0.13	21.61
AJ 3	2.98 ± 0.13	12.86	2.83 ± 0.13	20.72	2.72 ± 0.09	25.06*	2.58 ± 0.07	25.64*
AJ 4	2.9 ± 0.11	15.20	2.78 ± 0.07	22.12	2.68 ± 0.07	26.17*	2.55 ± 0.10	26.51*
AJ 5	2.93 ± 0.15	14.32	2.83 ± 0.1	20.72	2.72 ± 0.07	25.06*	2.57 ± 0.08	25.93*
AJ 6	3.35 ± 0.15	2.04	3.28 ± 0.13	12.53	3.13 ± 0.15	13.77	3.05 ± 0.13	12.10
AJ 7	2.72 ± 0.09	20.46	2.55 ± 0.05	28.57*	2.45 ± 0.05	32.50*	2.25 ± 0.05	35.15*
AJ 8	3.27 ± 0.17	4.38	3.17 ± 0.17	11.20	3.01 ± 0.15	17.07	2.93 ± 0.12	15.56
AJ 9	2.82 ± 0.11	17.54	2.83 ± 0.08	20.72	2.72 ± 0.07	25.06*	2.45 ± 0.10	29.39*

** Significant protection at P < 0.05 (n=8)*

1. *Compounds: AJ3, AJ4, AJ5 and AJ9 -→ Significant at 3hr and 4hr time point*
2. *Compound: AJ7 -→ Significant at 2hr, 3hr and 4hr time point*
4. *In the above series IIA, lead molecules is AJ7*

Tables-3

Anti-inflammatory activity of 3[(4-Chlorophenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)Indolin-2-ones] (Y)

Initial *Mean ±SD (1.58 ± 0.07)*	*1hr*		*2hr*		*3hr*		*4hr*	
	Mean ±SD	*% red*	*Mean ±SD*	*% red*	*Mean ±SD*	*% red*	*Mean ±SD*	*% red*
Control	3.32±0.18	NA	3.47±0.19	NA	3.57±0.17	NA	3.27±0.25	NA
Standard	2.33±0.16	29.81*	2.13±0.16	38.61*	2.07±0.1	42.01*	1.83±0.13	44.03*
AJ 10	3.17±0.15	4.51	3.02±0.13	12.96	2.93±0.1	17.92	2.78±0.11	14.98
AJ 11	2.8±0.17	15.66	2.7±0.2	22.19	2.62±0.16	26.61*	2.48±0.18	24.15*
AJ 12	2.73±0.16	17.77	2.63±0.15	24.20*	2.5±0.11	29.97*	2.37±0.15	27.52*
AJ 13	2.53±0.17	23.79*	2.42±0.09	30.25*	2.27±0.1	36.41*	2.12±0.09	35.16*
AJ 14	2.65±0.21	20.18	2.45±0.21	29.39*	2.33±0.24	34.73*	2.2±0.25	32.72*
AJ 15	3.1±0.11	6.62	2.95±0.1	14.98	2.83±0.15	20.72	2.7±0.16	17.43
AJ 16	2.45±0.15	26.20*	2.25±0.19	35.15*	2.15±0.13	39.77*	2.02±0.04	38.22*
AJ 17	2.87±0.16	13.55	2.73±0.10	21.32	2.83±0.11	20.72	2.52±0.09	22.93
AJ 18	2.52±0.19	24.09*	2.38±0.13	31.41*	2.22±0.11	37.81*	2.10±0.08	35.78*

** Significant protection at P < 0.05 (n=8)*

1. *Compound: AJ11 -→ Significant at 3hr and 4hr time point*
2. *Compounds: AJ12 and AJ14-→ Significant at 2hr , 3hr and 4hr time point*
3. *Compounds: AJ13, AJ16 and AJ18 -→ found significant all time points (1hr, 2hr, 3hr and 4hr)*
4. *In the above series IIB, lead molecules are AJ13, AJ16 and AJ18*

Tables-4

Anti-inflammatory activity of 3[(4-Hydroxyphenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)Indolin-2-ones] (Z)

