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Research Article

Synthesis, Analgesic, Anti-inflammatory and Antimicrobial Activities of Some Novel Pyrazoline Derivatives

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Abstract

Purpose: Microbial infections often produce pain and inflammation. Chemotherapeutic, analgesic and anti-inflammatory drugs are prescribed simultaneously in normal practice. The compound possessing all three activities is not common. The purpose of the present study was to examine whether molecular modification might result in detection of new potential antirheumatic drugs having antimicrobial activities.

Method: A series of novel 4-(5'-substituted aryl-4', 5'-dihydropyrazole-3'-yl-amino) phenols **2a-f** have been synthesized by treating substituted aryl-N-chalconyl amino phenols **1a-f** with hydrazine hydrate. The starting materials were synthesized from p-aminoacetophenone. Their structures were confirmed by IR, ¹H NMR spectral data. The synthesized compounds were investigated for analgesic, anti-inflammatory and antimicrobial activities.

Result: The data reported in Tables 2, 3 & 4 shows that effect of variation in chemical structure on activity was rather unpredictable. Seldom did a particular structural modification lead to uniform alteration in activity in all tests. The substitution which appeared to be most important for high order of activity in the greatest number of test was the p-choloroaryl group. The introduction of p-nitro and p-hydroxy group in aryl moiety of the pyrazole analogs **2c** and **2e** produce compounds with potent analgesic, anti-inflammatory and, in a few cases, antimicrobial properties.

Conclusion: The observed increase in analgesic, anti-inflammatory and antimicrobial activities are attributed to the presence of 4-NO₂, 2-OH and 4-Cl in phenyl ring at 5-position of pyrazoline ring of synthesized compounds. In some cases their activities are equal or more potent than the standard drugs.

Keywords: Pyrazole, Analgesic, Anti-inflammatory, Antibacterial activity.

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INTRODUCTION

Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. The recent success of pyrazole COX-2 inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry. A systematic investigation of this class of heterocyclic lead revealed that pyrazole containing pharmacoactive agents play important role in medicinal chemistry. The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead. The treatment of pain continues to be the subject of considerable pharmaceutical and clinical research. Microbial infections often produce pain and inflammation. Chemotherapeutic, analgesic and anti-inflammatory drugs are prescribed simultaneously in normal practice. The compound possessing all three activities is not common. It has been reported that pyrazoline possess analgesic, anti-inflammatory¹⁻³ and antimicrobial⁴⁻⁶ activities. In view of these above, an attempt has been undertaken for the synthesis of the some novel 4-(5'-substituted aryl-4', 5'-dihydropyrazole-3'-yl-amino) phenols possessing potent biological activities. The synthesized compounds were tested for their possible analgesic, anti-inflammatory and anti-microbial activities.

EXPERIMENTAL

Equipment

Melting points were determined in open capillaries and were uncorrected by melting point determining apparatus (SISCO). Purity of the compounds were checked by TLC. IR spectra (KBr, cm^{-1}) were recorded on a JASCO FT/IR 410 spectrophotometer. ^1H NMR (CDCl_3) on a Bruker DPX 300-MHz spectrometer using TMS as an internal reference (chemical shifts in δ ppm). C, H and N analysis were carried out on a Euro EA (Italy) analyzer.

Materials

Pure paracetamol (ODCL, India), ciprofloxacin (Alkem, India), clotrimazole (Glenmerk, India). Methanol, Hydrazinehydrate, ethanol (all from (SD-Fine Chemical, India), Sodium Hydroxide benzaldehyde, furfuraldehyde, 4-nitrobenzaldehyde, p-anisaldehyde, salicylaldehyde, 4-cholorobenzaldehyde, Carrageenan (all from Merck, Germany), carboxymethylcellulose (Sigma, India), Dimethylformamide (Aldrich), Mullar hinton agar and Sabouraud dextrose agar (Hi-Media, India).

