STUDIES ON ANTI-INFLAMMATORY, ANALGESIC AND ANTIPYRETIC ACTIVITIES OF SOME INDAN ACIDS

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Summary : A series of indan-1-acids were synthesized and screened for anti-inflammatory activity. All the reported compounds showed varying degrees of anti-inflammatory activity in carrageenin-induced paw oedema test. They also exhibited appreciable antipyretic and analgesic activity in various animal test models. Among these compounds 6-methoxy-indan-1-acetic acid (compound 11) and 5,6-dimethoxy-indan-1-acetic acid (compound 12) showed activity profile close to that of phenylbutazone having prolonged action and lower toxicity than the latter.

Key words: analgesic anti-inflammatory antipyretic indan-1-acids

INTRODUCTION

Arylakanoic acids are currently the most widely investigated class of compound in the area of non-steroidal anti-inflammatory agents. Indan acids which belong to this class, have assumed a special significance primarily because of its peculiar molecular framework making it a highly sensitive ring moiety towards various pharmacological actions (3) besides being isosteric with indolidine, another pharmacologically active chemical nucleus. Excelient anti-inflammatory activity of some substituted indan acids have already been reported in some recent communications (1,5,7). In the present study we examine the anti-inflammatory activity of some simple and substituted indan-1-carboxylic acids and indan-1-acetic acids with a view to obtain less toxic compounds than those reported earlier.

The indan acids reported here were synthesized by the cyclo-dehydration of the corresponding simple and substituted phenylsuccinic acids and phenylglutaric acids with polyphosphoric acid or anhydrous aluminium chloride (6). All these acids showed significant anti-inflammatory, analgesic and antipyretic activity in suitable screening models as detailed below.

MATERIALS AND METHODS

Male albino rats and mice both of Wistar strain were used after acclimatization for 8 days to the laboratory environment.

Chemicals :

The following chemicals were used :

Carrageenin (Marine Colloids Inc., U.S.A.), aspirin and indomethacin (IDPL, India), phenylbutazone (Albert David, India), phenylquinone (SIGMA, U.S.A.), dried yeast (Shaw Wallace, India), sodium chloride and sodium hydroxide (I.P.) and the indan acids (synthesized in our laboratory).

Methods :

All the compounds were administered by either ip or sc injection dissolving them in aqueous sodium hydroxide solution at a pH of 7.5 $\pm$ 0.2.

Acute toxicity :

Male albino mice, 25-30 *g* were used, 6 animals per dose level. Approximate LD_{50} was determined by inspection from mortalities occuring within 24 hr after ip administration of the compounds.

Anti-inflammatory activity :

Carrageenin-induced paw oedema test : The method is essentially that of Winter *et al.* (8) with some modification in the procedure of paw volume determination. The initial paw volumes upto the level of lateral malleolus of the rats were determined by simple mercury displacement technique with the help of a travelling microscope. The compounds were administered ip immediately before the injection of 0.1 *ml* of a 1.0% solution of carrageenin in 0.9% saline into the plantar surface of right hind paw. Then the paw volumes were determined every hr upto 4 hr and at 24 hr. The increase in paw volume minus the volume injected gave the oedema volume. The average oedema volumes in both the control and drug-treated groups were compared using Student's t-test. The percent inhibition of paw oedema against saline treated control was determined for each drug-treated group from the average oedema volumes obtained at hourly intervals as shown below.

$$\% \text{ inhibiton} = \frac{V_c - V_t}{V_c} \times 100$$

where V_c and V_t are average oedema volumes in control and treated groups respectively.

Analgesic activity by phenylquinone-induced writhing method :

The method is essentially that of Hendershot and Forsaith (4) with minor modifications. Male albino mice, 18-22 g were injected intraperitoneally with 0.25 *ml* of 0.02%

phenylquinone solution and observed during the next 20 min for writhing. Animals giving 20 or more writhes were selected. After 6 days, these animals were divided at random into groups of 10 mice each. Compounds were administered subcutaneously at different doses using saline for the control group. After 1 hr, 0.25 *ml* of 0.02% phenylquinone solution was injected ip and observed during the next 20 min for writhing. Control experiments were repeated several times and the data were pooled to determine average control level. The percent protection by individual compounds as well as reference standard drugs at each dose level against control was calculated by the formula below.

$$\% \text{ protection} = \frac{W_c - W_t}{W_c} \times 100$$

where W_c and W_t are total number of writhes per group in control and treated group respectively.

