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Aromatic amide derivatives of 5,6-dimethoxy-2,3-dihydro-1*H*-inden(-1-yl)acetic acid as anti-inflammatory agents free of ulcerogenic liability

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Abstract—Amide derivatives of 5,6-dimethoxy-2,3-dihydro-1*H*-inden(-1-yl)acetic acid were synthesized and evaluated for their anti-inflammatory and analgesic activity. Few selected compounds were also screened for their antipyretic, anti-arthritic, and ulcerogenic potential. Most of the compounds exhibited good activity profile and were free of gastrointestinal toxicity of common NSAIDs. However these compounds failed to decrease secondary lesions of adjuvant induced arthritis and also did not inhibit TNF-α in lipopolysaccharide induced pyresis.

Indan is one such molecular framework which serves as an inert carrier for holding various biologically active molecules in a stereospecific manner. The indan nucleus thus fixes the relative position of functional groups and imparts greater specificity of biological activity.[1] A number of indan and indene derivatives have been synthesized which incorporate structural features required for various pharmacological activities, for example, diuretic,[2] hypoglycemic,[3] antihypertensive,[4] antiproliferative,[5] antimicrobial,[6] acetyl cholinesterase inhibitors,[7] HIV-1 Integrase inhibitors,[8] anticancer,[9] anticonvulsant,[10] muscle relaxant,[11] and in the treatment of Alzheimer's disease.[12]

Various indan derivatives possessing anti-inflammatory activity have been reported.[13,14] Indan-1-carboxylic acid seems to involve essential conformation of phenyl acetic acids for exerting the anti-inflammatory activity.[15] Research in this area has led to the development of Clidanac, 6-chloro-5-cyclohexylindan-1-carboxylic acid, with an ED_{30} of 0.85 mg/kg.[16] However due to gastrointestinal side effects of nonsteroidal anti-inflammatory drugs (NSAIDs), research has been shifted to the development of nonulcerogenic, selective cyclooxygenase-2 (COX-2) inhibitors. Among all the Indan derivatives tested to date only 6-[(2,4-difluorophenyl)-thio]-5-methanesulfonamido-1-indanone, Flosulide,[17] has been identified as a potent selective COX-2 inhibitor.

Recently the biochemical differences between the COX-isoforms have been exploited to improve upon the selectivity of carboxylate-containing NSAIDs.[18] It has been reported that derivatization of carboxylate moiety of Indomethacin,[19] Meclofenamic acid[20] and Ketoprofen[21] to corresponding amides produced selective COX-2 inhibitors.

Based on the above-reported facts and our earlier work with aliphatic amide derivatives of Indan-1-acetic acid, we designed, synthesized, and biologically evaluated some aromatic amide derivatives of 5,6-dimethoxyindan-1-acetic acid for anti-inflammatory and related biological activities. The idea behind derivatization was to lower the side effects of gastric irritation and ulceration, which is associated with free carboxyl group. Neutralization of the carboxyl group by amidation was expected not only to enhance absorption by increasing lipophilicity but also to impart COX-2 selectivity.

The starting reagent for the preparation of the key intermediate, 5,6-dimethoxy-2,3-dihydro-1*H*-inden(-1-yl)acetic acid **(6)**, was vanillin **(1)**. The hydroxyl group of vanillin was methylated using dimethyl sulfate under alkaline conditions to get the methylated product-