Methods

Preparation of N-(4-hydroxyphenyl)-3-phenylacrylamide (1a)

To a mixture of p-hydroxyacetoaminophenone (0.01 mol) and benzaldehyde (0.01 mol) in ethanol, 2 % sodium hydroxide solution (1 ml) was added drop wise with constant stirring over a period of 30 min. and the reaction mixture was stirred for another 10 h at room temperature and then refluxed for 6 h. The excess solvent was distilled off and the solid obtained was poured into ice- cold water. The solid thus obtained was filtered, dried and recrystallised from ethanol. Compounds **1b-f** were prepared similarly by using different arylaldehydes. Their melting points, % yields and molecular formula are given in Table-1

1a (R = $-\text{C}_6\text{H}_5$): m.p. 150°C , yield: 72%, IR(KBr in cm^{-1}): 3452 (Ar-OH str.), 3301 (NH str.), 3016 (C-H str.), 1610 (C=C str.), ^1H -NMR (δ ppm) (CDCl_3), 7.1-7.8 (2H,d,CH), 6.11 (1H,s,N-H), 7.70 (1H,s,N-H), 5.35 (1H, s, Ar-OH), 6.76 – 8.00 (m, Ar-H). Analysis ($\text{C}_{15}\text{H}_{13}\text{O}_2\text{N}$) cal(found)%: C 75.30(75.52) H5.48(4.98) N5.85(6.21).,MS:(m/z) : 239(M^+).
1b (R = - Furyl): IR(KBr in cm^{-1}): 3300 (Ar-OH str.), 3253 (NH str.), 2922 (CH_2 str.), 1476(C=C str.), 1137 (C-O-C str.); ^1H -NMR (δ ppm) (CDCl_3), 7.13-7.21(2H,d,CH), 6.21 (1H,s,N-H), 7.38 (1H, s, N-H),,5.65 (1H, s, Ar-OH),6.76 – 8.00 (m, Ar-H). Analysis ($\text{C}_{13}\text{H}_{11}\text{O}_3\text{N}$) cal(found)%: C 68.11(68.43) H 4.84(4.49) N 6.11(5.89).,MS:(m/z): 229. **1c** (R=p- NO_2 - C_6H_4):- IR(KBr in cm^{-1}): 3490 (Ar-OH str.), 3291 (NH str.), 3099 (C-H str.), 2851(CH_2 str.), 1560 (C- NO_2 asym. str.),

1485(C=C str.); .), ¹H- NMR (δ ppm) (CDCl₃), 7.1-7.8 (2H,d,CH), 6.13(1H,s,N-H), 7.68 (1H,s, N-H), 5.35 (1H, s, Ar-OH),6.76 – 8.02 (m, Ar-H) Analysis (C₁₅H₁₂O₄N₂) cal(found)%: C 63.38(63.42) H 4.25(4.52) N 9.85(9.53). MS :(m/z) 284(M⁺). **1d** (R = p- OCH₃-C₆H₄) IR(KBr in cm⁻¹) : 3431(Ar-OH str.), 3211 (NH str.), 2831 (CH₂ str), 1493(C=C str), 1101(C-O-C str); ¹H- NMR (δ ppm) (CDCl₃) 7.1-7.8 (2H,d,CH), 6.14 (1H,s,N-H), 7.52 (1H, s, N-H), 5.35 (1H, s, Ar-OH),6.76 – 8.01.(m, Ar-H).):- Analysis (C₁₆H₁₅O₃N) cal (found) %: C 71.36(71.57) H 5.61(6.02) N 5.20(4.99). MS:(m/z): 269(M⁺).**1e** (R= 2-OH-C₆ H₄):- IR(KBr in cm⁻¹) : 3412 (Ar-OH str.),3208(NH str.), 2834(CH₂ str.), 1505.7(C=C str.); ¹H-NMR (δ ppm) (CDCl₃), 7.1-7.8 (2H,d,CH), 6.23 (1H,s,N-H), 7.48 (1H, s, N-H), 5.35 (1H, s, Ar-OH),6.56 – 8.00 (m, Ar-H) Analysis (C₁₅H₁₃O₃N) cal(found)%: C 70.58(70.82) H 5.13(5.34) N 5.49(5.26). MS :(m/z) 255(M⁺). **1f** (R = p-Cl-C₆H₄): IR (KBr in cm⁻¹): 3417(Ar-OH str.), 3278(NH str.), 2932 (C-H str.), 2836(CH₂ str.), 742 (C-Cl.) ¹H- NMR (δ ppm) (CDCl₃), 7.19-7.21 (2H, d, CH), 6.21(1H, s, N-H), 7.40 (1H, s, N-H), 5.38 (1H, s, Ar-OH), 6.76 – 8.00 (m, Ar-H). Analysis (C₁₅H₁₂O₂NCl) cal (found) %: C 65.82(66.12) H 4.42(4.63) N 5.12(5.43), MS :(m/z) 273(M⁺).

