IJPSR (2012), Vol. 3, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 September, 2011; received in revised form 19 October, 2011; accepted 26 December, 2011

SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF 1-BENZ-HYDRYL PIPERAZINE DERIVATIVES

Atul Kumar Thakran*[1], Sushil Gupta[1], Shilpa Kumari[2] Abhay Kumar Mourya[3] and Shashi Alok[3]

College of Pharmacy, IFTM [1], Moradabad, Uttar Pradesh, India
Department of Chemistry, Ramjas College, Delhi University [2], New Delhi, India
Institute of Pharmacy, Bundelkhand University [3], Jhansi, Uttar Pradesh, India

Keywords:
1-benzhydryl piperazine,
Acyl chlorides,
Antihistaminic activity,
Antihelmintic activity

Correspondence to Author:

Atul Kumar Thakran

College of Pharmacy, IFTM, Moradabad, Uttar Pradesh, India

ABSTRACT

In order to explore the antihistaminic and anthelmintic activity associated with piperazine framework, several 1-benzhydryl piperazine derivatives and 1- benzhydryl piperazine acyl derivatives were synthesized. Their chemical structure was characterized and confirmed by H^1 nuclear magnetic resonance (NMR), Fourier-transform infrared (FTIR). The target compounds were synthesized by the nucleophilic substitution reaction of 1-benzhydryl piperazine with various acyl chlorides. The intermediate (AT-1) was prepared by reaction of benzhydryl chloride and piperazine in presence of anhydrous potassium carbonate in N-N dimethylformamide. Further 1-benzhydrylpiperazine was reacted with various acyl chloride in presence of triethylamine in dichloromethane afforded target compounds (AT5 -9). The anthelmintic activity of compounds were evaluated by Garg and Atal method while antihistaminic activity was evaluated by *in- vitro* guinea pig ileum.

INTRODUCTION: Benzhydryl are pharmacologically highly therapeutic potential class of compounds and have broad biological profile. Compounds containing the benzhydryl ring have been reported to possess different biological activities such as anticonvulsant, antibacterial, antifungal, anticholinergic, antihistaminic and activity depending on the substutions in the ring system [1].

Literature survey showed that benzhydryl is a versatile lead molecule for design of potential bioactive agents. Piperazine and its congeners are important pharmacophores that can also found in biologically actives compounds across a number of different therapeutic areas such as anti-fungal, anti- bacterial, antimalarial, antipsychotic, HIV protease inhibitors, antidepressant, and anti-tumor [2].

The development of novel antihistaminic agents with more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry. Antihistaminic therapy however is neither universally effective nor invariably safe. The traditionally antihistaminic drugs have troublesome sedative and antimuscarinic effects [3, 4]. Most of existing drugs are effective as local anaesthetics and also block sodium channels in excitable membranes. Attempts have been made going to develop an H_1 receptor antagonist devoid of these properties.

During past decade, heterocyclic structures have received special attention because they belong to class of compounds with proven utility in medicinal chemistry. Benzhydryl moiety has been extensively utilized as drug like scaffold in medicinal chemistry, and as such the benzhydryl skeleton is considered to be privileged structure. Molecules based on the benzhydryl exhibit a multitude of interesting pharmacological activities, including anticonvulsant, antifungal, analgesic, anticholinergic, anti-

hypertensive, anti-migraine, anti-allergic, disinfectant and antiseptics [5].

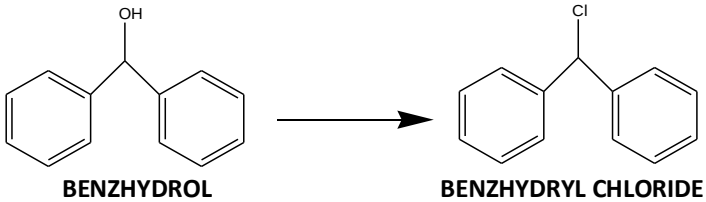
Benzhydryl are important class of compounds and large number of unnatural benzhydryl skeletons with variety of substituent has been prepared via synthetic strategies.

