Synthesis and structure-activity-relationships of indan acid derivatives as analgesic and anti-inflammatory agents

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ABSTRACT

Indan ring system, also known as indane or benzocyclopentane, is an important chemical feature associated with various biological activities. Among the drugs possessing an indan ring system, 1*H*-indene-3-acetic acid-5-fluoro-2-methyl-1-[4-(methylsulfinyl)-phenyl]methylene (Sulindac) and 6-chloro-5-cyclohexyl indan-1-carboxylic acid (Clidanac) are well known anti-inflammatory agents, whilst indan-1,3-dione is an anticoagulant. Over the years, several indan derivatives, particularly indan acid derivatives, have been synthesized and their potential analgesic and anti-inflammatory properties have been studied. This review critically appraises various synthetic protocols and structure-activity-relationships of indan acids as analgesic and anti-inflammatory agents with low ulcerogenicity.

Keywords: Indan acid derivatives; Analgesic; Anti-inflammatory; Structure-activity-relationships (SAR); Synthesis

CONTENTS

1. INTRODUCTION

Indan (also known as indane or benzocyclopentane) ring system (Figure 1) is regarded as an ideal chemical feature associated with various biological activities [1-3]. Over the years, several indan derivatives have been synthesized with the expectation of generating pharmacologically active compounds as new drug candidates. Some of these compounds have eventually turned out to be pharmacologically active with any practical uses [1, 4].

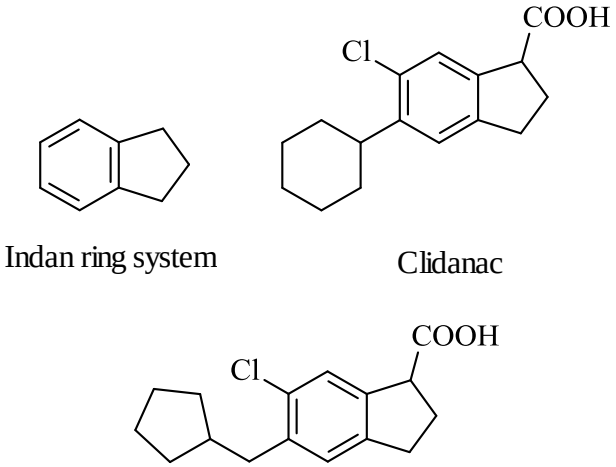


Figure 1. Indan ring system, and some indan acid-based anti-inflammatory agents

Many indan derivatives are indan acids, and they were synthesized as potential analgesic and anti-inflammatory agents [1, 5-15]. For example, the analogues of *p*-alkylphenylacetic acids and 5-alkyl-1-indan-carboxylic acids were synthesized as anti-inflammatory agents, and among them, 6-chloro-5-cyclohexyl-1-indancarboxylic acid was found to possess the highest level of analgesic, anti-inflammatory and antipyretic activities [16]. Later, 6-chloro-5-cyclohexyl-1-indancarboxylic acid was introduced into the market as Clidanac as an anti-inflammatory drug (Figure 1) [5, 7, 17]. However, this compound displayed significant ulcerogenicity along with anti-inflammatory activity at a dose of 400 mg/kg. Interestingly, an isomer of this compound, known as 6-chloro-5-(cyclopentanylmethyl)-indan-1-carboxylic acid (Figure. 1) displayed anti-inflammatory activity, but no detectable ulcerogenicity in the acute or chronic treatment models in rats and monkeys [7]. It was also noted that 1,2,3,4-tetrahydro-1-naphthoic acid derivatives did not have potent activity as that of corresponding

1-indan-carboxylic acids [5, 17]. Apparently, 1-indan-carboxylic acid may have the essential conformation of the phenylacetic acids for exhibiting the anti-inflammatory activity.

Ketoprofen (Figure 2), a *meta*-substituted aryl-aceitc acid derivative, was found to be an effective anti-inflammatory agent [18]. This finding gave birth to the hypothesis that a new anti-inflammatory agent could be obtained by introducing an appropriate substituent at either 4- or 6-position of 1-indan-carboxylic acid, which corresponds to the *meta*-position in phenylacetic acid [19]. As a result, in the search for more potent, less toxic and new analgesic and anti-inflammatory agents, indan acids with various substitutions, *e.g.*, halogenation or methoxylations, on the benzene ring of the indan nucleus have been synthesised [1, 5-15, 17, 19].

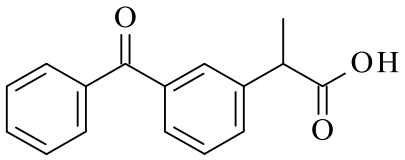


Figure 2. Ketoprofen, a potent anti-inflammatory agent

Electrophilic substitutions, particularly, halogenations on the indan nucleus received considerable attention with respect to their relative reactivities and orientation on the aromatic ring [20]. The substitution takes place predominantly on the 6-position of the indan ring or 3-position of the starting materials benazaldehyde [10, 21]. Owing to electrochemical nature, halogens exert a pronounced influence on the biological behaviour of organic compounds. Thus, it was predicted that halo-substituted indan-1-acids should have similar activity profile as that of halo-substituted indole-3-acetic acid [1, 10, 12, 15, 21]. Pal *et al.* [1] carried out dichloro substitution at 5- and 6-positions of the indan ring with starting material 3,4-dichlorobenzaldehyde, and evaluated the anti-inflammatory activity of the products. Since aromatic halogen substitution is a reasonable means of increasing the activity and widening the margin of safety, a number of chloro- and bromo-substituted analogues of indan-1-carboxylic acid and that of indan-1-acetic acid were synthesized to investigate the effect of halo-substitution on the biological activity of the indan-1-acids [1, 10, 12, 15, 21].

Like halo-substitution, methoxy-substitution was also considered as an option for increasing the potency of indan acids. A number of methoxy-substituted indan derivatives were synthesized to evaluate various pharmacological activities like hypoglycemic, antilipidemic, analgesic, antipyretic and anti-inflammatory [22-28]. The methoxy-substitutions were found to exhibit necessary pharmacological activities and binding affinity at the melatonin receptor molecules [29]. The steric and the electronic properties of the substituent on the phenyl ring necessary for the receptor recognition were investigated by introducing different groups at the 4-position on the ring for better activity. The effects of the position of chloro- or methoxy-substitution on the resulting pharmacological activity were also evaluated [30].

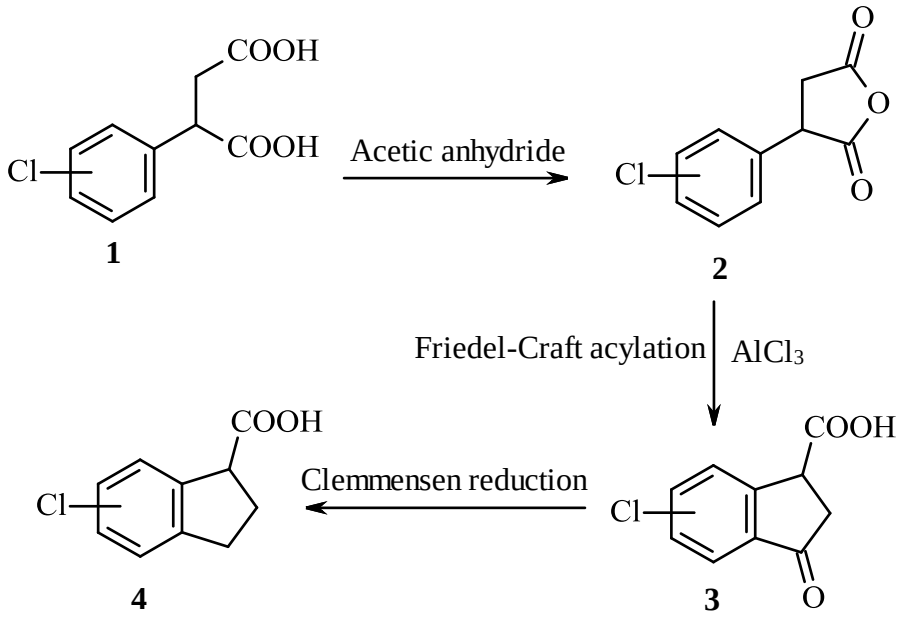
This review critically appraises various synthetic protocols and structure-activity-relationships of indan acid derivatives as analgesic and anti-inflammatory agents with low ulcerogenicity.