Preparation of 4-[(5'-phenyl-4', 5'-dihydropyrazol-3'-yl) amino] phenol (2a)

A mixture of compound **1a** (0.01mol) and hydrazine hydrate (0.01mol) in ethanol (30ml), were refluxed for 6 h on a water bath. The reaction mixture was concentrated, cooled and poured into ice-cold water. The resulting solid **2a** was filtered, dried and recrystallised from ethanol. Compounds **2b-f** were prepared similarly. Their melting points, % yields and molecular formula are given in Table-1. **2a**(R = -C₆ H₅): IR (KBr in cm⁻¹): 3462 (Ar-OH str.), 3293 (NH str.), 3261(NH str.), 3022(C-H str.), 1630 (C=N str.), ¹H- NMR (δ ppm) (CDCl₃), 2.20-2.25 (1H, t, CH), 6.15 (1H,s,N-H), 7.43 (1H, d, N-H), 4.71- 4.86 (2H, d, CH₂), 5.31 (1H, s, Ar-OH), 7.31 – 7.65 (m, Ar-H). Analysis (C₁₅H₁₅N₃O) cal (found) %: C 71.13(70.75) H 5.97(5.76) N 16.59(16.39). MS

:(m/z): 253(M⁺). **2b** (R=Furyl): IR (KBr in cm⁻¹): 3312 (Ar-OH str.), 3261 (NH str.), 3264 (NH str.), 3065 (O-H str.), 2927 (CH₂ str.), 1630 (C=N str.), 1464 (C=C str.), 1137 (C-O-C str.); ¹H- NMR (δ ppm) (CDCl₃),2.13-2.22 (1H, t, CH), 6.24 (1H,s,N-H), 7.38 (1H, d, N-H), 4.54- 4.61 (2H, d, CH₂), 5.63 (1H, s, Ar-OH), 6.63 – 7.87 (m, Ar-H). Analysis (C₁₃H₁₃N₃O₂) cal (found) %: C 64.19(64.23) H 5.39(4.99) N 12.27(12.63).MS :(m/z) 243 (M⁺). **2c** (R = p-NO₂-C₆H₄ IR(KBr in cm⁻¹) : 3497 (Ar-OH str.), 3298 (NH str.), 3241 (NH str.), 3073 (C-H str.), 2832 (CH₂ str.), 1634 (C = N str.), 1570 (C-NO₂ asym. str.), 1489 (C=C str.); ¹H- NMR (δ ppm) (CDCl₃),2.22-2.24 (1H, t, CH),/6.11(1H,s,N-H), 7.68 (1H,d, N-H), 4.11- 4.16 (2H, d, CH₂), 5.28 (1H, s, Ar-OH), 6.78 – 8.24 (m, Ar-H).):- Analysis (C₁₅H₁₄N₄O₃) cal(found)% : C 60.40 (60.49) H 4.73 (4.87) N 18.78 (18.43). MS :(m/z) 298(M⁺). **2d** (R = p-OCH₃-C₆H₄):- IR(KBr in cm⁻¹) : 3431 (Ar-OH str.), 3207 (NH str.), 2843 (CH₂ str), 1613 (C=N str), 1499 (C=C str), 1093 (C-O-C str); ¹H- NMR (δ ppm) (CDCl₃),2.1-2.4 (1H, t, CH), 6.17(1H,s,N-H), 7.52 (1H, d, N-H), 4.36- 4.41 (2H, d, CH₂), 5.47 (1H, s, Ar-OH), 6.71 – 8.11 (m, Ar-H). Analysis (C₁₆H₁₇N₃O₂.) cal (found) %: C 67.83 (68.01) H 6.05 (5.88) N 14.83 (14.72). MS:(m/z) 283(M⁺).**2e** (R=2-OH-C₆H₄):- IR(KBr in cm⁻¹) : 3409 (Ar-OH str.),3202 (NH str.), 2834 (CH₂ str.), 1638 (C=N str.), 1500 (C=C str.) ; ¹H- NMR (δ ppm) (CDCl₃),2.12-2.6 (1H, t, CH), 6.26 (1H,s,N-H), 7.48 (1H, d, N-H), 4.15- 4.18 (2H, d, CH₂), 5.34 (1H, s, Ar-OH), 6.68 – 8.13 (m, Ar-H). Analysis (C₁₅H₁₅N₃O₂) cal (found) %: C 66.96(66.64) H 5.61(5.47), N 15.60 (15.34). MS :(m/z) 269 (M⁺). **2f** (R=p-Cl-C₆H₄): IR(KBr in cm⁻¹) : 3411 (Ar-OH str.), 3271 (NH str.), 2922 (C-H str.), 2922 (CH₂ str.), 1024 (C=N str.), 742 (C-Cl str.), ¹H- NMR (δ ppm) (CDCl₃),2.21-2.23 (1H, t, CH), 6.24(1H,s,N-H),7.43 (1H, d, N-H), 4.23- 4.28 (2H, d, CH₂), 5.46 (1H, s, Ar-OH), 6.82 – 8.16 (m, Ar-H). Analysis (C₁₅H₁₄N₃OCl) cal (found) %: C 62.61(62.78) H 4.90(4.92) N 14.60(14.29), MS :(m/z) 287(M⁺).