Chemical formula $(C_6H_5)_2CH_2$ and Molecular weight 168.23. Chemistry of benzhydryl contains two benzene ring which substitute hydrogen atoms in the methane molecule. This structure does not allow the fusion of benzene ring. This nomenclature system is particularly useful to describe the groups attached to the benzene rings and the additional substituent on the methane. The benzhydryl structure features as the motif for modified fibers, polymers and curing agents.

As a general method for synthesis of Benzhydryl is Benzylation of excess of benzene is carried out with the benzyl chloride at 120°C in presence of nanocomposite catalyst Nafion/SiO_2 and another is Diphenylmethane reacting Dibenzylether with benzene in the presence of protonic acid catalysts which contain a phosphoric acid.

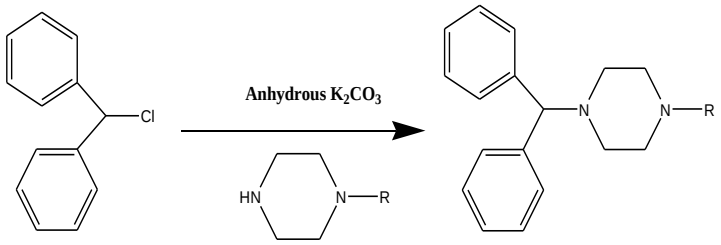
MATERIALS AND METHODS:

Synthesis of benzhydryl chloride: To a cold solution of thionyl chloride (11.9 ml, 0.1 mole) in two neck round bottom flask, the benzhydrol (0.1mole, 18.5 gm) in di chloro methane wad added drop wise maintaining the temperature at 0-5°C. The reaction mixture was stirred for 4-6 hrs on magnetic stirrer until the HCl fumes ceases out. The reaction mixture was heated on the water bath to evaporate the solvent to get final product.

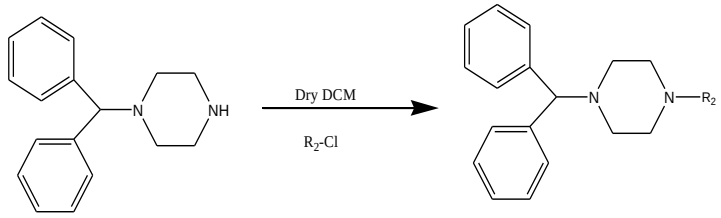


BENZHYDROL **BENZHYDRYL CHLORIDE**

Synthesis of 1-benzhydryl piperazine derivatives (AT1-5): A solution of R (methyl piperazine, piperazine anhydrous, ethyl piperazine, phenyl piperazine) in dimethyl formamide was taken, anhydrous potassium carbonate (27.6gm, 0.2mol) was added to solution and stirred for 10 min and then benzhydryl chloride (16.08 ml, 0.1mol) in DMF was added. The reaction mixture was refluxed at 80°C for 10 hrs.



Synthesis of 1-benzhydryl piperazine acyl derivatives (AT 5-9): A solution of 1- benzhydrylpiperazine (2.52gm, 0.01mol) in dry dichloromethane was taken and cooled to 0-5°C in an ice bath. Triethylamine (4.2ml, 0.03mol) was added to cold solution and stirred for 10 min. Then R_2 (acetyl chloride, benzoyl chloride, chloro acetyl chloride, valeryl chloride, phenyl acetyl chloride) was added to the solution. The reaction mixture was allowed to stir at room temperature for 5-6 hrs.



RESULTS AND DISCUSSION:

Chemical Studies: Four derivatives of 1-benzhyrdyl piperazine and five derivatives of 1- benzhydryl piperazine acyl were prepared according to scheme. Percentage yields of all the compounds were calculated and tabulated in **table 1 & 2**. Their physical constants and thin layer chromatography primarily conformed purity of the synthesized compounds. Melting points and R_f values are also given in the table **3 and 4**.

