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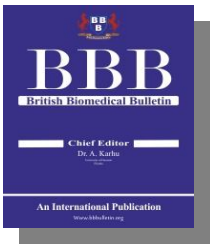

Original

Synthesis with Antibacterial and Antifungal Screening of 4-Hydroxy-4- Phenyl Piperidine Derivatives

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ABSTRACT

The present study was aimed to develop Piperidine analogues having high impact medicinal significance. As the outstanding position of piperidine and its derivatives has proven them an important core in the structures of pharmaceutically active molecules and as synthetic intermediates with interesting biological, physical and pharmacological behaviors. Hence a new sequence of 4-Hydoxy -4- Phenyl piperidine derivatives (II-VI) were synthesized with different phenacyl halide. The newly synthesized compounds were structurally proved by various analytical and spectroscopic methodologies. Furthermore these compounds were screened for their *in vitro* antibacterial and antifungal activities against different pathogens and the structure-activity relationship (SAR) was studied according to the attitude of synthesized compounds towards microbes. The outcome of study reveals the resistance of the parent compounds for organisms but the substitution specifically of pthalamide led to a prominent enhancement of both the activities.

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Introduction

The medicinal use of piperidine is very ancient. Because of being an alkaloid and a fragment of morphine, piperidine itself and its derivatives are pervasive component for the synthesis of many significant pharmaceuticals. Furthermore piperidine fragment was substituted via variety of synthetic reactions to develop more improved moieties with enhanced activities and to suppress the side effects when taken as medicine for different ailments[1,2].

Many naturally occurring piperidine compounds have been experimentally proved excellent antibacterial agents[3] as like black pepper (*Piper nigrum Longum*), the main source of piperidine, showed 75% bactericidal inhibition against different generas of bacteria obtained from oral cavity[4,5]. Various derivatives of piperidine molecule are used as antimicrobial agents and were found to show activity at a minimum inhibitory concentration[6,7]. Nalidixic acid was the first nitrogen containing antibacterial agent[8]. Another were fluoroquinolones, broad-spectrum antibiotics that were well known drug for bacterial infections. The strong growth inhibition against *Mycobacterium tuberculosis* was examined by two substituted derivatives of the antihistaminic agents, Bamipine and Diphenylpyraline, both containing piperidine ring and also have strong H_1-receptor antagonistic activity[9]. As in some pathogens the presence of urease is a dangerous reason for certain abnormal conditions like kidney stones, pyelonephritis and peptic ulcers, hence depending on these facts different piperidine derivatives were discovered having urease inhibition activity[10].

Different antibacterial targets are selected to achieve bacterial inhibition successfully that are aimed while developing structure of molecule via synthesis as like the inhibition of bacterial immunoglobulin G (IgG) of pyrogenes, by IdeS cleaving enzyme. Peptides demonstrated negative inhibition against IdeS enzyme but prominently proved as a potent inhibitor when glycine residue of peptides was replaced by piperidine moiety and on the basis of this criteria a variety of antibacterial compounds were developed[11,12].

Materials and Methods

To conduct the present designed reactions reagents of Sigma Aldrich Chemical Company and solvents of analytical grade were used. In methanol-d, UV spectra was taken on 1601 spectrophotometer. IR was taken on spectra on Jasco 302 Fourier transform FTIR spectrophotometer. Mass spectras were determined on electron impact (EI) condition by Varian Massen spectrometer MAT 312, MAT 113DMASPEC system. The instrument used for HNMR spectra Bruker AM 300 spectrophotometer and the solvent was DMSO-d6/MeOD. The ^{13}C spectra were scanned by the same instrument as for HNMR.

For conducting the designed reactions 4-Hydroxy-4-phenyl piperidine compound was selected as parent and was reacted with corresponding phenacyl halides in (0.01 moles) equimoler quantities (Table: 1, Figure:1). The reaction mixture (solvent and reactants) was kept on hot plate magnetic stirred for 24-48 hours at temperature 60°C-80°C. Afterwards the product was recrystallized and further was confirmed through spectral structural elucidation.