2. SYNTHESIS OF INDAN ACID DERIVATIVES

2.1. Indan acids

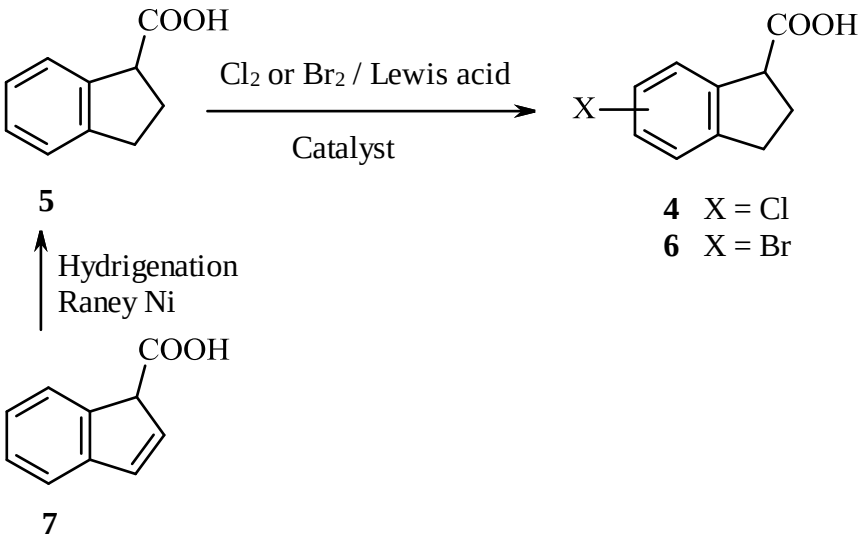
2.1.1. Indan-1-carboxylic acids

4-Chloroindan-1-carboxylic acid (**4a**), 5-chloroindan-1-carboxylic acid (**4b**), 6-chloroindan-1-carboxylic acid (**4c**), 7-chloroindan-1-carboxylic acid (**4d**), 4-bromoindan-1-carboxylic acid (**6b**) and 6-bromoindan-1-carboxylic acid (**6a**) were synthesized by Aono *et al.* [19]. Different (chlorophenyl)-succinic anhydrides (**2**) were prepared from corresponding substituted (phenyl)-succinic acids (**1**), *e.g.*, 2-(chlorophenyl)-succinic acid (**1a**), 3-(chlorophenyl)-succinic acid (**1b**) and 4-(chlorophenyl)-succinic acid (**1c**), by refluxing with acetic anhydride (Scheme 1). The anhydrides (**2**) were subjected to the Friedel-Crafts acylation to afford 5-chloro-3-oxo-indan-1-carboxylic acid (**3a**), 6-chloro-3-oxo-indan-1-carboxylic acid (**3b**) and 7-chloro-3-oxo-indan-1-carboxylic acid (**3c**). 4-Chloro-3-oxo-indan-1-carboxylic acid (**3d**) was obtained as a by-product of **3b** from its organic layer (CH_2Cl_2-$CHCl_3$ mixture) after washing it with water, extracted with Na_2CO_3 (5%) and finally acidified with dil. HCl. The 3-oxo derivatives (**3**) were then reduced to the respective acids (**4**) using the Clemmensen reaction (Scheme 1).



Scheme 1. Synthesis of various chloroindan-1-carboxylic acids

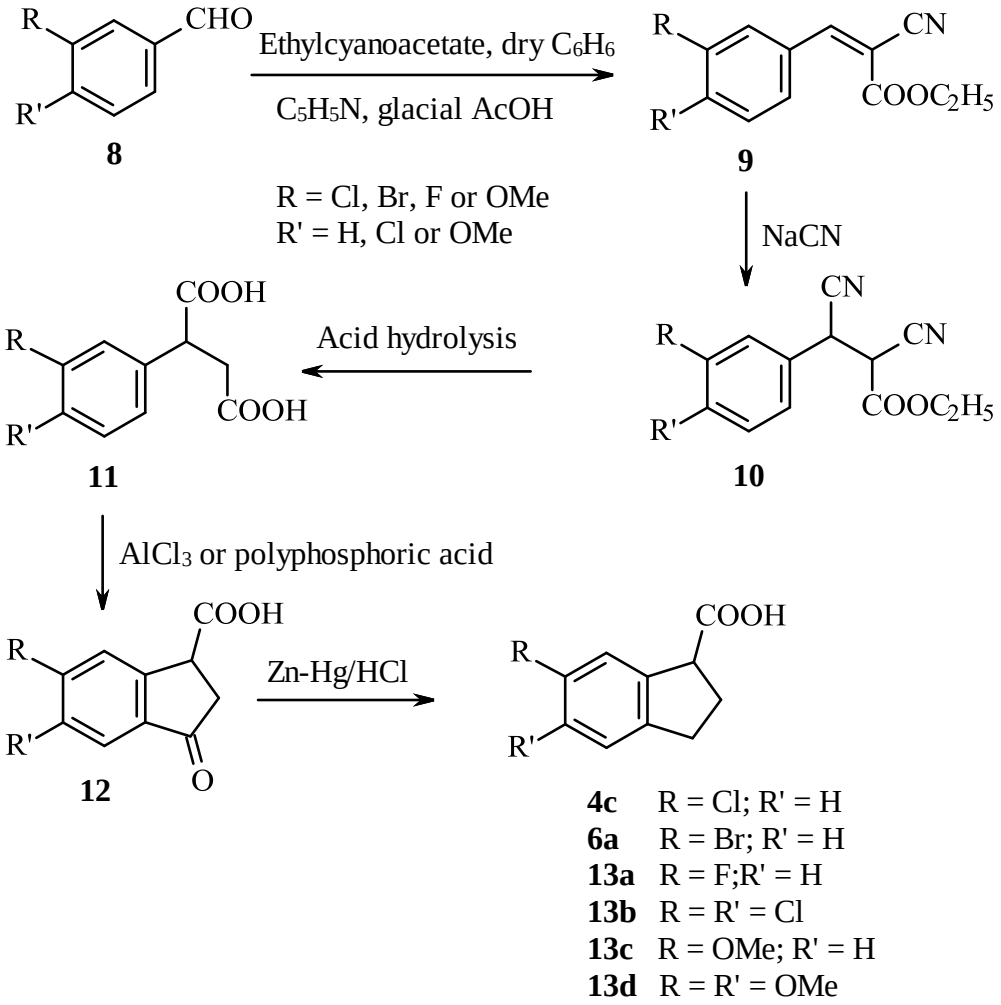
Aono *et al.* [19] also reported the synthesis of chloroindan-1-carboxylic acids (**4a-d**) using a different synthetic approach (Scheme 2). Chlorination of indan-1-carboxylic acid (**5**) produced these compounds. To a stirred, ice-cooled mixture of **5** and catalyst ($FeCl_3$, $TiCl_4$, $ZnCl_2$ and $SnCl_4$), Cl_2 solution was added drop-wise. The mixtures were stirred for 1.3 h under cooling and then poured into ice-water. The mixtures were extracted with ether, washed with water, dried over anhydrous $MgSO_4$ and evaporated to dryness. Similarly, 6-bromoinadan-1-carboxylic acid (**6a**) was prepared by bromination in presence of catalyst, and 4-bromoindan-1-carboxylic acid (**6b**) was obtained as a by-product (Scheme 2). The indan-1-carboxylic acid (**5**) could easily be synthesized by hydrogenation of indene-1-carboxxylic acid (**7**) using the Raney nickel catalyst [31] (Scheme 2).