Structures of synthesized compounds were confirmed by infrared and ^1H NMR spectroscopy. IR spectra were obtained by preparing KBr pellets on PERKIN Elmer spectrum of RXI FTIT system and are expressed in terms of wave number (cm^{-1}). The proton NMR spectra of the synthesized compounds were obtained by using

MODEL Bruker Avance II 400 MHz NMR at using DMSO solvent are also given below the each spectra.

TABLE 1: PHYSICAL CONSTANTS OF 1-BENZHYDRYLPIPERAZINE DERIVATIVES

R	Designation	% Yield	Melting* Point range (°C)	R_f value$^+$
H	AT-1	83.58	190-194	0.68
Methyl	AT-2	74.56	138-140	0.54
Ethyl	AT-3	71.40	148-151	0.39
Phenyl	AT-4	77.90	220-223	0.63

TABLE 2 PHYSICAL CONSTANTS OF 1-BENZHYDRYL PIPERAZINE ACYL DERIVATIVES

R	Designation	% Yield	Melting* Point range °C	R_f value$^+$
CH_3	AT-5	71.42	198-201	0.70
C_6H_5	AT-6	73.31	231-234	0.63
CH_2Cl	AT-7	78.84	229-231	0.50
C_4H_9	AT-8	74.23	232-235	0.57
$CH_2C_6H_5$	AT-9	65.87	245-248	0.71

IR spectra of 1-Benzhdryl piperazine (AT-1): (cm^{-1})-3323.98(NH str of piperazine), 3163.65(C-H str in aromatic), 2850-2960(C-H str in aliphatic), 1624.15(NH bend of piperazine), 1599.67(NH bend of piperazine), 1462.64(C-C str, skeleton), 1202.04(C-N str).

^{1}H PNMR Spectra of (AT-1): Chemical shift δ (ppm)-7-8(10H, Two phenyl rings attached), 5.19(1H, CH attached to piperazine), 2.50-2.59(8H, Methylene group in piperazine), 1.18 (1H, NH of piperazine),

IR spectra of 1-Benzhdryl -4-methyl piperazine (AT-2): 3328.41(NH str of piperazine), 3328.41(NH str of piperazine), 3095.38(C-H str in aromatic), 2850-2960(C-H str in aliphatic), 1549.67(C=C str in aromatic), 1459.38(C-C str, skeleton), 1128.56(C-N str)

^{1}H NMR Spectra of (AT-2): δ (ppm)-7-8(10H, Two phenyl rings attached to –CH-N), 5.12(1H, CH attached to piperazine), 2.28-2.49(8H, Methylene group in piperazine), 1.1(3H, Methyl group attach to piperazine).

IR spectra of 1-Benzhdryl -4-ethyl piperazine (AT-3): 3334.04(NH str of piperazine), 3045.27(C-H str in aromatic), 2850-2960(C-H str in aliphatic) 1624.63 (NH bend of piperazine), 1488.08(C=C str in aromatic), 1455.38(C-C str skeleton), 1237.54 (C-N str)

^{1}H NMR Spectra of (AT-3):7-8(10H, Two phenyl rings attached to –CH-N), 5.14 (1H, H attached to piperazine), 2.59(8H, Methylene group in piperazine), 2.43-2.49(2H, Methylene attached to piperazine), 1.0(3H, Methyl group).

1-Benzhdryl -4-phenyl piperazine (AT-4): 3323.98(NH str of piperazine), 3163.65(C-H str in aromatic), 2964.64(C-H str in aliphatic), 1616.15(NH bend of piperazine), 1590.27(C=C str in aromatic), 1455.38(C-C str, aromatic), 1214.54 (C-N str).

^{1}H NMR Spectra of (AT-4): δ (ppm) -6.1-7.8(15H, Three phenyl rings), 2.19-3.35(8H, Methylene group in piperazine), 5.07(1H, CH attached to piperazine)

IR spectra of 1-(4- benzhydrylpiperazin- 1- yl) ethanone (AT-5): 3328.41(NH str of piperazine), 3146.75(C-H str in aromatic), 2887.73(C-H str in aliphatic), 41633.0(Ketonic group of $–CH_2$), 1549.41(C=C str in aromatic), 1455.38(C-C str, skeleton), 1193.3(C-N str).