Compound II

1-(1″-Phenoxypropyl)-4-phenyl-4-hydroxy piperidinium Hydrobromide, Yellow crystalline powder, mp 200°C. UV, λ_{max} (MeOH) nm (log ε):233, 277. IR ν_{max} (KBr) $cm^{-1:}$ 3356, 2925, 1597, 1492, 1248,762, 696. H^1-NMR(MeOD- 300MHz) δ: 8.55 (1H, s,

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N-H) , 7.69-9.61(1H, m, *H-4″*),7.57-7.52 (2H, m, *H-3″/ H-5″*), 7.48 (2H, d, *J*=8.1 Hz, *H-2′/H-6′*), 7.41 (2H, d, *J*=8.1 Hz, *H-3′/H-5′*), 7.26 (2H, m, *H-2″/H-6″*),7.21 (1H, t, *H-4′*), 4.32(1H, s, *H-4*) ,4.13 (2H, t, *J*=7.1 Hz, *H-9*), 3.31 (2H, m, *H/7*), 3.27-3.13 (4H, m, *H_2-2/H_2-6*), 2.30 (2H, m, *H/8*), 2.21 (2H, dt, *J*=13.6, 4.8, Hz, *H-3 α /H-5 α*), 1.92 (2H, m, *H-3 ß /H-5 ß*). ^{13}C NMR (CD_3OD, 75 MHz): 208.0 (C-8), 159.9 (C-1″), 147. (C-1′), 1129.78 (C-2′/C-6′), 130.5 (C-2″/C-6″),127.8 (C-3′/C-5′),125.74 (C-4′),122.2 (C-4″), 115.1 (C-3″/C-5″), 69.3 (C-4), 66.1 (C-9), 59.54 (C-7), 49.84 (C-2/C-6), 39.08 (C-3/C-5). E.I-MS m/z: 306.1(M^+-HBr), 293.2, 216.2, 190.2, 172.1.Anal calcd. for $C_{20}H_{26}BrNO_2$ (391.12): C, 61.23; H,6.68, Br,20.37; N,3.57; O,8.16

Compound III

1-(6″-Methyluracil)-4-phenyl-4-hydroxy piperidinium Hydrochloride, White amorphous powder, 60; mp: 250°C. UV, λ_{max} (MeOH) nm (log ε): 230. IR ν_{max} (KBr) cm^{-1}: 3425, 2811, 1709, 1493, 1429,762, 696. H^1-NMR(MeOD- 300MHz) δ: 8.41(1H, s, *N-H*), 7.51 (2H,d, *J*,8.4 Hz, *H-2′/H-6′*), 7.36 (2H, d, J, 8.4 Hz, *H-3′/H-5′*), 7.21 (1H, t , *H-4′*), 5.66(2H,s, *H-1″/H-3″*), 4.65(1H, dt, *H-5″*),4.34(1H, s, *H-4*), 3.37 (2H, s, *H-7*), 3.42-3.34 (2H, m, *H-2 α /H-6 α*), 2.75-2.62 (2H, m, *H-2ß /H-6ß*), 2.22-2.12 (2H, m, *H-3 α /H-5 α*), 1.97-1.91 (2H, m, *H-3 ß /H-5 ß*). ^{13}C NMR (CD_3OD, 75 MHz): 147.1 (C-1′), 129.77(C-2') , 125.74 (C-4′), 125.75(C-5'/C-3′), 129.77 (C-6′), 101.29 (C-5″), 155(C-2″/C-4″), 102(C-6″), 71.42 (C-4), 49.84 (C-6/C-2), 59.546(C-7) , 39.08 (C-3/C-5). E.I-MS m/z: 301.1(M^+-HCl), 283.1, 206, 176.1. Anal calcd. for $C_{16}H_{20}ClN_3O_3$(337.12):C, 56.89, H,5.97; Cl,10.51; N,12.44; O,14.21

Compound IV

1-(1″-Adamantan acyl)-4-phenyl-4-hydroxy piperidinium Hydrobromide , Off white crystalline powder , 74% mp 210 °C. UV, λ_{max} (MeOH) nm (log ε): 213,252,257. IR ν_{max} (KBr) cm^{-1}: 3425, 2924, 2811,1709,1429,1251, 825.

