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ANTI-HISTAMINE ACTIVITY OF NEWLY SYNTHESIZED PYRIMIDINES

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ABSTRACT

Pyrimidines are one of the most important class of heterocyclic compounds with a variety of biological activities. Keeping this in view, it was proposed to synthesize some novel pyrimidines from chalcones. The condensation of chalcones of 4'-piperzine acetophenone with guanidine hydrochloride gives pyrimidines. The structures of the synthesized compounds RCP_{1-5} were assigned on the basis of elemental analysis, IR and ^1H NMR spectroscopy data. These compounds were also screened for their anti-histamine activity. The recorded % of histamine inhibition showed significant anti-histamine activity, when compared with standard antihistamine drug mepiramine.

Key words : Chalcone, Pyrimidine, Anti-histamine activity

INTRODUCTION

Pyrimidines are heterocyclic compounds, which posses wide range of biological activities such as antibacterial[1,2], anticancer[3,4], antitubercular[5], antiviral[6,7], antiinflammatory[8], antihistamine[9,10], antimalarial activity, etc. To synthesize pyrimidine derivatives we selected starting material as Chalcone. Generally chalcones are 1, 3-diaryl-2-propene-1-ones. In the present communication, we report the reaction of different Chalcone derivatives **(1)** with guanidine. HCl **(2)** to form pyrimidines RCP_{1-5}. 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 antihistamine activity.

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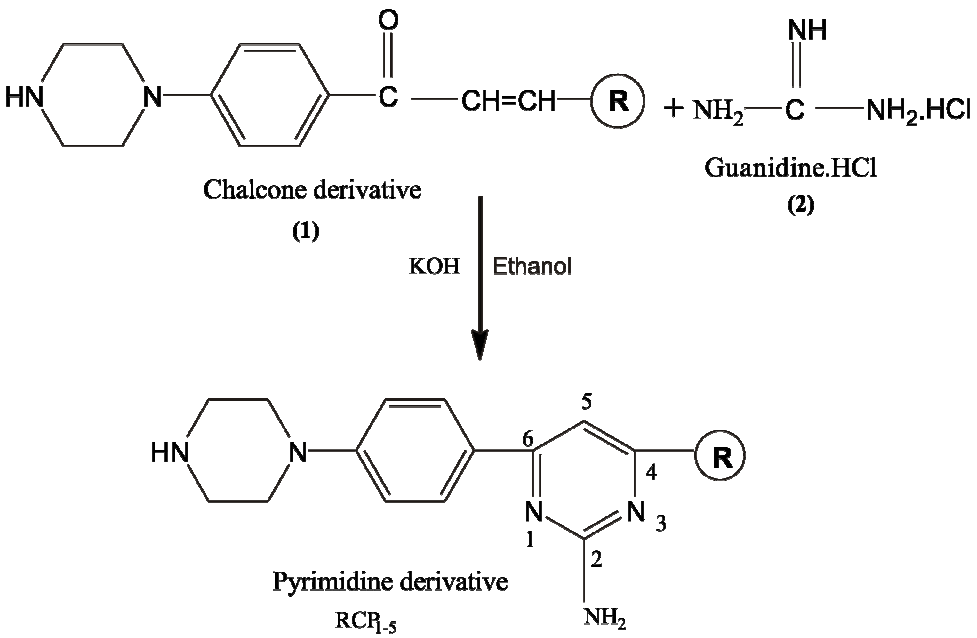
EXPERIMENTAL

All the melting points were determined by digital melting point apparatus. The ^1H NMR spectra 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 pyrimidines RCP_{1-5}

A mixture of chalcones of 4'-piperizino acetophenone (1 eq.) and guanidine hydrochloride (1 eq.) in absolute ethanol (10 mL) were refluxed on a water bath for 6 hours. The solvent was completely evaporated and the residue was poured into ice cold water. The precipitated solid was collected by filtration and crystallized from suitable solvent to give the pyrimidine derivatives RCP_{1-5}.