^{1}H NMR Spectra of (AT-5): δ (ppm)- 7-8(10H, Two phenyl rings), 5.41(1H, -CH attached to piperazine), 2.69-3.38(8H, Methylene group in piperazine), 20.3(3H, CH_3CO)

IR spectra of (4-benzhydrylpiperazin-1-yl) (phenyl)methanone(AT-6): 3455.70 (NH str of piperazine), 3159.48 (C-H str in aromatic), 2850-2960 (C-H str in aliphatic), 1656.15 (Ketonic group of $–CH_2$), 1624.63(NH group of piperazine), 1096.08(C-Nstr).

^{1}H PNMR Spectra of (AT-6): 7-7.84(15H, Three phenyl rings), 5.10(1H, C-Three phenyl rings), 2.31-3.35(8H, Methylene grp in piperazine)

IR spectra of 1-(4-benzhydrylpiperazin-1-yl)-2chloroethanone (AT-7): 3415.70 (NH str of piperazine), 3138.31(C-H str in aromatic), 2850-2960(C-H str in aliphatic), 1633.04(Ketonic group of $–CH_2$), 1596.55(C=C str in aromatic), 1455.38(C-C str, aromatic), 1193.18(C-N str), 748.64(C-Cl str)

^{1}H NMR Spectra of (AT-7): δ (ppm)-7-8(10H, Two phenyl rings attached to –CH-N), 5.19(1H, CH attached to piperazine), 2.58-3.39(8H, Methylene grp in piperazine), 4.23(2H, CH_2Cl).

IR spectra of 1-(4- Benzhydrylpiperazin-1-yl) pentan-1-one (AT-8): 3328.41 (NH str of piperazine), 3159.43(C-H str in aromatic), 2887.73(C-H str in aliphatic), 1645.80(C=O group), 1618.53(C=C str in aromatic), 1440.38(C-C str, aromatic), 1108.52(C-N str)

^{1}H NMR Spectra of (AT-8): δ (ppm)-7-8(10H, Two phenyl rings attached to –CH-N), 5.19(1H, CH attached to piperazine), 2.49-3.35 (8H, Methylene grp in piperazine), 1-3(6H, methylene in butyl), 0.85 (3H, Methyl group).

IR spectra of 1-(4-benzhydrylpiperazin-1-yl)-2-phenylethanone(AT-9) : 3455.70(NH str of piperazine), 3196.16(C-H str in aromatic), 2850-2960(C-H str in aliphatic), 1638.39(C=O group), 1602.64(C=C str in aromatic), 1463.18(C-C str, aromatic), 1190.60(C-N str).

^{1}H NMR Spectra of (AT-9): δ (ppm)-7-8(15H, Three phenyl ring), 5.19 (1H, CH attached to piperazine), 2.69(8H, Methylene group in piperazine), 3.30(4H, Methylene group in piperazine), 3.39(2H, CH_2 attached to phenyl ring).

Biologicals studies:

Antihelmintic activity [4, 5, 6]:

Animals: Indian adult earthworms were collected from moist soil in the I.F.T.M campus & washed with normal saline to remove all fecal matter were used for antihelmintic activity. The earthworm of 3-5 cm in length and 0.1-0.2 cm in width were used for all the experimental protocols due to their anatomical and physiological resemblance with the intestinal round worm parasites of human beings.

Method: Antihelmintic studies were carried out against *Eudrilus species* of earthworms by Garg and Atal method at 4 mg/ml concentrations. Suspensions of samples (AT1-AT9) were prepared by triturating synthesized compounds (200 mg) with Tween 80 (0.5 %) and distilled water. The resulting mixtures were stirred using a mechanical stirrer for 30 min. The suspensions were diluted to contain 0.4 % w/v of the test samples. Suspension of reference drug albendazole was prepared with same concentration in a similar way. Five earthworms of almost similar sizes were placed in petri plates of 4 inch diameter containing 50 ml of suspension of test samples and reference drug at room temperature. Another set of five earthworms was kept as control in 50 ml suspension of distilled water and Tween 80 (0.5 %). Observation was made for the time taken to paralysis and death of individual worms. Time for paralysis was note when no movement of any sort could be observed except when the worms were shaken vigorously. The death time was ascertained by placing the earthworms in warm water (50°C), which stimulate the movement if the worm was alive (**fig. 1**).

