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Original article

# Synthesis and biological evaluation of amide derivatives of (5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-yl)acetic acid as anti-inflammatory agents with reduced gastrointestinal ulcerogenecity

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**Abstract**

A variety of amide derivatives of (5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-yl)acetic acid were synthesized and screened for their analgesic and anti-inflammatory activities. The compounds were found to have longer activity profile exceeding that of indomethacin in carrageenan-induced rat paw edema model. Few selected compounds were also screened for their antipyretic, anti-arthritic and ulcerogenecity potential. From these studies it can be concluded that these compounds though have significant antipyretic activity did not act through the inhibition of TNF-α. The test compounds failed to prevent the development of secondary inflammation in adjuvant-induced arthritis assay. However, these compounds showed no ulcer formation at the tested dose level of 100 mg/kg p.o.


*Keywords:* Indene; Amides; Anti-inflammatory; Ulcerogenecity

## 1. Introduction

Of all the chemical classes that have been examined in recent years as potential non-steroidal anti-inflammatory agents, none has received wider attention than the aryl- and hetroarylalkanoic acids. Features of a typical molecule, which are important for activity, include a carboxyl group separated by one or more carbon atoms from a flat aromatic nucleus that is further substituted by a lipophilic group. The lead compound for aryl acetic acids is ibufenac from which ibuprofen and (*S*)-(+)-2-(3-chloro-4-cyclohexylphenyl) propionic acid have come up [1]. Ring chain modification of the aryl propionic acid has led to the development of indan moiety. Indan ring system has been found to act as an inert carrier, which serves to hold biologically active functional moieties in a stereospecific manner [2]. This congener of indene is isosteric and bioisosteric with indolidine and indole, respectively, which are also pharmacologically active chemical nuclei.

Among the various indan-1-alkanoic acids [1,3,4] prepared as potential anti-inflammatory agents some of the compounds not only showed anti-inflammatory activity comparable to phenylbutazone but were also found to be much less ulcerogenic. The research in this area led to the development of Clidanac [1], having $ED_{30}$ of 0.85 mg/kg, which showed better gastrointestinal tolerability. An isomer of Clidanac, 6-chloro-5-(cyclopentylmethyl)indan-1-carboxylic acid, was also devoid of any mucosal damage in the rat stomach up to highest tested dose of 400 mg/kg [5].

It has been shown that the biochemical differences between the COX isoforms can be exploited to improve upon the selectivity of carboxyl containing NSAIDs as COX-2 inhibitors. Successful transformation of indomethacin and meclofenamic acid into selective COX-2 inhibitors by a single chemical derivatisation (amidation or esterification) has been reported [6]. Structurally diverse indomethacin amides inhibited purified human COX-2 with $IC_{50}$ values in the low nanomolar range but did not inhibit ovine COX-1 activity at concentrations as high as 66 μM [7].

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Keeping the above points in view, we designed (Fig. 1), synthesized and biologically evaluated some amide derivatives of 5,6-dimethoxyindan-1-acetic acid for anti-inflammatory and related biological activities. The idea behind derivatisation was to further 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 to increase the activity profile of indan-1-alkanoic acids by not only enhancing absorption due to increased lipophilicity but also by imparting COX-2 selectivity.

## 2. Chemistry

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 by dimethyl sulphate under alkaline conditions to get the methylated product veratraldehyde (**2**). Compound **2** was reacted with 2 mol of ethylacetoacetate (EAA) in the presence of catalytic amount of piperidine at room temperature to obtain the bisacetoacetate (**3**). Acidic hydrolysis of **3** was carried out with 6 N potassium hydroxide (KOH) in 90% ethanol to get the diacid **4**. The IR spectra of **4** showed broad OH stretch at 3300–2400 $cm^{-1}$ and C=O stretch at 1710 $cm^{-1}$. $^1H$ NMR of **4** showed singlets at $\delta$ 3.84 and 3.86 ppm corresponding to methoxyl protons, doublet of doublet at 2.59 and 2.70 ppm as well as quintet at 3.59 ppm for $CH_2$ and CH of glutaric acid side chain, respectively, multiplet at $\delta$ 6.81 ppm for aromatic protons and small broad singlet at $\delta$ 10.08 ppm indicating the presence of carboxyl group.

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**. Presence of doublet of doublet at 2.46 and 2.57 ppm and doublet of doublet at 2.79 and 2.91 ppm corresponding to $CH_2$ of side chain and $CH_2$ of the indan ring, respectively, as well as the presence of quintet at 3.79 ppm indicates the ring closure. The presence of methoxyl protons (singlets at 3.91 and 3.98 ppm), aromatic protons (singlets at 7.00 and 7.15 ppm) and acid protons (broad singlet at 10.12 ppm) further supports the proposed structure of compound **5**.

The ketone group of compound **5** was finally removed using Clemmensen's reduction to give (5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-yl)acetic acid (**6**). Because of the different conformational arrangement of proton present on CH of indan ring both neighbouring $CH_2$ peaks got split into two peaks (two doublets of doublets at 2.49 and 2.80 ppm, and two multiplets at 1.81 and 2.43 ppm). The presence of multiplet at 2.89 ppm equivalent to two protons in addition to peaks obtained for compound **5** indicates the reduction of carbonyl group and formation of indan ring system. The presence of aromatic protons (singlets at 6.76 and 6.78 ppm) and acid protons (broad singlet at 10.11 ppm) further supports the structure of compound **6**.The mass spectrum of this compound showed the base peak at 236 corresponding to its formula weight. Compound **6** was treated with oxalyl chloride in the presence of catalytic amount of dimethylformamide to