Animals

Wistar albino mice (20-30 g) and Swiss albino rats (100 – 140 g) of either sex were selected

for the experiments. Animals were allowed to be acclimatise for a period of 2 weeks in our laboratory environment prior to the study. Animals were housed in polypropylene cages (4 animals per cage), maintained under standard laboratory conditions (*i.e.* 12:12 hour light and dark sequence; at an ambient temperature of $25\pm 2^{\circ}\text{C}$; 35-60% humidity); the animals were fed with standard rat pellet diet (Hindustan Liver Ltd.Mumbai) and water *ad libitum*. The principles of Laboratory Animal Care (NIH, 1985) were followed and instructions given by our institutional animal ethical committee were maintained throughout the experiment.

Analgesic activity

The analgesic activity was determined by tail flick method ⁷. Wistar albino mice of either sex (20-30g) in the groups of six animals each were selected by random sampling technique. Paracetamol at a dose level of 100 mg/kg was administered as a reference drug for comparison. The test compounds at dose level of 100mg/kg were administered orally by intragastric tube. The animals were held in position by a suitable restrainer with the tail extending out and the tail (up to 5 cm) was then dipped in a beaker of water maintained at $55 \pm 5^{\circ}\text{C}$. The time in seconds taken to withdraw the tail clearly out of water was taken as the reaction time. The reading was recorded at 30, 60, 120 and 180 min. after administration of compounds. A cut off point of 10 sec. was observed to prevent the tail damage. The results are presented in Table-2.

Anti-inflammatory activity

The anti-inflammatory activity was determined by carrageenan-induced rat paw oedema method ⁷ in albino rats (n=6) of either sex (100-140 g). Rats were selected by random sampling technique. Paracetamol (100mg/kg) was administered as a reference drug. The test compounds were administered at dose level of 100 mg/kg orally 30 min. prior to the administration of carrageenan in the right hind paw of the rats. The paw thickness was measured using vernier callipers at 30, 60, 120 and 180 min. after carrageenan

administration. The results are presented in Table-3.

