SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF SOME NEW 2-(SUBSTITUTED PHENYL)-4H-CHROMEN-4-ONE DERIVATIVES

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ABSTRACT

A new series of some new 2-(substituted phenyl)-4H-chromen-4-one derivatives were synthesized. The structures of these synthesized compounds were confirmed by IR, NMR and CHN analysis. All the values and results of these spectral and elemental analysis are found to be in the normal range. These compounds are subjected to anti-inflammatory activities by carragennan induced paw edema method, using diclofenac sodium as a standard drug. Most of these compounds have shown excellent anti-inflammatory activities.

Key words: Chromone derivatives, Anti-inflammatory activity, CHN analysis.

1.INTRODUCTION

A number of natural and synthetic benzopyrone derivatives have been reported to exert notably antimicrobial, antitubercular and anti fungal activity (Albert J Chullia, 1995; Gournelis,1995; Ramesh,1995;). Benzopyrone having chromone (γ -Benzopyrone) moieties are associated with interesting physiological activities such as anti microbial, anti tubercular, anti inflammatory, anti diabetic, antiviral,anticancer etc.(Amzad,2001;Basu,2002; Jehan,1998; Khan,1993; Liu, 1991; Notel, 2005; Satyanarayan, 1991;Vinay,2003; Ye-Shi Li,1990.)

In view of these observations and our interest in the synthesis of biologically active bi heterocycles possessing chromone nucleus, we have modified 5-amino-6-hydroxy-2-phenyl-4H-Chromen-4-one (V) by reacting it with thiourea to yield 2-amino-7-phenyl chromen (5,6-d) imidazol-9 (3H)-one A_1 for its versatile biological activity. Compound V was treated with urea to yield 7-phenyl-1H-Chromeno (5,6-d) oxazole-2, 9-dione A_2. Compound V was treated with chloroacetyl chloride to get 8-phenyl chromeno (6,5-b) (1,4) oxazine-2, 10 (1H, 3H)-dione A_3. Compound V was treated with substituted aldehydes to yield 2-(4-substituted phenyl)-7-phenyl-9H-chromeno (5,6) oxazol-9-one A_4 and A_5 to explore activities associated with this nucleus and screened them for anti-inflammatory activity. The unique structure of compound V has facilitated for getting compound A_1 to A_5, which would possess the promising anti-inflammatory activity.

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2.MATERIALS AND METHODS

EXPERIMENTAL

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was checked on Silica gel TLC plates. IR spectra were recorded on Thermo Nicolate IR 200 spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on Bruker AMX-400, DMSO d6 as internal standard. Combustion analysis were found to be within the limits of permissible errors.

Synthesis of 1-(2,5dihydroxy phenyl)-3-phenyl-1, 3-propanedione (II)

54 gm (0.15 mole) of 2,5-dibenzoyloxy acetophenone I was dissolved in 325 ml of dry pyridine and was heated to 50°C in a flask. Further 7.3 g (0.13 moles) of finely powdered potassium hydroxide were added with stirring. Stirring was continued till the solid separated out. The reaction mixture cooled to room temp. Acidified with 187 ml of 10% acetic acid solution and the solid separated out was filtertred, dried and recystallized from rectified spirit to get the product (24.4 g), yield 64% (Notel,2005).

Synthesis of 6-hydroxy-2-phenyl-4H-chromen-4-one (III)

25.6 g (0.1 mole) of 1-(2,5-dihydroxyphenyl)-3-phenyl-1, 3-propanedione II was dissolved in 75 ml of glacial acetic acid in a 500 ml of round bottom flask and 4 ml of conc. Sulphuric acid was added with constant stirring. The reaction mixture was refluxed for 2hr and cooled. The contents of the flask were poured in to beaker containing crushed ice. The solid separated out was filtered and it was recrystallized from n-hexane to get the (17.2 g), yield 68%, m.p 240-42^{0}c (Notel,2005).