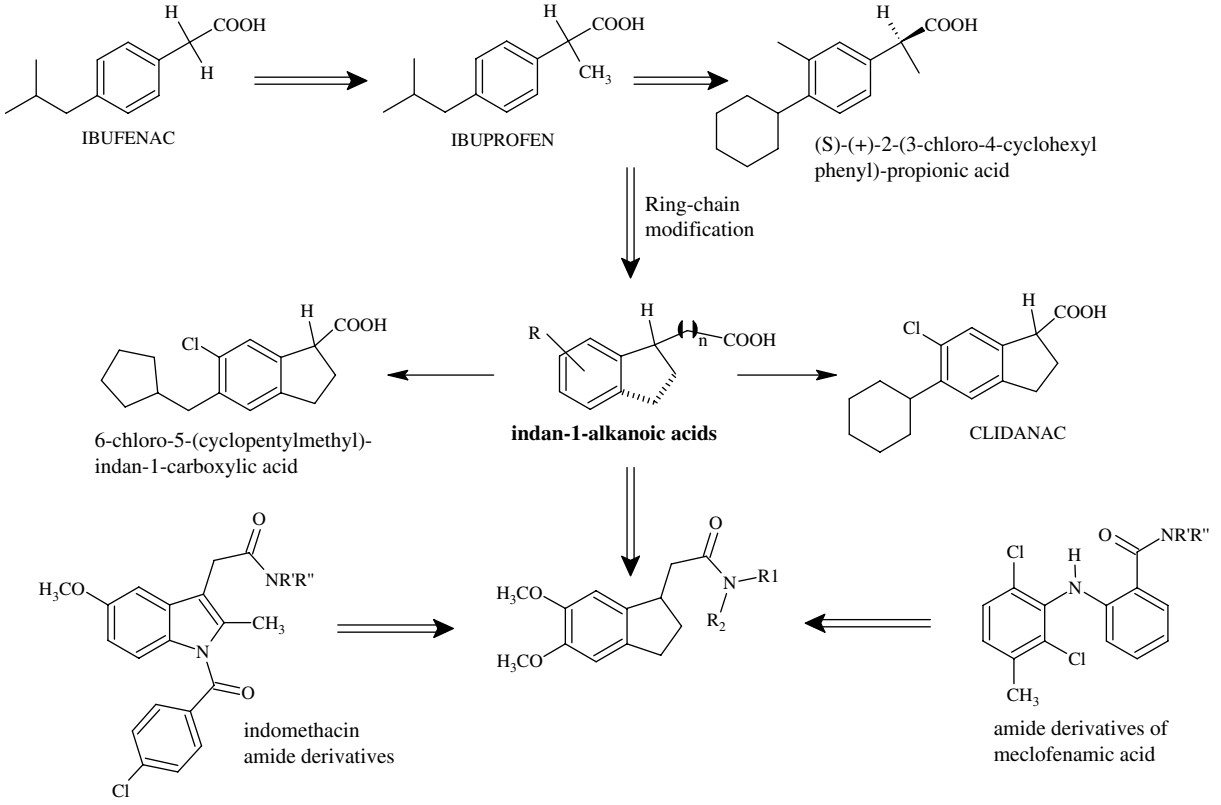



Fig. 1. Design of (5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-yl)acetic acid amides.

convert carboxyl group of **6** into acyl halide. The acyl halide thus obtained was not isolated or characterized. It was used directly in the next step. The acyl halide was reacted with various primary and secondary amines under Schotten–Baumann conditions for the formation of desired amides **7a–t**. The structure of amide derivatives was confirmed by the presence of two, one or no peak around 3300 $cm^{-1}$ (NH stretch) corresponding to primary, secondary and tertiary amides. Also disappearance of broad OH stretch at 3400–2400 $cm^{-1}$ indicates the formation of amide bond. The formations of amides were further confirmed by the presence of a small singlet at 5–6 ppm in $^1H$ NMR. In most of the cases there was an overlap of two peaks at around 2.2–2.4 ppm corresponding to doublet of doublet and multiplet. The mass spectrum of all amides showed the peaks corresponding to the molecular ion. Either $M^+$ or M + 1 peak was observed as the base peak with the maximum intensity.

## 3. Results and discussion

### 3.1. Anti-inflammatory activity

The anti-inflammatory activity of the test compounds was evaluated by carrageenan-induced rat paw edema model. The results (Table 1) 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 at 24 h after a single oral dose. The 1st hour data indicate that the test compounds are slow acting and the activity of these compounds reaches peak after 3–4 h of oral administration, however, residual activity is very high and the duration of action often exceeded 24 h. The peak activity as well as residual activity is maximal in case of long chain amides (**7j** and **7k**) having comparatively high calculated log *P* values (Table 1). However, the peak activity of the test compounds was found to be lower than that of indomethacin (10 mg/kg, p.o.) but their residual activity at 24th hour exceeded that of the latter.

It was found that the activity increased with increasing bulk of the amide function. The dimethyl (**7c**), diethyl (**7e**), isopropyl (**7g**) and tertiary butyl (**7i**) derivatives were comparatively more active than methyl (**7b**), ethyl (**7d**), propyl (**7f**) and butyl (**7h**) derivatives. The cyclic analogs (**7m** and **7n**) were more active as compared to their linear counterparts (**7j** and **7k**). The ethanolamine derivative (**7t**) showed least activity which may have resulted from its low log *P* value and hence poor absorption. Among the cyclic amine derivatives, the piperazino derivative (**7r**) showed good activity besides having low log *P* value, which may be correlated to some hydrogen bonding interactions of –NH of piperazine ring system with the receptor. Based on the anti-inflammatory activity profile of the test compounds (Table 1) we selected compound **7k** for dose–response studies. Compounds **7k** and **7n** were found to have an $ED_{30}$ value of 24 and 20 mg/kg, respectively.

### 3.2. Analgesic activity

The analgesic activity was determined by acetic acid-induced writhing assay. The results (Table 2) reveal that the beneficial effect of increasing chain length was also apparent for analgesic activity of these compounds. The activity increased with increasing chain length and reaches the maximum with the hexyl derivative, compound **7k**. The cyclic analogs (**7m** and **7n**) were comparatively less active than their linear counterparts (**7j** and **7k**). The cyclic amine derivatives showed intermediate activity while the piperazino derivative (**7r**) exhibited good analgesic properties. The compounds (**7j**, **7k**, and **7r**) were found to have good analgesic activities compared to the standard drugs indomethacin and aspirin.

### 3.3. Antipyretic 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 [8,9]. It is well known that LPS produces a biphasic response in the rat. It shows an initial hypothermia up to 3rd hour of its administration. It has been shown that this hypothermia is triggered by tumour necrosis factor-α (TNF-α) [10]. The test compounds (Table 3) exhibited significant antipyretic property, but none of these compounds exhibited antagonism of the initial LPS-induced hypothermia as indicated by first temperature index in Table 3 thus indicating that the antagonism of TNF-α is not possibly involved in the mechanism of action of these compounds [11]. However, the test compounds were able to significantly reduce the hyperthermia induced by LPS as shown by the second temperature index in Table 3. Compounds **7k** and **7r** were found to be the most potent in this regard.

### 3.4. Anti-arthritic activity

Compounds were selected for adjuvant-induced arthritis assay based on the inhibition of carrageenan-induced edema, analgesic and antipyretic activity profile. Adjuvant-induced arthritis test in rats produced a biphasic response. The initial response started immediately after adjuvant administration and reached maximum on 3rd day and then it started subsiding. The 2nd phase started from the 9th day and continued till the end of the experiment (14th day). Secondary lesions (appearance of nodules, and erythema in tail, nose and ears) started developing from the 10th day. Results of this test summarized in Table 4 show that compound **7k** has the best profile in this assay.

Examination of Table 4 reveals that the compounds selected for adjuvant arthritis assay exhibit almost uniform appreciable anti-inflammatory activity over the hours. Compound **7n** was found to be active and the animals did gain more weight than those treated with indomethacin indicating a better toxicity profile compared to the reference drug. In this biomodel compounds **7k** and **7n** significantly reduced the primary inflammation of the right hind paw but as with

