INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

SYNTHESIS AND ANTI INFLAMMATORY ACTIVITY OF SOME NEW PRENYLATED 5, 7-DIHYDROXY FLAVONOID ANALOGS

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ABSTRACT

5,7-dihydroxy-2[2-(3-methylbut-2-en-1-yl)phenyl]-2,3-dihydro-4*H*-1-benzopyran-4-onewere prepared with different chloro phenyl acetic acid under mild conditions to give corresponding prenylated flavones, the title compounds in good yields. Lead compound synthesized were characterized by physical (R_f values, Melting point, Molecular weight, Molecular formula) and spectral data (^{1}H NMR, IR, Mass spectra). In carageenan induced paw edema compounds 4,7,10 significantly inhibited the edema in a dose dependent manner. The paw volume in rats pretreated with lower dose of compounds 4,7,10 (100 mg/kg/day), higher dose of compounds 4,7,10 (200 mg/kg/day) and indomethacin (10 mg/kg/day) at 2nd hr were found to be 0.191 ± 0.0061 ml, 0.158 ± 0.0042** ml and 0.1369 ± 0.0054** ml.

Key Words: prenylated 5,7-dihydroxy flavonoid, anti inflammatory activity.

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INTRODUCTION

On the account of the reported anti inflammatory agents of prenylated flavones, a new series of prenylated flavones derivatives were synthesized and tested for in-vivo anti inflammatory agents[1]. Prenylated flavones derivatives have attracted the attention of numerous researchers over many years due to their important biological activities. The structural similarity of prenylated flavones with many luteolin[2] have made them a prime target forscientific research and in this context several reports dealing with the synthesis of these fused heterocyclic compounds Have appeared in the literature[2]. An array of biological activities such anti diabetic, antibacterial, antifungal[3,4] antiphlogistic, antitumor[5], anti inflammatory agents, and Herbicidal has been reported to be shown by various flavones. It has been proved that these flavones compounds are effective as inhibitors of inflammatory mediators in intact cells[6], M. tuberculosis[7]and humanenterovirus[8]. They also show inhibitory activity towards both tubulin polymerization, cyclin-dependent kinase [9]and enzymatic assays on Src and Abl tyrosine kinases. Prompted by these claims and in continuing our synthetic studies on bioactive flavones, we have now synthesized a new series of some novel5,7-dihydroxy-2[2-(3-methylbut-2-en-1-yl)phenyl]-2,3-dihydro-4*H*-1-benzopyran-4-oneto test their ability as anti inflammatory agents.

MATERIALS AND METHODS

Synthesis of 1-(2-chlorophenyl)-5,7-dihydroxy-2,3-dihydro-4*H*-1-benzopyran-4-one(3)

Compound 2 was taken in round bottomed flask to which pyridine (30ml) was added and HCL 0.5ml was added drop by drop as catalyst and then refluxed for two hours. Then the reaction mixture was quenched in to solid ice and then obtained solid crystals are filtered and washed with petroleum ether and stored (Fig-1).

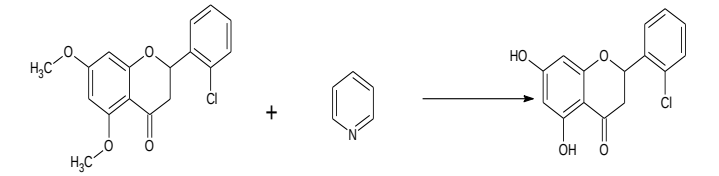


Fig-1 Syntheis of 1-(2-chlorophenyl)-5,7-dihydroxy-2,3-dihydro-4*H*-1-benzopyran-4-one(3)

Synthesis of 5,7-dihydroxy-2[2-(3-methylbut-2-en-1-yl)phenyl]-2,3-dihydro-4*H*-1-benzopyran-4-one(4) :

Compound 3 was taken in a beaker and dissolved in ethanol and stirred at room temperature for 8 hours and then mixture was transferred in to round bottomed flask and boiled for 3 hours and cooled to room temperature excess ethanol was distilled of under reduced pressure. Obtained crude was transferred in to ice cold water then crystals where extracted by ethyl acetate and recrystallised by ethanol (Fig-2).