Scheme of general reaction

Where (R) is –

RCP_1 = 4' - Fluoro phenyl,

RCP_2 = 2' – Chlorophenyl,

RCP_3 = 2', 4' - Dichloro phenyl

RCP_4 = 4' – Chlorophenyl and

RCP_5 = 2' – Hydroxyl - 4' - methoxyphenyl

Table 1. Characterization data of compounds $RCP_{(1-5)}$

Compound	Molecular formula	M. Wt.	M. P. (°C)	Yield (%)
RCP_1	$C_{20}H_{20}N_5F$	348.0	110-112	72.00
RCP_2	$C_{20}H_{20}N_5Cl$	365.5	117-119	78.00
RCP_3	$C_{20}H_{19}N_5Cl_2$	400.0	128-130	80.12
RCP_4	$C_{20}H_{20}N_5Cl$	365.5	124-126	84.50
RCP_5	$C_{21}H_{23}N_5O_2$	377.0	155-156	69.00

Table 2. IR and ^{1}H NMR spectral data of compounds RCP_{1-5}

Compound	IR (cm^{-1}) (KBr)	^{1}H NMR (DMSO) (δ ppm)	
RCP_1	N-H str --- 3356.00	1.863	(1H, s, aliphatic N-H)
	C=N str --- 1570.89	4.197	(2H, bs, 1°NH_2)
	C=C str --- 1601.87	2.507	(4H, piperzine protons)
	C-F str --- 1229.48	2.933	(4H, piperzine protons)
		7.609	(1H, s, C- 5H)
		6.582-8.287	(8H, aromatic protons)
RCP_2	N-H str --- 3370.08	1.666	(1H, s, aliphatic N-H)
	C=C str --- 1683.49	2.508-2.806	(8H, piperzine protons)
	C=N str --- 1567.93	3.71	(2H, bs, 1o NH_2)
	C-Cl str --- 651.48	7.631	(1H, s, C-5H)
		6.859-7.520	(8H, aromatic protons)
RCP_3	N-H str --- 3365.35	1.842	(1H, s, aliphatic N-H)
	C=C str --- 1594.27	2.507-2.967	(8H, piperzine protons)
	C=N str --- 1527.99	3.977	(2H, bs, 1o NH_2)
	C-Cl str --- 669.55	7.227	(1H, s, C-5H)
		6.705 – 8.062	(7H, aromatic protons)

Compound	IR (cm^{-1}) (KBr)	^1H NMR (DMSO) (δ ppm)	
RCP_4	N-H str --- 3400.69	1.742	(1H, s, aliphatic N-H)
	C=N str --- 1574.04	2.507-2.850	(8H, piperzine protons)
	C-Cl str --- 653.89	3.616	(2H, bs, 1o NH_2)
		8.456	(1H, s, C-5H)
		6.998–8.227	(8H, aromatic protons)
RCP_5	N-H str --- 3407.17	1.896	(1H, s, aliphatic N-H)
	C=C str --- 1604.30	2.506, 2.938	(8H, piperzine protons)
	C=N str --- 1572.58	3.885	(3H, s, -OCH_3)
	C-O str --- 1248.41	4.100	(2H, s, NH_2)
		7.518	(1H, bs, C-5H)
		6.881-8.116	(8H, aromatic protons)

Anti-histamine activity

Antihistamine drugs act on H_1 receptors. Pharmacological actions of histamine on H_1 receptors are smooth muscle contractions (bronchi, smooth muscle of ileum) and dilates the blood vessels. The widely used antihistamine drugs are mepiramine, chlorpheniramine, diphenhydramine, cyclizine, meclizine and buclizine. Among these drugs cyclizine, meclizine and buclizine contain piperzine heterocyclic nucleus. The newly synthesized pyrimidine derivatives RCP_{1-5} also showed antihistaminic activity because they contain piperzine nucleus.

