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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SUBSTITUTED PYRAZOLINE DERIVATIVES

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Abstract: **In the present study, the chalcone intermediates are synthesized by Claisen-Schmidt condensation reaction between acetanilide and appropriate aromatic aldehydes. Further, these chalcone intermediates were cyclized with phenylhydrazine in glacial acetic acid to give new pyrazolines derivatives using ultrasonic irradiation with higher yields in lesser time. All the synthesized derivatives are characterized and screened for anti-inflammatory activity.**

Keywords: **Chalcones, Pyrazolines, Anti-inflammatory activity.**

1. INTRODUCTION

Chalcones are α, β-unsaturated ketones which contain two aromatic groups and bridged by an enone linkage. They form the central core for a variety of important biological compounds. They are mainly intermediates in the synthesis of various biologically active compounds 1, 2. The modifications on the chalcone backbone result in the generation of various heterocyclic systems. The acetamido group containing compounds have been found as essential pharmacophore, and thus incorporation of these in chalcone backbone may result in compounds with significant activity 3, 4. When synthesized chalcones are subsequently cyclized with hydrazines, gives Pyrazolines 5, 6. Among Pyrazoles, 2-pyrazolines are widely used as useful synthons in organic synthesis and having various biological activities 7, 8.

Most of the synthetic methods for 2-pyrazolines suffer from several disadvantages such as long reaction times, expensive reagents, drastic reaction conditions, low yields, tedious workup procedures, and formation of byproducts. Nowadays, the application of Ultrasonic irradiation has aroused more and more interest in synthetic chemistry, which overcome the disadvantages and accelerates the reactivity millions fold and many synthetically useful reactions were accomplished 9-11.

Given this, the present investigation involves the synthesis of Pyrazoline derivatives through cyclization of synthesized chalcones having acetamido pharmacophore under ultrasonic irradiation in search of potential anti-inflammatory compounds 12-15.

2. MATERIALS AND METHODS

The starting materials and solvents used for each reaction are of synthetic grade . All the chemicals and synthesized products were characterized for their purity by physical constant and Thin Layer Chromatography (TLC). All the reactions were monitored by using thin layer chromatography on pre-coated TLC plates (Silica gel 60-120#) by using solvent system Benzene: Ethanol [8:2] for Step-1 compounds and Dichloromethane: Ethyl acetate [9:1] for Step-2 compounds. The obtained TLC plates were observed under a long UV lamp in a UV chamber. All reactions were carried

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out ultrasonic irradiation by using sonicator made of Labman Scientific Instruments. The synthesized compounds were characterized by spectroscopic method FTIR and 1H NMR for elucidation and confirmation of their structures.

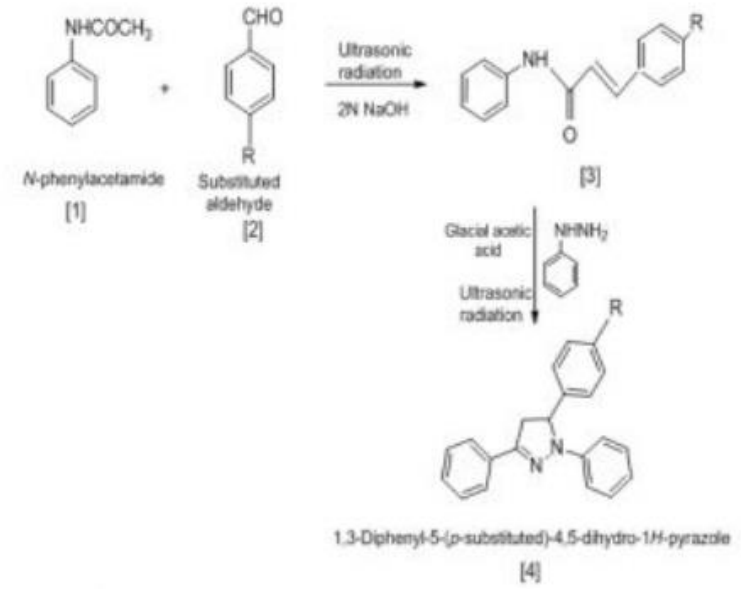
Synthesis Under Ultrasonic Irradiation:

