ANTI-INFLAMMATORY ACTIVITY OF NOVEL ISATIN ANALOGUES

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Summary

In present study several N, N-disubstituted acetyl isatin hydrazones were synthesized by condensation of chloro acetyl isatin hydrazones with different N, N-disubstituted amines. All the synthesized compounds showed good anti-inflammatory activity in Sprague Dawley rats. The anti-inflammatory activity was performed by carrageenan induced rat paw edema method. Thus among the Ic with N, N-dimethyl substitution have shown most significant activity. Among all the compounds, the compound with dimethyl substitution Ib has shown less activity.

Key words: Indoles, Anti-inflammatory activity, Isatin hydrazones.

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Introduction

Isatin (1H-indole-2, 3- dione) was first discovered by Erdmann and Laurent in 1841, independently as a product from oxidation of indigo by nitric and chromic acids. Isatin (1H-indole-2, 3- dione) is a versatile molecule and possesses wide range of biological activities like antimicrobial, analgesic, anti-inflammatory, anti-convulsant, antidepressant, antipsychotic, anticancer (1-7). In the present study we synthesized N, N-disubstituted acetyl isatin hydrazones which were prepared by condensing chlroacetyl isatin hydrazones with two different secondary amines and screened for the anti-inflammatory activity by carrageenan induced rat paw edema. The compound with N, N-Dimethyl substitution (Ic) was the most active among the series at a dose of 100mg/Kg body weight with 84.3 percent inhibition of carrageenan induced rat paw edema, comparable to that of ibuprofen 50mg/Kg body weight.

Materials and Methods

Chemicals:

Chemicals used for the experiments were all AR grade obtained from Loba Chemicals. Carrageenan and Ibuprofen were obtained from sigma chemicals. For testing anti-inflammatory activity the standard drug and test compounds were made into suspension with 0.1% Carboxy methyl cellulose. The physical data of test compounds were shown in table-1.

Animals:

Male Sprague Dawley rats maintained under controlled conditions of temperature (23±2ºC) and humidity (50±5%) and a 12 hour light –dark cycle were used for the experiment. The animals were housed in sanitized polypropylene cages containing sterile paddy husk as bedding. They had free access to standard rat food and water. The studies were conducted with the prior approval of Institutional Animal Ethics Committee.

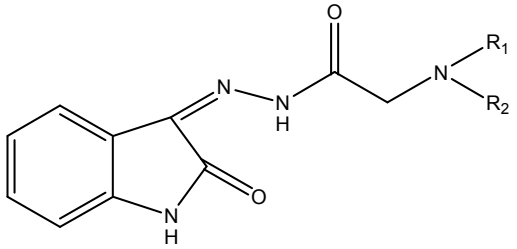
Anti-inflammatory activity:

Healthy male Sprague Dawley rats weighing 200-250grams were used as experimental animals. Animals were fasted overnight and divided into standard, test and control groups of six animals each. 0.05ml of 1% solution of carrageenan was administered into the planar side of the left hind paw of the rats. Thirty minutes later standard drug (50mg/kg body weight of Ibuprofen), test compound (100mg/kg body weight) and control vehicle (0.1% Carboxy methyl cellulose) were administered to the rats by intraperitonial injection (8, 9).

The paw is marked with ink at the level of the lateral malleolus and immersed in mercury up to this mark to measure the paw volume. The paw volume was measured plethysmographically in 0 hour (before carrageenan injection), 1 hour, 2 hours, 4 hours and 6 hours. The results were compared with control and standard drug.

Percentage reduction in paw edema = (1- difference in the paw volume of right and left paw of the drug treated / difference in the paw volume of right and left paw of the control) × 100

Table 1: Physical data of N, N-disubstituted acetyl isatin hydrazones



Compounds	R	R1	R2	Molecular Formula	Molecular weight	Melting Point (°C)	Percentage Yield
Ia	H	CH_3	CH_3	$C_{10}H_{13}N_4$	169	200	75
Ib	H	C_2H_5	C_2H_5	$C_{12}H_{15}N_4$	191	210	71
Ic	5-CH3	CH_3	CH_3	$C_{11}H_{15}N_4$	181	216	78
Id	5-CH3	C_2H_5	C_2H_5	$C_{12}H_{17}N_4$	193	219	60
Ie	7-CH3	CH_3	CH_3	$C_{11}H_{15}N_4$	181	225	58
If	7-CH3	C_2H_5	C_2H_5	$C_{12}H_{17}N_4$	193	280	50

Results and Discussion

Evaluation of anti-inflammatory activity

The test compounds were evaluated for anti-inflammatory activity by carrageenan induced paw edema method in rats. The rat paw edema volume (ml) and percentage reduction in paw edema of all the test compounds are presented in the tables 2 and 3 and figure 1 respectively. The increased paw volume was observed after injection of the carrageenan as it is phlogestic agent causes inflammation. The increased paw volume was observed in time dependent manner. Significantly decreased paw volume was observed in test and standard group of animals when compared to control group.