H^1-NMR(MeOD- 300MHz) δ: 9.02 (1H, s, *N-H*) 7.50 (2H, d, *J*,8.4 Hz, *H-2′/H-6′*), 7.37 (2H,d, *J*,8.4 Hz, *H-3′/H-5′*), 7.21 (1H,t , *H-4′*), 4.51(2H, s, *H-7*), 4.34(1H, s, *H-4*) 3.52 (4H, m, H-2/H-6), 2.37 (4H,dt , *J*, 15.0, 4.5 Hz, H-3/H-5), 2.06 (3H, m, *H-3″/H-5″/H-8″*), 1.97 (6H, m, *H-2″/H-6″/H-10*), 1.79 (6H, m, *H-7″/H-4″/H-9″*). ^{13}C NMR (CD_3OD, 75 MHz): 208.3 (C-8), 146.1 (C-1′), 125.74 (C-4′), 129.5 (C-3′/C-5′), 127.4 (C-2′/C-6′), 72.1 (C-4), 62.5 (C-7), 51.3 (C-2/C-6), 47.1 (C-1″), 38.9 (3C-2″), 37.2 (3C-4″), 36.5 (C-3/C-5), 29.2 (3C-3″). EIMS *m/z*: 354(M^+ -HBr), 340, 224, 206. Anal calcd. for $C_{23}H_{32}BrNO_2$ (434.41) C, 58.92; H,6.66; Br,17.04; N,2.99; O,6.82.

Compound V

1-(1″- Propiophenone)-4-phenyl-4-hydroxy piperidinium Hydrochloride

White crystalline powder, 73%, mp 214°C. UV, λ_{max} (MeOH) nm (log ε): 280. IR ν_{max} (KBr) cm^{-1}: 3327, 2925, 1596, 1492, 1247,762, 696. H^1-NMR(MeOD- 300MHz) δ: 8.55 (1H, s, N-H) , 7.69-9.61(1H, m, H-4″),7.57-7.52 (2H, m, H-3″/ H-5″), 7.48 (2H, d, J,8.1 Hz, H-2′/H-6′), 7.49 (2H, d, J,7.9 Hz, H-3′/H-5′), 8.02-8.01 (2H, m, H-2″/H-6″),7.21 (1H,t , H-4′), 4.32(1H, s, H-4), 3.41 (2H, m, H/7), 3.32-3.23 (4H, m, H_2-2/H_2-6), 3.72 (2H, m , H/8), 2.58-2.33 (4H, m, H-3 /H-5).^{13} C NMR (CD_3OD, 75 MHz):159.9 (C-1″), 147. (C-1′), 128.78 (C-2′/C-6′), 130.5 (C-2″/C-6″), 127.8 (C-3′/C-5′),125 (C-4′), 126 (C-4″), 114.1 (C-3″/C-5″), 69.3 (C-4), 206(C-9), 53.54 (C-7) , 49.84 (C-2/C-6), 39.08 (C-3/C-5), 36.5 (C-8). Anal calcd. for $C_{20}H_{24}ClNO_2$ (345.15) ; C, 69.45; H,6.99; Cl,10.25; N,4.05; O, 9.25.E.I-MS m/z: 310(M^+-HCl), 253, 223, 205.