TABLE 3: ANTIHELMINTIC STUDIES OF COMPOUND AGAINST *EUDRILUS SPECIES*

Code of Compounds	Mean paralyzing time ± S.D. *(min)	Mean death time ± S.D. *(min)
AT-1	14.59 ± 0.06	21.58 ± 0.14
AT-2	14.06 ± 0.15	33.38 ± 0.10
AT-3	14.05 ± 0.13	36.38 ± 0.16
AT-4	16.88 ± 0.22	27.67 ± 0.11
AT-5	16.06 ± 0.05	31.56 ± 0.15
AT-6	17.04±0.65	29.32 ±0.91
AT-7	17.12 ± 0.11	32.74 ± 0.36
AT-8	15.63 ± 0.16	26.18 ± 0.20
AT-9	13.11 ± 0.18	34.05 ± 0.30
Albendazole (Std)	9.35 ± 0.12	21.15 ± 0.17

n=5, p<0.05, Concentration = 4 mg/ml

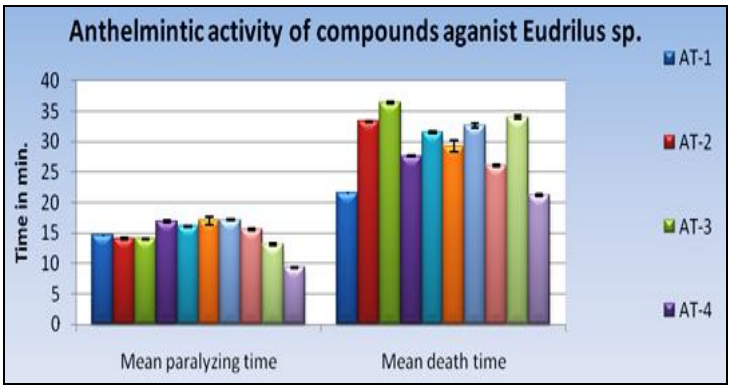


FIG. 1: GRAPH SHOWING ANTIHELMINTIC ACTIVITY OF SYNTHESIZED COMPOUNDS

Antihistaminic Activity: All synthesized compounds were evaluated for antihistaminic activity. Results are recorded in cm as the height of contraction and are shown **Table 4 & fig. 2**.

TABLE 4: ANTIHISTAMINIC STUDIES OF COMPOUND AGAINST GUINEA PIG ILEUM

Drug	Height of contraction (in cm)			
	0.1 ml	0.2 ml	0.4 ml	0.8ml
Histamine	2.1	2.7	3.0	3.1
Histamine+ Mepyramine	0.5	0.7	1.0	1.3
Histamine+AT-5	1.5	1.6	2.7	3.0

Histamine+AT-6	2.0	2.4	2.8	2.7
Histamine+AT-7	1.8	2.2	2.6	3.0
Histamine+AT-8	1.7	2.2	2.9	2.8
Histamine+AT-9	2.0	2.3	3.0	3.0