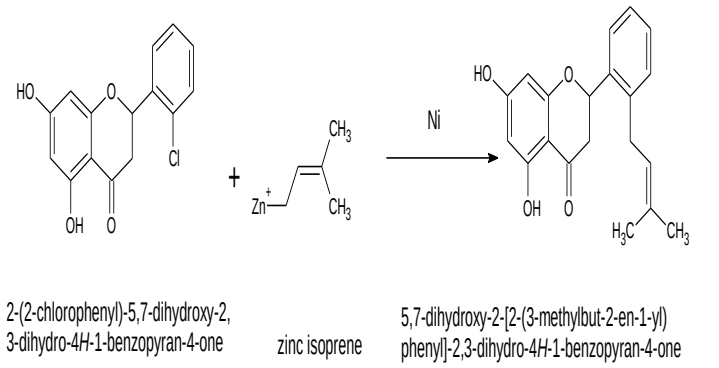


Fig-2 Synthesis of 5,7-dihydroxy-2[2-(3-methylbut-2-en-1-yl)phenyl]-2,3-dihydro-4*H*-1-benzopyran-4-one

Anti-inflammatory activity

Experimental Animals and Housing of Animals

Albino Wistar rats weighing 150 ± 25 g of either sex were used for the study in different models. The animals were procured from National institute of Nutrition (hyderabad) at least 2 weeks prior to the study, so that animals could acclimatize to the new environment. Animals kept in well-maintained room under standard hygienic conditions. Commercial pellet diet and water were made available *ad libitum*. They were housed in propylene cages (32 x 24 x 16 cm) with stainless steel grill top,

Selection of Doses and Preparation of Drug for Study

Since the lethal dose was found at 2000mg/kg body weight, the $1/10^{th}$ of the preceeding dose i.e 100mg/kg body weight was taken as the testing dose for this study and the double of the dose i.e 200mg/kg body weight also tested to find out was there any dose dependent pharmacological effect or not.

Screenings of anti-inflammatory activity

Albino Wistar rats weighing between 150-200gms were divided into 5 groups of 6 rats each; three animals being housed in labeled cage each. Animals were given a period of time to adjust to the new environment provided with food & water ad libitum

Group I: Animals were administered 0.1ml saline p.o; Group II: Animals were administered 0.1ml saline p.o; Group III: Animals were administered standard (Indomethacin 10 mg/kg) p.o; Group IV: Animals were administered *drug sample of compound 1,2,3,4.* (100 mg/kg) p.o; Group V: Animals were administered *drug sample of compound 1,2,3,4* (200 mg/kg dose) p.o

All rats of II, III, IV & V (except I group) groups were injected with 0.1ml of carageenan (1%) in normal saline into sub planter area of right hind paw. All the drugs were given orally 1hr prior to carageenan injection. Paw volume was measured by mercury plethysmograph at 0, 1, 2, 3, 6, hrs after the carageenan injection.

RESULTS AND DISCUSSION

The synthesis of 5,7-dihydroxy-2[2-(3-methylbut-2-en-1-yl)phenyl]-2,3-dihydro-4*H*-1-benzopyran-4-one were synthesized using the appropriate synthetic procedures.

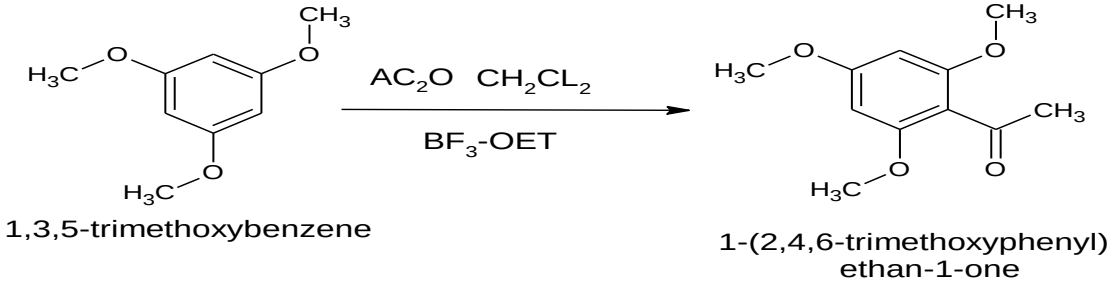


Fig-3 Synthesis of 1-(2,4,6-trimethoxyphenyl)ethan-1-one

The reactants 1,3,5-trimethoxybenzene, borontrifluride diethyl etherate and acetic anhydride were taken and stirred at room temperature for 6 hours then refluxed for 50min. The excess solvent was distilled off at negative pressure and finally, crushed ice was added and extracted by ethyl acetate and concentrated and washed 10% sodium bicarbonate and dried over megnisium sulphate product to give the yield of 85.75%. Acetic anhydride extracts proton from 1,3,5 trimethoxy benzene which in turn attacks ketone group on to the moiety. This results in liberation of 1-(2,4,6,-trimethoxyphenyl)ethan-1-one (Fig-3).