Antimicrobial activity

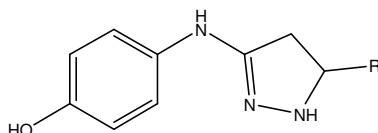
In vitro antimicrobial study was carried on Muller hinton agar (Hi-media) plates (37°C , 24 h) by agar diffusion cup plate method ⁸. All the compounds were screened for antimicrobial activity at 100 $\mu\text{g/ml}$ concentration against the following bacterial strains: *Staphylococcus aureus*, *Staphylococcus feacalis*, *Escherichia coli*, and *Salmonella typhi*. Antifungal activity was tested on Sabouraud dextrose agar (Hi-media) plates (26°C , 48-72 h) by cup plate method ⁸ against *Candida albicans* and *Aspergillus niger* at the concentration level of 100 $\mu\text{g/ml}$. Ciprofloxacin and Clotrimazole were used as standards for comparison of antibacterial and antifungal activity under the similar conditions. DMF was used as a solvent control for both antibacterial and antifungal activities. The results are presented in Table-4.

Statistical analysis

Data were analyzed by one -way ANOVA followed by Dunnett's *t*-test using computerized Graph Pad InStat version 3.05 (Graph Pad software, U.S.A.).

RESULTS

Biological results are reported in Table 2, 3 and 4, which also records the effects of the standard drug included for comparison, Series of compound are prepared in this study exhibited significant pharmacological properties in different biological models. The general pattern of pharmacological activity encountered in this synthesized compounds was seen mainly in their effect on pain perception and local inflammation. However, there was a small, well defined antimicrobial activity range associated with many of these compounds. Considerable variation of these effects were seen with each structural change, varying from agents that had less activity to those with high potency, and significant changes in potency resulted even from minor change in chemical structure as shown in Table 2, 3 and 4.

Table 1: Characterization data of compounds **1a-f** and **2a-f**

Compound	(R)	Mol. Form.	M.P. (°C)	Yield (%)
1a	-C ₆ H ₅	C ₁₅ H ₁₃ O ₂ N	148-150	72
1b	-2-furyl	C ₁₃ H ₁₁ O ₃ N	160-162	63
1c	-4-NO ₂ -C ₆ H ₄	C ₁₅ H ₁₂ O ₄ N ₂	108-110	81
1d	-4-OCH ₃ -C ₆ H ₄	C ₁₆ H ₁₅ O ₃ N	152-154	74
1e	-2-OH-C ₆ H ₄	C ₁₅ H ₁₃ O ₃ N	142-144	72
1f	-4-Cl-C ₆ H ₄	C ₁₅ H ₁₂ O ₂ NCl	150-152	75
2a	-C ₆ H ₅	C ₁₅ H ₁₅ N ₃ O	161-163	62
2b	-2-furyl	C ₁₃ H ₁₃ N ₃ O ₂	159-161	73
2c	-4-NO ₂ -C ₆ H ₄	C ₁₅ H ₁₄ N ₄ O ₃	182-184	69
2d	-4-OCH ₃ -C ₆ H ₄	C ₁₆ H ₁₇ N ₃ O ₂	143-145	72
2e	-2-OH-C ₆ H ₄	C ₁₅ H ₁₅ N ₃ O ₂	164-166	66
2f	-4-Cl-C ₆ H ₄	C ₁₅ H ₁₄ N ₃ OCl	190-192	78