Step I: Synthesis of Chalcones: Acetanilide (1, 1 mmole), dissolved with appropriate aromatic aldehydes (2, 1 mmole) in 95% of ethanol solvent (10 mL) and N sodium hydroxide (3 mL), taken into a 100 ml conical flask. The mixture was irradiated by an ultrasonic generator in a water-bath at 40-45 °C for 20 min. The reaction mixture so formed was diluted with water and neutralized with *N* hydrochloric acid. Collect the precipitate by filtration and washed well with cold water . Further, recrystallization of crude product was carried out by using ethanol and collect the yellow crystals of chalcone 3a-e. Their physical characteristics data of these are reported in **Table 1**.

Step II: Synthesis of Pyrazolines: Synthesized chalcones 3a-e (1 mmole), phenylhydrazine, (2 mmoles) and glacial acetic acid (10 mL) were taken into a 100 mL conical flask. This reaction flask was suspended in the ultrasonic bath to get the ultrasound energy and sonicated until complete disappearance of chalcone. Further, the reaction mixture was poured into crushed ice and keep overnight. The obtained precipitate was collected by filtration and washed well with cold water . Purification of crude product was carried out by recrystallization by using ethanol to give crystals of pyrazolines 4a-e. The products were characterized by IR and 1H NMR spectral data. The physical characteristics data of these are reported in **Table 2**.

The following sequence of reaction appears to afford a satisfactory explanation of the mode of formation of the products. This reaction involves the initial formation of aryl hydrazones with the subsequent attack of nitrogen upon the carbon-carbon double bond.

Scheme:



Biological Activity:

Anti-inflammatory Activity: The anti-inflammatory of the test compounds 4a-e was carried out using the carrageenan-induced rat paw oedema inhibition method. Acute inflammation was produced by sub plantar injection of 0.1 ml of 1% suspension of carrageenan in the right hind paw of the rats, 30 min after oral administration of the drugs. The paw volume was measured at 1, 2, 3, and 4 h after the carrageenan injection. Ibuprofen was used as the standard drug at a dose level of 10 mg/kg. The percentage inhibition of oedema was calculated using the formula 16, 20.

$$\% \text{ Inhibition} = (1 - Vt/Vc) \times 100$$

Where *V*t is oedema volume in treated groups, and *V*c is oedema volume in control groups.

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3. RESULTS AND DISCUSSION

All chemicals and products have shown single spot on TLC plate when observed under UV light . The melting points were taken in open capillaries on melting point apparatus and were found uncorrected.

TABLE 1: PHYSICAL CHARACTERISTICS DATA OF SYNTHESIZED CHALCONE INTERMEDIATES

Comp. No.	R	Temp. (ºC)	Time (Min.)	% Yield
3a	-NO2	30	30	84
3b	-Cl	25	40	81
3c	-F	25	40	78
3d	-CH3	40	35	80
3e	-OH	35	30	86

TABLE 2: PHYSICAL CHARACTERISTICS DATA OF SYNTHESIZED PYRAZOLINE DERIVATIVES

Comp. No.	R	Temp. (ºC)	Time (Min.)	% Yield
4a	-NO2	35	40	77
4b	-Cl	40	30	72
4c	-F	40	35	69
4d	-CH3	35	40	75
4e	-OH	40	30	70

Spectral Data: The characterization with IR and 1H NMR spectra of the synthesized compounds confirmed the anticipated structure. The spectral data of synthesized pyrazolines has been shown in **Table 3**.