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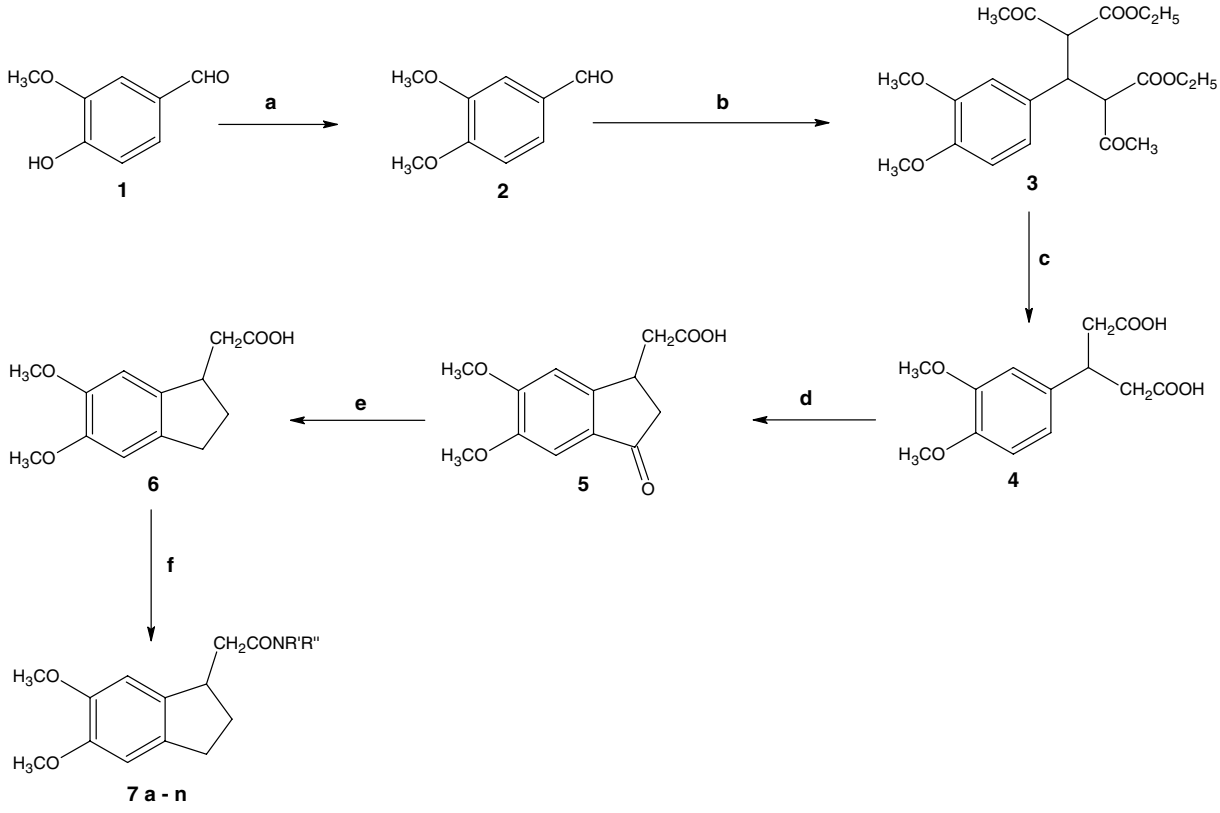
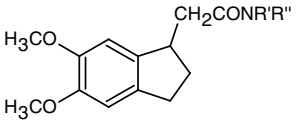
veratraldehyde[22] **(2)**. Veratraldehyde was reacted with two moles of ethylacetoacetate (EAA) in the presence of catalytic amount of piperidine at room temperature; as a result the aldehydic group of **2** was converted into bisacetoacetate **(3)**. Acidic hydrolysis of **3** was carried out with 6 N potassium hydroxide (KOH) in 90% ethanol to get the diacid **4**. Compound **4** was treated with polyphosphoric acid (PPA) when intramolecular Friedel Crafts cyclization and hence ring closure took place to give the ketonic product **5**. The ketone group of compound **5** was reduced using Clemmensen's reduction to give 5,6-dimethoxy-2,3-dihydro-1*H*-inden(-1-yl)acetic acid[23] **(6)**. Compound **6** was treated with oxalyl chloride in the presence of catalytic amount of dimethylformamide to convert the carboxyl group of **6** into acyl halide. The acyl halide thus obtained was reacted with various aromatic amines following Schotten Bauman's principle for the formation of desired amides **7a–n**[24] (Scheme 1). The proposed structure of the amide derivatives was confirmed by the disappearance of the broad OH stretch at 3400–2400 cm^{-1} and presence of a peak around 3300 cm^{-1} (NH stretch) corresponding to secondary amides. The formations of amides were further confirmed by the presence of a small singlet at 7–8 ppm in ^1H NMR. All the synthesized compounds were characterized by elemental microanalysis and spectroscopic data. The physical data of all the synthesized compounds are given in Table 1. Experimental details and data for synthesis are cited in the References and Notes.[25–29]

The anti-inflammatory activity of the test compounds was evaluated using carrageenan-induced rat paw edema model.[30] The results (Table 2) show that the test compounds exhibit variable anti-inflammatory activity, and a few among them have significant acute as well as residual anti-inflammatory activity even at 24 h after a single oral dose. Though the peak activity of the test compounds was found to be lower than that of Indomethacin (10 mg/kg, p.o.) their residual activity at 24 h exceeded that of the latter. The activity seemed to be dependent on the type and position of substituents on the phenyl ring of these aromatic amides. 4-Chlorophenyl derivative (**7c**) was found to be most active and showed longer activity profile with 70.0% inhibition at 24 h. Replacements of chloro group at para position with the bulkier bromo group (**7d**) as well the chloro group at the meta position (**7b**) decreased the activity. However, the compounds **7b** and **7d** showed good anti-inflammatory activity at 24 h. There was substantial decrease in activity with electron donating substituents (**7g**, **7i**, and **7k**) at para position. The ortho substituted derivatives (**7e**, **7h**, and **7l**) showed poor activity possibly because of steric hindrance. The higher residual activity may be associated with the high lipophilicity of the amide derivatives (Table 1) in comparison to the free acid **6**having log *P* value of 2.11. Due to high lipophilicity these amide derivatives are likely to form lipid depots in the body which may be responsible for longer activity profile of these compounds. In order to find out if some active metabolite is responsible for higher activity at lat-



Scheme 1. Reagents and conditions: (a) Me_2SO_4/KOH; (b) ethylacetoacetate/pyridine, 3 days at room temperature; (c) alcoholic KOH, 1 h reflux (d) PPA, 4 h heating on waterbath with intermittent stirring; (e) Zn/Hg/HCl, 8 hrs reflux; (f) i—$(COCl)_2$/DMF, 24 h rt; ii—NHR′R″/triethylamine, 12 h room temperature.