Scheme 2. Synthesis of various haloindan-1-carboxylic acids

6-Fluoroindan-1-carboxylic acid (**13a**), 6-chloroindan-1-carboxylic acid (**4c**) and 6-bromoindan-1-carboxylic acid (**6a**), 5,6-dichloroindan-1-carboxylic acid (**13b**), 6-methoxyindan-1-carboxylic acid (**13c**) and 5,6-dimethoxyindan-1-carboxylic acid (**13d**) were synthesized starting from respective substituted benzaldehydes (**8**) [1, 12, 21, 22] (Scheme 3). The substituted benzaldehydes (**8**) were reacted with ethylcyanoacetate in dry benzene (C_6H_6) in presence of pyridine (C_5H_5N) and glacial acetic acid (AcOH). The reaction mixtures were refluxed in an oil bath, and then evaporated to dryness under reduced pressure. The solid residues, substituted-phenyl cyanoacrylic esters (**9**), were filtered, washed sequentially with water, HCl (5%) and cold water, dried and crystallized in aqueous ethanol (EtOH). The substituted-phenyl cyanoacrylic esters (**9**) were allowed to react with sodium cyanide (NaCN) using water as a solvent. The reaction mixtures were refluxed in presence of 50% aqueous EtOH, cooled, poured in water, conc. HCl was added to it and kept for overnight. The mixtures were then extracted three times with chloroform ($CHCl_3$). The individual extract was washed with water, dried over baked sodium sulphate and evaporated to dryness. The products, substituted-phenyl α,β-dicyanoethylpropionates (**10**), were hydrolyzed by refluxing with conc. HCl to obtain corresponding substituted-phenyl succinic acids (**11**), separated as a white solid on cooling. The white solids were then filtered, washed with cold water, dried and re-crystallized from hot water. The respective diacids (**11**) were converted to diacylchlorides by refluxing them with thionylchloride ($SOCl_2$) in dry C_6H_6. The benzene and excess $SOCl_2$ were removed under vacuum to obtain diacylchlorides as liquid. Anhydrous aluminium

chloride was poured immediately into the reaction mixtures of diacylchlorides in portion wise in well stirred condition using carbon disulfide (CS_2) as a solvent. The reaction mixtures were stirred at r.t., and decomposed in ice water mixture. CS_2 was evaporated on a hot water bath. The 3-oxo compounds (**12**) precipitated after cooling of the mixtures, filtered, washed thoroughly with water, dried and re-crystallized. The respective 3-oxo-indan-1-carboxylic acids (**12**) were reduced to corresponding substituted indan-1-carboxylic acids (**4c**, **6a**, **13a-d**) following the Clemmensen reduction. The compounds were separated from the reaction mixture through solvent extraction.



Scheme 3. Synthesis of various halo- and methoxyindan-1-carboxylic acids from respective substituted benzaldehydes

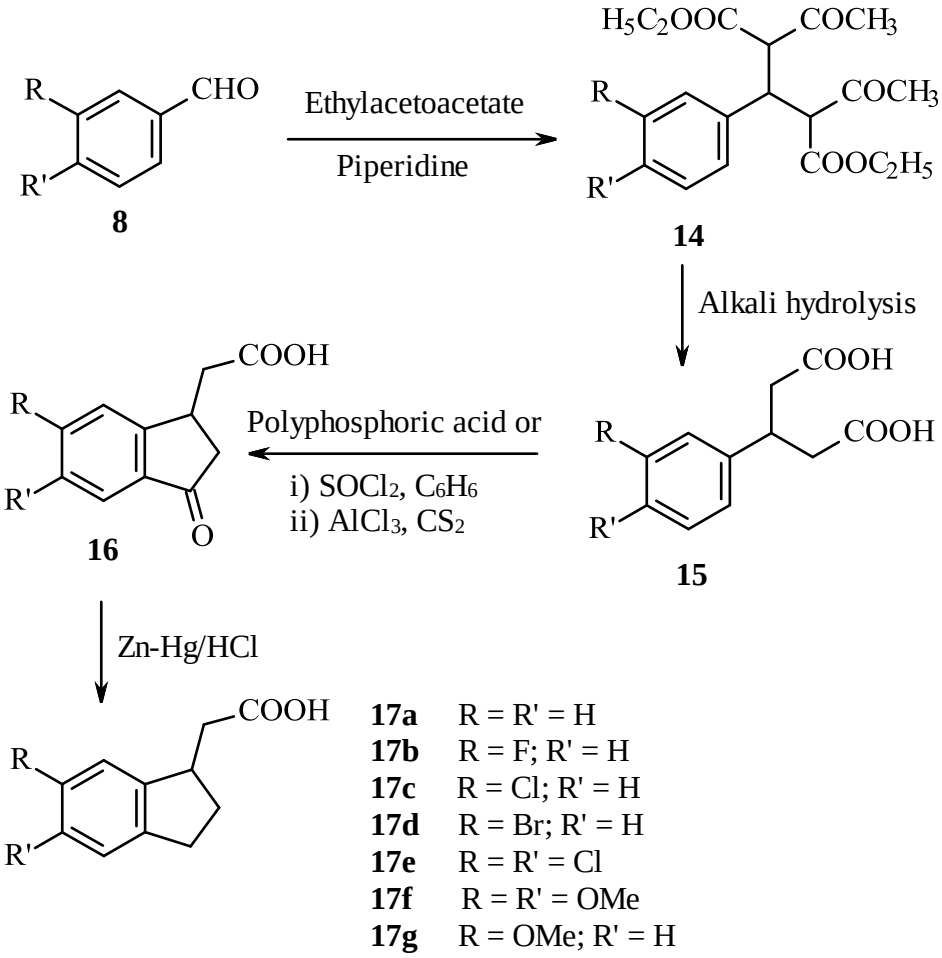
An improved method for the synthesis of various substituted indan-1-carboxylic acid derivatives involved cyclization of phenyl succinic acid and reduction of the indanon-1-carboxylic acid with triethylsilane in trifluoroacetic acid. However, the synthesis was not targeted toward generation of new anti-inflammatory or analgesic compounds [32]. Fujimura *et al.* [33] synthesized 6-chloro-5-cyclohexyl-1-indancarboxylic acid as an anti-inflammatory agent. Similarly, several 5-substituted 1-indancarboxylic acids were prepared as potential anti-inflammatory agents [34].