Table 2: Analgesic activity (tail flick method) of compounds **2a-f**

Compd.	Dose mg/kg	Percentage of analgesic activity			
		30 min.	1 hour	2 hour	3 hour
2a	100	27 ± 0.12 [*]	30 ± 0.23 [*]	35 ± 0.43 [*]	30 ± 0.11 [*]
2b	100	33 ± 0.25 ^{**}	42 ± 0.09 ^{**}	44 ± 0.40 ^{**}	38 ± 0.31 ^{**}
2c	100	38 ± 0.54 ^{**}	43 ± 0.23 ^{**}	47 ± 0.43 ^{**}	38 ± 0.29 ^{**}
2d	100	44 ± 0.23 ^{**}	53 ± 0.29 ^{**}	58 ± 0.33 ^{**}	45 ± 0.36 ^{**}
2e	100	36 ± 0.32 ^{**}	43 ± 0.36 ^{**}	47 ± 0.38 ^{**}	38 ± 0.42 ^{**}
2f	100	42 ± 0.23 ^{**}	45 ± 0.73 ^{**}	50 ± 0.87 ^{**}	38 ± 0.65 ^{**}
Paracetamol	100	38 ± 0.42 ^{**}	47 ± 0.82 ^{**}	52 ± 0.71 ^{**}	33 ± 0.31 ^{**}
Control	—	3 ± 0.26	6 ± 0.44	4 ± 0.57	4 ± 0.91

Results are expressed in mean ± SEM (n=6) significance levels * P<0.05, ** P < 0.01 and *** P < 0.001 as compared with the respective control.

Analgesic Activity: Some of the compounds in this series exhibited activity in experimental models used. The particular interests are the results obtained in the Glassman's procedure which utilizes selective inhibition of inflammatory pain as a creation for anti-inflammatory drugs. When the structure of this synthesized compound is compared, it would appear that replacement in R with a p-nitro, p-

methoxy and p-chloro aryl groups (2c, 2e & 2f) showed promising analgesic activity.

Anti-inflammatory Activity: A number of agents caused marked reduction of the carrageenan induced edema of the rat foot, however, with exception of compounds 2f (R = p-Nitro phenyl). In this test also only analogs with a p-Methoxy phenyl group in R (2d) showed equal to that exhibited by the standard paracetamol. Compounds 2f, in

Table 3: Anti-inflammatory activity (carrageenan induced rat paw oedema method) of compounds **2a-f**.

Compd.	Dose mg/kg	Percentage inhibition			
		30 min.	1 hour	2 hour	3 hour
2a	100	26± 0.10 [*]	32± 0.62 [*]	39± 0.10 [*]	33± 0.07 [*]
2b	100	28± 0.19 [*]	37± 0.17 [*]	43± 0.78 [*]	36± 0.17 [*]
2c	100	27± 0.41 ^{**}	33± 0.81 [*]	38± 0.67 [*]	29± 0.24 [*]
2d	100	26± 0.40 [*]	32± 0.36 ^{**}	35± 0.96 ^{**}	27± 0.66 ^{**}
2e	100	28± 0.27 ^{**}	35± 0.49 ^{**}	41± 0.11 ^{**}	32± 0.53 ^{**}
2f	100	29± 0.78 ^{**}	33± 0.27 ^{**}	34± 0.42 ^{**}	27± 0.62 ^{**}
Control	-	5.11± 0.28	6.13± 0.26	5.68± 0.36	3.30± 0.91
Paracetamol	100	26± 0.29 ^{**}	30± 0.22 ^{**}	34± 0.91	28± 0.62 ^{**}

Results are expressed in mean ± SEM. (n=6) significance levels * P<0.05, ** P < 0.01 and *** P < 0.001 as compared with the respective control.

Table 4: Antibacterial and antifungal activity of compounds **2(a-f)**

Compd.	Conc.(µg/ml)	Zone of inhibition (mm)					
		<i>S. a</i>	<i>S. f</i>	<i>E. c</i>	<i>S. t</i>	<i>C. a</i>	<i>A. n</i>
2a	100	14	16	16	12	13	13
2b	100	13	12	15	11	12	11
2c	100	18	20	21	19	17	19
2d	100	16	15	17	14	14	13
2e	100	21	16	17	19	20	17
2f	100	18	18	19	18	21	24
Ciprofloxacin	10	29	31	32	26	-	-
Clotrimazole	20	-	-	-	-	28	27

*Average of three readings

S. a = *Staphylococcus aureus*; *S. f* = *Staphylococcus faecalis*; *E. c* = *Escherichia coli*; *S. t* = *Salmonella typhi*; *C. a* = *Candida albicans*; *A. n* = *Aspergillus niger*

addition to being the most potent agents of this series against rat-foot inflammation, were also found to be among the most active analgesic when assayed in Glassman's analgesic model.

