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EFFICACY OF 2, 6-DIARYL-1-(2-(THIOPHENE-2-YL) ACETYL) PIPERIDIN-4-ONE OXIME ON WOUND INFECTING BACTERIA

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Abstract

Background: Etiological classification of wounds may belong to acute or chronic.In these types tissue damage will lead to pathogenic infections and cause inflammation.Targeting fast healing of wounds by the control of pathogenic microflora and treatment with the heterocyclic compounds.

Objectives: The present study aimswith the objectives of synthesizedpiperidine oxime were profiled by 1H NMR and 13C NMR spectral experiments.It was investigated for its antibacterial potentiality against wound infecting bacteria.

Materials and Methods: The synthetic piperidine oxime was characterized by NMR. The concentrations of piperidine oxime were tested from 10µg/ml to 125 µg/mlagainst bacterial pathogens of wounds.Antibacterial activity was assessed by the zone of inhibition(ZOI). All the data were analysed by SPSS -IBM for the statistical significance.

RESULTS: NMR spectral studies revealed that the nitrogen site of 2,6-diphenyl piperidin-4-one ring exerted a minor change in the chemical shifts of the ring carbons and their attached protons. Furthermore, the benzylic protons at C-2 and C-6 position act as highly functionalized scaffolds.The zone of inhibition for Streptococcus pyogens is 26.5 mm,for Staphylococcus aureus is 25.9mm . ZOI was resulted at 27.2mm for Pseudomonas aeruginosa and the effect on Escherichia coli was recorded at 26.3 mm.

Conclusion: From the current research it had been proved that 100 µg of piperidin oxime could be sufficient to kill the wound pathogenic bacterial flora and piperidin oxime could be used an effective antibiotic as an alternative to amoxicillin.

Keywords: Piperidine 4-one oxime, NMR spectral study, wound bacterial isolates, antibacterial activity.

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Introduction

Vital role of natural and synthetic piperidine in pharmaceutical industry is ubiquitous. Heterocyclic ring systems having piperidin-4-one nucleus have treated as pharmacophore due to their wide variety of bioactive alkaloids. [1-5]. Multi-component reactions are efficiently evolved in organic synthesis to generate yield in a single synthetic operation. Thus heterocyclic compounds having piperidin–4-one skeleton are theimportant target of organic synthesis owing to their pharmacological activity and their wide occurrence in nature. Specifically many substituents at carbon C-2 and C-6 of the piperidin ring have been well documented as potent microbial agents [6-9].

With this back ground we have synthesized N-substituted 2, 6-diaryl piperidin-4-one oxime. The synthesized compound was characterized by ^{1}H NMR and ^{13}C NMR spectral studies. 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. The synthesized compound further experimented for antibacterial potential against wound infecting bacteria.

Materials and Methods

Synthesis of 2,6-diaryl-1-(2-(thiophene-2-yl)acetyl) piperidine-4-one oxime

To a well-stirred solution of 2,6-diphenyl piperidin-4-one with triethylamine (1 mol) in 30ml of dry benzene, thiophene-2-acetyl chloride (1 mol) in 20 ml of benzene was added drop wise through the separating funnel for about half an hour. Stirring was continued with mild heating using magnetic stirrer. After completion of reaction, it was poured into water and extracted with ether in three 50 ml portions. The combined ether extract was washed well with 3% sodium bicarbonate solution and dried over anhydrous sodium sulphate. This upon evaporation and subsequent recrystallization in distilled ethanol (Figure-1).