Synthesis of 6-hydroxy-5-nitro-2-phenyl-4H-chromen-4-one (IV)

A mixture of 6-hydroxy-2-phenyl-4H-chromen-4-one III (5.1 g, 0.02 mole) and concentrated sulphuric acid (30 ml) was stirred at 0^0c for 30 min . Then a mixture of conc. Nitric acid (1.5 ml) and sulphuric acid (5 ml 98%) were added. The temperature was kept at 0-5 ^{0}c during the period of addition and the mixture was then continuously stirred for 2 hr at 5^0 C .The reaction mixture was poured into ice cold water, the precipitate formed was filtered, dried and recrystallized from acetone to get the product (4.02 g), yield 78%, m.p. 210-12^0c (Hodgetts,2000).

Synthesis of 5-amino-6-hydroxy-2-phenyl-4H chromen 4- one

Iron powder (8g) was added portion wise to a hot mixture of 6-hydroxy-5-nitro-2-phenyl-4H-chromen-4-one (IV) (5.66 g, 0.02 moles) in ethyl alcohol (20 ml) and conc. Hydrochloric acid (30 ml) at reflux temperature. After completion of the addition, the refluxing was continued for 6hr. Upon colling a white precipitate formed was filtered off washed with water, dried and recrystallized from methanol to get product (3.1g), yield 56%, m.p. 180-82^0c (Notel,2005).

Synthesis of 2-amino-7-phenyl chromen (5,6-d) imidazol-9- (3H)-one (A_1)

A mixture of V (0.5 g 0.002 mole) and thiourea (2.28 g, 0.03 mole) was heated at 130-140 ^{0}c for 15 min, the reaction mixture melted and re-solidified, treated with hot water, filtered off and recrystallized from ethanol to get the prduct (0.3 g), yield 62%, m.p. 194-95^0c.

Synthesis of 7-phenyl-1H-chromeno (5, 6-d) oxazole-2, 9-dione (A_2)

A mixture of V (0.5 g, 0.002 mole) and urea (1.8 g, 0.03 mole) was heated at 100^0c for 15 min, the reaction mixture melted and re-solidified, treated with hot water, filtered off and recrystallized from ethanol to get the product (0.24 g), yield 48%, m.p. 208-09^0c .

Synthesis of 8-phenyl chromeno (6, 5-b) (1, 4) oxazine-2, 10 (1H, 3H)-dione (A_3)

A mixture of V (0.5 g, 0.002 moles), chloroacetyl chloride (0.17 ml, 0.002 moles) and anhydrous potassium carbonate (0.5g) in dry acetone (20 ml) was refluxed for 3hr, cooled then poured into ice-cold water. The precipitate formed was filtered off and recrystallized from ethanol, yield 57% (0.28 g), m.p. 231-32^0c .

Synthesis of 2-(4-substituted phenyl)-7-phenyl-9H-chromeno (5, 6) oxazol-9-one A_4, A_5

To a solution of V (0.5g, 0.002 mole) in glacial acetic acid and the appropriate aldehydes namely nitro benzaldehyde and p-chloro benzaldehyde (0.002 mole) was refluxed for 15 hrs, cooled and poured into ice-cold water. The precipitate formed was filtered off and recrystallized from pet. Ether, A_4: yield 39% (0.19 g), m.p. 178-79^0c, A_5: yield 41% (0.21g), m.p.136-37^0c .

BIOLOGICAL EVALUATION

ANTI-INFLAMMATORY ACTIVITY

Anti-inflammatory activity was determined by Carragennan Induced Rat hind Paw edema method of winter ,1962. wistar rats (120-150 g) was used for the experiment. The drugs were prepared as a suspension by triturating with water and 0.5% sodium CMC .

Method: Carragennan Induced Rat hind Paw edema.