Table 1. Physical data of compounds (**7a–7n**)



Compound	R′	R″	Molecular formula	Yield (%)	Mp (°C)	Recrystallization solvent	Log *P*
7a	H	C_6H_5	$C_{19}H_{21}NO_3$	72.8	148–149	Dil. alcohol	2.98
7b	H	C_6H_4(*m*-Cl)	$C_{19}H_{20}ClNO_3$	65.6	104–106	Dil. alcohol	3.84
7c	H	C_6H_4(*p*-Cl)	$C_{19}H_{20}ClNO_3$	70.6	118–120	Dil. alcohol	3.79
7d	H	C_6H_4(*p*-Br)	$C_{19}H_{20}BrNO_3$	65.2	151–152	Dil. alcohol	3.82
7e	H	C_6H_4(*o*-CH_3)	$C_{20}H_{23}NO_3$	69.5	132–134	Dil. alcohol	3.26
7f	H	C_6H_4(*m*-CH_3)	$C_{20}H_{23}NO_3$	72.6	146–148	Dil. alcohol	3.40
7g	H	C_6H_4(*p*-CH_3)	$C_{20}H_{23}NO_3$	75.7	128–129	Dil. alcohol	3.49
7h	H	C_6H_4(*o*-OCH_3)	$C_{20}H_{23}NO_4$	71.5	118–120	Dil. alcohol	2.97
7i	H	C_6H_4(*p*-OCH_3)	$C_{20}H_{23}NO_4$	60.1	180–181	Dil. alcohol	3.06
7j	H	C_6H_4(*p*-NO_2)	$C_{19}H_{20}N_2O_5$	57.5	164–166	EtOAc/hexane	3.08
7k	H	C_6H_4(*p*-$NHCOCH_3$)	$C_{21}H_{24}N_2O_4$	60.7	206–208	EtOAc	2.38
7l	H	2-Pyridyl	$C_{18}H_{20}N_2O_3$	54.6	112–114	Dil. alcohol	2.19
7m	H	3-Pyridyl	$C_{18}H_{20}N_2O_3$	55.7	120–122	Dil. alcohol H	2.16
7n	H	4-Pyridyl	$C_{18}H_{20}N_2O_3$	58.6	104–106	EtOAc/hexane	2.19

Log *P* values were calculated using www.logp.com.

