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# Synthesis and antimicrobial studies of some new *N*- benzyl piperidin-4-one derivatives

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**ABSTRACT**

*In a wide search program towards new and efficient antimicrobial agents, some of new N-benzyl piperidine-4-one derivatives were synthesized by the condensation of respective reagents (hydroxylamine hydrochloride, hydrazine hydrochloride, phenyl hydrazine, semicarbazide and thiosemicarbazide). The synthesized compounds were initially identified by their analytical and IR/mass spectral data. For all the synthesized compounds $^{1}H$ and $^{13}C$ NMR spectra were recorded at 500 MHz and 100.6 MHz respectively in DMSO. All the synthesized compounds were tested for their in vitro antibacterial and antifungal activities. The antimicrobial activities of the synthesized compounds showed very potent activity against the fungi, Aspergillus niger and the bacteria, Escherichia coli.*

**Keywords:** Piperidone, Oxime, Hydrazone, Phenyl hydrazone Semicarbazone, Thiosemicarbazone, IR, NMR.

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## INRODUCTION

Many valuable natural products with carbonyl groups are crystallized out only in the form their oximes and semicarbazones form their biological sources. Biological evaluation of hetero cyclic compounds presents an eloquent picture. Drugs in clinical development include modified azoles and a new class of echinocandins and pneumocandins[1-2]. Benzo[*b*]thiophenes are found to possess various biological activities such as antimicrobial[3-4], antioxidant[5], anti-HIV[6], anticancer[7] and antiviral[8] activities. Several bio organic chemists have attempted to study the synthesis and biological evaluation of many hetero cyclic compounds. Perusal of literature shows that work on biological activities of N-benzyl piperdine-4-one derivatives as antimicrobial agent is conspicuously lacking. Hence the present study is concerned with the aim of throwing more light on structural elucidation and antimicrobial activity of N-benzyl piperidine -4-one derivatives.

## MATERIALS AND METHODS

All the chemicals were analytical grade and solvents were distilled before use. Melting points of all the synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity of the compounds were checked by TLC using silica gel. The IR spectra were recorded on SHIMADZU FT-IR spectrometer using KBr pellet. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on Bruker (AMX-400 MHz) using DMSO as solvent and TMS as an internal standard (chemical shifts in δ ppm). The synthesized compounds were tested for their in vitro antimicrobial activity beside the gram positive and gram negative .The primary screen was carried out by agar disc- diffusion method using nutrient agar medium fluconazole and chloromphenical were used as control drug [9].

## RESULTS AND DISCUSSION

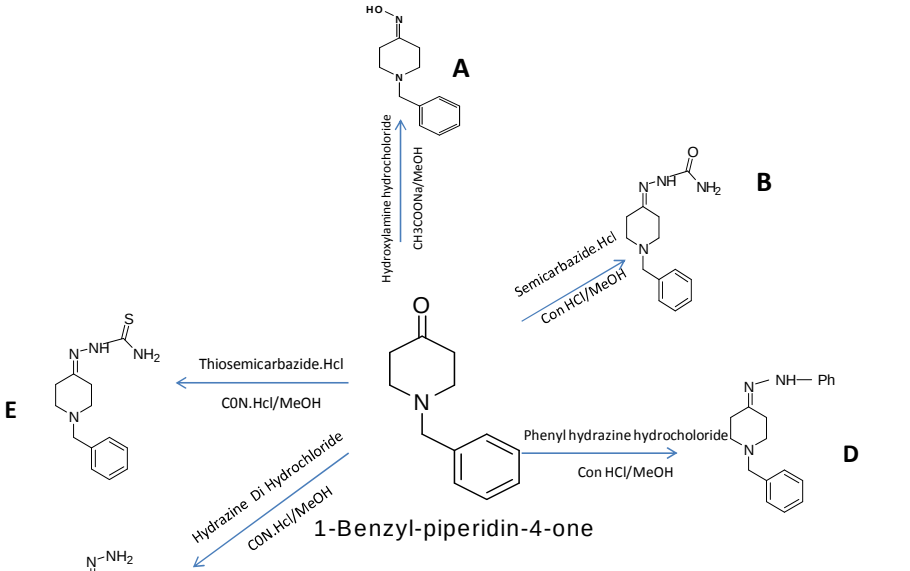
### 3.1 Preparation of compounds

The N-benzyl piperidine-4-one derivatives were synthesized by condensing the N-benzyl piperidine-4-one (0.01mol) in methanol (45ml) and sodium acetate with respective reagents hydroxylamine hydrocholoride, hydrazine hydrocholoride, phenyl hydrazine ,semicarbazide, and thiosemicarbazide . The reactions were refluxed for 3 hours and finally poured into water. The synthesized compounds were recrystallised from ethanol and water and duly characterized using $^{1}H$, and $^{13}C$ nuclear magnetic resonance (NMR) spectra.