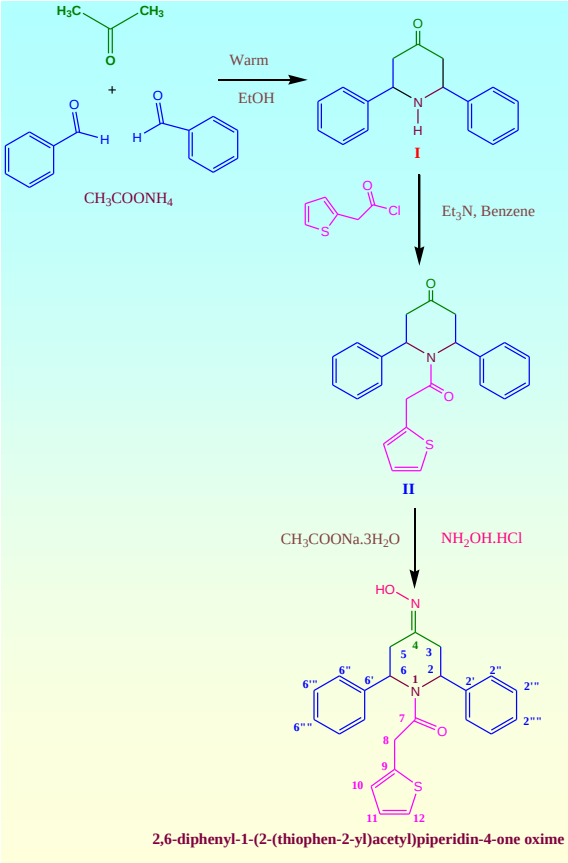


Figure-1.Synthetic route for piperidine 4-one oxime

Spectral Measurements

The reagents used were purchased from commercial suppliers without further purification. Melting points were determined by using an open capillary method and are uncorrected. Thin layer chromatography (TLC) was performed with Aluminium sheet–silica gel 60F254 purchased from Merck. The column chromatography with silica gel (100-200 mesh) using Benzene: Petroleum ether (9:1) as eluent, NMR spectrum was run by BRUKER-400MHZ Spectrophotometer by using $CDCl_3$ as a solvent.

Antibacterial Studies

Collection of Microbes

Bacterial pathogens such as *Escherichia coli*, *Streptococcus pyogens, Pesudomonas aeruginosa, Staphylococcus aureus* were isolated from diverse wounds of 30 persons which were collected on cotton swabs. The isolated microbes were maintained in nutrient agar broth and cultured in nutrient agar medium.

Preparation of Medium and Inoculums

Nutrient agar medium was prepared by dissolving 2.8g of nutrient agar in 100ml of distilled water. The solution was sterilized in an autoclave at 121°C for 15min. It was cooled and poured into sterile Petri dishes to solidify. Each wound infecting bacterium is inoculated on agar by streaking with the swab containing inoculums. Rotate the plate by 60° and repeat the rubbing procedure. This will ensure an even distribution of the inoculum. Whatman No.1 discs (6mm in diameter) were impregnated in the test compound dissolved in DMSO (25,50,75,100 and 125µg/ml) for about half an hour. Commercially available drug disc (amoxycillin 10mg/disc) was used as positive reference standard. Negative controls were also prepared by impregnating the disc of same size on the inoculated agar plates and incubated at ±37°C for about 18-24h.

All the tests were conducted in triplicates. The diameter of zone of inhibition was measured in mm. All the data obtained from the present study were analysed by SPSS -IBM for the statistical significance.

Results and discussion

Spectral analysis of piperidin-4-one oxime

The synthetic method of preparation of 2, 6-diphenyl-1-(2-(thiophen-2-yl) acetyl) piperidin-4-one oxime represented in Scheme 1. Synthesized compound was confirmed by their 1H and ^{13}C NMR spectral studies.Types of spectrum recorded for the synthesized compounds are given in Table-1.

Table 1: Type of the spectrum recorded for the synthesized compound2, 6-diphenyl-1-(2-(thiophen-2-yl) acetyl)piperidin-4-one oxime

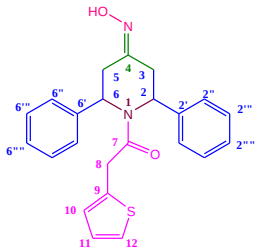
Compound	^{1}H NMR	^{13}C NMR	C=N (cm^{-1})	OH (cm^{-1})	Aliphatic and Aromatic C-H (cm^{-1})
Piperidin-4-one oxime	√	√	1615	3247	3090-2903

