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Synthesis and Pharmacological Evaluation of Some Indanone-3-acetic acid Derivatives

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Synthesis of a series of nine compounds of the class indanone-3-acetic acid derivatives was undertaken with compounds containing indane ring moiety which itself is well known as a potential carrier for inducing biological activity in organic molecules. In fact, indane derivatives are known to have a wide spectrum of biological activity such as analgesic, antiinflammatory, monoamino oxidase inhibitory, antidepressant, antibacterial activity etc. In the present work, nine indanone-3-acetic acid derivatives were prepared in the laboratory by the steps: conversion of 3-hydroxy-4-methoxy benzaldehyde to a bis(acetoacetate), hydrolysis of the bis(acetoacetate) to yield the corresponding β-phenylglutaric acid and cyclization to indanone-3-acetic acid. Condensation of different amines was effected *via* acid chloride formation by refluxation with thionyl chloride followed by treatment with appropriate amines for different optimum periods in benzene. Elemental analysis and IR, NMR data characterized the synthesized compounds. All the synthesized compounds were allowed to undergo antiinflammatory activity by carrageenan induced hind paw method. Some of the compounds showed appreciable activity.

Key Words: Synthesis, Antiinflammatory agent, Indanone-3-acetic acid.

INTRODUCTION

Indane is one such molecular framework, which acts as an inert carrier and holds the biologically active moieties in a stereospecific manner and thus imparts a greater specificity for biological activity[1–3]. These compounds are reported to have a wide spectrum of biological activity such as analgesic, antiinflammatory, monoamine oxidase inhibitory, antidepressant, hypertensive, antibacterial, etc. The present work encompasses the synthesis of certain indanone-3-acetic acid *via* β-phenylglutaric acid preparation. Here, β-phenylglutaric acid was prepared in

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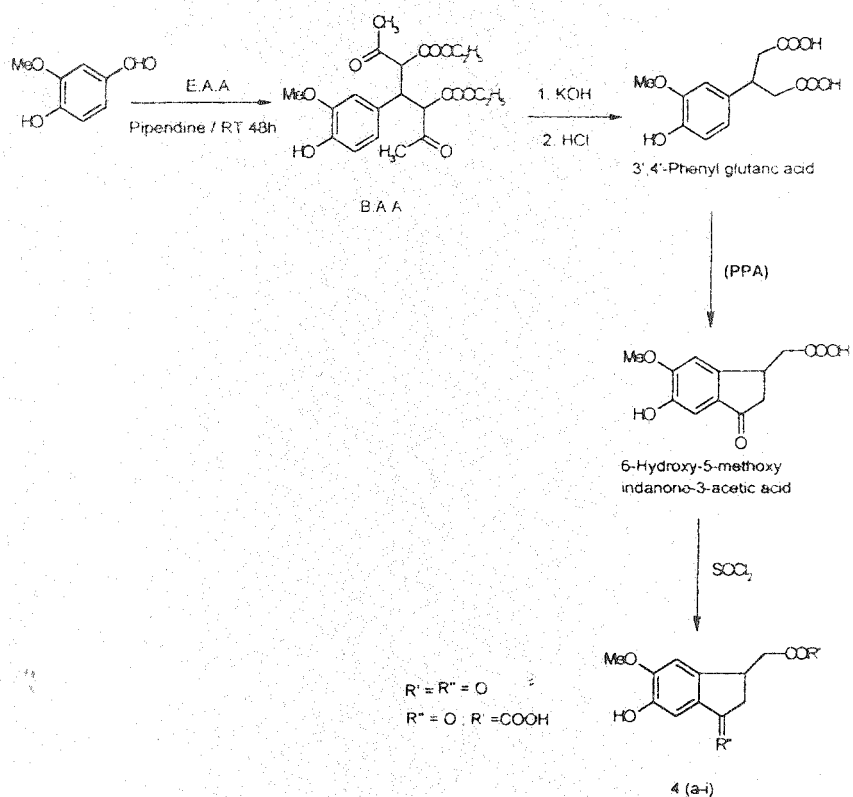
the laboratory, using 3-hydroxy-4-methoxy benzaldehyde in presence of ethylacetoacetate and piperidine to yield a bis(acetoacetate) first; hydrolysis of the bis(acetoacetate) yielded β-phenylglutaric acid. The former was then converted to 3-acetyl substituted-6-hydroxy-5-methoxyindane-3-acetic acid followed by condensation with different amines *via* acid chloride intermediate by refluxation with thionyl chloride for different optimum periods in benzene[4]. The structures of the compounds were characterized by elemental analysis, IR and NMR spectral data[5]. The nine synthesized compounds were allowed to undergo antiinflammatory activity by carrageenan induced hind paw method[6]. Some of the compounds showed appreciable activity.