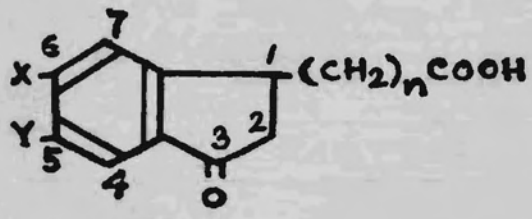
Antipyretic activity :

Yeast-induced pyresis method : Male albino rats (140-160 *g*) were kept fasting for 18 hr. They were divided at random into groups of 6 animals each and the rectal temperature was recorded as the base temperature. Then the animals were given a 15% suspension of dried brewer's yeast in physiological saline (10 *ml/kg*, sc) keeping a control group without yeast (non-pyretic control). Each yeast administered group received either saline (pyretic control) or compound at different doses 1 hr after yeast administration. Temperature index was calculated following the method of Winter *et al.* (9) from the sum changes in rectal temperatures from the base temperature every hr upto 4 hr after administration of the compounds or the reference drug.

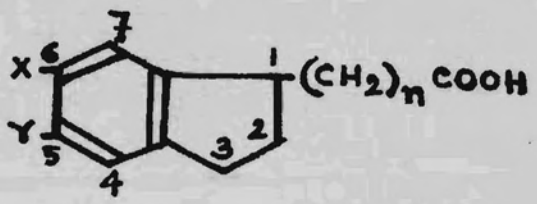
RESULTS AND DISCUSSION

The data on the anti-inflammatory activity of indan acids alongwith aspirin, phenylbutazone and indomethacin as reference standard are detailed in Table I. Their analgesic and antipyretic activities are summarized in Table II, taking aspirin and phenylbutazone as reference standard. All these compounds exhibited significant anti-infammatory, analgesic and antipyretic activity in carrageenin-paw oedema test, phenylquinone-writhing test and yeast pyresis method respectively. The activities were dose-related (50-200 *mg/kg* dose range).

Table I : Percent inhibition of carrageenin-induced rat paw oedema by a series of indanacids compared to other standard anti-inflammatory drugs. Compounds were given as their sodium salts in aqueous solution (pH at 7.5±0.2) immediately before carrageenin administration (01. *ml* of 1.0% in 0.9% saline). The average oedema volumes in control (saline) and drug-treated groups of animals were compared using Student's t-test (.05>P values>.01) and used in calculation of percent inhibition of oedema.



TYPE-I



TYPE-II

Compound no.	*Compound Type*	*Approx. LD_{50} ip*	*Dose mg/kg ip*	*Percent inhibition of rat paw oedema*				
				1 hr	*2 hr*	*3 hr*	*4 hr*	*24 hr*
1	I; X=Y=H; n=0	1650	200	18.54	38.64	27.23	14.78	NS
2	I; X=OMe, Y=H; n=0	1700	200	22.64	48.07	35.31	23.41	NS
3	I; X=Y=OMe; n=0	1400	200	21.51	40.72	26.27	15.83	NS
4	I; X=Y=H; n=1	1500	200	19.39	40.68	31.35	18.37	NS
5	I; X=OMe, Y=H; n=1	1400	200	29.96	50.37	38.89	30.24	NS
6	I; X=Y=OMe; n=1	1300	200	38.54	54.30	41.63	32.95	NS
7	II; X=Y=H; n=0	1250	200	23.67	43.18	32.39	20.17	NS
8	II; X=OMe, Y=H; n=0	1200	200 100	34.77 29.82	58.24 46.67	47.32 38.18	36.74 27.31	20.78 NS
9	II; X=Y=OMe; n=0	1125	200	21.83	44.39	33.65	20.26	NS
10	II; X=Y=H; n=1	1250	200	24.72	45.57	39.82	25.60	NS
11	II; X=OMe, Y=H; n=1	1125	200 100	39.51 30.64	62.85 54.36	51.13 45.62	43.72 37.43	26.08 22.04
12	II; X=Y=OMe; n=1	1050	200 100	45.19 36.24	67.05 58.13	56.35 47.61	49.42 38.82	30.25 25.34
Aspirin		1000	200	34.14	48.54	40.67	29.81	15.12
Phenylbutazone		500	100	38.64	56.23	45.14	36.15	20.53
Indomethacin		25	8	36.47	54.58	45.23	36.05	22.27

NS indicates percent inhibition less than 15.0.

