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

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

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

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

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

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

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

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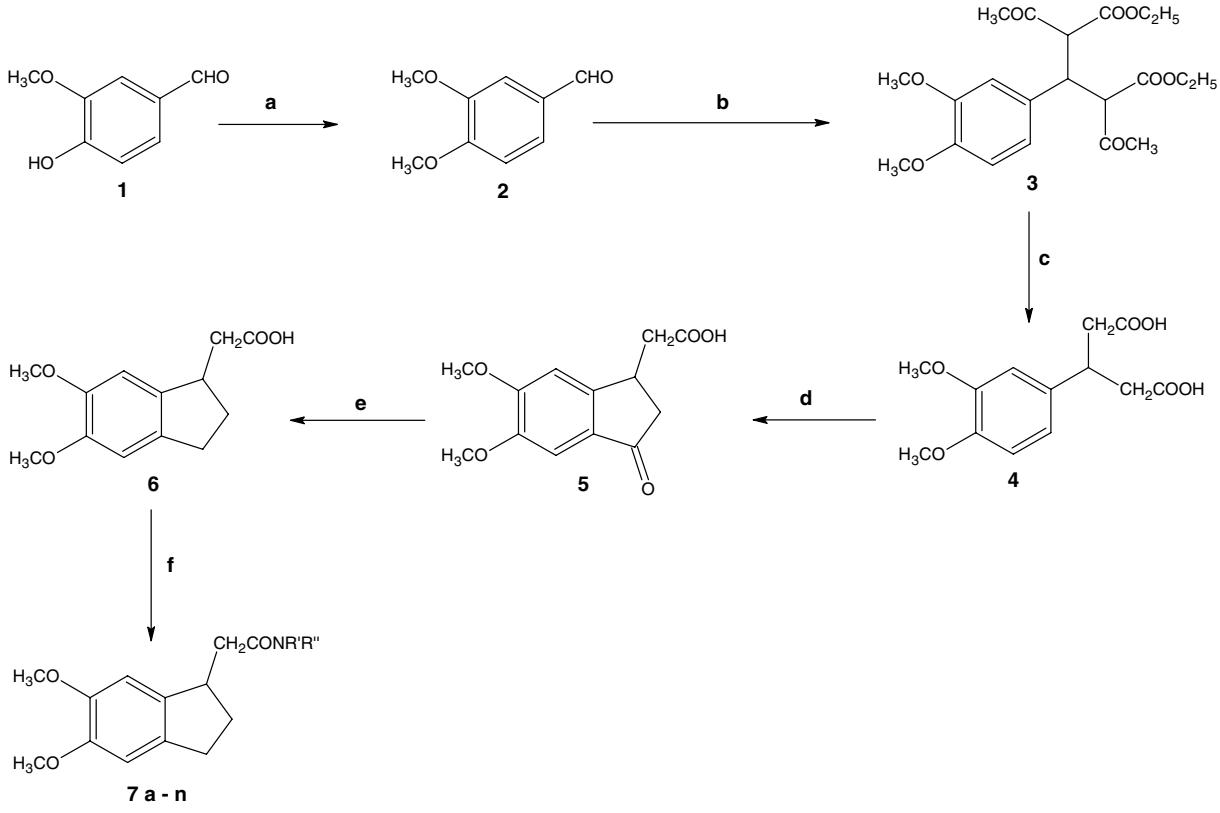
veratraldehyde[22] **(2)**. Veratraldehyde was reacted with two moles of ethylacetoacetate (EAA) in the presence of catalytic amount of piperidine at room temperature; as a result the aldehydic group of **2** was converted into bisacetoacetate **(3)**. Acidic hydrolysis of **3** was carried out with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

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



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