EXPERIMENTAL

The melting points of synthesized compounds were taken in open capillary tubes on a Gallenkamp-5 melting point apparatus and are uncorrected. The IR spectra were recorded in the 4000–400 cm^{-1} range using KBr disks on a Perkin-Elmer 297 spectrophotometer. The ^1H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer in $CDCl_3$.



Scheme-1

Synthesis of some carboxy indanones and their oximes

For the synthesis of this series of compounds **(Scheme-1),** indanone-3-acetic acid was prepared in the laboratory using a three step reaction: (i) conversion of 3-hydroxy-4-methoxy benzaldehyde to a bis(acetoacetate) (BAA), (ii) hydrolysis of the BAA to yield the aryl substituted dicarboxylic acid (DCA) and (iii) cyclization of DCA to indanone-3-acetic acid. All other reagents used in this scheme, namely, amine compounds, inorganic compounds like potassium hydroxide, mineral acids, etc. were obtained from commercial sources. Polyphosphoric acid (PPA) was also prepared in the laboratory by mixing equal amounts of phosphorous pentoxide and syrupy phosphoric acid by weight, shaking vigorously, then keeping the mixture on a boiling water bath for 3 h with occasional shaking.

(a) Preparation of bis(acetocetate): 1 mol of 4-hydroxy-3-methoxy benzaldehyde (152 g) (m.p. 81–83°C) was reacted with 260 g, *i.e.*, 2 mol of ethylacetoacetate (b.p. 181°C, d. 1.021) in presence of piperidine at room temperature for 48 h with occasional shaking. The resulting yellow crystalline solid (bisacetoacetate) was broken into small pieces, crushed and then washed with solvent ether. This crude bis(acetoacetate) was crystallized from benzene to yield 440 g of pure product; m.p. 145°C.

(b) Preparation of β-phenylglutaric acid: The pure bis(acetoacetate) (100 g) was mixed with an aqueous solution of potassium hydroxide (50 g in 1000 mL). The mixture was stirred for 1/2 h at room temperature. The resulting red coloured solution was acidified with concentrated hydrochloric acid to give the crude acid. It was filtered under suction, washed with a little volume of cold water and recrystallized from hot water to yield 70 g of pure product; m.p. 108°C.

1-Indanone-3-acetic acid

To 40 g of β-phenylglutaric acid, 400 g of polyphosphoric acid (PPA) was added in 1 : 10 ratio and the combined mixture was heated over a wire gauze and a Bunsen burner at 120°C for 10 min with occasional shaking. It was then cooled and poured slowly with constant stirring on crushed ice to yield the required cyclized product (1-indanone-3-acetic acid). The crude product was extracted with chloroform and washed thoroughly with cold water to remove acid. The chloroform extract was dried over anhydrous sodium sulphate and then distilled; yield 38 g; m.p. 52°C. Some minor procedural differences in the manipulations during working up of the individual compounds were done.

15 g of 1-indanone-3-acetic acid were taken in an RB flask and 50 mL of benzene was added to it. Then after the addition of a solvent of thionyl chloride in benzene to this mixture, it was heated to boiling and refluxed for 30 min. The reaction mixture was allowed to cool. Benzene layer was distilled until the temperature reached about 100°C and the resulted yellow liquid was distilled under vacuum at 150–160°C at 20 mm Hg; yield 88%.

(a) 3-Acetylamino (3′-nitrophenyl)-6-hydroxy-5-methoxy indane-3-acetic acid: 10 g of benzene mixture were taken in an RB flask and 6 g of *m*-nitro aniline were added slowly; everything passed into the solution. The reaction mixture was allowed to stand overnight at room temperature. The crude product was filtered, washed with a little benzene; yield 72%; m.p. 122°C.