In the present investigation the aromatic and ipso carbons were identified by their characteristic absorption in the region of 125-142.1ppm. The two signals of the target compound were exhibited in the most down field region 155.3 and 172.1 ppm. Among these two signals the lower frequency region signal (155.3ppm) was attributed to C=N carbon while the signal observed at in higher frequency region (172.1) was ascribed to amide (N-CO) carbonyl carbon. A signal observed with very low intensity at 58.1 ppm was assigned to C-2 and C-6 carbons of the piperidin ring. Whereas the signals observed at 27.5 ppm and 29.7 ppm was assigned to C-3 and C-5 carbons of the piperidin ring. Similarly, the high intensity signal observed at 36.3 ppm is characteristic for thiophene connected methylene carbon(C-8). Analytical and spectral data of 2,6-phenyl-(1-(2-thiophen-2-yl)acetyl)piperidin-4-one oxime are given in Table 1 and 2.Elemental analysis of 2,6-diphenyl-1-(2-(thiophen-2-yl)acetyl)piperidin-4-one oxime by NMR spectra revealed the following data:In the synthetic piperidine derivative, the substituted electron withdrawing thiophene acetyl group at the nitrogen site of 2,6-diphenyl piperidin-4-one ring is known to exert a minor change in the chemical shifts of the ring carbons and their attached protons. Heterocyclic benzylic protons at C-2 and C-6 position act as highly functionalized scaffolds and the piperidine moiety are used as pharmacophore for preparation of drugs that are in demand to treat various illnesses [10-12].

Performance of 2, 6-diphenyl-1-(2-(thiophene-2-yl) acetyl) piperidin-4-one oxime against wound infecting bacteria

Wound healing capacity of the drugs/biocomposites depend on the control over wound infecting pathogens [13-15]. So that the inflammation is prevented and healing of wound is effected. Hence the present investigation had been focused on the control of growth of wound infecting bacterial flora in terms of zone of inhibition (ZOI) and the results with regard to NMR profiling revealed the nature of synthetic compound.

Table 2: Analytical and spectral data of 2, 6-diphenyl-1-(2-(thiophen-2-yl) acetyl) piperidin-4-one oxime

M.F.: $C_{23}H_{22}N_2O_2S$	**m.p. (^{0}C) : 196-198**	**Yield (%): 50**	**Structure**
IR(KBr, cm^{-1}); 1615 (C=N), 1636 (N-C=O), 3090-2903(C-H aromatic and aliphatic)3247(OH)			
^{1}H NMR(CDCl$_3$, ppm);δ: 2.82 (d, 2H, H-3), 2.61 (d, 1H, H-5a),3.43(d,1H,H5e) 3.80 (s, 2H, H-8),5.13 (s,1H,H-2) 6.30 (s, 1H, H-6), 10.00(s,1H,OH),6.69-7.73 (aromatic protons);			
^{13}C NMR (CDCl$_3$, ppm); δ: 36.3 (C-8), 27.5(C-3)29.7(C-5), 58.0 (C-2, C-6), 172.1 (C-7), 155.3 (C=N), 125.0-142.1 (aromatic carbons).			
Mass : 390.5 (calculated),			

Substitution on the piperidin-4-one by thiophene and amides are considered to be key factors in controlling the wound infecting pathogens. Thiophene and amides high intensive moieties which modulate the electronic effects on heterocyclic rings of the synthesized compound. These atoms may also influence the steric characteristics and the hydrophilic–hydrophobic balance of the molecule and effectively controlling various pathogens at diverse environment [16-18].The concentrations of piperidine oxime were tested from 10µg/ml to 125 µg/ml. There was no or less activity below 25µg/ml where as the concentrations ranging from 50 to 125 µg/ml of piperidine oxime were effectively control the wound pathogens.Pharmacological activity of synthetic piperidine oxime at 100 µg/ml against bacterial isolates from wounds in terms of zone of inhibition in mm was resulted in the following order:

Pseudomonas aeurigenosa>*Escherichia coli* and *Streptococcuspyogens*> *Staphylococcus aureus*

