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Pharmacological Activity of Synthetic Piperidine against Bacterial Isolates of Cigarette Smoking Men

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Abstract: ***Piperidine is a saturated heterocyclic ring, considered as a privileged scaffold in view of its role in wide range of biological activities. The planar nature of this heterocyclic nucleus allows the introduction of substituent groups at different positions on the ring. In the present study, 3-allyl 2, 6-bis (4-fluorophenyl) piperidine-4-one had been synthesized and its antibacterial activity was assessed. Piperidine, either from the natural sources or in the synthetic form attracted many researchers due to its antioxidant, antiplatelet, anti-inflammatory, antihypertensive, antihelminthic, antitumor, and antiasthmatic activities. Synthesis of 3-allyl 2, 6-bis (4-fluorophenyl) piperidine-4-one revealed a new horizon towards the pharmacological actions against the bacterial flora of cigarette smoking persons. The promising pharmacological activity at 25mg/ml concentration against bacterial isolates had shown the greater zone of inhibition ranging from 20.1 to 26 mm for E. coli, 22-24mm for Staphylococcus aureus, 23.3-26.4 mm for Bacillus subtilis, 24.7-27.5mm for Streptococcus spand 24.8-28 for Pseudomonas aeurigenosa. The present investigation on antibacterial activity of the synthetic piperidine against the pathogenic bacteria of cigarette smoking persons demonstrated synthetic piperidine is a suitable candidate for pharmacological formulations.***

Keywords: Piperidine, Synthesis, cigarette smokers, bacterial isolates, antibacterial activity

1. Introduction

Synthetic piperidines are classified into piperidine nitroxides, substituted piperidines, unsaturated piperidines, N-acyl substituted piperidines, diarylsubstitutedpiperidinones, piperidinone oximes, and piperidine hydrazides. A huge value of piperidine in the medical and pharamacology is focused by the researchers due to its antioxidant, anti-inflammatory, antihypertensive, antihelminthic, antitumor, and antiasthmatic activities [1-7]. In the present study 3-allyl 2, 6-bis (4-fluorophenyl) piperidine-4-one was synthesized to find out the reaction time and efficient purification procedures.

Cigarette smokers are prone to the bacterial infections and the bacterial pathogens alters the beneficial microbes responsible for host defence mechanism. The presence of these bacterial pathogens cause formation of bacterial film which increase the risk of respiratory infections [8-14]. Binding of bacterial biofilm on the epithelial cells of upper respiratory tract predominantly resistant to the antibiotics. Further the cigarette smoking persons lack antibiotic resistance and loss of beneficial microbes in the mucosal surface. With this background, the present study was carried out to evaluate the response of bacterial pathogens of cigarette smoking men at age group ranging from 21 to 60 against 3-allyl 2, 6-bis (4-fluorophenyl) piperidine-4-one.

2. Materials and Methods

2.1 Synthesis of 3-allyl 2, 6-diphenylpiperidine-4-one

0.05 mol of hexene-2-one, 0.1 mol of benzaldehyde, 0.05 mol of ammonium acetate and 40ml ethanol were mixed well, heated gently and poured into 50ml ether. The mixture was treated with 25 ml concentrated hydrochloricacid. The precipitated hydrochloride was washed with ethanol-ether mixture. The base was liberated by suspending strong ammonia till the hydrochloride dissolved. A free base was afforded on dilution with water. After recrystallization from benzene-petroleum ether the compound was melted at 56-58°C.

For this synthesized compound, the effect of substituent on the ring conformation and orientation of the substituent and the chemical shift of the carbon and their associated protons are discussed with the help of NMR Spectral data [15].

2.2 Collection of pathogens

Pathogens were collected from the upper throat of smoking men (selected from Chennai city of India) by a sterile swab. The samples were grouped as S1-21-30; S2 31-40; S3 41-50 and S4 51-60. These isolates were stored for further characterisation. All bacterial isolates were identified by conventional microbiological method and tested for in vitro antibiotic susceptibility by modified Kirby-Bauer disc diffusion method [16]. Triplicates were maintained in each sample.

2.3 Antibacterial studies

Pharmacological activity of synthetic piperidine evaluated in vitro for its antimicrobial activity against bacterial pathogens of upper respiratory tract of smoking men. These men were selected from Chennai city of Tamilndu, India. The age group ranging from 21 to 60. Bacterial isolates (S1, S2, S3 and S4) from the throat swab of smoking men were maintained on nutrient agar slants in an incubator at 37 ºC and subcultured prior to testing.