TABLE II : The comparative analgesic and antipyretic activities of a series of indan acids in phenylquinone induced-writhing and yeast-induced pyresis methods respectively. The average temperature before yeast administration was taken as the base temperature. The temperature index was calculated from the sum of the temperature changes from the base tempearture every hr upto 4 hr after drug administration.

*Compound no.**	*Dose mg/kg*	*Analgesic activity*		*Antipyretic activity*				*Temperature index*
		Total no. of writhes per group	*Percent Prortection*	*Average change in body temperature (°C) after drug administration*				
				1 hr	*2 hr*	*3 hr*	*4 hr*	
1	200	123	62	—0.08	+0.19	+0.44	+0 86	+1.41
2	200	117	64	—0.11	+0.27	+0.48	+0.75	+1.39
3	200	149	54	—0.04	+0.54	+0.85	+1.09	+2.44
4	200	104	68	—0.22	+0.03	+0.45	+0.64	+0.90
5	200	78	76	—0.46	—0.04	+0.15	+0.65	+0.30
	100	149	54	—0.32	+0.09	+0.44	+0.78	+0.99
6	200	65	80	—0.32	+0.21	+0.48	+0.78	+1.15
	100	136	58	—0.14	+0.35	+0.66	+0.98	+1.85
7	200	100	69	—0.33	—0.11	+0.38	+0.64	+0.58
8	200	78	76	—0.34	+0.20	+0.41	+0.68	+0.95
	100	117	64	—0.18	+0.37	+0.56	+0.85	+1.60
9	200	91	72	—0.08	+0.13	+0.67	+0.89	+1.61
10	200	81	75	—0.41	—0.16	+0.32	+0.59	+0.34
	100	123	62	—0.23	+0.07	+0.46	+0.77	+1.07
11	100	91	72	—0.38	—0.12	+0.16	+0.47	+0.13
	50	139	57	—0.16	+0.09	+0.41	+0.60	+0.94
12	100	71	78	—0.31	—0.03	+0.25	+0.49	+0.40
	50	110	66	—0.12	+0.16	+0.48	+0.76	+1.28
Aspirin	100	120	63	—0.38	—0.15	+0.19	+0.54	+0.20
	50	178	45	—0.10	+0.13	+0.55	+0.86	+1.44
Phenyl-butazone	100	81	75	—0.71	—0.29	—0.14	+0.28	—0.86
	50	156	52	—0.42	—0.06	+0.20	+0.57	+0.29
Control Saline		324	—	+0.10 (Non-pyretic)	+0.05	0.0	0.0	+0.15
				+0.50 (Pyretic)	+1.09	+1.54	+1.68	+4.81

* Compound nos. are the same as in Table I.

+ and — means increase and decrease respectively.

Their anti-inflammatory activity reached the maximum at 2 hr after drug administration and in some cases the activity persisted even after 24 hr. Their antipyretic activity reaches its maximum within 2-3 hr after drug administration.

From the accompanying Tables it is generally observed that the presence of a keto function at 3-position of indan-1-acids decreases activity. Contrary to earlier report on the position of carboxyl function in indan-1-acids for anti-inflammatory activity (5), it is found that indan-1-acetic acids (Compound, 4,5,6,10,11,12) are more active than the corresponding indan-1-carboxylic acids (Compounds 1,2,3,7,8,9). Further, the introduction of methoxy group at 6 position or both 5,6-position of indan-1-acetic acid increases activity (Compounds 5,6,11,12).

Acute toxicity studies (Table I) suggest that they are much less toxic than indomethacin and phenylbutazone and do not show any toxic symptom at therapeutic doses as high as 200 *mg/kg*, ip.

Another distinct advantage of therapeutic use of these acids is that they do not disturb the normal pH of blood (7.4) and even may act as buffer since their pKa values lie between 6-7(2). Though it is not known whether their dissociated or undissociated form is active, their prolonged action may be due to slow release of protein-bound undissociated molecules when the dissociated forms are used up with time.

From these studies it is revealed that two compounds namely 6-methoxy-indan-1-acetic acid (Compound 11) and 5,6-dimethoxy-indan-I-acetic acid (Compound 12) possess maximum anti-inflammatory, analgesic and antipyretic activity among all the compounds reported here. They exhibit an acivity profile similar to that of phenylbutazone having longer duration of action and less toxicity than the latter. Therefore, they deserve detailed pharmacological and toxicological investigation to explore their possible use as therapeutic agents.

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