Table 1
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 | Log *P* |
| **7a** | 0.26 ± 0.0158 [18.75]ns | 0.345 ± 0.016 [31.0]* | 0.48 ± 0.0126 [30.43]* | 0.44 ± 0.0127 [31.25]* | 0.39 ± 0.0145 [27.78]* | 0.22 ± 0.0126 [26.67]* | 1.45 |
| **7b** | 0.27 ± 0.006 [15.62]ns | 0.35 ± 0.0072 [30.0]* | 0.49 ± 0.0152 [28.99]* | 0.45 ± 0.0179 [29.69]* | 0.41 ± 0.0179 [24.07]* | 0.20 ± 0.0153 [33.33]* | 1.92 |
| **7c** | 0.24 ± 0.0367 [25.0]ns | 0.32 ± 0.0148 [36.0]* | 0.40 ± 0.0273 [34.78]* | 0.41 ± 0.0273 [35.94]* | 0.36 ± 0.0165 [33.33]* | 0.23 ± 0.0125 [23.33]ns | 2.29 |
| **7d** | 0.27 ± 0.0058 [15.62]ns | 0.37 ± 0.0216 [26.0]* | 0.51 ± 0.027 [26.09]* | 0.47 ± 0.0225 [26.56]* | 0.43 ± 0.212 [20.37]* | 0.20 ± 0.0159 [33.33]* | 2.44 |
| **7e** | 0.22 ± 0.0138 [31.25]* | 0.30 ± 0.0086 [40.0]* | 0.43 ± 0.0154 [37.68]* | 0.40 ± 0.085 [37.5]* | 0.37 ± 0.0195 [31.48]* | 0.24 ± 0.0308 [16.67]ns | 3.21 |
| **7f** | 0.26 ± 0.0203 [18.75]ns | 0.36 ± 0.0157 [28.0]* | 0.49 ± 0.0148 [28.98]* | 0.47 ± 0.212 [26.56]* | 0.42 ± 0.0212 [22.22]* | 0.22 ± 0.0083 [26.67]* | 2.90 |
| **7g** | 0.22 ± 0.0115 [31.25]* | 0.315 ± 0.019 [37.0]* | 0.48 ± 0.0143 [30.43]* | 0.39 ± 0.0125 [39.06]* | 0.34 ± 0.0191 [37.03]* | 0.21 ± 0.0065 [30.00]* | 2.72 |
| **7h** | 0.22 ± 0.016 [31.25]* | 0.35 ± 0.0240 [24.0]* | 0.47 ± 0.013 [27.54]* | 0.45 ± 0.0178 [25.0]* | 0.39 ± 0.0105 [24.07]* | 0.19 ± 0.0141 [36.67]* | 3.36 |
| **7i** | 0.22 ± 0.0158 [31.25]* | 0.34 ± 0.0203 [32.0]* | 0.46 ± 0.0173 [33.33]* | 0.43 ± 0.0167 [32.81]* | 0.37 ± 0.0155 [31.48]* | 0.18 ± 0.0151 [40.00]* | 3.24 |
| **7j** | 0.21 ± 0.0134 [34.38]* | 0.33 ± 0.018 [34.0]* | 0.43 ± 0.013 [37.68]* | 0.38 ± 0.0105 [40.62]* | 0.35 ± 0.0156 [35.19]* | 0.14 ± 0.0073 [46.67]* | 3.83 |
| **7k** | 0.17 ± 0.0186 [46.88]* | 0.345 ± 0.017 [31.0]* | 0.41 ± 0.014 [40.58]* | 0.39 ± 0.0183 [39.06]* | 0.325 ± 0.015 [39.81]* | 0.17 ± 0.0173 [43.33]* | 4.31 |
| **7l** | 0.25 ± 0.006 [21.88]ns | 0.43 ± 0.0108 [14.0]ns | 0.56 ± 0.0142 [18.84]ns | 0.53 ± 0.0142 [17.19]* | 0.48 ± 0.0084 [11.11]ns | 0.33 ± 0.0154 [0]ns | 2.63 |
| **7m** | 0.18 ± 0.0169 [40.62]* | 0.19 ± 0.0189 [52.0]* | 0.39 ± 0.0204 [43.48]* | 0.39 ± 0.0196 [45.31]* | 0.32 ± 0.018 [40.74]* | 0.16 ± 0.019 [46.67]* | 3.34 |
| **7n** | 0.10 ± 0.0073 [50.0]* | 0.20 ± 0.0183 [56.0]* | 0.32 ± 0.0171 [49.27]* | 0.30 ± 0.0142 [50.0]* | 0.26 ± 0.0185 [48.15]* | 0.14 ± 0.0131 [53.33]* | 3.83 |
| **7o** | 0.20 ± 0.01 [18.75]ns | 0.38 ± 0.0206 [24.0]* | 0.59 ± 0.0128 [14.45]ns | 0.52 ± 0.0105 [18.75]* | 0.375 ± 0.015 [30.55]* | 0.17 ± 0.0133 [43.33]* | 2.95 |
| **7p** | 0.305 ± 0.016 [4.69]ns | 0.40 ± 0.017 [20.0]ns | 0.51 ± 0.0182 [26.09]* | 0.485 ± 0.013 [24.22]* | 0.42 ± 0.0147 [22.22]* | 0.20 ± 0.00963 [33.33]* | 2.75 |
| **7q** | 0.20 ± 0.0152 [18.75]ns | 0.39 ± 0.0167 [22.0]ns | 0.47 ± 0.017 [31.88]* | 0.435 ± 0.012 [32.03]* | 0.37 ± 0.158 [31.48]* | 0.18 ± 0.013 [40.00]* | 3.28 |
| **7r** | 0.12 ± 0.0131 [62.5]* | 0.28 ± 0.0125 [44.0]* | 0.40 ± 0.022 [42.03]* | 0.36 ± 0.0197 [40.62]* | 0.36 ± 0.0197 [33.33]* | 0.105 ± 0.0099 [65.00]* | 1.54 |
| **7s** | 0.27 ± 0.0068 [15.62]ns | 0.43 ± 0.0154 [14.0]ns | 0.47 ± 0.0247 [19.57]* | 0.555 ± 0.034 [13.28]ns | 0.46 ± 0.0265 [14.8]ns | 0.23 ± 0.0154 [23.33]* | 1.90 |
| **7t** | 0.35 ± 0.012 [0]ns | 0.52 ± 0.0208 [0]ns | 0.605 ± 0.021 [12.31]ns | 0.58 ± 0.0114 [9.37]ns | 0.47 ± 0.0208 [12.96]* | 0.26 ± 0.0193 [13.33]ns | 0.88 |
| **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]* | 2.11 |
| 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]ns | 2.98 |
| 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 | |

Data were analyzed by one-way ANOVA followed by post hoc test. *Represents the significance level of $p < 0.05$, ns represents not significant at $p < 0.05$. Each value represents the mean ± SEM ($n = 6$). Log *P* values were calculated from website www.logp.com.

Table 2
Acetic acid-induced writhing assay: analgesic activity

| Compound | Writhing ± SEM | % Age inhibition | Compound | Writhing ± SEM | % Age inhibition |
|---|---|---|---|---|---|
| **7a** | 26.13 ± 1.41** | 24.62 | **7k** | 6.17 ± 1.17* | 82.20 |
| **7b** | 27.33 ± 1.36**** | 21.17 | **7l** | 23.33 ± 1.28** | 32.71 |
| **7c** | 26.83 ± 1.19**** | 22.61 | **7m** | 21.83 ± 2.07** | 37.03 |
| **7d** | 26.5 ± 1.78**** | 23.57 | **7n** | 19.17 ± 1.78** | 44.70 |
| **7e** | 25.17 ± 1.94*** | 27.40 | **7o** | 18.0 ± 2.65** | 48.05 |
| **7f** | 25.33 ± 1.76*** | 26.94 | **7p** | 28.0 ± 0.73**** | 19.24 |
| **7g** | 24.5 ± 1.23** | 29.33 | **7q** | 19.17 ± 2.80** | 44.70 |
| **7h** | 21.0 ± 0.97** | 39.43 | **7r** | 11.0 ± 1.06* | 68.83 |
| **7i** | 20.19 ± 1.37** | 41.76 | **7s** | 26.5 ± 1.91*** | 23.56 |
| **7j** | 9.83 ± 1.47* | 71.65 | **7t** | 24.33 ± 2.08** | 29.82 |
| **6** | 19.41 ± 1.68* | 44.01 | Aspirin | 13.33 ± 1.09* | 61.55 |
| Indo | 16.83 ± 1.30* | 51.46 | Control | 34.67 ± 1.67 | |

Data were analyzed using student's *t*-test: *$p < 0.0001$, **$p < 0.001$, ***$p < 0.005$, ****$p < 0.01$. Each value represents the mean ± SEM ($n = 6$).

indomethacin these were not able to reduce the secondary inflammation of left hind paw.