Table 2. Carrageenan induced rat paw edema: anti-inflammatory activity

Compound	Increase in paw volume (ml) ± SEM (% inhibition of edema)					
	1 h	2 h	3 h	4 h	6 h	24 h
7a	0.22 ± 0.0113 [31.25]*	0.34 ± 0.0058 [32.0]*	0.44 ± 0.0071 [36.23]*	0.40 ± 0.008 [37.5]*	0.33 ± 0.0174 [38.88]*	0.21 ± 0.0087 [30.0]*
7b	0.22 ± 0.0141 [31.25]*	0.36 ± 0.0198 [28.0]*	0.52 ± 0.0250 [24.64]*	0.475 ± 0.016 [25.78]*	0.33 ± 0.0213 [38.88]*	0.11 ± 0.006 [63.33]*
7c	0.09 ± 0.0125 [71.88]*	0.185 ± 0.014 [63.0]*	0.27 ± 0.0123 [60.88]*	0.25 ± 0.0108 [60.94]*	0.21 ± 0.0088 [61.11]*	0.09 ± 0.008 [70.00]*
7d	0.16 ± 0.0130 [50.00]*	0.30 ± 0.0117 [40.0]*	0.39 ± 0.0138 [43.48]*	0.38 ± 0.0125 [40.62]*	0.29 ± 0.0131 [46.30]*	0.10 ± 0.0019 [66.67]*
7e	0.25 ± 0.0136 [21.88]ns	0.41 ± 0.0186 [18.00]ns	0.51 ± 0.0164 [26.09]*	0.48 ± 0.0182 [25.0]*	0.40 ± 0.0135 [25.93]*	0.23 ± 0.0158 [23.33]*
7f	0.20 ± 0.0163 [37.5]*	0.355 ± 0.0143 [29.0]*	0.43 ± 0.0151 [37.68]*	0.38 ± 0.0137 [40.62]*	0.335 ± 0.008 [37.96]*	0.175 ± 0.0112 [41.67]*
7g	0.21 ± 0.0129 [34.38]*	0.37 ± 0.0256 [26.0]*	0.45 ± 0.0154 [34.78]*	0.43 ± 0.0254 [32.81]*	0.34 ± 0.0102 [37.04]*	0.21 ± 0.0065 [30.00]*
7h	0.23 ± 0.0142 [28.12]*	0.42 ± 0.0204 [16.0]	0.54 ± 0.0161 [21.74]	0.49 ± 0.0168 [23.44]*	0.41 ± 0.0135 [24.07]*	0.21 ± 0.0143 [30.0]*
7i	0.21 ± 0.0117 [34.38]*	0.41 ± 0.0093 [18.0]ns	0.51 ± 0.0073 [26.09]*	0.465 ± 0.0171 [27.34]*	0.38 ± 0.0137 [29.63]*	0.18 ± 0.0106 [40.00]*
7j	0.20 ± 0.0181 [37.50]*	0.32 ± 0.0364 [36.0]*	0.43 ± 0.0275 [37.68]*	0.40 ± 0.0131 [37.5]*	0.34 ± 0.0215 [37.04]*	0.17 ± 0.0056 [43.33]*
7k	0.24 ± 0.014 [25.0]*	0.41 ± 0.0138 [18.0]ns	0.53 ± 0.0169 [23.19]*	0.495 ± 0.0149 [22.66]*	0.41 ± 0.0184 [24.07]*	0.20 ± 0.0119 [33.33]*
7l	0.24 ± 0.0161 [25.0]*	0.34 ± 0.0138 [32.0]*	0.48 ± 0.0142 [30.43]*	0.45 ± 0.0152 [29.69]*	0.38 ± 0.0114 [29.63]*	0.20 ± 0.0154 [33.33]*
7m	0.24 ± 0.0147 [25.0]*	0.35 ± 0.0058 [30.0]*	0.46 ± 0.0176 [33.33]*	0.42 ± 0.0148 [34.38]*	0.35 ± 0.0208 [35.18]*	0.19 ± 0.0114 [36.67]*
7n	0.185 ± 0.013 [42.19]*	0.28 ± 0.013 [44.0]*	0.40 ± 0.0068 [42.03]*	0.35 ± 0.0143 [45.31]*	0.29 ± 0.0183 [46.29]*	0.16 ± 0.0143 [46.67]*
6	0.26 ± 0.034 [18.75]ns	0.38 ± 0.034 [24.0]*	0.50 ± 0.0335 [27.53]*	0.49 ± 0.0256 [23.94]*	0.43 ± 0.0226 [20.37]*	0.22 ± 0.0125 [26.67]*
Indomethacin	0.16 ± 0.0145 [50]*	0.21 ± 0.0125 [58]*	0.24 ± 0.0131 [65.22]*	0.27 ± 0.0113 [57.8]*	0.28 ± 0.0154 [48.15]*	0.26 ± 0.0141 [13.33]
Control	0.32 ± 0.0221	0.50 ± 0.0187	0.69 ± 0.0263	0.64 ± 0.0169	0.54 ± 0.0196	0.30 ± 0.0154

Anti-inflammatory activities of the test compounds and indomethacin were tested at 100 mg/ kg and 10 mg/kg, respectively, in male Wistar rats weighing 170 ± 20 g.

One hour after oral dosing, 0.1 ml of 1% carrageenan was administered into the subplantar region of the right hind paw and the paw volumes were measured using an Ugo Basile plethysmometer at 0, 1, 2, 3, 4, 6, and 24 h after the carrageenan injection.

Each value represents means ± SEM ($n = 6$).

Significance level $^{*}p < 0.05$ as compared with the control group.

ter hours we also studied the anti-inflammatory activity of compound **7c** in carrageenan induced rat paw edema model using SKF-525A,[31] a standard hepatic microsomal enzyme inhibitor, pretreated rats. Examination of Table 7 reveals that there is no significant difference between data generated from this test and those generated using standard protocol. This indicates that probably the test compound par se is the active species.

The analgesic activity was determined by acetic acid induced writhing assay.[32] From the results described in Table 3 it was seen that the activity was dependent on the type and position of substituents on the phenyl ring of the aromatic amides. The 4-chlorophenyl (**7c**) and 3-pyridyl (**7m**) derivatives were found to have good analgesic activity compared to the standard drug aspirin. The 4-methoxyphenyl (**7i**) derivative which showed poor anti-inflammatory activity was found to have relatively good analgesic activity.

