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SHORT COMMUNICATION

Synthesis and anti-histaminic activity of some novel pyrimidines

Sk.A. Rahaman [a,*], Y. Rajendra Pasad [b], Phani Kumar [b], Bharath Kumar [b]

[a] *Department of Pharmaceutical Chemistry, KVSR Siddhartha College of Pharmaceutical Sciences, Siddhartha Nagar, Vijayawada 520 010, AP, India*
[b] *University College of Pharmaceutical Sciences, Andhra University, Vishakapatnam 530 003, AP, India*

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KEYWORDS

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Abstract Novel pyrimidines were prepared by the condensation of chalcones of 4′-piperazine acetophenone with guanidine HCl. The structures of the synthesized compounds **RP 1–5** were assigned on the basis of elemental analysis, IR, ^{1}H NMR and mass spectroscopy. These compounds were also screened for anti-histaminic activity. The recorded percentage of histamine inhibition showed a significant anti-histaminic activity when compared to the reference anti-histaminic drug mepiramine.

1. Introduction

Pyrimidines are an important class of heterocyclic compounds, which possess a wide range of biological activities such as anticancer (Mattew et al., 1984; Yamakawa et al., 1990), antibacterial (Isida et al., 1960), anti-inflammatory (Hogale et al., 1986), antiviral (Ahluwalia et al., 1987), antitubercular (Bhat et al., 1972), antihypertensive (Ishitsuka et al., 1982) and anticonvulsant (Ninomiya et al., 1990) activities.

* Corresponding author.
E-mail address: rahaman_pharma@rediffmail.com (Sk.A. Rahaman).

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2. Experimental

All the melting points were determined by a digital melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin–Elmer 377 spectrophotometer, ^{1}H NMR spectra were measured on Bruker AV 400 MHz using DMSO as a solvent and TMS as an internal standard.

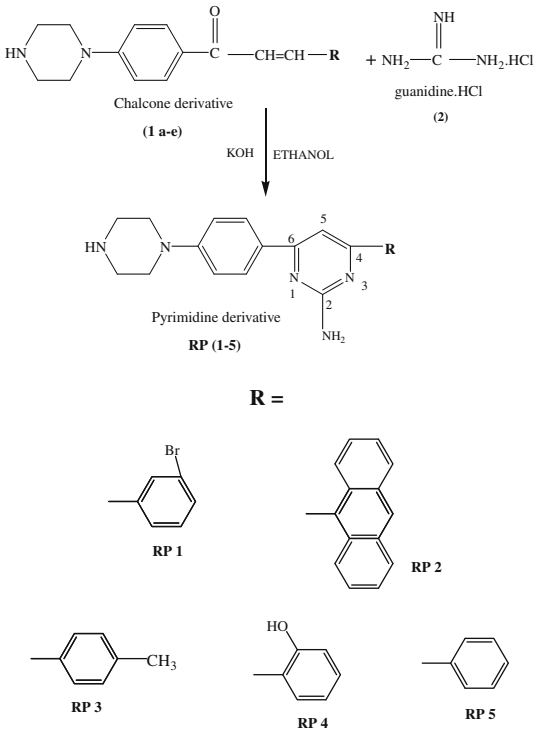
2.1. Preparation of chalcone derivatives (*1a–e*)

A mixture of 4′-piperazine acetophenone (0.01 mole) and aryl aldehyde (0.01 mole) was stirred in methanol (15 ml), then an aqueous solution of 40% KOH (10 ml) was added. The mixture was kept overnight at room temperature, poured into crushed ice and then acidified with HCl. The solid separated was filtered and crystallized from ethylacetate and methanol mixture (8:2).

2.2. General procedure for the preparation of pyrimidines *RP (1–5)*

A mixture of appropriate chalcones of **1a–e** (1 e.q.) and guanidine hydrochloride (1 e.q.) in absolute ethanol (10 ml) was

refluxed on a water bath for 6 h (Meazza et al., 1993). The solvent was completely evaporated and the residue was poured into ice cold water. The precipitated solid was collected by filtration, purified on silica gel column using methanol and ethylacetate mixture (1:9) solvent system.



2.3. Estimation of anti-histaminic activity

Anti-histaminic activity of the synthesized pyrimidine derivatives was estimated on guinea pigs of either sex 400–550 mg. They were sacrificed by stunning and exsanguinations (Kulkarni, 2002). The abdomen of guinea pig was opened with scissors and the caecum was lifted 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 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 2–3 cm long. One piece of ileum was taken and a thread was tied to top and bottom ends without closing the lumen and the tissue was mounted in the organ bath containing tyrode solution. The organ bath temperature was maintained at 37 °C and bubbled with oxygen air. A tension of 0.5 g was applied and the tissue was allowed to equilibrate for 30 min before adding drugs to the organ bath.

The concentration dependent responses due to histamine were recorded using frontal writing lever. A contact time of 30 s and 5 min time cycle were kept for proper recording of the responses. Initially histamine dose was given with a concentration of 0.1 μg/ml, then 0.2 μg/ml, 0.4 μg/ml and 0.8 μg/ml. Among these concentrations 0.4 μg/ml was selected as submaximal dose.

2.4. Test solution preparation

10 mg of each test sample was dissolved in 10 ml DMSO solvent. The resulting solutions were diluted with DNS (dextrose normal saline) solution to get concentrations of 0.1 μg/ml, 0.2 μg/ml, 0.4 μg/ml and 0.8 μg/ml.