Procedure

Antihistamine activity was done on guinea pig for the synthesized pyrimidine derivatives RCP_{1-5}. Guinea pig of either sex 400 g – 550 g are used. They are sacrificed by stunning and exsanguinations[10]. The abdomen is opened with scissors and lifted the caecum to trace the illeo-caecal junction. A required length of the long ileal portion was cut and 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 2-3 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 and the temperature was maintained at 37°C. Then the solution was bubbled with oxygen (air). A tension of 0. 5 g is applied and the tissue is allowed to equilibrate for 30 minutes 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 sec and 5 min time cycle are 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. From these concentrations 0.4 µg/mL concentration was selected as sub maximal dose.

Test solution preparation

10 mg of each test sample was dissolved in 10 mL of DMSO solvent. Then different dilutions were made 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.

Standard solution preparation

10 mg of sample was 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.

Table 3. % Histamine inhibitions of newly synthesized pyrimidines RCP_{1-5}

Sample code	% Inhibition			
	0.1 µg	**0.2 µg**	**0.4 µg**	**0.8 µg**
RCP_1	4.32	8.30	38.88	83.30
RCP_2	3.81	7.10	29.52	61.20
RCP_3	0.00	2.77	30.55	55.55
RCP_4	8.90	28.48	49.80	68.50
RCP_5	11.30	47.60	52.30	71.42
Standard	17.60	100.00	100.00	100.00

The responses were recorded on a kymograph. The graph was plotted as concentration (X-axis) Vs % inhibition (Y axis). The % inhibitions were calculated and values are showed in Table 3. DMSO solvent not showed any % histamine inhibition.

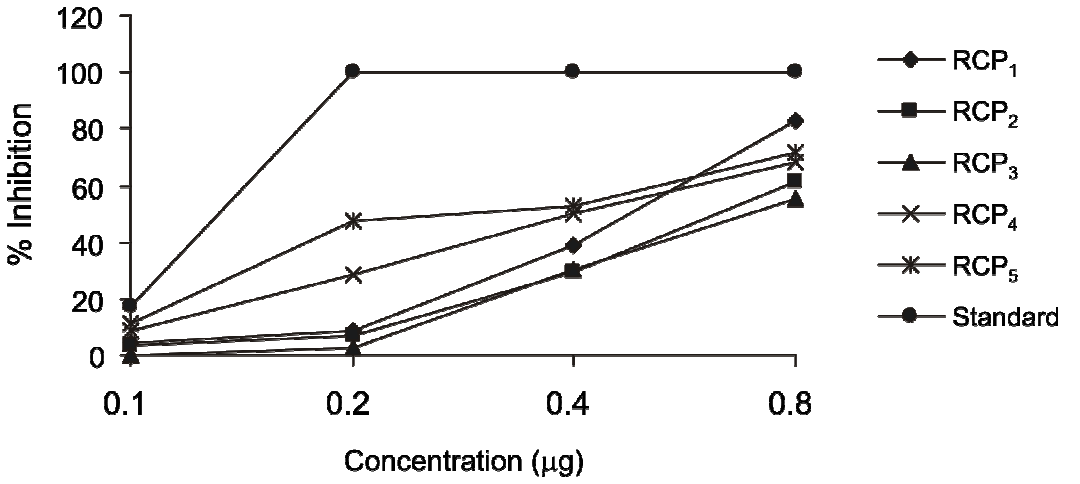


Fig. 2 : % Hitamine inhibition of newly synthesized pyrimidines

RESULTS AND DISCUSSION

(i) Five newly synthesized pyrimidines showed significant antihistamine activity, when compared with standard anti-histamine drug mepiramine. If the concentration of pyrimidines RCP_{1-5} was increased from 0.1 µg/mL to 0.8 µg/mL, the % histamine inhibition also increased.

(ii) Among the five pyrimidine derivatives RCP_{1-5} only flourine substituted pyrimidine RCP_1 showed greater antagonistic activity.

(iii) The moderate anti-histamine activity was found in chlorine substituted compounds.

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