2.1.2. Indan-1-acetic acids

The synthesis of several substituted indan-1-acitic acids (**17a-f**) has been reported [1, 15, 21, 22] (Scheme 4). The respective substituted benzaldehydes (**8**) were condensed with ethyl acetoacetate in 1:2 molar ratios in presence of piperidine allowing the reaction mixtures in anhydrous condition at r.t. After completion of the reaction, yellow solids were obtained. The solid masses were crushed, and washed with ether. The white crystalline powders were obtained and re-crystallized from acetone-water as substituted benzylidine-*bis*-acetoacetates (**14**), which were hydrolyzed by refluxing with alcoholic KOH solution. The alcohol was then distilled off under reduced pressure, diluted with water, washed with $CHCl_3$ and neutralized by conc. HCl in cold condition with stirring. The precipitations thus formed as substituted β-phenylglutaric acids (**15**), were filtered and re-crystallized from alcohol-water as crystalline solids. The respective diacids (**15**) were cyclized to substituted 3-oxo-indan-1-acetic acids (**16**) using polyphosphoric acid as dehydrating agent by heating at 120°C with stirring for 10-15 min or anhydrous $AlCl_3$ using CS_2 as a solvent. The reaction mixtures were poured into ice-water mixture. The solids were filtered, washed with cold water and re-crystallized from aqueous EtOH. The compounds as substituted-3-oxo-indan-1-acetic acids (**16**) were then subjected to the Clemmensen reduction using C_6H_6. The benzene layers were washed with water and dried over anhydrous magnesium sulphate ($MgSO_4$). After removal of the solvent under reduced pressure, the target compounds (**17a-f**) were obtained. The products were re-crystallized from aqueous EtOH.

Similarly, a series of indan acetic acid derivatives were synthesized as potential selective insulin sensitizers [35, 36]. Zhang *et al.* [37] reported the *enantio*-selective synthesis of an indan acetic acid derivative, methyl (2*S*)-2-[(1*S*)-5-hydroxy-2,3-dihydro-1H-inden-1-yl]-

butanoate. The main indene acetic acid framework was constructed *via* a robust, unprecedented Reformatsky process. One stereogenic center was set *via* a resolution, and the other *via* a diastereoselective hydrogenation of the indene acetic acid. However, the synthesis was not linked to any pharmacological activity assessment.



Scheme 4. Synthesis of substituted indan-1-acetic acids

2.1.3. Indan-1-propionic acids and indan-1-butyric acids

Mukhopadhyay *et al.* [28] synthesized several long-chain indan acid analogues, 2-(indan-1-yl)-propionic acid (**21a**), 2-(6-methoxyindan-1-yl)-propionic acid (**21b**), 2-(5,6-dimethoxyindan-1-yl)-propionic acid (**21c**), 3-(indan-1-yl)-butyric acid (**21d**), 3-(6-methoxyindan-1-yl)-butyric acid (**21e**), and 3-(5,6-dimethoxyindan-1-yl)-butyric acid (**21f**), by the consecutive Arndt-Eistert reaction starting from respective indan-1-acids (**18a-f**)

(Scheme 5). The Arndt-Eistert reaction is a series of chemical reactions designed to convert a carboxylic acid functionality to a higher carboxylic acid homologue (*i.e.*, contains one additional carbon atom) and is considered a homologation process. In indan-1-acids the increased aliphatic chain length could separate the hydrophobic indan ring system from the pharmacophoric carboxyl group.

Indan-1-acetic acid (**18a**), 6-methoxyindan-1-acetic acid (**18b**) and 5,6-dimethoxyindan-1-acetic acid (**18c**) were refluxed with $SOCl_2$ to obtain various indan-1-acetyl chlorides (**19**), which were then dissolved in dry ether, added slowly to a cold ethereal solution of diazomethane (CH_2N_2) under reflux. The mixtures were stirred continuously and kept below 5°C during addition, and allowed to stand overnight at r.t. Ether was distilled off under reduced pressure, indan-1-actyl diazoketone, 6-methoxyindan-1-actyl diazoketone and 5,6-dimethoxyindan-1-actyl diazoketone were dissolved in MeOH, and a slurry of silver oxide (prepared from $AgNO_3$ and NaOH) in MeOH was added in portions at 30-40°C, and the progress of reactions were followed by N_2 evolution. When the addition was over, temperature of the bath was raised to 60-70°C and the mixture was refluxed for 0.5 h. The solutions were boiled with charcoal, filtered and the methanolic solution was concentrated. The resulting esters (**20**) were extracted in ether, washed consecutively with dil. HCl, alkali and water, dried and distilled under reduced pressure. The esters were refluxed with 10% KOH solution for 3 h. MeOH was removed and the aqueous layer washed with ether, and the resulting 3-(indan-1-yl)-propionic acid (**21a**), 3-(6-methoxyindan-1-yl)-propionic acid (**21b**) and 3-(5,6-dimethoxyindan-1-yl)-propionic acid (**21c**) were precipitated with dil. HCl. The precipitated acids were re-crystallized from alcohol-water. 4-(Indan-1-yl)-butyric acid (**21d**), 4-(6-methoxyindan-1-yl)-butyric acid (**21e**) and 4-(5,6-dimethoxyindan-1-yl)-butyric acid (**21f**) were synthesized following the same procedure as outlined above, but using the starting materials 3-(indan-1-yl)-propionic acid (**18d**), 3-(6-methoxyindan-1-yl)-propionic acid (**18e**) and 3-(5,6-dimethoxyindan-1-yl)-propionic acid (**18f**), respectively (Scheme 5).

Several non-methoxy and methoxyindan-1-propionic acids, as potential anti-hypercholesterolemic agents, were synthesized also from their corresponding benzaldehyde *via* indan-1-acetic acid as an intermediate [38]. 3-(5,6-Dimethoxyindan-1-yl)-propionic acid (**18f**) showed better activity profile than their homologues, but none of them was found to be

superior to standard drug Clofibrate (Figure 3). Earlier, the same group also synthesized trimethoxy analogs of indan-1-acetic acid [39] and alpha-alkyl substituted derivatives [40]. Witiak *et al.* [41] reported the synthesis of indan-propionic acids as uterine relaxants.

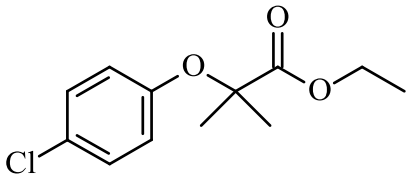
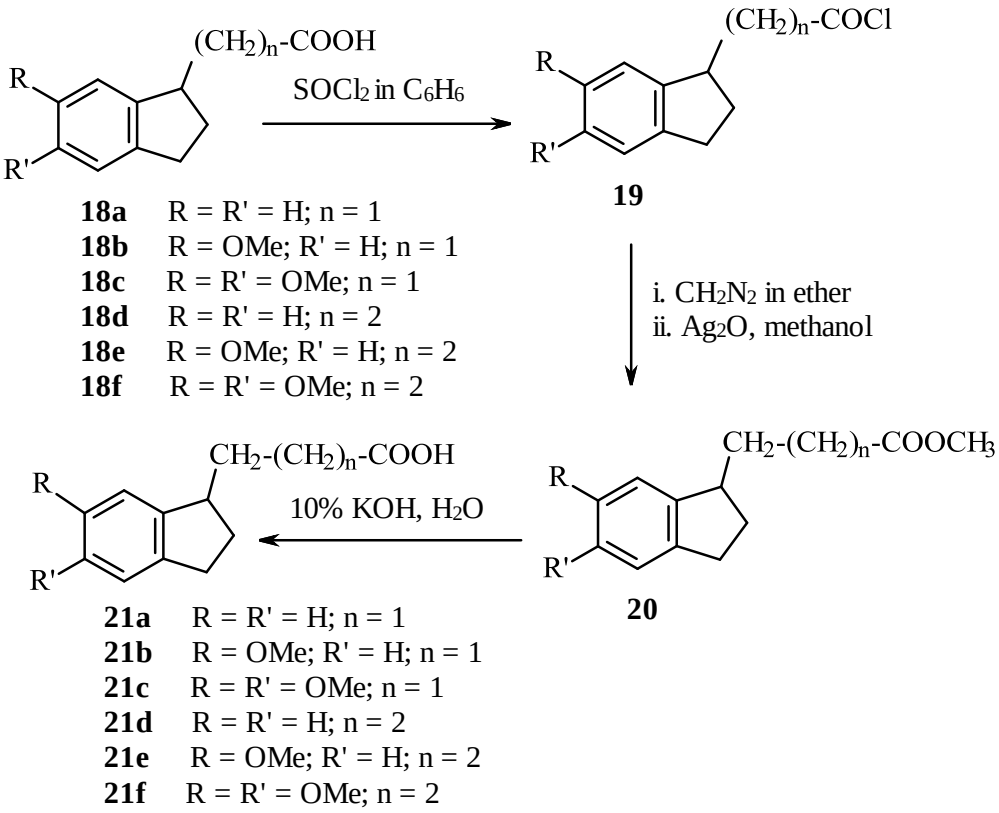


