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SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF NOVEL 1-(4-BENZHYDRYL PIPERAZIN-1-YL)-3-(DI-SUBSTITUTED) PROPAN-1-ONES AS ANTIHISTAMINIC AGENTS

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In order to explore the antihistaminic effect associated with the piperazine framework, several 1-benzhydryl piperazine derivatives **1**(a-f) were synthesized. Variation in the functional group at N-terminal of the piperazine led to final compounds. Their chemical structures were confirmed by ^{1}H NMR, ^{13}C NMR, Mass and elemental analysis. The antihistaminic effect of the compounds were evaluated in isolated guinea pig Ileum.

Among the pharmacologically active compounds the arrangement of atoms >N-C-C-C-N<, >N-O-C-C-C-N<, >N-C-C-O-NH- and >N-C-C-C-NH- are of importance, as inhibitors of histamine. Our interest in 1-benzhydrylpiperazine-4-substituted piperazines as biologically active compounds prompted us to prepare the title compounds having above arrangement and to undertake their biological evaluation for antihistaminic activity.

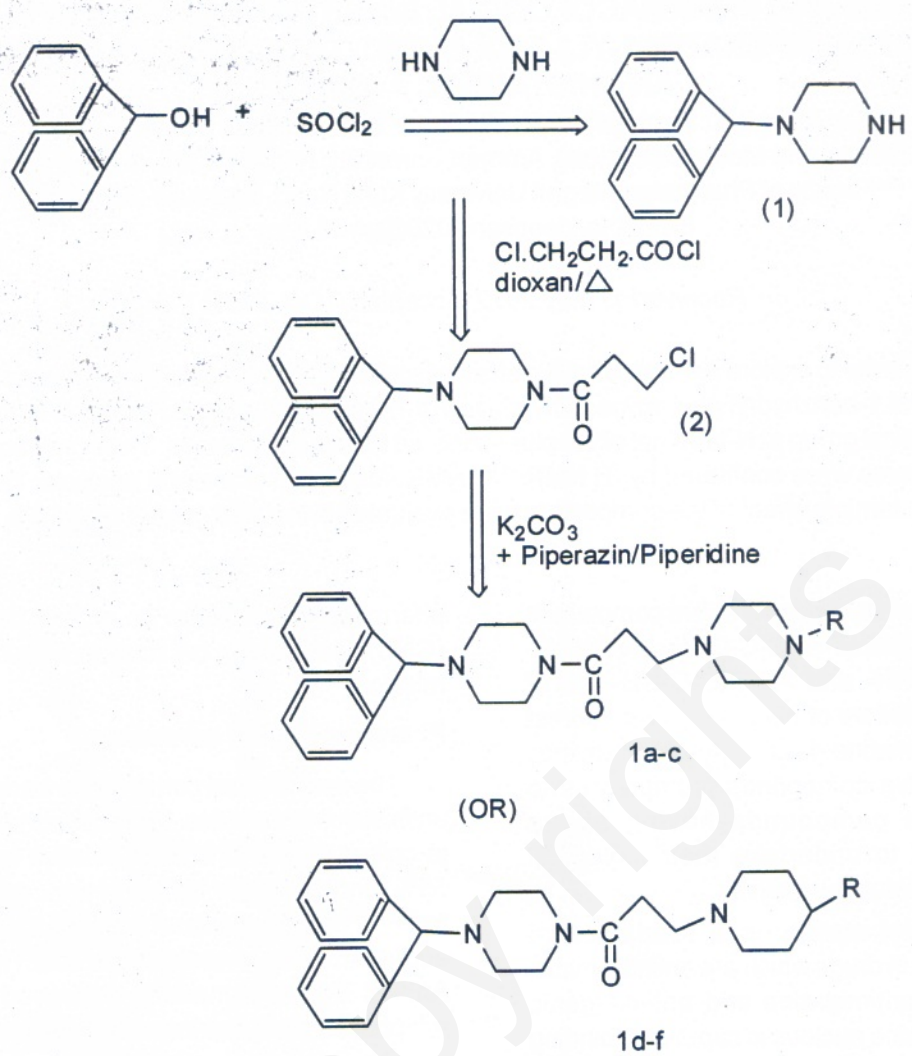
The benzhydryl moiety is a fundamental component present in drugs which are antihistaminic, antihypertensive, antimigraine and antiallergenic agents. The piperazine nucleus is capable of binding to multiple receptors with high affinity and therefore it has been classified as a privileged structure. Piperazines are found in various biologically active compounds across a number of different therapeutic areas which include antifungal, antibacterial, antimalarial, antipsychotic and antidepressant agents. They are reported to possess good antitumor activity against colon, prostate, breast, lung and leukemia tumors. The piperazine ring and its derivatives are important cyclic components in the field of industry since they are used as raw materials for hardening of the epoxy resins, corrosion inhibitors, insecticides, accelerators for rubber, urethane catalysts and anti oxidants. 1-Benzylpiperazine was originally synthesized as a potential anthelminthic agent. These derivatives of piperazine are found to possess excellent pharmacological activities such as vasodilator, hypotensive, antiviral and cerebral blood flow increasing actions. They are found to have broad pharmacological action on central nervous system (CNS), especially on dopaminergic neurotransmission.