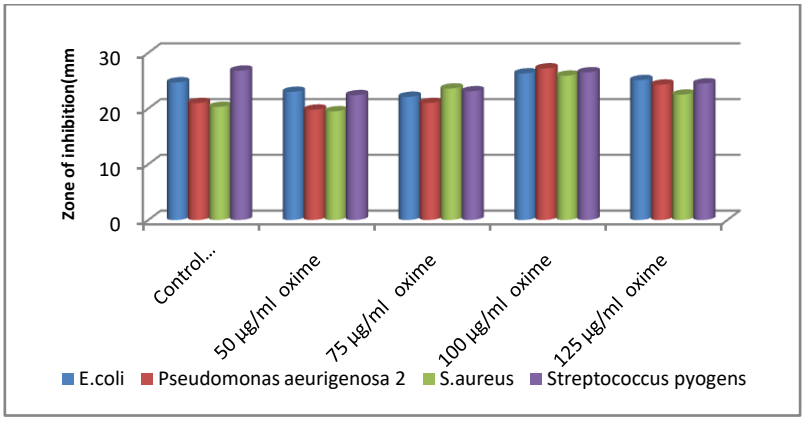


Figure-2.Pharmacological activity of piperidin oxime against wound infecting bacteria

The pharmacological activity in terms of maximum zone of inhibition by the amoxycillin (10mg/ml) for the selected pathogenic bacterial flora was effected from 20.3mm to 26.8mm. When compared to control (amoxicillin), 100 µg/ml of piperidine oxime had effected the maximum control over all wound infecting pathogens.At this concentration the zone of inhibition for *Streptococcus pyogens*is 26.5mm ,for *Staphylococcus aureus* is 25.9mm . ZOI is 27.2mmfor *Pseudomonas aeruginosa*and the effect on *Escherichiacoli* was recorded at 26.3 mm .When compared to 10mg of amoxicillin, 100 µg of piperidinoxime is sufficient to kill the wound pathogenic bacteria (Figure 2).

50 and 75µg/ml of piperidine oxime had effected the control over wound infecting pathogens as ZOI in the following order: Streptococcus *pyogens* (22.4mm) >*Escherichia coli* (23mm) >*Pseudomonas aeruginosa*& *Staphylococcus aureus* (19.6mm).

Table-3. Pharmacological effect of Amoxycillin and Piperidine 4 -one oxime against Wound Bacterial pathogens

Bacterial Pathogens	Amoxycillin (10mg/ml)	Piperidine 4 -one oxime (100µg/ml)
Escherichia coli	24.7 ±0.05	26.3 ±0.02
Pseudomonas aeruginosa	21.1 ±0.02	27.6 ±0.04
Staphylococcus aureus	20.3 ±0.01	25.9 ±0.03
Streptococcus pyogens	26.8 ±0.02	26.5 ±0.01

* Data represented as mean values ± standard derivation, Significance level at $p<0.05$

Various piperidine derived/substituted compounds such as piperidin-4-one oxime ethers, azole 1,4-benzothiazine, *N*-[2-(thiophen-3-yl)ethyl] piperazinyl quinolones,Penta-1,4-diene-3-one derivatives and 4-(1-Pyrrolidinyl) piperidine containing quinazoline and oxime ethers were experimented by many researchers [19-21] revealed that the piperidine nucleus is an essential pharmacophore against a diverse pathogenic microflora.

In the present study, compare to control amoxicillin (10mg/ml) the synthetic piperidine derivative (100µg/ml) was more efficient to inhibit the growth of wound bacterial pathogens(Table-3).

Conclusion

Significant results of the present study revealed the pharmacological activity of synthetic piperidine oxime against bacterial isolates from wounds in terms of zone of inhibition in mm was resulted in the following order: *Streptococcus pyogens*> *Pseudomonas aeurigenosa*> *Escherichia coli* >*Staphylococcus aureus.* Control of inflammation is a major challenge in the wound-healing process that prevents growth of fibroblast and collagen in the damaged tissue. Novel Compounds with aromatic heterocyclic rings employed the steric characteristics and the hydrophilic–hydrophobic balance of the electronic atoms effecting an antinflammatory potential on wound infecting bacteria. Hence from the present study it had been proved that synthetic piperidine oxime can be used in controlling the wound pathogens of various types of infections that prevent the healing process.

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Conflict of Interest

Authors declare that there are no conflicts of interest.

Informed Consent

Yes

Ethical Statement

Not Applicable.

Author Contribution

Dr.T.Yasodha: Project administration, Methodology, Writing – original draftreview & editing, Ms.Vijayalakshmi M.S: Methodology, Writing – review & editing. Mr.Hemachandran M: review & editing, Validation, Data curation.

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