Figure 3. Structure of Clofibrate

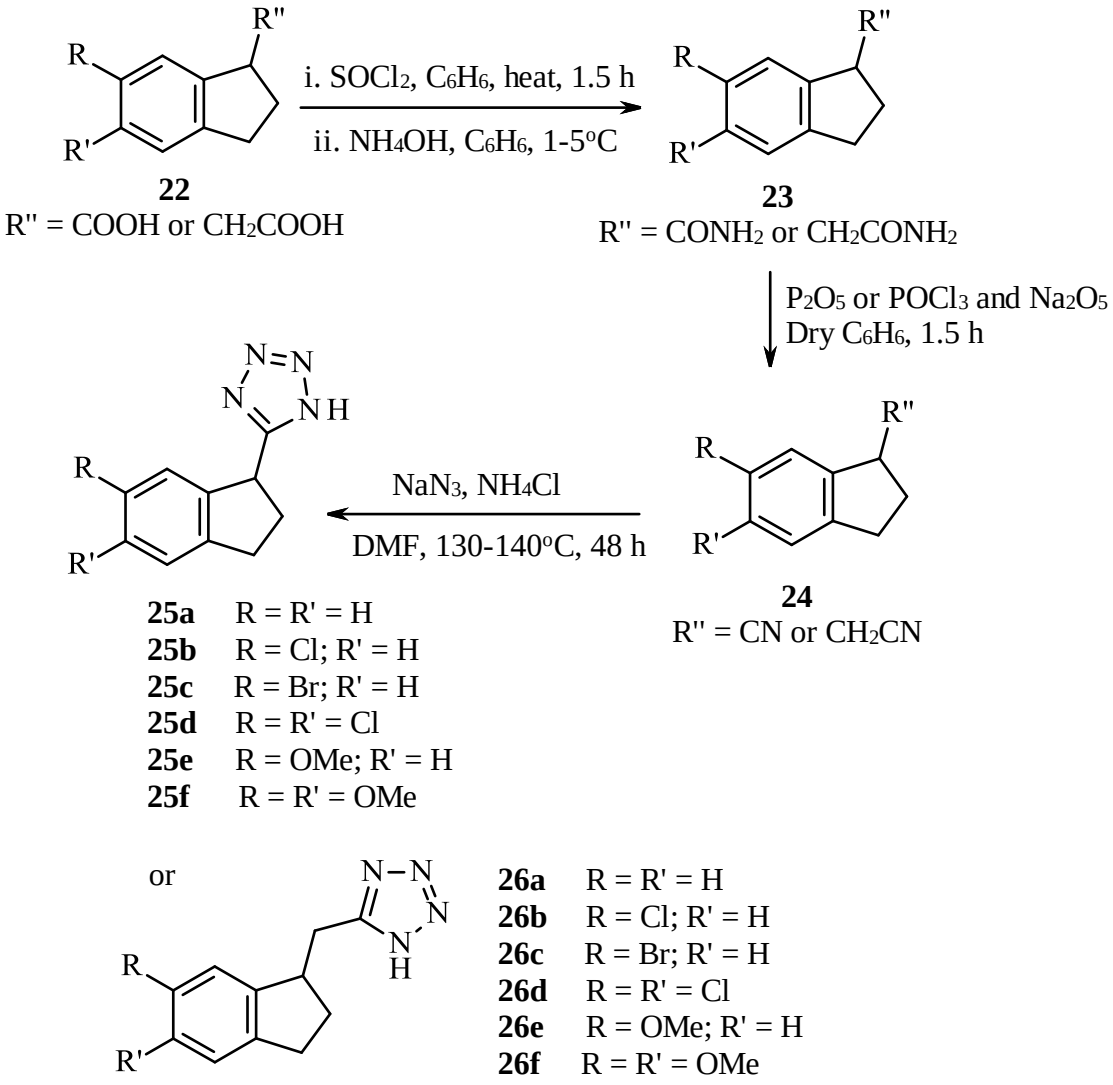


Scheme 5. Synthesis of substituted indan-1-propionic and butyric acids

2.2. Indan acid derivatives with extra heterocyclic rings

The respective acids (**22**) were treated with $SOCl_2$ to prepare acid chlorides, which were treated immediately with NH_3 solution at 1-5°C to afford respective amides (**23)** in excellent yields. The amides (**23**) were dehydrated with P_2O_5 in dry C_6H_6 or in a mixture of $POCl_3$ and NaS_2O_5 (10:1 ratio) by refluxing for 2-4 h. After decomposing the reaction mixtures and

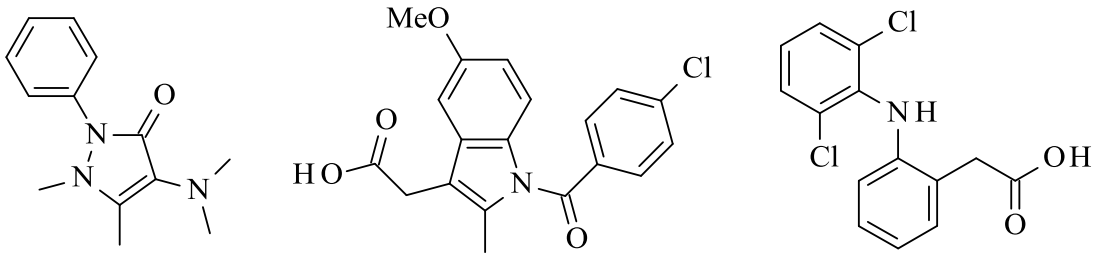
working up, the respective nitriles (**24)** were obtained. Subsequently, the nitriles were allowed to react with activated NaN_3 in presence of NH_4Cl in DMF at 130-140°C for 48 h to afford the target tetrazole derivatives **(25a–f)** and **(26a-f)** as crystalline solids [1, 10, 27, 42, 43] (Scheme 6).



Scheme 6. Synthesis of indan acid derivatives with extra heterocyclic rings

3. ANALGESIC ACYTIVITY OF INDAN ACID DERIVATIVES AND THEIR STRUCTURE-ACTIVITY-RELATIONSHIPS

The analgesic activity of compounds 6-fluoroindan-1-carboxylic acid (**13a)** (Scheme 3) was assessed by the acetic acid induced writhing in Swiss albino mice [12], and this compound was found to significantly reduce the writhing induced by acetic acid in a dose dependent manner. 6-Fluoroindan-1-carboxylic acid (**13a)** exhibited ~22% inhibition at the dose of 25 mg/kg body weight and 36% inhibition at the dose of 50 mg/kg body weight. Another indan acid derivative, 6-fluoroindan-1-acetic acid (**17b)**, showed 38% inhibition at the dose of 25 mg/kg body weight and 47% inhibition at the dose of 50 mg/kg body weight [15]. From these findings, it could be suggested that an increase in carbon number, i.e., acetic acid (-CH_2COOH as in **17b**) [15] instead of a carboxylic acid (-COOH in **13a**) [12] functionality, might have contributed to the increased analgesic potency of compound **17b**. The analgesic activity of these fluoroindan acids was comparable to those of the positive controls, *e.g.*, Aminopyrine, Indomethacin and Diclofenac (Figure 4).