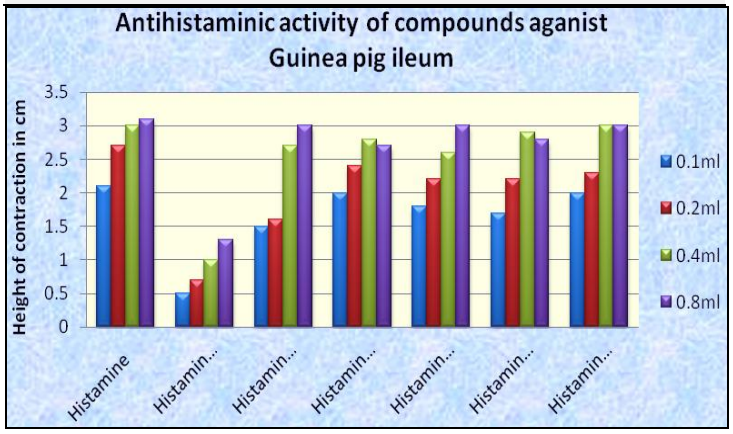


FIG. 2: GRAPH SHOWING ANTIHISTAMINIC ACTIVITY OF SYNTHESIZED COMPOUNDS

DISCUSSION & CONCLUSION: Various workers had synthesized benzhydryl derivatives and their findings suggest that derivatives of benzhydryl or substituted benzhydryl posses different types of biological activities including, analgesic, antiallergic, antibacterial. Antihistaminic activity promoted us to synthesize some new derivatives of 1-benzhydryl piperazines, which would include more effectiveness and specific antihistaminic activities.

Four different derivatives of 1-benzhydrylpiperazines were synthesized. The synthesis of benzhydryl chloride was accomplished by the reaction of benzhydrol and thionyl chloride in di chloro methane and stirred for 6 hours at temp of 0-5^{o}C. The intermediate benzhydryl chloride reacted with various substituted piperazines in the presence of anhydrous potassium carbonate in DMF and refluxed for 10 hrs. Derivatives (AT-1, AT-2, AT-3, AT-4, and AT-5) were obtained. Five different derivatives of 1-benzhydryl acyl piperazine were synthesized. The 1-benzhydrylpiperazine (AT-1) derivative was reacted with various acyl chlorides in the presence of anhydrous potassium carbonate in DMF and reaction mixture was stirred for 6 hrs. Derivatives AT-5, AT-6, AT-7, AT-8, AT-9 were obtained.

The purity and homogeneity of all compound were confirmed their sharp melting points and TLC.

In all cases, these derivatives were obtained in solid states. Yields obtained from 65.87% to 83.58%. The structures of these compounds were established on the bases of IR spectral analysis and ^{1}H NMR studies.

All the above results positively confirm the formation of the synthesized compounds and hence correctness of the anticipated structures drawn for synthesized compounds.

The biological properties are concerned antihelmintic activity was carried out on compounds (AT 1-9) while antihistaminic activity was carried out on (AT 5-9). Biological results data have showed that compounds (AT-1, AT-4, AT-6, and AT-8) take similar time to kill parasite as that of standard drug albendazole takes. Compound (AT-5, AT-8) significantly reduces the action of histamine at the minimum dose of 0.1 ml and 0.2 ml.

REFERENCES:

1. Vogel H. Gerhard: Drug Discovery & Evaluation. 2nd edition, Springer-Verlag Berlin Heidelberg-2002, 2
2. Patrik G. L: An Introduction to Medicinal Chemistry. 2nd edition, Oxford University Press 2001, 1
3. William David A. Foye: Principles of Medicinal Chemistry. 5th edition, Lippincott Williams & Wilkins, U.S.A,2005, 15
4. Singh Harkishan and Kapoor VK: Medicinal and pharmaceutical Chemistry. 1st edition,1996, 211-488
5. Kimara M, Masuda T and Yamada K: Bioorg Med Chem.11:3953-3963.
6. Thomas G, Suzanne R, Kesten: Journal of medicinal chemistry. 1999, 42, 3718-3725.
7. Bolton S, Bon C: Pharmaceutical Statistics Practical and Clinical Application. 2004, 4th edition, 215-265.
8. Kalsi PS: Spectroscopy of Organic Compounds. New Age International Publications, Fifth Edition, 149 – 157 and 383 – 388.
9. William Kemp: Organic Spectroscopy. Palgrave, Third Edition, 58 – 86 and 307 – 385.
10. Robert M Silverstein and Francis X Webster: Spectrometric Identification of Organic Compound. John Wiley & Sons Inc, Sixth Edition.

****