Pharmacological screening

The synthesized compounds were evaluated for antihistaminic activities. The animals were maintained in colony cages at 25± 2°, relative humidity of 45-55%, under a 12 hr light and dark cycle; they were fed with standard animal feed. All the animals were acclimatized for a week before use. The Institutional Animal Ethics committee approved the protocol adopted for the experimentation of animals.

Antihistaminic activity

A healthy adult guinea-pig (500 g) were stunned by a sharp blow on head, neck vessels cut and the animal was bled out. Abdomen was opened through a mildline incision, the ileocecal junction was exposed and the terminal ileum was cut (20-25 cm) after discarding 10 cm nearest to the ileocaecal junction to eliminate the excitatory adrenoreceptors. The mesenteric attachment was removed as far as possible without injuring the gut. A small portion of the ileum (4-5 cm) was then separated out and the lumen was thoroughly cleaned by running warm thread was passed through the wall of the lumen at each end with the help of a fine sewing needle and tied securely without occluding the lumen. One end of the segment was tied securely to the tissue holder and transferred to the organ bath (20 ml capacity), filled with Tyrode solution maintained at 36° ± 0.5°. It was aerated by



SCHEME-1

bubbling air through it. The other end of thread was fixed to a frontal writhing lever adjusted suitably for tension and magnification (Tension 0.5 to 1.0 g, magnification 5-10). After 15 min it was added to the organ bath and the contraction of the ileum was recorded. Different concentrations of the compounds were allowed to act on the tissue for one minute before the addition of histamine and the contraction was recorded. Cyproheptadine was used as a reference drug.

The experiments showed that in *in vitro* conditions the compounds had antihistamine activity on isolated guinea pig Ileum. Overall 1-(4-benzhydrylpiperazin-1-yl)-3-(2,6-dimethylpiperidin-1-yl) propan-1-on (**1e**) was more active than 1-(4-benzhydrylpiperazin-1-yl)-3-(4-methylpiperazin-1-yl) propan-1-one (**1a**).

The most active compound was 1-(4-benzhydrylpiperazin-1-yl)-3-(4-(piperidin-2-yl) piperazin-1-yl) propan-1-one (**1c**). The compounds with piperidinyl piperazine & ethyl piperazine showed significantly greater activity than cyproheptadine. The compound 1-(4-benzhydrylpiperazin-1-yl)-3-(4-methylpiperidin-1-yl) propan-1-one (**1f**) was least active compound.

Experimental

Melting points were determined by using melting point apparatus of Scientech company. Reactions were monitored by thin layer chromatography (TLC) on silica gel G plates using ethyl acetate-hexane (5:5), cyclohexane-ethylacetate (1:1) (iodine vapours and UV chamber as visualizing agent). ^{1}H NMR spectra were recorded on a Bruker DRX-300 and chemical shifts (δ ppm) are relative to TMS as an internal standard. Mass spectra were recorded on a JEOL-Accu TOF JMS-T100 LC mass spectrometer. Dry

Table-1
Antihistaminic activity of compounds on isolated guinea pig ileum

Compd	Concentration		Height (cm)		% inhibition
	Compound (μg)	Histamine (μg)	Histamine	Compound + Histamine	
1a	20	10	3.0	2.0	33.0
1b	20	10	3.2	0.4	87.5
1c	20	10	3.5	0.2	94.28
1d	20	10	2.8	1.8	35.71
1e	20	10	2.5	1.0	60.00
1f	20	10	2.8	2.0	28.57
Cyproheptadine	20	10	.2	0.5	84.37

helium was used with 4LPM flow rate for ionization at 350°. Silica gel column chromatography was performed using Merck silica gel (60-120 mesh) and Merck made TLC plates.