(b) 3-Acetylamino (3′-phenyl)-6-hydroxy-5 methoxy indane-3-acetic acid: 10 g of benzene mixture were taken in an RB flask and 6 g of aniline were added slowly; everything passed into the solution. The reaction mixture was allowed to stand overnight at room temperature. The crude product was filtered and washed with a little benzene; yield 57%; m.p. 102°C.

(c) 3-Acetylamino-methyl (phenyl)-6-hydroxy-5-methoxy indane-3-acetic acid: 10 g of benzene mixture were taken in an RB flask and 6 g of benzylamine were added slowly; everything passed into the solution. The reaction mixture was allowed to stand overnight at room temperature. The crude product was filtered and washed with a little benzene; yield 64%; m.p. 94°C.

(d) 3-Acetyl morpholine-6-hydroxy-5 methoxy indane-3-acetic acid: 10 g of benzene mixture were taken in an RB flask and 6 g of morpholine were added slowly; everything passed into the solution. The reaction mixture was allowed to stand overnight at room temperature. The crude product was filtered and washed with a little benzene; yield 67%; m.p. 131°C.

(e) 3-Acetylamino-6-hydroxy-5-methoxy indane-3-acetic acid: 10 g of benzene mixture were taken in an RB flask and 6 g of ammonia were added slowly; everything passed into the solution. The reaction mixture was allowed to stand overnight at room temperature. The crude product was filtered and washed with a little benzene; yield 77%; m.p. 117°C.

(f) 3-Acetyl piperidine-6-hydroxy-5-methoxy indane-3-acetic acid: 10 g of benzene mixture were taken in an RB flask and 6 g of piperidine were added slowly; everything passed into the solution. The reaction mixture was allowed to stand overnight at room temperature. The crude product was filtered and washed with a little benzene; yield 52%; m.p. 127°C.

(g) 1-Hydroxylamino-6-hydroxy-5-methoxy indane-3-acetic acid: 1 g of hydroxylamine hydrochloride, 2 g of crystallized sodium acetate, 0.5 g 1-indanone-3-acetic acid were dissolved in 10 mL of water. The combined mixture was refluxed for 3 h with occasional shaking on an oil bath at 110°C. It was then cooled and poured slowly with constant stirring on crushed ice to yield the required oxime, washed thoroughly with cold water and recrystallized from ethanol; yield 80%; m.p. 121°C.

(h) 1-N-Hydrazino-(2′,4′-dinitrophenyl)-6-hydroxy-5-methoxy indane-3-acetic acid: 0.25 g of 2,4-dinitrophenylhydrazine was suspended in 5 mL of methanol and 0.5 mL of concentrated sulphuric acid was added cautiously. The warm solution was filtered and a solution of 0.1 g of the 1-indanone-3-acetic acid in a small volume of methanol was added and was heated just to boiling. It was

allowed to cool to room temperature; the crude product was filtered at the pump, and recrystallized from dilute ethanol; yield 73%; m.p. 138°C.

(i) 1-Semicarbazo-6-hydroxy-5-methoxy indane-3-acetic acid: 2 g semicarbazide hydrochloride and 3 g crystallized sodium acetate were dissolved in 20 mL of water; 1 g of 1-indanone-3-acetic acid was added and shaken[5]. The mixture was turbid, so alcohol was added and a clear solution was obtained. The mixture was shaken for 5 min and allowed to stand overnight; the crystals was filtered off, washed with a little cold water and recrystallized from benzene; yield 70%; m.p. 161°C.

Antiinflammatory activity

In recent years, there has been a great interest to develop new non-steroidal antiinflammatory drugs (NSAIDs) which could specifically inhibit cyclooxygenase-2 (COX-2), the enzyme responsible for the production of prostaglandins and other mediators which are directly associated with inflammation process. Some selective inhibitors for COX-2 have already been found[6–9] and the research in this direction continues with a view to discover new drugs for inhibiting this enzyme. The aim is to have drugs with better efficacy, less toxicity and fewer side effects.

Experimental determination of antiinflammatory activity

All compounds were evaluated for their anti-inflammatory activity following the procedure developed by Levy[10]. The inflammation was introduced by administering (0.1%) carrageenin in aqueous saline (0.9% NaCl) solution on the hind paws of the white male Swiss albino mice of species *Mus muscullus*, having approximate weight of 30.00 g each. After 30 min, the synthesized compounds were administered intraperitoneally in one dose of 250 mg/kg of the animal's weight to one group of five animals. Simultaneously, for positive and negative controls, acetyl salicylic acid and vegetable oil were injected intraperitoneally. The animals were sacrificed 4 h after drug administration and the antiinflammatory activity determined by amputation of the hind paws of the region, which were weighed and the difference was obtained from the control groups.