### 3.5. Evaluation of ulcerogenic potential

Some selected compounds (based on anti-inflammatory and analgesic activity profile) were tested for their ulcerogenecity potential. No animal treated with test compounds at the level of 100 mg/kg p.o. developed ulcer (Table 5). It may, however, be noted here that the administration of the test compounds at the dose level of 100 mg/kg p.o. even 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.

### 3.6. Studies with SKF-525A

We hypothesized that the high residual anti-inflammatory activity of compounds could be due to higher protein binding of its active metabolite(s). These metabolites may arise via their hydrolytic metabolism to demethylated and/or deamidated product. We, therefore, studied the anti-inflammatory activity of compound **7k** in carrageenan-induced rat paw edema model using SKF-525A, a standard hepatic microsomal enzyme inhibitor [12], pretreated rats (Table 6). Examination of Table 6 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.

### 3.7. Acute toxicity study

The rats employed in anti-inflammatory screening were observed during 24 h. No mortality was present with any of these compounds at the end of observation period. The compounds **7k** and **7n** were also studied for their toxicity profile at higher dose levels. No toxicity was observed with these compounds up to the highest tested dose of 1000 mg/kg.

## 4. Conclusions

From the anti-inflammatory activity results it was found that compounds **7k**, **7n**, and **7r** exhibited good anti-inflammatory activity. The compound **7n** showed maximum inhibition of 50% at 4th hour and the compound **7r** showed maximum inhibition of 65% at 24th hour. Among the compounds screened for analgesic activity **7k** was found to be most active with 82.20% inhibition. From the results it can be hypothesized that the better biological activity profile compared to the parent acid compound **6** might be due to better lipophilicity thus better absorption of the derivatives. These compounds didn't inhibit TNF-$\alpha$ but showed significant antipyretic activity in LPS-induced pyresis and compound **7r** showed lowest temperature index. The adjuvant-induced arthritis study reveals that these compounds though have long duration of

Table 3
Lipopolysacchride-induced pyresis: antipyretic activity

| Compound | Change in rectal temperature (°C) and temperature index | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 h | 2 h | 3 h | TI | 4 h | 5 h | 6 h | 7 h | TI |
| **7t** | −0.65 | −1.93 | 0.17 | *−2.72* | 0.34 | 0.57 | 0.65 | 0.66 | *2.22* |
| **7r** | −0.45 | −1.23 | −0.85 | *−2.53* | −0.18 | 0.11 | 0.19 | 0.16 | *0.28* |
| **7n** | −0.33 | −1.26 | −0.67 | *−2.26* | 0.05 | 0.51 | 0.45 | 0.43 | *1.44* |
| **7k** | −0.56 | −0.94 | −0.23 | *−1.73* | 0.11 | 0.38 | 0.53 | 0.54 | *1.56* |
| **7g** | −0.41 | −1.51 | −0.39 | *−2.31* | 0.19 | 0.43 | 0.55 | 0.59 | *1.76* |
| Aspirin | −0.43 | −1.45 | −0.51 | *−2.39* | 0.05 | 0.11 | 0.17 | 0.23 | *0.56* |
| Indomethacin | −0.39 | −1.03 | −0.11 | *−1.53* | 0.22 | 0.30 | 0.35 | 0.55 | *1.42* |
| Control | −0.61 | −1.28 | −0.19 | *−2.08* | 0.34 | 0.76 | 1.03 | 1.30 | *3.43* |

Table 4
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[a] | | |
| **7r** | 1.45 ± 0.0156 [35.27]* | 1.41 ± 0.0169 [28.79]* | 2.08 ± 0.0159 [2.35] | 1.55 ± 0.181 [1.90] | Severe | 3.11 ± 0.132 |
| **7n** | 1.59 ± 0.0175 [29.02]* | 1.35 ± 0.0179 [31.82]* | 1.42 ± 0.0168 [33.33]* | 1.10 ± 0.0203 [30.38]* | Moderate | 6.84 ± 0.154 |
| **7k** | 1.54 ± 0.0164 [31.25]* | 1.41 ± 0.0176 [28.79]* | 1.29 ± 0.0185 [39.44]* | 1.02 ± 0.0163 [35.44]* | Moderate | 7.64 ± 0.167 |
| 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 |

Significance level *$p < 0.05$ as compared with the control. Each value represents the mean ± SEM ($n = 6$).
[a] Uninjected left paw.

action are not effective in preventing the formation of secondary lesions. The compounds were found to be free from ulcerogenecity liability of common NSAIDs. Considering the results from the battery of the screening tests employed, it can be said that the test compounds **7k**, **7n** and **7r** have the potential to turn out as drug candidates and thus they warrant further detailed studies regarding their pharmacological profile.

## 5. Experimental

### 5.1. Chemistry

Melting points were determined in open capillaries in a Buchi 520 melting point apparatus and are uncorrected. Identity and purity of the compounds were ascertained by TLC, elemental microanalysis and spectral analysis. Infrared spectra were recorded with a Shimadzu IR Prestige-21 FT-IR Spectrometer in KBr using powder diffraction technique. $^1$H NMR spectra were recorded on a 400 MHz Brucker Avance II NMR Spectrometer. Mass spectra of the compounds were recorded in a Jeol SX 102/DA-6000 Spectrometer. Elemental microanalysis was done in a Perkin–Elmer 2400 CHN analyzer. Scheme 1 was followed for the synthesis of 5,6-dimethoxyindan-1-acetic acid amides.

#### 5.1.1. 3,4-Dimethoxybenzaldehyde (**2**) [13]

Commercially available vanillin (**1**) 15.2 g (0.1 mol) was placed in a 500 ml three-necked flask equipped with a magnetic stirrer, two dropping funnels and a reflux condenser. One funnel was charged with potassium hydroxide (8.2 g in 12 ml) and the other funnel with dimethyl sulphate (12 ml, 0.104 mol). Vanillin was melted by warming on water bath then KOH was added at the rate of two drops a second. After 20 s dimethyl sulphate was also added at the same rate. The heating was stopped after few minutes as the mixture continued to reflux gently from the heat of the reaction. The reaction mixture was vigorously stirred throughout. After all reagents have been added the reaction mixture became turbid and separated into two layers. Pale reddish brown color of the reaction mixture indicating the alkaline conditions was maintained throughout the reaction. The yellow reaction mixture was poured into a porcelain basin and was left overnight. The hard crystalline mass thus obtained was ground, washed thoroughly with cold water to make it free of basicity, filtered and dried in a vacuum desiccator to get veratraldehyde in 70–75% yield, mp 43–44 °C.