To prepare the media, 23.0 grams of nutrient agar media weighed and dissolved in 900 ml of distilled water, stirred well and made up to one litre with addition of distilled

water. The media was autoclaved at 121^{o} C at 15 PSI for 20 minutes. The medium was poured into petri dishes under aseptic conditions in a laminar flow chamber and left to solidify. The cultures of test organisms were maintained on nutrient agarmedia.

Screening of antibacterial activity of synthetic piperidine was done by disc diffusion technique. The Petri dishes were inoculated with 0.5 ml of 24 hour old cultures of bacteria. After inoculation, zone of inhibition were measured after 24 hours. The antibiotic erythromycin (50mg) was used as standard and control**.** Triplicates were maintained for each treatment.

All the data obtained from the present study were analysed by SPSS-IBM for the statistical significance.

3. Results and Discussion

3.1. Synthesis of 3-allyl 2, 6-diphenylpiperidine-4-one

An efficient method for the synthesis of 3-allyl 2, 6-diphenylpiperidine-4 – one had been arrived. In the present study 3-allyl 2, 6-bis (4-fluorophenyl) piperidin-4-one (Figure-1) was synthesized by the condensing hexane-2-one, 4-fluoro benzaldehydes and ammonium acetate in 1: 2: 1 ratio. This synthetic approach for piperidine scaffold resulted in a practically efficient, shorter reaction times and simple purification procedures. There is a huge and significant consideration for piperidine moiety due to its importance in drug discovery and pharmacological applications [17-24].

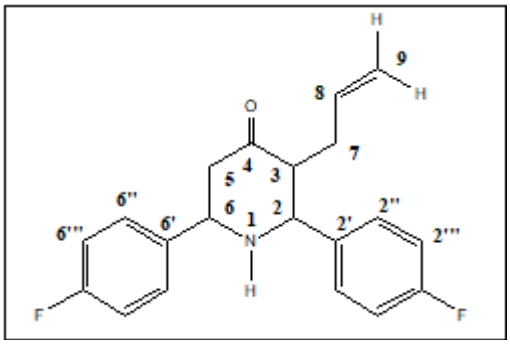

Figure 1: Structure of 3-allyl 2, 6-diphenylpiperidine-4-one

3.2 Antibacterial studies

The antibacterial potentiality of synthetic piperidine was examined via disc diffusion assay, using pathogenic bacterial isolates of smoking men (Table 1). Antibacterial tests using synthetic piperidine from concentrations 10mg to 50 mg were conducted to identify the minimum inhibition concentration (MIC). From The results of MIC indicated that piperidine tetra substituents had a significant effect at 25mg on the bacterial pathogens of smoking men of age group ranging from 21 to 60 (Table-2).

Table 1: Analytical and spectral data of synthetic piperidine

M. F.: $C_{20}H_{19}F_2NO$	m. p. (^{0}C): 56-58	Yield (%): 70
IR (KBr, cm^{-1}); 1715 (C=O), 3300 (N-H), 3075-2804 (C-H aromatic and aliphatic)		
^{1}H NMR (DMSO, ppm); δ: 2.00 (s, 1H, NH), 2.08 (d, 2H, H-7), 2.55 (d, 2H, H-5), 3.19 (s, 2H, H-2 and H-3), 4.2 2 (s, 1H, H-6), 4.72 (d, 1H, H-9a), 4.86 (d, 1H, H-9b) 5.61 (m, 1H, H-8), 7.19-7.71 (m, 8H, aromatic protons)		

Table 2: Antibacterial activity of synthetic piperidine (MIC) against bacterial isolates (Zone of inhibition in mm).

Bacterial isolates	Erythromycin (50mg)	Synthetic piperidine (25mg)
E. coli	28± 0.02	20.1-26 ± 0.01
Staphylococcus aureus	26± 0.05	22-24 ±0.02
Bacillus subtilis	27±0.01	23.3-26.4 ±0.05
Streptococcus sp	27±0.02	24.7-27.5 ± 0.04
Pseudomonas aeurigenosa	28±0.03	24.8-28 ± 0.02

*Results are expressed as the mean value of triplicates ($p>0.05$)

In general synthetic piperidine could be able to control *E. coli, Staphylococcus aureus, Bacillus subtilis, Streptococcus sp and Pseudomonas aeurigenosa* in smoking persons of different age group (21-60). Pharmacological activity of synthetic piperidine against bacterial isolates in terms of zone of inhibition in mm is ranging in the following order:

Bacillus subtilis >Escherichia coli >Staphylococcus aureus > Streptococcus sp and *Pseudomonas aeurigenosa.*

Synthetic piperidine at 25mg of concentration was more effective against *Streptococcus sp* and *Pseudomonas aeurigenosa* and it was on par with the results for the standard erythromycin at 50mg.