Initial *Mean ±SD (1.83 ± 0.10)*	*1hr*		*2hr*		*3hr*		*4hr*	
	Mean ±SD	*% red*	*Mean ±SD*	*% red*	*Mean ±SD*	*% red*	*Mean ±SD*	*% red*
Control	*3.38±0.14*	*NA*	*3.50±0.14*	*NA*	*3.58±0.14*	*NA*	*3.42±0.13*	*NA*
Standard	2.40±0.12	28.99*	2.22±0.13	36.57*	2.10±0.08	41.34*	1.93±0.08	43.56*
AJ 19	3.28±0.09	2.95	3.20±0.08	8.57	3.10±0.11	13.40	2.90±0.08	15.20
AJ 20	3.25±0.08	3.84	3.15±0.10	10.0	3.05±0.10	14.80	2.95±0.10	13.74
AJ 21	3.15±0.08	6.80	3.05±0.08	12.85	2.95±0.08	17.59	2.82±0.04	17.54
AJ 22	3.02±0.07	10.65	2.85±0.10	18.57	2.75±0.10	23.18*	2.67±0.08	21.92
AJ 23	2.93±0.05	13.31	2.77±0.05	20.85	2.63±0.05	26.53*	2.55±0.05	25.43*
AJ 24	3.22±0.11	4.73	3.13±0.10	10.57	3.03±0.10	15.36	2.93±0.08	14.32
AJ 25	2.67±0.10	21.00	2.53±0.08	27.71*	2.45±0.10	31.56*	2.35±0.10	31.28*
AJ 26	3.25±0.08	3.84	3.18±0.07	9.14	3.10±0.08	13.40	2.95±0.05	13.74
AJ 27	2.77±0.10	18.04	2.63±0.13	24.85*	2.53±0.12	29.32*	2.40±0.12	29.82*

** Significant protection at P < 0.05 (n=8)*

1. *Compounds: AJ22 -→ Significant at 3hr time point*
2. *Compound: AJ23 -→ Significant at both 3hr and 4hr time point*
3. *Compounds: AJ25, AJ27-→ found significant at 1hr, 2hr and 3hr*
4. *In the above series IIC, lead molecules are AJ25, AJ27*

Tables-5

Anti-inflammatory activity of 3[(4-Methoxyphenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)Indolin-2-ones] (X_1)

Initial *Mean ±SD (1.43 ± 0.10)*	*1hr*		*2hr*		*3hr*		*4hr*	
	Mean ±SD	*% red*	*Mean ±SD*	*% red*	*Mean ±SD*	*% red*	*Mean ±SD*	*% red*
Control	*3.42 ± 0.16*	*NA*	*3.52±0.14*	*NA*	*3.60±0.12*	*NA*	*3.42±0.11*	*NA*
Standard	2.40±0.17	29.82*	2.25±0.13	36.07*	2.15±0.13	40.27*	2.02±0.11	40.93*
AJ 28	3.28±0.11	4.09	3.20±0.08	9.09	3.12±0.09	13.33	3.0±0.07	12.28
AJ 29	3.22±0.07	5.84	3.12±0.10	11.36	3.08±0.07	14.44	2.98±0.07	12.86
AJ 30	3.15±0.10	7.89	3.07±0.12	12.78	2.93±0.08	18.61	2.9±0.11	15.20
AJ 31	3.02±0.07	11.69	2.90±0.08	17.61	2.80±0.12	22.22	2.68±0.11	21.63
AJ 32	2.9±0.07	15.20	2.80±0.08	20.45	2.72±0.11	24.44*	2.6±0.14	23.97*
AJ 33	3.18±0.07	7.01	3.10±0.08	11.93	3.0±0.07	16.66	2.9±0.07	15.20
AJ 34	2.68±0.07	21.63	2.55±0.08	27.55*	2.44±0.08	32.22*	2.3±0.08	32.74*
AJ 35	3.10±0.16	9.35	3.0±0.12	14.77	3.0±0.11	16.66	2.92±0.11	14.61
AJ 36	2.77±0.05	19.00	2.62±0.07	25.56*	2.53±0.05	29.72*	2.43±0.05	28.94*

** Significant protection at P < 0.05 (n=8)*

1. *Compounds: AJ32 -→ Significant at 3hr and 4hr time point*
2. *Compounds: AJ34 and AJ36-→ Significant at 2hr, 3hr and 4hr*
3. *In the above series IID, lead molecules are AJ34 and AJ36*

Tables-6

Anti-inflammatory activity of 3[(3-Nitrophenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidin[1H]-2-one)Indolin-2-ones] (Y_1)

