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Synthesis and Analgesic Studies of Some New 2-pyrazolines

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Abstract: A new series of 2-pyrazolines **(4a-j)** were synthesized by reacting chalcones **(3a-j)** with phenyl hydrazine in the presence of pyridine and ethanol. All these compounds were characterized by means of their IR, ^{1}H-NMR spectral data and microanalyses. When these compounds were evaluated for analgesic activity, some of them were found to possess significant activity, when compared to standard drugs.

Keywords: Pyrazolines, Analgesic activity.

Introduction

Pyrazoline derivatives constitute an interesting class of organic compounds with diverse pharmacological activities like antimicrobial, anti-inflammatory, analgesic, antidepressant, antitubercular and antimalarial activities[1-5]. Many of the therapeutically useful compounds such as phaenylbutazone, oxyphenbutazone, celecoxib, belonging to pyrazoles exhibited antipyretic, anti-inflammatory and analgesic properties[6]. Among various pyrazoline derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type compounds. Earlier studies by Ratnadeep et al, demonstrated analgesic activity of 3,2-(4,5-dihydro-5-(4-morphilinophenyl)-1*H*-pyarazol-3-yl)phenols[7], Suresh et al, reported a novel series of 5-substituted aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines as novel anti-inflammtory and analgesic agents[8], Manna et al, reported analgesic and antipyretic activity of some new N-acetyl-Δ^2-pyrazolines and dihydrothienocoumarines[9]. The reaction of an α, β-unsaturated ketone with phenylhydrazine became a generally used, simple and convenient procedure for the synthesis of pyrazolines[10].

In view of these observations and in continuation of our research programme on the synthesis of chalcones and their derivatives[11], we report herein the synthesis of some new pyrazoline derivatives which have been found to possess an interesting profile of analgesic activity. Synthetic methods for the preparation of pyrazoline derivatives **(4a-j)** are summarized in **scheme-1.** Chalcones were synthesized by the reaction of 3-acetyl-2,5-dimethylfuran and various substitud aromatic and hetero cyclic aldehydes in presence of aq.KOH and ethanol. Pyrazolines were obtained in good yields by reacting chalcones **(3a-j)** with phenylhydrazine in hot pyridine. The structures of the various synthesized compounds

were assigned on the basis of elemental analyses, IR and ^{1}H NMR spectral data. These compounds were also screened for their analgesic activity.

Material and Methods

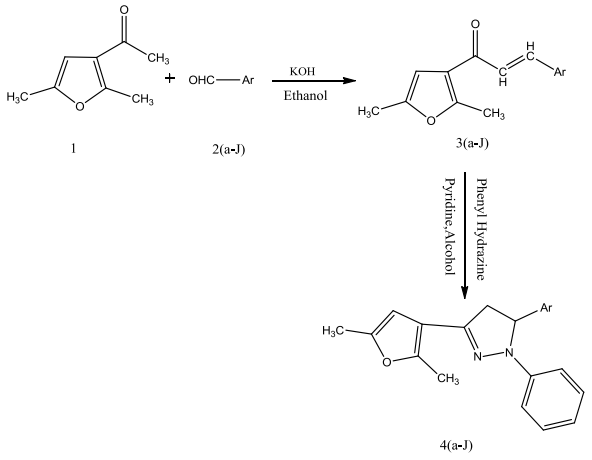
All the chemicals used in the synthesis were obtained from standard commercial sources. Melting points were determined on an open capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded (KBr) on a Perkin-Elmer AC-1 spectrophotometer. Micro analyses were performed on Carlo Erba E–1108 element analyzer and were within the ± 0.4% of the theoretical values. Reaction completion was identified by TLC using silica gel for TLC (Merck). All the chalcones have been purified by column chromatography performed on silica gel columns (100-200 mesh, Merck).

General procedure for preparation of 1-(2',5'-dimethyl-3'-furyl) -3-(aryl)-2-propen-1- one 3(a-j)

A mixture of 3-acetyl-2,5-dimethylfuran (0.005 mol) **(1)** and appropriate aldehyde (0.005 mol) **(2a-j)** was stirred in ethanol (7.5 mL) and then an aqueous solution of potassium hydroxide (50%, 7.5 mL) was added to it. The mixture was kept for 24 h and it was acidified with 1:1 HCl and H_2O. Then it was filtered under vacuum and the solid was washed with water, purified by column chromatography and crystallized from a mixture of ethyl acetate and hexane.