Aminopyrine Indomethacin Diclofenac

Figure 4. Structures of Aminopyrine, Indomethacin and Diclofenac

Indan acids, *e.g.*, indan-1-carboxylic acid (**5**), 6-methoxyindan-1-carboxylic acid (**13c**), 5,6,-dimethoxyindan-1-carboxylic acid (**13d**), indan-1-acetic acid (**17a**), 5,6,-dimethoxyindan-1-acetic acid (**17f**), were also screened for analgesic activity [12, 15, 25]. Roy *et al.* [25] evaluated the analgesic activity of various indan acids using the phenylquinone-induced writhing in mice at varying dose levels. Generally, the indan-1-carboxylic acid derivatives (**5**, **13c** and **13d**), exhibited less potent analgesic effects than corresponding indan-1-acetic acids,

e.g., **17a** and **17f**. It was also observed that the introduction of a methoxy group at 6 or both at 5- and 6-positions of indan-1-acetic acid enhanced remarkably the analgesic activity.

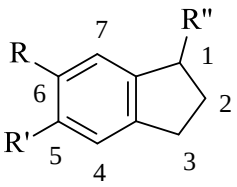
Mukhapadhyay and Lahiri [8] observed the analgesic activity of 3-(indan-1-yl)-propionic acid (**21a**), 3-(6-methoxyindan-1-yl)-propionic acid (**21b**), 3-(5,6-dimethoxyindan-1-yl)-propionic acid (**21c**), 4-(indan-1-yl)-butyric acid (**21d**), 4-(6-methoxyindan-1-yl)-butyric acid (**21e**) and 4-(5,6-dimethoxyindan-1-yl)-butyric acid (**21f**) in phenyl-*p*-quinone induced writhing in mice (Scheme 5). It was noted that indiscriminate chain lengthening was not necessarily beneficial to biological activity. Among the compounds, **21a**, **21b** and **21c** exhibited analgesic activity at a dose of 200 mg/kg body weight, which was comparable to that of phenylbutazone.

The analgesic activity of 5,6-dichloroindan-1-carboxylic acid (**13b)** and 5,6-dichloroindan-1-acetic acid (**17e)** was measured by the acetic acid-induced writhing in *Swiss albino* mice [1]. The analgesic activity, exhibited by **13b** with the doses of 50 and 100 mg/kg body weight, appeared to be better than that of the reference compounds, Phenylbutazone, Indomethacin and Aminopyrine (Figure 4), with the doses of 100, 50 and 30 mg/kg body weight, respectively. With the dose of 25 mg/kg body weight, **13b** exhibited almost similar potency to that of Indomethacin. 5,6-Dichloroindan-1-acetic acid (**17e)** at the doses of 50 and 100 mg/kg weight, also showed good therapeutic activity, but was less than that of **13b**. This investigation showed that both compounds (**13b** and **17e**) had good peripheral analgesic activity with the doses of 25, 50 and 100 mg/kg body weight, and thus concluded that introduction of chloro-functionalities at 5- and 6-positions of the indan nucleus could increase the analgesic activity compared to that of mono chloro-substituted nucleus, *e.g.*, 6-chloroindan-1-carboxylic acid (**4c**). At the same time, it was noted that an increase in carbon number, *i.e.*, acetic acid (-CH_2COOH as in **17c**) instead of a carboxylic acid (-COOH in **4c**) functionality, decreased the analgesic potency of the compound.

Ray and Lahiri [42-44] reported the analgesic activity of 5-(indan-1'-yl)-tetrazole (**25a**), 5-(6'-methoxyindan-1'-yl)-tetrazole (**25e**) and 5-(5',6'-dimethoxyindan-1'-yl)-tetrazole (**25f**) in the phenyl-*p*-quinone induced writhing reflex in mice model. All three compounds exhibited

variable analgesic activities with, respectively, 28.2%, 25.3% and 20.7% protection in comparison to reference standard Phenylbutazone (52.2% protection) and Aspirin (60.2% protection). Significant analgesic activity was also observed with other tetrazole derivatives, 5-(indan-1′-yl)-methyltetrazole (**26a**), 5-(6′-methoxyindan-1′-yl)-methyltetrazole (**26e**) and 5-(5′,6′-dimethoxyindan-1′-yl)-methyltetrazole (**26f**) in the phenyl-*p*-quinone induced preliminary test with low ulcerogenecity [44]. The ED_{50} dose for **26e** and **26f** were determined 117 and 166 mg/kg (p.o.), respectively, compared to positive control Phenylbutazone (41 mg/kg) [44]. However, the compounds did not show any response in the hot plate and the tail clip methods. From these studies [26, 27, 42, 43], it could be concluded that the introduction of a methoxy group at 6 or both at 5- and 6-positions of the compounds, as well as an increase of one carbon between the indan nucleus and tetrazole group increases the activity.

The analgesic activity of 5-(5′,6′-dichloroindan-1′-yl)-tetrazole (**25d**) and 5-(5′,6′-dichloroindan-1′-yl)-methyltetrazole (**26d**) was assessed by the acetic acid-induced writhing in Swiss albino mice [1]. The significant ($p < 0.001$) analgesic activity, exhibited by the compound **25d** with the doses of 50 and 100 mg/kg body weight, was better than that of the reference compounds, Phenylbutazone, Indomethacin and Aminopyrine, with the doses of 100, 50 and 30 mg/kg body weight, respectively. The methyltetrazole derivative **26d** also displayed good therapeutic activity at 50 and 100 mg/kg weight, but was less potent than that of **25d**. This finding also suggested that an introduction of a chloro group at both 5- and 6-positions of the indan nucleus could increase the analgesic activity compared to that of mono chloro substitution only at 6-position. At the same time, it could also be inferred that an increase in carbon number between indan nucleus and tetrazole ring i.e., 5-(5′,6′-chloroindan-1′-yl)-methyltetrazole (**26d**), could decrease the analgesic potency of the compound. The structural features of indan acid derivatives that influence the analgesic potency of these compounds can be summarized as follows (Figure 5).



	R	R’	R’’
Fig. 5a	H	H	-$(CH_2)_n$-COOH
Fig. 5b	Cl	H	-$(CH_2)_n$-COOH
Fig. 5c	Cl	Cl	-$(CH_2)_n$-COOH
Fig. 5d	OMe	H	-CH_2-COOH
Fig. 5e	OMe	OMe	-CH_2-COOH
Fig. 5f	OMe	H	-$(CH_2)_n$-tetrazolyl
Fig. 5g	OMe	OMe	-$(CH_2)_n$-tetrazolyl

Figure 5. Summary of structural features of indan acid derivatives that influence the analgesic potency

i. An increase in carbon number on the acid functionality increases the analgesic potency of indan-1-acids (refer to R’’ on Figure 5a). However, indiscriminate chain lengthening may not be beneficial to activity.

ii. For chloroindan-1-acids, an increase in carbon number on the acid decreases the analgesic potency (refer to R’’ on Figure 5b).

iii. An introduction of chloro functionality both at 5- and 6-positions (Figure 5c) of the indan nucleus increases the analgesic activity compared to that of mono chloro substituted nucleus (Figure 5b).

iv. An introduction of a methoxy group at 6 (Figure 5d) or both at 5- and 6-positions (Figure 5e) of indan-1-acetic acid enhances the analgesic activity remarkably.

v. In indanyl tetrazoles, an introduction of a methoxy group at 6 (Figure 5f) or both at 5- and 6-positions (Figure 5g) of the indan nucleus, as well as an increase of one carbon between the indan nucleus (refer to R'' on Figures 5f and 5g) and tetrazole group increases the activity.

