Synthesis and Anti-Inflammatory Activity of Pyrazolines

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Abstract: Some new pyrazoline derivatives were synthesized by reacting chalcones of 2-acetyl thiophene with phenyl hydrazine hydrochloride in the presence of alcohol. The synthesized compounds were identified by spectral data and screened for anti-inflammatory activity. Some of these compounds showed moderate to considerable anti-inflammatory activity.

Keywords: Synthesis, Pyrazolines, Anti-inflammatory activity.

Introduction

Compounds with pyrazoline structures are known to possess antimicrobial¹⁻³, anti-inflammatory⁴, antidepressant^{5,6}, anti-tubercular⁷ activities. In the present study some new pyrazoline derivatives (**1-5**) have been synthesized by the reaction of chalcones of 2-acetyl thiophene and phenyl hydrazine hydrochloride. The structures of the various synthesized compounds are assigned on the basis of elemental analysis, IR and ¹H NMR spectral data. These compounds were also screened for their anti-inflammatory activity.

Experimental

Melting points were determined on a capillary melting point apparatus and are uncorrected. ¹H NMR spectra was recorded in the indicated solvent on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer AC-1 spectrophotometer. Microanalyses were performed on Carlo Erba EA-1108 element analyzer and were within the $\pm 0.5\%$ of the theoretical values. Column chromatography was performed on silica gel (Merck, 60-120 mesh).

General procedure for the preparation of 2-pyrazolines (1-5)

A chalcone of 2-acetyl thiophene (0.001 mol) dissolved in 20 mL of ethanol and phenyl hydrazine hydrochloride (500 mg) was added to it. To this mixture 0.3 mL of pyridine was added drop wise at room temperature. After that the mixture was refluxed for 5-6 hours and

the solvent was evaporated completely. The reaction mixture was poured into ice-cold water and the solid mass that separated out was filtered, dried and purified by column chromatography with ethyl acetate/ hexane and recrystallized from chloroform.

Scheme 1. Synthesis of some new 2-pyrazoline derivatives

Table 1. Physical data of compounds (1-5)

Compound	M.F.	M.P, °C	Yield, %	Elemental analyses, %					
				C		H		N	
				Calcd	Found	Calcd	Found	Calcd	Found
1	C ₁₇ H ₁₂ N ₂ S ₂	210	71	66.23	66.12	3.89	3.81	9.09	9.06
2	C ₂₁ H ₁₉ N ₃ S	137	74	72.07	71.86	5.80	5.61	12.61	12.54
3	C ₁₉ H ₁₃ N ₂ SCl	239	74	67.65	67.64	3.8	3.74	8.30	8.28
4	C ₁₉ H ₁₂ N ₂ SCl ₂	246	73	60.96	60.81	3.2	3.04	7.48	7.42
5	C ₁₉ H ₁₃ N ₂ SF	227	68	71.47	71.42	4.07	4.04	8.77	8.74

Table 2. Spectral data of the compounds (1-5).

Compound	IR (KBr, cm ⁻¹)	¹ H NMR (CDCl ₃ , ppm)
1	1594 (C=N), 1112 (C-N), 706 (C-S).	3.25 (1H, dd, HA), 3.80 (1H, dd, H B), 5.50 (1H, dd, H X), 6.80 – 7.50 (11H, Ar-H).
2	1520 (C=N), 1080 (C-N), 690 (C-S).	3.10 (6H, s, N(CH ₃) ₂), 3.21 (1H, dd, HA), 3.80 (1H, dd, HB), 5.50 (1H, dd, HX), 6.70-8.10 (12H, Ar-H).
3	1595 (C=N), 1097 (C-N), 689 (C-S), 822 (C-Cl).	3.18 (1H, dd, HA), 3.85 (1H, dd, HB), 5.30 (1H, dd, HX), 6.40-7.90 (12H, Ar-H).
4	1645 (C=N), 1350 (C-N), 716 (C-S), 855 (C-Cl).	3.05 (1H, dd, HA), 3.91 (1H, dd, HB), 5.6 (1H, dd, HX), 6.70–7.60 (11H, Ar-H).
5	1640 (C=N), 1352 (C-N), 680 (C-S), 8.70 (C-F).	3.18 (1H, dd, HA), 3.88 (1H, dd, HB), 5.28 (1H, dd, HX), 6.80 – 7.45 (12H, Ar-H).

Anti-inflammatory activity

Synthesized compounds (**1–5**) were tested for their anti-inflammatory activity. Male albino rats weighing between 200–250 g were used for the experiment. Carragenan induced paw oedema method described by Singh and Ghosh⁸ was followed for the acute anti-inflammatory model and the results are presented in Table 3.

Table 3. Anti-inflammatory activity of the compounds (**1–5**).

Compound	% increase in paw thickness of various time intervals					
	0.5 h	01 h	2 h	3 h	4 h	6 h
Standard	20.26 ±0.64	23.95 ±0.66	58.02 ±1.54	67.93 ±1.65	97.09 ±1.95	98.98 ±1.98
Control	15.65±	21.95±	38.13±	43.15±	66.26±	75.85±
1	1.42	2.30*	2.61	3.40*	3.96**	1.53
2	20.62± 2.57*	31.34± 2.46*	46.38± 1.52	65.64± 3.85**	71.63± 2.85***	78.98± 1.87
3	18.84± 1.52	27.85± 3.42*	42.85± 3.84**	58.67± 2.02	79.7± 1.73	93.63± 1.65
4	19.87± 2.29*	31.48± 3.65**	57.85± 2.42	62.12± 1.45	86.93± 3.14*	96.4± 1.97
5	20.06± 1.48	31.69± 2.86*	46.85± 3.76**	58.84± 1.75*	61.94± 2.74**	92.75± 1.85

Control: 1% sodium CMC gel, standard: aceclofenac standard and sample solution is 100 mg/ kg body weight, values are expressed as mean $\pm$ (n = 6)* = 2.28, ** = 3.75, *** = 4.35. P* < 0.05, P** < 0.01, P*** < 0.001 compared to control student t-test

Results and Discussion

The screening results revealed that the compounds (**1–5**) exhibited moderate to considerable activity when compared with reference standard aceclofenac. The synthesized compounds showed anti-inflammatory activity in the range of 50–80% whereas standard drug showed 80–85% inhibition in paw edema. The results of anti-inflammatory activity indicated that compounds **3**, **4** and **5** showed maximum anti-inflammatory activity.

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