Table 5
Evaluation of ulcer index

| Compound | Dose (mg/kg) | Time | Ulcer index |
|---|---|---|---|
| Control | | 6 h | 0 |
| Indomethacin | 30 | 6 h | 31.37 ± 2.56 |
| **7k** | 100 | 6 h | 0 |
| **7n** | 100 | 6 h | 0 |
| **7r** | 100 | 6 h | 0 |
| **7g** | 100 | 6 h | 0 |
| Control | | 14 days | 0 |
| Indomethacin | 1 | 14 days | 72 ± 4.33 |
| **7k** | 100 | 14 days | 0 |
| **7n** | 100 | 14 days | 0 |

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

#### 5.1.2. Diethyl 2,4-diacetyl-3-(3,4-dimethoxyphenyl)-pentanedionate (**3**)

Veratraldehyde (**2**) (33 g, 0.2 mol) was dissolved in ethylacetoacetate (56 g, 0.43 mol) in a dry conical flask and piperidine (2.5 ml) was added slowly at ambient temperature and then kept for 3 days or more (up to 7 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 desired product in 70–75% yield [14]. Recrystallization from dil. alcohol gave the analytical product, mp 129–131 °C, IR ($cm^{-1}$): 1720 (C=O stretching), 1145 ($OCH_3$), H NMR $\delta$ (ppm) ($CDCl_3$) $J$ in Hz: 1.28 (t, $CH_3$, 6H, J 7.12), 2.10 (s, $CH_3$, 6H), 3.02 (d, CH, H, $J$ 12.1), 3.63 (d, CH, H, $J$ 12.6), 3.85 (s, $OCH_3$, 3H), 3.87 (s, $OCH_3$, 3H), 3.93 (qr, $CH_2$, 4H, $J$ 2.4), 4.18 (t, CH, 1H), 6.64 (s, ArH, H), 6.73 (s, ArH, 2H).

#### 5.1.3. 3-(3,4-Dimethoxyphenyl)pentanedioic 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 by distillation, and after dilution with water it was cooled and washed with solvent ether. The aqueous layer on acidification with cold conc. HCl and cooling gave crude **4** which was filtered and recrystallized from hot water [14]. Yield 65–70%; mp 189–191 °C; IR ($cm^{-1}$): 3300–2400 (br, OH stretch), 1710

Table 6
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 and **7k** | 0.10 ± 0.0168 [52.38] | 0.26 ± 0.0154 [36.58] | 0.37 ± 0.0147 [43.08] | 0.35 ± 0.0127 [38.60] | 0.28 ± 0.0145 [40.42] | 0.12 ± 0.0161 [45.45] |
| **7k** | 0.11 ± 0.0124 [47.62] | 0.24 ± 0.0172 [41.46] | 0.36 ± 0.0144 [44.62] | 0.33 ± 0.0179 [42.10] | 0.29 ± 0.0159 [38.29] | 0.12 ± 0.0153 [45.45] |
| Control | 0.21 ± 0.0267 | 0.41 ± 0.0148 | 0.65 ± 0.0173 | 0.57 ± 0.0203 | 0.47 ± 0.0165 | 0.22 ± 0.0135 |

Each value represents the mean ± 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.

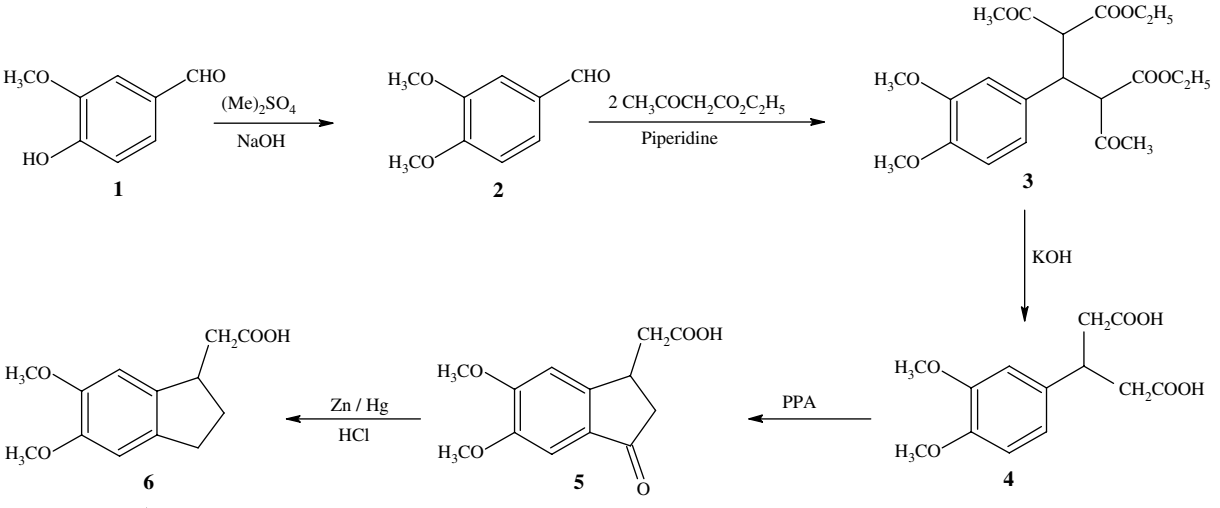
(C=O stretching), 1225(C–O stretch of $OCH_3$), 1260 (C–O stretch of COOH), 1010 (C–O stretch of $OCH_3$); $^1$H NMR $\delta$ (ppm) ($CDCl_3$) *J* in Hz: 2.59 (dd, $CH_2$, 2H, *J* 7.5), 2.70 (dd, $CH_2$, 2H *J* 7.9), 3.59 (qn, CH, 1H, *J* 7.51), 3.84 (s, $OCH_3$, 3H), 3.86 (s, $OCH_3$, 3H), 6.81 (m, ArH, 3H), 10.08 (br s, COOH, 2H).

### *5.1.4. (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 $OCH_3$); $^1$H NMR $\delta$ (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).

### *5.1.5. (5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)acetic acid (**6**)*

Compound **5** was subjected to Clemmensen's reduction. Compound **5** (0.1 mol) was treated with 50 g of zinc amalgam, 50 ml of conc. HCl and 75 ml of water. Around 200 ml of benzene was added as a co-solvent. The reaction mixture was refluxed on steam bath for about 8 h (until the reaction mixture became keto-negative). The organic layer was separated, and the aqueous layer and zinc granules were further extracted with benzene. The pooled organic phase was then dried over




| Compound | R' | R" | Compound | R' | R" |
|---|---|---|---|---|---|
| 7a | H | H | 7k | H | n-hexyl |
| 7b | H | Me | 7l | H | cyclopropyl |
| 7c | Me | Me | 7m | H | cyclopentyl |
| 7d | H | Et | 7n | H | cyclohexyl |
| 7e | Et | Et | 7o | H | benzyl |
| 7f | H | n-Pr | 7p | - | pyrrolidino |
| 7g | H | i-Pr | 7q | - | piperidino |
| 7h | H | n-Bu | 7r | - | piperazino |
| 7i | H | tert-Bu | 7s | - | morpholino |
| 7j | H | n-pentyl | 7t | H | $CH_2CH_2OH$ |

Scheme 1. Synthesis of (5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-yl)acetic acid amides.

anhydrous sodium sulphate and was finally distilled off to get the reduced acid. The analytical product was obtained on recrystallization from benzene. Yield 75–80%; mp 152–153 °C (benzene); IR ($cm^{-1}$): 3400–2800 (br, OH stretch), 1712(C=O stretching), 1040, 1256 (C–O stretch of $OCH_3$); $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.81, 2.43 (m, $CH_2$, 2H), 2.49 (dd, $CH_2$, 1H, *J* 9.3), 2.80 (dd, $CH_2$, 1H, *J* 5.4), 2.89 (m, $CH_2$, 2H), 3.55 (qn, CH, 1H, *J* 7.7), 3.86 (s, $OCH_3$, 3H), 3.88 (s, $OCH_3$, 3H), 6.76 (s, ArH, 1H), 6.78 (s, ArH, 1H), 10.11 (br s, COOH, 1H); MS 236 ($M^+$).