Compound VI

1-(1″-Ethyl pthalamide)-4-phenyl-4-hydroxy piperidinium Hydrobromide White

crystalline powder, 58% mp:250°C**.** UV, λ_{max} (MeOH) nm (log ε): 230

IR ν_{max} (KBr) cm^{-1}: 3512, 2535, 1706, 1432, 1360, 989, 768. H^1-NMR(MeOD-300MHz):8.02(1H, s, *N-H*),7.93(2H, m, *H-7″/H-8″*), 7.85(2H, m, *H-7″/H-8″*), 7.51(2H,d, J,7.5, *H-2′/H-6′*), 7.36(2H, d, J,8.41Hz, *H-3′/H-5′*), 7.27(1H, dt, *H-4′*), 4.51(2H, t, *H-8*) 4.34(1H, s, *H-4*), 3.53(2H, t, *H-7*), 3.77 (2H, m, *H-2 α / H-6 α*), 3.55 (2H, m , *H-2ß/H-6ß*), 2.28(2H, m, *H-3 α H-5 α*), 2.04(2H, m, *H-3ß/H-5ß*).^{13}C NMR (CD_3OD, 75 MHz): 169.85(C-5″/C-2″), 135.75(C-7″/C-8″), 133.41(C-1′), 131.29 (C-3″), 129.5 (C-3′/C-5′), 128.49(C-4″), 127.4 (C-2′/C-6′), 125.56 (C-9″), 125.74 (C-4′), 125.56(C-6″), 69.33(C-8), 72.1 (C-4), 50.66 (C-2), 36.71 (C-3/C-5), 50.66(C-6), 33.70(C-7). Anal calcd. for $C_{21}H_{23}BrN_2O_3$(431.32)C, 58.84; H,5.73; Cl,18.53; N,6.49; O,11.13. EIMS *m/z*:351 (M^+ -HBr), 330, 234, 206.

Method of Antibacterial Activity

The antibacterial activity of synthesized compounds against gram positive and gram negative bacteria were examined by agar-well method. All the bacterial isolates were checked for purity and kept on nutrient agar at 4°C in the refrigerator until required for use. Antibacterial activity of parent compound and their synthetic derivatives II-VI against pathogenic bacteria was determined. Autoclaved Muller Hinton broth (Oxoid, Basingstoke-UK) was used to refresh the bacterial culture, later wells were punched into Muller Hinton Agar and 10 microliters of culture were poured into the wells[13]**.** All plates were incubated at 28 ± 2°C for 24-48 hours and after incubation the zone of inhibition was noted by Vernier calliper. Gentamicin antibiotic was used as a standard drug in study.

Method of antifungal Activity

The test organisms for this study were isolated, identified, maintained and stored in the Microbiology Department, Federal Urdu University (FUUAST) selected for the antifungal study were the members of the saprophytic fungi, dermatophytic fungi and yeast fungi. All the fungal isolates were checked for purity and maintained on Sabourd Dextrose agar (SDA) (Oxoid, Basingstoke-UK) at 4°C in the refrigerator until required for use. Antifungal activity of parent compounds 4-Hydroxy-4-phenyl piperidine and their synthesized derivatives II-VI against human, environmental and phyto-pathogenic fungi was determined by using agar-well method. Autoclaved distilled water was used for the preparation of fungal spore suspension and transferred aseptically into each SDA plates[14]. All plates were incubated at 28± 2°C for 24 -48 hours and after incubation diameter of zone of inhibition was measured by Vernier calliper. Gresiofulvin antifungal agent was used as standard drug.

Results and Discussions

As piperidine derivatives are very well known to produce antibacterial response against a range of bacterial strains including gram positive and gram negative and have proven as potent antibiotics[15,16] Variety of compounds have been synthesized by the substitution of piperidine and were found more better than gemifloxacin and vancomycin[17]. As far as the antifungal response is concerned it was proved that the benzimidazole derivative having p-fluorobenzyl substitution at phenyl piperidin, found to inhibit strongly the growth of *Candida albicans* (yeast-like fungus). Similarly, through Mannich reaction and esterification a series of vanillin derivatives of piperidin were produced and some of these analogues were discovered more potent antimicrobials than fluconazole[18]. These discoveries led to evaluate the anti microbial response of synthesized piperidine derivatives.

The results of antibacterial bioassay were reported in tables 2,3 & 4 which showed that the parent compounds 4-Hydroxy-4-phenyl piperidine did not show any significant antibacterial and antifungal activity against the test strains whereas highly potent and vital activity was shown by the compound, 1-(1″-Ethyl pthalamide)-4-phenyl-4-hydroxypiperidinium Hydrobromide (V) against gram positive bacteria including *Bacillus cereus, Bacillus subtilis, Bacillus thruingiensis, Staphylococcus epidermidis, Streptococcus saprophyticus* and as well as against gram negative bacteria as like *Campylobacter jejuni, Campylobacter coli* and *Vibrio cholera*. The maximum zone of inhibition against these specific strains of gram positive and gram negative. Confirms the effectiveness of synthesized compounds.