Few selected compounds were subjected to lipopolysaccharide(LPS)-induced hyperthermia assay. It is generally accepted that the NSAIDs exhibit their anti-inflammatory effect primarily through inhibition of prostaglandin synthesis. However, relatively recent in vitro studies have indicated that NSAIDs also interfere with peripheral proinflammatory cytokine production. It is well known that LPS produces a biphasic response in the rat. It shows an initial hypothermia up to 3 h of its administration. It has been shown that this hypothermia is triggered by tumor necrosis factor-α (TNF-α).[33] The test compounds (Table 4 and Fig. 1) exhibited significant antipyretic property, but none of these compounds exhibited antagonism of the initial LPS-induced hypothermia as shown by first temperature index in Table 4 thus indicating that antagonism of TNF-α is not possibly involved in the mechanism of action of these compounds. However, the test compounds were able to significantly reduce the hyperthermia in-

Table 3. Acetic acid-induced writhing assay: analgesic activity

Compound	Writhing ± SEM	% Age inhibition	Compound	Writhing ± SEM	% Age inhibition
7a	19.83 ± 2.48*	42.80	**7h**	26.17 ± 1.12*	24.52
7b	16.83 ± 0.79*	51.46	**7i**	14.33 ± 1.17*	58.67
7c	9.17 ± 1.85*	73.55	**7j**	15.33 ± 1.54*	55.78
7d	21.67 ± 0.49*	37.50	**7k**	24.00 ± 1.37*	30.78
7e	24.26 ± 1.85*	30.03	**7l**	18.00 ± 2.25*	48.05
7f	15.83 ± 1.33*	54.34	**7m**	10.17 ± 1.56*	70.67
7g	20.33 ± 1.15*	41.36	**7n**	13.83 ± 2.09*	60.11
Aspirin	13.33 ± 1.09*	61.55	**6**	19.41 ± 1.68*	44.01
Indomethacin	16.83 ± 1.30*	51.46	Control	34.67 ± 1.67	

Male Swiss albino mice, 20 ± 5 g, were administered the test drugs orally at 100 mg/kg. and the standard indomethacin and aspirin at 10 mg/kg and 100 mg/kg, respectively.
One hour after the oral dosing they were injected i.p. with 0.1 ml/10 g of 1% v/v acetic acid.
Five minutes after the injection the writhings were noted for next 15 min.
Each value represents means ± SEM ($n = 6$).
Significance level $^{*}p < 0.05$ as compared with the control group.

Table 4. Lipopolysaccharide-induced pyresis: antipyretic activity

Compound	Rectal temperature (°C) ± SEM (change in rectal temperature °C)									
	0 h	1 h	2 h	3 h	TI	4 h	5 h	6 h	7 h	TI
7b	36.96 ± 0.21	36.61 ± 0.15 [−0.35]	35.34 ± 0.16 [−1.62]	36.72 ± 0.14 [−0.24]	**−2.21**	37.01 ± 0.11 [0.05]	37.19 ± 0.09 [0.23]	37.40 ± 0.13 [0.44]	37.38 ± 0.18 [0.42]	**1.14**
7c	36.79 ± 0.15	37.26 ± 0.19 [−0.47]	35.10 ± 0.23 [−1.69]	36.25 ± 0.24 [−0.54]	**−2.70**	36.68 ± 0.18 [−0.11]	36.96 ± 0.21 [0.17]	7.20 ± 0.17 [0.41]	37.19 ± 0.14 [0.40]	**0.87**
7f	37.0 ± 0.13	36.81 ± 0.12 [−0.19]	35.66 ± 0.19 [−1.34]	36.49 ± 0.15 [−0.51]	**−2.04**	37.22 ± 0.20 [0.22]	37.46 ± 0.23 [0.46]	37.71 ± 0.19 [0.71]	37.82 ± 0.17 [0.82]	**2.21**
7i	36.64 ± 0.18	36.62 ± 0.14 [−0.12]	34.80 ± 0.17 [−1.84]	35.98 ± 0.22 [−0.66]	**−2.62**	36.49 ± 0.19 [−0.15]	36.78 ± 0.17 [0.14]	36.90 ± 0.20 [0.26]	37.07 ± 0.16 [0.43]	**0.68**
7n	36.85 ± 0.16	36.74 ± 0.20 [−0.11]	34.62 ± 0.13 [−2.23]	35.98 ± 0.17 [−0.87]	**−3.21**	36.98 ± 0.21 [0.13]	37.20 ± 0.23 [0.35]	37.59 ± 0.16 [0.74]	37.27 ± 0.19 [0.42]	**1.64**
Aspirin	37.11 ± 0.17	36.68 ± 0.13 [−0.43]	35.66 ± 0.14 [−1.45]	36.60 ± 0.16 [−0.51]	**−2.39**	37.22 ± 0.15 [0.11]	37.31 ± 0.11 [0.20]	37.36 ± 0.12 [0.25]	37.42 ± 0.15 [0.31]	**0.87**
Indomethacin	36.81 ± 0.12	36.42 ± 0.15 [−0.39]	35.78 ± 0.18 [−1.03]	36.70 ± 0.19 [−0.11]	**−1.53**	37.03 ± 0.14 [0.22]	37.11 ± 0.20 [0.30]	37.16 ± 0.13 [0.35]	37.36 ± 0.17 [0.55]	**1.42**
Control	37.13 ± 0.14	36.52 ± 0.17 [−0.61]	35.85 ± 0.20 [−1.28]	36.94 ± 0.16 [−0.19]	**−2.08**	37.47 ± 0.15 [0.34]	37.89 ± 0.18 [0.76]	38.16 ± 0.21 [1.03]	38.43 ± 0.13 [1.30]	**3.43**

