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SYNTHESIS AND ANTIHISTAMINIC ACTIVITY OF NOVEL PYRAZOLINE DERIVATIVES

S.A.RAHAMAN*[2],Y.RAGJENDRA PRASAD[1],K.BHUVANESWARI[2], PHANI KUMAR[1]

[1]UNIVERISTY COLLEGE OF PHARMACEUTICAL SCIENCES, ANDHRA UNIVERSITY,VISHAKHAPATNAM-530003,A.P.,INDIA.

[2]DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, KVSR SIDDARTHA COLLEGE OF PHARMACEUTICAL SCIENCES, SIDDARTHA NAGAR, VIJAYAWADA-520010,A.P.,INDIA.

Corres.author: rahaman_pharma@rediffmail.com

ABSTRACT: Pyrazolines are one of the heterocyclic compounds with very important biological activities. In this view, it was proposed to synthesize some novel pyrazolines from chalcones. The condensation of chalcones of 4[1]-piperazine acetophenone with phenyl hydrazine hydrochloride gives pyrazoline derivatives(RP_{1-8}). The structures of the synthesized RP_{1-8} were assigned on the basis of elemental analysis, IR and ^1H NMR spectroscopy data. These compounds were also screened for their anti-histaminic activity. The recorded % of histamine inhibition showed significant anti-histaminic activity, when compared with standard antihistamine drug mepiramine.
Key words: Chalcone, pyrazoline,anti-histaminic activity.

INTRODUCTION

Pyrazolines are heterocyclic compounds which posses wide range of biological activities such as anti bacterial[1,2], anti depressant[3,4], anti tubercular[5,6], anti amoebic[7,8], anti inflammatory[9], herbicidal & insecticidal[10,11], cardiovascular[12] activity etc. To synthesize pyrazoline derivatives, we selected chalcone as starting material. Generally chalcones are 1,3-diaryl-2-propene-1-ones. In the present communication, we report the reaction of different chalcone derivatives**(1)** with phenylhydrazine hydrochloride**(2)** to form pyrozalines $RP_{(1-8)}$ .The structures of various synthesized compounds were assigned on the basis of elemental analysis, IR and ^1H NMR spectral data. These compounds were also screened for antihistaminic activity.

EXPERIMENTAL

All the melting points were determined by digital melting point apparatus. The ^1H NMR spectral data were recorded on Bruker AV 400 MHZ in DMSO using TMS as an internal standard. The IR spectra were recorded on Perkin-Elmer 377 spectrophotometer.

General procedure for the preparation of pyrazoline derivatives $RP_{(1-8)}$:

A mixture of chalcones of 4[1]-piperazino acetophenone(1eq.) and phenylhydrazine hydrochloride(1eq.) in absolute ethanol (10ml) were refluxed on a water bath for 6 hours[13]. The solvent was completely evaporated and the residue was poured into ice cold water. The precipitated solid was collected by filtration and crystallized from methanol as solvent to give pyrazoline derivatives RP_{1-8}.

Table-1: Physical Data of Compounds (RP_1-RP_8)

Compund	R	R^1	R^2	Molecular Formula	M.P. (^oC)	Yeild (%)
RP_1	H	H	H	$C_{25}H_{26}N_4$	164-166	68.5
RP_2	H	H	Cl	$C_{25}H_{25}N_4Cl$	196-198	71.45
RP_3	H	Br	H	$C_{25}H_{25}N_4Br$	204	65.8
RP_4	OH	H	H	$C_{25}H_{26}N_4O$	173-175	72
RP_5	OH	H	$-OCH_3$	$C_{26}H_{29}N_4O_2$	138-140	67.4
RP_6	H	H	$-N(CH_3)_2$	$C_{27}H_{30}N_5$	184-185	71.8
RP_7	H	H	$-NO_2$	$C_{25}H_{25}N_5O_2$	214-216	76
RP_8	Cl	H	Cl	$C_{25}H_{24}N_5Cl$	222-224	81

Table-2: IR[14] & ^{1}H NMR[15] Spectral Data of Compounds (RP_1-RP_8)

Compound	IR (cm^{-1})	^{1}H NMR($CDCl_3$)(SPPM)
RP_1	3422.4 -------N-H str 1597.4 ------C=N str 1515.6 ------C=C str	(i)2.5 (1H , bS , N-H) (ii)3.19 & 3.37 (8H ,piperazinylprotons) (iii)3.37 (1H , dd , $4H_A$) (iv)3.85 (1H ,dd , $4H_B$) (v)5.5(1H , dd , $5H_C$) (vi)6.97-7.62(14H,m, aromatic Protons)
RP_2	3427 --------N-H str 1599.5 ------C=N str 1496 --------C=C str	(i)2.46 (1H , bS , N-H) (ii)3.18 & 3.47 (8H, piperazinyl protons) (iii)3.0 (1H , dd , $4H_A$) (iv)3.91 (1H , dd , $4H_B$) (v)5.41 (1H , dd , $5H_C$) (vi)6.6-7.83(13H,m, aromatic protons)
RP_3	3399.3---------N-H str 1596.6 --------C=N str 1496 -----------C=C str	(i)2.5 (1H , bS , N-H) (ii)3.17 & 3,54 (8H, piperazinyl protons) (iii)3.09 (1H , dd , $4H_A$) (iv)3.9 (1H , dd , $4H_B$) (v)5.4 (1H , dd , $4H_B$) (vi)6.68-8.0(13H,m, aromatic protons)
RP_4	3399.3 --------N-H str 1596.6 --------C=N str 1506.6 --------C=C str	(i)1.9 (1H , bS , N-H) (ii)2.6&3.4(8H,piperazinyl protons) (iii)3.1 (1H , dd , $4H_A$) (iv)3.84 (1H , dd , $4H_B$) (v)5.56 (1H , dd , $5H_C$) (vi)6.7-7.7(13H,m, aromatic protons)
	3403 ---------N-H str	(i)2.5 (1H , S , N-H) (ii)3.2&3,47(8H, Piperazinyl protons)