In sample 1 (S1) throat bacterial isolates of 21-30 age group of cigarette smoking persons were controlled by 20-25 mg of synthetic piperidine. When compared to the standard erythromycin the zone of inhibition for *Staphylococcus aureus* (24mm) was moderately susceptible. Susceptibility of *Streptococcus sp* and *Pseudomonas aeurigenosa* to synthetic piperidine was maximum and on par to the standard erythromycin. Moderate susceptibility was demonstrated by *Bacillus subtilis* and *E. coli (*Figure-2).

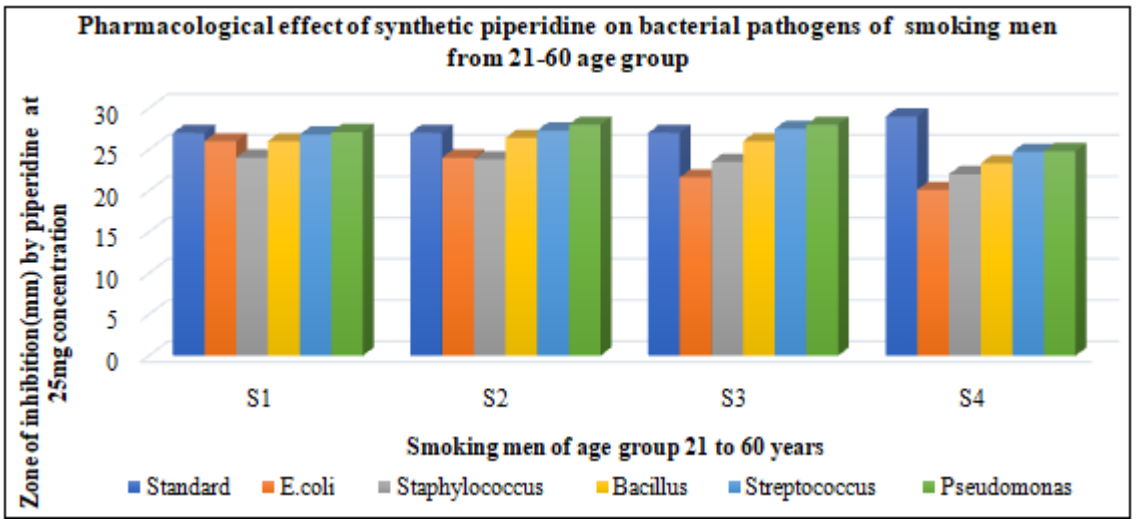

Figure 2: Pharmacological effect of synthetic piperidine on bacterial pathogens of smoking men from 21-60 age group

In S2 and S3 similar trend of results were obtained for zone of inhibition for the bacterial pathogens (Figure-2). In the age group 51-60 years response of the bacterial pathogens was the least. This might be due to the changes in bacterial virulence in the aged smoking persons and also needed higher concentrations of synthetic piperidine to inhibit the activity of pathogenic bacteria.

Bacterial profiling of young adult cigarette smokers in the previous studies [25-28] revealed the high risk of oxidative stress and other pulmonary diseases. In the earlier experiments, cigarette smokers of age group of 31 to 50 were studied for bacterial profiles of saliva, oral, nasopharyngeal and mucosal surface of upper respiratory tract. Loss of immunity promotes the formation of dense pathogenic bacterial colonies as biofilm. From the earlier literature [29-32] it was confirmed that biofilm attachment on the epithelial cells of upper and lower respiratory tracts enhanced the changes in the virulence of bacterial pathogens of aged persons belong to 41 – 60 years.

4. Conclusion

In the present study 3-allyl 2, 6-bis (4-fluorophenyl) piperidin-4-one was synthesized by condensing hexane-2-one, 4-fluoro benzaldehydes and ammonium acetate in 1: 2: 1 ratio. It was demonstrated by an economic and efficient method with shorter reaction times and simple purification procedures. Synthetic piperidine showed a noticeable activity against the bacterial isolates of smoking men of age group from 21 to 60. With reference to the zone of inhibition synthetic piperidine is sufficient to kill the different bacterial pathogens. The identified compound synthetic piperidine 25mg/mlhad significant influence over control of throat infecting bacteria from smoking men. Hence from the present study it is demonstrated that synthetic piperidine could be used to treat the upper throat infections of smoking persons.

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Data Availability Statement
All experimental data of this study are available within the research article itself.

Conflict of Interests
There are no conflicts of interest.

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