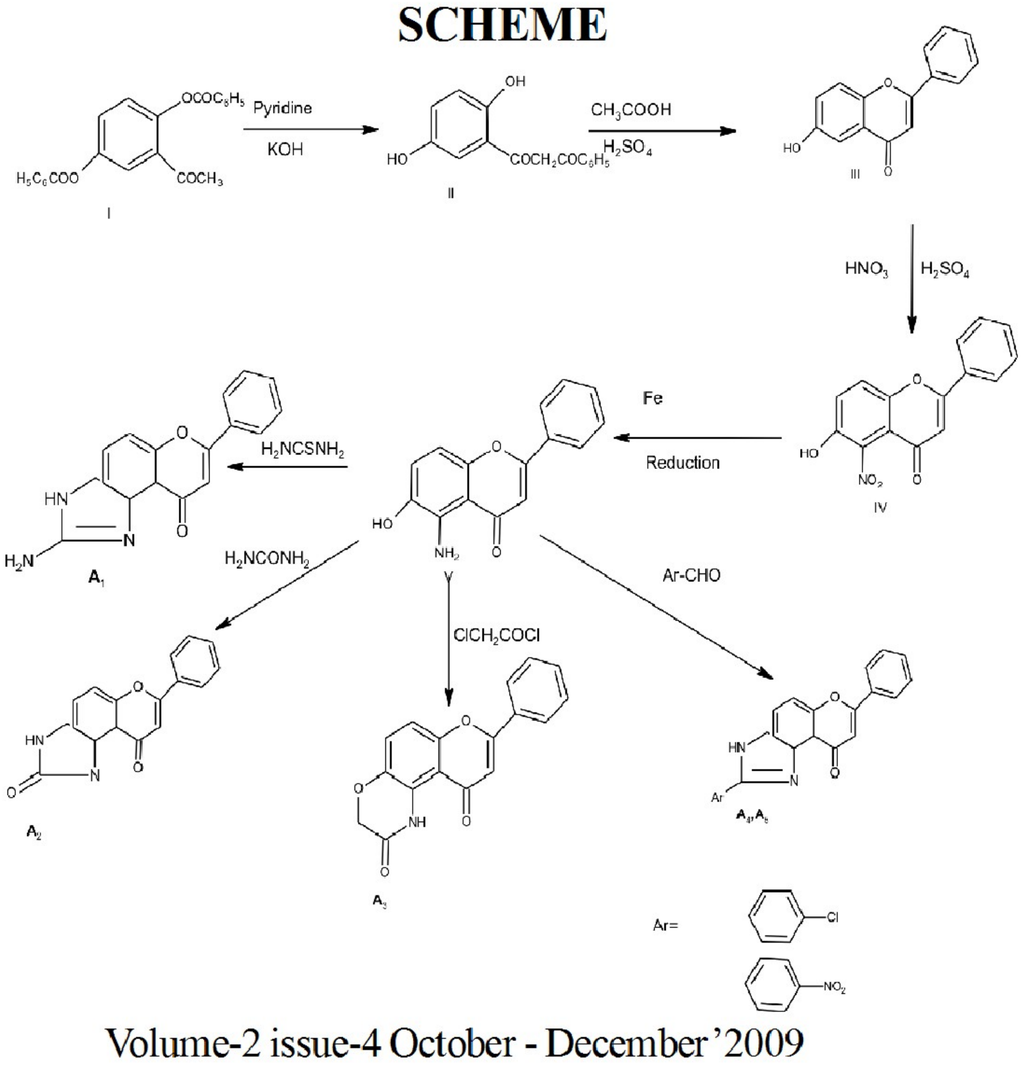
3.RESULTS AND DISCUSSION

A new series of some new 2-(substituted phenyl)-4H-chromen-4-one derivatives were synthesized. The synthesized compounds were subjected to anti-inflammatory activity by Carragennan induced paw edema method result obtained were found to be promising A_1,A_2,A_3,A_4 have shown excellent anti-inflammatory activity against Diclofenac sodium as a standard drug. These compounds exhibit a wide range of activities like anti-oxidant and immunomodulating; anti-inflammatory activities of these compounds are being exploited with suitable molecular modifications these compounds may prove as potent anti-inflammatory agents in future.