Male Wistar rats (170 ± 20 g were administered orally the test drugs at 100 mg/kg. and the standard indomethacin and aspirin at 10 mg/kg and 100 mg/kg, respectively.
After half an hour of oral administration of the drugs LPS dissolved in apyrogenic saline was injected at dose of l00 μg/kg i.p.
The rectal temperature was determined using telethermometer probes immediately before and 1, 2, 3, 4, 5, 6, and 7 h after LPS administration.
Each value represents means ± SEM ($n = 6$).
TI represents the temperature index.

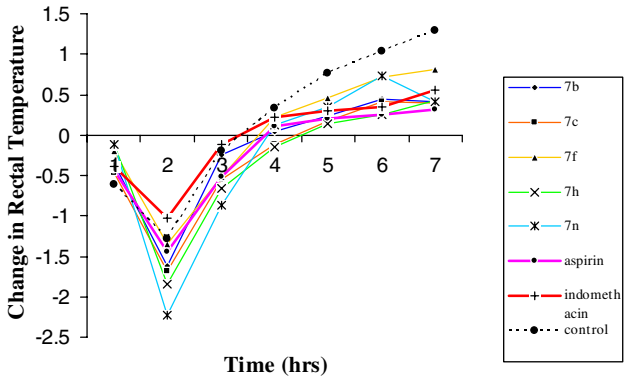


Figure 1. Antipyretic activity profile against LPS-induced pyresis.

duced by LPS as shown by the second temperature index in Table 4. Compounds **7c** and **7i** showed antipyretic activity comparable to standard aspirin.

Compounds were selected for adjuvant-induced arthritis assay based on the inhibition of carrageenan-induced edema, analgesic and antipyretic activity profile. Adjuvant-induced arthritis producing a biphasic response in rats was used for the evaluation of activity against arthritis.[34] Results of this test are summarized in Table 5. The compound **7b** showed moderate activity and the animals did gain more weight than those treated with Indomethacin indicating a better toxicity profile compared to the reference drug. Other compounds were not able to reduce the secondary inflammation of left hind paw and hence were considered to possess poor anti-arthritic activity.

Some selected compounds (based on anti-inflammatory and analgesic activity profile) were tested for their ulcerogenicity potential.[35] No animal treated with test compounds at the level of 100 mg/kg developed ulcer (Table 6). The compound **7c** did not produce any ulcers at the highest tested dose of 500 mg/kg. It may, however, be noted here that chronic administration of the test compounds at the dose level of 100 mg/kg for 14 days did not cause any ulceration of the gastric mucosa as revealed in the post mortem studies of sacrificed animals at the end of the adjuvant-induced arthritis study.

In conclusion, the aromatic amide derivatives of 5,6-dimethoxy-2,3-dihydro-1*H*-inden(-1-yl)acetic acid exhibited good anti-inflammatory and analgesic activity. These compounds were found to be long acting and their residual anti-inflammatory activity at 24 h exceeded that of Indomethacin. The anti-inflammatory and analgesic activity was dependent on position and type of substituents on the phenyl ring of the aromatic amides. These compounds did not inhibit TNF-α but showed signifi-

Table 6. Evaluation of Ulcer index

Compound	Dose (mg)	Time	Ulcer index
Control		6h	0
Indomethacin	30	6h	31.37 ±4.56
7b	100	6h	0
7c	100	6h	0
7c	500	6h	0
7g	100	6h	0
7j	100	6h	0
Control		14 days	0
Indomethacin	1	14 days	42 ± 5.33
7f	100	14 days	0
7b	100	14 days	0

Twenty-four hour fasted Wistar male rats (175 ± 25 g) were given the test compounds and indomethacin at the dose level of 100 mg/kg p.o. and 30 mg/kg p.o., respectively.
After six hours of oral dosing the rats were sacrificed and the stomachs were taken out and cut along the greater curvature and were examined for any ulcers.
Each value represents means ± SEM ($n = 4$).