### 5.1.6. General methods for the synthesis of amide derivatives (**7a–t**)

A solution of compound **6** in dry dichloromethane and catalytic amount of dimethylformamide was treated with oxalyl chloride in 1:2.5 molar ratios 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 or isolated and was used directly in the next step. To a solution of the acyl halide in dry 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 sulphate and then distilled to obtain the title compounds [15].

*5.1.6.1. 2-(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)acetamide (**7a**).* Yield 54% (water); mp 166–168 °C; IR: 3391, 3216 (NH), 1640 (C=O), 1268, 1087 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.77, 2.42 (m, $CH_2$, 2H), 2.35, 2.64 (dd, $CH_2$, 2H), 2.85 (m, $CH_2$, 2H), 3.62 (qn, CH, 1H), 3.83 (s, $CH_3$, 3H), 3.84 (s, $CH_3$, 3H), 5.49 (s, NH, 2H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 235 [$M^+$]. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.15; H, 7.25; N, 5.93.

*5.1.6.2. 2-(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)-N-methylacetamide (**7b**).* Yield 59.6% (water); mp 137–138 °C; IR: 3310 (NH), 1642 (C=O), 1266, 1088 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.76, 2.43 (m, $CH_2$, 2H), 2.15, 2.47 (dd, $CH_2$, 2H), 2.73 (s, $CH_3$, 3H), 2.85 (m, $CH_2$, 2H), 3.57 (qn, CH, 1H), 3.82 (s, $OCH_3$, 3H), 3.84 (s, $OCH_3$, 3H), 5.36 (s, NH, 1H), 6.75 (s, ArH, 1H), 6.76(s, ArH, 1H); MS (*m/z*): 249 [$M^+$]. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.71; H, 7.70; N, 5.63.

*5.1.6.3. 2-(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)-N,N-dimethylacetamide (**7c**).* Yield 60.4% (dil. alcohol); mp 117–118 °C; IR: 1643 (C=O), 1274, 1084 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.77, 2.32 (m, $CH_2$, 2H), 2.16, 2.48 (dd, $CH_2$, 2H), 2.88 (m, $CH_2$, 2H), 2.93 (s, $CH_3$, 6H), 3.60 (qn, CH, 1H), 3.82 (s, $OCH_3$, 3H), 3.84 (s, $OCH_3$, 3H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 263 [$M^+$]. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.25; H, 8.07; N, 5.31.

*5.1.6.4. 2-(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)-N-ethylacetamide (**7d**).* Yield 61.8% (dil. alcohol); mp 104–105 °C; IR: 3314 (NH), 1646 (C=O), 1270, 1085 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.22 (t, $CH_3$, 3H), 1.79, 2.31 (m, $CH_2$, 2H), 2.18, 2.49 (dd, $CH_2$, 2H), 2.88 (m, $CH_2$, 2H), 3.24 (qr, $CH_2$, 2H) 3.58 (qn, CH, 1H), 3.84 (s, $OCH_3$, 3H), 3.86 (s, $OCH_3$, 3H), 5.38 (s, NH, 1H), 6.75 (s, ArH, 1H), 6.76 (s, ArH, 1H); MS (*m/z*): 263 [$M^+$]. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.68; H, 8.01; N, 5.30.

*5.1.6.5. 2-(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)-N,N-diethylacetamide (**7e**).* Yield 64.9% (dil. alcohol); mp 62–63 °C; IR: 1644 (C=O), 1267, 1089 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.20 (t, $CH_3$, 6H), 1.79, 2.34 (m, $CH_2$, 2H), 2.21, 2.50 (dd, $CH_2$, 2H), 2.86 (m, $CH_2$, 2H), 3.23 (qr, $CH_2$, 4H) 3.59 (qn, CH, 1H), 3.84 (s, $OCH_3$, 3H), 3.86 (s, $OCH_3$, 3H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 291 [$M^+$]. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.81; H, 8.68; N, 4.79.

*5.1.6.6. 2-(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)-N-propylacetamide (**7f**).* Yield 66.7% (dil. alcohol); mp 107–108 °C; IR: 3324 (NH), 1648 (C=O), 1267, 1085 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 0.91 (t, $CH_3$, 3H), 1.51 (m, $CH_2$, 2H), 1.77, 2.31 (m, $CH_2$, 2H), 2.24, 2.51 (dd, $CH_2$, 2H), 2.84 (m, $CH_2$, 2H), 3.24 (t, $CH_2$, 2H), 3.60 (qn, CH, 1H), 3.83 (s, $OCH_3$, 3H), 3.85 (s, $OCH_3$, 3H), 5.45 (s, NH, 1H), 6.75 (s, ArH, 1H), 6.76 (s, ArH, 1H); MS (*m/z*): 277 [$M^+$]. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.50; H, 8.38; N, 5.06.

*5.1.6.7. 2-(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)-N-isopropylacetamide (**7g**).* Yield 66.6% (benzene); mp 140–141 °C; IR: 3285 (NH), 1644 (C=O), 1265, 1082 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.45 (d, $CH_3$, 6H), 1.81, 2.33 (m, $CH_2$, 2H), 2.21, 2.47 (dd, $CH_2$, 2H), 2.88 (m, $CH_2$, 2H), 3.58 (qn, CH, 1H), 3.83 (s, $OCH_3$, 3H), 3.85 (s, $OCH_3$, 3H), 3.94 (m, CH, 1H) 5.22 (s, NH, 1H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 277 [$M^+$]. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.35; H, 8.35; N, 5.04.

*5.1.6.8. N-Butyl-2-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)acetamide (**7h**).* Yield 59.2% (cyclohexane); mp 103–104 °C; IR: 3329 (NH), 1643 (C=O), 1270, 1083 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 0.97 (t, $CH_3$, 3H), 1.30 (m, $CH_2$, 2H), 1.53 (qn, $CH_2$, 2H), 1.80, 2.19 (m, $CH_2$, 2H), 2.21, 2.52 (dd, $CH_2$, 2H), 2.90 (m, $CH_2$, 2H), 3.20 (t, $CH_2$, 2H), 3.59 (qn, CH, 1H), 3.83 (s, $OCH_3$, 3H), 3.85 (s, $OCH_3$, 3H), 5.43 (s, NH, 1H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 291 [$M^+$]. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.79; H, 8.68; N, 4.83.

*5.1.6.9. N-(tert-Butyl)-2-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)acetamide (**7i**).* Yield 65.2% (cyclohexane); mp 156–157 °C; IR: 3295 (NH), 1642 (C=O), 1269, 1081 ($OCH_3$)

$cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.32 (s, $CH_3$, 9H), 1.81, 2.38 (m, $CH_2$, 2H), 2.25, 2.52 (dd, $CH_2$, 2H), 2.91 (m, $CH_2$, 2H), 3.60 (qn, CH, 1H), 3.83 (s, $OCH_3$, 3H), 3.85 (s, $OCH_3$, 3H), 5.31 (s, NH, 1H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 291 [$M^+$]. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.87; H, 8.68; N, 4.82.