RP_5	1581.4 ------C=N str 1508.3 -------C=C str	(iii)3.02 (1H , dd , $4H_A$) (iv)4.0 (1H , dd , $4H_B$) (v)5.5 (1H , dd , $5H_C$) (vi)6.71-7.7(12,m, aromatic protons)
RP_6	3418 -------- N-H str 1581.4 -------C=N str 1513 --------- C=C str	(i)2.5 (1H , s , N-H) (ii)3.2 & 3.47 (8H , piperazinyl protons) (iii)3.02 (1H , dd , $4H_A$) (iv04.05 (1H , dd , $4H_B$) (v)5.34 (1H , dd , $5H_C$) (vi)6.64-7.07 (13H , m, aromatic Protons)
RP_7	3420.6 -------- N-H str 1596 ---------- C=N str 1521 ----------C=C str	(i)2.5 (1H , bS , N-H) (ii)3.21(8H,piperazinyl protons) (iii)3.1 (1H , dd , $4H_A$) (iv)3.97 (1H , dd , $4H_B$) (v)5.62 (1H , dd , $5H_C$) (vi)6.69-8.28(13H, m,aromatic protons)
RP_8	3428 --------- N-H str 1597.5 -------- C=N str 1501 ----------C=C str	(i)1.85 (1H , bS , N-H) (ii)3.34 & 3.47 (8H, piperazinyl protons) (iii)2.9 (1H , dd , $4H_A$) (iv)3.82 (1H , dd , $4H_B$) (v)5.47 (1H , dd , $5H_C$) (vi)6.87-7.57 (12H , m, aromatic protons)

ESTIMATION OF ANTI-HISTAMINIC ACTIVITY

The compounds(RP_1-RP_8) were evaluated for their anti-histaminic activity on guinea pig ileum. Guinea Pig of either sex 400-500 grms., were used in this study. These animals were sacrificed by stunning and exsanguinations. The abdomen was opened with scissors and lifted the caecum to trace the illeo-caecal junction. A required length of the long ileal portion was cut, removed and immediately placed on the watch glass containing tyrode solution. Then the mesentery was trimmed and with gentle care the contents of the ileum were cleaned by pumping the tyrode solution into the lumen of the ileum. The ileum was cut into small segments of 2 to 3 cms., length. One piece of ileum was taken and a thread was tied to the top & bottom ends without closing the lumen and the tissue was mounted in the organ bath containing tyrode solution, maintained at 37 ^{0} C and bubbled with oxygen air. A tension of 0.5grm is applied and the tissue is allowed to equilibrate for 30 minutes before adding drugs to the organ bath.

The concentration dependent Reponses due to histamine were recorded using frontal writing lever. A contact time of 30 seconds and 5 minutes are kept for proper recording of the responses. Initially histamine dose was given with a concentration of 0.1 ug/ml, 0.4 ug/ml and 0.8 ug/ml. From that 0.4 ug/ml concentration was selected as sub-maximal dose.

Test Solution Preparation: 10 mg of each test sample was dissolved in DMSO solvent. Different solutions were made with DNS (Dextrose Normal Saline), solution to get a concentration of 0.1 ug/ml, 0.2 ug/ml, 0.4 ug/ml and 0.8 ug/ml.

Standard Solution Preparation: 10 mg of mepiramine sample was dissolved in DNS solution. The different dilutions of standard solutions were prepared to get concentrations of 0.1 ug/ml, 0.2 ug/ml, 0.4 ug/ml and 0.8 ug/ml.

The responses were recorded on a kymograph. The graph was plotted taking concentration of the test or standard on X-axis and % inhibition on Y-axis. The % inhibitions were calculated and values are shown in the table.

$$\% \text{ histamine inhibition} = \frac{a-b}{a} \times 100$$

Where a=height of histamine response (in cm)
b= height of test or standard response (in cm)

% Histamine inhibiton of newly synthesized Pyrazolines

Sample code	% inhibition			
	0.1 ug	**0.2 ug**	**0.4 ug**	**0.5 ug**
RP_1	4.5	10.6	21.4	42.8
RP_2	11.3	25.2	49.7	66.66
RP_3	10.8	27.8	44.9	58.0
RP_4	7.4	21.5	33.33	49.02
RP_5	6.2	20	28.4	49.8
RP_6	9.4	22.24	32.5	47.6
RP_7	2.5	10.8	26.7	37.2
RP_8	15.25	38.9	52.4	74.6

RESULTS AND DISCUSSION

- The eight novel pyrazolines were synthesized by condensation of various chalcones of 4'-piperazine acetophenone with phenyl hydrazine hydro chloride in ethanol and pyridine. After that the compounds were purified either by crystallization (or) column chromatography. The structures of the synthesized compounds were established on the basis of spectral data.

- The newly synthesized pyrazoline derivatives showed moderate to considerable anti-histaminic activity.Among the eight pyrazoline derivatives only electron with drawing substituent i.e. halogen substituted compounds RP_2, RP_3& RP_8 showed better antagonistic activity.

- The significant out come of the study is the emergence of pyrazolines with piperazine nucleus as promising anti-histaminic agents in general. An extension of the study in future may contribute to the development of useful anti-histaminic agents in this series.

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