The writhing reflex in mice induced by acetic acid and phenylquinone is a sensitive procedure to evaluate the potential analgesic activity of drugs. It has been suggested that acetic acid and phenylquinone act by releasing endogenous mediators, which stimulate the nociceptive neurons in mice. Acetic acid is sensitive to cyclooxygenase inhibitors and has been used to evaluate the effect of analgesic agents, which primarily inhibit the cyclooxygenase involved in prostaglandin synthesis. Acetic acid and phenylquinone are also sensitive to non-steroidal anti-inflammatory drugs (NSAIDs) and to narcotics and other centrally acting drugs. Recently it has been found that the nociceptive activity of acetic acid and phenylqinone may be due to the release of cytokines, such as TNF-α, interleukin-1β and interleukin-8, by resident peritoneal macrophages and mast cells. Based on this, it can be assumed that in the antinociceptive action showed by compounds in the acetic acid and phenylquinone induced writhing test might be due to inhibition of the release of TNF-α, interleukin-1β and interleukin-8, by resident peritoneal macrophages and mast cells. The writhing response observed after the treatment with various indan derivatives was assumed to be mediated through peritoneal mast cell [45], acid sensing ion channels [46] and the prostaglandin pathways [47].

4. ANTI-INH;AMMATPRY ACTIVITY OF INDAN ACID DERIVATIVES, AND THEIR STRUCTURE-ACTIVITY-RELATIONSHIPS

The anti-inflammatory activity of indan-1-carboxylic acids (**4-6, 13a-d**) was evaluated for anti-inflammatory activity in the carrageenan induced rat paw edema model. The reference standards Indomethacin, Aspirin, Diclofenac and Phenylbutazone were used as standard drug and saline as control. Juby *et al.* [5] reported that indan-1-carboxylic acid (**5**) did not possess any significant anti-inflammatory activity. It was observed that 6-chloroindan-1-carboxylic acid (**4c**), 6-bromoindan-1-carboxylic acid (**6c**) [unpublished work of Paul and Bachar] and

5,6-dichloroindan-1-carboxylic acid (**13b**) [1] had statistically significant anti-inflammatory response with respect to inhibiting paw edema in comparison to control in a dose dependent manner. The percent inhibition of edema volume at the dose of 50 mg/kg body weight by the compounds **4c**, **6c** and **13b**, after the third hour of carrageenan administration, was 19.18%, 16.12% and 44.51%, respectively. Slightly better activity was exhibited by the compounds 6-chloroindan-1-acetic acid (**17c**), 6-bromoindan-1-carboxylic acid (**17d**) [unpublished work of Paul and Bachar] and 5,6-dichloroindan-1-acetic acid (**17e**) with percent inhibitions of 19.82%, 18.25% and 34.91%, respectively [1]. It could be suggested from this finding that a substitution at 6-position of the indan ring with a chloro or a bromo functionality could enhance the anti-inflammatory potency of indan acids. Chloro substitution at both 5- and 6-positions, *e.g.,* 5,6-dichloroindan-1-carboxylic acid (**13b**), showed slightly better activity than that of 5,6-dichloroindan-1-acetic acid (**17e**), indicating that increase of carbon length decreases the anti-inflammatory potency of indan acids.

Lahiri and Gupta [22] synthesized 6-methoxy and 5,6-dimethoxy-indan-1-acids (**13d** and **17f**) as potential oral hypoglycemic agents. Later, the anti-inflammatory activity of **13d** and **17f** as well as other indan acids was studied using the doses of 100 and 200 mg/kg body weight in animal model [23, 24]. The activity was compared after the third hour of the study for 200 mg/kg body weight. Among the compounds indan-1-acetic acid (**17a**) displayed better anti-inflammatory potency than that of indan-1-carboxylic acid (**5**). 6-Methoxyindan-1-carboxylic acid (**13c**, 47.32% inhibition) and 5,6-methoxy-indan-1-carboxylic acid (**13d**, 33.65% inhibition) showed less anti-inflammatory activity than 6-methoxyindan-1-acetic acid (**17g**, 51.13% inhibition) and 5,6-dimethoxyindan-1-acetic acid (**17f**, 56.35% inhibition). On the basis of the above findings, further investigations were carried out with **17g** and **17f** in various acute, sub-acute and chronic inflammation models including the carrageenan induced rat paw edema, kaolin-induced rat paw edema, formalin induced rat paw edema, 5-hydroxytryptamine induced edema, cotton-pellet granuloma and adjuvant-induced arthritis [23-25]. Both compounds showed the highest level of activity at the third hour of the study and significant activity of the compounds were observed even at 24 h after the drug administration in comparison to Phenylbutazone. This longer duration of action of those indan acid derivatives might be due to their rapid binding to the plasma protein and subsequent slow release when the unbound acids having high pKa values (6.66 to 6.74) as slowly dissociated to their anions which were expected to be the pharmacophore [49]. From

this finding it was concluded that a methoxy substitution at 5- and 5, 6-positions with one carbon increased between indan ring and tetrazole functional group could be essential for better anti-inflammatory activity.

The anti-inflammatory activity was also studied with the compounds, 3-(indan-1-yl)-propionic acid (**21a**), 3-(6-methoxyindan-1-yl)-propionic acid (**21b**), 3-(5,6-dimethoxyindan-1-yl)-propionic acid (**21c**), 4-(indan-1-yl)-butyric acid (**21d**), 4-(6-methoxyindan-1-yl)-butyric acid (**21e**) and 4-(5,6-dimethoxyindan-1-yl)-butyric acid (**21f**) on the carrageenan induced rat paw edema model along with indan-1-carboxylic acids (Scheme 3) and indan-1-acetic acids (Scheme 4) [1, 15, 26]. It was observed that indiscriminate chain lengthening did not enhance the potency of anti-inflammatory activity, as the activity appeared to reside in a small structural framework. The anti-inflammatory activity was more prominent in indan-1-acetic acids, *e.g.*, indan-1-acetic acid (**17a**, 42.88% inhibition), 6-methoxyindan-1- acetic acid (**17f**, 55.22% inhibition) and 5,6,-dimethoxyindan-1- acetic acid (**17g**, 54.91% inhibition), and indan-1-propionic acids, *e.g.*, indan-1-propionic acid (**21a**, 40.14% inhibition), 3-(6-methoxyindan-1-yl)-propionic acid (**21b**, 54.91% inhibition) and 3-(5,6-dimethoxyindan-1-yl)-propionic acid (**21c**, 57.54% inhibition). The indan-1-carboxylic acids, e.g., indan-1-carboxylic acid (**5**, 28.83% inhibition), 6-methoxyindan-1-carboxylic acid (**13c**, 40.11% inhibition) and 5,6,-dimethoxyindan-1-carboxylic acid (**13d**, 43.56% inhibition), and indan-1-butyric acids, *e.g.*, 4-(indan-1-yl)-butyric acid (**21d**, 30.19% inhibition), 4-(6-methoxyindan-1-yl)-butyric acid (**21e**, 48.12% inhibition) and 4-(5,6-dimethoxyindan-1-yl)-butyric acid (**21f**, 52.18% inhibition), exhibited less activity. This indicated that one carbon separation between the indan ring and the carboxylic acid functionality is probably the optimum feature for anti-inflammatory activity of indan acid; less or more carbon than one seems to reduce the activity. The anti-inflammatory activity in this series could also be potentiated by the incorporation of methoxyl substitutions at 5- and 6-positions of the indan nucleus. It was found that the onset of action of these compounds were relatively slow, compared to that of Phenylbutazone; the anti-inflammatory activity of these compounds reached its peak after 3 h of their oral administration and in some cases was retained even after 24 h.