The remaining derivatives demonstrated no any pronounced inhibition against bacterial strain hence proved feeble antibacterial agent. AS far as the antifungal activity is concerned only the compound, 1-(1″-Ethyl pthalamide)-4- phenyl-4-hydroxy piperidinium Hydrobromide (VI) exhibited potent inhibition against *Candida albicans, Candida albicans ATCC 0383, Candida galbrata, Candida tropicalis* and *Aspergillus niger*. Whereas, medium activity was shown against *Candida kruzei, Aspergillus flavus*. The remaining derivatives illustrated no activity against any fungal strain. These observations reveals that fact that although the parent compound is inactive against micro-organisms but the presence of pthalamide in the structure will be responsible for the enhancement of activity.

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Table 1. Substituents of 4-Hydroxy-4-phenyl piperidine

Compound No.	R	X
II	OC_9H_{11}	Br
III	$O_2C_5H_5N_2$	Cl
IV	$OC_{12}H_{17}$	Br
V	OC_8H_7	Cl
VI	$O_2C_{10}H_8N$	Br

Table 2. Antibacterial Activity of 4-Hydroxy-4-phenyl piperidine Derivatives (I-VI) against gram positive bacteria

Gram Positive Bacteria	Zone of inhibition (mm)					
	I	II	III	IV	V	VI
Bacillus cereus	4	5	4	R	R	14
Bacillus subtilis	4	R	3	5	5	14
Bacillus thruingiensis	4	5	R	5	5	11
Staphylococcus epidermidis	R	5	R	4	5	17
Streptococcus saprophyticus	5	5	6	5	R	16

Table 3. Antibacterial Activity of 4-Hydroxy-4-phenyl piperidine Derivatives (I-VI) against gram negative bacteria

Gram Negative Bacteria	Zone of inhibition (mm)					
	I	II	III	IV	V	VI
Campylobacter jejuni	6	R	R	R	R	15
Campylobacter coli	4	R	3	7	R	14
Vibrio cholerae	R	R	R	R	R	13

Table 4. Antifungal Activity of 4-Hydroxy-4-phenyl piperidine Derivatives (I-VI) against Fungi

Fungal species	Zone of inhibition (mm)					
	I	II	III	IV	V	VI
Aspergillus flavus	R	R	R	R	R	7
Aspergillus niger	5	4	R	5	R	10
Penicillium specie	R	R	R	R	R	6
Fusarium specie	4	R	3	R	R	5
Candida albicans	R	R	R	R	R	12
Candida albicans ATCC R383	3	R	R	R	R	9
Candida galbrata	5	R	R	R	R	9
Candida tropicalis	R	3	6	R	4	9
Candida kruzei	R	R	R	R	R	7
Microsporum canis	R	R	R	R	R	R

Activity Key (For Table 2, 3 & 4)

Concentration of compound: 01mg/ml of DMSO
No zone of inhibition = resistant (R)
Below 5mm inhibition = not significant
From 7-10 mm inhibition = significant
Above 10 mm inhibition = highly significant