Synthesis of benzhydryl piperazine (1)

Benzhydrol was dissolve in CH_2Cl_2 (70 ml). After addition of $SOCl_2$ (5 ml, 0.69 mol) the reaction mixture was stirred at 40° for 3 hr. The solvent was evaporated under vacuum and the residue was dissolved in MeCN (80 ml). Then, piperazine (24.6g, 0.29 mol) was added and the mixture was refluxed for 12 hr. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate (250 ml) and washed with water (100 ml) followed by 1N HCl (100 ml). The acid phase was washed with ethyl acetate (3x60 ml). The ethyl acetate layer was discarded and the remaining water layer was neutralized with 3N NaOH aq solution (40 ml) to pH> 10. The aqueous solution was extracted with CH_2Cl_2 (3x 80 ml). The combined CH_2Cl_2 layer was washed successively with brine, dried over Na_2SO_4 and evaporated under vacuum to provide compound **1** as a yellow oil.

Synthesis of 1-(4-benzhydryl-1,4-diazepan-1-yl)-3-chloropropan-1-one (2)

A solution of benzhydryl homopiperazine (10 mmol) in dioxan was heated for 10 minutes. Then it was cooled to 0-5° in an ice bath. Then chloro propanoyl chloride (13 mmol) was added with stirring. The reaction mixture was stirred at RT for 4-6 hr. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride solution and finally with water . It was dried with anhyd sod. suphate, solvent was removed under reduced pressure to give **2**.

Synthesis of 1-(4-benzhydryl piperazin-1-yl)-3-(di-substituted) propan-1-ones compound (1a-f)

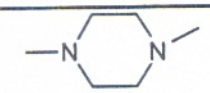
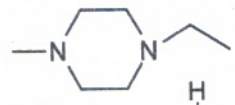
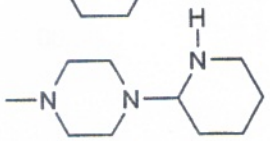
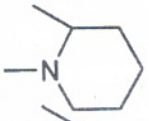
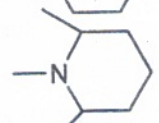
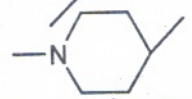
A mixture of **2** (0.01 mol), various substituted piperazine/piperidine (0.01 mol) and dry K_2CO_3 (0.012 mol) in DCM (10 ml) was stirred for 1 hr at 25°. After stirring the mixture it was refluxed for 6-12 hr. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with distilled water three times and dried with anhyd sod. sulphate, solvent was removed under reduced pressure.

Spectral data :

1a: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.34 (10H, m, ArH), 2.50 (t, 4H, piperazine), 2.49 (t, 2H, -CH_2 at α of C=O), 3.44 (t, 4H, piperazine), 3.67 (t, 2H, -CH_2 at β of C=O), 4.22 (1H, s, -CH of benzhydryl moeity), 2.35 (8H, m, piperazine at β of C=O), 2.26 (s, 3H, N-CH_3). MS: (ESI$^+$): m/z 406 (M^+), 407 (M^++1), 408 (M^++2). ^{13}C NMR ($CDCl_3$): 45.5, 52.9 (2), 54.8, 46.0(2), 30.6, 51.4 (2), 169, 76.5, 127 (2), 128.4 (4), 141.9 (2), 129.2 (4). [Found : 73.83, H, 8.46, N, 13.78, $C_{25}H_{34}N_4O$ requires C, 73.85, H, 8.43, N, 13.78%]

1b: ^{1}H NMR (300 MHz, $CDCl_3$): 7.24-7.34 (10H, m, ArH), 2.50 (t, 4H, piperazine), 2.49 (t, 2H, -CH_2 at α of C=O), 3.44 (t, 4H, piperazine), 3.67 (t, 2H, -CH_2 at β of C=O), 4.23 (1H, s, of benzhydryl moeity), 2.35 (8H, m, piperazine at β of C=O), 2.39 (q, 2H, N-CH_2),

Table-2
Physical data of compounds (1)

Compd	R	Yield (%)	R_f value
1a		50	0.71
1b		54	0.73
1c		60	0.70
1d		65	0.77
1e		70	0.71
1f		60	0.64

All the compounds were liquid

1.02 (t, 3H, N-C-CH_3 of piperazine). [Found : 74.20, H, 8.61, N, 13.34 $C_{26}H_{36}N_4O$ requires C. 74.25, H, 8.63, N, 13.32%]