*5.1.6.10. 2-(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)-N-pentylacetamide (**7j**).* Yield 65.1% (cyclohexane); mp 102–103 °C; IR: 3319 (NH), 1646 (C=O), 1268, 1086 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 0.98 (t, $CH_3$, 3H), 1.30 (m, $CH_2$, 4H), 1.51 (qn, $CH_2$, 2H), 1.76, 2.24 (m, $CH_2$, 2H), 2.27, 2.53 (dd, $CH_2$, 2H), 2.86 (m, $CH_2$, 2H), 3.24 (t, $CH_2$, 2H), 3.58 (qn, CH, 1H), 3.84 (s, $OCH_3$, 3H), 3.86 (s, $OCH_3$, 3H), 5.41 (s, NH, 1H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 305 [$M^+$]. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.91; H, 8.89; N, 4.60.

*5.1.6.11. 2-(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)-N-hexylacetamide (**7k**).* Yield 57.9% (cyclohexane); mp 94–95 °C; IR: 3323 (NH), 1648 (C=O), 1267, 1083 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 0.98 (t, $CH_3$, 3H), 1.31 (m, $CH_2$, 6H), 1.53 (qn, $CH_2$, 2H), 1.78, 2.24 (m, $CH_2$, 2H), 2.26, 2.52 (dd, $CH_2$, 2H), 2.86 (m, $CH_2$, 2H), 3.20 (t, $CH_2$, 2H), 3.60 (qn, CH, 1H), 3.84 (s, $OCH_3$, 3H), 3.86 (s, $OCH_3$, 3H), 5.39 (s, NH, 1H), 6.75 (s, ArH, 1H), 6.76 (s, ArH, 1H); MS (*m/z*): 319 [$M^+$]. Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.115; N, 4.38. Found: C, 71.60; H, 9.14; N, 4.40.

*5.1.6.12. N-Cyclopropyl-2-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)acetamide (**7l**).* Yield 62.7% (ethyl acetate); mp 128–129 °C; IR: 3316 (NH), 1643 (C=O), 1267, 1090 ($OCH_3$), 1003 (cyclopropyl) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 0.45 (m, $CH_2$, 4H), 1.76, 2.22 (m, $CH_2$, 2H), 2.19, 2.46 (dd, $CH_2$, 2H), 2.41 (m, CH, 1H), 2.88 (m, $CH_2$, 2H), 3.60 (qn, CH, 1H), 3.82 (s, $OCH_3$, 3H), 3.84 (s, $OCH_3$, 3H), 5.37 (s, NH, 1H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 275 [$M^+$]. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.80; H, 7.70; N, 5.10.

*5.1.6.13. N-Cyclopentyl-2-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)acetamide (**7m**).* Yield 72.5% (cyclohexane); mp 136–138 °C; IR: 3321 (NH), 1646 (C=O), 1271, 1083 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.45 (m, $CH_2$, 4H) 1.76 (m, $CH_2$, 4H), 1.81, 2.27 (m, $CH_2$, 2H), 2.31, 2.54 (dd, $CH_2$, 2H), 2.88 (m, $CH_2$, 2H), 3.57 (qn, CH, 1H), 3.65 (qn, CH, 1H), 3.82 (s, $OCH_3$, 3H), 3.84 (s, $OCH_3$, 3H), 5.31 (s, NH, 1H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 303 [$M^+$]. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.54; H, 8.34; N, 4.63.

*5.1.6.14. N-Cyclohexyl-2-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)acetamide (**7n**).* Yield 70.5% (cyclohexane); mp 152–153 °C; IR: 3327 (NH), 1645 (C=O), 1269, 1086 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.11 (qn, $CH_2$, 2H), 1.35 (m, $CH_2$, 4H), 1.71(m, $CH_2$, 4H), 1.79, 2.30 (m, $CH_2$, 2H), 2.19, 2.46 (dd, $CH_2$, 2H), 2.88 (m, $CH_2$, 2H), 3.58 (qn, CH, 1H), 3.65 (qn, CH, 1H), 3.82 (s, $OCH_3$, 3H), 3.84 (s, $OCH_3$, 3H), 5.29 (s, NH, 1H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 317 [$M^+$]. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.86; H, 8.58; N, 4.42.

*5.1.6.15. N-Benzyl-2-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-yl)acetamide (**7o**).* Yield 77.4% (dil. alcohol); mp 146–147 °C; IR: 3333 (NH), 1643 (C=O), 1272, 1084 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.80, 2.48 (m, $CH_2$, 2H), 2.36, 2.57 (dd, $CH_2$, 2H), 2.88 (m, $CH_2$, 2H), 3.63 (qn, CH, 1H), 3.81 (s, $OCH_3$, 3H), 3.83 (s, $OCH_3$, 3H), 4.46 (s, Bnz $CH_2$, 2H), 5.71 (s, NH, 1H), 6.74 (s, ArH, 1H), 6.75 (s, ArH, 1H), 7.26 (m, ArH, 5H); MS (*m/z*): 325 [$M^+$]. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.91; H, 7.14; N, 4.31.

*5.1.6.16. 1-[(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)acetyl]-pyrrolidine (**7p**).* Yield 64.3% (ethyl acetate and *n*-hexane); mp 114–115 °C; IR: 1643 (C=O), 1275, 1086 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.97 (m, $CH_2$, 4H), 1.81, 2.29 (m, $CH_2$, 2H), 2.31, 2.57 (dd, $CH_2$, 2H), 2.84 (m, $CH_2$, 2H), 3.46 (t, $CH_2$, 4H), 3.59 (qn, CH, 1H), 3.84 (s, $OCH_3$, 3H), 3.86 (s, $OCH_3$, 3H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 289 [$M^+$]. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.33; H, 8.03; N, 4.85.

*5.1.6.17. 1-[(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)acetyl]-piperidine (**7q**).* Yield 57.5% (chloroform); mp 101–102 °C; IR: 1646 (C=O), 1268, 1089 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.65 (m, $CH_2$, 6H), 1.75, 2.45 (m, $CH_2$, 2H), 2.72, 2.46 (dd, $CH_2$, 2H), 2.88 (m, $CH_2$, 2H), 3.37 (t, $CH_2$, 4H), 3.66 (qn, CH, 1H), 3.84 (s, $OCH_3$, 3H), 3.86 (s, $OCH_3$, 3H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 303 [$M^+$]. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.45; H, 8.33; N, 4.64.

*5.1.6.18. 1-[(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)acetyl]-piperazines (**7r**).* Yield 63.7% (ethyl acetate and *n*-hexane); mp 212–213 °C; IR: 3345 (NH of piperazine), 1645 (C=O), 1269, 1087 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.83, 2.26 (m, $CH_2$, 2H), 2.13 (s, NH 1H), 2.79 (t, $CH_2$, 4H), 2.23, 2.50 (dd, $CH_2$, 2H), 2.88 (m, $CH_2$, 2H), 3.33 (t, $CH_2$, 4H), 3.60 (qn, CH, 1H), 3.84 (s, $OCH_3$, 3H), 3.86 (s, $OCH_3$, 3H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 304 [$M^+$]. Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.99; H, 7.97; N, 9.18.