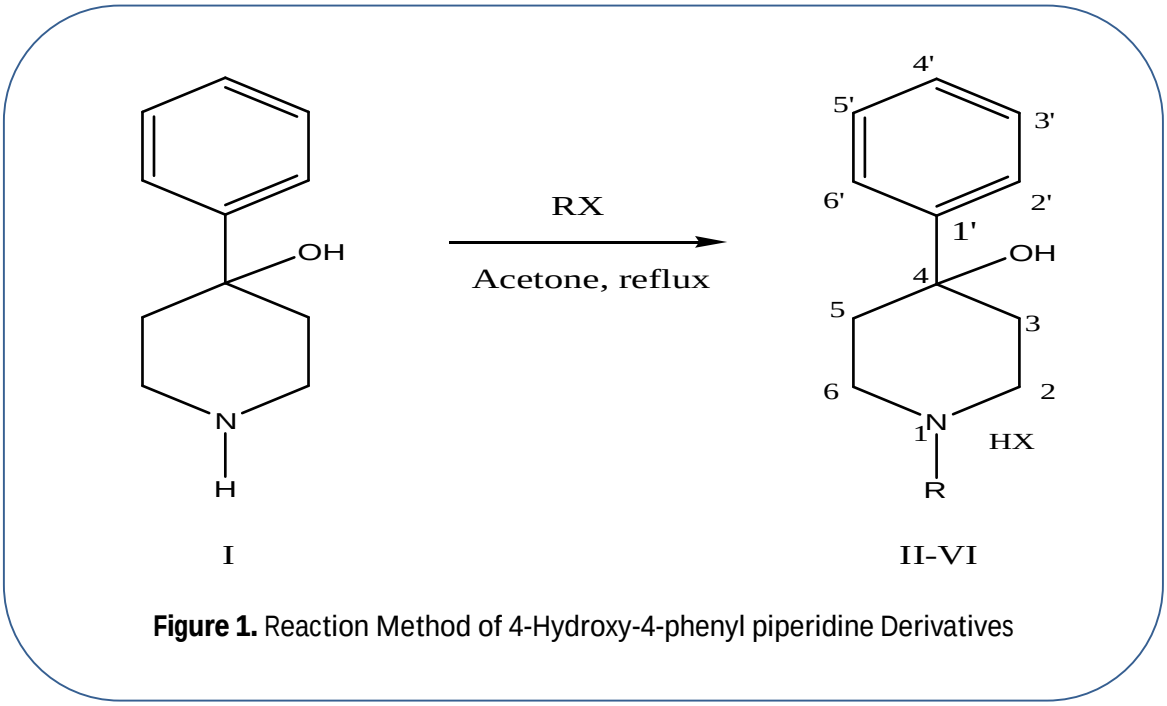

Figure 1. Reaction Method of 4-Hydroxy-4-phenyl piperidine Derivatives

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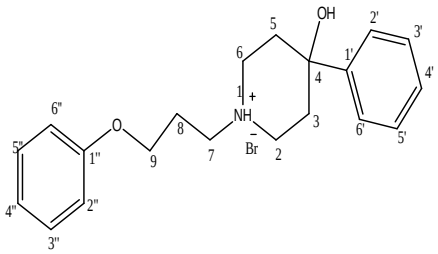

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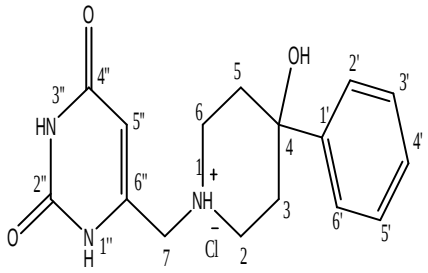

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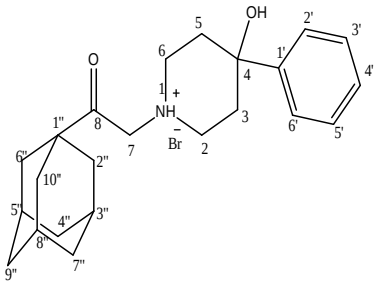

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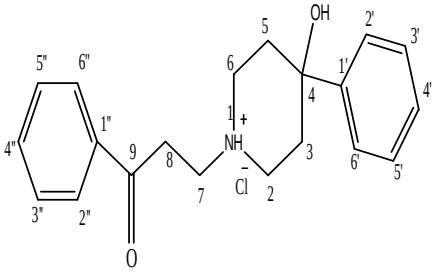

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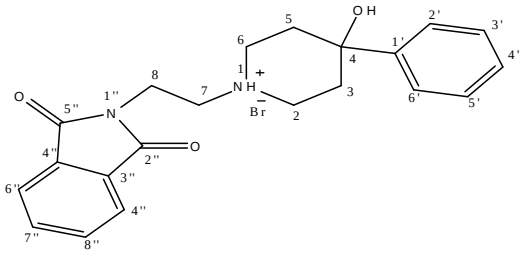

Compound VI

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