TABLE 3: SPECTRAL DATA OF SYNTHESIZED PYRAZOLINES

Compound 4a: 1,3-diphenyl-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole: M.P: 146 ºC Rf: 0.8		
IR (KBr cm-1)	:	3211 (C–H), 1624 (C=N), 1332 (C–N), 1538(C=C), 1358 (NO2)
Compound 4b: 1,3-diphenyl-5-(4-chloroophenyl)-4,5-dihydro-1H-pyrazole: M.P:182 ºC **Rf:** 0.7		
IR (KBr cm-1)	:	3216 (C–H), 1640 (C=N), 1326 (C–N), 1542 (C=C), 710 (C–Cl)
1H NMR (δ ppm)	:	3.109 (dd, 1H), 3.814 (dd, 1H), 5.210 (dd, 1H), 6.912–7.808 (m, 12H, Ar–H)
Compound 4c: 1,3-diphenyl-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole: M.P:160 ºC **Rf:**0.6		
IR (KBr cm-1)	:	3248 (C–H), 1637 (C=N), 1328 (C–N), 1568 (C=C), 1212 (C–F)
1H NMR (δ ppm)	:	3.126 (dd, 1H), 3.832 (dd, 1H),5.224 (dd, 1H), 6.908-7.823 (m, 12H, Ar–H)

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Compound 4d: 1,3-diphenyl-5-(4-methylphenyl)-4,5-dihydro-1H-pyrazole: M.P:156 ºC **Rf:**0.8		
IR (KBr cm-1)	:	3256 (C–H), 1629 (C=N), 1364 (C–N), 1554 (C=C)
Compound 4e:1,3-diphenyl-5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole: M.P:134 ºC **Rf:**0.7		
IR (KBr cm-1)	:	3248 (C–H), 1637 (C=N), 1328 (C–N), 1568 (C=C), 3542 (OH)

Biological Activity:

Anti-inflammatory Activity of Pyrazolines: Assessment of anti-inflammatory action was completed *via* carrageenan-induced rat paw edema inhibition method. The rate of edema hindrance was computed from the mean impact in control and treated creatures agreeing on the accompanying condition. Anti-inflammatory activity data of the synthesized Pyrazoline derivatives 4a-e are presented in **Table 4** .

TABLE 4: ANTI-INFLAMMATORY ACTIVITY OF PYRAZOLINES

Compound	Mean paw Oedema Volume (ml) ± SE						
	0 hr	**½ h**	**1h**	**2 h**	**3 h**	**4 h**	**% inhibition after 4 h**
Control	0.122±0.0502	0.411±0.0749	2.14±0.163	2.84±0.279	2.60±0.318	1.42±0.314***	--
Drug	0.0826±0.0762	0.615±0.237	1.12±0.236	1.54±0.178	1.24±0.271	0.956±0.182***	51
4a	0.124±0.0462	0.356±0.0823	1.55±0.432	1.86±0.139	1.42±0.326	1.29±0.243***	32
4b	0.142±0.0514	0.339±0.0627	1.38±0.210	1.59±0.130	1.30±0.318	1.27±0.128***	36
4c	0.110±0.0420	0.358±0.0524	1.43±0.136	1.58±0.216	1.42±0.114	1.26±0.135***	39
4d	0.124±0.0414	0.255±0.129	1.39±0.182	1.67±0.232	1.34±0.428	1.26±0.224***	34
4e	0.161±0.0429	0.242±0.109	1.78±0.136	1.52±0.249	1.41±0.132	1.21±0.132***	34

Values are expressed as mean ± SEM of six animals in each group. *Statistically significant ($P \leq 0.05$). **Statistically significant ($P \leq 0.001$)

4. CONCLUSION

Some of the new Pyrazoline derivatives were synthesized under ultrasonic irradiation and characterized by various analytical methods. These are successfully evaluated for their anti-inflammatory activity. Spectral data confirm the structure of the synthesized pyrazolines as expected. From the results, it can be concluded that the modified pyrazolines shows remarkable anti-inflammatory action and having the potential to study further.

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