General procedure for preparation of 1-phenyl-3-(2',5'-dimethyl-3'-furyl)-5-(aryl)-2-pyrazoline 4(a-j)

1-(2',5'-dimethyl-3'-furyl)-3-(aryl)-2-propen-1-one (0.001 mol) **3(a-j)** was condensed with phenyl hydrazine (0.001 mol) in the presence of pyridine (0.002 mol) in absolute ethanol (5 mL) at reflux temperature on a water bath for 2 to 6 h. The solvent was evaporated in vacuum and crushed ice was added to the residue while mixing thoroughly, were upon a bright yellow solid separated out. This solid was filtered under vacuum, dried and purified by column chromatography to give a pure pale yellow solid. The physical and spectral data of the pyrazolines were shown in table 1 and table 2.



Scheme 1 : synthetic procedure for preparation of title compounds

Analgesic Activity

Tail immersion test method [12,13] was adopted for the evaluation of analgesic activity of the test compounds. 60 spraygue-dawley rats (M/S Gosh Enterprises, Calcutta, West Bengal, India) of either sex weighing between 180-200 g were used in the experiment and these were divided into 12 groups of 5 animals each and they were numbered individually. The animals were fasted for 24 hrs before administering the drug with water *ad libitum.* The group I was administered with only 2% v/v tween 80 solution which served as control. Group II was administered with 100 mg/kg body weight of ibuprofen suspension orally which served as a standard. Group III to group XII were administered with test compounds respectively, the dose being 100 mg/kg body weight selected on the basis of the standard drug used. All the animal tails were dipped into a beaker containing water maintained at 55 $\pm 1^{o}$C and the time taken for the animals to flick the tail from the hot water completely is recorded at 15 minutes, 30 minutes, 1 hour, 2 hours and 3 hours respectively. The percentage of protection in the control, standard and drug treated animals were recorded and calculated by using the formula.

$$\% \text{ Analgesic activity (PAA)} = [(Rt/Rc) - 1] \times 100$$

Where Rt and Rc are the reaction time in test and control respectively.
The results and statistical analysis of the analgesic activity of ibuprofen and the compounds tested are shown in Table 3 and Fig1.

Table 1. Physical data of the prepared compounds 4 (a-j).

S. No.	Ar	Mol. Formula	(RMM)	M.P. (^{o}C)	Yield %	(% Calc.)			(% found)		
						C	H	N	C	H	N
4a	4″-methoxyphenyl	$C_{22}H_{22}N_2O_2$	346	106-108	67	76.28	6.40	8.09	76.23	6.38	8.17
4b	3″,4″-dimethoxyphenyl	$C_{23}H_{24}N_2O_3$	376	145-147	72	73.38	6.43	7.44	73.28	6.39	7. 46
4c	4″-fluorophenyl	$C_{21}H_{19}FN_2O$	334	96-98	78	75.43	5.73	8.38	75.41	5.71	8.29
4d	4″-nitrophenyl	$C_{21}H_{19}N_3O_3$	361	157-159	75	69.79	5.30	11.63	69.74	5.27	11.72
4e	2″-thienyl	$C_{19}H_{18}N_2OS$	322	115-117	67	70.78	5.63	8.69	70.72	5.63	8.58
4f	3″,4″,5″-trimethoxyphenyl	$C_{24}H_{26}N_2O_4$	406	134-136	78	70.92	6.45	6.89	70.87	6.45	6.94
4g	4″chlorophenyl	$C_{21}H_{19}ClN_2O$	350	121-123	73	71.89	5.46	7.98	71.85	5.42	7.95
4h	4″-methylphenyl	$C_{22}H_{22}N_2O$	330	92-94	69	79.97	6.71	8.48	79.96	6.68	8.56
4i	9″-anthryl	$C_{29}H_{24}N_2O$	416	223-225	75	83.63	5.81	6.73	83.58	5.76	6.84
4j	2″,4″-dichlorophenyl	$C_{21}H_{18}Cl_2N_2O$	384	89-91	73	65.46	4.71	7.27	65.41	4.68	7.36

Table 2. Spectral data of the prepared compounds 4 (a-j).