2.5. Standard solution preparation

Ten milligrams of sample were dissolved in 10 ml DNS solution. Then different dilutions of standard solution were prepared to get concentrations of 0.1 μg/ml, 0.2 μg/ml, 0.4 μg/ml and 0.8 μg/ml.

The responses were recorded on a kymograph. The graph was plotted taking the concentration of test/standard on *X*-axis and % inhibition on *Y* axis (see Tables 1 and 2).

Formula for calculation:

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

where *a* is the height of the histamine response (in cm) and *b* is the height of test/standard response (in cm).

By using the above-mentioned formula percentage of histamine inhibition was calculated and the values are given in Table 3.

3. Results and discussion

To prepare new pyrimidine derivatives we used chalcone as a starting material. Chalcones are 1,3-diaryl-2-propene-1-ones. In the present communication, we reported that the reaction between different chalcone derivatives (**1a**–**e**) and guanidine HCl (**2**) gives pyrimidine derivatives **RP** (**1**–**5**). The structures of various synthesized compounds were assigned on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral analysis. These compounds were also screened for their anti-histaminic activity.

Table 1 Characterization data of compounds **RP** (**1**–**5**).

Compound	Molecular formula	M.wt.	M.P. (°C)	Yield (%)
RP 1	$C_{20}H_{20}N_5Br$	407	107–108	64.5
RP 2	$C_{28}H_{25}N_5$	431.4	145–148	82
RP 3	$C_{21}H_{23}N_5$	345	95–98	77.4
RP 4	$C_{20}H_{21}N_5O$	347	144–145	71.5
RP 5	$C_{20}H_{21}N_5$	331	135–137	85.7

Table 2 IR and ^{1}H NMR Spectral data of compounds **RP 1–5**.

Compound	IR (cm^{-1}) (KBr)	^{1}H NMR (DMSO) (δ ppm)
RP 1	(i) N–H str – 3341 (ii) C═N str – 1598 (iii) C═C str – 1564 (iv) C–Br str – 536	1.867 (1H, s, aliphatic N–H) 2.507 and 2.880 (8H, piperazine protons) 4.263 (2H, bs, 1°NH_2), 8.423 (1H, s, C–5H) 6.646 (1H, s, C–2^{1}H), 6.929–8.236 (7H, aromatic protons)
RP 2	(i) N–H str – 3392 (ii) C═N str – 1602 (iii) C═C str – 1567	1.873 (1H, s, aliphatic N–H) 2.507 and 2.853 (8H, piperazine protons) 4.145 (2H, bs, 1°NH_2), 7.208 (1H, s, C–5H), 6.751–8.699 (13H, aromatic protons)
RP 3	(i) N–H str – 3398 (ii) C═N str – 1603 (iii) C═C str – 1575	1.879 (1H, s, aliphatic N–H), 2.506 and 2.877 (8H, piperazine protons) 2.377 (3H, s, benzylic protons), 3.740 (2H, bs, 1°NH_2) 7.564 (1H, s, C–5H), 6.520–8.110 (8H, aromatic protons)
RP 4	(i) N–H str – 3400 (ii) C═N str – 1572 (iii) C–Cl str – 655	1.894 (1H, bs, aliphatic N–H) 2.506 and 2.99 (8H, piperazine protons) 3.939 (2H, bs, 1°NH_2), 7.482 (1H, s, C–5H) 6.375 (1H, s, C–2′OH), 6.732–8.113 (8H, aromatic protons)
RP 5	(i) N–H str – 3405 (ii) C═N str – 1602 (iii) C═C str – 1575	1.871 (1H, s, aliphatic N–H) 2.506 and 2.865 (8H, piperazine protons) 3.999 (2H, bs, 1°NH_2), 7.606 (1H, s, C–5H) 6.584–7.838 (9H, aromatic protons)

Table 3 Percentage of histamine inhibition of the newly synthesized pyrimidines **RP (1–5)**.

Tested compound	% Inhibition			
	0.1 μg	0.2 μg	0.4 μg	0.8 μg
RP 1	9.5	33.33	46.66	60
RP 2	0	2.1	27.4	42.6
RP 3	3.2	12.4	29.81	49.32
RP 4	10.81	41.8	51.94	67.4
RP 5	0	0	14.8	29.5
Mepiramine	17.6	100	100	100

DMSO was used as a control.

The newly synthesized pyrimidines showed significant anti-histaminic activity. If the concentration of pyrimidine derivatives **RP (1–5)** increases, the percentage of histamine inhibition also increases. Among the five pyrimidine derivatives **RP (1–5)**, only bromine-substituted and 2-hydroxyphenyl-substituted pyrimidines showed greater anti-histaminic activity.

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تشييد واختبار الفاعلية المضادة للهستامين لبعض مركبات البيريميدين الجديدة

سك. أ. رحمن[1*] ، ي. راجندرا باساد ، فاني كومار[2] و بهاراث كومار[2]

ملخص البحث

تم تحضير مركبات بيريميدين جديدة وذلك بتكثيف تشالكونات مركب 4- بايبرازين أسيتوفينون مع جوانيدين هيدروكلوريد. وتم تعيين الصيغ البنائية للمركبات المشيدة RP(1-5) على أساس تحليل العناصر، ومطياف الأشعة تحت الحمراء، والرنين النووي المغناطيسي ^1H، ومطياف الكتلة. وتم اختبار هذه المركبات لفاعليتها المضادة للهستامين. وأظهرت نسبة تثبيط الهستامين المسجلة وجود فاعلية معنوية مضادة للهستامين عند مقارنتها بالدواء المرجعي المضاد للهستامين ميبيرامين.

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* المؤلف المراسل.