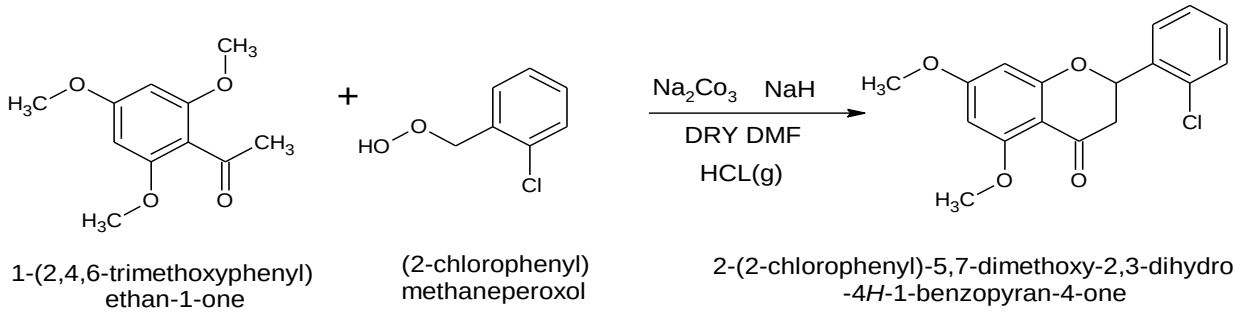


Fig-4 Synthesis of 1-(2-chlorophenyl)-5,7-dimethoxy-2,3-dihydro-4*H*-1-benzopyran -4-one

The product (Fig-4) of step 1 (1-(2,4,6-trimrthoxyphenyl)ethan-1-one is reacted with (2-chlorophenyl)methane peroxol in dimethyl foramide as the solvent and cooled for 0^oc by using ice and salt and acetone mixture in which dry hydrochloride gas was passed through it which is readily prepared by reacting hydrochloric acid and sulphuric acid evolves hydrochloric acid gas. The reaction was continued for 3 hours and stored in ice chest for two days the solid precipitate was extracted by ether and distilled under reduced pressure and the product was obtained with an yield of 75.65% . The reaction under goes Friedal Crafts coupling reaction and cyclises the flavone ring.

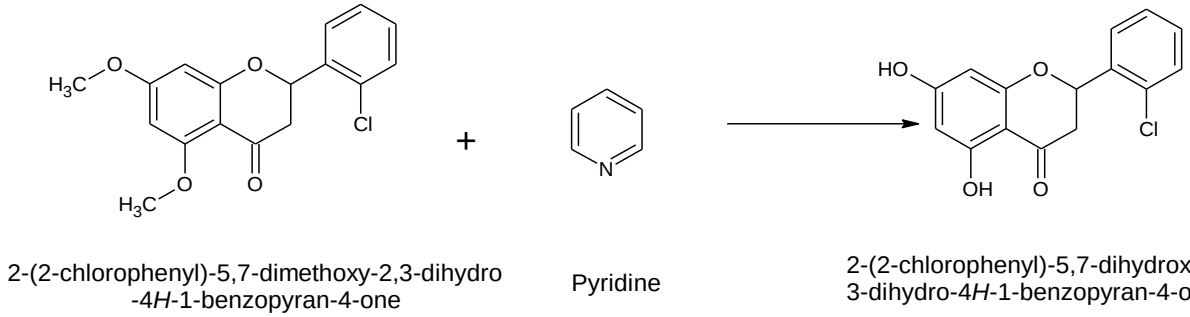
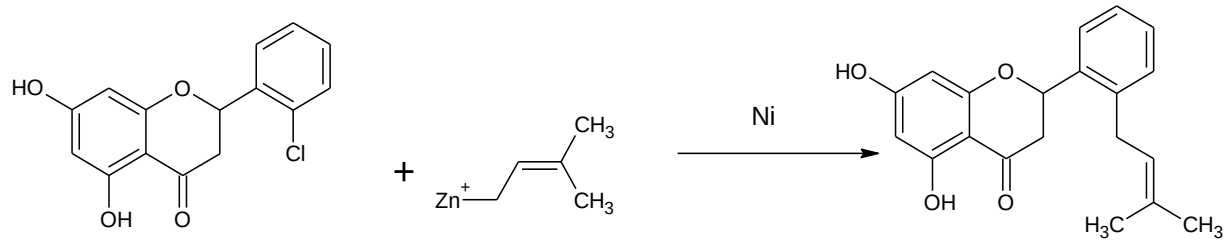