4.ACKNOWLEDGEMENTS

Authors wish to thank Honorable Shri.Radhakrishna Vikhe Patil, Minister for Education, Law and Justice, Govt. of Maharashtra for his constant encouragement and support.

SCHEME



SPECTRAL DATA

A_1 : IR (KBr) cm^{-1} : 3232(-NH str.), 3055 (Ar-CH str.), 1652 (C=O pyrone), 1500 (Ar-C-C str.), 1331 (C-O str.). **^{1} H NMR (δ ppm):** 11.89 (s, 1H, NH), 7.0-7.63 (m, 8H, Ar-H), 6.56 (d, 2H, NH_2)

A_2 : IR (KBr) cm^{-1}: 3238(-NH str.), 3046 (Ar-CH str.), 1689 (C=O pyrone), 1501 (Ar-C-C str.), 1331 (C-O str.). **^{1} H NMR (δ ppm):** 11.59 (s, 1H, NH), 7.52-7.62 (m, 8H, Ar-H).

A_3: IR (KBr) cm^{-1}: 3238(-NH str.), 3085(Ar-CH str.), 1651 (C=O pyrone), 1501 (Ar-C-C str.), 1301 (C-O str.). **^{1} H NMR (δ ppm):** 10.73 (s, 1H, NH), 7.0 - 7.63 (m, 8H, Ar-H), 6.96 (d, 2H, CH_2).

A_4: IR (KBr) cm^{-1} :3073 (Ar-CH str.), 1661 (C=O pyrone), 1516 (Ar-C-C str.), 1280 (NO_2.) ,679 (-Cl str.). **^{1} H NMR (δ ppm):** 6.94-7.64 (m, 8H, Ar-H).

A_5: IR (KBr) cm^{-1}:3062 (Ar-CH str.), 1682 (C=O pyrone), 1588(Ar-C-C str.), 1452 (C-N str.), 1360 (C-O str.), 1263 (-CN str.). **^{1} H NMR (δ ppm):** 6.94-7.64 (m, 8H, Ar-H).

Table no 1: Analytical data of synthesized compounds (A_1-A_5)

Compd.	Mol. Formula	Mol. Wt.	Yield %	m.p. ° C	Elemental analyses Calcd.(Found)		
					C	H	N
A_1	$C_{16}H_{11}N_3O_2$	277	62	194-195	69.3 (69.52)	4.0 (3.92)	15.15 (15.21)
A_2	$C_{16}H_9N_3O_4$	279	48	208-209	68.82	3.25	5.02
A_3	$C_{17}H_{11}NO_4$	293	57	231-232	69.62	3.48	4.78
A_4	$C_{22}H_{12}NO_3Cl$	373	39	178-179	70.69 (70.42)	3.24 (3.58)	3.75 (4.00)
A_5	$C_{16}H_{12}N_2O_5$	384	41	136-137	68.75	3.15(3.50)	7.29

The combustion analysis of compounds synthesized is within the limits of permissible errors.

Table no.2: Effect of synthesized compounds (Scheme I) and Diclofenac Sodium on carragennan induced rat paw edema by oral administration.

S.No	Compound (100mg/kg)	± SE			
		0 hr	1st hr	2nd hr	3rd hr
1	Control	3.72 ± 0.019	4.83 ± 0.23	4.64 ± 0.062	3.57
2	Standard (Diclofenac)	3.77 ± 0.070	3.43 ± 0.108	3.07 ± 0.13	2.79 ± 0.17**
3	A_1	3.78±0.069	3.24±0.090	2.98±0.13	2.63±0.19**
4	A_2	3.69±0.057	3.19±0.089	2.78±0.17	2.49±0.17**
5	A_3	3.67±0.053	3.47±0.079	2.69±0.19	2.37±0.13**
6	A_4	3.88±0.069	3.74±0.090	3.28±0.13	2.93±0.19**
7	A_5	3.79±0.057	3.59±0.089	3.28±0.17	3.19±0.17

*** p < 0.05 Non Significant**

**** p < 0.01 Significant**

*** ** p < 0.0001 (ANOVA followed by Dunnet't' test)**

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