### 3.2 The analytical and physical data of the compounds

**Table-1**

| Compound Name | Yield(%) | Melting point($^{0}C$) | Elemental analysis |
|---|---|---|---|
| 1-benzyl piperidin-4-one oxime | 96 | 160-162 | C(%) **70.53** H(%) **7.60** N(%) **13.79** |
| 1-benzyl piperidin-4-one hydrazone | 96 | 196-198 | C(%) **70.83** H(%) **8.40** N(%) **20.79** |
| 1-benzyl piperidin-4-one phenylhydrazone | 86 | 163-165 | C(%) **77.53** H(%)**7.10** N(%) **15.19** |
| 1-benzyl piperidin-4-one semicarbazone | 92 | 165-167 | C(%) **63.43** H(%)**7.29** N(%) **22.65** |
| 1-benzy lpiperidin-4-one thiosemicarbazone | 95 | 158-160 | C(%) **59.69** H(%)**7.09** N(%) **21.28** |




| COMPOUND NAME | LETTERS |
|---|---|
| 1-benzylpiperidin-4-one oxime | A |
| 1-benzylpiperidin-4-one semicarbazone | B |
| 1-benzylpiperidin-4-one hydrazone | C |
| 1-benzylpiperidin-4-one phenylhydrazone | D |
| 1-benzylpiperidin-4-one thiosemicarbazone | E |

SCHEME:1 SYNTHESIS OF *N*- BENZYL PIPERIDIN-4-ONE DERIVATIVES

### 3.3 SPECTRAL ANALYSIS

#### 3.3.1 1-benzylpiperidin-4-one oxime:

Yield: 96% ; **IR ($cm^{-1}$): 3114** (O-H stretching); 1635 (C=N stretching); **$^{1}H$ NMR (δ ppm) :** 3.17 (t, 2H, H-2, J = 5.2 Hz); 3.02 (t, 2H, H-6, J = 5.4 Hz); 2.74 (t, 2H, H-3, J = 5.3 Hz); 2.49 (t, 2H, H-5, J = 5.4 Hz); 4.30 (s, 2H, -N-C$\underline{H}_2$-Ph); 10.78 (s, 1H, OH proton); 7.64-7.42 (m, 5H, aryl protons); **$^{13}C$ NMR (δ ppm) :** 50.69 (C-2); 49.41 (C-6); 27.17 (C-3); 20.63 (C-5); 149.53 (C=N); 58.24 (-N-C$\underline{H}_2$-Ph); 129.32, 131.25, 128.67 (aromatic carbons).

#### 3.3.2 1-benzyl piperidin-4-one hydrazone:

Yield: 96% ; **IR ($cm^{-1}$): 3259** ($NH_2$ stretching); 1622 (C=N stretching); **$^{1}H$ NMR (δ ppm) : yield :96%** 3.68 (d, 2H, H-2, J = 6.0 Hz); 3.49 (t, 2H, H-6); 3.11 (m, 2H, H-3); 2.76 (t, 2H, H-5); 4.67 (s, 2H, -N-C$\underline{H}_2$-Ph); 7.48-7.43 (m, 5H, aryl protons). **$^{13}C$ NMR (δ ppm) :** 49.10 (C-2); 48.29 (C-6); 32.97 (C-3); 27.43 (C-5); 155.31 (C=N); 60.81 (-N-C$\underline{H}_2$-Ph); 131.38- 128.24 (aromatic carbons).

#### 3.3.3 1-benzyl piperidin-4-one phenyl hydrazone:

**yield:86%; IR ($cm^{-1}$) ;** 3195 (C-H stretching); 1597 (C=N stretching); **$^{1}H$ NMR (δ ppm) :** 4.47 (t, 2H, H-2, J = 6.0 Hz); 3.17 (t, 2H, H-6); 2.72 (t, 2H, H-3); 2.00 (t, 2H, H-5); 4.36 (s, 2H, -N-C$\underline{H}_2$-Ph); 4.29 (s, 1H, OH proton)7.48-

7.43 (m, 10H, aryl protons). **$^{13}$C NMR (δ ppm) :** 51.82 (C-2); 49.81 (C-6); 30.08 (C-3); 23.19 (C-5); 145.57 (C=N); 60.26 (-N-$\underline{C}H_2$-Ph); 131.18- 115.59 (aromatic carbons).

**3.3.4 1-benzyl piperidin-4-one semicarbazone: :**
**yield:92%; IR (cm$^{-1}$) 3409,3252** (N-H stretching); 1684 (C=O stretching); 1620 (C=N stretching); **$^1$H NMR (δ ppm) :** 4.38 (t, 2H, H-2); 3.15 (t, 2H, H-6); 2.73 (t, 2H, H-3); 1.98 (t, 2H, H-5); 4.30 (s, 2H, -N-C$\underline{H}_2$-Ph); 4.29 (s, 1H, NH proton)7.48-7.65 (m, 10H, aryl protons); **$^{13}$C NMR (δ ppm):** 51.58 (C-2); 49.20 (C-6); 30.08 (C-3); 23.54 (C-5); 152.77 (C=N); 159.01 (C=O); 60.21 (-N-$\underline{C}H_2$-Ph); 131.33- 128.29 (aromatic carbons).