Initial Mean ±SD (1.72±0.07)	1hr		2hr		3hr		4hr	
	Mean ±SD	% red	Mean ±SD	% red	Mean ±SD	% red	Mean ±SD	% red
Control	*3.38±0.16*	*NA*	*3.57±0.15*	*NA*	*3.53±0.19*	*NA*	*3.32±0.19*	*NA*
Standard	2.45±0.08	27.51*	2.20±0.12	38.37*	2.07±0.10	41.35*	1.85±0.08	44.27*
AJ 37	3.25±0.12	3.84	3.12±0.14	12.60	2.95±0.10	16.43	2.78±0.17	16.26
AJ 38	3.15±0.15	6.80	3.05±0.08	14.56	2.90±0.08	17.84	2.77±0.13	16.56
AJ 39	2.95±0.15	12.72	2.75±0.18	22.96	2.68±0.19	24.07*	2.55±0.19	23.19*
AJ 40	2.82±0.08	16.56	2.73±0.08	23.52*	2.65±0.10	24.92*	2.55±0.05	23.19*
AJ 41	2.78±0.09	17.75	2.65±0.08	25.77*	2.60±0.17	26.34*	2.42±0.14	27.10*
AJ 42	3.28±0.09	2.95	3.12±0.09	12.60	3.0±0.05	15.01	2.88±0.09	13.25
AJ 43	2.62±0.13	22.48	2.43±0.15	31.93*	2.33±0.10	33.99*	2.15±0.08	35.24*
AJ 44	3.22±0.13	4.73	3.03±0.13	15.12	3.0±0.09	15.01	2.78±0.13	16.26
AJ 45	2.68±0.09	20.71	2.53±0.08	29.13*	2.45±0.08	30.59*	2.28±0.16	31.32*

** Significant protection at $P < 0.05$ (n=8)*

1. *Compound: AJ39 -→ Significant at 3hr and 4hr time point*
2. *Compounds: AJ40, AJ41, AJ43 and AJ45-→ Significant at both 2hr, 3hr and 4hr time point*
3. *In the above series IIE, lead molecules are AJ40, AJ41, AJ43 and AJ45*

DISCUSSION

Among the X series, Compound AJ7 ($R=R_2=Br,R_1=H$) was identified as more potent compound comparatively against carragenan induced rat paw edema at 2hr, 3hr and 4hr time points with percentage inhibition of (28.57, 32.50 and 35.15) followed by compounds AJ4($R=Br,R_1=H$), AJ9($R_2=Cl,R=R_1=H$), AJ5($R=Br,R_1=R_2=R_3=H$) and AJ3($R=Cl,R_1=R_2=R_3=H$) were found to be significant at only 3hr and 4hr time points with percentage inhibition of (26.17 and 26.51), (25.06 and 29.39), (25.06 and 25.93) and (25.06 and 25.64) respectively. Among Y series, compound AJ16 ($R=R_2=Br,R_1=H,R_3=Cl$)was found to be comparatively the most potent compound among all the compounds of this series, aganaist carrageenan induced rat paw edema with percent inhibition of (26.20, 35.15. 39.77 and 38.22) at 1hr, 2hr, 3hr and 4hr followed by compound AJ18($R=R_1=H,R_2=Cl,R_3=Cl$) with percent inhibition of (24.09, 31.41, 37.78 and 35.78) at 1hr, 2hr 3hr and 4hr respectively. Compounds of Z and X1 showed moderate antii-inflammatory activity. 5($R=R_2=Br,R$ Among the five series of compounds, this series (Y1) of compounds was found to be next in the order of anti-inflammatory activity after the second group of series. Among this series of compounds, compound AJ43($R=R_2=Br,R1=H,R_3=NO_2$) showed significant percentage inhibition of rat paw edema (31.93, 33.91 and 31.24) at 2hr, 3hr and 4hr time points respectively. Compound AJ45($R_2=Cl,R=R_1=H,R_3=NO_2$) was next in the order of inhibition of edema with percentage of (29.13, 30.15 and 31.52) at 2hr, 3hr and 4hr respectively.

CONCLUSION

Among all the 45 compounds, series of Y [having 4-chlorobenzaldehyde substituent at 5-position of pyrimidine ring] have shown more anti-inflammatory activity [AJ_{16}>AJ_{15}> AJ_{14}> AJ_{15} and AJ_{12}] followed by Y_1, Z, X_1 and X series. Among Isatins, 5,7-disubstituted halogens are more active than mono substituted halogens Br,C1,F against anti-inflammatory activity Compound AJ16($R=R_2=Br,R_1=H,R_3=CI$) was the most potent anti-inflammatory compound with percent inhibition of (26.20, 35.15, 39.77 and 38.22) at 1hr, 2hr, 3hr and 4hr. Compounds AJ18($R=R_1=H,R_2=CI,R_3=CI$) with percent inhibition of edema (24.09,31.41,37.81 and 35.78) and AJ13$R_1=R_2=H,R=CI,R3=CI$) with percent inhibition of(23.79,30.25,36.41 and 35.16) were potent compounds comparatively among all the forty five compounds. The rest of the compounds showed mild to moderate activity and statistically significant. The anti-inflammatory was less than the standard Diclofenac sodium

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