S.No.	IR spectral data	^{1}H NMR spectral data Chemical shift (δ) in ppm
4a	1598 (C=N), 1503 (C=C), 1225 (C-O-C), 1157 (O-CH_3), 1122 (C-N)	3.05 (1H, dd, H_A), 3.78 (1H, dd, H_B), 5.28 (1H, dd, H_X), 3.75 (3H, s, OCH_3), 6.45-7.22 (10H, Ar-H), 2.2(3H,s,Ar-CH_3), 2.5(3H,s, Ar-CH_3).
4b	1573 (C=N), 1565 (C=C), 1233 (C-O-C), 1185 (O-CH_3), 1133 (C-N)	3.1 (1H, dd, H_A), 3.69 (1H, dd, H_B), 5.18(1H, dd, H_X), 3.75 (3H, s, OCH_3),3.85 (3H,s,OCH_3), 6.35-7.49 (9H,Ar-H), 2.3(3H,s, Ar-CH_3), 2.6 (3H,s, Ar-CH_3).
4c	1592 (C=N), 1570 (C=C), 1110 (C-F), 1060 (C-O-C) , 1130 (C-N)	3.05 (1H, dd, H_A), 3.78 (1H, dd, H_B), 5.22(1H, dd, H_X), 6.44-7.47 (10H, Ar-H), 2.18(3H,s, Ar-CH_3),2.5(3H,s, Ar-CH_3).
4d	1583 (C=N), 1563 (C=C), 1541 (N=O , asymmetric), 1325 (N=O, symmetric), 1105 C-N), 1055 (C-O-C)	3.08 (1H, dd, H_A), 3.80 (1H, dd, H_B), 5.27 (1H, dd, H_X), 6.75-7.66 (10 H, Ar-H), 2.2(3H,s, Ar-CH_3),2.6(3H,s, Ar-CH_3).
4e	1597 (C=N), 1573 (C=C), 1125 (C-N), 1063 (C-O-C) , 675 (C-S)	3.18 (1H, dd, H_A), 3.77 (1H, dd, H_B), 5.46 (1H, dd, H_X), 6.45-7.48 (9H, Ar-H), 2.2(3H,s, Ar-CH_3),2.5(3H,s, Ar-CH_3).
4f	1598 (C=N), 1504 (C=C), 1223 (C-O-C), 1160 (O-CH_3) ,1125 (C-N)	3.11 (1H, dd, H_A), 3.72 (1H, dd, H_B), 5.12 (1H, dd, H_X), 3.79 (6H, s, 2 x OCH_3), 3.82 (3H, s, OCH_3), 6.45-7.49 (8H , Ar-H), 2.25(3H,s, Ar-CH_3),2.55(3H,s, Ar-CH_3).
4g	1596 (C=N), 1553 (C=C), 1123 (C-N), 1055 (C-O-C) , 855 (C-Cl)	3.02 (1H, dd, H_A), 3.75 (1H, dd, H_B), 5.17(1H, dd, H_X), 6.41-7.45 (10H, Ar-H), 2.5(3H,s, Ar-CH_3),2.65(3H,s, Ar-CH_3).
4h	1597 (C=N), 1524 (C=C), 1106 (C-N) , 1058 (C-O-C)	3.10 (1H, dd, H_A), 3.68 (1H, dd, H_B), 5.20 (1H, dd, H_X), 2.29 (3H, s, Ar-CH_3) 6.41-7.46 (10H, Ar-H), 2.3(3H,s, Ar-CH_3),2.55(3H,s, Ar-CH_3).
4i	1593 (C=N), 1563 (C=C), 1110 (C-N) , 1063 (C-O-C)	3.53 (1H, dd, H_A), 3.89(1H, dd, H_B), 5.51 (1H, dd, H_X), 6.50-8.47 (15 H, Ar-H), 2.45(3H,s, Ar-CH_3),2.8(3H,s, Ar-CH_3).
4j	1595 (C=N), 1553 (C=C), 1121 (C-N),1065 (C-O-C), 863 (C-Cl)	3.02 (1H, dd, H_A), 3.67 (1H, dd, H_B), 5.17 (1H, dd, H_X), 6.41-7.45 (9H, Ar-H), 2.2(3H,s, Ar-CH_3), 2.6(3H,s, Ar-CH_3).
(J_{AB} = 16.50 , J_{AX} = 7.30 and J_{BX} = 9.5Hz).		