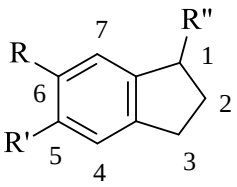
The non-steroidal anti-inflammatory activity of the indan-1-propionic acid derivatives (**21a-c**) were found to be dose dependant, and was comparable to that of Phenylbutazone in the carrageenan induced rat paw edema model [8]. The inhibition of paw oedema appeared to be its maximum level at the third hour of the study. Among these compounds, 3-(6-methoxyindan-1-yl)-propionic acid (**21b**) and 3-(5,6-dimethoxyindan-1-yl)-propionic acid (**13c**) showed better anti-inflammatory activity in the Kaolin induced paw edema and the immunological (granuloma) models [8], indicating the importance of the methoxy substituent(s) on the indan nucleus for this activity. Compounds **21b** and **21c** exhibited better anti-inflammatory potency in the cotton pellet granuloma study, particularly at lower dose levels, than that of Phenylbutazone. They exhibited high LD_{50} values with low ulcerogenecity, specially the compounds **21c** due to its more lipophilic nature.

The anti-inflammatory activity of chloro-and bromo-substituted (indanyl)-tetrazoles, *e.g.,* 5-(6′-chloroindan-1′-yl)-tetrazole (**25b**) and 5-(6′-bromoindan-1′-yl)-tetrazole (**25c**), and (indanyl)-methyltetrazoles, *e.g.,* 5-(6′-chloroindan-1′-yl)-methyltetrazole (**26b**) and 5-(6′-bromoindan-1′-yl)-methyltetrazole (**26c**) was evaluated in the carrageenan-induced rat paw edema model at the dose of 100 mg/kg of body weight [10, 49]. Compounds **26b** (39.98% inhibition) and **26c** (33.06% inhibition) showed better activity than that of **25b** (19.66% inhibition) and **25c** (18.15% inhibition), indicating the significance of one carbon separation between the tetrazole and the indan moieties for better anti-inflammatory profile. The percentage inhibitions produced by compounds were compared with that of the positive control phenylbutazone. Compounds **26b** and **26c** were further studied at the dose of 50 mg/kg, where promising activity was exhibited by **26b,** suggesting that a chloro as opposed to a bromo substitution contributes more to the anti-inflammatory potency of indanyl-tetrazole compounds. Other indanyl-tetrazole derivatives, *e.g.,* 5-(indan-1′-yl)-tetrazole (**25a**) and 5-(6′-methoxyindan-1′-yl)-tetrazole (**25e**) and 5-(5′,6′-dimethoxyindan-1′-yl)-tetrazole (**25f**) were also assessed for anti-inflammatory activity, and at the third hour of study the percent inhibitions caused by these compounds were 28.03%, 6.79% and 12.84%, respectively [42, 43]. Similar studies on the indan-methyltetrazole derivatives, *e.g.,* 5-(indan-1′-yl)-methyltetrazole (**26a**) and 5-(6′-methoxyindan-1′-yl)-methyltetrazole (**26e**) and 5-(5′,6′-dimethoxyindan-1′-yl)-methyltetrazole (**26f**), revealed that **26e** (37.08% inhibition) and **26f** (41.51% inhibition) had more potent activity than that of **26a** (24.35% inhibition) [26, 27].

The compounds showed dose dependent activity in both the carrageenan induced oedema and the adjuvant-arthritis test models.

Roy and Lahiri [44] further studied the anti-inflammatory, analgesic, anti-pyretic activities, gastric ulcerogenicity and acute lethal toxicity of 5-(6′-methoxyindan-1′-yl)-methyltetrazole (**26e**) and 5-(5′,6′-dimethoxyindan-1′-yl)-methyltetrazole (**26f**). It was observed that the ED_{50} values of **26e** in the adjuvant arthritis and the cotton pellet granuloma models were almost similar to that of Phenylbutazone. Pal *et al.* [1] synthesized 5-(5′,6′-dichloroindan-1′-yl)-tetrazole (**25d**) and 5-(5′,6′-dichloroindan-1′-yl)-methyltetrazole (**26d**) and evaluated the anti-inflammatory activity in the carrageenan induced rat paw edema model with the doses of 25 and 50 mg/kg body weight. A significant ($p < 0.001$) anti-inflammatory activity was observed with **25d** at the dose of 50 mg/kg body weight, and was comparable to that of reference standard Phenylbutazone (dose of 100 mg/kg body weight) after 3 h of carrageenan administration. Compound **26d** with the doses of 25 and 50 mg/kg body weight also displayed almost similar anti-inflammatory activity as that of Phenylbutazone in 1, 2 and 3 h after carrageenan administration. It was concluded that the introduction of a chloro substituent both at 5- and 6-positions of the indan nucleus could increase the anti-inflammatory activity more than just one chloro substitution at 6-position.

The structural features of indan acid derivatives that influence the anti-inflammatory potency of these compounds can be summarized as follows (Figure 6).



	R	R’	R’’
Fig. 6a	Cl or Br	H	- COOH
Fig. 6b	Cl or Br	Cl or Br	- COOH
Fig. 6c	Cl or Br	H	$-(CH_2)_n$-COOH
Fig. 6d	OMe	H	$-(CH_2)_n$-COOH
Fig. 6e	OMe	H	$-CH_2$ -tetrazolyl
Fig. 6f	OMe	OMe	$-CH_2$ -tetrazolyl

Figure 6. Summary of structural features of indan acid derivatives that influence the anti-inflammatory potency

i. Halogenation on the indan nucleus of indan-1-carboxylic acid offers increased anti-inflammatory potency, *e.g.*, a substitution at 6-position of the indan ring with a chloro or a bromo functionality enhances the anti-inflammatory potency of indan acids (Figure 6a).

ii. Halogenation at both 5- and 6-positions of the indan nucleus slightly increases potency (Figure 6b).

iii. In haloindan-1-acids (Figure 6c), an increase of carbon length (refer to R’’ on Figure 6c) decreases the anti-inflammatory potency.

iv. In methoxyindan-1-acids (Figure 6d), an increase of carbon length (refer to R’’ on Figure 6d) increases the anti-inflammatory potency.

v. Methoxy substitution at 5- (Figure 6e) and 5, 6-positions (Figure 6f) with one carbon increased between indan ring and tetrazole functional group (refer to R'' on Figures 6e and 6f) is essential for better anti-inflammatory activity.

vi. One carbon separation between the tetrazole and the indan moieties is essential for better anti-inflammatory profile (refer to R'' on Figures 6e and 6f).

5. CONCLUSIONS

Various synthetic protocols for the synthesis of bromo-, chloro-, fluoro- and methoxy-derivatives of indan-1-carboxylic, indan-1-acetic, indan-1-propionic and indan-1-butyric acids, as well as of indanyl-tetrazole and indanyl-methyltetrazole have been reported to date. The analgesic and anti-inflammatory properties of these derivatives have been studied *in vivo*, mainly using various rat models. From those studies, some patterns of structure-activity-relationships, *e.g.*, the importance of the substituents on the indan nucleus or the carbon length of acids, related to analgesic and anti-inflammatory properties have begun to emerge. However, there is no report on any *in vitro* mechanistic studies involving various enzymes, *e.g.*, COX-1 and COX-2, available to date, and thus, much work is probably needed in this area to have a clear understanding about the mechanism of action of these indan-based promising analgesic and anti-inflammatory compounds.

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