Table 2: Anti inflammatory Activity: Effect of various compounds on carrageenan induced rat paw edema (Rat paw volume)

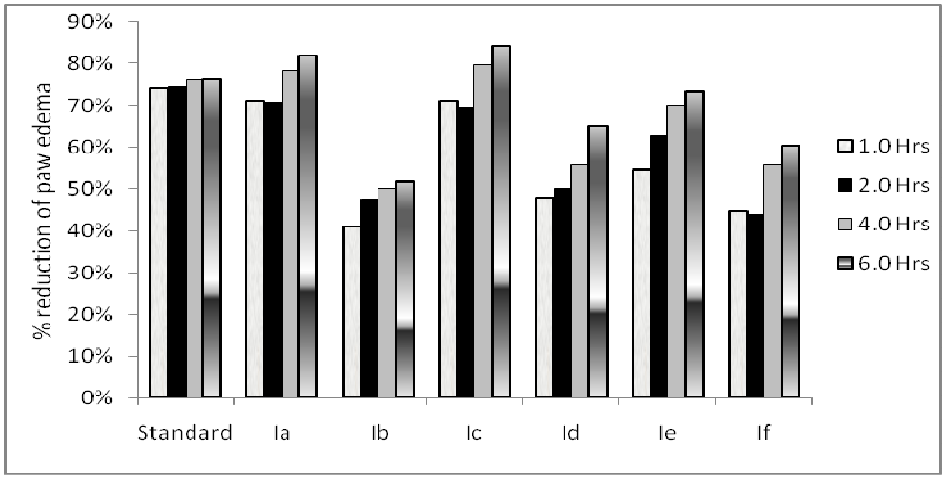
compounds	Rat paw volume (ml)			
	1hr	2hrs	4hrs	6hrs
Control	0.73 ± 0.050	0.82 ± 0.035	0.88 ± 0.029	0.89 ± 0.025
Standard	0.19 ± 0.025	0.21 ± 0.030	0.21 ± 0.048	0.20 ± 0.040
Compound Ia	0.21 ± 0.031	0.24 ± 0.043	0.19 ± 0.035	0.16 ± 0.025
Compound Ib	0.43 ± 0.064	0.43 ± 0.050	0.44 ± 0.048	0.43 ± 0.050
Compound Ic	0.21 ± 0.048	0.25 ± 0.001	0.18 ± 0.008	0.14 ± 0.011
Compound Id	0.38 ± 0.095	0.41 ± 0.062	0.39 ± 0.103	0.31 ± 0.062
Compound Ie	0.25 ± 0.039	0.29 ± 0.045	0.24 ± 0.035	0.20 ± 0.024
Compound If	0.39 ± 0.050	0.47 ± 0.030	0.39 ± 0.057	0.34 ± 0.050

The data on the anti inflammatory activity of N, N-disubstituted acetyl isatin hydrazones indicate that all the compounds exhibited anti-inflammatory activity. The compounds Ia, Ib, Ic, Id, Ie and If have shown 82%, 51.7%, 84.3%, 65.2%, 73.4% and 60.5% reduction in paw edema respectively after 6 hours. Among all the compounds, the Ic with N,N-Dimethyl substitution have shown most significant activity with the percentage reduction in paw volume of 84.3%. The compounds Ia, Ie are next in the order of anti- inflammatory activity. Among all the compounds, the compound with di ethyl substitution (Ib) has shown less activity with the % reduction of paw edema of 51.7%. The data of anti-inflammatory activity was given in table 2 & 3 and figure 1.

Table 3: Anti inflammatory Activity: Effect of various compounds on carrageenan induced rat paw edema (Percentage reduction)

compound	Percentage reduction (%) of rats paw edema			
	1hr	2hrs	4hrs	6hrs
Standard	74%	74.4%	76.1%	76.4%
Compound Va	71.2%	70.7%	78.4%	82.0%
Compound Vb	41.1%	47.6%	50.0%	51.7%
Compound Vc	71.2%	69.5%	79.5%	84.3%
Compound Vd	47.9%	50.0%	55.7%	65.2%
Compound Ve	54.6%	62.7%	70.0%	73.4%
Compound Vf	44.7%	43.9%	55.8%	60.5%

Figure 1: Anti-inflammatory activity of various compounds on carrageenan induced rat paw edema (Percentage reduction)



Conclusion

The present study results suggest the anti-inflammatory activity of all the six N, N-disubstituted acetyl isatin hydrazone analogues. Among the compounds tested, Ia and Ic showed potent anti-inflammatory activity by carrageenan induced rat paw edema method.

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