Table 3. Analgesic activity of 2-pyrazolines 4 (a-j).

Compound code	Ar	Analgesic Activity				
		15min	30min	1hr	2hr	3hr
4a	**4″-methoxyphenyl**	97 ± 2*	98 ± 1*	102 ± 2*	114 ± 2**	117 ± 2
4b	**3″,4″-dimethoxyphenyl**	91 ± 1	94 ± 2*	97 ± 1	94 .± 2	86 ± 1
4c	**4″-fluorophenyl**	102 ± 1*	98 ± 2*	91 ± 1	88 .± 2	74 ± 1
4d	**4″-nitrophenyl**	94 ± 2	88 ± 2	83 ± 1	84 .± 1	77 ± 2
4e	**2″-thienyl**	95 ± 1	92 ± 1	92 ± 2	85 .± 1	74 ± 1
4f	**3″,4″,5″-trimethoxyphenyl**	98 ± 2*	112 ± 2**	112 ± 2***	117 ± 2**	101 ± 1**
4g	**4″chlorophenyl**	96 ± 2	88 ± 2	77 ± 2	81 .± 1	75 ± 2
4h	**4″-methylphenyl**	91 ± 1	96 ± 1	99 ± 2*	98 ± 1*	92 ± 1
4i	**9″-anthryl**	98 ± 2	95 ± 2	96 ± 2	87 .± 1	81 ± 2
4j	**2″,4″-dichlorophenyl**	85 ± 1	88 ± 2	91 ± 2	92 ± 2	81± 2
IBUPROFEN		101 ± 1**	111 ± 2***	151 ± 2***	162 ± 1***	171 ± 2***
Control		-	-	-	-	-

Values are expressed as mean ± SEM (n=5). *p<0.05; **p<0.01; ***p<0.001 compared to controls. Students's t-test.

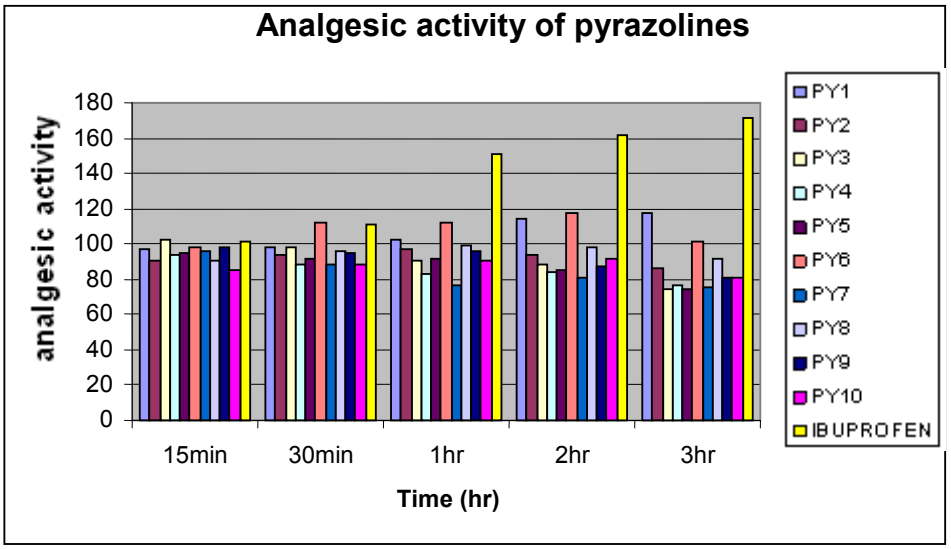


Figure 1. Analgesic activity of 2-pyrazolines 4 (a-j).

Results and Discussion

The title compounds 1-Phenyl-3-(2',5'-dimethyl-3'-furyl)-5-(4(-substituted phenyl)-2-pyrazoline (4a-n) were synthesized in good yields (scheme-I). All these compounds were tested for analgesic activity showed considerable activity when compared to the standard drug ibuprofen. It is interesting to note that the compound 4f, having a 3,4,5-trimethoxyphenyl and 4a, having a 4-methoxyphenyl ring at the 5-position of the 2-pyrazoline ring possessed the maximum activity. It clearly indicates the favorable effect of electron releasing substituent's on the analgesic activity of the 2-pyrazolines.

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