1c : ^{1}H NMR (300 MHz, $CDCl_3$): 7.27-7.36 (10H, m, ArH), 2.49 (t, 2H, CH_2 at α of C=O), 3.44 (t, 4H, piperazine), 3.68 (t, 2H, -CH_2 at β of C=O), 4.13 (1H, s, -CH of benzhydryl moiety), 2.71 (8H, m, piperazine at β of C=O), 2.0 (s, 1H, N-H of pyridyl piperazine), 3.87 (t, 1H, N-CH of pyridyl), 2.79 (t,2H, -CH_2 at α of NH), 1.49 (m, 2H, -CH_2 at β of NH), 1.55 (m, 2H, -CH_2 at of -NH), 1.69 (m, 2H, -CH_2 at δ of NH). [Found : C, 73.24, H, 8.67, N, 14.754 $C_{29}H_{41}N_4O$ requires C, 73.23, H, 8.69, N, 14.72%]

1d: ^{1}H NMR (300 MHz, $CDCl_3$): 7.24-7.36 (10H, m, ArH), 2.51 (t, 2H, piperazine), 2.28 (t, 2H, -CH_2 at α of C=O), 2.64 (2H, t, CH_2 at β of C=O), 1.12 (d, 3H, CH_3 of piperidine), 1.55-2.51 (m, 9H, piperidine), 4.21 (1H, s, -CH of benzhydryl moeity). [Found : C, 77.02, H, 8.71, N, 10.33 $C_{26}H_{35}N_3O$ requires C, 77.00, H, 8.70, N, 10.36%]

1e : ^{1}H NMR (300 MHz, $CDCl_3$): 7.24-7.36 (10H, m, ArH), 2.51 (t, 2H, piperazine), 2.28 (t, 2H, -CH_2 at α of C=O), 2.64 (2H, t, -CH_2 at β of C=O), 1.12 (d, 3H, CH_3 of piperidine), 4.21 (1H, s, -CH of benzhydryl moeity), 1.55-2.41 (m, 9H, piperidine). MS (ESI+): m/z 419 (M^+), 420 (M^++1), 421 (M^++2). ^{13}C NMR ($CDCl_3$): 20.5 (2), 24.1, 33.4(2), 53.8(2), 45.5, 45.7(2), 51.5(2), 169.9, 76.05, 128.4 (4), 126.7(2), 127.5(4), 142.53(2), 30.63. [Found :C, 77.30, H, 8.87, N, 10.02, $C_{27}H_{37}N_3O$ requires C, 77.28, H, 8.89, N, 10.01%]

1f: ^{1}H NMR : (300 MHz, $CDCl_3$): 7.25-7.37 (10H, m, ArH), 3.44 (t, 4H, piperazine), 2.49 (t, 2H, -CH_2 at α of C=O), 3.68 (2H, t, -CH_2 at β of C=O), 0.99 (d, 3H, -CH_3 of piperidine), 4.19 (1H, s, -CH of benzhydryl moiety), 1.31-2.52 (m, 9H, piperidine). [Found : C, 77.01, H, 8.69, N, 10.36 $C_{27}H_{37}N_3O$ requires C, 8.70, H, 8.70, N, 10.36%]

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References

1. A. Bali, S. Malhotra and A. Kumar, *A. AMC letter,* **19** (2009), 3041.
2. K.M. Basawaraja and V.P. Vaidya, *E-J. Chem.,* **5** (2008), 567.
3. M.L. Bolognesi, A.A. Cavalli, B.M.Vincenza and R. Banzi, *Il Farmaco,* **58** (2003), 917.
4. M.I. Dorokhova, E.N. Alekseeva and I.A. Kuznetsova, U.D.C. 615.31:547.361.3, 012.1.
5. E. Ernesto, S. Lourdes and Eugeniouriata, *Struc. Chem.*, **2** (2005), 4.
6. K. Jerzy and K.S. Mariola, *Molecules,* **11** (2006), 615.
7. T.A. Ozlem, O. Aliye and Y. Ismail, *Arch Pharm. Chem. Life science,* **338** (2006), 105.
8. B. Roberta and B. Laura, *Bioorg. Med. Chem.,* **10** (2002), 361.
9. A.K. Shakya, G.K. Patnaik and P. Mishra, *Eur. J. Med. Chem.*, **27** (1991), 67.
10. M. Tao, W. Jue, P. Hongli and F. Guanghua, *Eur. J. Med. Chem.,* **45** (2010), 1133.
11. R.S. Upadhayaya and J.K. Vandavasi, *Eur. J. Med. Chem.*, **45** (2010), 1854.

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