Antimicrobial Activity: The in-vitro antimicrobial activity of compounds (2a-f) were determined by agar cup plate method, The results of which are summarized in Table 4. The antimicrobial data in table 4 clearly showed that the halogen, nitro & hydroxyl phenyl groups is by far the most active substituted R group. The methoxy group

generally confers weak antimicrobial activity. Phenyl and Furyl substitution are weakly active to inactive among the synthesized compounds. Compounds 2c, 2e and 2f showed good activity against *S. aureus* and *S. typhi*. The compound 2c & 2f exhibit promising activity against *C. albicans* and *A. niger*. However, the tested compounds were less active in comparison to Ciprofloxacin and Clotrimazole (standard Drugs).

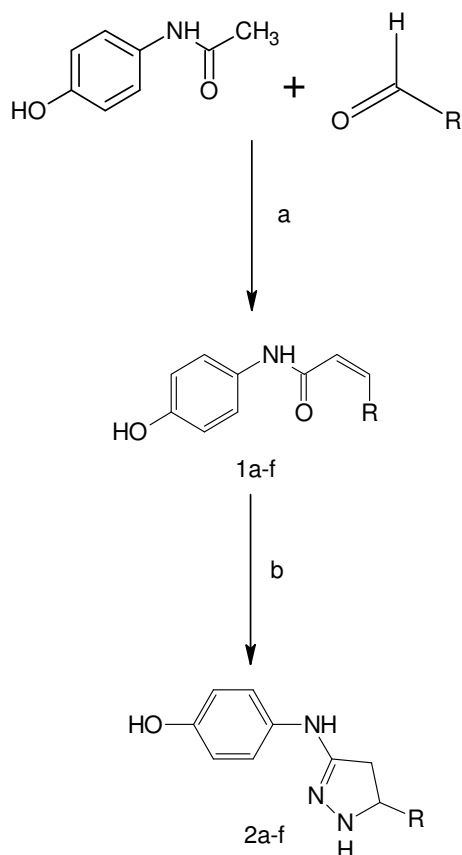


Fig 1: R = -C₆H₅ (**1a**, **2a**)
 -2-furyl (**1b**, **2b**)
 -4-NO₂-C₆H₄ (**1c**, **2c**)
 -4-OCH₃-C₆H₄ (**1d**, **2d**)
 -2-OH-C₆H₄ (**1e**, **2e**)
 -4-Cl-C₆H₄ (**1f**, **2f**)

DISCUSSION

The purpose of the present study was to examine whether molecular modification might result in detection of new potential antirheumatic drugs. A series of compounds were prepared and assayed in a variety of biological test for analgesic, anti-inflammatory and antimicrobial activity. The data reported in Table 2, 3 & 4 shows that effect of variation in chemical structure on activity was rather unpredictable. Seldom did a particular structural modification lead to uniform alteration in activity in all tests. However some point of interest did emerge and a few generalizations can be made. The substitution which appeared to be most important for high order of activity in the greatest number of test was the p-chloroaryl group. The introduction of Para nitro and p-hydroxy group in aryl

moiety of the pyrazole analogs 2c and 2e produce compounds with potent analgesic, anti-inflammatory and, in a few cases, antimicrobial properties.

CONCLUSION

In conclusion, the results of this investigation revealed that *the observed increase in analgesic, anti-inflammatory and antimicrobial activities are attributed to the presence of 4-NO₂, 2-OH and 4-Cl in phenyl ring at 5-position of pyrazoline ring of synthesized compounds.* Obviously, the comparative evaluation of active compounds will required further studies; the data reported in this article may be helpful guide for the medicinal chemist who are working in this area.

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