**3.3.5 1-benzyl piperidin-4-one thiosemicarbazone:**
**Yield:95% ; IR (cm$^{-1}$) 3387** (N-H stretching), 1599 (C=N stretching); 3206 ($NH_2$ stretching); **$^1$H NMR (δ ppm) :** 4.51 (t, 2H, H-2); 3.15 (t, 2H, H-6); 2.71 (t, 2H, H-3); 1.90 (t, 2H, H-5); 3.98 (s, 2H, -N-C$\underline{H}_2$-Ph); 8.1 (s, 1H, NH proton); 10.34 (s, 2H, NH proton)7.47-7.43 (m, 10H, aryl protons). **$^{13}$C NMR (δ ppm):** 51.48 (C-2); 50.37 (C-6); 31.70 (C-3); 25.21 (C-5); 168.22 (C=N); 178.84 (C=S); 59.30 (-N-$\underline{C}H_2$-Ph); 140.44, 130.36 and 128.58 (aromatic carbons).

**3.4 Antimicrobial assay**
Antibiogram was done by disc diffusion method using chemical sample. Petri plates were prepared by pouring 30 ml of NA /PDA medium for bacteria/fungi. The test organism was inoculated on solidified agar plate with the help of micropipette and spread and allowed to dry for 10 mints [10]. The surfaces of media were inoculated with bacteria/fungi from a broth culture. A sterile cotton swab is dipped into a standardized bacterial/ fungi test suspension and used to evenly inoculate the entire surface of the Nutrient agar/PDA plate. Briefly inoculums containing *Escherichia coli*, *Staphylococcus auerus*, *Pseudomonas aeruginos* and *Bacillus subtilis* specie on Nutrient agar plates for bacteria and *Candida albican* and *Aspergillus niger* for fungi were spread on potato dextrose agar for fungus strains. Using sterile forceps, the sterile filter papers (6 mm diameter) containing the crude extracts (50µl) were laid down on the surface of inoculated agar plate. The plates were incubated at 37°C for 24 h for the bacteria and at room temperature (30±1) for 24-48 hr. for yeasts strains. Each sample was tested in triplicate. [11]

**3.5 Measurement of zone of inhibition**
The antimicrobial potential of test compounds was determined on the basis of mean diameter of zone of inhibition around the disc in millimeters. The zones of inhibition of the tested microorganisms by the extracts were measured using a millimeter scale.

**Table:2 Antimicrobial activity**

| Samples | *Escherichia coli* (mm) | *Staphylococcus auerus* (mm) | *Pseudomonas aeruginos* (mm) | *Bacillus subtilis* (mm) | *Candida albican* (mm) | *Aspergillus niger* (mm) |
|---|---|---|---|---|---|---|
| 1-benzylpiperidin-4-one oxime (50µl) | 4.31±0.30 | 5.19±0.36 | 3.75±0.26 | 4.02±0.28 | 4.86±0.34 | 3.23±0.22 |
| 1-benzylpiperidin-4-one semicarbazone (50µl) | 3.72±0.26 | 3.12±0.21 | 2.34±0.16 | 2.01±0.14 | 2.16±0.15 | 1.93±0.13 |
| 1-benzylpiperidin-4-one hydrazone (50µl) | 6.57±0.45 | 4.61±0.32 | 5.14±0.35 | 2.23±0.15 | 3.62±0.25 | 2.56±0.17 |
| 1-benzyllpiperidin-4-one phenylhydrazone (50µl) | 8.06±0.56 | 7.02±0.49 | 6.53±0.45 | 5.79±0.40 | 5.27±0.36 | 5.02±0.35 |
| 1-Phenylpiperidin-4-one thiosemicarbazone (50µl) | 2.39±0.16 | 1.22±0.08 | 1.07±0.07 | 1.82±0.12 | 1.03±0.07 | 2.08±0.14 |
| Control (30µl) | 0 | 0 | 0 | 0 | 0 | 0 |
| Standard (Chloromphenical for bacteria) (30µl) | 11.25±0.78 | 10.87±0.76 | 11.08±0.77 | 10.64±0.74 | - | - |
| Standard (fluconazole for fungal) (30µl ) | - | - | - | - | 10.74±0.75 | 9.53±0.66 |

*Values were expressed as Mean ±SD.*

## CONCLUSION

Some novel N-benzyl piperdine-4-one derivatives (A to E) have been synthesized and evaluated for antimicrobial activities .The results of antimicrobial studies of newly synthesized compounds reveal that the compound 1 – benzyl piperidin- 4-one hydrazone and 1-benzyllpiperidin-4-one phenylhydrazone exhibited significant antibacterial activity and compound 1-benzylpiperidin-4-one oxime, 1-benzyllpiperidin-4-one semicarbazone and 1-benzylpiperidin-4-one thiosemicarbazone showed moderate antifungal activities. The outstanding properties of this new class of antibacterial reagents deserve further investigation in order to clarify the mode of action at molecular

level, responsible for the activity observed. More extensive study is also warranted to determine additional physico chemical and biological parameters to have a deeper insight into structure activity relationship and to optimize the effectiveness of this series of derivatives.

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