*5.1.6.19. 4-[(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)acetyl]-morpholines (**7s**).* Yield 61.6% (dil. alcohol); mp 137–138 °C; IR: 1648 (C=O), 1270, 1081 ($OCH_3$) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 1.74, 2.43 (m, $CH_2$, 2H), 2.68, 2.45 (dd, $CH_2$, 2H), 2.85 (m, $CH_2$, 2H), 3.47 (t, $CH_2$, 4H), 3.60 (qn, CH, 1H), 3.69 (t, $CH_2$, 4H) 3.84 (s, $OCH_3$, 3H), 3.86

(s, $OCH_3$, 3H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 305 [$M^+$]. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.69; H, 7.56; N, 4.60.

*5.1.6.20. 2-(5,6-Dimethoxy-2,3-dihydro-1H-inden-1-yl)-N-(2-hydroxyethyl)acetamide (**7t**).* Yield 64.4% (benzene); mp 72–74 °C; IR: 3311 (NH), 1644 (C=O), 1273, 1084 ($OCH_3$), 3615 (OH) $cm^{-1}$; $^1H$ NMR $\delta$ (ppm) ($CDCl_3$): 2.01 (s, OH, 1H), 1.81, 2.30 (m, $CH_2$, 2H), 2.19, 2.50 (dd, $CH_2$, 2H), 2.88 (m, $CH_2$, 2H), 3.41 (t, $CH_2$, 2H), 3.60 (qn, CH, 1H), 3.75 (t, $CH_2$, 2H) 3.82 (s, $OCH_3$, 3H), 3.84 (s, $OCH_3$, 3H), 5.50 (s, NH, 1H), 6.76 (s, ArH, 1H), 6.77 (s, ArH, 1H); MS (*m/z*): 279 [$M^+$]. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.62; H, 7.60; N, 5.02.

## 5.2. Biological evaluation

All synthesized compounds were evaluated for analgesic and anti-inflammatory activity and few selected compounds were screened for antipyretic, ulcerogenecity and anti-arthritic activity. The test compounds, **7a–t**, and standard drugs (indomethacin and aspirin) were administered orally as suspensions in 0.5% carboxymethylcellulose sodium in distilled water. Each group consisted of six animals. The animals were maintained at temperature of 24 ± 2 °C, relative humidity of 45% and kept under a 12 h light and dark cycle. The animals were fasted overnight for analgesic and anti-inflammatory assays and 24 h for antipyretic and ulcerogenecity studies. During fasting they had free access to water. The data obtained in pharmacological experiments were subjected to statistical analysis using student's *t*-test, one-way ANOVA, post hoc test, and the chosen level of significance was $p < 0.05$. The protocol for the animal experiments was approved by the Institutional Animal Ethics Committee (IAEC) as registered under Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Govt. of India.

### 5.2.1. Acute anti-inflammatory activity: carrageenan-induced edema

The anti-inflammatory activity of the test compounds (**7a–t**) was determined by carrageenan-induced rat hind paw edema assay as described by Winter et al. [16]. Female Wistar rats weighing 170 ± 20 g were administered the test compounds and standard indomethacin orally equivalent to 100 and 10 mg/kg, respectively. One hour after dosing, 0.1 ml of 1% carrageenan was administered into the subplantar region of the right hind paw. The paw volumes were measured using an Ugo Basile plethysmometer at 0, 1, 2, 3, 4, 6 and 24 h after carrageenan injection. The results (Table 1) are expressed as percentage inhibition of edema formation. The percentage inhibition of edema in each drug treated group was calculated using the formula given below:

$$\%\text{Inhibition} = 100(1 - V_t/V_c)$$

where $V_c$ and $V_t$ are average edema volumes in control and treated groups, respectively.

### 5.2.2. Analgesic activity

The analgesic activity of the compounds **7a–t** was determined by acetic acid-induced writhing test in mice as described by Collier et al. [17] with minor modifications. Female Swiss albino mice, 20 ± 5 g, were administered the test drugs orally at 100 mg/kg and the standard indomethacin and aspirin at 10 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 writhing (full extension of hind limbs) was noted for next 15 min. Animals giving 20 or more writhes were selected for the study. The percentage inhibition by individual drug as well as by the reference standard drugs was calculated using the following formula,

$$\%\text{Inhibition} = 100[1 - W_t/W_c]$$

where $W_c$ represents the average writhing produced by the control group and $W_t$ represents the average writhing produced by the test groups.

### 5.2.3. Antipyretic activity

The antipyretic activity of the compounds was evaluated by lipopolysaccharide-induced pyrexia. The method was that of Dogan et al. [11] with minor modifications. Adult female Wistar rats (170 ± 20 g) were used. Phenol extracted LPS from *Escherichia coli* serotype 0111: B4 (Difco) was used. The experiment was started at 09:00 am. Test compounds and aspirin were given orally at dose level of 100 mg/kg. Indomethacin was given at a dose level of 10 mg/kg. After half an hour of oral administration of the drugs LPS dissolved in apyrogenic saline was injected at dose of 100 μg/kg i.p. The rectal temperature was determined using telethermometer probes immediately before and 1, 2, 3, 4, 5, 6, 7 h after LPS administration. For evaluation of antipyretic activity, the temperature index was calculated following the method of Winter et al. [18].

### 5.2.4. Chronic anti-inflammatory activity: adjuvant-induced arthritis

The method used was essentially that of Newbould [21]. Only three compounds were selected for this study. Female albino rats weighing 160 ± 10 g were chosen for the study. The animals were given the test compounds at the dose level of 100 mg/kg p.o. once daily for 14 days starting from the day before the administration of 0.1 ml Freund's complete adjuvant (Genie, Bangalore, India) into the subplantar surface of right hind paw of each rat. Indomethacin was taken as the standard drug and was given for 14 days at the dose level of 10 mg/kg p.o. Both hind paw volumes up to the fixed mark at the level of lateral malleolus were measured before and daily after adjuvant administration. The formation of nodules and appearance of erythema in tail, nose and ears were observed and graded as mild, moderate and severe for

comparison. Change in body weight of the animals during the test period was also recorded for comparison. The results are presented in Table 4.

*5.2.5. Ulcerogenecity test*

Only few amides from the series **7a–t** were selected for ulcerogenic studies. The method used to evaluate the ulcerogenic potential of the test compounds was that of Velázquez et al. [19] with minor modifications. Twenty-four hour fasted Wistar female rats ($175 \pm 25$ g) were used. The test compounds and the standard drug indomethacin were dosed orally at 100 and 30 mg/kg, respectively. After 6 h of oral dosing the rats were sacrificed using cervical dislocation. The stomachs were taken out and cut along the greater curvature. After washing with saline the stomach mucosa was examined for ulcers using a hand lens. The gastric lesions were counted, and an ulcerative index (UI) for each animal was calculated according to Szelenyl and Thiemer [20].

$$\mathrm{UI} = (n\text{lesion I}) + (n\text{lesion II})2 + (n\text{lesion III})3$$

where I = presence of edema, hyperemia and single, submucosal, punctiform hemorrages(petechiae); II = presence of submucosal, hemorrhagic lesions with small erosions; and III = presence of deep ulcer with erosions and invasive lesions.

*5.2.6. Metabolism inhibition study using SKF-525A [10]*

The rats were pretreated with SKF-525A (50 mg/kg i.p.). One hour later, the rats were dosed orally the test drug **7k** at 100 mg/kg. The remaining protocol followed was the same as that of anti-inflammatory screening by carrageenan-induced rat paw edema model.

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