Table 5. Adjuvant-induced arthritis: anti-arthritic activity

Compound	Increase in paw volume (ml) ± SEM (% inhibition of edema)				Secondary lesions	Weight change (g)
	3rd day	8th day	13th day	13th day[#]		
7b	1.40 ± 0.0213 [37.5]*	1.47 ± 0.0191 [25.76]*	1.37 ± 0.0206 [35.68]*	1.08 ± 0.0196 [31.65]*	Moderate	7.21 ± 0.140
7c	1.60 ± 0.0182 [28.57]*	1.82 ± 0.0225 [8.08]	2.03 ± 0.0219 [4.69]	1.53 ± 0.0179 [3.16]	Severe	3.51 ± 0.131
7f	1.87 ± 0.0221 [16.52]*	1.60 ± 0.0235 [19.19]*	1.69 ± 0.0197 [20.66]*	1.32 ± 0.0213 [16.46]*	Severe	4.56 ± 0.129
7j	1.63 ± 0.0203 [27.23]*	1.63 ± 0.0217 [17.68]*	1.90 ± 0.0239 [10.80]	1.46 ± 0.0175 [7.60]	Severe	4.01 ± 0.133
7n	1.86 ± 0.0188 [16.96]*	1.76 ± 0.0196 [11.11]	1.71 ± 0.0261 [19.72]	1.35 ± 0.0179 [14.56]	Severe	4.25 ± 0.154
Indomethacin	1.40 ± 0.0178 [37.50]*	1.11 ± 0.0185 [43.94]*	1.14 ± 0.0213 [46.48]*	1.02 ± 0.0181 [35.44]*	Moderate	5.68 ± 0.124
Control	2.24 ± 0.0175	1.98 ± 0.0189	2.13± 0.0201	1.58 ± 0.0165	Severe	2.88 ± 0.117

Male Wistar rats weighing 160 ± 10 g were given the test compounds and indomethacin at the dose level of 100 mg/kg p.o. and 10 mg/kg p.o. once daily for 14 days starting from the day before the administration of 0.1 ml Freund's complete adjuvant into the subplantar surface of right hind paw of each rat.
Each value represents means ± SEM ($n = 6$).
Significance level $^{*}p < 0.05$ as compared with the control.
Each value represents means ± SEM ($n = 6$).
[#] Uninjected left paw.

Table 7. Study with Cytochrome P450 enzyme inhibitor

Compound	Increase in paw volume (ml) ± SEM (% inhibition of edema)					
	1 h	2 h	3 h	4 h	6 h	24 h
SKF-525A & **7c**	0.075 ± 0.0138 [64.29]	0.18 ± 0.0151 [56.10]	0.26 ± 0.0183 [56.67]	0.24 ± 0.0169 [57.89]	0.19 ± 0.0135 [59.57]	0.07 ± 0.0114 [68.18]
7c	0.07 ± 0.0147 [66.7]	0.17 ± 0.0176 [58.53]	0.24 ± 0.0154 [60.0]	0.23 ± 0.0143 [59.65]	0.185 ± 0.0161 [60.63]	0.07 ± 0.0125 [68.18]
Control	0.21 ± 0.0267	0.41 ± 0.0148	0.60 ± 0.0173	0.57 ± 0.0203	0.47 ± 0.0165	0.22 ± 0.0135

Male Wistar rats were pretreated with SKF 525A (50 mg/kg i.p.) and one hour later, test drug **7c** was administered at 100 mg/kg p.o.
The remaining protocol followed was the same as that of anti-inflammatory screening by carrageenan induced rat paw edema model.
Each value represents means ± SEM ($n = 6$).
The results obtained were analyzed by Student's *t*-test and the difference between the two groups was not found to be statistically significant.

cant antipyretic activity in LPS induced pyresis. The adjuvant induced arthritis study reveals that these compounds though have longer activity profile are not effective in preventing the formation of secondary lesions. The compounds were found to be free from ulcerogenicity liability of common NSAIDs. Further evaluation of COX-2 inhibition is required for establishing the mechanism of their low gastrointestinal toxicity.

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25. *Synthesis of diethyl 2,4-diacetyl-3-(3,4-dimethoxyphenyl)pentanedionate* **(3)**: Veratraldehyde (**2**) (34 g, 0.2 mol) was dissolved in ethylacetoacetate (60 g, 0.43 mol) in a dry conical flask and piperidine (2.5 ml) was added at ambient temperature and then kept for 3 days or more (up to seven days, depending on room temperature) with the mouth stoppered. The solid product thus obtained was crushed and then washed with solvent ether to get the product in 70–75% yield. Recrystallization from dil. alcohol gave the analytical product. Mp 129–131 °C, IR (cm^{-1}): 1720(C=O stretching), 1145 (OCH_3), ^1H NMR: δ (ppm) ($CDCl_3$):1.28 (t, CH_3, 6H), 2.10 (s, CH_3, 6H), 3.02 (d, CH, H), 3.63 (d, CH, H), 3.85 (s, OCH_3, 3H), 3.87 (s, OCH_3, 3H), 3.93 (qr, CH_2, 4H), 4.18 (t, CH, 1H), 6.64 (s, ArH, H), 6.73 (s, ArH, 2H).
26. *Synthesis of 3,4-dimethoxyphenylpentanedioic acid* **(4)**: Compound **3** (40 g, 0.089 mol) was dissolved in a hot solution of KOH (160 g in 120 ml of water) and 80 ml of 90% ethanol was added. The hot reaction mixture was refluxed on a water bath for 1 h. Alcohol was then removed as far as possible by distillation under reduced pressure, and after dilution with water it was cooled and washed with solvent ether. The aqueous layer on acidification with cold conc. HCl with cooling gave crude 4