Fig- 5 Synthesis of 1-(2-chlorophenyl)-5,7-dihydroxy-2,3-dihydro-4*H*-1-benzopyran-4-one

The product (Fig-5) of step 2 was dissolve in pyridine solution and Hydrochloric Acid was added as catalyst which under goes reduction reactions and eliminates methyl groups from the terminal methoxy groups of the molecules then the required flavones being obtained .with an yield of 86.65%



2-(2-chlorophenyl)-5,7-dihydroxy-2, 3-dihydro-4*H*-1-benzopyran-4-one

zinc isoprene

5,7-dihydroxy-2-[2-(3-methylbut-2-en-1-yl) phenyl]-2,3-dihydro-4*H*-1-benzopyran-4-one

Fig- 6 synthesis of 5,7-dihydroxy-2[2-(3-methylbut-2-en-1-yl)phenyl]-2,3-dihydro-4*H*-1-benzopyran-4-one

The product of step 3 flavone was reacted with zinc isoprene unit under mild conditions which under goes coupling reaction with the flavones and gives the product 4 Which is the targeted prenylated flavonoid moiety, with a yield of 56.65% The above reaction are repeated with changes in the reagent in the step 2 which yields flavones with halogens at different positions of the phenyl ring substituted at 1 postion of the flavones and the remaining procedures are repeated and derivatives of prenylated derivatives of flavones.

ANTIINFLAMATORY ACTIVITY

Carageenan induced paw edema in rats

In carageenan induced paw edema compounds 4,7,10 significantly inhibited the edema in a dose dependent manner as shown in below table-1. The paw volume in normal control group rats on 2nd hr was found to be 0.2148 ± 0.0122ml. The paw volume in rats pretreated with lower dose of compounds 4,7,10 (100 mg/kg/day), higher dose of compounds 4,7,10 (200 mg/kg/day) and indomethacin (10 mg/kg/day) at 2nd hr were found to be 0.191 ± 0.0061 ml, 0.158 ± 0.0042** ml and 0.1369 ± 0.0054** ml

Table-1 Anti-inflammatory effect of *compounds 1-5* on carageenan induced paw edema in rats

Treatment	Paw volume in ml at different Hrs (Mean ± S.E.M.)				
	0	1	2	3	6
Normal Control	0.101± 0.0058	0.101± 0.0058	0.101± 0.0058	0.101± 0.0058	0.101± 0.0058
Inflammatory controlControl	0.1225± 0.0079^{+++}	0.1876± 0.007^{+++}	0.2148± 0.0122^{+++}	0.2083± 0.0094^{+++}	0.165 ± 0.0076^{+++}
Indomethacin 10mg/kg, p.o.	0.1249 ± 0.0061	0.1427± 0.0071**	0.1369*± 0.0054**	0.1442± 0.007**	0.1449 ± 0.0060
Compound1 (100mg/kg)	0.1210 ± 0.0186	0.152 ± 0.008	0.191 ± 0.0061	0.196 ± 0.006	0.159 ± 0.009*
Compound2 (200mg/kg)	0.1016 ± 0.0070	0.132± 0.0057**	0.158 ± 0.0042**	0.1542 ± 0.0071**	0.1542 ± 0.0136

Values are expressed as (Mean±S.E.M) n=6; One way ANOVA followed by Dunnet's test.
+++ P<0.001 Vs Normal control & ** P< 0.01 Vs Inflammatory Control

The development of edema in the paw of the rat after injection of carageenan is a biphasic event. The initial phase of the edema has been attributed to the release of histamine and serotonin, the edema maintained during the plateau phase to kinin like substances and the second accelerating phase of swelling to the release of prostaglandin like substances. Inhibition of edema observed in various inflammatory models induced experimentally in the present study may, therefore be attributed to the ability of the compound 1 to inhibit various chemical mediators of inflammation like histamine and 5-HT during the initial phase.

CONCLUSION

5,7-dihydroxy-2[2-(3-methylbut-2-en-1-yl)phenyl]-2,3-dihydro-4*H*-1-benzopyran-4-onewere prepared with different chloro phenyl acetic acidunder mild conditions to give corresponding prenylated flavones, the title compounds in good yields. A facile method under mild conditions has been developed for the synthesis of the title compounds. Lead compound synthesized were characterized by physical (R_f values, Melting point, Molecular weight, Molecular formula) and spectral data (^{1}H NMR, IR, Mass spectra). The title compounds were screened for antinflammatory activity. The obtained antinflammatory activity results were analyzed statistically. All compounds showed similar antinflammatory activity. This acts as a lead for further optimization.

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