RESULTS AND DISCUSSION

Preliminary antiinflammatory and toxicity tests of indanone-3-acetic acid derivatives (4a–i)

Preliminary antiinflammatory activity tests have been performed for compounds **4a–i**. All of them except compounds **4e, g, h** and **i** exhibited antiinflammatory properties when compared with acetylsalicylic acid. Indanones **4a** and **4f** were 50% less effective than aspirin while **4b** and **4d** were *ca.* 70% less effective. Compound **4c** gave significant results and is comparable with aspirin (Table-1).

A comparative analysis of the antiinflammatory test results of compounds **4a–d, f** and aspirin is shown in Fig. 1.

The acute toxicity test in mice produced an interesting phenomenon. The animals demonstrated a sign of nervous system excitation (piloerection, cardiac acceleration, psychomotor agitation with repeated shivering), and soon after a light sedation. These phenomena were exacerbated with the gradual increase in dose administration. Meanwhile, no animal of any group died after 48 h with the dose tested (125–1000 mg/kg of body weight) except in the case of **4e, g, h** and **i** where more than 50% of the animals died (Table-2).

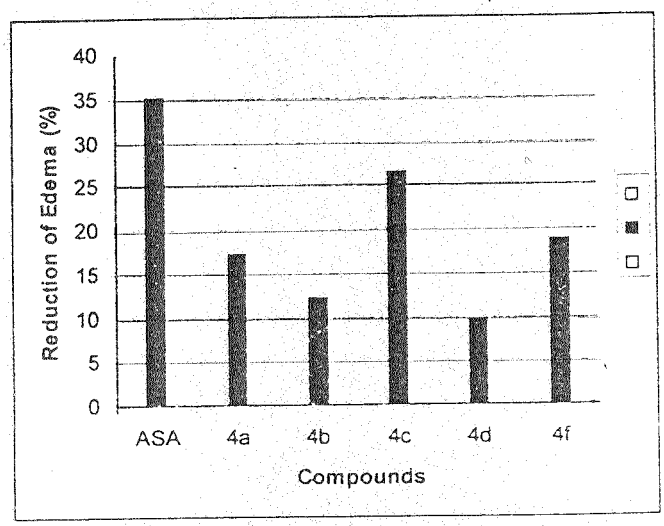


Fig. 1. Comparative analyses of the antiinflammatory activity of compounds **4a–d, f** and acetyl salicylic acid (ASA).

TABLE-1
ANTIINFLAMMATORY TEST RESULTS OF COMPOUNDS **4a–d, f** AND ACETYLSALICYLIC ACID (ASPIRIN)[a]

Compound	Average deference in paw weights (g) (standard deviation)	Edema reduction (%)
ASA	0.06392–0.00449	35.17
4a	0.08160–0.00609	17.24
4b	0.08666–0.01096	12.17
4c	0.07240–0.00427	26.57
4d	0.08516–0.00874	9.73
4f	0.08008–0.00827	18.78

[a]Compounds **4e, g, h** and **i** did not show any antiinflammatory activity.

TABLE-2
ACUTE TOXICITY TEST RESULTS OF COMPOUNDS **4a–i**

Compound	Dose (mg/kg)	Number of dead/batch. after 72 h	DL-50
4a	125	0/5	
	250	0/5	
	500	0/5	not found
	1000	0/5	
4b	125	0/5	
	250	0/5	
	500	0/5	not found
	1000	0/5	
4c	125	0/5	
	250	0/5	
	500	0/5	not found
	1000	0/5	
4d	125	0/5	
	250	0/5	
	500	0/5	not found
	1000	0/5	
4e	125	4/5	
	250	4/5	
	500	5/5	—
	1000	5/5	
4f	125	0/5	
	250	0/5	
	500	0/5	not found
	1000	0/5	
4g	125	3/5	
	250	3/5	
	500	4/5	
	1000	5/5	—
4h	125	2/5	
	250	3/5	
	500	5/5	
	1000	5/5	—
4i	125	2/5	
	250	3/5	
	500	5/5	
	1000	5/5	—

DL-50: lethal dose for 50% of the animals.

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