which was filtered and recrystallized from hot water. Mp 189–191 °C, yield 65–70%, IR (cm^{-1}): 3300–2400 (br OH stretch), 1710 (C=O stretching),1225 (C–O stretch of OCH_3), 1260 (C–O stretch of COOH), 1010 (C–O stretch of OCH_3), ^1H NMR: δ (ppm) ($CDCl_3$): 2.59, 2.70 (dd, CH_2, 4H), 3.59 (qn, CH, 1H), 3.84 (s, OCH_3, 3H), 3.86(s, OCH_3, 3H), 6.81 (m, ArH, 3H), 10.08 (br s, COOH, 2H).

27. *Synthesis of 5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden(-1-yl)acetic acid* **(5)**: Cyclization of compound **4** was effected by treating the powdered acid (15 g, 0.056 mol) with polyphosphoric acid (PPA) (225 g) on a steam bath for 4 h with stirring. After decomposition of the hot reaction mixture with crushed ice, the keto acid (**5**) was isolated by extraction with chloroform. The solvent was distilled off to get the crude keto acid. The crude product was finally recrystallized from acetone to get the pure compound. Yield 75–80%; mp 177–178 °C; IR (cm^{-1}): 3400–2400 (br OH stretch), 1724 (C=O stretching), 1045, 1255 (C–O stretch of OCH_3), ^1H NMR: δ (ppm) ($CDCl_3$) *J* in Hz: 2.46 (dd, CH_2, 1H, *J* 3.0), 2.52 (dd, CH_2, 1H, *J* 9.3), 2.79 (dd, CH_2, 1H, *J* 5.2), 2.91 (dd, CH_2, 1H, *J* 7.3), 3.79 (qn, CH, 1H, *J* 1.86), 3.91 (s, OCH_3, 3H), 3.98 (s, OCH_3, 3H), 7.00 (s, ArH, 1H), 7.15 (s, ArH, 1H), 10.12 (br s, COOH, 1H).
28. *Synthesis of 5,6-dimethoxy-2,3-dihydro-1H-inden(-1-yl)acetic acid* **(6)**: Compound 5 was subjected to Clemmensen's reduction. 0.1 mol of compound **5** was treated with 50 g of zinc amalgam, 50 ml of conc. HCl, and 75 ml of water. About 200 ml of benzene was added as a co-solvent. The reaction mixture was refluxed on steam bath for 8 h. The organic layer was separated and the aqueous layer and zinc granules were further extracted with benzene. The pooled organic phase was dried over anhydrous sodium sulfate and was finally distilled off to get the reduced acid. Mp 152–153 °C (benzene); yield 75–80%; IR (cm^{-1}): 3400–2800 (br OH stretch), 1712 (C=O stretching),1256(C–O stretch of OCH_3), 1210 & 1183 (C–O stretch of COOH), 1040 (C–O stretch of OCH_3); ^1H NMR: δ (ppm) ($CDCl_3$): 1.81, 2.43 (m, CH_2, 2H), 2.49, 2.80 (dd, CH_2, 2H), 2.89 (m, CH_2, 2H), 3.55 (qn, CH, 1H), 3.86 (s, OCH_3, 3H), 3.88 (s, OCH_3, 3H), 6.76 (s, ArH, 1H), 6.78(s, ArH, 1H), 10.1 (br s, COOH, 1H) M.S 236(M^+).
29. *General methods for the synthesis of amide derivatives* **(7a–n)**: A solution of compound 6 in dry dichloromethane and catalytic amount of dimethylformamide was treated with oxalyl chloride in 1:2.5 molar ratio under ice-cold conditions. The solution was allowed to stand for 24 h at room temperature with occasional stirring. Excess oxalyl chloride was removed by co-distillation with dry benzene under reduced pressure. The acyl halide thus obtained was not characterized and was used directly in the next step. To a solution of the acyl halide in dichloromethane was added a mixture of triethylamine (1.1 mol) and the appropriate amine in dichloromethane with constant stirring under ice-cold conditions. The mixture was kept at ambient temperature for 12 h. The resulting reaction mixture was then extracted with 0.1 N HCl, water, saturated solution of $NaHCO_3$, brine, and water. The organic phase was dried with anhydrous sodium sulfate and then distilled off to obtain the amides.
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